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Educational guide to
"INDUSTRIAL DRUG TECHNOLOGY OF SOLID PHARMACEUTICAL FORMS"

(for independent work)

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Reviewer:

Manual to practical lessons in Drugs technology (industrial technology) "INDUSTRIAL DRUG TECHNOLOGY OF SOLID PHARMACEUTICAL FORMS" / Borisyuk I.Yu., Fizor N.S., Zamkovaya A.V., Kutasevych N.V. - Odessa, ONMedU, 2022. – P.-46.

According to the content of the Drug Technology program, this manual presents the basic theoretical questions required to complete the course and also tests items to check the assimilation of educational material by students.
The publication is recommended for the students of pharmaceutical faculties also for medical high school students.

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INTRODUCTION

Human health depends on the availability of safe, effective, and affordable medicines. The choice of the dosage form, the method of its introduction into the body is an important task of pharmacotherapy. The correctly selected dosage form is the key to the success of treatment, which is associated with the biopharmaceutical properties of the drug, the patient's feelings, and the characteristics of his body. Therefore, the pharmaceutical industry faces the task of increasing the range and improving the quality of finished medicines.

Currently, an important problem in pharmaceutical technology is the prolongation of the duration of action of drugs. Recently, several advances have been made in the development of new drug delivery methods. Along with the creation of new dosage forms and drugs, new technologies and equipment are being developed all over the world

The aim of the discipline "Drugs technology" (industrial technology) is giving to students theoretical knowledge about trends in pharmaceutical production development.

This discipline includes five lectures (10 hours), twenty practical lessons (40 hours), and eighty hours of independent work of students.

This manual consists of **fivetopics**. Upon termination of each unit to students are offered the test for self-checking knowledge. The test includes "Krok-2" tests questions. To each question, there are 5 variants of answers from which correct is only 1. If the student has answered correctly on 80% of questions, the material is acquired well, 80% - it is good, 90% - is excellent. If there are fewer than seven right answers, it is recommended to work the text of the unit repeatedly.

The glossary of terms which meet in the given unit with the explanation of their value and questions which are taken out on seminar also is resulted.

MODERN PRODUCTION OF SOLID PHARMACEUTICAL FORMS. DEVELOPMENT PROSPECTS

СУЧАСНЕ ВИРОБНИЦТВО ТВЕРДИХ ЛІКАРСЬКИХ ФОРМ. ПЕРСПЕКТИВИ РОЗВИТКУ.

Controlled drug release

The main problem of pharmaceutical technology is the prolongation of drugs action time that in many cases have extended maintenance of strictly some concentrations of preparations in bioliquids and tissues of an organism is necessary.

Appreciation of the advantages of controlled drug release, development of many novel controlled release systems, and also the interest of major pharmaceutical enterprises in protecting marketed drug products, has led to increased interest in this type of dosage form. Most controlled-release products currently market include diuretic agents, cardiovascular and respiratory drugs, and compounds acting on the central nervous system (CNS). Less attention was received to antimicrobial agents.

Medicine's prolonged action can be reached by changing medicinal substance's chemical structure (complexing, polymerization, etherification), due to selection of the carrier with particular properties, changes of a solution viscosity, selection of the medicinal form type.

In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under- and overdosing. On the upper hand the controlled-delivery systems used can include:

- maintenance of the desired range of drug levels;

-the need for fewer administrations;

- optimal use of the drug in question;

- and increased patient compliance.

While these advantages can be significant potential disadvantages cannot be ignored: the possible toxicity or non-biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations.

Providing control over drug delivery can be the main factor when traditional oral or injectable drug formulations cannot be used. These include situations requiring the slow release of water-soluble drugs, the fast release of low- solubility drugs, drug delivery to specific sites, drug delivery using nanoparticulate systems, delivery of two or more agents with the same formulation, and systems based on carriers that can dissolve or degrade and be readily eliminated. The ideal drug delivery system should be inert, biocompatible, hard mechanically, comfortable for the patient, capable of high drug loading attain, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize.

In recent years, controlled drug delivery formulations and the polymers used in these systems have become much more sophisticated,

with the ability to do more than only extend the effective release period for a particular drug. For example, current controlled-release systems can respond to change in the biological environment and deliver — or cease to time. The traditional tablets or injections, the drug level in the blood follows the profile shown in Fig. 1.1 (A). The amount that rises after each administration of the drug is that the blood level of the agent should remain between a and then maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective. In controlled drug delivery systems designed for long-term administration, the drug level in the blood follows the profile shown in a month (Lupron Depot) to 5.

In recent years, controlled drug delivery formulations and the polymers used in these systems have become much more sophisticated, with the ability to do more than only extend the effective release period for a particular drug. For example, current controlled-release systems can respond to changes in the biological environment and deliver — or cease to decrease until the next administration. The main point with traditional remaining constant, between the desired maximum and minimum, for an extended period. Depending on the formulation and the application, this time may be all over from 24 hours (Procardia XL) to 1 year (Norplant).

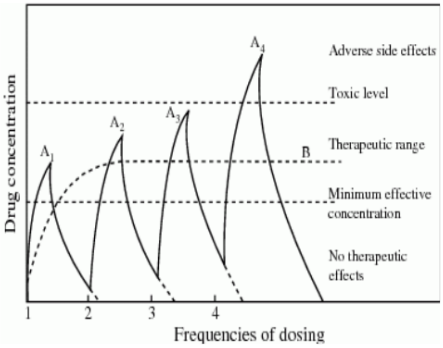

Fig. 1.1. Drug concentration profiles in the systemic circulation as a result of taking a series of multiple doses of a conventional drug-delivery system (Ai, A_2, ...) in comparison with the ideal drug concentration profile (B).

The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of delivery — drug-based on these changes. In addition, materials were developed, that should lead to targeted delivery systems, which can be directed a particular formulation to the specific cell, tissue, or site where the drug it contains is to be delivered. Till much of this work is still in its early stages, emerging technologies offer possibilities that scientists have only begun to explore.

Advantages of controlled drug release. The high cost of controlled-release dosage forms can be justified, just only if they can offer therapeutic advantages, i.e.:

-improved maintenance of therapeutic drug levels in the circulation;

- reduced dosing frequency;
- reduced fluctuation in circulating drug levels;
- increased convenience to the patient;
- reduced patient care time;
- less nighttime dosing
- more uniform-pharmacologic response
- reduced GI irritation;
- and reduced side effects.

The second of these, reduced dosing frequency, has often been claimed as a sufficient rationale for the development of a controlled release dosage form but has become unacceptable as a sole criterion. This is understandable given the current emphasis on cost containment in health care.

Disadvantages of controlled drug release. Possible disadvantages of controlled release dosage forms include the possibility of dose dumping, less facile dose adjustment, increased potential for hepatic first-pass metabolism, possible delay in onset of action, possibly lower system availability, and time of drug release limited (o residence time of formulation in the optimum absorption region(s) of GI tract.

Dose dumping, or inadvertent rapid release of the drug, is significant for potent drugs with this narrow therapeutic index. Good manufacturing practice (GMP) generally reduces the probability of this happening. Fine dose adjustment is often difficult with controlled release formulations. Controlled release tablets that use a granule matrix may be

subdivided to reduce the dose, but repeat action tablets or osmotic pump devices lose their controlled release properties once the dosage form is fractured. Increased first-pass metabolism may occur with drugs that are cleared by the liver, but only if hepatic clearance is saturable following rapid absorption from conventional dosage forms. Reduced systemic availability is common with controlled release dosage form, availability generally being 80-85% of that from conventional formulations. Limited residence time in the GI tract is a potential disadvantage of oral controlled release product, and this distinguishes oral from other controlled release dosage forms (e.g., skin patches, which can provide a slow release of drug over a prolonged period).

Drugs that are unsuitable for controlled release. Some drugs are unsuitable for controlled release formulations. Typical characteristics of such drugs include short biological half-life, long biological half-life, potent drug with narrow therapeutic index, large dose, poorly absorbed, low or slow dissolution, active absorption, the time course of activity not the same as that of circulating drug levels, and extensive first-pass metabolism.

A controlled release form of a drug has a short biological half-life, <2 h, or administered in large doses may need to contain a prohibitively large amount of drugs. A long biological half-lives medicinal (>8 h) are generally sufficiently sustained in the body from conventional doses, and prolonged-release is unnecessary. Incorporating the slowly dissolving compounds into a controlled release formulation is likely counterproductive since dissolution is rate-limiting anyway. Administering drugs like warfarin, whose' pharmacologic effect is prolonged relative to its blood profile, offers no therapeutic advantage. Incorporating such compounds as some beta-lactam antibiotics, fluorouracil, and some amino acids, which appear to be absorbed predominantly from the proximal intestine, is likely to reduce their efficacy and achieve little or no prolongation of effect. Based on what was said earlier, if a drug undergoes saturable first-pass metabolism from conventional doses, its systemic availability may be decreased after controlled release.

Although the above arguments provide utility general rules, there are many exceptions. Nitroglycerin has a biological half-life of less than 0.5 h. It is generally considered to be poorly absorbed and is rapidly metabolized by the liver, with obvious first-pass implications. However,

a large number of oral controlled nitroglycerin products are marketed. Low circulating levels of nitroglycerin obtained from these products appear to provide adequate prophylaxis against angina attacks, but not against acute angina episodes.

Many advancements have been made recently in the development of new techniques for drug delivery.

These techniques are capable of regulating the rate of drug delivery, sustaining the duration of therapeutic action, and/or targeting the delivery of drugs to a specific

tissue. These advancements have already led to the development of several novel drug delivery systems that could provide one or more of the following benefits:

1. Controlled administration of a therapeutic dose at a desirable rate of delivery
2. Maintenance of drug concentration within an optimal therapeutic range for a prolonged duration of treatment
3. Maximization of efficacy-dose relationship
4. Reduction of adverse side effects
5. Minimization of the need for frequent dose intake
6. Enhancement of patient compliance

Based on the technical sophistication of the controlled-release drug delivery systems (CrDDSs) that have been marketed so far, or that are under active development, the *CrDDSs can be classified* as follows:

1. Rate-preprogrammed drug delivery systems
2. Activation-modulated drug delivery systems
3. Feedback-regulated drug delivery systems
4. Site-targeting drug delivery systems

Further, the scientific concepts and technical principles behind the development of this new generation of drug-delivery systems are outlined and discussed.

Rate-preprogrammed drug delivery systems. In this group of CrDDSs, the release of drug molecules from the delivery systems has been preprogrammed at a specific rate profile. This is accomplished by system design, which controls the molecular diffusion of drug molecules in and/or across the barrier medium within or surrounding the delivery system. Pick's laws of diffusion are often followed. These CrDDSs can further be classified as follows:

1. Polymer membrane permeation-controlled drug delivery systems

2. Polymer matrix diffusion-controlled drug delivery systems

3. Polymer (membrane/matrix) hybrid-type drug delivery systems

4. Microreservoir partition-controlled drug delivery systems

Polymer Membrane Permeation-Controlled Drug Delivery Systems. In this type of CrDDS, a drug formulation is either totally or partially encapsulated in a drug reservoir compartment whose drug-releasing surface is covered by a rate-controlling polymeric membrane. The drug reservoir can be drug solid particles, a dispersion of drug solid particles, or a concentrated drug solution in a liquid- or solid-type dispersing medium. The polymeric membrane can be fabricated from a homogeneous or a heterogeneous nonporous polymeric material or a microporous or semipermeable membrane. The encapsulation of drug formulation inside the reservoir compartment can be accomplished by molding, capsulation, microencapsulation, or other techniques. Different shapes and sizes of drug delivery systems can be fabricated.

The release of drug molecules from this type of CrDDS is controlled at a preprogrammed rate by modulating the partition coefficients (the partition coefficients for the interfacial partitioning of drug molecules from the reservoir to the membrane and from the membrane to the aqueous diffusion layer), the diffusivity of drug molecule in the rate-controlling membrane and the aqueous diffusion layer, the rate-controlling membrane and the thickness of the membrane. For microporous membrane, the. porosity and tortuosity of the pores in the membrane should be included in the estimation of the diffusivity of drug molecules in the rate-controlling membrane and the thickness of the membrane.

Several CrDDSs of this type have been successfully mar.

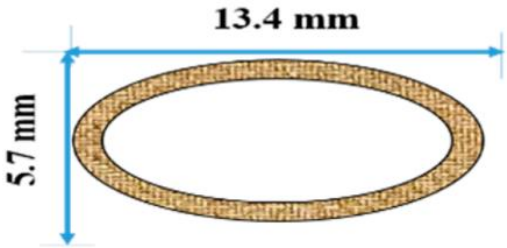

Fig. 1.2. Diagrammatic illustration of a unit of Ocusert system

Transderm-Nitro7 system. In this controlled-release transdermal therapeutic system the drug reservoir, which is a dispersion of nitroglycerinlactose triturate in a silicone (medical grade) fluid, is encapsulated in ellipsoid management of glaucoma.

Ocusert® system. In this controlled-release ocular insert, the drug reservoir is a thin disc of pilocarpine-alginate complex sandwiched between two transparent discs of microporous membrane fabricated from ethylene-vinyl acetate copolymer (Fig. 1.2). The microporous membranes permit the tear fluid to penetrate the drug reservoir compartment to dissolve pilocarpine from the complex. Pilocarpine molecules are then released at a constant rate of 20 or 40 pg/h for a 4- to 7-day shaped thin patch. The drug reservoir is sandwiched between a drug-impermeable metallic plastic laminate, as the backing membrane, and a constant surface of drug- permeable, rate-controlling membrane of ethylene-vinyl acetate copolymer (Fig.1.3). This device is fabricated by an injection-molding process. A thin layer of silicone adhesive is further coated on the drug-permeable membrane so that intimate contact of the drug-releasing surface with the skin surface is achieved and maintained. It is engineered to have nitroglycerin delivered transdermally at a rate of 0,5 (mg/cm2) /day for the daily relief of angina.

The same technology has been utilized in the development of the following: 1) the Estraderm® system, which administers a controlled dose of estradiol transdermally over 3-4 days for the relief of postmenopausal syndrome and osteoporosis; 2) the Duragesic system, which provides a transdermal-controlled administration of fentanyl, a potent narcotic analgesic, for 72-h relief of chronic pain; and 3) the

Androderm* system, which provides a transdermal-controlled delivery of testosterone, through nonscrotal skin, for the 24-h replacement therapy of testosterone-deficient patients.

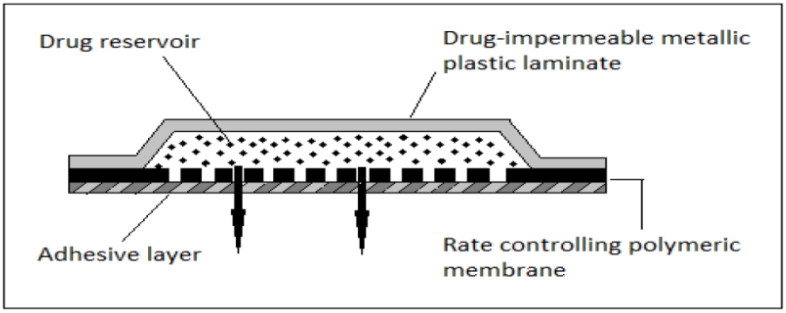

Fig. 1.3 - Cross-sectional view of Transderm-Nitro system

Polymer Matrix Diffusion-Controlled Drug Delivery Systems. In this type of CrDDS, the drug reservoir is a viscous liquid (or a semisolid) polymer, followed by a crosslinking of polymer chains or 2) mixing drug solids with a melted polymer at an elevated temperature. The resultant drug-polymer dispersion is then molded or extruded to form drug delivery devices of various shapes and sizes designed for a specific application. It can also be fabricated by dissolving the drug and the polymer in common solvent, followed by solvent evaporation, at an elevated temperature and/or under a vacuum, in a mold.

The release of drug molecules from this type of CrDDSs may be controlled at a preprogrammed rate by controlling the loading level and the polymer solubility of the drug and its diffusivity in the polymer matrix. Several CrDDSs of this type have been marketed successfully for therapeutical uses, and some representatives are outlined later for illustration.

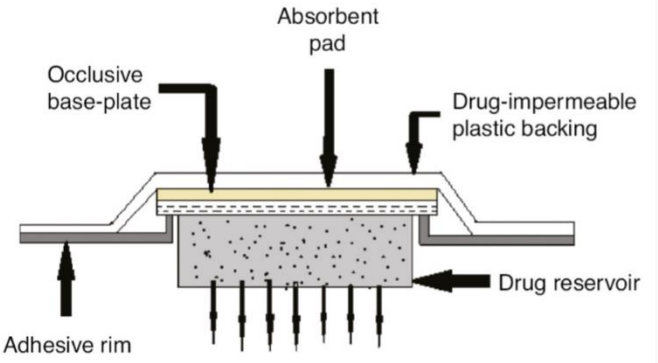

Fig. 1.4. Cross-sectional view of Nitro-Dur® system, showing various structural components.

Nitro-Dur® System. This controlled-release transdermal therapeutic system is fabricated by first heating an aqueous solution of a water-soluble polymer, glycerol, and polyvinyl alcohol and then lowering the temperature of the mixture to form a polymer gel. Nitroglycerin/lactose triturate is dispersed in the gel, and the mixture is then solidified at room temperature to form a medicated polymer disc by a moulding and slicing technique. After assembly onto a drug-impermeable metallic plastic laminate, a patch-type transdermal therapeutic system is produced with an adhesive rim surrounding the medicated disc (Fig. 1.4). It is designed for application onto intact skin to provide a continuous transdermal infusion ' of nitroglycerin, at a daily dose of 0.5 mg/cm2, for angina pectoris prevention.

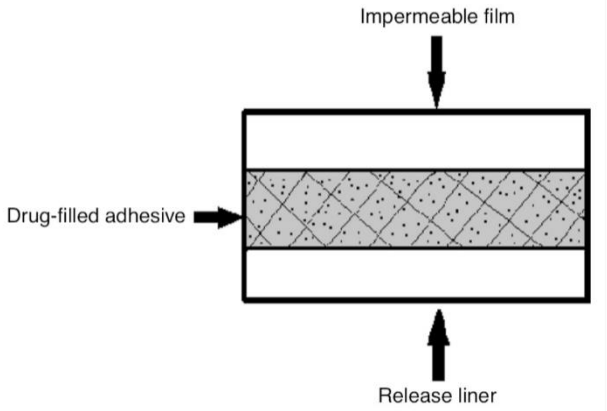

Fig. 1.5. Cross-sectional view of Nitro-Dur II, showing various

structural components.

The drug reservoir can also be formulated by directly dispersing the drug in an adhesive polymer, such as poly(isobutylene) or poly(acrylate) adhesive, after that spreading the medicated adhesive by solvent casting or softening, onto a flat sheet of drug-impermeable backing support to form a single- or multiple-layer drug reservoir. This type of transdermal CrDDS (TDD) is best illustrated by the development and marketing of an isosorbide dinitrate-releasing TDD system, named Frandol* tape, by Toaeiyo/Yamanouchi in Japan, and of a nitroglycerin-releasing TDD system, this the name Nitro-Dur® IT system by Key in the United States, for once-a-day medication for angina pectoris. This second generation of TDD system (Nitro-Dur Π) has also received FDA approval for marketing. Nitro-Dur II compares favourably with Nitro-Dur (Fig. 1.5) and has gradually replaced the first-generation Nitro-Dur from the marketplace.

Also, the same technical basis has been utilized in the development of the following: I) Habitrol® and Nicotrol® systems, which provide a controlled dose of nicotine transdermal over 24 h for smoking cessation; 2) Minitran® system which administers a dose-controlled of nitroglycerin transdermal over 24 h for the relief of anginal attacks; 3) Testoderm® system, which a controlled delivery administers of testosterone for transdermal permeation through a scrotal skin for the replacement therapy of testosterone-deficient patients for 24 h; and 4) Climara system, which provides a controlled delivery of 170-estradiol for transdermal permeation for once-weekly treatment of vasomotor systems associated with menopause.

To improve the drug release profiles, this polymer matrix diffusion-controlled CrDDS can be modified to have the drug-loading level varied, incrementally, to form a gradient of drug reservoir along the diffusional path in the polymer matrix. A constant drug release profile is thus achieved. This type of CrDDS is best illustrated by the

nitroglycerin-releasing Deponit® system (Fig. 1.6), first marketed by Pharma-Schwartz/Lohmann in Europe.

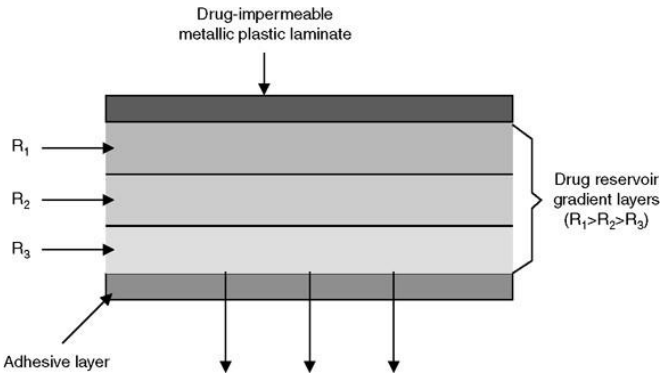

Fig. 1.6 - Cross-sectional view of a unit of Deponit* system

Furthermore, it was recently demonstrated that the release of a drug, such as propranolol, from the multilaminate adhesive-based TDD system can be maintained at zero-order kinetics by controlling the particle size distribution of the drug crystals in the various laminates of the adhesive matrix.

Polymer (Membrane/Matrix) Hybrid- Type Drug Delivery Systems. This type of CrDDS is developed to combine the constant drug release kinetics of polymer membrane permeation-controlled drug delivery systems with the mechanical superiority of polymer matrix diffusion-controlled drug delivery systems. The release profile of the drug from a sandwich-type drug delivery system is constant.

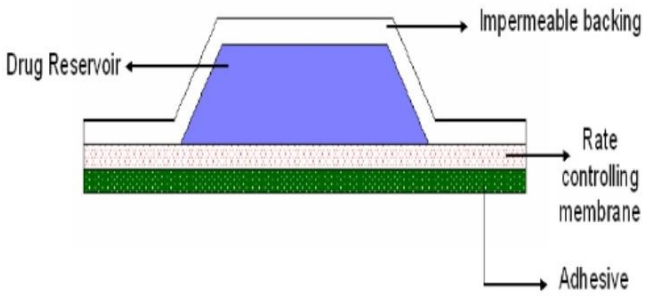

Fig. 1.7. Cross-section view of various structural components in the Transderm-Scop® and Catapres- TTS® systems.

The hybrid system is exemplified by the development of clonidine-releasing and scopolamine-releasing transdermal therapeutic systems (Catapres-TTS® and Transderm-Scop® (Fig. 1.7), in which a rate-controlling nonmedicated polymeric membrane is added to coat the surface of the drug-dispersing polymer matrix, and the release of drug molecules thus becomes controlled by membrane permeation instead 'of matrix diffusion.

Microreservoir Partition-Controlled Drug Delivery Systems. In this type of CrDDS the drug reservoir is a suspension of drug solid particles in an aqueous solution of a water-miscible polymer, like polyethene glycols. This forms a homogeneous dispersion of many discrete, unreachable, microscopic drug reservoirs in a biocompatible polymer, like silicone elastomers (Fig. 1.8). The microdispersion is achieved by. applying a high-energy dispersion technique. Different, shapes and sizes of drug-delivery devices can be fabricated from this micro reservoir-type CrDDS by moulding or extrusion techniques. Depending upon the physicochemical properties of drugs and the desired rate of drug release, the device can be further coated with a layer of biocompatible polymer to modify the mechanism and the rate of drug release.

The release of drug from the microreservoir-type CrDDS can follow either a dissolution- or a matrix diffusion-control process, depending upon the relative magnitude of the solubilities of the drug in/the liquid compartments and in the polymer matrix. Representatives of this type of CrDDS are outlined below.

Nitrodisc system.* In this transdermal CrDDS (Fig. 1.8), the drug reservoir is a suspension of nitroglycerin/lactose triturate in an aqueous solution of 40% polyethene glycol 400. It is dispersed homogeneously by a high-energy mixing technique, with isopropyl palmitate, a skin permeation enhancer, in a mixture of viscous silicone elastomer and catalyst. The resultant drug-polymer dispersion is then formed in situ into a solid medicated disc on a drug-impermeable metallic plastic laminate, with an adhesive rim, by an injection-moulding technique and application of instantaneous heating. It is engineered to provide a

transdermal administration of nitroglycerin at a daily rate of 0.5 mg/cm2 for the once-a-day medication of angina pectoris.

Activation-modulated drug delivery systems. In this group of CrDDSs, the release of drug molecules from the delivery systems is activated by some physical, chemical, or biochemical processes and/or facilitated by energy supplied externally. The rate of drug release is then controlled by regulating the process applied or energy input.

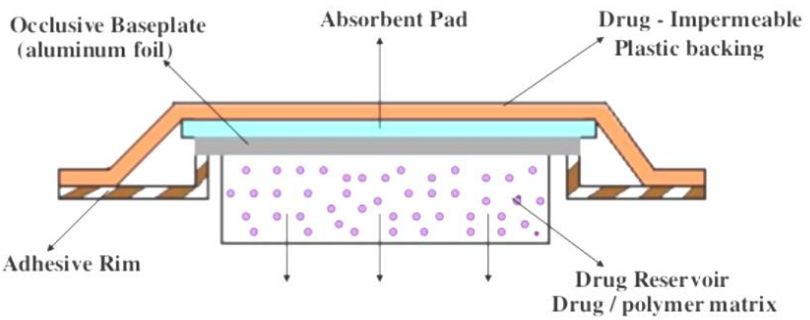

Fig. 1.8. Cross-sectional view of a unit of Nitrodisc® system, showing various structural components

Based on the nature of the process applied or the type of energy used, these activation-modulated CrDDSs categorize following categories:

1. Physical:
a. Osmotic pressure-activated drug delivery systems
b. Hydrodynamic pressure-activated drug delivery systems
c. Vapour pressure-activated drug delivery systems
d. Magnetics-activated drug delivery systems
e. Sonophoresis-activated drug delivery systems
f. Iontophoresis-activated drug delivery systems
g. Hydration-activated drug delivery systems

2. Chemical means
a. pH-activated drug delivery systems
b. pH-activated drug delivery systems
c. Ion-activated drug delivery systems

d. Hydrolysis-activated drug delivery systems

3. Biochemical means
a. Enzyme-activated drug delivery systems.
b. Biochemical-activated drug delivery systems

Several CrDDSs have been developed successfully and applied clinically to the controlled delivery of pharmaceuticals and biopharmaceuticals. These will be outlined and discussed below.

Osmotic Pressure-Activated Drug Delivery Systems. In this type of CrDDSs, the drug reservoir, which can be either a solution or a solid formulation, is contained within a semipermeable housing with a controlled water permeability. The drug in solution has been released through a particular laser-drilled delivery orifice at a constant rate under a controlled gradient of osmotic pressure.

The release of drug molecules from this type of CrDDS has been activated by osmotic pressure and controlled at a rate determined by the water permeability and the effective surface area of the semipermeable housing in addition to the osmotic pressure gradient. Several CrDDSs of this type has been marketed successfully for therapeutical uses. Some representatives will outline later.

Acutrim® tablet. In this oral CrDDS, the drug reservoir, which is a solid tablet of water-soluble and osmotically-active phenylpropanolamine (PPA) HC1, is enclosed within a semipermeable membrane of cellulose triacetate. The surface of the semipermeable membrane is coated further with a thin layer of immediately releasable PPA dose. In the alimentary tract, the gastrointestinal fluid will dissolve away the immediate release layer of PPA to provide an initial dose of PPA and then penetrate through the semipermeable membrane to dissolve the sustained-release dose of PPA. Under the osmotic pressure created, the PPA solution is released continuously at a controlled rate, through an orifice pre-drilled by a laser beam. It is designed to provide controlled delivery of PPA throughout 16 h for appetite suppression in a weight-control program. The same delivery system has also been utilized for the oral controlled delivery of indomethacin. An extension of this technology is the development of a push-pull type osmotic pressure-activated CrDDS for the oral controlled delivery of nifedipine and metoprolol. It has been further extended to the delayed-onset and

controlled oral delivery of verapamil to produce a maximum plasma concentration in the morning hours.

Hydrodynamic Pressure-Activated Drug Delivery Systems. In addition to the osmotic pressure systems, hydrodynamic pressure has also been explored as the potential source of energy to modulate the delivery of therapeutic agents.

A hydrodynamic pressure-activated drug-delivery system can be fabricated by placing a liquid drug formulation inside a collapsible, impermeable container to form

a drug reservoir compartment. This is then contained inside a rigid, shape-retaining housing. A laminate of an absorbent layer and a swellable, hydrophilic polymer layer is sandwiched between the drug reservoir compartment and the housing. In the gastrointestinal tract, the laminate will imbibe the gastrointestinal fluid through the annular openings at the lower end of the housing and become swollen. This generates a hydrodynamic pressure in the system. The hydrodynamic pressure, thus created, forces the drug reservoir compartment to reduce in volume and causes the liquid drug formulation to release through the delivery orifice.

The release of drug molecules from this type of CrDDS is controlled at a rate determined by the fluid permeability and effective surface area of the wall with annular openings as well as by the hydrodynamic pressure gradient.

Vapor Pressure-Activated Drug Delivery Systems, Magnetic-Activated Drug Delivery Systems, Sonophoresis-Activated Drug Delivery Systems are presented parenteral preparations.

QUESTIONS ON THE TOPIC

1. Characteristics of tablets as a dosage form. Types and groups of tablets.
2. Positive and negative sides of direct pressing.
3. The basic directions of manufacture of tablets by direct pressing.

4. Stages of the technological process of obtaining tablets by direct pressing.

5. Goals and the main types of granulation in the production of tablets.

6. Wet granulation. The positive and negative aspects of this process.

7. Methods of structural granulation.

8. Cases of using dry granulation (granulation by grinding).

9. Groups of excipients in the production of tablets.

10. Stages and equipment of production of tablets with preliminary granulation.

11. The objectives of coating the tablets.

12. Types of coatings and technology for their application.

13. Excipients used in the coating of tablets by shells.

14. Suspension method of coating. Its advantages.

15. Requirements for the geometric form of tablets-nuclei during coating.

16. Parameters influencing the coating process of tablets by coatings during coating.

17. Film coating. Types and properties. Ways of application.

18. Pressed coatings. Stages of technological process and equipment.

19. Determination of granules and dragees as dosage forms.

20. Auxiliary substances used in the production of granules and pellets.

21. Technology of obtaining granules and pellets.

22. Quality control of pellets and pellets.

23. Determination of capsules as a dosage form.

24. Types of capsules, their purpose.

25. Methods of making capsules. Used equipment.

26. Characteristics of soft gelatin capsules. Tubatins.

27. Technological scheme of production of soft gelatin capsules.

28. Characteristics of hard gelatin capsules.

29. Packing and storage of capsules.

30. Characteristics of the microcapsule shell, its varieties.

31. Physical methods of microencapsulation.

32. Characteristics of chemical methods for obtaining

microcapsules.

33. Standardization of microcapsules.

34. Medicinal forms from microcapsules.

TEST YOURSELF

1

At the pharmaceutical company make tablets. The time of disintegration of the tablets not covered by the shell is not more than:

* A) 15 minutes

B) 20 minutes

C) 30 minutes

D) 5 minutes

E) 10 minutes

2

Trituration tablets are made in the tablet shop. What quality indicators do not determine these tablets?

* A) Erasure, resistance to crushing

B) The uniformity of the content

C) Microbiological purity

D) Disintegration and dissolution

E) Uniformity of dosage

3

Pharmaceutical enterprises produce tablets coated with enteric membranes. Indicate that for a long time they SHOULD NOT decompose in acidic environment according to the requirements of HFC:

* A) 1 year

B) 2 years

C) 4 years

D) 3:00

E) 5:00

4

Dosage form for internal use in the form of grains of round or irregular shape, containing a mixture of medicinal and auxiliary substances, not covered with a shell, called:

* A) Granules

B) Dragee

C) Powder

D) Tablets

E) Spansuli

5

The pharmaceutical company manufactures Septefril tablets. Specify the device for determining the abrasion of tablets according to HFC:

* A) Drum Wiper (Friabilizer)

B) Areometer

C) Appliance with basket

D) Polarimeter

D) Densitometer

6

Specify the excipient to be added to the tabletting mass in excess of 1% according to HFC:

* A) Aerosil

B) Twin-80

C) Stearic acid

D) Calcium stearate

E) Magnesium stearate

7

Pharmaceutical enterprises produce tablets coated with entericcoating. Specify during which time they MUST NOT decompose in an acidic environment as required by the HFC:

* A) 1 hours

B) 2 hours

C) 6 hours

D) 3 years

E) 5 hours

8

In the tablet shop make trituration tablets. What Quality Score does not determine these tablets?

* A) Erasure, resistance to crushing

B) The uniformity of the content

C) Microbiological purity

D) Disintegration and dissolution

E) Uniformity of dosage

9

The pharmaceutical company produces drugs with thermolabile substances. Specify the drying method to be used in the preparation of these preparations:

* A) Sublimation

B) Radiation

C) Drying with high frequency current

D) Infrared

E) Ultrasound

10

The pharmaceutical company manufactures Septefril tablets. Specify the device for determining the abrasion of tablets according to HFC:

* A) Drum Cleaner (Friabilizer)

B) Areometer

C) Appliance with basket

D) Polarimeter

E) Densitometer

11

The medication should be prepared with 5.0 g of Etilmorphine hydrochloride trituration (1: 100). Specify the amount of poisonous substance and lactose to be taken:

* A. 0.05: 4.95

B. 1.0 4.0

C. 0.1: 4.9

D. 0.5: 4.5

E. 0.01: 4.99

12

At the pharmaceutical company make tablets. Specify for which tablets do not oppose mechanical strength:

* A. Nitroglycerin tablets

B. Sodium chloride tablets

C. Streptocide tablets

D. Acetylsalicylic acid tablets

E. Potassium bromide tablets

13

In the tablet shop produce tablets. In Tell the time of disintegration of soluble tablets in accordance with the requirements of the State Fund of Ukraine:

* A. 15 min

B. 5 minutes

C. 3 minutes

D. 60 min

14

At the pharmaceutical company make tablets. The disintegration time of tablets not coated is not more than:

* A. 15 minutes

B. 5 minutes

C. 10 minutes

D. 20 minutes

E. 30 minutes

15

Dosage form for internal use in the form of round or irregular grains containing a mixture of medicinal and auxiliary substances, not coated, is called:

* A. Granules

B. Tablets

C. Powder

D. Spansuli

E. Dragee

16

Specify the excipient to be added to the tabletting mass in an amount greater than 1% according to HFC:

* A. Aerosil

B. Twin-80

C. Stearic acid

D. Calcium stearate

E. Magnesium stearate

17

One of the above medicines, when heated to 180° C and when blown, explodes, resulting in care and care is it:

* A. Nitroglycerin solution
B. Coal activated
C. Alcoholic solution of iodine
D. Barium chloride
E. Calcium chloride

18

At the pharmaceutical company make tablets. In as sliding things in other pill production use:

* A. Calcium stearate
B. Starch paste
C. Water
D. Navy solutions
E. Tartrazine

19

The pharmaceutical company plans to release potassium bromide tablets. Is the receiving method optimal?

* A. Direct pressing
B. Formation
C. Direct pressing with excipients
D. Pressing with pre-wet granulation
E. Pressing with pre-dry granulation

20

As a binder for wet granulation use:

* A. Starch paste
B. Pectin
C. Gum
D. Slime
E. Aerosil

21

The physicochemical methods of obtaining microcapsules include:

* A. Coacervation method
B. Method of coating
C. Method of spraying
D. Spraying in the fluidized bed

E. Method of liquid dispersion

22

Modern methods of microencapsulation are divided into three main groups: physical, chemical and physico-chemical. Specify a method that applies to physical:

* A. Extrusion

B. Coacervation

C. Polymerization

D. Polycondensation

E. Spray drying

23

Physical methods of microencapsulation include:

* A. Spray in the fluidized bed

B. Physical adsorption

S. Coacervation

D. polymerization

E. Extraction Substitution

24

According to HFC, the content of solid drugs - capsules can be:

* A. Solid, liquid or pasty

V. Solid

S. Soft

D. Gaseous

E. Tver, soft

25

Medicinal preparations in capsule form, the shell of which is formed from rice flour, are called:

* A. Clouds

V. Medula

S. Spansuli

D. Tubatins

E. Caplets

26

In the manufacture of capsules, auxiliary substances of different groups are introduced into the gelatin base. Specify a group of excipients that is used to increase strength and reduce the fragility of the capsules:

* A. Plasticizers

B. Water repellents

C. Dyes

D. Preservatives

E. Adhesives

27

In the manufacture of phytochemicals, the extraction of extractives from vegetable raw materials occurs at the expense of:

* A) Molecular and convective diffusion

B) A adsorption and adsorption of the extractant by plant raw materials

C) Molecular and cellular diffusion

D) to onvective and cellular diffusion

E) Coacervation

28

The company manufactures soft gelatin seamless capsules. Specify the method of receipt:

* A) Drip

B) M ection

C) Stamping

D) Pouring

E) Dissolution.

29

Improve them properties of the filler in filling hard gelatin capsules added excipients slippery - 0.1% - 0.3% Eros or magnesium stearate with 0.5% - 1% talc?

* A) Loose flow

B) The ability to contact formation

C) Regulation of moisture content

D) Homogeneity

E) Homogeneity of mixing

30

In the manufacture of phyto-chemicals the extraction of extractives from vegetable raw materials occurs at the expense of:

* A) Molecular and convective diffusion

B) Absorption and adsorption of the extractant by plant material

C) Molecular and cellular diffusion

D) convective and cellular diffusion

E) Coacervation

31

The company manufactures soft gelatin seamless capsules. Specify the method of receipt:

* A) Drip

B) Wetting

C) Stamping

D) Pouring

E) Dissolution

32

To improve the properties of the filler when adding solid gelatin capsules add slippery excipients - 0.1% - 0.3% aerosil or magnesium stearate together with 0.5% - 1% talc?

* A) Loose flow

B) The ability to contact formation

C) Regulation of moisture content

D) Homogeneity

E) Homogeneity of mixing

33

Define the dosage form of tubatine:

*A. Soft capsules with elongated neck.

B. Soft rectal capsules in the form of an elongated drop.

C. Spherical capsules obtained by immersion

D. Egg-shaped capsules obtained by pressing

E. Hard capsules with lid, Filled with microcapsules

34

In the manufacture of capsules, auxiliary substances of different groups are introduced into the gelatin base. Specify the substance belonging to the group of plasticizers:

* A. Polypropylene

B. Potassium metabisulphate

C. Eosin

D. The essence is aromatic

E. Mint oil

35

In the manufacture of capsules, auxiliary substances of different groups are introduced into the gelatin base. Add a group of adjuvants, used to increase strength and reduce brittleness capsules:

* A. Plasticizers

B. Hydrofinizers

C. Preservatives

D. Adhesives

36

What is the technological technique for delivering the drug inside the cells?

* A. Liposomalisation

B. Coating

C. Solubilization

D. Microencapsulation

E. Granulation

37

The pharmaceutical company produces gelatin capsules. To ensure the antimicrobial resistance of the shells in the gelatin mass is introduced:

* A. Preservatives

B. Plasticizers

C. Film-forming agents

D. Dyes

E. Stabilizers

38

Various principles are based on the production of gelatin capsules. What are the features of the technological process of capsule production by immersion method:

* A. The capsule is formed by means of pins

B. Capsule formation with the help of two concentric camshafts

C. Formation of a spherical droplet with simultaneous incorporation of a liquid active substance in it

D. Formation of gelatin ribbon, capsule halves formation with

simultaneous filling and sealing

E. Preparation of capsules by coaceration

39

Immersion method is used to obtain hard gelatin capsules. Specify the equipment used for this method: indentation

* A. Macaque tub, frames with pins

B. Capsule Pressing Machine, Drying Machine Drykota Machine, Ball Mill

D. Installation of fluidized bed, pruning assembly

E. RPA, piston for

40

The pharmaceutical company manufactures solid hard gelatin capsules. I cue the method used to obtain hard shell capsules?

* A. Immersion

C. Casting

C. Pressing

D. Rotary-matrix

E. Formation

41

In the organoleptic evaluation of the shell of hard gelatin capsules contained a splash of air. What a technological mistake is made in the manufacture of gelatin mass

* A. Vacuum not connected B. Speed exceeded

C. Temperature increased

D. Long moving time

E. Insufficient number of stabilizers

42

The pharmaceutical company produces gelatin capsules. To ensure the antimicrobial resistance of the shells in the gelatin mass is introduced:

* A. Preservatives

B. Plasticizers

C. Film-forming agents

D. Dyes

E. Stabilizers

43

In the manufacture of hard gelatin capsules I use the immersion method. What are the technological equipment used for this capsule method:

*A. "Tub", frames with pins, drying unit, automatic cutting unit

B.Diskey, plunger for pushing, metered hopper

C. Grids, drying unit, cutting unit

D. Frame, chassis, drying unit, rotor with scrapers E. Matrix table, hopper for filling, receiver

44

The pharmaceutical company organizes the release of an oily solution of retinol acetate in capsule form. Specify the method that is appropriate for the manufacture of this drug:

* A. Drip method

B. Method of pressing

C. Rolling Method

D. Casting Method

E. Layering Method

45

Modern methods of microencapsulation are divided into three main groups: physical, chemical and physico-chemical. Specify the method of production for microcapsules containing tormolabile substances:

* A. Vacuum deposition

B. Dredging

S. Suspension

D. Extrusion

E. Dispersion

46

To prevent possible loss of volatile fillers, 40 capsules are further sealed. Specify sealing methods to do this:

* A. Thermo-mechanical welding

B. Real filling

C. Drying

D. Removal of solvent

E. Coating of capsules with metals

47

Immersion method is used to obtain hard gelatin capsules. Specify the equipment used for this method:

*A. "Tub", frames with pins

B. Capsule pressing machine drying unit

C. Drycott machine, ball mill

D. Set fluidized layer unit for trimming

E. RPA, a piston for strangulation

48

Different methods are used in the production of microcapsules. What methods are related to chemical:

* A. Polymerization, polycondensation

B. Simple coacervation

C. Dispersion

D. Dissolution

E. Dropping

49

According to the technology of drip method of capsule production, and encapsulation are subject to:

* A) Fluid non-aqueous non-aqueous medicinal substances

B) horoshkoobraznye substance

C) granulated medicinal substances

D) microgranular substance

E) pastes and liquids with high viscosity

50

The farm produces gelatin capsules. What is the purpose of glycerol in the composition of the gelatin mass?

* A) gives the shell elasticity

B) increases the porosity of the shells

C) increases resistance to gastric juice

D) has antimicrobial properties

E) accelerates the disintegration of shells

51

At the pharmaceutical enterprise, microcapsules are produced by the method of coating. Specify the equipment that is used when receiving microcapsules by this method.

* A) Dragee boiler
C) Friabilizer
C) Disintegrator
D) Granulator mixer
E) a dysmembrator

52

To improve the properties of the filler when filling solid gelatin capsules add sliding excipients - 0.1% - 0.3% aeosil or magnesium stearate together with 0.5% -1% talc.

* A) To enhance flowability
B) For the ability to compact formulation
C) To regulate moisture
D) For uniformity
E) For homogeneity of mixing

53

Modern microencapsulation methods are divided into three main groups: physical, chemical and physico-chemical. Specify the retention for microcapsules containing thermolabile:

* A. Vacuum deposition
B. Dredging
C. by suspending
D. Extrusion
E. Dispersion

54

Different methods are used in the production of microcapsules. What are the methods of chemical:

* A. Polymerization, polycondensation
B. Simple coacervation
C. Dispersion
D. Dissolution
E. Dragee

55

Give the name of the finished dosage form, which is a gelatin capsule filled with microcapsules:

* A. Spansuli

B. Tubatins

C. Pearls

D. Pills of the ARD type

E. Microcapsules

56

In the manufacture of capsules, auxiliary substances of different groups are introduced into the gelatin base. Specify the group of excipients that is used to increase the strength and reduce the fragility of the capsules:

* A. Plasticizers

B. Waterproofing agents

C. Dyes

D. Preservatives

E. Adhesives

57

When assessing the quality of gelatin capsules determine the solubility. Specify in which case the series is considered standard when determining this metric:

*A. If at least 75% of the active substance has dissolved in water within 45 minutes

B. If within 60 minutes 75% of the active substance has dissolved in water

C. If at least 55% of the active substance has dissolved in water within 30 minutes

D. If at least 85% of the active substance has dissolved in water within 90 minutes

E. If at least 10% of the active substance has dissolved in water within 90 minutes

58

Define the dosage form of tubatine:

*A. Soft capsule with a long neck

B. Spherical capsules obtained by immersion

C. Capsule ovate, obtained by pressing

D. Solid capsules with a cap filled with microcapsules

E. Soft rectal capsules in the form of an elongated drop

59

When controlling the quality of the capsules determine the average weight. Specify the number of capsules that should be taken to determine this indicator according to HFC:

* A. 20

B.15

C.10

D.5

E.3

60

The basis of gelatin capsule production is based on different principles. What is the feature of receiving capsules by pressing:

* A. Capsule formation by concentric nozzles

B. Capsule formation by dipping pins

C. Formation of a spherical droplet with simultaneous incorporation of the active substance

D. Formation of capsules from gelatin tapes by punching

E. Formation of capsules by evaporation of a volatile solvent

61

Farm. company produces gelatin capsules. To ensure the antimicrobial resistance of the shells in the gelatin mass is introduced:

* A. Preservatives

B. Plasticizers

C. Film-forming agents

D. Dyes

E. Stabilizers

62

Different principles are based on the production of gelatin capsules. What are the features of the technological process of capsule production by immersion method:

* A. Capsule formation is done with pins

B. Formation of capsules by means of two concentric gear shafts

C. Obrazovanie spherical droplets with simultaneous inclusion in it of liquid active substance

D. Formation of ribbons of gelatin mass, the formation of halves of capsules with simultaneous filling and sealing

E. Capsule preparation by coacervation

63

Changing what conditions can lead to a coacervation process

* A. All answers are correct

B. Coacervation of the electrolyte

C. Changes in the co-occurrence of the Navy

D. Changing the pH of the medium

E. Change in temperature

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GLOSSARY OF TERMINOLOGY

Batch: A specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits.

Standard Term

Standard Terms for describing the pharmaceutical form of a medicinal product, the routes of administration and the containers used have been established by the European Pharmacopoeia Commission and are provided in a separate publication on Standard Terms.

Active substance

Equivalent terms: active ingredient, drug substance, medicinal substance, active pharmaceutical ingredient.

Vehicle

A vehicle is a carrier, composed of one or more excipients, for the active substance(s) in a liquid preparation.

Basis

A basis is a carrier, composed of one or more excipients, for the active substance(s) in semi-solid and solid preparations.

Conventional-release dosage forms Conventional-release dosage forms are preparations showing a release of the active substance(s) which is not deliberately modified by a special formulation design and/or manufacturing method. In the case of a solid dosage form, the dissolution profile of the active substance depends essentially on its intrinsic properties. Equivalent term: immediate-release dosage form.

Modified-release dosage forms

Modified-release dosage forms are preparations where the rate and/or place of release of the active substance(s) are different from that of a conventional-release dosage form administered by the same route. This deliberate modification is achieved by a special formulation design and/or manufacturing method. Modified-release dosage forms include prolonged-release, delayed-release and pulsatile-release dosage forms.

Prolonged-release dosage forms

Prolonged-release dosage forms are modified-release dosage forms showing a slower release of the active substance(s) than that of a conventional-release dosage form administered by the same route. The

prolonged-release is achieved by a special formulation design and/or manufacturing method.

Equivalent term: extended-release dosage form.

Delayed-release dosage forms

Delayed-release dosage forms are modified-release dosage forms showing a release of the active substance(s) which is delayed. The delayed-release is achieved by a special formulation design and/or manufacturing method. Delayed-release dosage forms include gastro-resistant preparations as defined in the general monographs on solid oral dosage forms.

Pulsatile-release dosage forms

Pulsatile-release dosage forms are modified-release dosage forms showing a sequential release of the active substance(s). The sequential release is achieved by a special formulation design and/or manufacturing method.

Large-volume parenteral

Infusions and injections are supplied in containers with a nominal content of more than 100 ml.

Small-volume parenterals

Infusions and injections are supplied in containers with a nominal content of 100 ml or less.

Drug Product: A drug product is a finished dosage form (e.g., tablet and capsule) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. A solid oral dosage form includes but is not limited to tablets, chewable tablets, enteric-coated tablets, capsules, caplets, encapsulated beads, and gelcaps.

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effects in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure of any function of the human body, but does not include intermediates used in the synthesis of such ingredient.

Enteric Coated: Intended to delay the release of the drug (or drugs) until the dosage form has passed through the stomach. Enteric-coated products are delayed release dosage forms.

Equipment: Automated or nonautomated, mechanical or nonmechanical equipment used to produce the drug product, including equipment used to package the drug product.

Extended-Release: Extended-release products are formulated to make the drug available over an extended period after ingestion. This allows a reduction in dosing frequency compared to a drug presented as a conventional dosage form (e.g., as a solution or an immediate release dosage form).

Formulation: A listing of the ingredients and composition of the dosage form.

Immediate Release: This allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

Types of Extract

The Liquid Extract is the strongest type of plant liquid made, its ratio, of the-plant material to solvent is 1:1, i.e., 1 gram crude drug represents 1 ml of the liquid extract. For technical reasons, it may only be further concentrated by evaporation of the solvent. Occasionally a 1:2 preparation, i.e., 1 g crude drug equals 2 ml liquid is called an extract, this is incorrect and leads to confusion. When the term extract is used here, it means a 1:1 preparation.

The Tincture is the most common form of plant liquid. An official definition of a tincture is that it has a drug/solvent ratio of 1:4 and that the solvent is a minimum of 45% by volume. There are some difficulties with that definition because there are strong tinctures, i.e., 1:2 or 1:3, or they may go from 1:5 through 1:10. International protocol on potent plant drugs, e.g., Belladonna, Digitalis, Strophanthus etc., are agreed upon 1:10. The international protocol was established for obvious reasons. Preparations above 1:10 are little more than preserved concentrated infusions.

The Essential Oils represent a fraction of 1% of the total plant constituents and are not representative of a plant's therapeutic range. They are undoubtedly the finest natural bactericide, that because of their potency can be dangerous in the wrong hands. Therefore, if taken internally they can be extremely toxic and if used without dilution externally, the result will be damage to dermal or mucous tissue.

The Expressed Plant Juices enjoyed popularity in the early years of the 20th century but were gradually abandoned because of their limitations. They are brisk and vigorous in action; this may be attributed to the live enzyme content and as such bear comparison with fresh fruit

and vegetable juices, however strict dosage restraints must be adopted otherwise harm may result. The preserved juices are problematic.

The Concentrated Infusions and Decoctions were prepared with water as the solvent. If taken in that form they are classed as retention (recent) or they are preserved with alcohol 20%.

The Pasty or Dry Extracts are prepared from liquid extracts by evaporation. They must be prepared with extreme care lest irremediable damage occurs. There are three types;

(1) Soft. (2) Semi-soft. (3) Dry.

They are the basis of pills and ointments.

Dry Yield Converted to Liquid Yield

On the assumption of 100 kg of dried material, a liquid extract will yield 100 litres of extract.

On the same amount of dried material, 1 in 4 tinctures will yield 400 litres of the tincture. A Homeopathic mother tincture is 1 in 10. (There are a few odd exceptions). Therefore, the original 100 kg of dried material will yield 1000 litres of the mother tincture. It may be seen that the original 100 kg of dried material has suddenly started to be commercially viable.

THE ENGLISH-UKRAINIAN VOCABULARY OF TERMINOLOGY

airbubblenucleation-заповітрювання(виникненнягазовихпузирів)

anginapectoris-серцеванедостатність

biocompatibility-біосумісний

buccal-той,щовідноситьсядоротаабощоки

casting-лиття

crosslinking-перехреснозшитий

extruded-пресований;видавлений

fluidization-псевдозрідження

injectable-ін'єкційний

massexchange,

masstrasfer–масообмін

mass-transfer-масопереніс

melting-плавлення
molded-формований
mullercontainer-мюлерівськабочка
multistagely-багатостадійно
Permeation, penetration-проникнення
predesigned-запланований
Prolonged-прил.пролонгований,довгий
Rate-preprogrammed-зпрограмованоюшвидкістюrotary-pul satingdevice-роторно-пульсаційнийапарат
Site-targeting-доставкадомісця
semifinisheditems-напівпродукти
semipermeable-напівпроникний
swell-набрякати
transdermally-трансдермально,підшкіру
trans-mucosal-черезслизовуоболонку
vortical-вихровий
wall–пристінний

THE UKRAINIAN-ENGLISH VOCABULARY OF TERMINOLOGY

багатостадійно-multistagely
біосумісний-biocompatibility
вихровий–vertical, vortex
доставкадомісця-Site-targeting
запланований-predesigned
заповітрювання(виникненнягазовихпузирів)-airbubblenuclea tion
зпрограмованоюшвидкістю-Rate-preprogrammed
ін'єкційний-injectable
лиття-casting
масообмін-massexchange,masstransfer
масоперенiс-mass-transfer
мюлерівськабочка-mullercontainer
набрякати-swell
напівпродукти-semifinisheditems
напівпроникний-semipermeable
перехреснозшитий-crosslinking
плавлення-melting

пролонгований,довгий-Prolonged
проникненйя-Permeation,penetration
пресований;видавлений-extruded
пристінний-wall
псевдозрідження-fluidization
роторно-пульсаційнийапарат-rotary-pulsatingdevice
серцеванедостатність-anginapectoris
той,щовідноситьсядоротаабощоки-buccal
трансдермально,підшкіру-transdermally
формований-molded
черезслизовуоболонку-trans-mucosal