ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF DRUGS TECHNOLOGY

APPROVE
Head of Department

_____ (Borisyuk I.Yu.)
signature
«29» august 2022 y.

METHODICAL DEVELOPMENT OF THE LECTURE

Course: 5 Faculty: Pharmaceutical

Course : **Biopharmacy**

Lecture № 1 Topic: **"Biopharmacy as a scientific field and its importance in the development of composition and technology of dosage forms. Stages of biopharmacy development. Basic terms of biopharmacy. "**

The lecture was developed by:
Ph.D. of Pharmaceutical Sciences
_____ (Fisor N.S.)
The lecture was discussed at the methodical meeting of the department
«29» august 2022y.
Protocol № 1

Odessa – 2022

Lecture: "Biopharmacy as a scientific field and its importance in the development of composition and technology of dosage forms. Stages of biopharmacy development. Basic terms of biopharmacy."- 4 hours.

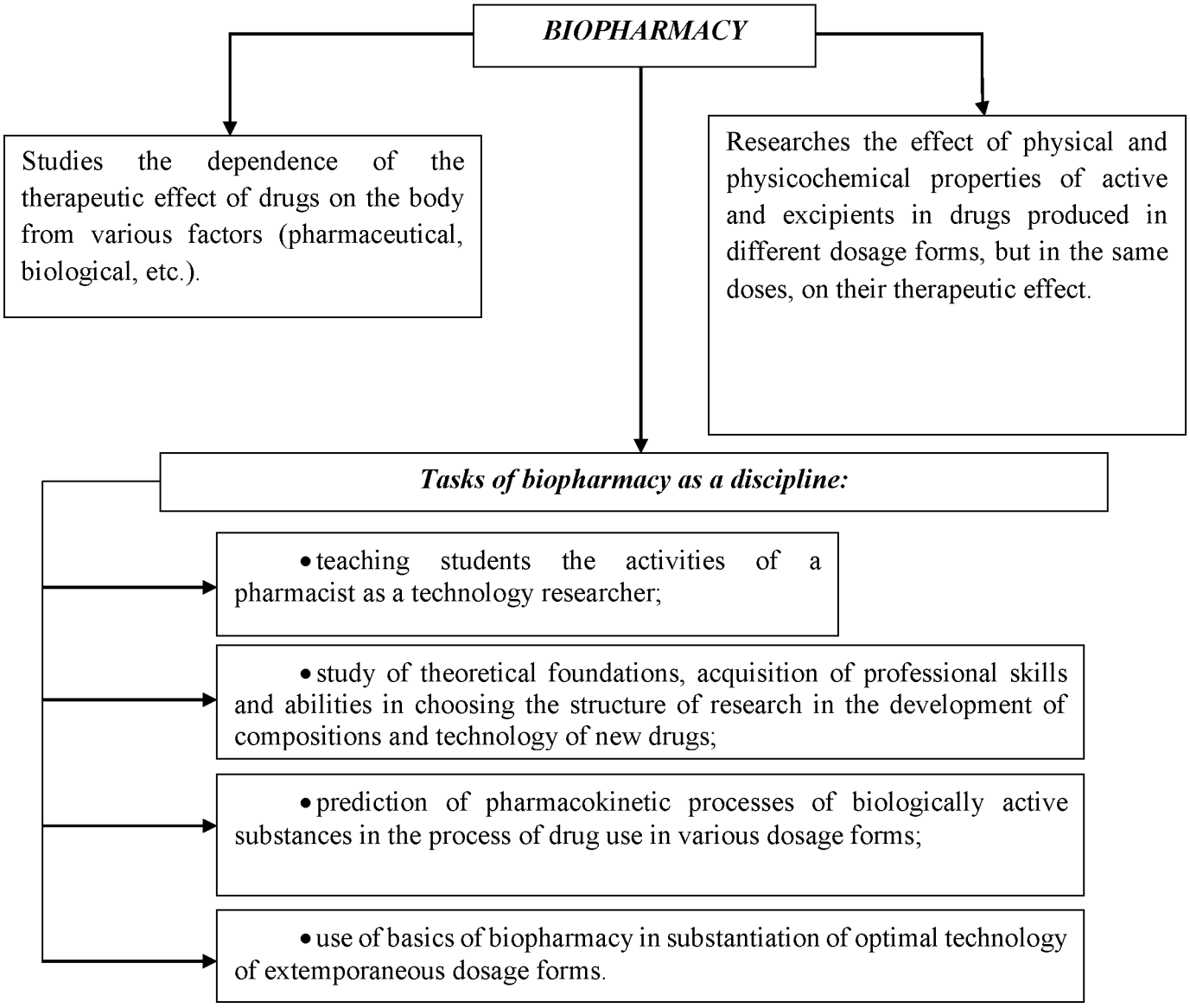
The purpose of the lecture: to get acquainted with the concept of biopharmacy.

Basic concepts: Biopharmacy, LADMER, efficacy, equivalence, pharmacokinetics.

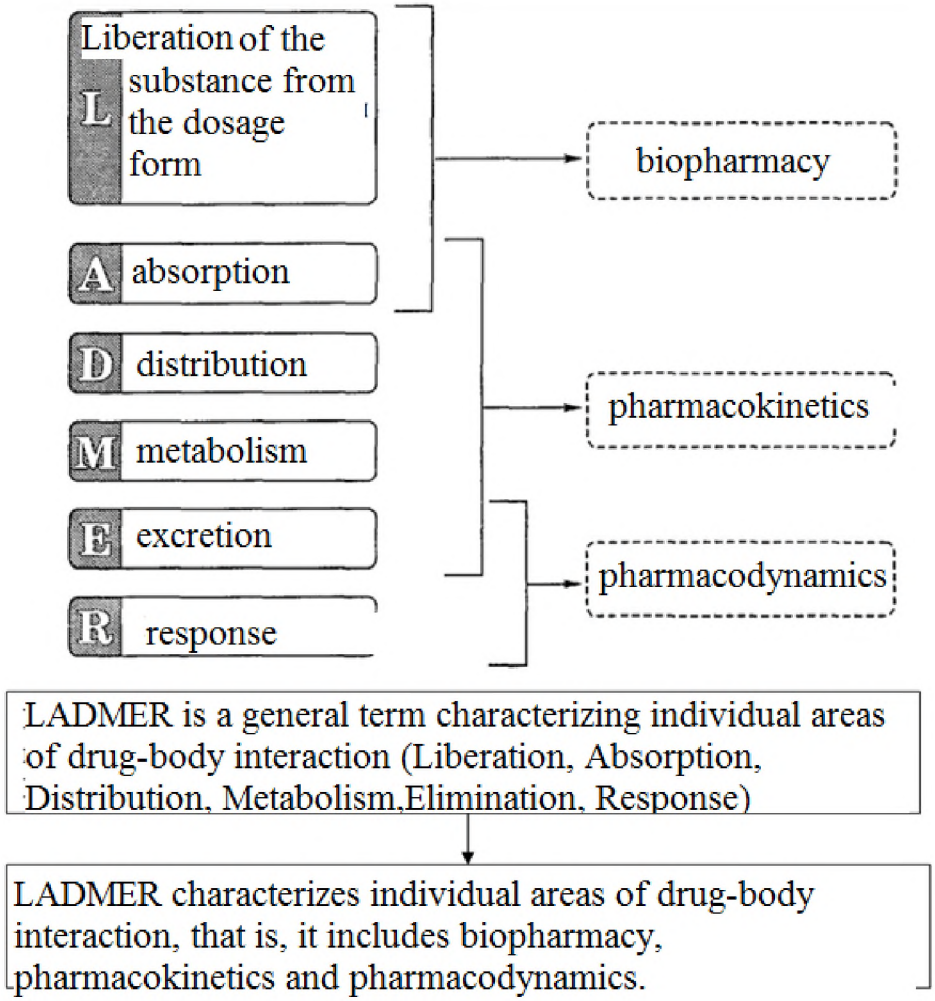
Plan:

1. Biopharmacy as a scientific direction and its importance in the development of the composition and technology of dosage forms.
2. Stages of biopharmacy development.
3. Basic terms of biopharmacy.

1. Biopharmacy as a scientific direction and its importance in the development of the composition and technology of dosage forms.



The main task of biopharmacy in drug technology is to maximize the therapeutic efficacy of drugs and minimize their possible side effects on the body.



Biopharmacy is now the theoretical and practical basis for the development of new drugs, allowing to predict the type and strength of the expected pharmacological activity and possible side effects, taking into account the type of dosage form, excipients, method of manufacture and more.

Biopharmacy is based on knowledge of mathematics, physics, inorganic and organic chemistry, pharmaceutical chemistry, physiology, anatomy, biochemistry, pharmacology, drug technology, so its terminology often uses pharmacological, chemical and technological terms.

Unlike pharmacology, biopharmacy does not study the mechanisms of action and site of administration of a drug or excipient.

It investigates the exceptional effect of variables on the pharmacodynamics and pharmacokinetics of drugs.

Scientific research of biopharmacy is developing in the following areas:

- Development of experimental-theoretical bases of biopharmaceutical screening;
- Study of the influence of pharmaceutical and other variables on the processes of release and absorption of drugs from dosage forms;
- Study of pharmacokinetics of drugs to optimize the composition of excipients and methods of drug administration;
- Study of the mechanisms of biopharmaceutical processes that occur during the interaction of the components of the finished dosage form with proteins and lipids of the membranes of different cells;
- Development of highly sensitive and selective methods of analysis of pharmacologically active substances in biological fluids of humans and animals;
- Search for new bioavailability modulators;
- Creation of new dosage forms with specified biopharmaceutical properties, which should ensure optimal bioavailability of active substances;
- Study of drug bioequivalence.

2. Stages of biopharmacy development.

From the history of pharmacy it is known that in 1838 Professor AA Iovsky first applied the concept of "technology" in the science of drug manufacturing, meaning by this term the science designed to enrich the production of drugs. At the beginning of the last century there was a great importance of the technology of the production process, the process of converting the original drugs into a dosage form designed to help the body weaken, destroy or prevent disease.

By the 1950s, the improvement of industrial technology made it possible to intensify various stages of pharmaceutical production (micronization, ultraemulsification, ultrasonic, and other types of sterilization, etc.), which also

affected the surface properties and formation of metastable modifications of drugs and excipients. It is the introduction into practice of new highly active drugs, excipients and advanced technological processes and formed the material basis of the unusual phenomenon, which in the scientific literature is called "Therapeutic inequality or inadequacy of drugs." The essence of such inequality (inadequacy) is that the same doses of (often highly active) drugs, prescribed in identical dosage forms prepared by different companies, have a different pharmacotherapeutic effect. for example, tablets containing the same doses of chloramphenicol, phenyl butazone, digoxin, tetracycline, prednisolone, thyroidin, etc., produced by one plant, have a therapeutic effect, produced by another plant - toxic, and the third - do not have the proper effect.

Careful study of known cases of therapeutic drug inequality,
showed that the activity of the active substance, its behavior in the process of release from the dosage form, diffusion to the site of absorption, and the process of absorption are closely dependent on the nature and amount of excipients and technological operations that take place in obtaining drugs.

Studies of cases of therapeutic non-equivalence of drugs have greatly contributed to the establishment of new ideas, biopharmaceutical, based on the recognition of biological (medical) significance of all components of the dosage form and consideration of drugs as a complex physicochemical system consisting of dialectical unity of factors and changes that accompany the preparation of drugs.

In the late 50's and a new direction in pharmacy was launched - biopharmaceutical. Biopharmacy is defined as the science that studies the biological action of drugs depending on the physicochemical properties, type of dosage form, cooking technology, and others. variables.

The founders of biopharmacy in the CIS and Ukraine are Professors JI Hajai and DP Salo. Research in this area was continued and developed by Professors IM Pertsev, GS Bashura, AI Tikhonov, NA Lyapu-Novy, GV Obolentseva, MV Steingardt, NA . Kazarinov, DI Dmitrievsky, VA Spiridonov, and others.

Biopharmacy - a science that studies the dependence of the therapeutic effect of drugs on the body from various factors (pharmaceutical, biological, etc.).

Biopharmacy is a scientific discipline of pharmacy that studies the effect of physical and physicochemical properties of active and excipients in drugs produced in different dosage forms, but in the same doses, on their therapeutic effect.

The emergence of biopharmacy was prepared throughout the progressive development of pharmacy, medicine, chemistry and other sciences. It is at the junction of several branches of knowledge and biopharmacy originates.

It appeared after establishing the facts of therapeutic non-equivalence of drugs, ie drugs of the same composition, but prepared by different pharmaceutical companies, differed in therapeutic efficacy. This was due to a number of reasons: the degree of grinding of drugs, the selection of excipients and the difference in technological processes, the so-called pharmaceutical factors. In the special literature, the term "pharmaceutical factors" has become widespread primarily in connection with the

clinical confirmation of experimental data on the existence of a relationship between the effectiveness of drugs and methods of obtaining them.

The founders of biopharmacy are considered to be the American scientists Levy and Wagner, thanks to whose work the term "biopharmacy" was adopted, which is used in most European countries as the equivalent of the English term "biopharmaceutics".

The term "biopharmacy" first appeared in scientific pharmacy in the United States in the 60s of XX century and soon gained general international recognition.

The word "pharmaceutics", used in English literature, is not synonymous with "pharmacy", its designation - galenic pharmacy. "Biopharmaceutics" and the adjective "biopharmaceutical" formed from it are literally translated as "biogalenics" and "biogalenic".

The addition of the prefix "bio" to the term "pharmaceutics" does not mean that we are talking about the biological evaluation of products of galenic pharmacy or biological pharmacy in general.

This capacious word "biopharmacy" successfully and fully defines the complex of dependencies that exist between the drug substance and the therapeutic effect of the prepared drug.

Despite the fact that the term "biopharmacy" is not quite accurate, it is used both in our country and abroad and is introduced into a single standard international biopharmaceutical terminology.

3. Basic terms of biopharmacy.

Modern biopharmacy has its own internal terms that denote its basic concepts.

Factors - simultaneously acting forces, states or other circumstances that affect the final result of the studied processes, data or parameters.

The active *substance* is a biologically active part of the drug that is responsible for the therapeutic effect.

Efficacy - the ability of a drug or drug to achieve the desired effect.

Due to the fact that the therapeutic efficacy is significantly influenced by variable biological (physiological, biochemical) factors, biopharmacy also pays attention to their study using the bioavailability test.

Thus, the definition of biopharmacy at the first stage of its development can be formulated as follows: *science, the subject of which is the study of the influence of a wide range of variables (pharmaceutical and biological) factors on the interaction of drugs and the body.*

The main purpose of biopharmacy is to obtain a lasting effect, maximize the effectiveness and minimize the adverse effects of drugs on the body.

Numerous international symposia on biopharmacy and pharmacokinetics (Czechoslovakia, 1970, 1974, 1978 and 1982), which regularly took place due to the organizational skills of the Slovak scientist L. Zathurecky, as well as due to regional scientific quorums, contributed to the rapid development of biological pharmacy and the formation of new thinking. devoted to this problem.

The influence of pharmaceutical and biological variables on the degree of efficacy of drugs can be traced according to a typical pharmacokinetic scheme:

the amount of active substance in the drug

↓

release and amount of substance at the site of absorption

↓

absorption, biotransformation and the amount of active substance in the bloodstream and tissues

↓

excretion of the active substance (metabolites) from the body

Before the process of absorption of the active substance, it must be released from the pharmaceutical system (tablets, suppositories, ointments), diffuse to the absorption surface. The absorption process itself is also diffusion and depends on many factors: the amount, properties and physical state of the active substance, the overall composition and properties of the pharmaceutical system, as well as technological factors and the physiological state of the absorption surface.

Therefore, the effectiveness of drugs can be determined only by careful study of both pharmaceutical and biological variables, each of which determines the dominant influence at certain stages of "life" of the pharmaceutical drug, from creation and production to rational use, including the possibility of its interaction with exogenous, endogenous components and elements of the organism.

Clinical factors - factors that occur during pharmacotherapy in a clinical setting (choice of dosing regimen, time of drug administration, side effects, interaction of simultaneously or sequentially administered drugs, bedriddenness, physical activity, severity of the disease, gastrointestinal disorders tract, liver, kidneys, heart, etc.).

Equivalence - the correspondence of the amount of drug (drug) or drug indicated in the analytical regulations or the identity of the effect of the studied drug of comparison.

The pharmaceutical equivalent is a drug that contains the same amount of therapeutically similar substance in a particular dosage form and meets the requirements set by technological standards.

Clinical equivalent - the equivalent of a drug, which after the use of the same doses gives the same therapeutic effect, tested on any symptom or treatment of the disease.

Bioequivalence - the equivalent of drugs prepared by different manufacturers or the same plant, but different series, after the introduction of which in the same dosage form to the same patients in the same doses, the same biological (therapeutic) effect.

Therapeutic non - equivalence - the inequality of therapeutic action of the same drugs in the same doses, prepared by different manufacturers or the same plant, but different series.

Bioavailability is a condition that allows a drug substance introduced into the body to reach the site of exposure.

Relative bioavailability - expressed as a percentage of the amount of drug released from the dosage form, which after administration reaches the receptor in an amount sufficient to cause a biological effect.

Absolute bioavailability is the amount of drug administered intravenously or intravascularly that enters the bloodstream without the effect of the first pass effect or after correlation to this effect, and the rate of this process.

Physiological availability is synonymous with "bioavailability" or "bioavailability".

Systemic availability is the part of the total absorbed dose of the drug that enters the circulatory system after oral administration. Synonymous with "bioavailability" and "bioavailability".

Absorption (absorption) - the process of transition of the drug from the place of reception into the bloodstream.

Resorption is synonymous with "absorption".

The release rate constant is a general constant that determines the rate of penetration of a drug substance from the site of ingestion through the biological membrane.

Biotransformation - a complex process in which lipoid-soluble molecules of the drug in the process of biochemical reactions are replaced by catalytic enzymes (oxidation, reduction, hydrolysis, synthesis) into metabolites.

Purity - the hypothetical volume of the body, which was deprived of the corresponding substance per unit time.

Purity of the whole body - the purity of the hypothetical volume of plasma in milliliters (volume of distribution), through which the body is released from the drug, releasing it through the kidneys, bile, lungs, skin and metabolism.

Distribution is the process by which a drug is distributed or dispersed from the blood into one or more parts, into tissues and organs of the body.

Distribution rate constant - the rate constant of the transition of a drug substance from the circulatory system to any or any part of the body.

The area under the pharmacokinetic curve is the surface, which in the coordinate system is limited by a segment (x-axis and curve), which characterizes the concentration of the drug in the blood (serum, plasma, urine) depending on time. It is limited in time or extrapolated to infinity.

Excretion (excretion) - a process during which the drug (drug) is excreted from the circulatory system through the kidneys into the urine, through bile and saliva into the intestines and feces, through the skin, breast and sweat glands.

Absorption constant is a general constant that determines the rate of penetration of a drug substance from the site of administration through the biological membrane into the body.

Elimination constant - the rate constant of the process during which the effective substance is removed from the body by excretion or biotransformative processes.

Pharmacokinetics - a description of changes over time in the concentrations of the administered drug and its metabolites in the body; covers such transport processes of the active substance and its metabolites in the body as absorption, distribution, biotransformation and elimination.

Thus, the main purpose of biopharmacy as a science is a theoretical and experimental justification for the creation of new drugs and improvement of existing ones, taking into account the increase of their therapeutic effect and reduction of side effects on the body.

Significant scientific achievements in the field of biopharmacy include the following:

1. The connection between the type of ointment bases and the effectiveness of antiseptics, antibiotics, biologically active substances of bee products and other chemotherapeutic substances. This allowed to develop and implement in medical practice of the CIS ointments "Levosin", "Levomicol", "dioxicol" and many others.

2. The relationship between the distribution of drug molecules, in particular corticosteroids, in different phases of dispersed dosage forms depending on the structure of these phases and between the release, bioavailability, efficacy and side effects of drugs. The results of these studies were used in the development of ointments and liniments of sinaflan, hydrocortisone and prednisolone ointments, Triacort ointments, Cortonisol aerosols, Trimistin ointments, Cortonitol ointments, and others.

3. The connection between the supramolecular structure of surfactant associations (surfactants), physicochemical properties of dispersed systems, release, bioavailability, activity and the manifestation of toxic effects of various drugs. The results of research have purposefully managed the pharmacological and toxicological properties of drugs in various dosage forms: ointments, foams, suppositories, gels and others - and formed the basis for the creation of drugs such as "Suliodopyrone", suppositories "Propofen", "Polenfen", ointments Lipovit "," Prolidoxide "and others.

4. The correlation between affinity of medicinal and auxiliary substances to different biomembranes, structure of biomembranes, bioavailability and efficiency of pharmacological action of medicinal pre-Paraty is established.

5. The regularities of pharmacokinetic, pharmacokinetic and toxicodynamic interaction of drugs in combined drugs are studied, as well as the influence of excipients and tablet technology on the release of drugs from tablets and their bioavailability is studied. The results of the research formed the basis for the creation of a group of combined preparations with paracetamol, solid dosage forms with bee products (tablets "Propolin", "Propoltin", "Feprogit"), and others.

6. The influence of chemical modification of medicinal substances with the help of amino acids on their bioavailability and efficiency of action has been studied. For example, acelysin (Domestic soluble aspirin) and its dosage forms have been introduced into production and medical practice.

Interest in biopharmacy as a scientific field is becoming deeper, and more and more scientists are engaged in biopharmaceutical research.

To date, biopharmacy has successfully solved a number of problems of scientific pharmacy and medicine and have a significant impact on the further development of the theory of modern drug management.

Questions for self-control

1. What does the scientific discipline of pharmacy - biopharmacy?
2. Define the basic concepts: efficiency, clinical factors, bioequivalence, relative bioavailability, absolute bioavailability, absorption, metabolism.
3. The concept of bioavailability. The main indicators of bioavailability of drugs.
4. Factors affecting the bioavailability of drugs:

1) Influence of drug routes on bioavailability: parenteral, oral, rectal, inhalation route of administration;

2) The influence of body temperature and environment;

3) Influence of a magnetic field and meteorological factors;

4) Influence of age, sex, biorhythms and pathological processes;

5) The effects of alcohol and smoking.

Main:

1. .Biopharmaceutics. Збірник текстів лекцій./ Tikhonov A.I., Yarnykh T.G., Yuryeva A.B., Podorozhna L.N., Zuykina S.S., НФаУ Оригінал, 2011. – 140 с.
2. Biopharmaceutics. Практикум / Tikhonov A.I., Bogutskaya Ye.Ye., Yarnykh T.G., Kotenko A.M., Garkavtseva O.A., НФаУ Оригінал, 2011. – 80 с.
3. Janicki S., Sznitowska M., Zielinski W. Dostepnosc farmaceutyczna I dostepnosc biologiczna lekow. – Warshawa, 2001.–242 s.
4. Biopharmaceuticals: Biochemistry and Biotechnology, 2nd Edition. – 2013. – 544 p

ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF DRUGS TECHNOLOGY

APPROVE
Head of Department
_____ (Borisyuk I.Yu.)
signature
«29» august 2022y.

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. "**

The lecture was developed by:
Ph.D. of Pharmaceutical Sciences
_____ (Fisor N.S.)
signature
The lecture was discussed at the methodical meeting of the department
«29» august 2022y.
Protocol № 1

Odessa – 2022

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

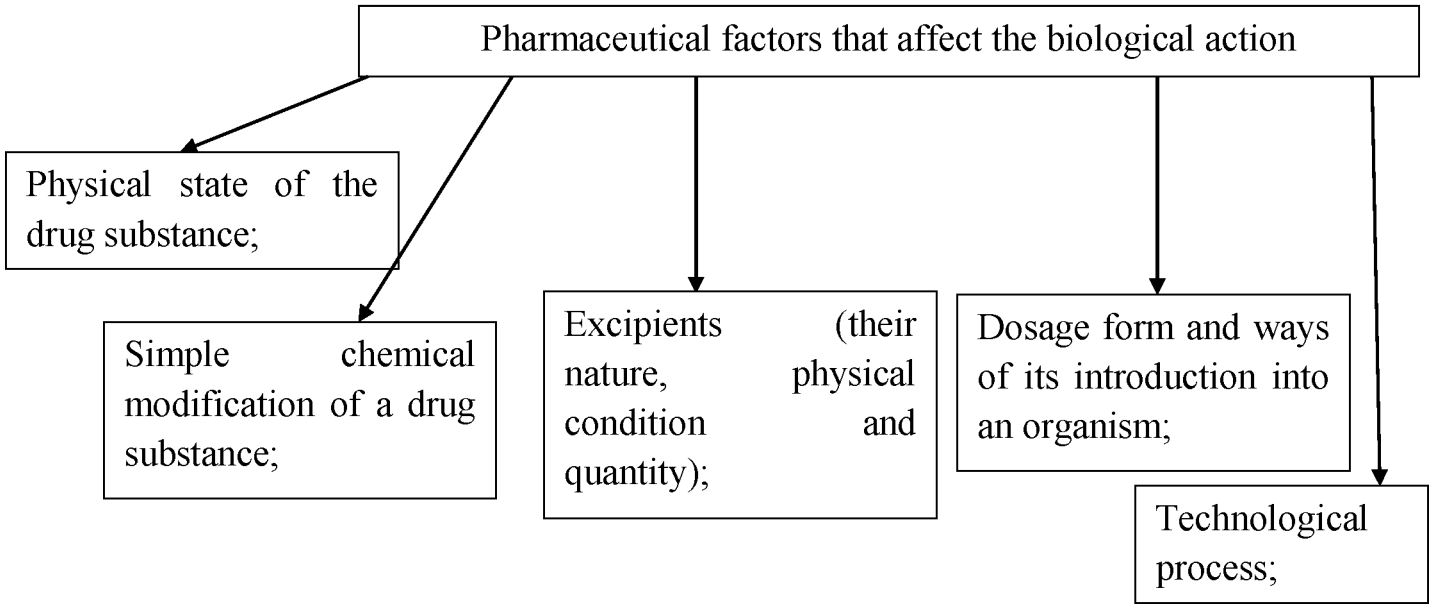
The purpose of the lecture: to get acquainted with all pharmaceutical factors and their influence on the action of drugs;

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.

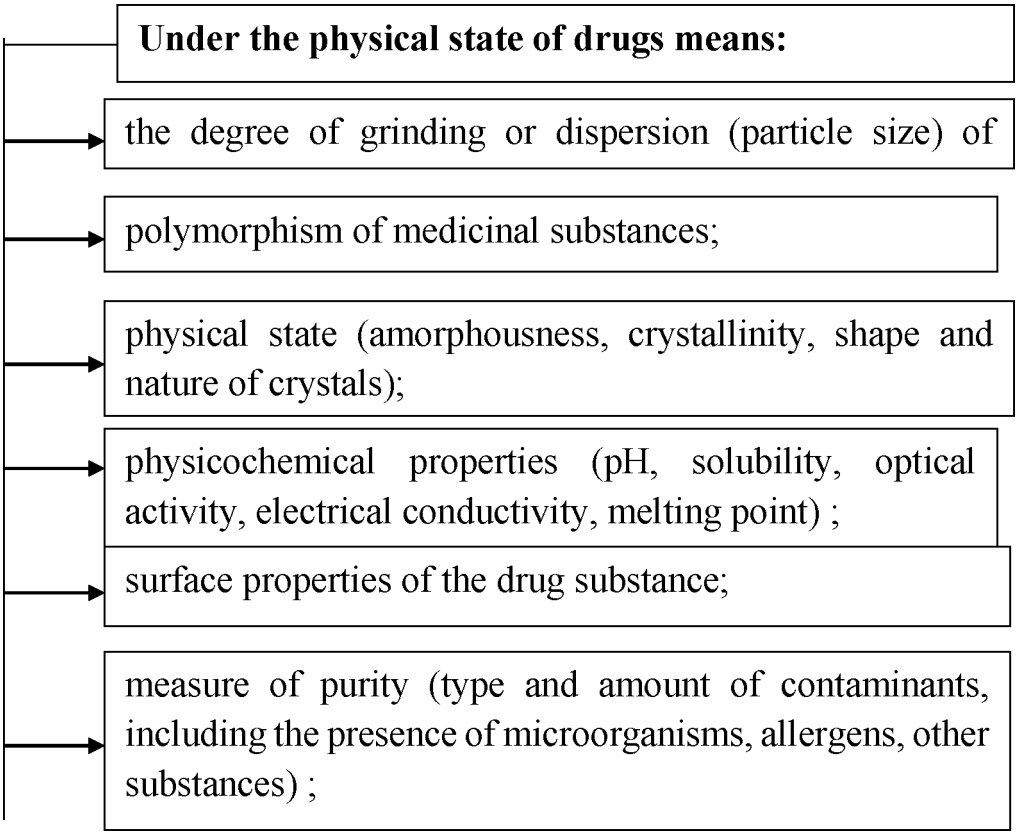
Heterogeneous - two-phase coarse systems with a particle size of 100 to 1000 nm (0.1-1 μm) and more.

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. A review of works on the study of polymorphism in medicinal substances is given in the works of AI Tentsova, Halebleyne, Bush, Halabala.

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_cH, -CH_2RO_cN. 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.

The phenomenon of electoral resorption is clearly illustrated in the experiments of prof. A.I. Tentsova, when in all experiments the results testifying to influence of correcting substances (cherry syrup, raspberry essence, citric acid) on speed of absorption of calcium chloride are received.

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:

1. .Biopharmaceutics. Збірник текстів лекцій./ Tikhonov A.I., Yarnykh T.G., Yuryeva A.B., Podorozhna L.N., Zuykina S.S., НФаУ Оригінал, 2011. – 140 с.
2. Biopharmaceutics. Практикум / Tikhonov A.I., Bogutskaya Ye.Ye., Yarnykh T.G., Kotenko A.M., Garkavtseva O.A., НФаУ Оригінал, 2011. – 80 с.
3. Janicki S., Sznitowska M., Zielinski W. Dostepnosc farmaceutyczna I dostepnosc biologiczna lekow. – Warshawa, 2001.–242 s.
4. Biopharmaceuticals: Biochemistry and Biotechnology, 2nd Edition. – 2013. – 544 p

ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF DRUGS TECHNOLOGY

APPROVE
Head of Department

_____ (Borisyuk I.Yu.)
signature
«29» august 2022y.

METHODICAL DEVELOPMENT OF THE LECTURE

Course: 5 Faculty: Pharmaceutical

Course: **Biopharmacy**

Lecture № 3 Topic: **"Bioavailability of drugs."**

The lecture was developed by:
Ph.D. of Pharmaceutical Sciences
_____ (Fisor N.S.)
signature name

The lecture was discussed at the methodical meeting of the department
«29» august 2022y.
Protocol № 1

Odessa – 2022

Lecture: "Bioavailability of drugs" - 2 hours.

The purpose of the lecture: to get acquainted with the modern definition of bioavailability of drugs, the factors that affect it.

Plan

1. Definition of bioavailability.
2. Factors affecting the bioavailability of drugs.
3. Influence of routes of administration on bioavailability.
4. Influence of body temperature and environment
5. Influence of age and sex.
6. Influence of biorhythms.
7. Influence of magnetic field and meteorological factors.
8. Influence of pathological processes and individual features of an organism.
9. Influence of alcohol.
10. The effects of smoking.
11. The effect of drug interactions on bioavailability.

1. Definition of bioavailability.

Bioavailability (BA) is the degree to which a drug is absorbed from the site of entry into the systemic circulation and the rate at which this process occurs.

According to the WHO recommendations, the measure of bioavailability is the ratio (in percent) of the amount of absorption of the drug administered in the test dosage form (A) to the amount of absorption of the same drug administered in the same dose but in the standard dosage form (B), ie BA = (A: B) * 100

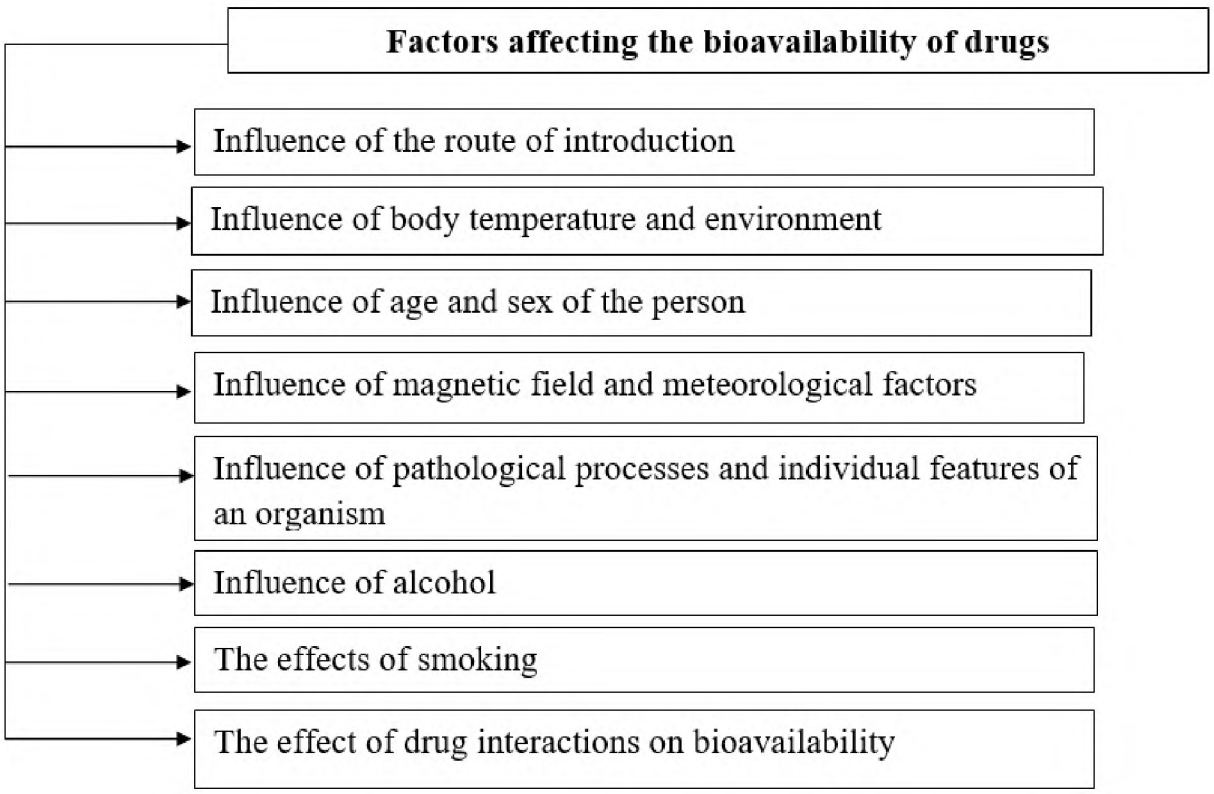
Absolute — **Bioavailability** — *Relative*

General bioavailability

It can be calculated if a solution for internal administration is used as a dosage form, which provides 100% bioavailability.

Characterizes the relative degree of absorption of the drug substance of the study drug and the comparison drug.

Part of the oral dose of the drug, which reached the systemic blood flow in unchanged form and in the form of metabolites formed in the process of absorption as a result of presystemic metabolism ("first-pass effect").



Biopharmacy, along with the pharmaceutical availability test, proposes to establish a specific criterion for assessing the effect of pharmaceutical factors on drug absorption - *bioavailability* - the degree to which a drug is absorbed from the site of entry into the systemic circulation and the rate at which this process occurs.

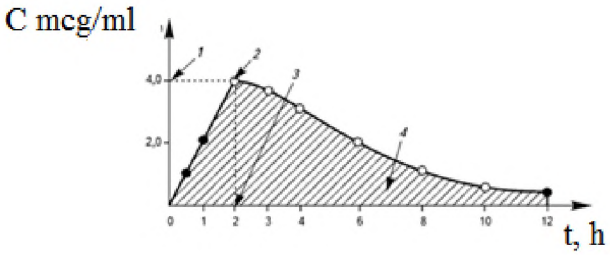
Bioavailability (DB) is the part of the administered drug that enters the systemic bloodstream by oral, intramuscular, inhalation and other routes of administration. It is obvious that with intravascular administration the DB of the substance will be equal to 100%, and with other routes of administration (oral, rectal, intramuscular, etc.) - much lower and almost never reaches 100%.

According to the WHO recommendations, the measure of bioavailability is the ratio (in percent) of the amount of absorption of the drug administered in the test dosage form (A) to the amount of absorption of the same drug administered in the same dose but in the standard dosage form (B), ie DB = (A: B) · 100. Most often, the bioavailability of drugs is determined by a comparative study of changes in the concentration of the drug in plasma when prescribing the study and standard dosage forms.

When studying the bioavailability of drugs, the most important are the following parameters:

- maximum (peak) concentration of the drug in the blood;
- time to reach maximum concentration;
- area under the curve of change in the concentration of the drug in plasma or serum over time.

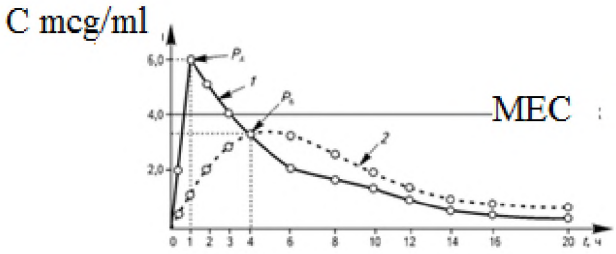
The main parameters of pharmacokinetics used in the study of bioavailability of drugs are presented in Fig. 1.



1- max concentration
2-peak
3-time (t) to reach maximum concentration
4- area under the "concentration-time" curve

Fig.1. The main parameters of pharmacokinetics used in the study of bioavailability of drugs.

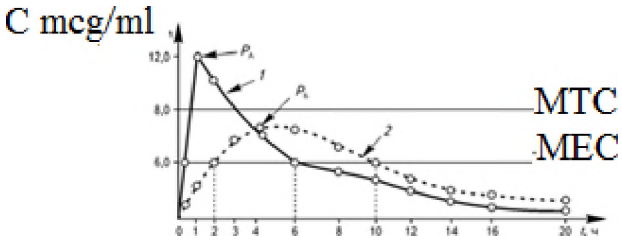
The practical value of the concentration peak is well illustrated in Fig. 2, in which two curves depict the kinetics of the concentration in the blood of the same substance contained in different dosage forms (A and B). The horizontal line indicates the minimum effective concentration (IEC) at which this substance has a therapeutic effect (4 μg / ml). It is seen that in dosage form B, the drug substance, although completely absorbed, but does not have a therapeutic effect, because it does not reach the MEC.



1- dosage form A;
2-dosage form B;
3-peak concentration of the drug;
MEC-minimum effective concentration.

Fig. 2. The dynamics of the concentration (C) of the drug after its use in two dosage forms:

In small. 3 shows the kinetics of a drug substance having an IEC b μg / ml and a minimum toxic concentration (MTC) of 8 μg / ml, when used in two dosage forms A and B. When using dosage form A, the concentration of the substance exceeds the ITC, and therefore it has a toxic effect. When using dosage form B, the drug substance is contained in the blood in therapeutic concentrations, but does not reach toxic concentrations and does not have a harmful effect on the body.



1- dosage form A;
2-dosage form B;
3-peak concentration of the drug;
AUCA=34,4(mcg/ml)-hour,
AUCB=34,2(mcg/ml)-hour-

Fig. 3. Determination of the minimum toxic concentration (MTC) and the minimum effective concentration (MEC) of the drug by the dynamics of its concentration in the blood when used in two dosage forms (A and B):

The second important parameter is the time to reach the maximum concentration of the substance in the biological fluid P, as it reflects the rate of absorption of the substance and the rate of onset of therapeutic effect. From fig. 3. it follows that P when

using dosage form A is achieved after 1 hour, and in dosage form B - after 4 hours. Suppose that in this case the drug is a hypnotic. It reaches the minimum therapeutic concentration and has a soporific effect in the first case after 30 minutes, and in the second case - only after 2 hours. At the same time, the effect of the hypnotic substance in the first case (when using dosage form A) lasts 5.5 hours, in the second case (when using dosage form B) lasts 8 hours.

Thus, taking into account the peculiarities of the pharmacokinetics of the same hypnotic, in different dosage forms differ indications for their use. Dosage form A should be used in case of sleep disturbance, while dosage form B - in case of sleep disturbance.

Third, the most important parameter of bioavailability is the area under the curve "concentration - time" (AUC), which reflects the amount of drug that entered the blood after a single injection of the drug.

In small. 3 presents the curves characterizing the bioavailability of two different dosage forms of the same substance. These curves have different shapes, different peaks and different time to reach the IEC. At the same time, the areas under these curves are the same [AUC for dosage form A is 34.4 (μg / ml) -hour, for B - 34.2 (μg / ml) -hour], therefore, both dosage forms provide revenue in blood of the same amount of drug substance. However, they differ in the degree of absorption and the rate of achievement of the IEC of the drug, which has a great influence on both quantitative and qualitative parameters of their therapeutic action, which means that they can not be attributed to bioequivalent drugs. This qualitative characteristic should be taken into account when prescribing and using drugs of similar composition and action, but manufactured by different pharmaceutical companies.

Fig. 4. The relative bioavailability of the drug when used in three dosage forms:

In small. Figure 4 shows the curves that reflect the kinetics of the same substance when used in three different dosage forms - A, B and B.

The area under the curve that characterizes dosage form A is larger than under curve B and much larger than under curve B. It follows that dosage form A provides absorption into the blood of the drug much better than dosage forms B and B.

Thus, to compare different generic drugs, dosage forms, to address the issue of replacing the drug with an analogue, it is necessary to take into account the parameters of bioavailability. Differences in the degree of absorption and the rate of reaching the maximum concentration of the drug can have a significant impact not only on the quantitative parameters of the therapeutic effect of the drug, but also on its qualitative characteristics.

2. Factors affecting the bioavailability of drugs

The drug immediately enters the systemic bloodstream only when administered intravascularly. With all other methods of administration, this is preceded by a number of different processes. First of all, the drug substance must be released from the dosage form - tablets, capsules, suppositories, etc. The tablets are first destroyed, only then the drug goes into solution. The capsule first dissolves the shell, then releases the drug, which only then passes into solution. When administered as a suspension, the drug substance dissolves under the influence of body fluids (saliva, gastric juice, bile, etc.). The base of the suppositories melts in the rectum, and then the drug becomes capable of dissolving and absorbing. The rate of absorption may decrease and the duration of action may increase if the drug is administered in the form of insoluble complexes, which then disintegrate in the injection area, forming a form soluble in water. An example is benzylpenicillin sodium, protamine-zinc-insulin.

The drug, administered orally or rectally, is absorbed by the capillaries of the gastrointestinal tract (GI tract), and then through the mesenteric veins enters the portal vein and liver. If the drug is rapidly metabolized in the liver, then some of it is converted into metabolites before it is found in the systemic circulation. This position is even more true for drugs that are metabolized in the intestinal lumen, its wall or mesenteric veins. This phenomenon is called presystemic metabolism or first-pass effect (EPP).

According to physiologists, the greatest distance at which cells in tissues defend from capillaries is about 0.125 mm. Since the cells of the human body have an average diameter of 0.01 mm, the drug molecule after entering the systemic bloodstream must overcome the biological barrier, consisting of approximately 10-12 cells, before entering into a specific interaction with the receptor. In order to get into the brain, eye, breast milk and a number of other organs and tissues, drugs must also overcome special biological barriers, such as blood-brain, hematoophthalmic, placental and others.

Thus, when drugs are administered extravascularly, a number of chemical-pharmaceutical and medical-biological factors are able to have a significant impact on its bioavailability. In this case, physiological factors are important both in themselves and in interaction with pharmaceutical factors.

Consider the most significant medical and biological factors that can affect the bioavailability of drugs, and hence their therapeutic efficacy and toxicity.

3. Influence of routes of administration on bioavailability

Oral route of administration of drugs

Most drugs are administered orally, ie by mouth. This way of drug administration is the simplest and most convenient. At the same time, the number of factors that may affect the bioavailability of drugs is the largest in this way of introduction.

Influence of enzymes of the gastrointestinal tract . Drugs affect the body differently, depending on when they are taken: before meals, during or after meals, due to changes in the pH of the gastrointestinal tract, the presence of various enzymes and active substances released from the bile to ensure the digestive process .

During and after meals, the acidic environment of the stomach reaches pH = 2.9 ... 3.0, and the small intestine - 8.0 ... 8.4, which significantly affects the ionization, stability of drugs, the speed of their passage through digestive tract and absorption into

the blood. Thus, acetylsalicylic acid at a gastric pH of 1 to 3 is almost completely in non-ionized form and as a result (due to the high solubility in lipids) is almost completely absorbed. Taking aspirin with food increases the amount of the drug, which is converted into a salt form, the rate of absorption in the stomach is reduced to values approximately coinciding with the rate of absorption of aspirin in the small intestine, and bioavailability is generally reduced.

Erythromycin, benzylpenicillin, pancreatin, pituitrin, insulin and a number of other drugs are inactivated under the influence of acidic environment and gastric enzymes. Hexamethylenetetramine is completely decomposed into ammonia and formaldehyde.

Therefore, most orally administered drugs are significantly affected by enzymes and various highly active substances of the gastrointestinal tract, released during and after meals, which can significantly affect their bioavailability.

Influence of composition and temperature of food .

The composition and temperature of food have a great influence on the effectiveness of drugs. Ordinary mixed food contains substances of plant, animal and mineral origin: proteins, fats, carbohydrates, amino acids, fatty acids, glycerin, tannins (in tea, persimmons), caffeine (in tea, coffee), serotonin (in nettles, peanuts, bananas). , pineapples), tyramine (in cheese, bananas, beans, herring, coffee, beer, wine, chicken liver), oxalates (in rhubarb, celery, sorrel, spinach), sterols, phytosterols, heavy metal ions and other chemically and pharmacologically active substances. Depending on the composition of food in different ways affects the peristalsis and secretory function of the digestive tract, which depends on the degree and rate of absorption of drugs.

Protein foods (eggs, cheese, milk, peas, beans) reduce the pharmacological effect of digitoxin, quinidine, cimetidine, caffeine, theophylline, tetracycline and penicillin, anticoagulants, cardiac glycosides and sulfonamides.

Fats (especially those containing higher fatty acids) reduce the secretion of gastric juice, slow down the peristalsis of the stomach, which leads to delayed food processes and transportation of food mass. Under the influence of foods rich in fat, the absorption of many drugs is significantly increased, especially fat-soluble, such as anthelmintics, anticoagulants, sulfonamides, griseofulvin, anaprilin, diphenine, fat-soluble vitamins A, D, E, carbamazepine, lithium metro, and lithium, and lithium. . Deficiency in eating fats slows down the metabolism of ethylmorphine hydrochloride. Preliminary intake of fatty foods reduces the activity of salol and besalol.

Influence of the nature of the liquid used for drinking drugs.

The nature of the liquid with which the drug is washed plays a role in the bioavailability of drugs. Often, to mask the unpleasant taste and smell of drugs, use a variety of fruit or vegetable juices, tonics, syrups, milk. Most fruit and vegetable juices are acidic and can destroy acid-fast compounds, such as ampicillin sodium, cycloserine, erythromycin, benzylpenicillin, potassium salt. Juices can slow down the absorption of ibuprofen, furosemide, enhance the pharmacological effect of adebit, barbiturates, diacarb, nevigramon nitrofurans, salicylates.

When sweetening drugs with syrups or milk sugar, the absorption of isoniazid, ibuprofen, calcium chloride, tetracycline hydrochloride, furosemide is sharply slowed

down. Some drugs that have an irritating effect on the mucous membrane of the gastrointestinal tract, washed down with milk. Medicines are mixed with milk and dairy products for infants. Some patients, taking medication, do not drink them at all, which is not recommended, because the capsules, tablets, pills, sticking to certain parts of the inner surface of the esophagus and gastrointestinal tract, are destroyed before reaching the site of absorption. In addition, they cause irritation at the site of adhesion, and the lack of sufficient fluid delays their absorption.

Rectal route of administration of drugs

The rectal route of administration of drugs (through the rectum) ensures their rapid absorption (after 7 - 10 minutes). It is used for both local and general action. At a rectal way of administration of medicinal substances in 5-15 min. the minimum therapeutic concentration is created in blood. This is due to the presence in the rectum of a dense network of blood and lymphatic vessels, good absorption of drugs, soluble in both water and fat, through the mucous membrane of the rectum. Substances, absorbed in the lower part of the rectum, through the inferior hemorrhoidal veins enter the systemic bloodstream, bypassing the hepatic barrier. The fact that the rectal route of administration of drugs are not destroyed by the enzyme system of the liver as a result of the "primary effect", significantly increases their bioavailability compared to oral administration.

The process of intestinal absorption is influenced by the autonomic nervous system (adrenergic agonists stimulate absorption, and cholinergic antagonists - secretion), endocrine system, biologically active peptides. Endocrine, autonomic nervous and neuropeptide systems also regulate the motor activity of the colon, which, in turn, determines the duration of the drug in the intestine. In addition, a number of diseases of the rectum (hemorrhoids, cracks in the anorectal region, proctitis) impair the bioavailability of drugs administered rectally.

Inhalation route of drug administration

During the inhalation route of administration, the drug is rapidly absorbed into the systemic bloodstream through the bronchial mucosa without affecting the primary metabolism in the liver. With this route of administration, the bioavailability of drugs may be affected by concomitant diseases of the bronchopulmonary system, smoking (as a factor contributing to the development of chronic bronchitis with appropriate restructuring of the bronchial wall structure), and circulatory status in the bronchopulmonary system.

4. Influence of body temperature and environment

The increase in body temperature is accompanied by a sharp excitation of the CNS, respiration and blood circulation, increased metabolism. Excessive sweating leads to dehydration, blood clotting, decreased volume of circulating fluid, electrolyte imbalance. All this, in turn, affects the processes of absorption, distribution and metabolism of drugs, their bioavailability after oral administration.

With increasing absorption temperature, metabolism and transport of drugs proceed faster, and with decreasing - slow down. Local cooling of body tissues leads to vasospasm, resulting in a sharp slowdown in absorption, which should be borne in mind when local administration of the drug. The influence of temperature factor on the

pharmacokinetics of drugs must be taken into account in clinical practice in cases where drugs are prescribed to patients with severely impaired thermoregulation.

5. Influence of age and sex

A person's age also affects the bioavailability of drugs. For young patients are characterized by higher rates of absorption, excretion, the shortest time to reach the maximum concentration of drugs; for the elderly - a higher value of the half-life of drugs.

When prescribing drugs to children, it is important to remember that in children under one and a half years of age, the bioavailability of drugs taken orally is only slightly different from that of adults. However, their absorption (both active and passive) is very slow. As a result, small concentrations are created in the blood plasma, often insufficient to achieve a therapeutic effect. In children, the delicate, easily irritated mucous membrane of the rectum, because the reflexes that occur, lead to rapid bowel cleansing and reduced bioavailability of drugs.

6. Influence of biorhythms

One of the most powerful factors influencing a person and the effectiveness of drug therapy is also the action of biorhythms. Every cell of our body experiences time - the alternation of day and night. For a person is characterized by an increase during the day and a decrease in night physiological functions (heart rate, minute blood volume, blood pressure, body temperature, oxygen consumption, blood sugar, physical and mental performance). Biological rhythms cover a wide range of periods: age, annual, seasonal, monthly, weekly, daily. They are all strictly coordinated. The circadian, or round-the-clock, rhythm at the person is shown, first of all, in change of the periods of a dream and wakefulness. There is a biological rhythm of the body with a much lower frequency than the daily, which affects the reactivity of the body and affects the action of drugs. Such, for example, hormonal rhythmics (female menstrual cycle).

During the day there is a different sensitivity of the body to optimal and toxic doses of drugs. The experiment found a 10-fold difference in mortality of rats from elenium and other drugs in this group at 3 o'clock in the morning compared with 8 o'clock in the morning. Tranquilizers show maximum toxicity in the active phase of the day, coincide with high motor activity. Their lowest toxicity was observed during normal sleep. Acute toxicity of adrenaline hydrochloride, ephedrine hydrochloride, mezaton and other adrenomimetics increases during the day and decreases significantly at night. And the acute toxicity of atropine sulfate, platyphylline hydrotartrate, metacin and other cholinolytics is much higher at night, in the inactive phase of the day. High sensitivity to sleeping pills and anesthetics is observed in the evening, and to anesthetics in dentistry - at 14-15 o'clock in the afternoon (at this time it is recommended to remove teeth).

7. Influence of magnetic field and meteorological factors

- significantly affect the higher centers of nervous and humoral regulation, biocurrents of the heart and brain, the permeability of biological membranes. Men are more sensitive to the activity of the Earth's magnetic field than women. Patients with disorders of the nervous and cardiovascular systems are most sensitive to magnetic

storms in the Earth's atmosphere. In the days of magnetic storms, they have an exacerbation of the disease, there is a hypertensive crisis, cardiac arrhythmias, angina attacks, reduced efficiency, and so on. In turn, changes in the work of the heart, the intensity of blood circulation and, above all, the permeability of biomembranes can significantly change the bioavailability of drugs with different routes of administration, both in the direction of its reduction and increase.

Meteorological factors (absolute humidity, atmospheric pressure, wind direction and strength, average daily temperature, etc.) affect the elasticity of blood vessels, viscosity and clotting time. A decrease in atmospheric pressure by 1.3-1.6 kPa (10-12 mm Hg) can lead to vascular disorders, rainy weather causes depression.

8. Influence of pathological processes and individual features of an organism

Significant in the body's response to drugs is its initial state. The influence of pathological conditions and diseases of the gastrointestinal tract and liver on the processes of absorption and metabolism of drugs are discussed above.

First of all, these are pathological processes that promote free radical (peroxide) oxidation of lipids, inflammatory processes that lead to the activation of phospholipases and their hydrolysis of membrane phospholipids. Also important are the processes that are accompanied by changes in electrolyte homeostasis of tissues, which causes mechanical (osmotic) stretching of membranes. General stress reactions of the body also lead to a mandatory change in the properties of all biological barriers, which inevitably affects the bioavailability of drugs and the effectiveness of drug therapy in patients of this category.

9. Influence of alcohol

Alcohol adversely affects the therapeutic effect of many drugs and is the cause of dangerous complications. Ethanol affects the pharmacodynamics and pharmacokinetics of drugs in different ways. The bioavailability is directly affected by the following factors: changes in the permeability of histohematological barriers due to impaired fluidity of lipid membranes when interacting with ethanol; changes in the structure and function of cell membranes, impaired penetration of drugs through biomembranes; change in the structure and function of enzymes (acetylcholine esterase, mitochondrial electron transport chain enzymes); increased secretion of gastric mucus and decreased absorption of drugs in the stomach; switching the microsomal system of the nonspecific enzymatic system of the liver (MEOS - microsomal ethanooxidation system) to the oxidation of ethanol, resulting in a decrease in the level of oxidation of other endogenous and exogenous ligands; induction of liver microsomal enzymes and, as a consequence, changes in the rate and level of biotransformation of drugs.

At simultaneous appointment of drugs and ethyl alcohol their interaction can occur at once on several mechanisms that has important clinical value. The effect of the interaction of alcohol and drugs on the body depends on their concentration in the blood, pharmacodynamic properties of drugs, dose and time of administration. In small quantities (up to 5%) alcohol increases the secretion of gastric juice, and in concentrations of more than 30% clearly reduces its secretion and inhibits digestive

processes. The absorption of many drugs increases as a result of increasing their solubility under the influence of ethanol. Possessing lipophilic properties, alcohol facilitates the penetration of drugs through the phospholipid membranes of cells, and in higher concentrations, affecting the gastric mucosa, further increases the absorption of drugs. As a vasodilator, ethanol accelerates the penetration of drugs into tissues. Inhibition of many enzymes, which occurs with alcohol consumption, enhances the effect of drugs and leads to severe intoxication at the usual therapeutic doses. This applies to neuroleptics, analgesics, anti-inflammatory, hypnotics, diuretics, as well as antidepressants, insulin, nitroglycerin. The combination of the above groups of drugs and alcohol is accompanied by severe poisoning, often fatal.

10. **The effects of smoking**

The action of drugs can be affected by substances entering the body during smoking. Nicotine as an H-cholinomimetic leads to the activation of sympathetic and parasympathetic ganglia, the cerebral layer of the adrenal glands, CNS dysfunction. Stimulation of the cerebral layer of the adrenal glands leads to narrowing of peripheral blood vessels, which disrupts the blood supply to many organs and tissues. Nicotine, benzpyrene and their derivatives alter the activity of metabolic enzymes. Smoking stimulates the oxidative metabolism of phenacetin, propranolol, theophylline, noxiron, aminazine, diazepam, resulting in reduced efficiency. Smoking reduces the therapeutic effect of dexamethasone, furosemide (lasix), propoxyphene and oral contraceptives. Flavored cigarettes contain coumarins, which can enhance the effect of anticoagulants - coumarin derivatives

In a number of cases, the effect of smoking on the bioavailability and therapeutic efficacy of drugs requires further study. Thus, when prescribing drugs and assessing their therapeutic efficacy and toxicity, it is necessary to take into account the effects of numerous external and internal environmental factors.

11. **The effect of drug interactions on bioavailability**

Such interaction means a qualitative and quantitative change in the effect of one drug under the influence of another. From a practical point of view, it is important to remember that even pharmacologically indifferent components of a drug can interact with another substance, affecting its bioavailability. The drug is also able to interact with itself. When re-ingested, it can induce microsomal oxidation of a foreign substance and thus accelerate its own metabolism (a classic example is barbiturates). Medications can also worsen their own effects on organs (an example is the emergence of opiate tolerance). In clinical practice, the phenomenon of drug interactions must be constantly considered for the following reasons: - almost every hospitalized patient during a hospital stay receives several drugs (sometimes up to 40! Substances prescribed to one patient), numerous finished drugs are a combination of two or more substances, a significant number of patients in outpatient treatment, consume drugs such as laxatives, analgesics, hypnotics, etc. Of all possible interactions, only about 1-10% pose a risk of adverse effects, but the risk of mutual reduction in efficiency is significantly higher. New reports of drug interactions should always be treated with great care. The number of possible interactions at first glance is extremely large,

although not everyone has clinical significance. There are three types of interactions: pharmaceutical, pharmacokinetic and pharmacodynamic.

Questions for self-control

1. Biopharmacy as a scientific discipline and its importance in the development of composition and technology of dosage forms.
2. History of biopharmacy development.
3. Basic concepts and terms of biopharmacy.
4. The main tasks of biopharmacy at the present stage and their role for practical health care.
5. The concept of pharmaceutical factors influencing the therapeutic efficacy of drugs, their classification.
6. The physical state of drugs and excipients in dosage forms and its effect on the rate of release and absorption of drugs.
7. The influence of the physical state of drugs on the pharmacological action.
8. The influence of the degree of dispersion of drugs on the therapeutic effect of drugs.
9. The effect of crystal structure and polymorphism of drugs on the pharmacological activity of drugs.
10. The influence of the nature of the solvent, solubility, degree of viscosity and pH of the medium on the absorption of drugs.
11. The degree of purity of the drug and its effect on pharmacotherapy.
12. Dependence of therapeutic activity of drugs on the type and quality of packaging.

Main:

1. .Biopharmaceutics. Збірник текстів лекцій./ Tikhonov A.I., Yarnykh T.G., Yuryeva A.B., Podorozhna L.N., Zuykina S.S., НФаУ Оригінал, 2011. – 140 с.
2. Biopharmaceutics. Практикум / Tikhonov A.I., Bogutskaya Ye.Ye., Yarnykh T.G., Kotenko A.M., Garkavtseva O.A., НФаУ Оригінал, 2011. – 80 с.
3. Janicki S., Sznitowska M., Zielinski W. Dostepnosc farmaceutyczna I dostepnosc biologiczna lekow. – Warshawa, 2001.–242 s.
4. Biopharmaceuticals: Biochemistry and Biotechnology, 2nd Edition. – 2013. – 544 p