MINISTRY OF HEALTH OF UKRAINE
ODESSA NATIONAL MEDICAL UNIVERSITY

Faculty Pharmacy
(faculty name)
Department Pharmaceutical Chemistry and Drug Technology
(name of department)

APPROVE
Vice-Rector for Scientific and Pedagogical Work
_____ Eduard BURYACHKIVSKY
« 28 » August 2024

METHODOLOGICAL DEVELOPMENT TO LECTURE AND FROM THE ACADEMIC DISCIPLINE

Faculty, course Pharmaceutical, course V
Academic discipline Biopharmacy
(name of academic discipline)

Approved:

Meeting of the Department of Pharmaceutical Chemistry and Drug Technology

Odessa National Medical University

Protocol No. 1 dated “ 28 ” August 2024.

Head of the Department _____ Volodymyr HELMBOLDT

(signature) (First name, last name)

Developers:

Candidate of Biological Sciences, Associate Professor Zamkovaya A.V.

Lecture No. 1 -3

Topic: " Biopharmacy as a scientific direction and its importance in the development of the composition and technology of dosage forms. Stages of development of biopharmacy. Basic terms of biopharmacy" - 6 hours.

Relevance of the topic: biopharmacy is one of the fundamental natural sciences. It helps to understand natural phenomena, participates in the formation of the worldview of each person. Biopharmacy is a theoretical basis necessary for the study of special disciplines, instills skills in predicting the properties and reactivity of medicinal substances used in pharmacy and medicine.

Objective: As a result of the lecture, applicants should become familiar with the subject, objectives, methods and history of the development of biopharmacy, form knowledge about the place of biopharmacy in the system of natural sciences and in the educational process of future pharmacists, as well as the basic concepts and laws of pharmacists, the history of the emergence, development, modern interpretation and application of the significance of biopharmacy for medicine and pharmacy; master the concept of biopharmacy.

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

Lecture plan and organizational structure:

No. No. p.p.	**The main stages of the lecture and their content.**	**Goals in levels of abstraction.**	**Type of lecture, lecture equipment.**	**Time allocation.**
1	**2**	**3**	**4**	**5**
I 1.	***Preparatory stage*** Defining learning goals. Providing positive	I	 Combined lecture	1%

2.	motivation. ***Main stage*** Presentation of lecture material. Plan: 1. Biopharmacy as a scientific direction and its importance in the development of the composition and technology of dosage forms . 2. Stages of development of biopharmaceuticals . 3. Ba ***Final stage*** Lecture summary, general conclusions. The lecturer's answers to possible questions. Tasks for student self-study.	II III	Slides Bibliography, questions, assignments.	2% 90% 2% 3% 2%
II 3. III				

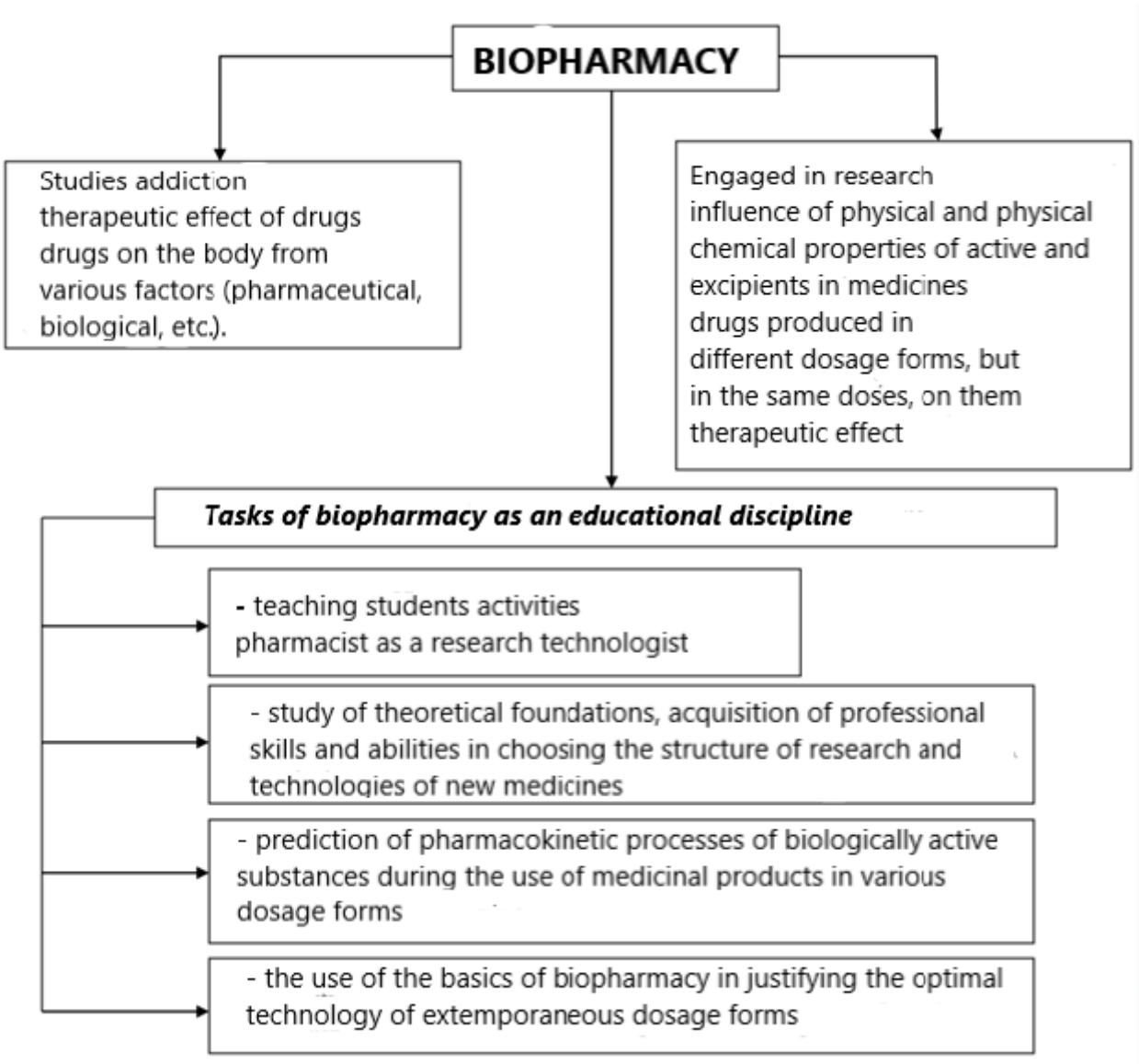
Structural and logical diagram of the lecture content

Plan:

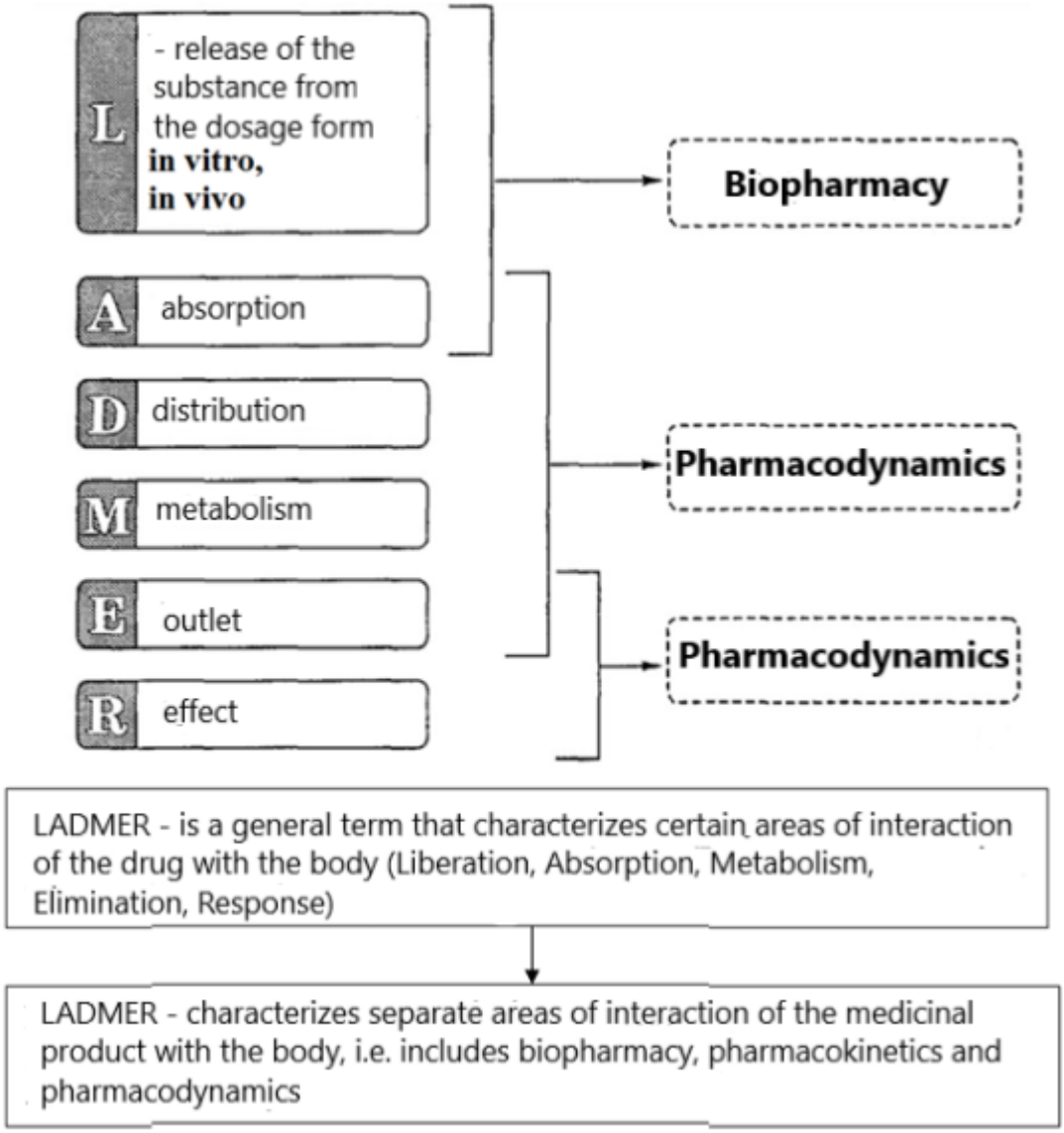
1. Biopharmacy as a scientific direction and its importance in the development of the composition and technology of dosage forms.
2. Stages of development of biopharmacy.
3. Basic terms of biopharmacy.

Content of the lecture material (lecture text)

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



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

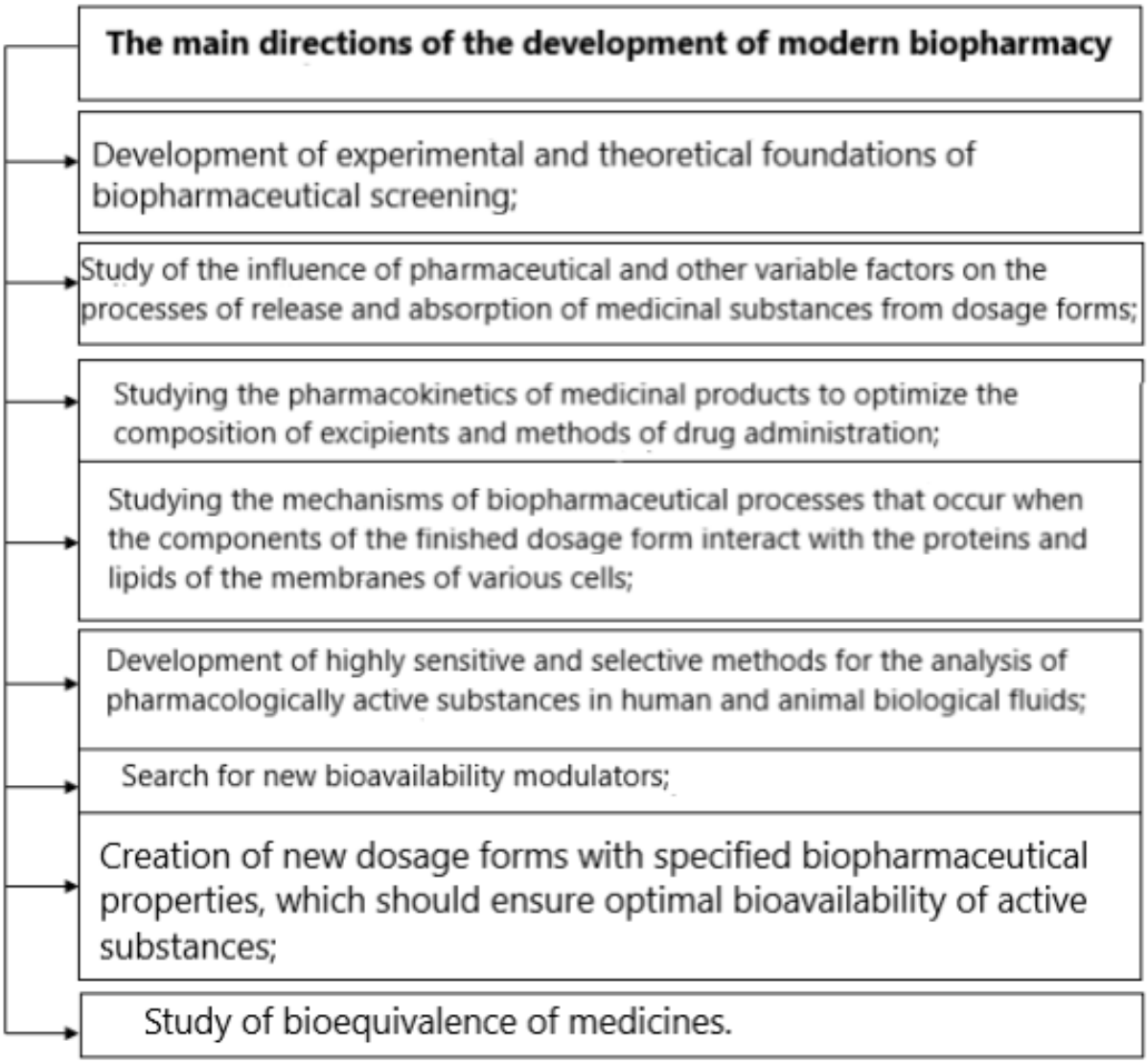


Biopharmaceutics currently constitutes the theoretical and practical basis for the development of new drugs, allowing for the prediction of the type and strength of the expected pharmacological activity and possible side effects, taking into account the type of selected dosage form, excipients, manufacturing method, etc.

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

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

It investigates the unique influence of variable factors on the pharmacodynamics and pharmacokinetics of drugs.



1. Stages of development of biopharmacy.

From the history of pharmacy it is known that back in 1838 Professor A.A. Iovsky first used the concept of "technology" in the science of drug production, meaning by this term the science designed to enrich the production of drugs. Back at the beginning of the last century, the great importance of the technology of the production process, the process of transforming the initial medicinal substances into a medicinal form designed to help the body weaken, destroy or prevent diseases, was noted.

By the 50s of the 20th century, 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 the formation of metastable modifications of medicinal and

auxiliary substances. It was the introduction into practice of new highly active medicinal substances, auxiliary materials and advanced technological processes that formed the material basis of that unusual phenomenon, which received the name "Therapeutic inequivalence or inadequacy of drugs" in the scientific literature. The essence of such inequivalence (inadequacy) is that the same doses of (often highly active) medicinal substances, prescribed in identical dosage forms prepared by different enterprises, have different pharmacotherapeutic effects. For example, tablets containing the same doses of chloramphenicol, phenylbutazone, digoxin, tetracycline, prednisolone, thyroidin, etc., produced by one factory, have a therapeutic effect, those produced by another factory have a toxic effect, and those produced by a third factory have no proper effect at all.

A thorough investigation of known cases of therapeutic non-equivalence of drugs, showed that the activity of the active substance, its behavior during release from the dosage form, diffusion to the site of absorption, and the absorption process itself are closely dependent on the nature and amount of excipients and technological operations that take place during the preparation of the drug.

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

In the late 1950s, a new direction in pharmacy was launched - biopharmaceuticals. Biopharmacy is defined as the science that studies the biological effect of drugs depending on their physicochemical properties, type of dosage form, preparation technology, and other variable factors.

The founders of biopharmacy in the CIS and Ukraine are Professors Ya. I. Khadzhai and D. P. Salo. Research in this area was continued and developed by Professors I. M. Pertsev, G. S. Bashura, A. I. Tikhonov, N. A. Lyapunov, G. V. Obolentseva, M. V. Shteyngardt, N. A. Kazarinova, D. I. Dmitrievsky, V. A. Spiridonov, etc.

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

Biopharmacy is a scientific discipline of pharmacy that studies the influence of the 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 by the entire course of progressive development of pharmacy, medicine, chemistry and other sciences. It is at the junction of several fields of knowledge that biopharmacy originates.

It appeared after establishing the facts of therapeutic non-equivalence of drugs, i.e. drugs of the same composition, but prepared by different pharmaceutical enterprises, differed in therapeutic efficacy. This was due to a number of reasons: the degree of grinding of medicinal substances, the selection of excipients and the difference in technological processes, the so-called pharmaceutical factors. In the special literature, the term "pharmaceutical factors" became widespread primarily in connection with the clinical confirmation of experimental data on the existence of a relationship between the effectiveness of drugs and the methods of their production.

The founders of biopharmacy are considered to be 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" itself first appeared in scientific pharmacy in the United States in the 1960s and soon gained general international recognition.

The word "pharmaceutics", used in English literature, is not a synonym for "pharmacy", its designation is galenic pharmacy. "Biopharmaceutics" and the adjective "biopharmaceutical" derived 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 galenic pharmacy products or about biological pharmacy in general.

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

Despite the fact that the term "biopharmacy" is not entirely accurate, it is used both here and abroad and has been introduced into a single standard international biopharmaceutical terminology.

2. 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 processes, data, or parameters being studied.

An active ingredient is the biologically active part of a medicinal product that is responsible for the therapeutic effect.

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

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

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

The main goal of biopharmacy is to obtain a stable effect, maximize efficiency, and minimize the undesirable effects of drugs on the body.

The rapid development of biological pharmacy and the formation of new thinking among scientists were facilitated by numerous international symposia on biopharmacy and pharmacokinetics (Czechoslovakia, 1970, 1974, 1978 and 1982), which were held regularly thanks to the organizational abilities of the Slovak scientist L. Zathurecky, as well as thanks to regional scientific quorums dedicated to this problem.

The influence of pharmaceutical and biological variables on the degree of drug efficacy can be traced through a typical pharmacokinetic scheme:

the amount of active ingredient in the drug

↓

release and amount of substance at the site of absorption

↓

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

↓

excretion of the active substance (metabolites) from the body

Before the active substance can be absorbed, it must be released from the pharmaceutical system (tablet, suppository, ointment) and diffuse to the absorption surface. The absorption process itself is also diffusional 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 individual stages of the "life" of a pharmaceutical drug, starting from its creation and production and ending with rational use, including the possibility of its interaction with exogenous, endogenous components and elements of the body.

Clinical factors - factors that arise during pharmacotherapy in clinical conditions (choice of dosage regimen, time of drug administration, side effects, interaction of simultaneously or sequentially administered medicinal substances, patient's bedriddenness, physical activity, severity of the disease, dysfunction of the gastrointestinal tract, liver, kidneys, cardiac activity, etc.).

Equivalence - compliance of the amount of medicinal substance (agent) or medicinal product with that indicated in the analytical regulatory documentation or identity of the effect of the investigated agent with the reference drug.

A pharmaceutical equivalent is a medicinal product that contains the same amount of a therapeutically similar substance in a specific dosage form and meets the requirements determined by technological standards.

Clinical equivalent - an equivalent of a medicinal product that, after using the same doses, produces the same therapeutic effect, tested on any symptom or in the

treatment of a disease.

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

Therapeutic inequivalence is the inequality of the therapeutic effect of the same drugs in the same doses, prepared by different manufacturers or the same factory, but of different batches.

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

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

Absolute bioavailability - the amount of a drug substance administered in a dosage form intravenously or intravascularly, which enters the bloodstream without the influence of the first-pass effect through the liver (the "first pass" effect) or after correlation with this effect, and the rate of this process.

Physiological availability is a synonym for "biological availability" or "bioavailability."

Systemic availability - the portion of the total absorbed dose of a drug substance that enters the circulatory system after oral administration. Synonymous with "biological availability" and "bioavailability."

Absorption is the process of transferring a medicinal substance from the site of administration into the bloodstream.

Resorption is a synonym for "absorption."

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

Biotransformation is a complex process in which lipid-soluble molecules of a drug substance are transformed into metabolites by catalytic enzymes (oxidation, reduction, hydrolysis, synthesis) during biochemical reactions.

Purity is the hypothetical volume of a body area that has been deprived of the corresponding substance per unit of time.

Whole body clearance is the purity of the hypothetical plasma volume in milliliters (volume of distribution) through which the body gets rid of the drug substance by excreting it through the kidneys, bile, lungs, skin, and metabolism.

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

Distribution rate constant - the rate constant of the transfer of a drug substance from the circulatory system to any or all parts of the body.

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

Excretion (excretion) is the process by which a drug (drug) is removed from the circulatory system through the kidneys into the urine, through bile and saliva into the intestines and feces, and through the skin, mammary 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 a biological membrane into the body.

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

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

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

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

1. A connection has been established between the type of ointment bases and the effectiveness of antiseptics, antibiotics, biologically active substances of beekeeping products and other chemotherapeutic substances. This allowed the development and introduction into medical practice of the CIS ointments "Levosin", "Levomikol", "Dioxykol" and many others.

2. The relationship between the distribution of molecules of medicinal substances, in particular corticosteroids, in different phases of dispersed dosage forms depending on the structure of these phases and between the release, bioavailability, effectiveness of action and side effects of medicinal products has been established. The results of these studies have been used in the development of Sinaflan ointment and liniment, hydrocortisone and prednisolone ointments, Triacort ointment, Cortonizol aerosol, Trimistin and Cortonitol ointments, etc.

3. The relationship between the supramolecular structure of surfactant associates (surfactants), the physicochemical properties of dispersed systems, release, bioavailability, activity of action and the occurrence of toxic effects of various medicinal substances has been established. The results of the research allowed to purposefully manage the pharmacological and toxicological properties of medicinal products in various dosage forms: ointments, foams, suppositories, gels and others - and formed the basis for the creation of such drugs as "Sulyodopyron", suppositories "Propofen", "Polenfen", ointments "Lipovit", "Prolidoxide" and others.

4. A correlation has been established between the affinity of medicinal and excipients to various biomembranes, the structure of biomembranes, the bioavailability and effectiveness of the pharmacological action of medicinal preparations.

5. The regularities of pharmacokinetic, pharmaco and toxicodynamic interaction of medicinal substances in combination preparations were studied, and the influence of excipients and tableting technology on the release of medicinal substances from tablets and their bioavailability was also studied. The results of the studies formed the basis for the creation of a group of combined preparations with paracetamol, solid dosage forms with beekeeping products (tablets "Propolin", "Propoltin", "Feprogit"), etc.

6. The effect of chemical modification of medicinal substances using amino

acids on their bioavailability and effectiveness has been studied. For example, acelizin (Domestic soluble aspirin) and its dosage forms have been introduced into production and medical practice.

Interest in biopharmacy as a scientific direction is becoming increasingly profound, and an increasing number of scientists are engaged in biopharmaceutical research.

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

Materials for activating higher education students during lectures: questions, situational tasks, etc.:

Question:

1. What does the scientific discipline of pharmacy - biopharmacy - study?

2. Define the basic concepts: efficacy, clinical factors, bioequivalence, relative bioavailability, absolute bioavailability, absorption, metabolism.

3. The concept of bioavailability. The main indicators of bioavailability of drugs.

General material and methodological support for the lecture:

- educational premises – the department's auditorium;
- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials – presentation, slides.

Questions for self-control :

Name the factors that affect the bioavailability of drugs:

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

2) Influence of body temperature and environment;

3) Influence of the magnetic field and meteorological factors;

4) The influence of age, gender, biorhythms and pathological processes;

5) The influence of alcohol and smoking.

List of sources used:

Main literature:

1. Gladyshev V.V., Davtyan L.L., Drozdov A.L., Byryuk I.A., Kechyn I.L. Biopharmacy. Textbook for pharmaceutical universities and faculties. 2nd ed. Edited by V.V. Gladyshev. Dnipro: ChMP "Economica". 2018.- 250 p.
2. Guideline ST-N MOZU 4242-7.1:2005 "Medicines. Guideline on clinical trials. Bioavailability and bioequivalence studies" - Kyiv, 2018.
3. Guideline ST-N MOZU 4242-7.1:2005 "Medicines. Guideline on clinical trials. Bioavailability and bioequivalence studies" - Kyiv, 2018.
4. Guideline ST-N MOZU 42-7.2:2018 Medicinal products for bioequivalence studies. – Kyiv, 2018. – 77 p.
5. Modern pharmaceutical technologies: teaching aids for laboratory classes of undergraduates of full-time, evening and correspondence forms of study in the specialty 8.110201 "Pharmacy" / edited by O.A. Ruban. – Kh.: Publishing house of the National University of Physics and Technology, 2016. – 256 p.
6. Biopharmacy: textbook / edited by: Borysyuk I.Yu., Fizor N.S., Akisheva A.S. Odesa, ONMedU, 2020. - 98 p.

Additional literature:

1. Pharmaceutical Encyclopedia / Chairman of the Editorial Board and author of the foreword V.P. Chernykh. – 3rd ed. – K.: “MORION”, 2016. – 1952 p.
2. Polovko N.P., Vyshnevska L.I., Shpychak O.S. Assessment of biopharmaceutical factors in the development and production of new drugs // Modern advances in pharmaceutical technology and biotechnology: collection of scientific papers, issue 2. – X.: Publishing house of the National University of Physics and Technology, 2017. – pp. 155-160.

Excipients in the production of medicines: a teaching aid for students of higher pharmaceutical schools /O. A. Ruban, I. M. Pertsev, S. A. Kutsenko, Yu. S. Masliy; edited by I. M. Pertsev. Kh.: Zoloti storyni, 2016. 720 p.

Lecture No. 4-5

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

Relevance of the topic: biopharmacy is one of the fundamental natural sciences. It helps to understand natural phenomena, participates in the formation of the worldview of each person. Biopharmacy is a theoretical basis necessary for the study of special disciplines, instills skills in predicting the properties and reactivity of medicinal substances used in pharmacy and medicine.

Objective: As a result of the lecture, applicants should become familiar with the subject, objectives, methods and history of the development of biopharmacy, form knowledge about the place of biopharmacy in the system of natural sciences and in the educational process of future pharmacists, as well as the basic concepts and laws of pharmacists, the history of the emergence, development, modern interpretation and application of the significance of biopharmacy for medicine and pharmacy; master the concept of biopharmacy. Become familiar with all pharmaceutical factors and their influence on the action of medicines.

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

Lecture plan and organizational structure:

No. No. p.p.	**The main stages of the lecture and their content.**	**Goals in levels of abstraction.**	**Type of lecture, lecture equipment.**	**Time allocation.**
1	**2**	**3**	**4**	**5**
I 1. 2.	***Preparatory stage*** Defining learning goals. Providing positive motivation.	I	Combined lecture	1% 2%

II 3.	***Main stage*** Presentation of lecture material. Plan: 1. Types of pharmaceutical factors that affect bioavailability . 2. Physical state of biopharmaceutical medicinal substances . 3. Grinding of medicinal substances 4. Polymorphism of medicinal substances 5. Solubility of medicinal substances 6. Chemical modification 7. Excipients 8. Types of dosage form and routes of administration 9. Technological processes ***Final stage*** Lecture summary, general conclusions.	II	Slides	90% 2% 3% 2%
III	The lecturer's answers to possible questions. Tasks for student self-study.	III	Bibliography, questions, assignments.	

Structural and logical diagram of the lecture content

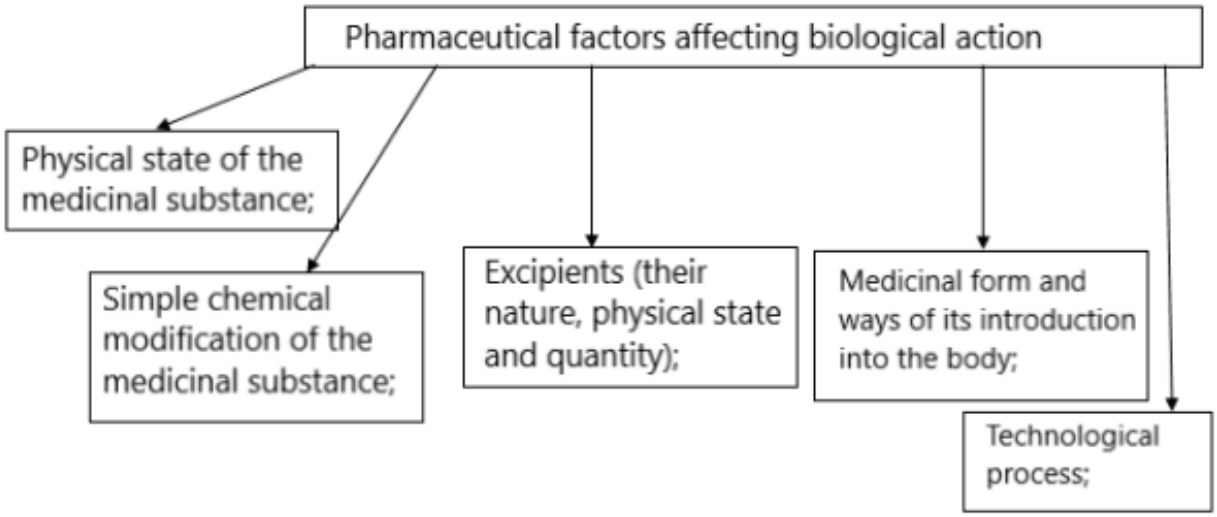
Plan:

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 medicinal substances
6. Chemical modification

7. Excipients
8. Types of dosage form and routes of administration
9. Technological processes

Content of the lecture material (lecture text)

1. Types of pharmaceutical factors that affect bioavailability.



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

- physical state of the medicinal substance;
- simple chemical modification of the medicinal substance;
- excipients (their nature, physical state and quantity);
- dosage form and routes of administration 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 from the point of view of biopharmaceutics due to their significant impact on the dynamics of bioavailability of medicinal substances, the stability of medicinal products during storage, and many other indicators.

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

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

Homogeneous - single-phase ionic or molecularly dispersed systems. These are true solutions with a particle size of DF for low-molecular compounds up to 1 nm, for high-molecular compounds - from 1 to 100 nm (0.001-0.1 μm). A special group includes colloidal systems and solutions of high-molecular compounds (HMCs) with a particle size of up to 100 nm, which retain homogeneity only under certain conditions, taking into account temperature, pressure, solvent, pH of the medium and other factors.

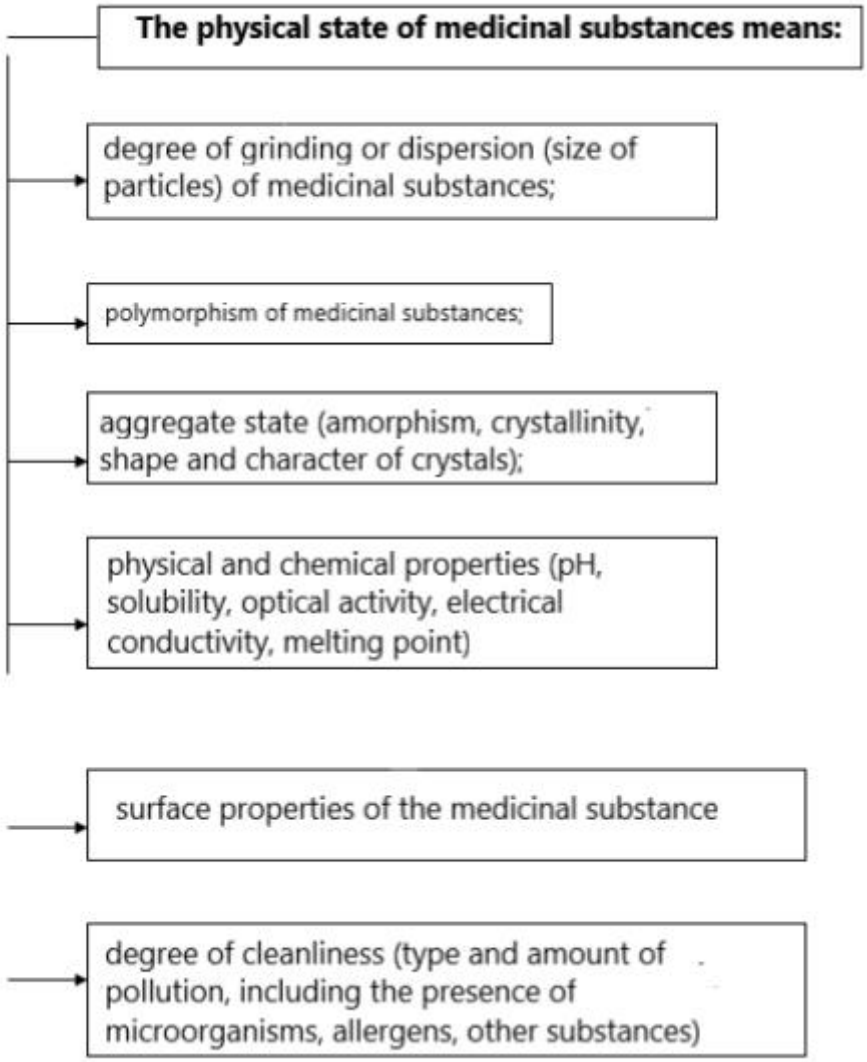
Heterogeneous - two-phase coarsely dispersed systems with particle sizes from 100 to 1000 nm (0.1-1 μm) and more.

From the point of view of biopharmaceutics 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, homogeneous disperse systems (solutions, aerosols, etc.) are most acceptable. If the drug substance is in a coarsely dispersed state, it is necessary to create conditions in the dosage form or at the time of use in the patient's body for the transfer from the coarsely dispersed state to the ionic or molecularly dispersed state.

For this purpose, various technological techniques, excipients, special dosage forms with specified pharmacokinetic properties are used, and the physiological characteristics of the body are also used (pH of the stomach and intestines, lipid solubility, blood buffer systems, etc.).

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

2. Physical state of medicinal substances.



The physical state of medicinal substances is understood to mean:

- the degree of grinding or dispersion (particle size) of medicinal substances;
- polymorphism of medicinal substances;
- aggregate state (amorphism, crystallinity, shape and nature of crystals);
- physicochemical properties (pH, solubility, optical activity, electrical conductivity, melting point);
- surface properties of the medicinal substance (surface tension, philicity, etc.).
- degree of cleanliness (type and amount of contamination, including the presence of microorganisms, allergens, binders, etc.).

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

The degree of grinding and polymorphism of medicinal substances have the most significant impact on pharmacotherapy.

3. Grinding of medicinal substances

Grinding of medicinal substances is the simplest, but at the same time one of the most important technological operations performed by a pharmacist when preparing various dosage forms. The dispersion of a medicinal substance affects not only the flowability of powdered materials, bulk density, mixing uniformity, and dosing accuracy. It is especially important to note that the speed and completeness of absorption of a medicinal substance, as well as its concentration in biological fluids, mainly in the blood, depends on the size of the particles, with any methods of its administration in the form of various dosage forms.

For example, in tablets that disintegrate in the stomach, the particle size is significantly larger than the particle size of the powder, as a result of which the concentration of the active substance after taking the tablet is lower than after taking the powder. The particle size of drugs in suspensions, emulsions and liniments is one of the main characteristics of these dosage forms.

The influence of particle size on therapeutic activity was first proven for sulfonamides, and then steroid drugs, as well as furan derivatives, salicylic acid, antibiotics and currently - for anticonvulsants, analgesics, diuretics, antituberculosis, antidiabetic and cardiotonic agents. Thus, it was established that when using micronized sulfadiazine, its maximum concentration in the blood of people is achieved two hours earlier than when it is administered in the form of a powder of the usual degree of grinding. At the same time, the maximum concentrations of sulfadiazine in the blood are 40% higher, and the total amount of the substance absorbed is 20% more. The drug calciferol is able to be absorbed and have a therapeutic effect only when the particle size is less than 10 microns.

When reducing the particles of griseofulvin from 10 to 2.6 microns, its absorption in the gastrointestinal tract increases sharply, which allows you to reduce its therapeutic dose by half. By obtaining a molecular degree of dispersion of griseofulvin in polyvinylpyrrolidone, it was possible to increase the bioavailability of

this antibiotic by 7-11 times, 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 absorption process is particularly evident in ointments and suppositories prepared on the same basis, but using fractions of the medicinal substance, the particle size of which is noticeably different.

4. Polymorphism of medicinal substances

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

As is known, polymorphic modifications form many chemical and, including, medicinal substances. Since the discovery of polymorphism of carbon Davy (1809) (graphite, coal and diamond) transitions of some polymorphic modifications into others have been studied in detail. It is emphasized that *the chemical composition remains unchanged,* which is mainly taken as an assessment of quality. A review of works on the study of polymorphism in medicinal substances is given in the works of A. I. Tentsova, Halebleyne, Busheva, Khalabala.

Particles of medicinal substances in a powdered solid state have a different structure (crystalline or amorphous), which depends on the peculiarities of the molecular structure of a particular substance. Electron microscopic studies have shown that medicinal substances in most cases have a crystalline structure, due to the fixed arrangement of atoms in the molecule and the directional growth of crystals under certain conditions during the crystallization process. The amorphous state is less common. Any medicinal substance 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 size of particles, etc.). When the conditions change, the substance crystallizes in a different system and has other physicochemical characteristics, and therefore other indicators of biological accessibility. Such physical characteristics of powders in the existing AED

as “crystalline”, “fine-crystalline”, “amorphous”, “light powder” are sufficient for the technological process, but to identify their effect on therapeutic activity, more precise definitions are required, which is provided by crystal chemistry.

There are seven crystallographic systems (syngonia): monoclinic, diclinic, trigonal, tetragonal, hexagonal, rhombic, cubic, they are used to identify medicinal substances. Andronyk I. Ya. and Babilev F. V. published an atlas of diffractograms of crystalline medicinal substances and developed an information search system for identifying crystalline medicinal substances by their diffraction spectra. The use of the atlas and the automated system allows to accelerate the identification of medicinal substances.

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

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

There are many examples of polymorphic modifications of drugs. For example, there are two polymorphic modifications of acetylsalicylic acid, one of which is 1.5 times more biologically active than the other.

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.

In this case, *the solubility of* various polymorphic modifications is of particular importance, because the absorption of medicinal substances depends on it.

The dissolution process also affects the effectiveness of medications.

The drug substance as a dispersed phase undoubtedly interacts with the liquid, i.e. with the dispersion medium. This causes one or another chemical reaction

responsible for changing the biological activity of the substances.

Liquids are classified as polar, semipolar and nonpolar. Depending on the chemical nature of the drug substance and the solvent, the interaction energy in liquid dosage forms, ionic, molecularly dispersed systems or coarsely dispersed suspensions can be formed. During the preparation process, exo- or endothermic phenomena, contraction can be observed. All this must be taken into account when preparing liquid dosage forms, scientifically substantiating technological methods and the composition of the drug.

5. Solubility of medicinal substances

The solubility of substances depends largely on their *surface* properties, including *the degree of their grinding.* Significant differences in the size of drug particles can lead to different rates of absorption and content in biological fluids of the same drug, and therefore, to its possible clinical non-equivalence.

The solubility of medicinal substances can vary depending on *the methods of their recrystallization*, and in finished medicines - on the presence of *excipients used* and *the technology of* dosage forms. The solubility of medicinal substances in dosage forms is also affected by *the choice of dosage form.* Thus, when using very poorly soluble medicinal substances in the case of their oral administration, a rational dosage form is a thin suspension; such medicinal substances are best administered in the form of elastic capsules filled with a suspension.

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

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

2. Using individual or mixed solvents (benzyl benzoate, benzyl alcohol, propylene glycol, polyethylene glycol, ethyl cellulose, dimexide, glycerin, etc.).

3. Using hydrotropy, which provides the formation of hydrophilic complexes with organic substances containing electron-donating substituents - polar radicals.

Examples of hydrotropic substances include sodium salicylate, sodium benzoate, hexamethylenetetramine, novocaine, antipyrine, urea, glycerin, amino acids, oxyacids, proteins, etc. 4. By the formation of salts and complexes:

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

obtaining aqueous iodine solutions using readily soluble iodine complexes with alkali metal iodides;

c) to obtain aqueous solutions of polyene antibiotics (nystatin, levorin, etc.) polyvinylpyrrolidone is used, 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 the relationship "drug substance-excipient" in complex physicochemical systems, which are drugs.

5. Synthetic route - introduction of hydrophilic groups into the structure of the molecule: -COOH, CH_2-COOH, -HPO_ZH, -CH_2PO_ZH. Example: unithiol.

The therapeutic activity of medicinal substances is also significantly influenced by their *optical properties.* There is no chemical difference between optical isomers, but each of them rotates the plane of polarization of light in a certain direction. Despite the fact that chemical analysis fully confirms the presence of the same substance in medicinal products with different isomers, they will not be therapeutically equivalent.

When a drug is absorbed in the gastrointestinal tract, *the degree of ionization of the substance plays a major role.* Depending on *the concentration of hydrogen ions*, medicinal substances can be in ionized or non-ionized form, pH also affects solubility, distribution coefficient of medicinal substances, membrane potential and surface activity.

6. Simple chemical modification

The term *simple chemical modification* of drugs is understood to mean when the same substance can be used as a drug in different chemical compounds (salt, base, acid,

ester, complex compound, etc.), in which the part of the substance molecule responsible for the pharmacological effect is fully preserved.

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

Simple chemical modification (replacing a drug in the form of a salt with one cation with a chemically similar drug in the form of a salt with another cation or a drug in the form of an acid, ester, etc.) more often takes place in factory production.

Biopharmaceutics pays the most serious attention to the study of the factor of simple chemical modification, because taking into account its influence on the pharmacokinetics of medicinal substances allows to significantly increase the effectiveness of medical intervention, reduce the consumption of medicinal products, and dramatically increase the stability of many medicinal substances and their preparations.

Based on biopharmaceutical experiments, it has been proven that *arbitrary replacement of any ion in a molecule of a medicinal substance, based on purely technological or economic considerations, is unacceptable.*

7. Excipients

Excipients are of natural, synthetic and semi-synthetic origin. When preparing dosage forms, they can perform various functions: solvents, solubilizers, stabilizers, bases, surfactants, thickeners, emulsifiers, preservatives, flavoring agents, dyes, etc.

Such substances include: starch, glucose, purified water, ethyl alcohol, petroleum jelly, oil, cocoa, talc, bentonite, aerosil, paraffin, wheat flour, polyethylene oxides, various cellulose derivatives, etc.

Throughout the centuries-old history of pharmacy, excipients were considered as indifferent substances in pharmacological and chemical terms, which play the role of form-forming agents. They were added to medicinal substances in order to give them a suitable form, convenient for use, transportation and storage. In the production of medicinal products, the most accessible and cheap substances were used. At the same time, the influence of the nature and quantity of excipients on the biological activity of medicinal substances was not taken into account.

Based on biopharmaceutical work, it was established 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 medicinal substances* under the influence of various causes and combinations (complexing and adsorption, molecular reactions, etc.), as a result of which the speed and completeness of absorption of the medicinal product can change dramatically. The interaction between medicinal and excipients can occur both in the process of preparing medicinal products and in the process of their preservation.

Thus, the mechanism of influence 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 polymer complexes, micelles, micelle associations, macromolecules of the Navy, chemisorption, etc. The compounds formed can be quite strong or, conversely, easily destroyed, characterized by high surface activity or balanced energy of the system, enhance or weaken the main pharmacological reaction of the drug substance, etc.

As is known, the degree of interaction is determined by the energy of the physicochemical or chemical bond. If *the bond is weak* (van der Waals forces - 1 kcal/mol (4-10 ^{3} J) or hydrogen bond 7-10 kcal/mol), then the process can be reversible, since the body will cope with this bond, can split, modify and the medicinal substance will be utilized.

But if *a strong bond is formed,* covalent with an energy of 100-140 kcal/mol, the process may become irreversible, because there are no conditions in the body to destroy this bond. Therefore, *excipients can minimize the therapeutic effect of the drug substance, enhance it to the point of toxicity, or completely change it.*

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

Phenobarbital is poorly soluble in polyethylene glycol and, as a result, is not absorbed. Theophylline-phenobarbital complexes and tetracycline calcium are poorly soluble compounds and are practically not absorbed.

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 medicinal substances.

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

The sequence and rate of resorption are determined by various factors: *the time of taking the drug before or after meals, the type of food, the amount and nature of the liquid consumed, the time of day, the physiological state of the mucous membranes, the chemical and physicochemical characteristics of the drugs,* etc.

Among the above factors, it is necessary to consider the latter, all other things being equal. It is known from the literature that the best resorptive ability is possessed by dissociating low-molecular compounds, substances having a diphilic structure with metal, ethyl, phenyl, etc. radicals, substances with a high affinity for the body's bioenvironment.

The phenomenon of selective resorption is clearly illustrated in the experiments of Prof. A.I. Tentsova, when in all experiments the results were obtained, indicating the influence of corrective substances (cherry syrup, raspberry essence, citric acid) on the rate of absorption of calcium chloride.

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

For example, mannitol acts as a filler in tablets, and in liquid dosage forms it acts as a laxative. And active ingredients such as urethane, antipyrine, quinine are used to solubilize and prolong the action of a number of medicinal substances, changing the

level of pharmacokinetics.

It is impossible to draw a clear line between the active substance and the excipient in a dosage form, and therefore modern pharmaceutical science sets a requirement when developing new medicines: *to establish the degree of influence of excipients on the therapeutic efficacy of the medicine.* In other words, the excipient should not be used in general, but specifically with an individual substance. *Unjustified use* of an excipient *can lead to a decrease, increase, change in the therapeutic effect or complete loss of the therapeutic effect of the medicinal substance*.

8. Types of dosage form and routes of administration

Numerous studies on the influence of dosage form on the therapeutic efficacy of drugs have shown that the optimal activity of a drug substance is achieved only when it is administered in a rational dosage form. In addition, in this case, many side effects of drugs on the body can be avoided.

A dosage form is a pharmacologically rational, convenient form of a medicinal substance for administration and storage, which ensures its optimal therapeutic effect with a minimum of side effects.

According to modern concepts, a dosage form is a material norm for the manifestation of the dialectical unity of active and auxiliary substances, as well as technological operations that ensure the optimal therapeutic effect of a medicinal product.

The 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 and intestines and interaction with their secretions. According to the degree of release and, accordingly, better bioavailability, all oral drugs can be placed in the following series: 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 made it possible to give a scientific explanation of the role of technological processes, methods of obtaining drugs in the development of the effect. Before the formation of biopharmacy, this issue was practically not paid attention to.

It has now been proven that the method of obtaining a medicinal product largely determines the stability of the medicinal substance, the rate of its release from the dosage form, the intensity of absorption and, ultimately, its therapeutic efficacy.

Depending on the physicochemical, physicomechanical and other characteristics of the dosage forms, specific methods of their preparation and equipment are used. For example, when preparing suppositories, grinding, sieving of medicinal substances, melting of the base, mixing, pouring of the suppository mass into molds, cooling, etc. are carried out; when obtaining tablets - grinding, drying, sieving, mixing, granulation, pressing, 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 20th century and turned out to be the most studied in pharmaceutical and biopharmaceutical terms. Moreover, all stages of obtaining tablets are widely studied in order to clarify the influence of stage-by-stage operations on their physicomechanical properties and pharmacotherapeutic efficacy. Such operations as granulation, pressing, drying, etc. have been subjected to particularly thorough experimental study. Theoretically and experimentally, the need for a rational selective approach to the use of tableting stages in the preparation of tablets was substantiated already in the 60s of the last century.

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

In the technological process of preparing dosage forms, there are also repetitive operations common to a number of stages of the production of medicinal products. In the production processes of preparing medicinal products in pharmacies or factories, unique technological techniques are used: grinding, dissolving, drying, filtering, sterilization, freezing, etc.

Subjective factors also play an important role in the preparation of medicinal

products. This is especially true for 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, the situation, and so on, and all these factors can affect the quality of the manufactured products.

A pharmacist must have a high level of training to take into account various variable factors when preparing medications.

Materials for activating higher education students during lectures: questions, situational tasks, etc.:

Question:

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.

General material and methodological support for the lecture:

- educational premises – the department's auditorium;
- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials – presentation, slides.

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. In vitro methods (direct diffusion through the membrane, agar plates, chromatographic, solubility test, etc.).
5. "In vivo" methods, which are carried out on laboratory animals, healthy human volunteers, isolated organs with single and multiple administration.
6. Modern methods for determining the concentration of medicinal substances in biological fluids (blood, urine, body secretions).

7. Microbiological and acanthosis tests.

8. Graphical method for calculating the area of the pharmacokinetic curve and the degree of absorption of drugs. Determination of the absorption and elimination constant.

9. Radioisotope method.

10. Correlation of "in vitro" and "in vivo" methods in determining the bioavailability of medicinal substances.

List of sources used:

Main literature:

7. Gladyshev V.V., Davtyan L.L., Drozdov A.L., Byryuk I.A., Kechyn I.L. Biopharmacy. Textbook for pharmaceutical universities and faculties. 2nd ed. Edited by V.V. Gladyshev. Dnipro: ChMP "Economica". 2018.- 250 p.

8. Guideline ST-N MOZU 4242-7.1:2005 "Medicines. Guideline on clinical trials. Bioavailability and bioequivalence studies" - Kyiv, 2018.

9. Guideline ST-N MOZU 4242-7.1:2005 "Medicines. Guideline on clinical trials. Bioavailability and bioequivalence studies" - Kyiv, 2018.

10. Guideline ST-N MOZU 42-7.2:2018 Medicinal products for bioequivalence studies. – Kyiv, 2018. – 77 p.

11. Modern pharmaceutical technologies: teaching aids for laboratory classes of undergraduates of full-time, evening and correspondence courses in the specialty 8.110201 "Pharmacy" / edited by O.A. Ruban. – Kh.: Publishing house of the National University of Physics and Technology, 2016. – 256 p.

12. Biopharmacy: textbook / edited by: Borysyuk I.Yu., Fizor N.S., Akisheva A.S. Odesa, ONMedU, 2020. - 98 p.

Additional literature:

10. Pharmaceutical Encyclopedia / Chairman of the Editorial Board and author of the foreword V.P. Chernykh. – 3rd ed. – K.: “MORION”, 2016. – 1952 p.

11. Polovko N.P., Vyshnevska L.I., Shpychak O.S. Assessment of biopharmaceutical factors in the development and production of new drugs // Modern

advances in pharmaceutical technology and biotechnology: collection of scientific papers, issue 2. – X.: Publishing house of the National University of Physics and Technology, 2017. – pp. 155-160.

Excipients in the production of medicines: a teaching aid for students of higher pharmaceutical schools /O. A. Ruban, I. M. Pertsev, S. A. Kutsenko, Yu. S. Masliy; edited by I. M. Pertsev. Kh.: Zoloti storyni, 2016. 720 p.

Lecture No. 6-7

Topic: "Bioavailability of medicinal substances" - 4 hours.

Relevance of the topic: biopharmacy is one of the fundamental natural sciences. It helps to understand natural phenomena, participates in the formation of the worldview of each person. Biopharmacy is a theoretical basis necessary for the study of special disciplines, instills skills in predicting the properties and reactivity of medicinal substances used in pharmacy and medicine.

Objective: As a result of the lecture, applicants should become familiar with the subject, objectives, methods and history of the development of biopharmacy, form knowledge about the place of biopharmacy in the system of natural sciences and in the educational process of future pharmacists, as well as the basic concepts and laws of pharmacists, the history of the emergence, development, modern interpretation and application of the significance of biopharmacy for medicine and pharmacy; master the concept of biopharmacy. Become familiar with all pharmaceutical factors and their influence on the action of medicines.

Basic concepts: bioavailability, AUCA .

Lecture plan and organizational structure:

No. No. p.p.	The main stages of the lecture and their content.	Goals in levels of abstraction.	Type of lecture, lecture equipment.	Time allocation.
1	2	3	4	5

I 1. 2. II 3.	***Preparatory stage*** Defining learning goals. Providing positive motivation. ***Main stage*** Presentation of lecture material. Plan: 1. Definition of the concept of bioavailability. 2. Factors affecting the bioavailability of drugs. 3. Effect of routes of administration on bioavailability. 4. Influence of body temperature and environment 5. The influence of a person's age and gender. 6. The influence of biorhythms. 7. The influence of the magnetic field and meteorological factors. 8. The influence of pathological processes	I II	Combined lecture Slides	1% 2% 90% 2%

III	and individual characteristics of the organism. 9. The influence of alcohol. 10. The impact of smoking. 11. The impact of drug interactions on bioavailability. ***Final stage*** Lecture summary, general conclusions. The lecturer's answers to possible questions. Tasks for student self-study.	III	Bibliography, questions, assignments.	3% 2%

Structural and logical diagram of the lecture content

Plan:

1. Definition of the concept of bioavailability.
2. Factors affecting the bioavailability of drugs.
3. Effect of routes of administration on bioavailability.
4. Influence of body temperature and environment
5. The influence of a person's age and gender.
6. The influence of biorhythms.
7. The influence of the magnetic field and meteorological factors.
8. The influence of pathological processes and individual characteristics of the organism.
9. The influence of alcohol.

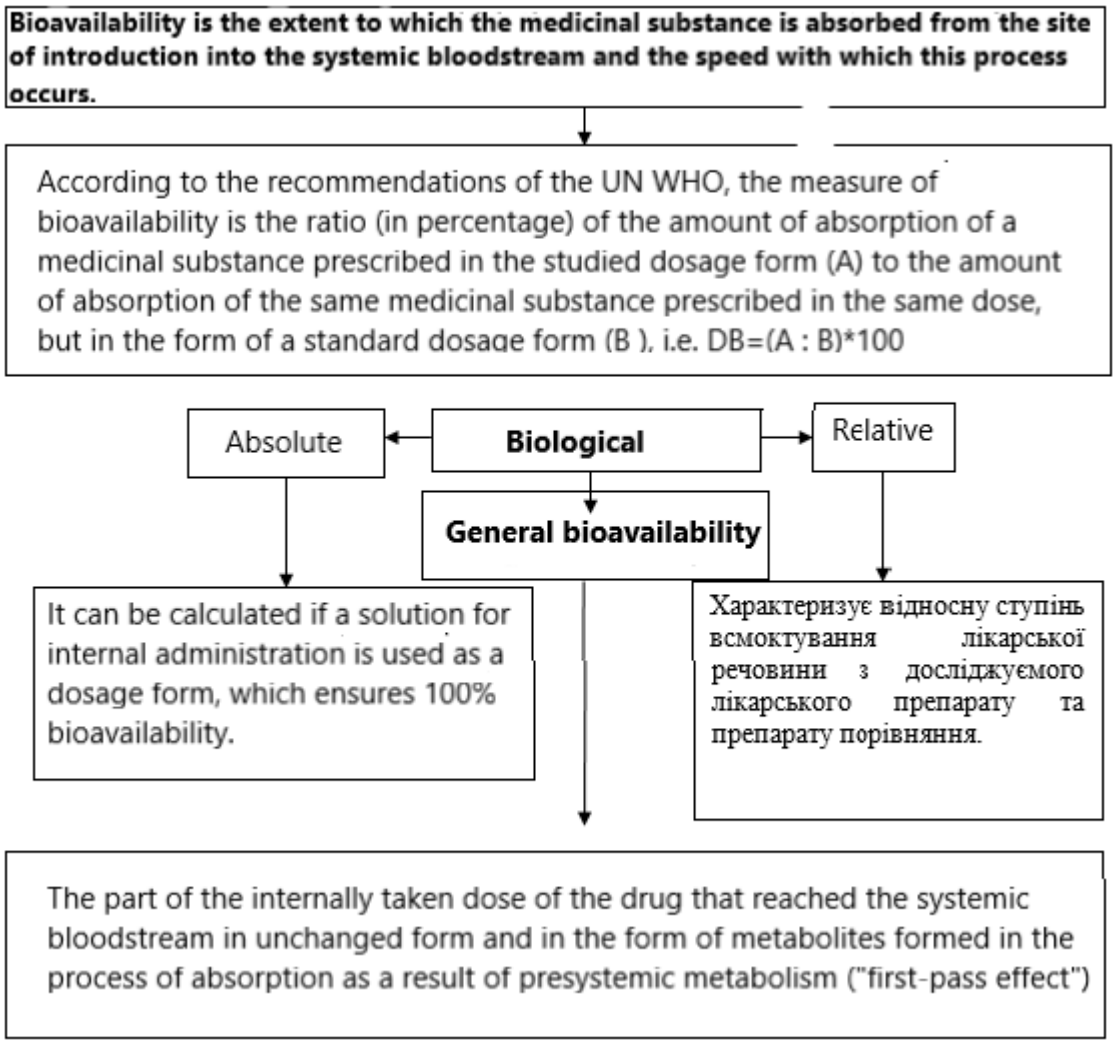
10. The impact of smoking.

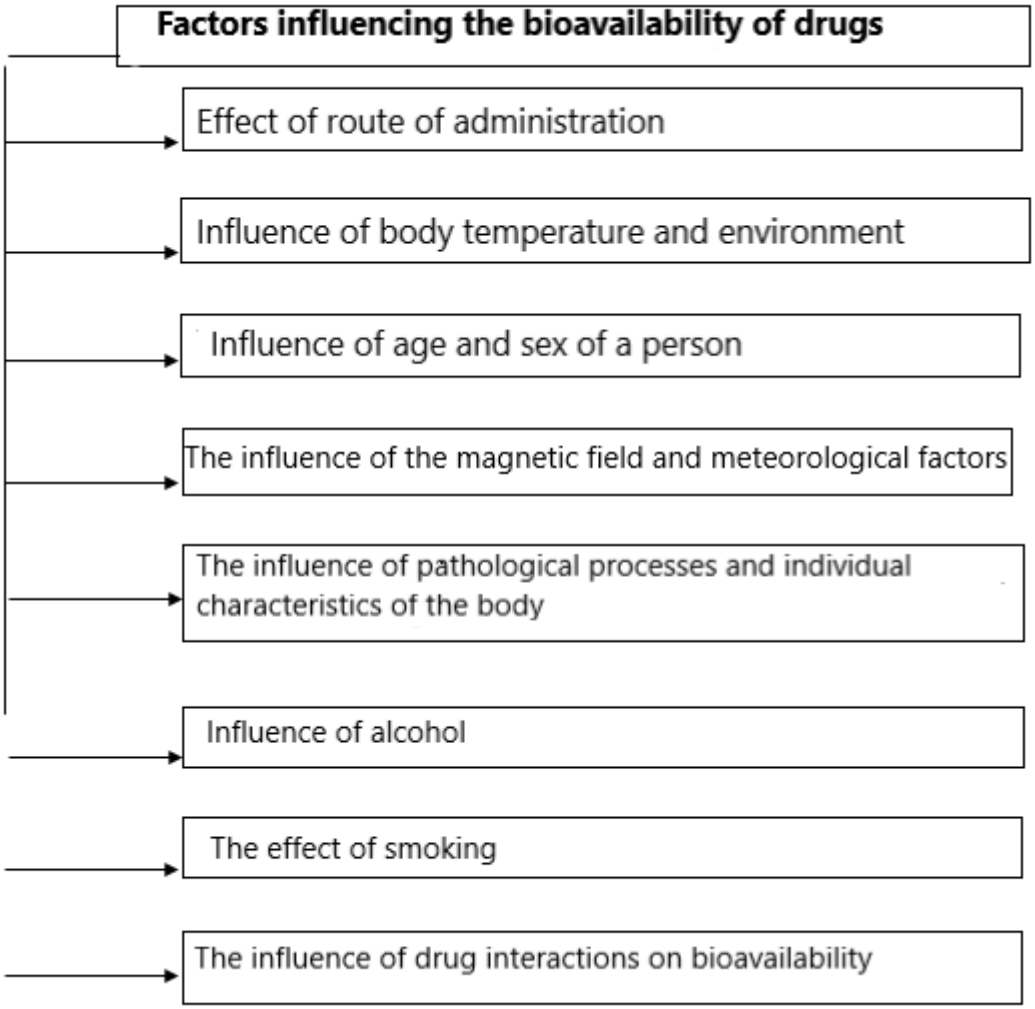
The impact of drug interactions on bioavailability.

Content of the lecture material (lecture text)

Biopharmacy, along with the pharmaceutical availability test, proposes to establish a specific criterion for assessing the influence of pharmaceutical factors on the absorbability of a drug - *bioavailability* - the degree to which a drug substance is absorbed from the site of administration into the systemic bloodstream and the speed at which this process occurs.

Bioavailability (BA) is the part of the administered drug substance that enters the systemic bloodstream when administered orally, intramuscularly, inhaled, or by other routes. It is obvious that with intravascular administration, the BA of the substance will be equal to 100%, while with other routes of administration (oral, rectal, intramuscular, etc.) it is much lower and almost never reaches 100%.



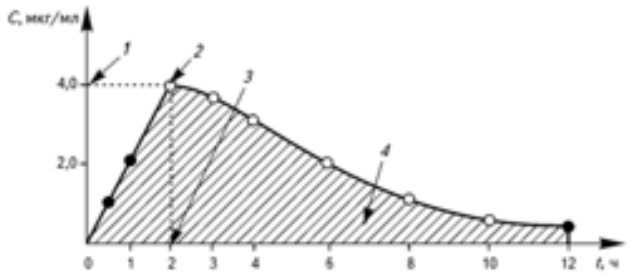


According to the recommendations of the WHO, the measure of bioavailability is the ratio (in percent) of the amount of absorption of a medicinal substance prescribed in the studied dosage form (A) to the amount of absorption of the same medicinal substance prescribed in the same dose, but in the form of a standard dosage form (B), i.e. BD = (A: B) · 100. Most often, the bioavailability of drugs is determined by comparative study of changes in the concentration of the medicinal substance in the blood plasma when prescribing the studied and standard dosage forms.

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

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

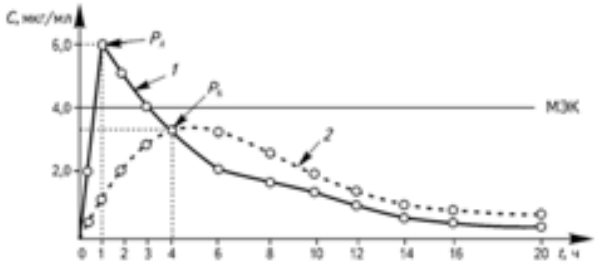
The main pharmacokinetic parameters used in the study of drug bioavailability are presented in Fig. 1.



1 - maximum concentration (C);
2 - peak;
3 - time (t) of reaching the maximum concentration;
4 - the area under the "concentration-time" curve.

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

The practical value of the peak concentration indicator 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 marks the minimum effective concentration (MEC) at which this substance has a therapeutic effect (4 μg / ml). It can be seen that in dosage form B, although the drug substance is completely absorbed, it does not have a therapeutic effect, because it does not reach the MEC.



1 - pharmaceutical form A;
2 - medicinal form B;
P - peak concentration of the substance;
MEC - minimum effective concentration.

Fig. 2. Dynamics of concentration (C) of the medicinal substance after its use in two dosage forms:

Fig. 3 shows the kinetics of a drug substance with an IEC of 6 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 MTC, and, therefore, it has a toxic effect. When using dosage form B, the drug substance is contained in the blood in a therapeutic concentration, but does not reach a

toxic concentration and does not have a harmful effect on the body.

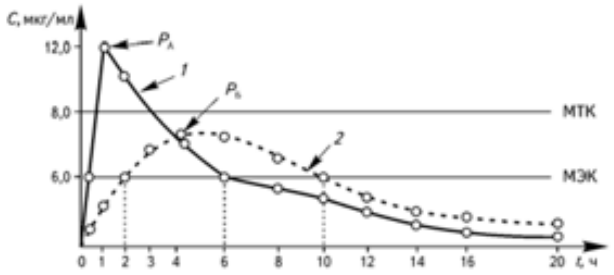


Fig. 3. Determination of the minimum toxic concentration (MTC) and minimum effective concentration (MEC) of a medicinal substance based on the dynamics of its concentration in the blood when used in two dosage forms (A and B):

The second important parameter is the time of reaching the maximum concentration of the substance in the biological fluid P, since it reflects the rate of absorption of the substance and the rate of onset of the 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. Let us assume that in this case the medicinal substance is a hypnotic. It reaches the minimum therapeutic concentration and has a hypnotic effect in the first case after 30 minutes, and in the second case - only after 2 hours. At the same time, the action 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 pharmacokinetics of the same sleeping pill, the indications for its use differ in different dosage forms. Dosage form A is advisable to use in case of difficulty falling asleep, while dosage form B is advisable to use in case of difficulty staying asleep.

The third, most important parameter of bioavailability is the area under the concentration-time curve (AUC), which reflects the amount of drug that has entered the bloodstream after a single administration of the drug.

Fig. 3 presents curves characterizing the bioavailability of two different dosage forms of the same substance. These curves have different shapes, different peaks and different times of reaching the MEK. At the same time, the areas under these curves are the same [AUC for dosage form A is 34.4 (μg / ml)-h, for B - 34.2 (μg / ml)-h], therefore, both dosage forms provide the same amount of drug substance into the blood.

However, they differ in the degree of absorption and the speed of reaching the MEK of the drug substance, which has a great influence on both the quantitative and qualitative parameters of their therapeutic action, which means that they cannot be attributed to bioequivalent drugs. This qualitative characteristic should be taken into account when prescribing and using drugs of similar composition and action, but produced by different pharmaceutical companies.

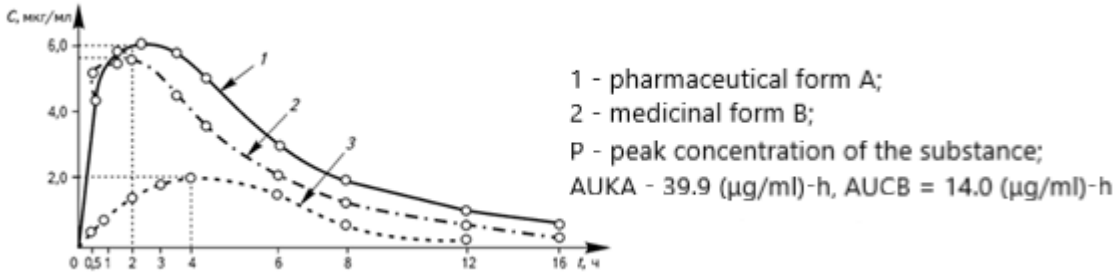


Fig. 4. Relative bioavailability of a drug substance when used in three dosage forms:

Fig. 4 presents curves reflecting the kinetics of the same substance when used in three different dosage forms - A, B and C.

The area under the curve characterizing dosage form A is larger than that under curve B and significantly larger than that under curve B. It follows that dosage form A ensures the absorption of the drug substance into the blood much better than dosage forms B and C.

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

1. 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. Tablets first disintegrate, only after that the drug substance goes into solution. In capsules, the shell first dissolves, then the drug

substance is released, which only then goes into solution. When administered in the form of 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 dissolution and absorption. The absorption rate 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 area of administration, forming a form soluble in water. Examples include benzylpenicillin sodium salt and protamine-zinc-insulin.

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

According to physiologists, the greatest distance that cells in tissues are separated 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 a 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 hematoencephalic, hematoophthalmic, placental, etc.

Thus, when a drug is administered extravascularly, a number of chemical-pharmaceutical and biomedical factors can have a significant impact on its bioavailability. Physiological factors are important both on their own and in interaction with pharmaceutical factors.

Let's consider the most significant medical and biological factors that can affect the bioavailability of drugs, and therefore, their therapeutic efficacy and toxicity.

2. Effect of administration routes on bioavailability

Oral route of drug administration

Most drugs are administered orally, i.e. through the mouth. This route of administration is the simplest and most convenient. At the same time, this route of

administration has the greatest number of factors that can affect the bioavailability of drugs.

The effect of gastrointestinal enzymes . Drugs do not affect the body in the same way, depending on when they are taken: before meals, during or after meals, which is explained by changes in the pH of the gastrointestinal tract, the presence of various enzymes and active substances secreted with bile to ensure the digestive process.

During and after meals, the acidic environment of the stomach reaches pH = 2.9 ... 3.0, and of the small intestine - 8.0 ... 8.4, which significantly affects the ionization, stability of drugs, the speed of their passage through the digestive tract and absorption into the blood. Thus, acetylsalicylic acid at a stomach pH of 1 to 3 is almost completely in a non-ionized form and as a result (due to its high solubility in lipids) is almost completely absorbed. Taking aspirin with food increases the amount of the drug converted into the salt form, the rate of its absorption in the stomach decreases to values approximately coinciding with the rate of aspirin absorption in the small intestine, and bioavailability as a whole decreases.

Under the influence of the acidic environment and stomach enzymes, erythromycin, benzylpenicillin, pancreatin, pituitary, insulin and a number of other drugs are inactivated. Hexamethylenetetramine completely decomposes into ammonia and formaldehyde.

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

The influence of food composition and temperature .

The effectiveness of medicinal substances is greatly influenced by the composition and temperature of food. 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 nettle, 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 chemical and pharmacologically active substances. Depending on the composition, food has different effects on peristalsis and

secretory function of the digestive tract, which determines 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 a delay in food processes and transportation of food mass. Under the influence of food rich in fats, the absorption of many drugs, especially fat-soluble, for example, antacids, anticoagulants, sulfonamides, griseofulvin, anaprilin, diphenin, fat-soluble vitamins A, D, E, carbamazepine, lithium preparations, seduxen, metronidazole, etc., increases significantly. Deficiency in dietary fats slows down the metabolism of ethylmorphine hydrochloride. Prior intake of fatty food reduces the activity of salol and besalol.

The influence of the nature of the liquid used to wash down the medication.

A certain role in the bioavailability of medicinal substances is played by the nature of the liquid with which the medicine is taken. Often, to mask the unpleasant taste and smell of medicinal substances, various fruit and berry or vegetable juices, tonic drinks, syrups, milk are used. Most fruit and berry and vegetable juices are acidic and can destroy acid-resistant compounds, for example, ampicillin sodium salt, 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 medicines with syrups or milk sugar, the absorption of isoniazid, ibuprofen, calcium chloride, tetracycline hydrochloride, furosemide is sharply slowed down. Some medicines that have an irritating effect on the mucous membrane of the gastrointestinal tract are washed down with milk. Medicines are mixed with milk and dairy products for infants to take. Some patients, when taking medicines, do not wash them down at all, which is not recommended, since capsules, tablets, dragees, sticking to individual parts of the inner surface of the esophagus and gastrointestinal tract, collapse without reaching the place of absorption. In addition, they cause irritation at the place of adhesion, and the lack of a sufficient amount of

liquid delays their absorption.

Rectal route of drug administration

The rectal route of administration of drugs (through the rectum) ensures their rapid absorption (after 7-10 minutes). It is used for the purpose of both local and general action. With the rectal route of administration of drugs, a minimum therapeutic concentration is created in the blood after 5-15 minutes. This is explained by the presence of a dense network of blood and lymphatic vessels in the rectum, good absorption of drugs soluble in both water and fats through the mucous membrane of the rectum. Substances, absorbed in the lower part of the rectum, enter the systemic bloodstream through the lower hemorrhoidal veins, bypassing the hepatic barrier. The fact that with the rectal route of administration, drugs are not destroyed by the liver enzyme system as a result of the "first-pass 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), the endocrine system, biologically active peptides. The endocrine, autonomic nervous and neuropeptide systems also regulate the motor activity of the colon, which, in turn, determines the duration of drug residence in the intestine. In addition, a number of diseases of the rectum (hemorrhoids, anorectal fissures, proctitis) impair the bioavailability of drugs administered rectally.

Inhalation route of drug administration

When administered by inhalation, the drug is rapidly absorbed into the systemic bloodstream through the bronchial mucosa, without being subjected to primary metabolism in the liver. With this route of administration, the bioavailability of drugs can be affected by concomitant diseases of the bronchopulmonary system, smoking (as a factor contributing to the development of chronic bronchitis with a corresponding restructuring of the structure of the bronchial wall), as well as the state of blood circulation in the bronchopulmonary system.

3. Influence of body temperature and environment

An increase in body temperature is accompanied by a sharp excitation of the CNS, respiration and blood circulation, increased metabolism. Profuse sweating leads to

dehydration of the body, thickening of the blood, a decrease in the volume of circulating fluid, and electrolyte imbalance. All this, in turn, affects the processes of absorption, distribution and metabolism of drugs, their bioavailability after oral administration.

When the temperature of absorption increases, the metabolism and transport of medicinal substances occur faster, and when it decreases, they slow down. Local cooling of the body's tissues leads to vasospasm, as a result, absorption is sharply slowed down, which should be remembered when administering the drug locally. The influence of the temperature factor on the pharmacokinetics of drugs must be taken into account in clinical practice in cases where drugs are prescribed to patients with sharply impaired thermoregulation.

4. The influence of a person's age and gender

Age also affects the bioavailability of drugs. Younger patients are characterized by higher rates of absorption, excretion, and shorter time to reach maximum drug concentration; older patients have higher half-lives.

When prescribing medications to children, it is necessary to remember that in children under one and a half years of age, the bioavailability of drugs taken orally differs only slightly from that in adults. However, their absorption (both active and passive) occurs very slowly. As a result, small concentrations are created in the blood plasma, often insufficient to achieve a therapeutic effect. Children have a delicate, easily irritated rectal mucosa, because the reflexes that arise lead to rapid bowel cleansing and a decrease in the bioavailability of drugs.

5. The influence of biorhythms

One of the most powerful factors affecting humans and the effectiveness of drug therapy is also the action of biorhythms. Every cell in our body feels time - the alternation of day and night. For humans, an increase in daytime hours and a decrease in nighttime physiological functions (heart rate, minute blood volume, blood pressure, body temperature, oxygen consumption, blood sugar content, physical and mental performance) are characteristic. Biological rhythms cover a wide range of periods: age, annual, seasonal, monthly, weekly, daily. All of them are strictly coordinated. The circadian, or round-the-clock, rhythm in humans is manifested, first of all, in the

change of periods of sleep and wakefulness. There is also a biological rhythm of the body with a much lower frequency than the daily one, which affects the reactivity of the body and affects the effect of drugs. Such, for example, is hormonal rhythms (female menstrual cycle).

During the day, the body's sensitivity to optimal and toxic doses of drugs is different. The experiment established a 10-fold difference in the lethality of rats from elenium and other drugs of this group at 3 a.m. compared to 8 a.m. Tranquilizers exhibit maximum toxicity during the active phase of the day, coinciding with high motor activity. Their lowest toxicity is noted during normal sleep. The acute toxicity of adrenaline hydrochloride, ephedrine hydrochloride, mezaton and other adrenomimetics increases during the day and significantly decreases at night. And the acute toxicity of atropine sulfate, platifillin hydrotartrate, metacin and other anticholinergics is much higher at night, in the inactive phase of the day. Great sensitivity to hypnotics and anesthetics is observed in the evening, and to anesthetics in dentistry - at 2-3 p.m. (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, permeability of biological membranes. Men are more sensitive to the activity of the Earth's magnetic field than women. The most sensitive to magnetic storms in the Earth's atmosphere are patients with disorders of the nervous and cardiovascular systems. On the days of magnetic storms, they have an exacerbation of the disease, hypertensive crisis, heart rhythm disturbances, angina attacks, reduced working capacity, etc. 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 decrease and increase.

Meteorological factors (absolute air humidity, atmospheric pressure, wind direction and strength, average daily temperature, etc.) affect the elasticity of blood vessels, viscosity and blood 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. The influence of pathological processes and individual characteristics of the organism

The initial state of the body is of great importance in the body's response to a drug. The influence of pathological conditions and diseases of the gastrointestinal tract and liver on the processes of absorption and metabolism of drugs has been discussed above.

First of all, these are pathological processes that contribute to free radical (peroxide) oxidation of lipids, inflammatory processes that lead to the activation of phospholipases and their hydrolysis of membrane phospholipids. Also important are processes that are accompanied by a change in the 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 cannot but affect the bioavailability of drugs and the effectiveness of drug therapy in patients of this category.

9. The impact of alcohol

Alcohol negatively affects the manifestation of the therapeutic effect of many drugs and is the cause of dangerous complications. Ethanol affects the pharmacodynamics and pharmacokinetics of drugs in various ways. The following factors directly affect bioavailability: change in the permeability of histohematological barriers due to disruption of the fluidity of lipid membranes when interacting with ethanol; change in the structure and function of cell membranes, disruption of the penetration of drugs through biomembranes; change in the structure and function of enzymes (acetylcholinesterase, enzymes of the mitochondrial electron transport chain); increased secretion of gastric mucus and reduced absorption of drugs in the stomach; switching of the microsomal system of the nonspecific enzymatic system of the liver (MEOS - microsomal ethanol oxidation 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 result, a change in the rate and level of biotransformation of medicinal substances.

When drugs and ethyl alcohol are administered simultaneously, their interaction can occur through several mechanisms, which is of important clinical importance. The effect of the mutual influence of alcohol and drugs on the body depends on their

concentration in the blood, the pharmacodynamic properties of the drugs, the 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%, it significantly reduces its secretion and inhibits digestive processes. The absorption of many drugs increases as a result of an increase in 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, it further increases the absorption of drugs. Being 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 intoxications when taking normal therapeutic doses. This applies to neuroleptics, analgesics, anti-inflammatory, hypnotics, diuretics, as well as antidepressants, insulin, nitroglycerin. The combination of taking the above groups of drugs and alcohol is accompanied by severe poisoning, often fatal.

10. **The impact of smoking**

The effect of drugs can be influenced by substances that enter the body during smoking. Nicotine as an N-cholinomimetic leads to activation of sympathetic and parasympathetic ganglia, adrenal medulla, and CNS dysfunction. Stimulation of the adrenal medulla leads to constriction of peripheral vessels, which disrupts the blood supply to many organs and tissues. Nicotine, benzpyrene, and their derivatives change the activity of metabolic enzymes. Smoking stimulates the oxidative metabolism of phenacetin, propranolol, theophylline, noxiron, aminazine, and diazepam, resulting in their reduced effectiveness. 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 effect of numerous factors of the external and internal environment.

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

Such interaction is understood as 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. A drug is also capable of interacting with itself in a peculiar way. When taken repeatedly, it can induce microsomal oxidation of a foreign substance and thereby accelerate its own metabolism (a classic example is barbiturates). Drugs can also worsen their own effects on organs (an example is the development of opiate tolerance). In clinical practice, the phenomenon of drug interactions must be constantly taken into account for the following reasons: - almost every hospitalized patient receives several medications during his stay in the hospital (sometimes there are up to 40! substances prescribed to one patient), numerous ready-made drugs are a combination of two or more substances, a significant number of patients undergoing outpatient treatment consume such drugs as laxatives, analgesics, hypnotics, etc. Of all possible interactions, only about 1-10% pose a risk of developing undesirable effects, but the risk of mutual reduction of effectiveness is significantly higher. New reports of drug interactions should always be treated very carefully. The number of possible interactions at first glance is extremely large, although not all of them are clinically significant. There are three types of interactions: pharmaceutical, pharmacokinetic and pharmacodynamic.

Materials for activating higher education students during lectures: questions, situational tasks, etc.:

Question:

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

General material and methodological support for the lecture:

- educational premises – the department's auditorium;

- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials – presentation, slides.

Questions for self-control:

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

2. History of the development of biopharmacy.

3. Basic concepts and terms of biopharmacy.

4. The main tasks of biopharmacy at the present stage and their role in practical healthcare.

5. The concept of pharmaceutical factors that influence the therapeutic efficacy of drugs, their classification.

6. The physical state of medicinal and excipients in dosage forms and its effect on the rate of release and absorption of drugs.

7. The influence of the aggregate state of drugs on the pharmacological action.

8. The influence of the degree of dispersion of medicinal substances on the therapeutic effect of medicinal products.

9. The influence of the crystal structure and polymorphism of medicinal substances on the pharmacological activity of medicinal products.

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 a medicinal product and its impact on pharmacotherapy.

12. Dependence of therapeutic activity of drugs on the type and quality of packaging.

List of sources used:

Main literature:

13. Gladyshev V.V., Davtyan L.L., Drozdov A.L., Byryuk I.A., Kechyn I.L. Biopharmacy. Textbook for pharmaceutical universities and faculties. 2nd ed. Edited by V.V. Gladyshev. Dnipro: ChMP "Economica". 2018.- 250 p.

14. Guideline ST-N MOZU 4242-7.1:2005 "Medicines. Guideline on clinical trials. Bioavailability and bioequivalence studies" - Kyiv, 2018.
15. Guideline ST-N MOZU 4242-7.1:2005 "Medicines. Guideline on clinical trials. Bioavailability and bioequivalence studies" - Kyiv, 2018.
16. Guideline ST-N MOZU 42-7.2:2018 Medicinal products for bioequivalence studies. – Kyiv, 2018. – 77 p.
17. Modern pharmaceutical technologies: teaching aids for laboratory classes of undergraduates of full-time, evening and correspondence forms of study in the specialty 8.110201 "Pharmacy" / edited by O.A. Ruban. – Kh.: Publishing house of the National University of Physics and Technology, 2016. – 256 p.
18. Biopharmacy: textbook / edited by: Borysyuk I.Yu., Fizor N.S., Akisheva A.S. Odesa, ONMedU, 2020. - 98 p.

Additional literature:

1. Pharmaceutical Encyclopedia / Chairman of the Editorial Board and author of the foreword V.P. Chernykh. – 3rd ed. – K.: “MORION”, 2016. – 1952 p.
2. Polovko N.P., Vyshnevska L.I., Shpychak O.S. Assessment of biopharmaceutical factors in the development and production of new drugs // Modern advances in pharmaceutical technology and biotechnology: collection of scientific papers, issue 2. – X.: Publishing house of the National University of Physics and Technology, 2017. – pp. 155-160.
Excipients in the production of medicines: a teaching aid for students of higher pharmaceutical schools /O. A. Ruban, I. M. Pertsev, S. A. Kutsenko, Yu. S. Masliy; edited by I. M. Pertsev. Kh.: Zoloti storyni, 2016. 720 p.

Lecture No. 8

Topic: " The influence of the route of administration and simple chemical modification of drugs on the process of their absorption **"** - 2 hours.

Relevance of the topic: biopharmacy is one of the fundamental natural sciences. It helps to understand natural phenomena, participates in the formation of the worldview of each person. Biopharmacy is a theoretical basis necessary for the study

of special disciplines, instills skills in predicting the properties and reactivity of medicinal substances used in pharmacy and medicine.

Goal: to master theoretical material and acquire practical skills in taking into account the influence of various exogenous and endogenous factors on the bioavailability of drugs; to know their classification and mechanisms of influence on bioavailability and the possibility of preventing the action of undesirable factors in the technological process.

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

Lecture plan and organizational structure:

No. No. p.p.	**The main stages of the lecture and their content.**	**Goals in levels of abstraction.**	**Type of lecture, lecture equipment.**	**Time allocation.**
1	**2**	**3**	**4**	**5**
I 1. 2. II 3.	***Preparatory stage*** Defining learning goals. Providing positive motivation. ***Main stage*** Presentation of lecture material. Plan: 12. Types of pharmaceutical factors that affect bioavailability . 13. Physical state of	I II	Combined lecture Slides	1% 2% 90%

	biopharmaceutical medicinal substances . 14. Grinding of medicinal substances 15. Polymorphism of medicinal substances 16. Solubility of medicinal substances 17. Chemical modification 18. Excipients 19. Types of dosage form and routes of administration 20. Technological processes ***Final stage*** Lecture summary, general conclusions. The lecturer's answers to possible questions. Tasks for student self-study.			2% 3% 2%
III		III	Bibliography, questions, assignments.	

Structural and logical diagram of the lecture content

Plan:

1. Characterization of pharmaceutical factors affecting bioavailability.

2. Optimal degree of dispersion of medicinal substances.

3. Optical, electrophysical properties of the active substance.

4. Examples of polymorphism of medicinal substances.

5. Conditions for the formation of various polymorphic modifications.

6. The influence of excipients on the modification of pharmacokinetic parameters of drugs.

7. The influence of technological processes on bioavailability.

8. The influence of the dosage form and the route of administration on bioavailability

Content of the lecture material (lecture text)

Biopharmacy (biopharmacy) is a science that studies the dialectical relationships of drugs as physicochemical systems and the macroorganism as a biological system, taking into account the variable pharmaceutical and biological factors that accompany the transportation of drugs and significantly affect the effectiveness of pharmacotherapy. The ultimate and main task of Biopharmacy is associated with the optimization of the action of drugs - increasing their therapeutic activity and safety by creating optimal dosage forms in terms of composition, properties and type. Therefore, as a scientific direction, it is closely related to pharmaceutical technology, pharmacokinetics, pharmacology and toxicology. The term "biopharmacy" was adopted in 1961 mainly thanks to the works of J. Levi and J. Wagner, dedicated to establishing the phenomenon of therapeutic non-equivalence of drugs that fully met the requirements of the pharmacopoeia and other specifications, had the same composition, identical dosage forms, but differed in manufacturing methods or excipients used. It was impossible to explain the therapeutic inequivalence of such drugs without a radical revision of the entire heritage of pharmacy and the formation of a new pharmaceutical mindset. This new view of the action of drugs was later formulated in the form of a biopharmaceutical concept, which was based on accurate experimental data obtained using highly sensitive methods and the introduction of new techniques (devices) in biomedical and pharmaceutical research. This concept recognized the biological significance of the influence of variable

pharmaceutical factors on the manifestation of the therapeutic efficacy of drugs, which should be taken into account at the stage of forming their composition and production. Therefore, pharmaceutical factors are often called "technological" or "production".

The influence of pharmaceutical and biological (physiological, biochemical) variables can be traced to the following pharmacokinetic scheme of oral drugs: the amount of drug substance in the drug → release and its amount at the site of absorption → biotransformation and the amount of drug substance (metabolites) in the bloodstream and tissues → excretion of the drug substance (metabolites) by various routes (through the kidneys, gastrointestinal tract, lungs, skin) from the body. The above scheme demonstrates the close relationship of all variable factors and their influence on the effectiveness of drugs. Before being absorbed, the drug substance must be released from a certain dosage form (tablets, suppositories, ointments, etc.), diffuse to the absorption surface. It is at this stage that technological factors determine the speed and completeness of the release of the substance from the pharmaceutical system, which depends on its composition, technology and properties. The absorption process itself (see Absorption *of drugs)* is mainly also diffusional and depends on many factors of both technological and biological (age, gender, state of the organism, etc.) nature. Biochemical factors dominate at the final stage - excretion of the active substance (metabolites) from the body. The study of biochemical factors (the prerogative of pharmacogenetics) is important for assessing the enzymatic fullness and degree of activity of the body's response to the administration of drugs, which include certain medicinal substances. Therefore, the effectiveness of drugs can be determined only when studying both pharmaceutical and biological variable factors, each of which determines the dominant influence at individual stages of their "life", starting from creation and production and ending with rational use (see Interaction of *drugs, Interaction of drugs and food, Therapeutic nutrition).* Therefore, special biopharmaceutical research is the study of the influence on the effectiveness of drugs of such pharmaceutical factors as the chemical (see Simple *chemical modification)* and physical state of active substances, the optimal use of excipients, the type of dosage form, and technological operations and processes.

The physical state of an active substance from the point of view of the biopharmaceutical concept is a set of its properties: the ability to polymorphism, dispersity; optical, electrophysical and other characteristics (aggregate state, philicity, crystal shape, etc.), which determine the intensity of the processes of dissolution, diffusion, phase transition, absorption, etc., which, in turn, affects bioavailability (see *Bioavailability*). The most significant of this group of factors are polymorphism, dispersity and optical activity.

Polymorphism is the ability of substances to form several crystalline modifications that are chemically identical but different in crystal structure, as a result of which they have different physical properties. The formation of numerous polymorphic modifications is explained by different conditions of technological processes (temperature, pressure, nature of the solvent, nature of the impurities present, etc.) when obtaining active substances, especially during crystallization and purification, drying, grinding, granulation, tableting. This confirms the need to comply with certain requirements of Good Manufacturing Practice when obtaining them. The phenomenon of polymorphism is widespread in nature among many organic substances, especially among hormones, antibiotics, sulfonamides, derivatives of barbituric and salicylic acids, etc. Thus, riboflavin and norsulfazole have 2, cortisone acetate - 5, acetylsalicylic acid - 6 polymorphic forms, which have different solubility, T_{pl}, resistance to oxidation and destructive processes, etc. Such a difference in physical properties, in turn, affects both the speed and degree of absorption of active substances and the stability of the drug. Knowledge of the phenomenon of polymorphism is an important section of biopharmaceutics and allows you to actively influence the effectiveness of pharmacotherapy.

that *the dispersion of active substances* can affect the rate of their dissolution and absorption, but the scientific interpretation of the medical significance of this factor was formulated during the period of research into cases of therapeutic nonequivalence of drugs. Grinding a substance leads to an increase in the surface area, and therefore to an increase in free surface energy (the forces of unbalanced molecular forces on the surface of a substance). According to the second law of thermodynamics, every body tends to reduce free surface energy. In this regard, finely ground active substances

dissolve better, are absorbed, better adsorb skin secretions, etc., i.e. tend to saturate free surface energy and have greater therapeutic activity regardless of the dosage form in which they are found. It has been proven that the analgesic effect of micronized particles of acetylsalicylic acid is 2 times higher than that of particles obtained by conventional mechanical grinding; This is also true for many active substances with anticoagulant, antiseptic, diuretic and other effects. When using the same doses of micronized and conventionally ground sulfadimezine, it is determined in the blood by 40% more in the first case, and the maximum concentration is observed 2 hours earlier. The smaller the size of chloramphenicol particles, the faster it accumulates in the bloodstream, and in the molecular state of dispersion (in PEG 400) its therapeutic activity increases several times. However, in some cases, an increase in the degree of dispersion of active substances (with oral administration of penicillin, erythromycin) can lead to a decrease in the therapeutic activity of drugs, which is explained by the intensification of the processes of their hydrolytic destruction or a decrease in stability in the presence of biological fluids and other components of the gastrointestinal tract. There are cases when, with increasing dispersion of the active substance, undesirable toxic reactions increase (nitrofuranthion) or, conversely, when irritation of the digestive tract mucosa is significantly reduced (acetylsalicylic acid). Therefore, in the production of drugs in each specific case, the starting substance must be ground to such an extent that optimal therapeutic efficacy is ensured and minimal undesirable side effects of the drug are detected.

The optical and electrophysical properties of the active substance also affect the manifestation of their pharmacological activity. There is no chemical difference between the optical isomers of chloramphenicol and synthomycin, which will be confirmed by chemical analysis, but in clinical practice, chloramphenicol has been found to be 2 times more effective than synthomycin. And the levorotatory isomer of propylnoradrenaline exhibits a bronchodilator effect even 800 times higher than its dextrorotatory isomer. Therefore, the pharmacological activity of a substance is determined not only by the structure and size (mass) of the molecule, but also by its structural and steric (position of individual substituents of the molecule in space) properties. Thus, trans-amine (granylcypromine) exhibits an antidepressant effect with

an excitatory effect, while cis-amine retains an antidepressant effect, but is a tranquilizing component and is less toxic, which is very much appreciated in practical medicine. When absorbed through a lipid barrier (the walls of the stomach, intestines, skin), *the degree of ionization, the distribution coefficient of the active substance,* etc. have a noticeable effect. Anhydrous modifications of theophylline, caffeine, ampicillin, and some hormones are more stable, dissolve faster (no energy is spent on the destruction of crystals) and are absorbed, providing a higher concentration of the substance in biofluids compared to the corresponding crystal hydrates.

Excipients are a large group of materials of natural and synthetic origin, with the help of which various dosage forms are obtained, where they determine the technological, consumer, economic characteristics and therapeutic effectiveness of drugs. They are included in large quantities in some dosage forms (ointments, suppositories, etc.) and significantly affect the manifestation of the therapeutic effect of drugs. The greatest achievement of biopharmacy is the rejection of the dominant concept of the role of excipients as indifferent form-forming agents. Being a kind of carrier (matrix), excipients are able to interact with both active substances (see *Interaction of excipients*) and the external environment (gastrointestinal contents, vessel walls, tissue fluid, oxygen, etc.) in the process of manufacturing, storing and using drugs. Depending on the nature of the interaction between the components of the pharmaceutical system, its effectiveness may or may not change significantly (table). Therefore, an unjustified combination of active and excipients is unacceptable. It is necessary to study their possible interaction and the impact of the latter on the manifestation of the effectiveness and stability of the drug.

Table. The influence of the interaction of active and excipients on the manifestation of drug efficacy

Active ingredient	**Excipient**	**Pharmaceutical system efficiency**
Phenobarbital sodium	PEG 4000	Missing
Sodium barbital	PEG 4000	Present

Active ingredient	Excipient	Pharmaceutical system efficiency
Chloramphenicol	Polyvinylpyrrolidone	Lower than that of an antibiotic
Chloramphenicol	PEG 400	Ten times higher than that of an antibiotic

One of the main tasks of biopharmaceutical research is to study the selective effect of excipients on the modification of the pharmacokinetic parameters of the drug and obtaining its optimal dosage form. Scientific justification of the rational use of excipients is important in developing the composition of any drugs, especially drugs for children and geriatric patients, predicting their action and stability.

The therapeutic significance of the type of dosage form as a structural unit not only of commodity science, but also of pharmacotherapy was highlighted in the second half of the last century. Previously, it characterized the main indicators (stability, identity and amount of substance in the drug) of the official specification, as well as the convenience of using drugs, dosage accuracy, appearance, smell, taste, economy (completeness, transportation, storage conditions) and destruction (disintegration, period of complete deformation). Today, without rejecting the above characteristics, the dosage form has a new interpretation as a factor that determines the convenience of using and storing the drug, ensures its optimal therapeutic effect with minimal undesirable effects, as well as optimal conditions for the release with subsequent absorption of the active substance. All other requirements for the dosage form as the main "implementer" of the pharmacotherapeutic effect are subordinate to this (therefore, its empirical choice or unjustified replacement is prohibited). Today, there are known cases when only the optimal dosage form allows to ensure the desired result and avoid undesirable side effects of the drug.

Technological processes are understood as purposeful production actions: technological techniques and percolations associated with the processing (processing) of starting materials (API, excipients, LRS), intermediates used in the production of drugs in a certain dosage form. B.f. requires theoretical justification of the influence of the used technological processes on the pharmacokinetic and pharmacodynamic

indicators of the finished product (drug). It has been proven that even the simplest technological techniques can significantly affect the nature of the action of drugs. Thus, by changing the temperature when mixing the oil dispersion medium and the aqueous dispersed phase, it is possible to obtain a cooling effect of different strengths of pseudoemulsions and cold creams. Adding IUD to eye drops changes their viscosity, adhesive ability and duration of contact with the mucous membrane, as a result of which the duration of their therapeutic action increases. Coating tablets, dragees, and granules with shells allows you to avoid irritating the mucous membrane, protect the active substance from the destructive effects of various environmental factors, or localize its release site and create a higher concentration in the stomach or intestines, which is of certain importance when using laxatives, anthelmintics, and other drugs, or to obtain a prolonged-acting drug.

Thus, the biopharmaceutical concept has enriched pharmaceutical technology with new theoretical provisions and ideas regarding the rational use of the active substance in order to create such drugs that would maximally meet the requirements of modern pharmacotherapy. In *the educational direction*, it requires the training of pharmaceutical personnel with a broader medical outlook and constant improvement of professional knowledge. Based on this, biopharmaceutics should be considered a modern pharmaceutical theory, knowledge of the basic provisions of which is mandatory for all specialists in this field.

Various factors affecting the bioavailability of drugs significantly change the degree of their therapeutic effect. They can enhance it or, conversely, reduce it. In addition, pharmaceutical factors can eliminate the side effect of the drug or contribute to its manifestations. The processes of absorption, biotransformation and elimination of drugs from the body depend on pharmaceutical factors. Therefore, when developing the composition and technology of new drugs and improving existing ones, it is necessary to take into account the possible influence of pharmaceutical factors on their pharmacodynamics and pharmacokinetics.

Pharmaceutical factors that affect the degree and duration of the pharmacological action of drugs are divided into 5 main groups: the physical state of medicinal substances, simple chemical modification, excipients, the type of dosage

form and the route of its administration into the body, technological processes. All these factors significantly change the degree of therapeutic effect of drugs. They can enhance or, conversely, reduce it. In addition, physical factors can eliminate the side effect of drugs or contribute to its manifestations. The processes of absorption, biotransformation and elimination of drugs from the body depend on physical factors. Therefore, when developing the composition and technology of new drugs and improving existing ones, it is necessary to take into account the possible influence of physical factors on their pharmacodynamics and pharmacokinetics. The physical state of a drug substance includes such factors as particle size (dispersity), aggregate state, optical activity, surface tension, solution pH, polymorphism, etc. Simple chemical modification of a drug substance is a state in which the same drug substance is used in different chemical forms: salt, acid, base, ester, complex compound, etc. Excipients used in drug technology also affect the pharmacological action, and their nature and quantity are important. Therefore, from the existing wide range of excipients, their choice should be individual for each drug. Optimal drug activity is achieved by prescribing it in a rational dosage form, which, in turn, determines the route of administration. Technological processes (operations, equipment) used in the preparation of a drug also change the strength of its therapeutic action. The method of obtaining a drug determines its stability, i.e., storage duration and quality, and affects its biotransformation in the body. Failure to comply with certain conditions of production technology leads to the emergence of therapeutic inequivalence.

Materials for activating higher education students during lectures: questions, situational tasks, etc.:

Question:

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.

General material and methodological support for the lecture:

- educational premises – the department's auditorium;
- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials – presentation, slides.

Questions for self-control:

1. When preparing an oil emulsion, the pharmacist weighed camphor in a mortar, ground it with a few drops of ethyl alcohol, added Tween-80, purified water, and castor oil. He mixed thoroughly with a pestle. Evaluate the correctness of the pharmacist's actions.

2. The doctor prescribed a 33% sulfuric acid ointment to the patient to treat scabies, the pharmacist prepared an ointment based on petroleum jelly. Indicate the pharmacist's error

3. The pharmacist carefully ground bismuth subnitrate with some water, added the rest of the water. He mixed some of the prepared suspension with sugar syrup and transferred everything to a dispensing bottle. Give a critical assessment of his actions.

List of sources used:

Main literature:

19. Gladyshev V.V., Davtyan L.L., Drozdov A.L., Byryuk I.A., Kechyn I.L. Biopharmacy. Textbook for pharmaceutical universities and faculties. 2nd ed. Edited by V.V. Gladyshev. Dnipro: ChMP "Economica". 2018.- 250 p.

20. Guideline ST-N MOZU 4242-7.1:2005 "Medicines. Guideline on clinical trials. Bioavailability and bioequivalence studies" - Kyiv, 2018.

21. Guideline ST-N MOZU 4242-7.1:2005 "Medicines. Guideline on clinical trials. Bioavailability and bioequivalence studies" - Kyiv, 2018.

22. Guideline ST-N MOZU 42-7.2:2018 Medicinal products for bioequivalence studies. – Kyiv, 2018. – 77 p.

23. Modern pharmaceutical technologies: teaching aids for laboratory classes of undergraduates of full-time, evening and correspondence forms of study in the

specialty 8.110201 "Pharmacy" / edited by O.A. Ruban. – Kh.: Publishing house of the National University of Physics and Technology, 2016. – 256 p.
24. Biopharmacy: textbook / edited by: Borysyuk I.Yu., Fizor N.S., Akisheva A.S. Odesa, ONMedU, 2020. - 98 p.

Additional literature:

3. Pharmaceutical Encyclopedia / Chairman of the Editorial Board and author of the foreword V.P. Chernykh. – 3rd ed. – K.: “MORION”, 2016. – 1952 p.
4. Polovko N.P., Vyshnevska L.I., Shpychak O.S. Assessment of biopharmaceutical factors in the development and production of new drugs // Modern advances in pharmaceutical technology and biotechnology: collection of scientific papers, issue 2. – X.: Publishing house of the National University of Physics and Technology, 2017. – pp. 155-160.
Excipients in the production of medicines: a teaching aid for students of higher pharmaceutical schools /O. A. Ruban, I. M. Pertsev, S. A. Kutsenko, Yu. S. Masliy; edited by I. M. Pertsev. Kh.: Zoloti storyni, 2016. 720 p.

Lecture No. 9-10

Topic: " Molecular mass, solubility, acidity, alkalinity, state of aggregation and polymorphism as physicochemical factors affecting the bioavailability of drugs" - 4 hours.

Relevance of the topic: biopharmacy is one of the fundamental natural sciences. It helps to understand natural phenomena, participates in the formation of the worldview of each person. Biopharmacy is a theoretical basis necessary for the study of special disciplines, instills skills in predicting the properties and reactivity of medicinal substances used in pharmacy and medicine.

Goal: To acquire practical skills in predicting the influence of physicochemical factors on pharmacokinetic characteristics, dynamics of bioavailability, therapeutic effect of drugs and stability of drugs during storage. To master methods for determining the main physicochemical properties that affect the bioavailability of drugs. To be able to analyze the possible effect of a substance on the body, taking into account certain quantitative characteristics.

Basic concepts: Molecular weight, solubility of drugs. .

Lecture plan and organizational structure:

No. No. p.p.	**The main stages of the lecture and their content.**	**Goals in levels of abstraction.**	**Type of lecture, lecture equipment.**	**Time allocation.**
1	**2**	**3**	**4**	**5**
I 1. 2. II 3.	***Preparatory stage*** Defining learning goals. Providing positive motivation. ***Main stage*** Presentation of lecture material. Plan: 1. Medicinal substances that are well soluble and well absorbed. For such substances, it is not necessary to determine the “dissolution” test, because the active substance goes into solution within a few minutes. 2. Medicinal substances that are well soluble, but poorly absorbed. 3. Medicinal substances that are	I II	 Combined lecture Slides	1% 2% 90%

	poorly soluble, but well absorbed. ***Final stage*** Lecture summary, general conclusions. The lecturer's answers to possible questions. Tasks for student self-study.			2% 3% 2%
III		III	Bibliography, questions, assignments.	

Structural and logical diagram of the lecture content

Plan:

1. Medicinal substances that are well soluble and well absorbed. For such substances, it is not necessary to determine the “dissolution” test, because the active substance goes into solution within a few minutes.
2. Medicinal substances that dissolve well but are poorly absorbed.
3. Medicinal substances that are poorly soluble but well absorbed.

Content of the lecture material (lecture text)

Molecular weight and solubility of drugs are important physicochemical factors that affect the absorption, distribution and excretion of a drug substance. The degree of

absorption and the choice of the appropriate route of administration of the drug depend on solubility. Four groups of drugs are distinguished by solubility and absorption: 1. Drugs that dissolve well and are well absorbed. For such substances, it is not necessary to determine the "dissolution" test, because the active substance goes into solution within a few minutes. 2. Drugs that dissolve well, but are poorly absorbed. 3. Drugs that dissolve poorly, but are well absorbed. To prevent the insolubility of substances in liquid dosage forms, simple chemical modification can be used: An example of the effect of simple chemical modification can be the use of active substances in the form of acids, alkalis, salts, ethers, etc., in the structure of which the part of the molecule responsible for the pharmacological action does not change. To improve solubility, the following are used: a) replacement of an insoluble drug substance with its pharmacological analogue (codeine - codeine phosphate, theophylline - euphylline, barbital - sodium birbital, erythromycin with its ester - erythromycin propionate, sodium salt of benzylpenicillin - potassium salt, ascorbic acid with sodium ascorbate); b) addition of excipients capable of improving solubility due to complexation (for example, potassium iodide for dissolving crystalline iodine in aqueous and alcoholic solutions); c) addition of substances that create an optimal pH value (sodium bicarbonate, boric acid, buffer solutions). So, the study of simple ONMedU, Department of Drug Technology Practical lesson No. 10. "Molecular mass, solubility, acidity, alkalinity, aggregate state and polymorphism as physicochemical factors affecting the bioavailability of drugs." Methodological development of a practical lesson, OPP "Pharmacy, industrial pharmacy", 5th year, Faculty of Pharmacy, Discipline: "Biopharmacy" p. 2 chemical modification of the active substance allows to increase the effectiveness of pharmacotherapy by improving bioavailability. 4. Medicinal substances that are poorly soluble and poorly absorbed. For this group of drugs, it is preferable to use parenteral methods of administration. Among the physicochemical characteristics of medicinal substances that affect absorption and excretion, the relative molecular mass is of great importance. For example, according to Hirom and co-authors, only substances with a molecular mass less than 300 are excreted in the urine. In cases where the molecular mass of the substance is more than 300, a proportional part of the medicinal product is excreted in the bile. One of the

indicators of the ability of a substance to penetrate the blood-brain barrier, in addition to molecular weight, is the polarity of the surface of the molecules. A simple chemical modification can have a significant impact on the biotransformation pathways of a medicinal product. A new functional group introduced into the molecule of the substance, as a result of chemical reactions occurring in the body, can change its solubility and, in turn, the nature and strength of the therapeutic effect both in the direction of increasing its pharmacological activity (prodrug) and in the direction of decreasing it. At the same time, the effect of the first passage through the liver, which is the main organ of metabolism of most medicinal products, changes. As a result of metabolism, the substance can become electrophilic in chemical nature and interact with biological macromolecules, causing toxic phenomena, mutagenesis, carcinogenesis, etc. An example of a simple chemical modification can be conversion into salts. For example, the alkaloid quinine-base can be converted into salts: sulfate, chloride, bromide. Their solubility is different and is 1: 800, 1:34, 1:16, respectively, which, in turn, determines the unequal bioavailability and severity of antimalarial action. The pharmaceutical industry produces the following dosage forms of quinine hydrochloride: tablets of 250 and 500 mg and a 50% solution in ampoules of 1 ml. Quinine hydrobromide, the solubility of which is twice as high as that of quinine hydrochloride, is practically not used due to the possibility of a side effect - the phenomenon of "bromism". The pH of drugs has a significant effect on excretion. Drugs that have acidic properties are quickly excreted in alkaline urine. Conversely, weak bases - in acidic urine. For example, the elimination of morphine hydrochloride, codeine phosphate, quinine sulfate, and novocaine increases with an acidic urine reaction, and in an alkaline environment, barbituric acid derivatives, salicylates, and sulfonamide drugs are excreted more quickly.

Drug efficacy (Latin: *Effectus* - action or *efficio* - action) is an indicator that characterizes the sum of the positive effects of the manifestation of the desired therapeutic effect of a certain drug. The therapeutic effect of drugs is determined by their qualitative and quantitative composition, which is formed during the development and production process and is evaluated during preclinical studies and clinical trials and is usually supplemented by certain technological standards of production and

quality control. Efficacy, as well as safety, are the main indicators of their quality, for which the holder of the registration certificate is responsible in accordance with current legislation, which is a resource for pharmacovigilance.

The factors on which the effectiveness of drugs depends are divided into *main* [chemical structure, mol. m., dose, degree of hydration, structural, spatial (position of individual substituents of the molecule), electrophysical (degree of ionization, distribution coefficient in biofluid) and other characteristics of the API] and *secondary* (*variable*) *factors* , which can significantly affect both qualitative and quantitative indicators of the E.l. According to the biopharmaceutical concept, all variable factors have a biological significance of the impact on the E.l. and, in turn, are divided into pharmaceutical (technological, production) and biological (physiological and biochemical), which are closely interconnected and determine the speed and completeness of the release and absorption of the API from the pharmaceutical system.

The following pharmaceutical factors dominate the stage of drug creation and production: *physical state of the API* (ability to polymorphism, dispersibility, aggregate state, philicity, crystal shape, etc.), which determines the intensity of diffusion processes (release and absorption), which affects bioavailability *The optimal combination of API with excipients* affects technological, consumer, economic characteristics and therapeutic effect; *scientifically based choice of technology and type of dosage form* , which provide the intended physicochemical, pharmacokinetic and pharmacodynamic indicators of the drug or controlled release and targeted delivery of API, allow avoiding undesirable effects of environmental factors, ensure the convenience of use and storage of the drug.

The effectiveness of drugs is also significantly influenced by interrelated *biological* (physiological and biochemical) variable factors (age, gender, body weight, immune status, genetic characteristics of the patient; the presence of beneficial microflora in the gastrointestinal tract and the activity of enzymes, coenzymes and vitamins, the presence of concomitant diseases, especially liver and kidney, the characteristics of the course of the underlying disease, etc.). It is necessary to take into account the irrational use of drugs, especially their incompatibility and interaction with other drugs when taken simultaneously, drugs, alcohol, dietary supplements, food

products, etc. The effectiveness of drugs can also be influenced by the environment (temperature, radiation energy, magnetic field, meteorological, hypo- and hyperbaric conditions), chronopharmacological features of drugs, the patient's biorhythmic status, time and conditions of drug use during the day; the awareness of specialists (doctor, pharmacist) regarding the patient's pharmacotherapeutic dossier, the latter's willingness to follow the recommendations provided regarding the use of drugs, economic and many other factors.

Biological rhythms are fluctuations in the change and intensity of vital processes, which are based on changes in the metabolism of biological systems, caused by the influence of external and internal factors. The nature, mechanisms and significance of biological rhythms are studied by chronobiology (Greek *chrynos* - time). External factors include: changes in illumination (photoperiodism), temperature (thermoperiodism), possibly the magnetic field, the intensity of cosmic radiation; tides, seasonal and solar-lunar influence. Internal factors are neurohumoral processes that occur at a certain, hereditarily fixed pace and rhythm. Most biological rhythms are characterized by endogenous generation, small variability of the constant duration of cycles during ontogenesis. The frequency of biological rhythms ranges from a few fractions of a second to several years. B.r., caused by internal factors of changes in activity with a period of 20 to 28 hours, are called round-the- clock , or circadian, rhythms. Most physiological processes in the human body are subject to periodic fluctuations, of which daily fluctuations in body temperature have been studied in detail. The hypothalamus, pineal gland, striatum, hippocampus and some other brain structures participate in the regulation of the daily periodicity of functions. In pathology, distortions of many physiological processes are noted. For example, in people with hypertension of stages II and III at night, there is not a decrease, as in healthy people, but an increase in all indicators of blood pressure, peripheral resistance with a simultaneous decrease in systolic and minute blood volumes. These hemodynamic changes lead to a deterioration in the condition of patients at night. The mismatch of the rhythm of biological clocks and photoperiodism in the autumn and spring seasons is the cause of exacerbation of chronic diseases of the respiratory system, cardiovascular system, gastrointestinal tract, etc. The reproduction of some

parasites in the body also has a pronounced periodicity, which is partly determined by the biological rhythms of the "host". Fluctuations in metabolism with a period of tenths and hundredths of a second are characteristic of neural biological clocks. These rhythms are manifested in changes in the reactive properties of neurons. They also determine some psychophysiological patterns, in particular the duration of simple and complex sensorimotor reactions, the dependence of the magnitude of sensation on the intensity of signals, the limiting values of the information volume of short-term memory, etc. Biological rhythms are cyclic oscillations in various systems of the body.

The main characteristics of biological rhythms are: the period or frequency of oscillations (the number of oscillations per unit of time), their amplitude (the magnitude of the maximum deviation of the indicator in one direction or another from the average value or level of oscillations), level, phase and form. The period of oscillations is determined by the time interval between adjacent maxima or minima of the indicator of the state of the organism. The phase of oscillation characterizes the state of the oscillatory process at a point in time; it is measured in fractions of the period, and in the case of sinusoidal oscillations - in angular and arc units. The following types of physiological oscillations are conditionally distinguished by form: pulsed, sinusoidal, relaxation, mixed. The classification of physiological rhythms according to Halberg (F. Halberg) is based on the magnitude of the oscillation period. Biological rhythms are also classified according to their relationship with periodic changes in geophysical factors and are designated as functional (e.g. periodic changes in the intensity of transpiration and metabolism in plants, the rhythm of heart contractions, respiration, cycles of motor activity - walking). If the period of the rhythms coincides with the periods of geophysical cycles or is close to or a multiple of them, then they are called adaptive or ecological. These include daily, tidal, monthly and seasonal rhythms. In biology, adaptive rhythms are considered from the standpoint of the general adaptation of organisms to the environment, and in physiology - from the point of view of identifying the internal mechanisms of such adaptation and studying the dynamics of the functional state of the organism over a long period. Exogenous, acquired (habitual) and endogenous rhythms are distinguished by the degree of dependence on external periodic processes. The disease most often worsens

in spring and autumn. Worsening of the course of hypertension is more often observed in winter, the development of acute myocardial infarction is most likely in autumn and winter. The peak number of suicides in most countries falls on May. Thus, seasonal prevention of many diseases is promising. Biological rhythms determine the non-stationarity of the effects of drugs and their pharmacokinetic parameters. For example, morning administration of diazepam, amitriptyline, propranolol, nitrosorbide is accompanied by more complete and rapid absorption than evening or night administration. Cytostatics are more effective at those hours when mitotic activity is maximal (for tumors of the blood system, this is the second half of the day). Data have been obtained that the administration of cytostatics at 2 p.m. and 7 p.m. accelerates the onset of remission in acute leukemias compared to standard treatment regimens. The maximum effect of diuretics occurs in the first half of the day. The highest efficiency of taking glucocorticoids is noted in the morning hours due to increased sensitivity of hormonal receptors. On the other hand, drugs can affect B.r. Thus, one of the mechanisms of action of caffeine is reduced to inhibition of the enzyme phosphodiesterase, which causes an increase in the frequency of nerve cell discharges. Antibiotics, inhibiting protein synthesis in ribosomes, disrupt the rhythm of bacterial cell division. In modern conditions, chronobiology, chronomedicine and chronopharmacology are gaining increasing importance. Their development allows us to better understand the deep mechanisms of life and improve the quality of prevention and treatment of many diseases.

It should be noted that the potential (determined) effectiveness of drugs may change when stored in inappropriate (not specified in the NTD) conditions.

Materials for activating higher education students during lectures: questions, situational tasks, etc.:

Question:

1. Medicinal substances that are well soluble and well absorbed. For such substances, it is not necessary to determine the “dissolution” test, because the active substance goes into solution within a few minutes.
2. Medicinal substances that dissolve well but are poorly absorbed.

3. Medicinal substances that are poorly soluble but well absorbed.

General material and methodological support for the lecture:

- educational premises – the department's auditorium;
- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials – presentation, slides.

Questions for self-control:

1. The pharmacist carefully ground bismuth subnitrate with some water, added the rest of the water. He mixed some of the prepared suspension with sugar syrup and transferred everything to a dispensing bottle. Give a critical assessment of his actions.

List of sources used:

Main literature:

25. Gladyshev V.V., Davtyan L.L., Drozdov A.L., Byryuk I.A., Kechyn I.L. Biopharmacy. Textbook for pharmaceutical universities and faculties. 2nd ed. Edited by V.V. Gladyshev. Dnipro: ChMP "Economica". 2018.- 250 p.

26. Guideline ST-N MOZU 4242-7.1:2005 "Medicines. Guideline on clinical trials. Bioavailability and bioequivalence studies" - Kyiv, 2018.

27. Guideline ST-N MOZU 4242-7.1:2005 "Medicines. Guideline on clinical trials. Bioavailability and bioequivalence studies" - Kyiv, 2018.

28. Guideline ST-N MOZU 42-7.2:2018 Medicinal products for bioequivalence studies. – Kyiv, 2018. – 77 p.

29. Modern pharmaceutical technologies: teaching aids for laboratory classes of undergraduates of full-time, evening and correspondence forms of study in the specialty 8.110201 "Pharmacy" / edited by O.A. Ruban. – Kh.: Publishing house of the National University of Physics and Technology, 2016. – 256 p.

30. Biopharmacy: textbook / edited by: Borysyuk I.Yu., Fizor N.S., Akisheva A.S. Odesa, ONMedU, 2020. - 98 p.

Additional literature:

5. Pharmaceutical Encyclopedia / Chairman of the Editorial Board and author of the foreword V.P. Chernykh. – 3rd ed. – K.: “MORION”, 2016. – 1952 p.

6. Polovko N.P., Vyshnevska L.I., Shpychak O.S. Assessment of biopharmaceutical factors in the development and production of new drugs // Modern advances in pharmaceutical technology and biotechnology: collection of scientific papers, issue 2. – X.: Publishing house of the National University of Physics and Technology, 2017. – pp. 155-160.

Excipients in the production of medicines: a teaching aid for students of higher pharmaceutical schools /O. A. Ruban, I. M. Pertsev, S. A. Kutsenko, Yu. S. Masliy; edited by I. M. Pertsev. Kh.: Zoloti storyni, 2016. 720 p.