ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF DRUGS TECHNOLOGY

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«27» august 2021y.

METHODICAL DEVELOPMENT OF THE LECTURE

Course: 5 Faculty: Pharmaceutical

Course: **Biopharmacy**

Lecture № 2 Topic: **"Pharmaceutical factors. Physical state of medicinal substances. Polymorphism, solubility, chemical modification, excipients. "**

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Protocol № 1

Odessa – 2021

Lecture: "Pharmaceutical factors. Physical state of medicinal substances. Polymorphism, solubility, chemical modification, excipients "- 4 hours.

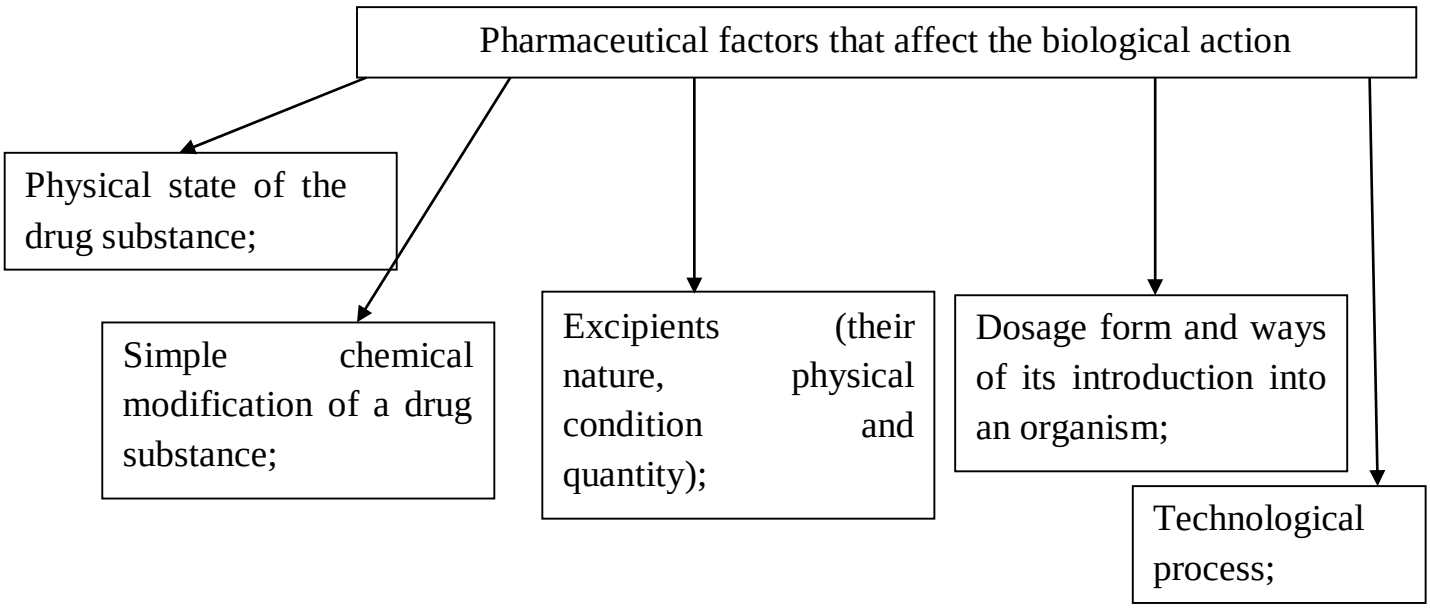
The purpose of the lecture: to get acquainted with all pharmaceutical factors and their influence on the action of drugs;

Basic concepts: Polymorphism, chemical modification, solubility.

Plan

1. Types of pharmaceutical factors that affect bioavailability.
2. Physical state of medicinal substances.
3. Grinding of medicinal substances
4. Polymorphism of medicinal substances
5. Solubility of drugs
6. Chemical modification
7. Excipients
8. Types of dosage form and ways of its introduction into the body
9. Technological processes

Types of pharmaceutical factors that affect bioavailability.



All pharmaceutical factors that affect the biological action of drugs can be divided into five groups:

- physical condition of the drug substance;
- simple chemical modification of the drug substance;
- excipients (their nature, physical condition and quantity);
- dosage form and ways of its introduction into the body;
-technological process.

A careful study of known cases of therapeutic non-equivalence of drugs has shown that the activity of the active substance (drug substance), its release from the dosage form and absorption are closely dependent on pharmaceutical factors.

Therefore, the study of the latter is mandatory in terms of biopharmacy due to their significant impact on the dynamics of bioavailability of drugs, the stability of drugs during storage and many other indicators.

Drugs according to the dispersological classification are characterized as comprehensive binary disperse systems consisting of a dispersed phase (DF) and a dispersion medium (DS). The drug substance in the form of DF can be in dosage form in solid, liquid or gaseous state. In turn, the dispersed medium can be an auxiliary component of the system (eg, base for ointment, solvent in liquid dispersed systems).

According to the degree of dispersion, drug dispersion systems are classified into homogeneous and heterogeneous.

Homogeneous - single-phase ionic or molecularly dispersed systems. These are real solutions with DF particle size for low molecular weight compounds up to 1 nm, for high molecular weight - from 1 to 100 nm (0.001-0.1 μm). In a special group are colloidal systems and solutions of macromolecular compounds (IMS) with a particle size up to 100 nm, which remain homogeneous only under certain conditions, taking into account temperature, pressure, solvent, pH and other factors.

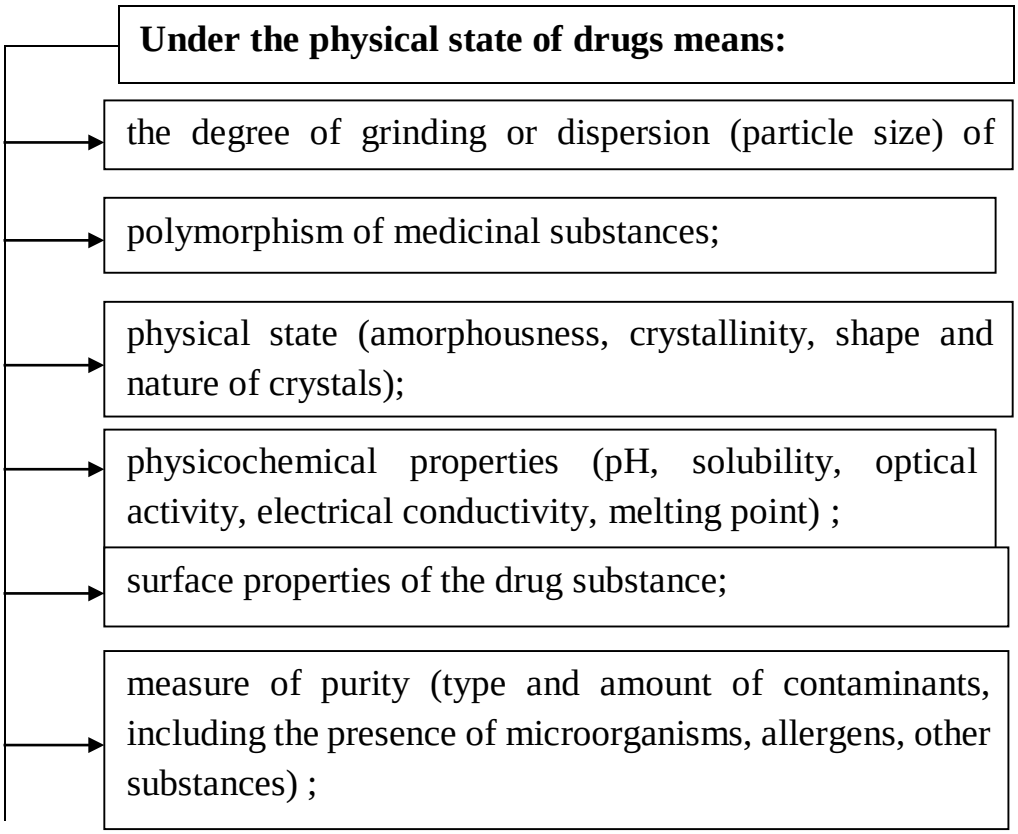
Heterogeneous - two-phase coarse systems with a particle size of 100 to 1000 nm (0.1-1 μm) and more.

From the point of view of biopharmacy and pharmacokinetics, the drug will have the necessary bioavailability only if the drug substance is presented in the most favorable state for the resorptive process (in ionic or molecularly dispersed form). Therefore, the most acceptable are homogeneous dispersed systems (solutions, aerosols, etc.). If the drug substance is in a coarse state, it is necessary to create conditions in the dosage form or at the time of use in the patient's body to transfer from the coarse state to ionic or molecularly dispersed.

For this purpose, and use various technological techniques, excipients, special dosage forms with specified pharmacokinetic properties, as well as use the physiological characteristics of the organism (pH of the stomach and intestines, lipoid solubility, buffer blood systems, etc.).

Polymorphic modifications also have a great influence on the therapeutic activity of drugs.

Physical state of medicinal substances.



Under the physical state of drugs means:

- the degree of grinding or dispersion (particle size) of drugs;
- polymorphism of medicinal substances;
- physical state (amorphousness, crystallinity, shape and nature of crystals);
- physicochemical properties (pH, solubility, optical activity, electrical conductivity, melting point);
- surface properties of the drug (surface tension, filler, etc.).
- degree of purity (type and amount of contaminants, including the presence of microorganisms, allergens, binders, etc.).

The physical state of drugs affects the stability of the drug during storage, therapeutic efficacy, rate of absorption, distribution and excretion from the body.

The most significant effect on pharmacotherapy is the degree of grinding and polymorphism of drugs.

3. Grinding of medicinal substances

Grinding of medicinal substances is the simplest, but at the same time one of the most important technological operations which is carried out by the pharmacist at at-made various dosage forms. The dispersion of the drug affects not only the

flowability of powdered materials, bulk density, mixing uniformity, dosing accuracy. It is especially important to note that the particle size depends on the speed and completeness of absorption of the drug, as well as its concentration in biological fluids, mainly in the blood, in any way of its appointment in the form of various dosage forms.

For example, in tablets disintegrated in the stomach, the particle size significantly exceeds the particle size of the powder, resulting in the concentration of the active substance after taking the tablet is lower than after taking the powder. The particle size of drugs in the mixture-suspensions, emulsions and liniment is one of the main characteristics of these dosage forms.

The effect of particle size on therapeutic activity was first proven for sulfonamide and then steroid drugs, as well as derivatives of furan, salicylic acid, antibiotics and now -for anticonvulsants, analgesics, diuretics, antituberculous, antidiabetic and antidiabetic drugs. Thus, it was found that when using micronized sulfadiazine, its maximum concentration in human blood is reached two hours earlier than when it is prescribed in the form of a powder of the usual degree of grinding. The maximum concentrations of sulfadiazine in the blood are 40% higher, and the total amount of absorbed substance is 20% higher. The drug calciferol is able to be absorbed and have a therapeutic effect only when the particle size is less than 10 microns.

At decrease in particles of griseofulvin from 10 to 2, 6 microns its absorption in a gastrointestinal tract sharply increases that allows to reduce twice its therapeutic dose. Obtaining the molecular degree of dispersion of griseofulvin in polyvinylpyrrolidone, it was possible to increase by 7-11 times the bioavailability of this anti-antibiotic, even in comparison with the micronized form of the drug. Therefore, the industry produces tablets of micronized griseofulvin, digoxin, acetylsalicylic acid.

The influence of the degree of grinding on the process of absorption is particularly pronounced in ointments and suppositories prepared on the same basis, but using fractions of the drug substance, the particle size of which is markedly different.

4. Polymorphism of medicinal substances

Polymorphism (from the Greek words " role " - many, "morphe" - form) - is the property of a chemical to form in different conditions of crystallization crystals that differ from each other by a class of symmetry or shape, physical and sometimes chemical properties.

It is known that polymorphic modifications form many chemicals and, including drugs. Since the discovery of the Devi carbon polymorphism (1809) (graphite, coal, and diamond), the transitions of one polymorphic modification to another have been studied in detail. It is emphasized that the *chemical composition remains unchanged,* which is taken mainly for quality assessment

The particles of medicinal substances in the powdery solid state have a different structure (crystalline or amorphous), depending on the peculiarities of the molecular structure of a substance. Electron microscopic studies have shown that drugs in most cases have a crystalline structure, due to the fixed location of atoms in the molecule and the directional growth of crystals under certain conditions during crystallization. The amorphous state is less common. Any drug under certain conditions *(solvent, temperature, pressure, etc.)* crystallizes in a certain system and has certain physicochemical characteristics (solubility, melting point, specific surface area, strength, shape and particle size, etc.). When conditions change, the substance crystallizes in another system and has other physicochemical characteristics, and hence other indicators of biological accessibility. Such physical characteristics of powders in the existing AND as "crystalline", "fine crystalline", "amorphous", "light powder" are sufficient for the technological process, but to identify their impact on therapeutic activity requires more accurate definitions, which gives the crystal chemistry.

There are seven crystallographic systems (syngony): monoclinic, diclinal, trigonal, tetragonal, hexagonal, rhombic, cubic, they are used to identify drugs. Andronyk I. Ya. And Babilev FV published an atlas of diffractograms of crystalline drugs and developed an information retrieval system for the identification of crystalline drugs by their diffraction spectra. The use of an atlas and an automated system can speed up the identification of drugs.

The formation of various polymorphic modifications can occur in both liquid and soft dosage forms. This is observed: when replacing solvents; when administered in liquid or soft dosage forms of various excipients; during drying, cleaning, preparation of drugs and in the process of their preservation.

The phenomenon of polymorphism among drugs is especially common among salicylates, barbiturates, sulfonamides, hormonal agents. For most modifications there are no special names and they are denoted by letters or numbers I, II, III, etc.

Examples of polymorphic modifications of drugs are many. Thus, there are two polymorphic modifications of acetylsalicylic acid, one of which is biologically more active than the other 1.5 times.

Accounting and rational use of the phenomena of polymorphism of medicinal substances are of exceptional importance for pharmaceutical and medical practice. Polymorphic modifications of the same substance are characterized by different *stability constants, phase transition temperature, solubility,* which ultimately determines both the stability of the substance and its pharmacological activity.

Of particular importance is the *solubility of* various polymorphic modifications, because it depends on the absorption (absorption) of drugs.

The dissolution process also affects the effectiveness of drugs.

The drug substance as a dispersed phase undoubtedly interacts with the liquid, ie with the dispersion medium. This is one or another chemical reaction responsible for changing the biological activity of substances.

Fluids are classified into polar, semipolar and nonpolar. Depending on the chemical nature of the drug substance and the solvent, the interaction energy in liquid

dosage forms can form ionic, molecularly dispersed systems or coarsely dispersed suspensions. Exothermic or endothermic phenomena and contraction may be observed during cooking. All this must be taken into account in the preparation of liquid dosage forms, scientifically substantiating the technological methods and compounds of the drug.

5. Solubility of drugs

The solubility of substances depends largely on their *surface* properties, including the *degree of their grinding.* A significant difference in the particle size of the drug substance can lead to unequal rate of absorption and content in the biological fluids of the same drug, and hence to its possible clinical non-equivalence.

The solubility of drugs may vary depending on the *methods of their recrystallization*, and in finished drugs - on the availability of used *excipients* and dosage form *technology* . The solubility of drugs in dosage forms is influenced by the *choice of dosage form.* Thus, when using very sparingly soluble drugs in the case of their oral administration, the rational dosage form is a thin suspension, such drugs are best administered in the form of elastic capsules filled with a suspension.

There are several ways to increase the solubility of sparingly soluble substances and thus bioavailability.

1. 3a by solubilization. Solubilization is defined as the process of spontaneous transition to a stable solution using surfactants insoluble or sparingly soluble in this solvent. In the domestic literature, this process is also called colloidal or combined solubility.

2. Using individual or mixed solvents (benzyl benzoate, benzyl alcohol, propylene glycol, polyethylene glycol, ethylcellulose, dimexid, glycerin, etc.).

3. With the use of hydrotropia, which provides hydrophilic complexes with organic substances containing electro-donor substituents - polar radicals. Examples of hydrotropic substances are sodium salicylate, sodium benzoate, hexamethylenetetramine, novocaine, antipyrine, urea, glycerin, amino acids, hydroxy acids, proteins, and others. 4. By the formation of salts and complexes:

a) sparingly soluble substances: bases, acidic form of compounds in alkali or with sodium bicarbonate turns into easily soluble salt. In this way, phenobarbital, norsulfazole, streptocide, osarsol, and others can be converted into soluble compounds. substances;

obtaining aqueous solutions of iodine using easily soluble complexes of iodine with iodides of alkali metals;

c) polyvinylpyrrolidone is used to obtain aqueous solutions of polyene antibiotics (nystatin, levorin, etc.), with which they form complex compounds, where the water-insoluble substance and the solubilizer are linked by a coordination bond. These complexes are well soluble in water. Scientific research initiated in this direction

allows us to reveal new patterns in relation to "medicinal substances-excipients" in complex physico-chemical systems, which are drugs.

5. Synthetic way - introduction into the structure of the molecule of hydrophilic groups: -COOH, CH_2-COOH, -HPO $_C$H, -CH_2RO $_C$N. Example: unithiol.

The therapeutic activity of drugs is also significantly influenced by their *optical properties.* There is no chemical difference between the optical isomers, but each of them rotates the plane of the polarizing ray in a certain direction. Although chemical analysis fully confirms the presence of the same substance in drugs with different isomers, they will not be therapeutically equivalent.

The *degree of ionization of the substance* plays *an* important role in the absorption of the drug in the gastrointestinal tract . Depending on the *concentration of hydrogen ions, the* drugs can be in ionized or non-ionized form, the pH also affects the solubility, drug distribution coefficient, membrane potential and surface activity.

6. Simple chemical modification

The term *simple chemical modification of* drugs means when one and the same substance can be used as a drug in various chemical compounds (salt, base, acid, ether, complex compound, etc.), which fully retains the part of the molecule responsible for the pharmacological effect. substances.

For example: novocaine - the basis and salt of novocaine hydrochloride; codeine - base and codeine phosphate - salt; caffeine - base and caffeine-sodium benzoate - salt.

Simple chemical modification (replacement of a drug in the form of a salt with one cation, chemically similar to a drug in the form of a salt with another cation or a drug in the form of an acid, ether, etc.) is more common in factory production.

Biopharmacy pays the most serious attention to the study of the factor of simple chemical modification, because taking into account its effect on the pharmacokinetics of drugs can significantly increase the effectiveness of drug intervention, reduce drug consumption, dramatically increase the stability of many drugs and their drugs.

On the basis of biopharmaceutical experiments it is proved that *arbitrary replacement of any ion in the molecule of a drug substance, based on purely technological or economic considerations, is unacceptable.*

7. Excipients

Excipients are of natural, synthetic and semi-synthetic origin. In the preparation of dosage forms, they can perform various functions: solvents, solubilizers, stabilizers, bases, surfactants, thickeners, emulsifiers, preservatives, correctors, dyes, etc.

Such substances include: starch, glucose, purified water, ethyl alcohol, vaseline, oil, cocoa, talc, bentonites, aerosil, paraffin, wheat flour, polyethylene oxides, various cellulose derivatives, and others.

Throughout the centuries-old history of pharmacy, excipients have been considered as indifferent substances in pharmacological and chemical terms, acting as formers. They were added to medicinal substances in order to give them an appropriate form, convenient for use, transportation and storage. The most available and cheapest substances were used in the production of medicines. This did not take into account the influence of nature and the amount of excipients on the biological activity of drugs.

On the basis of biopharmaceutical works, it was found that *excipients are not an indifferent* mass used in a purely technological sense. They have certain physicochemical properties and, depending on the nature of the substance *can enhance, reduce, change the nature of the action of drugs* under the influence of various causes and combinations (complexing and adsorption, molecular reactions, etc.), which can dramatically change the rate and complete absorption of the drug. The interaction between drugs and excipients can occur both in the process of preparation of drugs and in the process of their preservation.

Thus, the mechanism of action of excipients on bioavailability may be different.

The main reason for the change in biological activity is the chemical interaction between the ingredients in the "drug substance - excipient" system with the formation of complexes of polymers, micelles, micelle associations, IUD macromolecules, chemisorption, and others. The formed compounds can be quite strong or, conversely, easily destroyed, characterized by high surface activity or balanced energy of the system, to strengthen or weaken the main pharmacological response of the drug, etc.

It is known that the degree of interaction is determined by the energy of the physicochemical or chemical bond. If the *bond is weak* (vandervalt forces - 1 kcal / mol (4-10 ^{3} J) or hydrogen bond 7-10 kcal / mol), the process can be reversible, because the body can handle this bond, can split , modify and the drug substance will be disposed of.

But if a *strong bond is* formed , covalent with an energy of 100-140 kcal / mol, the process can become irreversible, because the body does not have the conditions to break this bond. Therefore, *excipients can minimize the therapeutic effect of the drug, enhance it to the point of toxicity or completely change it.*

For example, the complex of amphitamine with carboxymethylcellulose is practically not absorbed and, accordingly, does not provide a pharmacological effect.

Phenobarbital in polyethylene glycol is poorly soluble and, as a consequence, is not absorbed. Complexes of theophylline-phenobarbital and calcium tetracycline - sparingly soluble compound and practically not soaked up.

Clay minerals have adsorption properties and delay the release of alkaloids, anesthetics, antibiotics and other drugs. Magnesium trisilicate and magnesium oxide contribute to the destruction of steroid hormones.

Known antioxidants sodium sulfite, bisulfite and metabisulfite, introduced into a buffer solution of thiamine (pH = 3.5), destroy it to thiazole. Vitamin D in solid dosage forms in the presence of excipients is easily isomerized (talc, ammonium silicate, calcium phosphate, citric acid, etc.).

Selective resorption is also the cause of changes in the biological activity of drugs.

Biological membranes through which the process of drug absorption is carried out must be considered as a complex receptor mechanism through which resorption is carried out according to Fick's law based on the law of diffusion, but in strict order and at different speeds.

The sequence and rate of resorption are determined by various factors: *time of administration of the drug before or after a meal, type of food, amount and nature of the fluid to be washed, time of day, physiological state of mucous membranes, chemical and physicochemical characteristics of drugs* .

Among these factors it is necessary to consider the latter, all other things being equal. It is known from the literature that dissociating low-molecular compounds, substances having a diphilic structure with metallic, ethyl, phenyl, and others have the best resorptive capacity. radicals, substances with high affinity for the body's bioenvironment.

Sometimes, with a certain composition, the *excipients become the active ingredients and the active ingredients become the excipients.*

For example, mannitol acts as a filler in tablets, and in liquid dosage forms acts as a laxative. And such active substances as urethane, antipyrine, quinine are used for solubilization and prolongation of a number of drugs, changing the level of pharmacokinetics.

It is impossible to draw a clear line between the active substance and the excipient in the dosage form, and therefore modern pharmaceutical science requires the development of new drugs: to *establish the degree of influence of excipients on the therapeutic efficacy of drugs.* In other words, the excipient should not be used in general, but specifically with an individual substance. *Unreasonable use of the* excipient *may lead to a decrease, increase, change in therapeutic effect or complete loss of therapeutic effect of the drug substance.*

8. Types of dosage form and ways of its introduction into the body

Numerous studies on the effect of the dosage form on the therapeutic efficacy of drugs have shown that the optimal activity of the drug is achieved only when prescribed in a rational dosage form. In addition, in this case, you can avoid many side effects of drugs on the body.

Dosage form is a rational from a pharmacological point of view, convenient for reception and storage form of the drug, which provides its optimal therapeutic effect with minimal side effects.

According to modern ideas, the dosage form is a material norm of manifestation of the dialectical unity of active and auxiliary substances, as well as technological operations that provide the optimal therapeutic effect of the drug.

Dosage form is a structural unit of both pharmacotherapy and industrial production. The degree of influence of the dosage form on the absorption processes is determined by the ability to release the active substance from the oral dosage form and the possibility of contact with the mucous membranes of the stomach, intestines and interaction with their secretions. According to the degree of release and, accordingly, better bioavailability, all oral drugs can be arranged in the following order: solutions-emulsions-suspensions-powders-granules-tablets.

9. Technological processes

Technological (production) processes are methods that consist of certain technological techniques and operations. Biopharmaceutical research has provided a scientific explanation of the role of technological processes, methods of obtaining drugs in the development of the effect. Until the formation of biopharmacy, this issue was given almost no attention.

It is now proven that the method of obtaining the drug largely determines the stability of the drug substance, the rate of its release from the dosage form, the intensity of absorption and ultimately its therapeutic efficacy.

Depending on the physico-chemical, physico-mechanical and other characteristics of dosage forms, specific methods of their preparation and equipment are used. For example, in the preparation of suppositories carry out grinding, sieving drugs, melting the base, mixing, pouring the suppository mass into molds, cooling, etc .; upon receipt of tablets - grinding, drying, sieving, mixing, granulation, compression, coating of tablets with shells.

Due to the popularity of tablets, their predominant use compared to other dosage forms, they became one of the main dosage forms in the middle of the XX century and proved to be the most studied in pharmaceutical and biopharmaceutical terms. Moreover, all stages of obtaining tablets are widely studied in order to determine the effect of step-by-step operations on their physical and mechanical properties and pharmacotherapeutic efficacy. Operations such as granulation, compression, drying, etc. have been subjected to particularly careful experimental study.

The influence of technological operations on physico-mechanical and biopharmaceutical characteristics in obtaining other dosage forms (suspensions, emulsions, liniments, aerosols, etc.) has been studied to a lesser extent.

In the technological process of preparation of dosage forms there are repetitive operations common to a number of stages of production of drugs. In the production processes in the preparation of medicines in pharmacies or factories, one-time technological techniques are used: grinding, dissolving, drying, filtering, sterilization, freezing, and others.

Subjective factors also play an important role in the preparation of drugs. This is especially true of small-scale production. For example, in a pharmacy the choice of technological operations and techniques depends on the qualifications and level of knowledge of the specialist, his production experience, analytical thinking, situation and so on, and all these factors can affect the quality of products.

The pharmacist must have a high level of training to take into account various variables in the preparation of drugs.

Questions for self-control

1. Classification of excipients and their role in the preparation of dosage forms.
2. The influence of the nature of excipients on the rate of absorption of drugs and their therapeutic efficacy.
3. Modern methods for determining the effectiveness of drugs.
4. Methods "in vitro" (direct diffusion through the membrane, "agar plates", chromatographic, solubility test, etc.).
5. "In vivo" methods, which are performed on laboratory animals, healthy human volunteers, isolated organs with single and multiple injections.
6. Modern methods for determining the concentration of drugs in biological fluids (blood, urine, excretion).
7. Microbiological and acanthosis tests.
8. Graphical method of calculating the area of the pharmacokinetic curve and the degree of absorption of drugs. Determination of absorption and elimination constants.
9. Radioisotope method.
10. Correlation of methods "in vitro" and "in vivo" in determining the bioavailability of drugs.

Main:

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