Attila Dévay

The Theory and Practice of Pharmaceutical Technology

university textbook

University of Pécs
Institute of
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ATTILA DÉVAY

The Theory and Practice of Pharmaceutical Technology

Development of digital learning materials
for renewable pharmaceutical practice-oriented skills
in English and Hungarian.
Preparing university lecturers for educational challenges of the 21st century."
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Content

Preface

Regarding its past and present, pharmaceutical technology is characteristically a branch of *pharmaceutical science*, which is strongly connected to prevailing pharmaceutical work, the everyday practice of the pharmacist profession.

Most of the European pharmaceutical corporations have been founded in the age of industrialization of the 19^{th}-20^{th} centuries by pharmacists, who, following social demand, made use of centuries of officinal pharmacology experience in a new, industrial environment. A rigid division between officinal preparation of remedies and industrial manufacture of medicine is an erroneous approach. On one hand, it ignores the traditions of pharmaceutical technology; on the other hand it forgets that these fields have strong mutual ties to this day. Obviously, there are differences, but similarity outweighs differences by far.

Due to the ever increasing costs of research the number of new active agents is in global decline, which calls for new opportunities for satisfying therapeutic needs. Pharmaceutical technology must keep pace with this evolution. Traditional pharmaceutical technological procedures (such as tableting or encapsulation) will most assuredly be needed for a long time, but there is also increased interest in modern drug delivery systems. In addition to research on small molecular weight drugs, research on large molecule drugs is playing an ever increasing role, fostered by biotechnological developments. Consequently, such technological methods are needed, which are capable of satisfying the ever increasing demands of therapy with appropriate dosage forms for both small molecule and new type active agents.

Pharmaceutical technology, a branch of pharmaceutical science dealing with drug preparation and production, is an interdisciplinary field of science between technical and biological sciences. The fields of science in closest relation to pharmaceutical technology are *unit operations*, *biopharmacy* and *drug therapy*. These fields are in close interaction, playing a decisive role in the design, production and application of preparations.

This book presents the possibilities of reaching therapeutic goals by means of pharmaceutical technology. These two books are in addition marked to demonstrate and prove that pharmaceutical technology and drug therapy are closely linked but independent disciplines that mutually postulate and complement each other. Whatever approach one takes from either discipline to the other, the two will certainly be connected by a third, new branch of science just becoming independent, namely biopharmacy.

According to our objective, this book is confined to the elementary notions of pharmaceutical technology, with a brief survey of assaying aspects and methods of raw materials and preparations, dosage form theory, the generic and specific requirement systems of the preparation and production of drugs, quality management and packaging technology.

This is the first such electronically published book for pharmacy education, issued in Hungarian and English simultaneously. This format has several advantages over traditional printed books. The internet makes it available to both students of pharmacy and interested professionals anywhere and anytime, with the contents are open for subsequent improvements, supplementation or upgrading. The book exploits multimedia, supporting the transfer, understanding and consolidation of knowledge with illustrations, videos, animations and other ways.

I hereby thank Dr. Gabriella Ujhelyi PhD, hon. associate professor, Head of Pharmaceutical Development, Sanofi-Aventis, Dr. GyörgyUjfalussy, drug development director of EGIS Pharmaceuticals, and Dr. Mária Jelinekné Nikolics, assistant professor of Semmelweis University, University Pharmacy, Department of Pharmacy Administration for their professional advice and the staff of the Institute of Pharmaceutical Technology and Biopharmacy of the University of Pécs, Dr. Klára Mayer assistant professor and Dr. Szilárd Pál assistant lecturer, Dr. Rita Börzsei assistant lecturer, Dr. Nagy Sándor PhD research fellow and assistant lecturers Dr. Péter Diós és Dr. Tivadar Pernecker, for assisting me in compiling this book.

Pécs-Budapest, March 2013 Attila Dévay

The author

The author of this book is Attila Dévay, academic candidate, PhD, dr. hab. associate professor. He has experience in several fields of pharmacy: officinal preparation of remedies, industrial pharmaceutical production, medication supply, pharmaceutical researchand teaching both theoretical and practical subjects in under- and postgraduate collegiate education.

He began his pharmaceutical career in 1973 at EGIS Pharmaceuticals. Later he worked at the Department of Pharmaceutics of Semmelweis University. He spent 1990-1991 at Dalhousie University, Canada as visiting lecturer. He is the founder and director of the Institute of Pharmaceutical Technology and Biopharmacy of the University of Pécs since 2002.

His main fields of education and research are exploring and developing the interrelations of pharmaceutical technology, biopharmacy and drug therapy, design of new generation pharmaceutical products and modelling and optimization of pharmaceutical technological processes.

1 Concept and short history of pharmaceutical technology until present

Medicines are special products, therefore they require special production, shipping and storage conditions.

Technology in general means the mode of preparation of a product which includes all work-processes necessary for manufacturing as well as parameters of these, which are required to produce professional, reproducible, controlled product with guaranteed quality.

Pharmaceutical technology is a science dealing with the preparation and production of medicine. The production of medicines requires technology based on preliminary research and development, strict procuction conditions and *quality control (QA)*.

In the process of research and development, from pre-clinical phase the active pharmaceutical ingredient has already administered in several particular forms of preparation. While preparations do not ensure only accurate dosage, storage, and safe introduction of medicament, but it also do play role in the regulation of drug liberation. Therefore pharmaceutical, pharmaceutical technological, and biopharmacy development start in the initial phase of whole research and development process.

Research is the activity, which aims at expansion of scientific knowledge connected with active substances and preparations in order to improve the efficacy and manufacture of previous medicines.

The history of medicines and medicine making are as old as mankind. The vast body of knowledge, acquired from experience first and scientific research later, upon which modern drug therapy is based, has been amassing ever since prehistory.

Prehistoric man started learning the effects of herbs on the human or for that matter animal body millennia before.

Movie 1. Pharmaceutical memories

Ancient Chinese, Jewish, Mesopotamian, Indian, Native American civilizations have initially evolved on their own, but later civilizations, especially Egyptian, Greek and Roman influenced each other through migration, commerce, wars, conquests and later geographical discoveries (e.g. Native American cultures). As a result, ancient Arabic medicine used to be a great reservoire of Indian, Persian, Babilonian, Syrian, Egyptian, Greek, Jewish and Christian knowledge.

The oldest available herbal book, "De historia plantarum" by *Theophrastus* (371-286 BC) describes 455 plants alog with their effects and influences.

Fig. 1.1.
Theophrastus: De historia plantarum

A görög *Hippokratész* (Kr.e. 460-377) a gondos megfigyelésen és feljegyzéseken alapuló tapasztalati tudást helyezte a gyógyítás középpontjába. Gondos megfigyelésekkel írta le az egyes betegségek tüneteit, próbálta felderíteni a betegségek okait, a szervezet működését. A kos-i Aszklépionban a templomi gyógyítást, tudományos orvoslássá fejleszti. Gyógynövényekből készítettek gyógyszereket és speciális étrendet írtak elő.

The Greek physician *Hippocrates* (460-377 BC) made empirical knowledge based on careful observation and notes the focal point of healing. He made accurate notes on the symptoms of diseases, trying to explore the causes and the functions of the body.

There are frequent referencess to medicines, herbs in the *Bible*. The Book of Ecclesiasticus says: *"The Lord has brought forth medicinal herbs from the ground, and no one sensible will despise them."*

The book *Materia Medica* by another Greek author, *Pedanius Dioscorides* (40-90 AD) summarizes nearly 600 medicines of that age. It describes their ingredients, sources of supply and the way they are prepared. The authority of this book was practically irrefutable for nearly fifteen centuries.

Claudius Galenus (131-201 AD) is considered the "*father of pharmacy*". He had several hundred published books, describing the mode of preparation of preparations and the required tools. His name is preserved in the name of medicines of various ingredients and a particular composition called *galenicals*.

Fig. 1.2.
Claudius Galenus

Collected substances have been processed in manufactural ways; through the preparation of mixtures, extracts and pilula the foundations of modern pharmaceutical technology have been laid.

The Frankish king and Roman emperor *Charles the Great* (768-814 AD) made regular cultivation of herbs mandatory by decree.

Saint Benedict of Nursia considered healing the most important duty of the Benedictine order he founded, thus the first herb gardens had been planted in the monasteries of the order.

One of the most famous of Arabic physician-pharmacist scholars was *Avicenna* (981-1037 AD). His principal work is the five volume Canon of Medicine. It summarizes the main features of nearly 800 medicinal substances. According to his teaching there is no scientific healing without the analysis of the ailment and choosing the right medicines and procedures requires careful consideration.

Fig. 1.3.
Ibn Sīnā, Abū ʿAlī al-Ḥusayn ibn ʿAbd Allāh ibn Sīnā
(سينا ابو علی, سينا بن الله عبد بن الحسين علي أبو; Avicenna)

In the 12th century the decrees „*Constitutiones Melfi*" and „*Novae Constitutiones*" issued by the Holy Roman Emperor *Frederick II of Hohenstauffen* (1194-1250) regulated the processing of pharmaceutical substances and the preparation of medicines in a way that is up-to-date to this day. According to his regulations, pharmacists must

prepare medicines in a separate room (*apotheca*). They also regulated the conditions for preparation and quality of medicines.

At the end of the Reneissance age in the 16th century healing was guided by the teachings of *Galenus* and *Avicenna*, regardless of the effectiveness of their methods. Many patients died as a result of medical treatment. In the course of his hard life, *Paracelsus* (1693-1541) clashed with his contemporary physicians, calling them anti-physicians, who do more harm than good. He emphasized the importance of practice in healing, as opposed to the dead knowledge of books. He had his own errors, but many of his conclusions were essentially correct and lasting. According to him nature has formulas ready, physicians need not add to or take from it. ("*Since nature alone possesses [this] knowledge, it must be nature that compounds the recipe.*") He was the first to use otherwise poisonous compounds of mercury, sulphur and iron. "*All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy.*" He sums up his herbal lore in his book *Herbarius*. He believes that only particular pieces of herbs have potence, called "*quinta essentia*", which can be obtained from herbs through extraction, brewing or scalding.

The anatomy book of *Andreas Vesalius*, published in 1543, represented a new approach and scientific quality. *Anton van Leuwenhoek* (1632-1723) contributed to the exploration of microscopic life by perfecting the microscope.

In the early 18th century the European wealth of pharmacy held approximately one thousand different substances of plant, animal and mineral origin. Zoolite (i.e. of animal origin) drugs (e.g. honey, shellac, cuttle-bone, cod-liver oil, cantharides, cantharis tincture) constitute some ten percent of medicines obtained from nature.

Discoveries and inventions in physics, biology, medicine and pharmacology have laid the foundations for the industrial revolution which begun in the late 18th and culminated in the 19th century. In parallel with intensive social, economical and technological changes natural sciences, especially physics and chemistry, underwent significant developments.

In 1747 *James Lindt* developed a method for preventing scurvy.

In 1755 *Joseph Black* discovered carbon-dioxide and *Carl Wilhelm Scheele* oxygen. *Antoine Laviosier* formulated the law of indestructibility of matter in 1789.

Withering used digitalis for cardiac diseases in 1785.

Edward Jenner introduced pox vaccination in 1796.

In 1801 *Joseph Louis Proust* discovered the law of definite proportions, then in 1808 *John Dalton* the law of multiple proportions.

Antonio Avogadro established the correlations between the weight and number of particles in 1811.

Pelletier and *Caventou* isolated quinine from chinchona in 1820.

With the emergence of the *pharmaceutical industry* the evolution of pharmaceutical research, chemistry, analytics and technology have gathered significant momentum.

Heinrich Emanuel Merck decided in 1827 to produce alkaloids, herbal extracts and other chemicals in industrial quantities.

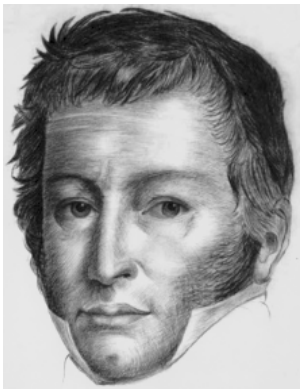

Fig. 1.4.
Heinrich Emanuel Merck

The *Schering* pharmaceutical works grew out from the "Green Pharmacy" of Berlin, winning a silver medal with its high purity chemicals in the Paris World Fair if 1855. The firm became renowned later for its hormonal products and leukemia-, tumor- and sclerosis multiplex drugs.

The isolation of morphine was *Friedrich Sertürner*'s achievement in 1804. By synthesizing carbamide, *Friedrich Wöhler* disproved the so-called "*vis vitalis*" principle in 1828.

Horace Wells used nitrous oxide as anaesthetic in 1845.

In 1847 *James Young* used chloroform.

In 1863 *Mátyás Rozsnyay* developed a method for the production of quinine tannate, a flavourless derivative of quinine, the only pediatric antipyretic of the period. By foregoing patent protection for his discovery, he fostered widespread propagation of the method.

Fig. 1.5.
Mátyás Rozsnyay

August Kekulé described the benzene ring in 1865.

The vaccine for rabies was developed by *Louis Pasteur* in 1885.

The history of acetylsalicylic acid goes back a long way, as the bark of *willow (Salix alba)* had been used, primarily for fever- and pain reduction, before Christ. The chemical structure of the active agent salicylic acid has been established by professor *Hermann Kolbe* of Marburg in 1859. He developed a chemical procedure for the production of salicylic acid, upgrading it to industrial grade synthesis in 1874. The *Kolbe* synthesis of salicylic acid is practically the inception of pharmaceutical industry.

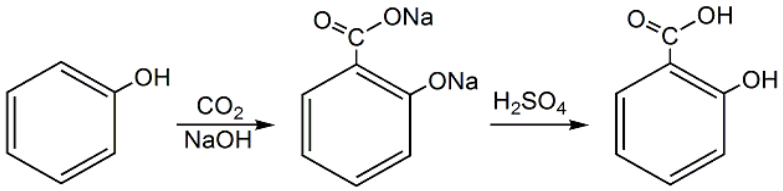

Fig. 1.6.
Production of salicylic acid according to the *Kolbe* synthesis method

Salicylic acid has an unpleasant side effect: taking it regularly caused severe stomach complaints. In 1897 *Felix Hoffmann*, researcher of the German firm *Bayer*, succeeded in producing a derivative by acetylating the phenolic hydroxyl group of salicylic acid. The effectiveness of the derivative was identical, without being so harmful to the mucous membrane of the stomach. This established the foundations of *acetylsalicylic acid* production.

Fig. 1.7.
Felix Hoffman

The great discoveries of the 20th century brought significant changes; primarily through the discovery of antibiotics, vitamins and hormones, which enabled medicine to prevent epidemics and find cures for until then incurable diseases.

In 1902 *Zoltán Vámossy* (1868-1953) discovered the laxative effect of phenolphthalein.

Research physician *Paul Ehrlich* and his Japanese assistant *Sachahiro Hata* tested arsenic compounds for effectivity against spirochaetes. Eventually they reached compound nr. 606. in 1909, employed succesfully in the treatment of the until then incurable disease, syphilis, under the brand name Salvarsan (to avoid adverse effects the improved Neo-salvarsan was issued later).

Fig. 1.8.
Paul Ehrlich

Alexander Fleming found penicillin by chance in 1929, which, along with other antibiotics developed later became the most effective remedy against syphilis and other bacterial infections. Fleming prevented patenting of the method and in the 1950's put it at the disposal of the whole world. In Hungary, it was Fleming himself to hand the penicillin-producing stock over to the National Istitute of Public Health.

By proving the antimicrobial effect of the industrial textile dye Prontosil in 1931-35 *Gerhard Paul Domagk* laid the foundation for the development of sulphonamides.

Waksman introduces streptomycin in 1944 to cure tuberculosis.

Brotzu isolated Cephalosporin C in 1948.

Vitamin B_{12} has been isolated in 1948.

Initially Penicillum notatum, later Penicillum chrysogenum was used to produce penicillin, the later yielding much more penicillin in the *fermentation* process. The first semisynthetic penicillins appeared in 1959. Semisynthetic penicillins are antibiotics, whose base molecule is produced by microorganisms, with a synthetically attached side-chain, which could not be added in fermentation.

The discovery, the structural exploration and production of vitamins A, B_1 and B_2, C, D_2 and E as well as K and P happened in the period between the two world wars. Several Nobel Prizes have been awarded for work done in this field, among others that of Albert Szent-Györgyi, who recognized that peppers from Szeged contain high concentrations of extractable hexuronic acid (later renamed to ascorbic acid).

Frederick Banting and *Charles Best* isolated and tested insulin in 1922. Due to their altruism insulin treatment has quickly spread all over the world. *Sanger* determined the molecular structure in 1955; it has been first synthesized in 1964-65. DNA recombinant synthesis became feasible in the USA in 1978.

Pharmacist *János Kabay* (1896-1936) established the *Alkaloida Chemical Works* in Büdszentmihály in 1927 with meager start capital. He developed a profitable method for the production of morphine from poppy chaff. (Morphine had been extracted from green poppy heads before that.)

Fig. 1.9.
János Kabay

Pharmacist *Gedeon Richter* (1872-1944), the founder of the Hungarian pharmaceutical industry, started his career of experiments and medicine preparation in the Eagle Pharmacy in Budapest. He realized that officinal medicine production will not be able to keep pace with demands in the long term and that industrial scale production is more economic. Initially his new factory produced preparations extracted from animal organs. The first two great success stories of the Chemical Works of Gedeon Richter were Kalmopyrin, patented in 1912, and the disinfectant Hyperol.

Fig. 1.10.
Gedeon Richter

The development of the drugs Mydocalm, Trioxazin, Grandaxin, Lycurim, Zitostop, Frenolon, Depersolon, Libexin, Phlogosam, Probon, Sensit and Cavinton are remarkable achievements of Hungarian pharmaceutical research.

Development in modern pharmaceutics is the aggregate of expedient, scheduled activities aimed at exploiting discoveries of pharmaceutical research, licensing and marketing medicines.

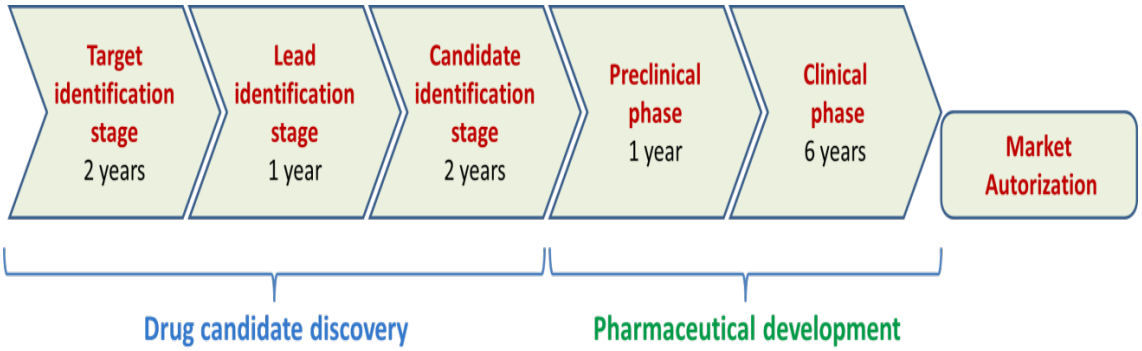

Fig. 1.11.
Main phases of drug development

The accurate implementation of technology and manufacturing of products of appropriate quality require such raw materials, equipment, production environment (building, premises, headroom, temperature, humidity) and last, but not least experienced and skilled workforce that make manufacturing possible. Therefore, *quality management* and *quality control* must consider all the parameters that are relevant to manufacturability and the quality of the end product.

Therefore, *preparation and manufacture of medicine* that conforms to international quality standards must be carried out by a skilled, professional staff, in properly designed and officially approved premises, using appropriate equipment and technology as well as quality management system that guarantees comprehensively safe and reproducible manufacturing for the product.

Today the production, handling, controlling, distribution and use of pharmaceutical substances and preparations require the establishment and application of such control systems that ensure that quality requirements are fulfilled. This induced the development of the following internationally accepted "good practice" policies:

- *GCP, Good Clinical (drug trial) Practice,*
- *GCLP, Good Clinical Laboratory Practice,*
- *GLP, Good Laboratory Practice,*
- *GMP, Good (Pharmaceutical) Manufacturing Practice,*
- *GAMP, Automated Manufacturing Practice,*
- *GVP, Good Pharmacovigilance Practice,*
- *GDP Good Distribution Practice,*
- *GPP, Good Pharmacy Practice*

Good Pharmaceutical Manufacturing Practice (GMP) is a segment of quality management which, if observed, guarantees that products are always manufactured and controlled according to such quality requirements that ensure that these products fulfill the requirements of the approval for trade and are suited for their intended purpose.

No kind of pharmaceutical production activity (including the production and packaging of acive pharmaceutical ingredients, production, quality control of pharmaceutical preparations) shall be performed without a valid licence for pharmaceutical manufacturing issued by the relevant authority.

Further historical aspects of the evolution of pharmaceutical technology are detailed in other chapters of this book.

Questions

1) What is pharmaceutical research?
2) What are the main characteristics of pharmaceutical development?
3) How would you define the notion of technology?
4) What are the objectives of preformulation studies?
5) What does „batch" mean?
6) What are the principal criteria of Good Pharmaceutical Manufacturing Practice (GMP)?

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Recommended websites

http://www.historylearningsite.co.uk/history_of_medicine.htm

http://books.google.hu/books?id=Btx3M5t6lDEC&printsec=frontcover&hl=hu#v=onepage&q&f=false

2 Substances for pharmaceutical use

Every organic or inorganic substance used as an active agent or excipient in the preparation of human- or veterinary medicinal products is a *substance for pharmaceutical use (Corpora ad usum pharmaceuticum)*. These substances can be obtained either from natural sources or they can be produced from various raw materials by extraction, chemical synthesis, distillation, fermentation, nano- or biotechnological methods.

Substances for pharmaceutical use can be applied as medicine in themselves or as raw material in the preparation of pharmaceutical preparations.

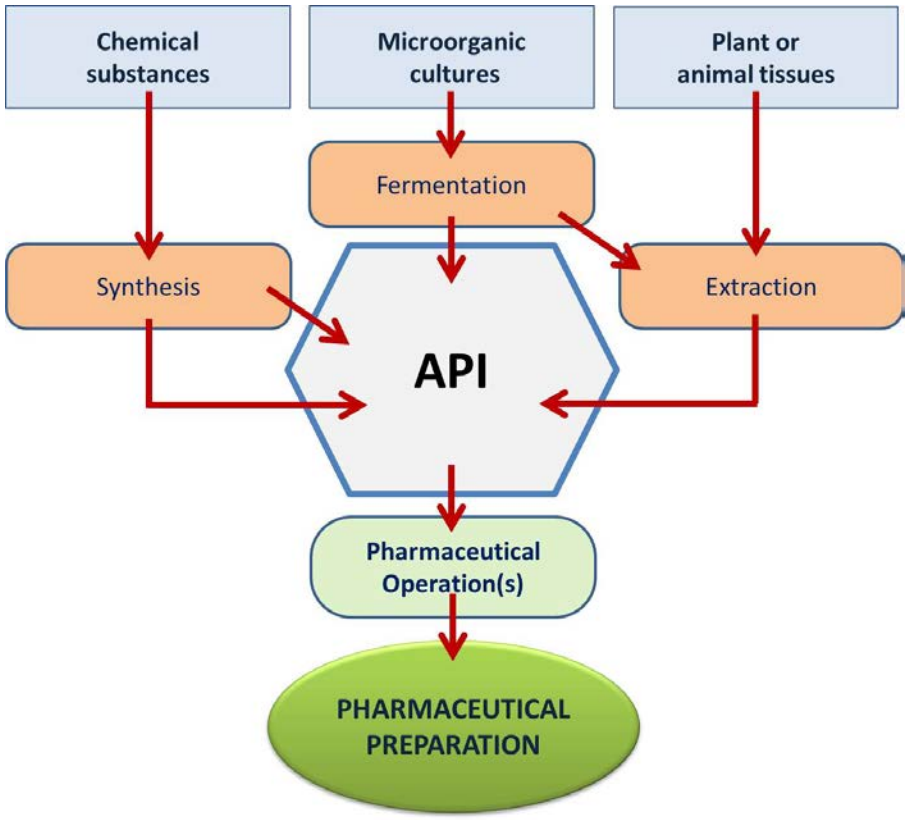

Fig. 2.1.
Production and employment of substances for pharmaceutical use

The history of substances for pharmaceutical use is concurrent with the history of healing, which is as old as mankind.

Thus the knowledge of nature, illnesses and uses for substances has been accumulating for ages. The evolution of pharmacology had been empirical for a long time, with skilled healers applying, enriching, methodizing and advancing this vast body of experience through the millennia. The usability of new substances of plant, animal or mineral origin as medicine were often the result of accidental observations. Scientific pharmacology evolved with other natural sciences, with its rate of development significantly accelerating in recent centuries.

In order to ensure safety and technological reproducibility, pharmaceutical substances (allowing for justified and permitted exceptions) need to be identified and their active ingredient content determined with appropriate methods.

According to their origin, *pharmaceutical substances* form the following groups:

- substances of mineral origin (e.g. white clay, paraffin, vaseline),
- herb-derived substances (e.g. chamomile blossom, valerian root),
- animal-derived substances (zoolite) (e.g. beeswax, pepsin, gelatine),
- synthetic compounds (e.g. acetyl-salicylic acid, diclofenac),
- semi-synthetic substances (e.g. morphine derivatives),
- biochemical pharmaceutical substances (e.g. antibiotics, vitamin B12),
- pharmaceutical substances produced with biotechnology (e.g. insuline, growth hormone),
- nano substances.

2.1 Substances of mineral origin

The body needs various minerals, which, usually in the form of salts, contain among others potassium, sodium, calcium, magnesium, phosphor and sulphur.

Table 2-I.
Pharmacopeial substances of mineral origin

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Alum	Alumen
Aluminium chloride hexahydrate	Aluminii chloridum hexahydricum (Alum. chlor. hexahydr.)
Aluminium oxide, hydrated	Aluminii oxidum hydricum (Alum. oxid. hydr.)
Aluminium sulphate	Aluminii sulfas (Alum. sulf.)
Ammonium bromide	Ammonii bromidum (Ammon. brom.)
Ammonium chloride	Ammonii chloridum (Ammon. chlor.)
Calcium carbonate	Calcii carbonas (Calc. carb.)
Calcium chloride hexahydrate	Calcii chloridum hexahydricum (Calc. chlor. hexahydr.)
Calcium gluconate	Calcii gluconas (Calc. glucon.)
Calcium glycerophosphate	Calcii glycerophosphas (Calc. glycerophosph.)
Calcium hydrogen phosphate dihydrate	Calcii hydrogenophosphas dihydricus (Calc. hydrogenophosph. dihydr.)
Calcium lactate pentahydrate	Calcii lactas pentahydricus (Calc. lact. pentahydr.)
Ferrous sulphate heptahydrate	Ferrosi sulfas heptahydricus (Ferros. sulf. heptahydr.)
Ferric chloride hexahydrate	Ferri chloridum hexahydricum (Ferri chlor. hexahydr.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Iron for homoeopathic preparations	Ferrum ad praeparationes homoeopathicas (Ferr. ad praep. hom.)
Iodine	Iodum (Iod.)
Potassium bromide	Kalii bromidum (Kal. brom.)
Potassium carbonate	Kalii carbonas (Kal. carb.)
Potassium chloride	Kalii chloridum (Kal. chlor.)
Potassium dihydrogen phosphate	Kalii dihydrogenophosphas (Kal. dihydrogenophosph.)
Potassium hydrogen carbonate	Kalii hydrogenocarbonas (Kal. hydrogenocarb.)
Potassium hydrogen tartrate	Kalii hydrogenotartras (Kal. hydrogenotartr.)
Potassium iodide	Kalii iodidum (Kal. iod.)
Potassium sodium tartrate tetrahydrate	Kalii natrii tartras tetrahydricus (Kal. natr. tartr. tetrahydr.)
Potassium nitrate	Kalii nitras (Kal. nitr.)
Potassium sulphate	Kalii sulfas (Kal. sulf.)
Magnesium carbonate, light	Magnesii subcarbonas levis (Magn. subcarb. lev.)
Magnesium chloride hexahydrate	Magnesii chloridum hexahydricum (Magn. chlor. hexahydr.)
Magnesium citrate anhydrous	Magnesii citras anhydricus
Magnesium citrate dodecahydrate	Magnesii citras dodecahydricus
Magnesium oxide, light	Magnesii oxidum leve (Magn. oxid. lev.)
Magnesium sulfate heptahydrate	Magnesii sulfas heptahydricus (Magn. sulf. heptahydr.)
Sodium bromide	Natrii bromidum (Natr. brom.)
Sodium carbonate decahydrate	Natrii carbonas decahydricus (Natr. carb. decahydr.)
Sodium chloride	Natrii chloridum (Natr. chlor.)
Sodium dihydrogen phosphate dihydrate	Natrii dihydrogenophosphas dihydricus (Natr. dihydrogenophosph. dihydr.)
Sodium metabisulfite	Natrii metabisulfis (Natr. metabisulfis)
Sodium fluoride	Natrii fluoridum (Natr. fluor.)
Sodium hydrogen carbonate	Natrii hydrogenocarbonas (Natr. hydrogenocarb.)
Sodium hydroxide	Natrii hydroxidum (Natr. hydroxid.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Sodium iodide	Natrii iodidum (Natr. iodid.)
Sodium nitrite	Natrii nitris (Natr. nitris)
Sodium sulfate decahydrate	Natrii sulfas decahydricus (Natr. sulf. decahydr.)
Calcium phosphate	Tricalcii phosphas (Tricalc. phosph.)
Potassium citrate	Kalii citras (Kal. citr.)
Sodium citrate	Natrii citras (Natr. citr.)

2.2 Herb-derived substances

Any plant, whether in whole, broken or cut to pieces as well as any unprocessed, fresh or dried plant part is considered a *herb-derived substance*. Untreated vegetal secretions are also considered substances of plant origin. Every substance, whose active ingredients are one or more herbal drugs or drug preparations and nothing else or the combination of such herbal drug(s) and drug preparation(s) are considered *herbal medicines*.

Table 2-II.
Pharmacopeial herbs

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Wormwood	Absinthii herba (Absinth. herb.)
Yarrow	Millefolii herba (Millefol. herb.)
Agar	Agar
Agrimony	Agrimoniae herba (Agrimon. herb.)
Aloes, cape	Aloe capensis (Aloe cap.)
Marshmallow leaf	Althaeae folium (Alth. fol.)
Marshmallow root	Althaeae radix (Alth. rad.)
Maize starch	Maydis amylum (Mayd. amyl.)
Potato starch	Solani amylum (Solan. amyl.)
Wheat starch	Tritici amylum (Trit. amyl.)
Angelica root	Angelicae radix (Angel. rad.)
Star anise	Anisi stellati fructus (Anis. stell. fruct.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Aniseed	Anisi fructus (Anis. fruct.)
Bitter-orange epicarp and mesocarp	Aurantii amari epicarpium et mesocarpium
Peru balsam	Balsamum peruvianum (Bals. peruv.)
Belladonna leaf	Belladonnae folium (Bellad. fol.)
Birch leaf	Betulae folium (Betul. fol.)
Calendula flower	Calendulae flos (Calend. fl.)
Capsicum	Capsici fructus
Caraway fruit	Carvi fructus (Carv. fruct.)
Clove	Caryophylli flos (Caryoph. fl.)
Centaury	Centaurii herba (Centaur. herb.)
Matricaria flower	Matricariae flos (Matricar. fl.)
Greater celandine	Chelidonii herba (Chelidon. herb.)
Cinchona bark	Cinchonae cortex (Cinchon. cort.)
Coriander	Coriandri fructus (Coriandr. fruct.)
Hawthorn berries	Crataegi fructus (Crat. fruct.)
Hawthorn leaf and flower	Crataegi folium cum flore (Crat. fol. cum flor.)
Dog rose	Rosae pseudo-fructus (Rosae pseudo-fruct.)
Equisetum stem	Equiseti herba (Equis. herb.)
Fennel, sweet	Foeniculi dulcis fructus (Foenic. dulc. fruct.)
Frangula bark	Frangulae cortex (Frang. cort.)
Gentian root	Gentianae radix (Gent. rad.)
Acacia	Acaciae gummi (Acac. gummi)
Couch grass rhizome	Graminis rhizoma (Gramin. rhiz.)
St. John’s wort	Hyperici herba (Hyperic. herb.)
Ipecacuanha root	Ipecacuanhae radix (Ipec. rad.)
Wild pansy (flowering aerial parts)	Violae herba cum flore (Viol. herb. cum flor.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Juniper	Juniperi pseudo-fructus (Junip. pseudo-fruct.)
Lavender flos	Lavandulae flos (Lavand. fl.)
Lovage root	Levistici radix (Levist. rad.)
Iceland moss	Lichen islandicus (Lichen island.)
Linseed	Lini semen (Lini sem.)
Liquorice root	Liquiritiae radix (Liquir. rad.)
Hop strobile	Lupuli flos (Lupuli fl.)
Mallow flower	Malvae sylvestris flos (Malvae sylv. fl.)
White horehound	Marrubii herba (Marrub. herb.)
Honey	Mel
Melilot	Meliloti herba (Melilot. herb.)
Melissa leaf	Melissae folium (Meliss. fol.)
Peppermint leaf	Menthae piperitae folium (Menth. pip. fol.)
Restharrow root	Ononidis radix (Ononid. rad.)
Red poppy petals	Papaveris rhoeados flos (Papaver. rhoead. fl.)
Ribwort plantain	Plantaginis lanceolatae folium (Plantag. lanc. fol.)
Primula root	Primulae radix (Primul rad.)
Oak bark	Quercus cortex (Querc. cort.)
Rhatany root	Ratanhiae radix (Ratanh. rad.)
Rhubarb	Rhei radix (Rhei rad.)
Sage leaf (Salvia officinalis)	Salviae officinalis folium (Salv. off. fol.)
Elder flower	Sambuci flos (Samb. fl.)
Senna leaf	Sennae folium (Sennae fol.)
Senna pods, alexandrian, tinnevelly	Sennae fructus angustifoliae (Senn. fruct. angustifol.), Sennae fructus acutifoliae (Senn. fruct. acutifol.)
Wild thyme	Serpylli herba (Serpyl. herb.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Stramonium leaf	Stramonii folium (Stramon. fol.)
Thyme	Thymi herba (Thymi herb.)
Lime flower	Tiliae flos (Tiliae fl.)
Tragacanth	Tragacantha (Tragacanth.)
Bogbean leaf	Menyanthidis trifoliatae folium (Menyanth. trifol. fol.)
Nettle leaf	Urticae folium (Urtic. fol.)
Bearberry leaf	Uvae ursi folium (Uvae ursi fol.)
Valerian root	Valerianae radix (Valer. rad.)
Mullein flower	Verbasci flos (Verbasci fl.)

2.3 Volatile oils

Due to their curative effect or fragrant components volatile oils extracted from herbs are an important portion of pharmaceutical substances.

Table 2-III.
Pharmacopeial volatile oils

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Anise oil	Anisi aetheroleum (Anis. aetherol.)
Sweet orange oil	Aurantii dulcis aetheroleum (Aurant. dulc. aetherol.)
Caraway oil	Carvi aetheroleum (Carvi aetherol.)
Clove oil	Caryophylli floris aetheroleum (Caryoph. flor. aetherol.)
Matricaria oil	Matricariae aetheroleum (Matricar. aetherol.)
Cassia oil	Cinnamomi cassiae aetheroleum (Cinnam. cass. aetherol.)
Citronella oil	Limonis aetheroleum (Limon. aetherol.)
Eucalyptus oil	Eucalypti aetheroleum (Eucal. aetherol.)
Bitter-fennel fruit oil	Foeniculi amari fructus aetheroleum (Foenicul. amar. fruct. aetherol.)
Juniper oil	Juniperi aetheroleum (Junip. aetherol.)
Lavender oil	Lavandulae aetheroleum (Lavand. aetherol.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Peppermint oil	Menthae piperitae aetheroleum (Menth. pip. aetherol.)
Rosemary oil	Rosmarini aetheroleum (Rosmar. aetherol.)
Thyme oil	Thymi aetheroleum (Thymi aetherol.)

2.4 Other herb-derived substances

There are numerous substances to be obtained by processing plants, extracting their substances, which can be used as active ingredients or excipients. Refining starch and gelatin, preparation of capsule shells is significant to this day.

Table 2-IV.
Other pharmacopeial herb-derived substances

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Agar	Agar
Sunflower oil, refined	Helianthi annui oleum raffinatum (Helianth. annui ol. raffinat.)
Linseed oil, virgin	Lini oleum virginale (Lin. ol. virgin.)
Castor oil, virgin	Ricini oleum virginale (Ricin. ol. virgin.)

2.5 Substances of animal-derived substances

Today the number of pharmaceutical substances of animal origin is insignificant.

Table 2-V.
Pharmacopeial animal-derived substances

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Beeswax, white	Cera alba (Cer. alb.)
Wool fat	Adeps lanae (Adeps lan.)
Cetyl palmitate	Cetylis palmitas (Cetyl. palm.)
Wool alcohols	Alcoholes adipis lanae
Cod-liver oil (Type A)	Jecoris aselli oleum A (Jecor. aselli ol. A)

2.6 Synthetic and other substances

Industrial pharmaceutical production and progress of the chemical industry gradually supplanted natural substances.

Table 2-VI.
Synthetic and other pharmacopeial substances

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Acetone	Acetonum (Aceton.)
Acetic acid, glacial	Acidum aceticum glaciale (Acid. acet. glac.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Acetylsalicylic acid	Acidum acetylsalicylicum (Acid. acetylsalicyl.)
Glycine	Glycinum (Glycin.)
Aspartic acid	Acidum asparticum (Acid. aspart.)
Benzoic acid	Acidum benzoicum (Acid. benzoic.)
Boric acid	Acidum boricum (Acid. bor.)
Hydrochloric acid, concentrated	Acidum hydrochloridum concentratum (Acid. hydrochlor. conc.)
Hydrochloric acid, dilute	Acidum hydrochloridum dilutum (Acid. hydrochlor. dil.)
Citric acid monohydrate	Acidum citricum monohydricum (Acid. citr.monohydr.)
Oleic acid	Acidum oleicum (Acid. oleic.)
Phosphoric acid, concentrated	Acidum phosphoricum concentratum (Acid. phosph. conc.)
Silica, colloidal anhydrous	Silica colloidalis anhydrica (Silic. coll. anhydr.)
Sorbic acid	Acidum sorbicum (Acid. sorb.)
Tartaric acid	Acidum tartaricum (Acid. tart.)
Trichloroacetic acid	Acidum trichloraceticum (Acid. trichloracet.)
Acriflavinium monochloride	Acriflavini monochloridum (Acriflavin. monochlor.)
Hard fat	Adeps solidus (Adeps solid.)
Hard fat	Adeps solidus (Adeps solid.)
Ethacridine lactate monohydrate	Ethacridini lactas monohydricus (Ethacridin. lact. monohydr.)
Ether	Aether
Ethyl acetate	Ethylis acetas (Ethyl. acet.)
Ethyl oleate	Ethylis oleas (Ethyl. oleas)
Ethylmorphine hydrochloride	Ethylmorphini hydrochloridum (Ethylmorphin. hydrochlor.)
Ethanol (96 per cent)	Ethanolum (96 per centum) (Ethanol. 96 %)
Cetyl alcohol	Alcohol cetylicus (Alc. cetyl.)
Cetostearyl alcohol	Alcohol cetylicus et stearylicus (Alc. cetyl. et stearyl.)
Isopropyl alcohol	Alcohol isopropylicus (Alc. isopropyl.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Poly(vinyl alcohol)	Poly(alcohol vinylicus) [Poly(alc. vinyl.)]
Alum	Alumen
Aluminium chloride, hexahydrate	Aluminii chloridum hexahydricum (Alum. chlor. hexahydr.)
Ammonia solution, concentrated	Ammoniae solutio concentrata (Ammon. sol. conc.)
Ammonium bromide	Ammonii bromidum (Ammon. brom.)
Ammonium chloride	Ammonii chloridum (Ammon. chlor.)
Apomorphine hydrochloride	Apomorphini hydrochloridum (Apomorph. hydrochlor.)
Water, purified	Aqua purificata (Aqu. purif.)
Water, purified	Aqua purificata (Aqu. purif.)
Water for injections	Aqua ad iniectabilia (Aqu. ad ini.)
Silver, colloidal, for external use	Argentum colloidale ad usum externum
Silver nitrate	Argenti nitras (Argent. nitr.)
Silver nitrate	Argenti nitras (Argent. nitr.)
Arsenious trioxide for homoeopathic preparations	Arsenii trioxidum ad praeparationes homeopathicas (Arsen. trioxid. ad praep. hom.)
Atropine sulfate	Atropini sulfas (Atrop. sulf.)
Barbital	Barbitalum (Barbital.)
Barium sulfate	Barii sulfas (Barii sulf.)
Benzalkonium chloride	Benzalkonii chloridum (Benzalkon. chlor.)
Benzocaine	Benzocainum (Benzocain.)
Benzyl benzoate	Benzylis benzoas (Benzyl. benzoas)
Bismuth subcarbonate	Bismuthi subcarbonas (Bism. subcarb.)
Bismuth subgallate	Bismuthi subgallas (Bism. subgall.)
Bismuth subnitrate, heavy	Bismuthi subnitras ponderosus (Bism. subnitr. pond.)
Bismuth subsalicylate	Bismuthi subsalicylas (Bism. subsalicyl.)
Calcium gluconate	Calcii gluconas (Calc. glucon.)
Calcium glycerophosphate	Calcii glycerophosphas (Calc. glycerophosph.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Calcium lactate pentahydrate	Calcii lactas pentahydricus (Calc. lact. pentahydr.)
Camphor, racemic	Camphora racemica (Camphor. racem.)
Carbomers	Carbomera
Carmellose sodium	Carmellosum natricum (Carmellos. natr.)
Cellulose acetate phthalate	Cellulosi acetas phthalas (Cell. acet. phthal.)
Cellulose, microcrystalline	Cellulosum microcristallinum (Cell. microcrist.)
Cetrimide	Cetrimidum (Cetrimid.)
Quinidine sulfate	Chinidini sulfas (Chinidin. sulf.)
Quinine hydrochloride	Chinini hydrochloridum (Chinin. hydrochlor.)
Quinine sulfate	Chinini sulfas (Chinin. sulf.)
Chloral hydrate	Chlorali hydras (Chloral. hydr.)
Chloramphenicol	Chloramphenicolum (Chloramphen.)
Chlorhexidine digluconate solution	Chlorhexidini digluconatis solutio (Chlorhexid. digluconat. sol.)
Chlorobutanol hemihydrate	Chlorobutanolum hemihydricum (Chlorobutanol. hemihydr.)
Cholesterol	Cholesterolum (Cholesterol.)
Clioquinol	Clioquinolum (Clioquin.)
Cocaine hydrochloride	Cocaini hydrochloridum (Cocain. hydrochlor.)
Codeine hydrochloride dehydrate	Codeini hydrochloridum dihydricum (Codein. hydrochlor. dihydr.)
Codeine phosphate sesquihydrate	Codeini phosphas sesquihydricus (Codein. phosph. sesquihydr.)
Copovidone	Copovidonum
Dithranol	Dithranolum (Dithranol.)
Emetine hydrochloride heptahydrate	Emetini hydrochloridum heptahydricum (Emetin. hydrochlor. heptahydr.)
Ephedrine hydrochloride, racemic	Ephedrini racemici hydrochloridum (Ephedrin. racem. hydrochlor.)
Ergotamine tartrate	Ergotamini tartras (Ergotamin. tartr.)
Erythromycin	Erythromycinum (Erythromycin.)
Erythromycin lactobionate	Erythromycini lactobionas (Erythromycin. lactobion.)
Fluorescein sodium	Fluoresceinum natricum (Fluorescein. natr.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Formaldehyde solution (35 per cent)	Formaldehydi solutio (35 per centum) (Formald. sol. 35 %)
Gentamicin sulphate	Gentamicini sulfas (Gentamicin. sulf.)
Glycerol monostearate 40-55	Glyceroli monostearas 40-55 (Glycerol. monostear. 40-55)
Hexobarbital	Hexobarbitalum (Hexobarbital.)
Homatropine hydrobromide	Homatropini hydrobromidum (Homatropin. hydrobrom.)
Hydrogen peroxide solution (30 per cent)	Hydrogenii peroxidum 30 per centum (Hydrogen. peroxyd. 30 per cent.)
Hydroxyethylcellulose	Hydroxyethylcellulosum (Hydroxyethylcell.)
Hydroxypropylcellulose	Hydroxypropylcellulosum (Hydroxypropylcell.)
Indometacin	Indometacinum (Indometacin.)
Isoprenaline hydrochloride	Isoprenalini hydrochloridum (Isoprenalin. hydrochlor.)
Potassium perchlorate	Kalii perchloras (Kal. perchlor.)
Potassium permanganate	Kalii permanganas (Kal. permang.)
Potassium sorbate	Kalii sorbas (Kal. sorb.)
Cresol, crude	Cresolum crudum (Cresol. crud.)
Lidocaine hydrochloride	Lidocaini hydrochloridum (Lidocain. hydrochlor.)
Lidocaine	Lidocainum (Lidocain.)
Lithium carbonate	Lithii carbonas (Lith. carb.)
Macrogol 400	Macrogolum (400-as típus)
Macrogol 1500	Macrogolum (1500-as típus)
Macrogol 4000	Macrogolum (4000-es típus)
Macrogol stearate	Macrogoli stearas
Magnesium aspartate dihydrate	Magnesii aspartas dihydricus
Magnesium peroxide	Magnesii peroxidum (Magn. peroxid.)
Magnesium stearate	Magnesii stearas (Magn. stear.)
Methenamine	Methenaminum (Methenamin.)
Methylcellulose	Methylcellulosum (Methylcellulos.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Homatropine methylbromide	Homatropini methylbromidum (Homatropin. methylbrom.)
Methyl parahydroxybenzoate	Methylis parahydroxybenzoas (Methyl. parahydroxybenz.)
Methyl salicylate	Methylis salicylas (Methyl. salicyl.)
Methylrosanilinium chloride	Methylrosanilinii chloridum (Methylros. chlor.)
Methylthioninium chloride	Methylthioninii chloridum (Methylthionin. chlor.)
Metronidazole	Metronidazolum (Metronidazol.)
Morphine hydrochloride	Morphini hydrochloridum (Morphin. hydrochlor.)
Naphazoline hydrochloride	Naphazolini hydrochloridum (Naphazolin. hydrochlor.)
Sodium acetate trihydrate	Natrii acetas trihydricus (Natr. acet. trihydr.)
Sodium benzoate	Natrii benzoas (Natr. benz.)
Sodium starch glycolate (type A, B, C)	Carboxymethylamylum natricum A, ~ B, ~ C
Disodium edetate	Dinatrii edetas (Dinatr. edet.)
Sodium hydroxide	Natrii hydroxidum (Natr. hydroxid.)
Sodium laurilsulfate	Natrii laurilsulfas (Natr. laurilsulf.)
Sodium nitrite	Natrii nitris (Natr. nitris)
Borax	Borax
Sodium thiosulfate	Natrii thiosulfas (Natr. thiosulf.)
Neomycin sulfate	Neomycini sulfas (Neomycin. sulf.)
Nikethamide	Nicethamidum (Nicethamid.)
Nitrofurantoin	Nitrofurantoinum (Nitrofurantoin.)
Metamizole sodium	Metamizolum natricum (Metamizol. natr.)
Nystatin	Nystatinum (Nystatin.)
Oxytetracycline hydrochloride	Oxytetracyclini hydrochloridum (Oxytetracyclin. hydrochlor.)
Papaverine hydrochloride	Papaverini hydrochloridum (Papaverin. hydrochlor.)
Paracetamol	Paracetamolum (Paracetamol.)
Paraffin, liquid	Paraffinum liquidum (Paraff. liqu.)
Paraffin, hard	Paraffinum solidum (Paraff. solid.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Paraldehyde	Paraldehydum (Paraldehyd.)
Phenazone	Phenazonum (Phenazon.)
Phenobarbital	Phenobarbitalum (Phenobarbital.)
Phenobarbital sodium	Phenobarbitalum natricum (Phenobarb. natr.)
Phenolphthalein	Phenolphthaleinum (Phenolphtalein.)
Phenol	Phenolum (Phenol.)
Phenylbutazone	Phenylbutazonum (Phenylbutazon.)
Phenylmercuric borate	Phenylhydrargyri boras (Phenylhydrarg. bor.)
Physostigmine salicylate	Physostigmini salicylas (Physost. salicyl.)
Pilocarpine hydrochloride	Pilocarpini hydrochloridum (Pilocarpin. hydrochlor.)
Polymyxin B sulfate	Polymyxini B sulfas (Polymyxin. B sulf.)
Polysorbate 20	Polysorbatum 20 (Polysorbat. 20)
Polysorbate 60	Polysorbatum 60 (Polysorbat. 60)
Polysorbate 80	Polysorbatum 80 (Polysorbat. 80)
Povidone	Povidonum (Povidon.)
Prednisolone	Prednisolonum (Prednisolon.)
Procaine hydrochloride	Procaini hydrochloridum (Procain. hydrochlor.)
Promethazine hydrochloride	Prometazini hydrochloridum (Prometazin. hydrochlor.)
Propylene glycol	Propylenglycolum (Propylenglycol.)
Propyl parahydroxybenzoate	Propylis parahydroxybenzoas (Propyl. parahydroxybenz.)
Resorcinol	Resorcinolum (Resorcinol.)
Rifampicin	Rifampicinum (Rifampicin.)
Saccharin sodium	Saccharinum natricum (Saccharin. natr.)
Scopolamine hydrobromide	Scopolamini hydrobromidum (Scopolamin. hydrobrom.)
Sorbitan laurate	Sorbitani lauras (Sorbitan. laur.)
Sorbitol	Sorbitolum (Sorbitol.)
Sulfacetamide sodium	Sulfacetamidum natricum (Sulfacetamid. natr.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Sulfadimidine	Sulfadimidinum (Sulfadimidin.)
Sulfathiazole	Sulfathiazolum (Sulfathiazol.)
Sulphur for external use	Sulfur ad usum externum
Talc	Talcum (Talc.)
Tetracaine hydrochloride	Tetracaini hydrochloridum (Tetracain. hydrochlor.)
Thiomersal	Thiomersalum (Thiomersal.)
Thymol	Thymolum (Thymol.)
Titanium dioxide	Titanii dioxidum (Titan. dioxid.)
Trolamine	Trolaminum (Trolamin.)
Paraffin, white soft	Vaselinum album (Vaselin. alb.)
Paraffin, yellow soft	Vaselinum flavum (Vaselin. flav.)
Zinc chloride	Zinci chloridum (Zinc. chlor.)
Zinc oxide	Zinci oxidum (Zinc. oxid.)
Zinc sulfate heptahydrate	Zinci sulfas heptahydricus (Zinc. sulf. heptahydr.)

At the beginning of the 21st century, biotechnology and nanotechnology open up new perspectives for research and production of pharmaceutical substances. The impending spread of nanomedicine and biotechnology may radically change drug therapy.

2.7 Medicines produced with biotechnology

Medicines produced with biotechnology use proteins, enzymes, antibodies and other natural substances in curing diseases. Other living organisms (vegetal and animal cells, bacteria, viruses and yeasts/fungi) are employed in the industrial production of these products.

Károly Ereky Hungarian scientist was the first to use the expression *biotechnology* (in German Biotechnologie) in a lecture he gave in 1918. The first published use also belongs to him. He is regarded by some as the "father" of biotechnology.

The insulin therapy of diabetic patients has been practically revolutionized by the invention of the first recombinant protein, human insulin made with recombinant DNA technology using bacteria. In effect this is the date of birth of the biotechnological industry.

Principal types of biological drugs:

- hormones (e.g. growth hormone)
- immunomodulators (e.g. interferon alfa)

- enzymes
- monoclonal antibodies
- coagulant factors (e.g. factor VIII)
- vaccines

Several attributes of drug compounds produced in "legacy" chemical synthesis are different from those of biological drugs.

Table 2-VII.
Main attributes of traditional chemical drugs and biological drugs

Conventional medicines	Biological medicines
Preparation	
by chemical sysnthesis, for quality control approx. 50 examinations are required	by fermentation (biosynthesis), for quality control approx. 50 examinations are required
Physico-chemica properties	
small and medium molecules Mw≤ 800 Daltons identifiable structure, usually stable	macromolecules, Mw > 800 Daltons characterization of the structure is not certain, instable (heat sensitive) structure
Pharmacological properties	
short acting, non-immunogenic, independent from races	long acting, immunogenic, race-dependent
Biopharmaceutical properties	
peroral administration, used in common practice	parenteral administration, used in hospitals

In the case of traditional drugs, in the authorization process of a generic drug it is easy to confirm that its active agent is identical with that of the original drug. In the case of biological drugs however, only *biosimilarity* can be established to the references product, as these substances are macromolecules, mostly proteins, which cannot be described with absolute precision, as their secondary and tertiary structure can easily change during production.

2.8 Nanomaterials

Nanomaterials are such natural, manufactured materials that contain at least 50% of unbound particles in the size range between 1 to 100 nm, which are either weakly (agglomerate) or strongly (aggregate) attached to each other.

Manufacturing traditional active ingredients in nano sizes and/or attaching them to nanocarriers can increase specific surface in extreme proportions, to up to 1.000 sqm/g. The increased surface is highly determinative for physical (melting point, conductance, ionization potential, magnetizability, surface tension, hydrophobic/hydrophilic

character), chemical (reactivity), pharmacokinetical and biopharmaceutical (e.g. solubility, rate of dissolution, interaction with bio-macromolecules) attributes.

Nanoparticles behave in a peculiar way in the body. As a result of surficial interactions their surface develops a protein coating (so-called protein crown) and this complex material system interacts in subsequent processes.

With the application of nanotechnology such new substances can be designed and produced that are either naturally present in the body or are capable of supplementing substances in a biocompatible way, can be used in regenerative medicine as structural materials, are capable of accomplishing new diagnostic objectives and/or exerting therapeutic effect. Drug delivery nanosystems can achieve targeted drug effects (passive and active targeting). They allow s significantly lower doses than systemic dosage and adverse effects can be greatly reduced.

2.9 Active agents

Pharmaceutical substances are either active agents or excipients.

Every ingredient or pharmaceutical substance of a pharmaceutical preparation, which is capable of taking pharmacological or other direct effect in the diagnosis, treatment or prevention of a disease, or is intended for the pharmacological manipulation of the structure or metabolism of the human or animal body is called an *active ingredient (AI, Active Pharmaceutical Ingredient API, active substance, drug substance*). One pharmaceutical preparation may contain multiple active agents.

WHO classifies active ingredients according to a coding system (*Anatomical Therapeutical Classification, ATC).*

Table 2-VIII.
Main groups of active ingredients according to ATC

ATC code	Application
ATC A	**Alimentary tract and metabolism**
ATC A01	Stomatological preparations
ATC A02	Drugs for acid related disorders
ATC A03	Drugs for functional gastrointestinal disorders
ATC A04	Antiemetics and antinauseants
ATC A05	Bile and liver therapy
ATC A06	Laxatives
ATC A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents
ATC A08	Antiobesity preparations, excluding diet products
ATC A09	Digestives, including enzymes
ATC A10	Drugs used in diabetes
ATC A11	Vitamins
ATC A12	Mineral supplements
ATC A13	Tonics
ATC A14	Anabolic agents for systemic use
ATC A15	Appetite stimulants
ATC A16	Other alimentary tract and metabolism products

ATC code	Application
ATC B	**Blood and blood forming organs**
ATC B01	Antithrombotic agents
ATC B02	Antihemorrhagics
ATC B03	Antianemic preparations
ATC B05	Blood substitutes and perfusion solutions
ATC B06	Other hematological agents
ATC C	**Cardiovascular system**
ATC C01	Cardiac therapy
ATC C02	Antihypertensives
ATC C03	Diuretics
ATC C04	Peripheral vasodilatators
ATC C05	Vasoprotectives
ATC C07	Beta blocking agents
ATC C08	Calcium channel blockers
ATC C09	Agents acting on the renin-angiotensin system
ATC C10	Lipid modifying agents
ATC D	**Dermatologicals**
ATC D01	Antifungals for dermatological use
ATC D02	Emollients and protectives
ATC D03	Preparations for treatment of wounds and ulcers
ATC D04	Antipruritics, including antihistamines, anesthetics, etc.
ATC D05	Antipsoriatics
ATC D06	Antibiotics and chemotherapeutics for dermatological use
ATC D07	Corticosteroids, dermatological preparations
ATC D08	Antiseptics and disinfectants
ATC D09	Medicated dressings
ATC D10	Anti-acne preparations
ATC D11	Other dermatological preparations
ATC G	**Genito-urinary system and sex hormones**
ATC G01	Gynecological antiinfectives and antiseptics
ATC G02	Other gynecologicals
ATC G03	Sex hormones and modulators of the genital system
ATC G04	Urologicals
ATC H	**Systemic hormonal preparations, excluding sex hormones and insulins**
ATC H01	Pituitary and hypothalamic hormones and analogues
ATC H02	Corticosteroids for systemic use
ATC H03	Thyroid therapy
ATC H04	Pancreatic hormones
ATC H05	Calcium homeostasis

ATC code	Application
ATC J	**Antiinfectives for systemic use**
ATC J01	Antibacterials for systemic use
ATC J02	Antimycotics for systemic use
ATC J04	Antimycobacterials
ATC J05	Antivirals for systemic use
ATC J06	Immune sera and immunoglobulins
ATC J07	Vaccines
ATC L	**Antineoplastic and immunomodulating agents**
ATC L01	Antineoplastic agents
ATC L02	Endocrine therapy
ATC L03	Immunostimulants
ATC L04	Immunosuppressants
ATC M	**Musculo-skeletal system**
ATC M01	Anti-inflammatory and antirheumatic products
ATC M02	Topical products for joint and muscular pain
ATC M03	Muscle relaxants
ATC M04	Antigout preparations
ATC M05	Drugs for treatment of bone diseases
ATC M09	Other drugs for disorders of the musculo-skeletal system
ATC N	**Nervous system**
ATC N01	Anesthetics
ATC N02	Analgesics
ATC N03	Antiepileptics
ATC N04	Anti-parkinson drugs
ATC N05	Psycholeptics
ATC N06	Psychoanaleptics
ATC N07	Other nervous system drugs
ATC P	**Antiparasitic products, insecticide and repellents**
ATC P01	Antiprotozoals
ATC P02	Anthelmintics
ATC P03	Ectoparasiticides, including scabicides, insecticides and repellents
ATC R	**Respiratory system**
ATC R01	Nasal preparations
ATC R02	Throat preparations
ATC R03	Drugs for obstructive airway diseases
ATC R05	Cough and cold preparations
ATC R06	Antihistamines for systemic use
ATC R07	Other respiratory system product
ATC S	**Sensory organs**
ATC S01	Ophthalmologicals
ATC S02	Otologicals
ATC S03	Ophthalmological and ontological preparations

ATC code	Application
ATC V	**Various**
ATC V01	Allergens
ATC V03	All other therapeutic products
ATC V04	Diagnostic agents
ATC V06	General nutrients
ATC V07	All other non-therapeutic products
ATC V08	Contrast media
ATC V09	Diagnostic radiopharmaceuticals
ATC V10	Therapeutic radiopharmaceuticals
ATC V20	Surgical dressings

Pharmacopeias usually include the most important, most frequently used active ingredients.

Table 2-IX.
Pharmacopeial active ingredients

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Acetic acid, glacial	Acidum aceticum glaciale (Acid. acet. glac.)
Acetylsalicylic acid	Acidum acetylsalicylicum (Acid. acetylsalicyl.)
Glycine	Glycinum (Glycin.)
Ascorbic acid	Acidum ascorbicum (Acid. ascorb.)
Boric acid	Acidum boricum (Acid. bor.)
Hydrochloride acid, dilute	Acidum hydrochloridum dilutum (Acid. hydrochlor. dil.)
Folic acid	Acidum folicum (Acid. fol.)
Lactic acid	Acidum lacticum (Acid. lact.)
Nicotinic acid	Acidum nicotinicum (Acid. nicot.)
Salicylic acid	Acidum salicylicum (Acid. salicyl.)
Tannic acid	Tanninum (Tannin.)
Acriflavinium monochloride	Acriflavini monochloridum (Acriflavin. monochlor.)
Ethacridine lactate monohydrate	Ethacridini lactas monohydricus (Ethacridin. lact. monohydr.)
Ether	Aether
Ethylmorphine hydrochloride	Ethylmorphini hydrochloridum (Ethylmorphin. hydrochlor.)
Alum	Alumen
Aluminium chloride, hexahydrate	Aluminii chloridum hexahydricum (Alum. chlor. hexahydr.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Aluminium oxide, hydrated	Aluminii oxydum hydricum (Alum. oxid. hydr.)
Aluminium sulfate	Aluminii sulfas (Alum. sulf.)
Ammonium bromide	Ammonii bromidum (Ammon. brom.)
Ichthammol	Icthammolum (Icthamm.)
Apomorphine hydrochloride	Apomorphini hydrochloridum (Apomorph. hydrochlor.)
Silver nitrate	Argenti nitras (Argent. nitr.)
Arginine hydrochloride	Arginini hydrochloridum (Arginin. hydrochlor.)
Arsenious trioxide for homoeopathic preparations	Arsenii trioxidum ad praeparationes homeopathicas (Arsen. trioxid. ad praep. hom.)
Atropine sulfate	Atropini sulfas (Atrop. sulf.)
Barbital	Barbitalum (Barbital.)
Benzalkonium chloride	Benzalkonii chloridum (Benzalkon. chlor.)
Benzocaine	Benzocainum (Benzocain.)
Benzyl benzoate	Benzylis benzoas (Benzyl. benzoas)
Bismuth subcarbonate	Bismuthi subcarbonas (Bism. subcarb.)
Bismuth subgallate	Bismuthi subgallas (Bism. subgall.)
Bismuth subnitrate, heavy	Bismuthi subnitras ponderosus (Bism. subnitr. pond.)
Bismuth subsalicylate	Bismuthi subsalicylas (Bism. subsalicyl.)
Kaolin, heavy	Kaolinum ponderosum (Kaolin. ponderos.)
Calcium glycerophosphate	Calcii glycerophosphas (Calc. glycerophosph.)
Calcium hydrogen phosphate, dihydrate	Calcii hydrogenophosphas dihydricus (Calc. hydrogenophosph. dihydr.)
Calcium lactate pentahydrate	Calcii lactas pentahydricus (Calc. lact. pentahydr.)
Camphor, racemic	Camphora racemica (Camphor. racem.)
Urea	Ureum
Charcoal, activated	Carbo activatus (Carbo activ.)
Quinidine sulphate	Chinidini sulfas (Chinidin. sulf.)
Quinine hydrochloride	Chinini hydrochloridum (Chinin. hydrochlor.)
Quinine sulphate	Chinini sulfas (Chinin. sulf.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Chloral hydrate	Chlorali hydras (Chloral. hydr.)
Chloramphenicol	Chloramphenicolum (Chloramphen.)
Chlorhexidine digluconate solution	Chlorhexidini digluconatis solutio (Chlorhexid. digluconat. sol.)
Chlorobutanol hemihydrate	Chlorobutanolum hemihydricum (Chlorobutanol. hemihydr.)
Clioquinol	Clioquinolum (Clioquin.)
Cocaine hydrochloride	Cocaini hydrochloridum (Cocain. hydrochlor.)
Codeine hydrochloride dihydrate	Codeini hydrochloridum dihydricum (Codein. hydrochlor. dihydr.)
Codeine phosphate sesquihydrate	Codeini phosphas sesquihydricus (Codein. phosph. sesquihydr.)
Caffeine	Coffeinum (Coffein.)
Copper sulfate pentahydrate	Cupri sulfas pentahydricus (Cupr. sulf. pentahydr.)
Dithranol	Dithranolum (Dithranol.)
Emetine hydrochloride heptahydrate	Emetini hydrochloridum heptahydricum (Emetin. hydrochlor. heptahydr.)
Ephedrine hydrochloride, racemic	Ephedrini racemici hydrochloridum (Ephedrin. racem. hydrochlor.)
Ergotamine tartrate	Ergotamini tartras (Ergotamin. tartr.)
Erythromycin	Erythromycinum (Erythromycin.)
Erythromycin lactobionate	Erythromycini lactobionas (Erythromycin. lactobion.)
Ferrous sulphate heptahydrate	Ferrosi sulfas heptahydricus (Ferros. sulf. heptahydr.)
Ferric chloride hexahydrate	Ferri chloridum hexahydricum (Ferri chlor. hexahydr.)
Iron for homoeopathic preparations	Ferrum ad praeparationes homoeopathicas (Ferr. ad praep. hom.)
Fluorescein sodium	Fluoresceinum natricum (Fluorescein. natr.)
Formaldehyde solution (35 per cent)	Formaldehydi solutio (35 per centum) (Formald. sol. 35 %)
Gentamicin sulfate	Gentamicini sulfas (Gentamicin. sulf.)
Hexobarbital	Hexobarbitalum (Hexobarbital.)
Homatropine hydrobromide	Homatropini hydrobromidum (Homatropin. hydrobrom.)
Indometacin	Indometacinum (Indometacin.)
Iodine	lodum (lod.)
Isoprenaline hydrochloride	Isoprenalini hydrochloridum (Isoprenalin. hydrochlor.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Potassium bromide	Kalii bromidum (Kal. brom.)
Potassium carbonate	Kalii carbonas (Kal. carb.)
Potassium hydrogen carbonate	Kalii hydrogenocarbonas (Kal. hydrogenocarb.)
Potassium iodide	Kalii iodidum (Kal. iod.)
Potassium permanganate	Kalii permanganas (Kal. permang.)
Cresol, crude	Cresolum crudum (Cresol. crud.)
Lidocaine hydrochloride	Lidocaini hydrochloridum (Lidocain. hydrochlor.)
Lidocaine	Lidocainum (Lidocain.)
Lithium carbonate	Lithii carbonas (Lith. carb.)
Magnesium aspartate dihydrate	Magnesii aspartas dihydricus
Magnesium carbonate, light	Magnesii subcarbonas levis (Magn. subcarb. lev.)
Magnesium chloride hexahydrate	Magnesii chloridum hexahydricum (Magn. chlor. hexahydr.)
Magnesium oxide, light	Magnesii oxidum leve (Magn. oxid. lev.)
Magnesium peroxide	Magnesii peroxidum (Magn. peroxid.)
Magnesium sulfate heptahydrate	Magnesii sulfas heptahydricus (Magn. sulf. heptahydr.)
Magnesium trisilicate	Magnesii trisilicas (Magn. trisilic.)
Levomenthol	Levomentholum (Levomenthol.)
Methenamine	Methenaminum (Methenamin.)
Homatropine methylbromide	Homatropini methylbromidum (Homatropin. methylbrom.)
Methyl salicylate	Methylis salicylas (Methyl. salicyl.)
Methylrosanilinium chloride	Methylrosanilinii chloridum (Methylros. chlor.)
Methylthioninium chloride	Methylthioninii chloridum (Methylthionin. chlor.)
Metronidazole	Metronidazolum (Metronidazol.)
Morphine hydrochloride	Morphini hydrochloridum (Morphin. hydrochlor.)
Naphazoline hydrochloride	Naphazolini hydrochloridum (Naphazolin. hydrochlor.)
Sodium bromide	Natrii bromidum (Natr. brom.)
Sodium fluoride	Natrii fluoridum (Natr. fluor.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Sodium hydrogen carbonate	Natrii hydrogenocarbonas (Natr. hydrogenocarb.)
Sodium iodide	Natrii iodidum (Natr. iodid.)
Sodium salicylate	Natrii salicylas (Natr. salicyl.)
Borax	Borax
Neomycin sulfate	Neomycini sulfas (Neomycin. sulf.)
Nikethamide	Nicethamidum (Nicethamid.)
Nitrofurantoin	Nitrofurantoinum (Nitrofurantoin.)
Metamizole sodium	Metamizolum natricum (Metamizol. natr.)
Nystatin	Nystatinum (Nystatin.)
Cod-liver oil (type A)	Jecoris aselli oleum A (Jecor. aselli ol. A)
Castor oil, virgin	Ricini oleum virginale (Ricin. ol. virgin.)
Oxygen	Oxygenium (Oxygen.)
Oxytetracycline hydrochloride	Oxytetracyclini hydrochloridum (Oxytetracyclin. hydrochlor.)
Pancreas powder	Pancreatis pulvis (Pancreat. pulv.)
Papaverine hydrochloride	Papaverini hydrochloridum (Papaverin. hydrochlor.)
Paracetamol	Paracetamolum (Paracetamol.)
Paraldehyde	Paraldehydum (Paraldehyd.)
Pepsin powder	Pepsini pulvis (Pepsin. pulv.)
Phenazone	Phenazonum (Phenazon.)
Phenobarbital	Phenobarbitalum (Phenobarbital.)
Phenobarbital sodium	Phenobarbitalum natricum (Phenobarb. natr.)
Phenolphtalein	Phenolphtaleinum (Phenolphtalein.)
Phenol	Phenolum (Phenol.)
Phenylbutazone	Phenylbutazonum (Phenylbutazon.)
Phenylmercuric borate	Phenylhydrargyri boras (Phenylhydrarg. bor.)
Physostigmine salicylate	Physostigmini salicylas (Physost. salicyl.)
Pilocarpine hydrochloride	Pilocarpini hydrochloridum (Pilocarpin. hydrochlor.)
Polymyxin B sulphate	Polymyxini B sulfas (Polymyxin. B sulf.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Prednisolone	Prednisolonum (Prednisolon.)
Procaine hydrochloride	Procaini hydrochloridum (Procain. hydrochlor.)
Promethazine hydrochloride	Prometazini hydrochloridum (Prometazin. hydrochlor.)
Resorcinol	Resorcinolum (Resorcinol.)
Rifampicin	Rifampicinum (Rifampicin.)
Rutoside trihydrate	Rutosidum trihydricum (Rutosid. trihydr.)
Scopolamine hydrobromide	Scopolamini hydrobromidum (Scopolamin. hydrobrom.)
Sulfacetamide sodium	Sulfacetamidum natricum (Sulfacetamid. natr.)
Sulfadimidine	Sulfadimidinum (Sulfadimidin.)
Sulfathiazole	Sulfathiazolum (Sulfathiazol.)
Sulphur for external use	Sulfua ad usum externum
Tetracaine hydrochloride	Tetracaini hydrochloridum (Tetracain. hydrochlor.)
Theobromine	Theobrominum (Theobromin.)
Theophylline	Theophyllinum (Theophyllin.)
Thiamine hydrochloride	Thiamini hydrochloridum (Thiamin. hydrochlor.)
Thymol	Thymolum (Thymol.)
Titanium dioxide	Titanii dioxidum (Titan. dioxid.)
Zinc chloride	Zinci chloridum (Zinc. chlor.)
Zinc oxide	Zinci oxidum (Zinc. oxid.)
Zinc sulfate heptahydrate	Zinci sulfas heptahydricus (Zinc. sulf. heptahydr.)

2.10 Excipients

Every pharmaceutical substance in a pharmaceutical preparation other than the active ingredient, which serves the production of the preparation or was used in the process of making the preparation is called an *excipient*. Regarding their role, excipients can be the carrier of the active ingredient or a component of the preparation. The purpose of using them may serve the preservation of the quality of the active ingredient (stability), the accuracy of dosage, biopharmaceutical attributes (e.g. release, absorption) or good appearance of the preparation. Usually multiple excipients may be used in the preparation of pharmaceutical preparations.

Over 10 000 different excipients are currently on the market, satisfying the demands of pharmaceutical industry. This contributed greatly to the progress of pharmaceutical technology and the development of new drug delivery systems.

Excipients used to be considered materials that enable the production of dosage forms, thus mostly playing a *carrier substance* role. Their widespread use in today's modern drug formulation practice is highly beneficial in solving biopharmacy-oriented technological problems:

1) they can enable or boost producibility of medicines (e.g. by increasing solubility, keeping in solution, lubrication of substances in tableting),
2) they can preserve the physical, chemical or microbiological stability of drugs (e.g. by increasing viscosity or buffer and preservative effect),
3) they can improve biological applicability of drugs (e.g. by controlling solubility or rate of dissolution),
4) they can optimize the therapeutic effect (e.g. by controlling the location, duration or pace of drug release),
5) they can facilitate tolerability (e.g. preparation of isotonic and isohydric eye drops).

Excipient substances are not always indifferent to the body. It has been found that gelatine extracted from skin is lower risk than gelatine extracted from bone. Lactose, which is frequently used as a tableting excipient, is broken down into dextrose and galactose by the lactase enzyme in the process of absorption in the epithelium of the small intestine. In the absence of lactase enzyme lactose intolerance may develop. In this case lactase is transferred to the colon undigested, causing abdominal bloating, cramps and flux. Adult lactose intolerance affects 15 percent of the populace in Northern Europe, 30 percent in Central Europe and up to 70 percent in the Mediterranean.

Table 2-X.
Parmacopeial excipients

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Acetone	Acetonum (Aceton.)
Acetic acid, glaciale	Acidum aceticum glaciale
Aspartic acid	Acidum asparticum (Acid. aspart.)
Hydrochloric acid, concentrated	Acidum hydrochloridum concentratum (Acid. hydrochlor. conc.)
Hydrochloric acid, dilute	Acidum hydrochloridum dilutum (Acid. hydrochlor. dil.)
Citric acid monohydrate	Acidum citricum monohydricum (Acid. citr.monohydr.)
Oleic acid	Acidum oleicum (Acid. oleic.)
Phosphoric acid, concentrated	Acidum phosphoricum concentratum (Acid. phosph. conc.)
Silica, colloidal anhydrous	Silica colloidalis anhydrica (Silic. coll. anhydr.)
Sorbic acid	Acidum sorbicum (Acid. sorb.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Tannic acid	Acidum tartaricum (Acid. tart.)
Hard fat	Adeps solidus (Adeps solid.)
Hard fat	Adeps solidus (Adeps solid.)
Ethyl acetate	Ethylis acetas (Ethyl. acet.)
Ethyl oleate	Ethylis oleas (Ethyl. oleas)
Ethanol (96 per cent)	Ethanolum (96 per centum) (Ethanol. 96 %)
Cetyl alcohol	Alcohol cetylicus (Alc. cetyl.)
Cetostearyl alcohol	Alcohol cetylicus et stearylicus (Alc. cetyl. et stearyl.)
Isopropyl alcohol	Alcohol isopropylicus (Alc. isopropyl.)
Poly(vinyl alcohol)	Poly(alcohol vinylicus) [Poly(alc. vinyl.)]
Ammonia solution, concentrated	Ammoniae solutio concentrata (Ammon. sol. conc.)
Purified water	Aqua purificata (Aqu. purif.)
Purified water	Aqua purificata (Aqu. purif.)
Water for injections	Aqua ad iniectabilia (Aqu. ad ini.)
Benzalkonium chloride	Benzalkonii chloridum (Benzalkon. chlor.)
Calcium hydrogen phosphate dihydrate	Calcii hydrogenophosphas dihydricus (Calc. hydrogenophosph. dihydr.)
Carbomers	Carbomera
Carboxymethylcellulose sodium	Carmellosum natricum (Carmellos. natr.)
Cellulose acetate phthalate	Cellulosi acetas phthalas (Cell. acet. phthal.)
Cellulose, microcrystalline	Cellulosum microcristallinum (Cell. microcrist.)
White beeswax	Cera alba (Cer. alb.)
Yellow beeswax	Cera flava (Cer. flav.)
Wool fat	Adeps lanae (Adeps lan.)
Cetyl palmitate	Cetylis palmitas (Cetyl. palm.)
Cetrimide	Cetrimidum (Cetrimid.)
Cholesterol	Cholesterolum (Cholesterol.)
Copovidone	Copovidonum

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Dipotassium phosphate	Dikalii phosphas (Dikal. phosph.)
Disodium phosphate dodecahydrate	Dinatrii phosphas dodecahydricus (Dinatr. phosph. dodecahydr.)
Fructose	Fructosum (Fructos.)
Gelatin	Gelatina (Gelat.)
Glucose, anhydrous	Glucosum anhydricum (Glucos. anhydr.)
Glycerol (85 per cent)	Glycerolum 85 per centum (Glycerol. 85%)
Glycerol monostearate 40-55	Glyceroli monostearas 40-55 (Glycerol. monostear. 40-55)
Hydroxyethylcellulose	Hydroxyethylcellulosum (Hydroxyethylcell.)
Hydroxypropylcellulose	Hydroxypropylcellulosum (Hydroxypropylcell.)
Potassium hydroxide	Kalii hydroxidum (Kal. hydroxid.)
Potassium sodium tartrate tetrahydrate	Kalii natrii tartras tetrahydricus (Kal. natr. tartr. tetrahydr.)
Potassium nitrate	Kalii nitras (Kal. nitr.)
Potassium sorbate	Kalii sorbas (Kal. sorb.)
Lactose monohydrate	Lactosum monohydricum (Lactos. monohydr.)
Wool alcohols	Alcoholes adipis lanae (Alc. adip. lan.)
Macrogol 400	Macrogolum (400-as típus)
Macrogol 1500	Macrogolum (1500-as típus)
Macrogol 4000	Macrogolum (4000-es típus)
Macrogol stearate	Macrogoli stearas
Magnesium stearate	Magnesii stearas (Magn. stear.)
Mannitol	Mannitolum (Mannit.)
Methylcellulose	Methylcellulosum (Methylcellulos.)
Methyl parahydroxybenzoate	Methylis parahydroxybenzoas (Methyl. parahydroxybenz.)
Sodium acetate trihydrate	Natrii acetas trihydricus (Natr. acet. trihydr.)
Sodium benzoate	Natrii benzoas (Natr. benz.)
Sodium carbonate decahydrate	Natrii carbonas decahydricus (Natr. carb. decahydr.)
Sodium chloride	Natrii chloridum (Natr. chlor.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Sodium dihydrogen phosphate dihydrate	Natrii dihydrogenophosphas dihydricus (Natr. dihydrogenophosph. dihydr.)
Sodium metabisulfite	Natrii metabisulfis (Natr. metabisulfis)
Sodium hydroxide	Natrii hydroxidum (Natr. hydroxid.)
Sodium laurilsulfate	Natrii laurilsulfas (Natr. laurilsulf.)
Sodium nitrite	Natrii nitris (Natr. nitris)
Sodium thiosulfate	Natrii thiosulfas (Natr. thiosulf.)
Sunflower oil, refined	Helianthi annui oleum raffinatum (Helianth. annui ol. raffinat.)
Linseed oil, virgin	Lini oleum virginale (Lin. ol. virgin.)
Triglycerides, medium-chain	Triglycerida saturata media (Triglyc. satur. med.)
Liquid paraffin	Paraffinum liquidum (Paraff. liqu.)
Paraffin, hard	Paraffinum solidum (Paraff. solid.)
Polysorbate 20	Polysorbatum 20 (Polysorbat. 20)
Polysorbate 60	Polysorbatum 60 (Polysorbat. 60)
Polysorbate 80	Polysorbatum 80 (Polysorbat. 80)
Povidone	Povidonum (Povidon.)
Propylene glycol	Propylenglycolum (Propylenglycol.)
Propyl parahydroxybenzoate	Propylis parahydroxybenzoas (Propyl. parahydroxybenz.)
Saccharin sodium	Saccharinum natricum (Saccharin. natr.)
Sucrose	Saccharum (Sacchar.)
Sorbitan laurate	Sorbitani lauras (Sorbitan. laur.)
Sorbitol	Sorbitolum (Sorbitol.)
Stearic acid	Acidum stearicum (Acid. stearic.)
Talc	Talcum (Talc.)
Thiomersal	Thiomersalum (Thiomersal.)
Calcium phosphate	Tricalcii phosphas (Tricalc. phosph.)

Ph. Eur.7. English name	Ph.Eur.7. Latin name and abbrev.
Paraffin, white soft	Vaselinum album (Vaselin. alb.)
Paraffin, yellow soft	Vaselinum flavum (Vaselin. flav.)

2.11 Vehicles

The carrier system of the active ingredient(s) of liquid state pharmaceutical preparations, consisting of one or more excipients, is called vehicles.

2.12 Basis

The carrier system of the active ingredient(s) of semisolid or solid state pharmaceutical preparations, consisting of one or more excipients, is called basis.
The excipients relevant to different operations are detailed in the respective chapters of the book.

Questions

1) How would you define the notion of pharmaceutical substance?
2) What are the main sources of pharmaceutical substances?
3) What animal-derived substances do you know?
4) What are the main characteristics of traditional chemical drugs and biological drugs?
5) How would you define the notion of nano materials?
6) How would you define the notion of active ingredient?
7) How would you define the notion of excipient?
8) What are the main benefits of using excipients?
9) What substances are rated as vehicles?
10) What is a basis?

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Recommended websites

http://online.pheur.org/EN/entry.htm

http://www.thieme-chemistry.com/ps/prod/

3 Operations and processes in pharmaceutical technology

The production of a certain *product* requires an appropriate *technology*, which is based on preliminary research and development. Technology in general stands for the method of a product's manufacturing, including all the necessary work-processes and their parameters, which are required for the professional, reproducible and controlled – therefore guaranteed quality - production of the end product.

Pharmaceutical products as *end products* are produced by using basic raw materials (active pharmaceutical ingredients, excipients) according to a developed technology.

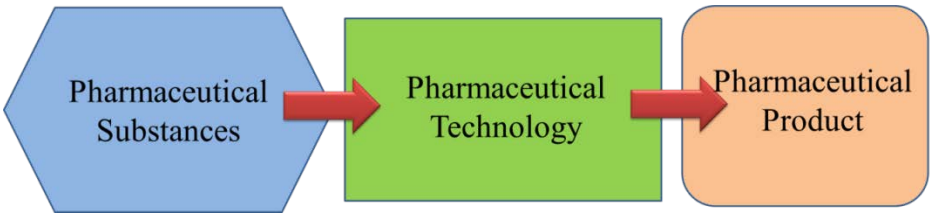

Fig. 3.1.
From basic materials to the end product

The physico-chemical properties of *pharmaceutical substances* (e.g. particle size, crystal form, habit, impurity, water content, stability and solubility) principally affect and determine the *manufacturability*, *quality parameters* and *shelf life* of the product.

Prudent and thorough, so-called *preformulation studies* are required for the detailed exploration, recognition and identification of different basic materials that paly an important role in the safe production and applicability in therapy of a preparation. The change or alteration of any attribute of a basic substance may jeopardize the whole technological process and/or therapeutic effect, as the set of requirements of the product's technological and biopharmaceutical testing can only be met by the technology whose parameters had been previously determined

The physico-chemical properties of *raw materials* (e.g. particle size, crystal form, habit, impurity, water content, stability and solubility) are fundamental in determining *manufacturability*, *quality parameters* and *shelf-life* of the product. Careful and thorough, so called *pre-formulation studies* are required to explore, recognize and determine the parameters of different substances in detail. These studies provide safe manufacturability and therapeutical applicability of the product. Any change occurring or applied to any parameter of a raw material may jeopardize the whole technological process and/or the therapeutic effect, as the requirement framework of the product's technological and biopharmaceutical testing can only be met by the technology whose parameters had been previously determined.

Therefore, identical quality parameters of the basic substances in manufactured batches are an important condition of the reproducibility of quality parameters. Any variation may result in a review and recalibration of the whole system of operation parameters in order to maintain quality.

A product's technology is attained through the *technological process*, making manufacturing of the product possible. Technological processes typically involve

stages, operations, their execution mode, procedures and the control of these through operation parameters.

Pharmaceutical technological processes generally belong to multi-step technological processes. *Manufacturing processes* can also be divided into process stages (e.g. preparation, composition, shape forming), during which several, different pharmaceutical technological operations are applied (e.g. measurement, sieving, granulation, compaction).

Essential steps of different technological processes are termed *unit operations*. From a unit operation aspect the process of pharmaceutical preparation and manufacturing can be divided into different *technological operations* and *procedures*. Pre-planned, reproducible and safe application of these is required to produce the preparation in appropriate quality and quantity every time.

Fig. 2 illustrates the system of relations in the pharmaceutical technological process, stage, operations and procedures in a generalized format. The entire process is under constant quality control: from raw materials on, through parameters of manufacturing, up to the end product.

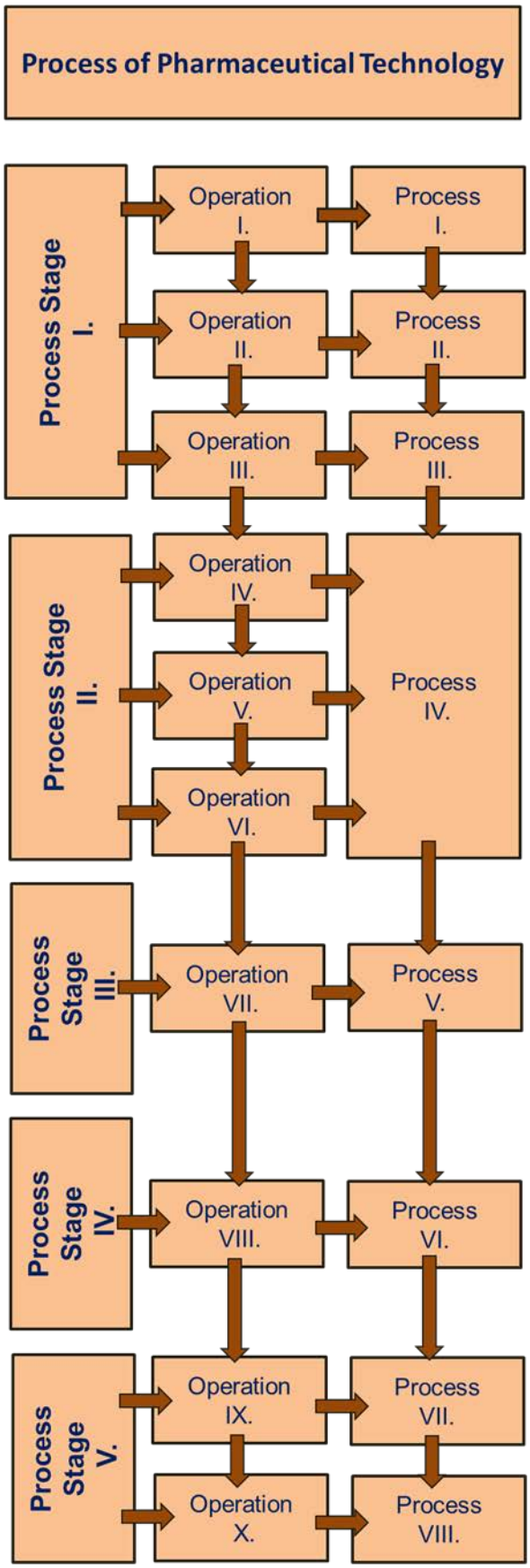

Fig. 3.2.
System of relations in a pharmaceutical technological process

The discipline dealing with this is called the *discipline of unit operations***,** created and its foundations laid in the early 20th century, when technological development and the increasing demand for quality necessitated it. According to the fundamental thesis of unit operations the wide range of operations involves relatively few *basic operations* (e.g. mixing, extracting, drying). Different operations and their implementation modes can be characterized and controlled according to the physical principles underlying each *procedure*.

For example the operation of mixing can be carried out manually (e.g. glass rod, pestle) or mechanically, for example by magnetic stirrer; a high-speed, high-shear force mixing device or planetary mixing method, capable of processing highly viscous media.

General technology and pharmaceutical technology, as well as the disciplines of general and applied unit operations (e.g. *pharmaceutical unit operations*) are closely interconnected, mutually enriching each other with experience, research results and scientific findings.

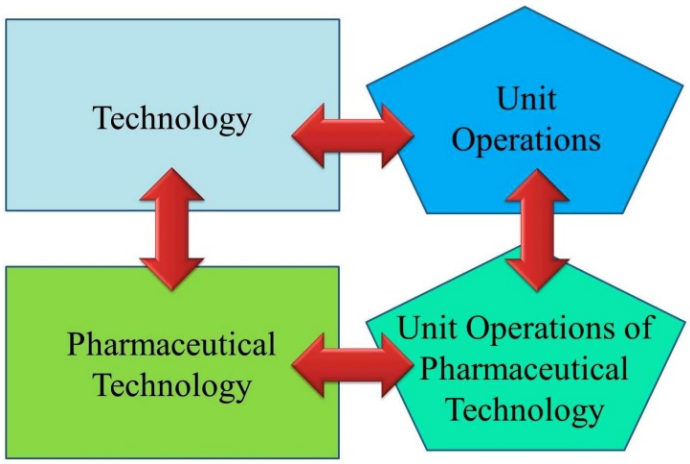

Fig. 3.3.
Connections of technology and unit operations

Unit operation can be considered as *abstracted technology*, as it is aimed at exploring the essence of operations, singling out typical and determinative parameters, finding correlations and setting up objective (mathematical) models, without regard to the actual individual technological solution, machinery or equipment. This describes the relationship between technology and unit operation well.

The individual operations are usually placed in a planned *technological row*. Their perfect harmonization and synchronization is one of the most important criteria of the quality of the end product. Therefore at the stage of developing the technology, the mutual relationship and interrelation of different operations and procedures has to be determined as well as possibility of their co-regulation. Similarly, unit operations of pharmaceutical technology usually connect in a consecutive, although concurrent, parallel applications may also occur.

Manufacturing products in different dosage forms requires various different technological units, devices, equipment, knowledge of their process- and operation unit parameters, as well as that of applicable materials, appropriate experience, skills and practice. This complex body of knowledge is also capable of advancing the technology of medicines, thereby developing and improving existing products further by the application of ever newer and more advanced procedures, materials and instruments.

As the capacity of devices and equipment determines the producible volume in a given unit of time (batch size) the intended product volume must be taken into account in the planning phase. Besides the designated dosage form and the amount of substances, the physico-chemical properties of the employed materials and material systems is also an important aspect in the configuration of the technological processes.

As far as possible, the *applied technology* should fulfil the following requirements:

- simple
- transparent
- easy to control
- controlled by a small set of parameters
- requires a low number of processes
- safe (reproducibility, reliability)
- cost effective (optimum use of material and energy)
- generates as little as possible by-product
- environment-friendly

Considering the method of execution, unit operations can be the following types:

1) *batch operations*, in which the steps of the operation are carried out separately, apart both temporally and spatially
2) *continuous operations*, in which different steps are carried out within the same apparatus and
3) *mixed operations*, in which some steps are carried out in batches and others continuously.

In spite of the many advantages of continuous operations, batch operations have retained importance, being applied in the production of small batches.

Continuous operations are important primarily in large-scale manufacturing, producing large batches, as it can be a cost effective solution due to its productivity.

Unit operations can also be grouped by their *characteristic features:*

1) *operations of material (component) transfer* (e.g. water demineralization using ion exchanger resin, dissolution, drying, crystallisation, wetting, granulation, fluidisation, coating),
2) *operations of separation* (*separation or extraction of a component:* distillation, extraction, filtering, decantation, centrifugation, drying, membrane filtering, reverse osmosis, dialysis),
3) *operations of integration* (*merging of components*: blending, dissolution, mixing, manufacture of ointments and suppositories, granulation, direct compression of tablets)
4) *operations of heat transfer* (*caloric operations*: heating, cooling, concentrating by evaporation, rectifying, drying, fluidisation),
5) *mechanical operations* (e.g. milling, sieving, granulation, compaction)
6) *hydrodynamic operations* (e.g. mixing of liquids, liquid transfer, centrifugation, fluidisation, decantation, filtering)

Some operations may belong to more than one group of unit operations, since more than one operation may occur concurrently, as in the case of mixing: blending, dissolution, fluidising, emulsification, heat transfer, milling and homogenisation).

Operations of *material transfer* are often considered *operations of diffusion*, if these processes are controlled by the laws of diffusion.

The purpose of *material transfer* operations may be:

1) extraction of valuable components (e.g. extraction, distillation)
2) removal of unwanted components (e.g. removing humidity by drying)
3) introduction of components into a medium (e.g. dissolution)
4) exchange of components (e.g. water demineralisation by ion-exchanging resin)

Operations of material transfer can be:

a) *equilibrium-stage operations* (e.g. distillation, rectification, absorption, extraction, adsorption, drying and crystallisation),
b) *non-equilibrium-stage operations* (e.g. membrane filtering, reverse osmosis, dialysis and electrodialysis)

During the *transport of components* in operations of material transfer the constituents of the system

a) flow in the same phase, or
b) flow from one phase to another, changing the quantitative proportions, i.e. the concentrations of the components.

Caloric operations are determined by differences in temperature. They can be explained and controlled by the laws of thermodynamics. Note that the operation of drying belonging to this group can also be classified as an *operation of material transfer, diffusion* (water molecules escaping through pores by diffusion and crossing the solid-gas interface).

Mechanical operations usually need mechanical force (e.g. impact, pressure, cutting) where the laws of solid mechanics are relevant. These operations are mostly used in pre-treatment, but depending on the manufacturing process they may be applied both in *compositional operations* and the preparation of intermediate- and end products (milling, compaction) Mechanical *separating operations* are also possible, such as sieving.

The characteristic parameter in *hydrodynamic operations*, based on the rules of hydrodynamics, is the energy of flowing liquids and gases.

In view of material- and heat transfer different kinds of operations have significant differences. There are several groups of operations according to the direction of the transfer:

1) parallel flow,
2) counterflow,
3) cross-flow,
4) vortex-flow operations.

Unit operations can be divided according to the participant *phases*:

1) vapour-liquid (e.g. distillation, rectification)
2) gas-liquid (e.g. absorption, desorption)
3) liquid-liquid (e.g. extraction)
4) liquid-solid (e.g. extraction, adsorption, ion-exchange)
5) solid-liquid (e.g. wetting, drying)
6) liquid-solid (e.g. dialysis, membrane filtering)
7) solid-solid (e.g. compaction) phase operations.

Unit operations of pharmaceutical technology can be divided into three main groups according to the *purpose of the working process*:

1) *basic operations*, effecting the production of the dosage form only indirectly (e.g. mixing, heat transmission, drying, fluidisation),
2) *shaping operations*, directly serving the production of the dosage form (e.g. preparation of solutions, suppository moulding, granulation, capsule filling, tablet compression),
3) *packaging operations,* playing no role in the production of the dosage form, serving the identification, dosing and protection of the product (e.g. blistering, boxing).

It is characteristic of pharmaceutical technology that each group of products, each dosage form (e.g. solution, ointment, tablet) and different preparations of the same dosage form require *specialised manufacturing technologies*. Certain products thus may require both common and special technological directions.

For example, it is a general practice to introduce components of a preparation in *ascending order of* their *weight*. However, in various cases this practice is ignored.

Foul-smelling substances are usually added last to the other components, regardless of their weight.

In case of preparations containing active pharmaceutical ingredients (API) applied in *small dose* (e.g. hormones, atropine, quinine, ergotamine), to achieve most accurate measurement of the required active ingredient and homogeneity, dilutions may be employed, prepared in advance by applying inert excipients. Manufacturing such preparations, the homogenous distribution of the active ingredient during granulation can be achieved by dissolving the active ingredient in the granulation liquid, processing the solution in a high-shear granulator or by spraying the solution of the active ingredient on the fluidized layer.

Previously applied dilution can also be used in compacting dangerous and *explosive substances* (e.g. nitro-glycerine). Homogeneous distribution and absorption of nitro-glycerine from transdermal patches can also be ensured by application of dilution (e.g. preparing 10% dilution with lactose).

Material systems containing *coloured substances*, in case of tablets ’inner’ and ’outer’ phases are granulated together (unlike general practice), as inhomogeneous distribution of the coloured substance would make the surface of the tablet spotted (e.g. in case of compacting yellow riboflavin, thiamine, nystatin, cliochinol, carotenoids ranging yellow to red depending on composition or black activated carbon).

Among several other alternatives *maintaining suspension* of active ingredients or excipients, preventing precipitation or re-crystallisation of suspended particles during storage, maintaining redispersibility can be included here.

Maintaining the physical, chemical and biological *stability* of the product, including the API and the excipients, requires specific intervention.

Adequate solutions have to be found to prevent *incompatibilities,* to *protect APIs* from the damaging effects of gastric juice (e.g. when supplementing enzymes active in the small intestine) or to *protect the human body* from irritative APIs (as with gastric irritative APIs).

According to the requirements of *therapeutic application* and based on the pharmacokinetic and biopharmaceutical parameters, the exact location of API release and the parameters of dissolution (e.g. rate, duration, repetition) have to be individually controlled in new generations of products.

Applied technology always refers to the manufacture of a particular product.

In addition to the general requirements of manufacturing and quality control, *technological specification* takes into consideration special technological and biopharmaceutical aspects, including the preparation's particular therapeutic purpose, the characteristics of the substances needed in the formulation of the active ingredient and the dosage form, required unit operations and processes, technological parameters of applied equipment, the entire scope of technological parameters – essentially, the particular *method of preparation* or *manufacture*.

To establish *an up-to-date framework of pharmaceutical technology*, it is important to emphasize the significance of *raw materials, intermediate and end products* and their correlations. Certain stages may be determinative, as their purpose is to contribute to the production of a pharmaceutical preparation of appropriate quality (indirectly) or intermediate products (e.g. granulates) of appropriate quality (directly) which are required for the production of this preparation.

Pharmaceutical technology is not simply a collection of knowledge of materials, equipment, process- and operation unit parameters, technological processes and quality management systems. It also considers – from planning to implementation, from raw materials to end product - *therapeutic purpose* and possibilities, *pharmacological attributes*, *dosage* and the *system of relations between the preparation and the living organism*.

Thus, especially in the past decades, a *biopharmaceutical and therapeutical approach* has been an integral part of pharmaceutics and pharmaceutical technology. This outlook allows the development of conscious, planned and *biologically compatible drug delivery systems*, capable of fulfilling therapeutic requirements perfectly, exploring new fields of employment, enabling, enhancing, widening and perfecting drug therapy.

Temporally and spatially controlled *new generation* drug delivery systems (e.g. chronotherapeutic preparations, self-regulating systems) are conceived in this theoretical and practical framework, enabling pharmaceutical technology to adopt further technological opportunities (e.g. nanotechnology, development of biotechnological drugs) and use them in therapy in the best possible ways.

Questions

1) What is the difference between operations and procedures?
2) What are the main, general requirements for applied technology?
3) What are the main classes of pharmaceutical technological operations?
4) How can operations of material transfer be classified?
5) How can pharmaceutical technological operations be classified according to the direction of flow?
6) What are caloric operations?
7) What are mechanical operations?
8) What are hydrodynamic operations?

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http://www.nzifst.org.nz/unitoperations/

4 Biopharmaceutical fundamentals of pharmaceutical technology

The human body contains, approximately 10^{14} billion cells of over 200 types. Each human cell contains around 2500 specific enzymes. Some $3x10^{16}$ chemical reactions happen inside the cells every single second. Currently the number of genes encoded in the human genome is estimated between 30-35 000, with 5-10 000 of these being potential pharmaceutical targets. Cells group in tissues and organs specialized to perform different specific functions and harmonize their activity to achieve a perfectly balanced distribution of labor in the body. Drugs intervene in this complex system of biological relations. Moreover, it is done using – apart from a couple of exceptions such as hormones – *xenobiotics* (substances normally not present in the body) as drug.

Biopharmacy is a pharmaceutical science dealing with the interactions between drug-preparations and the living body.

Biopharmacy has an important coordinative role in every level of pharmaceutical research, pharmaceutical development, design and therapeutic application of preparations.

LADME system describes the processes which follow a drug administration:

Liberation (L), the release of the drug from it's dosage form.
Absorption (A), the movement of drug from the site of administration to the blood circulation.
Distribution (D), the process by which drug diffuses or is transferred from intravascular space to extravascular space (body tissues).
Metabolism(M), the chemical conversion or transformation of drugs into compounds which are easier to eliminate.
Excretion (E), the elimination of unchanged drug or metabolite from the body via renal, biliary, or pulmonary processes.

1995 has been a milestone in the evolution of biopharmacy, when *Gordon L. Amidon* and his associates classified active agents to standard biopharmaceutical criteria by their solubility and permeability and established the *Biopharmaceutical Classification System, BCS*, which is used for predicting intestinal adsorption of drugs.

Table 4-I
Biopharmaceutical Classification System of Active Agents

Class	Solubility	Permeability
I.	good	good
II.	poor	good
III.	good	poor
IV.	poor	poor

The concept of drug evolves along with the evolution of drug therapy. Active agents as chemical substances are rarely applied on their own. Pharmaceutical preparations are in use now, whose application opportunities show similar significant progress. In previous decades preparations have been regarded as nothing but a carrier for the active agent, with the effects of this attitude lasting to this day. As a result, a thorough scientific exploration of the system of relations between body and pharmaceutical preparations was in little demand. The ability of pharmaceutical

technology satisfying the demands of therapy on a higher level had been established and enabled by biopharmacy. New generation pharmaceutical preparations developed on the basis of recent scientific achievements facilitated a significant progress in therapy by improving existing drug therapy methods and developing entirely new therapeutic facilities (e.g. compound preparations, controlled drug release systems, including autoregulatory and targeted release systems.)

The earlier *active agent – pharmaceutical effect* approach needs to be updated with the *pharmaceutical preparation – pharmaceutical effect* approach both for pharmacists and physicians, supplementing it with now available modern biopharmaceutical and drug therapy knowledge.

Modern *pharmaceutical preparations (dosage forms)* are likewise composed of active agents and excipients with a drug delivery function. However, owing to their specific composition, structure, in addition to introducing active agents in the body, they are also capable of optimizing drug therapy through altering the pharmacokinetic parameters of the active agents.

Drugs have two lives: one before administration, the other, in vivo, after administration. The first stage is there for the development and preparation of the drug, the second for the triggering of a therapeutic effect, the application of the drug. It is the harmonization of the administration of drug and the stages before and after administration that lead to the development of modern, *biocompatible* preparations and drug delivery systems. Both stages deserve examination and comparison from unit operation as well as biopharmaceutical aspect.

Regarding the primary purpose of pharmaceutical research and development or pharmaceutical production it manifests clearly that the in vivo part is dominant in the relationship of the two stages, where the first stage must fulfill the set of requirements defined by the stage after the administration of the drug with the utmost accuracy.

In the course of developing pharmaceutical technology, all the pharmacological, pharmacokinetic, physico-chemical, pharmacophysical, pharmacochemical and pharmaceutical technologic parameters of drugs (active agents and preparations) must be taken into consideration, which enables

- introduction of active agents, pharmaceutical preparations into the body,
- delivery of the preparation to the location of absorption,
- control of active agent release and
- exertion of the optimum therapeutic effect.

The dosage form, size, consistence, composition of the drug depend on the route of introduction.

Table 4-II.
Dosage forms and routes of administration

dosage form	dosage mode in latin	route of introduc-tion
tablet	*buccalis, sublingualis*	oral cavity
solution (gutta), emulsion, suspension powder, granulate, tablet, capsule	*per os*	oral (ingestion)

dosage form	dosage mode in latin	route of introduction
solution for injection	*intra venam*	vein
	intraarterialis	artery
	intracardialis	heart
	epiduralis	epidural space
	intraarticularis	joint
	intracutan	skin
solution, emulsion, suspension for injection	*intramuscularis*	muscle
solution, suspension for injection	*subcutan*	subcutaneous tissue
solution, suspension	*intraperitonealis*	abdominal cavity
solution, emulsion, suspension	*epicutan*	skin
ointment	*dermalis*	
patch	*transdermalis*	
aerosol	*inhalatio (pulmonalis)*	bronchi and alveola
eye drops, eye ointment in solution, suspension, emulsion	*conjuctivalis*	conjunctiva
nasal drops, gel, spray in solution, suspension, emulsion	*nasalis*	nasal cavity
ear drops in solution, suspension	*oticularis*	ear
suppository, enema	*rectalis*	rectum
vaginal suppository, vaginal tablet, globules	*vaginalis*	vagina
urethral sticks	*urethralis*	urethra

Getting the preparation to the location of effect may be achieved:

- directly (local application), or
- indirectly, assisted by vital functions (e.g. intestinal peristaltic, blood-stream, absorbing epithelial tissue).

In case of intravenous administration, the active agent is distributed in blood and, by the aid of the cardiovascular system, in tissues to achieve a systemic effect. Knowledge of parameters of solubility, blending and distribution after immission in blood are necessary for drug design.

In case of intravenous administration, the drug is homogenized and distributed in the body without absorption shortly after administration. This happens much slower in case of intramuscular administration, due to absorption. The composition, pH and volume of blood is practically constant.

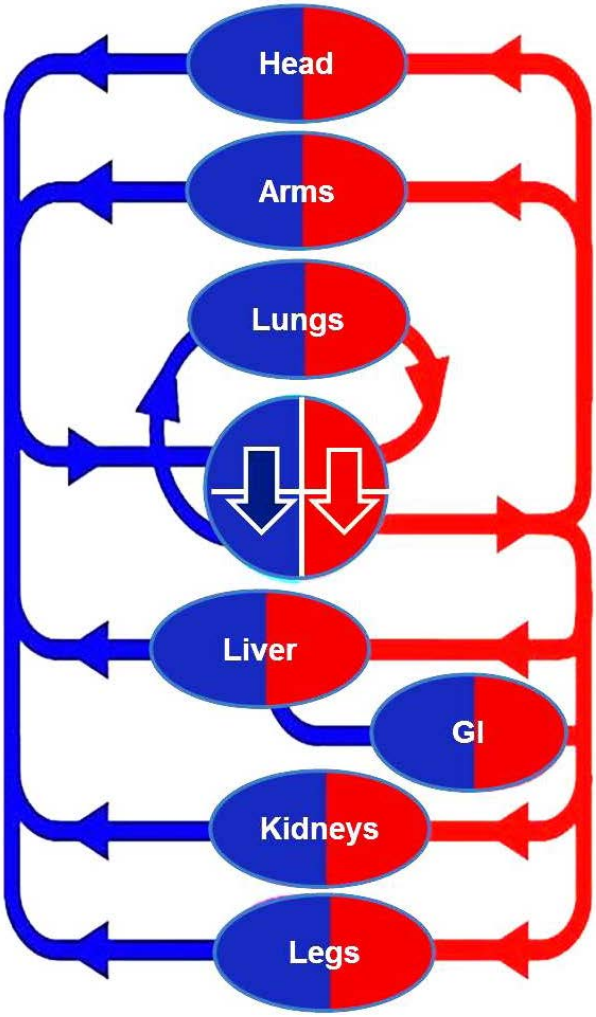

Fig. 4.1.
Schematic diagram of our cardiovascular system

From a technological and economic aspect it can be established that tablets are relatively easy and inexpensive to produce in mass quantities. Also, being so simple to administer, it is one of the most widely used dosage mode for *peroral* administration of *macro size dosage forms*.

From a biopharmaceutical and unit operations aspect our intestinal system is very diverse, rather complex and determined by several parameters, as required for the utilization of nutriments. According to its purpose, the anatomical structure of the intestinal system, its functional anatomical characteristics, different cytological structures, varying pH and enzyme composition of the internal fluids of its individual sections are fundamentally determining for the options of pharmaceutical therapy. Fittingly with its consecutive structure, the processes occurring in individual sections of the GI tract are particularly significant, as they influence and in many cases prepare the functions and options of the subsequent intestinal sections.

Designing *orally, perorally* or rectally administered preparations the conditions that surround the preparation after administration need to be considered. Therefore, the body of knowledge of pharmacological technologists and even attending pharmacists cannot rely solely on the operation of tablet compression or preparation of suppositories, the knowledge of active agents and excipients, equipment or quality management systems. They need to be aware of the role the preparation they make

plays in therapy, how it exerts its effect or what are the possible risks of administering an inadequate quality (e.g. release, disintegration) preparation.

If the whole dissolution and adsorption process is considered, not just administration alone, it becomes clear that contrary to common belief, the simplicity of peroral dosing is ostensible. Considering only the facts that it does not require professionally trained staff, goes without the difficulties (e.g. intravenous administration, pain) and risks (e.g. infections) of giving injections, this dosage mode is truly simple. Actually, the process following the taking of a tablet is rather complicated and complex as the fate of the tablet inside the body is influenced by several voluntary and involuntary factors.

From a unit operations aspect, in *peroral administration*, at the start of the above mentioned second stage (i.e. subsequent to administration) the act of *swallowing*, for example, is a complex action, influenced by several parameters, controlled in different ways. There is voluntary control over the first phase of swallowing, thus it cannot be positively guaranteed that the patient will ingest the drug at the designated time. The patient has an active, decision-making role in adhering to the prescribed, recommended therapy with this dosage form. This *subjective factor* needs to be considered in therapy.

Cooperation in therapy is expressed by the term *compliance*, describing the level of precision on the patient's side, the degree of adherence to prescriptions, which is a necessary condition of successful drug therapy. It is a common experience that little children protest the unusual, bitter taste of tablets. Others, often even adults, are averse to taking tablets due to personal conditions, incidental bad experience or illness, having difficulties with (or altogether incapable of) swallowing tablets, forget to take it, confuse different tablets or fail to thake the prescribed dose. If tablet ingestion is not a viable choice, or a difficulty, then splitting, crushing and flavoring of the tablet or substituting it with alternative dosage forms (e.g. effervescent tablet, soluble tablet or injection) is recommendable, unless otherwise contraindicated.

For biopharmaceutical reasons, to make swallowing easier, tablet shape is usually a flat cylinder or oblong with rounded edges in case of larger doses. Tablet size conforms to the dimensions of the pharynx and the esophagus.

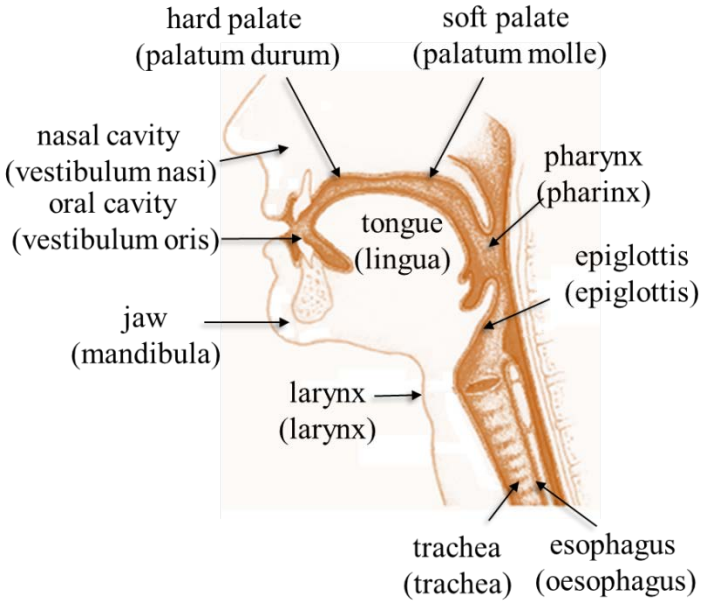

Fig. 4.2.
Anatomical structure of swallowing conditions

Tablets, just like food, are transferred to the pharynx by the downward movement of the tongue root. As of the arrival of the tablet in the pharynx, there are no further voluntary means of influencing its course. In addition to overcoming the psychic inhibition, placing the tablet on the rear end of the tongue and swallowing with a head slightly leaned back can help.

Contracting pharyngeal muscles direct the tablet towards the dilated upper tract of the esophagus and prevent it from returning to the oral cavity. As a result of the peristaltic contractions of the esophagus the tablet enters the stomach through the *cardia*. This ring of muscles, made up of skeletal muscle fibers, acts as a sphincter, preventing gastric content from returning to the esophagus (*reflux*). The sphincter opens only if the peristaltic wave running along the esophagus arrives to it. This is when the tablet can enter the stomach through the opening cardia.

Liquid dosage forms pass through the esophagus faster than the peristaltic movement, pulled on by their own weight. However, they cannot enter the stomach before the esophageal peristalsis opens the sphincter.

For the ingested tablet entering the digestive system, the stomach has an important "distributional", controlling function beyond its absorptive ability. Depending on their design, drugs behave in various ways in the stomach:

1) disintegrate, releasing the active agent partially or fully,
2) do not disintegrate and active agent release begins,
3) being gastroretentive, form a depot in the stomach by expanding or clinging to the gastric mucosa, blocking passage,
4) pass on unchanged to the subsequent parts of the GI tract.

Motion of the gastric content is controlled by the *antrum pyloricum*. By using coatings dissolving in different pH levels matching the various pH conditions in the GI tract, a retarded or targeted release of active agents can be achieved. Active agents sensitive to the gastric fluid require the development of dosage forms with *enteric* coating (e.g. coated tablet, coated pellet). Depending on the location of effect (e.g. enzymes) or the location of adsorption, active agent release can be controlled in the various sections of the small intestine in a planned manner, which significantly increases biological usefulness.

Non-absorbing expedients of pharmaceutical preparations used in the digestive system leave with the excreta. For injections and implants however it is advisable to use expedients that are present in the body anyway (e.g. water, phospholipids) or such polymers that are not toxic and break down in the body after a while.

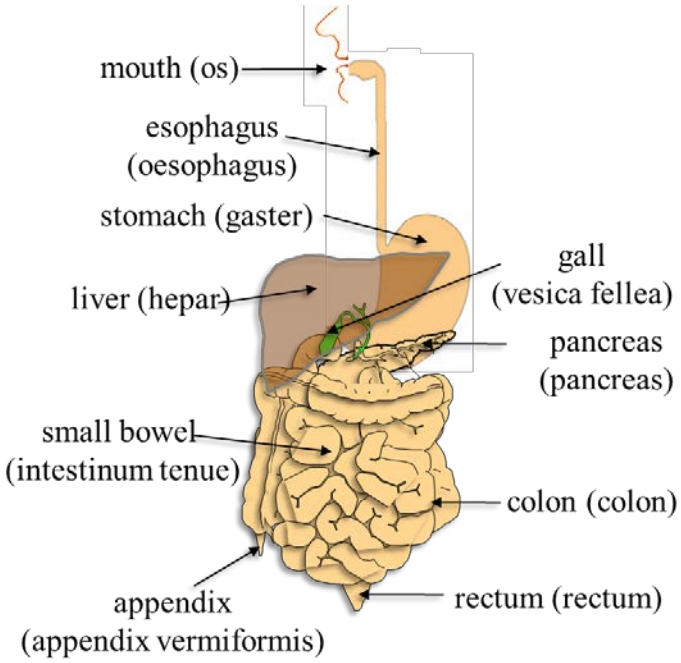

Fig. 4.3.
The digestive system

The above examples show that in addition to therapeutic requirements, biopharmaceutical parameters have a direct effect on the applicable dosage forms, the parameters of the drug, applicable expedients and production technology.

Biocompatible novel macro, micro and nano size drug delivery systems are the significant of connection of pharmaceutical technology and biopharmacy, which base and allow the optimization of pharmaceutical therapy by harmonization of dosage, blood level controlled by time, administration route require to treatment, and time interval of pharmacological effect. This type of pharmaceutical preparation is able to release active substances in planned and useful way based on modified biopharmaceutical properties. This kind of liberation is allowed by manufacture technology and biopharmacy properties of preparation. Release of active substance has to be possibly tailored to properties of administration site. Due to intense development and research activities of the last decades, novel preparation is appeared, which is called internationally drug delivery systems (DDS). These biocompatible preparations allow the design and optimization of therapeutic effect in the aspect of dosage form, dosage, speed and site of drug delivery, plasma level and applied excipients. Biopharmaceutcial based improvement of therapeutic effect extends pharmaceutical therapy significantly. Not only by having fewer side effects and less dosage, efficiency and tolerability of pharmaceutical treatment could be improved, but also there are possibilities for control of plasma level according to time and site of action. Basic requirement of development of DDS systems was the pharmaceutical technological view based on biopharmacy. Connection of these two sciences enriched each other in the last three decades, and due to this new drug delivery systems have been created, which are able to control drug release in time and according to site of action. These preparations are capable for continuous, discontinuous, accelerated, sustained, delayed drug delivery or which are controlled externally or self-control drug release due to safe and changeable dissolution profile, mechanism of drug delivery and programmability.

Questions

1) What is the difference between ADME and LADME systems?
2) What are the main aspects to be taken into consideration for pharmaceutical preparation design?
3) What are the requirements for product biocompatibility?
4) What are the advantages and disadvantages of peroral administration?
5) What compounds belong to class II. BCS?
6) What compounds belong to class III. BCS?
7) List the main characteristics of drug delivery systems!

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http://69.20.123.154/services/bcs/search.cfm

http://www.understandingnano.com/medicine.html

http://www.youtube.com/watch?v=kxSX6YJTS2I

5 Design and optimization in pharmaceutical technology

In pharmaceutical industry, in order to maintain safety of manufacturing and competitiveness modern technologies are required. Its primary criteria are conditions (skilled staff, rooms, equipments), optimization and profound knowledge of processes, operations and procedures applied in pharmaceutical production.

Design, operation and control of *modern technological systems* are based on information and their processing, thus understanding of procedures is carried out by data mining, which means knowledge discovery in database. *Data mining* is a scientific action, which aims at discovery of particular phenomena and procedures by data management and search and analysis of their correlations.

Afterwards discovery of procedures (*process analysis*) will take place the control of procedure, which can only be efficient, if factors can be determined, which are influencing quality parameters. The factors can be grouped accordingly how extent and in which way are able to affect on particular parameters.

In pharmaceutical research and development, tasks related to process analysis, operational examination of parameters and optimization are very frequent.

Optimization can be defined as search of the best and most favorable values of a phenomenon in order to create the necessary technological conditions. Size of manufacture batch, manufacturing time and particular operation parameters can also be obtained by optimization of parameters. Optimization can be done by numeric and/or graphic methods.

Optimization of pharmaceutical technological processes usually have two purposes:

1) minimization of parameters (e.g. usage of material and energy, contamination, standard deviation of tablet weight, difference in release of active substance, powder content, disintegration time)
2) maximization of parameters (e.g. cost-effectiveness, production yield, flow property of granules, stability of active substance and/or product).

The practice shows that quality parameters of particular batch are deviated even in optimized systems. Expectable and feasible reproduction of quality parameters of product is achieved in the deviation range. One of the reasons for optimization is to reduce this standard deviation.

In systems determined by several parameters, properties of research object (operation or process) are affected by several independent and dependent variable. "*Black box*" can be applied to describe their relationship, which is a model with unknown internal articulation, and real processes, thus directly cannot be quantified. Its function is evaluated by external reactions (input-output, feedback).

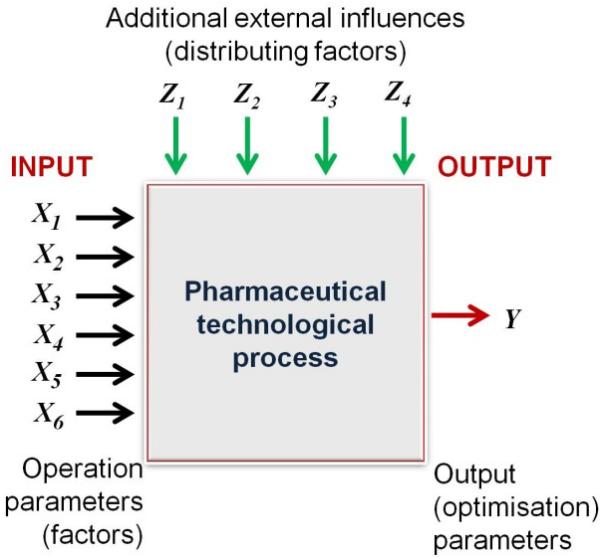

Fig. 5.1.
Scheme of a "black box"

By optimization, it is desired to know the relations between *independent* (*input*) and *dependent* (*output*) variables, furthermore how output values of optimization parameters are influenced by independent variables and different values of factors (*factor levels*).

The measurable, variable quantity, which has a particular, determined value in a certain moment and with which function of examined object can be influenced, is termed: *factor*.

With the usage of *factorial experimental design*, few numbers of experiments are enough to explore the correlation between independent and dependent variables. Requirements of chosen parameters and factors are:

- controllability,
- accuracy,
- factor has to be unambiguous and directed to the particular object,
- independence between factors.

Suppose that optimum of *Y* parameter is desired to determine in a technological process, and it is known that this parameter is affected by *n* number of factors. The mathematical model described by this function is:

$$Y = f(x_1, x_2, ..., x_n) \qquad (1.)$$

Y *optimization parameter (dependent variable)*,
x_n n^{th} *factor* (*independent variable*).

Typical property of pharmaceutical technological operations is that there are processes determined by a plenty of parameters. From the „*black box*" model, it can be clearly seen, that in order to eliminate disturbing external effects (e.g. steady temperature, maintain the same humidity), effective, less effective or completely ineffective factors have to be chosen. Simultaneously several factors can influence the result, in addition to their interaction can also occur.

Large number of experiments required for examinations (N) result from the fact that numbers of factors increase exponentially the possible values of factors (m).

Table 5-I.
Number of experiments in the function of *m* and *n*

n	m	N
2	2	4
4	2	16
6	2	64
8	2	256
2	3	9
4	3	81
6	3	729
8	3	6561
2	4	16
4	4	256
6	4	4096
8	4	65536

Profound consideration is necessary to determine in how many level these several factors has to be examined. Even high number of adjustment can also be inevitable. The task can be solved in the easiest way with experimental design methods developed and based on mathematics. If there are a plenty of factors, it is practical to make effort on decrease of their number.

Experimental design is the effective method of optimization and examination of several technological processes, which is able to design, analyze experiments and to conclude objectively. The point is that by systematic design of experimental settings, and from result obtained by changing result of this optimization parameter values leads us to construct a mathematical model, which is able to carry out processes with sufficient precision.

The *experimental design* (*ED*, or *Design of Experiment, DOE*) means plan or design containing settings and sequence, which has to be compiled even before beginning of experiment. This is an effective method, which allows planning and analysis of experiments, objective evaluation of obtained result, conclusion, after which follow the steps for optimization of particular process.

Full factorial experimental design is regarded if all possible factor level combination and fractional factorial experiments are performed. If just a part of the full, partial factor design is carried out. Latter one can significantly reduce the necessary number of experiments, which should be performed.

The linear model for two factors (x_1 and x_2):

$$Y = b_0 + b_1 x_1 + b_2 x_2 + b_{12} x_1 x_2 \qquad (2.)$$

b coefficient

for three factors (x_1, x_2 and x_3):

$$Y = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + b_{12}x_1x_2 + b_{13}x_1x_3 + b_{23}x_2x_3 + b_{123}x_1x_2x_3 \qquad (3.)$$

Mathematic model determined experimentally is appropriate to describe or characterize an examined system, if it meets with the criteria of adequacy. Namely there is no significant difference between output of system calculated according to computer and output of actual system.

Optimization can be performed by applying the gradient descent method developed by *Box and Wilson*. The principal of this method is that in order to determine the optimum, simultaneous change of significant factors is required.

Factorial experimental design is demonstrated by the following example.

During production of micropellets carried out by high-shear granulator, three parameters were changed. Their effect for the drug release from dosage form was monitored. Examined factors were excipient creating matrix: amount of carbomer (x_1), speed of stirrer (x_2), and flow speed of granulating fluid (x_3). 2^3 type factorial design needed altogether 8 experimental settings. Medium level of changed parameters then variation interval was determined, with which lower and upper level was ascertained.

Table 5-II.
2^3 type factor design for examination of production of micropellets

	x_1 **quantity of carbomer** (g)	x_2 **speed of stirrer** (rpm)	x_3 **liquid flow speed** (ml/min)
Medium level	1.0	1375	6
Variation interval	0.5	125	1
Upper level	1.5	1250	7
Lower level	0.5	1500	5

Table 5-III.
2^3 experimental settings of type factor design

Trial	x_1 **quantity of carbomer** (g)	x_2 **speed of stirrer** (rpm)	x_3 **liquid flow speed** (ml/min)
1	-1	-1	-1
2	1	-1	-1
3	-1	1	-1
4	1	1	-1
5	-1	-1	1
6	1	-1	1
7	-1	1	1
8	1	1	1

Examinations were carried out in randomized order in multiplicate according to the trial.

After experimental production, time of 50 % drug release ($t_{50\%}$) was determined, as an optimalization parameter, based on which the following function was concluded:

$$t_{50\%} = 0{,}56 + 0{,}045x_1 - 0{,}067x_2 - 0{,}25x_3 + 0{,}19x_1x_2 - 0{,}050x_1x_3 + 0{,}027x_2x_3 \qquad (4.)$$

Afterward statistical analysis, the model containing significant coefficients was:

$$t_{50\%} = 0{,}56 - 0{,}067x_2 - 0{,}25x_3 + 0{,}027x_2x_3 \qquad (5.)$$

According to the model, direct information can be acquired about the intense of effect based on number of absolute value of coefficient and about way of effect according to its sign. In the case of positive coefficient, optimization parameter increases with increased parameter, in the case of negative sign, it decreases.

The 3D graphs often provide more information than graphs in 2D. Visualization of the function of the relationship between a dependent and two independent variables chosen according to mathematical models occurs by the connection of data points producing 3D graphs, called *response surfaces*. Application of this method is recommended when optimal combination of two data sets should be determined. This graph is also suitable to represent the possible interactions.

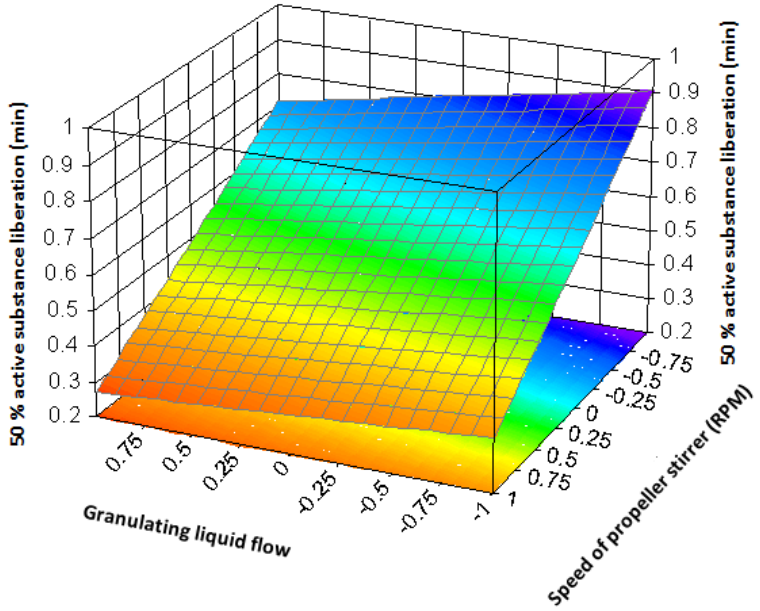

Fig. 5.2.
The effect of speed of stirrer and granulating liquid flow for drug release from micropellets

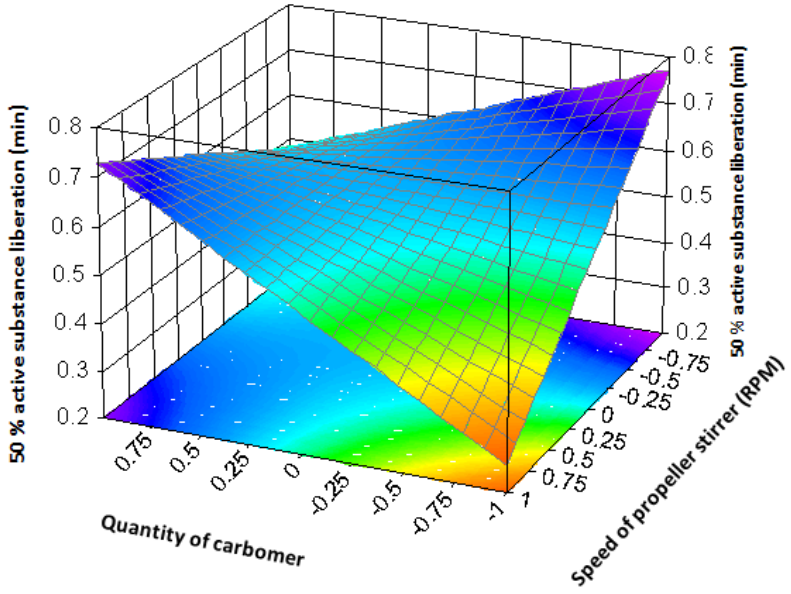

Fig. 5.3.
The effect of speed of stirrer and quantity of carbomer for drug release from micropellets

In another experiment production of liposomes was investigated. Effects of two parameters was examined on the particle size (d): time of ultrasonication (x_1) and quantity of cholesterol used as stabilizing agent. In this case *CCD*, namely *Central Composite Design* was applied.

Table 5-IV.
CCD type factorial design for examination of liposome production

	x_1 **time of ultrasonication** (min)	x_2 **quantity of cholesterol** (%)
Medium level	10	0,6
Variation interval	5	0,4
Upper level	15	0,2
Lower level	5	1,0

Table 5-V.
CCD type experimental settings of factor design

Trial	x_1 **time of ultrasonication** (min)	x_2 **quantity of cholesterol** (%)
1	-1.00	-1.00
2	1.00	-1.00
3	-1.00	1.00
4	1.00	1.00
5	-1.41	0.00
6	1.41	0.00
7	0.00	-1.41
8	0.00	1.41
9	0.00	0.00
10	0.00	0.00
11	0.00	0.00
12	0.00	0.00
13	0.00	0.00

The following quadratic model was obtained:

$$d = 314{,}00 - 140{,}62x_1 + 16{,}25x_2 + 13{,}00x_1^2 - 24{,}50x_2^2 + 7{,}50x_1x_2 \qquad (6.)$$

Afterward significance examination, it was ascertained that exposition time of ultrasound affect significantly the size of liposomes.

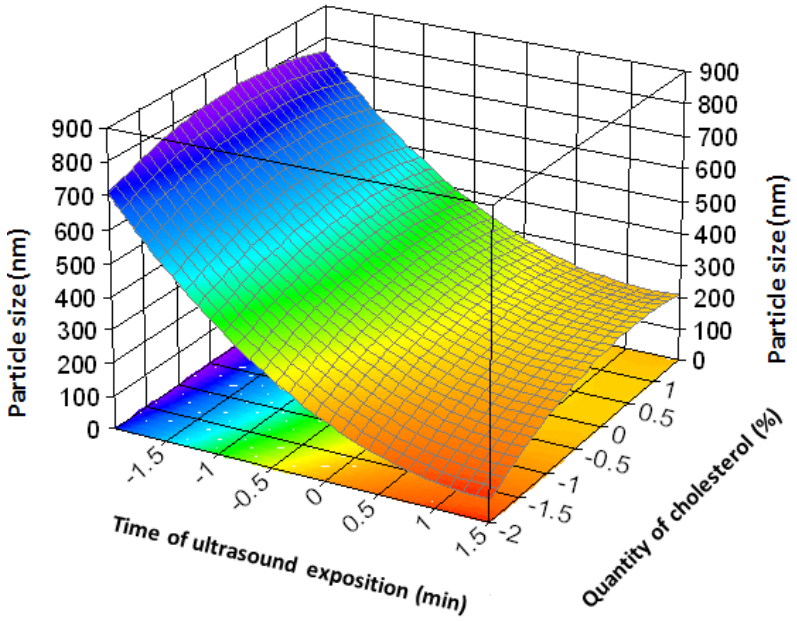

Fig. 5.4.
The effect of time of ultrasonication and quantity of cholesterol on particle size of liposomes

In pharmaceutical industry, or in research and development laboratories, besides the nowadays widely applied factorial experimental design, plenty of possibly having *artificial neural networks* are also used. The fundamental idea of its development was the human brain. Similarly to the brain the artificial neural network has adaptive properties due to its structure, namely it is able to learn. During the operation of the system, it is able to receive large number of samples (measurement data) and learns them with complex, series of mathematical functions with memory. During this process input variables are assigned to the measured output values.

The application possibilities of artificial neural networks:

1) classification tasks (text recognition, voice recognition, purpose recognition, diagnosis),
2) function approximation (process control, process modeling),
3) forecast (forecast of time-related dynamic systems, financial modeling),
4) data mining (data display, export, clasiification).

Among neural networks, several types are distinguished, and according to the nature of task it will be decided, which type should be used. The easiest artificial neural network is the MLP (M*ulti-Layer Perceptron*) network, which is consisted of an input, output and a hidden layer. In the first, input layer there are as many neurons as input variables. The part of MLP is the hidden layer, in which the number of layers and neurons is arbitrary (though policies exist to determine the number of neurons). The

third component of the network is the output layer, which is consisted of as many neurons as examined output values.

The neurons of particular layers are localized in three vertical columns, next to each other in the architecture of a neural network. In Fig. 5. there can be found on the left side two neurons of input layer, in the middle three neurons of hidden layer and on the right side one neuron of output layer. Originated from the number of neurons located in the different layers, this architecture is termed as a 2-3-1 architecture.

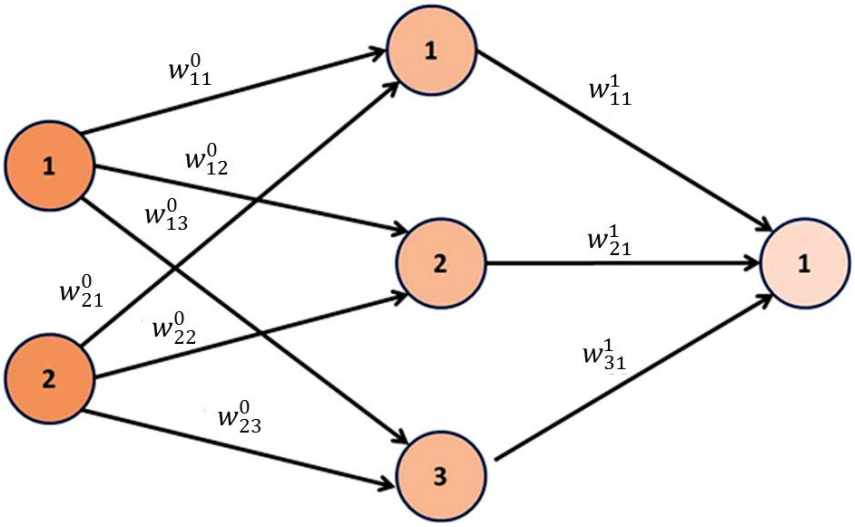

Fig. 5.5.
Architecture of a 2-3-1 type artificial neural network

The input neurons are connected to right located layers, namely in this case to the neurons of the hidden layer. This connection can be called as synapsis. System assigns weights (w_{mn}^i) to the connections (i is neural layer of the network, m and n indicate the connected neurons), which in every cases generates a multiplication with the input sign, and ultimately enters into the neuron found at the end of connection. Values entering into the neurons of the next layer are summed, and then after a transformation process pass on the neurons of the next layer. Afterwards the values are multiplied again with the weights of connections. In order to get the output data closer to real output values with the learning (which is often called training) process (n_t), the network can modify the weights.

During the operation of system, a learning curve is created, which indicates the success of the training process. The graph illustrates the mean squared error of calculated output values which is correlated with the real output values.

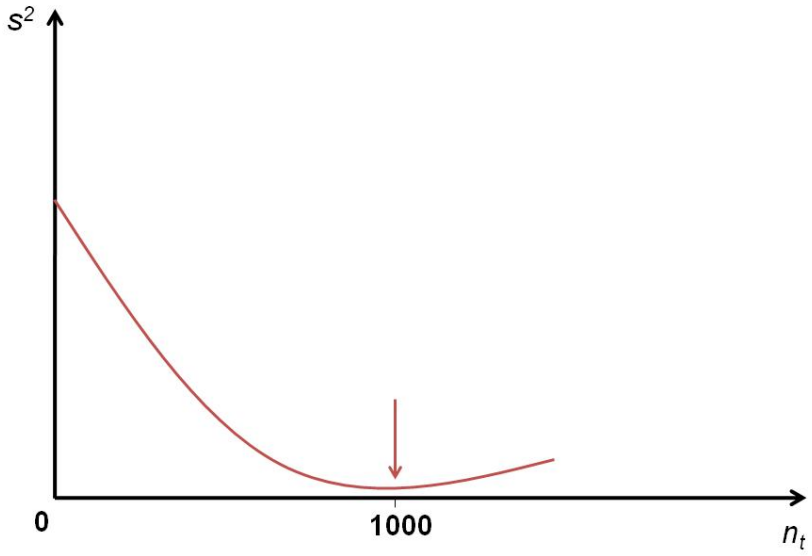

Fig. 5.6.
Typical training curve of an artificial neural network

Important factor in the training process of neural networks is to determine the sufficient amount of repetition. Appropriate learning method or process can be controlled by maximized amount of learning data, as well as by application of least square method within leaning data, or by decreasing below a particular value. Overtraining can also be achieved by choosing the number of learning repetition incorrectly, since the unnecessarily long training time causes the square errors to be raised.

During the first learning process of the system, the initial weights belonging to synapses are generated randomly, however second learning data is controlled according to the assessment of first learning data. The network calculates the difference between the real, measured value and value calculated by the system. According to the extent of difference, a learning algorithm can alter the values of weights, as long as only a minimal difference is observed. Sufficiently to the experimental data, applied architecture of neural networks has to be complied according to policy of models of neural networks, so that the possibly most accurate learning can be performed. Therefore in many cases several architecture is neccessitated to be tried.

Higher number of samples increases the accuracy of the artificial neural networks. After finding and creating the appropriate and controlled learning architecture of a system, will be able to conclude and predict the result of unperformed experiments, measurements, without any correlation between the input and output values.

Questions

1) What makes the application of mathematical statistical procedures necessary in the study of pharmaceutical technological processes?
2) What are the possible main goals of the optimization of pharmaceutical technological processes?
3) How would you define the notion of data mining?
4) What are the pharmaceutical technological problems that experimental design can solve?

5) How would you define the notion of „factor”?

6) What is the correlation between the number of experiments to be performed in factorial experimental design and the number and levels of factors?

7) What are the practical benefits of using response surfaces?

8) What are the greatest potentials of the application of artificial neural networks for pharmaceutical technology?

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Recommended websites

http://www.stat.yale.edu/Courses/1997-98/101/expdes.htm

http://www.itl.nist.gov/div898/handbook/pri/section1/pri1.htm

http://www.moresteam.com/toolbox/design-of-experiments.cfm

http://www.jmp.com/support/downloads/pdf/jmp_design_of_experiments.pdf

6 Measurement

Measurement is an action or sequence of actions during which a physical (e.g. mass, volume, density, rheological property, color, particle size, surface), chemical (e.g. pH, ion concentration, reactivity, polymerization degree), physicochemical (e.g. solubility, HLB value, surface activity) or biological (e.g. pharmacokinetic, pharmacologic, biopharmaceutical, pharmaceutical therapeutic) quantity is described by an appropriate value.

Discipline related with the measurement is called *metrology*.

Identification of active ingredients, determining their structure dose, or dissolution quantitative and qualitative analysis of pharmaceutical preparations, research and development, quality assurance, process control and optimizing, in-process controls are all based on reliable measurement techniques.

Quantities to be determined could be intensive and extensive. Extensive quantities are additive quantities proportional to the extent of physical quantities (e.g. weight, volume, heat quantity). Intensive quantities are equalized quantities independent from the size of the system (e.g. temperature, pressure). Specific amount should always be transformed to a unit mass. Quantities calculated to a unit amount of material are termed molar quantities.

Measuring technique is part of the metrology dealing with the practical execution of the measurement. Its technical level can promote the manufacture and the control.

Aim of the measurement is the determination of a quantity. During the measurement we collect reliable information from the subject of the measurement (physical, chemical quantity, state, process etc.). This information is termed the result of the measurement.

For measurement we need to choose a defined unit of quantity called dimensional unit. Essentially measurement means the comparison of the dimensional unit and the measured amount. Hence the result (X) is equal to the common part of the amount (m_a) and the dimensional unit (m_d).

$$X = m_a \cdot m_d \tag{1.}$$

The lawful dimensional units are specified in standards and statutory rules

The base units of The International System of Units (SI):

1) *meter (m)* is the unit of *length (l)*
2) *kilogram* (*kg*) is the unit of *mass (m)*
3) *second (s)* is the unit of *time (t)*
4) *ampere (A)* is the unit of *electric current (I)*
5) *kelvin (K)* is unit of *thermodynamic temperature (T)*
6) *mole (mole)* is the unit of *amount* of *substance (n)*
7) *candela (cd)* is the unit of *luminous intensity (Iv)*

Units derived from the SI base units is e.g. *the force [m.kg.s^{-2}]*. Units outside the SI like *volume (liter) or mass (tons)* are regulated by specific rules.

The SI derived units like *mass density [kg.m^{-3}]* are obtained from special equations and the seven SI base units. Furthermore there are prefixes by them the multiples and submultiples of SI units can be formed.

Table 6-I.
The SI prefixes used to form decimal multiples and submultiples of SI units

prefix	sign	vcalue
exa	E	10^{18}
peta	P	10^{15}
tera	T	10^{12}
giga	G	10^{9}
mega	M	10^{6}
kilo	k	10^{3}
hekto	h	10^{2}
deka	da (dk)	10
deci	d	10^{-1}
centi	c	10^{-2}
milli	m	10^{-3}
mikro	μ	10^{-6}
nano	n	10^{-9}
piko	p	10^{-12}
femto	f	10^{-15}
atto	a	10^{-18}

Next units outside of SI are used to expressing very low concentrations in analytical, pharmacokinetic and biopharmaceutical examinations:

- ppm (part per million): 10^{-6}g/g = 1μg/g,
- ppb (part per billion): 10^{-9}g/g = 1ng/g,
- ppt (part per trillion): 10^{-12}g/g = 1pg/g.

In several times the multiples or submultiples SI base units and units outside of SI are used in the pharmaceutical practice instead of the seven SI base units.

Units applied for measurement of length in pharmaceutical practice:

- millimeter (*mm*),
- micrometer (*μm*),
- nanometer (*nm*).

Millimeter (mm) and micrometer (μm) are used for the measurement of particle size or nanometer (nm) can be used as well in case of nanosystems.

Units applied for measurement of mass:

- gramm (*g*),
- centigramm (*cg*),
- milligramm (*mg*),
- microgramm (*μg*).

Units applied for measurement of volume:

- liter (*l*) (1 $l = 0{,}001\ m^3$)
- cubic centimeter (cm^3),
- milliliter (*ml*).

The SI base unit of amount of substance (n) is mole.

To express the concentration, mass percent (m/m%) or (in case of alcohols) volume percent (V/V%) are used in pharmaceutical practice.

The most common concentration types used in laboratory are mass percent, mole percent, volume percent, mole concentration, mass concentration and concentration calculated by Rauolt's law (molality).

Mole concentration (C_{ni}) is defined as how many moles solute are in one liter volume solution:

$$c_{ni} = \frac{n_i}{V} \tag{2.}$$

c_{ni} molarity of component i
n_i moles of component i
V solution volume

Mole fraction (X)

$$X_i = \frac{n_i}{n} \tag{3.}$$

$$1 = X_1 + X_2 + ... + X_n \tag{4.}$$

X_i mole fracttion of component i
n_i moles of component i
n total moles of solution

Mole percent (*X%*)

$$X_i\% = \frac{n_i}{n} 100 \tag{5.}$$

$$100 = X_1\% + X_2\% + ... + X_n\% \tag{6.}$$

$X_i\%$ mole percent of component i

Mass fraction (m/m; W)

$$W_i = \frac{m_i}{m} \tag{7.}$$

$$1 = W_1 + W_2 + ... + W_n \tag{8.}$$

Mass percent (w%)

$$W_i\% = \frac{m_i}{m} 100 \tag{9.}$$

$$100 = W_1\% + W_2\% + ... + W_n\% \tag{10.}$$

Mass concentration is defined as the amount of solute in one liter volume of solution.

$$c_{mi} = \frac{m_i}{V} \tag{11.}$$

C_{mi} mass concentration of component i
m_i mass of component i
V volume of solution

Volume fraction (γ):

$$\gamma_i = \frac{V_i}{V} \tag{12.}$$

$$1 = \gamma_1 + \gamma_2 + ... + \gamma_n \tag{13.}$$

Volume percentage (γ%):

$$\gamma_i\% = \frac{V_i}{V} 100 \tag{14.}$$

$$100 = \gamma_1\% + \gamma_2\% + ... + \gamma_n\% \tag{15.}$$

γ_i: volume fraction of component i
$\gamma_i\%$ volume percentage of component i
V_i volume of dissolved component i
V volume of solution

Concentration calculated by Raoult's law (Molality) (C_{Ri}):

$$c_{Ri} = \frac{n_i}{m} \tag{16.}$$

c_{Ri} molality of component i
n_i moles of component i (mol)
m 1000 g solvent

The unit of density used in pharmaceutical practice is:

- gram/ cubic centimeter (g/cm^3) = gram/ milliliter (g/ml)

The units of pressure (Pascal) used in pharmaceutical practice are:

- bar (*1 bar =100 kPa*),
- millibar (mbar) (*1 mbar = 100 Pa*),
- millimeter of mercury (*mmHg*) = *torr* (1 *mmHg* = 1,33322•10^2 *Pa*) = *133 Pa.*

One of the seven SI base units is the thermodynamic temperature. The Celsius (°C) temperature scale (t) is defined by the absolute temperature (T) on the Kelvin scale:

$$t = T - T_o \tag{17.}$$

$T_o = 273{,}15\ K$

Dimensional unit of dynamic viscosity (Pas) applied in pharmaceutical technology is:

- centipoise (*cP*) (*1 cP = 1 mPas*).

Dimensional unit of kinematic viscosity (m^2s^{-1}) is:

- centistokes (*cSt*) (*1 cSt = 10^{-6} m^2/s*).

Refractive index is the measure of refracting ability of a material, which is the ratio of the speed of the light in vacuum and in the examined material in relation with the sine of the incident (absolute refractive index). Relative refractive index, which has no dimensional unit, is the quotient of absolute refractive indexes of two materials.

Optical activity of optically active materials is measured by the degree of rotation of the linearly polarized light on the right side (+) or the left side (-) in degrees (°).

Measuring method is the principle according to which the measurement is planned and carried out.

Measuring process is a collective act carried out according to a definite measuring method using the proper device by properly skilled technicians. Measuring process is carried out by the proper measuring device.

Accuracy and deviation are opposite, inverse concepts. Measurement accuracy is the proximity of the true and the measured value.

Expected value is the center of the probability variable of the measured value. This center equals the arithmetic mean around which the measurement data oscillate.

Measurement error is the difference between the measured and the true value. The bigger the measurement error is, the smaller is the accuracy. Result of the measurement can only be given in view of the measurement data and the extent of the measurement error.

Main types of the measurement error:

1) absolute
2) relative
3) regular
4) accidental
5) crude

Absolute error (E) is the difference between the real value *(X_R)* and the true value (X_T) of the measured quantity:

$$E = X_R - X_T \tag{18.}$$

Relative error (e) is the quotient of the absolute error and the true value:

$$e = \frac{E}{X_T} = \frac{X_R - X_T}{X_T} \tag{19.}$$

True value (X_T) is the value of the measured amount, which can substitute the real value for the defined purpose in the sufficient accuracy.

Regular measurement error is the error returning every time during the measurement which cannot be excluded by carrying out parallel measurements. To solve this problem the correct setup of the device or the correction of the measurement data is required.

In case of *accidental error* measurement data are slightly oscillating. Accidental error is the type of error that is repeated accidentally in case of the measurement. Error can be excluded or decreased by making parallel measurements. Extent of the error is given by an interval (called confidence interval) with a definite probability (e.g. 99.74%) containing the real value.

Neglecting the regular errors can distort the measurement result. Neglecting the accidental errors make the measurement uncertain. During a carefully executed measurement, regular errors (as far as possible) should be determined and corrected, thus the uncertainty of the measurement depends only on the accidental errors.

Crude error occurs due to strong environmental impact or a personal mistake.

Mean of parallel measurements, the expected value, is the estimation of the real value. In order to carry out more accurate measurement, parallel measurements are required and their mean $(\bar{x})$ is accepted as the best estimation of the real value. The more measurement is carried out, the closer the mean gets to the real value.

$$\bar{x} = \frac{x_1 + x_2 + x_3 + x_4 + x_n}{n} \tag{20.}$$

n is the number of measurements

Accuracy of the measurement can be characterized according to the mean by the sum of the squares of deviations of each measured value:

$$s = \sqrt{\frac{(x_1 - \bar{x})^2 + (x_i - \bar{x})^2 + \ldots (x_n - \bar{x})^2}{n}} \tag{21.}$$

Measured data are considered as probability variables. For the calculation of the standard deviation of the measured results the probabilistic distribution should also be determined. These distributions can be normal, binomial, Poisson and exponential.

In practice most physical quantities show normal distribution which can be described by the Gaussian function.

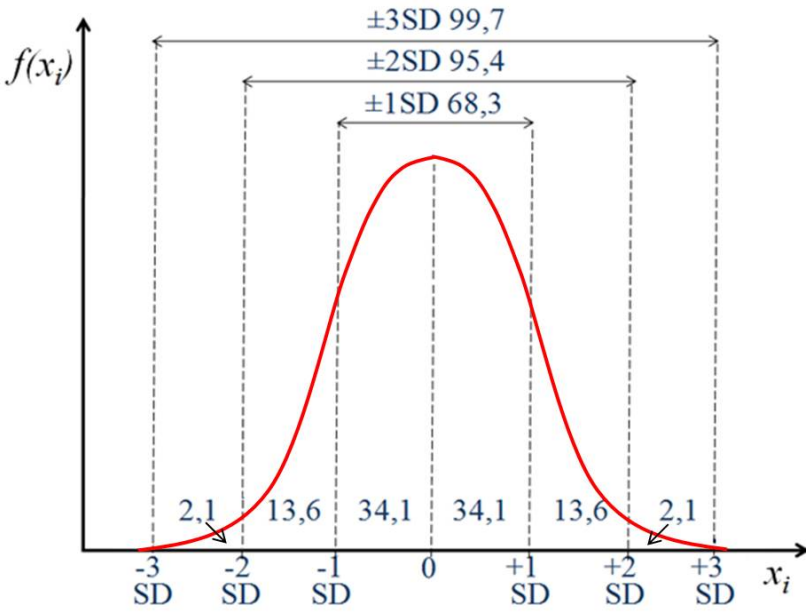

Fig. 6.1.
Normal distribution

$$f(x)=\frac{1}{\sigma\sqrt{2\pi}}exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right) \tag{22.}$$

σ standard deviation, the place of the point of inflection
μ expected value of the probability value
The *standard deviation* (*standard error, SD*) is:

$$SD=\sqrt{\frac{\sum_{i=1}^{n}(x_i-\bar{x})^2}{n-1}} \tag{23.}$$

Results of single measurements, depending on the distribution of the x_i random numbers are usually near the mean value ± 3SD.

Measuring signal represents the measured quantity according to a definite functional relationship. The *sensitivity of the device (S)* is the change in the *output sign* of the device *(da)* divided by the change of the *input sign (dx)*:

$$S=\frac{da}{dx} \tag{24.}$$

The sensitivity is characterized by the lowest measurable value and the limit of detection. The next table represents some values of a few analytical methods:

Table 6-II.
Limits of detection of analytical methods

method	detection limit
titrimetry	10^{-7} g
spectrophotometry	10^{-8} g
gas chromatography	10^{-12} g
mass spectrometry (MS)	10^{-16} g
atomic absorption spectrometry (AAS)	10^{-6}g/l
Inductively Coupled Plasm (ICP)	10^{-7}g/l
spectrophotometry	10^{-9}g/l

The measuring device usually transforms the measurable amount into a measuring signal. Sometimes it is needed to determine the instrument constant, which is a coefficient used to calculate the measurement value from the raw data by multiplication.

The instrument constant (C) is the inverse of the sensitivity:

$$C = \frac{1}{E} \tag{25.}$$

Measuring range of the measuring device determines the lowest and the highest signal which can be transmitted by the apparatus. Confirming the measuring ability *verification* and *calibration* is required by the law.

As a way of verification of measuring ability, validation and calibration is determined and regulated by law.

The aim of validation of measuring device is to evaluate the fact that whether the measuring device is valid and appropriate for its metrological standards. The most important requirement is its error limit, which aberration cannot be exceeded during the validation process.

The measured result is generally only valid and acceptable, if is created by measurement performed by a valid device with proofed conformance. That device can be regarded to be valid, which is validated by metrological authorities. Measuring device with expired validation is forbidden to use!

The validation processes have to be repeated, if:

- the validity period is expired,
- repair has been done in the device,
- the measurement technique properties of the device has been changed,
- the result done with controlling standard is not appropriate.

In pharmaceutical research and supply measuring devices are required, since in pharmaceutical industry application of measuring systems is needed besides the measuring devices. These measuring systems play a significant role in quality assurance, controlling and regulation of manufacture. Due to their importance, the measuring devices and systems have to be appropriately accurate for planned usage as well as measuring methods has to be validated suitably for the standards *of Good Laboratory Practice (GLP)* and *Good Manufacturing Practice (GMP)*.

The validation (proving control) is confirmation done by examinations and providence of objective evidences in order to be fulfilled the concrete criteria referring to the determined proper usage. The performance characteristics of method have to meet

with the required criteria and the measured values are suitable for their requirements. At the validation these are confirmed by methodized examinations. The validation procedure means the method to determine performance data such as precision, accuracy, linearity, detection limit, or selectivity. Briefly: the measured values have to be appropriate for determined criteria.

The verification (justifying control) is a confirmation done by examinations and providence of objective evidences, that the prescribed requirements are realized. At verification measurement and statistical evaluation are performed to prove the fact that, whether measurement done by the particular device (in the function of applied measurement method, used measuring system, and technical circumstances) is suitable for required accurate completion of the examined specification. Briefly: the measuring device has to be appropriate to perform the measurement tasks.

Table 6-III.
Control of functionality of several tools and devices

device	examined parameter	frequency of supervision
scales	linearity, zero reliability (with references masses)	depending on usage
volume measuring devices (burettes, pipettes)	reliability, precision	depending on usage
densitometer	single-point calibration with standard with known density	in every 5 years
thermometer	critical points of scale is supervised, compared to references	in every year

The calibration is the totality of those operations, with which the correlation between value shown by the measuring device, the measurement signal and measurable quantity can be determined. This knowledge is indispensable for the proper use of our devices and apparatus. At creation of calibration curve, the function relationship between the value of used standard, the dependent variable (e.g. concentration, mole) and independent variable (e.g. value show non device) is assessed experimentally. One of the most frequently performed calibration process usually uses five-six calibration sample with known concentration included the sample with „zero” concentration (so-called blank sample).

The shape of curve edited by this calibration method is usually monotonous increasing and saturating featured. On the saturating section of the curve the uncertainty of concentration determination increases, therefore preferably to carry out the measurement at most the yet acceptable linear section of the curve. Applying the least-squares method, specific parameters of the correlation curve are defined with linear regression calculation. In the case of if the calibration function can be linearized by the suitable transformation, then the linear regression method can be also used with the transformed values.

The *standard* means an extent or sample material, which plays a role as a references and define, accomplish, maintain or reproduce a unit of a quantity as well as one or more known values. At calibration used standard has to have current validity and must be more accurate than the controlled device.

The standard materials are usually the material, which is suitable to calibrate a device, qualify a measuring method, or appoint material specification.

It is usually occurs, that two samples have to be compared according to their deviation, assessed the fact that whether the measured difference is accidentally or can be effectively experienced. This assessment can be done by the application of Fisher's exact test. The test forms the ratio of variation of samples, so that in which the numerator is higher, the denominator is lower number.

$$F = \frac{s^2 higher}{s^2 lower} \tag{26.}$$

Subsequently F values belonged to desired significance level is determined from chart. If the calculated F value is lower, than the determined F-value from the chart, then there is no significant aberration between the two samples.

Firstly the variation coefficient *(s%)* has to be calculated to compare the deviance values belonged to variant order of magnitude, which shows that how many percent of the arithmetic mean is the deviation.

$$s\% = \frac{100 \cdot s}{\overline{X}} \tag{27.}$$

In case of the value between
0-10% little ~,
10-20% moderate ~,
20-30% intense ~,
30% extreme variability is considered.

During measuring the providence of appropriate number of sample data, elimination of accidental errors is also indispensable. Deviation of data has to be known to determine this, and then acceptable error probability (P%) has to be given as well as allowable estimation error (h).

According to this, sufficient number of data:

$$n = \frac{t_{P\%}^2 \cdot s^2}{h^2} \tag{28.}$$

In several cases variant, salient value can occur among the data of sample, which result in a statistical bias in conclusion. Dixon- method is used to monitor that bias in case of normal distribution. At the application of this method, data have to be listed according to the magnitude, which are signed with $X_1, X_2 \ldots X_n$.

The following forms are applied depending on the numbers of data (n):

If the numbers of data are between: 3-7, then $r_{10} = \frac{x_1 - x_2}{x_1 - x_2}$

If the numbers of data are between: 8-10, then $r_{11} = \frac{x_1 - x_2}{x_1 - x_{n-1}}$

If the numbers of data are between: 11-13, then $r_{21} = \frac{x_1 - x_3}{x_1 - x_{n-1}}$

If the numbers of data are between: 14-25, then $r_{22} = \frac{x_1 - x_3}{x_1 - x_{n-2}}$

The calculated r-values are compared with the crucial r-values from chart based on the Dixon method. If the calculated r-value is larger than r-value in a chosen P% from chart, it leads to salient value.

Measuring devices (appliance, apparatus, instrument) are used standalone or with their accessories to measure definite quantities with proper sensitivity, resolution and accuracy.

Measuring devices can be:

1) measuring apparatus,
2) measuring appliance,
3) measuring system.

Measuring system is the union of measuring devices and other apparatuses designed to carry out different types of measuring tasks. In parallel with the development solving the challenges on the field of research, design, manufacture and quality assurance leads to the development of novel, more advanced techniques (more precise, more sensitive) and methods, improving each other. This process is continuous.

Modern measuring devices are often able to analyze the measuring data. These functions are very important in case of measuring systems. Personal computers became one of the most important accessories of measuring systems, since they are able to collect, classify, analyze, summarize and interpret the measuring data. Automatic intelligent systems in addition are able to control other devices, peripheral units and processes according to definite quality requirements monitoring the measuring data continuously or in batches. This function facilitates decisions and various controls during the production and also the preparation of the documentation of the manufacture.

6.1 Weight measurement

One of the most major steps of preparation compounding, and manufacturing are weighting or compounding of particular substances of the composition. „Weighting" involves the measurement of materials necessary for technological processes in proper proportion and quantity according to the composition and also when a determined amount of material is separated from a dose of material. Compounding includes the processes, when several materials are measured in a row.

Sufficient number of scales, which is suitable for purpose, and have appropriate precision and sensitivity, are indispensable for not only compounding, manufacturing, but also controlling, quality assurance actions.

In pharmaceutical technological tasks, quite a few definitions are directly connected to the definition of weighting, during which substances or bodies with unknown weight have to generally be assessed.

Scales, balances have to be placed in measuring room providing protected, vibration-free place, and should not be easily moved, and exposed to direct sunlight, heating body, and naturally kept away from draught. The temperature of body should be measured, has to be the same as the weighting room. In case of non-equal temperature there appear such flows in ambient air, which interfere with weighting.

Condition and criteria of assuring appropriate quality involves the application of scales, balances, and naturally weight, which are validated and have suitable accuracy for standards. Weighting devices have to be controlled periodically, which should be possibly linked to service. Periodic control and validation of weight devices can be only done by authority having official permissions for this task. This period is 6 month in case of weighting devices and 12 month in case of weights.

Accoring to the principle of operation the weighting devices can be grouped into scales operating automatically and non-automatically. The latter one is regarded as the conventional one, necessitate the intervention of operator with placing weights. Automatic weighting devices can measure with automatic taring and indicate the result digitally. (see digital scale)

In pharmaceutical technological practice, the quantity which should be measured, determines the type of scales should be used, since the accuracy and loading capacity of devices are different.

In every case the quantities of materials have to be measured suitably for signed accuracy.

The loading capacity means the highest weight, which is measurable without any damage of scale. This value is given by manufacturer. All of the weighting devices can be loaded till a specified extent.

The *pharmaceutical hand-scales* are conventional pharmacy type of weighting devices, their measurement limit are different depending on their size, but their accuracy is at most 0,01 g. The material, which should be measured, has to be placed directly into pan of the scale. This type of devices is suitable for quick measurement of small doses of substances.

Fig. 6.2.
The pharmaceutical hand-scale

Analytical balance allows to measure with 1mg or 0,1 mg accuracy, usually measurement limit is 100-200g.

Fig. 6.3.
Analytical balance

Upper measurement limit of *pharmaceutical fast scale* is 50,00g and the smallest measurable amount is 0,05. The accuracy of measurement is 0,01g.

Fig. 6.4.
Pharmaceutical fast scale

Equal-arm balance is the used most known, conventional, equal arm type weighting device, which can measure maximum 1000,0 g of materials, although its accuracy is 0,1g. Quantities less than 1,0g are not measured with this type of balance. In these cases latter mentioned scales can be used due to their accuracy.

Fig. 6.5.
Equal-arm balance

Suitable pots have to be used when measuring components in solid, semi-solid, or liquid state of matter. Important to take into consideration that less the mass of pot is used at weighting the more precise is the weighting. At measurement of liquids flasks, in case of ointment or suppository basis patendulas are used. Weighting plastic cards are applied at measuring powders, which are thin, flexible, and the made of non-absorbent material. Squeezed at both longitudinal edges it can be form that the measured substance is able to slide and wash away from the surface. Ground measuring container should be used to weight absorbent or easily evaporable material.

Digital scales are more advanced and modern compared to latter ones; in their measuring cell strain gauge resistors measure the substances by transforming the deformation in proportion with mechanical load into electrical sign. Digital scales do sequential self-calibration, thus the weighting can ensure suitable accuracy in wide temperature interval. Their loading capacity is usually 500g (1000g), nevertheless their accuracy is generally 0,001g.

These devices provide faster and simpler work process, therefore suppress the conventional ones and are also capable to tare and to perform automatic, semi-automatic calibration done by internal or external calibration weights.

Fig. 6.6.
Digital laboratory scale

Digital laboratory scales and analytical scales are used with glass draft shield to avoid errors possibly arisen from air flows in order to achieve more accurate measurement.

Fig. 6.7.
Pharmacy type of digital scale

Fig. 6.8.
Laboratory scale with glass draft shield

Digital dosing spoon is capable to weight accurately powders, crystals, and granules digitally.

Fig. 6.9.
Digital dosing spoon

In electronic industrial scale, high speed microprocessor allows other functions besides accurate measurement such as process control, remoting. Integrated clock and memory can also provide appropriate data storage in the case of no power supply. In pharmaceutical industry, person, time of measurement performing measurement can be identified and retrieved by coded entry system. Components of compositions which should be measured can also be called in the cases of several batch or amount.

Fig. 6.10.
Electronic industrial scale

Fig. 6.11.
Measurement station

6.2 Volume measurement

Volume is the unit expressing the extent of subject, and describes the space which is occupied by the subject. The volume of containers for liquid materials is generally termed capacity.

At compounding, at the most of the cases weight measuring is preferred rather than volume measuring. Nevertheless this measuring method is applied at particular

technological steps (e.g. dilution, completion, titration or calculation with mixed percentage) furthermore at dosing and at administration of medicine.

In pharmacy practice, for dosing of liquid preparations variant spoons were used.

Table 6-IV.
Conventional volume measuring tools for dosing

tools	volume
1 coffe spoon	5 ml
1 dessert spoon	10 ml
1 tablespoon	15 ml

Nowadays, properly designed, calibrated measuring tool in the original box of medicine ensures the more accurate dosing, which eliminates the differences due to density differences.

Weight measurement depends less on actual temperature conditions. This is the practical reason that the amount of active substance and excipients on prescription is most frequently prescribed in weight unit. Temperature effect, principally heat expansion has to be considered at measuring of liquids.

Heat expansion is specific property for each material and can be characterized by linear and volume thermal coefficient.

Linear thermal coefficient (α) is in linear proportion with length change ($\Delta l/l_o$) per initial length unit (l_o) and in inversely proportion with temperature:

$$\alpha = \frac{\Delta l}{\Delta T l_o} \tag{29.}$$

Linear heat expansion developed after heat stress (l_k):

$$l_k = l_o(1 + \alpha \Delta T) \tag{30.}$$

Liquid thermometers operate based on linear heat expansion. These thermometers are able to measure linear expansion due to affected heat in closed container with the appropriate narrow tube, from which temperature can be concluded with appropriate calibration. The most frequently used thermometers are the mercury based from -30 °C to 300 °C, alcohol based till -100 °C, pentane based till -200 °C, but at most until 750 °C.(The usage of mercury in thermometer is now prohibited in EU and in USA) Besides the previously applied types of thermometer, digital, electronic ones have increasingly important role.

Volume thermal expansion is also important in the consideration of volume determination.

Volume thermal expansion (β):

$$\beta = \frac{\Delta V}{V_o \Delta T} \tag{31.}$$

Volume changed due to affected heat is in linear proportion with the initial volume (V_o):

$$V_k = V_o(1 + \beta \Delta T) \qquad (32.)$$

Table 6-V.
Heat expansion of several liquid, solvents being significant in pharmaceutical consideration (β)

liquid	β
acetone	1,43
benzine	1,06
ethanol	1,10
ether	1,62
glycerin	0,49
chloroform	1,28
paraffin	0,76
water	0,21

Temperature dependence of density and volume of alcohol and alcohol containing solutions is significant, and has to be considered for example at alcohol dilution.

Table 6-VI.
Temperature dependence of density of ethanol

tempreature *(°C)*	**density** *(g/cm^3)*
5	0,80207
10	0,79788
15	0,79381
20	0,78945
25	0,78522
30	0,78097
35	0,77671
40	0,77244

Volume measurement means actually the comparison with standardized volumes.

Two main groups of volume measuring devices can be differentiated based on their functions:

1) calibrated to input volume
2) calibrated to output volume

Flasks belong to the first group while graduated measure cup, measuring cylinders, burettes and pipettes create the second group.

Graduated measure cup can be made of glass, plastic or enameled porcelain and are used for measurement of larger amounts of liquid (100-1000g or ml).

Fig. 6.12.
Graduated porcelain measure cup

At volume measurement, bulb pipette, flask or burettes should to be used because of their accuracy if both the digit and the end of the digit number is zero after the decimal point (e.g. 10.0 or 0.50 ml). In other cases measuring cylinder or measuring pipette are sufficient as well.

Measuring cylinders are usually made of glass or plastic less often and are suitable for measuring 10–2000 ml volumes. They are more accurate (~1–2%) than graduated measure cup but less than pipettes.

Movie 2. Determination of apparent volume

The pharmaceutical usage of *pipettes* is widespread and they occur in several forms. Among the traditional pipettes there are different forms and sizes. Volumetric namely bulb pipettes and measuring types, namely graduated pipette can be differentiated. Bulb pipettes are used for measuring a single specific volume of liquid

and have one or two meniscus marks. Graduated pipettes are calibrated into small divisions so that various amounts of liquid can be measured with the same pipette. Because it can be dangerous to draw up the liquid by mouth, it is recommended to use either a rubber bulb (e.g. *Griffin's* rubber bulb) or pipette pumps/controllers (e.g. Pi pump).

The classic *macropipettes* are suited to measure liquid volumes more than 1000 µl.

Volumes specified in microliters should be measured by *micropipettes* or *microsyringes*.

Micropipettes are used for measuring liquids between 1 and 1000 µl volume. Similarly to measuring macropipettes these are essentially same cross-sectional capillary tubes.

For measuring of concentrated acids and basis, a so-called *acid pipette* should be used, which is similar to the volumetric pipette, but two ball-shaped dilatation can be found above the upper signal for security reasons.

Pipettors are more and more current in laboratory techniques. These piston devices require changeable, narrow plastic tubes called *pipette tips*. Pipettors can have analogue or digital display and can be treated mechanically or electrically.

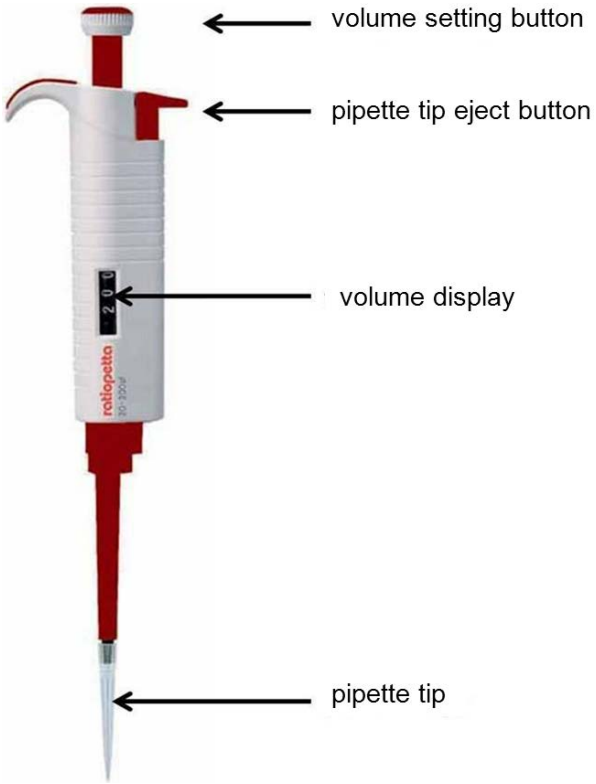

Fig. 6.13.
Main parts of pipettors

In the electronic pipettors both the pumping up and the dosage of the liquid are performed by a small electrical piston. Piston driven by microprocessor eliminates the inaccuracy arisen from doubtfulness of the human hand.

The single-channel pipettors are primarily suitable for single measurements or only for low number of series elements. These pipettors are extremely accurate thereby can be used in volume range between 0.2-5000 µl. For measuring higher number of

series, multi-channel pipettors can be applied because of their excellent repeatability and promptness. Multi-channel pipettors usually have 8 or 12 channels.

Fig. 6.14.
Single and multi-channel pipettes

Dispensers have a piston similarly to pipettors and their accuracy is the same like cylinders. Dispensers can operate mechanically or automatically. Their dispensing end can be put on glasses and needed volume can be set with the button being on the top of the dispenser. The needed volume can be controlled by the pointer on the scale. Drawing up the pump the set amount of liquid flows into the dosage space, from where it can be emptied by pushing down the pump.

Fig. 6.15.
Dispenser

Questions

1) What is measurement?
2) What are the main types of measurement error?
3) What is the correlation that describes minimum sample size?
4) How would you define the notion of validity?
5) How would you define the notion of verification?
6) What is calibration?
7) What is the measurement accuracy of various scales used in pharmacy and what is the maximum measurable quantity?
8) How would you define the notion of extensive and intensive quantities?
9) What are the base units of the International System of Units (SI)?
10) What are sensitivity, regular error and accidental error?
11) What are dispensers?

References

McCabe W. L., Smith J. C.: Unit Operations of Chemical Engineering, Mc Graw Hill.Companies Inc. 2005.

Recommended websites

http://www.radwag.com/pliki/artykuly/criteria_for_selection_of_a_weighing_instrument.pdf

http://pharmlabs.unc.edu/

7 Heat transfer

In pharmaceutical technology, in order to achieve a well-defined technological purpose, heat is frequently transferred to some material to change its temperature, state of matter, or any other physical-, chemical-, biological estate.

Most common compounding processes which also require the operation of heating:

- dissolving,
- melting,
- evaporation,
- distillation,
- extraction,
- drying,
- lyophilization,
- sterilization.

Temperature (T) is a non-additive physical property of materials. *Quantity of heat* (*Q*) is the quantity of energy absorbed or lost after thermal interaction. The amount of heat invested into heating a body, is in linear proportion with the mass of material (m) and the specific heat capacity (C) and the difference of temperatures (ΔT):

$$Q = mC\Delta t \tag{1.}$$

Specific capacity of heat defines how much heat has to be transferred to a body with unified mass in order to increase its temperature with one Celsius degree.

Heating can be performed directly or in an indirect way.

Most commonly, *direct heating* is done with flame or other heat source (e.g. immersion heaters), which means a heat transfer without any transfer medium. The most major disadvantage of this kind of heating is risk of overheating.

Indirect heating is slower, but allows a more even, consistent warming up. In this case, several transfer medium is used such as: air bath, liquid bath, sand bath. Air bath can be produced with hot air, liquid bath with heated water or oil depending on the temperature which should be achieved. Sand bath warms up much more slowly than the latter ones, but can provide temperature from room temperature to 200 Celsius degree deep in sand.

Mixing of the medium, which should be heated, assists the more even and consistent heat transfer in both cases.

At heat transfer, depending on material properties, and magnitude of transferred heat several phenomena can occur:

- phase transition,
- polymorphism,
- pyrolysis.

Heat can be transferred by:

- conduction
- convection
- radiation.

Conduction occurs in every case, if two bodies with different temperature contact with each other, or if temperature difference occurs between certain parts of the body. Heat transfer happens in molecular size, in which the particles connecting to each other give the energy to each other. During this process, the higher temperature molecules with higher kinetic energy give a part of their energy to the nearby molecules having less energy. Due to this, temperature of the particles having less energy is risen, thus the heat has been conducted. In solid medium this is the only way of heat transfer, though in fluid or in gas state of matter may also occur. During the process, heat is transferred due to movement of electrons, longitudinal vibration and crashing of molecules with different speed depending on state of matter. The conduction becomes equilibrium or steady state, if the temperature in all part of the body remains invariable (stationary conduction).

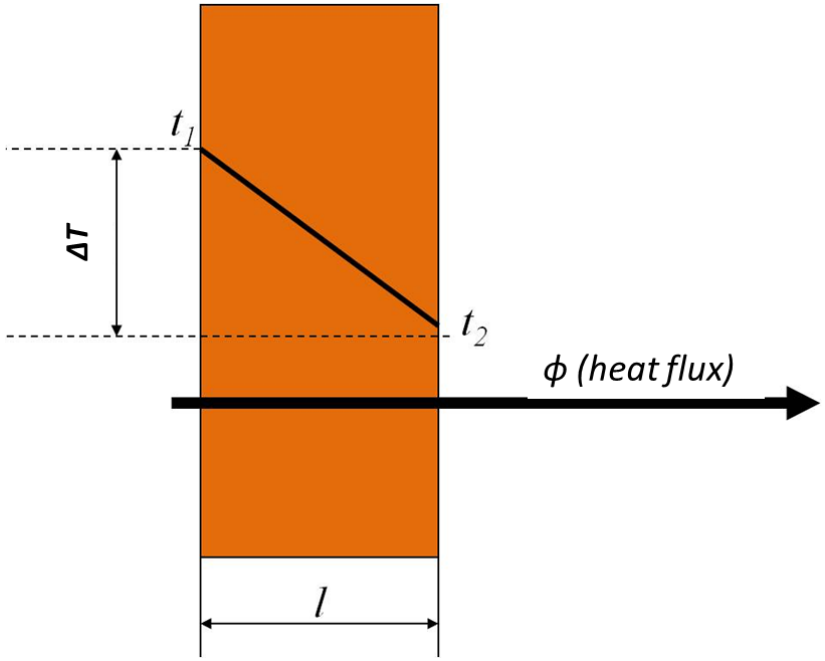

Fig. 7.1.
Most major determining parameters of conduction

Fourier's basic formula for conduction:

$$\varphi = \lambda \frac{A}{L} \Delta T \qquad (2.)$$

φ heat transfer
λ conduction factor
A surface
L thickness
ΔT temperature difference

Convective heat transfer (convection) means a heat transfer with transportation and can only occur in fluids (liquids, gases, steams). In these medium the particles of matter can move, consequently during this process can deliver their energy. Colder and warmer layers ensure the mixing of these layers due to the creating density difference.

According to the Newton's cooling law, the specific formula for convective heat transfer:

$$\varphi = \alpha A \Delta T \tag{3.}$$

α convection factor

On the 2. Fig. it can be seen, that in practice the main types of heat transfers can be appeared simultaneously, thus may be mixed. The heat energy (Bunsen burner, electric hot plate) comes with conduction through the wall of flask, which induces an internal movement (convection) in the medium, which should be heated (Fig. 2.).

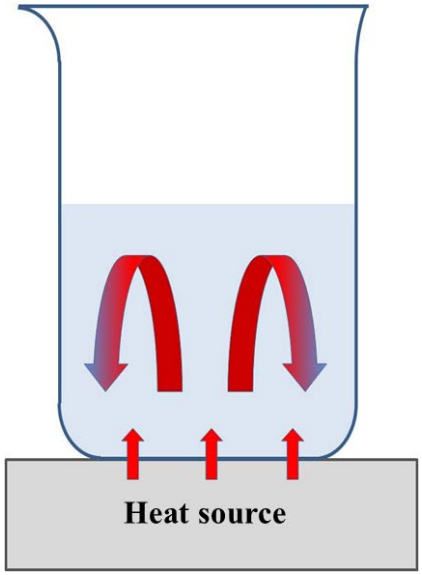

Fig. 7.2.
Convective heat transfer

In contrast with the previously mentioned heat transfers, the one developed by radiation can be prescinded from material, since it is a possibility of heat transfer *without any transfer medium*. Radiation spread with electromagnetic waves, which means that the radiation of warmer body is absorbed in the colder body.

The process of radiation can be specified by the *Stefan-Boltzman formula:*

$$\varphi = \varepsilon \sigma A T^4 \tag{4.}$$

ε emission capability
σ radiation constant of body
T absolute temperature

Two wavelength ranges of electromagnetic wave are used during compounding:

- *infrared rays* (10^{-12} -10^{-14} Hz), and
- *microwaves*(10^{-8} -10^{-12} Hz).

The infrared rays are inter alia used to *heat, melt, dry,* while the microwaves are principally used for *dielectric heating*.

At the *application of infrared ray*, penetrating rays and energy input warm up the material. Its advantage, that there is no need of intermediate transfer medium, therefore the material does not contact directly with heat source.

Fig. 7.3.
Melting of ointment basis by infra lamp

During heating with microwaves internal heating develops, thus the heat absorption is more even and consistent, and the process heat of transfer lasts much shorter. This method of heat transfer is considerable in many view of pharmaceutical applicability, thereby the energy of microwaves is not usually sufficient to degrade bonds of the molecules, but in certain circumstances it is able to modify biological structures (damaging in bonds of molecules, cell membrane).

The temperature increase of heated material depends on:

- time of heating,
- composition,
- dielectric properties of components,
- water and salt content of composition.

The disadvantage of process of heating with microwaves is the possibility of *"selective heating"* because of the dielectric properties of the different ingredients in the composition. The variant absorption capability of microwave, thus the different temperature within the material leads to difference in heating, so called *"selective heating"*.

The heat transfer can be carried out:

1) *directly* (e.g. cooling water with ice, warming it with addition of warm water) by contact of materials
2) *indirectly* (e.g. through wall of a tube) by without any contact of materials.

In the pharmaceutical technological practice indirect heating is principally used.

The heat exchanger provides careful, even and indirect heat transfer with avoiding local overheating, in addition to the possibility to supply cooling too. These are essentially the devices and equipment, in which the two medium flowing in different area is separated by a wall, therefore they will not mix with each other. The heat transfer occurs on the surface of the separating wall.

Absorbed and lost quantity of heat equal in the heat exchanger, therefore:

$$m_1 C_1 \Delta T_1 = m_2 C_2 \Delta T_2 \tag{5.}$$

from which the proportion of temperature differences:

$$\frac{\Delta T_1}{\Delta T_2} = \frac{m_2 C_2}{m_1 C_1} \tag{6.}$$

The heat exchanger can be warmed up by hot water or steam through its cape, and can also be suitable for cooling by the flow of cold water. Heat transferred to the wall in unit time is a proportion with contact surface through the medium (heating medium) with higher temperature and with the thickness of the created layer around the wall and with the conduction factor.

In continuous mode the flow speed of liquid has to be regulated to obtain enough time for heat transfer. The affected media are separated by a solid wall.

The heat exchanger devices can be grouped into three main groups:

1) *plate heat exchanger*
2) *cape heat exchanger and*
3) *tube bundle heat exchanger.*

Plate heat exchanger consists of series of internal, pressed patterned heat transferring plates, which are restricted between plates closed by external plates. This type of exchanger are used to heat and cool liquids. The waviness of plates allows the turbulence of liquids, thus the better heat transfer developed through the wall of plates. The heating and the medium which should be heated, flow in opposite direction in constrained path in two separated flow area and on different side.

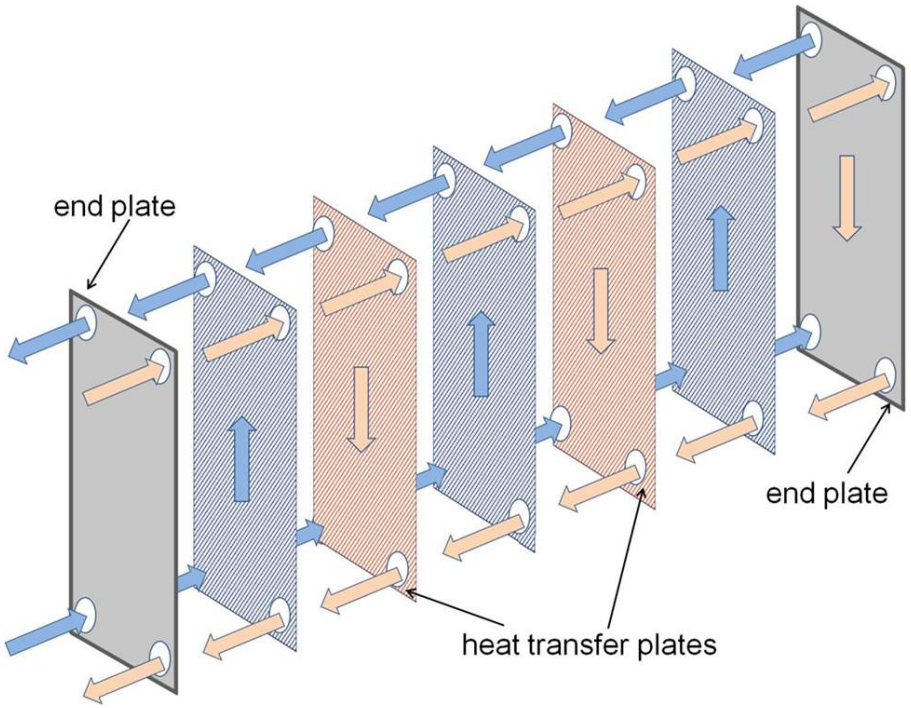

Fig. 7.4.
Structure of plate heat exchanger

The cape heat exchangers are essentially two-layered equipments (duplicators), which are considered containers, surrounded by the external covering plate, namely the cape area. In the duplicators a determined amount of material is generally processed in the same time. Heat transfer is provided by transmission of warmed water, steam or oil or perfusion, depends on desired temperature. Mixing of the media assists the heat transfer between the wall of container and medium, and the heat convection inside the fluid.

In laboratories in pharmaceutical practice, duplicators with double walls and made of glass are used for heating materials, careful tempering. Connected with perfusion thermostat, liquid is warmed to appropriate temperature, or kept in constant temperature. Heat transfer can be helped by mixing.

Fig. 7.5.
Glass laboratory duplicator

The cape heat exchanger depending on task and usage with or without mixer, are suitable to perform chemical, namely exothermic and endothermic processes including dissolution, melting, evaporation, crystallization, fermentation, or other operations in a closed structure. The control of processes can be carried out with several integrated sensor (e.g. pH, temperature), or with periodic sampling. There is a possibility of control via computer.

Industrial duplicators with upper and lower driven mixer can be distinguished based on the modes of mixing.

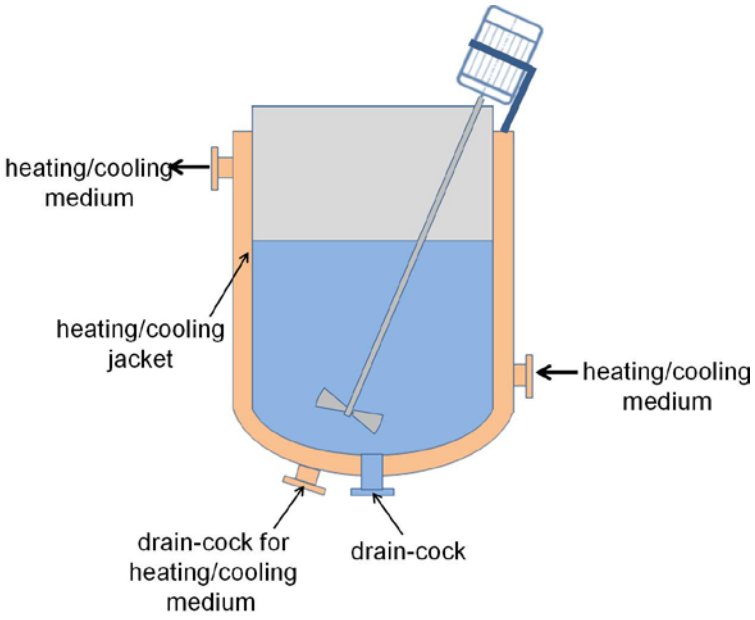

Fig. 7.6.
Jacketed heat exchanger

Contrary to duplicators, *tube bundle heat exchangers* are continuous operating and dynamic devices. The flow speed between the continuously flowing media (fluids) determines the time of stay in devices, during which develops the heat transfer. This type of heat exchangers are devices consisted of parallel assembled tubes, in which the heat transfer is provided by mantle of tubes. Heat exchangers can be vertical or horizontal type.

The tube bundle wall closes the space between tubes. Chamber at the end of bundle can be influent or effluent, and turning (recirculating) chamber according to its function.

The flow of heat develops invariably due to the temperature difference, therefore is a precondition of heat transfer. The process of heat transfer lasts only until the temperature difference is persistent.

According to the flow direction of heat transferring medium and the medium, which should be heated, the heat transfer can be:

- direct flow,
- counterflow
- cross-flow.

In case of *direct flow tube bundle heat exchanger*, heating medium, medium which should be heated flow in the same direction on the two side of separating wall. Upon entry, the heated medium meets with high temperature heating medium, thus the temperature difference is initially high and then more and more decreases. The effluent temperature of heated medium cannot reach the effluent temperature of heating (cooling) medium.

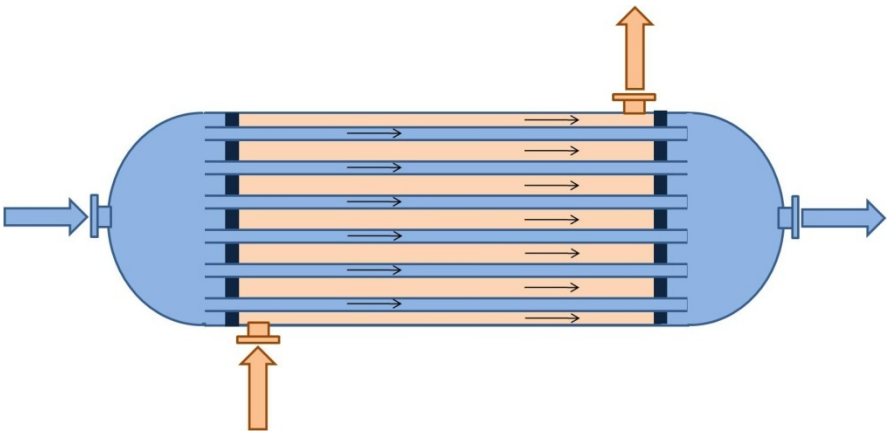

Fig. 7.7.
Inflexible tube bundle heat exchanger with direct flow

In case of *counterflow tube bundle heat exchanger*, the input and output points of materials participating in heat transfer are not on the same side. At influent, the heated medium meet with a medium with low temperature (but warmer than the heated), which allows a slower and more careful heating. While the two media flows in an opposite direction, hence the heated medium meets with warmer and warmer heating medium and consequently end-temperature of heated medium can be higher than temperature of heating medium.

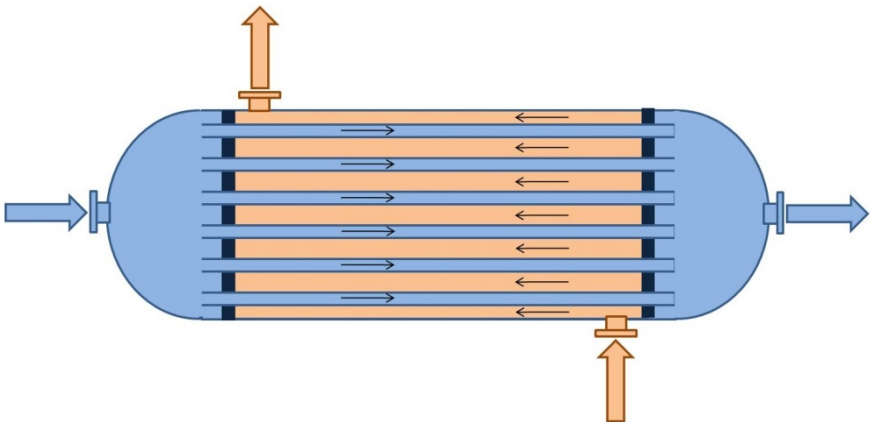

Fig. 7.8.
Inflexible tube bundle heat exchanger with counterflow

In case of *cross-flow tube bundle heat exchanger*, the two media flows in perpendicular direction to each other, thus the previously mentioned heating effect is mixed.

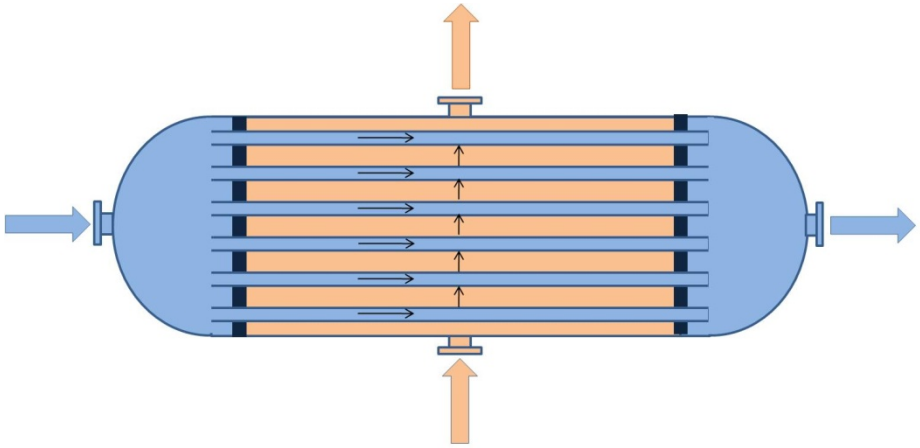

Fig. 7.9.
Inflexible tube bundle heat exchanger with cross-flow

Thermal expansion of inflexible tube bundle heat exchanger is limited. To achieve higher temperature, U-tube heat exchanger should be used, which is able to compensate developing internal tension by allowing thermal expansion of tubes.

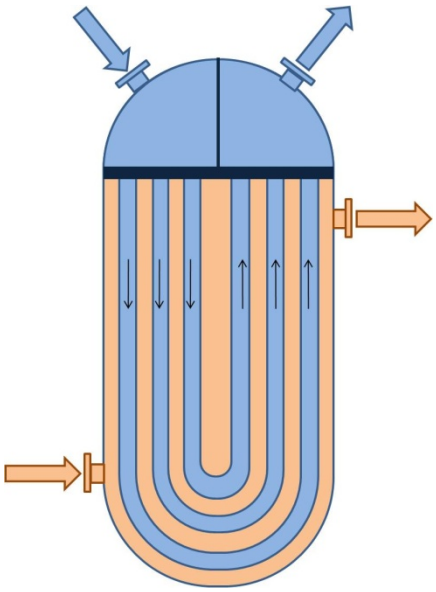

Fig. 7.10.
U-tube heat exchanger

Questions

1) What are the most common drug preparation operations that require heat transfer?
2) What are the principal methods and attributes of heat transfer?
3) What types of heat exchangers do you know of?
4) What are the possible types of heat exchange between the heating medium and the medium to be heated, according to their respective directions of flow?
5) To what type of flow does the Stefan-Boltzman law apply?

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Recommended websites

http://www.nzifst.org.nz/unitoperations/httrapps.htm

http://www.ubter.in/Curriculum/Chemical/Document/sem5.pdf

8 Heat reduction

In practice of pharmaceutical technology, the heat reduction or cooling is frequently used operation for example at storage of basic materials and preparations, distillation, crystallization, freeze-drying, preparation of solution which are heated, and application of technologies using melting (e.g. ointment, suppositories), or to condensate steams, and reducing solubility.

During process of cooling the desired properties of applied cooling media are:

- non-toxic,
- not environmentally harmful,
- not flammable and explosive,
- large heat of vaporization,
- specific volume of steam is to be low,
- evaporation on atmospheric pressure,
- low viscosity,
- not expensive,
- do not have unpleasant odor,
- do not cause corrosion.

Cooling can be carried out by suitable natural media: by air, water. These ways of cooling is termed natural cooling (such as at preparation of suppositories to enhance cooling by flowing tap water).

If there are no any available, suitable, natural cooling medium in appropriate amount and appropriate temperature or the temperature of cooled medium has to decreased more than the natural cooling medium, or has to kept ont hat temperature, artificial cooling is needed.

Frequently applied artificial cooling media:

Table 8-I.
Several cooling mixture in practice

Cooling medium	**Composition** (m/m%)	**Achievable temperature** (°C)
Dry ice		-79
Dry ice—aceton		-86
Dry ice—ether		-100
Liquid air		-187
Liquid nitrogen		-195,8
Liquid helium		-268,6
NaCl—ice	23,5 : 6,5	-40-70
NH_4CI—ice	19: 81	-21,2
$CaCl_2$—ice	59 :41	-15,8
36% HCl—ice	25 : 75	-54,9

The cooling process can be performed by cooling bath or perfusion of cooling medium. Both are used in pharmaceutical technological practice.

Cooling bath is used in cold water, crushed ice, mixture of eutectic salt and ice, dry ice (solid carbon-dioxide) or even in liquid nitrogen too.

In pharmacy circumstances, consistent and slow cooling of melted ointment materials is normally performed with manual mixing and in patendula with pestle, in order to create the appropriate gel structure. At preparation of higher amount of ointment, cooling and mixing have to be regulated and carried out in dedicated devices (frequently in duplicators). At the preparation of heated solutions, syrups, decoctions, infusions, cooling bath or perfusion of cooling medium are also used.

Laboratory refrigerators are able to condensate hot steams, which are operated by perfusion

of cooling medium. These refrigerators have different capacity of heat, which depends on their internal surface (e.g. Liebig cooler, cooling coil and ball). Continuous heat reduction is needed to maintain the cooling evenly, which is achieved by perfusion of cooling liquid, frequently by water. Even more amount of steams can be condensed by these cooler, than in case of air-cooled condenser, or retort.

Devices providing continuous heat reduction are termed to refrigerators. Temperature, which is lower than environmental can be developed and permanently maintained. Energy investment is needed for this process, while during this process, heat has to be reduced from a closed space what has to be transferred in another place. These devices are called as *heat pumps.*

Based on their operation, the most frequent used cooling devices can be:

- *vapor-compression-type and*,
- *absorption-type refrigerators*.

Vapor-compression-type of refrigerators is applied in many places for example as refrigerators in pharmacy, to store medicines, or in air conditioning systems. The refrigerators circulate the cooling medium (e.g. ammonia) in a closed space. During the process of cooling, the cooling medium absorbs heat from space, which should be cooled, then transfers and emits. Steam developed after evaporation of cooling medium is led to a compressor, which condenses the steams to an appropriate pressure. The high-pressure steam is revamped to overheated steam by compressor, then goes to condenser. The condenser is a special heat exchanger, where the steam is cooled and condensed by cooling air or cooling water, meanwhile the cooling medium emits the heat absorbed from system to water or air.

The condensed, liquid cooling medium is led through a controllable throttle, where pressure of liquid cooling medium decreases suddenly by adiabatic change. One part of cooling medium evaporates and cools down to the temperature of space, which should be cooled. Due to evaporation it absorbs the heat from its environment, as well as cools its environment too. The absorbed heat from cooled space is transferred to circulating in evaporator. From here the steam goes into compressor again and the entire process repeats.

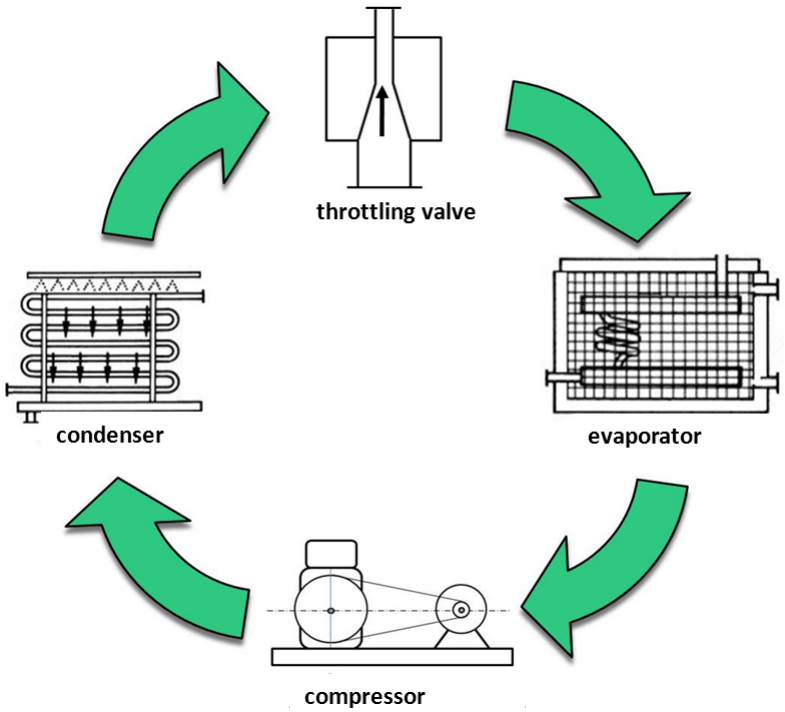

Fig. 8.1.
Operation of vapor-compression-type of refrigerators

The absorption-type refrigerators do not contain any moving parts, thus there is no noise, vibration and no internal oil contamination, with which has to be regarded in case of vapor-compression type. Their three major structural elements (condenser, throttle, evaporator) are the same as in the last mentioned type, but compressor are substituted by a new structural element. The essence of cooling process is the absorption and desorption process between gas and liquid. Absorption has to carried out in cold medium, while desorption in warm medium. If ammonia is used as a cooling medium, then water is the most suitable solvent. Firstly liquid ammonia goes into the evaporator (similarly to vapor-compressor type), where forms into steam, during which cools down its environment. Cooling medium coming from evaporator moves into dissolution container, in which dissolves in the proper chosen, and matched solvent, namely absorbs. The heat released during dissolution is absorbed by coil heat exchanger. The created solution is transferred by pump through the heat exchanger into boiler, where pressure is much higher than before. The released ammonia steam is transferred into condenser, and cooled with water, while ammonia liquefies. The pressure in condenser is determined by the temperature of cooling water. The liquefied ammonia is transferred through a throttle, while its pressure is decreasing. In evaporator, ammonia becomes steam again.

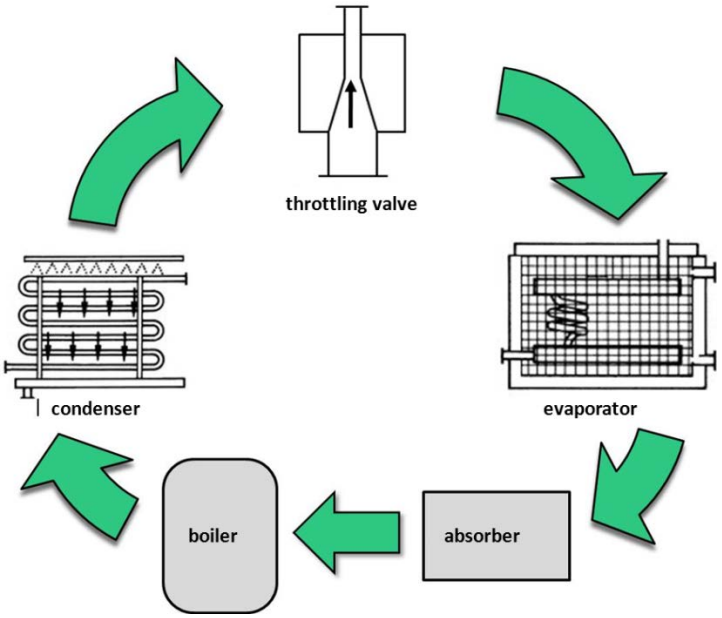

Fig. 8.2.
Operation of absorption-type refrigerators

One part of pharmaceutical materials and preparation is stored in room temperature (15–25°C), and the other has to be stored only in cooled area, when their it is justified due to their physical, chemical, microbiological stability, or heat sensitivity.

Material, or medicine in small amount, which should be kept in cool place has to be stored in refrigerators. According to standards insulin preparations and eye drops from FoNo have to be kept in refrigerators (2-8 °C).

Fig. 8.3.
Pharmacy refrigerator

Oculogutta rifampicini FoNoVII. preparation has to be stored in *freezer,* which means under -15 C°. Its expiry date besides this storage is 1 month, but after unfolding until only 5 day can be used. In the meantime it has to be stored on 2-8 °C.

In pharmacy, medicines in high amount are stored in cooling rooms, in the case of storage of higher stock in factories and wholesalers products are kept in cooling halls.

Cooling rooms and halls which are planned on stock amount and achievable, sustainable temperature, are rooms equipped with devices with suitable capacity and surrounded by appropriate insulated walls. Their internal temperature is adjustable and controllable. Medicines should be placed on internal shelving systems.

Mucuses (*Mucilago hydroxyaethylcellulosi, Mucilago methylcellulosi*), syrups (Sirupus *aurantii, Sirupus laxans, Sirupus liquiritiae, Sirupus simplex*), ointments (*Unguentum emolliens*) from Hungarian Pharmacopoeia (Ph. Hg. VII) and nutrition are stored in cool place, which means 8-15 °C.

Questions

1) What are the required properties of cooling media?
2) What are the media most frequently used for heat reduction, and what temperatures can they achieve?
3) What are the main types of the most commonly used cooling devices?
4) What are the main attributes of vapor compression type cooling devices?
5) What are the main attributes of absorption type cooling devices?

6) What is the required storage temperature of different kinds of pharmaceutical preparations?

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Recommended websites

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9 Evaporation and distillation

At laboratory examination, isolation, manufacture of basic preparations and products, frequently occurring task is to increase concentration of solution by removing solvent.

Evaporation is a caloric operation separating components, during which from a solution of non-volatile dissolved substance, the valuable component can be obtained or extracted by volatilization of solvent.

Evaporation is carried out, because

1) concentrated solution is desired to produce, or
2) dissolved substance is desired to store and use in dry form, or
3) pure solvent is valuable, and is wanted to be extracted.

Distillation is also a caloric operation separating components, which is suitable for separation components of principally liquids, solvents, based on their *difference in volatility*. One form of distillation is *fractional distillation*, when distillate is separated in time according to volatility of components during the distillation process. In the evaporation leftover, less volatile components are accumulated. If components have to be extracted very precisely, then rectification, namely multiple partial evaporation and condensation must be used.

In *reflux* mode, the steam -occurring due to the boiling- is not released into atmosphere, but is condensed by refrigerant and returned back to boiling container. Hence solvent loss can be prevented.

Evaporation is distinguished from distillation, while during evaporation, concentration of dissolved substance in steam is always zero.

At evaporation appropriate amount of heat is transferred to solution, due to which a part of solvent transforms to steam phase and departs from solution. Firstly the solution has to be heated until the boiling point belonging to the particular pressure, at this time steams create, depart from fluid phase. During this process, the leftover solution concentrates more and more. During evaporation, if the solution become totally concentrated, then by further steam removal, crystal form of substance (in solid state of matter) will appear.

During evaporation, the following parameters of solution are changing:

1) concentration of solution,
2) its density
3) its viscosity,
4) its boiling point.

At the end of evaporation, due to the increase in density as well as viscosity, bubble formation become gradually more difficult and more intense mixing is required to maintain appropriate mixed status. The internal circulation of liquid slows down because of increase of viscosity, thus performance of evaporator can be decrease. The heat transfer can be deteriorated by any deposition of viscous material on heating surface.

Individual accompanying phenomenon of evaporation process is the increase in boiling point during evaporation. Vapor pressure of solution is invariably less in the same temperature, than vapor pressure of solvent. The reason of phenomenon is that there are interactions between molecules of solvent and dissolved substances. Therefore the number of solvent molecules reduces in the air over the solution (getting into vapor space), thereby vapor steam over solution decreases too.

According to *Raoult*'s law, vapor pressure of any solution ($p_{solution}$) is in proportion with mole fraction ($X_{solvent}$) and vapor pressure of pure solvent ($p_{solvent}$).

$$p_{solution} = X_{solvent}\, p_{solvent} \tag{1.}$$

The boiling point is the temperature at which the vapor pressure of the liquid equals the environmental pressure surrounding the liquid. In case of solutions, the environmental pressure of solution decreases due to the interaction of particles of solvent and dissolved substances. Due to rise of boiling point because of pressure decrease, the solution has to heated more to achieve the certain vapor pressure, so that solution boils in higher temperature. The increase of boiling point (ΔT) is depending on concentration of dissolved substance besides pressure created in evaporator device.

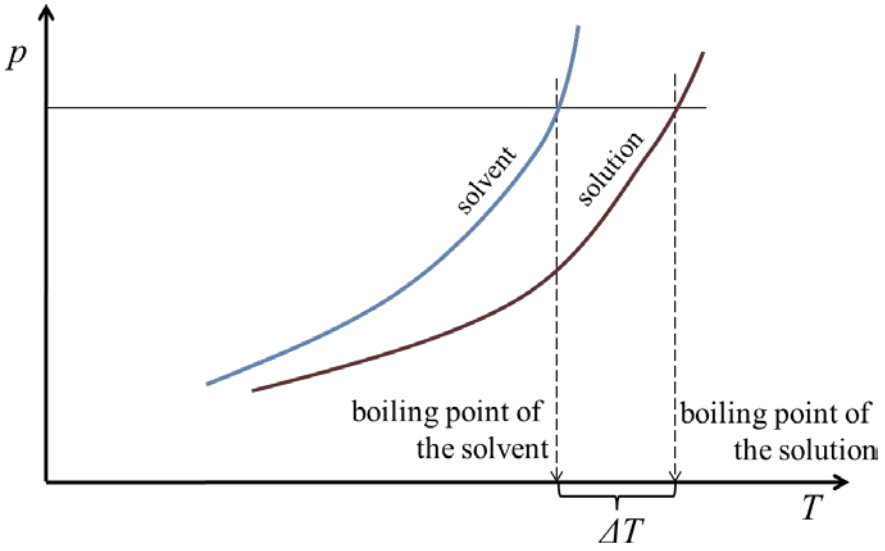

Fig. 9.1.
Rise of boiling temperature of solutions

The rise of boiling point increase generally the evaporation difficulties and cost, because to maintain boiling more attention and energy is needed, for example more and more intense heating has to be transferred in a form of heating steam.

In evaporator the heat commonly transferred through a special heat transferring surface. Applied heat source can be electricity, liquid, but most frequently heating steam. (Water steam has excellent heat transferring property, during its condensation, its evaporation energy is released.)

The evaporators can be classified into many groups:

1) heating cape,
2) tube,
3) plate,
4) film,
5) vacuum evaporators.

The one of the oldest evaporator is the heating cape evaporator. These are relatively low-power devices with cylindrical shape and works discontinuously. The efficacy of heat transfer can be increased by integration of a mixer.

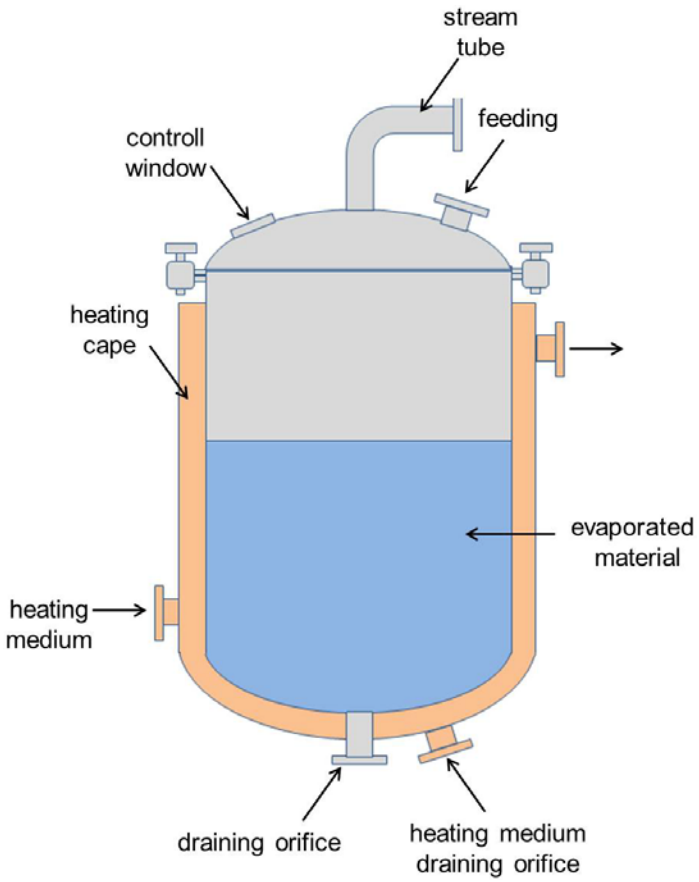

Fig. 9.2.
Heating cape evaporator

In the cylindrical *Robert evaporator* having cone-shaped bottom, an internal heating chamber, and more intense, free heat transfer can be carried out through vertical boiling tubes, which are located in parallel to each other. Among boiling tubes, one of with the largest diameter is termed *downcomer*. The evaporator is so filled with basic material, to infest boiling tubes. In downcomer, temperature of liquid is a little bit lower, than in boiling tubes, which in the boiling medium causes the flow of solution. Appearing solvent steam flows towards the upper steam concentrating device part. Liquid drops are detained by drip plate.

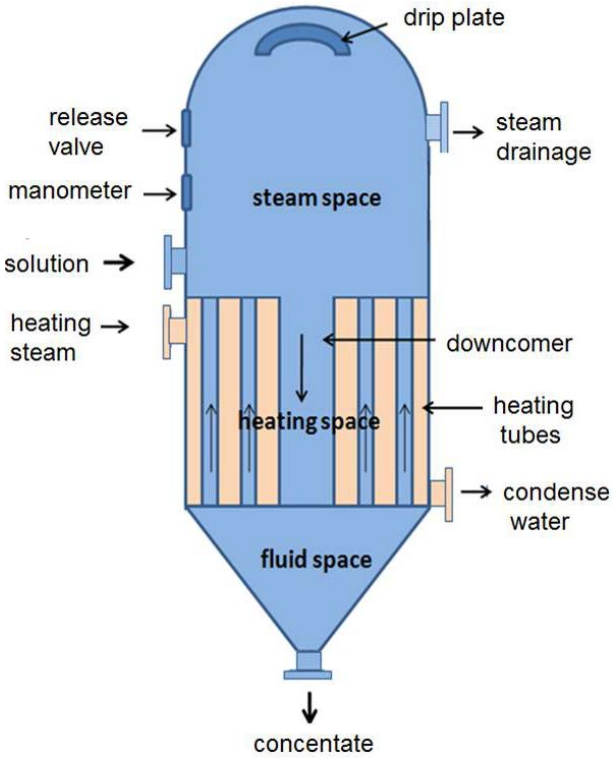

Fig. 9.3.
Robert evaporator

Plate evaporators are consisted of evaporator and an external plate-shaped heat exchanger.

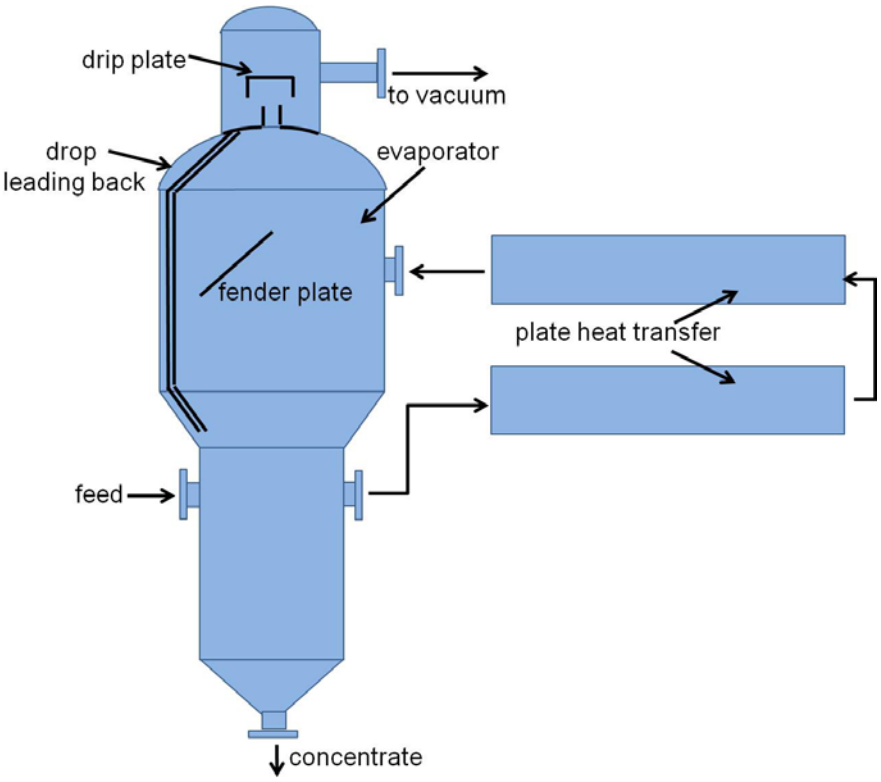

Fig. 9.4.
Plate evaporator

At evaporation solvent having low boiling point are removed from solutions on atmospheric pressure, but ones with high boiling point should be evaporated with the application of vacuum. The evaporation can be performed on lower temperature, thus the speed of distillation rises. In this case the material which should be evaporated, receives heat stress, which is especially beneficial in the case of unstable, heat-sensitive materials. On the internal surface of rotating flask developing solution-film layer provides great heat transfer and large surface.

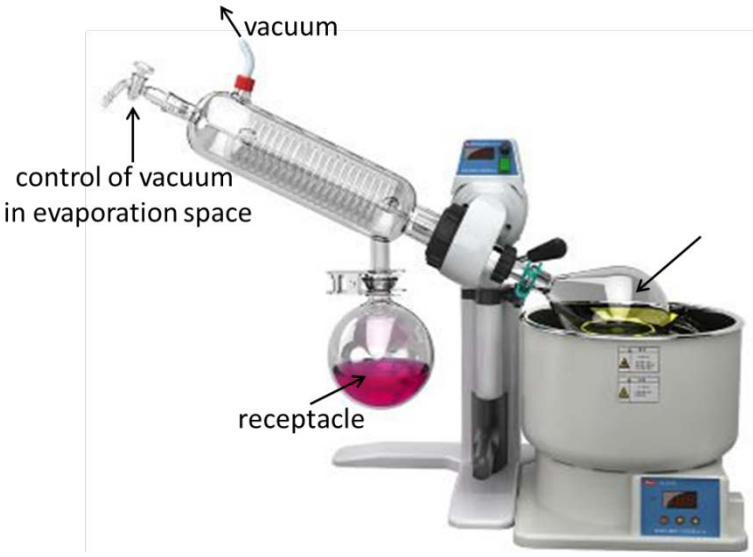

Fig. 9.5.
Rotation vacuum evaporator

Vacuum evaporation can be efficiently applied with mechanical elements in industrial dimensions.

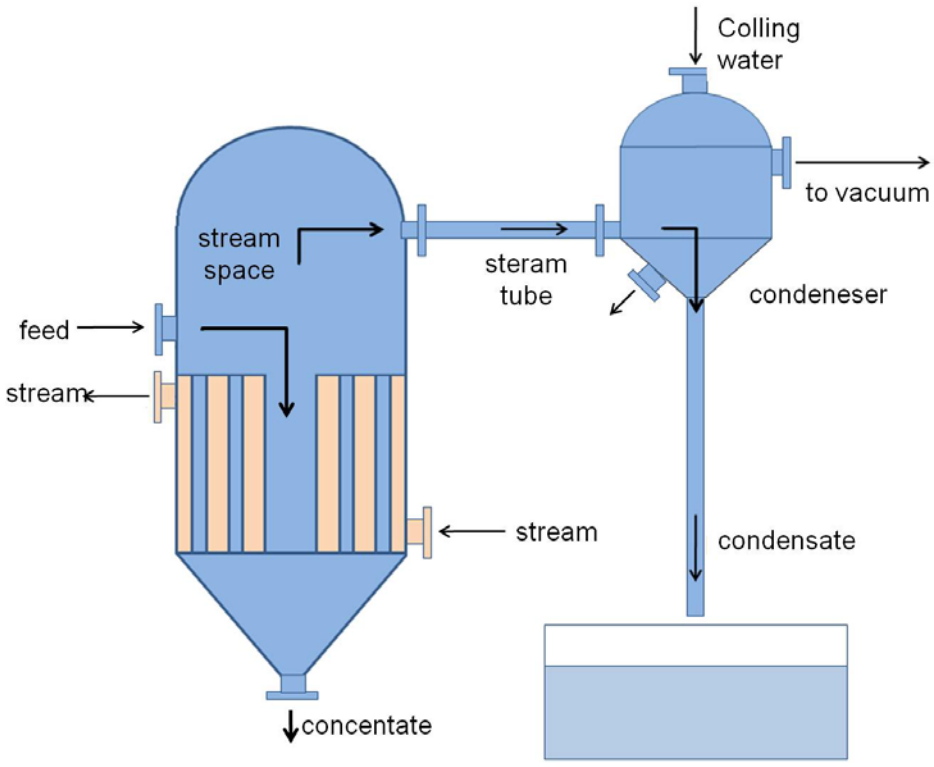

Fig. 9.6.
Industrial vacuum evaporator

Film evaporators generally are tube shaped and externally heated devices. In film evaporator, liquid film is created on the internal surface of evaporator body, which thickness are controlled by speed of filling, stirrer structure consisted of shovels to achieved the best heat transfer. The film created by the liquid pass downward. The occurring solvent steam goes upward in the middle of tube in an axial direction, and leaves the device on the top. In the case of low speed, thick film is created having inappropriate heat transferring property. Another extreme case, when too thin layer develops, which can be broken easily and, dry spots appears due to heating, which significantly deteriorates the efficiency.

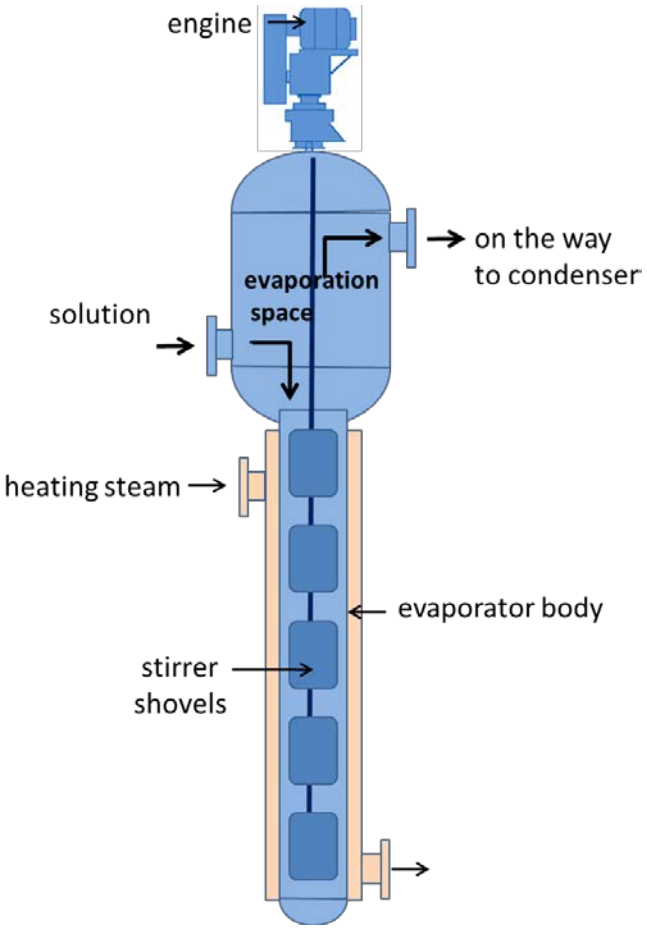

Fig. 9.7.
Film evaporator

Evaporators can be connected to each other, in which steam developing during boiling is used for heating another apparatus. According to connection, the flow can be direct, counter flow in atmospheric pressure or in vacuum.

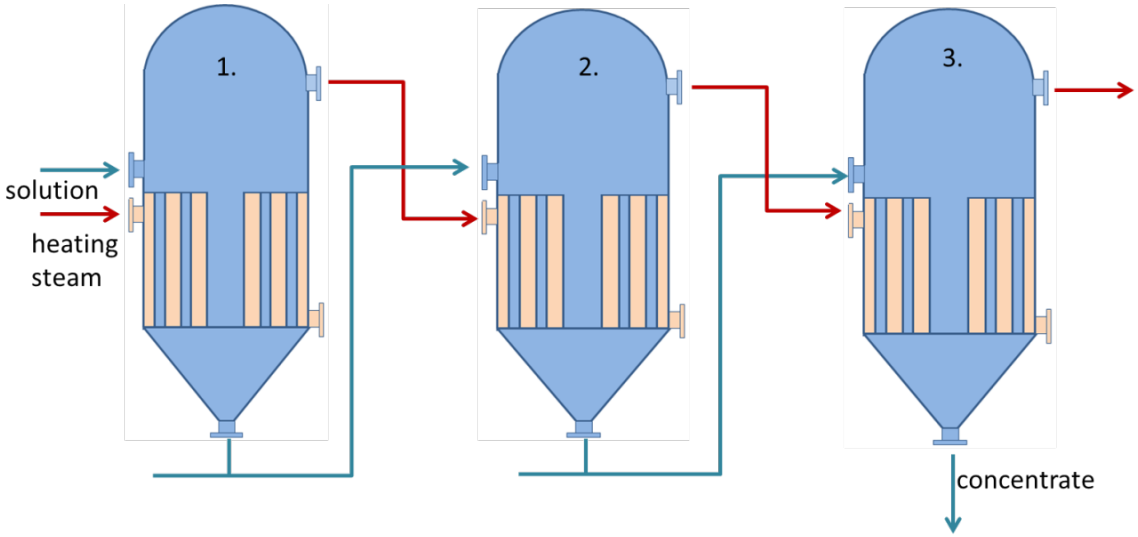

Fig. 9.8.
Connected evaporator appliances, working direct

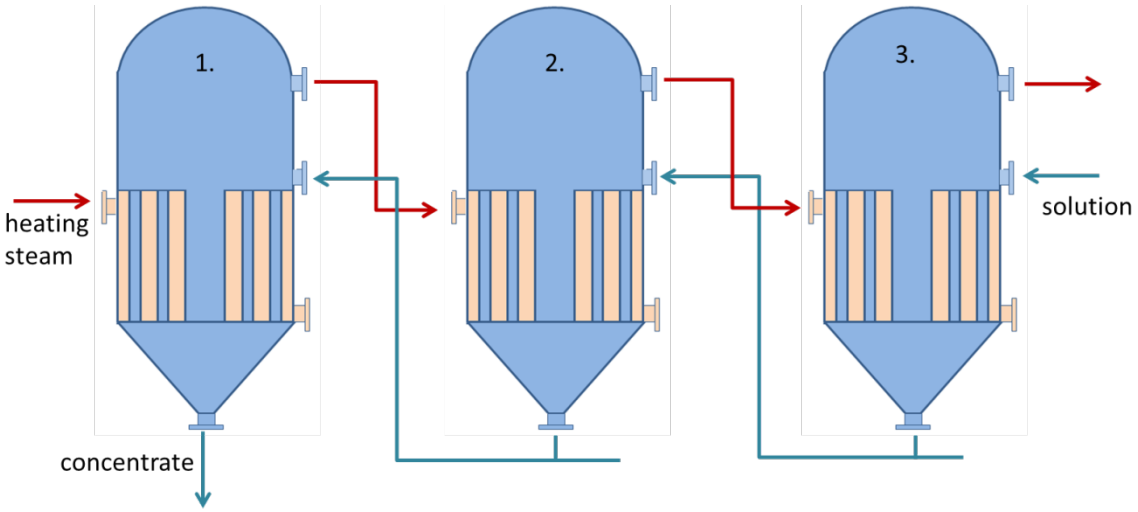

Fig. 9.9.
Connected evaporator appliances, working counterflow

The aim of distillation can be to:

- separate two or three liquids,
- purify a liquid from not volatile contaminations,
- extract a solid material form a solution of this solid material.

In the pharmaceutical practice, the most common application of distillation is the water purification. Production of small amount of distilled water or evaporation of other liquid is performed with glass distillation device.

Fig. 9.10.
Water distillation device

Questions

1) What is evaporation?
2) What are the possible purposes of evaporation?
3) What is distillation?
4) What are the main types of evaporators?
5) How do rotary vacuum evaporators work?
6) How do film evaporators work?
7) What types of distilled water do pharmacopoeias identify?
8) To what phenomenon does the Raoult law apply during evaporation?
9) What types of evaporators do you know of?

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Recommended websites

http://www.nzifst.org.nz/unitoperations/evaporation.htm

http://www.cbu.edu/~rprice/lectures/evap1.html

10 Mixing

Mixing is the most frequent applied pharmaceutical technological basic operation.

Mixing is such a mechanical operation, during which movement is achieved in order to promote the flow of liquid in a system. At mixing two or more material is moved, merged namely *homogenized* to meet the dispersion of certain components with the desired mixing rate in a particular smallest volume unit. The aim of mixing is to distribute the components of system in the available space, and to achieve a homogeneous mixture from the measured components. This means, that in the mixture, the components have to be in the prescribed proportion even in a small dose from total *manufacture batch*.

Mixing plays very significant role in the complex connection of living human organism and pharmaceutical preparation.

The peristaltic (inner circular and outer longitudinal) motion of gastrointestinal tract assists to transfer, mix, digest, absorb and to defecate the intestinal contents too. The liberation of API content occurs after or without disintegration (depending on applied composition and technology) after taking medication given per orally and API molecules continuously mix with the dissolving medium. API molecules get to the area of absorption during mixing with medium by peristalsis.

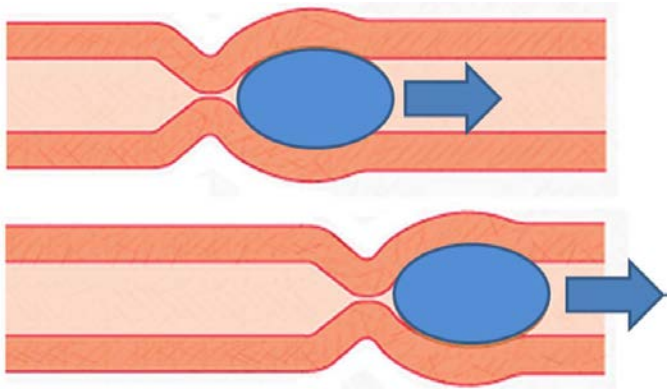


Fig. 10.1.
Mixture and transfer of intestine content by peristalsis

From chewable tablets, medical chewing gums, mixture of dissolving API is assisted by motion of teeth and tongue.

The quickest way without the process of absorption can be achieved by intravenous administration. During the process of distribution, the administered API is distributed quickly, within 2-3 minutes because of the circulation. After intramuscular administration, absorption occurs before API could distribute. The mixture with tissue liquid is much slower, which result in sustained therapeutic blood concentration. By the given injection containing crystals, the effect time can be extended due to longer dissolution time. Hence mixing is not only the important operation of pharmaceutical technological processes, but it is also essential in living human organism and development of pharmacological effect. The expected specific conditions of mixing have to be always considered at drug design and optimization of biopharmacy parameters.

10.1 Theory of mixing

At mixing of two or more materials, homogeneous and heterogeneous systems are created depending on the solubility properties of the particular materials.

The aim of mixing can be different depending on material and task:

- homogenizing (mixing of solutions, mixtures or mixture of powders, wetting),
- promoting heat exchange (e.g. dissolution accompanying endotherm or exothermic reaction, melting),
- mass transfer (e.g. dissolution, fluidization bed dying, crystallization),
- structure conversion (e.g. preparation of emulsions, suspension, skimming),
- dispersing (reducing drop size of emulsion-based preparation),
- chemical reaction acceleration (e.g. preparation of dendrimers by polymerization),
- changing rheological properties (e.g. transformation of internal structure).

At mixing in multi-component structures, structures being in identic or different state-of-matter, soluble or insoluble in each other, miscible or immiscible, or reacting or non-reacting materials, or components are made to move, therefore preparations or basic materials can be prepared.

In pharmaceutical practice, materials structure intended to mix can be:

- self-mixing -,
- non-self-mixing material structures.

In *self-mixing structures*, mixing occurs due to heat movements of molecules, which is generally a slow process. Such material structures are gases and liquids with low viscosity, in which inhomogeneity is resulted in unevenness of concentration or temperature difference, though inhomogeneity can be compensated.

Non-self-mixing material structures can be:

- *structures retaining mixture state.* These structures are for example: powders, liquid with high viscosity and stabile disperse structures,
- *structures non-retaining mixture state.* These structures include suspension and emulsion, which are separating into phases

At mixing of variant dosage forms, number of components and phases can also be changed.

At *dissolution*, before and after mixing numbers of components (n_k >1) are not, but the numbers of components can be changed above saturation concentration due to precipitation.

At *preparation of disperse systems* by high-shear granulation, significant shear, disintegration force is applied while preparation of emulsions and suspensions. Number of components and phases does not, but relationship of components and phases to each other, size of interface do significantly change with degree of dispersion.

In the case of *powder, solid particles*, at the mixing of solid-solid material, homogeneity of the system can be increased due to mixing, but number of components and phases cannot. Although in the case of substances with hygroscopic, or absorbent properties, or eutectic mixture can be changed.

In pharmaceutical practice, mixing is one of the most frequent used operations. The following application possibilities are highlighted:

- homogenization,
- dispersion (emulsifying, suspending),
- heat transfer,
- cooling,
- wetting,
- drying,
- crystallization,
- disintegration,
- granulation,
- preparation of ointment and suppositories,
- micro-encapsulation,
- preparation of micropellets,
- preparation of nano medicines,
- chemical reaction,
- biopharmacy examination (e.g. dissolution, membrane permeability),
- coating.

During the operation of mixing, several processes, phenomena can be regarded:

- *increase in particle size* (e.g. at granulation),
- *decrease in particle size* (e.g. at emulsifying),
- *deformation* (e.g. at disintegration)
- *flow of material.*

At the application of mixing, flow of material can be laminar and turbulent.

At *laminar flow*, vector of speed of particles is parallel along flow line (parallel with axle tube). Particles move orderly next to each other without any mixing. Laminar flow will occur, if frictional forces are higher than inertia forces.

During turbulent flow, movement of particles shows only overall the flow line. Due to the arbitrary, intertwining, swirling, whirling movement of the particles, the layers next to each other are blended.

Euler number is a specific non-dimensional number to flow occurring at mixing:

$$Eu = \frac{P}{d^5 n^3 \rho} \tag{1.}$$

P performance of stirrer
d diameter of stirrer
n speed of stirrer
ρ density of mixed material

Reynolds number (*Re*) is also a specific non-dimensional number for mixing. The value of *Re* in laminar interval is from 10 to 60, in turbulent interval is $>10^3$.

$$Re = \frac{d^2 n \rho}{\eta} \tag{2.}$$

d diameter of stirrer
n speed of stirrer
ρ density of material mixed
η viscosity of material mixed

In practice, *laminar and turbulent* flow frequently appears in the same time. According to this, a transitional interval can be distinguished between laminar and turbulent interval in the by Euler number illustrated in the friction of Reynolds number.

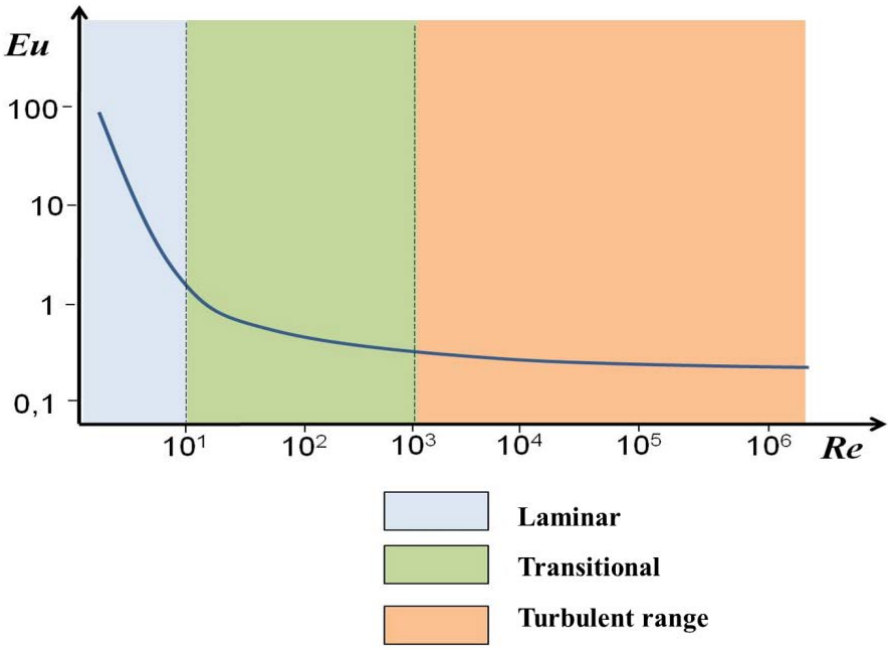


Fig. 10.2.
Euler-Reynold diagram

At the design and choice of stirrer, it has to be considered that, whether state of matter and other parameters of the material which should be mixed, influence the resistance against mixed medium. *Drag force* affecting a moving object depends on density of medium (F), and surface in a direction of movement (A).

$$F = \rho \cdot A \tag{3.}$$

The performance required for mixing can be characterized by the following expression:

$$P = N_e \cdot \rho \cdot n^3 \cdot D^5 \tag{4.}$$

N_e *Newton-number* (*resistance factor*) [number without dimension]
ρ density of material
n speed of stirrer
D diameter of stirrer

While before mixing the material which should be mixed, is in a rest state, but to move the material, and to initiate mixing more energy is needed than to maintain mixing speed.

Degree of mixing (M) can be calculated from relative standard deviation and can be characterized by the following first-order kinetic formula:

$$M = RSD_{\infty} + (RSD_o - RSD_{\infty})e^{-kt} \tag{5.}$$

RSD_o relative standard deviation in initial stage
RSD_{∞} relative standard deviation at the measured degree of mixing
k rate constant
t time

At mixing of solid materials, in practice can be noted, that further homogeneity can be achieved by increasing of mixing time, however opposite effect can occur, namely decrease of homogeneity (phase separation) can appear. This is not valid for preparation of diluted solution. In order to determine *optimal mixing time,* it can be assessed after evaluating relative standard deviance (RSD) calculated from data of samples, that change in RSD has a limit value.

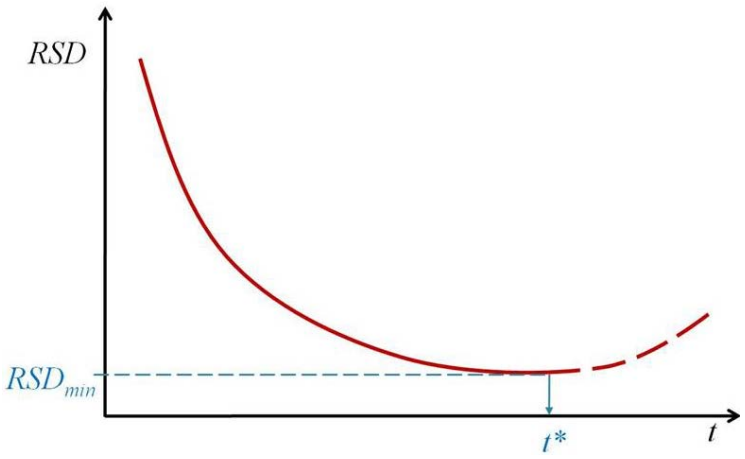


Fig. 10.3.
Determination of optimal mixing time

In the case of dense, viscous material when *over mixing* occurs, the consistency of material can be changed in an undesirable way due to its internal, structural modification (e.g. liquefaction, sticking, condensation).

By mixing it has to be achieved, that particular components of compositions have to be in a prescribed proportion, between allowable limits, even in a small dose from the total batch.

Heat transfer among liquid and heat transferring surface(s) can be significantly improved by mixing. In the case of liquids with low or medium viscosity, stirrers with high speed are applied, which ensures homogeneous heat transfer too. At viscous materials, stir of liquid is needed to be increased next to the heat transferring surface. This can be achieved by low speed stirrer mixing along the wall (gate stirrer, anchor stirrer). Liquids having low viscosity can be well stirred by water circulation pump.

In case of mixing operation, the following data is required in order to choose an appropriate method or apparatus or determine its technical parameters:

1) aim or task determination (e.g. mixing, dissolution, preparing suspension, emulsification, heat transfer),
2) physical properties of initial materials (e.g. quantity, density, viscosity, particle size, rheological property)
3) quality requirements of end product (e.g. homogeneity, particle size, stability, viscosity).

Mixing can be carried out *manually* or *by machines*. Manual mixing is only used in the case of small amount of materials (e.g. compounding preparation in pharmacy). For manufacture larger amount of products, suitable machines, apparatuses have to be applied.

Those stirrers have to be applied, with which the resistance between stirrer and medium can overcome and the desired degree of mixing can be achieved relatively rapidly.

The parameters of mixing operation fundamentally determine the quality of preparation as a product: such as homogeneity of solutions, stability of emulsions and suspensions, evenness of coating and content uniformity of divided dosage forms (injections, suppositories, divided powders, tablets, and capsules).

In the case of emulsions and suspensions, homogeneity/ homogenization is different from homogeneity of solution, it means:

- grinding of particles and drops, and decrease of their size,
- even dispersion of these small particles in dispersion area.

The disperse phase is stabilized mechanically, in order to hider and to minimalize sedimentation in suspensions and skimming in emulsions.

The surface tension can be reduced by using emulsifying agents, which assist to dissolve certain materials as well as to stabilize the disperse phase.

10.2 Mixing of liquids

Stirrer elements in variant size and shape installed on rotatable mixing shaft are applied for mixing liquids. Mixing assists to create of disperse systems, more even dispersion of particles, to accelerate the transfer of material and heat, to perform of chemical reaction. According to speed of stirrer, slow and fast stirrers are distinguished.

During dissolution, the removal of dissolved substance from the surface of the dissolving (not dissolved) material can be accelerated by mixing too. The mixing increases the rate of dissolution, so that it gradually disrupts and removes the creating concentrated boundary layer (stationary diffusion layer) on the surface of crystals.

The mixing time and speed or rpm of stirrer influence the achievable *homogeneity*.

During preparation of suspension, the increase of boundary surface can be assisted by mixing. In the case of emulsions, the aim is also to create appropriate boundary layers on the drops inside the liquid. The shear forces occurring at mixing are significantly able to disperse particles, to reduce their particle size, and to create new boundary surfaces.

Modes of mixing can be the followings:

a) mechanical (by a stir of mixing element e.g. agitating machine, or by rotary motion e.g. magnetic stirrer),
b) static (by a certain medium flow),
c) pneumatic (by air or inert gas),

Mixing modes by medium flow or pneumatic mixing are rarely or are not at all applied. In pharmaceutical technology, are less remarkable.

Mixing by *material flow* is classified into 3 main types:

a) *axial*
b) *radial and*
c) *tangential* flow.

It should be noted, that the three types of mixing do not commonly appear purely themself in practice, but in a mixed form.

Axial type of stirrers achieves the relatively high speed stir of liquid materials with low viscosity in a direction of an axis, which is parallel with spin axis. This vertical movement ensures an upward or in the direction of bottom of flask namely downward liquid motion, depending on direction of rotation and position of stirrer blade. In case of axial liquid movement, the liquid flow turns back at the bottom and top.

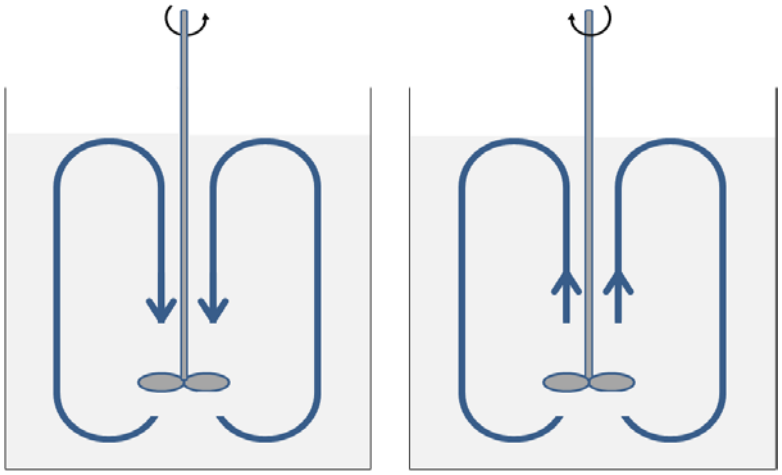


Fig. 10.4.
Axial flow

In container with installed stirrer, centrifugal and gravitational forces act on liquid, which can be expressed by Froude number:

$$Fr = \frac{n^2 d}{g} \tag{6.}$$

n speed of mixing element
d diameter of mixing element
g acceleration of gravity

As a resultant of these forces, bell-mouth entry can occur depending on position of stirrer blade and speed of stirrer, on the surface of liquid. If bell-mouth entry reaches

the stirrer, then air can be dispersed in the medium. In order to avoid bell-mouth entry, back flap has to be used, although increases the needed energy.

The number of stirrer blades can be two or more, but their size, shape and dip angle can be different, which result in variant flow conditions and consequently facilitate optimal mixture of materials with different physical properties.

Axial type stirrers are used generally at preparation of solutions, suspensions and emulsions. This type includes propeller and oblique stirrer.

Fig. 10.5.
Three-blade propeller stirrer

Fig. 10.6.
Four blade oblique stirrer

Radial type stirrers are able to mix liquids having lower and higher viscosity. The blades are parallel with spin axis. Flow of mixed medium firstly is directed at direction of radiation, then next to the wall of flask vertically upward and downward, then reverses in axial direction too. Especially with this type of stirrer, in the lower liquid zone, higher turbulence and shearing can be achieved, than with the axial stirrers.

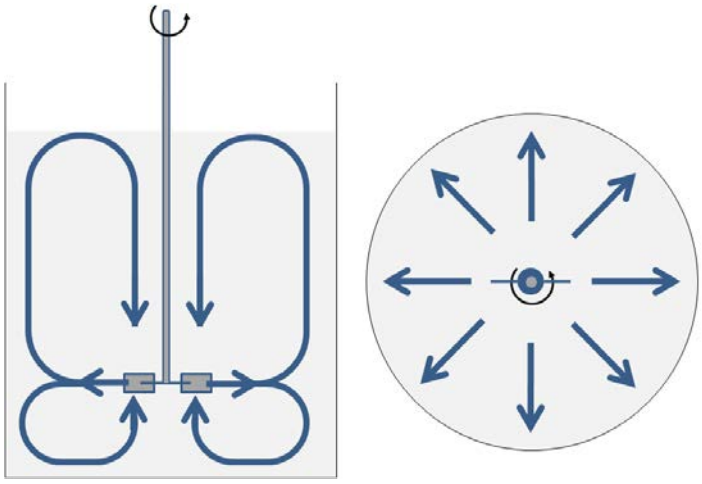


Fig. 10.7.
Flow conditions in case of radial type stirrers, in side and top view

By turbine stirrer intense mixing can be reached in the whole volume. The so called opened turbine stirrers are well applied during heating in order to improve heat transfer of liquid with low density, to hinder sedimentation in suspensions and at crystallization.

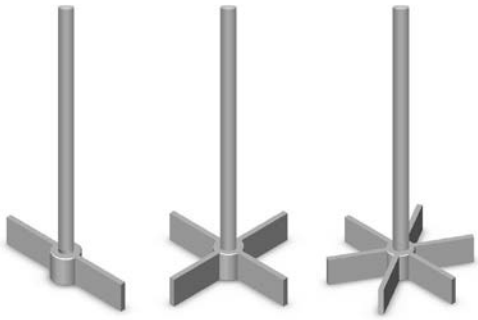


Fig. 10.8.
Opened turbine stirrers

The disc turbine stirrer is classified into high speed stirrers, it consist of vertical blades installed onto disc. At their usage, due to occurring shear forces are they suitable to disperse and to emulsify.

Fig. 10.9.
Disc turbine stirrer

Dissolver type stirrer is able to express more shear force and create significant turbulent flow.

Fig. 10.10.
Dissolver disc stirrer

Tangential, blade stirrers are used for slow mixing. The mixing is assisted by holes on blades and deflecting and baffle plates built in mixing vessel. Holes moderates the occurring resistance, and deflecting plates help the rotation of material, excluding any co-movement of the material.

Fig. 10.11.
Plate stirrer

To eliminate co-movement of material, baffle and deflecting plates are installed.

Tangential stirrers are applied principally to improve heat transfer in the case of liquids with low density, to hinder sedimentation in suspension, as well as in case of crystallization.

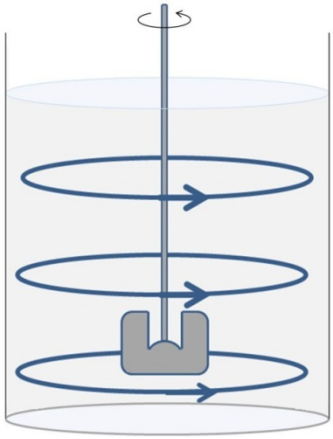


Fig. 10.12.
Flow conditions in the case of tangential type, blade stirrer

Vortex stirrers are used to mix a little amount of liquids, for example a test tube amount. Vertical axis of the stirrer connects excentrically to a rubber hat, which performs fast circular, oscillating movements, when the engine is switched on.

Fig. 10.13.
Vortex stirrer

Magnetic stirrers used in laboratory conditions, just express small torque, and their rpm cannot be controlled accurately, therefore are suitable for mixing of little amount and liquids with low viscosity. Certain types of magnetic stirrers are able to heat during mixing.

Fig. 10.14.
Magnetic stirrer

Laboratory stirrers are used to dissolve and disperse materials. More even and intensive stir is provided in the case of materials with different viscosity too. Their speed/rpm are controlled precisely, and are also able for operational and increasing "return to scale" examination of mixing processes.

Fig. 10.15.
Engine of a laboratory stirrer with digital display

Ultrasonic tanks are able to mix liquids effectively, to prepare solutions, to redisperse, and to clean surfaces of solid objects (metal, plastic, glass). The point of this procedure is that high frequency waves are generated by generator into the medium, which result in cavitation effect. Due to this process, low pressure bubbles in microscopic size are created, which lead to mixing and cleaning effect. Based on apparatuses, they work over the frequency range between 20 kHz to 200 kHz.

Fig. 10.16.
Ultrasonic tank

At operation of *vibration stirrer*, one or more perforated disks installed onto axis vibrate in a direction of axis. Intensive mixing can be achieved by relatively high frequency vibration, thus homogenization, dispensation, and dissolution can be performed within shorter time. During mixing, vortex is not occurring, the surface of liquid remains at rest.

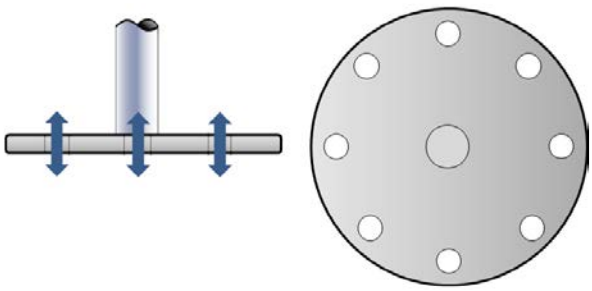


Fig. 10.17.
Vibration stirrer in side and over view

At preparation of mixtures, solutions with low viscosity laboratory orbital shakers are applied. Their advantage, which several vessels can be mixed simultaneously, and due to circular movement, the liquid materials receive the same influences. The location of fastening rods can be adjusted in vertical and horizontal direction, thus several, difference flasks can be fixed from the size of a small flask to larger ones. The speed and time of mixing is controllable.

Fig. 10.18.
Laboratory orbital shaker

In small-scale and industrial size higher amount of liquids can be mixed by apparatuses lower or upper powered. In this case, the required mixing time and speed have to be determined depending material nature and aim of mixing. The choice of suitable mixing elements and their position (depth / height) as well as direction of axis of blade are essential to be ascertained.

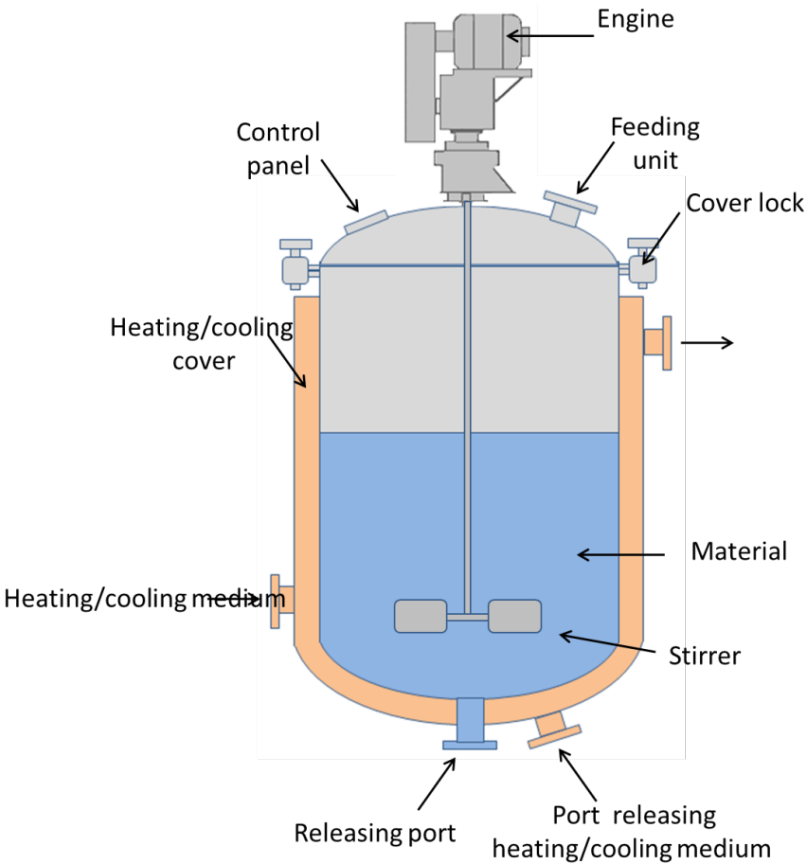


Fig. 10.19.
Small-scale and industrial duplicator stirrer heating/cooling medium

Essentially small-scale and industrial duplicator stirrers are similar to evaporator devices, *reactors* performing chemical reaction, *bioreactors* performing biotechnological tasks and *fermentors* applied for fermentation, which are suitable to perform the operation with their complementary accessories and to control operational parameters determining quality of end product.

Fig. 10.20.
Duplicator apparatus with propeller stirrer

Fig. 10.21.
Upper and lower powered industrial duplicators with oblique stirrer

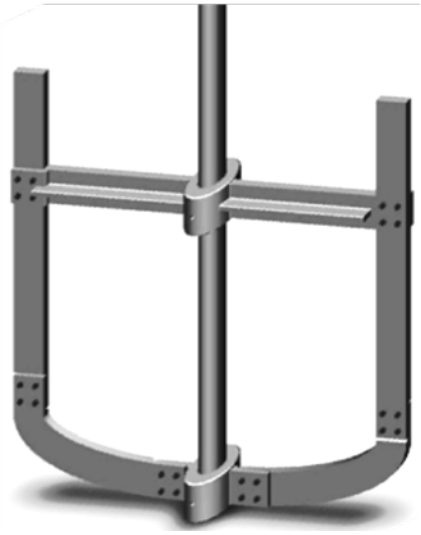


Fig. 10.22.
Anchor mixer

10.3 Mixing of semisolid materials

Mixing of these kind of materials will be discussed later in chapter 'Semi-solid preparations'.

10.4 Mixing of solid materials

Most frequently used dosage forms are the solid dosage forms. An inevitable and important step of the pharmaceutical technology is the mixing. The aim of mixing operation is to prepare homogeneous mixture from measured components, which is correspondent to the prescription. This means that particular components of compositions have to be in a prescribed proportion, between allowable limits, even in a small dose from the total batch.

The mixing is carried out to homogenize two or more solid material and to achieve system consisted of solid components. In case of powders or solid granular materials, homogenization means a spatial, even arrangement of particles. The effectiveness of mixing are influenced in the case of solid materials by the followings:

- quantity of material,
- chemical structure,
- density,
- water content,
- adhesion ability,
- electrostatic charging,
- size of particles,
- shape of particles.

At mixing of small dose, potent active substance, to ensure the appropriate homogeneity the active substance should be mixed firstly with a same amount of diluent, then should be added gradually further parts of diluent. Conversely, if high amount of active substance is applied, the preparation method should be also started to be mixed with the addition of same amount of diluent, and then continued with the leftover.

In the case of high moisture content, free moving of particles are hinders because of their adhesion, therefore the desired homogeneity cannot be ensured. Too low moisture content causes dust creation due to their abrasion.

At mixing powders can be *charged electrostatically* which can be dangerous. In industrial size, electrostatic charge of particles are risky on account of fire safety reasons, thereby electric discharge can occur due to the accumulation of electric charge and increase of e*lectric* field *gradient*. This charge can conclude an explosion, which should be hindered by grounding of devices, ensuring the airspace with controlled moisture content. In the view of dust explosion, fraction sized under 100 μm are risky, but explosion limit depends on certain material, but generally is between 10-50 g/m^3 and 1-5 kg/m^3.

Even dispersion of particular particles greatly depends on applied apparatus, particle size of mixed material, mixing time and intensity of mixing. The powder particles shaped spherical have better fluency, which promote homogeneity.

Kneading stirrers are suitable to homogenize solid granular material, wetting, kneading and mixing more dense suspension.

Fig. 10.23.
Kneading stirrer in lower view

Intensive kneading-stirring effect can be achieved by *Z-arm mixer*, in which arms rotate round two horizontal axes which is parallel to each other. In pharmaceutical technology, Z-arm mixers are principally used for preparation of granules, consistent and even wetting of dry powders.

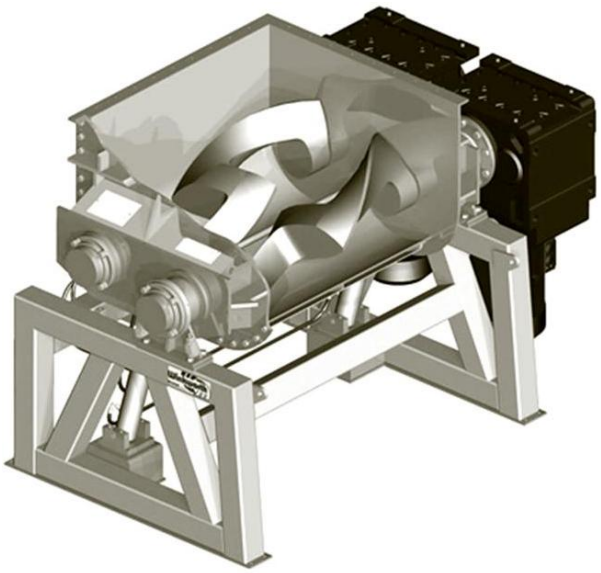


Fig. 10.24.
Z-arm kneader

High shear mixers are principally applied to homogenize dry powders, to wet powders and to knead intensively. Granulation can also be performed in high shear mixer with additional installed stirrers.

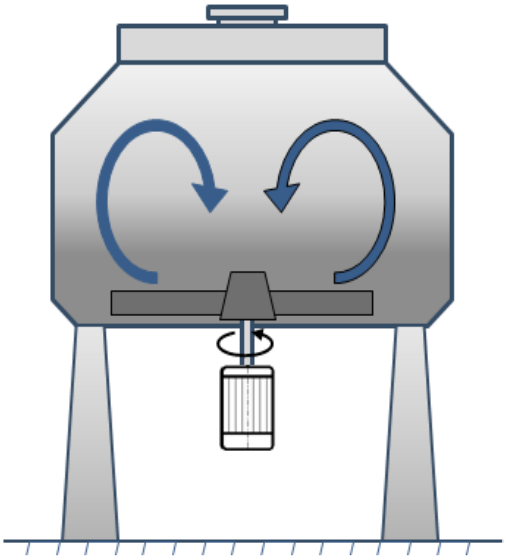


Fig. 10.25.
High shear mixer

The container of *screw mixer* has cylinder shape with a conical end. In the apparatus, the mixing material is forced to move in helix, so that rotates around the longitudinal axis of the apparatus and goes through. The resultant of two movement result in helical movement. The mixing screw causes intensive mixing effect, thereby is also suitable for kneading wet particle structure besides homogenization of powders.

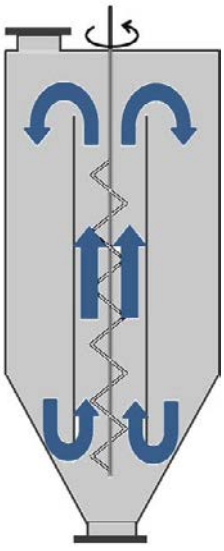


Fig. 10.26.
Vertical axis screw mixer

In the case of *oblique axis screw mixer*, its container has not cylinder shape, but cone shape with an oblique placed screw, which transfers upward and mixes the material. During which the container rotates around its own axis.

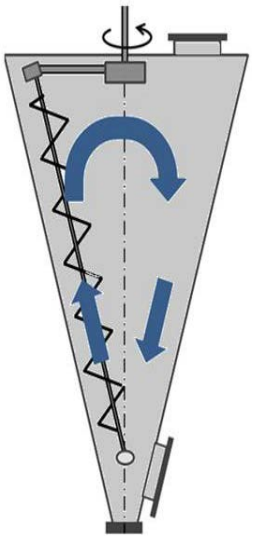


Fig. 10.27.
Oblique axis screw mixer

According to the shape of *drum mixers* can be tetrahedral, cylindrical, or a double cone and V shaped. These apparatuses are principally suitable for mixing materials having appropriate fluency, without adhesion tendency. During mixing, particle layers move together with the drum, then detach from the envelope of drum, slide down and roll onward on the material at the bottom. The load of drum mixers generally can be about 40-65%. The speed of mixing should not be increased over the *critical speed*, because at this time, particles or granules will not mix but rotate together with the drum.

To ensure the perfect homogeneity, in mixer having hexahedron or cubic shape, internal spreader rods help the further material to turn over and to roll onward.

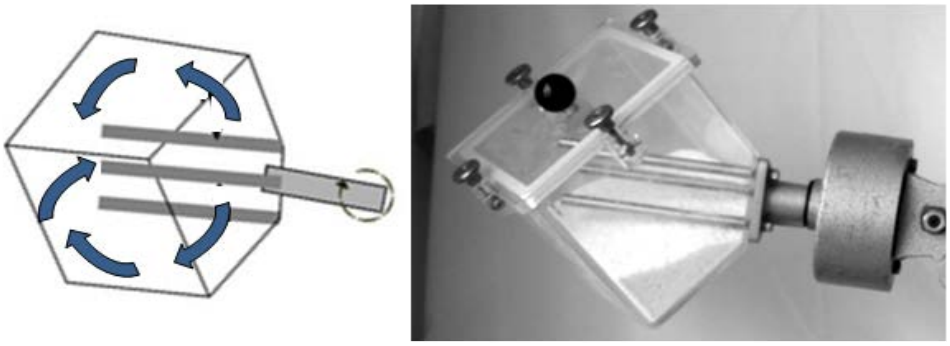
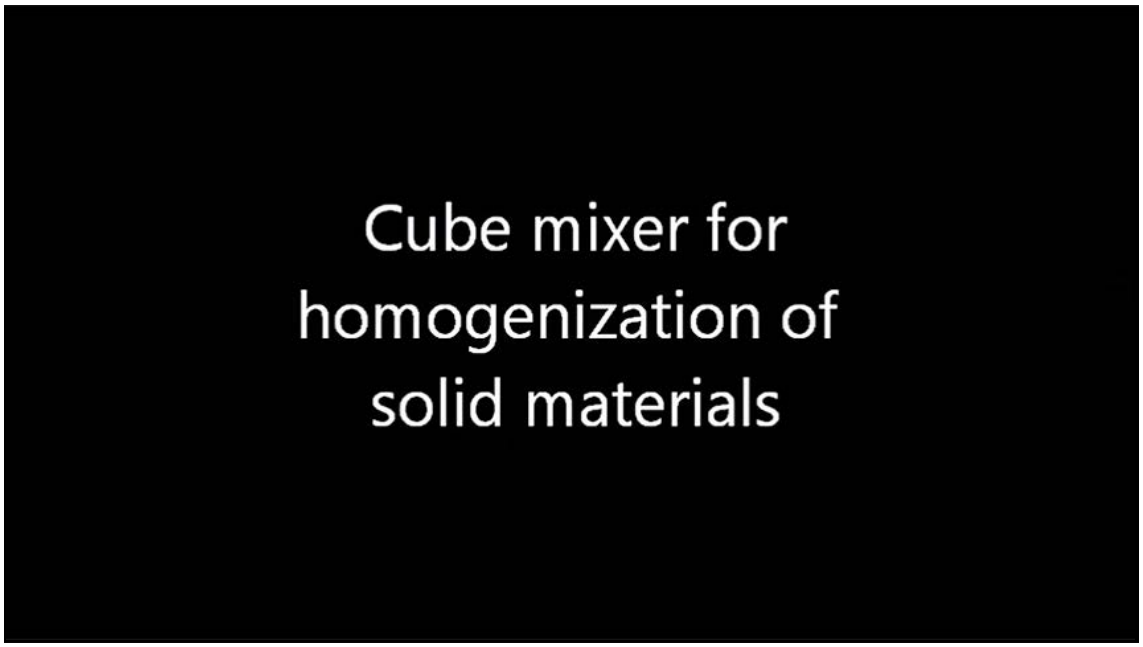


Fig. 10.28.
Cube mixer with spreader rods



Movie 3. Cube mixer for homogenization of solid materials

The cylindrical mixer homogenizes the material mass by turning over the layers, rolling forth and back and by symmetrically repeating rotations.

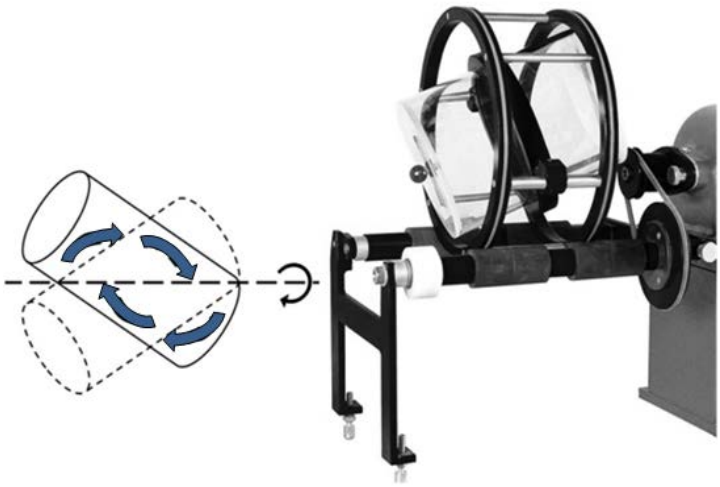


Fig. 10.29.
Cylindrical mixer

Mixing of solid particles with rolling and turning over the layers is also achieved by *double cone mixer*. Although the direction of roll can be varied with asymmetric or symmetric placement of drive axis.

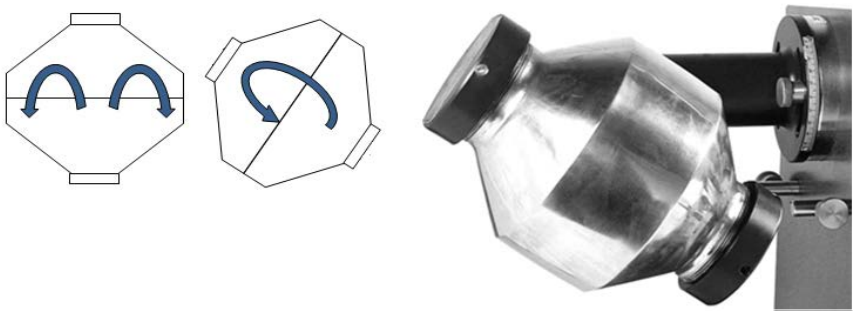


Fig. 10.30.
Double cone mixer with symmetric and asymmetric drive axis

Blind area or less mixing zones can occur around the rotation axis especially at symmetric rotation.

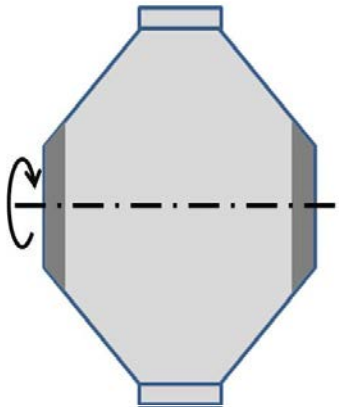


Fig. 10.31.
Blind areas of double cone mixer at symmetric mounting

Special types of mixers with rotating container are the *V-type mixers*. These apparatuses developed to mix especially solid materials are proved to be very effective. The particles move back and forth from a cylinder to another one, in both sides up and down due to the rotation. The cylinders fit V-shape to each other.

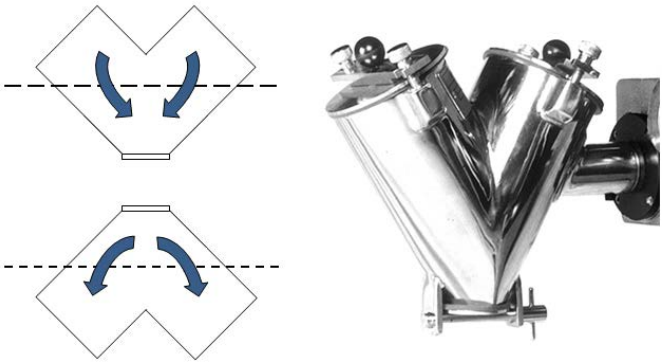


Fig. 10.32.
V-type mixer and its flow conditions

Along the rotation axis in the mixer, less mixing zone may develop in V-type mixer.

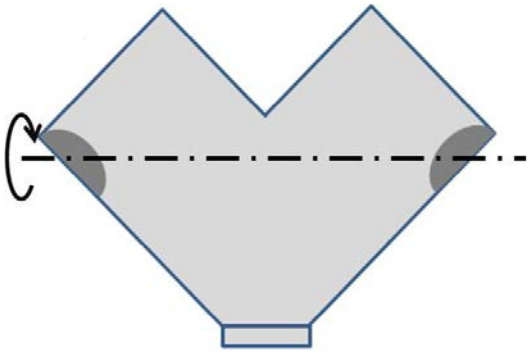


Fig. 10.33.
Blind areas of V-type mixer

Questions

1) What is mixing?
2) What does the Euler number express?
3) What are the possible material systems to be mixed in pharmacy practice?
4) A gyógyszerészi gyakorlatban milyenek lehetnek a keverendő, keverésre szánt anyagrendszerek?
5) How is optimum duration of mixing determined?
6) How is the performance required for mixing calculated?
7) What are modes of mixing?
8) What are the main types of material flow in mixing?
9) What are the main parts of the industrial agitator mixer?
10) What parameters influence the efficacy of mixing of solid granular materials?
11) How would you describe “self-mixing structures”?
12) What are laminar and turbulent flow? Which is more significant in mixing?
13) When does the phenomenon “phase separation” occur?
14) How do “dust explosions” come about in the course of mixing?
15) Which stirrers are suited for kneading wetted powders?
16) Which stirrers are most suited for making homogeneous solid powder mixes?

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Chowhana Z.T., Linna E.E.: Mixing of pharmaceutical solids. I. Effect of particle size on mixing in cylindrical shear and V-shaped tumbling mixers, Powder Technology,.24, 2, 237-244, 1979.

McCabe W. L., Smith J. C.: Unit Operations of Chemical Engineering, Mc Graw Hill.Companies Inc. 2005.

Recommended websites

http://nsdl.niscair.res.in/bitstream/123456789/751/1/Revised+mixing.pdf

http://www.stat.yale.edu/Courses/1997-98/101/expdes.htm

http://www.nzifst.org.nz/unitoperations/mixing.htm

http://dettk.ucoz.com/_ld/2/227_Vegyipari_mvele.pdf

http://www.postmixing.com/mixing%20forum/impellers/impellers.htm

http://mixmor.thomasnet.com/item/all-categories/custom-impellers-2/custom-impellers

11 Dissolution

Dissolution is the one of the most important basic and forming operation in pharmaceutical technology.

In a pharmaceutical technology, *dissolution* means the operation, during which a materials in solid, liquid or gas state of matter is dispersed in a solvent in molecular level. Thus to dissolve can regarded as a special form of to disperse. If the molecular size of dissolved material is lower, than 1nm, then molecular, if is higher than 500 nm, but not more than 1μm, then colloidal is the dissolution.

Absorption from preparation can develop directly from solution-type preparations (e.g. solutions, injections) or indirectly, when active ingredients have to liberate and dissolve previously to be ready to be absorbed.

In biopharmacy point of view, process of dissolution is one of the important criteria of absorption:

1) previously dissolved medicine before administration (e.g. effervescent tablet), and
2) dissolution process occurring in living organization, which can be:
   - 2.1) dissolution of active substance after taking or applying (e.g. medical powders),
   - 2.2) fast dissolving (e.g. sublingual preparation),
   - 2.3) dissolution or liberation can occur from preparation,
     - 2.3.1) uncontrolled way (e.g. suppository, conventional tablet) and
     - 2.3.2) controlled way
       - in space,
       - in time,
       - in space and time.

Dissolution of excipients (e.g. coating, matrix) frequently and significantly affects dissolution process and starts parallel with liberation of APIs.

From solutions and nano systems (e.g. dendrimers, inclusion complexes) absorption is faster; because molecules are ready to be absorbed in the view of molecular dispersion degree, and there is no need previous disintegration processes (as a criteria of dissolution process). Absorption of preparation regarded to *such molecular systems* is influenced and determined after per oral administration by quantity of API molecules in non-ionic state. The ionic and non-ionic state depends on *pH* value of local gastrointestinal tract and *pK*, based on *Henderson- Hasselbach equation.*

For perfect absorption of a particular molecule $t_{transit}$ time is only available. If dissolution (in the case of preparation, *liberation*) is just performed partially, then perfect, total absorption cannot be expected and biological availability/ bioavailability (*BA*) of the preparation will be low ($BA<1$,or $BA<<1$). Low *BA* can occur due to the fact that certain amount of administered *API* passes intestine section with absorption capability. These points of view have to be considered at design of biopharmacy parameters, control of location and speed of dissolution and at determination of required dosage.

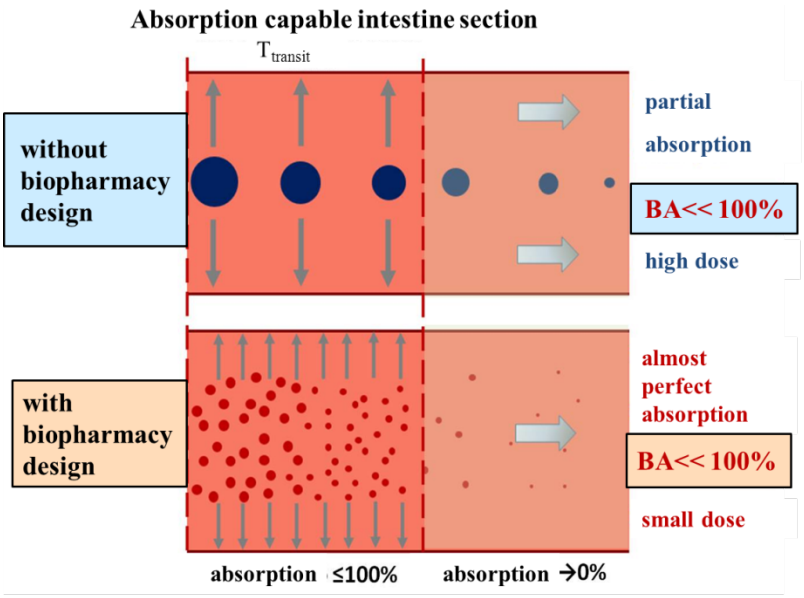


Fig. 11.1.
The effect of solubility, dissolution speed and transit time on bioavailability and applied dose

Solutions can be administered in the following ways:

1) *oral* (e.g. mouthwashes, gum preparations),
2) *peroral* (e.g. solutions, elixirs, mixtures, syrups, decoctions, infusions),
3) *dermal and transdermal* (e.g. solutions, decoctions, infusions, ointments, creams),
4) *ocular* (e.g. eye drops, eye washes),
5) *vaginal* (e.g. vaginal solutions and washes),
6) *rectal* (e.g. enema),
7) *parenteral* (e.g. injections, infusions).

The solutions, mixtures, or solution –type solid dispersions or mixture of gases are multicomponent (number of components, $n_k \geq 2$), monophasic (number of phases, $n_f = 1$) homogeneous materials structures.

Pharmaceutical solutions are homogeneous liquid dispersion of a solute (solid, liquid or gas) dissolved in a suitable vehicle (water, alcohol or any other solvent mixture).

General operation steps of dissolution shown in Figure 2.

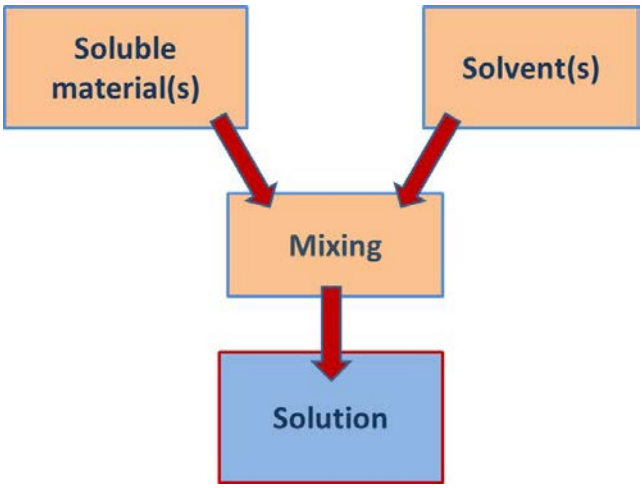


Fig. 11.2.
General operation steps of dissolution

Most important characteristics that need to be considered when compounding solutions are solubility and stability.

The majority of processes occurring in nature take place in solution. In laboratory -, and industrial sizes, implementation of chemical reactions, manufacture operations is generally in liquid phase, mostly in solutions.

Solutions, drops, eye drops are independent dosage forms, at preparation which solubility properties of materials have to be known. Operation of dissolution plays a significant role in pharmaceutical monitoring, control.

The process of dissolution can be performed in physical and in chemical way.

The point of *physical dissolution* is that during process, the two materials do not change the structure of each other (e.g. solution of sodium chloride or sucrose). The process is reversible, namely dissolved material can be extracted by evaporation of solution.

Chemical dissolution is when two material interact with each other in a chemical interaction, which result in a new structure material (e.g. $Fe + 2HCl = FeCl_2 + H_2$). The process is irreversible.

At physical dissolution, two or more phasic system may gradually turn into one phase and homogeneous status may be created. Before and after the operation, the number of components will not be changed, but number of phases can increase to the original value above the saturation concentration (due to separation of crystals).

In the case of liquids, which are *miscible unlimitedly* in each other, the dissolution is termed mixing. Before and after the operation, number of phases and components does not change for example the mixture of water-ethanol, or benzene and toluene.

Other type of liquids can be *mixed until a limit* in each other, such as water and phenol, or water and ether.

Dissolution is the result of interaction between the molecules of solvent and dissolving material. In both material, one part of the interparticle bonding (secondary) are broken and new bonding are created among solvent and dissolved material.

In dissolution process, *solvation* is created between molecules of dissolved material and solvent, in addition to the fact that in case of water solvent, is termed *hydration*. Solvation is the connection or interaction creation between the molecules of dissolved substance and solvent. The point of process is the creation of a solvation shell or a hydration shell around a molecule or an ion.

At solvation, different type intermolecular interactions can develop: hydrogen bonding, ion-dipole, dipole-dipole or *van der Waals* forces. Hydrogen bonding, ion-dipole, dipole-dipole forces occur only in polar, hydrophilic solvents. Ion-ion interactions present in ionic solvents. In case of lack of these, *van der Waals* forces present. The hydrate shells around ions (because the most frequent used solvent is water)" shroud" the opposite charged ions, hence ions cannot unite and create salt. The solutions of ions, which are able to move freely, are termed electrolyte solutions, while it conducts electricity.

At dissolution of salt type molecules in water, the molar free energy of solution can be calculated by this formula:

$$\Delta G_{solution} = \Delta G_{cation} + \Delta G_{anion} - \Delta G_{lattice} \qquad (1.)$$

ΔG_{cation} molar hydration free energy of the cation,

ΔG_{anion} molar hydration free energy of the anion,

$\Delta G_{lattice}$ free energy of crystal-lattice.

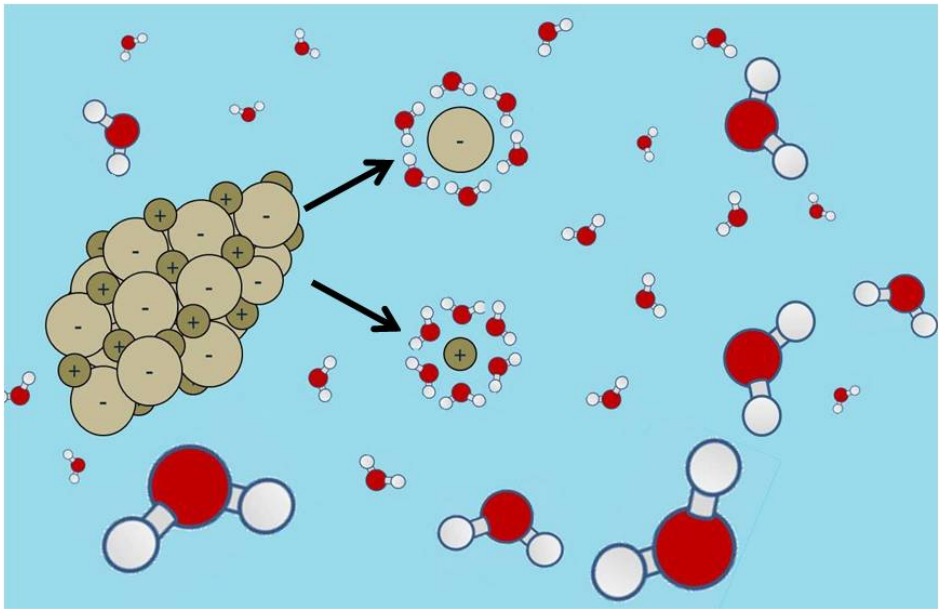


Fig. 11.3.
The process of hydration based on ion-dipole forces

In solvation process, the molecules of dissolving material have to escape from crystal-lattice in order to be stabilized in the solvent by the interaction with molecules of solvent.

In order to escape the units of crystal lattice, lattice energy ($E_{lattice}$) has to be exerted to overcome the force between the molecules of dissolving material.

Between the molecules of solvent are also cohesive forces, but their energy level is much lower than lattice energy.

Water as a solvent has a strong dipole force, and is built up by molecules connected with hydrogen bridges. Primarily water is able to create and maintain ion-dipole, dipole-dipole and hydrogen bridge bonding. Its dielectric constant (value of relative permittivity) is high (78,54), therefore ion-type substances present as ions in water-based solutions, and not as ion-pairs.

Water is able to separate opposite charged particles, and to stabilize ions and dipole-type molecules.

At dissolution, between particles of solvent and dissolved material, new coherent force is created, which is associated with energy release. This energy is *solvation energy* (E_{solv}), what is termed *hydration energy* (E_{hydr}) in the case of water.

Heat of solution is the heat, which is released or absorbed, if quantity of one mole material is dissolved in large excess of solvent. Heat of solution is characterized in dissolution process by algebraic sum of used lattice and released hydration energy:

$$\Delta H_{dissolv} = E_{lattice} + E_{hydr} \qquad (2.)$$

The sign of heat of solution can be positive, when the process is endothermic, and if it is negative, then it is an exothermic process. (Lattice, hydration energy and heat of solution is calculated per mole.)

In case of exothermic process, the system lose energy (during rearrangement of bonds, its total energy decrease), more energy is released during the dissolution process, than can be used. This energy rises the temperature of environment with the temperature of solution. At dissolution of crystalized material, the energy level of molecules goes from a higher energy lattice level to a lower, hydrated energy level, therefore energy is released:

$$E_{lattice} < E_{hydr} \qquad (3.)$$

Thus heat of solution is a negative value, because the material releases heat. For example heat of solution is at dissolution of NaOH: –42,2 kJ/mole, in the case of Na_2SO_4: -1,9 kJ/mol.

In the case of *endothermic dissolution process,* the situation is the opposite, because the internal temperature increase, during the dissolution process less energy is released, than is used:

$$E_{lattice} > E_{hydr} \qquad (4.)$$

Thus heat of solution is a positive value, because the material receives heat. For example heat of solution is at dissolution of KNO_3: +35,1 kJ/mole, in the case of NaCl:+4kJ kJ/mol.

The molecules of solvent are targeted to surround and separate dissolved molecules.

Dissolution takes place in at least three steps:

1) solvent and dissolving material has to get contact with each other,
2) chemical or physical processes of dissolution take place on the boundary surface with creating the most concentrated solution layer,
3) dissolved material has to move toward to the inside of solution, in order to assist continuation of dissolution process.

In the view of dissolution process, the structure of dissolving material and stability of the developing new structure are fundamentally important.

At dissolution of crystallized material, the entropy generally increases, while order of the system decrease when a less organized solution is created from an ordered crystalline status.

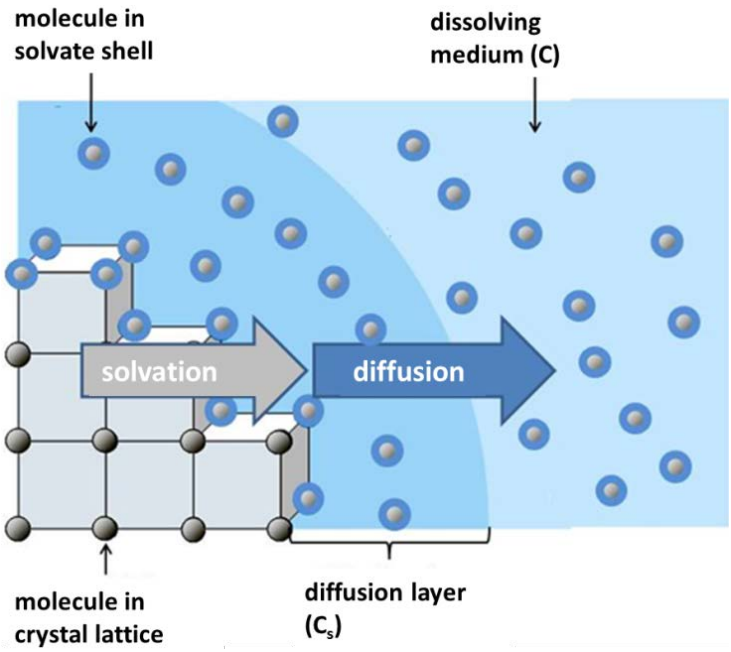


Fig. 11.4.
Dissolution mechanism of crystalline material

The pharmaceutical definition of solubility is the mass proportion of dissolved material and solvent in a saturated solution. It shows the dissolution, that a mass unit of dissolving material can dissolve in how many mass unit of solvent. In other words, the concentration of dissolved material in certain saturated solution in particular temperature and pressure. The solubility plays a very important role in design, implementation of several technological processes.

According to saturation concentration the following groups can be distinguished:

1) *unsaturated solution*, which is able to dissolve more additional material in it,
2) *saturated solution*, which contains the maximum of the particular material,
3) *oversaturated solution*, which contains more quantity of material than the saturated solution.

In the case of unsaturated solution ($c<c_t$), concentration can be increased until the saturation concentration. At saturation, dynamic balance develops among dissolving and separating material. Oversaturation ($c>c_t$) is only a temporary, instable status containing more material than saturated solution.

Table 11-I.
Most frequent applied solvent in pharmaceutical practice

Solvent	Specifications			
	Freezing point	Boiling point	Hydrophilic	Hydrophobic
acetone	-94.6	56.5	+	
acetonitrile	-40	82	+	
amyl alcohol	-78.5	137.9	Limited	
ammonia			+	

Solvent	Specifications			
	Freezing point	Boiling point	Hydrophilic	Hydrophobic
aniline	-6.2	184.4	Limited	
benzene	5.5	80.1		+
cyclohexane	6.5	83.3		+
diethyl ether	-116.3	34.6		+
diethyl amine	-38.9	55.5	+	
dimethyl sulfoxide	19	189	+	
ethanol	-112	78.4	+	
ethyl acetate	-82.4	77	Limited	
Ethylene glycol	-11.5	197.5	+	
phenol	42	181.8	Limited	
formaldehyde	-92	-21	+	
glycerol	17.9	290	+	
isopropyl ether	-60	67.5		+
isopropanol	-90	82.4	+	
isopropyl acetate	-73.4	89.4	Limited	
Isopropyl myristate	~5	140,2 (266Pa)		+
chloroform	-63.5	61.2		+
methanol	97	64.7	+	
methylene chloride	-96.7	40	Limited	
n-amyl acetate	-70.8	148.4	Limited	
n-butyl acetate	-76.3	125		+
n-butyl alcohol	-79.9	117		+
n-heptane	-90.6	98.4		+
n-hexane	-94	69		+
n-propanol	-127	97.8		+
octanol (n)	-16	194		+
pyridine	-42	115	+	
polyethylene glycol 600	15-25 (freezing)		+	
propylene glycol	-	188	+	
toluene	-95	110.8		+
triethyl amine	-114.8	89.4	+	
water	0	100	+	

Legend: ++ well miscible, + partially miscible, - inmiscibl

The expression, distilled water means that the water purified by distillation.

According to pharmacopoeias, several waters used in pharmaceuticals can be distinguished.

1) *Purified water* (*Aqua purificata*) is a water for preparation of those compounded medicines, which has not to be sterile and pyrogen-free (e.g. solutions, emulsions, suspensions, drops excluding eye drops),

excepted justified and officially approved cases. Two types of purified water are distinguished, purified water in bulk, and in containers.

1.1) *Purified water in bulk* is prepared by distillation, by ion exchange, by reverse osmosis or by any other suitable method from water that complies with the regulations on water intended for human consumption laid down by the competent authority. According to the criteria of pharmacopoeia, water in bulk has to be:

a.) clear and colorless liquid,
b.) met with criteria of microbial monitoring
c.) appropriate in pH, as well as its specific conductivity
d.) less nitrate, aluminum or heavy metal in it, than the allowed limit
e.) at most the concentration of bacterial endotoxin in it, than the allowed 0.25 IU/ml.

The storage and filling conditions has to be created to exclude proliferation of microorganisms and any other contamination.

1.2) *Purified water in container*, that has been filled and stored in conditions designed to assure the required microbiological quality. It is free from any added substances.

2) Water for injections (*Aqua ad iniectabilia)* can be in bulk and sterilized water for injection. Water for the preparation of medicines for parenteral application, when water is used as a vehicle (*water for injection in bulk*), and dissolving or diluting substances or preparation for parenteral administration (*sterilized water for injection*).

2.1) Water for injections in bulk is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority or which the parts in contact with water are of neutral glass, quartz or suitable metal and which is fitted with an effective device to prevent the entertainment of droplets. The correct maintenance if the apparatus is essential. The first portion of the distillate obtained when the apparatus begins to function is discarded and the distillate is collected. The assurance of water quality is controlled by validated methods, by in process conductivity measurements, and by gradual microbiological monitoring. Storage and distributing water for injection in bulk has to be managed to exclude growth of microorganisms and any other contamination. Based on the criteria of the Pharmacopoeia has to be:

a) clear and colorless liquid,
b) appropriate in pH, as well as its specific conductivity,
c) less nitrate, aluminum or heavy metal in it, than the allowed limit
d) at most the concentration of bacterial endotoxin in it, than the allowed 0.25 IU/ml.

2.2) Water for injection in bulk that has been distributed into suitable container, closed and sterilized by heat in condition which ensure that the product still complies with the test of bacterial endotoxins. Sterilized water for injection is free from any added substances and

has to be met with the criteria of sterilization. Sterilized water for injections is used to dissolve or dilute substances in parenteral preparation (e.g. in situ preparation of injection from vials). Based on the criteria of Pharmacopoeia, sterilized water for injection has to be:

a) clear and colorless liquid,
b) appropriate in pH, as well as its specific conductivity,
c) less oxidizable substances, chloride, nitrate, sulphate, aluminum, calcium, magnesium, and heavy metal in it, than the allowed limit
d) at most 4mg (0,004%) after evaporated (evaporation leftover)
e) at most the concentration of bacterial endotoxin in it, than the allowed 0.25 IU/ml.

3) Water, high purified (*Aqua valde purificata*) intended for use in preparation if medicinal product where water of high biological quality is needed, except where Water for injection is required.
4) Water for dilution concentrated hemodialysis solutions is obtained from potable water by distillation, by reverse osmosis, by ion exchange or by any suitable method. The conditions of preparation, transfer and storage are designed to minimize the risk of chemical and microbial contamination. When water obtained by one of the methods described above is not available, potable water may be used for home dialysis. Because the chemical composition of potable water varies considerably from one local to another, consideration must be given to its chemical composition to enable adjustment. Quality of water for dilution concentrated hemodialysis has to be controlled gradually including acidity, alkalinity, oxidizable substances, content of total available chlorine, chloride, fluorides, nitrates, sulphates, aluminum, ammonium, calcium, magnesium, mercury, potassium, sodium, zinc, heavy metals, and also microbial contamination as well as bacterial endotoxins.

11.1 Solubility

Solubility, the property of substances, means the amount of a substance that dissolves in a unit volume of a solvent to form a saturated solution under specified conditions of temperature and pressure.

The solubility of a substance fundamentally depends on the used solvent as well as on temperature and pressure. Solubility values in pharmacopoeia pertain to 15–25 °C temperature intervals.

Table 11-II.
Specific intervals of solubility

Descriptive term	Approximate volume of solvent in millilitres per gram of solute
very soluble	<1
freely soluble	1-10
sparingly soluble	10-100

Descriptive term	Approximate volume of solvent in millilitres per gram of solute
slightly soluble	100-1000
very slightly soluble	1000-10000
practically insoluble	>10000

The term *"partly soluble"* is used to describe a mixture where only some of the components dissolve. The term „miscible" is used to describe a liquid that is miscible in all proportion with the started solvent.

Solubility depends on several factors, such as solvent, dissolving material, temperature and in the case of solubility of gases it depends on partial pressure of the component. Therefore solubility is generally given in 20°C.

Solubility can be characterized in several ways:

a) *solubility equilibrium* or namely *thermodynamic solubility*, which means the concentration of a saturated solution in which the dissolved material is in redundancy.
b) *intrinsic solubility* is the balance solubility of free acid or alkali form of ion-type substances in a certain pH, in which the substance presents in totally unionized form.
c) *kinetic solubility* is the concentration value, in which substance is firstly separated from solution in insoluble form.
d) *apparent solubility* is determined in solutions or puffers in several pH, therefore apparent solubility depends on pH and ionic strength of the medium.

In order to determine thermodynamic solubility, the substance has to be mixed in redundancy to particular volume of aqueous medium, in particular temperature until a particular time (frequently until 24 or 48 hours), then concentration of saturated solution can be determined with a suitable analytical methods by extracting the filtrate (by filtering/ centrifugation).

Kinetic solubility can be ascertained that the solid material is dissolved in organic solvent in a low concentration, and then a small part of this solution is mixed with aqueous puffers. When the material firstly precipitates, then it has to be separated from the solution and concentration is determined.

Jain and Yalkowsky have introduced the *General Solubility Equation, GSE*, which gives the correlation of effective solubility:

$$\log S_0 = 0{,}5 - 0{,}01\,(T_m - 25) - \log P \qquad (5.)$$

S_0 effective solubility,
T_m melting point,
P octanol/ water partition coefficient.

Based on Henry-Dalton rule, solubility of gas without reacting with liquid depends on pressure:

$$c = kp \qquad (6.)$$

In the case of gases, temperature also influences the solubility besides pressure.

The higher is the concentration of dissolved material, bigger is the difference from this rule. The reason of behavior differing from ideal is due to interactions of molecules and ions in so called true solutions.

In the case of solutions, solubility depends principally rather on temperature and less on pressure. Temperature dependence of solubility of different materials is various. By rising temperature for example, solubility of saccharose and KNO_3 increase, but solubility of Na_2SO_4 decrease. In the case of NaCl, NaBr, KCl, solubility is not changed by temperature.

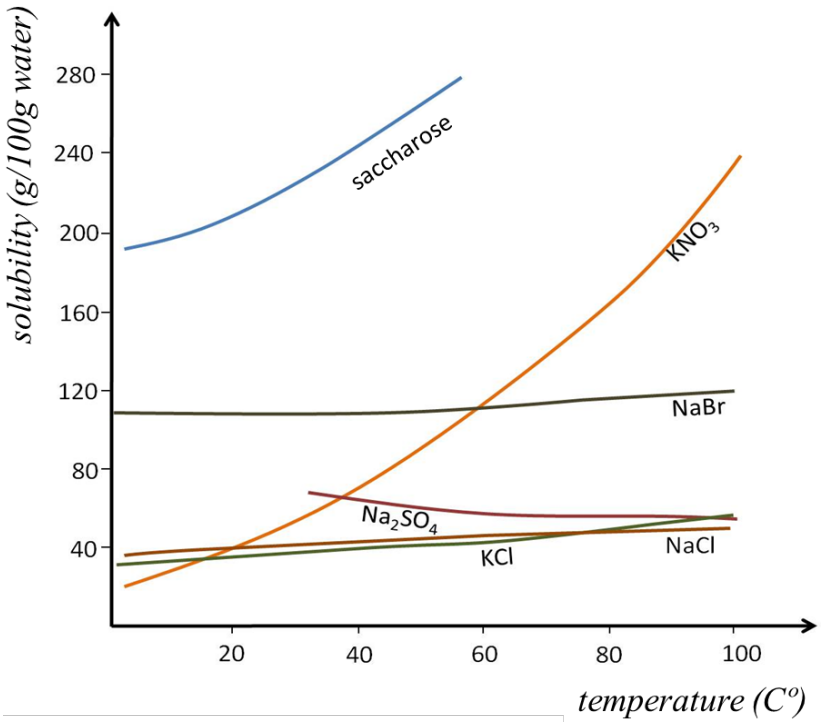


Fig. 11.5.
Change in solubility of several materials in the function of temperature

Temperature dependence of solubility is described in *Clausius-Clapeyron correlation:*

$$lg\frac{S_{T_1}}{S_{T_2}} = \frac{\Delta H_{diss}(T_2 - T_1)}{2{,}3RT_2T_1} \qquad (7.)$$

S_{T_1}, S_{T_2} solubility in certain temperatures (T_2,T_1)

If heat of solution has negative sign (exothermic dissolution), then solubility decrease, but if it is positive (endothermic dissolution), then solubility increases by rising temperature.

Most frequently the materials which should be dissolved belong to weak electrolyte type substances. In this case, pH of the medium is also a significant parameter in the view of solubility. According to dissociation equilibrium, the material presents in dissociated and not dissociated form at the same time. The sum of two solubility is (S_s):

in the case of weak acids:

$$S_t = S_0 + S_0 K_d 10^{pH} \tag{8.}$$

in the case of weak alkali:

$$S_t = S_0 + \frac{S_0}{K_d} 10^{-pH} \tag{9.}$$

11.2 Increase of solubility

Increase of solubility can developed with caution in every case. Physical chemical thereby biopharmacy properties of active substance can be modified by changing of molecular-chemical structure, increase or decrease of polar nature. These methods can be only applied, if original therapeutic effect of active ingredient is kept.

Polymorphism, hydration, solvation, and amorphous forms of solid crystals influence the speed of dissolution. One possibility to modify manufacturability, solubility and speed of dissolution is to turn the substance to amorphous form. This method is just considered, when the substance prones to form into polymorph form or the workability of certain crystal form is difficult. In amorphous state the chemical stability decreases due to absence of crystal lattice. The crystal lattice has a long term orientation, while material with amorphous structure has got only short-time orientation. In practice, this means that amorphous material has higher solubility. It is very important about amorphous materials that higher is the probability for recrystallization and to turn into another crystal form with lower solubility due to the instable status of amorphous structure. In order to maintain the amorphous structure, hindering of transformation of structure is needed in more stable state. The solution can be the dispersion of amorphous substance in a solid dispersion, which slows down the recrystallization process by hindering the internal movements.

One of the most common solutions for increase of solubility is salification or salt formation in the case of weak acid and alkali substances.

Choice of suitable salt form depends on:

- solubility,
- hygroscopic character,
- stability and
- toxicological properties.

With this solution, ephedrine can be formed to ephedrine hydrochloride and phenobarbital into phenobarbital sodium

Table 11-III.
Salification possibilities for increase of solubiltiy

name of active ingredients	type of salt
bases	hydrochloride
	methanesulphonate (mesylate)
	hydrobromide
	acetate
	fumarate
	sulfate
	succinate
	citrate
	phosphate
	maleate
	nitrate
	tartrate
	benzoate
	carbonate
	pamoate
acid	sodium
	calcium
	potassium
	tromethamine

Solubility (mg/ml) of several salt shows significant differences in water:

- codeine 8.3; codeine sulfate 33; codeine phosphate 445 mg/ml,
- atropin1.1; atropine-sulfate 2600 mg/ml,
- ibuprofen 0.02; ibuprofen hydrochloride 2000 mg/ml.

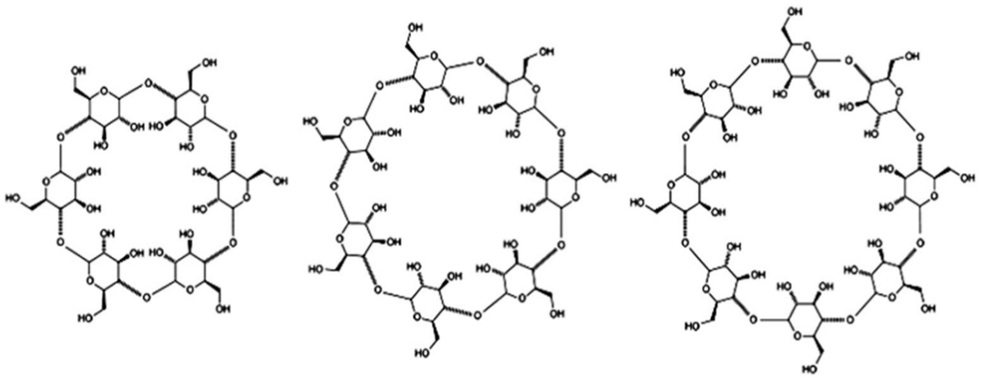
Solubility increasing effect of hydrotropic materials (single or polyvalent alcohols, their ethers and esters, hydroxyl acids and their salts, nitrogen compounds, or macromolecules) are the creation of loose complexes, decrease of boundary surface tension, creation of hydrogen bridges, and change in permittivity. Materials with hydrophobic character interact with the lipophilic part of the hydrotropic molecules, and their polar groups are hydrated in water via intermolecular hydrogen bridges. Pharmaceutical technological examples of hydrotropic are the followings:

- theobromine with sodium salicylate,
- oxytetracyclin with salicylate or with benzoate,
- theophylline with sodium salicylate,
- caffeine with sodium benzoate.

Water-soluble complexes can be prepared or formed with appropriate excipients. The ethylene diamine tetra acetate (EDTE) plays very important role in solubility increase by creating chelate complexes. It is important in the case of lead, arsenic and mercury poisoning. At creation of metal chelate complexes, chemical bond is created during a Lewis acid-base reaction among donor and acceptor molecules (e.g. Zn-ACTH, Zn-insulin and Fe-dextran). In the case of tetracycline and oxytetracycline, farmakon

metal chelate complexes can be easily created, which decrease their pharmacological effect.

Cyclodextrins are oligosaccharides consisted of six, seven or eight α-D-glucopyranose units with which structure assist to increase solubility. Cyclodextrins have polar surface character which allows the dissolution in water. Association type complexes can be created and as acceptor they can increase solubility of donor in water.



	α	β	γ
number of glucopyranose units	6	7	8
molecular weight (Dalton)	973	1135	1297
solubility in water (g/ml)	14,5	18,5	23,2
blank volume ml/1g	0,10	0,14	0,20

Fig. 11.6.
Main properties of cyclodextrins

Creation of inclusion complexes can be characterized with the followings:

- water molecules are displaced from the inside of cyclodextrin molecules by the less polar molecules, and the molecules with suitable shape and size are placed in the hole of cyclodextrin molecules.
- donor molecules get into an interaction with the hydrophobic hole (van deer Waals and hydrogen bridges are created)
- only certain groups or side chains of some, large molecules can fit into the hole of cyclodextrins
- Gibbs free energy of structure is decreased after creation of an inclusion complex.

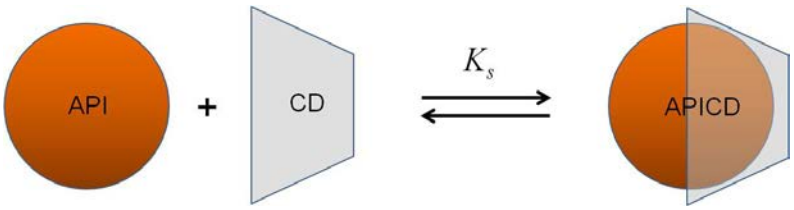


Fig. 11.7.
Equilibrium development at preparation of inclusion complex

At creation of inclusion complex, dissolving material, generally the active pharmaceutical ingredient (API) and molecule of cyclodextrin (CD) create a complex. The stability coefficient of this molecule complex can be calculated by the following formula (K_s)**:**

If the concentration of dissolved material is increased in the function of cyclodextrin concentration, the following linear function is received:

$$[API] = R[CD] + S_0 \qquad (10.)$$

R slope of the graph
S_o intersection ([CD]=0)

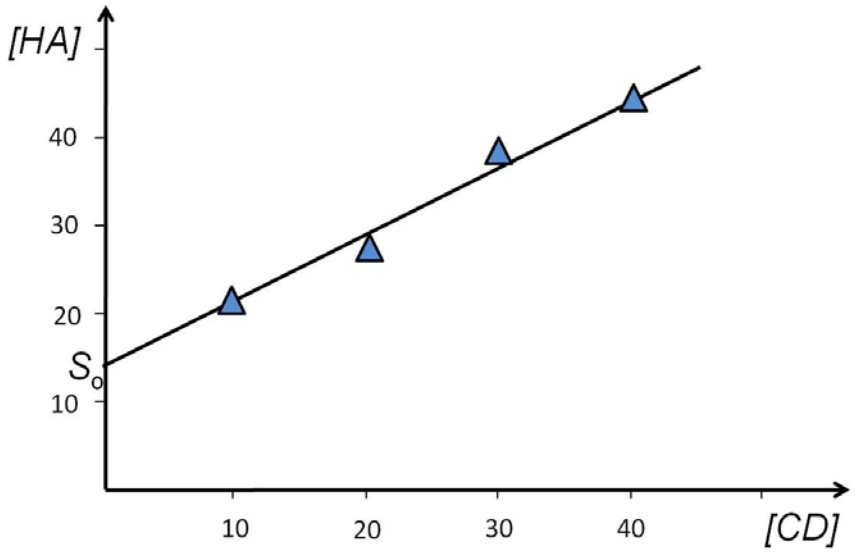


Fig. 11.8.
The increase of concentration of dissolved material in the function of cyclodextrin concentration

Based on experimental experiences, *Higuchi* és *Connors* ascertained following about the interpretation of the slop of the line:

$$[HA] = \frac{K_s S_o}{1 + K_s S_o}[CD] + S_o \qquad (11.)$$

K_s stability coefficient in the case of 1:1 proportion

One or more cyclodextrin can be connected with the molecule according to its configuration.

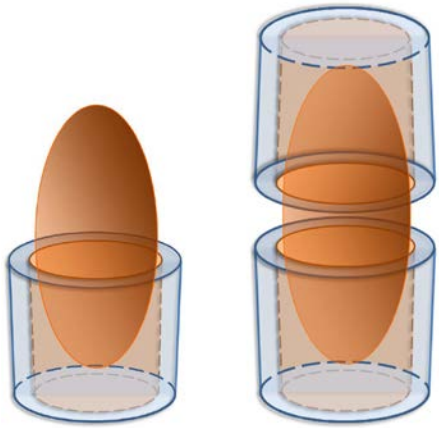


Fig. 11.9.
Cyclodextrin complexes with 1:1 and 1:2 proportion

The shape of cyclodextrin molecule develops according to its composition, functional groups and configuration.

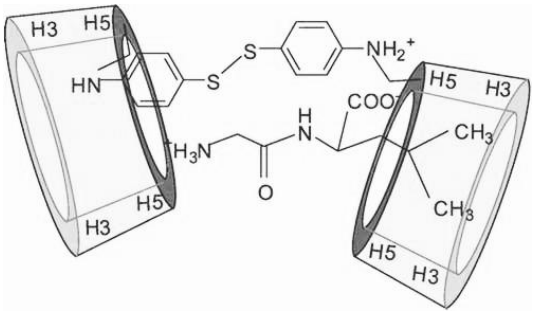


Fig. 11.10.
Aliphatic oligopeptide-cyclodextrin conjugate

Solubilization is also an important possibility to increase solubility, which is achieved by surface active compounds. According to the amphipathic structure of surface active substances, they can create micelles; the molecules of active substance with low solubility in water can be placed in this created micelle.

Based on the *Hardy-Harkins* theory, these types of structures are striven to energy minimum by orientation of surface active substances (by developing spontaneous aggregation with the increase of concentration and orientation).

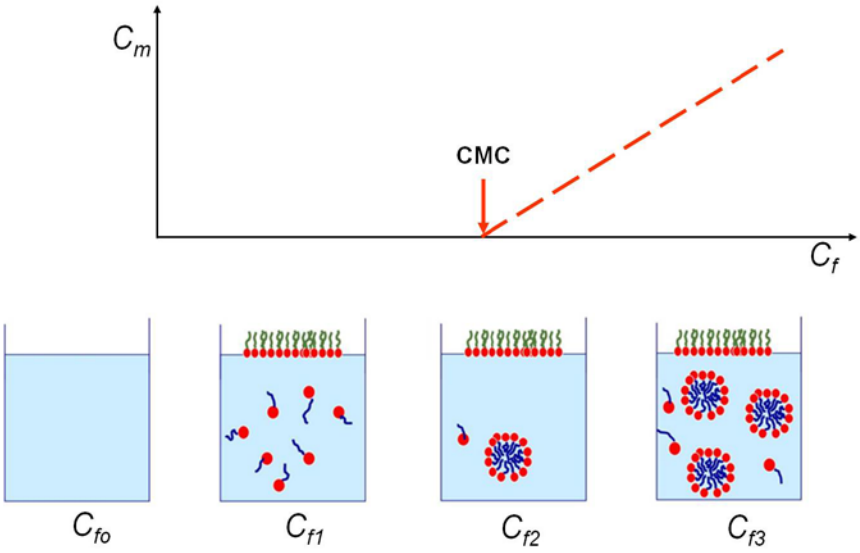


Fig. 11.11.
Micelle concentration in the function of concentration of surface active substance

Solubility of active pharmaceutical ingredients in the presence of micelles can be described by the following formula:

$$S = pS_w + K_{ms}(c_s - CMC) \tag{12.}$$

p other effects of surface active substance on solubility (e.g. change in pH, salting),
S_w solubility in water,
K_{ms} solubilization affinity of the certain micelle,
c_s concentration of surface active material,
CMC critical micelle concentration

Properties of amphiphilic surface active materials, tenzid are determined numerically by the proportion of hydrophilic and lipophilic groups of molecule. Thus surface active materials are characterized by HLB value (*Hydrophilic-Lipophilic Balance*). HLB value is essentially the proportion of hydrophilic and lipophilic molecule group, namely the polarity of the particular molecule. More is the HLB value, more polar is the molecule.

HLB scale developed by Griffin is from 0 to 20. Under 10 HLB value, the surfactants have lipophilic and over 10 have hydrophilic character. The emulsifying agents having 0-8 HLB value are applied to create W/O, and over 8 HLB value are used to create O/W emulsions. Emulsifying materials with more than 14 HLB are used as solubilization agents.

Table 11-IV.
Possibilities of usage of surface active substances

HLB	Usage
1-3,5	defoamers
3,5-8	W/O emulsifying agents
7-9	moistening agents
8-16	O/W emulsifying agents
13-16	detergents
15-40	solubilizing agent

Molecules with low HLB cannot dissolved in water, but with the increase of HLB will have more ability to dissolve in water. The HLB signs the water solubility of surface-active material.

Table 11-V.
Dispersion of surface active materials in water

HLB	dispersion rate
1-4	cannot be dispersed
3-6	slightly dispersible
6-10	milk-like dispersion
10-13	opalescent solution
15-40	clear solution

There are several methods for calculation of HLB values:

According to *Griffin*, proportion of mass of hydrophilic molecular parts and twenty times of total molecular mass has to be counted:

$$HLB = \frac{H_M}{M_t} \cdot 20 \qquad (13.)$$

H_M mass of hydrophilic molecular parts
M_t molecular mass

According to *Davies'* formula, HLB can be calculated from the numbers of hydrophilic and lipophilic group in molecule and their values based on the chemical structures which are specific for groups:

$$HLB = 7 + n_h H_h \cdot - n_l H_l \qquad (14.)$$

n_h number of hydrophilic groups in molecule
H_h value of hydrophilic groups in molecule
n_l number of lipophilic groups in molecule
H_l value of lipophilic groups in molecule

In the case of fatty acid esters of polyvalent alcohols, HLB value can be determined by the following correlation:

$$HLB = 20\left(1 - \frac{S}{A}\right) \tag{15.}$$

S saponification number
A acid number

HLB can be also calculated with ethoxy number and alcohol groups:

$$HLB = \frac{E + P}{5} \tag{16.}$$

E number of ethoxy groups
P number of alcohol groups in polyvalent alcohol

or with hydration heat:

$$HLB = 0{,}41Q + 7{,}5 \tag{17.}$$

Q hydration heat

The surface active materials can have natural or synthetic origin. According to their structure, ionic and non-ionic can be distinguished.

Natural surface active materials may be:

1) hydrocarbon derivatives (e.g. acacia, tragacanth, agar-agar, pectin)
2) protein types (such as gelatin, casein),
3) high molecular weight alcohols (e.g. stearyl alcohol, cetyl alcohol, cholesterol),
4) other (pl.: lecithin).
5) The ionic surface active materials can be cation or anion type.
6) Dispersion process of *anion type surface active materials* results in negative charged ions in water. Soaps (e.g. sodium palmitate, sodium stearate, sodium oleate), alkyl sulfates, alkyl phosphates are categorized to this group. Sodium lauryl sulfate has especially very great moistening and strong solubilizing and cleaning effect, with high HLB.

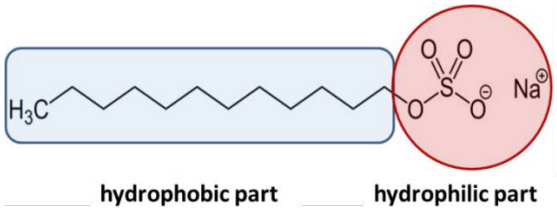


Fig. 11.12.
Structure of anion type surface active substances (Sodium lauryl sulfate)

Cation type surface active substances are quaternary ammonium bases, derived from the change of four hydrogen of ammonia and substituted with alkyl or aryl radicals. Their salts are the quaternary ammonium salts or invert soaps. These are rarely used as emulsifying agents, primarily as preservatives.

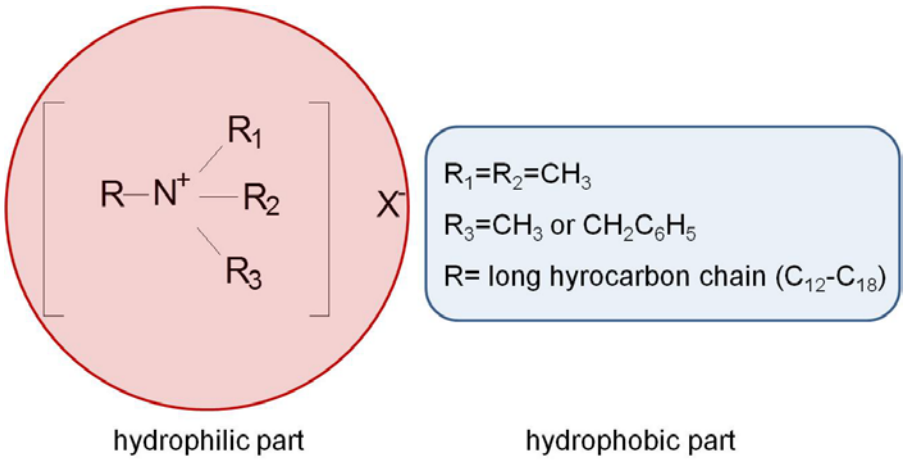


Fig. 11.13.
Structure of cation type surface active substance

Main type of cation type surface active substances:

1) cetavlon (cetrimide) type: alkyl trimethyl ammonium salts,
2) sapamin type: acyl amide alkyl trimethyl ammonium salts,
3) zephirol type: benzyl dimethyl alkyl ammonium salts,
4) sterogenol type: quaternary nitrogen compounds with long hydrocarbon chain that contain nitrogen aromatic ring, for example: benzalkonium chloride, cetyl bromide piridinum).

Amphoteric type emulsifying substances creates positive and negative ions after dissolution in water, such as compounds containing amino- and aromatic sulphonic acid and compounds with amino and carboxyl groups.

Non-ionic surface active substances do not create ions in water. Non-ionic surfactants includes: fatty acid esters of polyvalent alcohols (e.g. sorbitol, mannitol), polyoxyethylene derivatives, and compounds containing amide and ether bonds.

Main type of non-ionic surfactants:

1) polyethylene glycol ethers,
2) polyethylene glycol esters,
3) fatty acid esters,
4) sorbitan fatty acid esters and polyethylene glycol ethers

Polyethylene glycol-fatty alcohol ethers are so called Brij, generally esters of PEG and palmitic or stearic acid.

Table 11-VI.
Polyoxyethylene ether type non-ionic surface active substances and their HLB value

Polyoxyethylene ether type non-ionic surface active substances		
name	**name in pharmacopoeia**	**HLB**
Macrogol lauryl ether	Macrogoli aetherlaurilicum	10
Macrogol cetostearyl ether	Macrogoli aethercetostearylicus	16
Macrogol-18 stearyl ether	Macrogoli aetherstearylicus	18
Macrogol-15 oleyl ether	Macrogoli aetheroleicum	15

Table 11-VII.
Polyoxyethylene ester type non-ionic surface active substances and their HLB

Polyoxyethylene ester type non-ionic surface active substances		
name	**name in pharmacopoeia**	**HLB**
Macrogol stearate	Macrogoli stearas	16.0 (Macrogol-30-stearate)
Macrogol laurate	Macrogoli aethercetostearylicus	13.1 (Macrogol-8-laurate)
Macrogol oleate	Macrogoli oleas	11.1 (Macrogol-8-oleate)

The fatty acid esters of sorbitan are called Span.

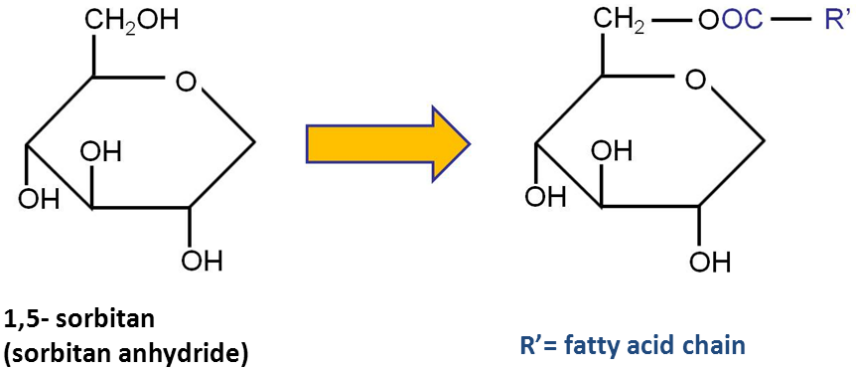


Fig. 11.14.
Sorbitan and its fatty acid ester

Table 11-VIII.
Fatty acid esters of sorbitan type non-ionic surface active substances and their HLB

Fatty acid esters of sorbitan type non-ionic surface active substances		
name	**name in pharmacopoeia**	**HLB**
Sorbitan laurate	Sorbitani lauras	8.6
Sorbitan palmitate	Sorbitani palmitas	6.7
Sorbitan stearate	Sorbitani stearas	4.7
Sorbitan sesquioleate	Sorbitani sesquioleas	3.7
Sorbitan oleate	Sorbitani oleas	4.3
Sorbitan trioleate	Sorbitani trioleas	1.8

The synonym name of fatty acid ester and polyoxyethene ether of sorbitan is Tween.

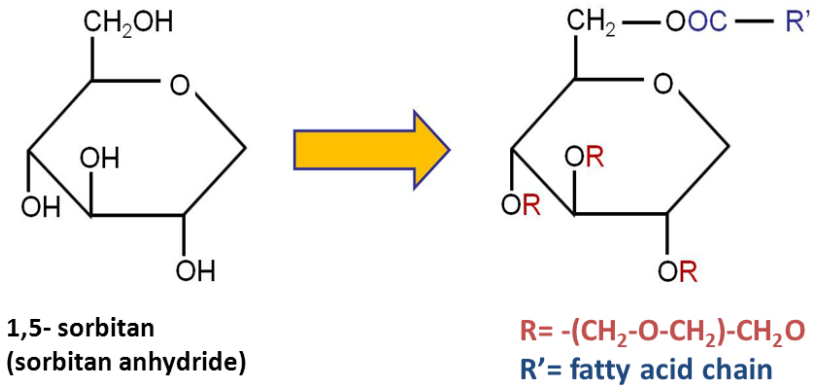


Fig. 11.15.
Sorbitan and fatty acid ester and polyoxyethene ether of sorbitan

Table 11-IX.
Fatty acid ester and polyoxyethene ether of sorbitan type non ionic surface active substances and their HLB

Fatty acid ester and polyoxyethene ether of sorbitan type non ionic surface active substances		
name	**name in pharmacopoeia**	**HLB**
PEG-sorbitan monolaurate	Polysorbatum 20	16.7
PEG-sorbitan monopalmitate	Polysorbatum 40	15.6
PEG-sorbitan monostearate	Polysorbatum 60	14.9
PEG-sorbitan monooleate	Polysorbatum 80	15.0

The application and usage of surface active substances is widespread in pharmaceutical technology. They are used to increase solubility besides solubilization, as antifoaming, moistening agent, to prepare emulsions, suspensions and to increase absorption. Some practical example for pharmaceutical technological application to assist the dissolution of material with low solubility in water:

- antibiotics (pl. penicillin-sulfosuccinate, tetracyclin in polysorbate solution, chloramphenicol Tween),
- sulphonamides,
- steroids (e.g. prednizolon in Triton WR solution),
- fat-soluble vitamins (e.g. vitamin A, D, E, K in polysorbate solution),
- barbiturates,
- salicylates.

Table 11-X.
Pharmaceutical technological task and the HLB value of chosen surfactant

Task	HLB
Mixing of oils	1-3
Preparation of W/O type emulsion	4-6
Powder moistening with oils	7-9
Preparation of self-emulsifying oils	7-10
Preparation of O/W type emulsion	8-16
Preparation of detergent solution	13-15
Solubilization, preparation of O/W micro-emulsion	13-18

11.3 Dissolution speed

Besides solubility, another important parameter of operation of dissolution is the dissolution speed. Dissolution speed is number of molecules dissolving into the solution within a particular time unit.

Several parameters influence the dissolution speed of solid material.

I Parameters depending on nature of material
1) crystal or non-crystal structure,
2) amorphism,
3) polymorphism,
4) hydration,
5) solvation,
6) particle size,
7) surface of particles

II External parameters
1) temperature,
2) pH,
3) viscosity,
4) presence of ions,
5) conditions of mixing (e.g. stirrer, speed, shape and size of container),
6) flow rate

Diffusion plays a significant role in the process of dissolution.

According to Fick 1st law diffusion connected to dissolution can be described with this formula:

$$\frac{dc}{dt} = \frac{DA(c_s - c_t)}{h} \qquad (18.)$$

c_s concentration in the diffusion layer surrounding the particles
c_t concentration in t moment
D diffusion coefficient
A diffusion surface
h thickness of diffusion layer

If $c_s >> c_t$, then high amount of clear solvent is in the solution, hence sink conditions/ criteria affecting factors are fulfilled. Its (c_s -c_t) importance is negligible in dissolution speed, therefore the former formula is simplified (thus effect of c_s prevails):

$$\frac{dc}{dt} = \frac{DAc_s}{h} \tag{19.}$$

Based on *Fick 1st law, Noyes and Whitney* have discovered the following equation according to dissolution from plane surface in order to characterize dissolution speed$\left(\frac{dc}{dt}\right)$:

$$\frac{dc}{dt} = k(c_s - c_t) \tag{20.}$$

k dissolution speed coefficient.

In order to determine the intrinsic dissolution speed, planar surface and constant surface reaching with solvent have to be ensured during the dissolution process. This can be achieved by a die, in which known amount of material is filled.

Two method are used, which are principally differed only in the conditions of mixing:

1) fixed disc and
2) rotating method

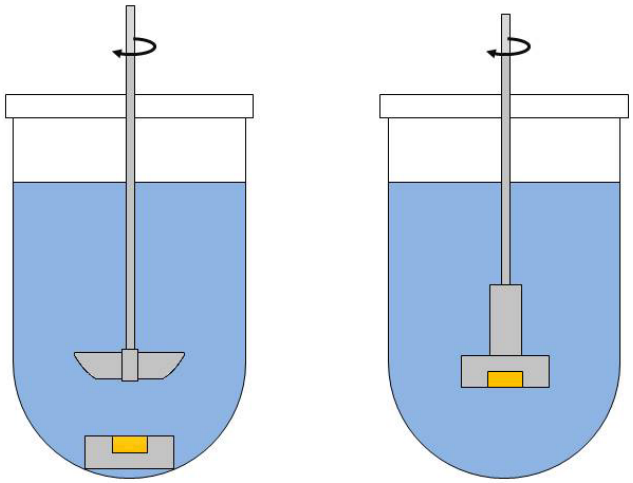


Fig. 11.16.
Examination of dissolution speed with rotating or fixed disc method

Dissolution speed can be increased by mixing, in order to inhibit the creation of process slowed by diffusion layers and to ensure high concentration difference. In this case turbulent flow is beneficial.

Dissolution surface may be raised by decreasing the particle size, thus dissolution speed will increase too.

Brunner és Tolloczko's Dissolution model regards the *Noyer-Whithney* equation and dissolution surface too:

$$\frac{dc}{dt} = k(c_s - c_t) = k_1 A(c_s - c_t) \tag{21.}$$

Nernst and Brunner had revealed the further components of previous dissolution speed constant:

$$\frac{dc}{dt} = k(c_s - c_t) = k_2 \frac{DA}{Vh}(c_s - c_t) \tag{22.}$$

D diffusion constant,
A surface of solid material,
V volume of medium,
h thickness of diffusion layer,
k_2 dissolution speed constant

Hixon and Crowell had approached the issue in another direction. They had described the cube root law:

$$m_o^{1/3} - m_t^{1/3} = k't \tag{23.}$$

k' dissolution model speed constant
m_o initial mass of dissolving particle,
m_t mass of dissolving particle in t moment.

With the interpretation of k' speed constant:

$$m_0^{1/3} - m_t^{1/3} = \frac{k'' N^{1/3} Dc_s}{h} t \tag{24.}$$

k'' speed constant
N particle number

Niebergall modified the cube root law:

$$\frac{dm}{dt} = k'' m^{2/3}(m_s - m_o + m_t) \tag{25.}$$

k'' dissolution speed constant,
m_S mass of solid material, which is needed to saturate a V volume solvent.

According to *Higuchi-Hiestand* correlation, in the case of particles with sphere shape the radius of dissolving particle is depending on the following factors:

$$r^2 = r_o^2 - \frac{2Dc_s}{\rho} t \tag{26.}$$

r_o radius of diffusion layer
D diffusion constant,

c_s concentration in the diffusion layer surrounding the particles
ρ density

Dispersions with solid, hydrophilic matrix are suitable to increase dissolution of material with low solubility, while the particles are dispersed in micro or nano size according to degree of reduction. This dispersion causes intensive and large surface for dissolution. If such matrix material is chosen, which has appropriate hydrophility and keep the API in dissolved status, and then *molecular dispersion (solid-liquid solution)* is prepared.

Surface therefore dissolution speed can significantly be increased by decrease of particle size by micronisation and nanonization.

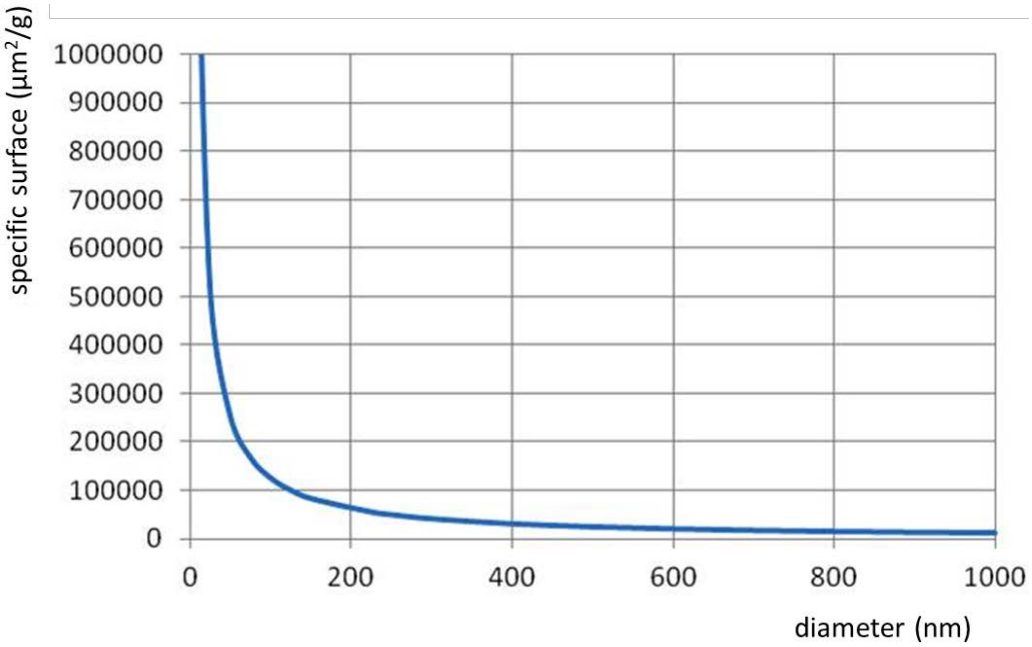


Fig. 11.17.
Surface of particle in the function of particle size

Nanocrystals can be prepared by the following methods:

1) controlled crystallization,
2) precipitation,
3) nano-milling (with ceramic milling balls, generally in aqueous medium, with high shear force),
4) high pressure homogenizer.

Nanonized crystals have much higher dissolution properties compared to micronized particles, thus dissolution speed, absorption, and biological availability of substances with low solubility can be increased.

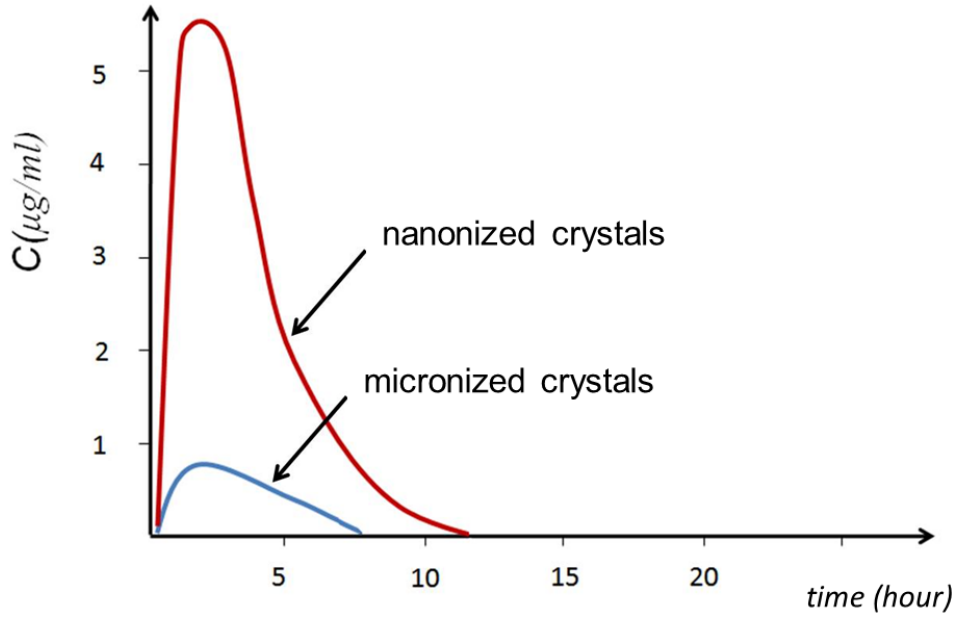


Fig. 11.18.
Blood level curve in the case of micronized $(\bar{d} \approx 2000\,nm)$ and nanonized $(\bar{d} \approx 120\,nm)$ crystals

The operation of dissolution is applied at drug delivery examination, in standard circumstances:

1) in prescribed flask (size, geometric properties),
2) with appropriate, suitable stirrer (plate, rotating basket dissolution apparatus),
3) with controlled speed,
4) in a medium on appropriate temperature, in certain volume, with an desired pH.

Movie 4. Dissolution

Colloidal solutions represent a transitional state among *true solutions* and *crude disperse* systems based on size of dispersed particle, internal structure, and physical properties. The majority of the physiological processes take place in colloidal systems.

Colloidal systems can be different based on the type of dispersed particles:

1) *colloidal dispersions* – particles separated by boundary surface can be found in some continuous phase such as gas, liquid, or solid microphase
2) *macromolecular colloids* – size of dissolved particles is already in the colloidal size interval (e.g. macromolecular polymers, or solutions of proteins)
3) *association colloids* – dissolved amphipathic molecules create micelles (e.g.: surfactants: create colloidal size associates, namely micelles)

If colloidal particles can move freely in liquid, then this kind of solution is termed to *sol*. If hydrate shells of particles can touch each other, and cannot move freely, then it is termed *gel*. Aqueous sols can be transformed to gel with deprivation of their hydrate shells (by adding salts). The gels have retention of shape and flexible structure in contrast with sols.

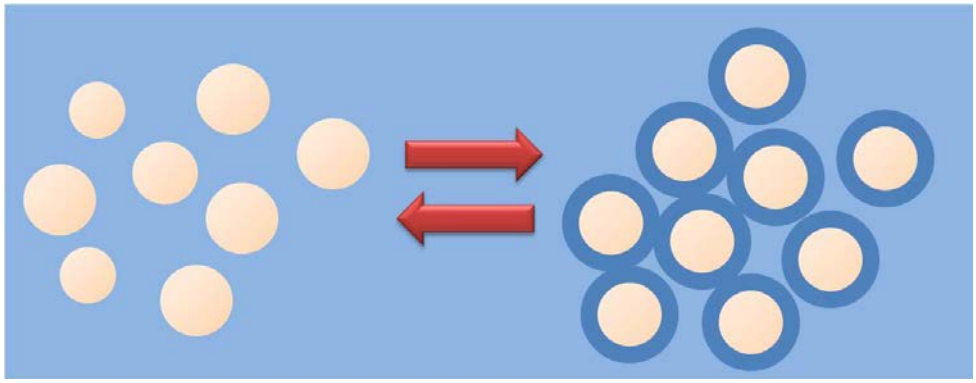


Fig. 11.19.
Sol-gel transformation

Liogels are heterogeneous systems containing liquid and solid components too, in which solid phase is greatly in hydrated status and liquid molecules are in fixed position around solid particles. Hence these structures have semisolid state of matter and are colloid structures having gelatinous texture.

Liogels undergo a slow transformation, namely dispersed particles get closer to each other, and thus the structure shrinks. One part of liquid forming the dispersion medium is crowded out from the structure. This process is called syneresis or ageing.

Xerogel is created, if liquid phase is separated from liogels. This transformation process can be reversible or irreversible by adding liquid. Xerogels have retention of shape and relatively flexible and solid. They are closer to the properties of solid bodies, than liogels.

Some gels represent thixotropic properties, namely liquefy after affected mechanical intervention, then in rest state and in isotherm condition and also in a certain time the original gelatinous texture is developed. This reconstruction is the process of regeneration.

Colloidal systems can be stabilized by the appropriate creation of boundary surface. The stabilizer and protective effect can inhibit the aggregation of colloidal particles and micelles. On one hand, this effect is due to the fact that long chains of macromolecules localized on boundary surface can hinder sterically the adhesion of particles. On the other hand, if overlap is even so developed, then dispersion medium flowing between particles distends them. This flow is due to high concentration of macromolecules and increased osmotic pressure.

Colloidal solution can be theoretically prepared by the following methods:

1) by milling from crude disperse systems (e.g. in colloid mill, or with ultrasound),
2) by precipitation from true solutions (e.g. change of temperature, concentration or solvent or with addition of precipitant)

In pharmaceutical practice, colloidal materials firstly are swollen in water (to be hydrated), then are also heated during slow mixing. At dissolution of colloidal particles, they obtain an aqueous hydrate shell and their conjunct solvate shell is created. At cooling the transparent, translucent solution transform into gel.

Sol-gel transition is also useful in the design and manufacture of depot preparations. For this purpose biocompatible and biodegradable polymers can be used, such as polyethyleneglycol-(lactic and glycolic acid copolymer)-polyethyleneglycol tribloc copolymers, which can be applied in im. injections. Vehicle of these preparations

congeals at body temperature and this gel acts like an in situ forming depot which regulates the liberation of the API by diffusion-biodegradation method.

Sol status is achieved by repeated heating because of increased kinetics energy of colloidal particles.

In the ’Mixing’ chapter, practice of dissolution is described in details in addition to its required tools and apparatuses.

Dissolution in a pharmacy is usually carried out in a beaker using a glass or magnetic mixer. Patendula is used in case of small amount of substances to increase the rate of dissolution using a pestle by grinding.

Under industrial conditions dissolution is carried out in glass or steel jars with motor-operated mixers.

Fig. 11.20.
Dissolution in glass bulb

Fig. 11.21.
Dissolution in stainless steel basins in the industry

Solutions are filled in clean bottles. Filling of huge volumes of liquid is done by automatic devices.

Fig. 11.22.
Filling of solutions with Erweka device

Preparation of solutions in industrial scale is carried out in batches or continuous operations. Dissolution, filling of the solution, closing the bottles takes place in controlled way, subsequently in the production line.

Fig. 11.23.
Dosing of solutions into bottles on a rotating table using a feeding pipe

Fig. 11.24.
Industrial device to fill solutions and close bottles

Pharmaceutical technological application of operation of dissolution:

1) intermediate products
    a) stock solutions,
    b) solutions for preparation of ointments,
    c) solutions for preparation of granulating fluid,
    d) syrups,
    e) mucilage for stabilization of suspensions.
2) end products
    a) per oral solutions,
    b) dermal solutions,
    c) painting solutions,
    d) injection solutions,
    e) infusion solutions,
    f) hemodialysis solutions,
    g) peritoneal solutions,
    h) dialysis solutions,
    i) solutions used for organ transplantation,
    j) perfusion solutions,
    k) enemas,
    l) eye wash solutions,
    m) decoctions,
    n) infusions,
    o) per oral drops,
    p) nose drops,
    q) ear drops,
    r) eye drops,
    s) inhalants,
    t) oral aerosols,
    u) nasal sprays,
    v) throat sprays,
    w) aerosols applied on intact skin and mucosa

Questions

1) What is dissolution?
2) What role does the process of dissolution play from a biopharmaceutical aspect?
3) How is the molar free energy of solutions calculated in case of saline compounds dissolving in water?
4) How would you define the notion of solubility from a pharmaceutical aspect?
5) What is the correlation that describes the temperature dependence of solubility?
6) What is the correlation that describes the solubility of weak acids and weak alkali?
7) What substances are hydrotropic?
8) What is the correlation that describes the stability constant of inclusion complexes?
9) What is the correlation that describes the solubility of the active ingredient in the presence of micelles?

10) To what purposes are surfactants for, according to their HLB value?
11) What are the main characteristics of nonionic surfactants?
12) What is heat of solution? What is its significance in dissolution processes?
13) What is solubility and what is the rate of solution? What notions are related to solubility?
14) Describe Jain and Yalkowsky's effective solubility equation!
15) What methods are available for increasing solubility? List actual methods!
16) What are the methods of determining rate of dissolution?
17) What substances are called xerogels?

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Recommended websites

http://www.pharmpress.com/files/docs/PCD2E_sample.pdf

http://www.chemeng.lth.se/exjobb/E272.pdf

http://www.bioscreening.net/2010/05/05/formulation-strategies-for-improving-drug-solubility-using-solid-dispersions/

12 Dispersing

Pharmaceutical technology frequently employs multicomponent systems. However, a significant fraction of substances are either altogether incapable of blending or dissolving in each other or only partially, therefore dispersions have an important role in pharmacy.

The term "*disperse system*" (*dispersion)* refers to a system in which one substance (the *dispersed phase,*) is distributed, in discrete units, throughout a second substance (the *continuous phase, matrix phase, dispersion medium).* Each phase can exist in solid, liquid, or gaseous state. The dispersed particles may be crystals, droplets, platelets, or bubbles among other things.

By employing disperse systems several challenges of pharmaceutical technology and biopharmacy can be solved, significantly enriching our pharmacy, improving, supplementing and developing possibilities in drug therapy.

With their particular structure, consistence and variable particle size disperse systems allow the development of extraordinary cosmetic products and drug delivery systems. Substances poorly solved by water can be administered perorally and rectaly using suspensions, emulsions. Sterilized emulsions and suspensions of appropriate particle size (d<1000nm) of water outer phase can be administered intravenously injections, only emulsions by infusions.

Suspensions achieve lower *bioavailability* than solutions, but higher than capsules or tablets:

solution > emulsion > suspension > capsule > tablet > coated tablet

Absorption can be controlled through the particle size of the suspended or emulsified particles, surface active substances and by coating particles individually.

There are several uses of disperse systems in drug therapy by:orális (pl.: ecsetelés nyálkahártyán),

1) *oral* (e.g suspensions for the mucous membrane),
2) *peroral* (e.g. O/W type emulsions for taste masking, antacid suspension),
3) *intravenous* (parenteral nutrition, nano products),
4) *dermal and transdermal* (e.g. medicinal ointments, creams, cosmetics),
5) *vaginal* (e.g. feminine washes),
6) *rectal* (e.g. enemas) routes.

The majority of medicines belong to either of various types of disperse systems in the field of pharmaceutical technology.

In the course of drug preparation or production, when two or more substances are dispersed their initial physical, rheological or chemical qualities may change.

In drug preparation mixing and dispersing are common operations. If the diameter (*d*) of the particles of the dispersed substance is smaller than 1 nm, it is called *dissolution* or *blending*; if it is between 1-500 nm, *colloidal dissolution*. If the particle size is larger than this, the process is specifically *dispersing*, where components are not dissolving with each other, but form so-called *coarse disperse systems* (d > 500 nm).

The disperse systems can characterized by particle size (the degree of dispersity) and particle size distribution. In practice, the most common systems heterodiszperse prepared.

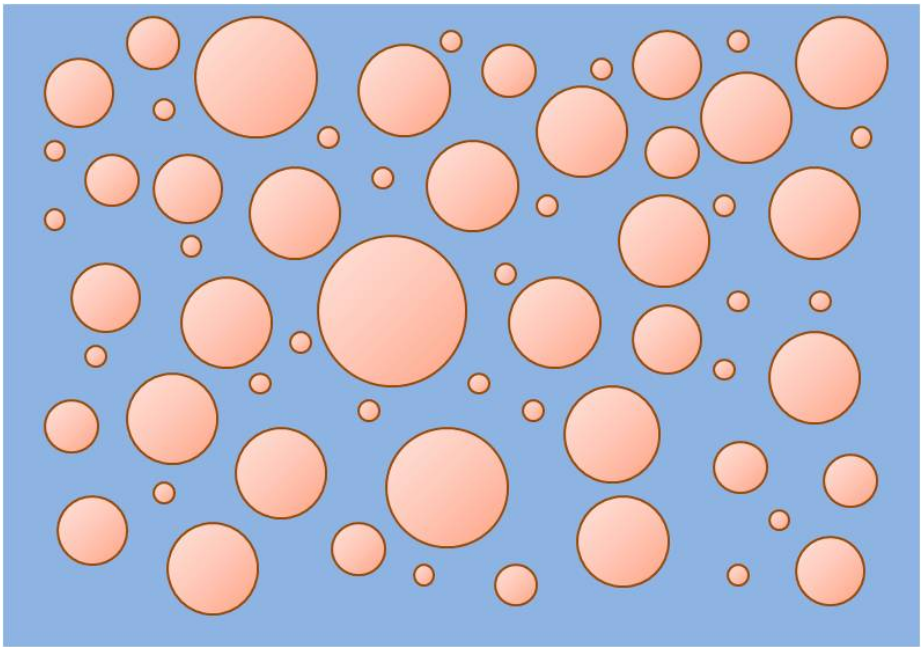


Fig. 12.1.
A heterodisperse system

Please note that this classification by particle size is relative, as there are numerous transitional forms between the above groups. Achieving uniform particle size requires very complicated and costly technology; therefore perfect homodispersity is not a priority in the practice of pharmaceutical technology.

However, particle distribution still remains heterodisperse. With solution depending on particle size, specifying a "between" range for particle size for sorting granulates and micropellets by particle size will result in a better approximation of homodisperse distribution.

Homodispersity, uniformity of particle size is a relative notion in practice, as it depends on the level of heterodispersity allowed or accepted in a granule system. Therefore, a part of pharmaceutical preparations is recognized as *multiparticulate systems*, confining particle size and size distribution within limits than can and must be observed.

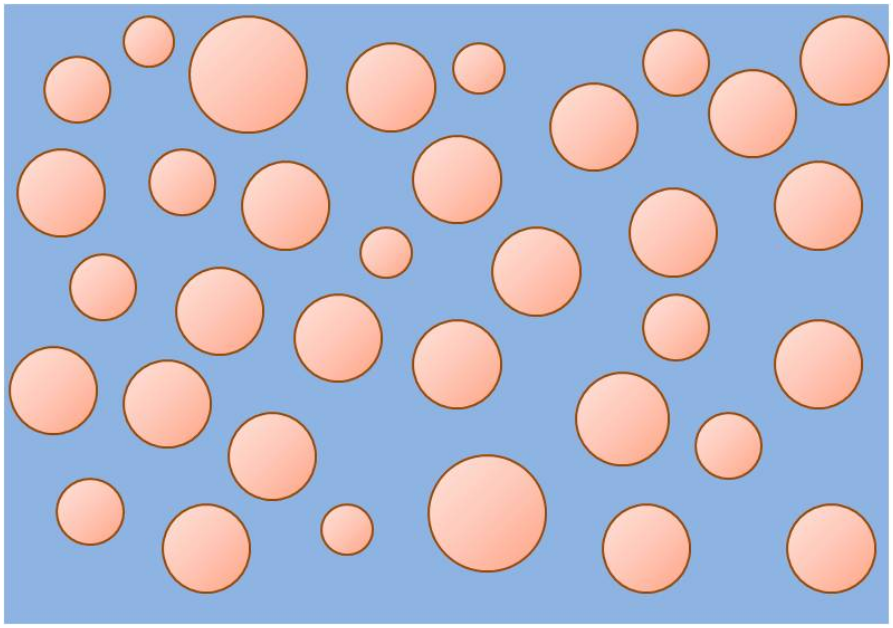


Fig. 12.2.
Heterodisperse system with a relatively homogenous distribution

Beyond the uniformity of particle size inside the disperse system, these systems themselves can be homogeneous or heterogeneous.

Single phase systems that fill the space they occupy completely and evenly, on a molecular level, without phase interfaces are considered *homogeneous systems*. Therefore they are physically homogeneous, do not contain discontinuities, so every part of the substance surrounded by the substance have identical physical parameters.

Multiphase systems that fail to fill the space they occupy evenly in the molecular range and there are interfaces between their components are *heterogeneous systems*. Therefore they are physically inhomogeneous, contain *discontinuities*, have different physical parameters. (Parts or particles in a system whose physical qualities are different from the qualities of the surrounding substances are called *discontinuities.*)

Homogeneous systems are single phase, heterogeneous are two- or multiphase. (Components of a system separated by interfaces are called *phases*.)

Pharmaceutical substances are mostly single-, sometimes multiphase, while *pharmaceutical preparations* are multicomponent systems in the majority of cases, as they are composed of active ingredients and excipients.

Coarse disperse systems (e.g. *suspensions*, *emulsions*) are multicomponent ($n_k \geq 2$), multiphase ($n_f \geq 1$) and considered heterogeneous, with at least two phases:

1) inner phase *(dispersed phase)*,
2) matrix-like outer phase (*continuous phase, dispersion medium, vehicle*).

According to the physical state of the dispersed phase and the dispersion medium, disperse systems can be gas, solid and liquid state.

Table 12-I.
Classification of disperse systems

Dispersion medium	Disperse phase	Number of phases	Number of components	Name of the disperse system
liquid	liquid	1	>1	mixture
liquid	solid	1	>1	solution
gaseous	liquid	>1	>1	aerosol (mist)
gaseous	solid	>1	>1	aerosol (fume)
liquid	gaseous	>1	>1	foam
solid	gaseous	>1	>1	foam
liquid	liquid	>1	>1	emulsion
liquid	solid	>1	>1	suspension, sol
solid	liquid	>1	>1	gel
solid	szilárd	>1	>1	solid mixture

Considering the stability of disperse systems it is important to highlight the electrical double layer forming around solid particles and *electrokinetic* or *zeta potential*. The reasons for its formation are the following:

1) solid particles are charged from the outset,
2) solid particles adsorb ions,
3) surface dissociation occurs,
4) polar molecules (e.g. tensides) settle directionally on the surface of the solid body.

Of the layers of the double layer one is fixed (*Stern* layer, "attracted" layer) to the surface of the solid phase, while the other is in the liquid phase, shifting with it. The double layer is diffuse in structure, with the potential *(ψ)* decreasing exponentially with the distance towards the bulk of the liquid.

$$\Psi = \Psi_o \cdot e^{(-\kappa x)} \qquad (1.)$$

x distance toward the bulk of the solution
κ the converse of the distance in which the potential ψ_0 decreases to the value of ψ/e.

When the dispersed phase or the medium flows, a thin layer of liquid remains attached to the solid surface. The potential appearing on the plane between the attached layer and the shifting liquid is the zeta potential. The electrical double layer also explains the repulsive effect occurring between the particles. Every factor that decreases the thickness of the double layer also decreases the repulsive forces acting between particles.

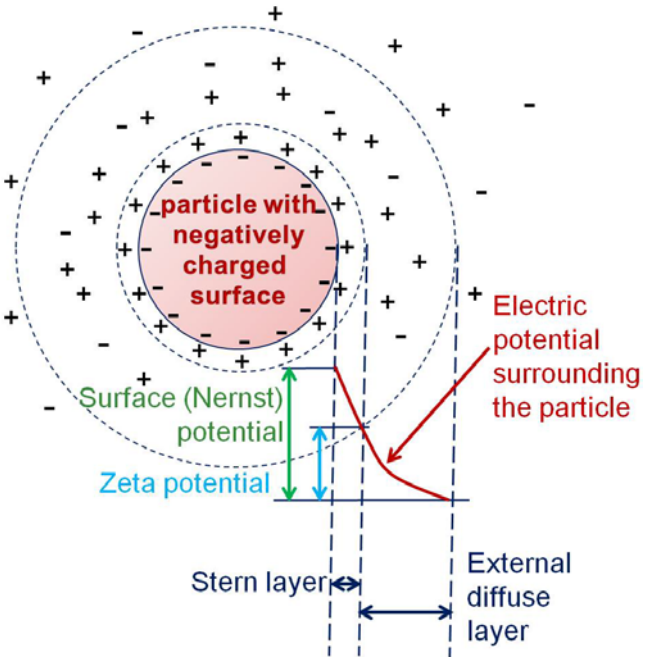


Fig. 12.3.
The electrical double layer and Zeta potential forming around a particle

The theory developed by *Derjagin, Landau, Verwey* and *Overbeek* (*DLVO-theory*) interprets the aggregate stability of disperse systems as the resultant of attractive and repulsive forces between particles, saying that attractive forces increase with distance according to the power function while repulsive force decreases exponentially.

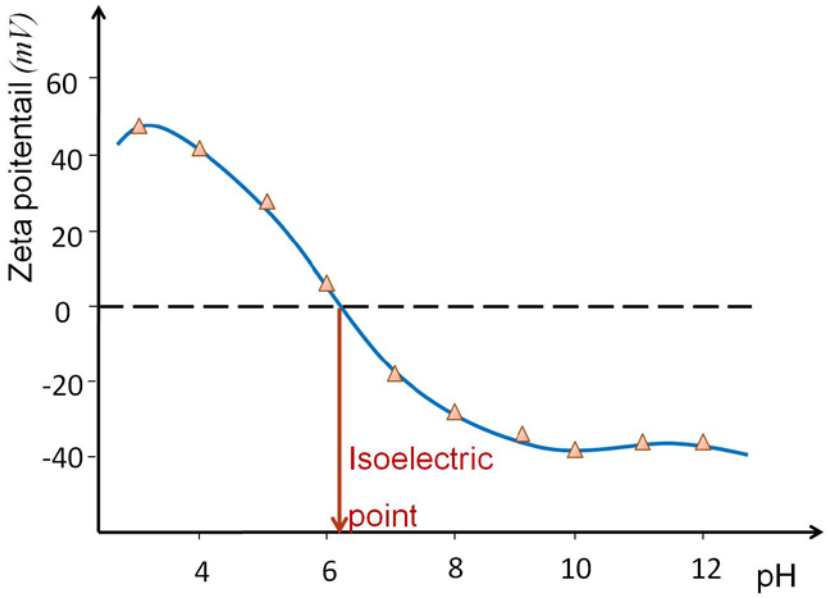


Fig. 12.4.
Zeta potential changes according to the pH of the medium

Resultant potential (V) is the algebraic sum of the attractive (V_v) and repulsive (V_t) potentials:

$$V = V_v + V_t \tag{2.}$$

There is a maximum at the resultant of the two forces, which indicates the thickness of the diffuse double layer that covers the particle. The points of primary and secondary minimum on the curve indicate the locations of irreversible and reversible coagulation, respectively.

The stability of the disperse system is appropriate when the thermal motion of particles approaching each other is insufficient for passing this potential barrier. This way system stability can be improved by increasing the thickness of the electrical double layer.

Oswald and *Buzágh* extended the theory to non-aqueous systems, as in such cases there is no electric double layer. According to their *theory of continuity*, the more continuously the solid dispersed phase fits the dispersing medium, the higher the stability of the disperse system.

In the following the operation of dispersing is illustrated with the pharmaceutical technology of *suspensions* and *emulsions*.

12.1 Suspensions

The particles of the dispersed phase in a suspension are undissolved, non-solvated. Their interaction with the dissolving medium is fundamentally determining for the properties and stability of pharmaceutical preparations. The three significant components of the interaction between the dispersed phase and the dispersing medium are wetting of the solid phase, electrokinetic potential and the adsorption of polymer excipients to the surface of particles.

Considering suspensions, an important parameter that characterizes phase boundaries is *wetting*. The degree of wetting is determined by the balance of adhesive and cohesive forces. Adhesive forces make liquids spread out, while cohesive forces work toward keeping liquids drop-shaped. In the course of wetting intramolecular interactions develop between the liquid and the solid surface.

The process of wetting is characterized by the *contact angle (θ)* that forms on the solid surface.

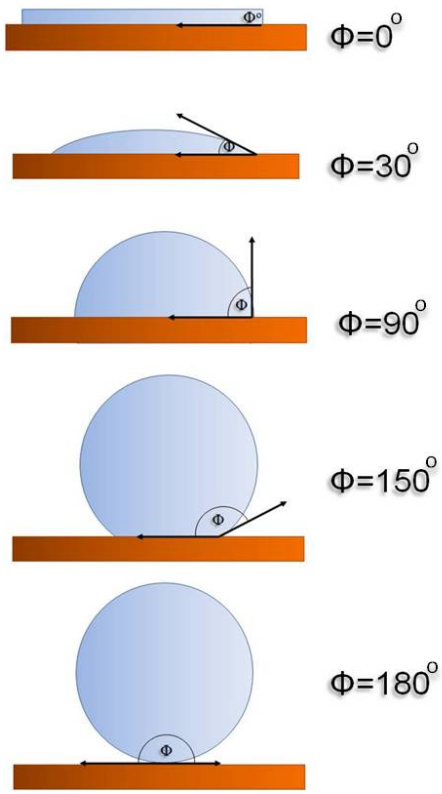


Fig. 12.5.
Contact angles

The equation established by the English scientist *Thomas Young* in 1804 is the following:

$$\gamma_{SG} = \gamma_{SL} + \gamma_{LG} \cdot \cos\theta \qquad (3.)$$

γ_{SG} interfacial surface tension between solid/gas,
γ_{SF} solid/liquid,
γ_{FG} liquid/gas.

Contact angle and the degree of wetting are inversely proportional. The smaller the contact angle, the more the given liquid wets the solid surface.

Table 12-II.
Parameters associated with the contact angle

Contact angle	Wetting	Strength of interactions	
		solid/liquid	liquid/liquid
0°	perfect	strong	weak
30°	goog	strong	weak
90°	medium	strong or weak	strong or weak
150°	poor	weak	strong
180°	non-wetting	weak	strong

In case of perfect wetting, when $\theta=0°$, The liquid forms a homogeneous film on the solid surface. If the liquid is polar and the surface is wetting, the solid surface is hydrophilic; if it wets poorly or does not wet, the surface is hydrophobic. A surface is *superhydrophobic* if $\theta>150°$, so practically there is no contact between the surface and water. If the liquid is other than water and the contact angle is small, the solid surface is lyophilic; if the contact angle is wide, it is lyophobic.

Table 12-III.
Contact angle values

Substance	Contact angle	Substance	Contact angle
acetyl-salicylic acid	74	cloramphenicol-palmitate (Form A)	122
aluminium stearate	120	cloramphenicol-palmitate (Form B)	108
aminophylline	47	lactose	30
ampicillin (anhydrous)	35	magnesium stearate	121
ampicillin (trihydrate)	21	nitrofurantoin	69
diazepam	83	prednisolon	43
digoxin	49	prednison	63
phenylbutazone	109	salicylic acid	103
indomethacin	90	succinyl-sulfathiazole	64
isoniazid	49	sulfadiazine	71
caffeine	43	sulfamethazine	48
calcium-carbonate	58	sulfathiazole	53
calcium-stearate	115	theophylline	48
chloramphenicol	59	tolbutamide	72

In addition to the *Young*-equation, another expression is useful for describing the thermodynamics of wetting. This expression is called *spreading coefficient (S)*.

$$S = \gamma_{SG} - \gamma_{LG} - \gamma_{SL} \qquad (4.)$$

Spreading coefficient can also be defined as the difference between adhesive (W_a) and cohesive (W_c) forces.

$$S = W_{a(SL)} - W_{c(LL)} \qquad (5.)$$

The spreading coefficient is positive, if the process of wetting occurs spontaneously, namely, net free energy decreases. If the value of *S* is negative, cohesive forces are dominant; the liquid remains lenticular, resulting in partial wetting.

When suspensions are prepared, the interaction occurring between solid particles and macromolecules has to be taken into consideration, as macromolecular substances applied to increase viscosity are important excipients of suspensions.

Macromolecules have two types of effects on suspended solid particles:

1) aggregating (*flocculating*) effect,
2) aggregation-inhibiting effect.

The basis of these opposite effects is the surface adsorption of macromolecules. Adsorption is determined by the structure of the solid surface and the chemical structure, shape, molecular weight and concentration of macromolecules.

Low concentration polymer particles cannot cover the entire surface, possibly causing aggregation. In case of higher concentration full covering may develop, providing protection from particle aggregation. Protective and flocculating effects largely depend on the shape of macromolecules. If the molecule clings to the surface of the particle, only an aggregation-inhibiting effect is possible. If, however, it has connectable segments protruding into the liquid, then bridge bonds or the adsorption of protruding chains to adjacent particles causes flocculation. Therefore, flocculation occurs if macromolecules adsorb to particle surfaces with some surface areas left uncovered and the polymer partially clinging to the surface has segments protruding into the dispersing medium.

The *stability of degree of dispersion (aggregative stability)* means the preservation of the discrete units of dispersed particles. On account of this any such interactions are to be avoided, which may cause the aggregation of particles.

When pharmaceutical suspensions are used, at least one minute long homogeneous state should be ensured after by approximately 8-10 times shaking (redispersion). On account of this, the sedimentation of particles has to happen in a controlled way, secured by distribution stability. *Stability of distribution* is actually the ability of particles to resist sedimentation, whose primary determining factors, aside from external mechanical action, are gravity and the thermal motion of particles.

The expression that applies to spherical particles, Stokes's Law, which declares that sedimentation rate depends on the diameter of particles, viscosity of the medium, gravitational acceleration and the difference in the density of particles and the medium, yields a good approximation for thin suspensions:

$$v = \frac{2\Delta\rho g r^2}{9\eta} \tag{6.}$$

$\Delta\rho$ the difference in the density of particles and the dispersion medium
g gravitational acceleration
r particle radius
η viscosity of dispersion medium

The *Kozeny-Carman* equation applies to thicker suspensions:

$$V = \frac{P}{L}\frac{1}{\kappa\eta S_s^2}\frac{\varepsilon}{(1-\varepsilon^2)} \tag{7.}$$

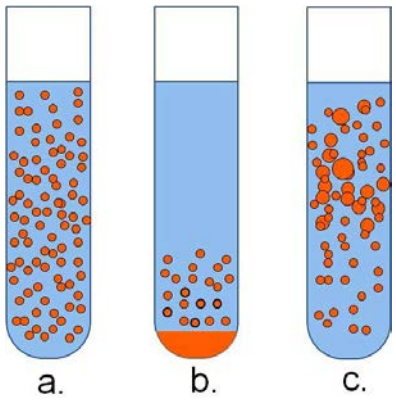
V flux rate of fluid streaming through the bed
P pressure
L total height of the bed
κ Kozeny-constant
η viscosity of the liquid
S_s specific surface
ε porosity of the solid particle bed

Medicinal suspensions have two types of sedimentation:

1) free settling,
2) hindered settling.

In *free settling* the particles in a thin suspension can sediment freely, without hindering each other, while the volume of sediment increases and settling particles obscure the system above the sediment. Sediments formed in this way may stick to the bottom of the medicine bottle. Cementing, which prevents appropriate resuspension, is also present. This phenomenon occurs when viscosity-increasing polymers are applied in excess.

In *hindered settling* the particles or the protective colloids and polymers covering the particles form a flocculated system, where, due to the interaction between particles, sedimentation is hindered, slowed.



a. newly made suspension
b. sedimentation of particles
c. aggregation of particles

Fig. 12.6.
Possible transformations for suspensions

A segédanyagokat a diszperziós közeg tartalmazza, melyek lehetnek:

1) oral (e.g. painting)
2) peroral (e.g. adsorbent, antacid, antibacterial)
3) dry poweders for suspension preparation

4) dermal (e.g. siccative ointment, antibiotic, antifungal)
5) auricular (e.g. antibiotic)
6) vaginal (e.g. flush, medicinal therapy)
7) nasal (e.g. mucous membrane treatments)
8) parenteral (crystalline injection)
9) ocular (rare due to irritation)
10) rectal (e.g. enema).

To determine the therapeutic applicability of medicinal suspensions the following aspects have to be taken into consideration:

- to ensure accuracy of dosage, homogeneous distribution of the active ingredient shall be available
- settled sediment shall be easily resuspendable,
- the size distribution of particles shall not have significant variation,
- viscosity shall hinder sedimentation, yet allow decanting from the bottle,
- shall have adequate microbial stability.

There are two methods for making medicinal suspensions:

1) precipitation/condensation from homogeneous system,
2) dispersion from heterogeneous system.

In the precipitation method a fine precipitation forms when the solutions of the two substances are blended, which is the solid dispersed phase of the suspension. This method can be implemented by changing the solvent or adjusting the acidity.

In the dispersion method the solid disperse phase of appropriate particle size is suspended in the dispersion medium in the presence of a wetting agent. The required particle size can be attained by using suitable grinding equipment: mortar on the officinal scale, various grinding-milling equipment (*e.g. ball grinder, cross-beater mill, colloid mill, jet mill*) on medium scale.

During the preparation of pharmaceutical suspensions number of excipients Can be used, whics contributes to the stability of the preparation and the patient compliance.

The following types of excipients are contained in the dispersion medium:

1) wetting agents
2) viscosity-increasing agents (mucilages, cellulose-ethers, e.g. methyl-cellulose and HPMC, alginate, carrageenan, polyacrilic acid derivatives, etc.)
3) protective colloids (mucilages, alginates, cellulose-ethers)
4) zeta-potential regulators (electrolytes, ionic tensides, dissociating ionic polymers)
5) buffering,
6) osmotic pressure regulators,
7) flavour enhancers,
8) coloring agents and
9) microbial preservatives.

The process of mechanical suspensions production consists of three basic operations:

1) grinding,
2) dispersing,
3) homogenizing.

The above operations may happen both consecutively and simultaneously during production.

Grinding can be performed using a colloid mill, ball brinder ot other mechanical grinding equipment capable of producing the particle size required for suspensions.

Dispersing and homogenization can be accomplished by mixing, using equipment for mixing liquids, such as plate-, propeller- and turbine stirrers as well as high-shear mixers-

12.2 Emulsions

Emulsions are liquid state heterogeneous disperse systems of L/L type liosols. These systems are multicomponent, consisting of a dispersing medium and the dispersed particles. If the diameter of dispersed liquid particles is in the colloid range, the liosol is called a colloid emulsion. Emulsions for external use are often referred to as *liniments* (e.g. Linimentum scabicidum), but it is important to note that not all liniments are emulsion systems.

The advantages of emulsion type pharmaceutical preparations are:

1) increase in bioavailability
2) make drug release controllable
3) protection of active ingredient from oxidizing and hydrolysis
4) make parenteral nutrition via infusion possible

formation does not change the number of components, phases, only the interface and the degree of dispersion.

The work (L) required for making emulsions is for scattering the liquid to be dispersed into small diameter spheres. This process implies a considerable increase of surface, with the invested work being exerted against surface tension (by shaking or agitation):

$$L = \gamma dF \tag{8.}$$

L energy required for increasing surface
γ surface tension
F surface

Emulsions usually include an aqueous phase, an oil phase and excipients. Either the oil or the water component is permanently dispersed in the other, therefore emulsions can be classified as simple and compound emulsions.

Simple emulsions:

1) *oil in water* emulsion (O/W), in which oil is the dispersed (internal) phase, permanently suspended in the continuous phase (external),
2) *water in oil* emulsions (W/O), which is the opposite of the previous.

Compound emulsions:

1) W/O/W emulsion and
2) O/W/O.

Identical phase emulsions:

1) O/O emulsions and
2) W/W emulsions, where components of the same phase type are dispersed in each other.

In the formulation of emulsions the two immiscible liquids are dispersed with each other by the application of mechanical energy, during which the dispersed phase assumes a spherical shape. In order to prevent droplets from coalescing and phases from separating the application of appropriate excipients, so-called *emulsifiers,* is required. Emulsifiers are dispersing excipients that facilitate the dispersion of one of two immiscible components in the other, prevent the coalescence of droplets, ease emulsification, decrease interfacial tension on the surface of droplets, make the borderline between the phases continuous and increase the stability of the preparation through all these properties.

The emulsion capacity of emulsifiers is described with the emulsion number:

$$E_{no} = \frac{V_E - V_0}{V_E} \cdot 100 \qquad (9.)$$

E_{no} emulsion number
V_E volume of emulsified oil
V_0 volume of separated oil

Usually surfactants are used as emulsifiers, which, due to their amphipathic character, are predisposed to bind with both phases.

According to *Bancroft*, in the course of emulsification external phases dissolve emulsifiers better. Emulsifiers can be classified according to their origin, chemical structure and properties.

There are three basic types of emulsifiers:

1) small molecule surfactants (tensides),
2) macronolecules,
3) solid, fine-grained dual wetting substances.

The resultant HLB of jointly employed emulsifier pairs is:

$$HLB = \frac{A\ HLB_\alpha + B\ HLB_\beta}{100} \qquad (10.)$$

HLB_α, HLB_β HLB values of α and β emulsifiers
A proportion of α emulsifier
B proportion of β emulsifier

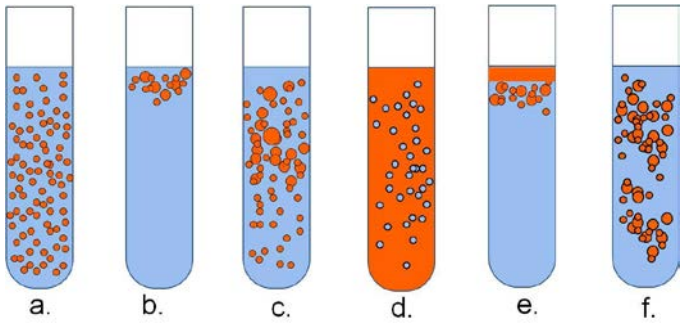
In a classical sense macromolecules belong to the group of so-called quasi-emulsifiers or pseudoemulsifiers, not emulsifiers, as they lack tensidic properties. Their stabilizing effect is based on the "protective bubble" formed around the droplets of the internal phase and the increase in the viscosity they induce in the dispersing medium, therefore they are not used as standalone emulsifiers. This group includes organic polymer carbohydrates like alginates, pectins, methyl-cellulose, casein, albumin as well as synthetic polyvinyl-alcohol and polyethylene-glycol.

Solid, fine-grained dual wetting substances, such as bentonite or fine dispersions of silicone-dioxide are likewise capable of forming a protective envelope on the surface of droplets, creating a stabilizing effect, but emulsifiers of this type are not on par with

the surface active mechanism of tensides either. Emulsions formed with finely distributed solid substances of smaller particle size than the emulsified droplets are also called *Pickering-emulsions*.

Emulsions have various types of transformation, such as *skimmering, creaming, aggregation (flocculation, coagulation, coalescence), phase inversion, phase separation and Ostwald ripening*.

Aggregation implies decreased degree of dispersion and increased particle size, which also means a decrease in surface free energy.



a. freshly made emulsion; **b.** creaming; **c.** coagulation, flocculation; **d.** phase inversion; **e.** coalescence, phase separation; **f.** Ostwald ripening

Fig. 12.7.
Transformations in emulsions

f. Ostwald ripening

The stability of the degree of dispersion and distribution apply to the stability of emulsions, just like with suspensions. A decrease in the degree of dispersion causes coagulation, which has two subtypes:

1) discontinuous coagulation
2) continuous coagulation.

There is externally induced impact coagulation in discontinuous coagulation, while in the case of continuous coagulation the phenomenon is attributable to the differences in solubility.

The stability of distribution describes the homogeneous distribution of emulsified droplets; the primary influence on this is sedimentation (*Stokes' law).*

The process of emulsification:

1) breaking up the internal phase into droplets by the application of mechanical energy
2) decreasing the amount of required energy by decreasing the interfacial tension, adding surface active agents
3) stabilization of droplets (altered surface charge, polymer protection)

There are various method of preparation. In the *English method* the emulsifier is dissolved in the external phase and the phase to be dispersed is emulsified in this solution. In the other method, called *Continental*, the phase to be dispersed is first blended with the emulsifier, and then a small amount of the external phase is added. After the preparation becomes homogenized, the rest of the external phase is added in small increments.

Various types of equipment are available for the preparation of emulsions, which can provide the mechanical work required for dispersing. Devices capable of exerting mechanical and sonic energy are most commonly used. Sonic energy usually means the application of ultrasound.

High-shear mixers are used for making large amounts of emulsion.

There are three basic types of devices transmitting mechanical energy to the system: mixer, homogenizer and colloid mill. Mixers are outlined in the chapter about solutions. Homogenizers force the blend to be emulsified through a small aperture, during which the internal phase disperses to small droplets in the external phase. The colloid mill forces the system to be emulsified through a narrow aperture between a stator and a rotor piece, exposing it to a high-shear effect.

On the officinal scale homogenization can be performed with pestle, milling with mortar.

On the laboratory scale the high-shear force between the *stator* piece and the *rotor* (5000-30000 rpm) makes the *Ultra turrax* device suited for performing quick and efficient dissolving and dispersing operations. The substance passes through the operating space repeatedly, enhancing the efficacy of blending and dispersing. Duration has significant impact on the eventual degree of dispersion.

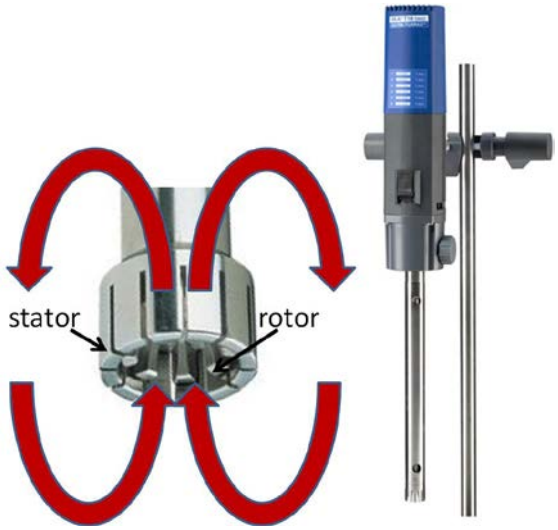
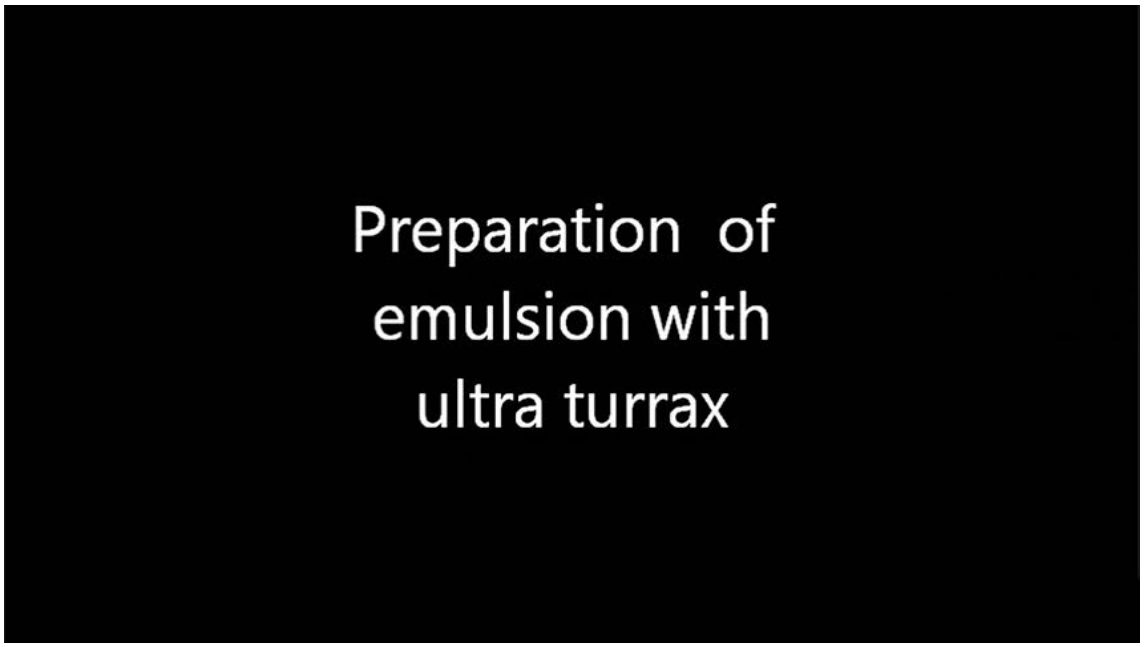


Fig. 12.8.
Ultra turrax



Movie 5. Preparation of emulsion with ultra turrax

Colloid size (in practice max. 500 nm diameter) particles are made with *colloid mills* on laboratory and medium scale. The operating space of the device contains a conically engaged rotor and stator.

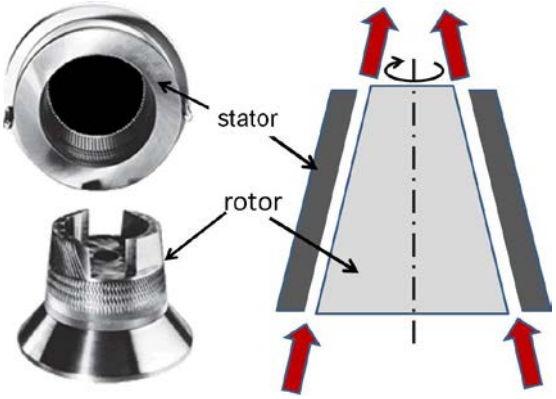
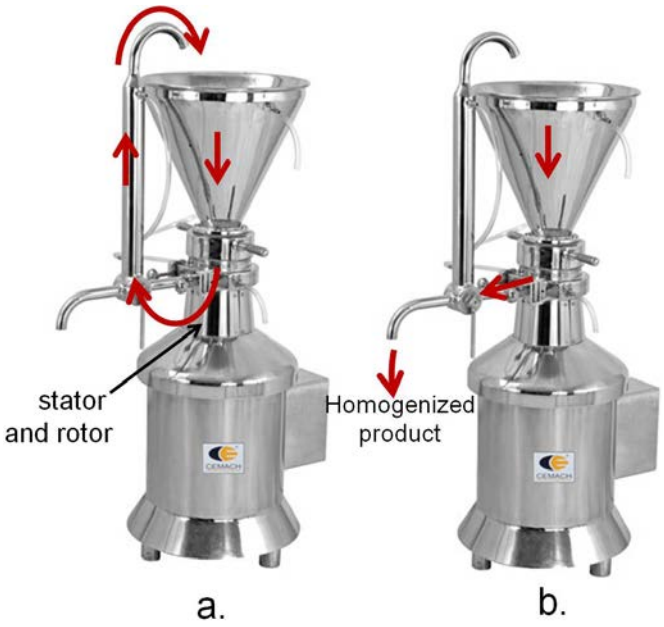


Fig. 12.9.
Main parts of colloid mill

In production mode the device recirculates the liquid to the operation space. More recycling, more effective blending and shearing and consequently higher degrees of dispersion can be achieved by decreasing the aperture between the stator and rotor pieces and by increasing the duration of recirculation.



a. production mode **b.** draining mode

Fig. 12.10.
Colloid mill

High pressure homogenizers are used both on the laboratory and industrial scale. These devices stream the disperse system through a narrow gap or aperture. There is very high shearing in the operation space, disintegrating droplets and particles to micron or sub-micron size. This requires high pressure energy. Besides material properties (e.g. density, viscosity) resulting particle size and size distribution of granules depend on pressure, feeding rate and the size and shape of the homogenizer valve.

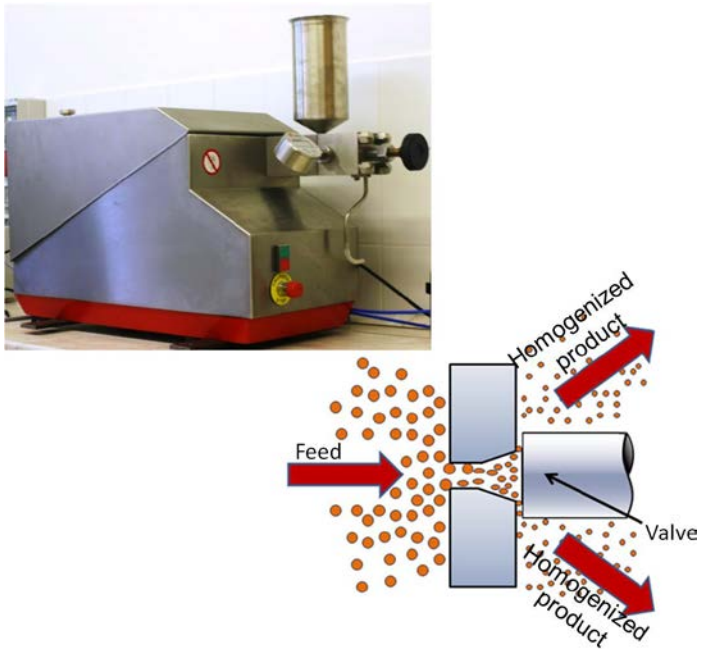


Fig. 12.11.
High-pressure homogenizer

The parameters of the technology developed for laboratory scale has to be adjusted to the subsequent step in scaling up by determining the necessary and sufficient conditions for reproducing the output parameters (e.g. homogeneity) of the product.

Fig. 12.12.
Industrial turboemulsifier

Fig. 12.13.
Industrial emulsion storage tank

Questions

1) How would you define the operation of dispersing?
2) What are the main reasons of the emergence of zeta potential?
3) What layers surround dispersed particles and what attributes do they have?
4) What are the principal findings of the DLVO theory?
5) What effect do macromolecules exert on suspended solids?
6) What are the main fields of application for suspension systems in drug therapy?
7) What are the main classes of excipients applicable for making medicinal suspensions?
8) What are the main advantages of emulsion type pharmaceutical preparations?
9) What types of transformations can emulsions undergo?
10) How does the Ultra turrax work?
11) How does the colloid mill work?
12) How does the high pressure homogenizer work?

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Recommended websites

http://www.firp.ula.ve/archivos/cuadernos/00_Book_Salager_Chap2.pdf

http://www.firp.ula.ve/archivos/cuadernos/00_Book_Salager_Chap3.pdf

13 Technology of semi-solid dosage forms

Melting and *freezing* are frequently used operations in solving pharmaceutical problems in the field of semi-solid dosage forms. Both are fundamental operations, although freezing can also be counted as a shaping operation, for example in suppository molding. These operations work oppositely, but their application in pharmaceutics justifies merging them in one chapter.

Substances changing their physical state from solid to liquid due to transmission of heat is called *melting*.

Substances changing their physical state from liquid to solid due to cooling is called *freezing*.

The properties of semisolid excipients are between liquid and solid state materials, forming a clearly circumscribable group. They share the attribute of being easy to melt at moderate temperatures ($T_{melt.}$<100C^{o}) and solidify if cooled to room temperature. They are used as matrix-materials, but they are useful in many other fields.

Changing phases, substances change from one state to another without chemical changes. In semisolid-melt transitions melting requires heat while freezing releases heat.

The temperature of a substance that is being melted remains constant until the transition to liquid is complete throughout the substance. The transition implies an increase in internal energy.

If a sample is heated or cooled in a steady rate with its temperature being measured, there is going to be a deviation from the linear during phase change. This deviation determines the latent heat required for melting and released at freezing, which, if adjusted to the mass of the sample, yields the material constant. Latent heat (specific melting heat) is absorbed or released when a substance undergoes a phase change at constant temperature, thus changing from solid to liquid (melting heat) or from liquid to gaseous (heat of evaporization).

The amount of heat required for the phase change (Q) is proportionate with the mass (m) of the substance undergoing the change.

$$Q = Lm \tag{1.}$$

L constant specific to the substance, phase-change heat, the amount of heat required for changing the physical phase of a unit mass of the substance

Substances used for making ointments and suppositories are not uniform chemically, thus further distinctive properties (e.g.slipping point, softening point, dropping point, congealing point) are needed for characterizing phase change. Their melting point, due to their inhomogeneous composition is specified in a temperature range, unlike the exact constant values of crystalline substances.

Table 13-I.
Melting ranges of Hydrophilic Meltable Materials

Hydrophilic Substances	Typical Melting Range (°C)
Gelucire® 50/13	44-50
Poloxamer® 188	51-52
Polyethylene glycol	
2000	42–53
3000	48–63
6000	49–63
8000	54–63
10000	57–64
20000	53–66
Polyethylene glycol stearate 6000 WL1644	46–58

Table 13-II.
Melting ranges of Hydrophobic Meltable Materials

Hydrophobic Substances	Typical Melting Range (°C)
Beeswax	61–68
Carnauba wax	75–83
Cetyl palmitate	47–50
Glyceryl behenate	67–75
Glyceryl monostearate	47–63
Glyceryl palmitostearate	48–57
Glyceryl stearate	54–63
Hydrogenated castor oil	62–86
Microcrystalline wax	58–72
Paraffin wax	47–65
Stearic acid	46–69
Stearic alcohol	56–60

Solidification is extended, structural transformation is not momentary. Cooling a melted substance at a steady rate will produce the phenomenon where the temperature of the substance first decreases below the congealing point then sets in at the congealing point.

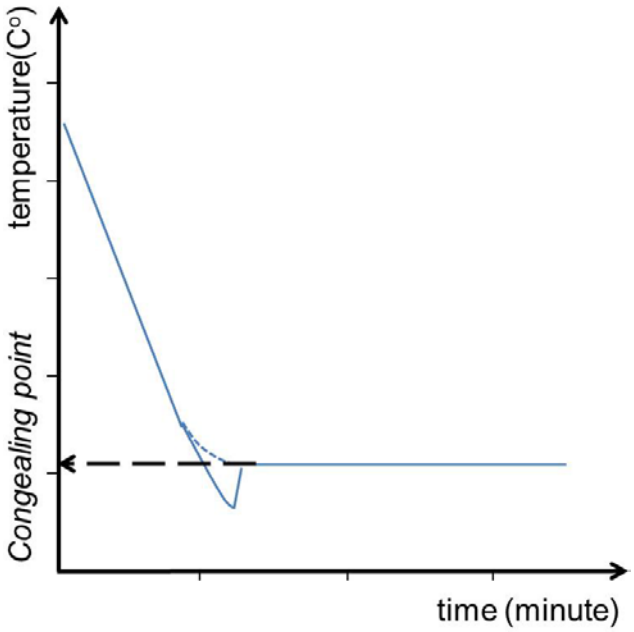

Fig. 13.1.
Determining the arrest point of melts

Substances of semi-solid (soft) consistence present several opportunities for preparation formulation and achieving local and systemic effects. There are malleable, pliable, easy to shape, sufficiently soft yet shape-reserving substances, which are indispensable for the preparation of certain dosage forms.
Drugs of local effect are used for treating the skin, eyes, vagina, urethra, rectum or external ear, but depending on conditions of absorption, systemic effects can be also achieved. By adjusting the composition of the preparation the rate of absorption, local or systemic effect can be controlled.

Semi-solid pharmaceutical preparations for the skin are:

- ointments,
- creams,
- gels,
- pastes,
- pouiltices and
- medicated plasters.

The following forms can be used for achieving a *local* effect *in body cavities:*

- nasal sticks,
- nasal gels,
- ear gels,
- vaginal suppositories
- globules,
- vaginal rods,
- sticks,
- sticks for wound care,
- urethral sticks and
- rectal suppositories.

The size, shape and composition of these types of preparations (e.g. sticks, ovules, suppositories) to be used in body cavities conform to the attributes of the respective cavity.

Medical preparations, such as vaginal pills, vaginal rods and ovules, melting or dissolving in the vagina are useful in gynecological treatments.

The shape of rectal suppositories can be cylindrical, conical and torpedo-shaped. Their tapered end facilitates rectal administration. Depending on its composition, the suppository in the rectum melts and/or dissolves in the mucous secretion.

The consistence of medicine must be appropriate for both the purpose and location of dosage. Therefore creams and ointments need to be easy to smear, while globules, suppositories, sticks must be as firm as necessary.

Soft dosage forms for opthalamological use are:

- eye ointments,
- medicated ophthalmic strips.

The following soft dosage forms can be used for achieving a *systemic effect* transdermally, via the mucous membrane of the mouth, gastric, small intestine or the rectum or the nasal mucous membrane:

- creams,
- ointments,
- gels,
- pastes,
- suppositories,
- transdermal patches,
- solid dispersions,
- granulates,
- micropellets,
- compressed dosage forms.

Transdermal patches are flexible medicated adhesive preparations for use on the skin. In addition to local effect they are also capable of achieving systemic effects. These controlled drug release systems are made for external (not implanted) use, which, due to being repeatable, can be used indefinitely in principle, without pain or surgical intervention. Their further major advantage is that patch therapy can be suspended any time.

Depending on the profile of the matrix, solid dispersions can expediate or retard the release rate of the active ingredient. Perorally administered *granulates, micropellets* and *molded/die-cast tablets* in a semi-solid matrix are capable of controlled drug release.

Depending on solubility conditions, the structure of preparations made with semi-solid excipients can be *solution*, *emulsion* or *suspension* type.

According to the pharmacopeal definition, ointments are semi-solid pharmaceutical preparations, containing solid or liquid substances dispersed in a single phase *preparation base* (*base cream*).

According to the interactions between hydrophilic and lipophilic phases and hydration there are:

a) hydrophobic,
b) water emulsifying and
c) hydrophilic ointments.

Hydrophobic ointments can absorb very small amounts of water. Such ointments contain no emulgent. Solid and liquid paraffins, vegetable oils, animal fats, artificial glycerides, waxes and liquid poly alkyl siloxanes are commonly used ingredients of these ointments.

In addition to the above listed base cream components *water emulsifying ointments* contain an emulgent/emulgents. This enables them of absorbing more water. Depending on the emulgent, they form a water-in-oil (W/O) or oil-in-water (O/W) type emulsion if mixed with water.

Hydrophylic ointments mix with water naturally, as this type of base creams are composed of hydrophilic components (usually a combination of liquid and solid macrogols) and possibly water.

Creams are multiphase preparations, consisting of lipophilic and water phases. They can be either lipophilic or hydrophilic in character.

Lipophilic creams contain W/O type emulgents (e.g. wool-wax alcohols, monglycerides, sorbitan esters) and the outer phase of the cream is lipophilic.

The outer phase of *hydrophilic creams* is the water phase. They contain O/W type emulgents, which can be sodium- or trolamine soaps, polysorbates, fatty alcohol sulphates, poly-oxy fatty acids and fatty acid ester derivatives. These emulgents, along with W/O type emulgents can be used as complex emulgents too.

Gels are high liquid content systems.

The main components of *lipophilic gels (oleogels)* are liquid paraffin, polyethylene or fatty oils, whose mix is gellified with colloid silicon dioxide or aluminum- or zinc soap.

The main components of *hydrophilic gels (hydrogels)* are water, gycerine or propylene glycol, whose mix can be gellified by adding aluminum-magnesium silicates, cellulose derivatives or starch.

Poultices consist of a hydrophilic base ointment and the solid or liquid components dispersed in it.

Pastes contain high amounts of finely dispersed solid components.

The applicability range of semi-solid pharmaceutical and cosmetic preparations largely depends of their yield properties. The majority of preparations (solutions, emulsions, suspensions, ointments, gels, mucilages, suppository components) are mostly viscous, viscoplastic. *Dilatation* is common in pastes.

Melting and freezing alters the *rheological* properties of substances.

13.1 Preparation of ointments and creams

Ointments are prepared by stirring at room temperature or by heating frequently. In the pharmacy laboratory melting of ointment ingredients is done in a patendula. To prevent local overheating, water-bath is applied, with stirring and temperature control. The application of infrared lamps for mild heat transfer is an established method (See also: chapter *Heat transfer*).

Depending on solubility, after preliminary melting of ingredients of different melting points, the active ingredient can be dissolved or suspended in the melt. In practice, pulverized substances of appropriate degree of fineness are first blended with a portion of the melted preparation base, adding the rest gradually, stirring until cooled. It must be borne in mind that depending on the properties and quantitative proportions of the substances, melted substances may precipitate or recrystallize after cooling, which may alter absorption.

Preparing emulsion ointments, the water phase, heated to the same temperature as the melted preparation base containing the emulgent, is dispersed in it by stirring, likewise stirring until cooled.

Planetary mixers are applied for mechanical blending, if melted ointment ingredients or combinations need steady, slow cooling (*"mixing"*). The movement of the blades of a planetary mixer is similar to the way planets orbit: the mixing blades *rotate around their own axis*, while *moving around a circular orbit*. These blenders are very effective in keeping cooling, increasingly viscous and therefore more resistant substances homogenous, with even steady cooling. The mixing blades are usually supplemented with a scraping blade, which moves along the side wall, removing deposited substance, pushing it to the inner layers of the medium, serving homogenization significantly.

Fig. 13.2.
Planetary mixer

Movie 6. Planetary mixer

Three roll mills (also called triple-roll mills) are useful for homogenizing ointments, removing inhomogeneities, "smoothing" the ointment. The three rolls are in contra-rotation on parallel horizontal axes. The ointment is forced through the adjustable gap rolls, homogenized by the shearing forces. This operation is also called *ointment (paste)-milling*.

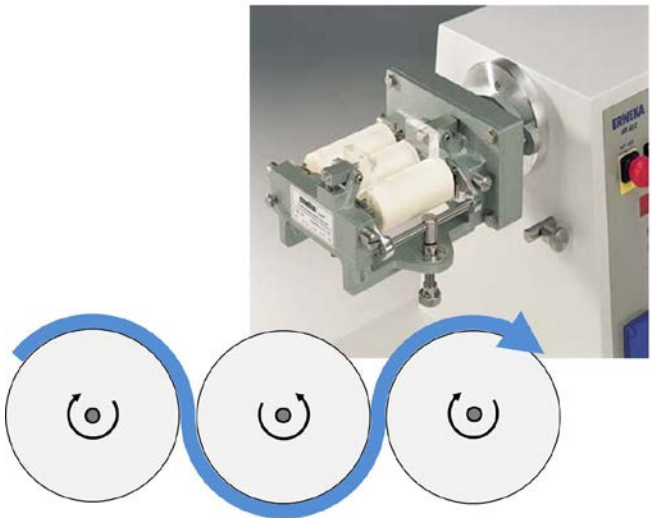

Fig. 13.3.
Three roll mill

Movie 7. Three roll mill

Duplicators equipped with appropriate mixing blades are widely used in industrial scale operations (see also chapter Mixing). The quality of cosmetic and pharmaceutical preparations is guaranteed by the combination of optimized composition and technology, appropriate conditions for production and closed production lines.

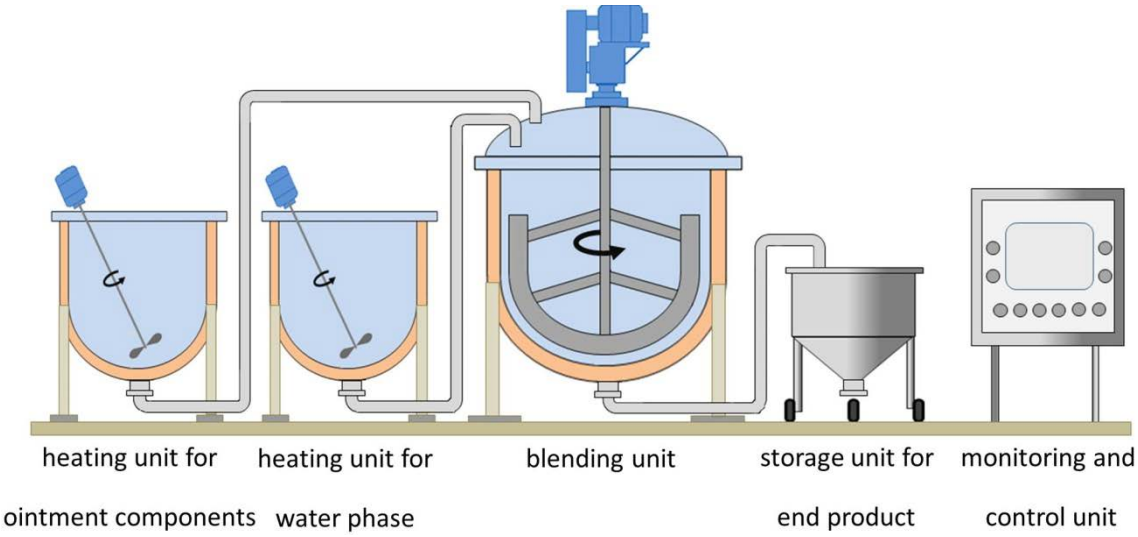

Fig. 13.4.
Automated production line for making ointments and creams

Duplicators making ointments and creams work in a closed system, in compliance with controlled unit operation parameters (e.g. temperature, blending time, stirring rotation speed, flow speed) with in-process control. To prevent bubbling in the melt and the end product, vacuum can be applied during blending. To control and operate this kind of computer controlled production line a specialist staff of one technologist operator and one machine-operator technician is sufficient.

Fig. 13.5.
industrial scale ointment production line

Ointments and creams are filled into tubes or jars after preparation. In the pharmacy or laboratory the preparation is filled in the tube with the appropriate tool (tube filler), the tube closed with crimping pliers afterwards.

Fig. 13.6.
Officinal ointment tube filler and crimping tools

There is machinery for loading larger amounts of ointment or cream, which fill preprogrammed amounts.

Fig. 13.7.
Erweka laboratory tube filler

On the industrial scale filling is done by closed production lines, which also cap tubes immediately after filling.

Fig. 13.8.
Industrial tube filler

13.2 Preparation of suppositories

The active ingredient of suppositories is solved or dispersed in an appropriate *suppository base*. Suppository pastes are water soluble or dispersible, or melt at body temperature. Preparations may contain additional excipients as necessary, such as fillers, adsorbents, surface active agents, microbiological preservatives and colorants as permitted by the relevant authority.

Suppositories are made without heat treatment by molding.

Active ingredients are first pulverized if necessary and sifted with an appropriate sieve. Various vehicles are available, such as solid fats, macrogols, cocoa butter and various gel-like blends consisting of, for example, gelatin, water and glycerin. For casting, the ingredients of the suppository are melted over a water-bath in a patendula. Heating and melting has to be performed under controlled conditions, as excessive heat can cause decomposition in heat-sensitive active ingredients and damage excipients (e.g. cocoa butter) irreversibly. The active ingredient is blended by adding small portions of the melt, then cast in a suitable mold and allowed to solidify. To prevent suppositories from sticking to the casting mold, it is advisable to apply a thin layer of paraffin to the inside of the suppository mold.

Rectal suppositories are solid, single dose pharmaceutical preparations. Their shape, size and consistence make them suited for rectal use. The weight of suppositories

for adults is usually 2-3 g, for children 1-1.5 g. Depending on the number of suppositories to be prepared single and multiple row suppository molds are available.

Fig. 13.9.
Single row rectal suppository molds

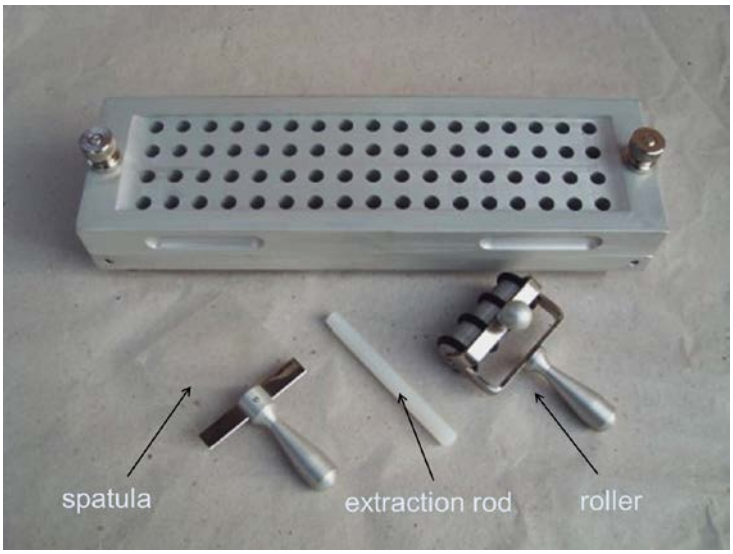

Fig. 13.10.
Four row suppository mold and appliances

To achieve uniform distribution, hot, melted substances, especially those of suspension-type suppositories, need constant stirring even in the course of casting.

Fig. 13.11.
Officinal suppository casting

Suppositories solidify with the cooling of the melt, in sol-gel transition. Cooling effect can be achieved by exposure to room temperature, circulation of water or, for accelerated cooling, refrigeration. To prevent sedimentation, accelerated cooling is be justified in case of suspension-type suppositories. The application of too rapid cooling or too cold cooling medium may result in rigid (cracked, brittle) suppositories.

Subsequent to cooling frozen excess material can be removed with a spatula.

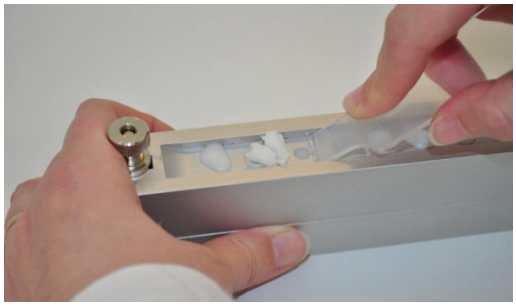

Fig. 13.12.
Removing excess after cooling

After the mold is carefully unfastened, the suppositories can be removed.

Casting large amounts of suppositories requires the use of temperature-controlled equipment capable of providing constant stirring, to maintain substance homogeneity in the course of casting. The arrangement of multiple mixing blades on a central shaft enhances stirring efficacy.

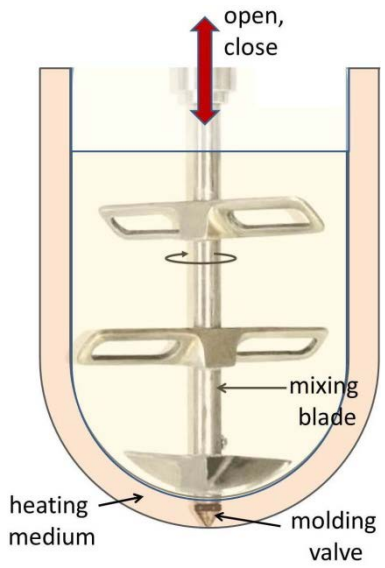

Fig. 13.13.
Operation principle of suppository molding machines

One or several molds can be placed under the molding valve, to be moved horizontally to achieve uniform filling.

Fig. 13.14.
Laboratory and medium-scale manufacturing of suppositories with an Erweka device

Movie 8. Manufacturing of suppositories with an Erweka device

For ease of removal, frozen suppositories can be dislodged from the mold after cooling by applying slight pressure at the top with an extraction rod or the mold's own roller.

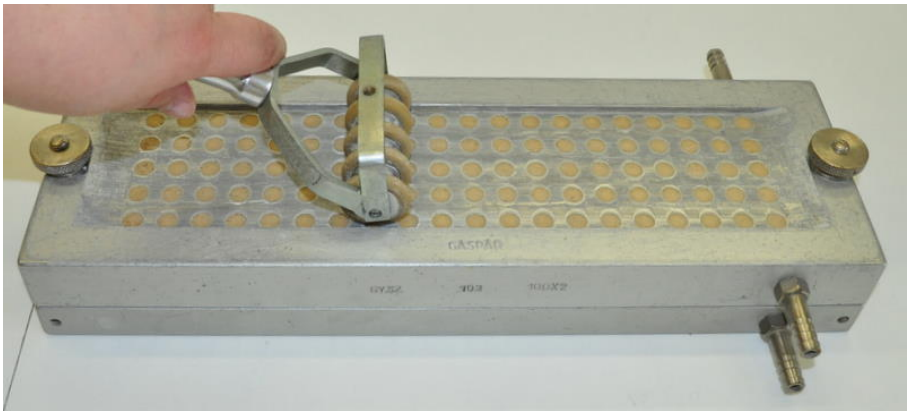

Fig. 13.15.
Preparation of suppositories for removal with roller

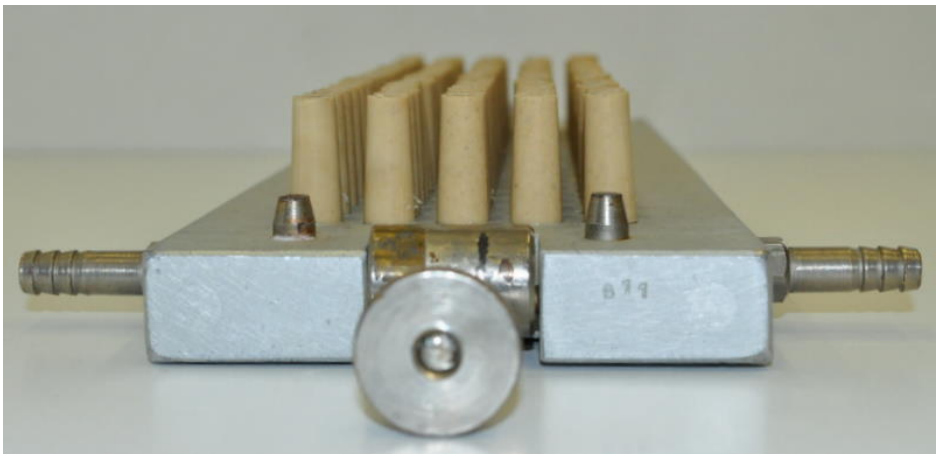

Fig. 13.16.
Suppositories prior to retrieval, in unfastened casting mold

Suppository making machines used in pharmaceutical production are capable of making up to 10 000 pieces per hour in batch and continuous operation.

Fig. 13.17.
Industrial suppository production line

Suppositories are individually packaged for mechanical protection. In industrial production suppositories are cast in plastic shells, which also serve as containers. This method boosts productivity.

Fig. 13.18.
Suppositories in plastic shell packaging

13.3 Preparation of vaginal suppositories

Pharmaceutical preparations melting or dissolving in the vagina are useful in gynecological treatments. According to their shape there are spherical (*globulus*), rod (*globulus longiformes*) and almond (*ovulum*) shapes. Vaginal suppositories, rods and spheres are semi-solid pharmaceutical preparations that melt in the body cavity and dissolve in bodily fluids, containing their active ingredient in the form of suspension, solution or emulsion.

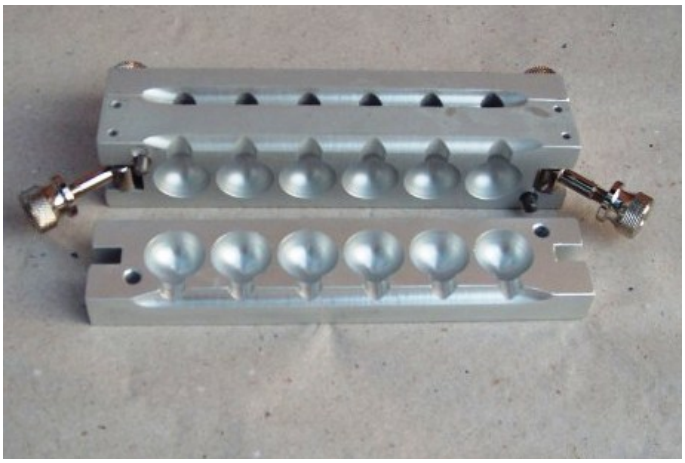

Fig. 13.19.
Casting mold for globules

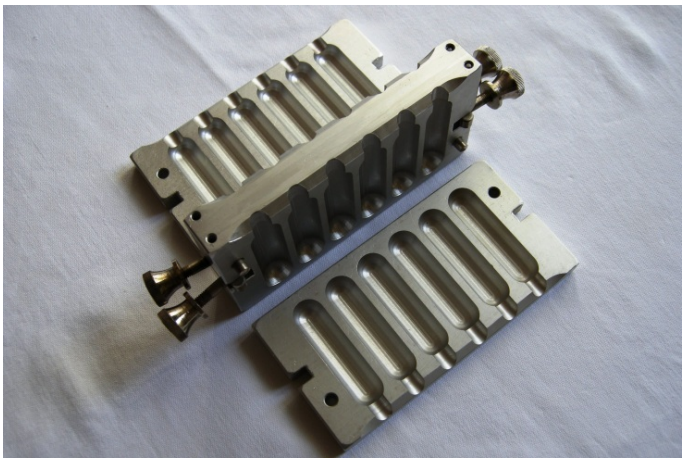

Fig. 13.20.
Casting mold for vaginal cylinders

Vaginal suppositories are semi-solid, single dose pharmaceutical preparations. They come in various shapes, but most often they are almond shaped and their size and consistence make them suited for vaginal use. Their suppository pastes are water soluble or dispersible, or melt at body temperature.

Fig. 13.21.
casting mold for vaginal suppositories

13.4 Preparation of sticks

Pharmaceutical sticks (styli) are rod- or cone-shaped preparations containing one or multiple active ingredients, meant for local treatment. The *stick* may be composed of the active ingredient(s) alone or a solution or dispersion of it/them in a suitable vehicle substance. Substances dissolving or melting at body temperature are used as vehicle. They are produced with pressing or casting. Sticks used on a wounded mucous membrane or meant for treating wounds must be sterilized.

13.5 Solid dispersions

To make solid dispersions, the meltable excipient, the polymer (matrix substance) has to be chosen according to the purpose of the preparation. The application of hydrophilic matrices and dissolution (active ingredient dispersed in molecular level) results in accelerated drug release. Suspending the active ingredient in a hydrophobic matrix yields long lasting, slow drug release solid dispersions.

13.6 Pelletizing

(See chapter 'Multiparticulate dosage forms')

13.7 Extrusion

The extruder is a modern instrument for blending and shaping melted substances. In pharmaceutical technology the device can be used for making solid dispersions using meltable excipients and as a preparatory operation in pelletizing and tableting. The extruder screw revolves in a heatable drum around a horizontal shaft, conveying and steadily blending the melt-dispersion of the active ingredient. The melted substance is thereby forced to move along the shaft. The drum ends in the extruder head. The product, called *extrudate*, leaves through the extruder head's apertures, cooling and freezing in cylindrical shape. Solidified extrudate can be chopped to required size by an attached cutter for further processing (e.g. pelletizing, pressing).

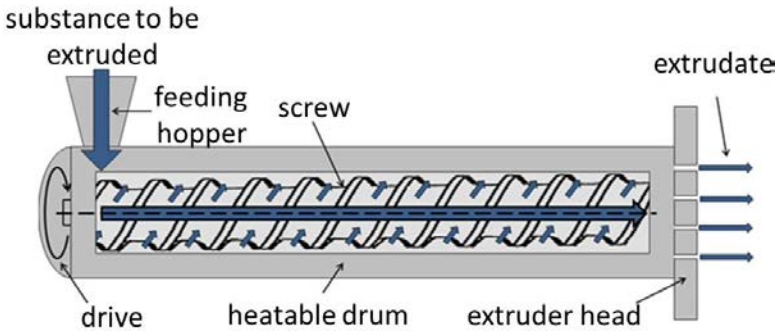

Fig. 13.22.
Extruder

Questions

1) What is the correlation that determines the amount of heat required for phase change?
2) In what direction does the planetary mixer move during blending?
3) For what technological tasks are three roll mills suited?
4) What are the advantages of the medium range Erweka suppository mold?
5) What is the output of modern suppository making production lines used in the pharmaceutical industry?
6) For what technological tasks are extruders suited?

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Recommended websites

http://www.firp.ula.ve/archivos/cuadernos/00_Book_Salager_Chap2.pdf

http://www.firp.ula.ve/archivos/cuadernos/00_Book_Salager_Chap3.pdf

http://www.ispesl.it/risk_profiles/_pharmaceutical_industry/

14 Extraction

Extraction is the removal process of one or more component from a liquid, semisolid or solid material. The operation of *extraction* is applied in almost every area of pharmaceutical and chemical industry.

Extraction is an essential step in herbal research, extraction of phytomedicine and manufacture of herbal based medicine, because the efficiency of preparations prepared from herbs can be increased by the extraction of their certain parts.

Pharmaceutical application of herbal- and material arisen from animal has a long history. Drugs generally provide important active ingredients (e.g. salicylic acid, vitamin C), but can be also used as excipients (e.g. cocoa butter, shellac, agar).

Thus *herbal drug, animal matters, teas and tea mixtures* are belonged to the oldest used medicines and created, discovered based on thousand years experiment as well as the knowledge has flared, which also supported the development of modern pharmaceutical technology.

In the middle Ages, pharmacists traded the drugs directly or after some processing, most frequently in the form of extracts. Their pharmaceutical application possibilities are also significant nowadays.

In traditional folk medicine, herbs are also used nowadays in home-made dosage forms (herbal tea, extraction containing alcohol, patch, ointment etc.). Important element of pharmacy preparations is the appropriate usage of the natural active substances and excipients.

These natural materials are constituted the majority of pharmaceuticals until the industrial size manufacture and the emergence of synthetic API in the beginning of XX. century.

Pharmacological therapy still cannot work without natural substances, materials. Modern medications are prepared after extraction of one or more active ingredients from significant part of herbs.

Herbal drug is the synonym of *herbal medicines*, *herbal preparations*, and *herbal medicinal products*.

Herbal drug can be derived from cultivated or wild plants. Herbal products can be entire, comminuted or plants chopped, herb parts, algae, fungi and lichens.

Herbal medicinal products include for example herb parts, or their pressed form, extracts, volatile oils, or those herbal teas, which are previously chopped to appropriate size, packed, or chopped in order to fill into capsule.

In herbal therapy, *herbal drugs* are used in processed or unprocessed, fresh or dried form, in order to administer externally or internally. They are applied in liquid, semisolid and solid preparations.

Isolation of novel, biological active fractions and molecules is important in the view of therapy as well as is a highlighted task of herbal research in order to prepare and develop new phytomedicine.

Herbal products can be prepared from herbal drug with variant procedures:

- extraction,
- distillation,
- pressing,
- fractionation,
- purification and

- concentration, or
- fermentation.

In pharmaceutical technology, several API can be extracted such as alkaloids, volatile oils, saponins, steroids, flavonoids, vitamins, glycosides, tannins, bitters etc. During extraction, depending on solvents and solubility conditions one or more other *escort substances* are extracted such as hydrocarbons (starch, sugars, pectin), waxes, resins, greases, proteins, mucus, enzymes or coloring substances.

Most frequently applied pharmaceutical technological test requiring extraction:

- purification of materials,
- extraction of materials,
- separation of materials.

In order to achieve appropriate therapeutic effect or to design the parameters of extraction, knowledge of quantity of components is also important besides the identification of particular compounds.

Extraction is a two- or multiphase transferring operation, which aims at the extraction of a valuable substance or purification of the material with removal of a not desired component. After extraction, the solution containing dissolved material is termed *extract* and the leftover solution is *raffinate*.

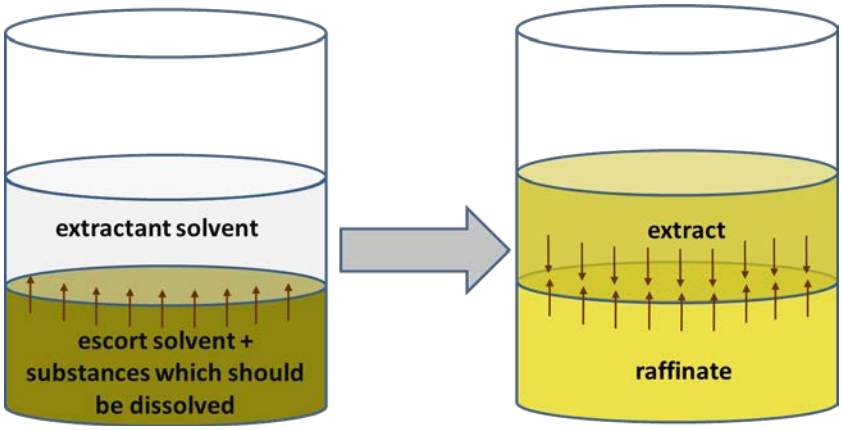

Fig. 14.1.
Liquid – liquid extraction

The separation is based on essentially the difference of physical properties (e.g. polarity) of materials, therefore deliberate choice of solvent or solvent compositions can make extraction selective.

Fundamental criterion of design of extraction operations is the appropriate knowledge of equilibrium condition of phases, because during the process, components distribute between phases based on polarity of phases. From one of the phases substances transfer to the other phase via phase boundary, consequently quantity proportions of components in phases is changed. In the viewpoint of further calculations it is important that total quantity of components is not changed.

The process and developing equilibrium can be characterized by *Nernst's distribution coefficient (k).* Based on this, if some material is dissolved in two immiscible but touching solvent, then after developed equilibrium the material distributes between the two solvents based on the following correlation:

$$k = \frac{x_e}{x_r} \tag{1.}$$

x_e equilibrium of concentration of distributing material in extract
x_r equilibrium of concentration of distributing material in raffinate.

Distribution coefficient depends on quality of material, temperature, but it is independent from material quantity.

The *phase proportion (f)* is the proportion of mass of base solution and extractant, or extract and raffinate:

$$f = \frac{m_e}{m_r} \tag{2.}$$

m_e mass of extract,
m_r mass of raffinate.

Extraction factor (E) can be calculated from the above mentioned formula. Extraction factor is in linear proportion with distribution coefficient and phase proportion in a particular temperature:

$$E = kf = \frac{x_e m_e}{x_r m_r} \tag{3.}$$

As it mentioned, choice of extractant plays a very important role in the process of extraction.

General requirements about extractants are the followings:

1) extracting material can be dissolved in extractant,
2) extractant and carrier solvent cannot possibly be mix with each other
3) not to be harmless for extract,
4) to be low its evaporation heat and boiling point
5) not to be corrosive,
6) not to be flammable or explosive,
7) not to be toxic,
8) to be cheap and recyclable.

Main tasks during extraction are:

1) intensive contact and mixing of delivering phase and absorbing phase,
2) insurance of appropriate time interval in order to perform the transport of valuable component,
3) separation of raffinate and extract, namely the two phases created during extraction

Classification of extraction operations:

1) at *liquid-liquid extraction, LLE* the initial material and solvent is in liquid state of matter (solvent extraction),
2) *at solid-liquid extraction, SLE* the initial material is a complex solid material and its soluble components are extracted by extractant
3) at *supercritical extraction, SCE* the initial material is solid (or liquid mixture), and the extractant is high pressure gas in fluid state

In the case of *liquid-liquid* type extraction, the transfer begins in liquid phase via the boundary surface of two immiscible liquid. A component or components of liquid mixture can be extracted with selective solvent based on distribution. In this operation, diffusion and distribution has a significant role.

Liquid-liquid extraction is especially reasonable if:

1) extracted component is sensitive to heat, or degrades in higher temperature,
2) liquid mixture has high boiling point,
3) low concentration component of the mixture is desired to be extracted,
4) boiling point difference of components of separated liquid mixture is low,
5) azeotrope mixture develops during distillation, rectification.

The method is also significant in the pharmaceutical point of view. If the purpose is to isolate valuable components from fermentation in a biotechnological process, then it is carried out by extraction. This operation is also regarded to concentrating process, since water namely the carrier solvent is removed and simultaneously the solvent get rid of contaminations soluble in water. Great advantage of application of extraction procedures that heat sensitive antibiotics (e.g. penicillin) avoiding any operation accompanied with high temperature (evaporation) can be extracted carefully without degradation. Extraction is typically more effective, if material is extracted with small amount of extractant in more times, than whole solvent quantity is used at once.

During extraction process, the quantity of extracted component increases in the extract due to interaction of phases, while decreases in the raffinate.

Liquid-liquid extraction can be continuous or discontinuous/phased similarly to solid-liquid extraction.

Liquid-liquid extractors operate with separation based on density difference.

According to their structure and operation, they can be classified to the following groups:

a) *column extractor*,
b) *centrifugal extractor*,
c) *mixer-settler extractor*

In column extractors, mixture of heavy and soft phases in counter flow and their transfer is assisted by baffle plates. The column contains the same segments in left and right side. Size of boundary, reaction surface and thereby efficiency of extraction can be increased more, if liquid column is mixed with stirrer simultaneously.

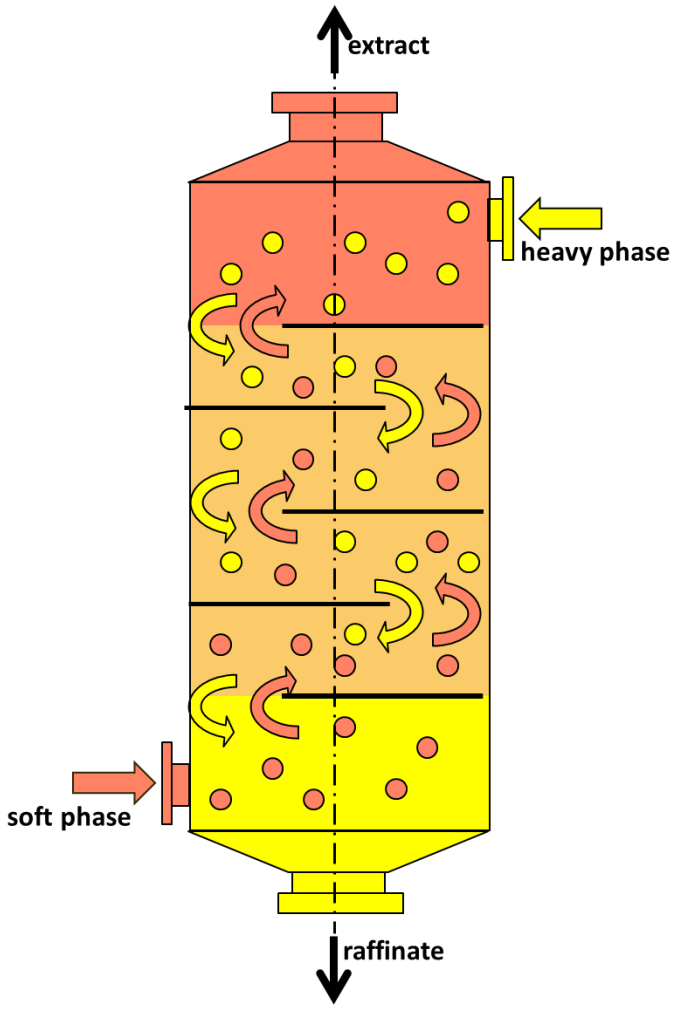

Fig. 14.2.
Column extractor with baffle plates

Mixer-settler extractors operate with gravitational separation based on the principle of counter flow. In continuous mode, heavy and soft phase is flowed opposite to each other, then after intensive mixing emulsion phase is separated in settler container. Main steps of process can be repeated in many times with recycling of phases.

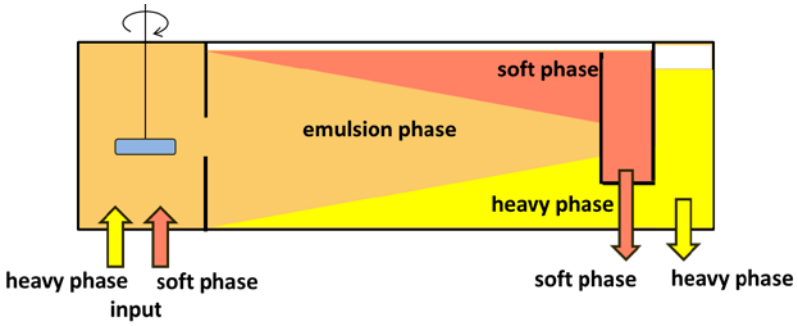

Fig. 14.3.
Mixer-settler extractor

Creation of emulsion frequently aggravates the process of extraction, which can be avoided by keeping avoid of emulsifying substances. If one of the solvents is water phase, then stability of emulsion can be impaired by change of pH value, or with increased ionic strength (e.g. adding salts).

Extract and raffinate cannot be separated only with gravitational settling, but also with centrifugation. Gravitational settling generally accompanies with difficulties, or almost impossible, if density difference is too little among two phases. In such case *centrifugal extractors* should be used.

Centrifugal extractors have the highest effectiveness. Separation of phases is assisted by centrifugal forces, during which liquids can be mixed and separated in many times in each other, thereby transfer and separation phases become faster and more complete.

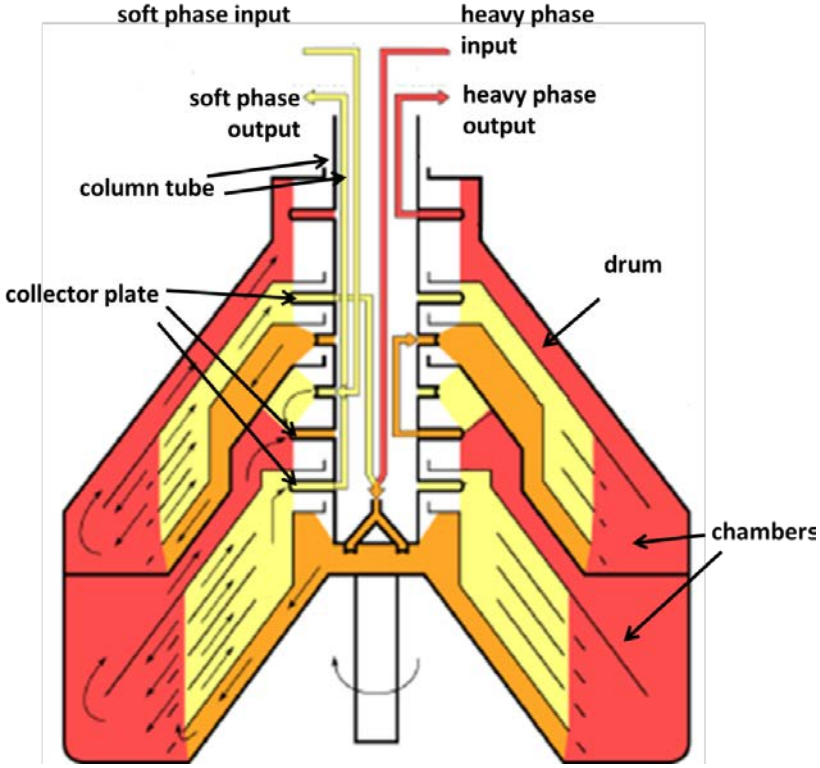

Fig. 14.4.
Process of Luwesta centrifugal extractor

Super centrifuge is special centrifuge with small diameter (45-150 mm) and high speed (10000-40000 rpm), but it is termed tubular bowl centrifuge. Liquid separator belongs also in the group of super centrifuges, which operates with 5000-10000 rpm. Radius of its bowl is 150-300 mm. These separators are able to separate liquid emulsions.

During solid-liquid extraction, one or more components of solid phase are dissolved in liquid extractant. During the process, osmosis and diffusion have highlighted role. Extraction is assisted frequently with heating, but heat sensitivity has to be carefully considered.

Main steps of extraction:

- contact with extractant,
- swelling,
- extracting,
- separation,
- re-extraction of solid phase,
- extraction of components from pooled liquid phase with variant separation methods (e.g. evaporation).

At extraction of API content from a certain drug, choice of solvent depends on the quality of components. The selectivity of solvent can pertain to one or more components as well, and have to been chosen according to which component of extraction is aimed.

At precondition of extraction, it has to be considered that only slow extraction with low efficiency is possible in the most cases via relatively thick and hardly permeable herbal cell wall, thereby previous chopping of drug should be performed in order to increase surface. With appropriate chopping it can be achieved that extractant is able to extract the valuable components faster from damaged cells. From intact cells, components can be extracted via cell wall due to concentration gradient, which is a slow diffusion process.

Speed of drug liberation ability of herbal (rarely animal) drugs is determined by the diffusion, thus Fick law is valid for this process:

$$M = DAt\frac{c_c - c_e}{l} \tag{4.}$$

M quantity of diffusing substance
D diffusion coefficient
A size of diffusion surface
1 thickness of diffusion layer
c_c cell concentration (intracellular concentration of API)
c_e extractant concentration (concentration of API in extractant)
t extraction time

Speed of extraction is influenced by temperature and speed of flow of extractant too.

During solid-liquid extraction, most frequently extraction of several or even more than thousand components can be extracted from herb parts, which necessitates further purification operations.

During extraction, intracellular concentration (c_{ic}) and concentration in extractant (c_e) determines the process, since diffusion only lasts until the concentration are equal.

Main steps of the process:

1) extractant penetrate into cells ($c_{ic} > c_e$),
2) substances are dissolved in extractant (active and escort substances) ($c_{ic} > c_e$),
3) components are diffused into extractant medium from created solution due to concentration gradient

Step 1-3. repeat continuously with decreasing the concentration difference, and dynamic equilibrium occurs ($c_{ic} \approx c_e$).

Several solvent can be applied for extraction such as isopropyl alcohol, ethyl alcohol, n-hexane and ethyl acetate. These solvent are included in list of solvent allowed by EU.

Methods of solid-liquid extraction:

- *soaking (maceration),*
- *turboextraction,*
- *vibroextraction,*
- *percolation,*
- *counterflow extraction.*

Soaking (maceration) is a discontinuous extraction method performed in room temperature. During this suitably chopped drug is moistened in order to loosen cell walls and swell the cells (generally 10 minutes). The amount of extractant solvent is 5 or 10 times of drug quantity in the most cases. Extract can be separated after several hours or days of soaking from herb parts. In well-sealed container should be the extraction performed to avoid evaporation. Extraction from drugs containing mucus is made within half an hour in room temperature. Rose hip tea preparation necessitates 10-12 minuses of soaking in order to preserve its Vitamin C component.

Concentration of maceratum *(c)* varies in the function of volume of extractant (*V*) according to this relation:

$$c = c_o V^k \tag{5.}$$

c equlibrium concentration of maceratum
c_o initial concentration of drug
V volume of solvent
k material constant

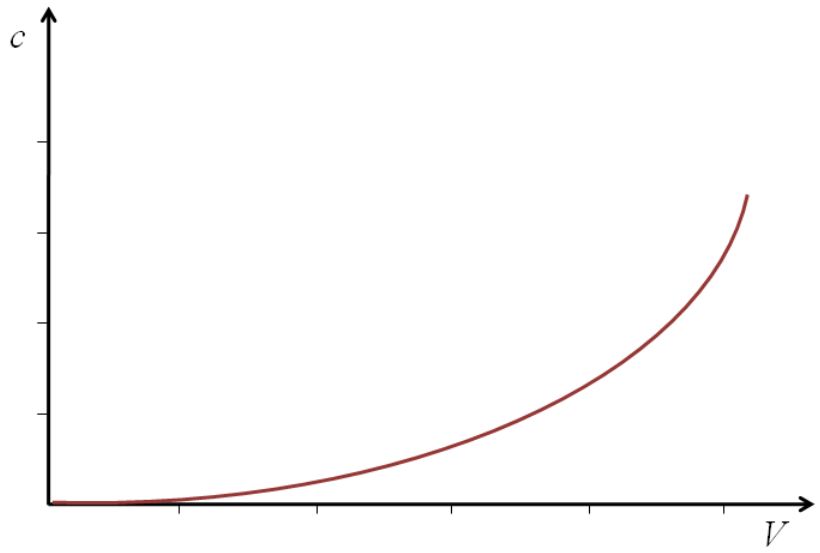

Fig. 14.5.
Change of concentration in maceratum (c) in the function of volume of extractant (*V*)

Decoctions (*decocta*) and *infusions (infusa)* are the aqueous extracts of herbal drugs performed in higher temperature. Extraction time depends on the properties of drug, namely softer and thinner is the drug, less time is required.

Main steps of their preparation:

1) herbal drug chopped to appropriate size is filled with prescribed volume of extractant into flask with or without previously performed soaking and it is moistened. (Extractant must not be hot, since it can result in the coagulation of proteins in cells and colloidal materials, which hinders extraction)
2) flask has to be taken into Schulek's steampot, and required period of time is allowed in steam chamber (till 20 min in the case of infusions, till 40 minutes at decoctions)
3) after prescribed time, decocts have to removed immediately and filtered while hot, and infusions are filtered after cooling down.

In the case of decoctions, extraction lasts longer (staying in steam chamber), but stops after filtering. At infusions, from removal from steam space until filtering after cooling, extraction continues.

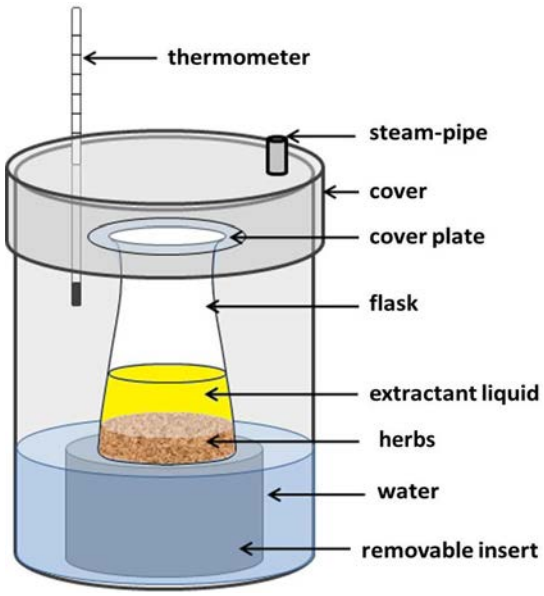

Fig. 14.6.
Schulek's steampot

Disadvantage of hot extraction can be that in the case of drugs containing volatile oil, particular heat sensitive active substances, extraction performed in cooled state should be carried out.

Preparations prepared by *dilution* of a tincture or *dissolution* of dry extract produced by lyophilization are equal to several decocts and infusions.

Percolation is that extraction method when extractant solvent goes through the permeable layer of herbal drug. Operation of percolation can be continuous or discontinuous. Percolation extraction is frequently performed in room temperature, and started with soaking of preconditioned (chopped) drug. Afterwards liquid containing extract is deflated in particular speed.

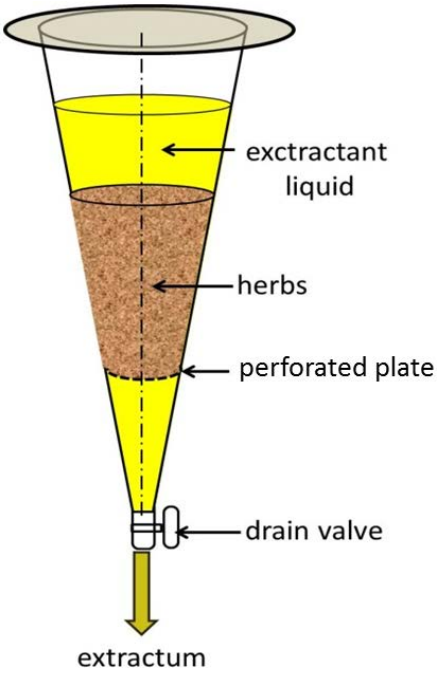

Fig. 14.7.
Percolator

Turboextraction means the extraction carried out by high speed mixing, which accelerates the diffusion greatly. (See Mixing chapter)

Vibroextraction is the extraction supported by ultrasound. Permeability of cell wall is increased by influencing ultrasound thereby diffusion process accelerated.

Soxhlet-type extraction apparatus allows the recirculation of solvent in many times. Herbal drug has to be placed into its socket. After the boiling of solvent, condensation of its steam flows back on the drug. At this place, solvent dissolves the components from sample. In extraction space, amount of extractant increases and after a particular time it changes, when its volume reach the level of opening of exhaust tube and flows back to round bottom flask. Extracted components from sample congregate in this flask, and pure solvent returns back again due to heating. So solvent transforms into steam gradually and condensed pure solvent can extract from drug with high concentration difference. Total extraction process requires generally approximately 15-20 hours. After finishing extraction, solvent is removed from round bottom flask by vacuum distillation.

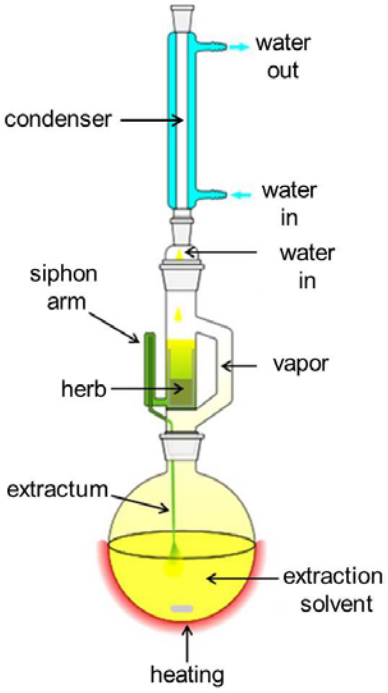

Fig. 14.8.
Laboratory size Soxhlet apparatus

Diffuser is among industrial devices for extraction operating discontinuously, and results in similar extraction compared to percolation. Lids of bowl can be easily opened due to easy filling and emptying. Upper lid is totally detachable, the lower can be tipped. Filled solid material is placed on a conical mantle made of perforated plated and fills the cylindrical diffuser body. Solvent is introduced from above, which penetrates through the drug, and then passing perforated plates is deflated through the socket on the bottom.

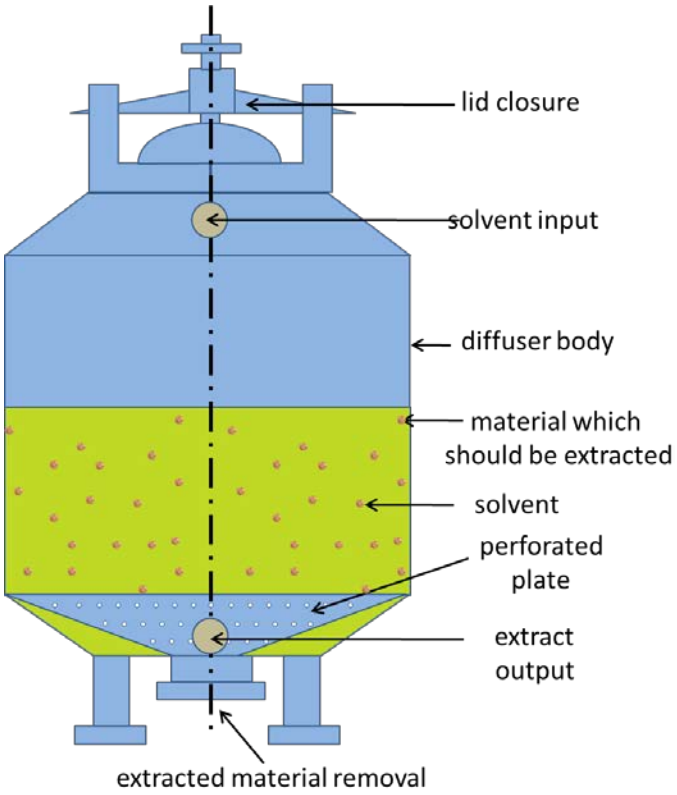

Fig. 14.9.
Diffuser

Mixer-settler extractor is used in the cases when material which should be extracted is granular. Solid material is filled through opened lid of apparatus, while extractant is filled into input manifold. In order to inhibit settling of particles and to increase efficiency, mixing is applied. At the end of extraction, mixing is stopped and particles start to settle on the filter inside the apparatus. Extract is deflated through output manifold; extracted solid material is removed through an emptying manifold.

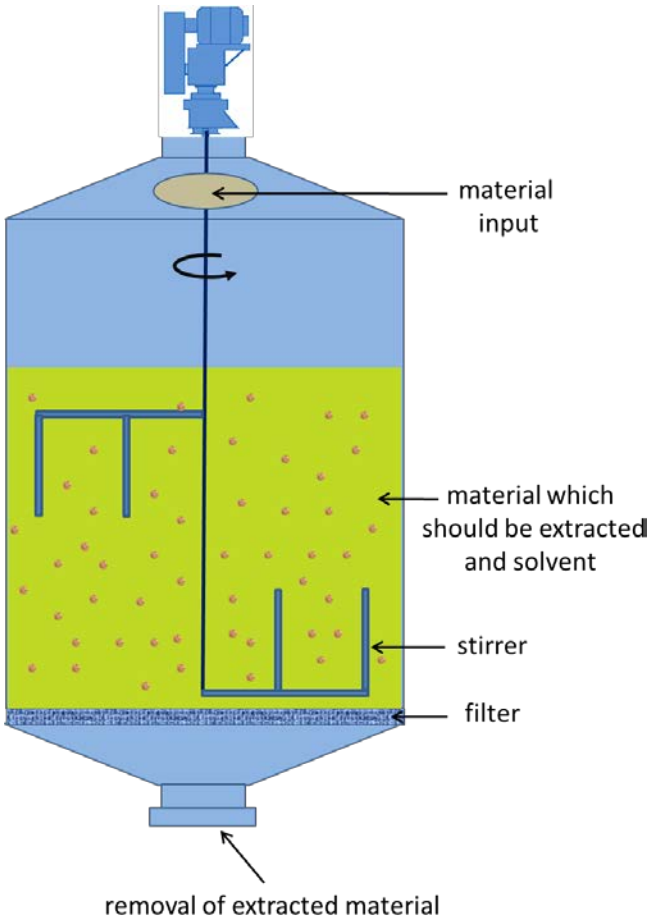

Fig. 14.10.
Mixer-settler extractor

Bonotto extractor allows continuous, counter flowing solid-liquid extraction. Solid material moves downward due to mixer, and falls down from plate to plate. Extracted material is removed by pulley system from the bottom of apparatus.

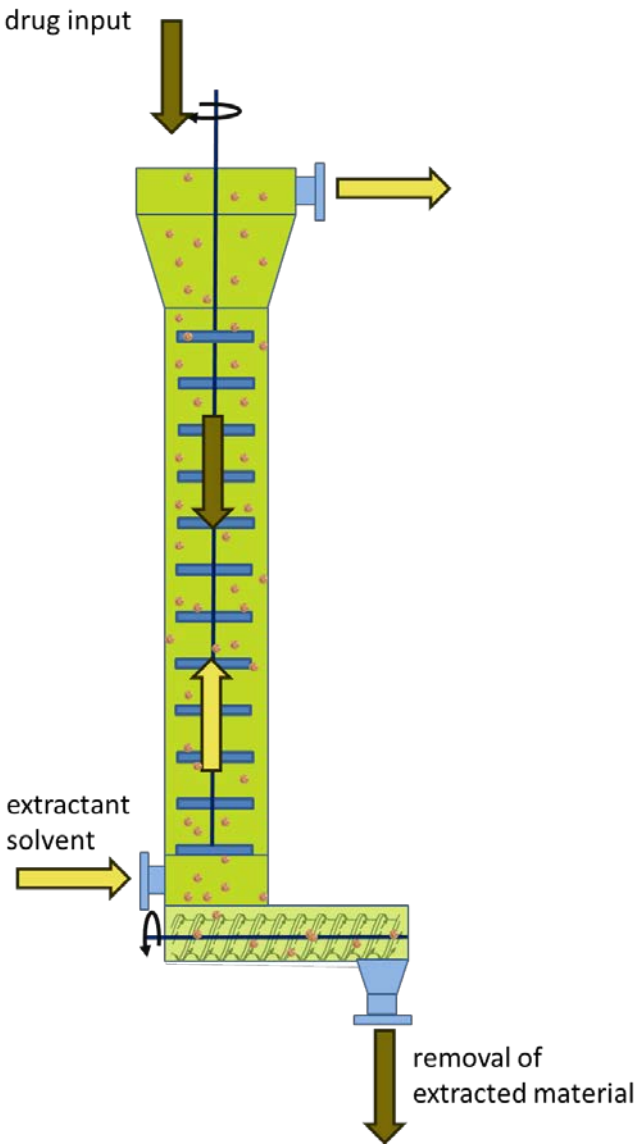

Fig. 14.11.
Bonotto extractor

Bollman extractor is continuously operating apparatus allowing solid-liquid extraction, in which bowls with perforated walls are moved in elliptical path, and driven by chain wheel. Solid material is delivered from input hopper to bowls. Solvent is sparged onto drug in direct flow in the input side; on the other side counter flow predominates because solvent is fed from the top. Although solvent from container is also delivered to the top by pump. Removal of extracted material from bowl takes place by tipping on the top of forced path.

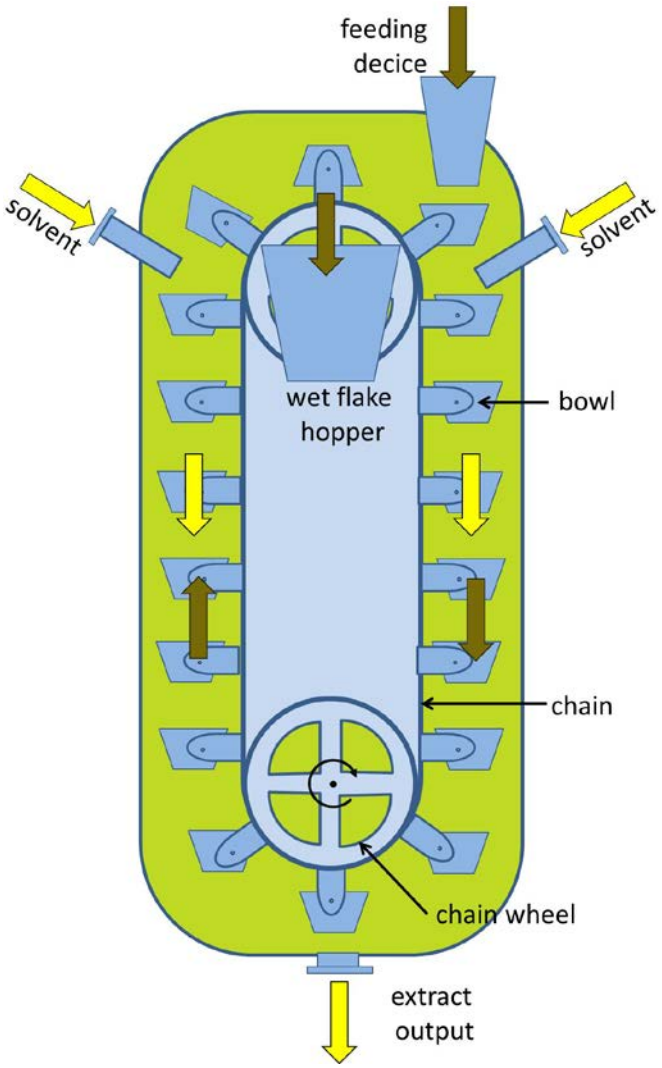

Fig. 14.12.
Bollman extractor

Hildebrand extractor with its U shape and screw conveyor system operates in counter flow. Apparatus consists of three tubes and screws made of perforated plates inside the tubes. Screws rotate with different speed, so that solid material is concentrated mostly on the bottom, horizontal section of the extractor.

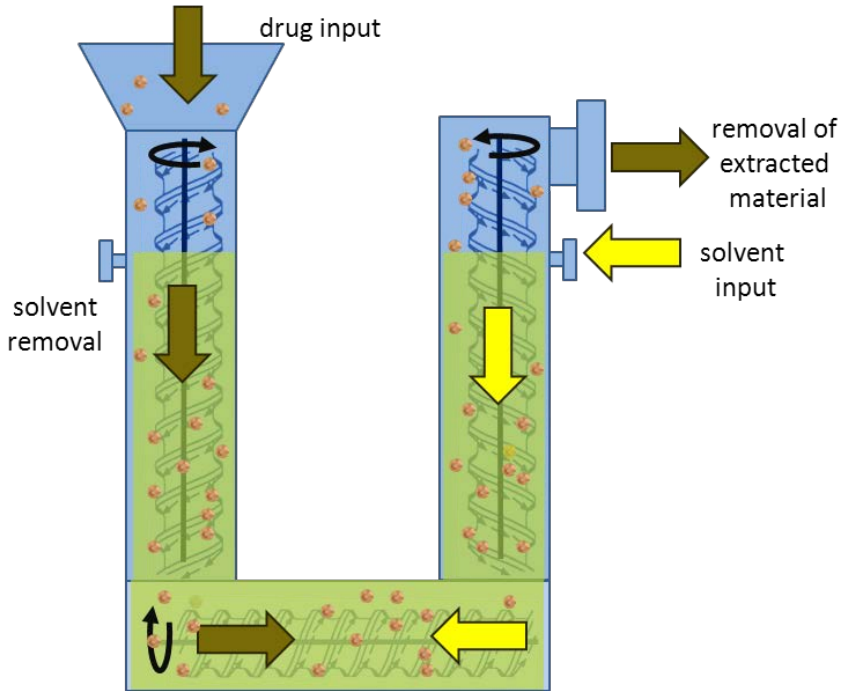

Fig. 14.13.
Hildebrand extraktor

Research team of Kőbányai Pharmaceutical Industry (Richter Gedeon) by *Kálmán Szász* (1910-1978) pharmacist's leadership carried out remarkable herbal extraction experiments, especially in the field of solvent extraction of *Vinca minor* in 1950's. With *Takács István* mechanical engineers, they invented a new type extractor, which can also be applied for multiple herbal drugs. The solid-liquid extractor got its name from its shape, thus it is termed U-extractor. Extraction of solid chopped grist, active ingredient of herbal drug can be performed with high efficiency with counter-flow and continuous operation.

Among Hungarian researchers, *Szabolcs Nyiredy* (1950-2006) pharmacy academician has to be mentioned, who was famous from his research in separation technique, herbal analysis and technology.

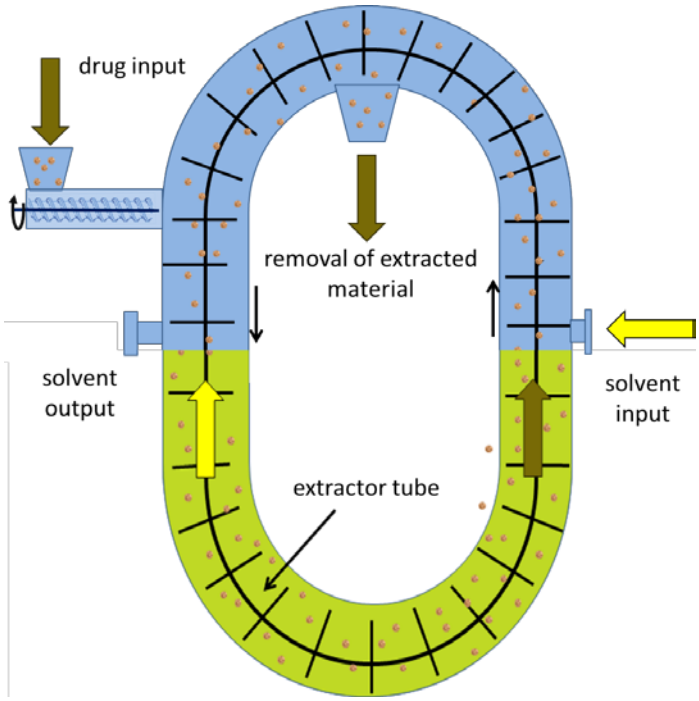

Fig. 14.14.
U-extractor

In Rotocell extractor, extraction can be performed in closed space and with counter-flow. The most concentrated solution drips from the recently loaded sieve plate. Solid material is moved onto tippable sieve plate in the trays. The rotating parts rotate slowly with trays containing drug, while delivers under solvent sprays. Solid material is emptied from trays into lower trays, from where it is removed. Solvent flows down to trays of lower container, from where is returned by pumps.

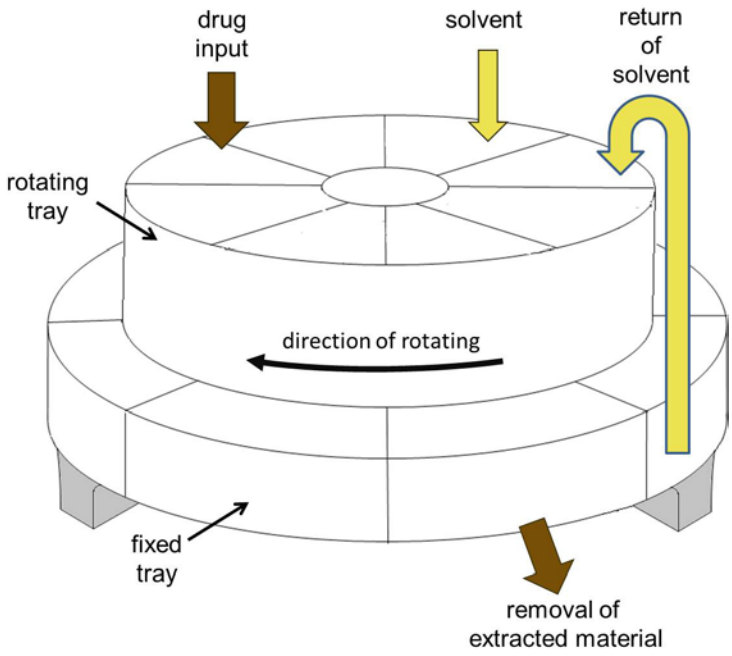

Fig. 14.15.
Rotocell extractor

Contrary to other separation operations (e.g. evaporation, crystallization), extraction does not result in pure components. Target substance can only be extracted from extract by further operations. Most frequently concentration, purification, drying, or separation from solvent is required.

At usage of high amount of organic solvent, extractant should be recovered from raffinate by regeneration.

Supercritical fluid extraction (SFE) is able to prepare extraction free from solvent, which good substitution for conventional extraction operations, primarily distillation and solvent extraction.

SFE can be realized with solvent from liquefaction of gases. Main aspects of solvent choice of conventional methods are also valid for SFE (to be cheap, not to be toxic, or harmful for product or environment and flammable).

By increase of pressure of gases and by decrease of their temperature, such a critical temperature and pressure can be achieved, that the gas liquefies. If gases are heated over critical temperature or pressure over critical is expressed, then material remains homogeneous. This temporary state among liquid and gas state of matter of material is very similar to properties of liquids.

In the viewpoint of selectivity is important that most of applied gases (carbon dioxide, methane, ethane, nitrous oxide, etc.) have apolar property, but composition of extractant can be modified by adding cosolvents (e.g. water, methanol, ethanol, acetone, hexane or other organic solvents).

Carbon dioxide can be used for extraction from herbs, since its critical temperature is low, thereby are especially able to extract biologically active, heat sensitive compounds. Extraction of APIs can be performed and realized on nearly room temperature (in the range of 31 – 60°C) without their transformation and degradation. In the end of extraction, carbon dioxide in gas state of matter leaves from extract without any remnant. In the viewpoint of solvent choice application of carbon dioxide have further advantages too:

- not harmless,
- not polluting,
- no reaction with treated material,
- not flammable ad corrosive,
- leaves without any remnant from preparation

Advantage of application of supercritical fluid extraction is that extraction can be carried out relatively fast, effectively, environmentally sound manner, within 30-120 minutes and without any remnant. Extraction can be made to selective for particular compound, and can result in almost 100% extraction rate. Its disadvantage compared to conventional procedures, that investment cost is high. This extractor operates most frequently discontinuously.

At extraction, drug is placed into extracting space bounded by filter plates. Extractant agent being in supercritical state is delivered from container containing liquid carbon dioxide, via cooled tubes by metering pumps. The temperature is ensured by coil in the mantle of metering pump. During extraction, solvent enriched with dissolved substances is delivered to separator, where dissolved substances can be separated from solvent by adjusted pressure. In the case of usage of more separators, it is a possibility for fractionation of extract too by adjusting pressure.

Solvent dissolves the soluble components from drug in the extractor. After that, solution is transferred to the first separator through pressure reducing valve and heat exchanger, where based on adjusted pressure, dissolved material and solvent are

separated partially or completely. Thereby fractionation of extraction can be achieved by adjusting pressure or application of two separators. In the end of process, pure carbon dioxide can be totally reclaimed and reused.

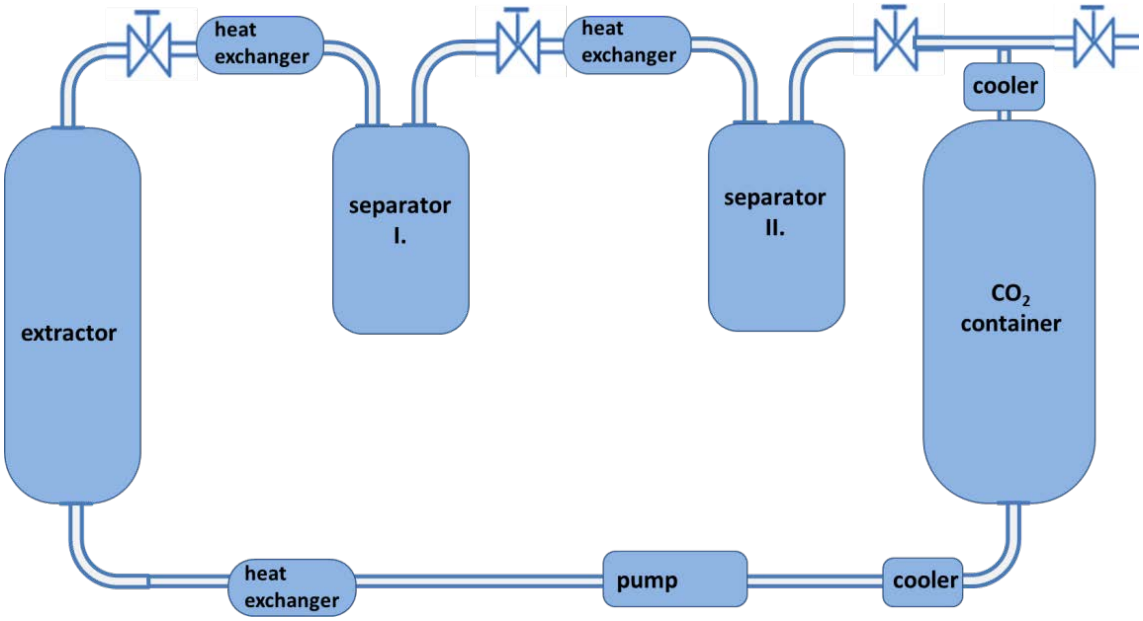

Fig. 14.16.
Supercritical carbon dioxide extraction

Questions

1) What is extraction?
2) What are the methods of herbal drug preparation?
3) What are extracts and raffinates?
4) What are the general requirements about extractants?
5) How can extraction operations be classified?
6) In what cases is liquid-liquid extraction justified?
7) What is the operating principle of mixer-settler extractors?
8) What are the principal methods of solid-fluid extraction?
9) What is the operating principle of the Soxhlet apparatus?
10) What is the operating principle of the U-extractor?
11) How is supercritical fluid extraction performed?

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Recommended websites

http://pharmlabs.unc.edu/

http://sfe.vemt.bme.hu/angol/supercritical.html

http://www.cyberlipid.org/extract/extr0008.htm

15 Extrusion

In pharmaceutical technology it is advisable to distinguish between *extrusion* and *pressing*. Both operations are separative operations, depending on whether solid and gas phases or solid and liquid phases are to be separated, but in pharmaceutical technology *pressing* is primarily used for the production of solid pharmaceutical preparations, tablets.

Extrusion is mostly used for the separation of solid and liquid phases in preparing galenicals (e.g. tinctures) from vegetable substances. In this sense extrusion means the separation of cell-fluids and cells lysated through crushing by the application of pressure.

This operation is employed if the valuable component can be extracted this way. If the liquid phase is needed, it is important to make sure that the value of the extruded substance is higher than the cost of work, energy and time invested in it. In the course of planning extrusion operations it is important to keep in mind that it has to stop before other, further unwanted components appear in the extruded liquid. If the solid phase is needed afterwards, extrusion is essentially done to reduce liquid content. In this case it can be interpreted as an operation of *desiccation* or a facilitating pre-desiccation operation.

The possibility of decreasing volume, compression is a fundamental condition of extrusion. With liquids being incompressible, the operation requires that liquids be able to escape from the press in the process.

The *efficacy of extrusion* (φ) can be calculated from the weight ratio of the extruded liquid (m_{juice}) and the substance to be extruded (m_{charge}):

$$\varphi = \frac{m_{\text{juice}}}{m_{\text{charge}}} 100\ \% \qquad (1.)$$

Factors affecting the *efficacy of extrusion* are:

1) liquid content of substance to be extruded
2) structure of substance to be extruded
3) scale of applied pressure
4) rate of pressure rise
5) duration of application of pressure

In general, it is advisable to extrude light textured drugs with higher speed, while substances of denser consistence with lower speed.

Distinguishing by the source of pressure, there are manual and machine powered extruders. The former are used primarily for extruding smaller amounts, the latter for industrial-scale application. They can be:

1) mechanical
2) hydraulic and
3) pneumatic devices.

There are batch- and continuous operation extruders.

Mechanical extruders exert the necessary pressure through various structural designs. Accordingly, there are spiral or screw type and excenter presses and extruders.

Basket type extruders are manually powered screw extruders, whose main feature is a steep-thread spindle through the rig, for the exertion of force. The extruded liquid can escape through the perforated cylinder cover surrounding the drug.

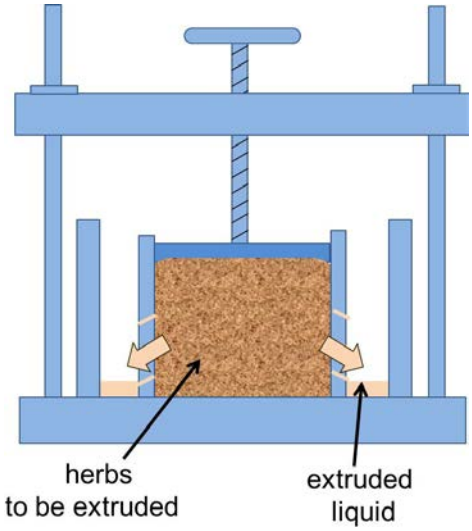

Fig. 15.1.
Basket type extruder

The substance to be extruded is placed between the divider plates of the platen-press. The substance may be wrapped in filter cloth beforehand. Pressure is transmitted evenly in the packets of the individual platens. The extruded liquid passes through the grooves to the main tank.

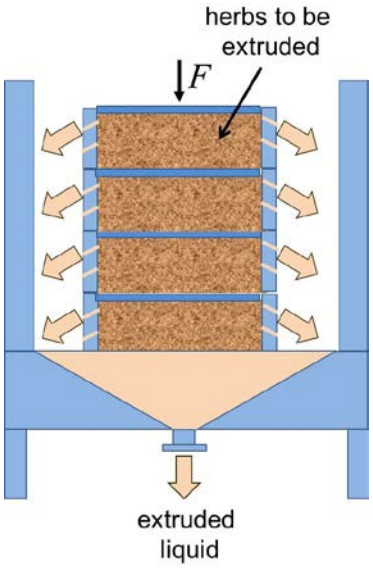

Fig. 15.2.
Platen-press

Screw extruders are machine powered. They can exert much greater force with adjustable speed of rotation. Theses devices are capable of both batch and continuous operation.

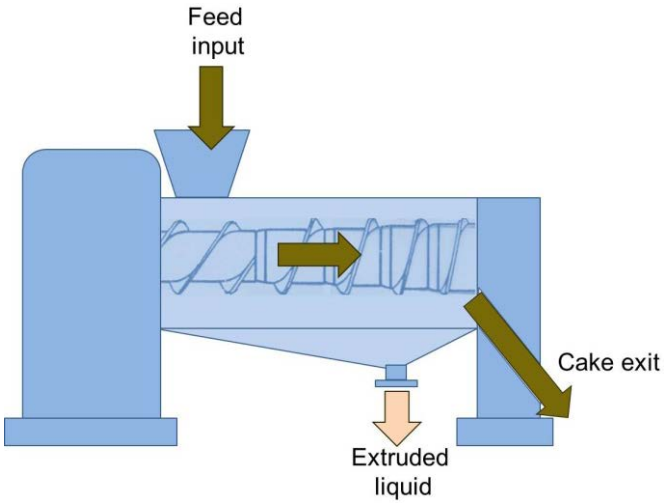

Fig. 15.3.
Screw extruder

The main part of pneumatic and hydraulic extruders is the slave cylinder. This is essentially a power conversion device, in which the compressive energy of the medium flowing into the cylinder is converted to extruding power. Pneumatic extruders are usually weaker, as compressed air is compressible; on the other hand, pneumatic slave cylinders are simpler, cheaper and capable of great operation speed.

Hydraulic extruders are capable of exerting far greater force, as hydraulic oil is not compressible, however, its operation speed is lower than that of pneumatic extruders.

Using a *Bramah press*, pressure is exerted on the substance, from which fluids are released in turn. The operation principle of this press is the fact that if pressure is applied to the liquid by a small diameter *control cylinder* in a closed system, then this pressure affects the large diameter *work cylinder*, moving it in proportion with the volume of liquid displaced. This way, high work pressures are achievable with the application of small control force. At the end of the process, following depressurization, the "cake" – i.e. remaining material - can be replaced with new material. With liquids being incompressible, the operation requires that extruded liquids be able to escape steadily from the system all through the process.

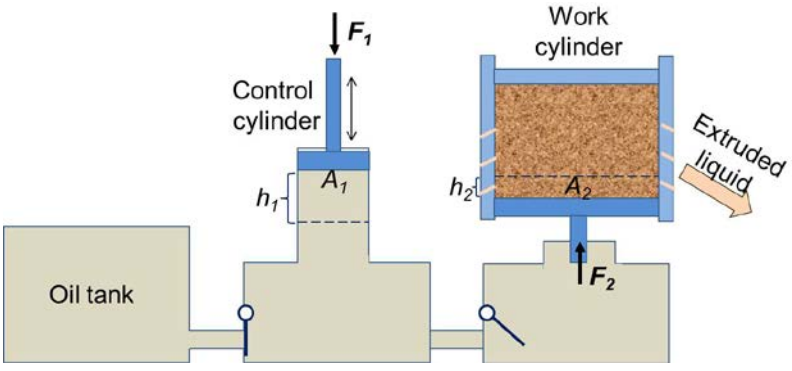

Fig. 15.4.
Bramah press

Pressures arising in the control and work cylinders in the *Bramah* press::

$$P_1 = \frac{F_1}{A_1} \tag{2.}$$

$$P_2 = \frac{F_2}{A_2} \tag{3.}$$

P_1 pressure of control cylinder
P_2 pressure of work cylinder
F_1 input force in control cylinder
F_2 output force in work cylinder
A_1 surface of piston in control cylinder
A_2 surface of piston in work cylinder

According to *Pascal's law,* pressure is transmitted equally in the liquid in all directions undiminished in the *Bramah press*, therefore:

$$P_1 = P_2 = P \tag{4.}$$

Values of volume change in the control and work cylinder:

$$\Delta V_1 = A_1 h_1 \tag{5.}$$

$$\Delta V_2 = A_2 h_2 \tag{6.}$$

ΔV_1 volume change in the control cylinder
ΔV_2 térfogatváltozás a munka hengerben

The volume change is identical in both cylinders due to the incompressibility of liquids:

$$\Delta V_1 = \Delta V_2 \tag{7.}$$

therefore

$$A_1 h_1 = A_2 h_2 \tag{8.}$$

h_1 motion of piston in the control cylinder
h_2 motion of piston in the work cylinder

Accordingly, the motion of the piston in the work cylinder is:

$$h_2 = \frac{A_1}{A_2} h_1 \tag{9.}$$

The force exerted in the work cylinder on the substance to be extruded (F_2):

$$F_2 = \frac{A_2}{A_1} F_1 \qquad (10.)$$

The application of hydraulic extrusion will not save work, but it yealds higher force with less motion:

$$F_2 = \frac{h_1}{h_2} F_1 \qquad (11.)$$

Questions

1) What is extrusion?
2) How is the efficacy of extrusion calculated?
3) What type of extruders are there according to the source of pressure?
4) What is the operation principle of the Bramah press?

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16 Crystallization

Most of our wealth of pharmaceutical substances are crystalline. This is why knowledge of the operation of crystallization is important: it is key to the production of crystals with pharmaceutically adequate parameters (crystal form, habit, grain size, crystal water content).

Reproducibility and identicalness of quality parameters of crystals in every manufactured batch is an important precondition of pharmaceutical production. The operation parameters of the crystallization process determine those physical (e.g. crystal water content, adhesiveness), chemical (e.g. stability), technological (e.g. facility, tablettability/pressability) and biopharmaceutical (e.g. solubility, absorption) characteristics of crystals, which must be taken into consideration in product design. Depending on the preparation type and the method of drug release (e.g. slowly or rapidly dissolving and/or absorbing preparation), the quality parameters of crystalline substances need to be optimized for particle size, crystal habit and solvation.

Crystal properties have a significant role in our pharmaceutical products. Among others plasticity, solubility, keeping quality, in fact even the biological employability depend on the crystallographic qualities of the active ingredients.

Crystals bear substantial important in several different dosage forms:

1) in *solution type preparations* (e.g. solutions, drops, injections, infusions)
   - 1.1) the solubility of the solute may decrease due to temperature changes, causing the formation of a new phase, crystallization, polymorphic transformation.
   - 1.2) concentration conditions may change, e.g. precipitation due to solvent evaporation,
   - 1.3) possibility of recrystallization during extended storage,
2) storing *suspensions*
   - 2.1) accelerated sedimentation and changed absorption due to unplanned particle size and distribution caused by crystal growth,
   - 2.2) recrystallization and unplanned particle size distribution may cause changed absorption,
3) in case of *ointments*
   - 3.1) in solution type ointments solutes may crystallize, precipitation may occur,
   - 3.2) in suspension type ointments recrystallization, change of particle size may happen, influencing absorption,
4) *suppositories*
   - 4.1) in solution type suppositories crystallization,
   - 4.2) in the course of suspension type suppository preparation the particle size of suspended particles may influence the distribution of active ingredients in the suppository,
5) isometric crystals are suited for making *microcapsulated* crystals,
6) during *tabletting*
   - 6.1) pressing properties may change with the change of crystal size or crystal form,
   - 6.2) crystallization or recrystallization may occur in tablets while in storage, changing the biopharmaceutical properties of the preparation.

Crytals are solid bodies, whose constituents (ions, atoms or molecules) form a three-dimensional structure, a so-called *space-lattice*. Unlike in *amorphous* substances, which are substances with entirely irregular internal structure.

The spatial description of the regular, structured layout of crystals is defined using a mathematical model, a *space-lattice*. According to this, the space-lattice is a regular, infinite array of zero-dimensional points (*lattice points*) in space.

Definition of crystal:

1) solid state material with space-lattice structure,
2) anisotropic in certain regards,
3) homogenous discontinuity.

Anisotropic, for crystals always exhibit directional properties. *Discontinuity*, for there is great distance between crystal-forming atoms, therefore space filling is discontinuous, imperfect.

Depending on their habit, crystals can be:

1) isometric,
2) needlelike,
3) columnar,
4) tabular or
5) lamellar.

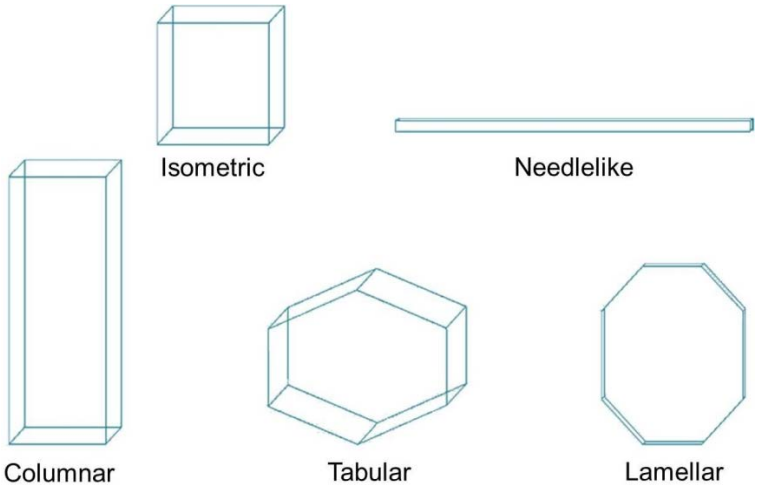

Fig. 16.1.
Crystal habits

Crystal habit is the shape, the external appearance of crystals. In pharmaceutical technology its significance is in its effect on pressability, facility and fluidity, while in terms of biopharmacy it can influence biological applicability.

Euler established a formula about the correlation between the numbers of a crystal's faces, vertices and edges:

$$f + v = e + 2 \qquad (1.)$$

f number of faces
v number of vertices
e number of edges

The concept of unit cell has been introduced by *Bravais*. Unit cells possess the attributes of the complete lattice structure and its symmetric relationships, thus it is the smallest unit of the crystal lattice. In theory, the whole crystal could be constructed by translating the unit cell in parallel with the three directions of space.

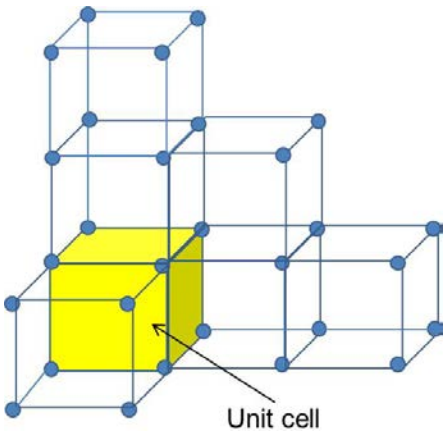

Fig. 16.2.
Unit cell

If a lattice node is selected as starting point, the other lattice nodes can be accessed by translation:

$$\vec{t} = n_1\vec{a} + n_2\vec{b} + n_3\vec{c} \qquad (2.)$$

$\vec{t}$ translation
$\vec{a},\vec{b},\vec{c}$ translations connecting the starting point with adjoining lattice nodes
n_1,n_2,n_3 integer

Based on the edge lengths (a, b, c) and the enclosed angles (α,β,γ), the volume *(V) of the unit cell is*:

$$V = abc\sqrt{(1 - \cos^2\alpha - \cos^2\beta - \cos^2\gamma + 2\cos\alpha\cos\beta\cos\gamma)} \qquad (3.)$$

In 1844 French physicist *August Bravais* established that theoretically there are 14 possible different types of unit cells, provided that only identical mass points are used in the construction of a crystal lattice.

Any conceivable crystal fits in one of the 7 types of coordinate systems or crystal systems: *triclinic, monoclinic, orthorhombic, tetragonal, trigonal, hexagonal* and *cubic*.

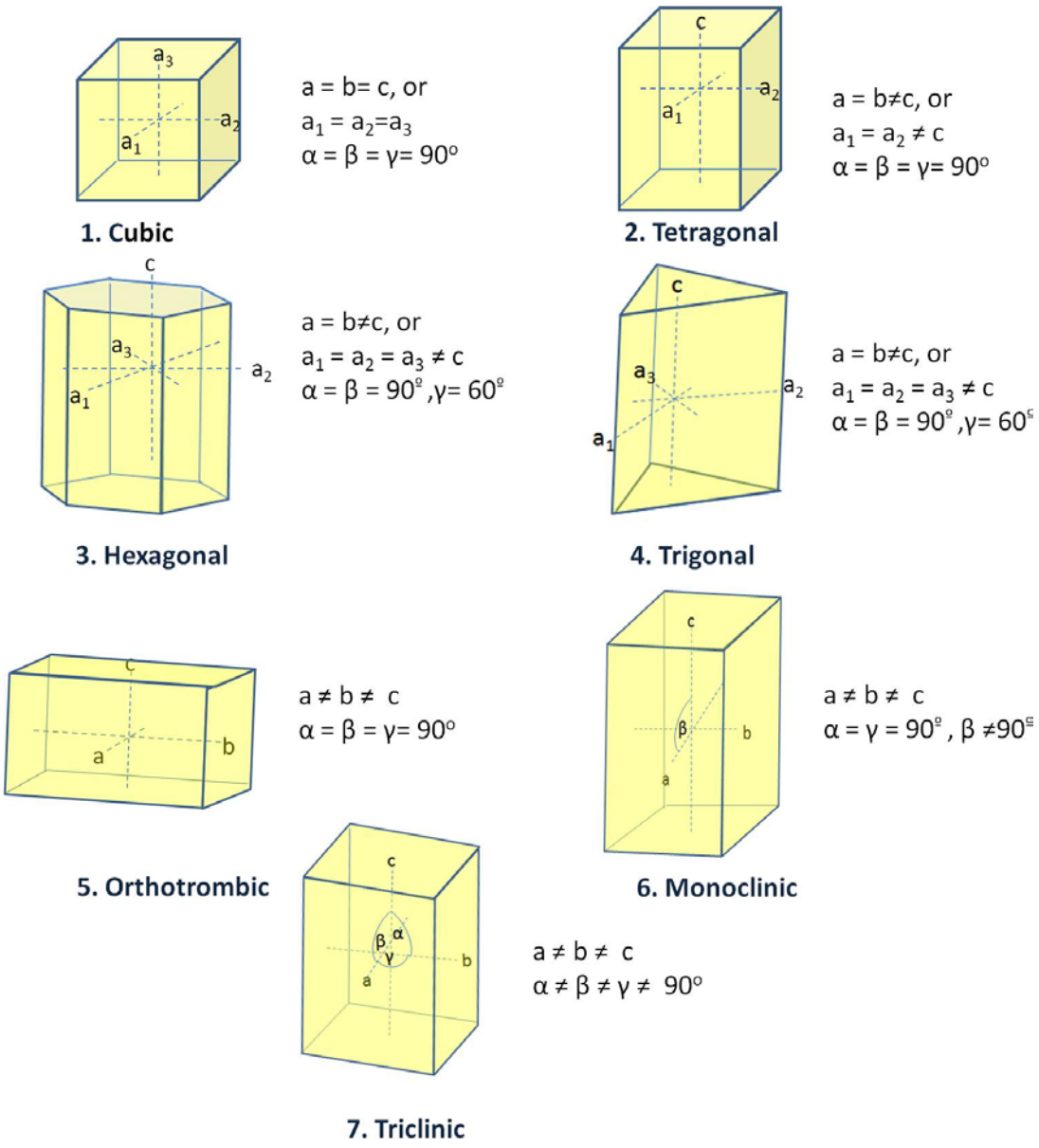

Fig. 16.3.
Crystal systems

In pharmaceutical technology the significance of *crystal form* is in the possible variation in solubility and pressability. In terms of biopharmacy, beyond solubility crystal form also has a role in absorption, thus, depending on the variation, it may cause accelerated absorption, even toxicity or on the contrary, decreased effectiveness.

Crystal form and habit combined are significant, each playing an important role in terms of pharmaceutical technology.

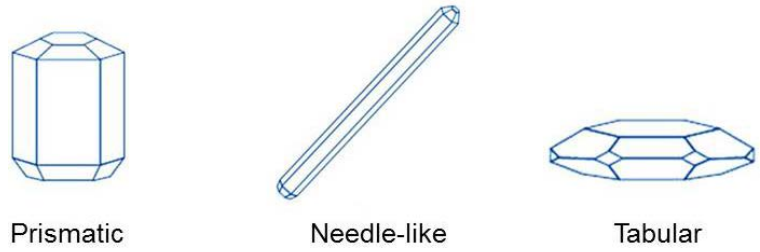

Fig. 16.4.
Different habits of hexagonal crystals

Numerous elements and compounds have multiple crystallographic forms. *Polymorphic crystals* have the same chemical composition, but their structure is different. *Isomorphy* means identical crystal structure but different chemical composition. Polymorphic transformations are usually reversible. Crystals with similar appearance and similar internal structure are called *isotypes* (e.g. NaCl, KCl). The phenomenon, when certain elements form allotropes of different crystal structures under the influence of external conditions (e.g. pressure, temperature) is called *allotropy*.

When a medicine is marketed, contingent *polymorphism* has to be taken into consideration. *Polymorphism* is a peculiar feature of elements and molecules: they form different crystal forms under different conditions. These allotropes have different physical and physico-chemical features, which can be described by different types of methods of investigation (e.g. x-ray diffraction, thermal analyses, spectroscopic methods, etc.). The formation of allotropes can be influenced through the operation parameters of crystallization. Crystal forms may morph into each other in the course of the preparation or storage of products, which can affect producibility and shelf life. From a biopharmaceutical aspect changes in solubility and absorbency can have grave consequences. Nitrofurantoin, chloramphenicol, various sulphonamide derivatives and cacluim carbonate crystals are particularly prone to polymorphism.

Crystallization is a process in which a solid state substance is precipitated from a noncrystalline liquid state compound (melt, solution).

The purpose of crystallization can be:

1) extraction of the given substance,
2) separation from other substances,
3) purification,
4) achieving the appropriate crystalline form required for further operations.

Solid crystalline active ingredients and excipients must be manufactured with their crystal form, habit, grain size and crystal water content complying with quality standards, as they are required for further technological processing.

Crystallization from liquid state can be either *melt crystallization* or *solution crystallization*.

Melt crystallization is a thermal separation operation. This method produces the required pure component from a melt compound of two or more components without the addition of solvents, in the form of a crystalline solid phase substance. The essence of the process is that nucleation starts when the temperature of the melt compound decreases to an appropriate level. The rate of nucleation is highest around the arrest point. In general, the difficulty of nucleation is proportional to the size and complexity of crystallizing molecules.

Solution crystallization occurs when the substance to be crystallized is supersaturated in the solution at the given temperature. Supersaturation of the solution can be achieved by cooling, distillation and precipitation.

Crystallization by cooling occurs when the solution's concentration reaches or exceeds the level of saturation at the given temperature as a result of cooling. This method is useful when the solubility of the substance to be crystallized decreases significantly with the reduction of temperature.

Saturation by distillation occurs when part of the solvent is gradually evaporated, making the solution more concentrated, more saturated and at a point supersaturated; this is where crystallization begins. Distillation is useful for crystallizing substances whose solubility is not or liminally influenced by variations in temperature.

In case of *precipitation* we add to the solvent of a definite substance another solvent which is a partial solvent or non-solvent of the substance. This method is useful when the solubility of the solute is practically independent of variations in temperature and there is a preferably inexpensive nontoxic solvent, which meets the above requirements.

Crystallization is a typically multi-stage process, defined by successive operations. The starting point is usually a singe phase compound system of multiple components (solute, solutes, solvent, solvent compound. Decreasing solubility induces a metastable state, which is stabilized in turn by the precipitation of a phase.

Crystallization begins with the formation of tiny crystals, called nucleation, followed by crystal growth. Occasionally, the process fails to start even in supersaturation. At such times the system needs to be pushed from this static condition; under laboratory conditions this can be achieved by scratching the glass crystallization dish with a glass rod or by seeding. If the solution is cooled gradually, large crystals are formed. If it is rapidly cooled or intensively shaken or agitated many small crystals are formed.

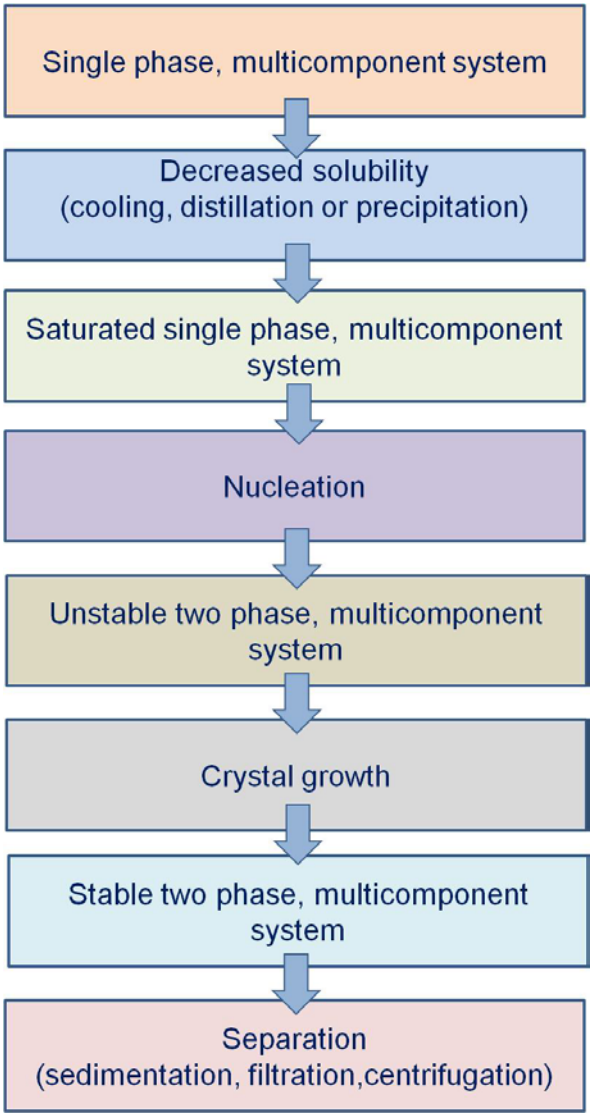

Fig. 16.5.
The process of crystallization

A solution is saturated, if it is in balance with the present solid state solute. There is no such balance in a supersaturated solution. According to *Ostwald* the saturation and supersaturation curves enclose a metastable zone. On the concentration-temperature graph the unstable range is above the supersaturation curve, the stable range below the saturation curve. The saturation curve indicates the emergence of dynamic equilibrium, where the quantity of crystals formed within a unit of time equals the quantity of crystals dissolved. Crystal formation is unlikely in the metastable zone (*Ostwald-Miers* region), but existing nuclei keep growing. There is spontaneous crystal formation in the unstable range, with the rate of nucleation abruptly increasing.

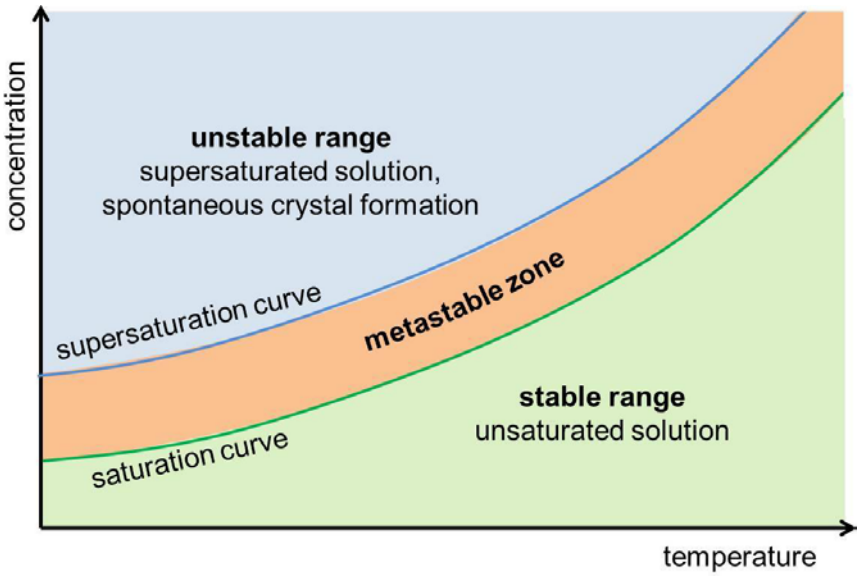

Fig. 16.6.
Saturation and supersaturation curves

The kinetics of the crystallization process can be described with nucleation and crystal growth rates. The way the process happens depends on the level of supersaturation in the solution, temperature, intensity of agitation and the presence of contaminants.

The *rate of crystallization* can be interpreted as the aggregate of the number of nuclei formed in a unit of time and the growth of existing crystals in a unit of time.

Crystal size and *particle size distribution* depend on the proportions of nucleation and crystal growth rates. If nucleation rate (V_g) is lower than crystal growth rate (V_{kn}) ($V_g < V_{kn}$), there are few nuclei formed and the process shifts toward growing large crystals. If, however, nucleation rate is higher than crystal growth rate ($V_g > V_{kn}$), the result is a mass of small crystals.

Nucleation is *homogenous*, if nucleation is spontaneous due to supersaturation in the solution. *Heterogenous nucleation* occurs when it is triggered by suspended foreign matter (e.g. mechanical contamination, seeding crystals) or external impulse (e.g. agitation or shaking). The two mechanisms are fundamentally different.

The driving force behind homogenous nucleation is supersaturation.

Nucleation rate is:

$$\frac{dn}{dt} = k_g (c - c_m)^i \tag{4.}$$

n number of nuclei,
t time,
c current concentration of solution,
c_m concentration of supersaturated solution,
k_g nucleation rate constant,
i empirical parameter.

Diffusion nucleation rate is:

$$\frac{dm}{dt} = k_{gn} A(c - c_f) \tag{5.}$$

m crystal mass,
t time,
k_{gn} nucleation rate constant,
A nucleus surface,
c concentration of solution,
c_f concentration on the nucleus surface.

Convection nucleation rate is:

$$\frac{dm}{dt} = \frac{1}{\frac{1}{k} + \frac{1}{\kappa}} A(c - c_f) \tag{6.}$$

k constant typical of circulation,
κ surface reaction rate constant.

The parameters of the end product of crystallization depend on the solvents used in recrystallization. Frequently used solvents, which are suited for being used for crystallization by themselves or as components of a compound:

- water,
- methanol,
- ethanol,
- acetic acid,
- acetone,
- ether,
- mineral ether,
- dioxane.

If the purpose of crystallization is purification, rapid cooling is advisable. Large crystals may contain residual solvent, mother-liquor and other impurities. To make pure, less contaminated large crystals, the system has to be redissolved and recrystallized using a pure solvent. This operation is called *recrystallization*. Cleaning (*washing*) of the surface of crystals may be necessary. This requires a solvent which does not solve the crystalline substance, but solves contaminants.

Solutions often contain components whose elimination requires boiling or the addition of a solid state absorbent. This operation is called *clarification*. It can prevent the contamination of crystals by keeping certain impurities from being enclosed or absorbing on the surface of crystals. *Clarifiants* (e.g. bentonite, activated carbon) usually have high specific surface area and are capable of adsorbing large quantities of matter to their own surface.

Depending on the crystallizer equipment, choice of solvent, temperature, operation parameters, general solubility conditions and parameters influencing crystallization, crystallization yields different quantities of crystals and product quality (e.g. impurities, crystal water content, crystal structure – polymorphic forms).

The following correlation indicates the *yield of crystallization*:

$$M = \frac{R[100m_{ds} - S(m_{solv} - E)]}{100 - S(R-1)} \qquad (7.)$$

M final crystal mass,
R molecular mass of hydrated solute / molecular mass of dry solute,
S solubility at the operation's terminal temperature,
m_{ds} initial mass of dry solute,
m_{solv} initial mass of solvent,
E quantity of solvent evaporated in the course of the operation.

The driving force of crystallization in crystallizer devices can be:

- internal conditions (spontaneous crystallization),
- cooling,
- distillation or evaporation (heat transmission),
- vacuum.

In crystallizer tanks cooling is done by spontaneous convection under atmospheric conditions, with or without agitation, with spontaneous crystallization in batches. Today, due to its slowness and unrepeatable cooling parameters this method is not used for industrial purposes.

In agitated tank crystallizers and scraped surface crystallizers heat transfer is conducted through the jacket of the crystallizer using surrounding air or the circulation of a cooling medium, as according to the theorem of duplicator. Built-in agitators and scraper blades are designated to ensure uniform cooling of the solution in the crystallization space, creating overall equal conditions for the process. These devices are capable of continuous operation.

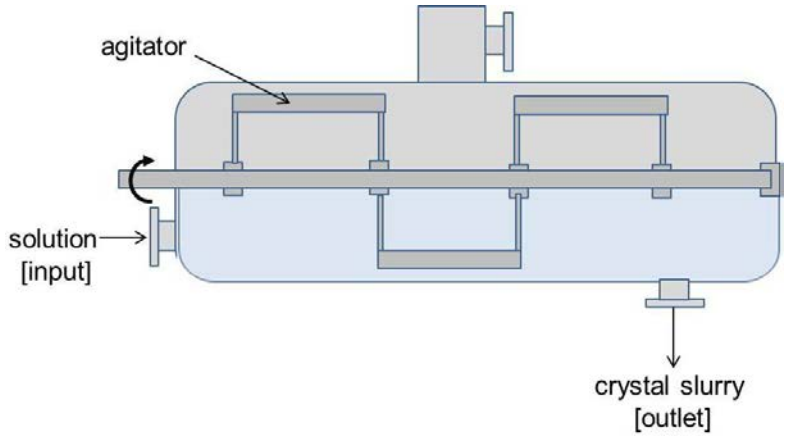

Fig. 16.7.
Agitated or scraped surface crystallizer

In open-duplicator crystallizers under atmospheric conditions, appropriate granulation and particle-size distribution can be maintained by controlling cooling and agitation speed or possibly by the installation of additional scraper blades.

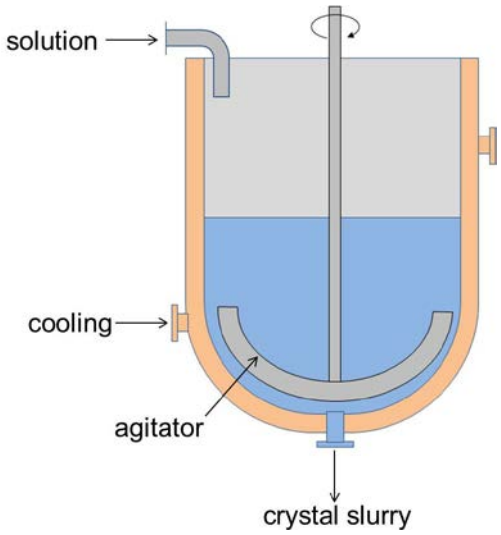

Fig. 16.8.
Open-duplicator crystallizer

Closed-duplicator crystallizers are principally used for crystallizing labile substances. In case of heat-sensitive substances the temperature required for distillation can be reduced by the application of vacuum.

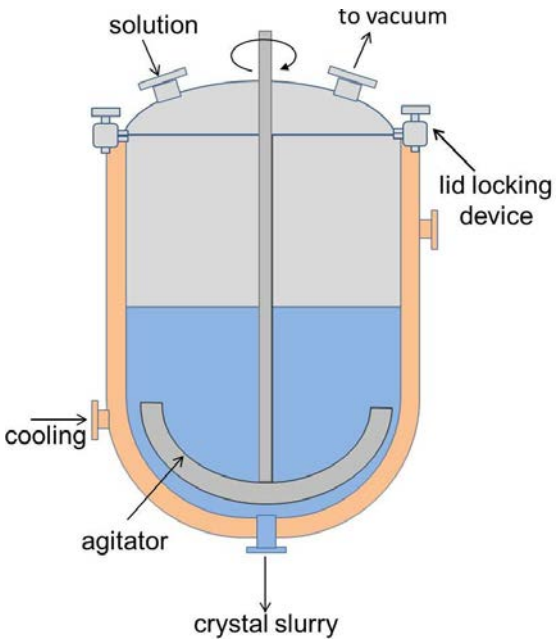

Fig. 16.9.
Closed-duplicator crystallizer

Immersed rotary drum crystallizers are continuous operation devices, as the solution is fed in the device steadily, with the optimum crystallization temperature maintained by hot water or steam heating. The substance crystallizing on the mantle surface of the cylinder immersed in the solution is steadily removed by a scraper blade. By creating reproducible parameters, this method is capable of producing nearly identical granularity crystals.

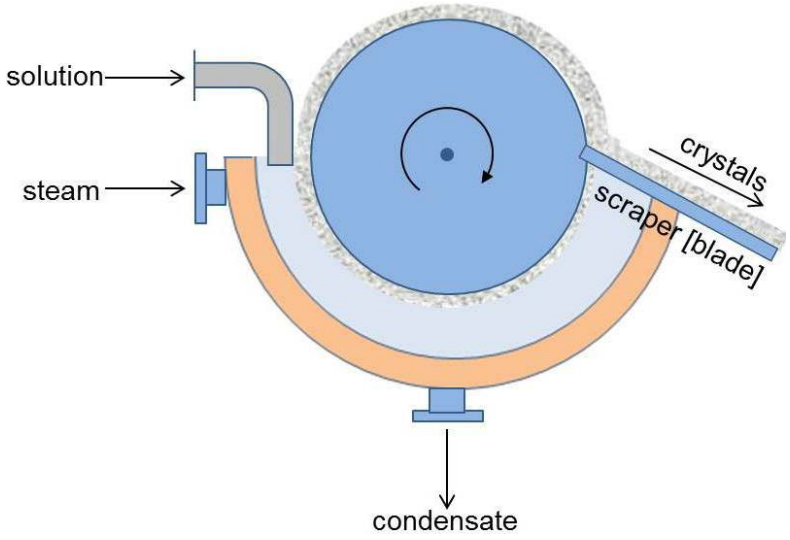

Fig. 16.10.
Immersed rotary drum crystallizer

They can be used for crystallizing *supercritical fluids* obtained by condensation of gases/vapours, producing crystals of very narrow size distribution, practically identical granularity, which is highly beneficial in tablet pressing.

As shown in the pressure-temperature state diagram, gases subjected to increasing pressure and decreasing temperature condensate when they reach a critical point of pressure and temperature. If the substance is heated beyond critical temperature and subjected to pressure beyond critical, the substance remains homogenous, becoming a supercritical fluid. This is a state between gas and liquid, where the fluid has properties very smilar to liquid properties.

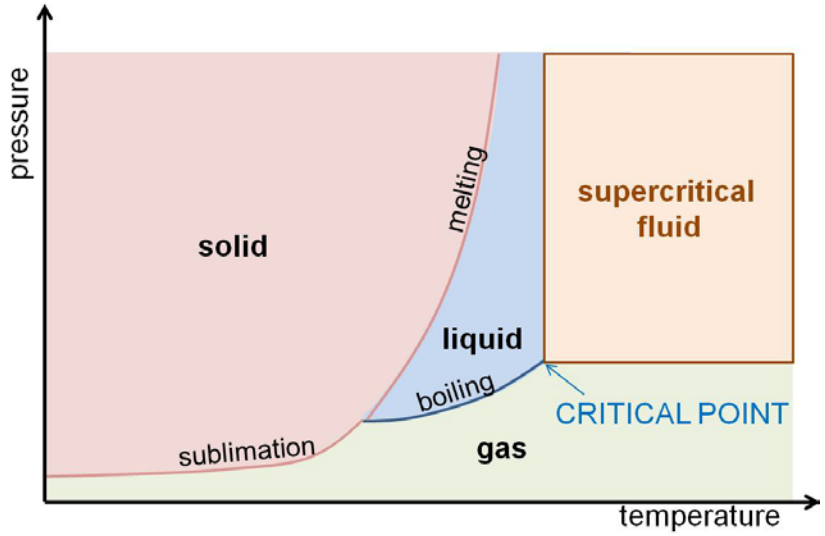

Fig. 16.11.
Pressure-temperature state diagram

Depending on whether the substance to be crystallized is soluble in the supercritical solvent, there are two available methods.

The *RESS* (*Rapid Expansion from Supercritical Solution*) method is useful if the substance to be crystallized is soluble in the supercritical solvent. First, the the substance to be crystallized is dissolved in the supercritical solvent, followed by spraying the solution through a special nozzle. At this point pressure is abruptly decreased, making the solute supersaturated in the solution, leading to the precipitation of small particles of narrow size distribution.

The *GAS* (*Gas-antisolvent Recrystallization*) method is useful in cases where the substance to be crystallized is not soluble in the supercritical solvent. First, the substance is dissolved in a liquid solvent (e.g. methanol), followed by the addition of a supercritical solvent as antisolvent, which rapidly precipitates the substance from the solution.

A further benefit of reactions with supercritical fluids is that the product can be separated from the solvent by fractionation, applying gradual reduction of pressure.

Crystallization is usually followed by the separation of mother-liquor, done by *filtration* or *centrifugation*, and finally *drying* completes the process.

Spherical crystallization procedures have been specifically developed for pharmaceutical purposes. Spherical crystals are important for their smoothness and flowability as well as enhancing pressability and taste-masking. Spherical agglomeration and [quasi-]emulsion solvent diffusion are techniques capable of producing spherical crystals.

Spherical agglomeration (SA) yields small crystal agglomerate particles by precipitation: the nearly saturated solution of the substance to be crystallized is mixed into a "solvent" that solves the substance poorly. The essence of the process is that the two liquids have to be able to blend and have higher cohesion between them than the cohesion between the substance to be crystallized and the original solvent, which is favourable for precipitation and the formation of bridges that facilitate agglomeration. Spherical agglomeration is facilitated by the addition of a small quantity of a third, so-called *bridging solvent*. An example for the application of this technique is the production of spherical crystals of salicylic acid from a compound of water, ethanol and choloform.

In the *emulsion solvent diffusion (ESD)* technique the substance to be crystallized is first dissolved in a solvent, then this solution is dispersed in an immiscible liquid medium in which the substance to be crystallized is not soluble, making an emulsion. Components have to be selected so that affinity between the substance to be crystallized and its solvent be stronger than between the solvents good and bad for the substance to be crystallized. In the course of mixing the solvent in the emulsion droplets starts to diffuse to the outer phase across the boundary surface. The solution inside the droplets becomes gradually more and more concentrated, eventually resulting in crystallization.

Questions

1) Define the crystals?
2) What role do crystals play in different dosage forms?
3) How crystals are characterized by Euler correlation?
4) What is the definition of polymorphism and allomorphism?
5) What is the purpose of doing crystallization?
6) What are the main steps of crystallization?
7) What is termed to Ostwald-Miers area?

8) With which correlation can be the output of crystallization characterized?

9) How does submerged cylindrical crystallizer operate?

10) How can be spherical crystals produced?

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17 Filtration

Filtration is process in which particles dispersed in liquid or gas are separated out.

Filtration is usually more expensive than sedimentation, but it has the advantage that it is applicable without regard to density differences and it allows enhanced separation.

The liquid produced after filtering is called *filtrate*, while the solid remaining in the filter is called *residue* (*retentate*, *filtrand)* or *filter cake*. The filtering device or the material of the filter is called *filter medium*. In such cases periodical or steady residue removal has to be ensured in the course of filtering operations.

Method of filtration should be chosen according to the size of particles to be filtered. *Macrofiltration* is used for separating particles larger than 1 µm, *membrane filtration* for particles smaller than 1 µm.

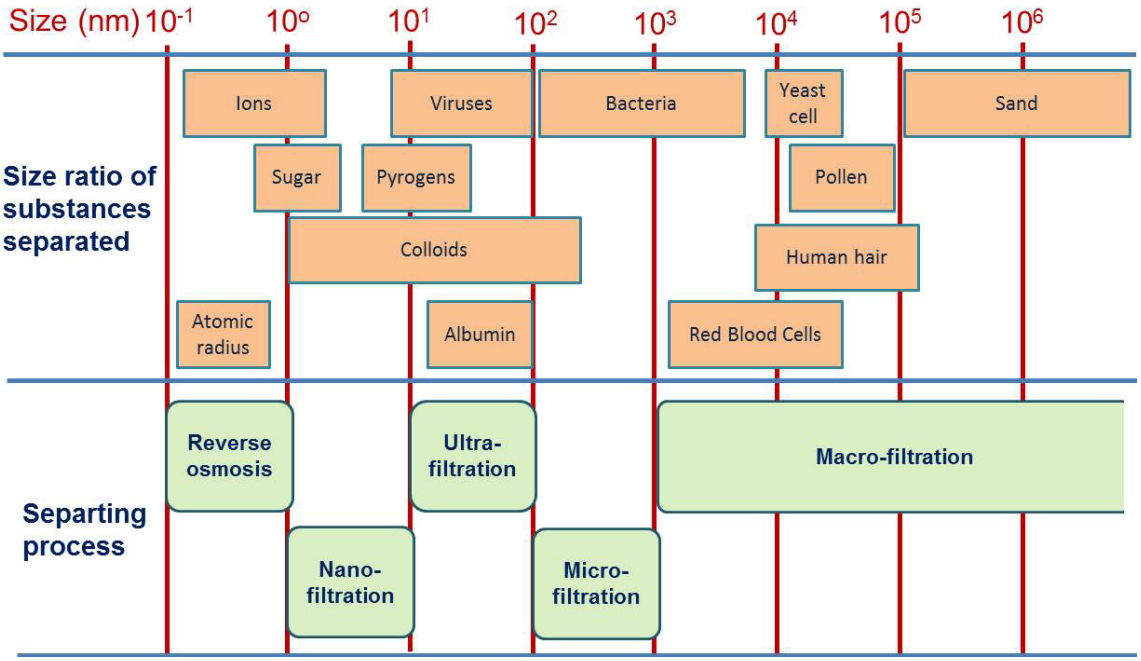

Fig. 17.1.
Particle size and possible methods of filtration

17.1 Macrofiltration

The purpose of macrofiltration can be:

- extraction of solid substance (e.g. precipitation, crystallization),
- extraction of residue (e.g. elimination of mechanical impurities),
- air purification (e.g. production of filtered air, aseptic workplace, air supply for clean room)

Besides particle size and particle size distribution, the macrofiltration method to be used is determined by the properties of the substance to be filtered.

Filtration can be *surface filtration* or *depth filtration*. In macrofiltration the liquid flow carrying suspended particles is usually perpendicular to the filter bed.

In *surface* filtration the filter medium initially retains particles larger than pore size, letting smaller particles through. These granules can cover most of the capillary inlets, moreover, if all the capillary inlets are blocked, filtration may halt. In such cases residue has to be removed.

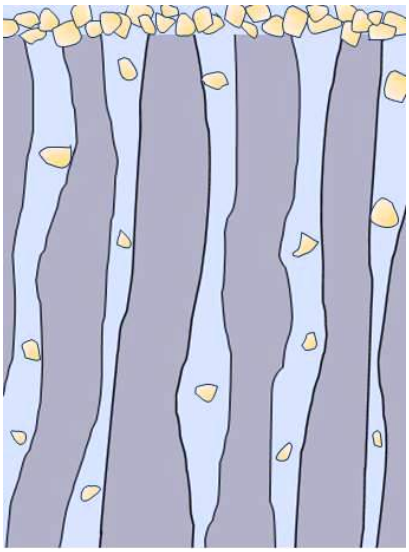

Fig. 17.2.
Surface filtration

It is more common that filtered particles form a bed of increasing thickness, retaining their permeability. At this point the solid substance forms a *cake* on the filter surface, itself functioning as a filter-bed. Filter cake formation starts with the largest particles of the substance to be filtered, with ever smaller particles settling on this layer, thereby forming the bed that is capable of filtering out finer particles. The texture of the filter bed is therefore an important factor in terms of filtration, playing a dominant part in the filtration process. Increasing filter resistance decreases the amount of liquid flowing through in a unit of time (filter performance).

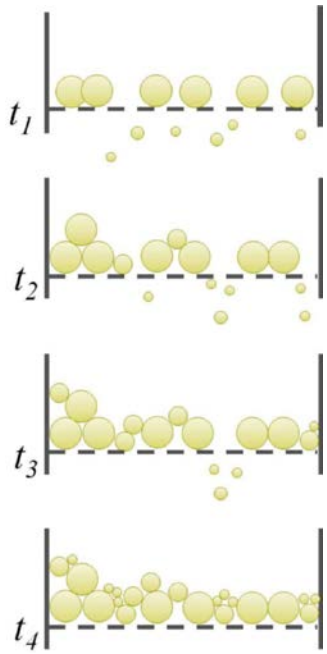

Fig. 17.3.
Filter cake formation in the function of time (t)

Homodisperse systems usually allow quicker filtration due to poor space filling and larger capillary diameters. On the other hand, heterodisperse particles fill space mor efficiently, being suited to filter finer grain fractions due to their lower cross-sectional area, thereby decreasing the speed of filtration. It is also characteristic of this type of filtration that the granule composition of the filter bed changes with time and its space filling varies; therefore repeating the filtration of the filtrate is advisable for the sake of better filtration.

Surface filtration can be performed with perforated plate, sieve plate, wire mesh, filter cloth, felt or filter paper. The primary function of the filter plate is therefore not full filtering, but enabling the formation of a filter cake by providing a suitable sustaining surface for the depositing mass of particles and withstanding the strain of vacuum or pressure.

In case of *depth filtration* (e.g. activated carbon filtration) the particles finer than the pore size of the filter medium enter the pores and channels of the grainy or fibrous filter medium and deposit there. Particles accumulate in the cavities of pores and capillaries due to direction breaks and changes in channel cross section, depositing due to inertial and surface forces. The cake forming on the surface is insignificant. Extremely fine particles are adsorptively bound by surface and capillary forces. In the course of filtration the permeable cross section and porosity of pores decreases and the resistance of the filter medium increases.

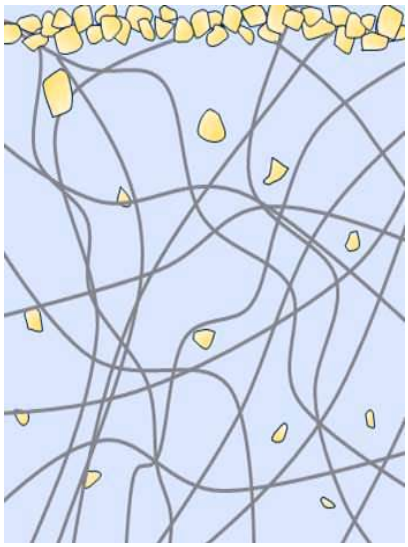

Fig. 17.4.
Depth filtration

The above mechanisms are often intermingled in real-life filtration processes, with the filter initially retaining only larger particles, acting as a surface filter, producing a cloudy filtrate. Later, with the formation and buildup of the filter cake the depth filtering mechanism prevails and subsequently the filtrate gradually clears up.

The *filter's performance* is described by the *filtration rate* (the amount of filtrate flowing through in a unit of time, *V/t*).

Filtration rate in correlation with unit filter surface (*A*) is:

$$v_{sz} = \frac{1}{A} \cdot \frac{dV}{dt} \tag{1.}$$

The *Hagen – Poiseuille* law is applicable in case of laminar, frictional and temporally constant flow. According to this, filtration can be considered a flow flowing through parallel capillaries and average rate is one half of maximum rate:

$$v_{átl} = \frac{v_{max}}{2} = \frac{r^4 \pi \Delta p}{8 \eta h} \tag{2.}$$

r radius of capillary,
η viscosity of liquid,
h length of capillary.

Darcy studied the flow of liquids through granular media at constant pressure and established that filtration rate is $\left(\frac{dV}{dt}\right)$:

$$\frac{dV}{dt} = B \frac{A \Delta p_l}{\eta L} \tag{3.}$$

V volume of filtrate,
t duration of filtration,

B permeability constant of the filter bed,
A filter surface,
Δp_l drop of pressure on the filter bed,
η dynamic viscosity of filtrate,
L width of filter bed.

Taking the resistance of the cake into consideration:

$$\frac{dV}{dt} = \frac{A\Delta p_l}{\eta(R_m + \frac{\alpha c V}{A})} \tag{4.}$$

R_m resistance of filter medium,
α specific cake-resistance,
c concentration of the substance to be filtered

The *Carman* equation is the base equation of filtration:

$$\frac{dV}{dt} = \frac{\Delta p_l A}{\eta\left(\alpha c \frac{V}{A} + R_m\right)} \tag{5.}$$

V volume of filtrate,
c mass of particles aggregating from a unit of filtrate,
R_m resistance of filter medium,
A filter surface.

Specific cake resistance (α) is:

$$\alpha = \frac{k(1-\varepsilon){a_f}^2}{\varepsilon^3 \rho_s} \tag{6.}$$

ε porosity,
ρ_s density of solid particles,
a_f specific surface of particles.

The *Kozeny-Carman* relation applies to laminar flow passing through agglomerated particles. According to the model the permeability constant is:

$$B = \frac{\varepsilon^3}{k(1-\varepsilon)^2 {a_f}^2} \tag{7.}$$

$$\frac{dV}{dt} = \frac{\varepsilon^3}{k(1-\varepsilon)^2 {a_f}^2} \cdot \frac{\Delta p}{\eta l_i} \tag{8.}$$

ε porosity,
η viscosity,
k *Kozeny-Carman* constant,

l_i width of sludge cake,
a_f specific surface of particles.

Filtration procedures can be intermittent and continuous operations.

In practice there are four types of filtration according to the driving force of filtration:

1) hydrostatic pressure (gravitational filter),
2) centrifugal force (filter centrifuge),
3) under pressure on the filtrate side of the filter bed (vacuum filter),
4) overpressure on the feed side of the filter bed (pressure filtration)

Gravitational macrofilters operate on hydrostatic pressure, deriving the force for filtration from the force of gravity at atmospheric pressure.

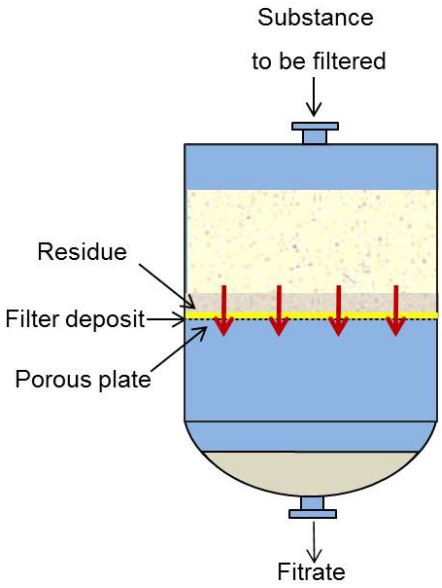

Fig. 17.5.
Gravitational filtration

Centrifugation is a separation process based on differences in density, executed in a centrifugal field of force. If the drum of the centrifuge is perforated, centrifugation is filtration by centrifugal force; if it is not perforated, it is sedimentation centrifugation.

Centrifugal macrofilters allow short time filtration due to high rotation speed.

The force (F_c) effecting the particle of m mass in a centrifugal field of force is:

$$F_c = \frac{mv^2}{r} \qquad (9.)$$

v peripheral speed of drum,
m mass of particle,
r radius of drum,
g gravitational acceleration.

$$v = \omega r = \frac{2\pi n}{60} r \tag{10.}$$

ω angular velocity of drum,
n rotation speed (revolutions per minute).

$$F_c = \frac{mv^2}{r} = \frac{Gv^2}{gr} = \frac{G}{gr}\left(\frac{2\pi n}{60} r\right)^2 \approx \frac{Grn^2}{900} \tag{11.}$$

G weight of particle

In centrifugal filtration the solid phase deposits on the inside of the mantle, forming a filter cake. The liquid phase passes through it under the influence of the centrifugal force.

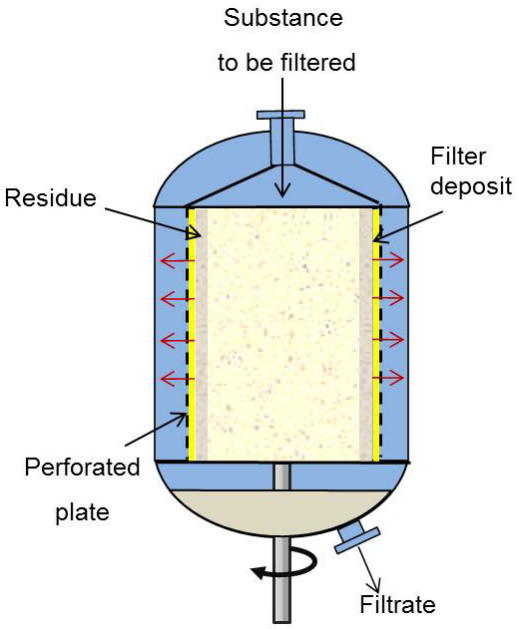

Fig. 17.6.
The operating principle of filtering centrifuges

Laboratory filtering centrifuges are suited to filter small volumes of difficult to filter samples.

Fig. 17.7.
Laboratory filtering centrifuge

Swing centrifuges are useful equipment under industrial conditions. Their vertical shaft is embedded in a base frame, with the driving motor also mounted on it. The centrifuge is suspended on three ball-jointed rods, thus the base plate is kept free of the strain of direct vibrations. The wall of the flanged rotor piece is perforated. It is enclosed in a reservoir mantle conFig.d for holding the filtrate.

Due to their hazardous nature, their operation requires special safety measures, as it is common with centrifuges in general. Centrifuges must not be started up with their cover open and brakes engaged.

Fig. 17.8.
Industrial centrifuge

When *vacuum* is employed, the process is accelerated by the application of pressure reduction or suction effect. In this case pressure above the filter (p_1) is higher than pressure below the filter (p_2), i.e. $p_2 < p_1$.

The simplest vacuum-driven filter-bed filters are the so-called v*acuum-filtration* used in laboratory practice.

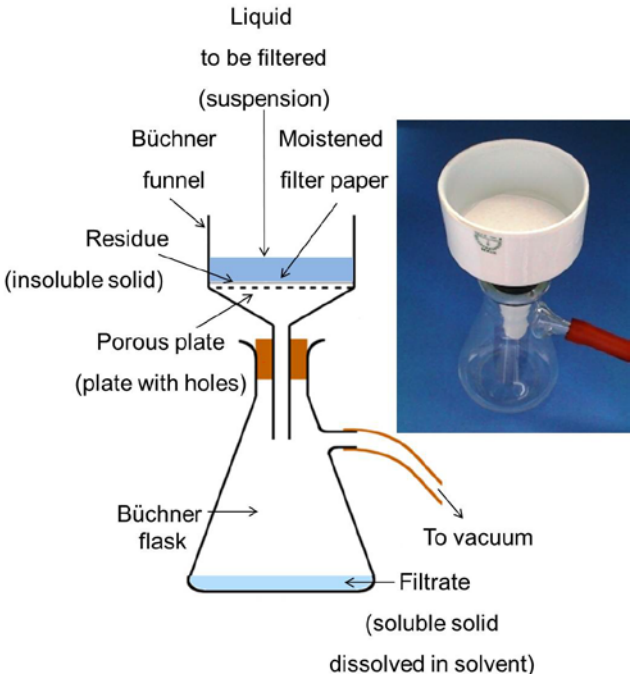

Fig. 17.9.
Laboratory vacuum-filtration

Vacuum-filters can also be applied well under industrial condidions.

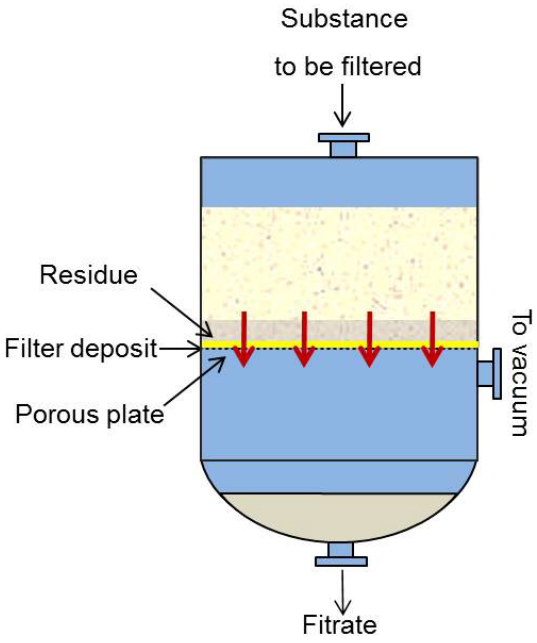

Fig. 17.10.
Operation principle of intermittently working vacuum-filters

Filtration happens on the mantle of *rotary vacuum-drum filters*, which are suited for industrial scale working in continuous operation. The drum that rotates around a horizontal axis is submerged in the suspension-filled tank. Vacuum makes suspended particles adhere to the mantle of the drum filter, which are washable and desiccable; finally, a scraper blade removes the filtered substance. The filtrate inside the drum is transferred to the central duct, from which it can be steadily drained.

The particle size distribution needs to be taken into consideration when rotation speed, and thereby the thickness of the forming bed, is selected. The reason for it is the fact that the device sucks the suspension to be filtered inward, making the smaller particles settle first, which may hinder filtration. The usual bed width for easy to filter (less heterodisperse) suspensions is 4-6 cm; for poorly filtering suspensions less than 1 cm. Having the substance to be filtered agitated in the duration of filtration is advisable.

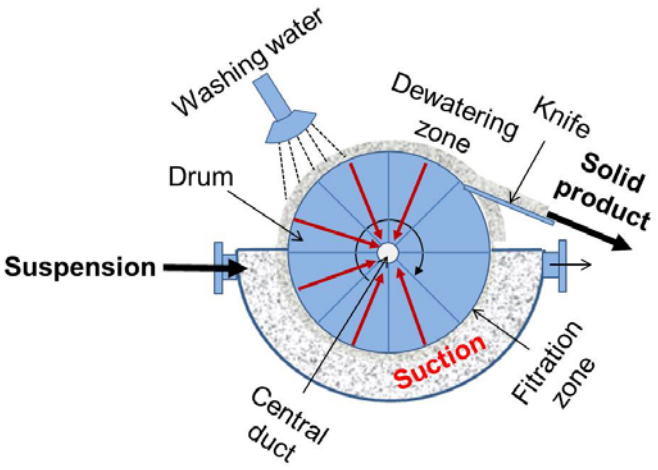

Fig. 17.11.
Continuous operation rotary vacuum-drum filter

In case of *pressurized filtration* the process is accelerated with the application of overpressure on the feed side of the filter. $p_1 > p_2$, pressure above the filter is higher than pressure below the filter, which can be atmospheric pressure. The filter must be able to withstand both the weight of filter sludge and the strain of overpressure.

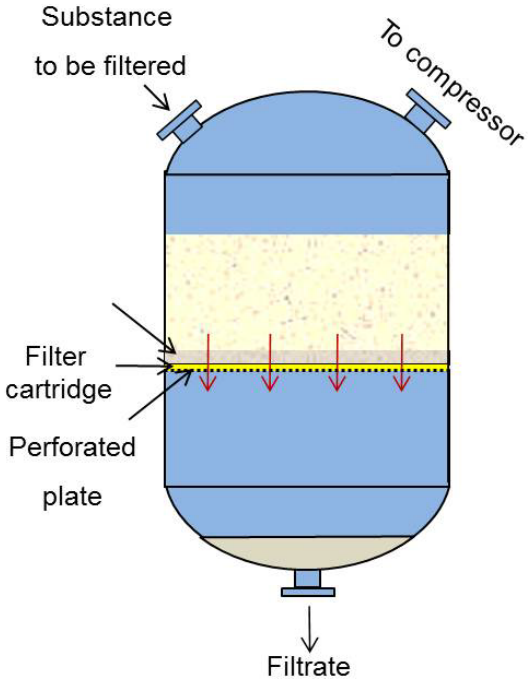

Fig. 17.12.
Operation principle of pressurized filters

The materials employed as filters are usually either *fibrous*, *solid body* or *membrane* type.

Filter paper, cotton wool, multi-layered gauze and filter cloth on filter frame (*tenaculum*) are *fibrous filter materials*. The system of internal pores is up to 70-80% of the bulk of Seitz filter sheets, allowing very effective depth, coarse, fine and sterile grade filtration. These filters were initially made of asbestos and cellulose, more

recently of pre-treated cellulose, diatomaceous earth and perlite. They are employed in pharmaceutical and biotechnological production.

Filter presses ae batch operation pressurized filtration devices, consisting of multiple filter plates working in parallel. Filter presses are versatile and their footprint is relatively small. Filtration occurs between compressed filter plates. Filtrate pressed through the filter medium is drained between the plate frames. Removal of the filtered substance is cumbersome. It is usually done by replacing the filters, so the device has to be stopped, opened and afterwards reassembled.

In the *chamber filter press* there are suitable chambers made for collecting the filter cake. Filtrate leaves through the filter bed (filter cloth) covering the chambers. It is usually used for filtering "thin", low dry-matter content suspensions.

Frame and plate is another type of filter press. It is another batch operation device made of stainless steel, equally suited for laboratory, medium scale and industrial environments. It is widely used in pharmaceutical technology. It consists of multiple closely fitted filter units, namely filter frames suspended on supports, and filter sheets in between. The row is closed on both ends by head plates. The assembly is squeezed by a spindle shaft. The liquid to be filtered can be circulated under pressure. The substance to be filtered is filled in the device with a hose. There are pressure gauges for tracking the filtering operation. Filtrate can be drained to a receiving vessel at the filter output. The filter cake can be washed out after filtering is complete. Frame and plate filters have a larger sludge containers than chamber filter presses, thus they are suited for filtering higher dry-content suspensions.

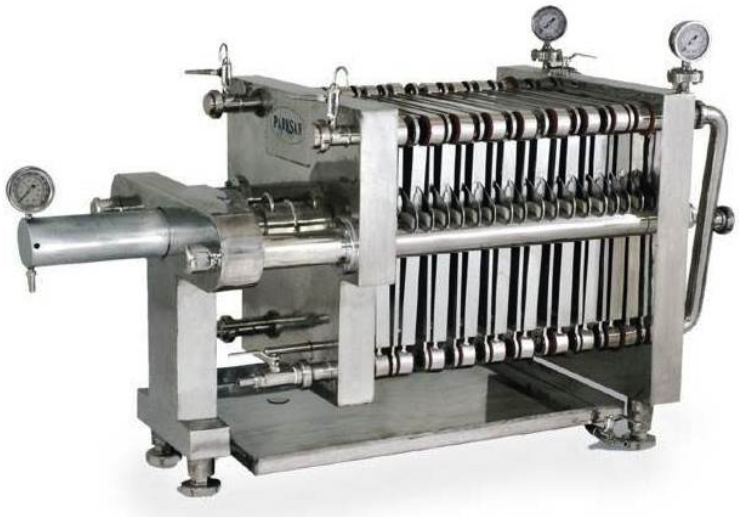

Fig. 17.13.
Frame and plate filter

Seitz filter sheets are made of high purity, carefully pre-treated cellulose, diatomaceous earth and perlite. Due to their material composition and structural design they are depth filters with a major (70-80%) part of their volume hollow inside, consisting of fine labyrinthine channels. Their capacity for absorbing floating particles is extremely high. Pre-filtering the solution on a screen filter can significantly extend the service life of membrane filters. In addition to coarse and fine filtration EK mark (Entkeimungsfilter, EK) provide sterilizing filtration.

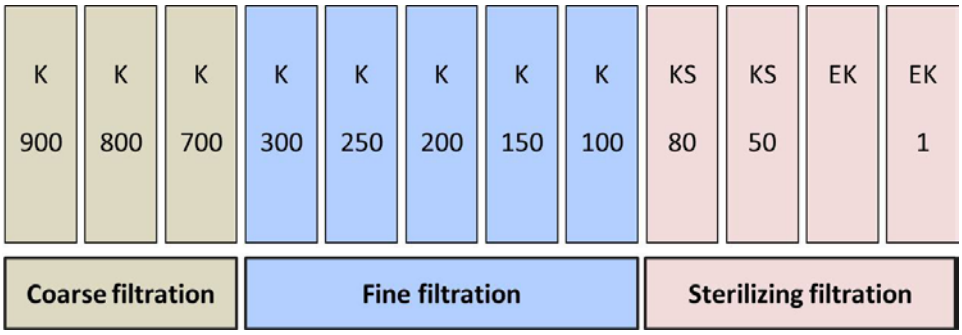

Fig. 17.14.
Seitz filters and their field of application

Pocket filters are composed of an airtight tank and filter elements, a.k.a. "pockets" in the tank. The bags are covered in filter cloth. Pressure forces the suspension to be filtered through the filter cloth of the pockets. The filtrate is collected in a central reservoir for later draining. The pockets are relatively easy to clean by water jetting.

Rigid filters are suited catch filaments in coarse to sterilize filtration. Their specific advantage is that they can be cleaned and sterilized in autoclave.

Table 17-I.
Essential glass filter information

type	**pore size** (μm)	**application**
G00	200-300	refining solutions
G0	150-200	refining solutions
G1	90-150	refining brews, infusions
G2	40-90	refining brews, infusions, syrups
G3	15-40	filtration of alcoholic and aqueous solutions
G4	3-13	filtration of eye drops
G5	1,0-1,5	sterilizing filtration of injection solutions

Glass filter plates and sheets are made out of pulverized glass of appropriate particle size by partial melting, a.k.a. sintering.

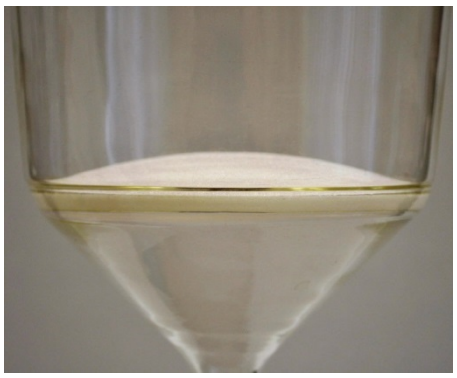

Fig. 17.15.
Glass filter

Berkefeld filters are made of diatomaceous earth. They are suited for sterilizing filtration of heat sensitive liquids (e.g. blood serum, enzyme solutions, antibiotics). *Chamberland* filters are made of unglazed porcelain. It is a high internal surface filter too.

In *candle filters* the parallel connected filter elements, the *filter candles* are arrayed in a pressure-tight shell. Pressure pushes the liquid to be filtered through the wall of the filter element. The filtrate proceeds from the individual candles to the filtrate reservoir, from which it can be discharged.

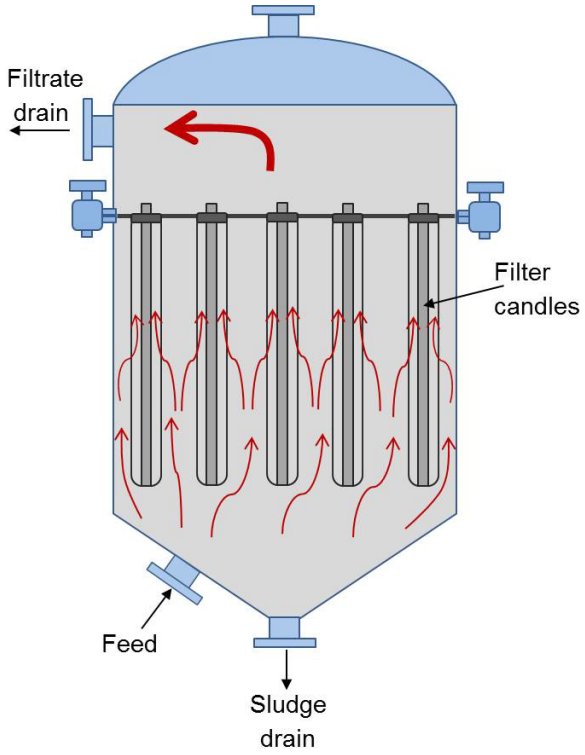

Fig. 17.16.
Candle filter

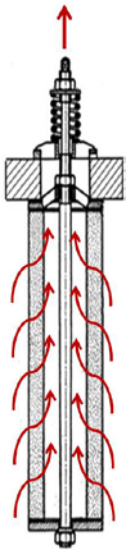

Fig. 17.17.
Filter candle element

17.2 Gas filtration

Besides liquid filtration, pharmaceutical practice also requires gas - most frequently air - filtration.

There are two main reasons for separating dust:

1) recovery of dust,
2) production of purified air by removing dust and other pollutants.

There are several methods available for gas filtration:

1) dry mechanical separation (dust chambers, cyclones),
2) wet scrubbing,
3) electrostatic gas purification,
4) filter cartridge dust separation.

In *dust chambers* the flow rate of gas decreases so much that gravity can settle dust particles to the bottom of the chamber, thus dust particles are separated from the gas flow.

In *wet scrubbers* the gas containing dust particles is forced through liquid in which they bind.

In *electrostatic gas purifiers* charged particles can be separated in an electic force field on the opposite polarity electrode.

In *cyclones* the application of centrifugal force affects moving particles, inducing separation.

In case of *filter cartridge dust separators* the material of the filter can be fabric, fibrous, grainy layered or porous.

The configuration of air venting technology for *cleanrooms* has to be designed to conform to technological processes and quality requirements for the production of pharmaceutical preparations. In cleanrooms, operating rooms and laboratories most commonly HEPA and ULPA filters are used.

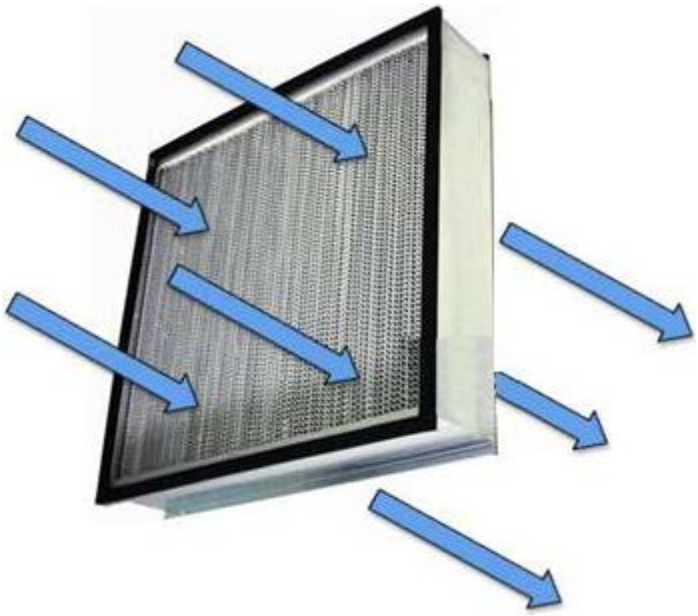

Fig. 17.18.
HEPA filter for room air filtration

Particularly large volumes of air are needed for the air treatment of *pharmaceutical factories*, as constant control, filtration, ventilation, streaming, regulation of temperature and humidity are elemental quality control tasks.

17.3 Membrane filtration

The elimination of particles and solutes of less than 1 μm diameter can be attained by *membrane separation*. It is different from macrofiltration methods in principle, because here a thin membrane accomplishes the separation.

The essence of membrane separation procedures is filtration by selective transport, through a membrane. A driving force effects the separation of substances, without chemical transformation. The method is suited mainly for filtering low viscosity liquids.

The firs membrane separation operation in history was done by the French physicist *Abbé Nollet* (also known as *Jean-Antoine Nollet)* in 1748. He observed that water enters into a wine-filled pig's bladder through the membrane when submerged in water.

Hungarian-born *Richárd Zsigmondy,* a Nobel laurate scientist in chemistry invented a membrane filter fit for colloid chemistry and biological studies in 1918 and ultrafilters in 1929. With these bacteria-sized particles can be separated from each other.

In addition to natural membranes, synthetic membranes appear as of 1855. Initially, the pores used to be the same size (isotropic) on both sides of membranes, with *anisotropic* membranes appearing later. Pore size is unequal on the two sides of the membrane, increasing towards the permeate side.

German physician *Georg Haas* was the first to treat kidney failure patients with dyalisis in 1924.

The ability of filtering microorganisms and ions makes membrane filtering ideal for water purification.

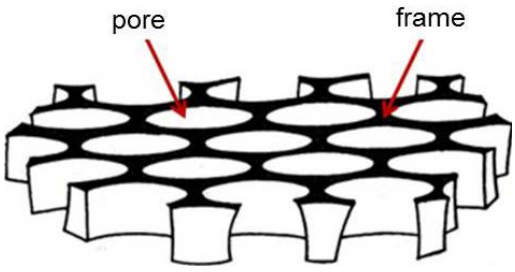

Fig. 17.19.
Structure of a membrane filter

Membrane flux (J) is the mass of permeate crossing the membrane in a unit of time:

$$J = \frac{m_p}{At} \tag{12.}$$

m_p mass of permeate,
A surface of membrane,
t duration of filtering.

The following relation indicates the *separation factor* (α):

$$\alpha = \frac{c_p(1-c_o)}{c_o(1-c_p)} \tag{13.}$$

c_p concentration level of permeate,
c_o a concentration level of feed solution.

The separation factor applies to the component passing through the membrane more rapidly.

Membrane filtering can separate complex material systems by molecular weight.

Membrane selectivity (β) can be calculated from the concentration levels of permeate (c_p) and feed solution(c_o):

$$\beta = 1 - \frac{c_p}{c_o} \tag{14.}$$

Surface filtering can be classified according to the directions of flow of the substance to be filtered (feed) and filtrate. They can be

1) unidirectional or
2) crossflow.

Traditionally, filtration is usually *unidirectional*, performed statically and in batches, generating sludge.

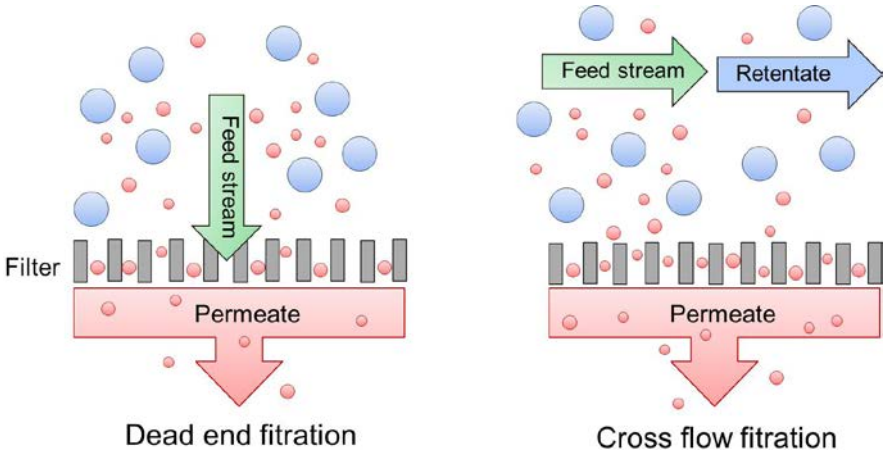

Fig. 17.20.
Main types of surface filtration

Membrane separation operations are usually performed with *crossflow* streaming. In such cases the feed liquid is streamed along the membrane in parallel and not perpendicular to it. The driving force carries some of the components from the substance to be filtered through the membrane and leave on the *filtrate (permeate, draw)* side. The components retained by the membrane (*residue, retentate, concentrate*) are enriched on the feed side of the membrane. The method is applicable in case of higher levels of concentration. In such cases the liquid to be filtered is streamed with high flux rate tangential to the surface. The driving force of the flux is the pressure differential created between the two sides of the membrane. The flux prevents the substances fed in from sticking to the membrane, thus there is no filter cake formation: some of the liquid phase flows through the membrane, while the mainstream carries the molecules caught on the membrane surface along. The efficacy of filtration is further enhanced by the membrane remaining clean and unclogged all through the operation. Filtration of the retentate can be perfected by recycling.

The various layers (membrane, spacer, residue collector) are rolled around a perforated pipe and arranged in bundles for larger surface area, which makes the system fit for continuous filtration of high volumes of liquid. Retentate can be separated or recycle.

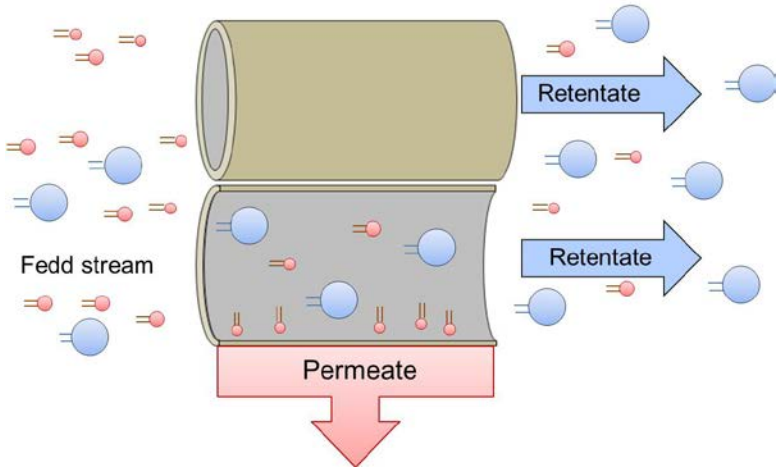

Fig. 17.21.
Operation principle of crossflow helix membrane filter

Main fields of application of membrane filtration:

1) microfiltration,
2) ultrafiltration,
3) nanofiltration and
4) reverse osmosis.

Microfiltration removes particles of 100-1000 nm size and 10^5-10^6 molecular mass. The method is generally fit for filtering suspended granules, flocculated substances, larger colloids and bacteria, while macromolecules and solutes can pass these microporous membranes.

Ultrafiltration is applicable mainly for the separation of macromolecules of 10-100nm size(1000-100000 Da). Colloids, microbial contaminations, bacteria, cells, viruses, proteins and larger organic molecules are retained, while smaller molecules can pass the microporous membrane.

Nanofiltration is applicable mainly for the separation of particles in the 1-10 nm particle size range. Nanofiltration is ranging between ultrafiltration and reverse osmosis. The skin-like membrane can retain larger (100-1 000 Da) molecules, saccharides, divalent ions.

Reverse osmosis provides the finest possible level of filtration. The application of external pressure creates the flow crossing the skin-like membrane; the direction of the flow is the reverse of that of osmosis. This method can separate 0,1-1 nm particles of 10-100 Da (solute salt, inorganic molecules). Reverse osmosis can be used for seawater desalinization and production of potable water as the size of viruses is nearly 200 times, of bacteria 2000 times larger than the pores of the filter. Retention of solute salts is 95-98%. The permeate can be made fit for drinking by subsequent remineralization.

Advantages of membrane filters:

1) long life,
2) low cost,
3) made of chemically uniform materials,
4) resistant to numerous organic solvent, acid and base,
5) good selectivity,
6) low filtration loss,
7) constant pore sizes,
8) they are suited for many kinds of filtration operations in pharmaceutical technology
   a) filament free filtration of solutions (d=0,45 - 0,8 μm)
   b) sterilizing filtration of solutions (d ≤0,2 μm),
   c) concentration of biological substances,
   d) purification of solutions

Disadvantages of membrane filters:

1) incidentally changing pore sizes
2) incidentally changing pore density
3) sensitivity to corrosion,
4) sensitivity to mechanical impact (liable to damage),
5) filtration requires pressurization or vacuum,
6) susceptible to clogging.

Being made of chemically uniform materials, being resistant to several organic solvents, acids and bases, low filtration loss, the filter material not absorbing solutes,

pore size being controllable within a relatively narrow range, lack of heat effect are manifest advantages of membrane filters. On the other hand, they also have disadvantages: they are liable to damage and require specialized filter equipment and vacuum or pressurization.

The material of *membranes* may be natural or artificial, out of which the layer of required thickness and permeability is produced by extraction, casting and bombardment with elementary particles. The first material of synthetic *membrane filters* was nitrocellulose ester. The more profitably applicable, less heat- and pH sensitive polysulphone membranes came later. Currently used membranes are made of various organic polymers (e.g. polyamide, polycarbonate, polyester), cellulose derivatives (e.g. cellulose acetate, cellulose nitrate) or derivatives of Teflon (e.g. polytetrafluoroethylene). There are filter membranes made of ceramics, metal and carbonaceous filaments now. Ceramic membranes are well suited for use in industrial micro- and ultrafiltration systems.

Quality analysis of membrane filters is performed by using *integrity tests* for various aspects. Testing is done with wet filters. For hydrophobic membranes alcoholic solutions can be used as lubricant. Integrity tests verify the actual bacterial filtering efficacy of filters. Upon validation a *bacterial "challenge"* test is employed, which examines the proportion of known bacteria penetrating the filter. Testing is done using *Pseudomonas diminuta* suspension, which contains known size cells.

In *diffusion testing* air of known pressure is passed through the lubricated membrane. The amount of diffused air is measured on the other side of the membrane.

In *pressure hold testing* the pressure drop the gas put on the lubricated membrane is measured. It is an informative method used before or after sterilization.

In the bubble point test air is pressed through the filter under increasing pressure, with bubbling observed on the other side. Bubble formation happens upon diffuse air transmission, only very slowly on visual observation. It becomes continuous after reaching bubble point. If gas pressure is increased gradually, then liquid will be squeezed first from the largest pore, thus the bubble point corresponding with the breaking pressure is characteristic of the size of the largest pore. This test does not establish the number and size of the largest pores, only an approximative value characteristic of the structure and pores of the membrane.

Questions

1) How would you define the notion of filtration?
2) What are the pharmaceutical technological purposes of macrofiltration?
3) What are the main characteristics of depth filtration?
4) What are the main characteristics of surface filtration?
5) What are the principal correlations that describe the filtration process?
6) What are the main classes according to the driving force of filtration?
7) How do vacuum drum filters work?
8) What are the methods of gas filtration?
9) Who invented the membrane filters used in colloid chemistry and biological studies?
10) What is membrane selectivity and how is it calculated?

11) What are the advantages of membrane filters?

12) What are the disadvantages of membrane filters?

13) What pore-size filters are suited for microbial decontamination in the production of injection solutions or infusions?

14) What are the methods of membrane filter quality testing?

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18 Sedimentation

Sedimentation is a method of material separation, which happens either in a gravitational or centrifugal force field due to density differential, or in an electrostatic force field (e.g. electrostatic dust separators) due to electric charge differential.

Sedimentation in practice is often the elimination of suspended solids.

Sedimentation is defined by the particle size of particles to be settled and the quantity of dispersed substance.

In easily separating, relatively thin, readily settling macroheterogene systems partial separation of liquid and solid particles may be achieved by *decanting*, in which part of the clear liquid is decanted from the settled substance, repeating the operation several times.

The elimination of small, for example of colloid size dispersed particles often requires preliminary *clarification* in practice.

The electric surface charge of particles and thereby the stability of the system depends on the pH of the medium and the addition of electrolytes. The separation of substances by coagulation and/or flocculation requires additives. With *coagulation* the electrostatic repelling interactions of particles are reduced, which facilitates the sedimentation of particles. With *flocculation* chain polymers of high molecular weight are employed, which attach to dispersed particles. Aggregates created this way are easier to separate.

The magnitude of particles determines the type of sedimentation. In case of thin suspensions there is *free settling*, where the effect of granules on each other is neglectable. In case of higher granule concentrations, however, sedimentation may be *hindered*, determined by other granules.

The advantage of gravity sedimentation is that the process does not require additional energy, it is relatively easy to implement on both laboratory and industrial scale, but it is slow.

According to *Stokes*' law, sedimentation rate is determined by particle size, gravitational force, viscosity of the dispersing medium and the difference between the density of the dispersing medium and the particles. Sedimentation occurs within a few minutes, a few hours (for example the sedimentation of precipitate in the manufacture of *Burow's* solution) or a few days, depending on the density difference.

In dispersing medium, particles move with accelerated motion for a short time, then with uniform motion, since the forces of gravity and counteracting buoyance and drag equalize.

Sedimentation rate (v) in this case is:

$$v = \sqrt{\frac{4dg}{3k}\frac{(\rho_1 - \rho_2)}{\rho_2}} \qquad (1.)$$

- d diameter of globular or approximately globular particles,
- k drag coefficient,
- ρ_1 density of particles,
- ρ_2 density of dispersing medium,
- g gravitational acceleration.

Drag coefficient depends on the *Reynolds (Re)* number of moving particles.

$$Re = \frac{vd\rho_2}{\eta} \tag{2.}$$

η viscosity

For diluted suspensions Re< 1 in the laminar interval Stokes's law applies. Ddrag coefficient in this case is:

$$C_d = \frac{24}{Re} \tag{3.}$$

In the C_d transitional interval:

$$C_d = \frac{12}{\sqrt{Re}} \tag{4.}$$

And in the C_d turbulent interval:

$$C_d = 0{,}44 \tag{5.}$$

Besides the size of settling particles the shape of particles is another important characteristic. If the shape of particles is not perfectly spherical, than the C_d parameter has to be multiplied with a shape factor.

Smaller particle surfaces are favorable for sedimentation.

Sedimentation can be

1) positive, if the density of particles is higher than the medium's ($\rho_1 > \rho_2$), with particles settling down or
2) negative, if the density of particles is lower than the medium's ($\rho_1 < \rho_2$), with particles moving in the opposite direction.

If $\rho_1 = \rho_2$, there is no sedimentation. In this case particles are suspended in the dispersing medium.

Depending on the properties of the suspension, the separation of phases can be done *in one step*, by means of gravitational sedimentation, centrifugation or filtration. Practice showed that the gravity sedimentation is not always capable of separating phases appropriately. In such cases separation is done *in two steps*, with centrifugation or filtration following up gravitational sedimentation.

Gravitational sedimentation is a low-cost, low power-intensity operation, but it is relatively slow and applicable only if density difference is high. Gravitational sedimentators can be batch and continuous operation.

*Dorr sedimentation tank*s work with low through-flow in continuous operation. Clarified, clear liquid leaves by overflowing the upper rim of the sedimentation tank. Sludge settled on the bottom is conveyed by the guide blades of the slow rotating (0.01-0.03 rpm) rake arm to the central discharge outlet, from where it can be removed through a conduit.

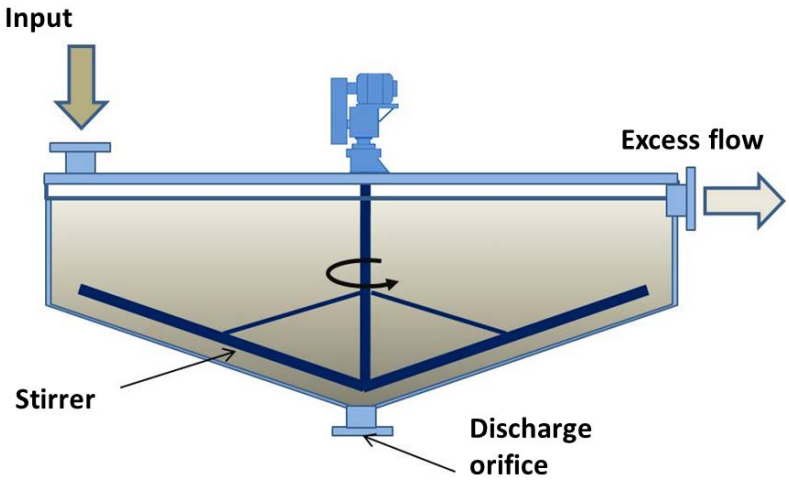

Fig. 18.1.
Dorr sedimentation (thickener) tank

Centrifugal force fields yield more effective separation. Sedimentation in a gravitational field is:

$$v_{grav} = \frac{d^2(\rho_1 - \rho_2)g}{18\eta} \tag{6.}$$

Rate of sedimentation in a centrifugal force field is:

$$v_{centr} = \frac{d^2(\rho_1 - \rho_2)r\omega^2}{18\eta} \tag{7.}$$

The index-number (φ) of the centrifuge signifies the efficacy of centrifugal sedimentation:

$$\varphi = \frac{r\omega^2}{g} \tag{8.}$$

ω angular velocity
r inner radius of centrifuge

Safety rules for operating centrifugal apparatuses must be observed at all times. Most important of these is that the device must not be turned on before its door or cover is closed and it must not be opened before it is fully stopped. The doors of modern, safe centrifugal apparatuses cannot be opened as long as the rotor is in motion.

Samples shall always be placed in the centrifugal apparatus in weight balanced pairs, positioned opposite to each other. Commonly used glass laboratory equipment (for example test glass, Erlenmeyer flask, spherical flask) cannot be centrifuged. For centrifugal spinning special polyethylene, polypropylene, polystyrene or Teflon centrifuge tubes shall be used. Ensuring slow, progressive access to working speed is also important.

In everyday laboratory practice centrifugation is applied for the elimination of materials difficult or impossible to filter (gelatinous, gluey, deformable grain).

Batch operation centrifugal apparatuses are useful in the rapid separation of disperse systems on laboratory level. In pharmaceutical technology centrifugal apparatuses are used for the separation of difficult or impossible to filter (fine-grain, gelatinous) materials. Plasma from blood samples is extracted by centrifugation for pharmacokinetic and biopharmaceutical analysis.

Centrifugal force pushes dispersed material to the bottom or side of the centrifuge depending on the angle of dip of the centrifuge tubes, thus clear fluid can be poured off easily.

Thermosensitive samples require the application of cooled centrifugal apparatuses.

Materials from the size of extremely small cellular components to the molecular level can be separated by using high-spin ultracentrifuges. Due to the high rotation speed aerodynamic drag is significant in these devices, requiring vacuum inside the centrifuge.

*Analytical ultracentrifuge*s are used for separating materials according to their molecular weight.

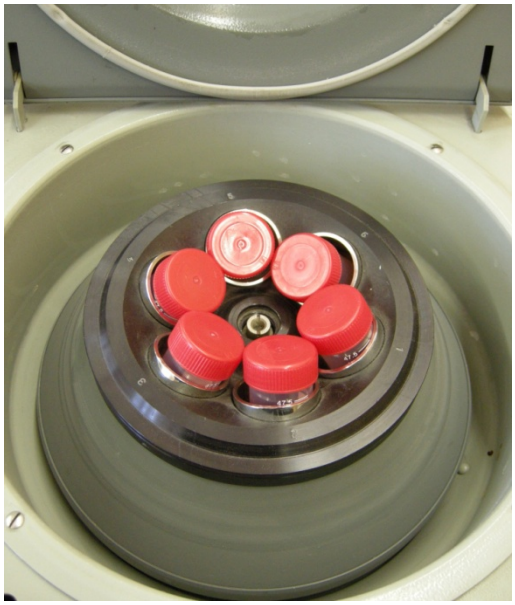

Fig. 18.2.
Laboratory centrifuge

On the industrial scale centrifugation is an effective method used principally in the synthesis of base materials, separation of suspensions and fermentation broths. It is advisable to install these centrifuges in dedicated rooms in order to prevent accidental damage or injuries (e.g. due to accidental structural failure).

Fig. 18.3.
Batch operation industrial centrifuge

Disk centrifuges are capable of separating large quantities of material. Their efficiency is highly increased by integrated conical discs, which decrease the length of sedimentation distance.

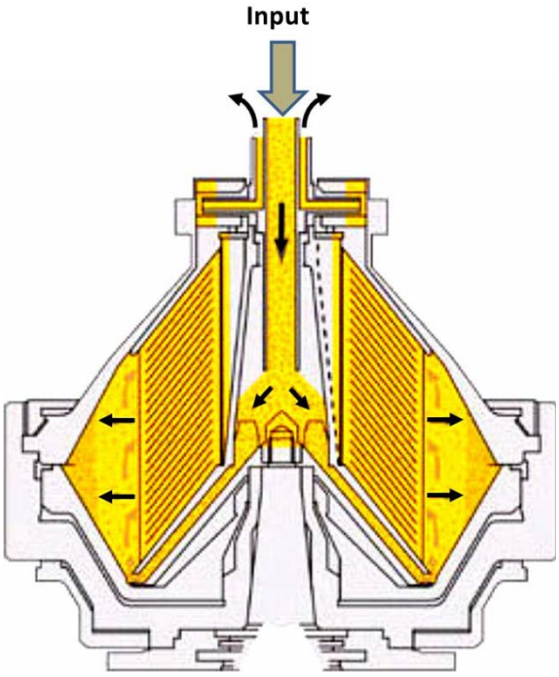

Fig. 18.4.
Continuous operation industrial disc centrifuge

Questions

1) What are the attributes of particles according to which they are separable in sedimentation?
2) How can coagulation be put to use for sedimentation?
3) What are the advantages and disadvantages of gravitational sedimentation?
4) How does the Dorr sedimentation tank work?
5) What does the index number of centrifuges mean and how is it calculated?
6) What are the principal safety considerations for centifuges?

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19 Drying

Drying is an operation of *mass transfer* and heat transmission in one, in which moisture is removed from the wet stock. The direction of component transfer (moisture evaporation) is from the stock to the air.

The process of drying is also an operation of *diffusion*, as moisture inside solid stock is transferred to the surface and eventually in the air by diffusion. Diffusion occurs due to the differential in vapor pressure between the vapor pressures of air and the water content of stock.

The application of external heat to speed up the evaporation process is common practice in drying. The heat transfer occurs from the outside toward the material In case of heat-sensitive substances the application of vacuum allows moisture withdrawal at lower temperatures.

The circumstances of drying and moisture content are highly influential on the properties of substances (e.g. density, adhesiveness, flow property, stability), making drying an important operation in medicine manufacturing. In pharmaceutical technology drying can be an intermediate (e.g. adjusting moisture content before granulation) or finishing (e.g. drying the film coating) operation in the technological row.

The principal aspects of the *stability* of substances and preparations:

1) physical (e.g. liquefaction – absorption of crystal water or due to dust accretion-overdrying)
2) chemical (e.g. decomposition – hydrolytic decomposition of substances sensitive to moisture)
3) biological (e.g. mould formation – the humidity is favorable for microbial proliferation)

The *purpose of drying* may be

1) preparation of substances for further technological operations. (e.g. tableting),
2) removing and keeping moisture off of substances reactive in the presence of moisture (e.g. effervescent preparations),
3) adjustment of moisture content of substances to the optimum value to achieve or preserve stability.

The initial moisture content of the substance, which usually stands for the amount of water included in a unit of stock volume or mass, has to be known.

Mass of wet substance (m):

$$m = m_d + m_m \tag{1.}$$

m_d Mass of moisture content,
m_m mass of dry substance.

Drying does not change m_d, while m and m_m decrease in proportion to the withdrawal of moisture.

Moisture content (W_d) correlated with dry content:

$$W_d = \frac{m_m}{m_d} \tag{2.}$$

According to the correlation, the value of W_d may vary in the range between 0 and ∞.

Quality requirements that specify the optimum, allowed minimum and maximum moisture content of raw materials, intermediate and end products are common in pharmaceutical technological development work, as appropriate moisture content is an important condition and attribute of material quality and manageability.

Moisture content correlated with wet stock (W_w):

$$W_w = \frac{m_m}{m} = \frac{m_n}{m_o + m_m} \tag{3.}$$

Accordingly, the moisture content of a substance may vary between 0 and 1 or 0 and 100%.

The ultimate moisture content achievable by drying depends on the binding characteristics of moisture and the *absorptiveness of drying air*. Latter depends on the pressure, temperature, moisture content, volume and flow speed of air.

Moisture in the drying substance may be solid, liquid and vapor phase. These phases change into each other by melting, freezing, evaporation, condensation, sublimation or desublimation. The balances of phase changes are shown in the phase diagram:

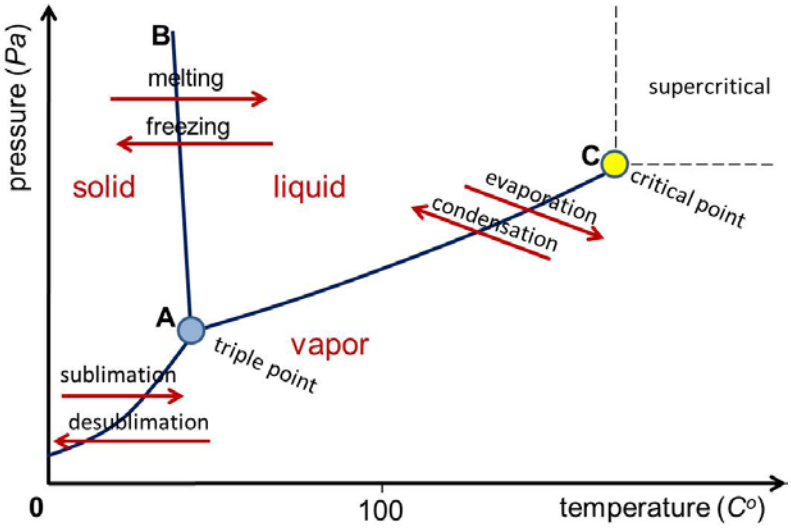


Fig. 19.1.
Phase diagram

The curves dividing the phases indicate phase changes. At the points of the curves, in case of various *pressure-temperature* data pairs, the two phases of the substance are in balance. The O-A curve indicates the phase boundary between solid and vapor. It is called *sublimation curve*. A-B is called *melting curve* (straight with good approximation). It divides the phases solid and liquid. The *tension curve* of A-C is between the phases liquid and vapor, characterizing boiling (evaporation).

The three curves meet at the *triple point*, where all three phases are in balance. This phenomenon is possible only at a single point of pressure-temperature (in case of water p= 611 Pa, T= 273,16 K).

Critical temperature is the highest temperature, at which a substance is liquid. The parameters relevant to this point are critical pressure and critical temperature.

Unbound moisture forms a continuous film on the surface of substances. It is also called adhesive surface moisture or free moisture. Moisture is generally bound by weak cohesive forces and its homeostatic vapor pressure over the whole surface in contact with the drying medium is equal with the pressure of identical temperature saturated vapor:

$$p_v = p_{vt} \tag{4.}$$

p_v vapor pressure,
p_{vt} pressure of saturated vapor

Bound moisture is bound in physical or chemical ways, which usually increases the energy and time demand of drying.

Physically bound moisture is usually bound in pores or capillary vessels. This type of bond is particularly significant for pharmaceutical technology, as drying is generally applied to porose materials (e.g. ganulates) with capillaries in their structure, which affects the drying process significantly. Removing moisture from such materials is a more difficult task, because after the elimination of surface moisture drying has to work against capillary forces. Transport of moisture from capillaries can be achieved by liquid and/or vapor diffusion.

In *macrocapillaries* ($d > 10^{-7}$ m) the effect of capillary force has little effect, but in *microcapillaries* ($d < 10^{-7}$ m) it is significant. In case of macrocapillaries the surface of moisture is flat or approximately flat, so vapor pressure is equal with the pressure of saturated vapor. These are usually not hygroscopical substances.

In microcapillaries vapor pressure is lower than the pressure of saturated vapor, due to the curved surface of moisture:

$$p_v < p_{vt} \tag{5.}$$

1) Substances capable of absorbing significant amounts of moisture from air are called *hygroscopic*. These substances, such as calcium chloride deliquesce, so it is advisable to use them in stock solution for pharmaceutical purposes.
2) *Crystal water*, which is *chemically* (strongest type) *bound*, classifies as difficult to remove. It is built in between lattice points of the crystal lattice in a strictly determined stechimetrical proportion characteristic of the substance (e.g. sodium borate ($Na_2B_4O_7 \cdot 10H_2O$), magnesium sulphate ($MgSO_4 \cdot 7H_2O$), Glauber's salt ($Na_2SO_4 \cdot 10H_2O$), gypsum ($CaSO_4 \cdot 2H_2O$), bluestone ($CuSO_4 \cdot 5H_2O$).

Beside the moisture content of stock, drying is also influenced by the humidity and temperature of surrounding air.

Absolute humidity is the mass of water vapor in a unit of air volume:

$$\varphi_a = \frac{m_v}{V} \tag{6.}$$

m_v mass of water vapor,
V volume of moist air.

The quotient of the partial pressure of air humidity and same temperature saturation vapor pressure is called *relative humidity*:

$$\varphi = \frac{p_v}{p_{vt}} \tag{7.}$$

p_v vapor pressure,
p_{vt} pressure of saturated vapor.

Humid air may be considered a two component blend (dry air and water vapor), whose components form a single phase under ordinary conditions. Available space is filled by the components. According to *Dalton's Law* in vapor phase the partial pressures of components are additive, therefore (total) air pressure is the sum of the partial pressures of components:

$$p = p_l + p_v \tag{8.}$$

p pressure of humid air,
p_l partial pressure of dry air,
p_v partial pressure of water vapor.

According to the *Clausius-Clapeyron* equation, the following correlation applies to vapor pressure and temperature:

$$ln\frac{p_1}{p_2} = \frac{\Delta H}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right) \tag{9.}$$

p_1 partial pressure of water at T_1 temperature,
p_2 partial pressure of water at T_2 temperature,
ΔH molar heat of evaporation of water,
R universal gas constant,
T temperature ($K°$).

Knowledge of the bonding and sorptive attributes of moisture is necessary for the design and implementation of drying processes. Drying or moistening of substances occurs through sorptive and desorptive processes in the function of the moisture content of the substance and surrounding air. In case of both processes a state of dynamic equilibrium develops as water escapes from the substance by evaporation while the same amount of water molecules condensate on the surface of the substance from the air.

Sorption isotherms follow the changes in the moisture content of substances at a given temperature, in the function of the relative humidity of air in contact with the substance. *Sorption* and *desorption* curves may or may not overlap, so hysteresis is possible.

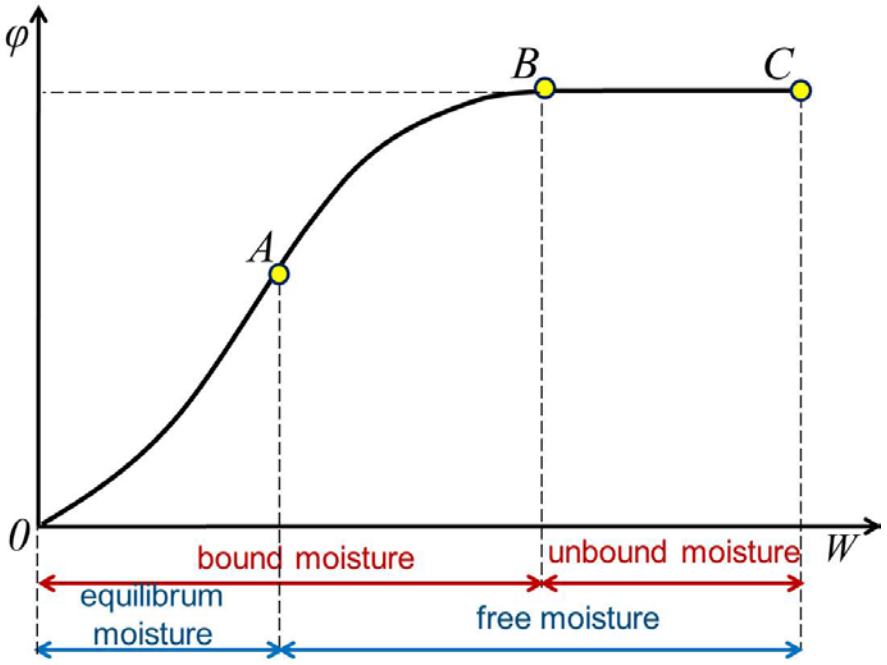


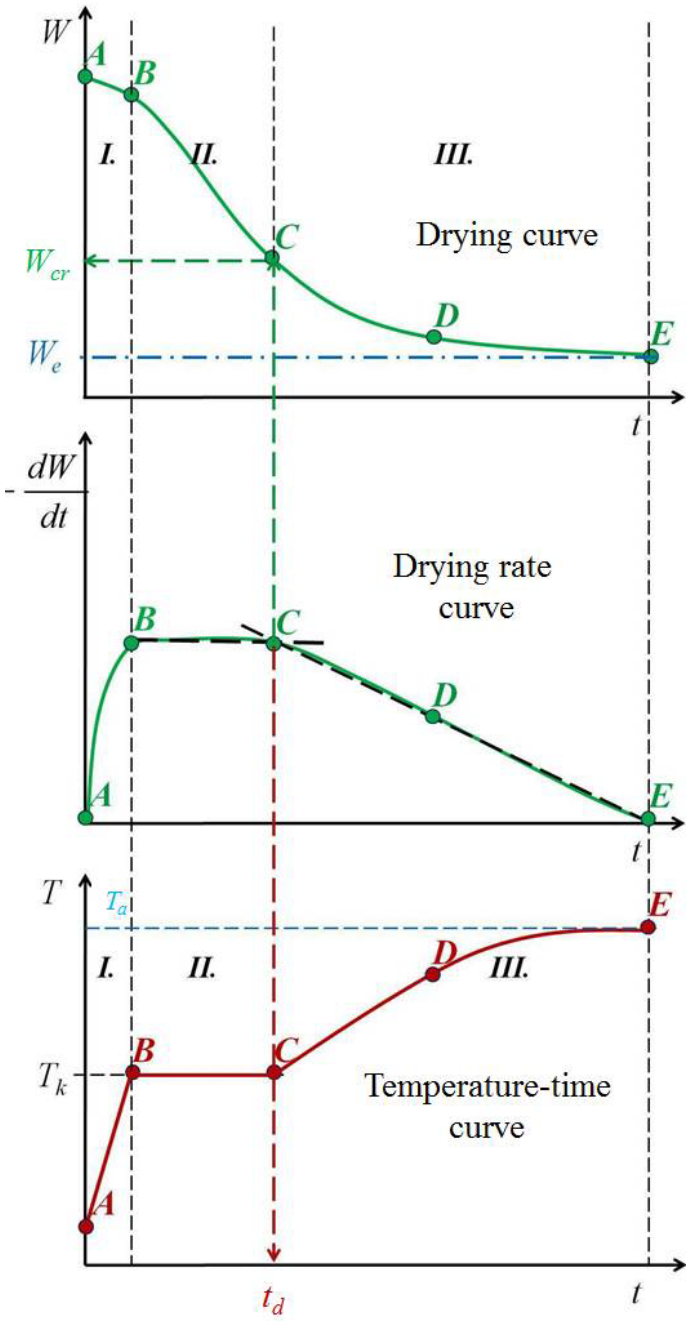
Fig. 19.2.
Sorption isotherm with moisture bonding types

The inflexion point (*A*) is a remarkable point of the isothermal curve, indicating the onset of *capillary condensation*. The *hygroscopic point* (*B*) indicates maximum moisture absorbable. Zone *0-A* of the curve indicates equilibrum moisture beyond which free or unbound moisture appears. The curve indicates bound moisture between points *0* and *B* and *unbound moisture* beyond point *B*, where the substance cannot take up any more moisture.

In the case of drying porose substances, the formation of a dry and a wet area can be observed. Their proportions change in the course of dryin, with the dry area growing and the wet shrinking, as their boundary draws toward the interior of the substance, with evaporation taking place at the boundary.

Changes of *moisture content* can be tracked by recording *drying* and *drying rate curves*. Drying starts at point *A* of curves and ends at point *E*.

The *temperature-time* curve shows that at point *E* the temperature of the substance reaches the temperature of warm drying air. Therefore in practice drying shall not be continued beyond point (critical point, *C*), because from this point on the heat-absorbing effect of drying decreases and the substance starts to heat up instead, which is potentially harful for the substance. Point *C* is the inflexion point of the drying curve. It is the meeting-point of *even* and *slowing rate sections*. A more exact value of *duration of drying* (t_d) can be obtained by differentiating the drying curve, recording a *drying rate curve*. It yields the value of moisture content that corresponds with the duration of drying (W_{cr}).



I. warming stage; ***II.*** linear rate stage; ***III.*** decreasing rate stage. $\boldsymbol{W_{cr}}$ moisture content corresponding to the critical point; $\boldsymbol{W_e}$ equilibrum moisture content; $\boldsymbol{T_a}$ temperature of drying air; $\boldsymbol{T_k}$ temperature of substance in the steady rate stage; $\boldsymbol{t_d}$ duration of drying. ***A-B*** initial leveling off; ***B-C*** linear rate section; ***C-E*** decreasing rate section; ***C-D*** section of unsaturated surface drying out

Fig. 19.3.
Dryin, drying rate and temperature-time curves

In the course of drying, in the *warming stage* (*I.*) the substance is warmed up by the warm drying air and drying begins. This stage usually does not take long, with small rate of drying.

The greater part of moisture can be eliminated in the *linear rate stage* (*II.*) The surface of the substance is steadily saturated with moisture in this stage. Moisture is evenly replenished from inside the substance, evaporation rate is steady.

In the *decreasing rate stage* (*III.*) after reaching the critical point the drying process *slows down*. The consisitent liquid film on the surface of the substance splits, dry areas appear, decreasing the surface of evaporation. Drying out of the unsaturated surface takes place in the C-D section and beyond point D the moisture content of the substance and the amount of evaporable moisture reaching the surface keep decreasing, thus dry areas increase in size and evaporation rate drops further.

Driers can be grouped according to various aspects:

1) *Mode of operation*
   1.1) batch operation (e.g. tray drier),
   1.2) continuous operation (e.g. tunnel dryer, belt drier)
2) *Movement of drying medium and substance*
   2.1) parallel flow,
   2.2) counterflow,
   2.3) cross-flow
3) *Movement of the substance to be dried*
   3.1) static bed (e.g. tray dryer),
   3.2) dynamic bed (e.g. fluidized bed dryer, spray dryer)
4) *Pressure inside the dryer*
   4.1) atmospheric (e.g. tray dryer),
   4.2) vacuum dryer
5) *Method of heat transfer*
   5.1) convection (e.g. meleg levegővel),
   5.2) radiated heat (e.g. infrared radiation),
   5.3) conducted heat,
   5.4) dielectrical, high frequency,
   5.5) combined methods.

Most dryers operate on atmospheric pressure. The required amount of substance to be dried is placed on the *dryer trays* and spread evenly. To extract larger amounts of moisture appropriately heated drying air is blown at the necessary rate. The direction of air flow is controlled by the arrangement of trays and baffles as well as the positions of feed-in and extraction of air. Drying air reaches the substance on the tray after heating, where it absorbs water and exits the apparatus by way of the humid air chamber. Air heating can be accomplished electrically, by steam or pre-heated liquid (water, oil) using a *heat exchanger*. Mixed with resh air drying air may be recycled.

The drying process can be controlled by monitoring the temperature of drying air.

The application of perforated trays provides air flow between the particles of the substance and thereby more uniform drying.

Fig. 19.4.
Industrial scale atmospheric tray dryer

There are dryer devices for industrial scale application in which the substance is placed on the trays of the device's cart, rolled in the drying chamber, from which it can be removed and rolled to the next operation unit after drying is complete. This type of dryers are generally batch operation devices.

Tunnel dryers and *belt dryers* are continuous operation devices.

In *tunnel dryers* the substance to be dried is placed on the shelves or trays of a train of carts. The movement of the cart train may be either in parallel- or counter flow with blown-in heated air.

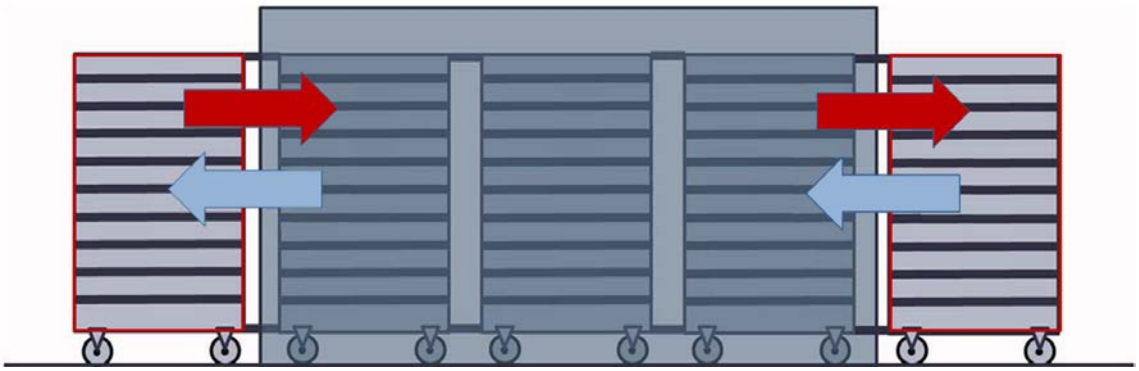


Fig. 19.5.
Industrial scale counterflow tunnel dryer

Belt dryers carry the evenly spread stock on a conveyor belt. Blown air drying is possible, although the risk of porkihordás is present, possibly influencing composition. It is therefore advisable to opt for *infrared* or *microwave* drying.

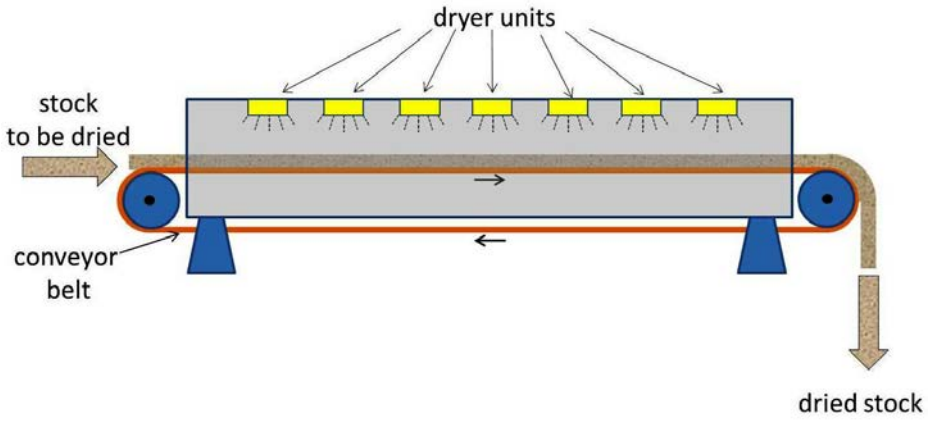


Fig. 19.6.
Continuous operation belt dryer

Infrared light does not use air as transmitting medium. It penetrates solid objects, warming them directly.

Drying by microwaves is made possible by the fact that water is a first rate dielectric. Water molecules generate heat by synchronized movement and rubbing in accord with the polarity of the electric field in the induced high-frequency space. This heat is suitable for extracting the moisture content of the substance. Microwave drying makes diffusion moisture flow much greater within the substance than in the layers near the surface, making drying more uniform.

Atmospheric drying is not a suitable and effective method in every case. *Vacuum drying* provides mild and homogeneous drying.

These dryers for two larger groups:

1) dryers that operate over and
2) dryers that operate under triple point pressure (sublimation)

Relatively little vacuum is required to decrease pressure from atmospherical to the triple point. Compared to atmospherical dryers, drying can be performed on lower temperatures. These dryers are primarily used for drying heat-sensitive substances, where drying may cause decomposition in the substance.

Fig. 19.7.
Vacuum dryer

The essence of *freeze-drying* is that moisture is eliminated by freezing and sublimation. The other name of the method, *lyophilization* indicates that freeze-dried substances are easily soluble.

Subsequent to freezing, the application of vacuum induces drying, which accomplished by sublimation, at the phase boundary between solid and vapor phases, along the *sublimation* (0-A on the phase diagram) *curve*.

The *Clausius–Clapeyron* equation can be applied to freeze-drying in the following form:

$$\frac{d \ln p}{dT} = \frac{\lambda_{subl}}{RT^2} \tag{10.}$$

p pressure,
λ_{subl} sublimation heat,
R universal gas constant,
T absolute temperature

Main steps of freeze-drying:

1) freezing,
2) sublimation of moisture from frozen stock,
3) heating of substance to be dried,
4) secondary drying,
5) sealing of container(s) of dried stock.

As the first step of the process the open containers holding the solution of the substance (e.g. ampullae, phials, infusion bottles) are placed in the device.

Temperature and pressure have to be controlled all through the process.

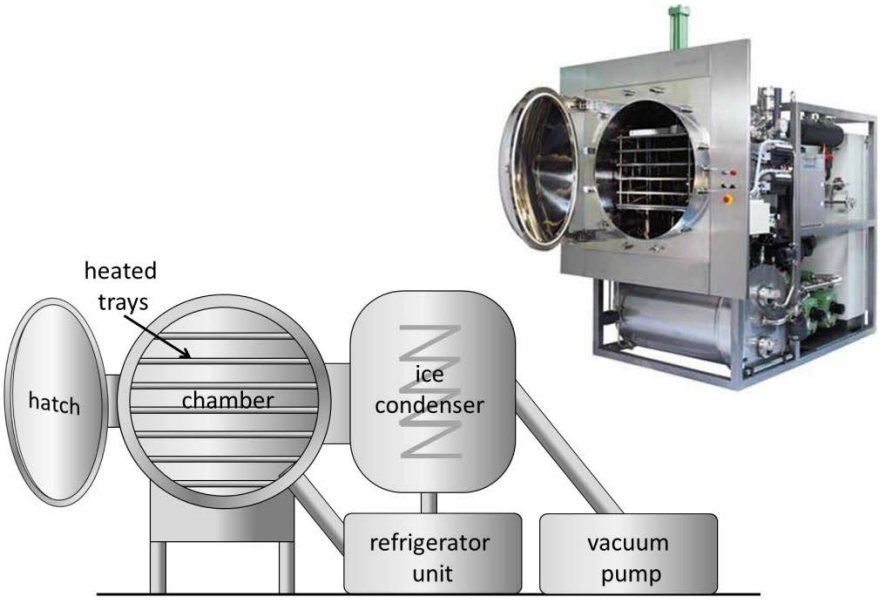


Fig. 19.8.
Freeze-dryer

In freeze-drying the heat lost to drying can be offset by careful warming of the substance, thereby preserving balance, because departing moisture cools the substance,

which slows the process significantly. Contingent overwarming leads to melting, resulting in dissolving. Extracted moisture is fixed on the surface of the refrigerated condenser, to be melted and removed from the system.

After reaching required moisture content the drying operation is concluded with the air- and moisture-tight sealing of the containers holding the substance.

This operation is well suited for preserving vaccines and moisture-sensitive substances that decompose in water. Freeze-drying makes products easy to store, easy to transport and nonperishable.

Fig. 19.9.
Freeze-dried products after sealing

The moisture content of freeze-dried products is usually below 1%.
Porous, spongy structure, high internal surface enables very quick dissolution.
Advantages of freeze-drying:

1) enables drying of thermolabile substances,
2) makes substances prone to chemical and/or biological decomposition in aqueous medium stabile for extended storage, to be dissolved directly before use,
3) biological substances retain their original biochemical, physiological and therapeutic qualities,
4) the addition of solvent dissolves the substance very quickly and without residue,
5) precise dosage becomes available.

Disadvantages of freeze-drying:

1) high investment costs,
2) high operation costs,
3) significant extra energy,
4) costly packaging for keeping out moisture.

Fluidized bed drying exploits fluidization (The method is described in chapter "Fluidization"). Firstly, fluidizing air keeps the substance to be dried in constant agitation, fluidized state; secondly, it warms particles and supplements heat lost to drying, meanwhile absorbing evaporated moisture and carrying it off. The rates of heat- and mass transfer processes increase significantly, which is beneficial to drying. Drying occurs as a result of intensive contact between wet particles and the drying medium, in convectional heat transfer.

In *fluidized bed drying*, if the *temperature of input air* (T_{in}) is steady, the changes in the *temperature of output air* (T_{out}) imitate the drying process. In the initial warm-up phase (t_o-t_1) it increases, barely changes in the drying phase (t_1-t_2) and after reaching the critical point, with moisture evaporated, it increases again (t_2-t_3) up to the temperature of input air, which, in case of compounds containing heat-sensitive ingredients, may lead to excessive, not allowable warming of stock. There is no further warming after reaching T_{in}.

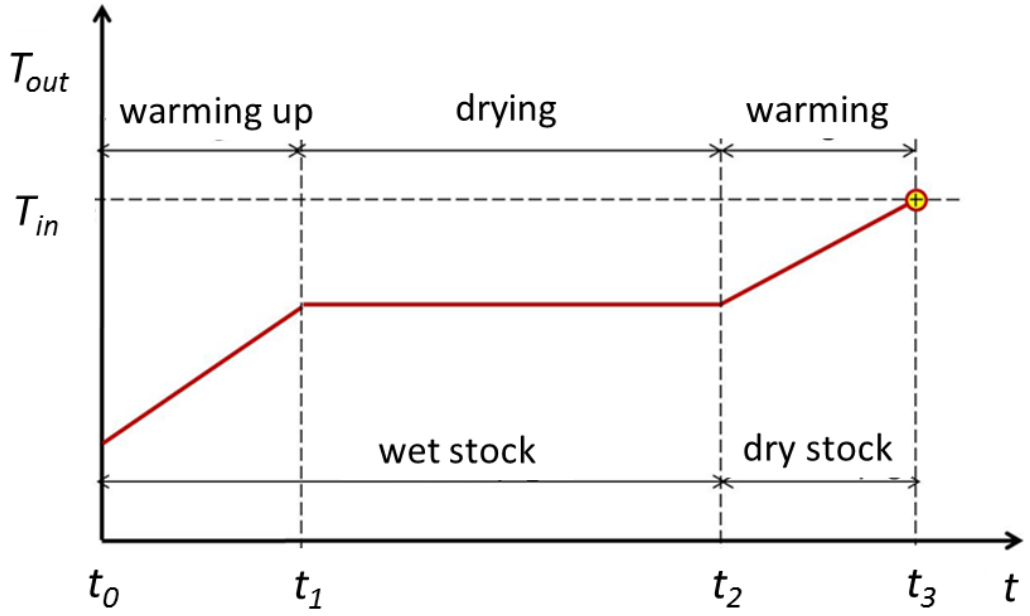


Fig. 19.10.
Changes in the temperature of output air during fluidized bed drying

Fluidized bed drying of granulates is a controllable process, provided that necessary technical conditions (installation of sensor and control units) are fulfilled.

Fig. 19.11.
Laboratory scale fluidized bed dryer

Fig. 19.12.
Industrial scale fluidized bed dryer

As the process of drying advances, the mechanical strength of particles decreases, which, due to collisions, is likely to increase *dust formation*, changing the original proportions of ingredients in turn. To avoid this, fluidized bed devices are outfitted with dust filter bags or cyclones, from which dust can be recycled to the particle system.

Fluidized bed dryers are generally batch operation devices.

The essence of *spray drying* is that the solution or suspension containing the substance to be dried is atomized to drops and dispersed in an appropriate amount of controlled temperature gas (usually air).

Atomization to drops greatly increases specific surface, resulting in significantly improved mass- and heat transfer between phases, allowing for relatively quick drying. Warm air retrieves moisture by convection heat transfer, carrying absorbed moisture away from the device.

In the *drying chamber*, where the liquid and the gas stream blend, solid particles begin to precipitate as allowed by solubility conditions, with gradual drying occurring first on the surfaces, then in internal capillaries. The end product remaining after the evaporation of the solvent is a fine distribution dry powder. As a result of intensive agitation, the collisions of particles to each other and the walls of the device decrease particle size further. A fragment of the dust may be carried off with air from the device, therefore it is advisable to employ a cyclone unit for retrieving this dust.

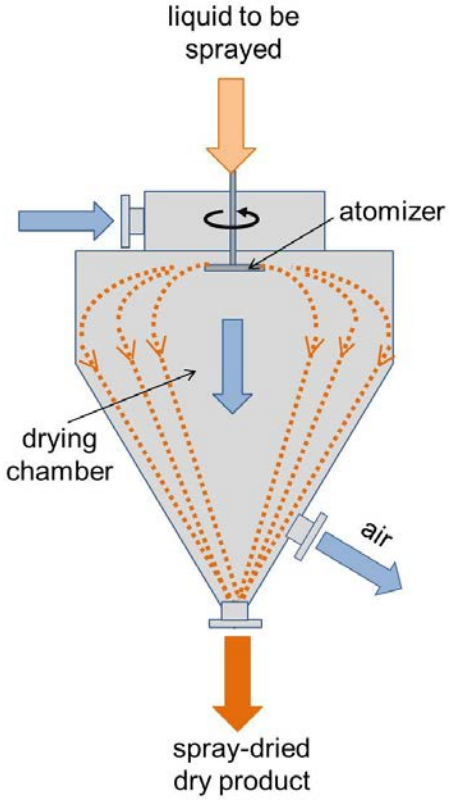


Fig. 19.13.
Operating principle of spray driers

In the course of the operation largest drops are the quickest to settle and slowest to dry, which must be taken into consideration in scaling spraying and controlling air velocity and temperature for the device. The drops created by spraying are varied in size, determined by the attributes of the substance to be sprayed and the operation parameters of spraying.

Drop formation takes place in the spray drying nozzle and it requires energy to overcome surface tension. Spray drying nozzles must be designed and scaled to the substance to be dried.

In its design the spray drying nozzle (a.k.a. atomizer) may be:

1) nozzled
   1.1) hydraulic-mechanical,
   1.2) pneumatic and
2) rotary.

Hydraulic-mechanical spray drying nozzles are single phase, as they operate without auxiliary air, on fed in liquid only. The liquid fed into the nozzle is forced into turbulent flow. Exiting the spray drying nozzle it forms a continuous liquid membrane cone, which tapers as it proceeds downward, until breaking up into droplets. Nearly monodisperse fine sprays can be produced in this way.

Fig. 19.14.
Mechanical spray drying nozzle

Pneumatic spray drying nozzles are two-phased, atomizing the solution or suspension to be sprayed with the aid of an air stream in the nozzle. Their lower sensitivity to variations in the substance parameters (e.g. viscosity, density) is an advantage. The droplet size they produce is less uniform and the apertures of these nozzles clog easily.

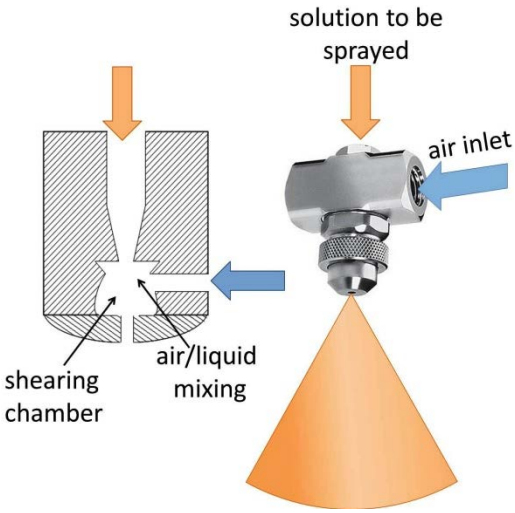


Fig. 19.15.
Pneumatic spray drying nozzle

Rotary disc atomizers are single phase. The solution or suspension to be sprayed is channeled to the middle of the disc, where it forms a thin film. This, affected by centrifugal force, proceeds outward through radial bores and breaks up into drops after leaving the atomizer. Rotary disc atomizers are applicable for spraying highly viscous liquids and even for paste-consistency substances.

Fig. 19.16.
Rotary disc atomizer

Spray drying is used both in pharmaceutical research and production. The product is retrieved in a dry format from a liquid medium after the application of various pharmaceutical technological (e.g. microcapsulation, nanotechnological,

biotechnological) Operations. The extraction of liquids containing organic solvents with gasses containing oxygen is explosive, therefore in such cases inert gases are used.

As a result of small particle sizes the end product is easy and quick to solve, which is an advantage in subsequent processing.

Spray drying is feasible both on laboratory and production scale.

Fig. 19.17.
Laboratory scale GEA spray dryer

Fig. 19.18.
Production scale GEA spray dryer

Questions

1) What pharmaceutically important material attributes are determined by moisture content?
2) What are the general pharmaceutical purposes of drying?
3) What determines the ultimate moisture content achievable by drying?
4) What are the main types of moisture according to the type of bonding?
5) What are the remarkable points of sorptive isotherms?
6) What are the remarkable points and sections of drying and drying speed curves?
7) What types of dryers are there, according to the method of heat transfer?
8) How can vacuum dryers be classified?
9) What are the main advantages and disadvantages of freeze drying?
10) What are the main steps of freeze drying?
11) What parameters can be used for controlling fluidized bed drying?
12) What is the operating principle of spray dryers?

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Recommended websites

http://www.nzifst.org.nz/unitoperations/drying.htm

http://www.geaniro.co.kr/geanirokr/cmsdoc.nsf/webdoc/ndkk5hmc6zspraydryersspraydryers

http://staff.sut.ac.ir/haghighi/download/documents/Drying.pdf

20 Particle size reduction

Particle size reduction operations plays important role in pharmaceutical technology (e.g. in preparation of solutions, emulsions, suspensions, ointments or pastes, as well as in granulation, pelleting, briquette-making, tablet compaction). It can be a finishing operation too, for example in making powder or granulate type end products.

Accordingly, *particle size reduction* means an important technological operation of processing raw materials, intermediate- and end products, in which the size of particles is reduced by using external action.

Size reduction increases particle surface, which is a dominant parameter of such important pharmaceutical technological material transfer processes as wetting, drying, extraction and dissolution. Size reduction increases specific particle surface significantly, which is important for interfacial effects (e.g. adsorption) as well as biopharmacy, as increased dissolution rates mean enhanced bioavailability of active ingredients.

Crushing, grinding, pulverizing of solid state materials are also disintegrating operations, in which external forces overcome the binding forces between and/or inside the particles of matter.

The primary consideration for particle size reduction is the behavior of substances concerning force impulses. Form the aspect of particle size reduction, according to their structural properties substances can be:

1) *rigid,*
2) *tough* and
3) malleable.

Rigid substances are not capable of forced permanent deformation. Their resilience is very low; if the force applied for particle size reduction exceeds this elastic limit the particles fall apart to smaller pieces. Glass and several crystals are for example rigid materials.

Tough substances are resilient, capable of permanent deformation. Rubber is such a material.

Malleable substances are not capable of forced elastic deformation, but, depending on their level of plasticity, they undergo permanent deformation. Such materials are, for example, ointments.

Particle size reduction in solid materials happens due to the application of the following types of force:

1) *cracking,*
2) *milling,*
3) *shearing,*
4) *cutting* and
5) *crushing.*

In *cracking* the substance is exposed to compressive force between flat surfaces. In *milling* the substance is exposed to an additional force, perpendicular to this compressive force. *Shearing* is similar to cracking, but the surfaces are sharp, not flat. In *cutting* size reduction is achieved by using sharp surfaces, in *crushing* by impacts. For particle size reduction it is therefore advisable to choose equipment that is most suited to the comminution properties of the substance as well as capable of exerting the above type forces.

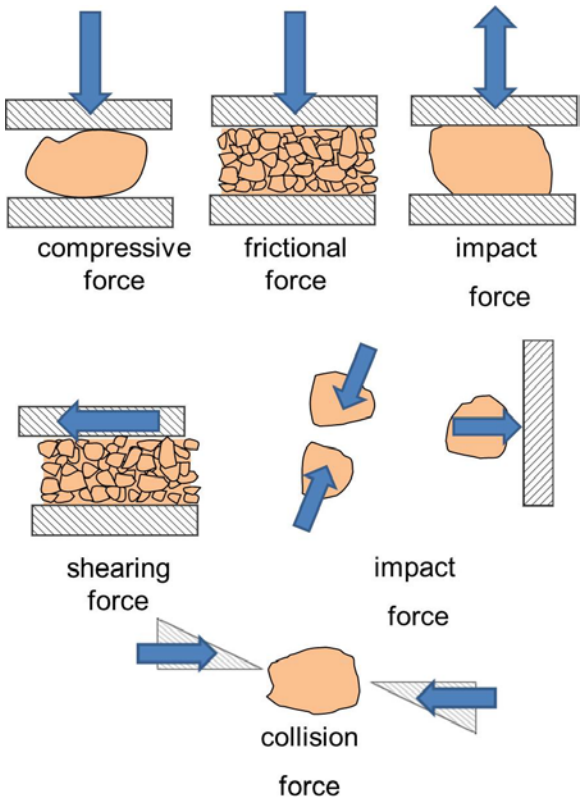

Fig. 20.1.
Forces applied in particle size reduction

The efficacy of size reduction is characterized by *reduction ratio (I)*, which is the quotient of the *initial typical mean diameter* ($\overline{d}$) and the *new typical mean diameter* (d_o) of the substance mass. Increased reduction ratio increases the energy demand of size reduction.

$$I = \frac{\overline{d}}{\overline{d}_o} \tag{1.}$$

The *mean diameter of particles* for *n* fractions can be calculated using the following relation:

$$\overline{d} = \frac{\sum_{j=1}^{n} \overline{d_j} \cdot a_j}{\sum_{j=1}^{n} a_j} \tag{2.}$$

$\overline{d_j}$ mean typical diameter of the j th fraction

a_j fraction mass of the j th fraction

In size reduction solid particles suffer volumetric deformations and split, mostly at the points of structural flaws, creating new surfaces.

In case of *coarse size reduction* required work is proportional to the volume of the particle to be reduced in size, which, in consideration of further parameters, can be determined using the *Kirpichev-Kick Law*:

$$W_{KK} = d_o{}^3 \frac{\sigma^2}{2 \cdot E} \tag{3.}$$

W_{KK} the work required for size reduction, according to the *Kirpichev-Kick* law
σ specific crushing strength of the substance,
d_o particle diameter,
E tensile modulus of the substance to be reduced in size

In *fine size reduction*, where surface area increase is dominant, the amount of work required for size reduction can be calculated using *Rittinger's* equation:

$$W_R = 3 \cdot d_o{}^2 \cdot W_f \left(\frac{d_o}{d} - 1 \right) \tag{4.}$$

W_R the work required for size reduction, according to *Rittinger's* Law
k constant, its value is between 1.2 and 1.7,
W_f specific work required for creating a unit of surface area in a unit volume of material,
d_o initial particle size,
d new particle size

According to *Bond*, the starting point shall be the geometric mean of the values received from the above surface-volume theory. According to his index, which applies primarily to particles in the 50 mm > d > 0,05 mm size range, the energy used in size reduction is proportional to the new crack length produced:

$$W_B = C_B \left(\frac{1}{\sqrt{d}} - \frac{1}{\sqrt{d_o}} \right) \tag{5.}$$

W_B work required for size reduction according to *Bond's* Law
C_B *Bond's* constant

The classical correlations of particle size reduction were summed up by *Charles* and *Hukki* in a *general formula*. According to this, the energy required to change unit particle size is:

$$\frac{\partial E}{\partial d} = C \frac{1}{d^n} \tag{6.}$$

E energy required for particle size reduction,
C constant

Relation 6 can be considered the *base equation of particle size reduction*: depending on the value of index n, either the *Kirpichev-Kick* Law (if n=1) or *Bond's* Law (if n=1.5) or *Rittinger's* equation applies.

The particle size of solids cannot be reduced infinitely, as the increase in applied mechanical energy will cease to reduce particle size beyond a certain value. This

phenomenon is called *size reduction resistance*. At this point the opposed forces of comminution and aggregation are equalized. Size reduction resistance can be decreased by changing surface energy conditions (e.g. by using additives).

Selecting from size reduction methods, the following aspects should be given due consideration:

1) volume of material,
2) purpose of size reduction,
3) structural attributes of the substance,
4) moisture content of substance,
5) initial and intended particle size,
6) particle size distribution,
7) intended degree of size reduction,
8) capacity of the apparatus,
9) further necessary operations.

Size reduction can be performed manually or with devices developed for this purpose.

Mortar (Latin: *mortarium*) is the traditional tool of particle size reduction. Besides size reduction, mortar and *pistle* are also used for blending substances, dispersion and preparation of liquid and semi-solid medicines.

In pharmacy, laboratory and small-scale production, for relatively small amounts of material size reduction is usually performed using china or sometimes agate mortars of coarse internal surface and roughened-end pistles. The substance to be reduced in size is pressed evenly to the wall of the mortar by the concentrical movement the pestle. The particle size defined by the prescription can be achieved by passing the comminuted substance through a sieve of the specified mesh size, continuing the size reduction with the residue caught on the sieve, until reaching the intended particle size.

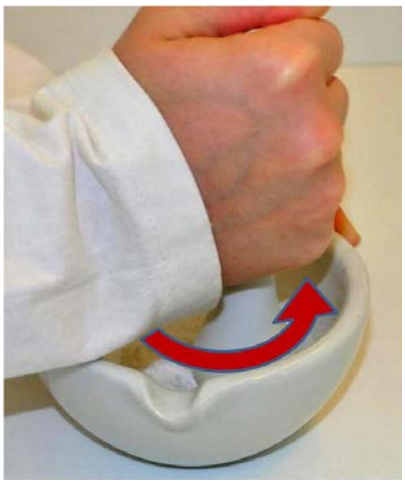

Fig. 20.2.
Manual trituration with mortar and pestle

To achieve higher levels of size reduction, particle size reduction can be done with power-driven *mortar mills*, with high hardness agate mortar and agate pestle. This method allows the production particle systems with finer particle size ranges and better reproduction of particle size and distribution, as the pestle's speed of circulation and

force of comminution are steady, with controllable milling duration. The device is suited for micronization.

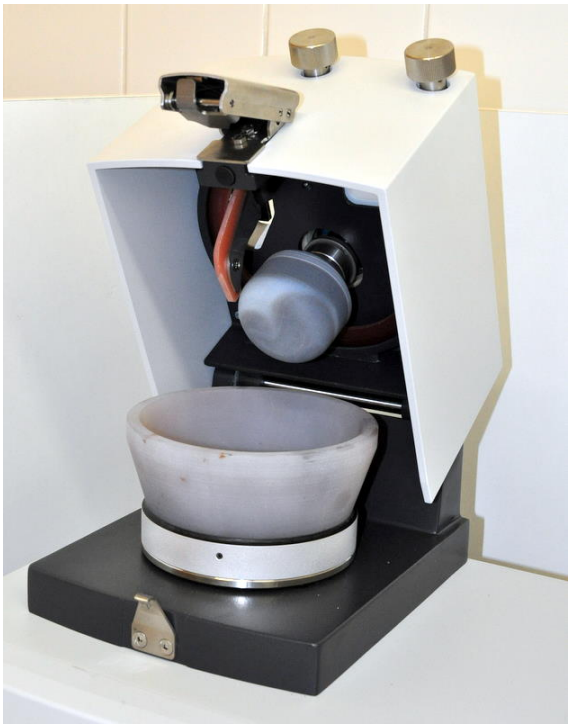

Fig. 20.3.
Mortar mill

Hammermills are suited for medium and fine size reduction. Their main parts are a rotating shaft on which hammers are mounted, a ribbed internal wall and a sieve on the bottom. The hammers are rotated in the mill at high peripherial speed, impacting the particles fed into the mill to the ribbed wall of the drum, smashing, cracking the particles in the process. Achieved particle size depends on the mesh (commutable) of the attached sieve. The device is capable of continuous operation.

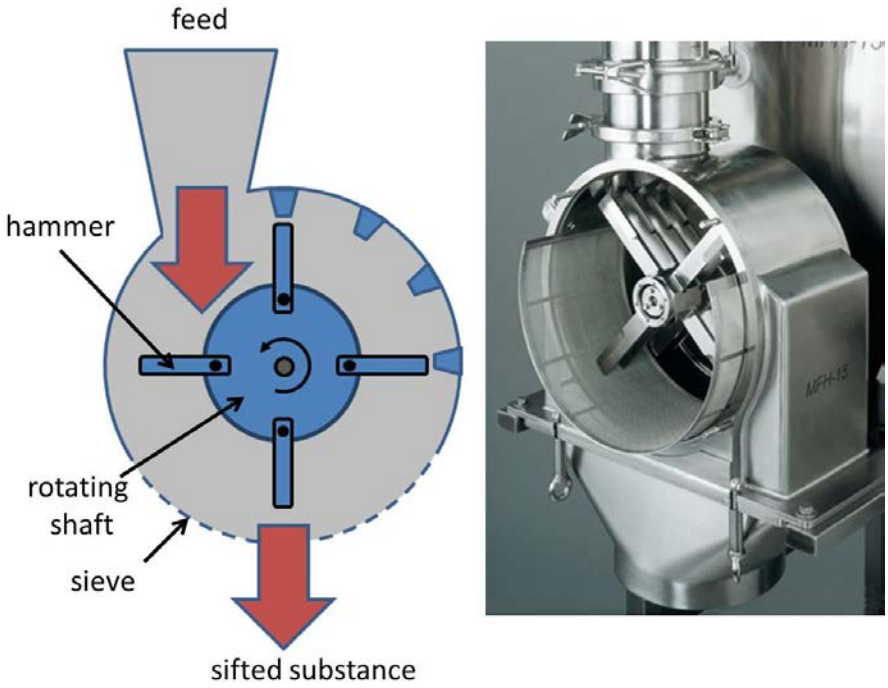

Fig. 20.4.
Hammermill

Ball mills, cylindrical or conical drums rotating on a horizontal shaft are for fine grinding. Size reduction is done by grinding bodies moving freely inside the drum, exerting impact, compression, attrition and friction effects. The movement of the balls is determined by the degree of charging and the angular speed of the mill. Energy consumption of ball mills is relatively high and a significant part of this energy is used for moving the balls. Due to friction some energy is converted to heat, resulting in warming of the system. These devices have the disadvantage of being noisy and bulky.

The balls moving in the mill are affected by gravity and centrifugal force. Centrifugal force depends on the rotation speed of the mill:

$$F = m\omega^2 r \tag{7.}$$

ω angular speed,
r radius of ball mill
v peripherial speed

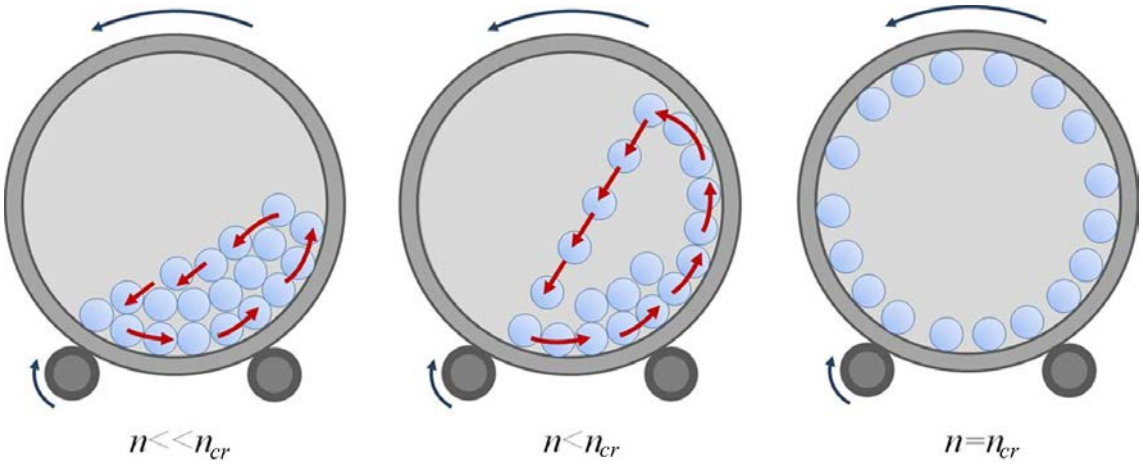

Fig. 20.5.
Movement and arrangement of balls in the mill at different rotation speeds

Movie 9. Ball mill for grinding

The rotation speed of the drum, at which the balls cease to fall down from the top position is called *critical rotation speed*. At this point the centrifugal force (F_c) is equal to the weight of the ball (F_g):

$$F_c = F_g \tag{8.}$$

$$F_g = mg \tag{9.}$$

$$mg = m\varpi^2 r \tag{10.}$$

$$\varpi = \frac{v}{r} \tag{11.}$$

$$g = \left(\frac{n_k \pi}{30}\right)^2 \frac{d}{2} \tag{12.}$$

$$n_k = \frac{42{,}3}{\sqrt{d}} \left[\frac{ford}{perc}\right] \tag{13.}$$

m mass of ball
d diameter of mill
n_k critical rotation speed

$n << n_{cr,}$ in case of low rotation speeds grinding is insufficient with the balls rolling over each other; the force exerted is mostly frictional, with very little grinding. At critical rotation speed there is no grinding as the balls are pressed to the wall of the drum.

The *working rotation speed* (n_w) of ball mills needs to be kept below the critical value ($n < n_k$). In practice this means 60-70% of the critical rotation speed, where the so-called *waterfall* mode emerges, yielding optimum grinding. This is the speed where rotation makes the balls rise and fall back, exerting significant impact force on the material to be reduced in size.

$$n_w = \frac{30}{\sqrt{d}} \tag{14.}$$

Fig. 20.6.
Laboratory scale batch operation ball mill

Hardinge conical ball mills, capable of continuous operation, are used in industrial-scale production.

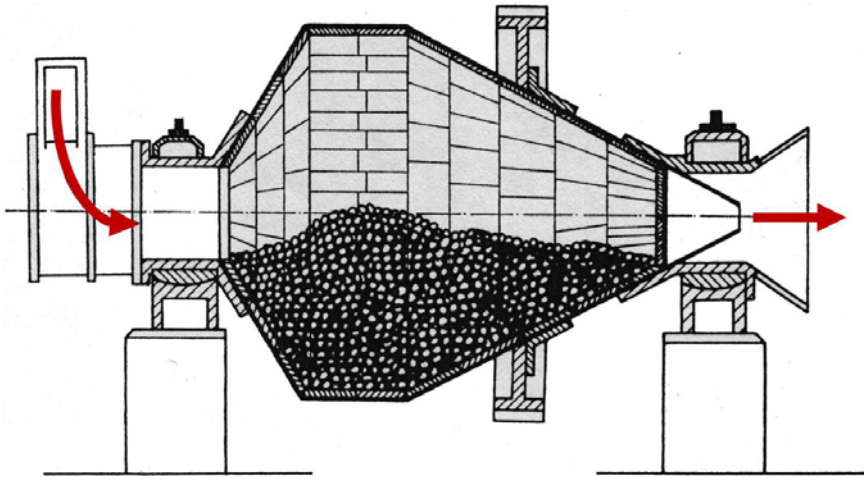

Fig. 20.7.
Hardinge conical ball mill

In *jet mills* high turbulences caused by blown-in air impact particles to each other, reducing their size in the process to as small as a few μm.

In the *Jet Mill* micronizer particles collide and erode each other in the vortex flow created by blown-in high pressure air or nitrogen. Larger particles move along the outer edge of the cylindrical grinding chamber, the smaller ones on an inner track, with the smallest leaving in the middle of the grinding chamber with exiting air through the dust bag that retains particles, letting air through. Particle size and particle size distribution can be controlled by adjusting the feed rate of the substance to be reduced in size and the pressure and speed of compressed air.

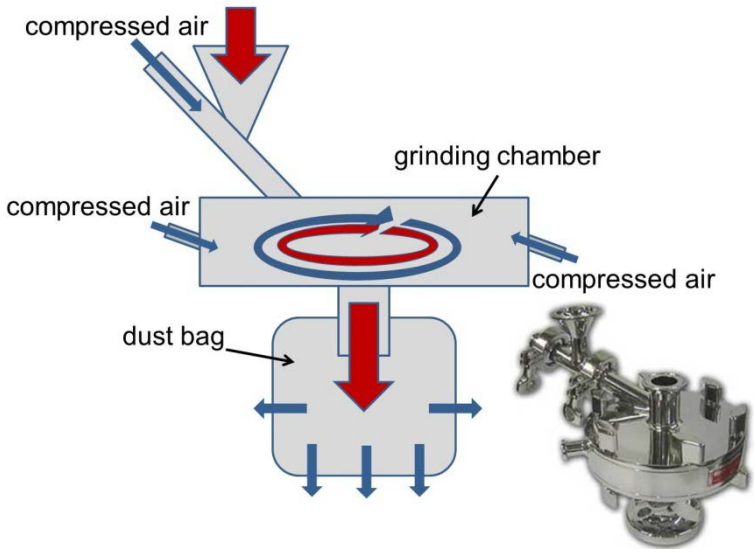

Fig. 20.8.
Jet Mill micronizer

Jet-O-mizer is another micronizer capable of continuous operation. It is a toroidal tube of 20-200 mm internal diameter, in which movement, grinding and separation of particles is carried out by blown-in air. At the bottom of the device various angle air injection makes particles collide, breaking up and eroding in the process. After the

straight section of the tube centrifugal force separates particles by size. Accordingly, larger particles move on the outside track, smaller on the inside track. Smaller particles leave the system after a while, larger ones are recycled to the grinding chamber. Particle size depends, in this case too, on the feeding speed of the substance to be reduced in size and the velocity of compressed air.

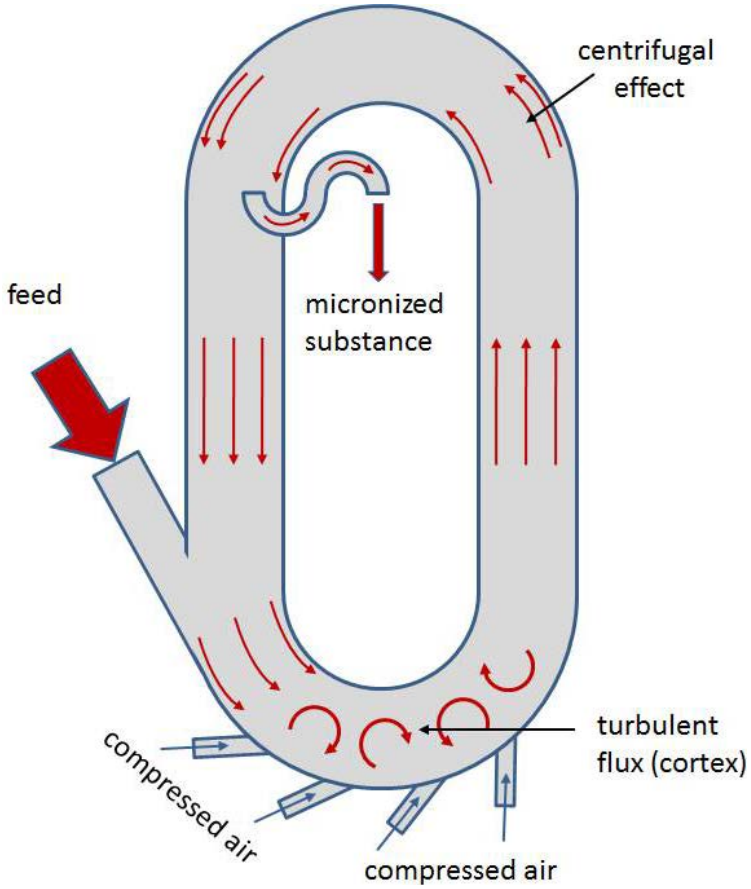

Fig. 20.9.
Jet-O-mizer micronizer

In the production of non-solid phase systems (e.g. emulsions, suspensions) the effect of grinding forces is dominant in increasing the degree of dispersion. The operation is performed by manual labor in mortar with pestle or high shear mixers (e.g. *Ultra Turrax*), colloid mills or high pressure homogenizers.

Questions

1) How can substances be classified from the aspect of particle size reduction?
2) According to the type of force applied, what particle size reduction methods are available?
3) To what instances does the Kirpichev-Kick Law apply and how is it formulated?
4) To what instances does Rittinger's equation apply and how is it formulated?
5) What are the aspects to be considered in selecting a size reduction method?
6) What type of size reduction can be performed by hammer mill?

7) How can the critical rotation speed of ball mills be determined?
8) How does the Hardinge ball mill work?
9) How does the Jet Mill work?
10) How does the Jet-O-mizer work?

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21 Sieving

Sieving is the separation of solid state particle systems by particle size.

From a *pharmaceutical technological* aspect particle size is a particularly important attribute of raw materials and intermediate products, which, among other things, determines the space filling, flow property and compactability of particles and the evenness of coatings.

Particle size and particle size distribution of preparations is also important, as particle size determines, for example, the stability and settling of suspensions. The parameters of particle systems are important from a *biopharmaceutical* aspect, as they have influence on local irritation, dissolution rate, the location of absorption (e.g. in the lungs) and absorption rate (e.g. intramuscular crystalline injections).

Therefore, on account of these technological and biopharmaceutical aspects, technological prescriptions define the average particle size of ingredients, allowed maximum and minimum particle sizes and particle size distribution data.

The purpose of sieving operations is:

1) *mid-production control* of the products of an operation (e.g. granulation, particle size reduction) for operation control and adhering to optimum parameters or
2) *assessment*, description of the *particle aggregate* (as end-product) by determining particle sizes and particle size distribution.

Particles should be able to slip over each other and shift on the sieve; this is a precondition of sieving operations.

During sieving the agglomeration separates into two parts:

1) the fraction *fallen* through sieve (*D*) and
2) the fraction *retained* on the sieve (*sieving residue, R*).

Sieves have rectangular or round mesh openings.

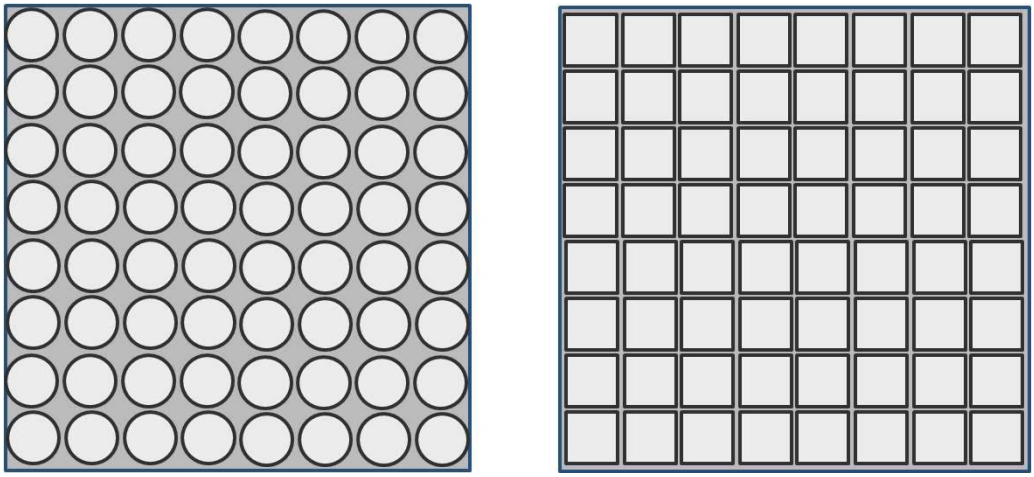


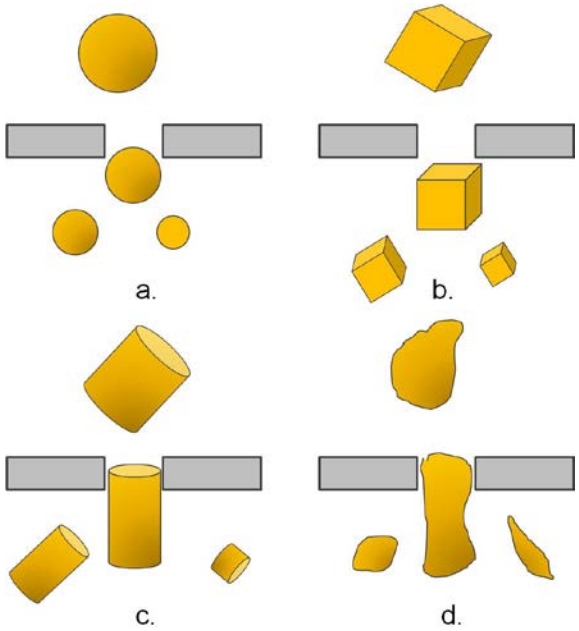
Fig. 21.1.
Round and rectangular sieve openings

In the course of sieving, particles pass through a given size and shape sieve opening according to their shape and size. The size of spherical particles (e.g

micropellets) is uniform in every direction, so they are relative easy to separate by sieving.

To make most of the non-spherical particles, whose size would allow passing the sieve actually pass the sieve the particles need to be properly aligned, which takes time. In case of cubical particles, larger particles need to be turned in the appropriate direction. The situation is similar with cylindrical (e.g. extruded and chopped products) and irregularly shaped particles (e.g. granules).

In the course of sieving the rate of throughput gradually decreases, while average particle size gradually increases. Larger particles may get stuck in the mesh, decreasing the number of available openings and hinder sieving. Particles capable of passing the openings need to assume appropriate orientation due to their shape. Finding this position may take hours for flat or oblong particles, but this usually does not affect the results of sieving substantially. There may be particles that are smaller than the sieve openings and yet they remain in the sieving residue even after prolonged sieving. Such are tiny dust particles adhering to larger particles.



a. spherical, **b.** cubical, **c.** cylindrical, **d.** irregular shape particles

Fig. 21.2.
Significance of particle shape

The *efficacy of sieving* (S_e) expresses the quality of separation, indicating the quantity that actually passed through the sieve, in proportion to the entire particle fraction of particles smaller than the actual sieve mesh (d):

$$S_e = \frac{D_{<d}}{D_{de}} \qquad (1.)$$

$D_{<d}$ particle fraction actually passed through the sieve,
D_{de} The entire particle fraction smaller than the actual d particle size.

The *efficacy of sieving* expresses the quality of the execution of the operation, which depends on the:

1) shape of the sieve openings,
2) mesh size of the sieve openings,
3) shape of particles,
4) moisture content,
5) adhesive power,
6) bed thickness of the substance on the sieve mesh,
7) character of motion of the substance to be sieved,
8) movement speed of a the substance to be sieved and
9) duration of sieving.

In *sieve analysis (a.k.a. gradation tests)* the particle aggregate is characterized by the quantitative distribution of the fractions separated on the sieve column. For this purpose a nested stack of sieves is used, with increasing mesh size from bottom to top. Sieves have to be selected in a way that covers the whole range of particle sizes present in the test sample.

It is worth to use such (logarithmic) sieve sets, in which the mesh size ratio (*multiplying factor*) of adjacent sieves is a constant value.

The sieve set conform with the $\sqrt{2}$ progression consists of …45, 63, 90, 125, 180, 250, 355, 500, 710, 1000, 1400, 2000, 2800, 4000… μm mesh sieves.

The studied sample is poured on the top (largest mesh size) sieve and the sieve column is subjected to agitation for an appropriate duration. Sieving is continued until reaching constant weight of fractions, as absolute separation is usually not feasible due to the imperfection of sieving.

After sieving is finished, the weight of particles retained in each sieve is precisely determined. The test indicates the distribution of size ranges of the particle system by weight.

In real-life aggregates particles are usually not spherical or cubical, but irregular. For standardization purposes the radius or diameter of particles considered spherical is specified, whose behavior is similar to that of the studied particle.

An m_1, $m_{2...}$ m_n weighted average is calculated from the weight of the particle fractions of sizes d_1, d_2 … d_n, which indicates the average particle size ($\overline{d}$) typical of the aggregate:

$$\overline{d} = \frac{m_1 d_1 + m_2 d_{2.} + ... + m_n d_n}{\sum m} \qquad (2.)$$

In case of small amounts the entire quantity, in case of large amounts (full scale production) an average sample is tested.

Fig. 21.3.
Sieve analysis apparatus

In practice, sieve analysis is appropriate for establishing particle size distribution if at least 75% of the particles are larger than 75 μm.

If the values (the quantity of *D* or *R*) received from sieve analysis are plotted on a graph where the abscissa represents the individual classes in $(\Delta d = d_n - d_{n-1})$ intervals and the ordinate the calculated (empirical) frequency, the result will be a *frequency histogram*.

The *particle size distribution curve* (a.k.a. *density function*) indicates the distribution frequency of different size particles.

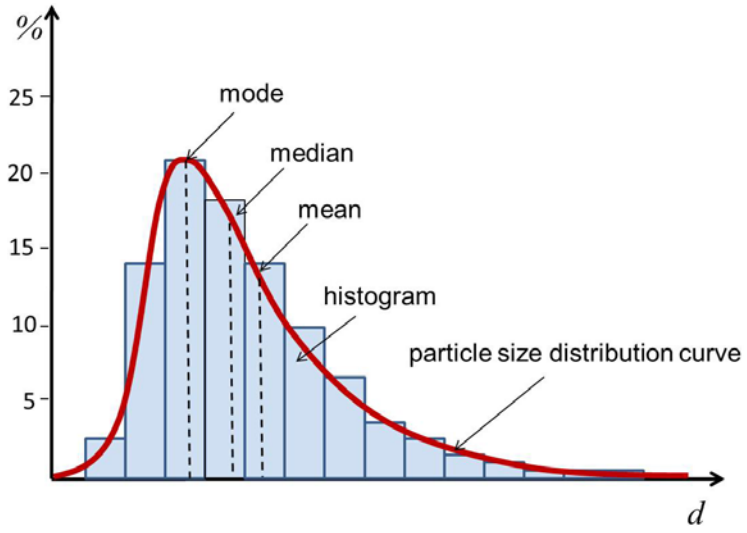


Fig. 21.4.
Histogram and density function of particle size data

The *median* is the middle, "halfway" value of numerically ordered values, with the number of values smaller and greater being equal. *Mode* means the most frequently found value. (As opposed to the other two mean values, there may be multiple modes, as multiple values with the same frequency may occur.) Finally, *mean* or *arithmetic mean* is the quotient of the total sum and the item count of the data.

In case of symmetrical distribution (e.g. normal distribution), the values of mode, median and arithmetic mean of particle size overlap, while in case of asymmetrical distribution they may be varied.

The sum of the amounts fallen through and retained by the sieve (D+R) equals the total substance quantity (1 or 100%):

$$D + R = 100\% \tag{3.}$$

Empirical distribution graphs or *granulometric curves* are derived from the graphical representation of accumulated frequencies. These curves indicate the weight of retained or fallen through particles at a given mesh size, expressed as a percentage of the total weight. In other terms, they indicate the probability of the occurrence of smaller or larger size particles than the value of a given mesh size.

Graphical differentiation of granulometric curves yields the *frequency* or *density distribution curve*.

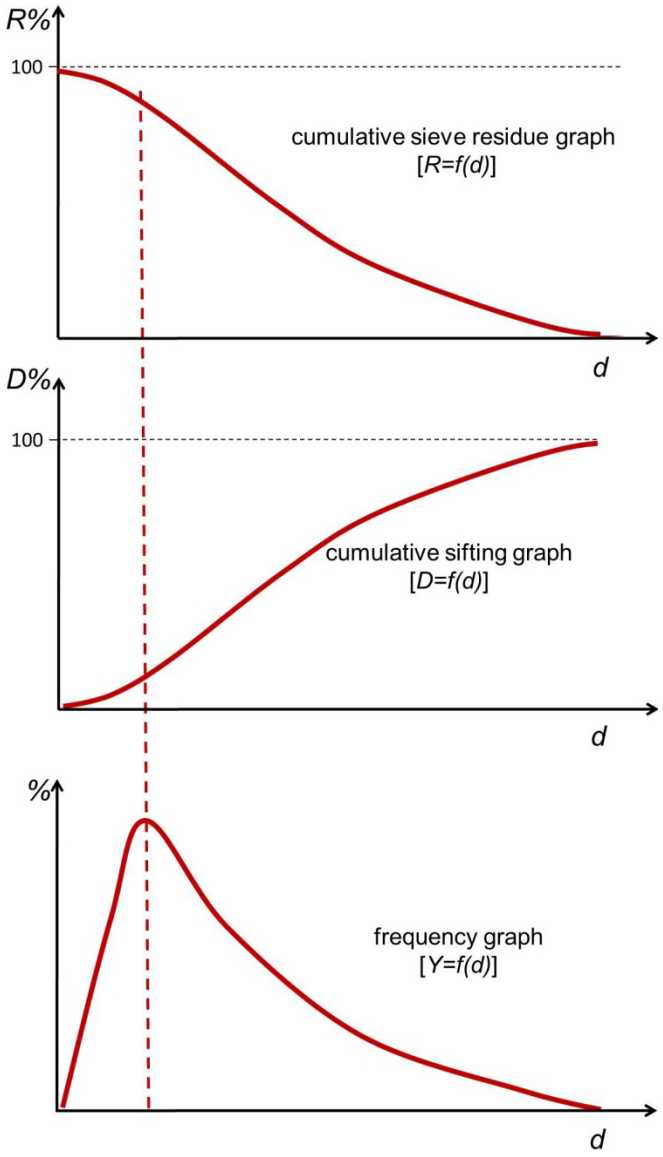


Fig. 21.5.
Cumulative curves of distribution and frquency

The character of particle aggregates can be approximated by various well-known function types.

In case of *normal distribution* distribution is symmetrical. Most of natural phenomena conform to the *Gauss* curve. The width and height of the curve are characteristically oblate, which implies homo- or heterodisperse distribution, while asymmetrical distribution is characterized by slantedness.

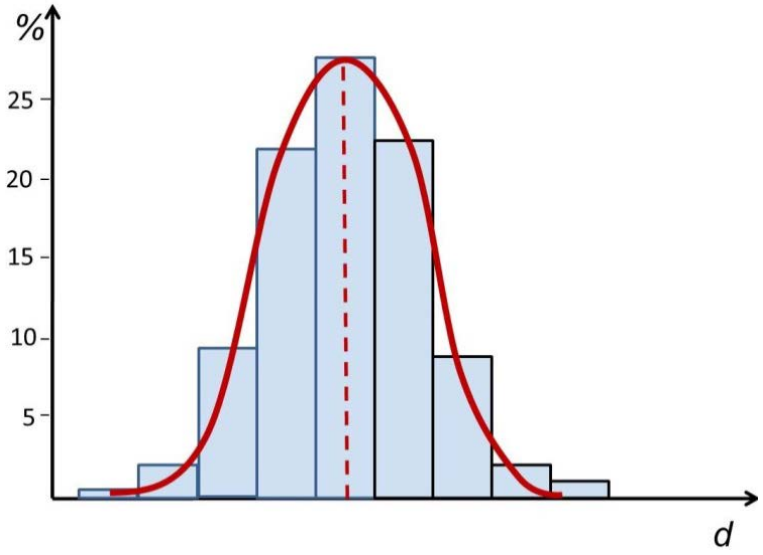


Fig. 21.6.
Histogram and density function of a normal distribution particle aggregate

Normal distribution particle aggregates can be described with the following function:

$$-D/d/ = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{x} e - \frac{(d - d_{50})^2}{2\sigma^2} d(\ln d) \tag{4.}$$

$$m = \frac{1}{\sigma} \tag{5.}$$

$$\sigma = \frac{d_{84}}{d_{50}} \tag{6.}$$

d particle diameter
d_{50} particle size of 50%
m direction tangent of the line
σ standard deviation

68.3% of the data being within ±1 dispersion (σ) distance of the mean value is an important characteristic of the normal distribution curve.

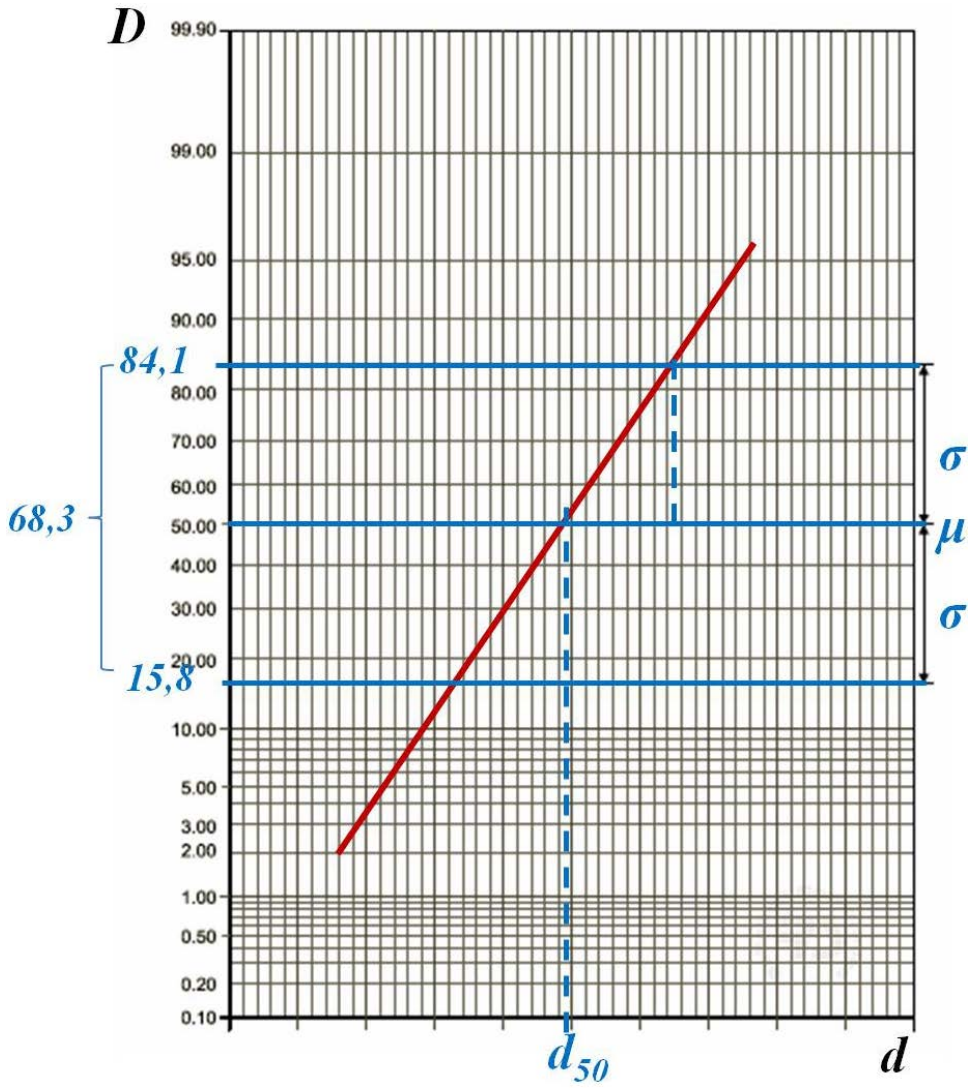


Fig. 21.7.
Normal distribution graph

Asymmetrical particle size distributions are common in pharmaceutical technological practice.

In case of *log-normal distribution* the classical bell-curve is obtained as a function of the logarithm of particle size (this is why it is advisable to use a sieve set of identical multiplying factors). By transforming it logarithmically, the originally asymmetrical distribution can be handled as symmetrical.

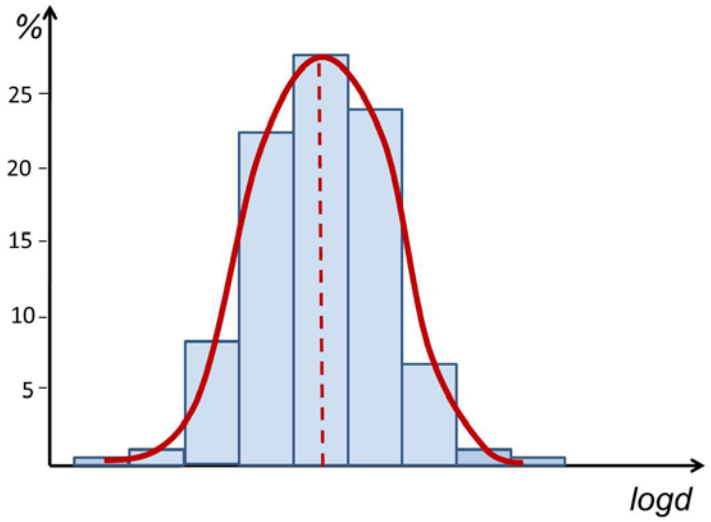


Fig. 21.8.
Histogram and density function of log-normal distribution particle aggregate

$$-D/d/ = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{x} e - \frac{(\ln d - \ln d_{50})^2}{2\sigma^2} d(\ln d) \tag{7.}$$

$$m = \frac{1}{\sigma} \tag{8.}$$

$$\sigma = \frac{\ln d_{84}}{\ln d_{50}} \tag{9.}$$

d particle diameter
d_{50} particle size of 50%
m direction tangent of the line
σ standard deviation

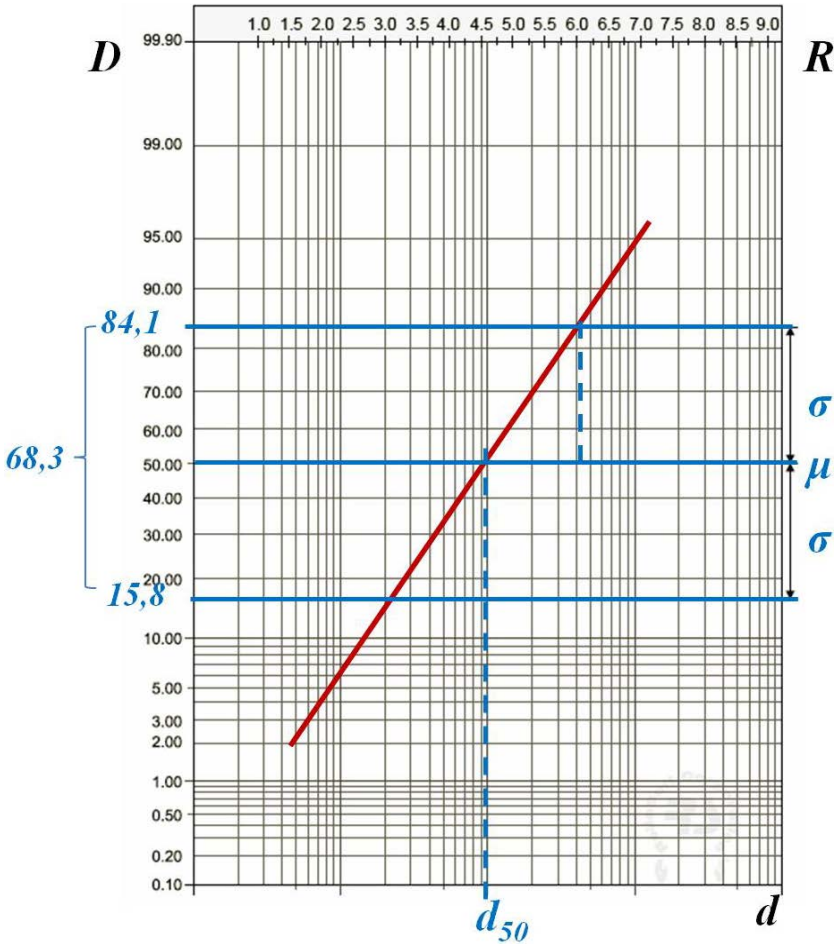


Fig. 21.9.
Log-normal distribution graph

The *GGSA (Gates-Gaudin-Schumann-Andrejev)* distribution function is applicable if the data indicate a linear correlation after a log-log transformation:

$$\frac{D}{100} = m\left(lg\, d - lg\, d_{max}\right) \tag{10.}$$

of which:

$$D = \left(\frac{d}{d_{max}}\right)^{m} \tag{11.}$$

d particle diameter
d_{max} largest particle size allowing 100%
m direction tangent of the line in case of log-log transformation

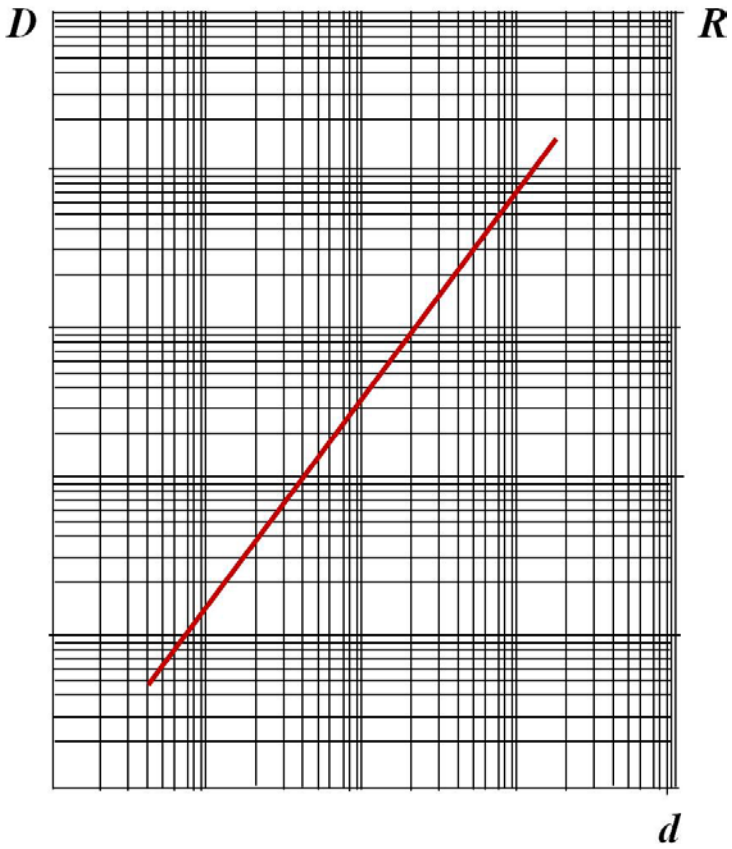


Fig. 21.10.
GGSA distribution graph

The *RRSB (Rosin-Rammler-Sperling-Benet)* distribution can be relatively frequently applied to describe particle size distribution. Data can be linearized with good approximation with it, if the log-log values of *R* or *D* are plotted against the logarithm of particle size.

$$ln\,ln\frac{100}{R} = m\left(ln\,d - ln\,d'\right) \tag{12}$$

of which:

$$R = 100 \cdot e^{-\left(\frac{d}{d'}\right)^m} \tag{13.}$$

R sieve residue (%)
d particle diameter
d' typical particle size associated with 63,2% passed (or 36,8% sieve residue)
m size distribution parameter

if *d*=*d'*, then

$$R = \frac{100}{e} = 36{,}8\% \tag{14.}$$

and

$$D = 63{,}2\% \qquad (15.)$$

Typical particle size is therefore the particle size associated with D= 63.2 or R = 36.8%-frequency, while size distribution parameter is derived from the direction tangent of the line: m = tg α.

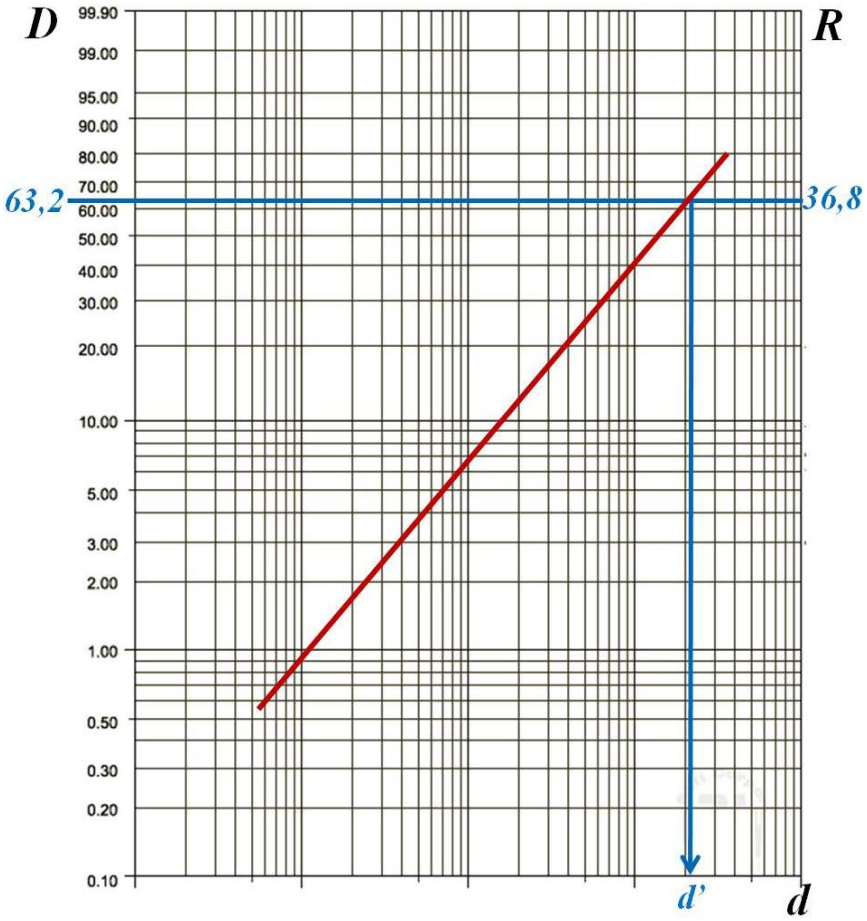


Fig. 21.11.
RRSB graph

For sieving small amounts in laboratory environment standing vertical position sieves are applicable.

Sieves are usually made of metal or in case of substances sensitive to metals (e.g. vitamin C) of plastic.

Fig. 21.12.
Sieve meshes of various sizes

The particles of the substance placed on the sieve are agitated with a card, which prompts them to sliding-rolling motion. The choice of sieve mesh depends on the particle size required for the medicine being prepared.

Fig. 21.13.
Manual sieving with card

Agitated sieving apparatuses are made for separating large quantities. Agitated sieves may be both drum and flat sieves.

Agitated flat sieves may be:

1) horizontal rotary motion sieves,
2) longitudinally or transversally shaken sieves (swinging sieves) and
3) oscillating or vibrating sieves.

Particles bounce on oscillating sieves according to the frequency of vibration. As a result smaller particles pass through the sieve and clogging particles stuck in the sieve easily break loose. The device is capable of both batch and continuous operation.

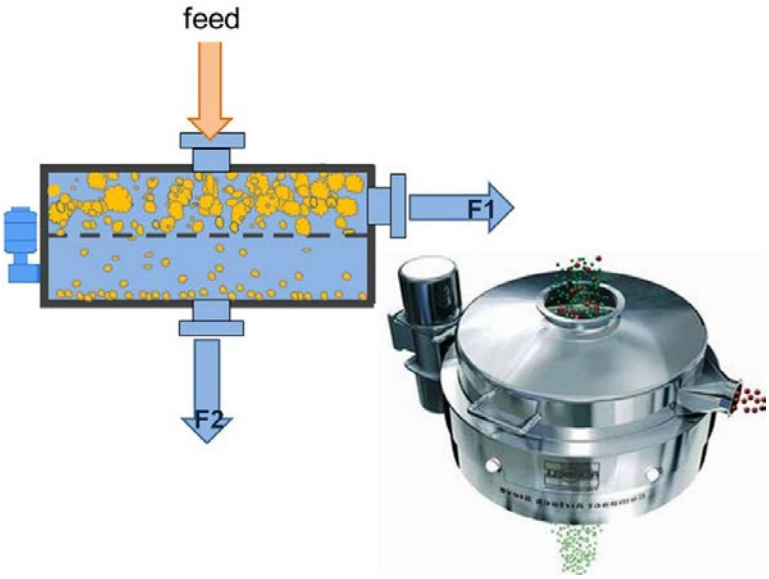


Fig. 21.14.
Continuous operation vibrating flat sieve

On drum sieves particles move in sliding, rotational and rolling motion. Larger particles may clog openings. The device is capable of continuous operation.

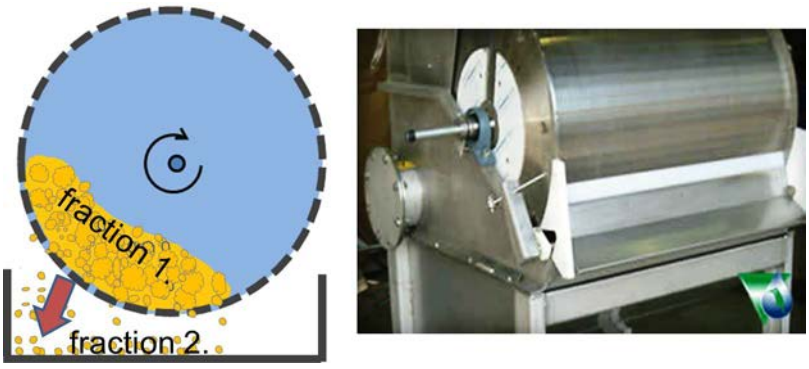


Fig. 21.15.
Drum sieve

Questions

1) What are the possible purposes of sieving?
2) How can the efficacy of sieving be determined and what does it depend on?
3) What is the formula of log-log distribution?
4) To what cases does the GGSA distribution apply and what is its formula?
5) To what cases does RRSB apply and what is its formula?
6) How do continuous operation sieving devices work?

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22 Fluidization

The first scientific observations regarding fluidization were published in 1878. The method was used by *Wurster* for granulation in 1960. Fluidization operations gained ground in pharmaceutics in the 1970s. Besides others, Hungarian authors *Ormos*, *Pataki* and *Blicle* deserve emphasized credit in laying the groundwork of fluidization theory with their fundamental theoretical and practical observations and descriptions of regularities of fluidization issues.

If a *fluid* (liquid or gas) is passed through a solid particle aggregate, then, depending on the flux rate, various states manifest.

The initial density of the particle aggregate is *packed density*, accompanied by *initial bed height* (L_o). The air flowing through the *distribution plate* (e.g. porous or perforated plate, sieve mesh) loosens up the bed, the distance between particles increases, volume and porosity of the bed grow, while its density recedes and a slightly higher than initial, *loose bed height* (L_l) forms.

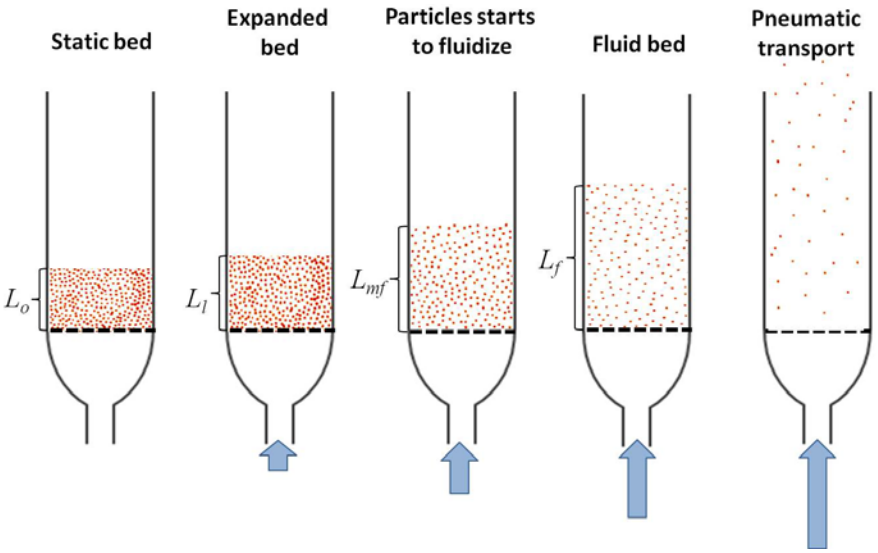

Fig. 22.1.
Bed states in the function of air velocity

As air velocity is increased, bed height, porosity and volume increase with it, the distance between particles grows, then the bed begins to move and particles start to move individually. This flux rate, required for reaching the initial state of fluidization is called *minimum fluidization velocity*. If air velocity is increased further, the actual fluidized state forms and the bed becomes *fluid bed*. Particles in the fluid bed change their position intensively in various directions; the particle system assumes a fluctuating state similar to boiling. Fluidized particle systems have surface tension and viscosity, just like liquids, their surface waves, exhibit hydrostatic pressure.

In fluid state particles float, as the forces affecting them are in balance; drag and *Archimedean* weight equal. At this point pressure drop in the charge is equal with the pressure weighing on the plate that sustains the charge.

If air velocity is further increased, the bed assumes *pneumatic transport* state, with porosity and bed height increased even further. This phenomenon can be employed in transporting granular and dusty products.

Particle systems fill available space discontinuously. If the space between particles has pores in it, the density of the substance is *aggregate density*.

Porosity of the fluid bed means the proportion of the void fraction in total volume:

$$\varepsilon = \frac{V_v}{V_v + V_p} = \frac{V_v}{V} \tag{1.}$$

V_v volume of void fraction in the particle system,
V_p poreless volume of particles,
V total volume of particle system

In case of known cross section (A) columns, porosity (ε) consists of the bed height of particles and pores:

$$\varepsilon = \frac{L_h}{L_h + L_p} = \frac{L_h}{L} \tag{2.}$$

L_h bed height of pores in the particle system,
L_p poreless bed height of particles,
L bed height of particle system.

In a fluidized system $L=L_f$, therefore:

$$\varepsilon = \frac{L_{gap}}{L_f} = \frac{L_f - L_p}{L_f} \tag{3.}$$

Poreless *bed height* of particles:

$$L_p = L_f(1-\varepsilon) \tag{4.}$$

$$L_f = \frac{L_p}{1-\varepsilon} \tag{5.}$$

Pharmaceutical technological practice also uses *ratio of bed height* (R), which indicates the change in bed height (L), relative to initial bed height:

$$R = \frac{L}{L_o} \tag{6.}$$

L_o initial bed height,

Pressure drop in the fluid (Δp):

$$\Delta p = L_f (1-\varepsilon)(\rho_p - \rho_f)g \tag{7.}$$

L_f height of fluid bed,
ε volume of void fraction,
ρ_p density of particle aggregate,
ρ_f density of fluid,
g gravitational acceleration

In substituted format:

$$\Delta p = \frac{L_{sp}}{1-\varepsilon}(1-\varepsilon)(\rho_p - \rho_f)g = L_p(\rho_p - \rho_f)g \tag{8.}$$

Fluidizers are usually powered by overpressure or vacuum. In overpressure-operated devices a compressor supplies the system with compressed air of appropriate pressure. The *buffer tank* eliminates the compressor's irregularities and provides a constant flux rate, which can be measured by a *rotameter*. The air is heated to the required temperature while passing through the heater unit. Air enters the fluidizer through the distribution plate and leaves through the dust bag. The *pressure drop* of the fluid is an important parameter, determined by *manometer*. Analysis of the operative parameters of fluidization makes the process and its regularities recognizable, making the system controllable in turn.

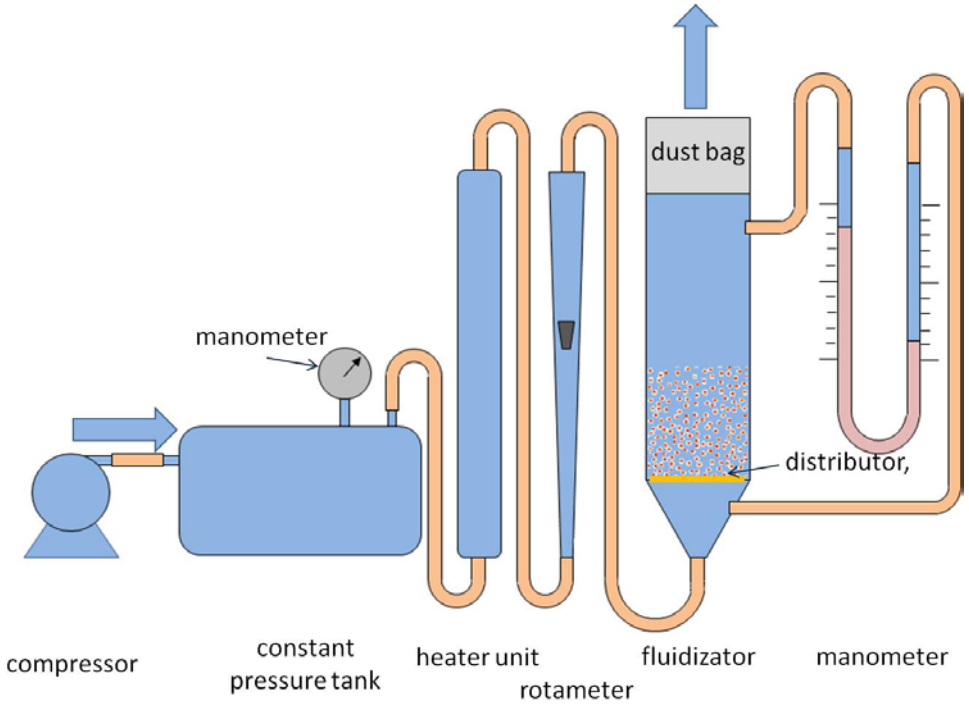

Fig. 22.2.
Apparatus for testing fluidization parameters

As the value of L_{sz} *is* constant during fluidization, *reduced unit pressure drop* $\left(\frac{\Delta p}{L_p}\right)$ can be used:

$$\frac{\Delta p}{L_p} = (\rho_p - \rho_f)g \tag{9.}$$

The changes in the fluid's pressure drop are ideal for tracking the process of fluidization. Analyzing the pressure drop of the fluid flowing through the particle system correlated with initial bed height *(L_o)* in the function of flow velocity, the fluid's pressure drop is initially proportionate with velocity up to point *A*, and then at higher velocity it increases by the square of velocity (*A*-*B*). Between points *B* and *C* particles start floating and arrange towards the direction of lesser resistance. After reaching maximum (*C*), with the bed loosening up resistance starts to decline, which is expressed in the decrease of pressure differential (*C*-*D*). Subsequent to reaching minimum fluidization velocity (point *D*) fluidization takes place between points *D*-*E*, with particles detaching from each other and floating individually in the fluid. Being independent of velocity and the loosening of the aggregate for a given amount of matter, *Δp* barely changes in this range.

After reaching *minimum pneumatic flow velocity* (v_{mpf}) pressure differential increases and pneumatic transport (*E*) starts.

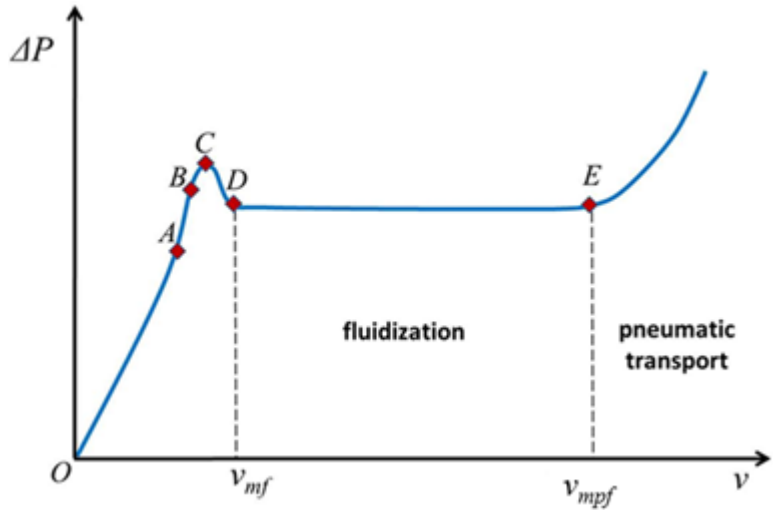

Fig. 22.3.
Pressure drop of fluid in the function of air flow velocity

Minimum fluidization velocity (v_o) can be calculated using the following correlation:

$$\frac{\Delta p}{L_{sz}} = 4 f_m \frac{1}{d} \frac{v_o^2 \rho_f}{2} \tag{10.}$$

f_m friction factor,
d particle diameter,
ρ_f density of fluid.

Fluidization technology is well suited for performing various

1) drying,
2) granulation and
3) coating operations.

In the course of designing a technological procedure, the following parameters must be determined for the given apparatus:

1) Charge
   a) weight,
   b) moisture content,
   c) particle size,
2) Fluidizing air
   a) velocity,
   b) pressure,
   c) temperature,
3) Vaporizing air
   a) velocity,
   b) pressure,
   c) temperature,
4) Solution (only for granulation and coating)
   a) volume,
   b) solvent components,
   c) concentration,
   d) temperature,
   e) feed rate.

There are often difficulties in attempting to scale-up from smaller scale to industrial units.

Fig. 22.4.
Glatt instrumented laboratory fluid bed device

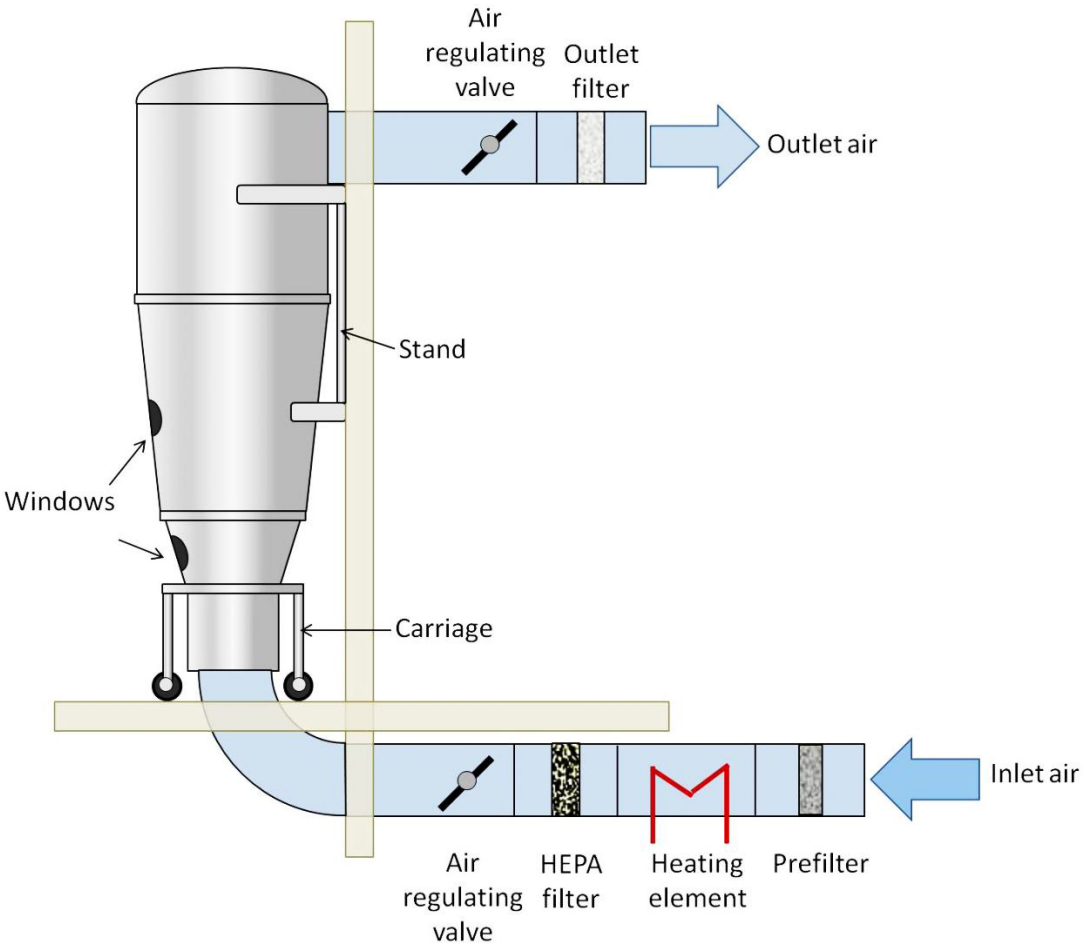

Fig. 22.5.
Industrial fluid bed device

22.1 Advantages of fluid bed technology

Due to the intensive mixing in the fluidized particle aggregate *distribution of temperature and concentration* is *more uniform* than in a static bed. The transfer of heat and matter takes place between particles as well as between particles and the fluid, expediting processes.

Fluidization is a *quick and efficient* technology, improving *productivity*. Multiple operations can be performed simultaneously (e.g. in granulation blending, wetting, agglomeration and drying), in the same device, significantly improving productivity and simplifying technology. Heat-sensitive substances dry at lower temperatures and granulate faster due to good blending and mass transfer.

The fact, that fluidization equipment is resistant to failures and cheaper than other devices due to the lack of moving parts and simple structure makes fluidization technology even more efficient.

Fluidization processes are controllable, devices are easy to instrument and automate.

Fluidization technology is capable of *continuous operation*, otherwise batch-operation production technologies can be converted to continuous operation.

22.2 Disadvantages of fluid bed technology

In the course of fluidization irregularities may occur in the fluid bed, setting back heat and mass transfer and thereby the reproducibility of the process.

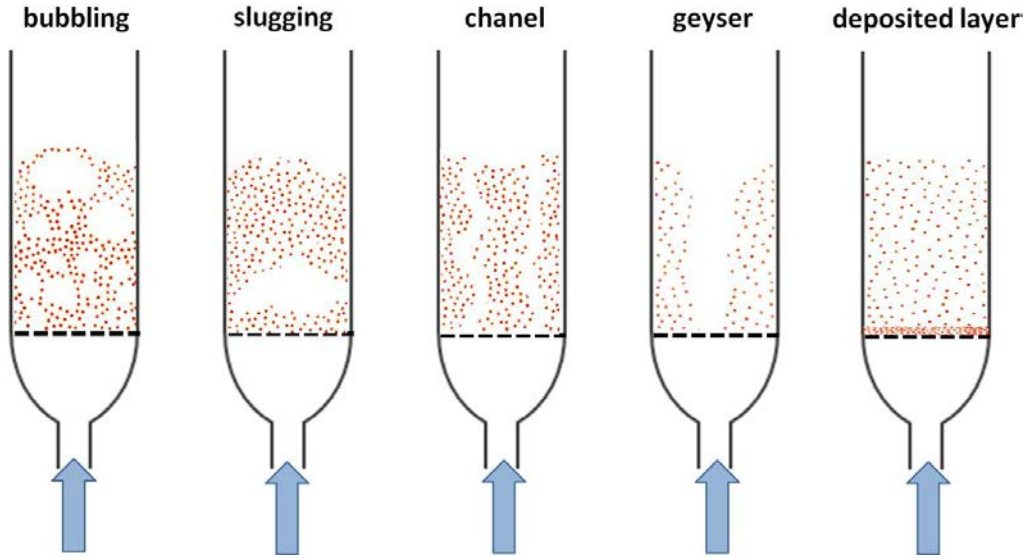

Fig. 22.6.
Fluid bed irregularities

In case of higher fluid flow rates sometimes *bubbles* form in the fluid bed, passing through the fluid bed causing inhomogeneity.

In case of excessive bed height sometimes large bubbles, filling the entire cross section and passing through the bed with bursting pulses. To prevent the occurrence of this phenomenon decrease the height of the fluid bed or use a higher cross section device.

In case of wet particles prone to clumping or fine powders sometimes *channels* form. Air tends to flow through these channels, reducing the homogeneity of the bed.

In case of *geyser formation* the high velocity fluid sweeps adjacent particles along and deposits them at the top of the bed. The phenomenon enables intensive drying.

Larger, heavy particles tend to settle on the distribution plate, forming a deposited layer decreasing the uniformity of fluid distribution.

Fluidization anomalies are usually removable or reducible by the optimization of flow, replacement of the distribution plate, application of vibration or installation of an agitator.

22.3 Entraining of solid

In the course of pharmaceutical preparation production using fluidization technologies the rate of entraining of solid, which may be significant.

Fluidizing air, flowing with adequately adjusted velocity keeps particles afloat in fluidized state, while carrying off adjacent small particles in pneumatic transport.

In practice, the rate of entrained solid can be reduced by controlling operative parameters, but it is usually unavoidable. It occurs in case of heterodisperse particle distribution in systems of high dust content. In drying operations rubbing creates dust,

especially in case of overdrying. Increased mass of entrained solid should be expected in granulating operations, if the initial elocity of fluidizing air is too high and if the vaporized solution wets the dry substance too slowly.

Entrained solid may alter composition of the preparation, therefore the solid has to be retrieved and returned to the fluidization space.

Mass of entrained solid shows up in pressure drop:

$$m_k = m_o\left(1 - \frac{\Delta p_t}{\Delta p_{mf}}\right) \qquad (11.)$$

m_o mass of charge,
Δp_{mf} pressure drop at minimum fluidization velocity,
Δp_t pressure drop at t point of time.

If $\Delta p_t = \Delta p_{mf}$, then according to the above relation $m_k = 0$, that is, amount of entrained solid is inconsiderable.

Solidt separation bags mounted at the top of the fluidizer in the path of outgoing air filter dust carried by air while letting outgoing air pass. Accumulated dust is returned to the fluidization space by manual or mechanical shaking off.

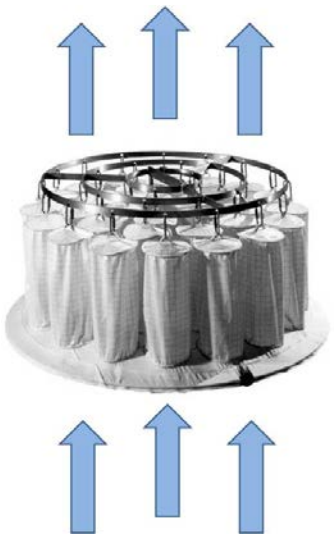

Fig. 22.7.
Filter bags

Air filter candles of various mesh sizes from which entrained solid can be reclaimed are used both in laboratory and production-scale equipment. They require cleaning before starting a new batch.

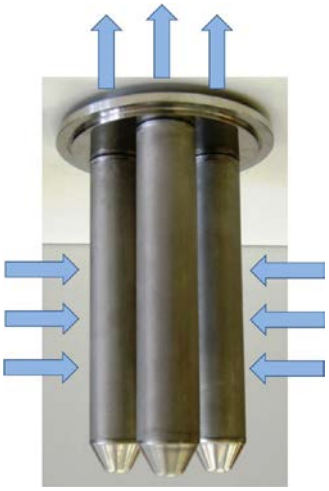

Fig. 22.8.
Air filter cartridges

Another frequently used method of entrained solid separation is channeling air through a *cyclone*. In the device, which is free of moving parts, dust is separated when flying particles are subjected to the effect of centrifugal force. Particles circulate on a decreasing circumference spiral course and eventually leave through the bottom of the device.

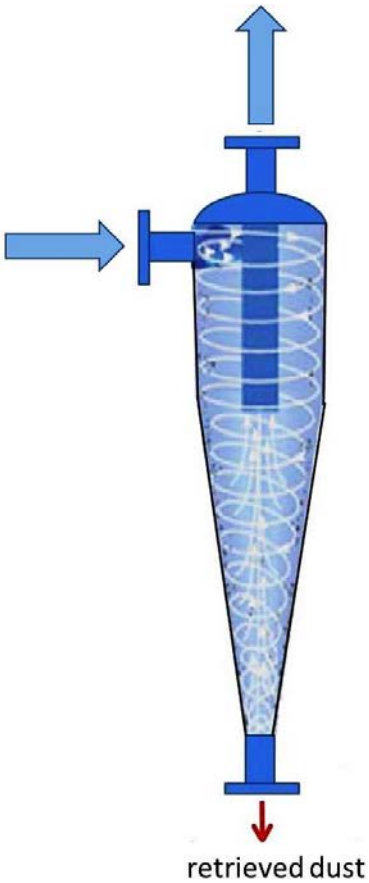

Fig. 22.9.
Cyclone dust separator

Questions

1) What types of bed state develop in the function of air velocity?
2) What does fluid bed porosity mean and what correlations characterize it?
3) What units constitute an apparatus for testing fluidization parameters?
4) What are the distinct stages of fluid pressure drop in the function of air flow velocity?
5) What is the correlation that determines minimum fluidization velocity?
6) What are the operative parameters that need to be determined in designing technological procedures of fluidization?
7) What are the main parts of an industrial-scale fluidizer?
8) What are the advantages and disadvantages of fluidization for pharmaceutical technology?
9) What are the main types of fluidization irregularities?
10) How does the cyclone dust separator work?

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Recommended websites

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http://www2.msm.ctw.utwente.nl/sluding/TEACHING/ParticleTechnology/vanOmmen_Fluidization.pdf

http://www.pharmainfo.net/free-books/fluidized-bed-systems-review

http://www.glatt.com/cm/en/process-technologies/drying.html

http://www.glatt.com/cm/en/process-technologies/agglomeration-granulation/spray-agglomeration.html

http://www.glatt.com/cm/en/process-technologies/coating/fluid-bed-coating.html

23 Granulation

Granulation in solid phase pharmaceutical technology is one of the most frequently applied *forming* operation, with which particles (granules) are created from powder.

Granulation according to its feature is a *forming operation*. Granulation can be an intermediate operation during manufacture of drugs, if granules will be used as an *intermediate product* (for compressing tablets, making capsules).

If granules are traded as final product, as separate dosage form, then granulation is the *finalizing* operation before packing. Granulation as a separate dosage form is chategorized into multiparticular dogase forms. (see chapter *Multiparticulate dosage forms*)

Aim of granulation can be:

1) to compress powders to reduce loss of powder and to improve dosing
2) to avoid separation and adhesion of powder mixture,
3) to improve compressibility of materials,
4) to form high dose active substances into granules,
5) to improve flowability of materials,
6) to prepare controlled drug delivery particles (e.g. delayed dissolution, sustained drug delivery) and
7) fast absorbing drug delivery systems (effervescent granules)

Granules may be marketed in:

1) in divided form,
2) in undivided form of preparation.

Liberation of active substance can be done:

1) externally (dissolving, dispersing, effervescent granules),
2) internally (in the form of spansule).

Dissolution of granules before administration ensures faster effect and better bioavailability than granules taken per orally. At administration of granules, which are coated or containing hydrophobic excipients, prolonged liberation of active substance can be achieved.

Typical particle size of pharmaceutical granules is generally between 0,1-0,8 mm. Their shape is spheric having good flowability, but their surface is usually uneven and have internal porosus structure.

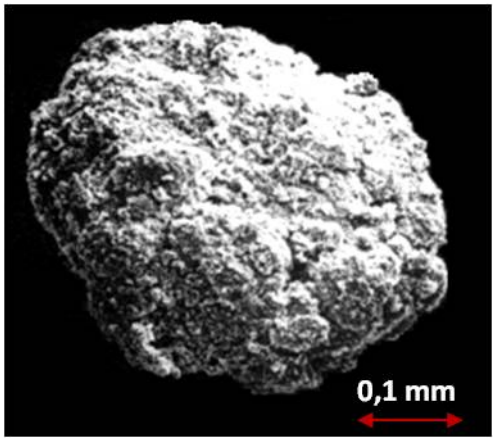


Fig. 23.1.
Granule

Granules may be created by aggregation from small particles (*building up granulation*), or by desaggregation from large particles (e.g. briquette).

Building up granules formation requires bindings created between primer particles. During preparation of granules, so strong bindings are created, which are able to base and to allow further growth of particles. An important practical aspect is the fact that these bindings are to ensure the required and steady mechanical strength for creating particles. Thereby granule particles will not crumble and are suitable to perform further operations (e.g. compressing, encapsulation).

23.1 Theory of forming bindings

Different type of association or connection possibilities could be identified based on previous practical experience and theoretical conclusions. Knowledge of connection possibilities is necessary to perform pharmaceutical granulation to solve solid phase dosage form development and to optimize operation parameters of manufacture.

Primary bindings are distinguished into the following types:

1) adhesion and cohesion forces in immobile liquid film created between primary powder particles,
2) boundary forces inside of granules in mobile liquid film
3) creation of solid bridges,
4) attraction force between solid particles
5) effect of mechanical connection.

23.1.1 Effect of adhesion and cohesion forces in immobile liquid film

With slightly moistening of dried powder mixture, absorption of moisture and creation of very thin *immobile* liquid layer will be performed. Due to effect of moisture dispersed by stirring, significant decrease occurs in distance between particles and contact surface of particles. Parallel binding force between particles increases, while magnitude of *van der Waals* attraction force is in linear proportion with diameter of particles and in inverse proportion with the square of distance.

At granulation, binding excipients should be used, while immobile layer developed due to granulating solution containing binding material and having high viscosity, can create stronger binding, than mobile layers discussed in section 2.

23.1.2 Effect of interfacial force in mobile liquid film

At wet granulation, *mobile film* is created around and between particles when more granulating material is added, than which is necessary for creation of immobile film.

In the case of low moisture content, *pendular* state occurs and lens-shape rings of liquid focuses the particles. In adhesion, suction effect caused by liquid/air boundary tension and hydrostatic pressure decrease plays a significant role.

At moistening of powders during stirring, started with pendular state, air is gradually forced out from pores, and granulating material replaces its place. Therefore pore space of particles decreases while density rises.

Initial three-phase system (air/liquid/solid) turns into biphasic system liquid/solid depending on quantity of liquid and dispersion. Solidity of granules increases three times more between pendular and capillary state.

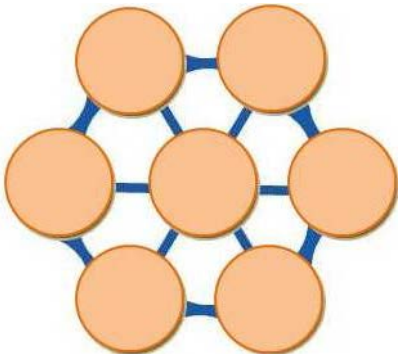


Fig. 23.2.
Pendular state

In *funicular* state, particles contains higher amount of liquid and less air compared to pendular state.

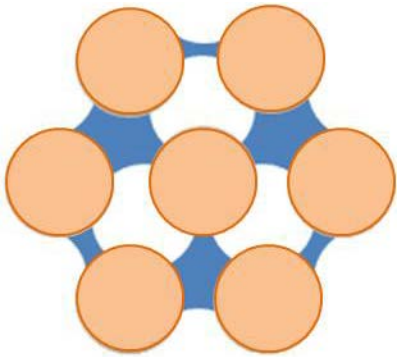


Fig. 23.3.
Funicular state

Funicular state represents an intermediate section between pendular and capillary state. Breaking stress of granule increases three times more between these two phases.

Capillary moisture state is created when moisture excludes all the air. Particles are held together on liquid/air boundary surface by capillary-suction effect, which prevails only on the surface of granule.

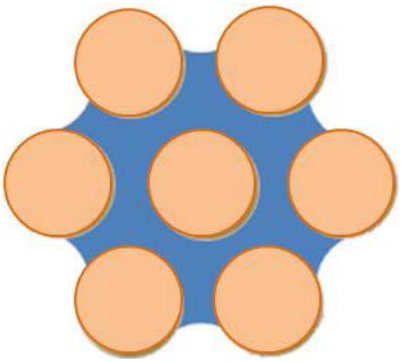


Fig. 23.4.
Capillary state

Due to the *exaggerated amount of moisture*, solid particles are suspended in granulating liquid.

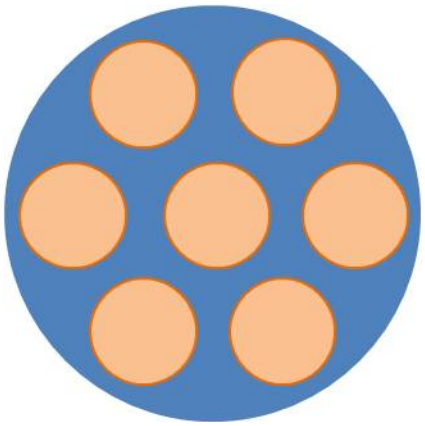


Fig. 23.5.
Over-moistened state

Practice shows that at wet granulation due to the effect of kneading-stirring operation which is for homogeneous moistening of particles, the material can transform from original pendular state into funicular or capillary state without adding further moisture. This phenomenon can be explained with more viscose and dense mass, which is created by decrease of pore-volume (excluding air), and particles can get closer to each other. Thus added amount of moisture is enough to achieve funicular or capillary state.

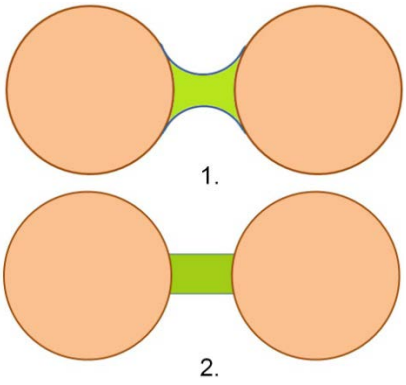
Hence actual state of moistened powders, powder mixtures is not only determined by moisture content, but also by parameters of stirring operation.

23.1.3 Creation of solid bridges

During granulation, solid bridges between particles are created by partial melting, partial dissolution of moistened powder material or with binding materials.

23.1.3.1 Dry granulation

In the case of use of excipient with low melting point, solid bridges are performed by *partial melting.* Between particles, molten bridges done by heating can be solidified by cooling. This operation is termed *sintering*, and granules created with this operation are sinter-granules.



1. molten liquid bridge; **2.** bridge solidified by cooling

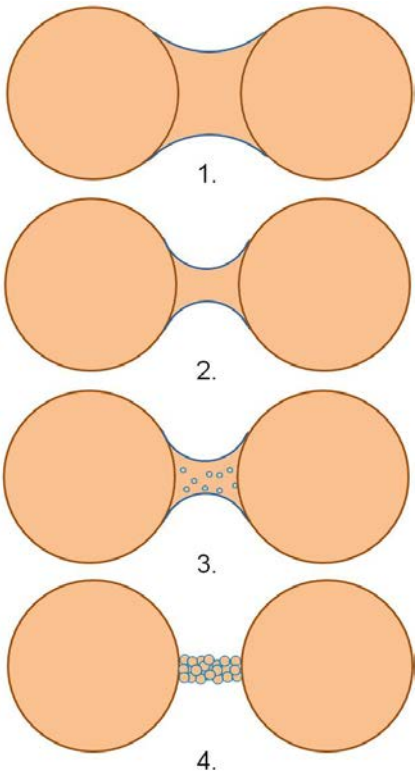
Fig. 23.6.
Creation of solid bridges at melting granulation

At dry granulation, in the case of materials with low melting point, partial melting can also be caused by applied pressure. After ceased pressure, particles connect to each other with created molten crystals. Attention has to be paid to the fact that, active ingredients having low melting point can also be molten and with cross-crystallization can participate in creation of bridges. Thus dissolution profile may be changed.

At wet granulation, accretion or adhesive granulation is applied depending on solubility conditions and excipients.

23.1.3.2 Partial dissolution

Partial dissolution of moistened powder material can only been counted, if at granulation applied moistening solution dissolves one or more component of powder material. After drying of moistened material, solid bridges are created from liquid bridges formed from own material of particles. This type of granules is called to *encrusted granules*.



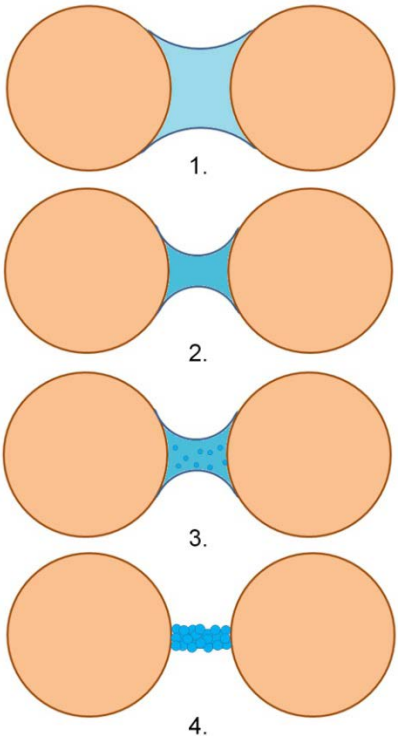
1. Creation of liquid bridges from the solution of own material of granule;
2. Evaporation of solvent from liquid bridge;
3. After turning solution into concentrated, starting of crystallization;
4. Solidification of bridges done by drying containing own material of granule.

Fig. 23.7.
Forming of solid bridges from liquid during encrustation

Development of concentration condition is significantly determined by speed of drying, thus size of crystals forming solid bridges. Larger crystals are formed with slower drying, while smaller ones created when faster drying is applied. Therefore if active substance is also dissolved in applied solvent, then recrystallization depending on operation parameters also influences dissolution and liberation of active substance.

23.1.3.3 Solidified binding agent

Solid bridges formed from *solidified binding agent* are created from liquid bridges consisted of solution of binding material after drying and solidification or crystallization of binding material. This technique called *adhesive granulation* is commonly used to for wet granulation of granules having high hardness and appropriate mechanical properties. Quantity of binding material has to be determined to produce granules with appropriate hardness but not slowed dissolution. According to publications, exaggerated amount of granulating material result in decelerated liberation of active ingredient.



1. formation of liquid bridges from solution of binding material;
2. concentration of binding materials solution-bridges by evaporation;
3. becoming solution to be concentrated,
then starting of crystallization of binding material;
4. solidification of bridges form crystals of binding material by drying.

Fig. 23.8.
Forming of solid bridges from liquid during adhesive granulation technique

23.1.4 Significance of attraction force between solid particles

Without any liquid or solid bridges consisted of binding material, attraction forces cohered the granules can be distinguished into two types:

a) *electrostatic* forces *and*
b) *van der Waals* forces.

Electrostatic forces play a significant role in cohesion between solid particles and forming of clods during stirring. Generally these do not assist in final hardness of granules.

Van der Waals forces compared to electrostatic forces are four orders of magnitude stronger and significantly assist in hardness of granules formed in dry way. These forces rise when distance between nearby surfaces decrease, which occur at dry granulation forced to particles by external pressure.

At compression, distance between particles is decreased by exclusion of air, which favor of enforcement of van der Waals forces. Attraction forces increase quadratically by decreasing of distance, which contributes to final hardness of compressed material.

23.1.5 Mechanical interconnection

In particle systems containing no water, form-closing bindings can be created too, which are mechanical ones based on shape of particles and surface unevenness. These are binding forces without adding excipients creating bridges, however are significantly weaker, than the solid bridges performed with binding agent.

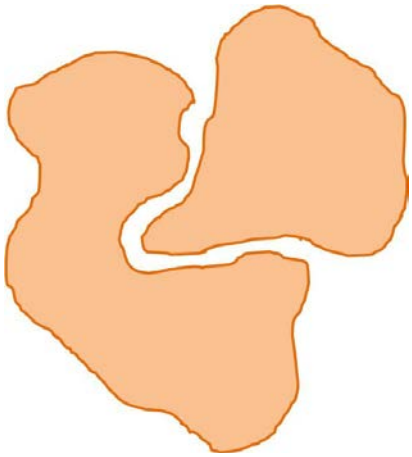


Fig. 23.9.
Form-closing bindings

According to the theory of *mechanical bindings*, criterion of creation of appropriate binding force the fact that solution of binding material does not only moisten the powder material, but also penetrates into pores of particles, thereby mechanical bindings can be made.

23.2 Mechanism of granule formation

At wet granulation, particular liquid is added to dry powder material and moisture is dispersed by stirring. Particles stick to each other due to creating liquid film and more particles can stick together by adding further liquid and applying more stirring.

Mechanism of granulation process can be divided to three phases:

23.2.1 Nucleation (creation of core)

Granulation is performed by adhesion of primer particles by creation of liquid bridges. Primer particles adhere to each other with pendular, funicular state then after further stirring with capillary state. Formed cores are the base of latter increase of granules.

23.2.2 Transformation

Following creation of core, granulation process can continue with two kind of transformation:

a) primer particles adhere to each other with pendular bridges or
b) cores adhere to each other.

Size of forming particles and proportion of smaller and larger particles are determined by operation parameters. Influence of these parameters can be characterized with average particles size and particle size dispersion. Not too large particle size and

particle size dispersion is beneficial for further compressing or encapsulation operations. Particles with larger size or too high portion of powder size (wide particle size dispersion) can result in complications during compression, such as causes non-uniform loading into bed-die.

23.2.3 Increase of particle size and conglobation

Continuation of granulation leads to increase of particle size and assists in creation of spherical particles which is beneficial to produce of pellets. Coalescence of particles continues due to further stirring, which ultimately cause formation of unusual mass. Development of this over-stirred state depends on quantity of granulation liquid and properties of applied powder beyond parameters of stirring (stirring time, speed).

At granulation, four possible mechanism of increase of particle size are distinguished.

23.2.3.1 Coalescence

Coalescence occurs, when two or more particles are combined to a larger one.

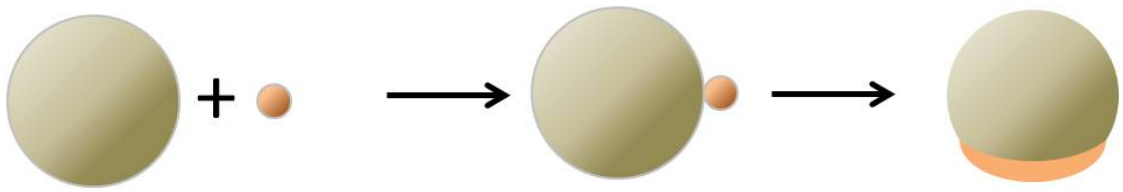


Fig. 23.10.
Coalescence

23.2.3.2 Breaking

Breaking means fracture of particles to smaller particles and stratification of these fragments stratification onto another particle

Fig. 23.11.
Breaking and stratification

23.2.3.3 Abrasive material transfer

Abrasive material transfer occurs, when some material wears out or crumbles from particular granules and adheres onto another granule.

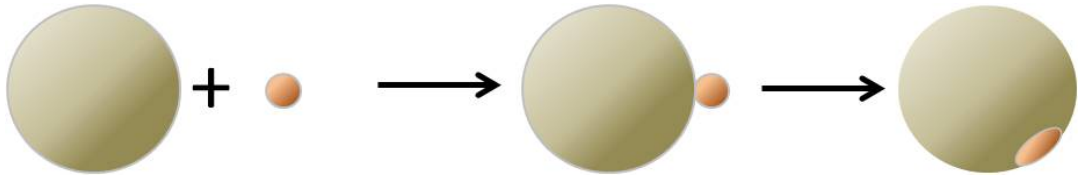


Fig. 23.12.
Abrasive transfer

23.2.3.4 Stratification

Stratification develops, when further powder material is introduced into granulation equipment during granulation process. These new particles stratify onto present granules which leads to smoother and more even surface while size is increased. This mechanism is beneficial for producing pellets.

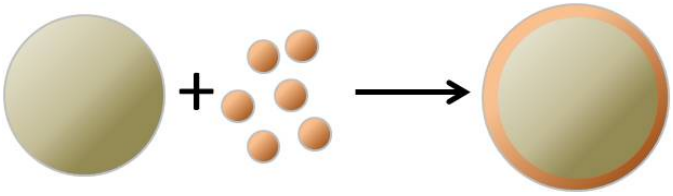


Fig. 23.13.
Stratification

23.3 Production of granules

Operation of granulation can be carried out agglomeration and/or desintegration.

Agglomeration is performed, when from a powder material, granules are typically produced in wet way of granulation by building up granules.

Disintegration is performedm, when particles produced by agglomeration in dry or wet way of granulation, are crushed to be granules.

In material structural point of view, granules can be regarded as particles adhered to each other, therefore theoretical, which deal with adhesion mechanism of primer particles and builind up particles, are significant in the aspect of quality of end product and reproducibility of manufacture.

23.3.1 Dry granulation

At dry granulation, granules are formed generally without adding binding material by compaction. Dry granulation can well be applied in the case of moisture or heat sensitive or unstable materials. Its advantage is to be a rapid method, requiring low energy. Hydrolytic decomposition or other undesirable processes due to heating can be avoided. Preformation of dry granulation needs few tools, small work place, and expensive drying operations are avoidable.

Disadavnatages of technology of dry granulation are the fact that it requires a special apparatus, the mechanical hardness of granules is lower, than in case of granulation with binding material, while the binding forces are weaker. Product shows a heterogeneous particle size dispersion because of high proportion of powder material, thus has relatively unappropriate flowablity.

23.3.1.1 Dry granulation by briquetting

Briquetting is a compressing operation, during which large size compressed material is performed as the first step. So called briquettes having approximately 20-30 mm diameter, flat and cylindrical shape with 5-15 mm thickness are produced by tableting machine performing high compressing force and which is equipped with special tools.

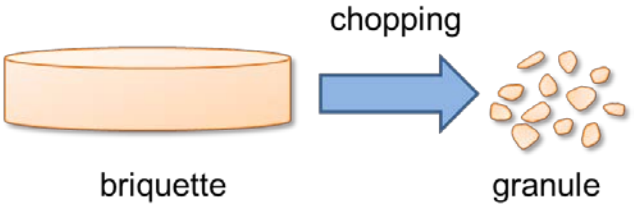


Fig. 23.14.
Dry granulation by briquetting

23.3.1.2 Dry granulation by compactor

Granulation is started with previously compaction of material. Solid bridges adhering granules are formed due to mechanical adhesion and compaction, compression, when compression forces act. Total operation including performance of sub-operations in several apparatuses or several units of a special apparatus can be performed sequentially.

Sub-operations of dry granulation:

1) compaction,
2) chopping,
3) sieving.

Powder materials are compressed by compactor cylinders. Binding forces are adjusted by appied compressing force (distance between cylinders). Chopping unit grinds the compressed material. Appropriate granule size can be set with distance between threads on sieve.

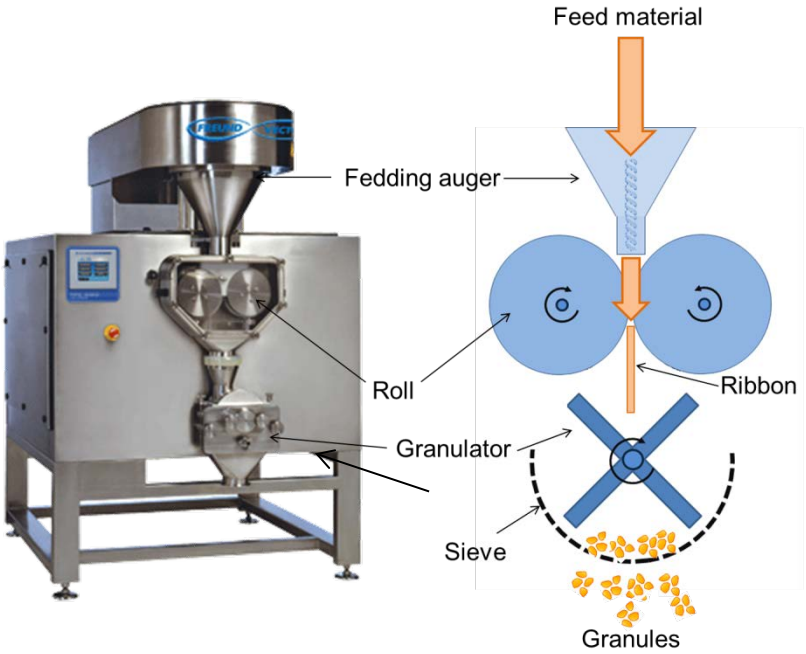


Fig. 23.15.
Compactor type dry granulator

These apparatuses can operate continuously or discontinuously.

After compounding, preparatory operations of dry granulation are the followings: chopping, sieving, compounding. Actual granulation are composed of the operations of stirring, briquetting, and chopping. As finalizing operation, separation of particles according to their particle size is carried out.

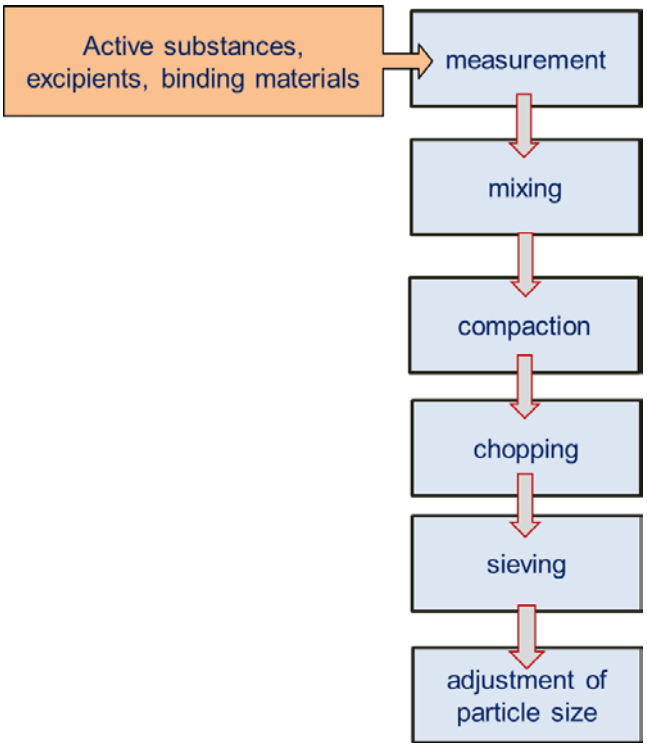


Fig. 23.16.
Dry granulation

23.3.2 Melting granulation (preparation of sinter granules)

In order to produce sinter granules, excipients having low melting point (e.g. macrogols) are used and with applied heating molten brides are formed, from which solid binding bridges are created after cooling.

In the case of heat sensitive materials, this method should be avoided. Storage temperature of granules or spansules which is made of this granule cannot overrun the melting point of sinter bridges.

Table 23-I.
Binding materials appropriate for sinter granulation

	Binding materials		Melting point (°C)
Melting hydrophilic binding materials	Gelucire50/13		44 – 50
	Poloxamer 188		50,9
	polyethylene glycols	PEG 2000	42 – 53
		PEG 3000	48 – 63
		PEG 6000	49 – 63
		PEG 8000	54 – 63
Melting hydrophobic binding materials	beeswax		56 – 60
	carnauba wax		75 – 83
	cetyl palmitate		47 – 50
	glycerol monostearate		54 – 63
	hydrogenated castor oil		62 – 86
	microcrystalline wax		58 – 72
	paraffin		47 – 65
	stearic acid		46 – 69
	stearyl alcohol		56 – 60

23.3.3 Wet granulation

Wet granulation similarly to dry granulation starts also with preparatory operation of active substances and excipients (compounding, chopping, sieving).

Firstly properties of active substance (e.g. dose, solubility, incompatibility, volume mass) should be considered at choosing granulation excipients.

Most frequently applied diluents during granulation:

- lactose (lactose content must be signed on box of tablets, in favor of patient having lactose intolerance)
- starch,
- cellulose,
- sucrose,
- glucose,
- mannitol,
- sorbitol
- urea,
- xylitol,

- maltitol,
- lactitol,
- dicalcium phosphate,
- tricalcium phosphate
- cyclodextrins.

Most commonly used binding materials, which create binding force between particles are the followings:

1) sugars
   - sucrose,
   - glucose,

2) polymers
   2.1) natural polymers
      - gelatin,
      - acacia,
      - tragacanth,
      - starch.

   2.2) Synthetic polymers
      2.2.1.) Cellulose derivatives

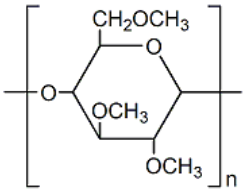


Fig. 23.17.
Methylcellulose

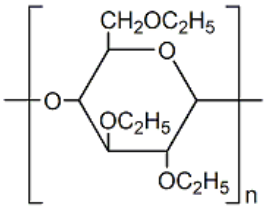


Fig. 23.18.
Ethylcellulose

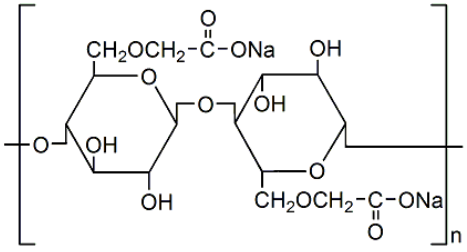


Fig. 23.19.
Sodium carboxymethylcellulose

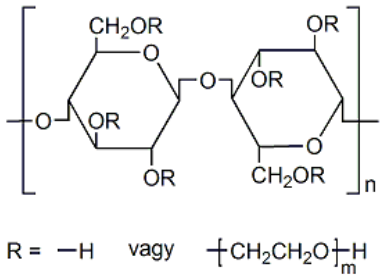


Fig. 23.20.
Hydroxyethyl cellulose

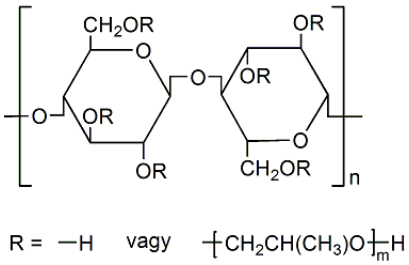


Fig. 23.21.
Hydroxypropyl cellulose

2.2.2.) Polividone derivatives

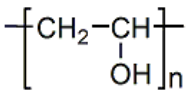


Fig. 23.22.
Polividone

2.2.3.) Polyoxyethene derivatives

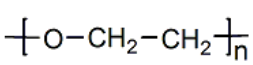


Fig. 23.23.
Polyoxyethylene

Further excipient which are necessary for preparation of solid dosage forms are summarized in *Tableting* chapter.

Several alternations of wet granulation are applied in pharmaceutical industry including kneading, high-shear granulation and fluidization procedures.

23.3.3.1 Kneading granulation

Actual granulation starts with homogenization of accurately measured dry powder mixture, which is followed by moistening and kneading with granulating fluid. Furthermore granulation (producing particles) of moistened mass which is done with breaking through a sieve, is carried out, and created granules are dried. At the end of

process, granules are broken through a sieve again to achieve the appropriate interval of granule size in order to reduce the size of granules adhered to each other.

The homogenization of powders may be performed in special barrel mixer (see chapter "*Mixing"*). Z-arm and high-shear mixers can express high force, which are able to do the operation of moistening and kneading too.

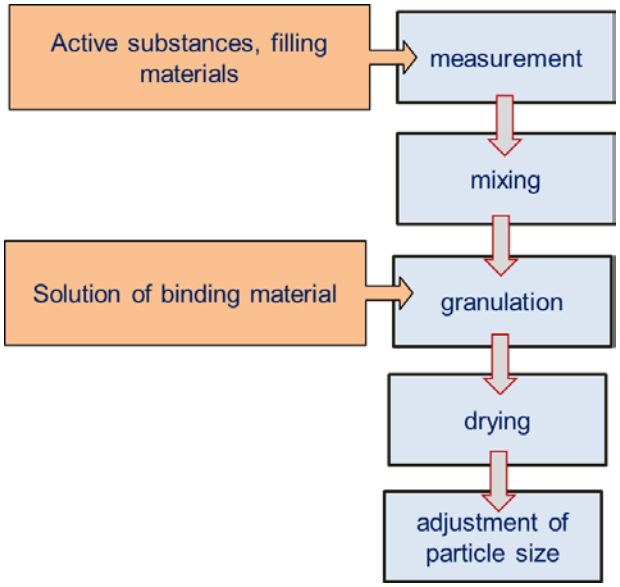


Fig. 23.24.
Flow chart of wet granulation

Undoubted advantage of wet granulation is the fact that hardness of granules is also high due to stronger binding material bridges,.

Disadvantage of application of this method is the high cost of investigation and operation, furthermore in the case of heat or moisture sensitive, unstable materials can not or can limitedly applied.

23.3.3.2 Manual granulation

At granulation performed in pharmacy or laboratory conditions, sieved, measured and homogenized powder mixture is moistened with granulating liquid and then broken through a sieve with expressing even pressure. Moistened granules can be dried in room temperature or in drying box. Then granules are broke through a sieve again to achieve the desired particle size.

Fig. 23.25.
Manual granulation, breaking through a sieve

23.3.3.3 Oscillating granulation

Oscillating granulation can be applied at wet or dry granulation. It name is arisen from four granulating rods placed horizontally and fitted to disks at their end, which mix the material circularly with back and forth movements and press the material through the sieve. The rods express consistent force, which result in homodisperse particle size dispersion.

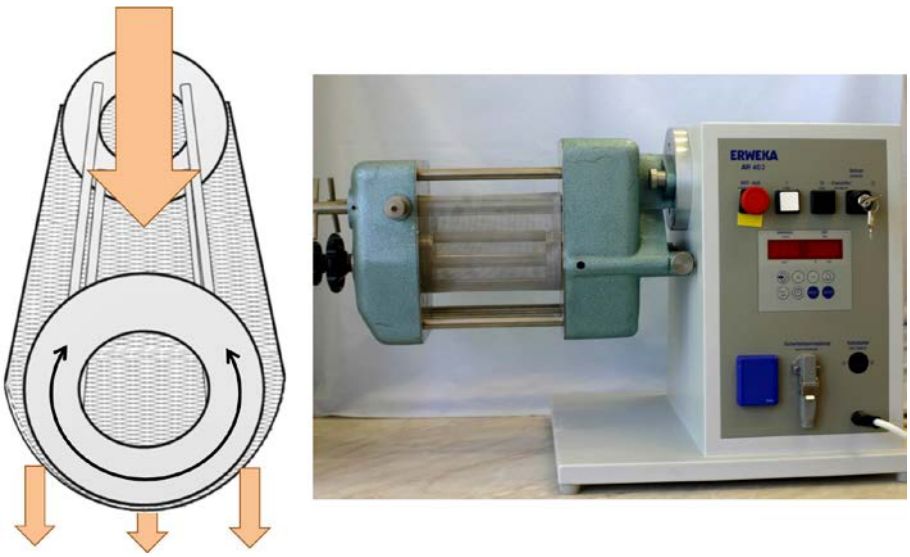
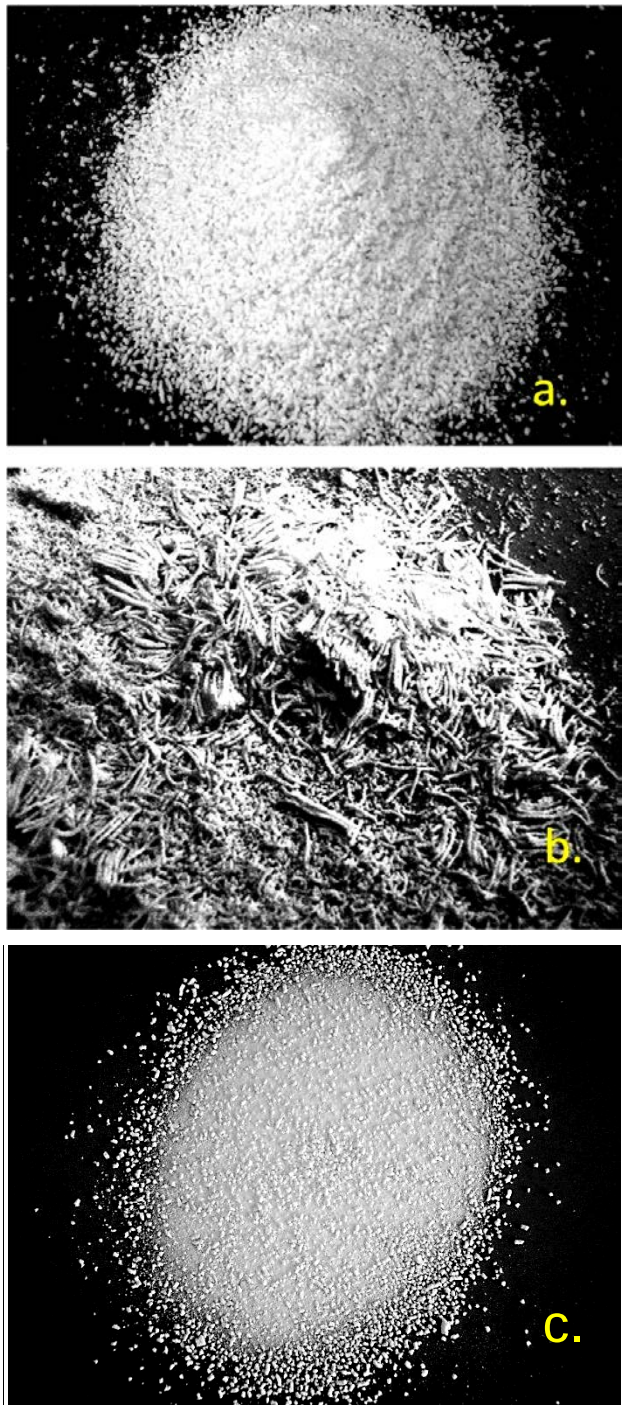


Fig. 23.26.
Erweka-type laboratory oscillating granulator

Shape, flowability, hardness and particle size dispersion are significantly influenced by moisture and binding material content of mass. If granulating fluid quantity, thus binding material quantity is low, and then particles will have heterodisperse dispersion due to weak binding forces and high powder content. Hence granules will have inappropriate flowability caused by large surface and low hardness.

If granulating fluid is present in high amount, then granules will have oblong shape therefore flowability will be inadequate.

In the case of appropriate operation parameters with optimal moisture and binding material, granules can be achieved with almost homodisperse particle size dispersion, having spherical shape, appropriate flowability and hardness.



a. with optimal amount of granulating fluid;
b. with exaggerated amount of granulation fluid;
c. with low or not appropriate amount of granulating fluid

Fig. 23.27.
Granules produced by oscillating granulator

23.3.3.4 High-shear granulator

One of the advantages of high-shear granulation is the fact that some steps of wet granulation such as homogenization, moistening, kneading and dispersing can be carried out in one apparatus, therefore operation time is less. Relatively strong binding

forces may be developed inside granules. In the case of high amount of active substance(s) or adhesive material, this method can also be applied. Beyond appropriate operation parameters (speed of stirrer, moisture content of material), spheronization occurs which result in pellets.

At stirring in high-shear granulator, high shear forces occur due to impeller and chopper, which play a significant role in building-up granules. Adding of granulating fluid can be done with pouring or spraying.

Froude number expresses the compaction due to centrifugal and centripetal force developing between wall of stirrer and particles of mass, acting on wet mass:

$$Fr = \frac{v^2 r}{G} \tag{1.}$$

Fr Froude number
v speed of homogenization stirrer
r radius of circle passed by prick of homogenization stirrer
G acceleration of gravity

In the case of high number of Fr value, developing granules or pellets will be denser.

Obviously high-shear granulation needs a further operation step, namely drying. Drying can be performed in combined kneading-drying apparatuses (so called processors), or in two separate apparatus, namely in high-shear kneading machine and in a drying apparatus such as in tray or fluidization dryer.

Disadvantage of high-shear granulator is that amount of granulating liquid can only be varied in narrow interval; thereby the mass can be easily over-moistened. Due to intensive mixing expressed by stirrer, temperature rises; solvent evaporates and mass becomes more dense.

Correlation of parameters related to high shear granulation can be well studied in laboratory apparatus.

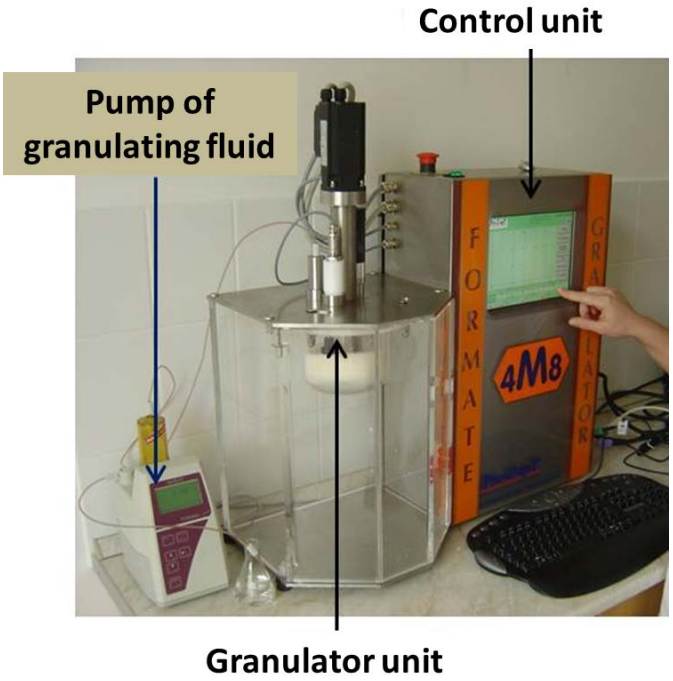


Fig. 23.28.
Procept-type laboratory high-shear granulator apparatus

Movie 10. High shear granulation

Technologies developed in laboratory scale can only be used in industry with some modification, with scale-up. Less modifications have to be done during scaling-up, better is the model determined experimentally.

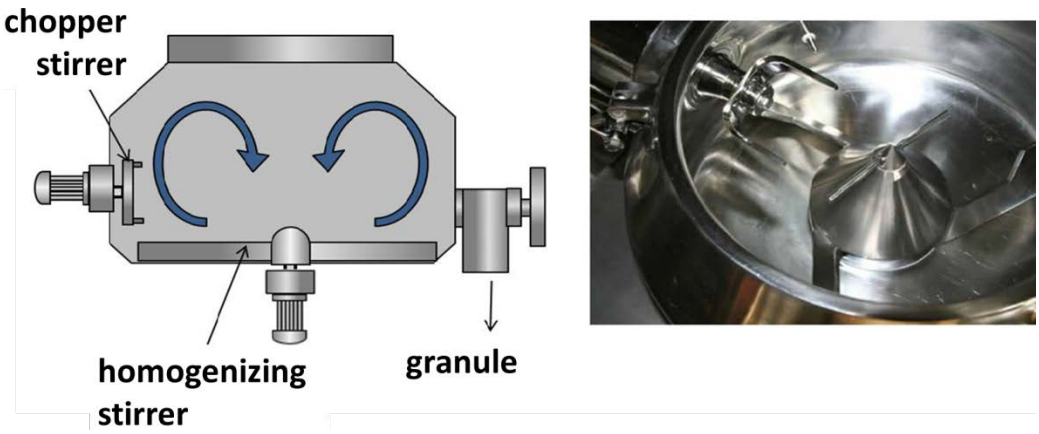


Fig. 23.29.
Diosna-type high-shear granulator

Fig. 23.30.
Industrial Diosna-type high-shear granulator with control unit

Parameters of *drying* during manufacture or at the end influences significantly the internal structure, hardness and dust content of particles. Mode of drying also affects quality parameters of particles. During the commonly applied fluidization drying, moistened particles are dried gradually from their surface to inside, their structure are porous therefore are compressed easily.

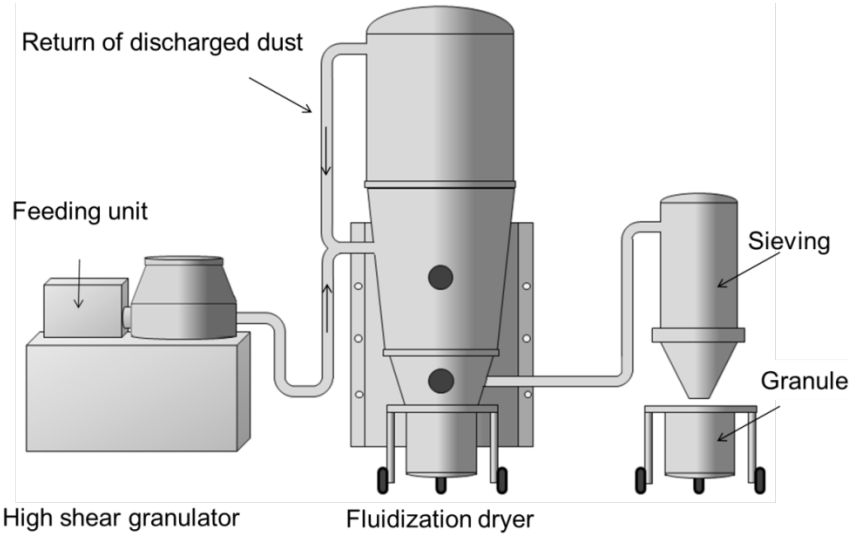


Fig. 23.31.
Industrial high-shear granulator with fluidization drier

As a result of new development, microwave and /or vacuum can be applied to dry wet granules. Drying of granules takes place from the inside of granules, which has to be considered. The result is denser, less porous, fragile granules, which can impair the compressibility of particles.

In high-shear granulator, there is a possibility for sintering by heating and cooling of the material. This needs a special double-walled (mantle) workspace, where heating or cooling medium can be flown with controlled temperature in mantle.

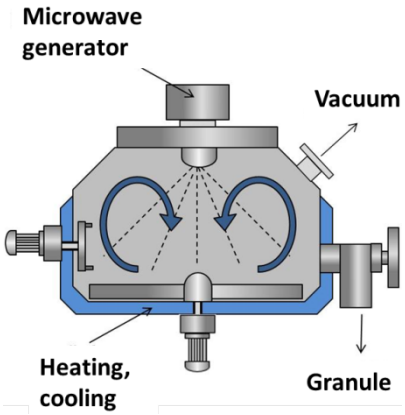


Fig. 23.32.
High-shear granulator with microwave and vacuum drying facility

Most important operation parameters of high-shear granulation:

1) mass of filling,
2) time of homogenization,
3) heating temperature (in the case of melting granulation),
4) speed of stirrers during homogenization,
5) granulation time,
6) speed of stirrers during granulation,
7) concentration of granulating solution,

8) composition of granulating solution,
9) amount of granulating solution,
10) viscosity of granulating solution,
11) temperature of granulating solution,
12) way of addition of granulating solution (melting or spraying),
13) speed of addition of granulating solution,
14) spray parameters in the case of spraying,
15) heating temperature during drying,
16) drying energy,
17) time of drying.

The most important process control and end-point parameters of high-shear granulation:

1) Observation of *energy consumption (power consumption)* of the apparatus is widely applied method to determine and scale-up wet granulation, while it is cost-effective and does not require special transformation and correlates appropriately with production of granules. Change in internal porosity has also a good correlation with power consumption.

2) In order to measure *torque of homogenization stirrer*, resistance-expansion measuring device is equipped between engine and the axis. While the axis rotates, so called parrel transports the signal to stationary detector.

3) Online measurement of torque required for rotation of stirrer is possible with *torque rheometer method*, with which developing rheological change can also be observed during granulation. Consistence of wet mass can also be concluded from measured data. This method is a widely used end-point determination as well.

4) Occurring sounds is examined by *acoustic methods* during manufacture. Application of piezoelectric acoustic emission sensors is started to spread in the beginning of 20^{th} century. This technique is very promising, non-invasive and cheap. Size, compaction and flowing properties of granules can be concluded from detected sounds by acoustic transducer.

5) *Near Infrared spectroscopy (NIR)* concludes for operation parameters of granulation with application of sensor determining moisture. Advantage of method is the fact that it provides data about chemical and physical properties of the sample. Change of homogeneity, particle size, as well as free and bound moisture content can also be observed. Disadvantage of the method is possibility to measure only a small amount of surficial sample.

6) With *focused ray reflectance measurement*, particle size can be determined. Ray moves circularly with particular speed, when meets a particle, then signal based on reflectance is detected. This variable is suitable for dynamic monitoring of the process in work space, which is in correlation with the shape, size and rheological properties of granules.

Measurement of torque and power consumption is usually thought to be correlated to each other during granulation in high-shear granulator, because they definitely is in proportion with each other. Both methods is applied in *Process Analytical Technology (PAT)*, which aims at understanding of manufacture and influencing of observed, measured data and online qualifying. Based on both methods, five phases of high-shear granulation/ pelletization is distinguished:

Phase I.: After starting of addition of granulating liquid, torque is not differed significantly from the value detected during stirring of dry material. In this phase, powder mixture moistens only slightly, does not really affect the observed parameters.

Phase II.: Torque graph shows steep rise. This phase is the sub-process of granule formation during which formation of core takes place.

Phase III.: Increase of torque curve stops and further significant rise is not shown, contrary to gradual addition of liquid. In this phase, formed cores adhere to each other and become more compact; however irregular cores and core fragments as well as heterogeneous particle system are formed.

Phase IV.: Steep increase in torque curve can be observed during this phase, which reach its maximum. This is the growth of particles (phase of sphere forming), where granules achieve their final size. This is regarded as the end-point of manufacture.

Phase V.: After reaching maximum of the curve, further addition of granulating liquid result in over-moistened mass and steep drop can be seen on graph, which indicates the conversion of system to suspension form.

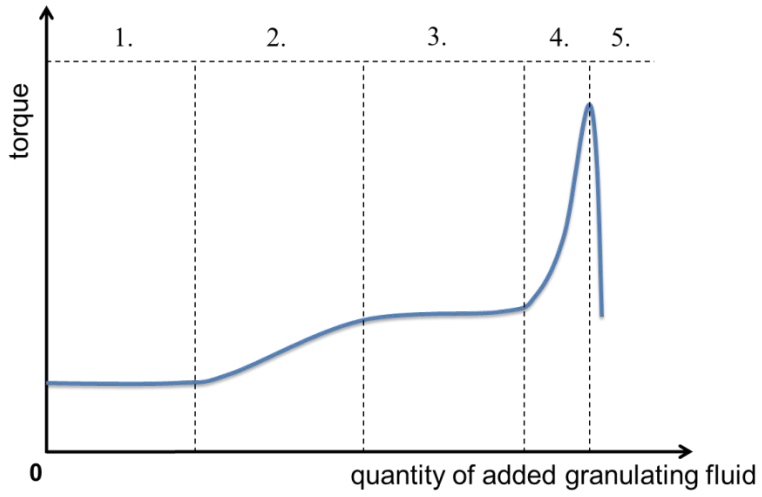


Fig. 23.33.
Process tracking and signaling end point in the case of high-shear granulation

23.3.3.5 Fluidization granulation

Several technological processes can be performed by fluidization method:

1) mixing,
2) granulation,
3) drying,
4) coating,
5) melting and freezing granulation.

The point of fluidization granulation is the fact that binding material is delivered into fluidized layer of solid material, which causes moistening, agglomeration and drying of particles, which are in gradual motion. At granulation, during moistening and drying, fine material and heat transfer are beneficial.

After homogenization of powder mixture performed by fluidization air, and reaching the required temperature, granulation fluid is sprayed on to powder.

Granulating fluid surrounds and coats the soaring solid particles, when getting contact with each other. If moistened particle interacts with another particle on fluidized bed, then liquid subsequently after drying solid binding bridges are created. This agglomeration steps repeat with statistical probability in several times and increase of granules is compensated by abrasion of particles due to collision. This balance can be controlled by quantity and concentration of granulating liquid.

Obvious advantage of fluidization granulation is that sub-processes of granulation can be carried out in one apparatus: homogenization, moistening, forming granules and drying. High active substance content and appropriate binding forces can be created.

Granules produced by fluidization method have generally appropriate flowability, hardness with relatively low powder content and with reproducible particle size dispersion.

High energy need can be considered as a disadvantage of this method.

An important, central part of fluidization granulator is the spraying unit. Among spraying parameters, *position of sprayer, distance, diameter of nozzle and spraying pressure* have to be highlighted.

At constant speed dosage, radius of spray circle increases by the increase of spraying distance (*h1*→ *h2*) and moistened area rises quadratically (r2π), however the same amount is distributed in larger conical volume and surface.

At increase of spray degree (α) in the case of same distance, the condition is the same. At downside spraying, position of sprayer (distance from fluidizing bed) and influence of conical degree are complementary to each other. Spraying conical degree has to be adjusted in the direction of fluidizator to be covered the two third of fluidizing layer by sprayed drops. In the case of too large angle, plenty of fluid is delivered onto fluidizator wall, but in the case of too small angle, dispersion of moisture is heterogeneous.

In the case of short distance, high amount of granulating fluid gets onto small surface within certain time unit, which causes local over-moistening/ inhomogeneous moistening. However in the case of long distance, sprayed particles can become dense due to evaporation, can increase in viscosity and their moistening ability can be changed.

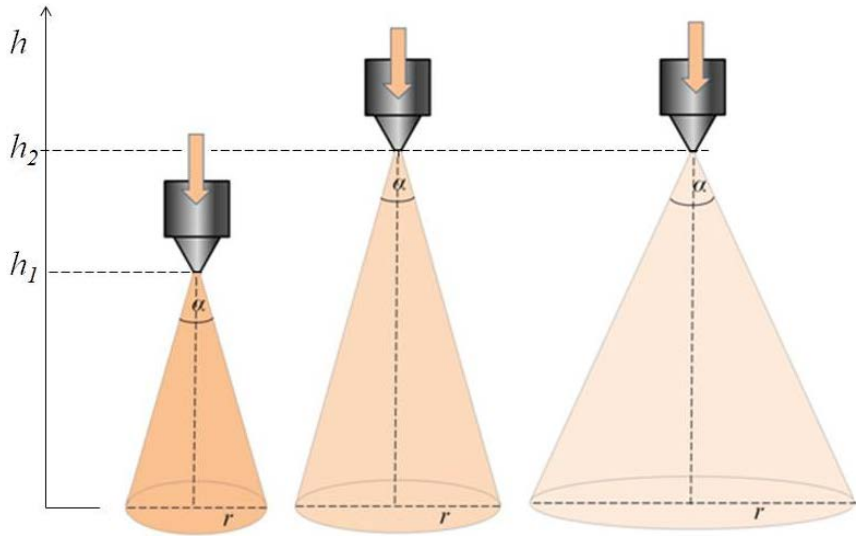


Fig. 23.34.
Effect of change of spraying distance and conical degree in spraying surface

By the control of addition speed of granulating solution, even moistening of particles and the time between two moistening phase for specific drying of particles two can be achieved. In the case of substantially different dosing speed, heterogeneous particle system is produced. When dosing speed is too fast, the material bed becomes over-moisture, particles adhere to each other, particle size increases, but at slow dosing speed, drying process dominates, which result in creation of powder and abrasion.

At downside spraying, that spraying pressure has to be chosen, which allows spray drops of granulating liquid to get to appropriate depth of fluidizing bed against the fluidization air flow and to moisten floating particles sufficiently.

In the case of *upside spraying*, direction of fluidization air flow and spraying is the same, furthermore spraying takes place in fluidizing bed, therefore lower pressure is also sufficient for appropriate moistening.

More recently, *lateral (tangential) spraying* is applied separately or combined with former ones in order to moisten particles more even.

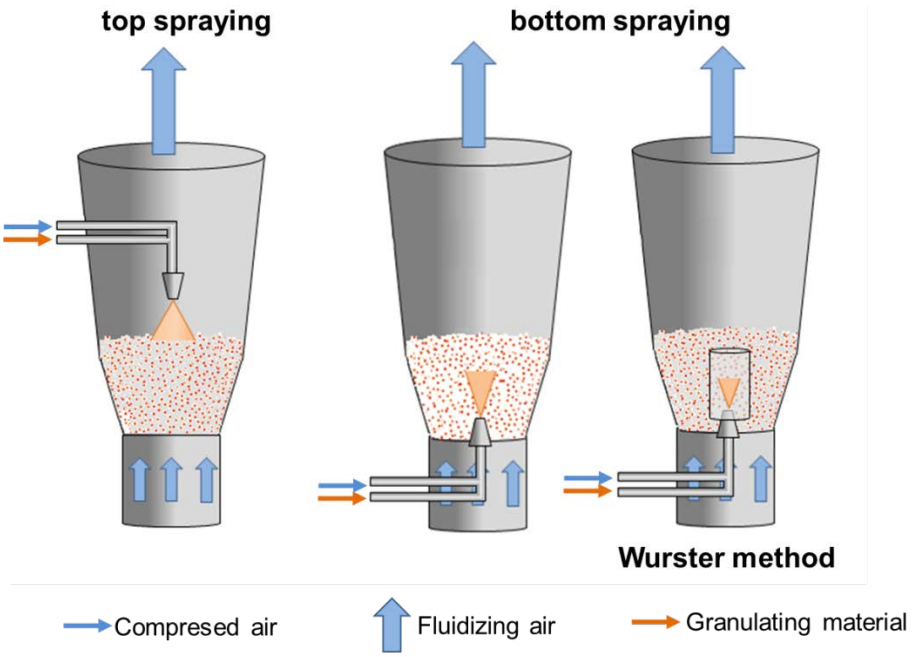


Fig. 23.35.
Spraying of granulating solution onto fluidizing bed

In fluidization apparatus, powder/dust delivered by fluidization is shaken off cyclically by operated dustbag or automated filter cartridges separates the dust.

At design of fluidization granulation techniques, scale-up and optimization of laboratory method parameters are generally indispensable in pilot and industrial level.

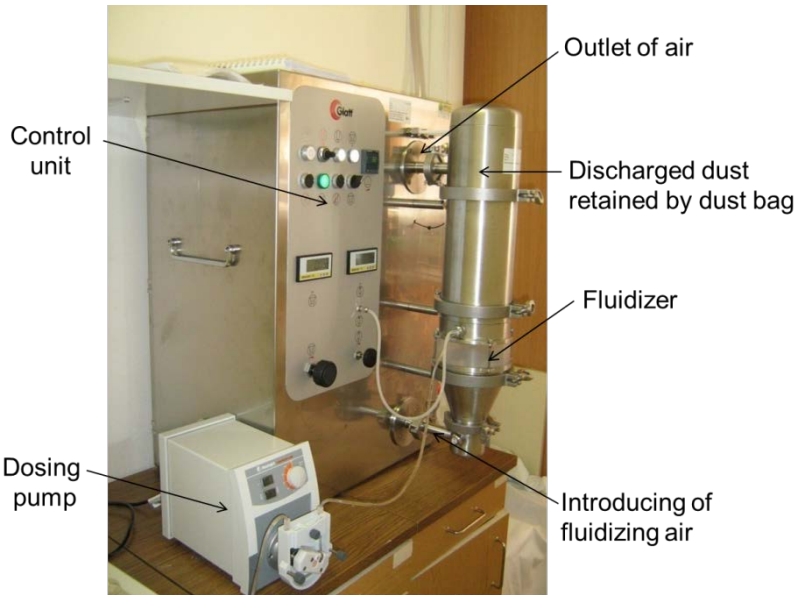


Fig. 23.36.
MiniGlatt-type laboratory fluidization granulator

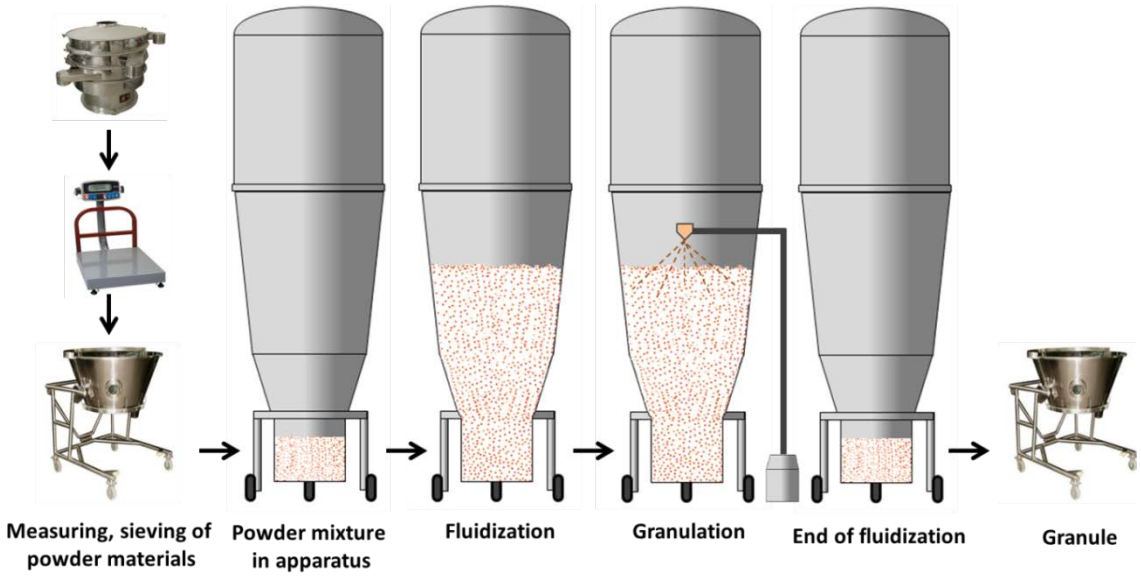


Fig. 23.37.
Industrial fluidization granulator

Several parameters influence the quality parameters of produced granules by fluidization method:

1) filler quantity,
2) homogenization time,
3) flow rate of fluidizing air,
4) temperature of fluidization air,
5) granulation time,
6) concentration of granulating solution,
7) its composition,
8) quantity,
9) viscosity,

10) temperature,
11) dosing speed,
12) spraying type,
13) spraying pressure,
14) spraying temperature,
15) speed of spraying air,
16) drying time,
17) temperature of drying.

Most important process control and en-point parameters of fluidization method:

1) output temperature of fluidization air,
2) input temperature of fluidization air,
3) moisture content of output fluidization air,
4) difference of moisture content of input and output fluidization air
5) pressure drop of fluidization air,
6) moisture content of fluidized material (PAT, on-line measurement with NIR)

In the beginning and end of granulation operation, *sieving* has an important function.

In the *beginning of granulation*, before measurement, average particle size of starting material, namely powder particles plays role in particle size of end-product, and particle size dispersion is important in internal structure and surficial evenness of end-product.

In the *end of granulation operation*, particle size and particle size dispersion of dried granules has to be adjusted based on technological needs of further operations (wrapping, encapsulation, tableting), which is determining in the view of filling volume and flowability. During drying process, average particle size can increase by adhesion of granule particles. By performance of „*regranulation*", particle size can be adjusted.

In practice, not exactly the same size, perfectly spherical, smooth particle system is expected, because it is not justified neither economically nor technologically. In technological documents, such particle size limits or acceptable size dispersion is given, which are able to meet with quality requirements of granules. At further processing, certain heterodispersity is needed and important in the view of more even space filling, and evenness of dosage (e.g. filling into capsules, mass of tablets).

Lower d_1 and upper d_2 particle size limits of granules are determined experimentally. Separation of granule set according to their size is carried out to three particle fractions (F_1, F_2, F_3):

- F_1 fraction ($d_{F1} > d_1$),
- F_2 fraction ($d_1 > d_{F2} > d_2$),
- F_3 fraction ($d_{F3} < d_2$).

Fraction F_1 contains larger granules than allowable one, fraction F_3 contains smaller particles. Particles size and size dispersion of fraction F_2 is suitable for further operations.

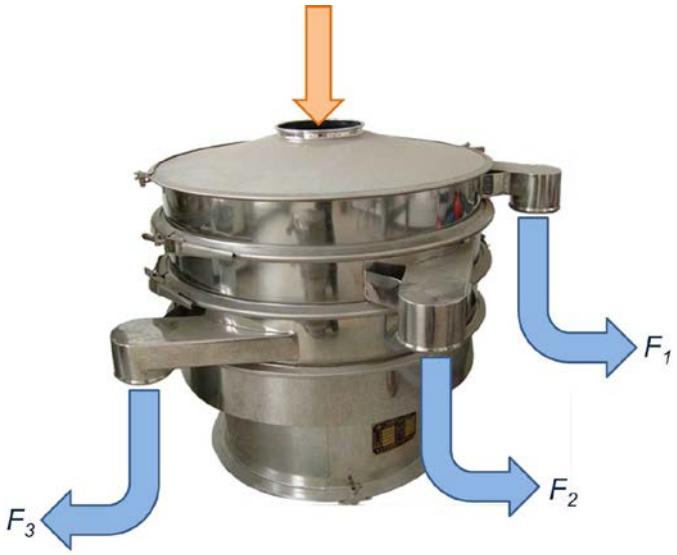


Fig. 23.38.
Continuously operating vibrating sieve for classification of granules according to their particle size

Physical-chemical properties of *active substances and excipients* influence process of creation of cores and particle increase, therefore determine quality parameters of end-product.

Most important properties of basic materials which affect the quality of end-product:

1) average particle size,
2) particle size,
3) contact angle,
4) shape of particles,
5) morphology of their surface,
6) solubility and dissolution speed,
7) crystallographic properties (polymorphism, hydrates).

In the case of low content of active ingredient (e.g. few milligrams), inert filling material (e.g. lactose, saccharose, starch, mannitol, glucose) is applied for easier handling, and dosing. Granulates may contain approved coloring agents, or flavoring ones as well.

Granulating liquid having appropriate moistening ability has to be chosen for particular composition, which as an internal matrix ensures evenness of granule increase by homogeneous dispersion of granulating agent. Too concentrated granulating liquid or having high viscosity results in inhomogeneous dispersion. Dispersion of granulating fluid affects hardness and particle-size dispersion of granules.

At addition of granulating fluid, properties of basic material may also be changed (e.g. solvation of crystal form, crystalline state), which affects biopharmacy parameters (e.g. solubility, dissolution speed) as well.

Such an example, glycine has α, β and γ crystalline modifications. α is metastable, and γ is the most stable form. At wet granulation, stable crystalline form of glycine transforms into α metastable form with polymorph transformation.

Theophylline has a maleficent solubility in water (8 mg/ml on 25C°). At its granulation, stable anhydrate form transforms into hydrate form, which may change back to anhydrate form. Dissolution speed from produced granules or compressed tablet may change, while metastable form dissolves faster, than the stable crystalline form. This phenomenon can be explained with the fact that metastable anhydrate form of theophylline transforms rapidly into monohydrate form.

Smaller are the particles of basic material, more binding excipient is needed to achieve appropriate granule size.

Hardness of granules can be increased by rising of binding force and quantity of binding excipients.

Nowadays, due to environmental reasons, primarily aqueous granulating agent is used. In the case of water sensitive namely hydrolytically instable materials, dry granulation is applied. If wet granulation and usage of organic solvents is still needed, then solvent decontaimation of output air has to be counted with.

Table 23-II.

Aspects of choice of granulating agent

Properties of granulating fluid	Advantage
granulating material dissolves quickly	dissolution time (preparation) is short
solubility of granulating material is fine	can be applied in a wide range of concentrations
solution has low viscosity	easy management of granulating fluid during pumping and spraying
high effectiveness of binding	good binding force can be achieved with relatively small amount of granulating agent

Operation of granulation is applied in the case of the following dosage forms:

1) medicated granules (simple granules, fast-dissolving granules, effervescent granules, granules for suspension)
2) coated granules,
3) spansules,
4) tablets,
5) coated tablets, dragees.

Questions

1) What does operation of granulation mean?
2) What is the aim of application of granulation technology?
3) Which are the primary binding mechanisms?
4) According to which mechanism is the creation of granules performed?
5) How are granules produced in dry way?
6) What are the most frequently applied filling materials during wet granulation?
7) What are the most common used binding materials in the process of wet granulation?

8) Which are the main steps of industrial wet granulation?
9) With which operation parameters can quality of granules produced by oscillation granulator be influenced?
10) With which operation parameters can quality of granules produced by high-shear granulator be influenced?
11) What are the most important process-control and endpoint possibilities of high-shear granulator?
12) With which operation parameters can be quality of granules manufactured by fluidizing granulator be influenced?
13) Which are the most important process-control and endpoint possibilities of fluidization granulator?
14) What are the main aspects of choice of granulating agent?

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24 Tabletting

Tablets are solid preparations manufactured by compression containing definite amount of active ingredient of a single or multiple dose.

Tablets belong to the most commonly used dosage forms due to their expansive use.

Progenitors of tablets, pilules, pastilles have been used through centuries in the pharmaceutical therapy. Development of the technology of pharmaceutical preparations allowed the industrial startup of these preparations by the appearence of eccentric and rotary tablet presses at the beginning of the 20th century. We can mention as an example the industrial manufacturer *Bayer's* active agent, the aspirin, which was originally introduced as powder, than after 1915 it was released as a tablet. By introducing tablets the dosing of active ingredients was much more safe, the counterfeit and the mass production decreased the price of medicines.

Application of the first tabletting machines required the use of a hammer in order to develop the compression force, but later several solutions were born to enhance the tabletting technology.

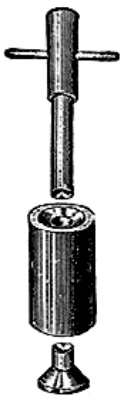


Fig. 24.1.
First hand tabletting machine for tabletting

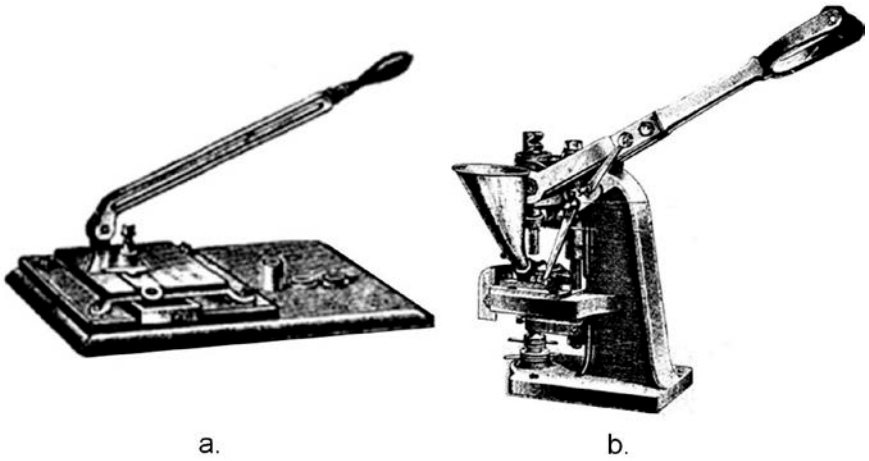
William Brockedon british pharmacist patented a manual driven machine which was able to compress medicinal preparations in 1843.

Javob Durnton developed a similar machine in 1864 and from 1869 he prepared and sold quinine tablets. During compression excipients, such as cocoa butter and mineral oil were also used to decrease the adhesion between the preparation and the wall of the die and punches.

The machine developed by *Joseph Remington* in 1875 was made especially for pharmacuetical purposes, for pharmacists to produce their own products.

Among several technological solutions the principal of the one-armed lift was also utilized which resulted more compression force by minor manual force. However first machines were unable for the mass production, because the manual filling between compression was very slow (1-5 pcs/min).

Significant progress was the invention of the feeder or feed cup, which function was synchronized with the movement of the punches. These hand-driven machines were much more reliable, they ensured uniform filling producing 10-15 tablets/min.



a. without feeder; **b.** with feeder

Fig. 24.2.
Hand-driven tabletting machine with the principal of one-armed lift

The manual drive was gradually changed to mechanical drive, thus the speed of the production could increase (40-100 pcs/min).

By the end of the 19. century the important mechanical elements, instruments and components developed which can be found in the modern tabletting machines. Compression takes place in the die by the punches. The role of the die is the reception of the substance to be compressed. The die also determines the diameter of the preparation, which is accurately regulated and can only be modified by the change of the die.

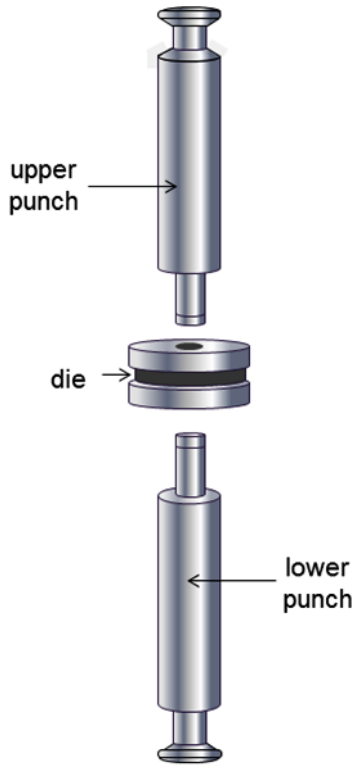


Fig. 24.3.
Tabletting tools

The size of the tablet, its geometrical property is determined by several factors, such as the dose of the API, the amount of the excipients to be used in order to carry out the compression, etc. Beyond that the biopharmaceutical viewpoints are also important. Tablets intended for oral chewing are usually flat and disk shaped. Effervescent tablets have similar shape, but their size is not terminated by anatomical factors, since before the application they are dissolved. Swallowing is eased by the proper diameter, roundness and the convexity. Higher dose is necessarily accompanied by increase in size, hence the swallowability should be ensured by oblong tablets. Excipients of implant tablets should be chosen so that after the drug release everything has to be absorbed without residuals. Tablets to be dissolved before the application and effervescent preparations should dissolve quickly and entirely. These requirements for the excipients are not necessary in case of peroral tablets, since they are eliminated from the organism.

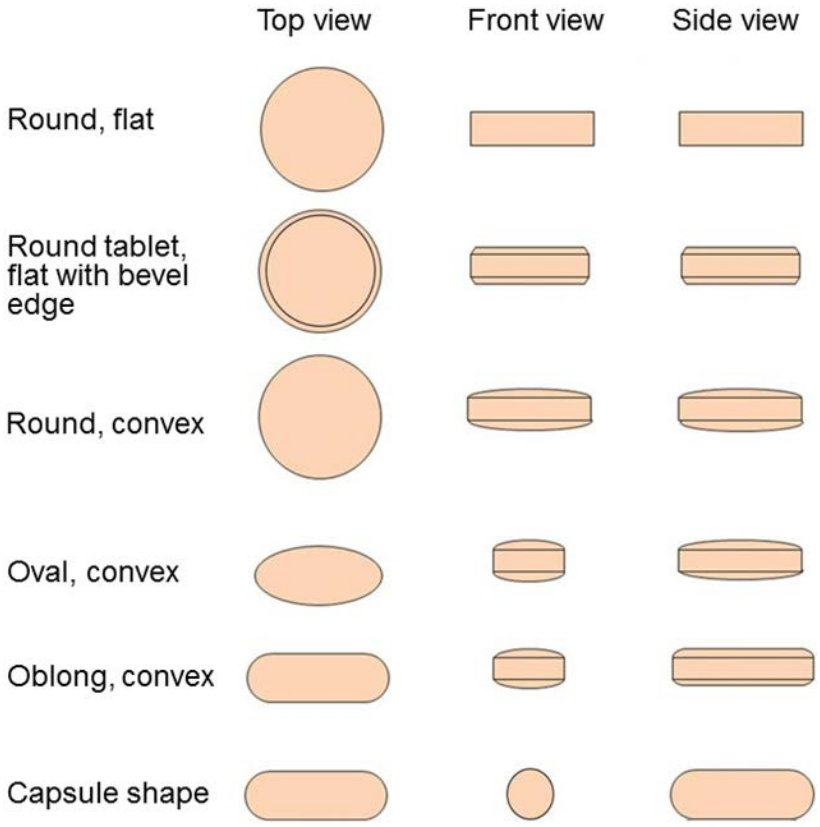


Fig. 24.4.
Shape of tablets

In case of administration of smaller amount of API in order to ease the splitting of the tablet, a bisector slot can be made. The name of the tablet, the API dose or the manufacturer's name also can be embossed on the surface of the tablet during compression.

Designing the composition of tablets biopharmaceutical viewpoints also have to be considered. Drug release has to be controlled according to the character of the API and the possibilities of the living organism regarding the biological and histological capabilities in order to reach the optimal therapeutic effect. In this case the local irritation can be avoided and the required API plasm level can be assured reaching a

systemic, local, quick, prolonged, chronotherapeutic effect, adapting the processes occuring in the human body.

Drug release from tablets can occur in several ways:

a) dissolution out of the body (dissolving, dispersible tablets) and
b) dissolution inside the body

The dissolution-type drug release can be:

1) oral (buccal, sublingual, chewable, orodispersible)
2) peroral
   2.1) normal (conventional) tablets without coating
   2.2) modified drug release tablets
      2.2.1) modified drug release in space
         a) gastric release (dissolving in gastric juice, swelling, gastroretentive, mucoadhesive)
         b) release in small intestines (dissolving, mucoadhesive)
         c) release in colon (dissolving, mucoadhesive)
      2.2.2) modified drug release in time
         a) continuous release (osmotic, retarded, accelerated, delayed)
         b) periodic release (pulsatile, chronotherapeutic)
3) locally acting in body cavities (i.e. vaginal tablets)
4) implants

Compressibility of substances is characterized by the decrease in volume under force. This character depends on the properties of substances, such as somposition, crystal form, habit, shape of particles, particle size and moisture content.

Well compressible substances have good compacting ability and they have little elasticity under compression force, since the plastic defromation results internal stress inside the tablet.

At the beginnig of the compression under the impact of little force particles can easily move, thus they adapt to the increasing pressure by the initial compactibility and better space filling, which is called together primary ordering.

Comparing to the initial (bulk) porosity and volume (V_0), the volume of the compressed substances gradually decreases: $V_o > V_1 > V_2$.

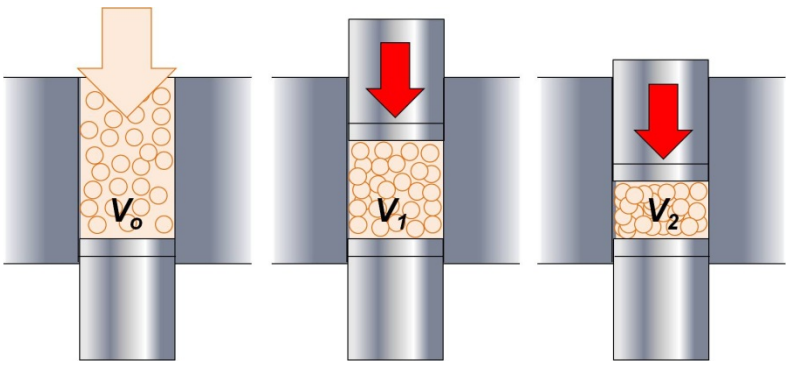


Fig. 24.5.
Change of volume of particles filled into the die during the primary ordering at the beginning of compression

During the compaction of powder particles the air between the particles and in the pores of particles squeezes and the solid particles get closer to each other, thus decreasing their moving and ordering ability. At a definite pressure, lacking the space to move, the movement of particles is impossible. After this point the particles decrease their size under further pressure.

Behaviour of majority of substances are plastic or elastic under outer force. These properties frequently occur in a mixed way and these plasto-elastic properties are reflected during compression.

In case of minor pressure the deformation can be reversible. In this case the substance restores to its original state after compression, showing elastic properties. Reaching the final threshold of deformation, particles became irreversible plastic and viscous flow of particles can be observed.

Distinction of well or poor compressible compositions during pharmaceutical technological development is based on the plastic or elastic behaviour of particles according to their material character. Ideal case is the plastic defrormation of particle compositions during compression. As plastic deformation is time-dependent process, short compression time results weak binding force. This phenomenon is critical especially in case of high-speed tabletting machines in the industry, where the dwell time of the particles during the compression is extremely short.

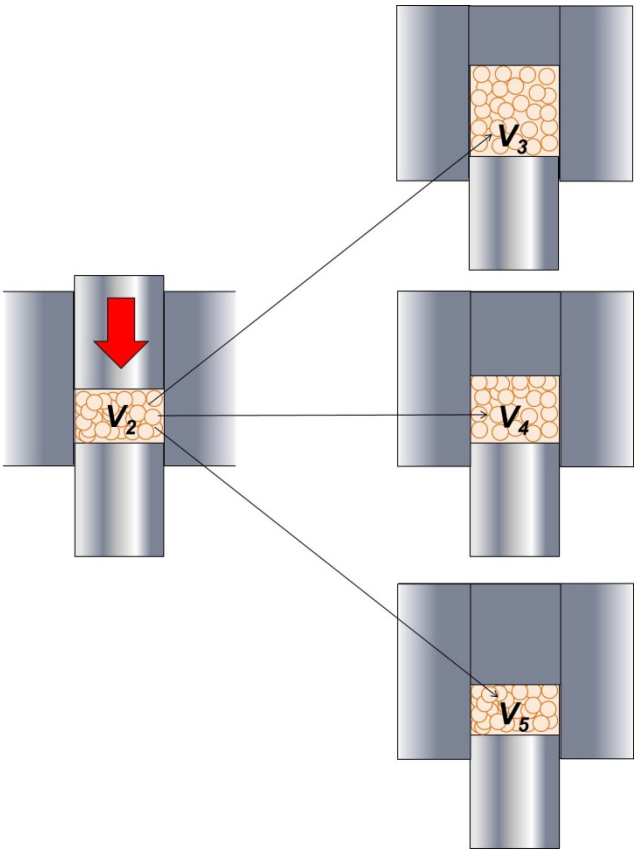


Fig. 24.6.
Change of volume of particles after termination of outer force in case of elastic (V_3), elasto-plastic (V_4) and plastic (V_5) deformation

After plastic deformation increasing the compression force, particles develop even bigger force to each other and brittle fracture occurs. In this phase, big particles break to

small particles. Grains can connect to each other due to compaction and contacting of new surfaces developed by breakage and fracture via solid bridges, mechanically and itermolecular forces.

Due to the change of particles' shape, breakage and slacking, new space filling and a secondery ordering occurs. Further fragmentation and ordering results a less porous, better space filled, compact structure, which is the tablet.

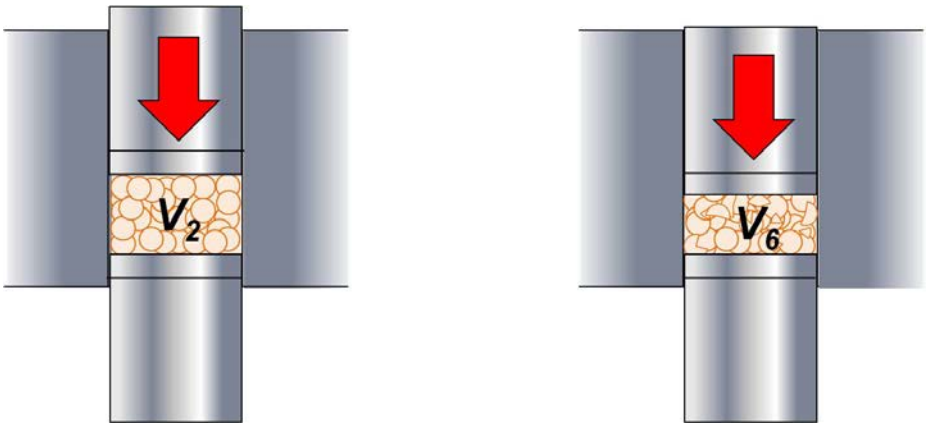


Fig. 24.7.
Formation of a tablet by fragmentation and secondery oredeing of particles under outer force

During compression of tablets, there is no need to produce perfectly coherent preparations without porosity, since disintegration of tablets and drug-release require definite inner structure and porosity.

Int he phase of decompression, after termination of force, particles or tablets can show elastic changes.

Force developed by upper punch acts across the substance mixture to be compressed, thus acting to the wall of the die and the lower punch.

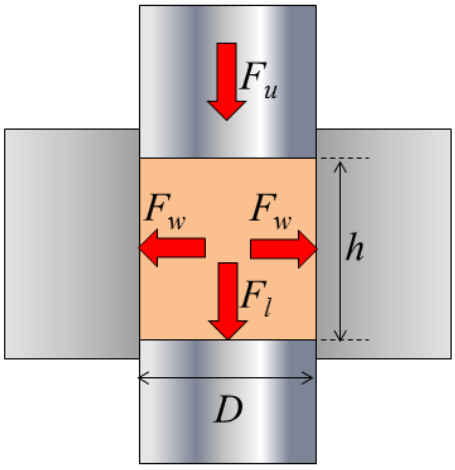


Fig. 24.8.
Effect of forces during tabletting in case of eccentric machine

Force developed by the upper punch (F_u) can be expressed:

$$F_u = F_l e^{\frac{Kh}{D}} \tag{1.}$$

F_l force acting to the lower punch,
h height of the substance mixture to be compressed,
D diameter of the die,
K abrasion constant between the particles and the wall of the die.

Compression force determines the biopharmaceutical parameters (disintegration, drug-release) excepting the porosity and the hardness.

Tabletting machines with *measuring instruments* offer the possibility of examination of compression forces, their action, compressibility of substances, detection of tabletting disorders in order to carry out different tests and optimize substance mixtures to be comressed.

Higuchi et al were the first scientists who instrumented an eccentric tabletting machine at the beginning of 1950.

Later it was possible to investigate the compression process by the instrumentation of the tabletting machine in case of rotary presses as well. A technological solution of this instrumentation is an attached strain-gauge to the pressure roll. In the production the centralized computer control of tabletting machines ensures the continuous monitoring and the termination of the tabletting process in case of disorders. This also solves the problem of filling disorders, since the force fluctuation registered on punches depends on the amount of substance filled int he die.

A portable equipment was also developed which has instrumented punches to be inserted between punches of the tabletting machines. They operate as transducers sending metering pulses to the central unit via infrared rays to be processed and evaluated by the computer.

Special appliances of compression process are the *compression simulators*. Usig these appliances the development time for optimization of a composition can be reduced. Various patameters and relationship can be investigated during the compression of the experimental composition:

1) movement of punches
2) compression force and pressure of punches
3) friction force
4) force acting on the wall of the die
5) rise of temperature of the tablet during compression
6) tablet ejection force

The control of the equipment is carried out by a computer.

Fig. 24.9.
Compression simulator for the invetigatation of tabletting process

Taking into consideration the *compression time*, which is very short t < 0.1s (in case of high performance machines it can be less, 10-50 ms), measurements require dynamic method which can be applied continouosly durig the compression process.

The easiest way to *measure the compression force* is to attach *strain-gauge* to the punch. The elastic deformation of the strain-gauge is in relationship with the induced change of resistance (*R*). This change can be monitored at equal current by measuring the change of voltage.

Since these fluctuations in voltage are very low, signals must be amplified.

Piesoelectric sensors also can be applied, in which the change of surface charge of crystals is in relationship with the compression force.

The energy of the compression is consumed by process-stages mentioned below:

1) compression of substances, forming the tablet
2) defeating the friction between the tablet and the wall of the die
3) rise in temperature of the upper punch at the end of the compression
4) ejection of the tablet from the die

The *work of compression* (W_c) can be calculated from the movement of the punch and the compression force:

$$W_c = F_u \cdot s \tag{2.}$$

F_u force,
s displacement of the punch (distance).

Difference of maximal forces (*RE*) measured on the lower ($F_{l,max}$) and the upper ($F_{u,max}$) punch:

$$RE = F_{u,max} - F_{l,max} \tag{3.}$$

In case of real particle aggregates the difference of forces can vary between 0 and 100%. In ideal case at perfectly irreversible deformity this value is 0, at substances with completely elastic behaviour this value is 100%

The *friction of ejection* can be expressed with the *lubrication coefficient* (*R*), which is the ratio of maximal force measured on the lower and the upper punch:

$$R = \frac{F_{l,max}}{F_{u,max}} \tag{4.}$$

In ideal case withoud friction, the value of *R* is 1. In real case at well-lubricated compositions its value is between 0.9-1.

By applying an instrumented tabletting machine, *the compression force-punch displacement* represents the relationship between the movement of the upper punch and its compression force. The area under the curve is the distance of movement multiplied by the force, which equals the work and energy produced by the machine.

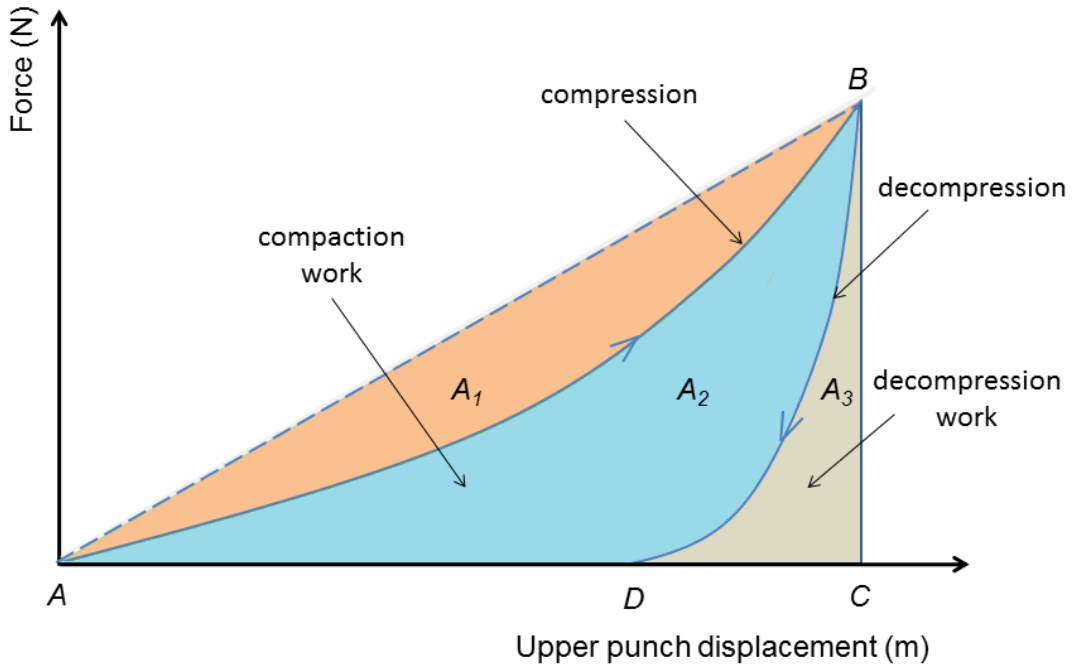


Fig. 24.10.
Compression force-displacement graph

The ideal *force-displacement* curve constitutes a triangle by connecting points *A*, *B* and *C*. Real curves differing from this ideal curve give information from the plastic and elastic properties of substances to be compressed. If the substance has no elastic properties, at the point when the upper punch reaches its lowest dead point position and it starts to move upwards, the force developed suddenly falls to zero. In case of elastic substances, the volume of the tablet slightly increases after the termination of the force, thus the force acting on the upper punch decreases only gradually.

Compression takes place along *AB* curve, which represents the *compactibility* of the particle aggregate. The smaller the A_1 area is (frictional work), the better is the compressibility.

Net compression work carried out by the upper punch takes into account the compaction at the beginning of the compression and the elastic rearrangement at the end of the process as well. The bigger the A_2 area is, the better the compressibility.

Decompression takes place along the *BD* curve, which is represented by area A_3, which is in relationship with the expansion work. Value of A_3 shows the elasticity of the substance, which predicts the layered separation of tablets after compression, the so-called layering and capping.

Apparent net compacting work (plastic deformation), which is important to defeat the friction on the wall of the die, is proportional with area A_2 (*ABD*). Gross work carried out by the upper punch is proportional with the sum of areas A_2 and A_3 (*ABC* triangle).

Tabletting process is also well described by the function representing the *compression force in function of time*. When the upper punch contacts the substance to be compressed, the force increases steeply until the maximum and falls to zero at the decompression stage. Changes of forces are also well-traceable on the lower punch and the wall of the die at the end of the cycle, during the tablet ejection.

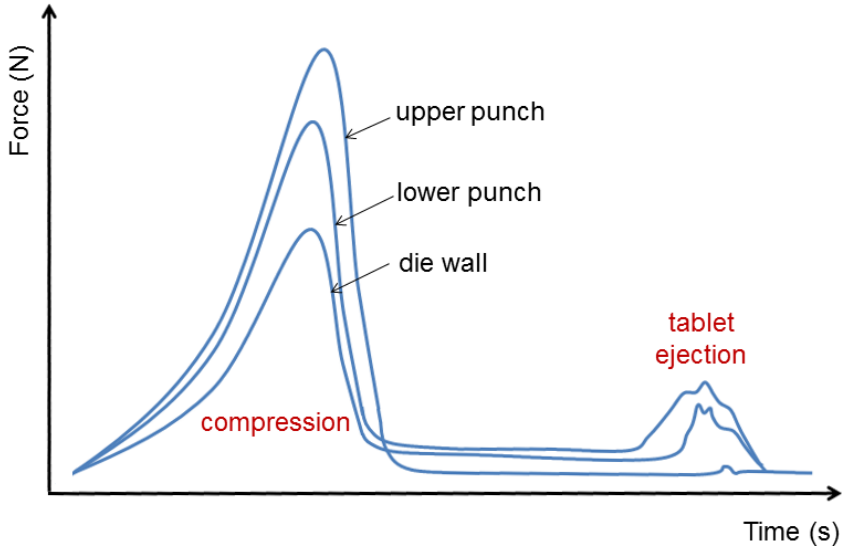


Fig. 24.11.
Change of force signals of punches and wall of the die during compression in function of time

Force-distance graphs are asymetric due to the irreversible plastic deformation of the substance to be compressed (Fig. 11. and 12.)

Relative elasticity (R_e) can be calculated by comparison of areas under the curve A_1 and A_3:

$$R_e = \left(1 - \frac{A_3}{A_1}\right)100 \qquad (5.)$$

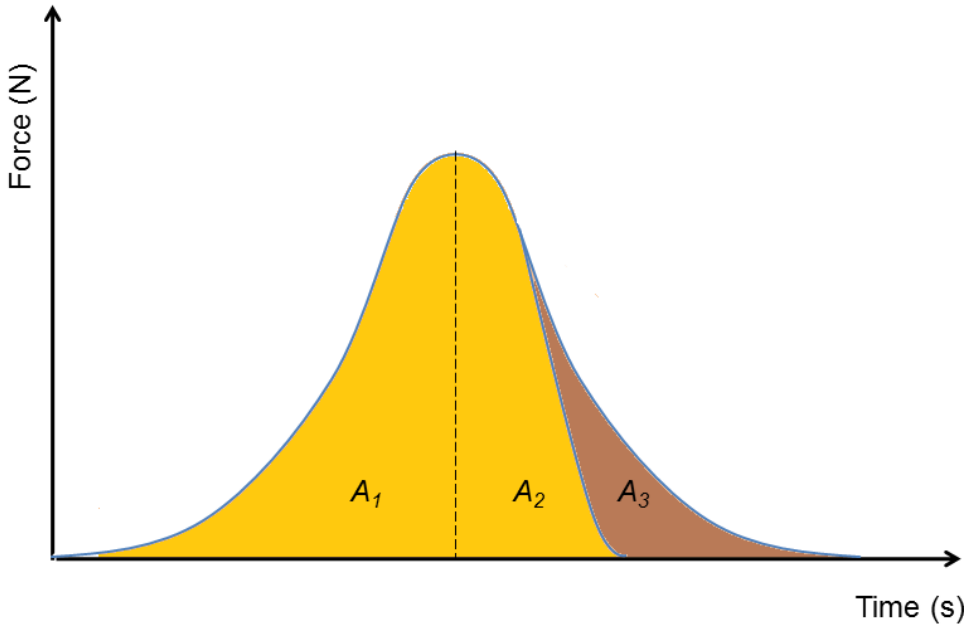


Fig. 24.12.
Graph of force-time of compression

A lot of scientists tried to describe the process of compression mathematically among which theory of *Heckel* is the most common.

Heckel stated that the change of density during the compression due to the pore-reduction follows first-order kinetics:

$$\frac{dD}{dP} = K \cdot (1 - D) \tag{6.}$$

dP change in pressure
D relative density of substances to be compressed,
K *Heckel* constant.

By logarithmisation of the equartion:

$$ln\left(\frac{1}{1-D}\right) = K \cdot P + A \tag{7.}$$

A constant (regression coefficient of the flat section according to the coordinate system of Heckel's relationship)

Since porosity is (ε):

$$\varepsilon = 1 - D \tag{8.}$$

after substitution:

$$ln\frac{1}{\varepsilon} = K \cdot P + A \tag{9.}$$

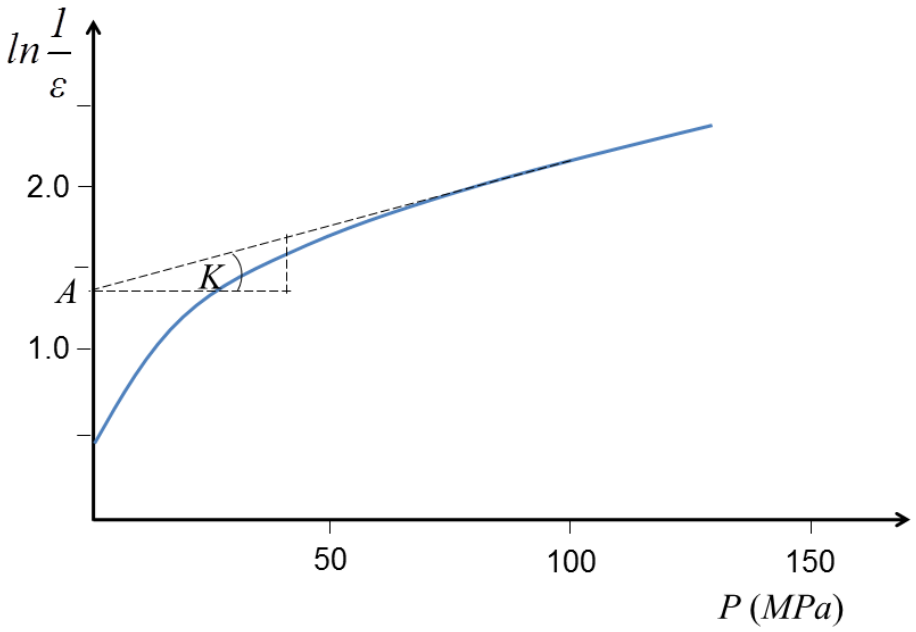


Fig. 24.13.
Pressure-porosity function with *Heckel* transformation

Slope of the line is the *Heckel constant* (*K*), which is chatacteristic for the substance to be compressed and it is inversely proportional to the minimal compression force necessery for the plastic deformation (so called yield-value of force). High values of *Heckel* constant indicate the ability of the substance for plastic deformation at low pressure. Intersection of the line represent the degree of compaction during the rearrangement of particles.

Heckel's theory was followed by further relationships, because calculated values were often independent from the measuring method and there were differences between the parameters of functions determined by exxentric and rotary presses.

Shapiro improved *Heckel's* model with an exponential part:

$$\ln \varepsilon = \ln \varepsilon_o - kP - lP^{0,5} \qquad (10.)$$

ε porosity,
ε_o initial porosity,
P pressure,
k, l constants,

Kawakita constructed the linear relationship below:

$$\frac{P}{C} = \frac{1}{ab} + \frac{P}{a} \qquad (11.)$$

The degree of decrease in volume (C):

$$C = \frac{V_o - V}{V_o} \tag{12.}$$

V_o initial volume,
V volume after compression,
P pressure,
a,b constants,

Compressibility properties and important viewpoints of examinations of tablets' parameters are following:

1) effect of substances used (e.g. crystallography parameters, mooisture content, particle size and distribution, flowability, elasto-plastic properties)
2) effect of compression force and force-distribution
3) effect of changes of substance components
4) effect of changes of conditions of compression

A paraméterek ismeretében kerülhet sor a kifejlesztendő tablettakészítmény préselési rendellenességeinek elkerülésével, az optimalizálására:

In view of parameters optimization can be carried out by avoiding tabletting disorders:

1) powder/granule composition (applied components, excipients and their ratio),
2) quality parameters (e.g. hardness and friability, disintegration time),
3) conditions of production (e.g. compression force, determining the compression time by optimizing the parameters)

Movie 11. Investigation of hardness of tablets

Movie 12. Tablet friability testing

Movie 13. Disintegration

24.1 Tablet presses

24.1.1 Eccentric tablet presses

Rotary motion can be converted to linear motion applying an eccenter. Using this theory a tabletting machine with reproducible controllable compression force was developed.

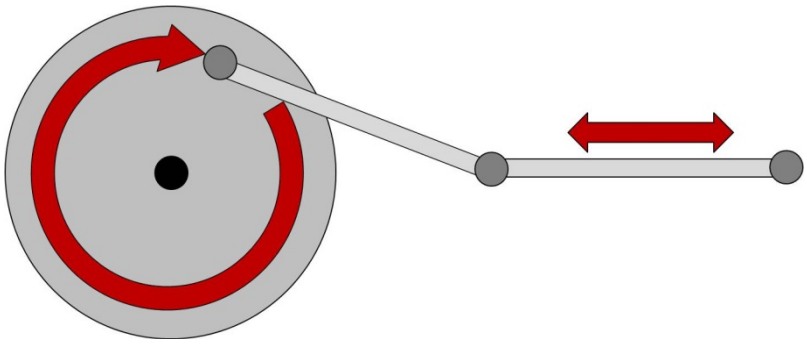


Fig. 24.14.
Principle of eccentric drive

Laboratory eccentric presses can be operated by manual or machine drive.

Fig. 24.15.
Laboratory eccentric press

During tabletting, we use proper die and punches according to the size of the tablet. Under equal circumstances of filling equal filling density can be achieved, thus the weight of the tablet can be controlled by the powder/granule's volume filled in the die. Since the inner diameter of the die is given, the volume of the chamber inside the die is determined by the filling height. This volume can be set by adjunting the *lowest dead point of the lower punch*. Movement of the feed cup helps to clear away the excess material from the surface of the die in order to assure the given weight of the tablet.

At the same time at the adjustment of the *upper dead point of the lower punch* care must be taken not to protrude above the surface of the die to avoid the collision of the punch with the feed cup at filling or tablet ejection. In practice the upper dead point of the lower punch should be a few millimeter lower than the level of the surface of the die.

Compression force is developed by the upper punch, the lower punch is only a counter-tool on case of eccentric machines. The extent of compression force can be set by the *lower dead point of the upper punch*, which is the immersion depth of the upper punch inside the hole of the die. When adjusting, weak force should always be applied

first to avoid damages of the machine. It is highly recommended to drive the machine manually very carefully at the first tablets and check the hardness of tablets after compression.

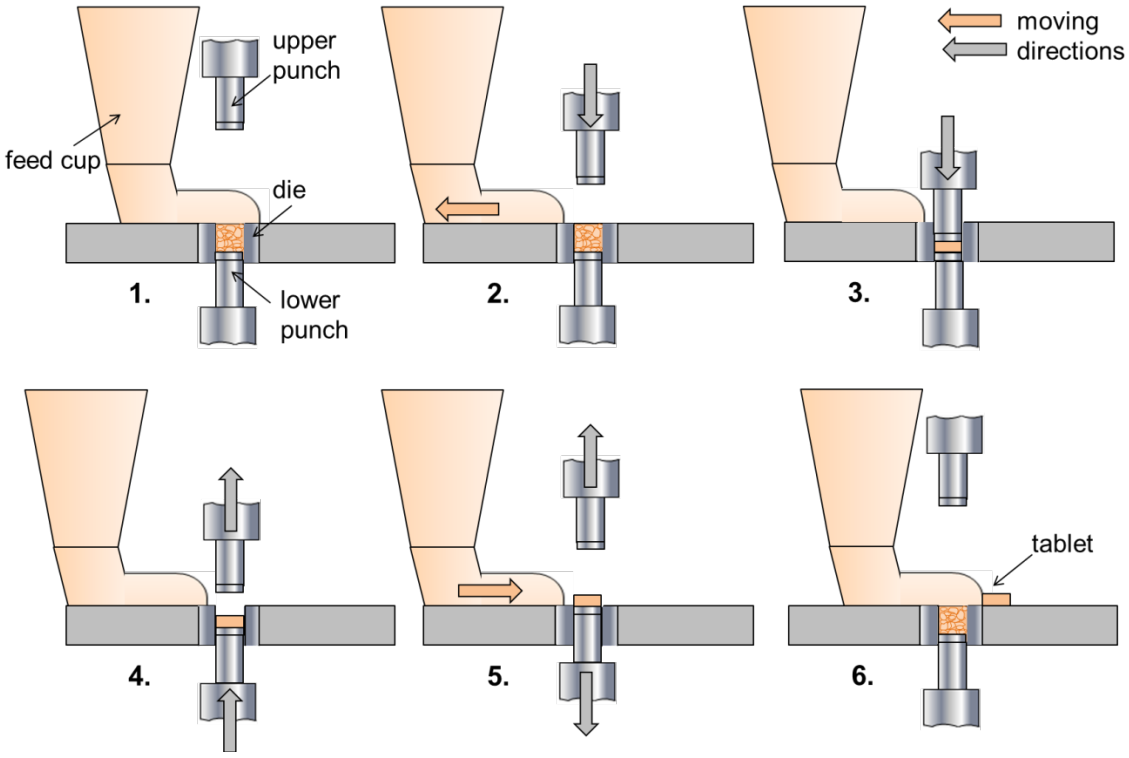


Fig. 24.16.
Operation cycle of eccentric tablet presses representing the direction of movement of the tools

Operation of eccentric tablet presses contain the steps below:

1) the feed cup fills the die,
2) in order to fill the same volume, the feed cup removes the excess material from the surface of the die and moves away to ensure the free movement of the upper punch,
3) the upper punch compresses the particle aggregate inside the die
4) the upper punch return to its initial upper dead point position, while the lower punch ejects the tablet from the die – reaching its upper dead point position
5) the feed cup rolls off the tablet
6) the lower punch returns to its lower dead point position and the feed cup fills the die

One of the most characteristic value regarding the tablet compression is the *hardness*, which is the rate of *cohesion ability* of substances inside the tablet. The required *hardness* of tablets can be adjusted by setting the proper compression force.

Average weight and *API content* of tablets should always be controlled and re-adjusted in case of need.

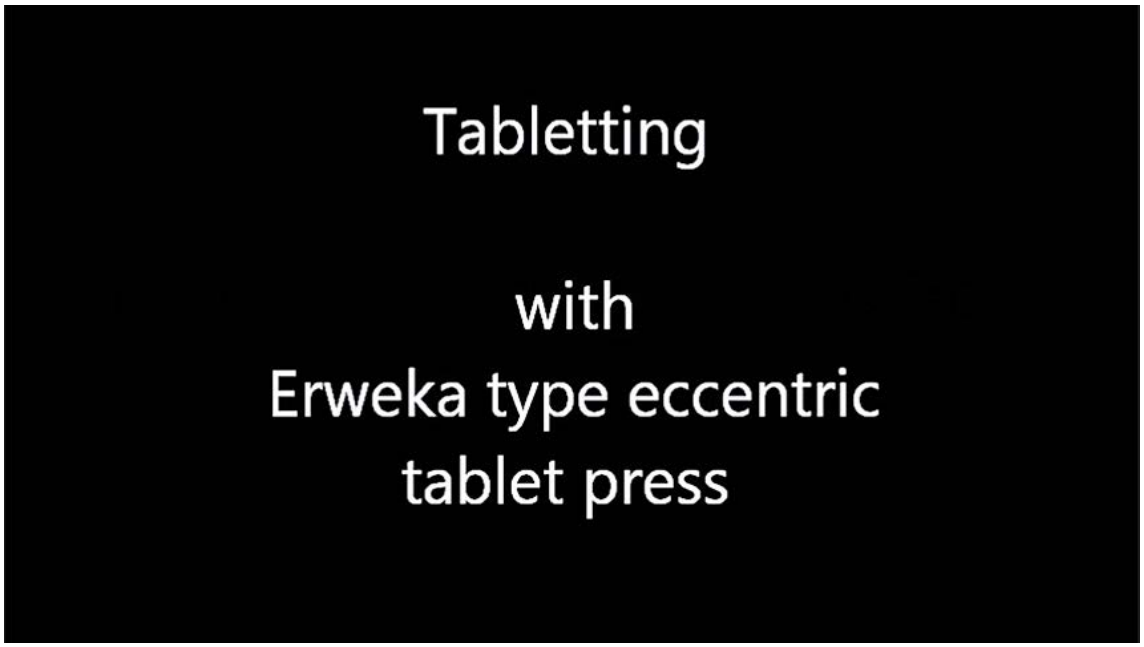
Filling uniformity can be monitored by the deviation of tablet weight.

Fig. 24.17.
Fette type pilot-plant eccentric tablet press

Capacity of machines in a tabletting cycle can be increased by application of multiple punches and dies increasing the production capacity up to 8 tablets/cycle. Application of these tools require much more precise setting and slower tabletting speed.

Fig. 24.18.
Multiple punch tools

Considering the biopharmaceutical viewpoints, such as route of administration, regarding the tablet's size, the swallowing ability should also be taken into account in case of peroral dosing. In case of effervescent or sublingual tablets, much bigger and smaller preparations can also be prepared than anatomically pre-determined peroral tablets.



Movie 14. Tabletting with Erweka type eccentric tablet press

Nowadays eccentric tablet presses are used only to produce smaller batches, instrumented bruiquetting and to investigate the compression process parameters.

24.1.2 Rotary tablet presses

It was *Henry Bower* who constructed the first *rotary tablet press* in 1872. This technological development was a revolutionary step increasing the productivity.

There are essential differences between rotary and eccentric machines. At the assembly dies must be fixed in the table of the machine, while punches are inserted into a lower and upper punch holder. During operation dies are moving synchronized together with punches on a circular path carrying out the same movement in every cycle. According to this the veretical position of lower and upper punches are determined by a constraint path in a counterrail, thus within a compression cycle they should always take up a definite position. Punches are moving around according to a programme in a counterrail also moving upwards a downwards, thus their free movement should be assured, which is a difference from eccentric machines where punches are fixed.

The compression force necessary for tabletting is developed by pressure rolls on both sides of the filling.

In order to produce more homogeneous structure, deaeration should be carried by a *pre-compression* process. At high performance machines phenomenon of capping has higher probability, since the high rotation speed shortens the compression time, that the air evacuates only partially. This is important especially in case of aerophil subsatnces or materials with high porosity. During compression the air is also compressed and if it stays inside the pores and particles, after the termination of the compression force expansion of air can cause capping. In order to avoid this disorder, size of dies and punches in chosen so that the air could evacuate from the die, in addition at pre-compression (when weak force is develooped) enough time must be ensured for the air to expel. This means without pre-compression operation speed should be much more slower.

At rotary presses feed cup is in a fixed position, it does not move and particles fill the die through a multiple guiding frame. To reach higher capacity and a uniform filling, there is a mixing element inserted inside the feed cup lately. When filling the die, the position of the lower punch determines te volume of the filling. There is always overfilling which is regulated by a stripper and the excess material is introduced back throug a recycling channel into the feed cup.

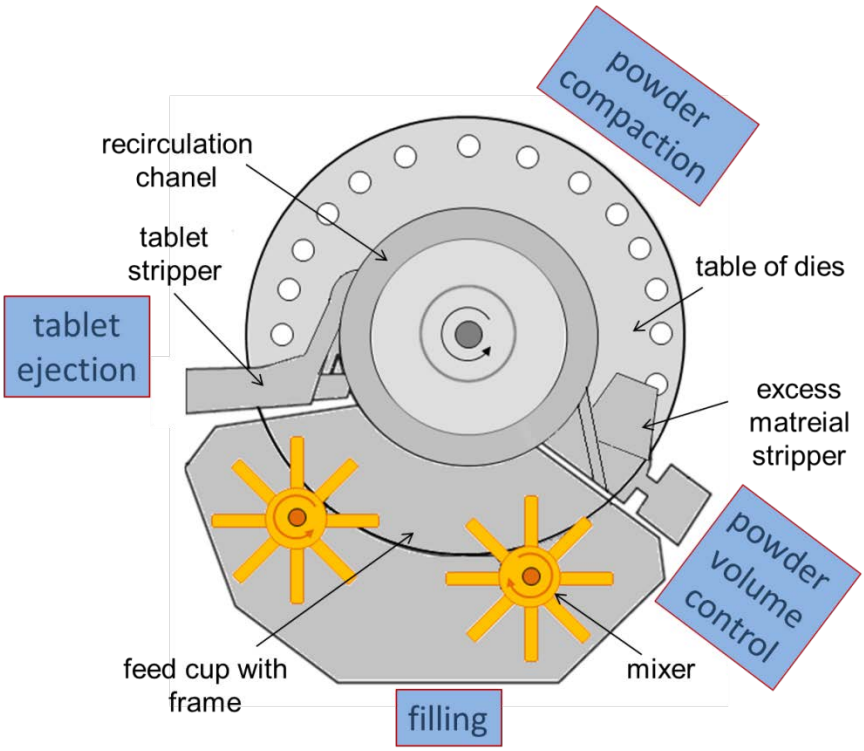


Fig. 24.19.
Operation of rotary press from top-view

Tabletting stages are the following at rotary presses:

1) filling,
2) pre-compression from both sides (at high performance machines),
3) compression through both punches,
4) ejection of the tablet.

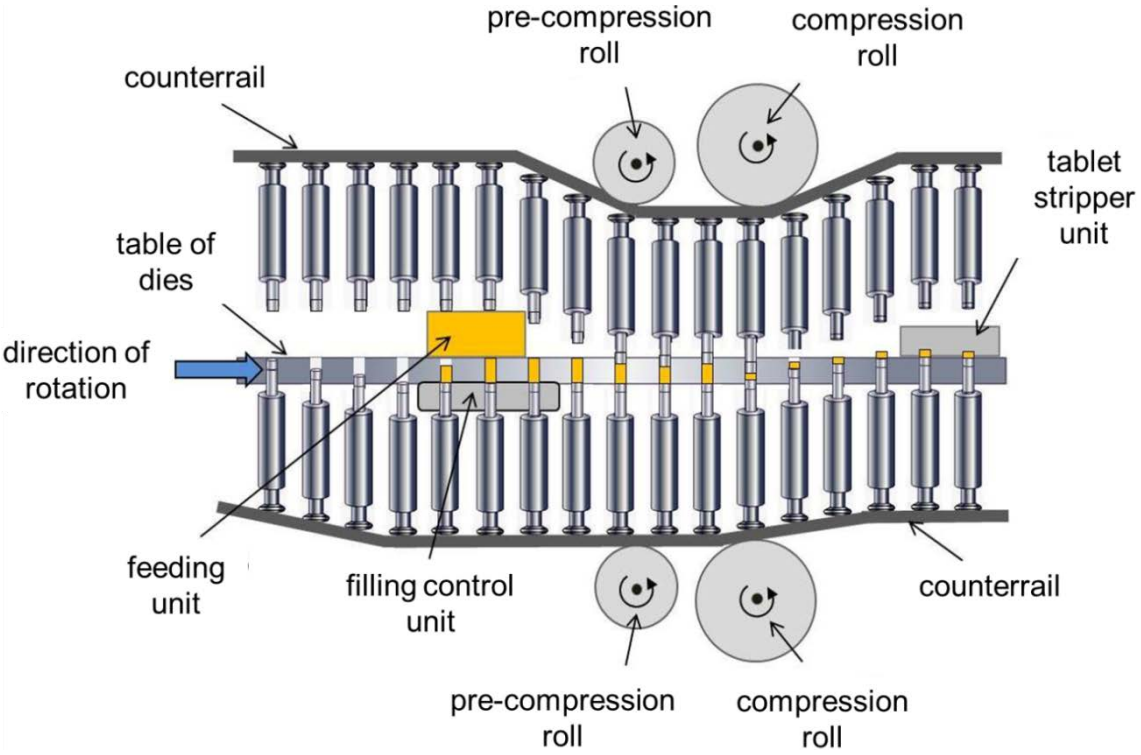
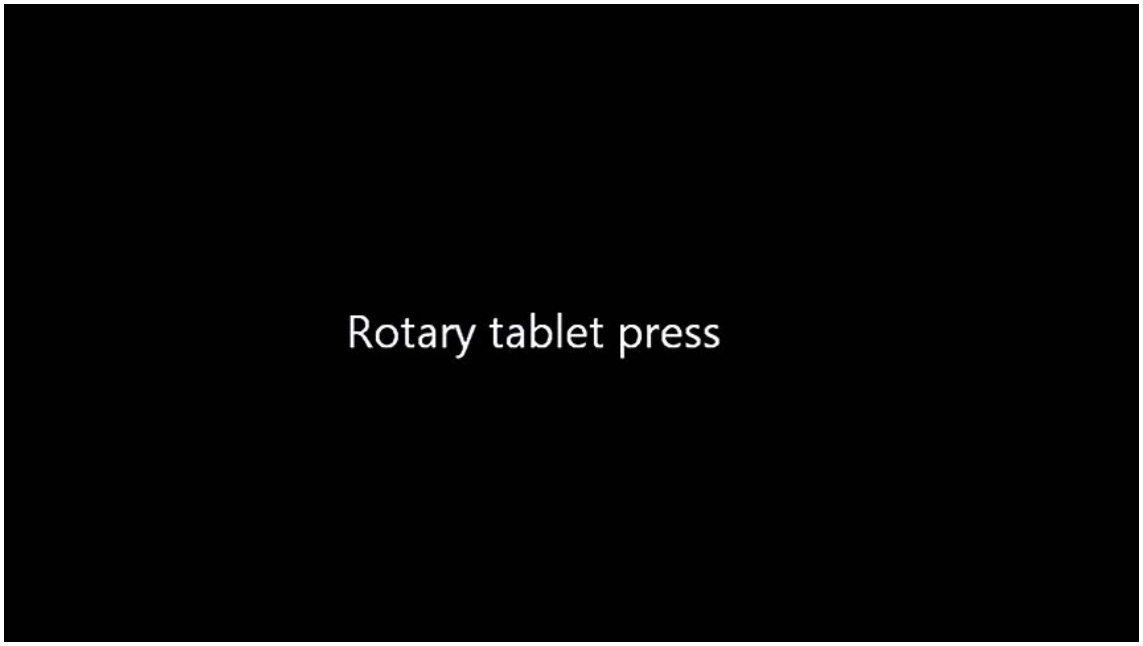


Fig. 24.20.
Operation of a rotary press from side view



Movie 15. Rotary tablet press

The regular operation is very important at rotary presses in order to avoid overcompression, thus initial manual drive is needed similarly to eccentric machines.

Capacity can also be increased by double rotary machines, when there are two feed cups and two pressure rolls against each odther above the table of dies and the compression is carried out at the same time.

Performance of these machines can reach the 200 000- 1 000 000 pcs/hr tablet.

According to examinations in practice the force acting ont he tablet has unequal distribution, which also influences these parameters. At rotary tablet presses force acting on both sides of the preparation results more homogeneous force distribution than at eccentric presses.

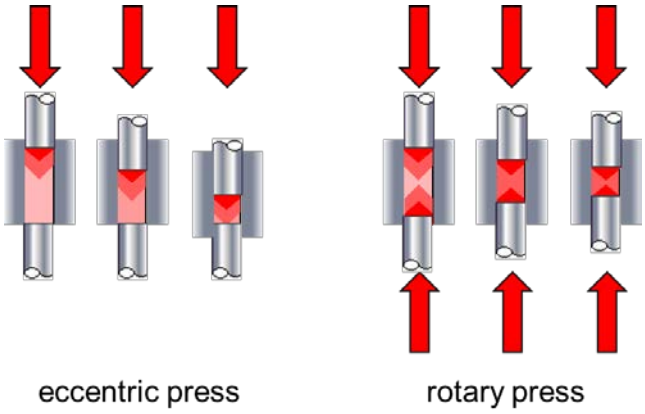


Fig. 24.21.
Distribution of force at compression

Utilization of capacity of high performance rotary presses can only be assured if substances has excellent quality and good flow properties.

Fig. 24.22.
Tabletting plant

Removal of dust from produced tablets can be carried out by compressed air, vibration, application of centrifugal force, using the so-called *deduster*.

Fig. 24.23.
Deduster

We can distinguish 3 main methods of tablet production:

1) direct compression method without preliminary granulation
2) tabletting from granules
   a) dry granulation method
   b) wet granulatio method

24.2 Tabletting

24.2.1 Tabletting by direct compression

If compacting and crystallographical properties of a substance are appropriate, long and expensive steps of tabletting process, the granulation can be by-passed. In practice it is possible only at a few substances (classic example is the sodium-chloride), when the preparatory step of tabletting is only the measurement of the substance.

In last decades breakthrough step was the introduction of excipients enhancing the compressibility properties at direct compression tabletting method. Using these excipients poor compressible substances can also be processed – up to a definite threshold. During their application mixing, flow properties and compressibility enhancing characters should be taken into account. From biopharmaceutical aspect it is important that tablets produced by direct compression have relatively short disintegration time.

Direct compression enhancer excipients:

- microcrystalline cellulose (Avicel, Vivacel, Vivapur),
- spray dried lactose (Tablettose, Spray dried Lactose, Lactose DC),
- composite mixture containing α-lactose monohydrate and cellulose (Cel-lactose),
- pregelatinized starch (partially hydrolised corn starch) (Starch 1500, Spress),
- carboxymethyl starch (Ultramilopektin, Primojel, Explotab),
- lactose (Ludipress) coated with povidone (Kollidon 30) and crospovidone (Kollidon CL),

- di- and tricalcium phosphate (Emcompress),
- spray dried spherical anhydro-dicalcium phosphate (Fujicalin),
- Macrogol 4000 and 6000,
- sodium-alginate (Manucol, Algipon).

At the application of these excipients only measurement and homogenisation is required before compression. If there are some insufficient properties regarding the compression process or quality, additional excipients (e.g. lubricant, glidant, antiadhesive materials) can be further applied for the enhancement of the compression.

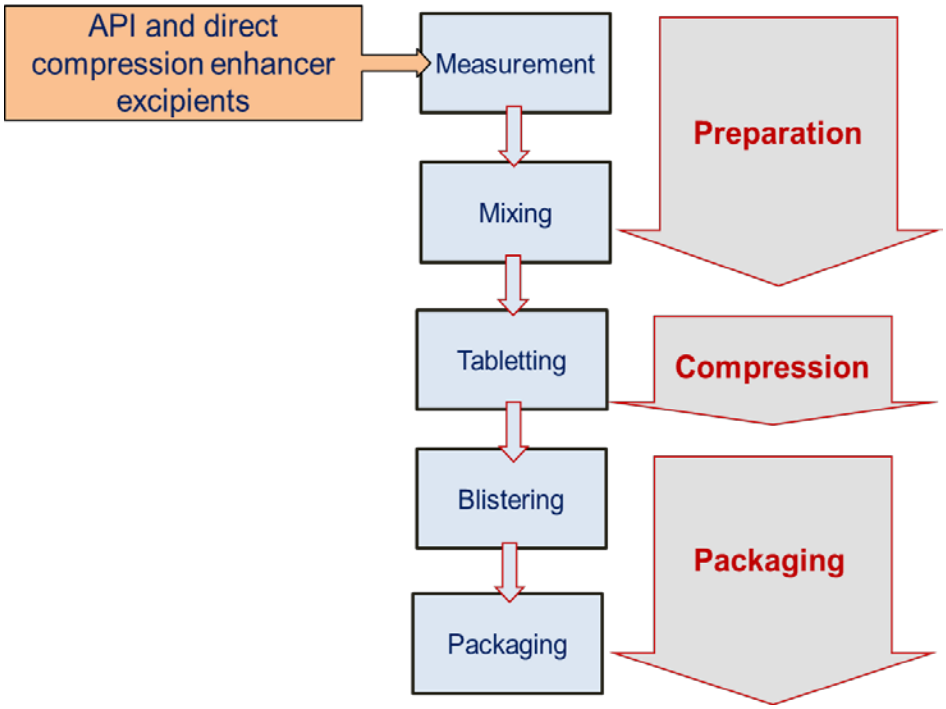


Fig. 24.24.
Flowchart of tabletting based on direct compression

24.2.2 Tabletting based on dry granulation

In case of moisture and heat sensitive substances dry method, inlcuding briquitting, compaction or sintering can be appplied to produce granules before tabletting. These granules have higher abrasion loss they have dust trouble and the binding character are not always sufficient to produce high quality tablets.

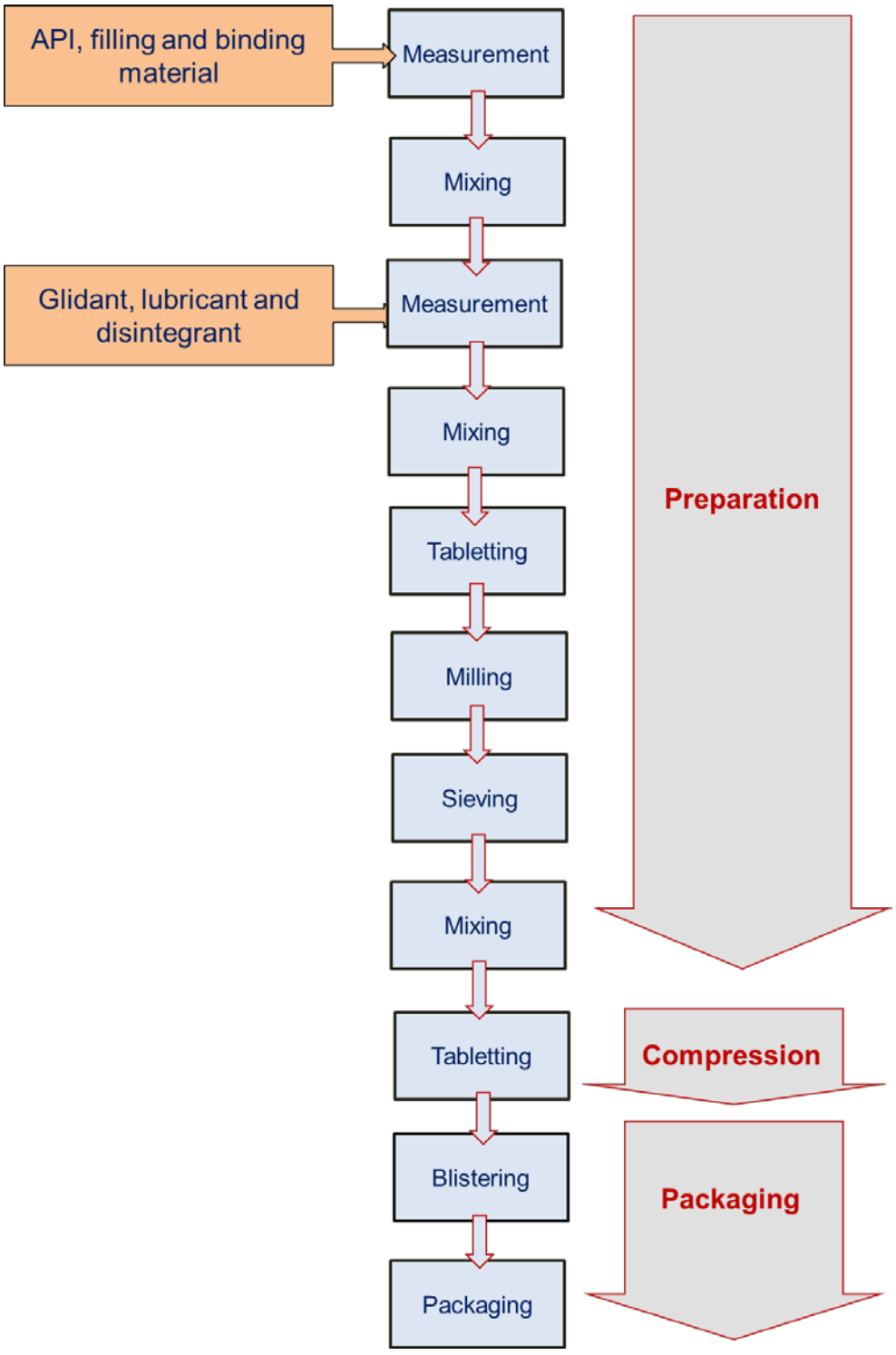


Fig. 24.25.
Flowchart of tabletting based on dry granulation

24.2.3 Tabletting based on wet granulation

Most common way of tabletting is the method based on wet granulation. It is mostly applied when the direct compression method cannot be used.

Common binder excipients are summarized in the chapter of *Tabletting*.

Binding bridges formed during wet granulation ensure good mechanical (friability and hardness) properties for the tablet. In practice it is often experienced that incresing

the binding excipient the hardness of the tablet also increases, at the same time disintegration time decreases and the drug release becomes slow, thus amount of the binder agent should be optimized taking into consideration these properties.

Granules prepared for tabletting are noted as the *inner phase* of the tablet, any other excipients (e.g. lubricant, glidant, disintegrant, antiadhesive agent) belong to the *outer phase*.

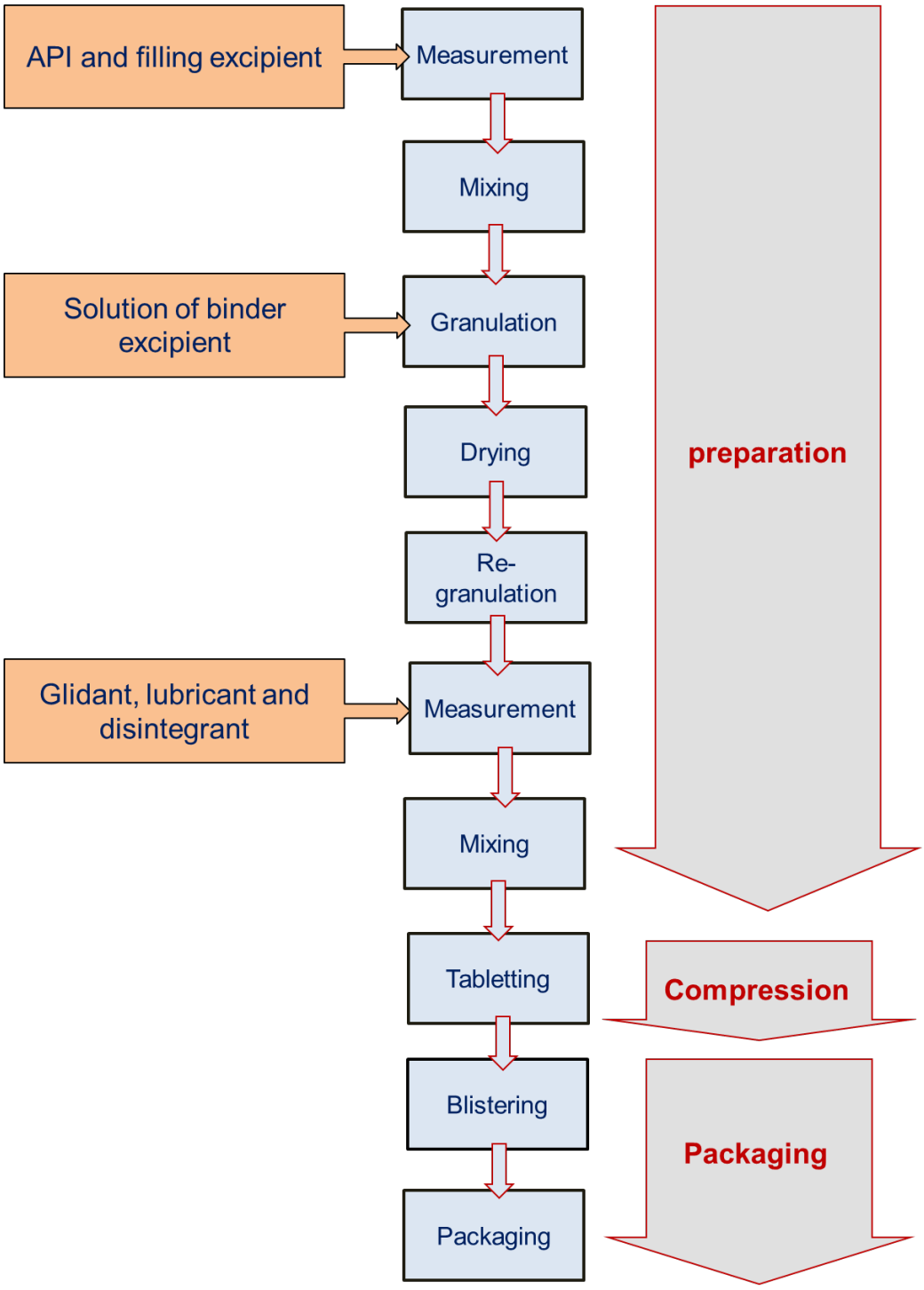


Fig. 24.26.
Flowchart of tabletting based on wet granulation

24.2.4 Special tabletting technologies

According to the commom pharmaceutical technology, measurement of the components is carried out in the order of increasing weight, but sometimes there are exceptions.

Odorous substances independently to their weight should always be added to other substances at the end of the measurement.

Preparations containing *low dose* active ingredients (e.g. hormones, atropin, quinine, ergotamine) can be diluted using inert excipients which are previusly prepared (triturations) in order to measure exact quantities. During production of these kind of preparations at granulation the API can be dissolved in the granulation liquid and after that application of a high-shear granulator or a fluid bed equipment ensures the homogeneous API distribution.

Preliminary dilution can be applied in case of *explosive substances* (e.g. nitroglycerine) before tabletting.

Mixtures containing coloured substances the inner and the outer phase is commonly granulated together differing from the general practice, because the inhomogeneous distribution causes spotty surface on the tablet (e.g. yellow riboflavine, thiamine, nystatin, clioquinol, carotenoids or activated carbon).

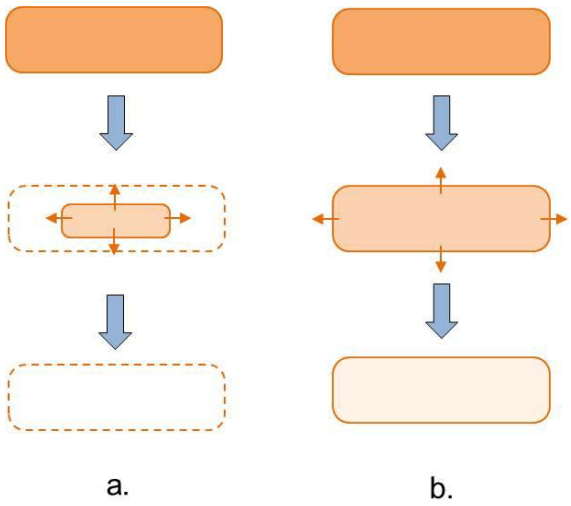
New technological developments can satisfy therapeutic and biopharmaceutical needs. Due to new technological solutions, controlled drug-release can be ensured with special structure of the preparation.

According to the structure of the tablets we can distinguish:

1) tablets without coating,
2) coated tablets,
3) matrix tablets,
4) layered tablets,
5) jacketed tablets,
6) osmotic tablets.

Coated tablets will be discussed later in the chapter *Coating*.

Release of the API form matrix tablets is happening by the erosion, dissolution of the tablets' frame structure or sometimes the structure stays intact.



a. dissolving matrix; **b.** non-dissolving matrix

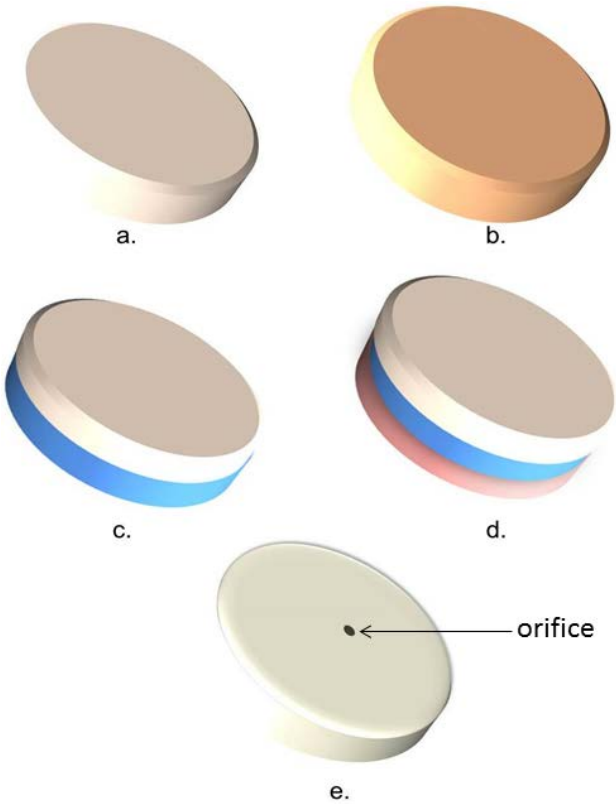
Fig. 24.27.
Possible mechanisms of drug-release of matrix tablets

Layered, jacketed and *osmotic tablets* are further broadening the pharmaceutical therapeutical possibilities.

Layered tablets can be applied in case of incompatible substances and at the developments of drug delivery systems controlled in time (e.g. pulsating systems), and/or systems with different drug release speed.

Jacketed tablets belong to the coated preparations. Since the coating is carried outusing a dry method, this procedure can be applied in case of moisture sensitive active ingredients (see chapter: *Coating*).

Osmotic tablets are practically layered and coated tablets consisting of a swelling layer and another layer containing the drug substance. The coating prepared by wet method or dry compression has a permeable and an unpermeable part. The permeable part is responsible for the swelling in the GI tract and the liquid intake. The coating acting as a semipermeable membrane allows the GI juice to get inside the tablet in order to induce the swelling and helps to dissolve or make a suspension from the active ingredient, which is slowly released through an orifice.



a. conventional; **b.** matrix; **c.** double layered; **d.** triple layered; **e.** osmotic tablet

Fig. 24.28.
Tablets with different strucrture

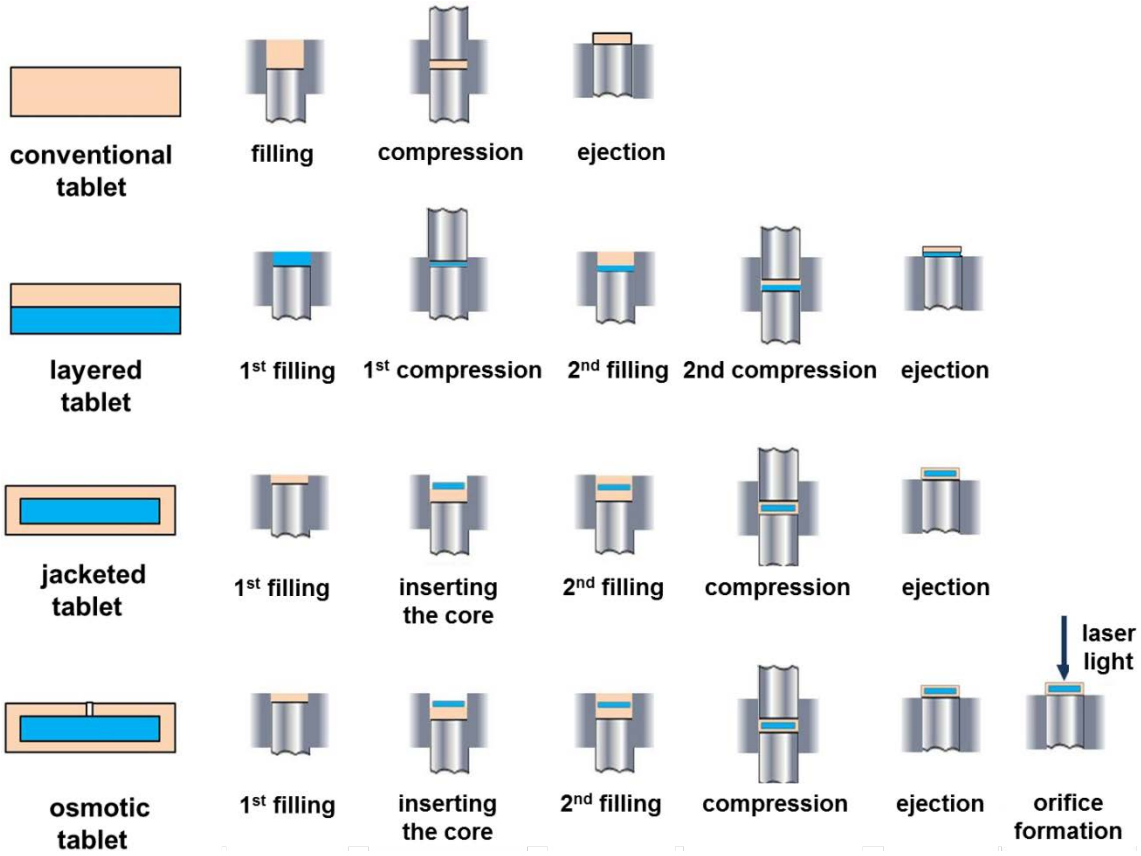


Fig. 24.29.
Main steps of production of conventional, layered, jacketed and osmotic tablets

24.3 Advantages of application of tablets

1) possibility of exact dosing of drug substances
2) simple route of administration
3) good compliance
4) productivity in huge amount
5) low production cost
6) well controllable parameters
7) the production os carried out in a solid phase, thus the sóchemical and physical stability of the product is good
8) small deviation of the amount of API
9) controllable disintegration time
10) controllable residence time
11) they can be covered with a protective coating
12) masking of smell and taste is possible
13) they are well identifiable by their colour, shape and label
14) they are easily packed and transferred

24.4 Disadvantages of application of tablets

1) problems at the production,
2) local irritation can be developed during the application
3) after intake, there is no perfect absorption from the GI tract (bioavailability is lower comparing to the intraveneous administration).

24.5 Possible applications of tabletting excipients

Within components of tablets, one of the most important excipient is the filling agent or diluent which fills up the body of the tablet, and it is important especially in case of APIs with very low amount. Its amount depends on the rate of other substances used at tabletting. Often it is impossible to produce tablets at extremely high doses of APIs. In this case, powder or granule can be prepared.

Application of diluents is important, because:

1) it ensures the given tablet weight containing the prescribed dose of API,
2) it improves the cohesion between particles,
3) it improves the flow properties of the particle aggregare,
4) sometimes it improves the compression characters in order to make direct compressed tablets

Tasks of modern diluents are not only to fill up the space inside the tablet, but also enhancing the tabletting properties.

Important excipient types during tableting:

1) diluents/filling agents (see chapter: *Granulation*),
2) binders (see chapter: Granulation),
3) lubricants,
4) disintegrants,
5) electrostatic dischargers,
6) glidants,
7) antiadhesive excipients,
8) moisture binders (to avoid drying and crumbling during storage),
9) taste enhancers (masking the unpleasant taste of the API),
10) colourants (in order to distinguish tablets and it also serves asethetic purposes)

During development of a preparation the compression disorders should be always eliminated. Sources of these disorders can be:

1) adverse characters of substances to be comressed
2) quality and quantity of tabletting excipients,
3) conditions of compression.

There are several excipients that can be used to improve tablets' compression and quiality proerties to avoid disorders.

24.6 Enhancement of lubrication after compression

Optimal lubrication coefficient (R>0.9) of a particle aggregate can be determined by an instrumented tabletting machine.

Proper lubrication of product batches is necessary.

In case of low amount of lubricant:

- tablet can stick to the punches and
- the tablet's firction to the wall of the die increases the force needed to eject the tablet.

Too small amount of lubricants can cause:

- decrease in tablet hardness,
- increase in disintegration time,
- decrease of drug release speed,
- the tabletting machine will be unable to compress the preparation.

There are two main types of lubricants:

a) hydrophil lubricants – they usually have less lubricant properties without glidant or antiadhesive character:
   - sodium-dodecyl-sulphate
   - sodium-stearyl-fumarate (e.g. *Pruv*),
   - glycerides with different degrees of estherification (e.g. glyceryl-palmito-stearate, *Precirol*)
   - polyethylene glycol 4000-6000 (PEG)

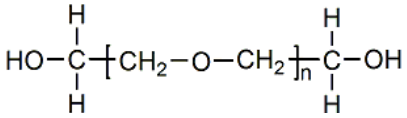


Fig. 24.30.
Polyethylene glycol

b) hydrophobic lubricants – they are usually good lubricants effective in small amount often with good glidant and antiadhesive properties:
   - stearic acid,
   - magnesium stearate,
   - calcium stearate
   - magnézium-alumínium szilikátok,
   - hydrogenated vegetable oils (e.g. *Cutina*),
   - glcyeryl behenate (e.g. *Compritol 888*)

According to the action of lubricants we can distinguish:

1) liquid or hydrodinamical type lubricants (e.g. fatty alcohols, vaseline, liquid and solid parafiine),
2) boundary layer lubricants (e.g. stearic acid, stearates, silicates)

Lubricant materials also ensure asthetic, glossy finish.

After compression different types of impacts can harm tablets (e.g. during coating, storage, transfer), thus tablets should have good mechanical (friabiity and hardness) properties to ensure the uniformity of weight and API content.

In order to reach proper mechanical character, size of granules and size distribution should be optimized. In case of majority of small particles, binding force is higher, thus mechanical solidity is higher. It is also necessary to set the moisture content, because too low or high moisture content can cause weak solidity of the preparation.

Application of talc and polyoxaethen improve, fatty acids or fatty alcohols decrease the mechanical stability. It is adviseable to regulate the compression force, incidentally to change geometrical parameters of the tablet.

Poor mechanical properties of tablets can be caused by:

- inappropriate particle size or ditribution,
- high porosity,
- inappropriate moisture content,
- inappropriate amount or quality of binder,
- presence of some glidants or lubricants,
- small compression force,
- inappropriate shape of the tablet.

Too high mechanical stability is also undesirable, because it caused long disintegration time and in case of splittable tablets bisection will be poor.

24.7 Biopharmaceutical and pharmaceutical technological viewpoints of tablets disintegration

One of the most important biopharmaceutical character of a tablet is the wetting and disintegration, which influences the drug release and the absorption, too. The balance should be kept within the composition from this viewpoint as well. Regulating the disintregration time, sometimes it is needed to add hydrophil substances and/or disintegrants to facilitate wetting.

Small particles with bigger surface slow down the disintegration because of the strong bining forces, thus the optimization of the particle size and/or amount of disintegrant is necessary.

The proper inner structure and porosity is also needed for the disintegration process. Too high compression force results more compact structure, which increases the disintegration time significantly.

During the disintegration the tablet falls apart to smaller particles ensuring a huge surface for the dissolution medium and the drug release.

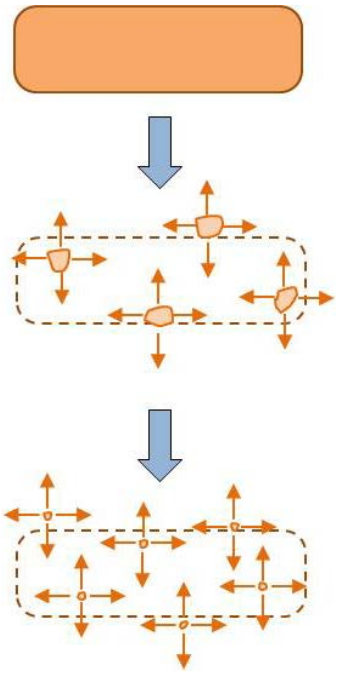


Fig. 24.31.
Mechanism of tablets' disintegration

Too slow disintegration can be caused by:

- aerophil or lipophil substances,
- excess presence of binding excipients,
- low amount or inappropriate disintegrant,
- high glidant content, application of lubricant,
- big particle size,
- small porosity,
- too big compression force.

Disintegration time can be increased or hindered with proper excipients slowing down this process (i.e. stearine, high molecular weight polymer substances, different hydrgenated fatty compounds, solid paraffin).

Disintegration time can be reduced by application of *disintegrants*:

- starch
- sodium carboxmethyl starch (Primojel, Ultraamolipektin, Explo-Tab),
- cross-linked carboxy methylcellulose, croscarmellose sodium (Ac-di-sol, Primellose, Vivasol),
- cross-linked starch,
- alginic acid, alginates (Manucol, Algipone),
- cross-linked PVP, crosspovidone (*Crosspovidone, Kollidon, Polyplasone*)
- hydroxy propylcellulose with low degree of substitution (*L-HPC*)

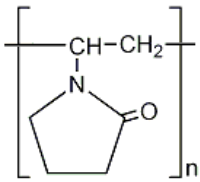


Fig. 24.32.
Crospovidone

24.8 Avoiding adhesion and picking during compression

Adhesion means bonding of the substance during compression to the punches or the wall of the die. Picking means a stronger adhesion to the punches accompanied by chipping.

This disorder can be caused by:

- too much moisture content,
- insuffucient binding force,
- insufficient antiadhesive property,
- surface failure of the punch.

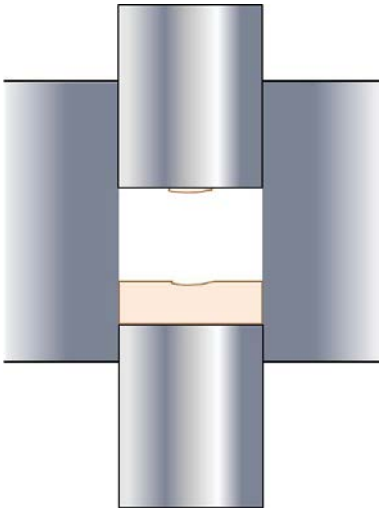


Fig. 24.33.
Sticking to the punch

Adhesion and picking can be avoided by regulating the granules moisture content, adding antiadhesive, anti-frictioning excipients or by cleaning, polishing or replacing the punch.

24.9 Avoiding capping and layering after tabletting

Detachment of the tablets' lower or upper part is called *capping*.

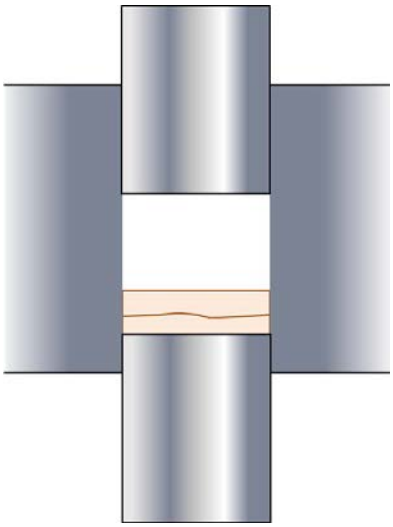


Fig. 24.34.
Layering

Layering means laminated detachment of the tablet.

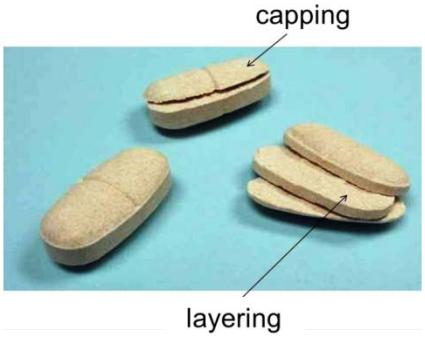


Fig. 24.35.
Capping and layering of tablets

Capping and/or layering can be caused by:

- low moisture content,
- presence of aerophil substances,
- high porosity of the granule,
- low amount of binder,
- high dust content,
- elastic properties of substances,
- high compression speed,
- high compression force,
- inappropriate tablet shape (too thick or extremely convex tablet).

Capping and layering can be avoided by the regulation of the moisture content of the granule, by adjusting the amount of binder exipient, adding substances increasing

elastic properties, applying pre-compression or increasing the compression time. In case of need, the shape of the tablet also can be changed, since too thick and too convex tablets are capping more easily. Decreasing the thickness and producing a lens-shaped tablet with a higher radius of curvature, the capping ability can be decreased. Decrease in the compression force and/or increase in the pre-compression force can also help to solve this problem.

By adding moisture binding excipients the decrease in moisture content below the optimal value (usually 5-7%) during storage can be avoided. Glycerol, propyleneglycol, sorbitol, different sugar syrups and the sodium-lactate can be used for this purpose as excipients. From this viewpoint the moisture content of the applied starch should also be taken into consideration.

24.10 Decrease of weight fluctuations of tablets

Fluctuation in tablet weight can be observed during compression, if:

- the particle size is inappropriate,
- there is high dust content,
- the particle shape is inappropriate,
- there is high moisture content,
- there is electrostatic charge,
- the flow properties of the granule is insufficient because of reasons mentioned above,
- there is too high compression speed.

High deviation in tablet weight is in relationship with the insufficient flow property of the granule, which results filling disorders. Poor flowability of the granule can be derived from the inappropriate particle size, moiture content, non-spherical particle shape, high dust content and electrostatic charge. Particle size and shape can be influenced by process parameters of the granulation. In order to decrease the dust content, conditions of the granulation should be precisely designed and/or increase in binding excipient may be also necessary.

Well known antistatic excipients:

- polyethylene-glycol,
- talc,
- colloidal silicone dioxide (e.g. *Aerosil*)

Glidant excipients act based on the decrease int he interparticular friction:

- talc,
- starch,
- macrogol 4000-6000,
- silicone oil,
- anhydrous colloidal silicone dioxide,
- silicified talc.

Effectiveness of glidants can be expressed by the flow factor (*f*):

$$f = \frac{t_g}{t_o} \tag{13.}$$

t_g flow time of granule containing glidant,
t_o flow time of granule without glidant.

Questions

1) Define the concept of tablets!
2) Which parameters determine the tablet's shape and size?
3) What kind of drug release can be carried out at tablets?
4) Which are the main changes during compression on the particles aggregate?
5) What is the relationship between the upper punch and the force developed by itself?
6) Which parameters can be investigated by compression simulators?
7) What is the relationship to calculate the compression work?
8) What kind of areas characterize the graph of movement/distance-force?
9) How can the Heckel constant be determined?
10) What is the model of Shapiro and Kawakita?
11) Describe the operation of an eccentric tablet press!
12) Describe the operation of a rotary tablet press!
13) When direct compression can be applied?
14) List some excipients of direct compression!
15) What are the main steps of tabletting applying the dry granulation method!
16) What are the main steps of tabletting applying the wet granulation method!
17) What are the advantages and disadvantages of application tablets?
18) List some lubricants!
19) List some disintegrants!
20) How adhesion and picking can be avoided during compression?
21) What kind of parameters can cause capping or layering? How can it be avoided?

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http://en.wikipedia.org/wiki/File:Tablet_press_animation.gif

http://www.techceuticals.com/Tousey_904TC.pdf

http://edoc.unibas.ch/16467/1/PhD_thesis_Go_Kimura_01032012_for_electronic_copy.pdf

25 Capsules

Medicinal capsules (*capsulae medicinales*) are pharmaceutical products containing solid or liquid medicine, made for peroral, in certain cases rectal or vaginal administration. The word capsule originates from Latin, meaning case. Therefore, in pharmaceutical technological practice *medical cachet* can be used for a synonym.

The invention and use of wafer cachets in pharmacy was the achievement of the Vienna pharmacist *de Paul* in 1730. He used these capsules to mask the foul taste of turpentine, used to cure gout at the time.

Frenchmen *Mothes*, a pharmacy student and *Dublanc*, a pharmacist, were the first to develop a method for making soft gelatin capsules in 1834, likewise for taste masking.

In 1846, Lehuby's patented invention of the "medical envelope" laid the ground for the production of two-piece hard gelatin capsules.

French engineer *Limousin* developed the first wafer capsule-making and -filling machine in 1872.

Plate-press capsule forming dates back to 1900, linked with *Colton*. The machines capable of filling and sealing capsules in mass production became available around the middle of the last century. A Park Davis&Co. started industrial scale capsule production after this time.

Scherer R.P. constructed a new device that made the mass production of single piece gelatin capsules possible.

Technological advantages of capsules:

1) odor- and taste masking,
2) easy administration due to their shape, good moistening and softness
3) attractive look,
4) the operation of encapsulation requires no or very little excipients,
5) capsule materials are physiologically inert, easy to digest,
6) encapsulation is feasible in pharmacies by manual or semiautomatic apparatus,
7) no such irregularities as in tablet compression,
8) capsule walls are easy to gloss (light protection) or color,
9) separation of incompatible ingredients,
10) easy to prepare sample doses for preclinical and clinical testing.

Disadvantages of capsules:

1) more expensive technology than tablet compression,
2) charge volume is limited,
3) hygroscopic active ingredients make hard gelatin shells brittle, as they draw moisture out of capsule walls,
4) hard gelatin capsules require 45-65% humidity for storage.

Capsule shells are made out of water solutions of jellifying substances:

1) animal proteins (e.g. gelatin),
2) vegetal polysaccharides and derivatives (e.g. starch, cellulose).

Gelatin is particularly suited for making capsules, as it has no taste and swells and disintegrates in the GI tract within a couple of minutes, enabling drug release.

According to the material of the capsule shell, from a technological aspect capsules can be classified into:

1) wafer capsules (cachets),
2) hard gelatine capsules
3) soft gelatine capsules.

Gelatin is suited for capsule making because it is not toxic, can be transformed into a xerogel, is capable of reversible sol-gel transition and dissolves in body fluids at body temperature. Gelatin capsule ingredients other than gelatin are water fixing agents (e.g. glycerine, sorbite), plasticizers that preserve the moisture content and strength of capsule wall, colorants and preservatives.

From a biopharmaceutical aspect capsules may be

1) rapidly disintegrating, rapidly solving (unmodified) or
2) modified drug release products.

Uncoated capsules made of *unmodified* water soluble materials rapidly disintegrate in gastric juice, releasing the active ingredient.

Capsules of *modified* drug release contain such excipients in their charge, capsule walls or both or are made using such specialized methods that make the speed, location and/or duration of drug release controllable.

Retarded and extended drug release capsules qualify as modified drug release capsules.

Capsules resistant to gastric juice are *intestinosolvent capsules* (*capsulae intestinosolventes*), gelatin shells hardened with formaldehyde or coated with a suitable excipient.

25.1 Capsules

25.1.1 Wafer capsules (cachets)

Wafer capsules (*capsula hostiae*) are used in magisterial medicine preparation, with decreasing frequency due to the rigidity and brittleness of the capsule walls. This type of capsule is usually made of unleavened rice flour dough. They belong to the group of rapidly disintegrating capsules. Immersing the capsule in water for a short period prior to ingestion makes the capsule walls soften and thereby easy to swallow. The following illustrations show the main steps of customized capsule preparation.

The following tool is capable of simultaneous filling and sealing of 12 capsules.

Fig. 25.1.
Laboratory wafer capsule filling device

Main types of gelatin capsules (*capsulae gelatinosae*):

1) soft shell capsules, usually filled with solutions, oils and suspensions,
2) hard shell capsules, usually employed with dry substances (e.g. powders, granulates, pellets, minitablet.

Soft gelatin capsules consist of a single piece, hard capsules of two parts, a body and a cap.

25.1.2 Soft gelatin capsules

Soft gelatin capsules (*capsulae elasticae*) are usually spherical, oval or oblong. Capsule walls are elastic with various levels of strength. Soft capsules have thicker shells than hard capsules.

Bioavailability can be improved and ease of swallowing increases patient compliance. Soft capsules filled with a liquid hydrophilic charge (e.g. PEG) can carry ibuprofen for active ingredient, which, by means of rapid dissolution and rapid adsorption of the molecular active ingredient dispersion, achieving analgesic effect in a short time.

This technology can mask the bad smell or taste of oily substances (e.g. garlic extract, cod liver oil, vitamins A, D, E)

Soft capsules have disadvantages too: higher cost than tablets or hard capsules, compatible solvents are scarce, as water solves the shell, strong acids and salts hydrolyze it, strong bases and aldehydes cross-link with it, decreasing the solubility of the capsule wall.

One of the production methods of soft capsules is dropping procedure, in which the active ingredient and hot-melt gelatin are dripped together into a medium that solves neither the active ingredient nor the excipients. Subsequent to cooling capsules can be filtered from the system with the liquid medium recycled. Capsules made with dropping procedure are spherical and seamless.

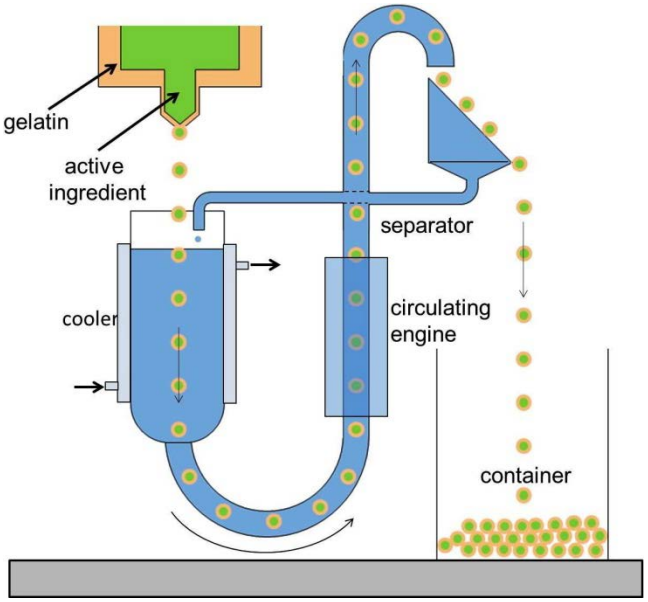

Fig. 25.2.
Capsule making machine (dropping procedure)

The concept of the continuous operation rotary die gelatin capsule filler is linked with *Scherer*. During this process hot liquid gelatin is continuously cast and formed into two thin wide ribbons. The ribbons and the fill material containing the active ingredient are fed between two counterrotating rolls, fashioned to cut, separate, seal, shape capsules one by one and cooling them. At the end of drying capsules have a residual water content of 4-10%. These capsules, depending on the mould, can be spherical or cylindrical, with a sealing seam along their side.

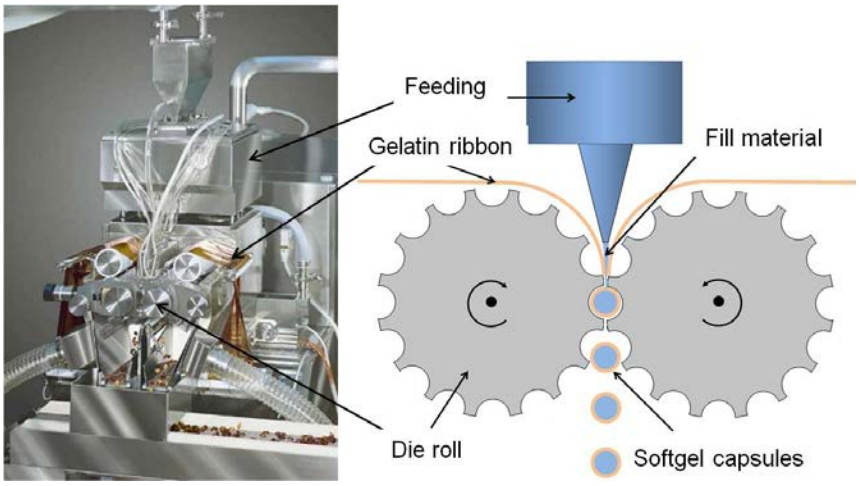

Fig. 25.3.
Rotary die gelatin capsule filler

25.1.3 Hard gelatin capsules

Hard gelatin capsules (*capsulae operculatae*) consist of two oblong cylindrical telescopic pieces, closed and rounded on either end.

There are various capsule sizes used in pharmaceutical technological practice.

Holding and protecting capsule content, preventing separation and spilling in transport and packaging and protection from external air and moisture require perfect sealing.

At the beginning hard gelatin capsules consist of two telescoping cylindrical parts, without any further sealing elements. With this type of capsule, appropriate sealing was achieved by precise fitting. However, as the two parts were telescoped, it was this very precise fitting that often caused overpressure in the capsule, which, on one hand made telescoping more difficult, on the other hand contributed to premature capsule separation. This was initially prevented by pasting capsule body and cap together after filling and closing. A gelatin solution heated to 60°C was used as sealant, dried with a warm air afterwards. The band created this way was colorable to preferences, which could be used for marking, aiding capsule identification.

These supplementary work phases required additional procedures, causing increased production time and costs. Mechanical processing required more efficient and safe solutions.

Fig. 25.4.
Traditional capsule open and closed, with and without sealing band

To perfect closure, capsule shape had to be altered to allow the proportion of enclosed air causing overpressure escape upon closure by implementing sealing elements.

The self-sealing or *Snap-Fit* capsule is one solution. There are locking rings around both the capsule body and cap, with an additional groove on the cap for pre-closure. These capsules remain closed without a sealing band and decrease the proportion of faults due to post-production separation significantly.

Their sealing is perfect from a safety aspect too; they cannot be reopened without irreversible damage.

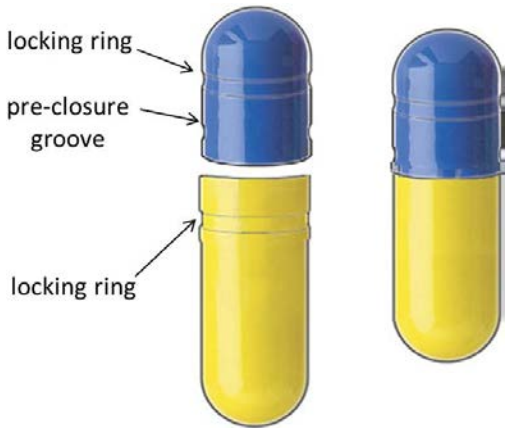

Fig. 25.5.
Snap-fit capsule open and locked

Coni-Snap capsules are an improved version of *Snap-Fit* capsules. Their bodies have a tapered rim that prevents faulty closure due to inaccurate assembly, where the capsule parts split each other. Closure is made more perfect and quick by two circular grooves and 4-6 additional interlocking serrations, safely enhancing the filling performance of high-speed filling machines.

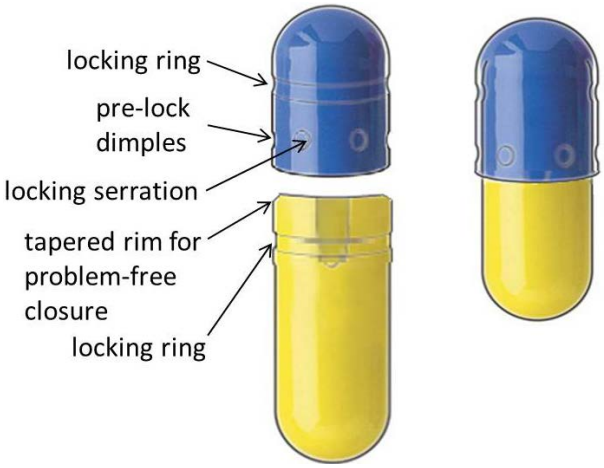

Fig. 25.6.
Coni-Snap capsule open and locked

As the filling speed of capsule filler machines increased, the open end of capsule bodies have been altered to a tapered shape to facilitate even safer closure.

25.2 Capsules

25.2.1 Officinal capsules

Encapsulation in laboratory is done either manually, individually filled capsules, or various capacity encapsulation tools.

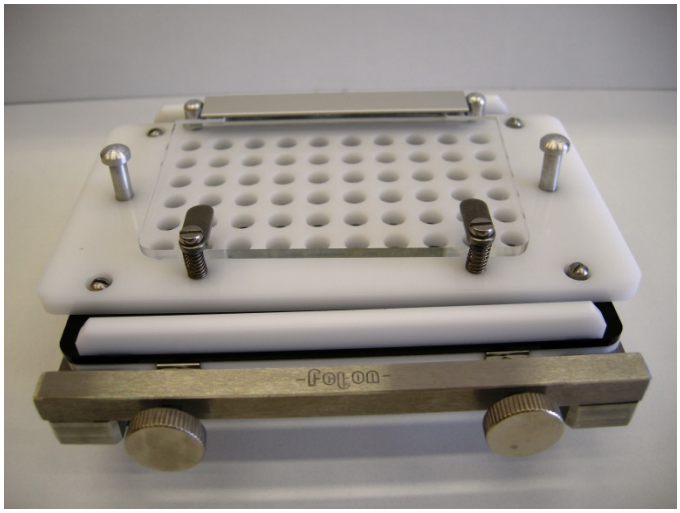

Fig. 25.7.
Manual capsule filling machine for laboratory-scale

The main steps of encapsulation using a laboratory-scale device capable of filling 50-100 hard gelatin capsules:

1) empty capsules loaded in the device with capsule bodies down,
2) capsule caps separated from bodies using the device,
3) charge spread out on the plate holding the capsule bodies, filling them even
4) charge material smoothed,
5) capsules closed by assembling the device,
6) filled capsules removed from device.

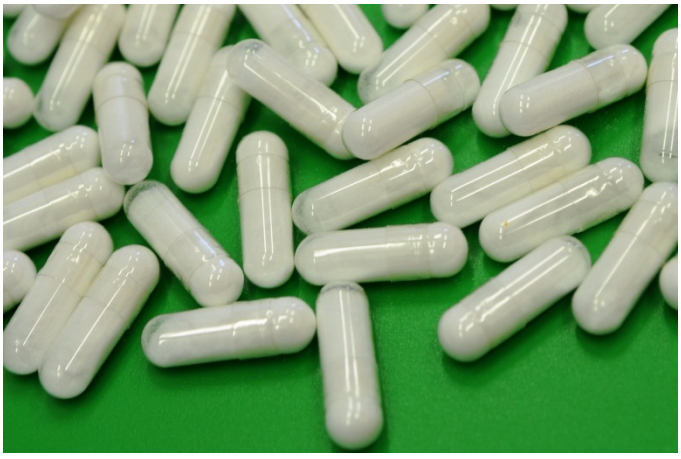

Fig. 25.8.
Filled hard gelatin capsules

25.2.2 Medium scale capsules

The higher performance manual devices are capable of filling larger quantities of 100-500 capsules.

Fig. 25.9.
Medium scale manual capsule filler

25.2.3 Industrial capsules

There are semi- and fully automatized industrial hard gelatin capsule filling machines. Their productivity may be up to 15 000 capsules/ hour.

Automatized filling machines generally work in continuous operation similar to that of rotary die capsule filling machines, with occasional linear movement operations in particular work phases.

These devices can open empty capsules before filling, separating capsule bodies from caps and aligning them. This is followed by filling, closure and discharging.

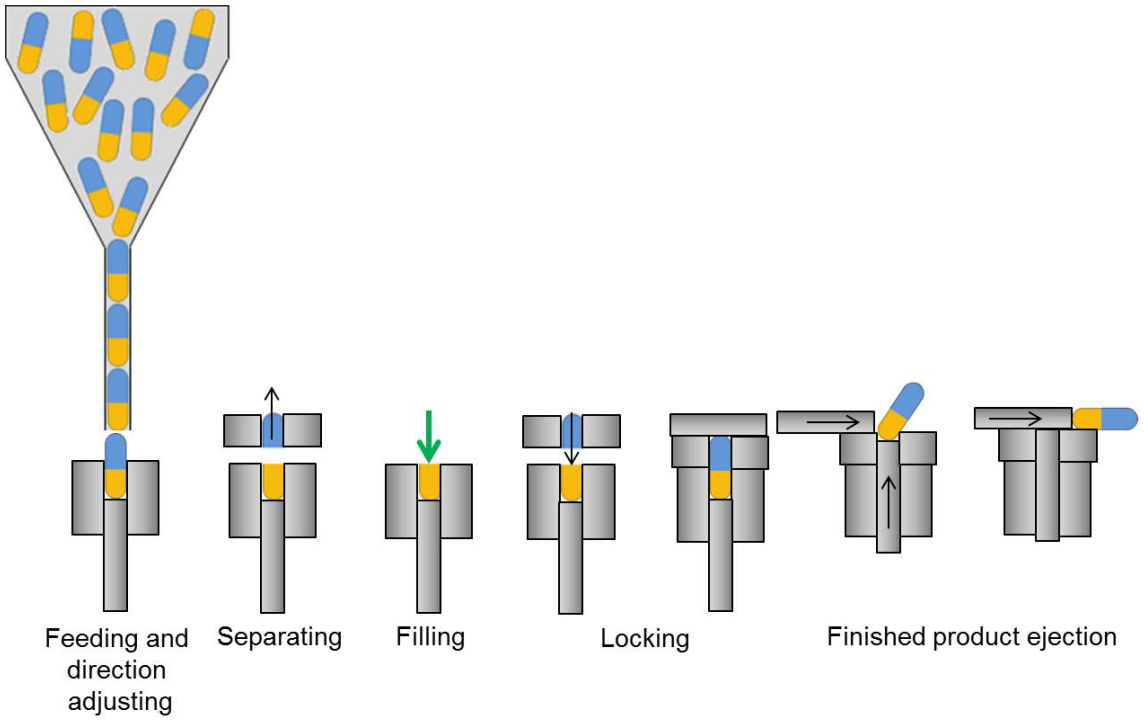

Fig. 25.10.
Main steps of mechanical encapsulation process

Mechanical encapsulation can be capsule size-adjusted and size-independent. In the first case charge volume or charge mass is determined by capsule size. In this case, to achieve uniformity of the fill weight the capsule body is fully filled and excess removed from the top. Dosing disc type systems follow this method.

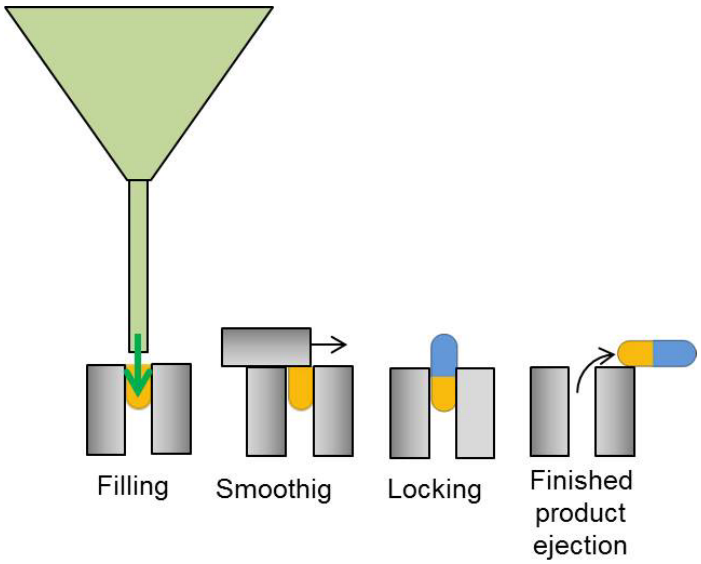

Fig. 25.11.
Dosing disc system

In size-independent encapsulation devices charge material is not filled directly into capsules. These devices first dose a single charge in a dosing tube and use this tube to fill capsules. In this case charge volume is usually smaller than capsule capacity.

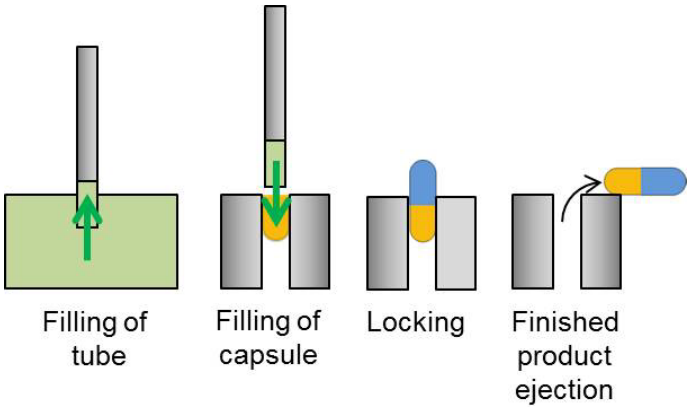

Fig. 25.12.
Dosing tube system

Frequently occurring technological problems of encapsulation, with solutions:

1) small portion substances are not suited for encapsulation. Required charge volume can be made by adding inert powders prior to encapsulation
2) hygroscopic powders draw moisture out of gelatin capsule shells, making capsule walls rigid and brittle, possibly causing cracks. This can be prevented by adding adsorbents such as magnesium carbonate or magnesium oxide.
3) liquefaction of eutectic mixtures may soften up capsule walls. Such substances are either separately encapsulated or adsorbents are added to them prior to preparing the mixture.
4) incompatible ingredients are encapsulated separately or separated by using a smaller capsule for one ingredient placed inside the bigger one holding the entire compound.

Excipients used in encapsulation may be the following:

1) diluents, e.g. lactose, corn starch,
2) lubricants and glidants, e.g. magnesium stearate, talcum,
3) wetting agents, e.g. sodium laureth sulphate,
4) disintegrants, e.g. crospovidone.

Blister packing provides protection to ready filled and sealed capsules against mechanical and other environmental impact (e.g. heat, moisture).

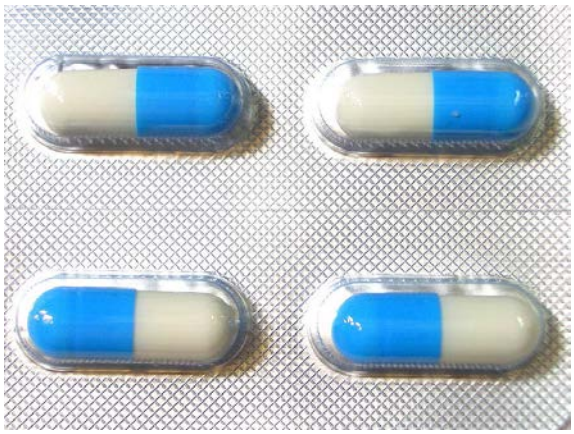

Fig. 25.13.
Blister packed capsules

Questions

1) How would you define the operation of encapsulation?
2) What are the technological advantages of capsules?
3) What are the technological disadvantages of capsules?
4) What are the biopharmaceutical advantages of capsules?
5) What substances are suitable as capsule material?
6) What are the advantages of soft gelatin capsules?
7) What are the methods of making soft gelatin capsules?
8) What are the main steps of officinal encapsulation?
9) What are the industrial methods of hard gelatin encapsulation?
10) What are the methods of hard gelatin capsule forming and sealing?

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Recommended websites

http://capsugel.com/media/library/ConiSnap_brochure_full.pdf

http://capsugel.com/media/library/hard-gelatin-capsules-today-and-tomorrow.pdf

http://65.23.159.214/products/conisnap.php

http://65.23.159.214/pdf/Consi-Snap-Brochure.pdf
http://www.medicaps.com/brochure_lems.pdf

26 Coating

In pharmaceutical technology coating means the covering of the external surfaces of medicinal particles or preparations (e.g. tablets, pellets) with a continuous layer of uniform thickness. This operation is suited to solve numerous biopharmaceutical and pharmaceutical technological problems and extends the therapeutic application opportunities of pharmacological research results, mainly in controlling drug release of pharmaceutical preparations.

Coated preparations (e.g. dragées, film tablets, coated pellets) consist of a core and a surrounding coating. The active ingredient is usually contained in the core, but in case of more complex preparations the coating may contain active ingredient for quick or staged drug release.

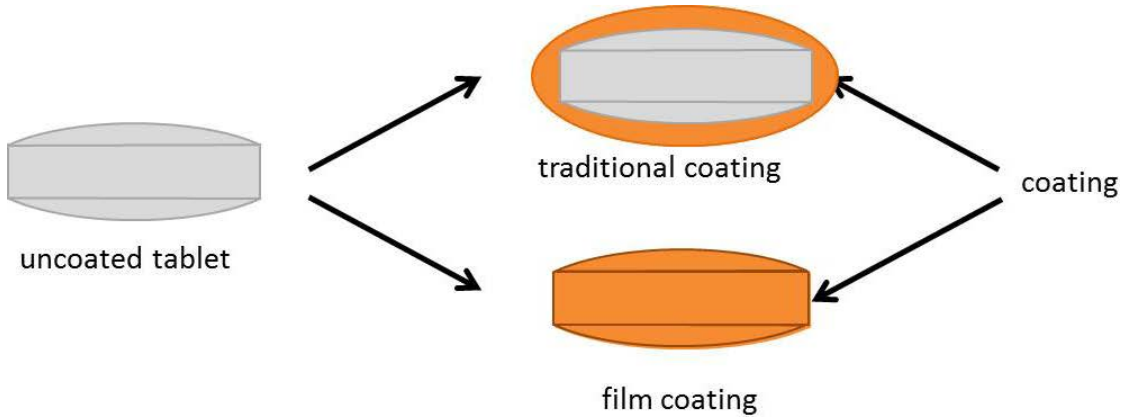


Fig. 26.1.
Structures of coated preparations

The operation of coating is employed for achieving the following main purposes:

1) attractive look,
2) coloring (e.g. for identification),
3) protection against environmental effects detrimental to the active ingredient (e.g. air, moisture, light), extension of shelf life,
4) protection of the preparation, enhancement of physical stability (e.g. from mechanical effects like impact, scratching, wearing, dust)
5) preparation of controlled drug release systems,

According to written records pill coating was in practice in ancient Egypt. *Avicenna* (981-1037) recommended coating pills with powdered silver and gold for taste masking and attractive looks for preparations. These procedures were improved later on, using silver and gold leaf (*Argentum foliatum, Aurum foliatum*) for a more perfect coating effect. in the middle ages honey and sugar were used as adhesives.

As of the mid-19th century, in conformity with social demand, coating became feasible on industrial scales. It required the development and application of devices and technology capable of coating massive quantities of tablet cores. The first devices essentially made for coating were manually rotated, naked flame-heated, tilt-axis copper drums, with power driving introduced later. In the course of technological developments *William Warner*, a pharmacist in Philadelphia developed a method in 1866 for sugar-coating tablets.

Up to the first third of the 20th century coating meant dragée-making (sugar glue coating, later suspension coating), essentially for the purposes of making preparations look attractive and taste masking. In this period the traditional drum method was employed, although organic solvent-based synthetic polymers have been put to use as coating materials and the introduction of cellulose nitrate and cellulose acetate made the preparation of intestinosolvent coatings possible.

Cole proposed the idea of *film coating* in 1930. The ongoing development and evolution of *technology* and *machinery*, the mutual influence of *chemical* and *pharmaceutical industry* resulted in further development. The first film-coated preparations appeared in 1954.

New, perforated-wall coating devices appeared in the 1960s, which allowed more efficient drying and the application of modern vaporization technology.

At the end of the 20th and the start of the 21st century *biopharmacy* gave a new impetus to the development and improvement of coating technologies by exploring and harmonizing the living body and the potentials of technology at a deeper level, developing biocompatible systems and expanding the opportunities of therapeutic application.

The biopharmaceutical advantages of coating are:

1) preventing the irritation of the oesophagus and the gastric,
2) protection of active ingredient (preventing disintegration or inactivation, e.g in the gastric),
3) achievement extended therapeutic effect (e.g. establishing depots)
4) achievement of targeted therapeutic effect (e.g. dissolution at a designated point of the GI tract),
5) drug release at the point of absorption,
6) increasing of bioavailability,
7) steady, pH-independent drug release (e.g. osmotic systems),
8) steady, retarded release (achievement of extended effect),
9) staged drug release (e.g. pulsatile systems),
10) easier ingestion,
11) enhancement of patient cooperation.

When biocompatible, peroral preparations are being designed, the starting point must be the specific relations, anatomical, physiological features and parameters of the digestive system.

The gastrointestinal tract is an approximately 8-9 meter long series of muscular organs, lined with mucous membrane. For the sake of perfect digestion the residence time, pH level and enzyme composition characteristic of various sections is diverse.

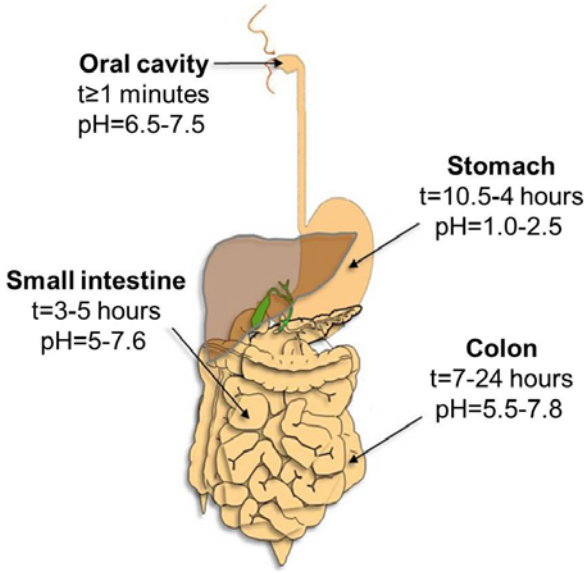
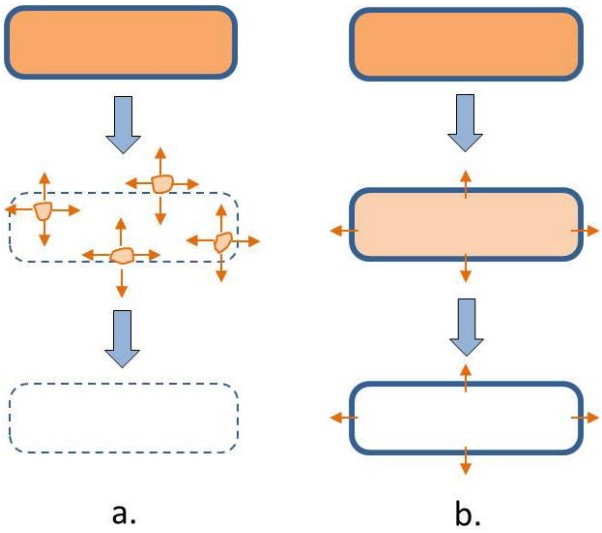


Fig. 26.2.
Residence times and pH levels in the digestive system

The fact, that the pH level of the highly acidic (pH=1-2,5) empty stomach gastric juice can increase to the range of 3-7, depending on the composition of food, has to be given due consideration. This changeable character of gastric pH level can have significant influence on drug release, stability and the absorption of active ingredients.



a. soluble coating; **b.** insoluble, permeable coating

Fig. 26.3.
The main mechanisms of drug release (coated preparations)

Beside the rate and location of absorption, the protection of the active ingredient and/or the intestinal tract as well as GI tract treatment opportunities can be controlled through the drug release parameters of preparations. Preparations containing aspirin, naproxen and diclofenac are often covered with enteric coatings to protect the gastric. Contact with acids disintegrates omeprazole, therefore it is delivered in enteric coated granulate capsules or tablets.

Drug treatment of the entire GI tract becomes feasible by employing preparations with insoluble coating that is permeable to the active ingredient. Targeted drug release is achievable for individual sections of the gastrointestinal system, making discrete drug therapies for the gastric and/or small intestine and further intestinal sections available.

For targeted colon treatment temporally controlled systems (retarded action) or systems covered with coatings insoluble in previous intestinal sections. Rectum is easy to treat locally.

Preparations with sulfasalazine are used for inflammatory intestinal ailments. Crohn's disease usually affects the end section of the small intestine and the first section of the colon, so using intestinoslovent coated preparations is beneficial to therapeutic effect.

From a production viewpoint coating is another technological step, coming with an increase in cost.

The pharmaceutical technological advantages of coating are:

1) masking of unpleasant tastes, smells or colors,
2) physical and chemical protection of medicine against external effects (light, moisture and air),
3) protection of the tablet core from external (e.g. mechanical) impact,
4) improvement of tablet appearance,
5) better identification of medicines,
6) making blister packaging easier.

In addition to drug therapy and biopharmacy aspects, jointly considering them all will decide whether coating a preparation is necessary or not.

Coating is achievable through the following methods:

1) wet coating
   1.1) dragée-making (in drum)
   1.2) film coating (in drum and by fluidization)
2) dry coating (by compacting)

26.1 Dragée-making

Dragée-making is a traditional coating method, which is essentially the application of various (e.g. subcoating, smoothing) layers of powders by means of a sugar syrup adhesive. This coating method enabled masking of the bitter taste of ibuprofen and quinine and the protection of active ingredients from light and moisture.

The thich coating layer of dragées provides good protection to the tablet core, but it can also impede decomposition, drug release and absorption, so this type of preparations cannot invariably fulfill the requirements of modern therapy.

Fig. 26.4.
Dragée

Dragée cores must have a rounded edge biconvex shape.

Initially, dragée-making was done by moulding, in sequentially repeated cycles of wetting dragée cores with sugar syrup, application of powder layer and subsequent drying. Sugar syrup serves both as moistener and adhesive layer needed for holding the powder coat.

Sugar syrup based coating procedures consist of five main phases:

1) Waterproofing and Sealing
   The first step is the creation of a waterproof sealing film, as a sort of base coating, on the dusted dragée cores, on which subsequent layers can be added without overmoistening or damaging the cores. Dragée cores are exposed to increased moistening effect in sugar syrup, therefore is is advisable to coat dragée cores with an organic solvent (e.g. alcoholic) solution of a polymer insoluble in water (earlier shellac, more recently polyvinyl-acetate-phtalate and acrylate polymers).

2) Subcoating
   The dragée cores previously coated with protective coating are evenly moistened with sugar syrup and sprinkle the cores, agitated in the drum, with subcoating powder, drying the new layer in the end. This workphase is repeated 3-5 times until core edges are sufficiently rouded. Sugar syrup suspensions are likewise applicable for subcoating, but in order to maintain dispersed particle size ($d<10$ μm) it is advisable to disperse and homogenize the subcoating suspension in a colloid mill before use.

3) Smoothing
   Smoothing makes the subcoated core surface even, concealing the irregularities of the underlying coating with smoothing syrup or thin suspension.

4) Coloring
   Dragées can be colored with dyes (pigments) soluble or insoluble in water (sugar syrup).

5) Polishing
   Dragées are polished with waxes (beeswax, carnauba wax, etc.) or their organic solvent solutions blended with cores. Wax solutions require subsequent drying.

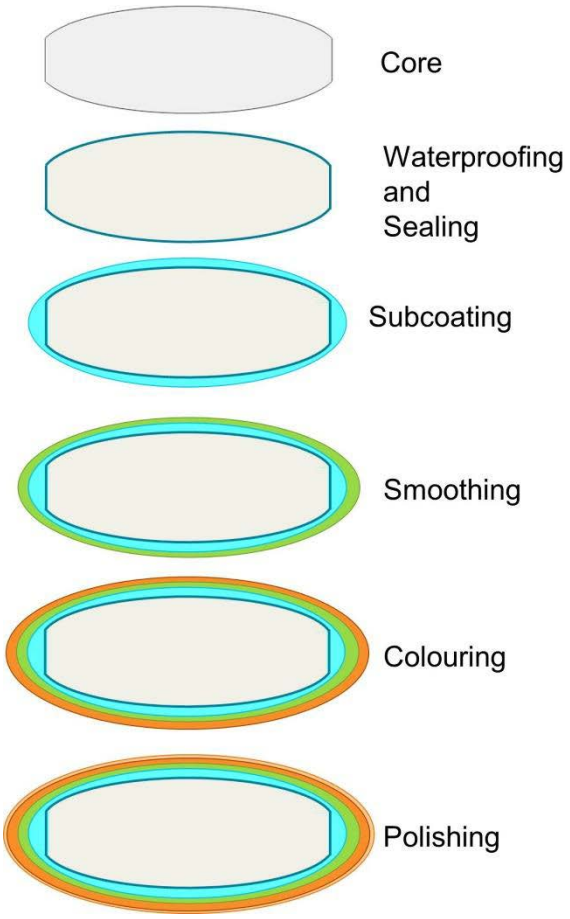


Fig. 26.5.
Layered structure of dragées

These procedures require room temperature or heating. The latter usually yields better looking, more uniform coatings and makes the rather slow operation quicker.

The preparation of consecutive layers, the crystallization of sugar and the establishment of interlayer bonds providing firmness to layers between coating cycles is time-consuming. on account of this drying of layers is often followed by extended agitation of dragée cores, a.k.a. “resting”. The fact that overdrying and excessive mechanical wear is damaging to coating layers must be observed. Therefore, performing this operation requires expertise and caution. The operation’s duration cannot be decreased beyond the optimum, so adding all the necessary coating layers may take as nlong as several days.

In case of old tilted axis coating drums the rotations speed had to be adjusted to provide appropriate blending of cores and uniform application of coating stock thereby. Too low rotation speeds fail to turn the dragée core bed over, resulting in fractional moistening of cores and due to the lack of mechanical impact moist cores tend to lump together. On the other hand, in case of too high drum rotation speeds centrifugal force hinders the free movement of cores, resulting in insufficient or missed core blending and irregular moistening.

In tilted axis drums the cores closest to the drum mantle move on an elliptical course, while the cores in the middle of the core bed move on a more circular course, the closer to the center of the bed the smaller the radius or the course.

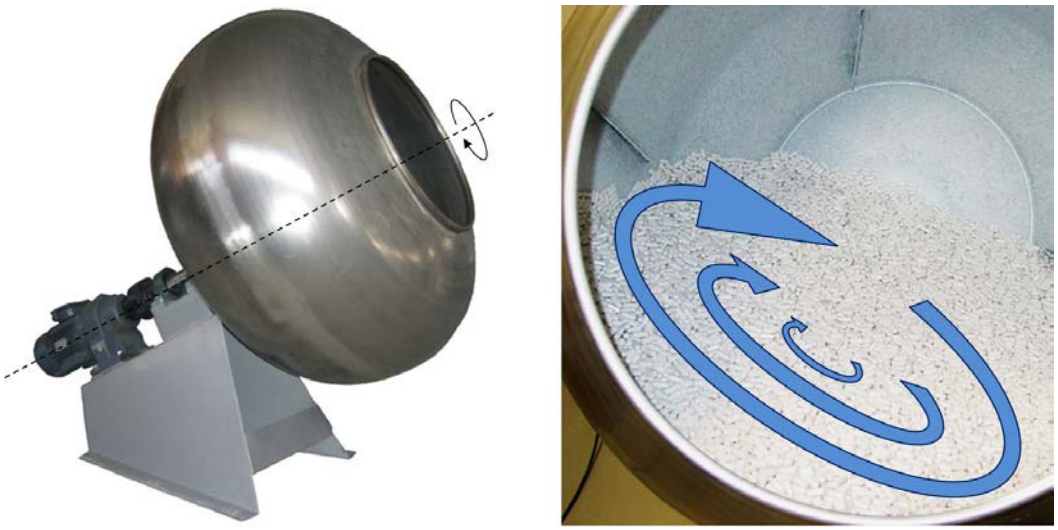


Fig. 26.6.
Movement of cores in a tilted axis drum

Installing baffle plates results in more thorough overturning of the core bed.

The distribution of blown-in drying air is not uniform in these devices, as it reaches only the surface of the core bed, with much slower drying below the surface and in contingent dead spots. The heat loss due to evaporation during drying with blown-in hot air can be compensated by keeping cores warm.

Fig. 26.7.
Tilted axis coating device with drying unit

26.2 Spray coating

As of the middle of the last century traditional moulding technologies have been gradually replaced by spray technologies. Their working principle is spraying the coating powder, previously suspended in sugary syrup, on the surface of agitated cores. To achieve most uniform coating, sufficient duration drying stages of blown-in hot air shall be inserted between applications of consequent layers. To achieve optimum operation parameters spraying periods must be long enough to allow applied suspension to spread evenly on the surface of cores without overmoistening. Excessive spraying periods may result in cores sticking together and previously applied layers of coating tearing away. Prevention of overmoistening and appropriate drying of coating layers are therefore just as important in this case. Frequent clogging of spray nozzles shall be expected when employing suspension spraying methods.

Careful study and optimization of operation parameters enable coating procedures to be improved, operation time decreased and automatization.

Fig. 26.8.
Computer-controlled sprayed dragée-making under industrial scale GMP conditions

26.3 Film coating

As of the 1970s the spreading of synthetic polymers created new potentials for developments in coating technologies. Synthesis and production of chemically stable film-forming polymers of appropriate mechanical properties suited for coating was one condition for this. For the sake of reproducible production developing new specialized equipment was necessary as well as the results of theoretical research on film coating. Implementation in practice brought the important steps of charting the influences of operation parameters, optimization of the parameters of coating processes and development of new film coating technologies.

Fig. 26.9.
Filmtablets

The introduction of thin (20-100 µm) coatings is significant for biopharmacy too, as they enable control over drug release, thereby expanding opportunities in drug therapy by making dosage safer and more reproducible. Nonstandard application (e.g. cutting, chewing) of such products is to be avoided, because doing so may result in drug release significantly different from intended.

The differences between earlier dragée-making techniques and film coating technologies are significant, especially in the substances, devices, equipment used, operation and end product quality parameters and applicability.

Table 26-I.
Quality parameters of dragées and film coated products

quality parameter	coating method	
	dragée making	film coating
odour masking	+	+
taste masking	+	+
protection (light, moisture, oxygen)	+	+
enhancing mechanical resistance (during packaging and transportation)	+	+
protecting active ingredient from the acidic effect of gastric juice	–	+
protecting the gastric mucous membrane from detrimental effects of the active ingredient (decreasing side effects)	+	+
control of drug release	–	+
shape	significant change (rounded)	minimum change
weight increase	significant (50-200%)	minimum (3-5%)
layer count	50-60	1
preparation time	24-36 hours	2-5 hours

As for equipment, the introduction of horizontal axis drums and the ongoing improvement of spray coating technologies tilted axis drums have been supplanted. Blending is more uniform in these drums, cores move on similar, nearly identical elliptical courses, their more thorough overturning aided by built-in baffle plates. Drum shape, baffle plates and drum rotation speed all work towards creating a uniform film coating.

Increasing the rotation speed of the drum enhances core blending. Drum rotation speed determines the uniformity of the coating, as it influences the residence time of cores in the spraying zone. Excessively high rotation speed increases the attrition of tablets and contributes to spalling.

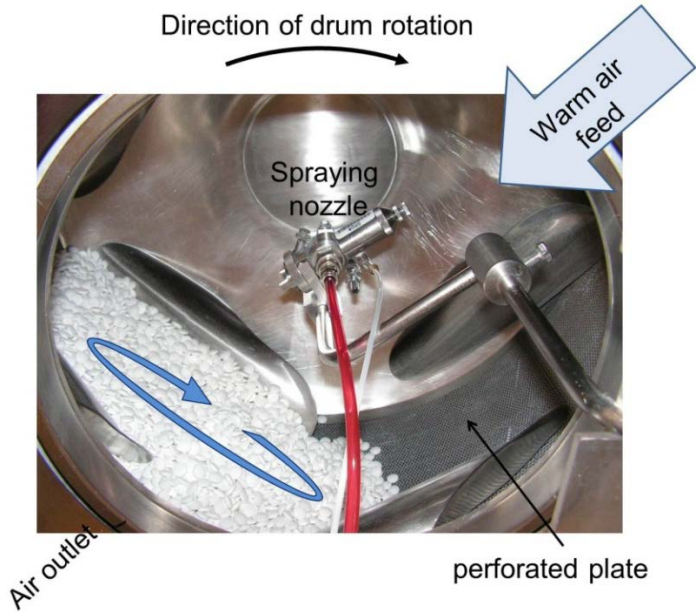


Fig. 26.10.
Coating in horizontal axis drum

Drying air can be fed in the drum from various directions. The efficacy, speed and uniformity of drying are greatly supported by the perforations of the coating drum's mantle. This way blown-in drying air can pass through the core bed, making drying more uniform, with air leaving through the perforated mantle of the drum, carrying along moisture vapor.

The temperature of blown-in air influences the uniformity of the coating. High temperature with high air flow rate may accelerate drying and film formation in excess, damaging coating quality. Too low input temperature, on the other hand, needlessly increases operation time, which increases particle attrition.

Low flow rate of atomized coating solution influences the coalescence of polymer molecules in the film, possibly resulting in rigid, fragile coating. Too high flow rate causes overmoistening, resulting in sticking. High atomization flow rate and too low tablet temperature combined delay film formation and subsequent rapid drying makes the film formed cracked.

Coating liquid is forwarded to the spraying head by a pump and it is vaporized with the help of compressed air. The flow rate of the coating liquid and spraying pressure determine spray fineness, which, along with spraying direction and bevel-angle, plays an important role in creating the film.

Increasing spraying air pressure generally decreases the roughness and variances of coated tablet surfaces, facilitating the formation of more densely structured, thinner films.

Excessive spraying pressure creates superfine spray, which, due to the increased evaporation surface, may dry prematurely, before reaching the surface of tablets. Too low spraying pressure, on the other hand, causes unwanted increase in the variances of film thickness. Large droplets cause local overmoistening and sticking.

Increasing the number of spraying heads enhances the uniformity of coating solution application.

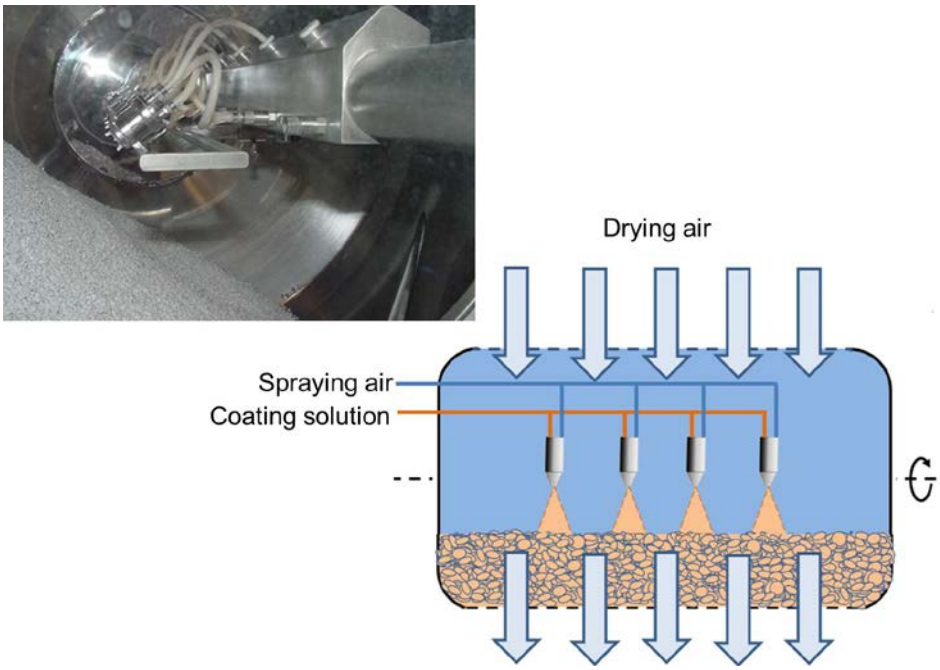


Fig. 26.11.
Modern horizontal axis coating drum with multiple spraying heads

The good quality of input drying air is an important prequisite of modern coating devices: it has to be free from dust, oily particles and other impurities. Air purification can be done by applying filtering systems of coarse and fine filters (e.g. HEPA filters). Decreasing moisture content can be accomplished by cooling (condensation) and/or adsorbents. Afterwards air is heated to the required temperature.

Operation time can be significantly decreased by fulfilling the above technical conditions, making production safer and product quality parameters more reproducible in production.

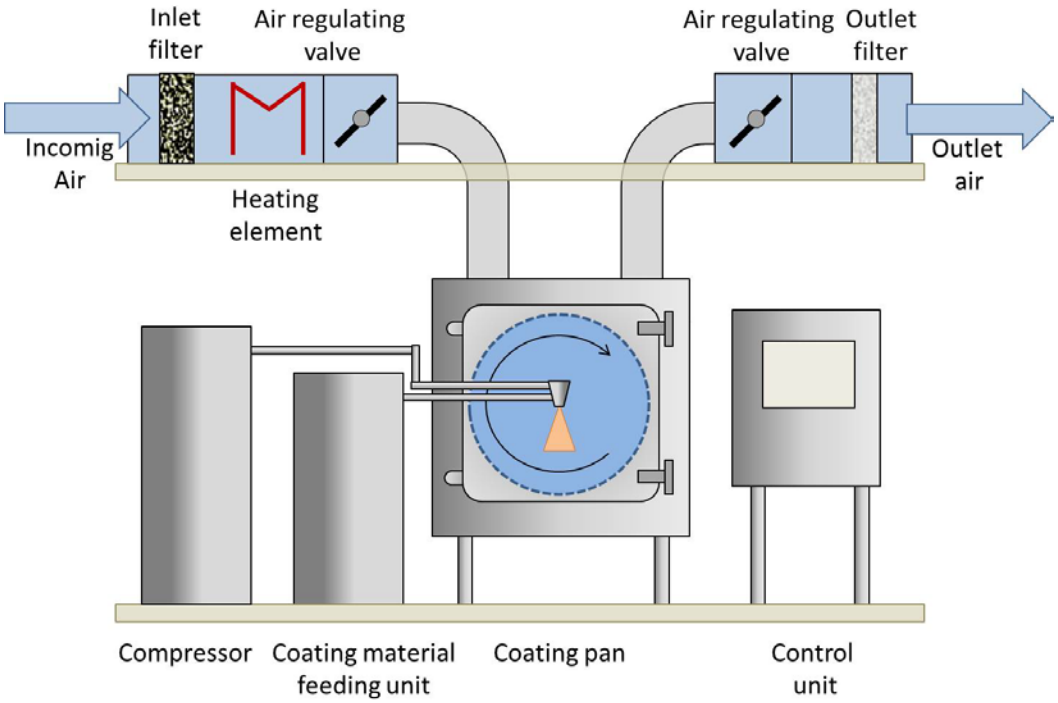


Fig. 26.12.
Main units of automatic horizontal axis coating machine

26.3.1 Excipients of film coating

Polymers applied as *protective coating* against environmental damage usually dissolve rapidly after ingestion. Polymer thickness shall be adjusted to provide adequate protection and dissolve in the body as rapidly as possible. Thicker films protect better, at the price of possible bioavailability loss. Such water soluble polymers are hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), polyvinyl acetate (PVA) and polyvinylpyrrolidone (PVP). Water soluble polymers are used for coating in water solution.

There are numerous synthetic polymers available for achieving *controlled drug release*.

Eudragit® E, a cationic methacrylic acid copolymer is gastrosolvent, insoluble in saliva but rapidly solving in gastric juice.

From a biopharmaceutical aspect there are multiple reasons for the application of *gastro-resistent* coatings:

1) protecting acid-sensitive substances from gastric juice. (e.g. enzymes and certain antibiotics),
2) prevention of nausea, gastic irritation and other destructive effects,
3) triggering drug release locally, at the designated spot (e.g. intestinal dis-infectants),
4) liberation of active ingredient at the location of absorption,
5) retarding drug release.

At low pH levels gastro-resistant, but enteric coatings are unionized, according to their the function groups (e.g. –COOH). In the gastrointestinal tract, as pH increases acidic function groups become ionized, the polymer swells and becomes soluble. This is how coated products can pass through the gastric without dissolution and drug release, releasing their active ingredients only after reaching the intestine.

These polymers react to changes in pH level just like any other substance undergoing ionization.

According to the *Henderson-Hasselbach* equation the concentration ratio of ionized (C_i) and unionized (C_{ni}) molecules depends on pH level and the value of PK_a.

$$\frac{C_i}{C_{ni}} = pH - pK_a \qquad (1.)$$

The application of insoluble diffusible films Eudragit® RL and RS enables pH-independently controllable drug release.

Prior to synthetic polymers, shellac was used for making *enteric* coatings. More recent coating materials have been designed to dissolve rapidly in the intestine, but not in the gastric The most effective way of creating this feature in synthetic polymers is adding carboxyl groups. The first such polymer was cellulose acetate phthalate (CAP), but it was unstable. More stable polyvinyl acetate phthalate (PVAP) and hydroxypropyl methyl cellulose phthalate (HPMCP) have been introduced later.

Currently the anionic methacrylate copolimers Eudragit® L and S are most used for this purpose. Based on solubility controlled by pH and chemical structure, the water based dispersions of Eudragit® L30 D-55 and Eudragit® L100-55 can be used for drug release in the duodenum. Eudragit L100® dissolves in the jejunum and Eudragit® S 100 in the ileum.

The polymers are permiscible, allowing even more precise control over drug release.

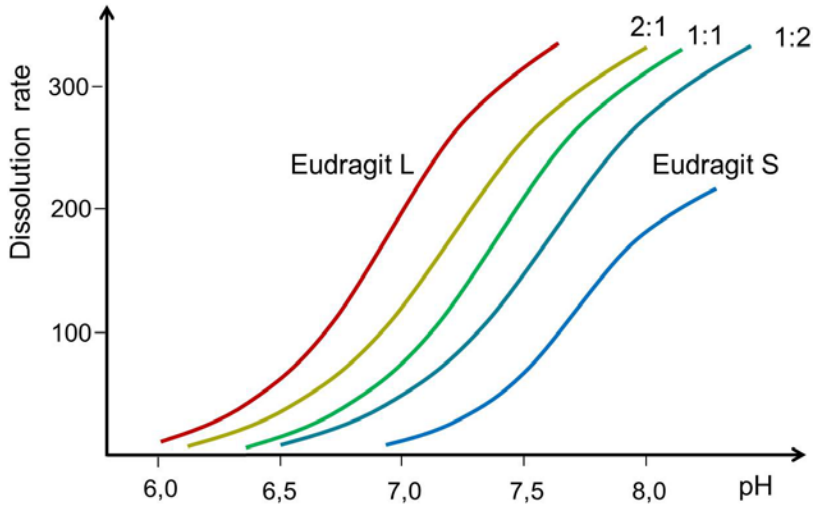


Fig. 26.13.
Dissolution behavior of enteric films

Eudragit® RL is insoluble, permeable and provides pH-independent dissolution. It can be used for creating *prolonged drug-release* just like its similar but less permeable counterpart, Eudragit® RS.

26.3.1.1 Chemical structure of frequently used film polymers

1) Cellulose derivatives

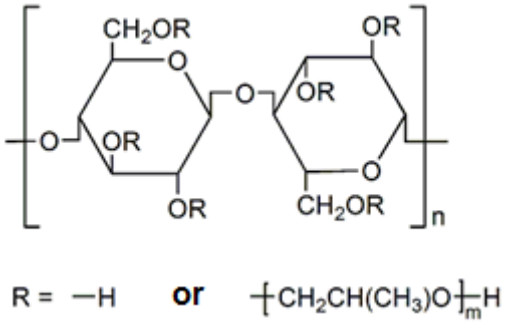


Fig. 26.14.
Hydroxyethyl cellulose

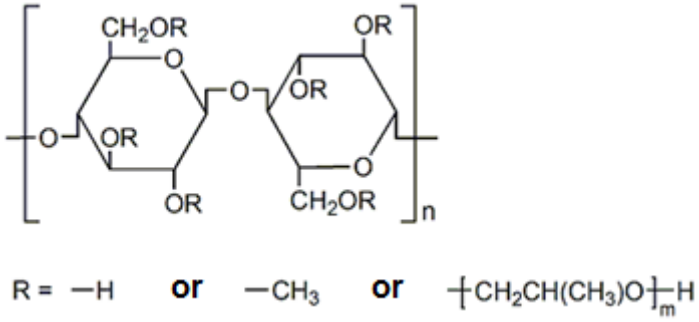


Fig. 26.15.
Hydroxypropyl cellulose

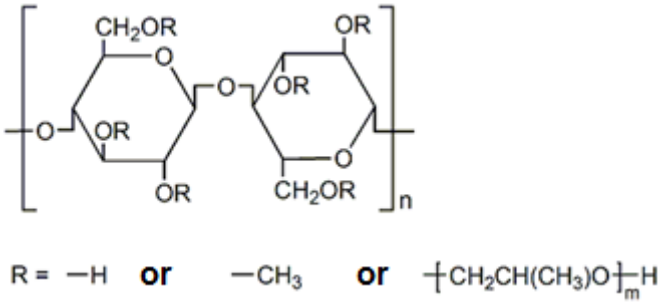


Fig. 26.16.
Hydroxypropyl methylcellulose

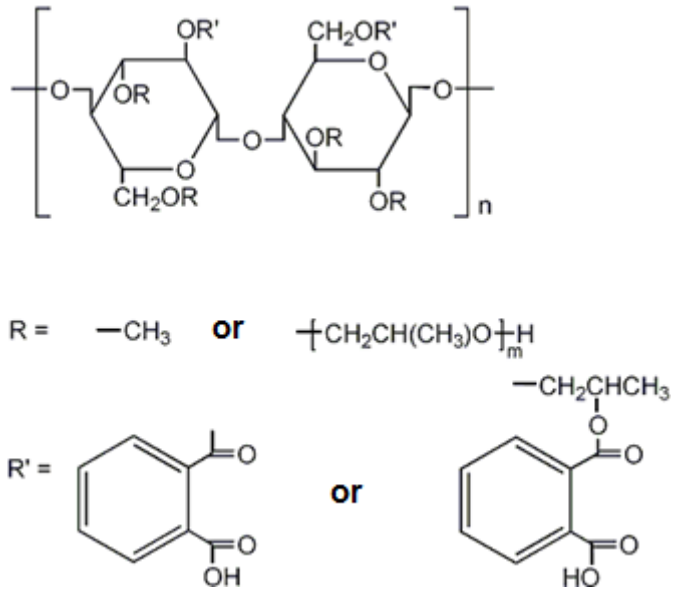


Fig. 26.17.
Hydroxypropyl methylcellulose phthalate

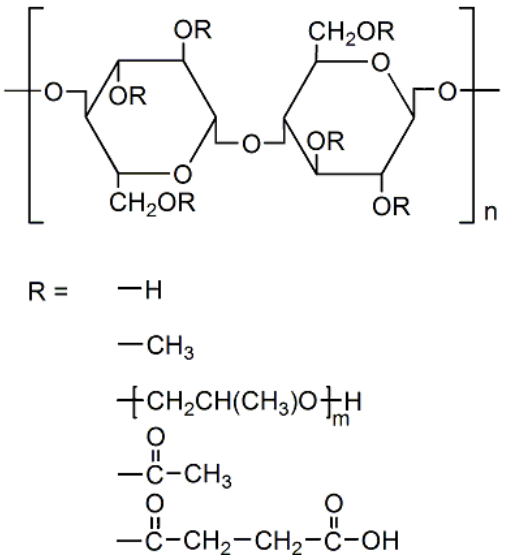


Fig. 26.18.
Hydroxypropyl methylcellulose acetate succinate

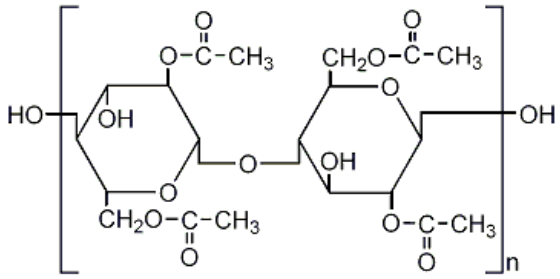


Fig. 26.19.
Cellulose acetate

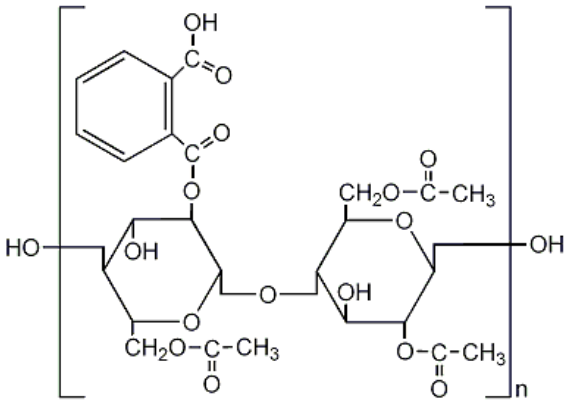


Fig. 26.20.
Cellulose acetate phthalate

2) Acrylate copolymers

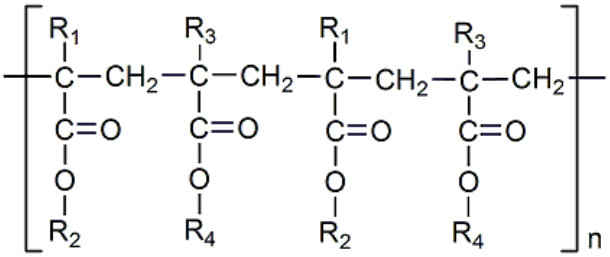


Fig. 26.21.
Generic structure of acrylate copolymers

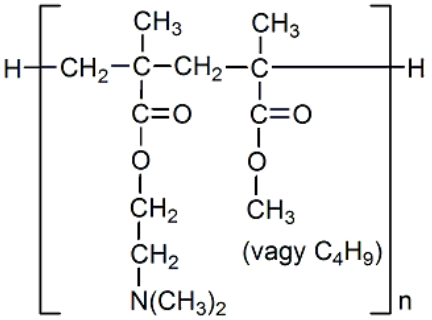


Fig. 26.22.
Eudragit E

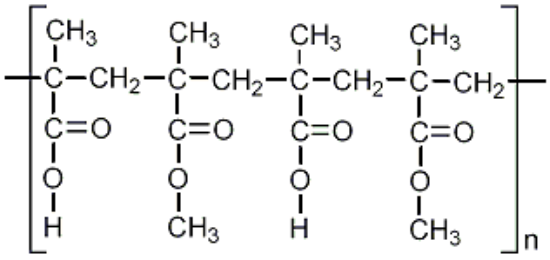


Fig. 26.23.
Eudragit LS/FS (methacrylic acid methylmethacrylate copolymer)

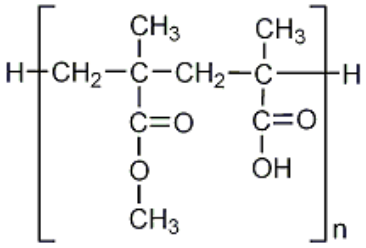


Fig. 26.24.
Eudragit S

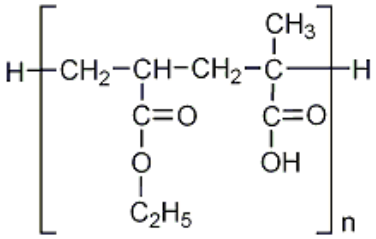


Fig. 26.25.
Eudragit L-55. Kollicoat MAE (methacrylic acid ethylacrylate copolymer)

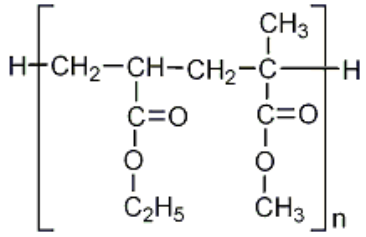


Fig. 26.26.
Eudragit NE, Kollicoat EMM (ethylacrylate methyilmethacrylate copolymer)

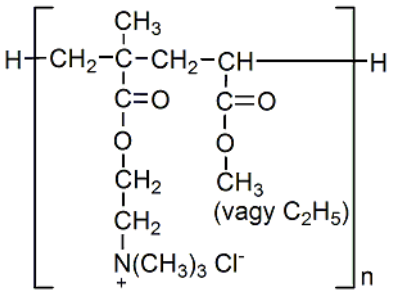


Fig. 26.27.
Eudragit RL/RS (ethyl acrylate : methyl methacrylate: trimethylammonium ethylmethacrylate chloride = 1:2:0,1)

3) Vinyl polymers/copolymers

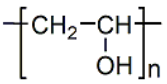


Fig. 26.28.
Polyvinyl alcohol

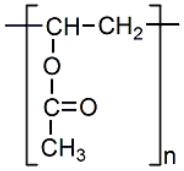


Fig. 26.29.
Polyvinyl acetate

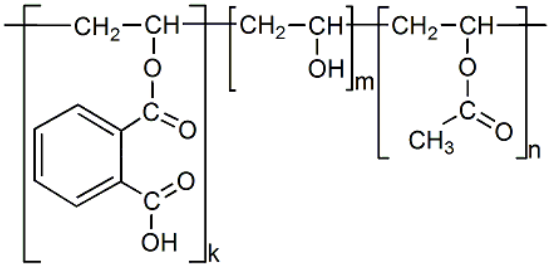


Fig. 26.30.
Polyvinyl acetate phthalate

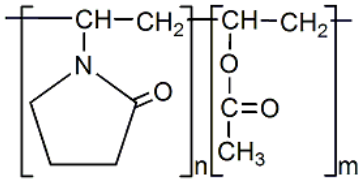


Fig. 26.31.
Vinylpyrrolidone-vinyl acetate copolymer (Copovidon, Kollidon VA 64, Plasdon S630)

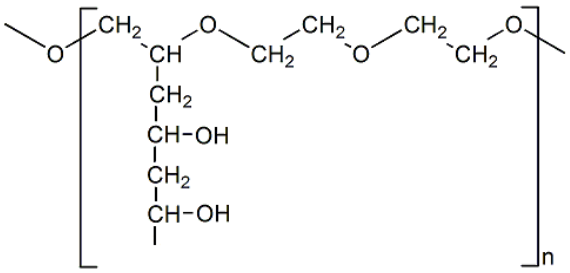


Fig. 26.32.
Polyvinyl alcohol-polyethylene glycol graft copolymer (Kolicoat IR)

Table 26-II.
Essential attributes of Eudragit varieties

Fuction	Polimer	Avalibilty	Dissolution properties
Moisture Protection and Odor/ Taste Masking	Eudragit® E 100	Granules	Soluble in gastric fluid up to pH 5.5
	Eudragit® E 12,5	Organic Solution 12.5%	Swellable and permeable above pH 5.0
	Eudragit® E PO	Powder	
Gastro-resistance and GI Targeting	Eudragit® L100-55	Powder	Dissolution above pH 5.5
	Eudragit® L 30 D-55	30% Aqueous Dispersion	
	Eudragit® L100	Powder	Dissolution above pH 6.0
	Eudragit® L 12,5	12.5% Organic Solution	
	Eudragit® S 100	Powder	Dissolution above pH 7.0
	Eudragit® S 12.5	12.5% Organic Solution	
	Eudragit® FS 30 D	30% Aqueous Dispersion	
Sustained realease	Eudragit® RL 100	Granules	Insoluble High permeability pH-independent swelling
	Eudragit® RL PO	Powder	
	Eudragit® RL 12.5	12.5% Organic Solution	
	Eudragit® RL 30 D	30% Aqueous Dispersion	
	Eudragit® RS 100 D	30% Aqueous Dispersion	Insoluble Low permeability pH-independent swelling
	Eudragit® RS PO	12.5% Organic Solution	
	Eudragit® RS 12.5	12.5% Organic Solution	
	Eudragit® RS 30 D	30% Aqueous Dispersion	
	Eudragit® NE 30 D	30% Aqueous Dispersion	Insoluble, low permeability, pH-independent swelling No plasticizer required Highly flexible
	Eudragit® NE 40 D	40% Aqueous Dispersion	
	Eudragit® NM 30 D	30% Aqueous Dispersion	

26.3.1.2 Plasticizers

Plasticizers are used in coating for improving the mechanical attributes, mainly the elasticity of polymer films or for influencing the drug release mechanism. Without plasticizers only rigid, brittle films could be made. Plasticizers are generally nonvolatile substances of high boiling point.

In water based dispersions they facilitate film formation.

Frequently used plasticisers:

1) glycerin and its esters (e.g. monoglycerides, triacetine),
2) phthalic acid esters (e.g. diethyl-, dibutylester),
3) citric acid ethers/esters (e.g. triethyl-, tributylether, acetyl triethyl-, acetyl-tributylether),
4) dibutyl-sebacate,
5) propylene glycol, polyethylene glycol.

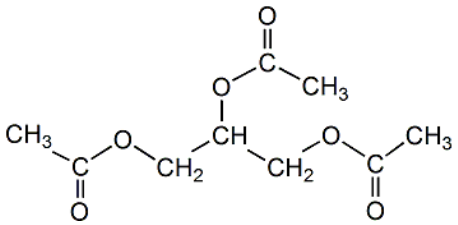


Fig. 26.33.
Triacetine, glycerin triacetate

26.3.1.3 Solvents

Being able to solve most of synthetic polymers is a definite advantage of organic solvents. They are no more (or only rarely) used in coating due to environmental protection reasons. Water soluble polymers or water based dispersions of polymers insoluble in water can be used instead, containing all the necessary auxiliary components (e.g. plasticizers, antifading antifoaming agents)

1) alcohols,
2) ketones,
3) esters
4) chlorinated carbohydrates,
5) water.

26.3.1.4 Colorants

To add color and decrease the light transmission factor of coatings *pigments* are used, primarily titanium dioxide. Talcum, previously in extensive use, is to be avoided now, due to its adverse health effects. Of dyes the use of water soluble so called food colorings is also restricted.

In case of organic solvent film formation the rapid evaporation of solvent from the surface of sprayed droplets starts instantly. On the surface to be coated droplets coalesce and evaporation gradually increases the viscosity of the coating solution. The solution has to be adhesive enough to adhere to the tablet surface. Further drying brings dissolved molecules closer to each other, with emerging cohesive forces making molecules coalesce, resulting in film formation and uniform film texture.

Water based polymer dispersions are made by emulsion polymerization or from water based emulsions of polymer solutions by evaporating the solvent. Film formation is based on the coalescence of particles. With the dispersion medium evaporating, dispersed polymer particles of 10-1000 nm gradually draw closer to each other, their free movement becoming restricted until they meet. They deform and combine in diffusion mass transfer, forming a continuous film.

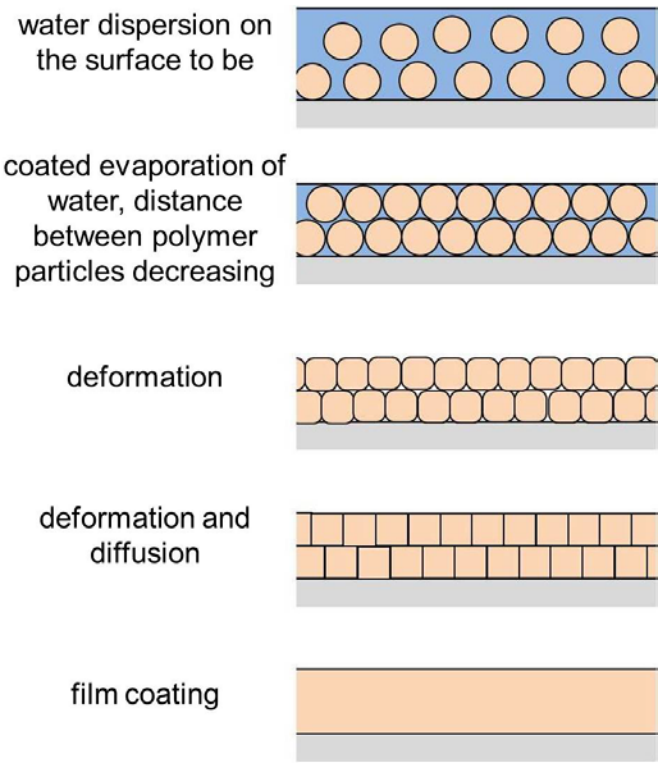


Fig. 26.34.
Film formation from water based dispersion

Making continuous and uniform quality film requires *minimum film forming temperature (MFFT)*. To achieve it, the temperature of cores has to be kept above *MFFT*, at around 35-45C^{o}. The MFFT is determined by experiment, its value is characteristic of the actual polymer.

According to the first law of thermodynamics, the thermal energy of input air (Q_{input}) is spent for warming the core bed ($Q_{core\ bed}$), the machine ($Q_{machine}$) and the coating substance ($Q_{coating\ material}$) as well as for offsetting heat loss (Q_{loss}) and warm output air (Q_{output}):

$$Q_{input} = Q_{core\,bed} + Q_{machine} + Q_{coatingmaterial} + Q_{loss} + Q_{output} \qquad (2.)$$

Coating procedures are easy to control and automatize by:

1) optimizing parameters (according to the cycles of application, drying and resting time),
2) tracking the moisture content and/or temperature of dragées and
3) monitoring the moisture content of air in the drum.

Fig. 26.35.
Coating apparatus for large scale production

The demand for decreasing production time and coating costs further made the development of fresh technologies necessary.

26.3.2 Fluidized bed coating

Dale Wurster has been first to employ fluidized bed technology for coating tablets in 1960.

The coating sprayed on cores fluidized by blown-in air dries quickly due to steady airflow, large surfaces and good heat- and mass transfer and cores become ready for the application of the next layer of coating. The liquid particles of the coating solution form a continuous film on the surfaces of solid particles. Fluidizing air thus serves a double purpose: it keeps particles afloat while drying them.

Coating substances are usually sprayed from the top or bottom, sometimes from a lateral direction.

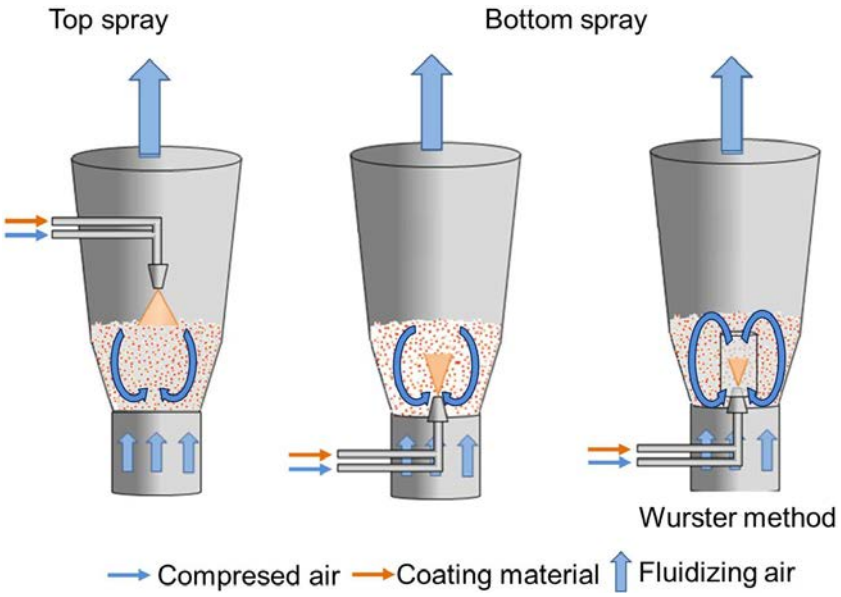


Fig. 26.36.
Working principles of various fluidized bed coating devices

The most important aspects to attend to in fluidized bed coating are making sure that coating particles be liquid state when contacting the surface of tablets or particles to be coated and providing sufficient time for moistened particles to dry before being recycled to the spray cone (see chapter *Granulation*).

The uniformity of coatings made with fluidization can be significantly enhanced by using a *Wurster adapter*. This is essentially a vertical pipe installed in the axis of spraying a small distance above the base plate that forces the flow of particles into a controlled recurring inescapable path. The particles entering at the bottom of the pipe are moved upwards by fluidizing air, being moistened with the coating liquid. They proceed to leave the pipe, then, as the buoyant force diminishes their weight makes them sink back to the bottom of the fluidizing chamber, drying in the process. The cycle is repeated as they ascend the pipe once again and another layer of coating is applied.

Besides tablets, fluidized bed coating devices are also used for coating powders, granulates and pellets in pharmaceutical industrial practice.

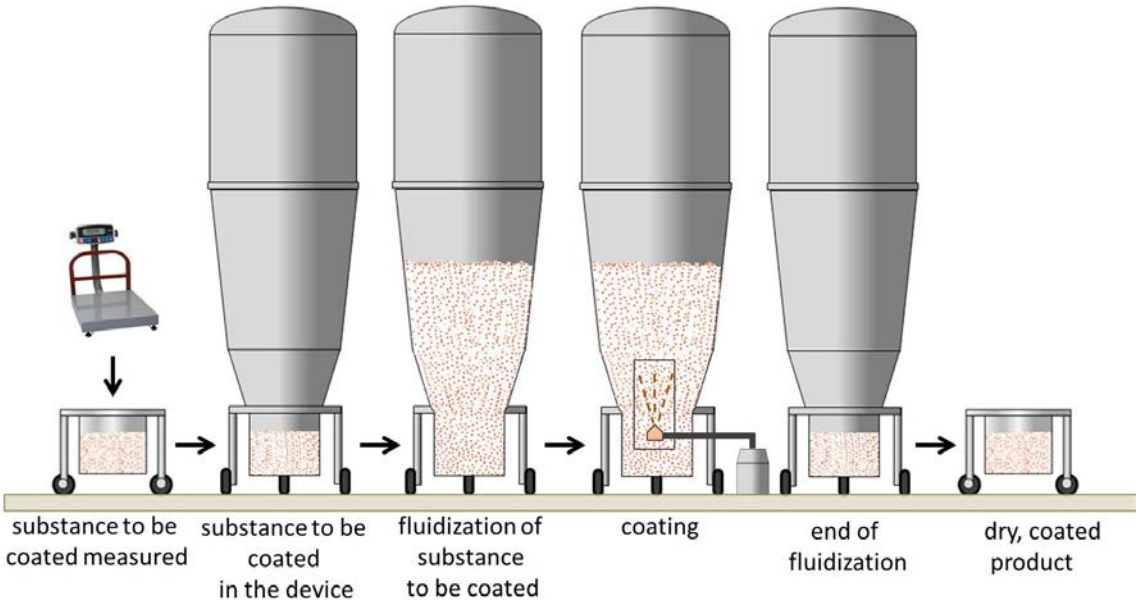


Fig. 26.37.
Main stages of fluidized bed coating in industrial production

26.3.3 Film coating flaws

If the core is not firm, its edges are too sharp or the cores are exposed to high mechanical stress (e.g. too high grum rotation speed) edges may chip and spalled fragments stuck in the coating form rough surfaces.

If the dye pigments lack sufficient opacity the product becomes spotted.

If adhesion is too low coating peels off the core.

Overmoistened, insufficiently dried cores lump together and/or rip coating layers off.

26.4 Dry coating

The compression coating method allows making coatings dry. Jacketed tablets (see in chapter *Tabletting*) are made by compressing the coating onto the tablet core.

The rotary devices developed for this purpose have the following working sequence: first the mould is filled with the coating substance, then the core is added, followed by the addition of the remaining coating. Compression makes the coating substance enfold the core.

The method has the disadvantage of requiring expensive equipment. However, it is an indisputable advantage that it eliminates the production problems characteristic of wet methods (e.g. atomization, drying, sticking).

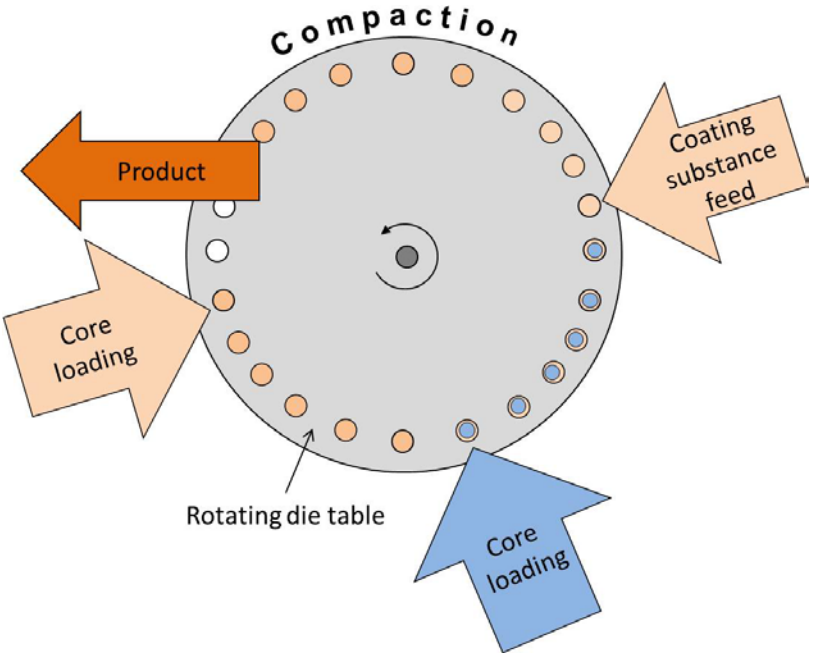


Fig. 26.38.
Compression coating with rotary tableting machine

Compression coating technology enables

1) coating of moisture-sensitive substances
2) dosing mutually incompatible pharmacons in the same product by putting one in the core, the other in the coating (e.g. the combination of vitamins B1-, B12- and C)
3) separately controlled release rates for initial and sustaining doses,
4) production of repeated effect (pulsating) multiphase products.

26.5 Packaging

Both uncoated and coated tablets require individual packaging for mechanical protection.

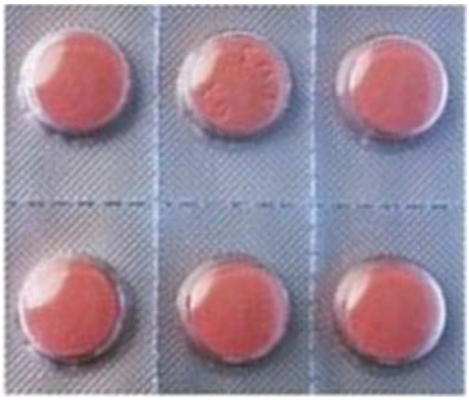


Fig. 26.39.
Coated tablets in blister packaging

Questions

1) How would you define the notion of coating?
2) For what purposes is coating used?
3) What are the biopharmaceutical benefits of using coatings?
4) What are the pharmaceutical technological benefits of using coatings?
5) What coating methods are there?
6) What are the main steps of dragee making?
7) What are the differences between tilted- and horizontal axis drums?
8) What are the differences between the technical parameters of dragees and film coated preparations?
9) What protective coating polymers do you know of?
10) What intestinosolvent coating substances do you know of?
11) What are the biopharmaceutical indicators for using gastric-resistant coatings?
12) What acrylate copolymers do you know of?
13) What type of vinyl polymers/copolymers can be used for film coating?
14) What cellulose derivatives do you know of that are suitable for film coating?
15) What are the main steps of the film formation process?
16) What are the parameters that allow control and automatization of coating procedures?
17) What is the Wurster adapter and what are the benefits of using it?
18) What are the most common film coating flaws?
19) How is dry coating feasible?

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27 Multiparticulate dosage forms

By improvement of medical therapy, macro drug delivery systems (e.g. tablets, drages) regarded to be conventional, can not completely be meet with the increasing requirements against preparations.

Conventional macro drug delivery systems are monolithic systems in which containing the whole amount of active substance(s) in one unit.

Multiparticulate preparations differ from macro systems in their size, structure, manufacture technology and mode of drug delivery as well. These contain the required amount of active substance in more individually controlled drug delivery units.

Multiparticulate, micro-pharmaceutical preparations in micrometer scale, are generally administered per oral. Their particles following administration, depending on control are dispersed in GI tract before releasing active substance(s), and then dissolution takes place with the same speed, in same place or with different speed in different location, and time.

Nano-pharmaceutical preparations in nano scale, are especially able to form such a drug delivery systems, with which many challange can be solved, such as increasing of bioavailability, artificial red blood cells, manufacture of nanorobots, reducing side effects, achivement of active and passive targeting)

27.1 Multiparticulate micro-pharmaceutical preparations

This group includes:

1) minitablets,
2) micro pellets and
3) microcapsules.

Biopharamceutical advantage of multiparticulate micro-pharmaceutical preparations:

1) after administration, homogeneous distribution in GI tract,
2) local irritation can be reduced,
3) controlled drug delivery can be achieved,
4) certain parts or entiry Gi tract can be treated medically,
5) bioavailability can be improved,
6) multiparticulate preparations have better reproducable properities, than conventional, monolithic preparations,
7) inter- and intrapersonal differences can be decreased,
8) safety of dosage can be increased, for example risks from failure of coating of macro preparations or different dissolution from design (slower, not complete or too fast release) can be reduced in multiparticluar systems,
9) granules of active substances can be coated differently inside one preparation, therefore dissolution profil can be provided according to therapeutical demand.

Due to their wide range dissolution profile, multiparticulate preparations are capable for sustained, modified, pulsative drug delivery. Based on these multiparticluar dosage forms larger and larger role can they get in pharmaceuicals. If diameter of these

drug delivery units is less than 2mm, then rapidly and continously leave stomach and transfer to further sections of GI tract.

In pharmaceutical technological aspect, further advantage is the aesthetic appearance, good flowability, furthermore the possibility of administraction of incompatible substances simultaneously.

27.1.1 Minitablets

Minitablets having appropriate size can be produced by compressing machine with die having 2-3 mm long diameter and with these tablets as a multiparticulate product, spansule form can be formed.

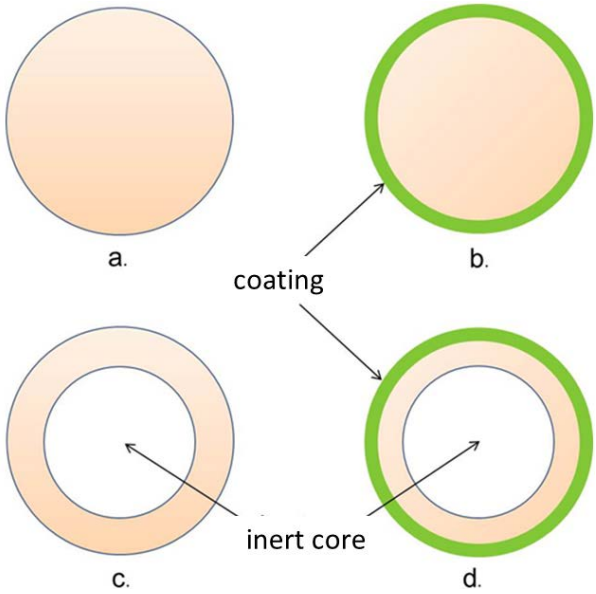
Fig. 27.1.
Minitablets in spansule form

27.1.2 Micropellets

Pharmaceutcial micropellets are spheric solid particles having 0,5-2 mm diameter. Structure of micropellets can be different.

One type of micropellets, namely spherical granules are consisted of active substance and excipients inside in homogeneous dispersion creating a unified matrix. Other structure is characterized by the fact that active substance is layered on the surface of inert core of pellet. Latter pellet type is neglected due to the limitation of caoting amount of material.

Based on biopharmaceutical or therapeutic demand, pellets can be provided with coating controlling dissolution or having protective layer



a. micropellet without coating; **b.** micropellet with coating; **c.** micropellet with inert core, without coating; **d.** micropellet with inert core, with coating

Fig. 27.2.
Different types of micropellets

In 1949 one researcher of *Smith Kline & French* has developed a brand new pelleting technology in order to achieve sustained drug delivery. This was carried out by application of layering onto a sugar core.

In 1964, spray freeting technology has been patented for production of pellets. In the asame year, spheronization pelleting technology was developed in Japan, with which amount of active ingredients in pellets can be singificantly increased even by 90%

First manufacture of micropellets in industry took place in 1970s.

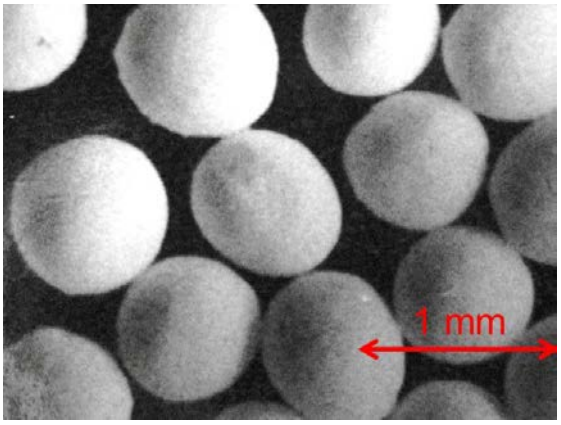


Fig. 27.3.
Micropellets

For introducing pelletization, special theoretical knowledge was required, which discovered mechanism of pellets creating/forming, and determinded the optimal operation and process parameters during manufacture.

27.1.2.1 Production of pellets

Manufacture, laboratory preparation and industrial production of micropellets can be carried out with several methods, with which parameters of preparation can be reproducable.

Practice shows that micropelleting technology with layering onto carrier sphere is less singificant in pharmaceutical aspect, because it is slow and expensive.

Similarly to creation of granules, forming of pellets can be performed by three different ways:

1) pelleting with solvent,
2) pelleting with binding material,
3) sinter pelleting.

Mechanism of pellet formation

Theory of revealing the machanism of micropellet formation is necessary for understanding pharmaceutical technological processe, but for controlling, optimalization, and end point detection of manufacture process.

Process of pellet formation in the aspect of creation of internal converging binding and growing of particles, takes place similarly as in the case of granulation at the beginning. (vide Granulation chapter).

Contrary to granulation processes, at pelletization, balance of aggregation and disaggregation process hav to be achieved that increase in particle size should be higher than its decrease due to friction, collisions at manufacture. On the other hand, mechanical forces and moistening forces have to be prevailed, which result in smoother surface and spherical shape. These aims can be reached by appropriate choice of pellet components (principally concentration f binding material and amount of solution) and optimalisation of manufacture technological parameters.

Prerequisite of occurrence of aggregation is the fact that the surface of particles has to be wet enought, which provides appropriate adherence and binding force for other particle. If it is too little, then consequently due to inverse effect, erosion will take place.

Desaggregation manifests in abrasion, breakage of bruise, drop, dust generation of the particles. During their motion, primarily protruding parts binding with less energy, therefore their sizes gradually approximate the spheric shape.

Surface smoothness is determined by particle size and particle size dispersion of dropout particles. Due to this, process have to be initiated so that protruding parts principally do not touch each other, but flatten larger particles by layering on them.

Aggregation and following abrasion occurs during intense movement of material. Particles move, rotate, touch each other in forced path, while scrub each other. Quantity of filling, mixing speed, moisture and binding material content of the material have determining importance in parameters of creating micropellet particles.

Aggregation and accompanying frictional processes occur during intense movement of the material. At this time particles are moving and spinning around a definite track, they collide to each other, thus abrading themselves. Amount of filling, speed of mixing, material moisture and amount of binding agent is essential in the parameters of the forming micropellet particles.

Multiparticulate systems are termed and handled as stochastic systems in which the coincidence has determinative role in the formation of discrete particles. Regularities during the preparation of particles are carreied out by coincidental changes of separate particles.

During the production of micropellets such mixing conditions should be ensured that the particles could move in the same environmental conditions in order to reach the same effect acting on a particle at the same time, the same way, the same strength and the same probability. Thus similarity of the particles can be achieved in their main quialitative properties (e.g. shape, smoothness, particle size, particle size distribution, density, porosity, hardness, fribility, surface properties, drug release). On the contrary, difference in the parameters of production decreases the reproducibility, which cannot be allowed neither from the viewpoint of pharmaceutical technology nor the biopharmacy.

Pelletizing with solvent

During pelletizing with solvent the applied liquid partially dissolves one or more components from the powder mixture. During liquid addition due to surface dissolution a concentrated solution forms ont he surface of the particles, which enables them to attach to other particles. This process is accompanied by particle size growth. After evaporation of the solvent, the dissolved substance forms crystals and bridges, creating the core for micropellets.

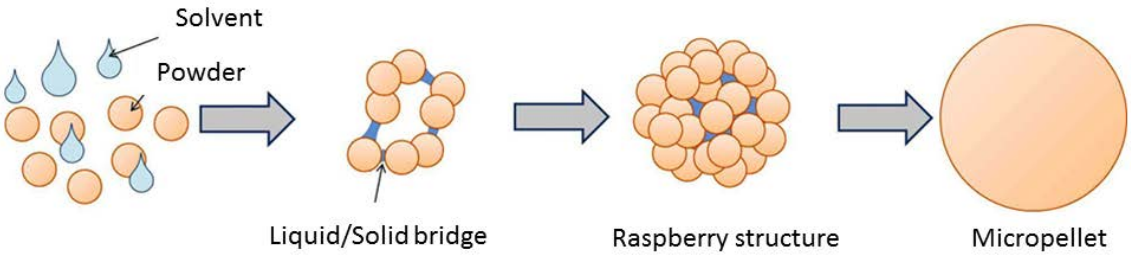


Fig. 27.4.
Mechanism of pelletizing with solvent

Pelletizing with binder agent

During pelletizing using binder agent high molecular weight polymers are used. Powder mixture is first wetted with the solution of the binder material in the proper concentration, then kneading is applied.

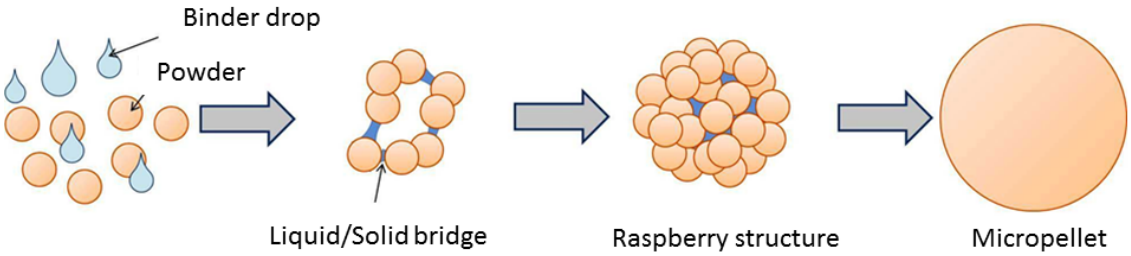


Fig. 27.5.
Mechanism of pelletizing with binder agent

Smooth surface of micropellets depends on the particle size of initial substances, the concentration of wetting agents, its the viscosity and amount.

Sinter pelletizing

During sinter pelletizing one component of the powder mixture has low melting point (e.g. high molecular weight macrogol). Heating the mixture partial melting occurs. Spraying and freezing the melt mass near spherical pellets are formed.

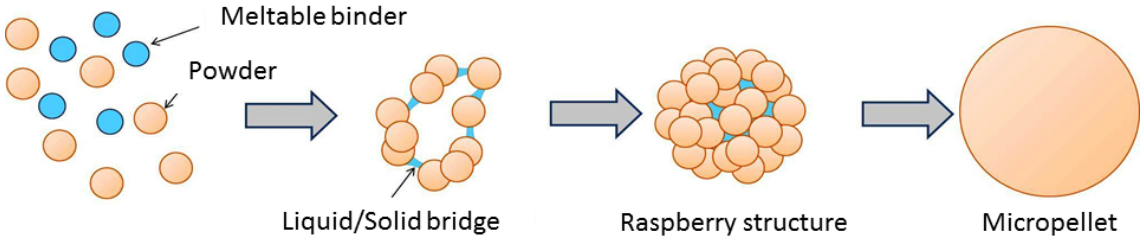


Fig. 27.6.
Mechanism of pelletizing with sintering

Coating of micropellets may be necessary in order to protect the API or achieve a controlled drug release (see chapter *Coating*).

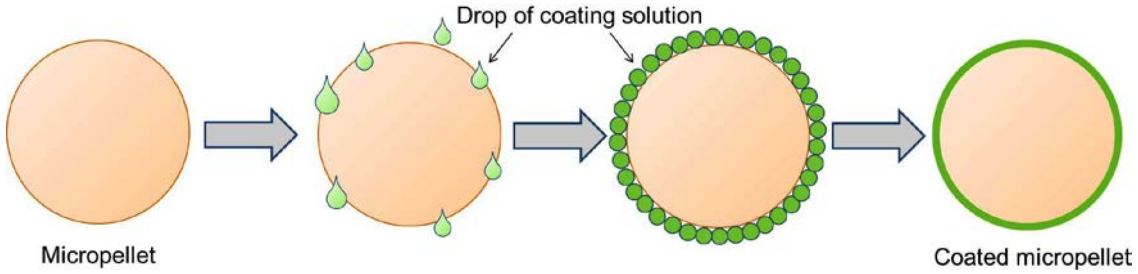


Fig. 27.7.
Mechanism of pellet coating

Several production process are available to carry out operations mentioned above.

Pelletizing processes

For the preparation of micropellets in pharmaceutical technology the following processes can be used:

1) rotating plate
2) extrusion-spheronisation
3) roto-fluid
4) spray-freeze-drying
5) high shear pelletizing
6) hot melt dispersion
7) drop pelletizing

Rotating pelletizer plate process

During operations of rotating plate granulating liquid is added to the powder rotating on a plate. Forming particles are rolling to the border of the plate, which results the spherical shape. End product is simply depleted by turning the plate. This method can be used both in case of pelletizing granules or extrudates.

Fig. 27.8.
Rotating micropelletizing equipment

Extrusion-spheronization process

During this widespread pelletizing process kneading of powder components and granulating liquid addition is executed. The produced wet mass is extruded through a perforated plate with 0.5-2.0 mm holes. The thikckness of the extrudate depends on the diameter of the holes.

Important parameter of the extrusion is its speed, which should be synchronized with the quality of the material and the hole size of the perforated plate. High speed and narrow hole size decreases the porosity, applying opposite parameters, particle density will be low.

Fig. 27.9.
Extruder

After extrusion plastic extrudate rod is cut to small cylinders then a spheronizer forms the spherical pellets. Collision force of wet particles is controlled by the rotation speed og the spheronizer unit. Optimal time and speed is determined by experiments. Operation is usually started with higher speed (abrasive forces are higher), then gradually slow down to reach uniform aggregation. In practice this process takes 5-15 minutes. Too long operation time can cause repeating desaggregation, abrasion and finally, dusting. Too much moisture can adhesion between particles and the wall of the plate. Too dry powder mixture can result high dust content in the end product. Proper

binder agent content ensures high inner cohesion forces, thus appropriate hardness of pellets, decreasing the dust, however high binder content can decrease the sphericity.

Fig. 27.10.
Spheronizer

Roto-fluid process

By application of roto-fluid process, grain formation, spheronization and drying occurs simultaneously in a single equipment. Due to the intense circular movement aggregation of particles is restricted, fluidization, centrufugal and gravitational force smoothens their edges, thus forming spherical particles.

A rotary disc is placed at the bottom of the equipment from which a conical body rises in the middle. Due to the fluid air, the rotating disc and the cone particles are moving round the disc. Granulation liquid is sprayed in the direction of the rotation towards the center of the disc.

At the border of the rotating disc particles are floating due to the fluid air, then fall back at the center. Reaching the required particle size the liquid addition is stopped, but the spheronization and drying continues.

Most important process parameters are the distance of the disc border from the side wall, rotation speed, fluid air speed, binder liquid addition speed and the pressure of the spraying air. Lifting force can be controlled by the amount of air flow, centrifugal force acting on pellets can be adjusted by the rotation speed of the disc.

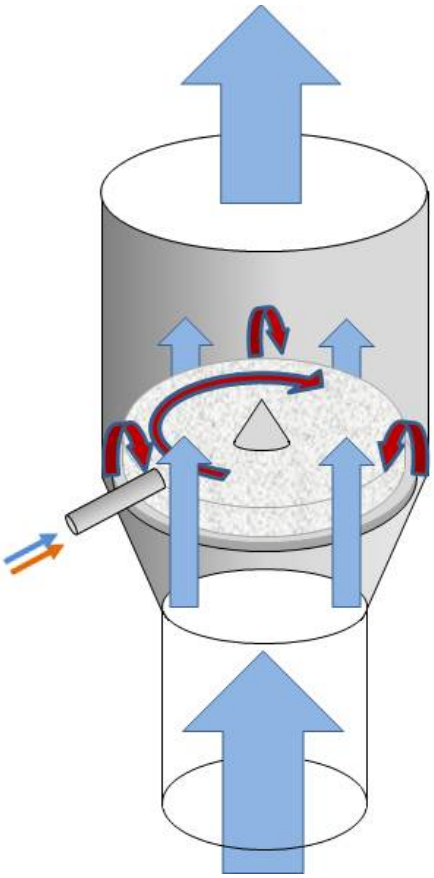


Fig. 27.11.
Principal of operation of Glatt-type roto-fluid equipment

Roto-fluid pelletizing requires a large amount of energy and a special equipment. Its advantage is the productivity and the single step operation.

Spray-freeze-drying

During this micropelletization process the API is dispersed in the melt liquid of the vehicle, then sprayed. Sphere droplets formed by this method are congealed by freezing.

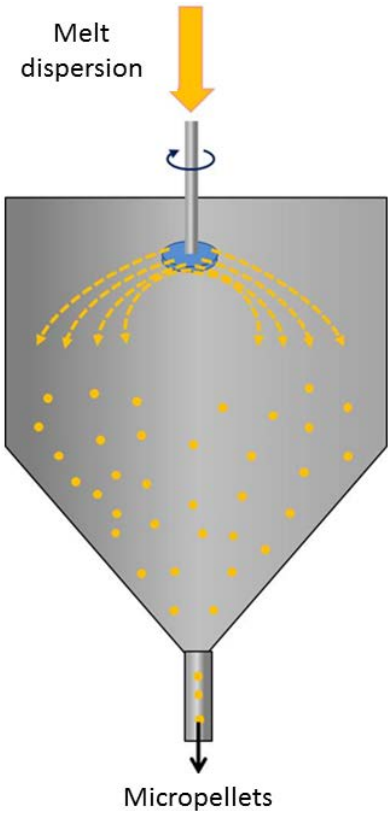


Fig. 27.12.
Scheme of spray-freeze-drying

Fig. 27.13.
Rotary atomiser

Fig. 27.14.
Industrial equipment for-spray freeze-drying

High-shear process

See chapter *Granulation*.

Hot-melt dispersion process

During hot-melt dispersion process API is dispersed in the mixture of the melt matrix material (e.g. cetyl-alcohol, stearyl-alcohol), then this melt suspension is emulsified in water above th emelting point of the matrix material. Cooling this melt emulsion forming micropellets are congealed and can be depleted by filtering.

This operation can be used for micropelletizing poor water soluble APIs. Drug dissolution can be controlled by the size and the matrix composition of the micropellets.

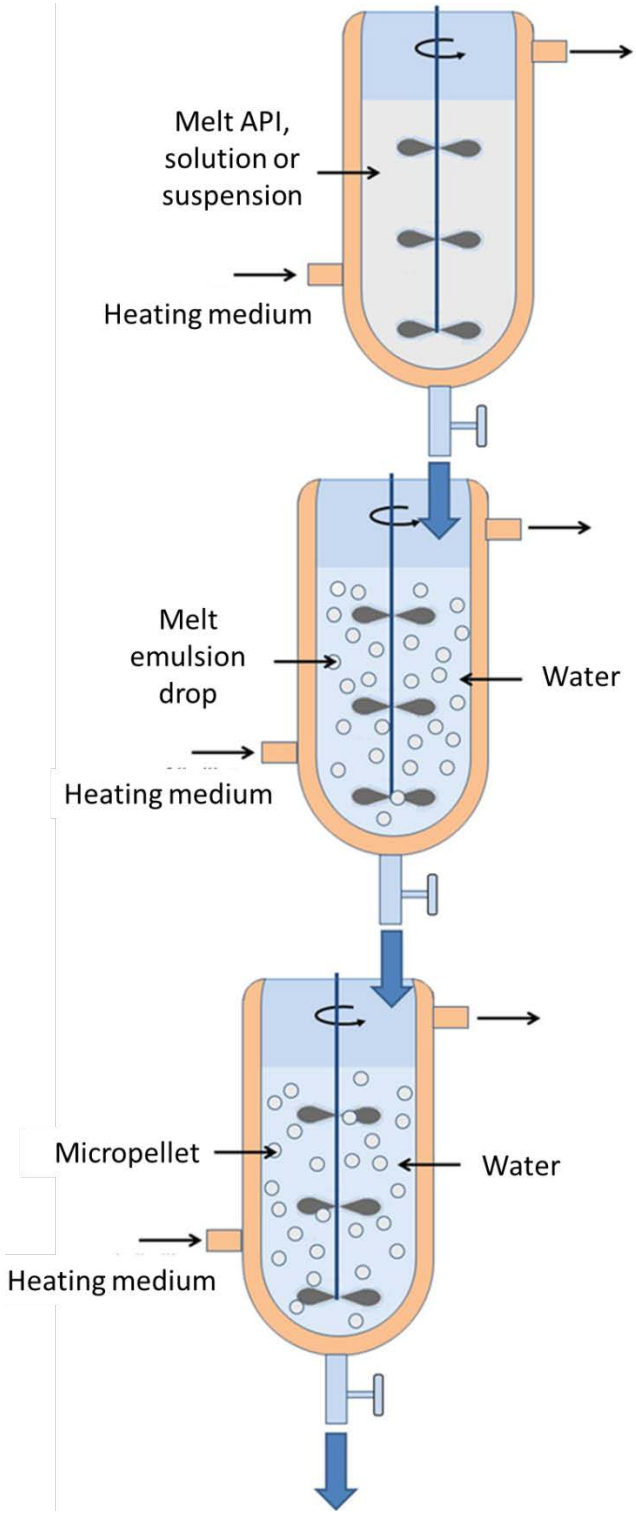


Fig. 27.15.
Hot-melt dispersion process

Drop pelletizing process

During this process API is dispersed in the melt matrix material by mixing or extrusion and droplets are formed inside a cylinder with refrigerated air. Micropellets can be collected at the bottom of the refrigerated tube. This process can be applied in case of water soluble and insoluble ingredients as well. Drug dissolution from micropellets can

be controlled by the size and matrix composition in a wider range comparing to the hot-melt dispersion process.

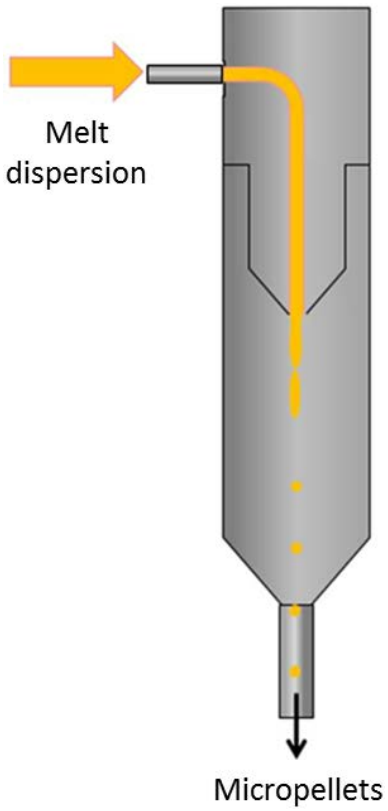


Fig. 27.16.
Preparation of micropellets by drop pelletizing process

Micropellets can both be intermediate and end products. They are commonly applied in preparations intended to dissolve or disperse in water, orodispersable tablets, modified release with zero-order-kinetic tablets and spansules.

Fig. 27.17.
Micropellets in spansule

27.1.3 Microencapsulation

Microcapsules are spherical particles with in range 1-1000 μm in which the API is in solid, liquid or gaseous form.

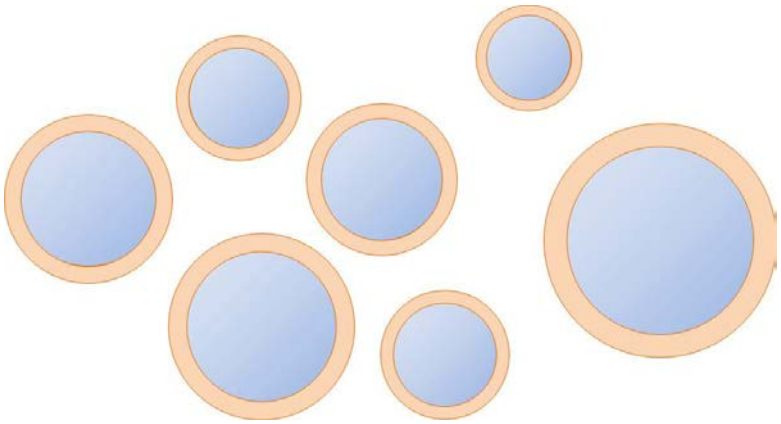


Fig. 27.18.
Shell-core type microcapsules

Coating a single particle of API within a microcapsule a typical shell-core structure is created. During production sometimes more particles are incorporated inside the microcapsule.

Pharmaceutical technological and biopharmaceutical aims of microencapsulation may be:

1) reaching modified drug release (e.g. isosorbid-dinitrate sustained release),
2) separation of components reacting with each other in case of incompatibility (e.g. vitamins),
3) handling volatile substances (e.g. methyl-salicylate, menthol, camphor, volatile oils),
4) taste and odour masking (e.g. erythromycin, cod liver oil),
5) protection of API against harmful environmental conditions (e.g. oxygen, humidity or light),
6) Transormation of liquid into solid material (A, E, D3 vitamin, cod liver oil),
7) reducing the irritative effect of substances (e.g. acetyl-salicylic acid, iron-sulphate, potassium-chloride).

Microencapsulation is also used int he field of agriculture, food industry, cosmetics and pharmaceutics.

Release of the API can occur due to:

1) dissolution of the shell
2) diffusion through the shell
3) erosion of the coating
4) osmosis.

27.1.3.1 Preparation of microcapsules

Choice of microcapsule as a dosage form in order to fulfill a therapeutic or technological aim requires careful consideration. Microencapsulation can be carried out

only by expensive processes which is basically determined by the character of the core. The substances of the core can be any active ingredient, a living cell, protein or a biotechnological product as well.

Most important properties of coating of microcapsules is the thickness, the cohesion to the surface of the core, the unity of the film structure, porosity, solubility, permeability, sorption ability of the moisture, stability, which all should be taken into account at the design of the preparation.

Pharmaceutical excipients of microencapsulation can be water soluble or water insoluble polymers.

1) water soluble polymers
   a) gelatine
   b) acacia gum
   c) starch
   d) polyvinyl-porrolidone
   e) polyvinyl-alcohol
   f) methylcellulose
   g) carboxymethylcellulose
   h) hydroxyethylcellulose
   i) polyacrilic acid
2) water insoluble polymers
   a) polyamide (e.g. nylon)
   b) polyethylene
   c) polyethylene-vinyl-acetate
   d) ethylcellulose
   e) polymethacrylate

The polymer should be chosen according to the solubility of the API, the aim and the method of microencapsulation. In case of water soluble API the excipient should be dissolved in a hydrophopic medium and the API should be dispersed. Water soluble polymers are applied in case of water insoluble or poor water soluble APIs to create the coating of microcapsules. The way of drug release is determined by the composition of the coating, its rate is controlled by the thickness and the structure of the coating.

Main methods of preparation of microcapsules are:

1) phase separation,
   1.1) water based medium,
      1.1.1) simple coacervation,
      1.1.2) complex coacervation,
   1.2) non-water based phase separation,
      1.2.1) solvent evaporation,
      1.2.2) solvent extraction,
2) interfacial polymerisation,
3) spry drying.

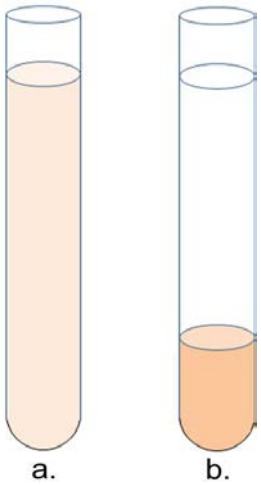
Phase separation

Phase separation processes according to the colloids taking part in the coating creation can be:

1) simple
2) complex

Bungeberg de Jong was the first who described the phenomenon of phase separation in aeqous medium, called *coacervation* in 1929.

The essence of the coacervation process is the separation of the part of the colloid in another phase due to an outer effect (e.g. salt addition, change in pH). One-phase system becomes two-phase and the homogeneous colloid solution separates into a colloid poor and a colloid rich liquid coacervation phase.



a. homogeneous colloidal solution;
b. separation into a colloid poor and a colloid rich phase

Fig. 27.19.
Coacervation

Base of practical utilization of phase separation was the observation of coating formation of droplets of colloid molecules (coacervate dops) layered on the surface of dispersed particles. At the end of the coacervation process the solidification of this layer is often needed (e.g. by cross-linking of the polymer).

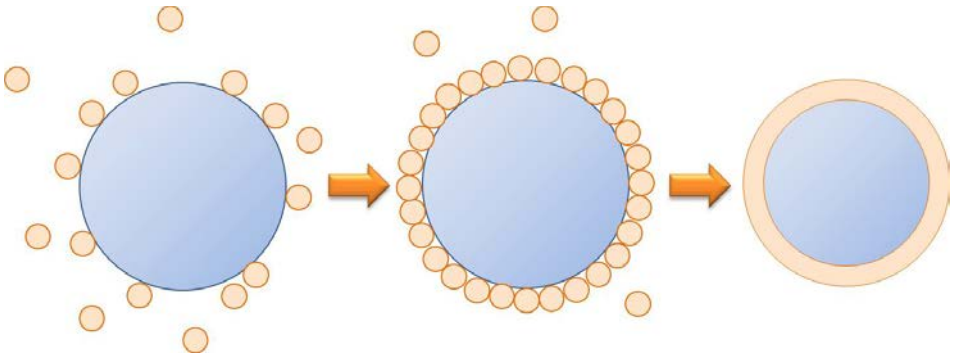


Fig. 27.20.
Phase separation on the surface of dispersed particles

Simple coacervation

Applying only one colloid simple coacervation can be achieved above the congealing point of the colloid by its dehydration. Simple coacervation in aqueous medium is due to hydrophil substances:

- ethanol, acetone, propanole, iso-propanole
- salts, e.g. Na_2SO_4

could be applied in case gelatine, polyvinyl-alcohol, methylcellulose coatings.

Complex coacervation

Complex coacervation occurs in a solution containing two or more hydrophil colloids with opposite charge.

During the process molecules with opposite charge (e.g. gelatine and acacia gum at a definite pH) join to each other and aggregate in the polymer rich coacervation phase.

Phase separation in non-aqueous medium

In case of water insoluble polymers phase separation in non-aqueous medium can by carried out from the polymer solution using a miscible solvent decreasing the solubility of the polymer. Evaporating the solvent and/or decreasing the temperature decreases the solubility of the polymer.

Interfacial polymerisation

Coating can be built applying chemical method of interfacial polymerisation. According to the *Schotten-Baumann* reaction, an acid-chloride and a molecule with an active hydrogen atom joins (amine, alcohol, polyesther, polyurea, polyurethane). The solubility of the formed polymer gradually decreases and creates a coating around the core. During microencapsulation of liquids before dispersing, one reactive component is dissolved int he liquid constituting the inner phase, after dispersing the component dissolving in the outer phase is added to the dispersion.

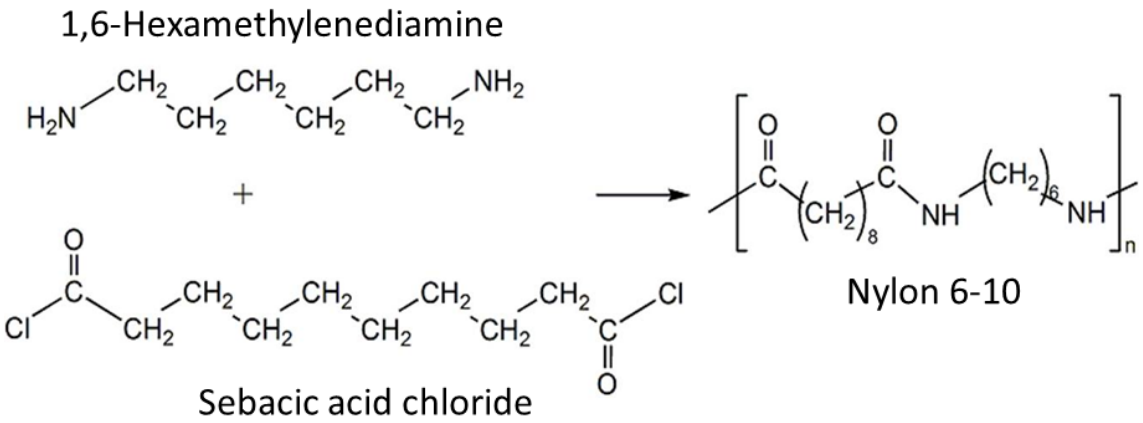


Fig. 27.21.
Formation of nylon coating

Cross-linking can be carried out by interfacial polyconensation of monomers.

In situ polymerisation differs from the interfacial polymerisation in the method of addition of reactive components to the outer, continuous phase.

Spray drying

Preparation of microcapsules can be carried out by spray drying using the method of dispersing the API in the polymer coating's solution, than spraying is performed. During this process after the evaporation of the solvent a polymer coating is created on the surface of the particles. Most important process parameters is the viscosoty of the solution, spraying tenperature, rotation speed of the spraying wheel. By application of supercritical carbon dioxide substances produced by biotechnological methods also can be microencapsulated.

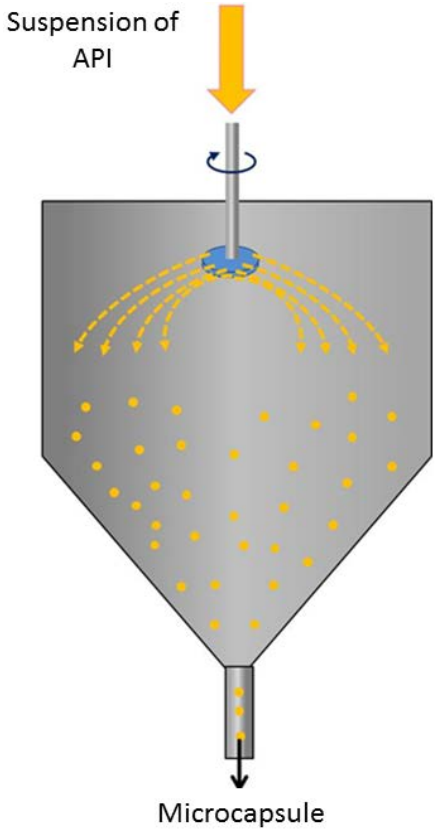


Fig. 27.22.
Spray drying

Particle size of microcapsules can be characterized by at least two statistical figures, which is the average particle size, the standard deviation and by determining the maximal and minimal acceptable limit.

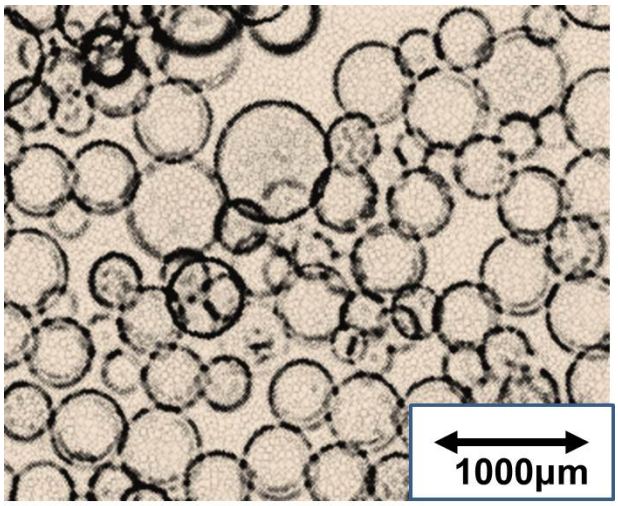


Fig. 27.23.
Optical microscopic picture of microcapsules

27.2 Multiparticulate pharmaceutical nano-preparations

Nanotechnology is the body of building operations in an atomic size, which recently became a hot field in the science.

Its pharmaceutical application offers new possibilities int he pharmaceutical technological development, including the preparation of nano materials and nano-carriers. Their application enables to solve several technological and therapeutical challenges which had no solution before.

Such molecules can be built which were unable to be built by chemical or biological methods previously. Significant solubility and dissolution rate enhacement can be reached in case of conventional active pharmaceutical ingredients as well, which influences the pharmacokinetical parameters, including the increase in the apsorption process. Bioavailability of substances can be enhanced taking into account the possible increase of toxic effect which should be further examined.

Nanotechnology can be applpied in several fields of dioagnostics, technology and therapy:

1) tissue surgery,
2) nanorobots,
3) biosensors,
4) biomarkers,
5) image enhancing diagnostic tools,
6) implant technology and
7) pharmaceutical nano-carriers.

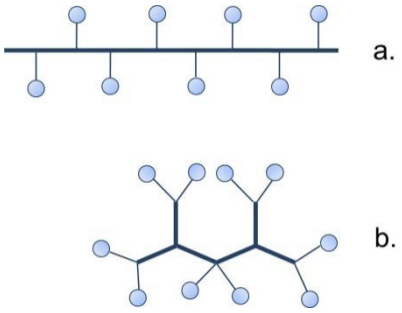
Pharmaceutical nano-carriers (1-1000nm) have different sctructure and application. Using these preparations the API can be transferred through the blood-brain barrier thus achieving a selective tissue targeting saving the other tissues. During chemotherapy accompanying poor-tolerable side effects can be reduced in a great extent, since lower doses can be applied reaching better effect.

Pharmaceutical nano-carriers include:

1) polymer conjugates,
2) micelles,
3) liposomes,
4) niosomes,
5) pharmacosomes,
6) ethosomes,
7) cochleates,
8) nano tubes,
9) quantum dots.

Small size and huge specific surface of *nanocrystals* may increase the solubility of poor soluble substances, dissolution speed may also increase which results a better absorption and bioavailability (see: Process of dissolving, preparation of pharmaceutical solutions).

Polymer conjugates can have linear or branched structure in which API is connected to the chains. Their application allows to produce drug delivery systems from which the dissolution of the API depends on the composition of the polymer molecule, the degree of polymerisation and the binding method of the API-polymer molecule.



a. linear and **b.** branched structure

Fig. 27.24.
Polymer conjugates

Micelles also can be pharmaceutical carriers, which are monolayer associates formed from ionic surface-active substances. Micelles are solubilising the active ingredients and the formed loose structure can be stabilized by cross-linking polymerization.

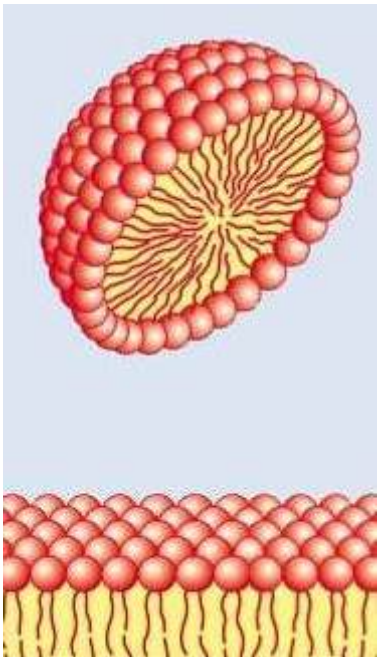


Fig. 27.25.
Cross-sectional view of a micelle, structure of a monolayer membrane

Liposomes were discovered by *Alec D. Bangham* (1921-2010), a british haematologist. Structure of their membrane and its chemical composition is similar to the living cell wall.

Membrane forming phospholipids belong to a special group of fats. One part of such molecules has a strong polar, the rest long carbon chain part has apolar character. One phosphoril-esther and two fatty acid chain is bound to the glycerin by esther bonding.

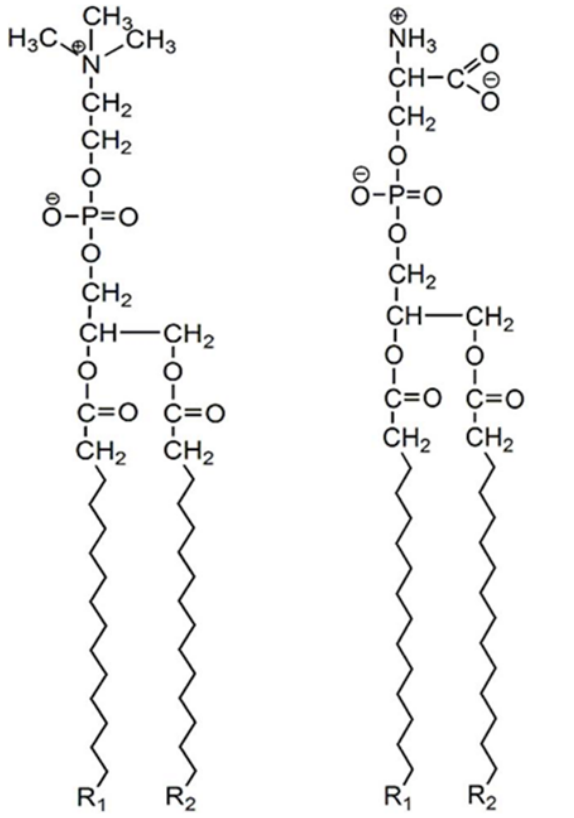


Fig. 27.26.
Membrane forming phospholipids

Polar and apolar part of phospholipid molecules are ordered according to their polarity in aqueous medium, forming a bilayer and engulfing polar and apolar APIs according to their amphipatic character.

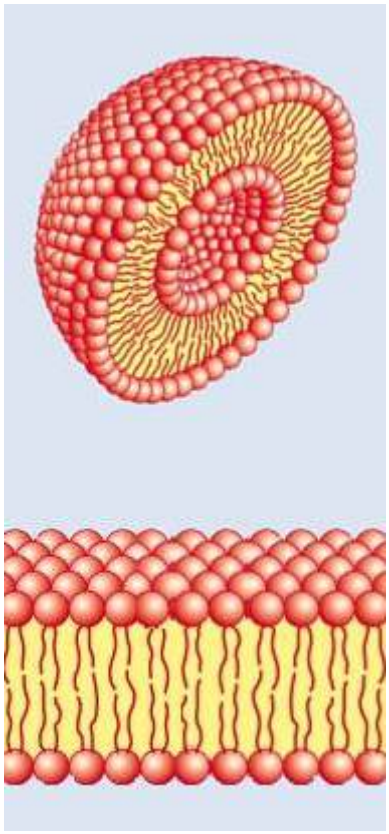


Fig. 27.27.
Cross-sectional view of a liposome and structure of the membrane bilayer

During the preparation of liposomes lipids are dissolved in organic solvents, after that they are hydrated with water above their phase transition temperature. Hydrated lipid molecules are ordered in space and after formation of membranes liposomes are also created. Organic solvent is extracted by appropriate methods (vacuum evaporation, dialysis, gel-filtration). The API is previously dissolved in the proper solvent according to its solubility.

Additional excipients, such as other lipids or cholesterin can be used to form the membranes in order to stabilize the wall of the membrane.

Process parameters determin the structure, size and the size distribution of liposomes. Conditions of hydration are particularly significant from the viewpoint wethermono- or multilayer vesicles are formed. Most important process parameters are:

1) amount of API,
2) applied excipients and their amount,
3) amount of organic solvents,
4) phase ratio,
5) mixing speed,
6) mixing time,
7) speed of hydration.

By observation of the canadian *Michael Mezei* of hungarian origin transdermal application of multilamellar liposomes can penetrate through the skin into the deep layers.

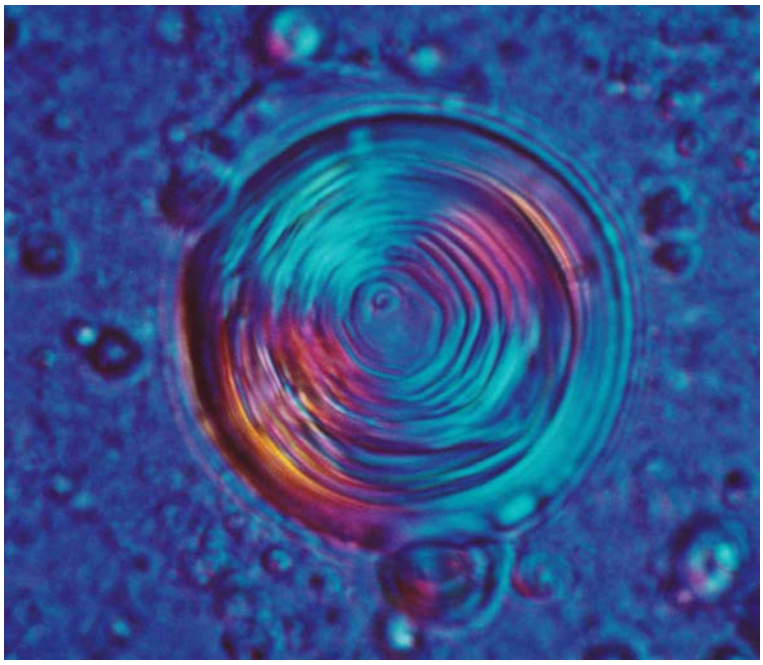


Fig. 27.28.
Optical microscopic picture of a multilamellar liposome

Multilamellar vesicles (*MLV*) can be transformed to *small unilamellar vesicles* (*SUV*) by extruding them through a polycarbonate microfilter.

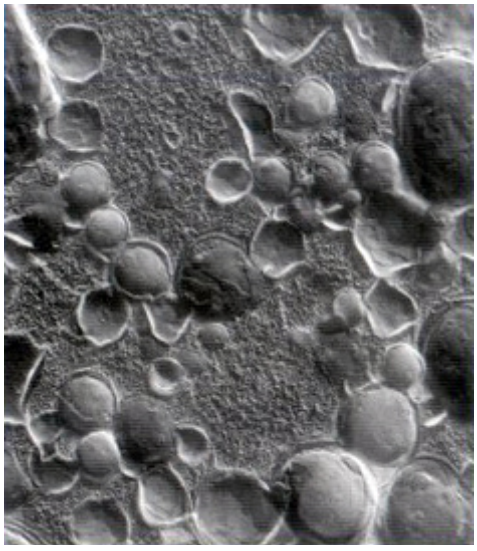


Fig. 27.29.
Electronmicroscopic picture of small unilamellar vesicles

By application of liposomes undesirable side effects and toxicity can be decreased, and the distribution of the API can be changed in space and time inside the body.

Importance of their application in chemotherapy, antifungal therapy, vaccination and gene therapy should be emphasised among different therapeutic applications.

Base of development of SUV type new generation liposomes is the observation on the basis of which cancer tissues are engulfing nano particles in a higher extent than

healthy tissues. Although m*ononuclear phagocyte system* (*MPS*) destructs them before their action after intravenous administration.

Important discovery was the observation that molecules, such as polyethyleneglycol, sialic acid, glucuronide derivatives attached to the surface of nano particles can temporarily hide them after intravenous administration. These sterically pegilaton stabilised secured liposomes, called *stealth liposomes* increase their own circulation time thus increasing the bioavailability in order to reach successful therapy, while effective dose and the prevalence of side effects decreases.

Doxorubicine's dosing is hindered by its cardiotoxicity during chemotherapy. *Caelyx*® is a preparation in which the API doxorubicine-chloride is included in liposomes with methoxypolyethylene-glycol (MPEG) on their surface.

Development of *Ambisome*® containing amphotericin-B was necessary in order to decrease the API's side effects (e.g. pain in muscles, renal impact, anaemy, thrombophlebitis). Applying liposomes, significant decrease of side effects can be observed.

Visudyne® was developed for the therapy of the age-related macular degeneration. Macula is responsible for the fine details of the vision, which is important during reading. The preparation contains porphirin-derivative, verteporphin encapsulated inside a liposome and can be applied in combination with laser therapy. Principal of photodynamic treatment is the activation of the API through the pupil on a localised area applying laser light at the fundus.

Other great possibility of the nanotechnology is the *pharmaceuticall active targeting*. Liposomes with proper ligands (antibodies, immunoglobulines, lectins, oligosaccharides) can find and destroy the targeted cells and tissues selectively.

Niosomes are vesicles with double layer built from non-ionic surfactants (i.e. sorbitane-esthers, cholesterol). They are accumulating primarily in the liver and the spleen, thus niosomes can be used in the treatment of these organs.They are also able to carry peptid-type active agents, hemoglobin in targeted drug delivery or transdermal systems.

Pharmacosomes are drug carriers int he colloidal range, in which the API attaches to the lipid with covalent bond, thus polar molecules can also be incorporated in the vesicles.

Ethosomes are vesicular, non-invasive drug carriers with high content of ethanol, which enables the penetration enhancement through the stratum corneum. They are able to penetrate into the deep layers of the skin and enter the systemic circulation.

Cochleate's name is derived from its wound shape. They are built from phospholipid bilayer membranes similarly to liposomes. Membranes are attached to each other by divalent ions (e.g. calcium), which results a stabile structure.

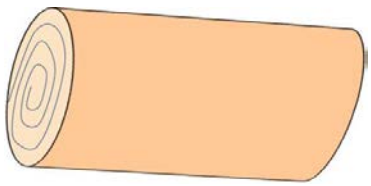


Fig. 27.30.
Cochleate

Dendrimers are macromolecules with branched structure derived from a central core. Further layers are attached to the core, which are called generations. The shape

and the consistence of the structure and the place of the API, its bonding strength inside the dendrimer is determined by end-chain functional groups.

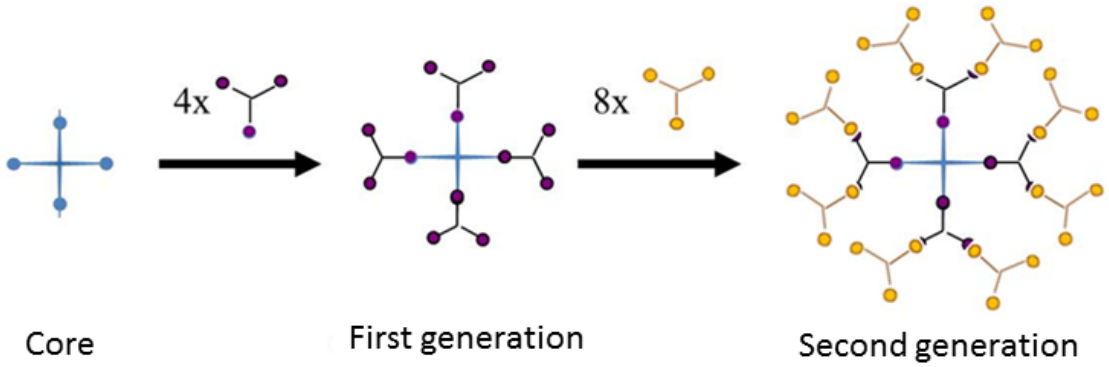


Fig. 27.31.
Preparation of dendrimers

Atoms of carbon can form stabile structure ordering in spherical or cylindrical structure. Nanotubes formed this way can act as carriers of APIs. One method of preparation is carried out by plasm technology. 3000°C temperture required to form nanotubes can be reached by electrical discharge. Peeling carbon atoms and their aggregation from the graphite electrode will create the nanotube structure. This process is catalized by metallic substances. Nanotubes also can be prepared by laser technology and catalitic decomposition in gaseous phase of carbohydrates.

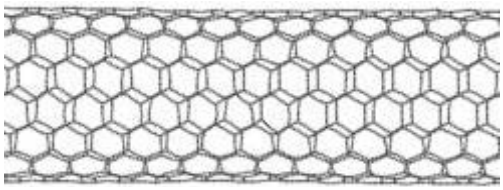


Fig. 27.32.
Nanotube

Quantum dots are nanocrystals within size 2-10 nm with semi-conducting chatacter built from 500- 10 000 atoms. Different functional groups are attached to their structure. Depending on the molecule attached they can be drug carriers and biosensors as well. Their therapeutic application is limited by their toxicity due to heavy metals in their structure (Cd, Te, Pb, etc.)

Questions

1) Which are the most important properties of pharmaceutical multiparticulate preparations?
2) Which preparations belong to the multiparticulate micro-drugs?
3) Which are the biopharmaceutical advantages of multiparticulate micro-preparations?
4) Which are the common excipients of pilule making?

5) List the methods of pelletizing!
6) Which are the main steps of rotating disk pelletizing?
7) Which are the main steps of extrusion.spheronisation method?
8) What kind of process parameters can influence the pelletization process in case of Roto-fluid method?
9) Which are the biopharmaceutical and pharmaceutical technological advantages of the microencapsulation?
10) What kind of polymers are used during microencapsulation methods?
11) Which are the main methods of microencapsulation?
12) Which are the multiparticulate nano-preparations?
13) What is the difference in the structure of micelles and liposomes?
14) Which are the most important process parameters during the preparation of liposomes?

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28 Aseptic and parenteral pharmaceutical products

Medicines are manufactured and applied with pathogenic and apathogenic microorganisms either warded off (*asepsis*) or killed (*antisepsis*) with appropriate methods.

Aseptic medicine production means that the sterility or low microorganism count state of the materials and products is established and maintained all through the production process.

Microorganisms can get into medicines from raw materials, production equipment and personnel or packaging materials in the course of medicine preparation, also upon administration.

Sterility means the state of being free of living microorganisms or microorganisms capable of reproduction, applying to pathogenic and apathogenic, as well as dormant (sporadic) forms.

Disinfection means the procedures that serve the elimination of pathogens or the termination of their pathogenicity (*inactivation*). Disinfection destroys only some of pathogenic and apathogenic microorganisms.

As early as the antiquity, cupping, the use of rectal irrigators and canulae, bloodletting and cerebral trepanation were known, beside other surgical procedures. Inadequate hygienic conditions, the lack of sterility made even the slightest medical operations high risk, taking a high toll for centuries.

The notion if immunity comes from *Thucydides* (460-395 BC). There was a plague epidemic in Athens in 430 BC and he observed that those who survived an earlier incidence of the disease could tend patients without falling ill a second time.

Ancient Romans used high temperatures to achieve sterility, which became de facto practice at the time. The significance of this was not recognized for centuries, which resulted in a significant increase of post-surgery deaths in the Middle Ages.

There are several sanitary and health-related rules in the *Bible* (disinfection of homes by whitewashing, prohibition of touching wounds by hand, personal and food hygiene).

According to Claudius *Galenus* (129- 201 A.D.*)* cupping shall be performed on veins close to the afflicted body part.

Inadequate hygiene caused successive waves of plague, pox, leprosy and cholera, especially in the Middle Ages.

Medieval Arabic physicians and their followers believed that any part of the body is suitable for cupping. On the other hand, *Andreas Vesalius* (1514-1564) was for Galen's opinion, supporting it with detailed anatomical charts.

The scientific work of English physician *William Harvey* (1576-1657 A.D.) on circulation established that blood, incessantly circulating in the body, is pumped by the heart in a closed system. This serves as the anatomical and physiological foundation for intravenous injections, infusions and transfusions, also laying the biopharmaceutical groundwork for injection therapy.

Anton van Leeuwenhoek (1632-1723), Dutch scientist, founder of microbiology is, among others, the inventor of microscope.

Christopher Wren (1632-1723) English scientist was the first to inject substances (a blend of wine, beer and opium tincture) in the veins of test dogs taking part in medical experiments in the course of his far-flung scientific activity.

Johann Daniel Major (1634-1693) German physician employed intravenous injections on humans with therapeutic intent.

It was a long way though that led to therapeutic injections becoming generally used and the importance of extreme quality requirements recognized. Until the significance of sterilization became recognized injections used to be very risky, with severe, often lethal adverse effects.

The first animal to animal blood transfusion is linked to *Robert Boyle* (1627-1691), an Irish-English physicist and chemist.

French physician *Jean-Baptiste Denys* (1643-1704) performed to human transfusions. His patients initially survived the transfusion of small amounts of animal blood (sheep) but receiving larger quantities killed them.

Carl Wilhelm Scheele (1742-1786) described the steam sterilization method in use to this day.

Charles Pravaz (1791- 1853) and *Alexander Wood* (1817-1884) invented the first syringe equipped with a needle and made infusions feasible.

Irish physician Francis Rynd (1801-1861) invented the subcutaneous injection needle.

Honoured as the savior of mothers, tragic fated *Ignác Semmelweis* (1818-1865) tried various disinfectant chemicals before proposing the institution of washing hands in chlorine water (solution of chlorinated lime). Eventually the labors of *Louis Pasteur* and *Robert Koch* did justice to his discovery.

Carl Friedrich Wilhelm Ludwig (1816-1895) developed methods for the perfusion of isolated organs.

Frenchman microbiologist and chemist *Louis Pasteur* (1822-1895), the founder of microbiology, immunology and epidemiology discovered bacteria. He also described the possibility of dry heat sterilization.

Englishman *Joseph Lister* (1827-1912), a surgeon, discovered and introduced antiseptic surgical operations. He successfully instituted the use of phenol (carbolic acid) in instrument and wound sterilization. His invention helped decreasing the post-operative mortality rate of patients.

The first ampullas were made by *Stanislas Limousin* (1831-1887).

The physiological solution named after British pharmacologist *Sydney Ringer* (1836-1910) is widely used to this day. His work laid the foundations of infusion therapy.

German bacteriologist *Robert Koch* (1843-1910) is the founder of modern scientific bacteriology. His postulates of the microbial origin of diseases, "Koch's postulates", are valid to this day.

Frenchman microbiologist *Charles Chamberland* (1851-1908) invented the autoclave.

The development of membrane filtering technology is linked to *Richárd Zsigmondy*(1865-1929), a Hungarian-born Austrian-German chemist.

Austrian biologist *Karl Landsteiner* (1868- 1943) discovered human blood-types and working ec

Penicillin, discovered by *Alexander Fleming* (1881-1955) in 1929 has been marketed in the 1940s as an antibiotic.

Progress went on in the 20^{th}-21^{st} centuries and now injections and infusions are an indispensable part of therapy. Achieving this required additional scientific effort and the establishment of such further, mostly technological, production conditions that allowed the introduction of fluid- and electrolyte therapy, blood- and volume replacement and parenteral nutrition.

American physicist and inventor *Willis Whitfield* (1919-2012), or as Time Magazine called him, *Mr. Clean*, invented clean space or clean room, which is required for aseptic production.

Based on the above, to improve therapy and compliance, as a result of the evolution of methods for administration and technology, disposable syringes, insulin pens for diabetes, precision dosing pumps and methods of administering drugs alternative to injections have been introduced.

It is the easy to reach body parts in contact with the the outside world (e.g. skin, eyes, mouth, ears, GI tract, respiratory organs, secretory and sexual organs) that are mnost used for administering drugs. It is their nature that due to their functions they have their own respective defensive mechanisms, which affects the level of microbiological purity various products are required to meet.

In case of *parenteral pharmaceutical products* (*Paernteralia*) the above defensive mechanisms are bypassed and products are introduced under the skin, into muscle tissue or intravenously directly into the bloodstream.

Product design, the conditions of production and the norms of quality management, quality control, storage and use are determined basically by *biopharmaceutical aspects*, dosage form and the interaction between the body and the pharmaceutical product.

Knowledge of the following is indispensable for being able to make aseptic products and design sterilization processes:

1) the notion of sterility,
2) the nature of pathogens,
3) the sources of microbial contamination,
4) sterilization methods,
5) the operation parameters of the applied sterilization method that determine sterility,
6) the set of requirements for controlling the process and the end product.

Sterilization is an operation through which germs and spores are perfectly eliminated from the materials and instruments to be used.

Sterility is a theoretical absolute notion, without stages. The goal is absolute sterility in the manufacture of aseptic pharmaceutical products, but achieving it is very difficult.

Pathogens have diverse sensitivity to heat, which decreases in the following order:

> prions > endospores of bacteria > mycobacteria > protozoa cysts > vegetative forms of protozoa > Gram-negative bacteria > fungi, fungal spores > viruses withot peplon > Gram-positive bacteria >viruses with peplons (they only bind to certain receptors).

In addition to the diversity of microorganisms, the variations in the effectiveness of various methods of sterilization depending on the sensitivity of microorganisms need due consideration.

The main types of effects sterilization has on microorganisms are the following:

1) germ count reduction effect,
2) bacteriostatic effect,
3) bactericide effect,
4) sporicide effect,
5) virucide effect,

6) fungicide effect,
7) parasiticide effect.

The only way of achieving safe sterilization conditions is knowing the attributes of the microorganisms to be eliminated by the operation.

Table 28-I.
Main attributes of microorganisms in terms of sterilization

Microorganism	Symptoms of life	Reproduction	Conditions of reproduction	Physical, chemical effects impeding
Bacteria	metabolism, biochemical activity	monogenesys, very rapid	oxygen (aerob) free of oxygen (anaerob)	freezing, sterilization by hot water or steam
Viri	no symptoms of life by themselves	intracellular	host cell	sterilization by hot water
Rickettsia	metabolism	scissiparity		
Fungi	metabolism	blastogenesis, monogenetic reproductive cells, syngenesys		sterilization by hot water or steam
Parasites	motion	monogenetic scissiparity or syngenesys		sterilization by steam

Keeping the risk of particle and pyrogen contamination to the minimum during production, storage and use is a fundamental principle.

There are several points in the course of production where materials, instruments or personnel can potentially cause microbial contamination of the product, but imperfectly performed aseptic production or sterilization can just as well result in the production of non-sterile grade products.

Therefore, manufacturing sterilized products requires the enforcement of such special requirements that keep the risk of microbial contamination in products at the minimum.

According to the principles of aseptic pharmaceutical production the probability of contamination has to be kept to the minimum both during the preparatory process and product preparation.

Therefore sterilization procedures have to be validated with particularly thorough care without exception.

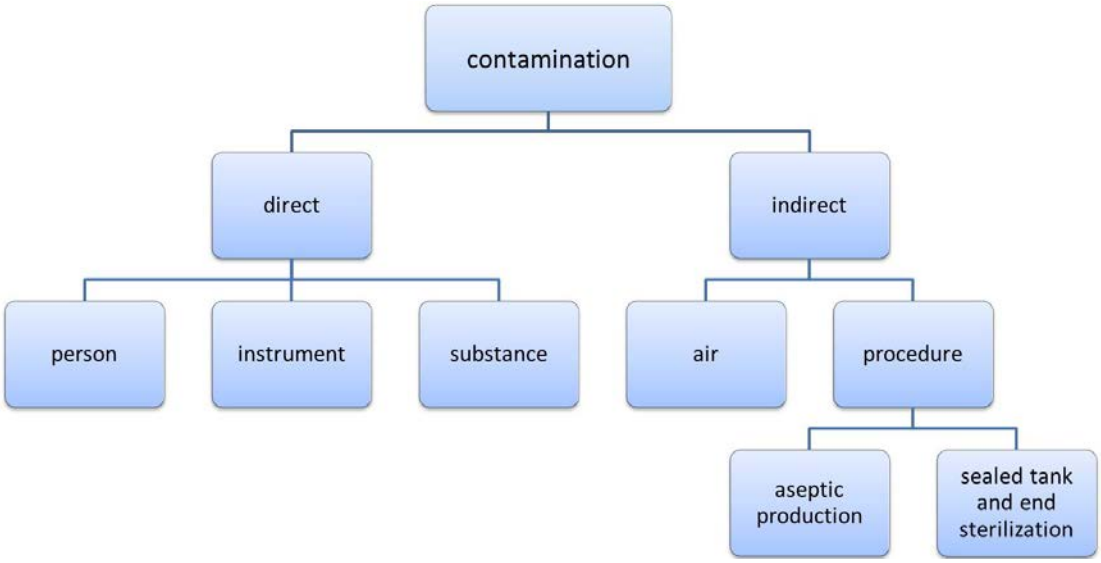

Fig. 28.1.
Possible sources of microbial contamination during aseptic medicine production

The sterility of parenteral products (e.g. infusion, injection, implant) must be maintained after production too, during transportation and use. Storing sterilized product in no other packaging but the one in which they had been sterilized is an important rule of thumb of storing. Sterilized packs require protective packaging or container for transportation. Sterilized packs must be opened only right before use. The contents of open packs can no more be considered sterile.

Aseptic pharmaceutical production takes place in an aseptic workplace in germ-free air.

Designing and performing sterilization procedures according to GMP requires particularly careful and thorough work:

1) qualified personnel with appropriate training,
2) arrangement, preparation and maintenance of rooms,
3) aseptic environment, minimum level of microbial contamination prior to sterilization,
4) production equipment designed for easy cleaning and sterilization,
5) validated procedures for all critical production steps,
6) uninterrupted registration of environmental contaminations,
7) in-process testing.

Keeping the number of production personnel (a potential contamination source themselves) to the necessary but sufficient minimum is an important aspect. The persons doing aseptic work must wash up, wear clothing washed with disinfectant or autoclaved, be free of infections and not be a latent pathogen host. Production personnel must be aware of the fact that even the slightest deviation from production protocols may have lethal consequences for patients.

In every room where production takes place, every surface must be smooth and impenetrable so that clinging and propagation of microorganisms could be minimized. Therefore, rooms must be furnished with washable walls and flooring, namely tiled and paved. Lately, jointless floors have been gaining ground. Perfectly fitting doors and windows are required. Furniture nust have easy to cleand and disinfect surfaces. Rooms and furniture must be washed and disinfected every day between shifts.

The regulations for antechambers of clean rooms, the so called "grey rooms" are less strict. Clothes and personal items not allowed in the clean room can be left here.

Entry to a clean room must be through an airlock after taking a preliminary shower, wearing appropriate clean room clothing (shirt, coat, cap, gloves and mask made of lint-free fabric, special smooth-soled shoes).

Clean rooms are environments in which air pressure relative to the atmosphere, direction of airflow, temperature, humidity, solid content and germ countof air are controlled according to strict rules and regulations. The air volume required for maintaining these, the ventilation rate of rooms (the number of times the entire air volume of a room is replaced in an hour) can be determined according to the stipulations of GMP.

In production various work phases must be carried out in separate rooms.

There are two types of clean rooms from the aspect of contaminations:

1) keeping out external contaminations (achieved by overpressure: air pressure in the room is higher than outside),
2) keeping contaminations from escaping outside (achieved by underpressure: air pressure in the room is lower than outside).

The air pumped in the clean room is filtered by high-efficiency HEPA and/or ULPA filters to eliminate dust, floating particles (see also Chapter *Filtration*). Uninterrupted air outflow from the room can be achieved by positive pressure. A thermostat regulates constant temperature (heating and cooling). Ventilation is often supplemented with a humidity regulating system.

These types of workspaces are classified according to their production work phase in order to decrease the risk of particle or microbial contamination of the handled substances (intermediate or end product) to the minimum. Trans- and crosscontamination of different class clean rooms must be avoided, therefore measurement, dissolution, filling and final sealing of products must be performed in separate rooms.

There are four classes of clean rooms:

Class „A" room, in which the risk of contamination is the greatest during operations (e.g. filling and sealing open ampullae or infusion bottles). They are usually laminar flow workplaces in which laminar airflow systems maintain 0,45 m/s ±20% homogenous air flow.

Class „B" room, in which aseptic preparations take place. Class "A" zones require this type of background environment.

Class „C" and „D" rooms are clean rooms designated for less critical production phases of parenteral products.

Laminar Air Flow (*LAF*) *cabinets* have the advantage of laminar airflow and small footprint combined; their workspace allows aseptic working. When harmless substances (e.g. injections, infusions) are being processed, the use of equipment providing positive pressure *Class "A"* workspace is required. Cabinets of *horizontal* (or vertical) *airflow* provide positive pressure quasi-sterile working conditions, but fail to protect the laborer.

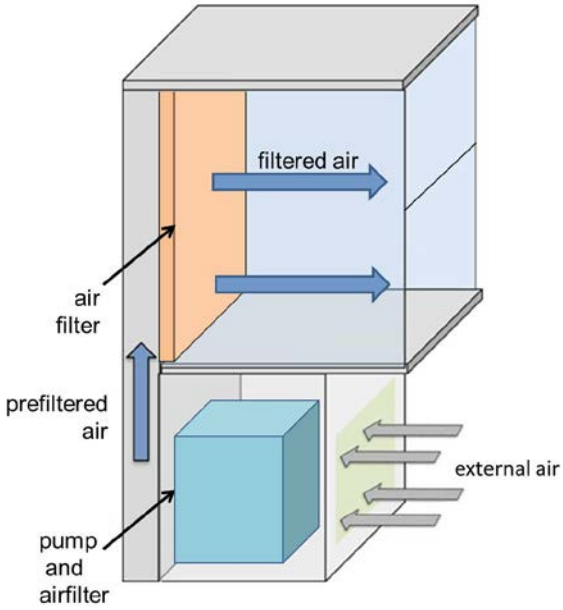

Fig. 28.2.
Horizontal airflow, positive pressure LAF device

When substances hazardous to the health of laborers are being processed (e.g. cytostatics, radiopharmacons, biological preparations – vaccines, toxoids -), in order to protect laborers only negative pressure Class "A" cabinets may be used. These have rear or bottom ventilation.

Fig. 28.3.
LAF device for preparing cytostatic compouds

Pharmaceutical industry builds cabins, sterile chambers or rooms for large scale aseptic work.

Fig. 28.4.
Laminar air flow room

Materials and instruments too enter clean rooms through airlocks. Making sterile products requires raw materials with acceptably low microbial contamination levels. Unlike materials, instruments are used again in processing subsequent batches. Being easy to clean and sterilize is a condition of their reusability.

In the course of sterile pharmaceutical production, in order to decrease the probability of contamination, the principle of "necessary minimum" shall be applied to instruments and devices too. Accordingly, products should be sterilized in the terminal container (e.g. sterile ampulla, infusion bottle).

28.1 Sterilization methods

There are several sterilization methods in use in pharmaceutical technology, which are, either individually or in combinations, suited for making a given sterilized product. Sterilization may take place at higher or lower temperatures, with or without overpressure, with or without employing chemically active substances or radiation.

The sterilization method of choice is basically determined by the microbial contamination and stability (e.g. heat tolerance) of the substance in question. There are standard conditions (e.g. temperature, pressure, gas concentration, duration) stipulated by pharmacopoeias for certain procedures, which alone however are not sufficient guarantee, so they can be disobeyed if validated procedures are used instead.

Therefore whenever a procedure is being designed, the critical conditions of the procedure have to be defined and steadily registered upon execution, in order to make sure that the pre-defined quality requirements are fulfilled. This registration duty certainly applies to procedures performed under standard conditions.

When *terminal sterilization* is used, products made of least possible germ count raw materials are sterilized in their sealed terminal container (e.g. ampulla, infusion bottle).

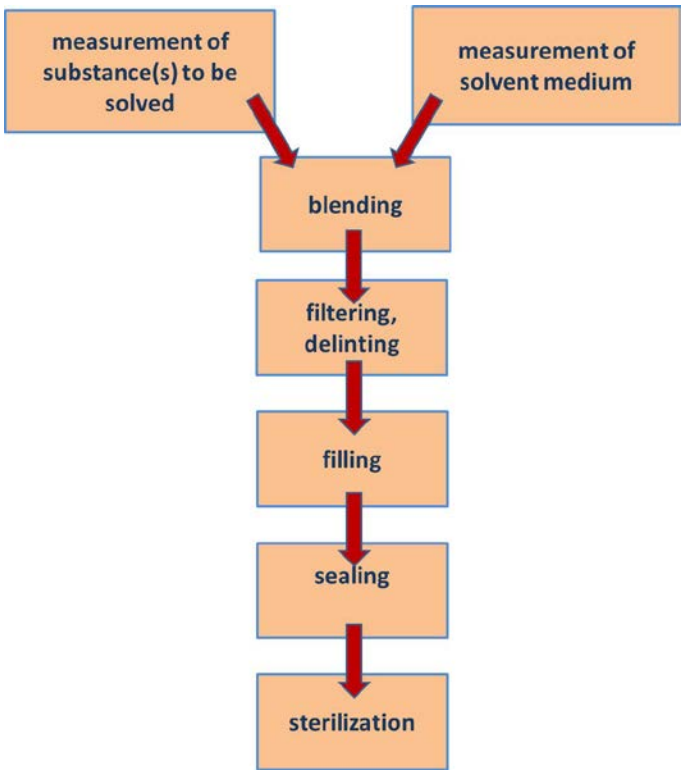

Fig. 28.5.
Flow diagram of parenteral solution preparation with therminal sterilization

Sterilization by filtration has to be performed before filling in the container, requiring *non-terminal sterilization*. In this case extremely strict aseptic production conditions must be maintained.

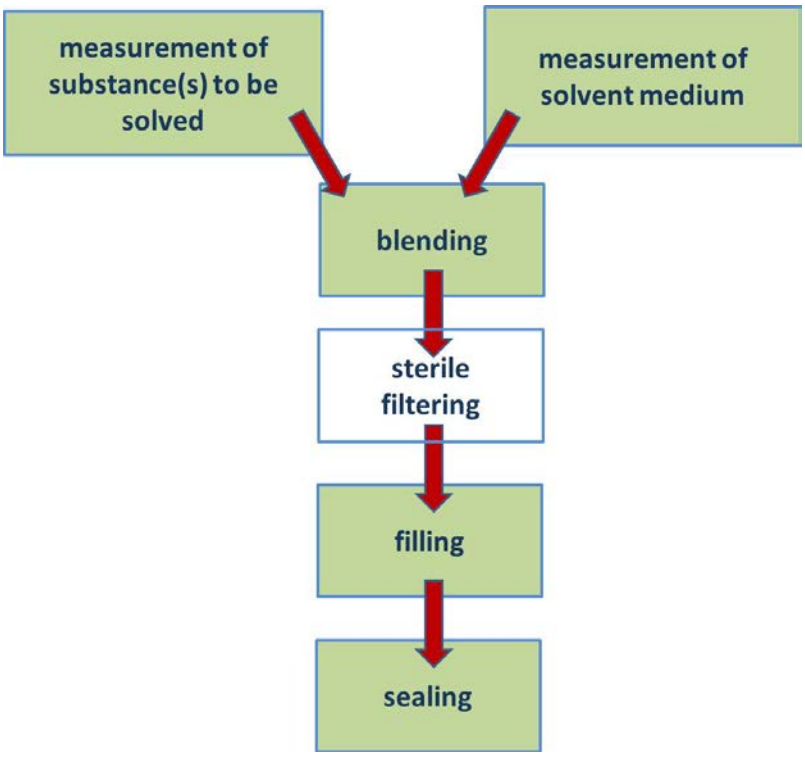

Fig. 28.6.
Flow diagram of parenteral solution preparation with közbenső sterilization

Sterilization methods can be grouped into physical (heat, filtration, radiation) and chemical methods.

28.1.1 Dry heat sterilization

Sterilization by heat is applicable only to substances that endure the heat of sterilization without disintegration or other transformation.

Sterilization in *naked flame* is used in microbiological work processes for disinfecting metal objects, instruments.

Dry heat sterilization is done in dry heat sterilizers, which are thermally insulated enclosures with adjustable temperature thermostate controlled air circulation.

Fig. 28.7.
Laboratory scale dry heat sterilizer

The pieces in the batch shall be allowed sufficient time to reach the required temperature before the clocking of the actual sterilization time is started. Dry heat sterilization requires at least 2 hours and minimum 160°C. Killing endospore-forming bacteria requires 120 minutes of treatment at 180°C. Dry heat treatment can eliminate pyrogens above 220°C.

Generally, temperature is controlled by thermal sensors, placed in the containers of product sampleas and the coldest spot of the workspace (determined in advance).

In the course of microbiological verification of sterilization procedures appropriate microbiological indicators (spores of *Bacillus subtilis*) shall be used.

Fig. 28.8.
Medium scale dry heat sterilizer

28.1.2 Moist heat sterilization

For sterilization purposes moist heat is more effective than dry heat, as water vapor is a far better heat conductor than air. It is advisable to use moist heat sterilization whenever higher temperatures would damage the instruments or substances to be sterilized.

Microorganisms are in general more sensitive to moist heat than to dry heat. Growth medium (eg. agar plus nutrients) to culture microorganisms can be sterilized by moist heat only.

Basic parameters to be used in moist heat sterilization: at 121°C for at least 15 minutes at 1 atm pressure.

The most effective form of sterilization is *high pressure saturated water vapor*. *Autoclaves* serve this purpose. Autoclaves are pressure-tight, hermetically sealed, valved devices in which steam is produced. Structurally, autoclaves can be single and double wall devices.

In single wall devices (e.g. stovetops, certoclavs) water is boiled in the workspace. The operating principle of double wall water jacket devices is identical, except that

saturated high pressure steam is produced between the two walls of the device, channeled into the workspace subsequently.

Being a closed system, any increase in internal temperature increases pressure too.

Air trapped inside the autoclave is the cause of most concern, as it is prone to create dead spaces. There are top loading vertical chamber- and front loading horizontal type autoclaves.

Fig. 28.9.
Laboratory scale single wall autoclave

Work space shall be filled up to 2/3 capacity and products shall be spaced loosely to allow free steam circulation between them.

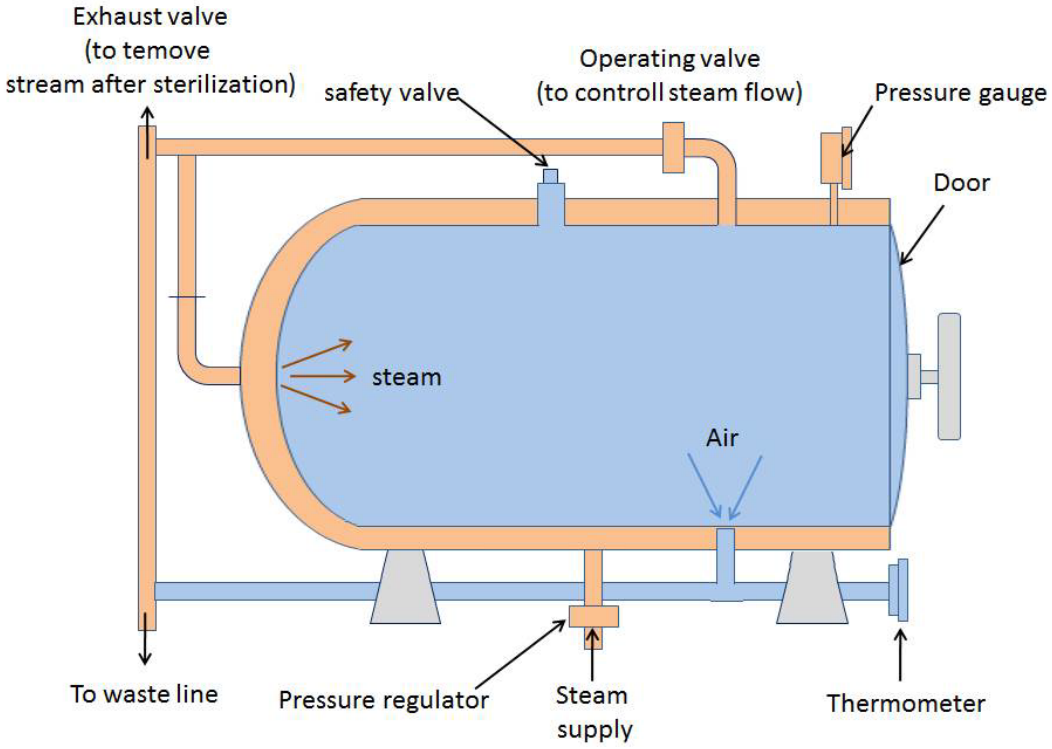

Fig. 28.10.
Industrial scale double wall autoclve

Products to be sterilized are inserted in the workspace on perforated shelves or in case of larger industrial scale devices on carriages.

Fig. 28.11.
Industrial autoclaving

Prior to heating up the autoclave is sealed airtight with locking screws. The products to be sterilized are heated to the required temperature by steam blown in the workspace. Rising pressure shall be monitored, with repeated short air-removal ventilation intermissions to eliminate trapped air. After reaching the validated temperature required for sterilizing the products to be sterilized are kept at this temperature.

After reaching the end of sterilization time the workspace is depressurized, letting out steam and condensed water. Heating is maintained for the duration of drying then turned off. The door of the autoclave workspace shall not be opened before internal and external pressure are equalized (overpressure is 0) and workspace temperature dropped below 60°C. The products removed from the autoclave workspace are placed on a thoroughly disinfected heat resistant table to cool.

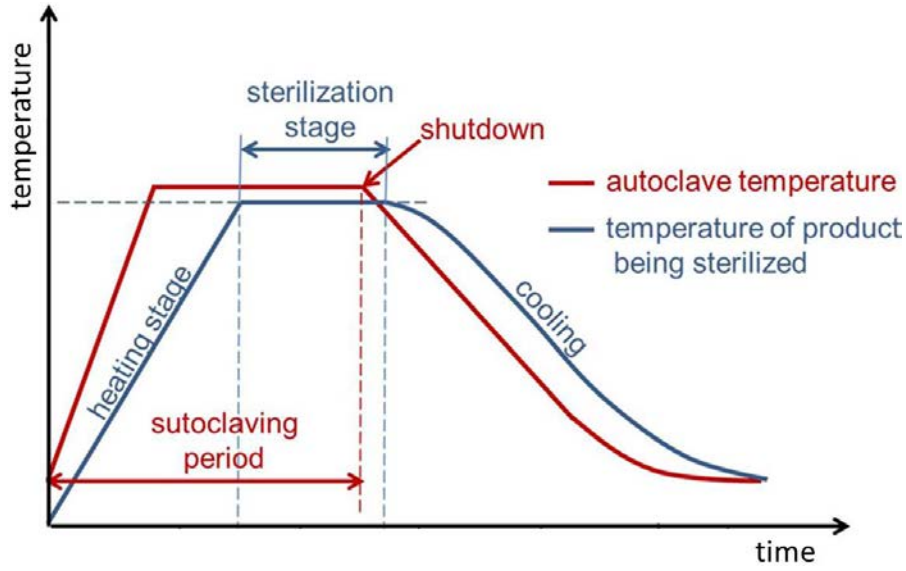

Fig. 28.12.
Stages of autoclaving

It is possible, that the conditions of sterilization inside the sterilization workspace are not uniform for a batch. Therefore the least accessible spot (e.g. coldest spot in an autoclave) for the sterilizing agent (e.g. heat, steam, chemical agent, radiation) must be determined. In the course of each sterilization process the physical - and wherever necessary chemical - conditions inside the workspace shall be tracked and registered. Minimum lethality produced by sterilization and the reproducibility of sterilization shall be indicated after sterilization.

28.1.3 Radiation sterilization

Advantages of radiation sterilization:

1) high penetrating power; sterilizing rays can penetrate packaging,
2) sterilization causing only minor rise in temperature,
3) sterilization of heat-sensitive substances possible,
4) no “residual matter”,
5) the number of parameters influencing the efficiency of sterilization is low.

28.1.3.1 Ionizing radiation

Low-energy *ionizing radiation* and electromagnetic radiation are not capable of ionizing, even at high flux. High flux ionizing radiations destroy living organisms. They induce ionization, dissolving cellular water molecules into reactive H+ and OH- radicals. Along with other cell constituents, DNA is particularly sensitive to ionizing radiation. The toxic agents created by radiation eventually destroy cells. Such are γ-, X-ray and β radiation.

In general practice the gamma radiation of an appropriate radioisotope (e.g. cobalt 60) or an electron beam from a suitable electron accelerator are used. The advantage of γ radiation is that it penetrates packaging, on the other hand it scatters in every direction, making it applicable only under special conditions. This method is suitable for sterilizing heat-sensitive pharmacons (e.g. antibiotics, hormones) and other substances (e.g. bentonite, charcoal, gelatine capsules, absorbable gelatine, eye ointments, polyethylene glycol-based creams, ointments), machinery and their parts, medicine containers.

The advantages of using γ radiation are the following:

1) sterilization is more effective than filtration and aseptic processing,
2) there is no residue as after for example ethylene oxide sterilization,
3) more penetrative than electron beams,
4) product temperature remains low,
5) easy to adjust sterilization process.

Sterilization by γ radiation is validated using the spores of *Bacillus pumilus*.

Fig. 28.13.
Sterilization by γ radiation

28.1.3.2 Non-ionizing radiation

Non-ionizing radiations excite molecules to higher energy level states, resulting in the formation of abnormal bonds. In the case of DNA it mostly leads to the formation of timidine dimers and mutations. The applicability of is method for sterilization is limited, as glass – thus the walls of glass containers – absorb biologically active waves. UV radiation is used primarily for the sterilization of the air and surfaces of clean rooms. It is damaging to eyes and carcinogenic, therefore nobody should stay in rooms with operating UV lights if possible. If it is unavoidable, wearing UV-protective spectacles is required.

The workspace of *aseptic enclosures* are sterilized and made suitable for aseptic work by using germicide lamps that emit ultraviolet radiation. In pharmacies 20-30 minute treatments are used for more effective sterilization. (90% of microorganisms within 0,25-1 m distance of the lamp are killed within 3-5 minutes.) Light-sensitive medicines shall not be subjected to the effect of germicide lamps.

Fig. 28.14.
Pharmaceutical aseptic enclosure for the preparation eye-drops

In addition to the above sterilization methods further physical methods are needed, which remove microorganisms instead of killing.

28.1.4 Filtration sterilization

Sterilization by filtration is a non-terminal method based on the size differential of microorganisms, in which microorganisms are not killed but separated. Membrane filtration is an absolute procedure that lets any particle smaller than a specific particle size pass.

In heat-sterilized products the disintegration of gram-negative bacteria may produce pyrogen substances or endotoxins. Pyrogen contamination can be prevented by filtration technology. Microbial filtration methods are capable of sterilization without using heat or radiation.

However, microorganisms without cell walls or steady shape (microplasms, rickettsia, viruses) can pass bacterial filters.

Filtration based sterilization is used for making heat-sensitive injections, ophthalmic solutions and biological products. In this case sterilization is not a finishing (terminal) operation of sterile solution preparation, unlike in case of heat- or radiation based sterilization. Alternatively, solutions can be first sterilized by heat without the heat-sensitive components (e.g. excipients, heparin, vitamins, volatiles), after which these components, subjected to a sterilizing filtration are added to the cooled sterilized solution.

Sterilization of air and other gases required for creating clean rooms is done by filtration. Sterilized gases are applicable for aerating industrial fermenters, centrifuges, autoclavs and freeze-dryers.

Membrane filtration time can be decreased by pre-filtration. Both depth and surface filtration are suitable for separating high volumes of particles. Fibrous, granular

and sintered substances are best for depth filtration while multiple layers of glass or polymer mesh filters are best for surface filtration.

Bacterial filtration is based on the adsorption of microorganisms and mechanical sieving, which do not change the composition of the filtered solutions, but separate not only microorganisms but particles, fibers suspended in the solution too (e.g. from pre-filtration).

The filtration requires high difference in pressure between the filrate and the solution to be filtered due to the small pore size (0.1-0.45 μm). To reach this we can pressurize from the side of the filter or we can apply vacuum from the side of the filtrate.

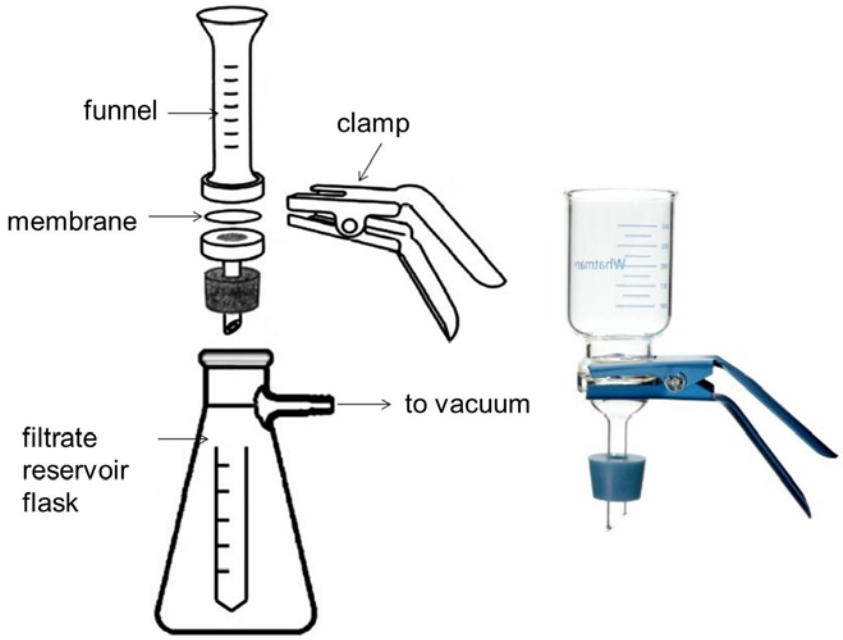

Fig. 28.15.
Laboratory-scale flat sheet membrane filtration

In the process of preparing injection solutions and infusions flat sheet membrane filters of 0,2-0,3 μm or smaller pore size (such are *Millipore* and *Sartorius* filters) can be used for *microbial decontamination* of solutions. Concentration and purification of biological substances can be done using such filters and they are useful in *biotechnological* work too.

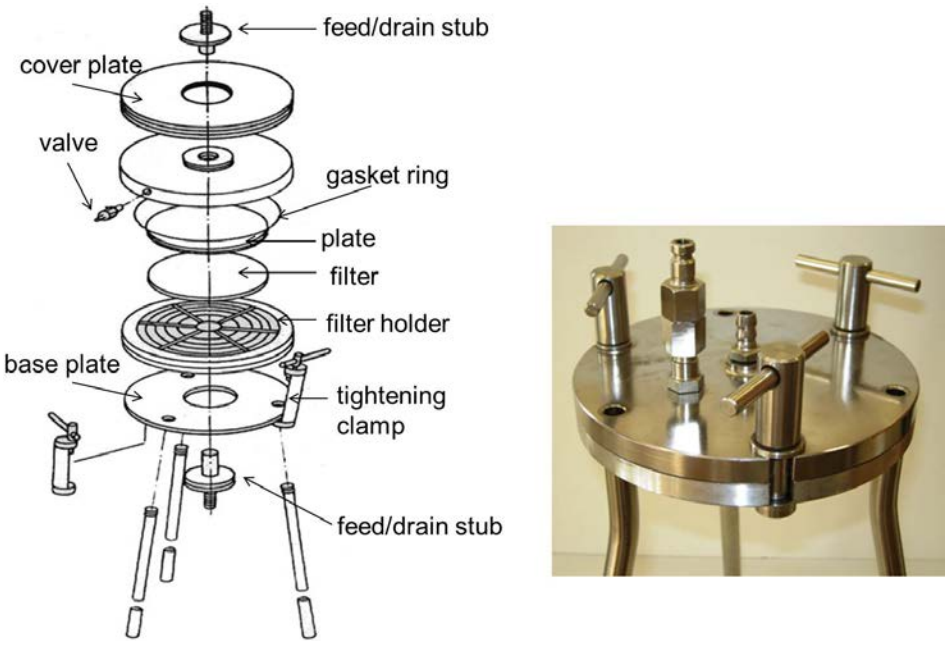

Fig. 28.16.
Flat sheet membrane filter kit for making injections and infusions

Pre-filtering solutions on a frame and plate filter using screen filters (pl. Seitz®KS80, KS50,EK, EK1, Europor® K 70, K 60, K 40) can significantly extend the service life of membrane filters (See also chapter *Filtration*).

When filtration sterilization production technology is designed, the following aspects shall be given due consideration:

1) the level of microbial contamination before filtration,
2) filtering capacity,
3) batch volume.

The adequate device and filter shall be chosen based on these and there are the unit operation parameters of filtration, filter pressure and filtration time to be determined.

The suitability of a filter depends on whether the test-microorganisms can pass it under production conditions.

The prime production conditions to be fulfilled in case of sterilizing filtration are the following:

1) filtration and filling must be located as close to each other as possible,
2) the application of filters of 0,2-0,3 μm (usually 0,22μm or smaller pore size or equivalent),
3) solute must not absorb to the filter,
4) filter must not release contaminants,
5) filter must be intact (e.g. “bubble point” shall be checked both before and after filtratrion).

Membrane filters are generally made of cellulose nitrate and ~acetate or polycarbonate.

In infusion production, when alternative filtration methods (e.g. frame and plate filter press) are used, it is advisable to use 0,40 - 0,80 μm membrane filters for additional delinting of the filtrate (using pre-shrunk glass filters if necessary).

28.1.5 Chemical sterilization

The *chemical agents* used for sterilization must have broad spectrum bactericidal effect, be harmless to humans, animals and plants, environmentally friendly, easy to handle and economical.

Required parameters of chemical sterilization:

1) the mode of action of the sterilizing agent,
2) the concentration required for achieving the sterilizing effect and
3) treatment time.

The agents used for chemical sterilization can be gaseous or liquid.

28.1.6 Gas sterilization

The applicability of gas sterilization in pharmaceutical technology is restricted, as gases might be absorbed by the sterilized substances and are difficult to remove. Subsequent to sterilization a certain duration of aereation is necessary to prevent any further tissue damaging effects.

About this method of sterilization:

1) It is used only in the absence of suitable alternative methods,
2) it requires gas concentration, humidity, temperature and duration to be recorded,
3) it requires the use of microbiological indicators,
4) a sample from each batch must be tested for sterility.

In case of gas sterilization gas and moisture must permeate the substance to be sterilized and leave after the process is finished.

Previously vapours of *formaldehyde* have been used for sterilizing instruments, device parts, rubber and reusable plastic instruments. In the course of sterilization with formaldehyde gas a formaline solution mixed to high pressure steam is introduced to the workspace from which air had previously been removed. The released formaldehyde gas kills or inactivates microorganisms in the 60-80°C workspace. The disadvantages of formaldehyde are weak penetrating force, highly irritating smell and difficulty of removal.

Ethylene oxide is gaseous state at room temperature (boiling point at 10,4 °C). It reacts with amino acids, proteins and DNA, thus preventing cellular reproduction. It is equally effective against spores and vegetative forms. It has strong penetrating force. Another advantage is that it is suitable for disinfecting heat-sensitive instruments (e.g. thermoplastic plastics). It has the disadvantage of causing oedema of lung if inhaled therefore it must be used with extra care. Its mutagenic and carcinogenic properties have been established in recent years, making it less used today.

Recently sterilization with *β-propiolactone* is used. Microbes are killed by its alkylating effect. It can be used at low temperatures, its vapors are less irritating; it is active in low concentrations, but carcinogenic, requiring days (min. 48 hrs) of aereation. It does not penetrate porous substances well. Polymerizes at temperatures above 50°C.

Fig. 28.17.
Gas sterilizer

28.1.7 Liquid antimicrobial chemicals

Liquid antimicrobial chemicals are mostly used for disinfecting surfaces, skin and hands.

Alcohols and *phenols* denaturalize proteins, havinging a membrane-damaging effect. Ethanol, isopropanol, benzyl alcohol, chlorobutanol, phenol, phenylethyl alcohol belong here.

Of *aldehyde* type compounds that are suitable for disinfection formaldehyde, glutaraldehyde, orto phtalaldehyde deserve emphasis. These compounds denaturalize proteins by reacting with amino radicals and forming cross-links.

Halogens and their derivatives, primarily the compounds of iodine (e.g. pvp-i) and chlorine (e.g. sodium hypochlorite) bond with thiol and amino radicals, damaging proteins.

Metals (e.g. Cu, Ag, Zn) and their salts are useful in antimicrobial surface treatment. Their applicability can be enhanced with nanotechnological methods (e.g. linings, wall paints containing nano silver).

Quaternary ammonium compounds work through their membrane-damaging effect.

28.1.8 Gas plasm sterilization

Gas plasm sterilization is ideal method for temperature-sensitive devices, equipments and materials.

In the course of plasma sterilization first vacuum is created in the workspace of the closed system device, then hydrogen peroxide is injected. Electric or magnetic field causes the cold hydrogen peroxide plasma state. These positively and negatively charged ions (free radicals or excited atoms) generated this way have antimicrobial – virucidal, bactericidal and sporacidal – effect.

The advantage of the method is that sterilization takes place at low temperatures (46±4 C°) in dry air, so it is compatible with heat- and moisture-sensitive substances. Sterilization takes 45-75 minutes. Residual O_2 and H_2O are nontoxic.

Subsequent to sterilization the contents of the device do not require additional treatment (e.g. cooling, aereation) as they are dry and ready to use.

Fig. 28.18.
Plasm sterilizer

This method is suitable for sterilizing medical instruments, metal appliances, radiotherapeutic devices, ultrasound heads. It is inappropriate for cellulose derivatives, linen, liquids, powders, substances not tolerating vacuum.

28.2 Controlling sterilization efficiency

There are various methods for *controlling sterilization efficiency*:

1) instrument control of physical parameters (temperature, pressure, time, moisture content),
2) chemical indicators that indicate changes in parameters by changing color (e.g. Browne's tubes, indicator tapes),
3) microbiological indicators.

The most reliable method for sterilizer validation and verification is using *biological indicators*. It is advisable to position indicators to the spot least accessible for the sterilizing agent. Microbiological indicators are microorganism-based standardized products used for evaluating the efficacy of sterilization methods. The rule of thumb for selecting the biological indicator is that it must have higher resistance to the specific sterilization method than the potential contaminant microorganisms in the product to be sterilized. The sterilization process is inadequate if, after sterilization, the test microorganisms produce growth after incubation on a culture medium.

Table 28-II.
Bacterium strains applicable as biological indicators with various methods of sterilization

Sterilization method	Microorganism
Steam	*B. stearothermophilus*
Dry heat	*B. subtilis var niger*
Gas	*B. subtilis var niger*
Radiation	*B. pumilus*

Microbes are not killed all at once in sterilization. Kill rate is often constant in time, in which case the same percentage of the initial living cell count survives at any examined interval. Kill rate, correlated with initial germ count in the function of time is characterized by a generally exponential process:

$$N_t = N_o e^{-kt} \tag{1.}$$

of which:

$$ln\, N_t = ln\, N_o - kt \tag{2.}$$

N_t germ count at t point of time
N_o initial germ count
k primary rate constant

According to the *Arrhenius* Equation:

$$k = Ae^{-\frac{E_a}{RT}} \tag{3.}$$

$$ln\, k = ln\, A - \frac{E_a}{R}\frac{1}{T} \tag{4.}$$

k primary rate constant
A constant
E_a apparent activation energy of thermal destruction (kJ/mol)

Sterilization had previously been considered a process in which all microorganisms are killed or eliminated. Today sterilization is defined as a process, which ends with the treated or sterilized product becoming free of viable microorganisms with a certain degree of probability. The reason for this shift is that it cannot be fully guaranteed or ascertained with currently available examination methods, that total sterilization is achieved for each and every unit of a sterilized batch.

The probability (P) of a single contaminated product after sterilization:

$$P = (1 - c)^n \tag{5.}$$

n number of samples
c contamination ratio

$$c = \frac{N_f}{N_s} \tag{6.}$$

N_f number of contaminated units
N_s number of units in batch

Sterility Assurance Level, (*SAL*) stands for the probability of a single unit of a batch remaining contaminated in the course of production. The lower this value is, the better the given method of sterilization. The methods used for sterilization or the adjustments of sterilization process parameters should yield a $SAL \geq 10^{-6}$ value. That is, the prevalence probability of a contaminated unit after sterilization should be $\geq 10^{-6}$, in other words maximum one viable microorganism in a population of 10^6 microorganisms.

When sterilized products are applied, the instruments used (e.g. scalpel, needle) and skin too have to be sterilized to the prescribed *SAL* level.

Inactivation Factor (IF) is the ratio of initial and final living cell counts of sterilization

$$IF = \frac{N_o}{N_t} = 10^{t/D} \tag{7.}$$

D value (decimal reduction value) is the duration required for reducing the number of viable microorganisms to 10% of the initial count. This value is affected by microbe type, applied temperature and the magnitude of radiation dose.

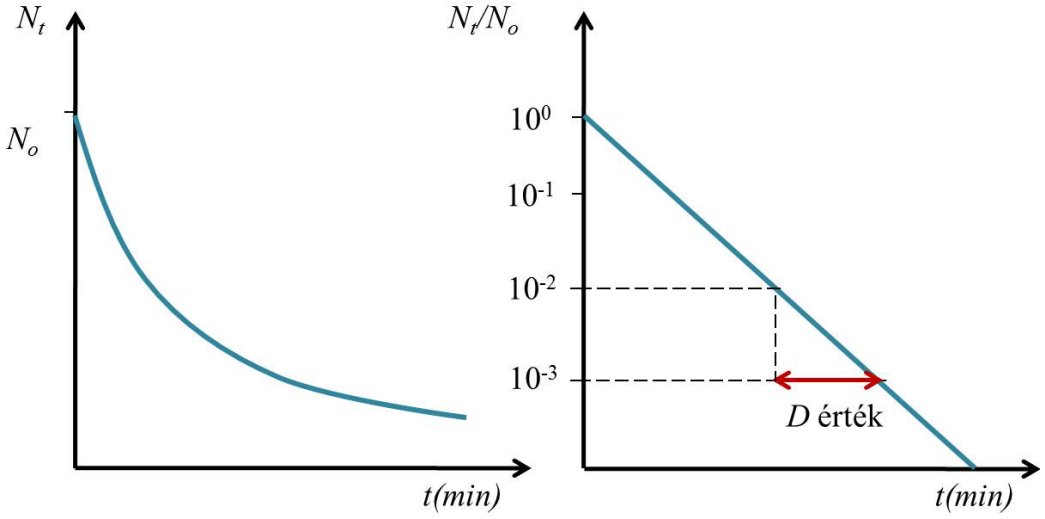

Fig. 28.19.
Bacteria killed in the function of time; establishing *D* value

The thermal destruction rate of microorganisms changes with time.

Z value is the change in temperature required to change *D value* by an order of magnitude. It expresses the thermal dependence of the heat resistance of microorganisms in case of steam sterilization:

$$Z = \frac{T_2 - T_1}{\log D_1 - \log D_2} \tag{8.}$$

Z value can be defined graphically in a semi logarithmic system:

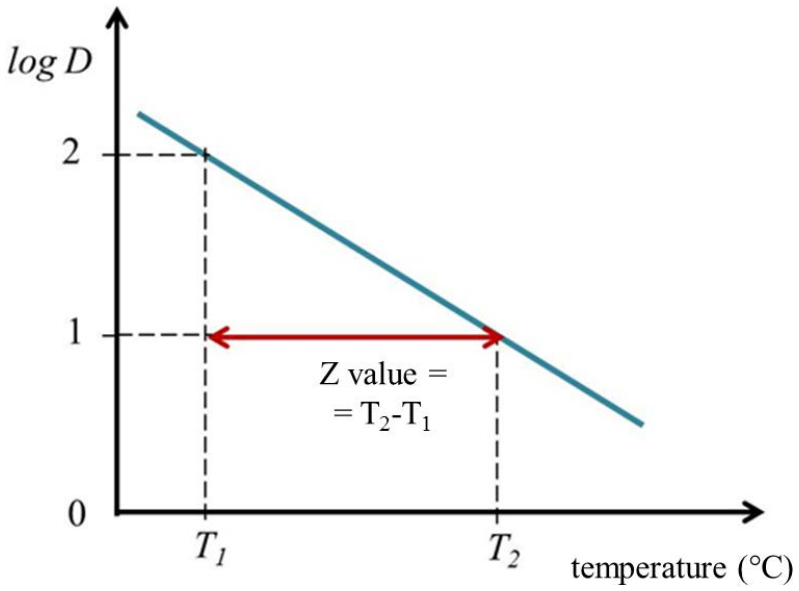

Fig. 28.20.
Bacteria killed in the function of time; establishing Z value

The F_o value of saturated steam sterilization is the lethality correlated to 121°C expressed in duration-equivalent minutes, which is achievable by a sterilization process executed in the terminal container.

The F_o value applies to microorganisms whose Z value is theoretically 10.

$$F_0 = D_{121}(logN_0 - logN_t) = D_{121}logIF \qquad (9.)$$

D_{121} a D value of 121 *C*

Parenteral pharmaceutical products must meet the general quality requirements for pharmaceutical products. There are additional special requirements and rules to fulfill:

1) sterility and
2) pyrogen-free state.

A sample must be taken from every batch for *sterility testing*. The test detects living microorganisms or their reproducible spores in medicinal products. (Not capable of detecting viruses.)

Heat sterilized or aseptically made injections, infusions, solutions, ointments, oily preparations, powder ampoules, vaccines, surgical bandages and suture materials and blood therapy preparations can be tested by direct grafting.

Prior to the test the sterility and susceptibility of the culture media shall be verified.

The tested product is flawed if there are microorganism cultures in two or more samples after the required incubation time.

In case of terminal sterilization sterility testing can be substituted by *parametric release,* which must be previously authorized by health authorities. To obtain a permit the appropriate validation of the manufacturing process must be certified, demonstrating that there is correlation between the test results of the end product and the monitoring of the process.

At the end of the 19th century it has been found that injecting watery solutions in the human body may cause a rise in temperature. The agent causing the fevered symptoms was named *pyrogen*. Pyrogen contaminations usually enter products in the course of heat sterilization.

Pyrogens are cell-membrane fragments of Gram-positive bacteria or lipopolysaccharides (*LPS*). Pyrogens of different structure may occur in low numbers. The most frequent pyretics are the endotoxins of these bacteria, also causing bacteremia, sepsis, septic shock, coagulation disorders or changed metabolism.

The chemical resistance of pyrogens is extraordinary, but they are sensitive to oxidation. High temperature treatments (200-250 °C) are applicable depyrogenation. Pyrogens can be tied to activated carbon sheets or powder.

Earlier the rabbit test was used for detecting endotoxins. A certain volume of the tested sample was injected in the ear vein of rabbits, monitoring rectal body temperature of the injected rabbits. In case of a pyretic reaction the sample contained endotoxin. This method is time consuming and not quantitative, a clear disadvantage.

The *Limulus Amebocyte Lysate (LAL)* test is for detecting and quantifying Gram-negative bacterial endotoxins. This test uses the lysate of the amebocytes of the horseshoe crab (*Limulus polyphemus*). *LAL*, exposed to endotoxins produces a gel precipitate and becomes opalescent. Measurements based on the *LAL test* are sensitive, reproducible and economical procedures.

28.3 Sterile pharmaceutical products

Pharmaceutical products have to be sterile only if the dosage form or the state of the administration's location justifies it. Accordingly, in case of injured or operated skin or mucous membrane only sterile products may be used instead of the otherwise used non-sterile products.

The dosage forms requiring a sterile production process are primarily injections, infusions, haemodyalysis solutions, peritoneal dialysis solutions, perfusion solutions used in organ transplant operations, ophthalmic products and inhalation aerosols, whose manufacturing process is supplemented with sterilization and depyrogenation.

The active agents in parenteral products may be "traditional" low molecular mass substances, proteins and other large molecule substances, biological substances, vaccines, monoclonal antibodies, oligonucleotides, nanotechnological preparations and genes in the not so distant future.

According to the pharmacopeial definition *injections* are sterile solutions, emulsions or suspensions. Their active ingredient(s) and the contingent excipients are dissolved, emulsified or suspended in water or an appropriate – if justifiable, non-sterile – non-water liquid or a compound of these vehicles.

Infusions are sterile water based solutions or O/W type emulsions which are usually isotonic with blood. Infusions are generally used in high volume. They must be free of microbiological preservatives.

Infusion products can be grouped according to the following classification:

1) solutions for liquid and electrolyte therapy,
2) blood- and volume substitutes, volume expanders,
3) compound infusions
   a) intravenous additives,
   b) cytostatic compounds,
   c) parenteral nutrition compounds.

4) solutions for osmotherapy,
5) solutions for dialysis.

Table 28-III.
Comparison of injections and infusions

Aspect	Injection	Infusion
purpose	parenteral administration of medicines	supplementation of water, electrolytes, plasma, parenteral nutrition, parenteral administration of medicines
volume	maximum 50 ml	50-500 ml
dosage form	practically to any body part	only i.v. and intraperitoneal (occasionally sc.)
physical-chemical classification	true solutions, colloid solutions, emulsions or suspensions	true solutions, colloid solutions or O/W type emulsions
solvent	water and/or other solvents	only water
isotonia	aspired, but often unachievable	required
isohydria	aspired, but often unachievable	required
isoionic	less important	expedient and important for certain types of infusions
colloid osmotic pressure	insignificant	important for plasma supplements
sterility	required	required
pyrogen-free state	required	required
preservatives	allowed	not allowed

The preparation, filtration and filling of parenteral solutions must happen in a closed system, strictly observing the requirements of aseptic production.

Preparation of injection and infusion solutions is a specialized application of dissolution, in which the goal is a sterile solution in the end, by observing the general aspects of dissolution and employing other operations as necessary (see also chapter *Dissolution*.)

The purity and cleanness of the substances and instruments used, operation parameters – in short the methods and circumstances of production greatly influence the chemical and mechanical purity, sterility and pyrogen-free state of infusion and injection solutions.

In the production of parenteral preparations universally required aseptic production means that the elimination of all pathogenic and non-pathogenic microorganisms is attempted all through the production process, even if the product is thoroughly sterilized. The process is started with sterile and pyrogenic-free materials and preserving this microbiologically pure state is in the course of production is a priority.

Excipients frequently used for making injections and infusions:

1) solvents (most often: Aqua ad iniectabilia, see chapter Dissolution),

2) cosolvents (e.g.: propylene glycol, glycerine, polyethylene glycol),
3) solubility enhancers s (e.g.: olubilizers, cyclodextrins)
4) isotonizing agents (sodium chloride, glycose),
5) pH correctors (e.g.: hydrochloric acid, sodium hydroxide, sodium bicarbonate, buffers),
6) microbiological stabilizers (e.g.: phenol, methyl paraben, chlorobutanol, benzalkonium chloride, thiomersal),
7) inert gases (e.g.: nitrogen, carbon dioxide),
8) antioxidants (e.g.: sodium bisulphite, sodium metabisulphite, ascorbic acid, glutathione),
9) viscosity agents (e.g.: methyl cellulose, carboxymethyl cellulose sodium, PVP, dextrane)

Suspension type injections belong either with heterogenous disperse or with suspensoid disperse systems. It is a suitable dosage form for incorporating insoluble or poor solubility pharmacons and for depo effect. If homogenization is appropriate, particle size is d<5 μm. For oily suspensions the dispersion medium is olive oil, sesame oil or peanut oil.

The stability and biocompatibility of emulsion type parenteral products are significantly affected by the particle size and size distribution of dispersed particles. Particle diameter must be d<1μm for intravenous administration. Particles bigger than 5 μm in the blood circulation may cause embolisms by blocking capillaries. Parenteral emulsions must be able to retain their particle size in storage by preventing particle coalescence.

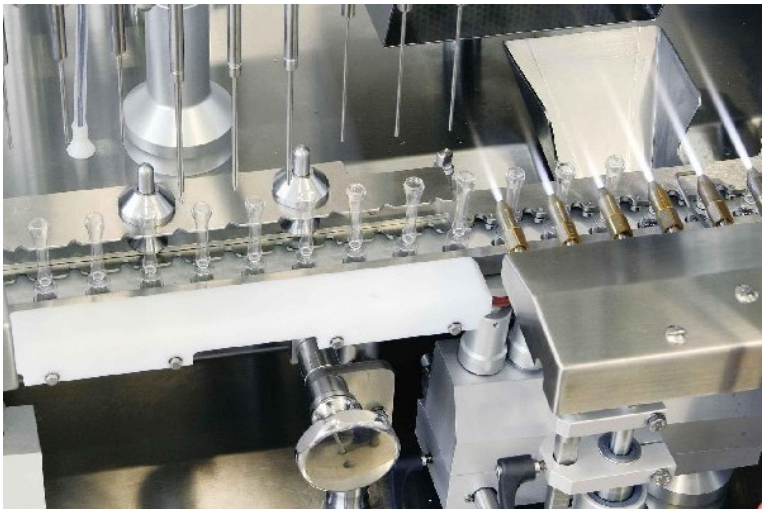

Fig. 28.21.
Filling and sealing injection ampoules

Injection and infusion concentrates are sterile solutions, of which injections or infusions are made via dilution. These preparations must be diluted with the prescribed solvent to the prescribed volume before use. The diluted solution must meet the test requirements for injections or infusions, respectively.

The *powders for making injections and infusions* are sterile, solid state substances marketed in containers fit for end use. Mixed with the prescribed volume of the prescribed solvent they form a clean, solution free of particle impurities or a homogeneous suspension. The resulting preparation must fulfill the test requirements

for injections and infusions. The solid components of these solutions to be solved immediately before use (ex tempore) can be micro- or nanocrystals or lyophilisates, which cannot be kept in solution for extended periods due to their lability. Aseptic handling of these solutions naturally applies to dissolving, syringe filling and giving the injection too.

Sol-gel transformation is suited for making *injectable gel preparations*. Aqueous solutions of poly(ethylene glycol-b-DL-lactic acid-co-glycolic acid-b-ethylene glycol) (PEG-PLGA-PEG) triblock copolymers at room temperature a free-flowing sol and become a gel at body temperature.

Parenteral medicinal implants (e.g.: *implantable tablets, Compressi implantablies*) are solid sterile products of suitable size and shape, intended for parenteral implantation. These implants provide steady release of the active ingredient over an extended period of time. Implants are marketed individually packaged in sterile containers. Their structural frame is composed of such *biocompatible and biodegradable* polymers that are capable of both controlling the release of the active ingredient and completely decompose, avoiding the need for posterior surgical removal. Such preparations can significantly enhance bioavailability, therapeutic effect and compliance while reducing adverse effects.

Adjustments to the ratio of monomers, average molecular weight and degree of crystallinity produces excipients of diverse physical qualities. This is how biological degradation becomes controllable and through it drug release rate and, over a period of days or months, the duration of effect too, as planned.

The commonly used biodegradable polymers, grouped by structure, are the following:

1) polyamide,
2) polyanhidride,
3) polyesther,
4) poly alkyl cyanoacrilate,
5) polyacetate,
6) polyphosphasene and
7) derivatives of polyurethane.

The polymers *Polyglycol acid (PGA)*, *polylactic acid (PLA)* and their copolymers *polylactate-co-glycolate (PLGA)* and *poly-ε-caprolactone (PCL)* are used most frequently for making controlled drug release parenteral medicinal implants. The advantage of these polymers is that their esther bonds get hydrolyzed in the body, forming lactic acid and glycolic acid. These substances are nontoxic and naturally present in the body.

PGA is a linear alpha polyesther. Polymerization of the glycol monomer yields in a high molecular weight substance. It is absorbed in 4-6 months completely.

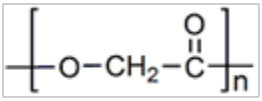

Fig. 28.22.
Polyglycol acid (PGA)

PLA is made from lactic acid, similarly by polymerization or polycondensation.

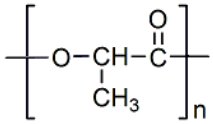

Fig. 28.23.
Polylactic acid (PLA)

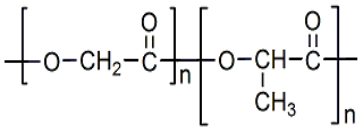

Fig. 28.24.
Polylactate-co-glycolate (PLGA)

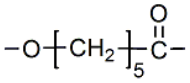

Fig. 28.25.
Poly-ε-caprolactone (PCL)

Sterility and depyrogenization are important requisites for parenteral nanomedicines too. Vaccines and parenterally administered biotchnological preparations too must be sterile and free of pathogens and pyrogens.

Questions

1) What does aseptic medicine production mean?
2) What is sterility?
3) What are the main types of effects affecting microorganisms during sterilization?
4) What is inactivation factor?
5) What is D value?
6) What is Z value?
7) What is the SAL value?
8) What is the Fo value?
9) What are the possible sources of contamination in the course of making sterile pharmaceutical products?
10) What clean room classes do you know of?
11) What operation parameters control sterility in dry heat sterilization?
12) What operation parameters control sterility in moist heat sterilization?
13) What are the advantages of γ-ray sterilization?
14) What are the primary production requirements of sterilizing filtration?
15) Under what conditions can gases be used for sterilization?
16) How would you define the notion of plasma sterilization?

17) What methods are there for detecting pyrogens?

18) What pharmaceutical products require sterile production?

19) What properties of injections and infusions are identical and which are different?

20) What biodegradable polymers do you know of?

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