ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF DRUGS TECHNOLOGY

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«29» august 2022 y.

METHODICAL DEVELOPMENT OF PRACTICAL LESSON

Course: 5 Faculty: Pharmaceutical

Course Biopharmacy

Practical lesson №1 Topic: " **Biopharmacy as a scientific and educational discipline. Subject and tasks of biopharmacy. The main indicators of bioavailability of drugs. Factors that affect the bioavailability of drugs. "**

The practical lesson was developed by:
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The practical lesson was discussed at the methodical meeting of the department
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Protocol № 1

Odesa – 2022

Purpose: Substantiation of the purpose and objectives of biopharmacy, history of its origin, basic terms and concepts, the concept of therapeutic inequivalence of drugs, purpose and objectives of biopharmacy as a new scientific field, as well as the definition of biopharmaceutical factors and their role in creating new drugs.
Basic concepts: Biopharmacy, Bioavailability, Minimum effective concentration, Minimum toxic concentration, AUCA.
Equipment: according to the requirements of Good Pharmacy Practice (GPP).
Study time: 4.0

Plan

I. Organizational moment.

II. Control of basic knowledge

2.1. Requirements for theoretical readiness of students to perform practical classes (knowledge requirements, list of didactic units):

Requirements for theoretical knowledge:

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

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

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

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

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

The term "biopharmacy" first appeared in scientific pharmacy in the United States in the 60s of the 20th century and soon gained general international recognition.

The word "pharmaceutics", used in English literature, is not synonymous with "pharmacy", its designation - galenic pharmacy. The literal translation of "biopharmaceuticals" and the adjective "biopharmaceutical" formed from it are the terms "biogalenics" and "biogalenic".

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

In this short word, biopharmacy successfully and quite fully defines the complex of dependencies that link the drug substance and the therapeutic effect of the prepared drug.

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

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

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

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

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

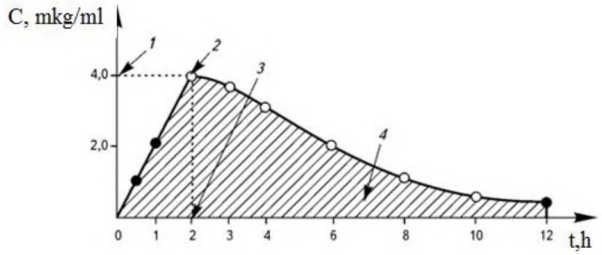


Fig.1. The main parameters of pharmacokinetics used in the study of bioavailability of drugs.

1 - maximum concentration (C);

2 - peak;

3 - time (t) to reach maximum concentration;

4 - area under the curve "concentration ■ - time".

The practical value of the concentration peak is well illustrated in Fig. 2, in which two curves depict the kinetics of the concentration in the blood of the same substance contained in different dosage forms (A and B). The horizontal line indicates the minimum effective concentration (IEC) at which this substance has a therapeutic effect

(4 μg / ml). It is seen that in dosage form B, the drug substance, although completely absorbed, but does not have a therapeutic effect, because it does not reach the MEC.

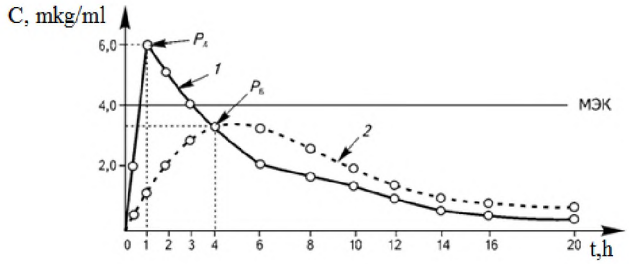


Fig. 2. The dynamics of the concentration (C) of the drug after its use in two dosage forms:

1 - dosage form A; 2 - dosage form B;

P is the peak concentration of the drug substance; IEC - the minimum effective concentration

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

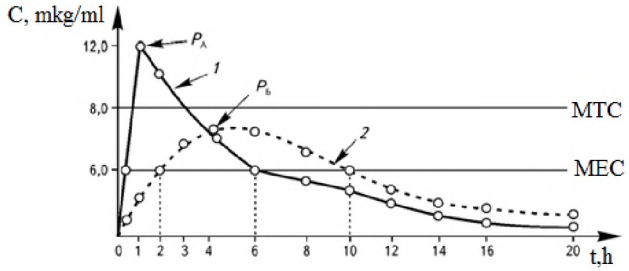


Fig. 3. Determination of the minimum toxic concentration (ITC) and the minimum effective concentration (IEC) of the drug by the dynamics of its concentration in the blood when used in two dosage forms (A and B):

1 - dosage form A;

2 - dosage form B;

P is the peak concentration of the drug substance; AUCA = 34.4 (μg / ml) -year, AUCB = 34.2 (μg / ml) -year

The second important parameter is the time to reach the maximum concentration of the substance in the biological fluid P, as it reflects the rate of absorption of the substance and the rate of onset of therapeutic effect. From fig. 3. it follows that P when using dosage form A is achieved after 1 hour, and in dosage form B - after 4 hours. Suppose that in this case the drug is a hypnotic. It reaches the minimum therapeutic concentration and has a soporific effect in the first case after 30 minutes, and in the second case - only after 2 hours. At the same time, the effect of the hypnotic substance

in the first case (when using dosage form A) lasts 5.5 hours, in the second case (when using dosage form B) lasts 8 hours.

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

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

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

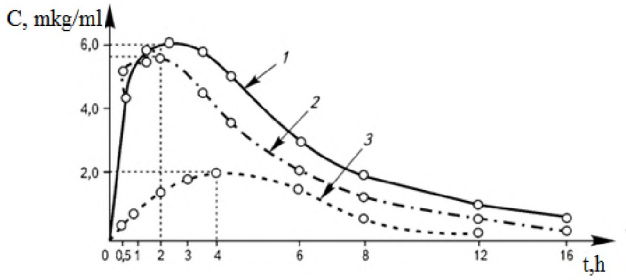


Fig. 4. The relative bioavailability of the drug when used in three dosage forms:

1 - dosage form A;

2 - dosage form B;

3 - dosage form B; AUCA = 39.9 (μg / ml) -year, AUCB = 32.2 (μg / ml) -year, AUCB = 14.0 (μg / ml) -year

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

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

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

Factors affecting the bioavailability of drugs

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

When the drug transitions to a soluble, absorbable form from the injection site, they have yet to cross a number of membranes before entering the capillary bed and entering the systemic circulation. Depending on the place of absorption, penetration into the capillary bed is not always equivalent to entering the systemic bloodstream.

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

Influence of routes of administration on bioavailability

Oral route of administration of drugs

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

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

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

Many drugs taken after a meal can lose or significantly reduce activity by interacting with digestive juices.

Erythromycin, benzylpenicillin, pancreatin, pituitrin, insulin and a number of other drugs are inactivated under the influence of acidic environment and gastric enzymes. Hexamethylenetetramine is completely decomposed into ammonia and formaldehyde. Preparations of cardiac glycosides (lily of the valley, strophanthus, sea onion) are completely destroyed, and the most stable of them - preparations of foxglove - significantly reduced activity under the action of enzymes of the gastrointestinal tract. However, in the presence of proteolytic enzymes, tetracycline and isoniazid are absorbed more rapidly. Gastric juice stimulates the absorption and acetylation (transition to an inactive form) of sulfonamide drugs.

A serious obstacle to the absorption of many drugs is mucin, which is released after a meal and covers a thin, highly viscous film of the mucous membranes of the mouth, stomach and intestines. Streptomycin sulfate, atropine sulfate, belladonna preparations, scopolamine hydrobromide, platyphylline hydrotartrate, antispasmodic, aprofen, metacin form poorly absorbed complexes with mucin.

Bile increases the solubility of some fat-soluble substances (vitamins) and at the same time is able to form sparingly soluble and non-absorbable complexes with neomycin sulfate, polymyxin B sulfate. Bile acids can bind to sodium paraaminosalicylate, activated charcoal, white clay, and so on, and their deficiency leads to impaired absorption of other drugs (diphenine, rifampicin, butadione, etc.).

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

Influence of composition and temperature of food . The composition and temperature of food have a great influence on the effectiveness of drugs. Ordinary mixed food contains substances of plant, animal and mineral origin: proteins, fats, carbohydrates, amino acids, fatty acids, glycerin, tannins (in tea, persimmons), caffeine (in tea, coffee), serotonin (in nettles, peanuts, bananas) , pineapples), tyramine (in cheese, bananas, beans, herring, coffee, beer, wine, chicken liver), oxalates (in rhubarb, celery, sorrel, spinach), sterols, phytosterols, heavy metal ions and other chemically and pharmacologically active substances. In addition, various food additives are introduced into food: preservatives (sorbic, acetic, citric acid), antioxidants, emulsifiers, dyes, sweeteners, substances that can actively interact with drugs and affect their bioavailability - in some cases increase solubility and absorption drugs, in others, forming insoluble or sparingly soluble complexes (eg, proteins, tannins, dipeptides) with food ingredients, reduce their absorption.

Depending on the composition of food in different ways affects the peristalsis and secretory function of the digestive tract, which depends on the degree and rate of absorption of drugs.

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

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

The presence of a large amount of carbohydrates in food (sugar, candy, jam) slows down the motility of the stomach, delays the absorption of isoniazid, calcium chloride in the intestine. The effect of food carbohydrates can be indirect - through intermediate metabolism.

Food slows down the absorption of phenoxymethylpenicillin, oxacillin sodium, ampicillin, rifampicin, lincomycin hydrochloride, acetylsalicylic acid, glibenclamide, isoniazid, and others. Sulfur-containing drugs interact with heavy metal ions that are constantly present in food to form insoluble compounds with low bioavailability. The absorption of drugs from the digestive tract is delayed by low-molecular products of hydrolysis of nutrients: glucose, amino acids, fatty acids, glycerin, as well as sterols contained in food. Foods rich in vitamins and minerals have a pronounced effect on drug metabolism. Foods containing ascorbic acid stimulate the function of oxidases, accelerating the metabolism of drugs, and sometimes reduces their toxicity; food containing folic acid accelerates the metabolism of pyridoxine hydrochloride, reduces the effectiveness of levodopa. In patients who eat foods rich in vitamin K (spinach, white cabbage), significantly changes the prothrombin time, as well as the metabolism of anticoagulants, barbiturates, nozepam, phenacetin. The temperature of food also has a certain effect. Very cold (below 7 ° C), as well as excessively hot (above 70 ° C) food and drinks cause digestive disorders. From cold food the excretory function amplifies and acidity of contents of a stomach with the subsequent decrease and weakening of digestive ability of gastric juice increases. Excessively hot food leads to atrophy of the gastric mucosa, accompanied by a sharp decrease in the secretion of enzymes of the gastrointestinal tract. These changes in the secretion of the gastrointestinal tract in turn affect the bioavailability of drugs.

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

diacarb, nevigramon nitrofurans, salicylates. Fruit juices and beverages contain tannins, which besiege digitoxin, caffeine-sodium benzoate. The tonic drinks "Baikal", "Pepsi-Cola" include iron ions, which in the gastrointestinal tract form insoluble complexes with lincomycin hydrochloride, oleandomycin phosphate, tetracycline hydrochloride, sodium thiosulfate, uniate thiosulfate, uni. Widely used for these purposes, tea and coffee, containing, in addition to caffeine and theophylline, tannin and various tannins and can enhance the pharmacological effect of paracetamol, acetylsalicylic acid, form insoluble compounds with aminazine, atropine sulfate, haloperidol, hydrophilicide and hydrodes. . Therefore, it is not recommended to drink the drugs they take, except for sleeping pills, which drink 1/2 cup of warm, weak and unsweetened tea.

When sweetening drugs with syrups or milk sugar, the absorption of isoniazid, ibuprofen, calcium chloride, tetracycline hydrochloride, furosemide is sharply slowed down. Some drugs that have an irritating effect on the mucous membrane of the gastrointestinal tract, washed down with milk. Medicines are mixed with milk and dairy products for infants. Milk can change the drug substance and reduce the bioavailability of, for example, benzylpenicillin, cephalexin. A glass of whole milk reduces by 50-60% the concentration in the blood of tetracycline hydrochloride, oxytetracycline and metacycline hydrochloride, having a slightly smaller effect on the absorption of doxycycline hydrochloride. It is not recommended to drink milk with drugs that have acid-resistant coatings (enteric), such as bisacodyl, pancreatin, pancurman, because of the risk of premature dissolution of the protective shell. For the same reason it is inexpedient to wash down the specified preparations with alkaline mineral waters (Borjomi, Luzhanskaya, Svalyava, Smirnovskaya). On the contrary, alkaline mineral waters should be washed down with pancreatin, PAS, salicylates, citramon, phthazine, novocephalin and sulfonamides. The latter are acetylated in the body, and acetylated compounds in a neutral and acidic environment do not dissolve and precipitate in the form of stones. In an alkaline environment, acetylated sulfonamides are in a dissolved state and are easily excreted from the body.

Children taking drugs mixed with milk can lead to a violation of the accuracy of their dosage. Drink milk those drugs that irritate the surface of the mucous membrane of the gastrointestinal tract, do not change their activity at milk pH (6.4), do not bind to milk proteins and calcium (butadione, indomethacin, prednisolone, reserpine, trichopol, salts potassium, nitrofurans, vibramycin, ethoxide, mefenamic acid, iodine preparations, etc.). Some patients, taking medication, do not drink them at all, which is not recommended, because the capsules, tablets, pills, sticking to certain parts of the inner surface of the esophagus and gastrointestinal tract, are destroyed before reaching the site of absorption. In addition, they cause irritation at the site of adhesion, and the lack of sufficient fluid delays their absorption.

Influence of food (diet) . In the vast majority of cases, when prescribing drugs, it is necessary to select an appropriate diet so that food components do not change the bioavailability of drugs and do not cause unwanted side effects.

Irrational nutrition during the illness affects the entire course of treatment, can contribute to disease of certain organs and cause relapses. For example, an excess of sodium chloride in food contributes to high blood pressure, animal fats - the development of atherosclerosis, diseases of the digestive system.

Irrational diet can lead to inactivation of drugs, the formation of complexes, as, for example, in the case of a combination of calcium ions (cheese, yogurt, milk) with tetracyclines. At the same time, eating vegetables and fruits can regulate intestinal function, supplement the deficiency of macro- and microelements, volatile oils, essential oils and aromatic substances that affect the immune status, regulate the secretion of digestive glands, lactation, etc. Potassium deficiency in the body can be filled with dried apricots, raisins, beets, apples, pumpkins, dried fruits. To increase the effectiveness of antianemic drugs can be the use of foods high in iron (strawberries, apricots, apples, beets, pomegranates) in combination with ascorbic acid. In the treatment of inflammatory diseases of the kidneys and urinary tract, the use of watermelons is recommended. The use of low-calorie vegetables (cabbage, carrots, turnips, cucumbers, tomatoes, eggplant, zucchini, etc.) reduces the caloric content of the diet, prevents the absorption of cholesterol, enhances its excretion from the body, helps to empty the intestines. The correct selection of therapeutic nutrition when prescribing drugs can significantly increase their bioavailability, and therefore reduce their dosage, avoid unwanted side effects while maintaining proper effectiveness.

Rectal route of administration of drugs

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

At a rectal way of introduction bioavailability can be influenced by individual features of blood supply of a rectum, a condition of its mucous membrane (with age at systematic use of laxatives and systematic lack of vegetable fiber in food the functional condition of a mucous membrane worsens). The glands of the mucous membrane of the colon secrete a liquid alkaline secretion (pH sometimes exceeds 9). Changes in intestinal pH, as well as changes in gastric pH, significantly affect the degree of ionization and absorption of drugs.

The process of intestinal absorption is influenced by the autonomic nervous system (adrenergic agonists stimulate absorption, and cholinergic antagonists - secretion), endocrine system, biologically active peptides. Endocrine, autonomic

nervous and neuropeptide systems also regulate the motor activity of the colon, which, in turn, determines the duration of the drug in the intestine. In addition, a number of diseases of the rectum (hemorrhoids, cracks in the anorectal region, proctitis) impair the bioavailability of drugs administered rectally.

Inhalation route of drug administration

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

Influence of body temperature and environment

Body temperature and environment have a significant impact on the course of physiological and biochemical processes in the body. In the conditions of increase of temperature and humidity of air heat transfer from an organism to environment becomes difficult and can be carried out only at power of mechanisms of physical thermoregulation (expansion of peripheral vessels, strengthening of sweating). Difficulty in heat transfer leads to overheating of the body. The increase in body temperature is accompanied by a sharp excitation of the CNS, respiration and blood circulation, increased metabolism. Excessive sweating leads to dehydration, blood clotting, decreased volume of circulating fluid, electrolyte imbalance. All this, in turn, affects the processes of absorption, distribution and metabolism of drugs, their bioavailability after oral administration. Even greater changes in the functions of organs and systems develop with fever. The excitability of the respiratory center changes, which can cause a decrease in alveolar ventilation and partial tension of oxygen in the blood. The heart rate increases. Spasm of the vessels of the skin at the beginning of the development of fascia increases the total peripheral vascular resistance of blood flow, which causes an increase in blood pressure. Later, due to vasodilation, increased sweating and fluid loss in the second stage of fever, blood pressure drops, sometimes significantly. The onset of fever is also accompanied by significant changes in metabolism: increased breakdown of muscle protein, increased gluconeogenesis, changes in protein synthesis in the liver, the rate of biochemical processes in hepatocytes, cells of other organs.

With increasing absorption temperature, metabolism and transport of drugs proceed faster, and with decreasing - slow down. Local cooling of body tissues leads to vasospasm, resulting in a sharp slowdown in absorption, which should be borne in mind when local administration of the drug. The influence of temperature factor on the pharmacokinetics of drugs must be taken into account in clinical practice in cases where drugs are prescribed to patients with severely impaired thermoregulation.

Influence of age and sex

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

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

When inhaled, the introduction of the mucous membrane of the respiratory tract is also easily irritated and responds to it with abundant secretion, which significantly complicates the absorption of drugs. At the same time, when applying the drug to the skin of children, it should be borne in mind that it is much easier than in adults, the absorption of any substances. Differences in the action of drugs due to sex have been noticed since ancient times. The residence time of drugs in the body of women is much longer than in men, respectively, and the level of concentration of drugs in the blood of women is higher. It is believed that this is due to the relatively high content of "inert" adipose tissue in women, which plays the role of depot.

Influence of biorhythms

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

The basis of the biological rhythm of the body is the rhythm of metabolism. In humans, metabolic (mostly catabolic) processes that provide the biochemical basis of activity reach a minimum at night, while biochemical processes that provide accumulation and energy resources reach a maximum during the day. The main factor that determines the biological rhythm is the conditions of existence of the organism. Seasonal and especially circadian rhythms act as if the conductors of all the oscillatory

processes of the body, and therefore the attention of scientists is most focused on the study of these rhythms.

Accounting for physiological rhythms is a prerequisite for justifying the optimal time of medication. The experience of pharmacotherapy has necessitated the consumption of drugs in a certain period of time of day, month, season and so on, for example, taking sleeping pills or sedatives in the evening or at night, tonics and stimulants - in the morning or afternoon.

The rapid development of medicine and biology in the second half of the XX century allowed to establish, explain and predict the influence of time factors or, rather, the phase of the body's biorhythm during which drugs were used, its effectiveness, increase side effects and identify the mechanism of this effect. The question of the effect of drugs on the body depending on the time of day, seasons of the year is studied by chronopharmacology, which establishes the principles and rules of rational administration of drugs, seeks schemes for their use in the treatment of desynchrony. Chronopharmacology is closely related to chronotherapy and chronobiology. The task of chronotherapy in general can be formulated as the organization of the treatment process based on the individual biorhythmological status and its correction using all the methods available in modern medicine. At inconsistency of biorhythms of an organism with time sensors desynchronosis which is a sign of physiological discomfort develops. It always occurs when moving from west to east or from east to west, in living conditions with unusual modes of work and rest (shift work), the exclusion of geophysical and social time sensors (polar day and night, space travel, deep dives), the impact stress factors (cold, heat, ionizing radiation, biologically active substances, mental and muscular tension, viruses, bacteria, food composition). Therefore, the rhythms of healthy and sick people are significantly different.

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

The intensity of absorption, transport and decomposition of various drugs is subject to significant fluctuations during the day. For example, the half-life of prednisolone when administered to patients in the morning is approximately 3 times longer than when administered in the afternoon. Changes in the activity and toxicity of drugs may be associated with the periodicity of liver enzyme systems and renal

function. The intensity of metabolic reactions and the complex interaction of the endocrine glands play a significant role in the daily changes in pharmacokinetics. An important factor is the susceptibility of biosystems to interaction. Due to the frequency of absorption, conversion, excretion of drugs and sensitivity, the question of the synchrony of time of the greatest activity of the drug and the maximum sensitivity to it is relevant. If these maxima coincide, the effectiveness of the drug will increase significantly.

Because during the acrophase (maximum function time) of daily, seasonal or other rhythms, increased efficiency or activity of systems, as well as the greatest sensitivity of cells and tissues to substances, the introduction of drugs before or at the beginning of acrophase allows to achieve a therapeutic effect in smaller doses and reduce their negative side effects.

Influence of magnetic field and meteorological factors

- significantly affect the higher centers of nervous and humoral regulation, biocurrents of the heart and brain, the permeability of biological membranes. Men are more sensitive to the activity of the Earth's magnetic field than women. Patients with disorders of the nervous and cardiovascular systems are most sensitive to magnetic storms in the Earth's atmosphere. In the days of magnetic storms, they have an exacerbation of the disease, there is a hypertensive crisis, cardiac arrhythmias, angina attacks, reduced efficiency, and so on. In turn, changes in the work of the heart, the intensity of blood circulation and, above all, the permeability of biomembranes can significantly change the bioavailability of drugs with different routes of administration, both in the direction of its reduction and increase.

Meteorological factors (absolute humidity, atmospheric pressure, wind direction and strength, average daily temperature, etc.) affect the elasticity of blood vessels, viscosity and clotting time. A decrease in atmospheric pressure by 1.3-1.6 kPa (10-12 mm Hg) can lead to vascular disorders, rainy weather causes depression. Thunderstorms and hurricanes have a particularly adverse effect on human health. In a cubic centimeter of air usually consist of 200 to 1000 positive and negative ions. They affect the intensity of the heart, respiration, blood pressure and metabolism. A high concentration of positive ions causes depression, shortness of breath, dizziness, decreased overall tone, fatigue and fainting. And the increased concentration of negative ions has a beneficial effect on the body: it improves mental state and mood. Of course, this is due to the fact that they prevent the formation of serotonin (a neurotransmitter associated with the sensation of pain). During a thunderstorm, the number of negative ions in the atmosphere increases. The state of the central nervous system, the general tone of the body regulate the intensity of blood circulation in various organs and tissues and to some extent the intensity of biotransformation of drugs into metabolites. This is reflected in changes in the absolute and overall bioavailability of drugs.

Influence of pathological processes and individual features of an organism

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

Many pathological processes lead to a violation of the barrier function of biological membranes, changes in the permeability of biological barriers.

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

The presence of pathological processes causes altered reactivity of cells and tissues in relation to drugs (often in combination with the effect on pharmacokinetics). For example, stress can increase the process of excitation and weaken the inhibition in the cerebral cortex. In diseases of the kidneys there is a slowing of excretion, in diseases of the gastrointestinal tract and liver, the processes of absorption and distribution of drugs are disrupted.

Individual sensitivity to drugs, such as butadione 6-7 times, to dicoumarin 10-13 times can vary widely. Differences in sensitivity to drugs are associated with different intensities of their metabolism due to genetic factors, with individual characteristics of the receptor mechanism.

Influence of alcohol

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

At simultaneous appointment of drugs and ethyl alcohol their interaction can occur at once on several mechanisms that has important clinical value. The effect of the interaction of alcohol and drugs on the body depends on their concentration in the blood, pharmacodynamic properties of drugs, dose and time of administration. In small

quantities (up to 5%) alcohol increases the secretion of gastric juice, and in concentrations of more than 30% clearly reduces its secretion and inhibits digestive processes. The absorption of many drugs increases as a result of increasing their solubility under the influence of ethanol. Possessing lipophilic properties, alcohol facilitates the penetration of drugs through the phospholipid membranes of cells, and in higher concentrations, affecting the gastric mucosa, further increases the absorption of drugs. As a vasodilator, ethanol accelerates the penetration of drugs into tissues. Inhibition of many enzymes, which occurs with alcohol consumption, enhances the effect of drugs and leads to severe intoxication at the usual therapeutic doses. This applies to neuroleptics, analgesics, anti-inflammatory, hypnotics, diuretics, as well as antidepressants, insulin, nitroglycerin. The combination of the above groups of drugs and alcohol is accompanied by severe poisoning, often fatal. Death occurs due to a sharp suppression of vital centers of the brain, respiratory and cardiovascular. Alcohol potentiates the action of anticoagulants (acetylsalicylic acid, dicoumarin, neodycoumarin, sincumar, etc.). It so intensifies their action that there can be heavy bleeding, hemorrhage in internal organs and a brain.

Alcohol has a multifaceted effect on the absorption and metabolism of hormonal drugs. In particular, the hypoglycemic effect of insulin and synthetic drugs for the treatment of diabetes is enhanced, resulting in the development of diabetic coma. Especially unacceptable use of alcohol and drugs that affect the function of the central nervous system: sedatives, hypnotics, anticonvulsants (bromides, chloral hydrate, diphenine, etc.), as well as tranquilizers (chlordiazepoxide, diazepam, oxazepam, meprobamate and others) . It is not recommended to drink alcohol at the same time as nitroglycerin, as this may lead to collapse. Antidiabetic sulfamides, chloramphenicol, griseofulvin, metronidazole give antabuse effect (teturam-alcohol reaction). Under the influence of alcohol, the effectiveness of vitamin therapy decreases. There is inactivation and reduction of the concentration of antibiotics in the tissues. Alcohol enhances the side effects of sulfonamides and anthelmintics, it is incompatible with anticonvulsants. From the given examples the negative effect of alcohol at treatment by medicines is visible. But in all cases, the effectiveness of pharmacotherapy is reduced or even lost.

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

cigarettes contain coumarins, which can enhance the effect of anticoagulants - coumarin derivatives

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

The effect of drug interactions on bioavailability by such interactions 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. The drug is also able to interact with itself. When re-ingested, it can induce microsomal oxidation of a foreign substance and thus accelerate its own metabolism (a classic example is barbiturates). Medications can also worsen their own effects on organs (an example is the emergence of opiate tolerance). In clinical practice, the phenomenon of drug interaction must be constantly considered for the following reasons: - almost every hospitalized patient during a hospital stay receives several drugs (sometimes up to 40! Substances prescribed to one patient), numerous finished drugs are a combination of two or more substances, a significant number of patients in outpatient treatment, consume drugs such as laxatives, analgesics, hypnotics, etc. The doctor can find out about it only after careful collection of medical history, some patients seek help from several doctors at once, without mentioning the recommendations of other doctors and their appointments, the elderly often suffer from several diseases, which leads to the objective need to use several different drugs. Of all possible interactions, only about 1-10% pose a risk of adverse effects, but the risk of mutual reduction in efficiency is significantly higher. New reports of drug interactions should always be treated with great care. The number of possible interactions at first glance is extremely large, although not everyone has clinical significance. There are three types of interactions: pharmaceutical, pharmacokinetic and pharmacodynamic.

Didactic units:

- Definition of biopharmacy
- Biological availability
- Bioavailability factors
- Ways of drug administration

2.2. Questions (tests, tasks, clinical situations) to test basic knowledge on the topic of the lesson:

Answer the question:

1. What does Biopharmacy study? The purpose and objectives of Biopharmacy?
2. Biopharmaceutical classification system of drugs .
3. What is the bioavailability of drugs, how to determine the bioavailability of drugs?
4. What parameters are important in determining the bioavailability of drugs?
5. Identify the factors that affect the bioavailability of drugs.

6. How does the bioavailability differ by different routes of administration: parenteral, oral, rectal, inhalation route of administration?

III. Formation of professional skills, abilities:

3.1. content of tasks:

Write recipes in Latin according to the current orders of the Ministry of Health of Ukraine. Justify the technology and make the appropriate calculations. Write a written control passport.

Take: Anesthesia 2.0
Boric acid 1.5
Tar 5.0
Castor oil 2.5
Ethyl alcohol 96% to 50 ml
Mix. Come on. Mark. Apply to hands.

3.2. recommendations (instructions) for performing tasks

4. Rp .: Anaesthesini 2,0
Boric acid 1.5
Picis liquidae Betulae 5,0
Oiei Ricini 2,5
Spiritus aethylici 96% ad 50 ml
Misce. Yes. Sign. Apply to hands.

Liquid dosage form for external use - alcohol liniment.

The composition of this recipe includes ingredients that are soluble in ethyl alcohol. Ethyl alcohol is dosed by volume, so the calculations are performed for castor oil and tar. The density of castor oil is 0.950 g, tar - 0.936. The volume of castor oil should be 2.6 ml (2.5: 0.950 = 2.6 ml), the volume of tar - 5.3 ml (5: 0.936 = 5.3 ml). To prepare this formulation of ethyl alcohol, it is necessary to take such an amount that after dissolving the anesthetic and boric acid, the volume of the alcohol solution does not exceed 42 ml (50 - 7.9 = 42.1 ml). 2.5 g of castor oil and 5.0 g of tar are weighed into a tared vial for tempering, an alcoholic solution of anesthetic 2.0 and boric acid 1.5 g, previously weighed into a stand with 95% ethyl alcohol 42.1 ml, is added. Shake thoroughly to a complete solution of ingredients. Make out labels "Keep in a cool place", "Shake before vacation", write a signature.

PPK

Date № recipe
Taken: Anaesthesini 2.0
Acidi borici 1.5
Spiritus aethylici 95% 42.1 ml
Oiei Ricini 2.5
Picis liquidae Betulae 5.0

In $_{total}$ = 50 ml
Prepared - (signature)
Checked - (signature)

3.3. requirements for work results, including before registration;
In accordance with the recommendations (instructions) for the tasks.

3.4. control materials for the final stage of the lesson: tasks, tasks, tests, etc.

1. In which years of the twentieth century in the scientific literature used the term "biopharmacy"?
   A. 50s
   B. 60s
   C. 80s
   D. 90s
   E. 40s
2. What is the known fact that underlies the emergence of biopharmacy?
   A. establishment of pharmacological incompatibility of drugs
   B. detection of technological incompatibility of drugs
   C. detection of therapeutic drug inequality
   D. detection of synergism of action
   E. detection of antagonism of action
3. Enter the name of the licensed drugs
   A. brandy
   B. generics
   C. generics
   D. copies
   E. forgeries
4. Indicate which term corresponds to the following statement: "Biologically active part of the drug that is responsible for the therapeutic effect."
   A. effective substance
   B. efficiency
   C. distribution
   D. biotransformation
   E. system availability
5. Indicate which term corresponds to the following statement: "Biologically active part of the drug that is responsible for the therapeutic effect."
   A. effective substance
   B. efficiency
   C. distribution
   D. biotransformation
   E. system availability

6. Indicate which term corresponds to the following statement: "The ability of a drug substance or drug to achieve the desired effect."
   A. effective substance
   B. bioavailability
   C. efficiency
   D. biotransformation
   E. clinical equivalent
7. Indicate which term corresponds to the following statement: "A condition that allows a drug substance introduced into the body to reach the site of exposure."
   A. therapeutic inequality
   B. equivalence
   C. pharmaceutical inequality
   D. bioavailability
   E. pharmaceutical equivalent
8. Indicate which processes relate to the direct study of biopharmacy?
   A. derivation, effect
   B. release of the substance from the dosage form, absorption
   C. metabolism, excretion
   D. absorption, distribution, metabolism, excretion
   E. destruction
9. Indicate which processes relate to the direct study of biopharmacy?
   A. derivation, effect
   B. release of the substance from the dosage form, absorption
   C. metabolism, excretion
   D. absorption, distribution, metabolism, excretion
   E. LADMER
10. Hard gelatin capsules are designed for dosing of loose powder, granular and microencapsulated substances. They have the shape of a cylinder and consist of two parts. Name them:
   A. stem and capillary
   B. body and capillary
   C. body and lid
   D. body and body
   E. pulp and lid
   10.1.

IV. Summing up

Main:

1. .Biopharmaceutics. Збірник текстів лекцій./ Tikhonov A.I., Yarnykh T.G., Yuryeva A.B., Podorozhna L.N., Zuykina S.S., НФаУ Оригінал, 2011. – 140 с.
2. Biopharmaceutics. Практикум / Tikhonov A.I., Bogutskaya Ye.Ye., Yarnykh T.G., Kotenko A.M., Garkavtseva O.A., НФаУ Оригінал, 2011. – 80 с.

3. Janicki S., Sznitowska M., Zielinski W. Dostepnosc farmaceutyczna I dostepnosc biologiczna lekow. – Warshawa, 2001.–242 s.
4. Biopharmaceuticals: Biochemistry and Biotechnology, 2nd Edition. – 2013. – 544 p

ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF DRUGS TECHNOLOGY

APPROVE
Head of Department

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

METHODICAL DEVELOPMENT OF PRACTICAL LESSON

Course: 5 Faculty: Pharmaceutical

Course Biopharmacy

Practical lesson №2 Topic: «**The influence of the physical state of drugs on the rate of their release from dosage forms. »**

The practical lesson was developed by:
Ph.D., Assoc.

_____ (Fizor. N.S.)
signature
The practical lesson was discussed at the methodical meeting of the department
«29» august 2022y.
Protocol № 1

Odesa – 2022

The purpose of the lesson: the formation of knowledge, skills, practical skills to study the effect of the degree of grinding of streptocide and polymorphic modifications of zinc-insulin on the rate of their release with the relative dosage form.
Basic concepts: polymorphism, physical state, optical activity, solubility, surface tension, amorphous modification.
Equipment: according to the requirements of Good Pharmacy Practice (GPP).
Study time: 2.0

Plan

I. Organizational moment.
II. Control of basic knowledge
2.1. Requirements for theoretical readiness of students to perform practical classes (knowledge requirements, list of didactic units):
Requirements for theoretical knowledge:

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

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

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

Grinding of medicinal substances is the simplest, but at the same time one of the most important technological operations performed by the pharmacist in the preparation of various dosage forms. The dispersion of the drug affects not only the flowability of powdered materials, bulk, homogeneity of mixing, dosing accuracy. It is especially important to note that the particle size depends on the speed and completeness of absorption of the drug, as well as its concentration in biological fluids, mainly in the blood, in any way of its appointment in the form of various dosage forms.

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

The effect of particle size on therapeutic activity was first proven for sulfonamide and then steroid drugs, as well as derivatives of furan, salicylic acid, antibiotics and now - for anticonvulsants, analgesics, diuretics, antituberculous, antidiabetic and antidiabetic drugs. Thus, it was found that when using micronized sulfadiazine, its

maximum concentration in human blood is reached 2:00 earlier than when it is prescribed in the form of a powder of the usual degree of grinding. The maximum concentrations of sulfadiazine in the blood are 40% higher, and the total amount of absorbed substance is 20% higher. The drug calciferol is able to be absorbed and have a therapeutic effect only when the particle size is less than 10 microns.

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

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

For example, AI Tentsova found that the release of sulfonamides, prednisolone, hydrocortisone, salicylic acid from ointments and their absorption through the skin are directly dependent on the particle size. VM Gretsky proved that streptocide, norsulfazole, anesthesia, grinding to 5-18 microns, are absorbed from ointments through the skin of rabbits in much larger quantities compared with substances crushed to 150-180 microns.

However, the choice of the degree of grinding of the drug must be scientifically justified. The desire to obtain micronized powder in each case cannot be considered, because in some situations a sharp decrease in the particle size of the drug can cause inactivation of the substance, its rapid excretion from the body or may have undesirable (toxic) effects on the body and reduced stability. In particular, with a sharp increase in the degree of dispersion of penicillin and erythromycin, their antimicrobial activity decreases when taken orally. This is due to increased processes of their hydrolytic destruction or reduced their stability in the presence of food juices, as well as increasing the contact surface of the drug with biological fluids.

Therefore, it is necessary to strictly regulate the particle size of the substance in the development of analytical regulations (AND) for drugs.

Thus, the drug substance in the drug should have the optimal degree of grinding, which depends on its bioavailability.

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

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

It is known that polymorphic modifications form most chemicals, including drugs. Since the discovery of the Devi carbon polymorphism (1809) (graphite, coal, and diamond), the transitions of some polymorphic modifications to others have been studied in detail. As emphasized by research, the chemical composition remains

unchanged, which is taken mainly for quality assessment. An overview of the study of polymorphism in drugs is presented in the works of AI Tentsova, Haleblein, Boucher, Halabal.

Particles of drugs in powdery solid state have a different structure (crystalline or amorphous), which depends on the molecular structure of a substance. Electron microscopic studies have shown that drugs 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 crystallization. The amorphous state is less common. Any drug substance under appropriate conditions (solvent, temperature, pressure, etc.) crystallizes in a certain system and has certain physicochemical characteristics (solubility, melting point, specific surface area, strength, shape and particle size, etc.). When conditions change, the substance crystallizes in another system and has other physicochemical characteristics and, accordingly, other indicators of bioavailability. The physical characteristics of powders in the existing AND, such as "crystalline", "fine crystalline", "amorphous", "light powder", are sufficient for the technological process, but to identify their impact on therapeutic activity requires more accurate definitions given by crystal chemistry.

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

The formation of various polymorphic modifications can occur in both liquid and soft dosage forms (for example, when replacing solvents; when introduced into liquid or soft dosage forms of various excipients; during drying, purification, preparation of drugs and in the process of their storage).

The phenomenon of polymorphism among drugs is characteristic of salicylates, barbiturates, sulfonamides, hormonal agents. For most modifications there are no special names and they are denoted by the letters a, (3, etc. or the numbers I, II, III, etc.

Examples of polymorphic modifications of drugs are many. Thus, there are two polymorphic modifications of acetylsalicylic acid, one of which is biologically more active than the other 1.5 times. Chloramphenicol has four polymorphic forms, of which one has 100% activity, phenobarbital has eleven, testosterone has six, etc. Amorphous modification also differs in its properties from crystalline. For example, novobiocin exists in crystalline and amorphous modifications. The amorphous form dissolves 10 times faster than the crystalline one.

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

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

The dissolution process also affects the effectiveness of drugs.

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

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

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

Usually more soluble substances are released faster from dosage forms, are absorbed faster, have a rapid therapeutic effect. At the same time, sparingly soluble drugs are more suitable for prolonging the action. To obtain such drugs, sometimes create an environment in which the drug does not dissolve. For example, when prescribing a solution of estradiol benzoate in oil, the drug has a therapeutic effect for three days, and when administered as an aqueous suspension - about three weeks.

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

The choice of excipients - solubilizers, co-solvents, surfactants, which in turn can increase the effectiveness of the drug, has a particularly significant effect on the solubility of drugs. This confirms the need for targeted use of excipients, as well as the choice of technological method of obtaining dosage forms.

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

1. By solubilization, which is defined as the process of involuntary transition to a stable solution using surfactants insoluble or sparingly soluble in this solvent compounds. In the domestic literature, this process is also called colloidal or bound solubility.

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

3. Using a hydrotrope, which provides hydrophilic complexes with organic substances containing electron-donating substituents - polar radicals. Examples of

hydrotropic substances are sodium salicylate, sodium benzoate, hexamethylenetetramine, novocaine, antipyrine, urea, glycerin, amino acids, hydroxy acids, proteins and others.

4. By the formation of salts and complexes:

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

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

b) to obtain aqueous solutions of polyene antibiotics (nystatin, levorin, etc.) use polyvinylpyrrolidone, with which they form complex compounds, where the water-insoluble substance and the solubilizer are connected by a coordinate bond. These complexes are well soluble in water. Scientific research initiated in this direction allows us to reveal new patterns of "drug substance - excipient" in complex physico-chemical systems, which are drugs.

5. Synthetic way - introduction into the structure of the molecule of hydrophilic groups: -OH; -COOH; -CH2-COOH; -CH2OH. Example: unithiol.

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

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

Anhydrous drugs and crystal hydrates have different solubilities, which leads to changes in their pharmacological action. For example, anhydrous forms of caffeine, ampicillin, theophylline dissolve faster than their crystal hydrate, and, accordingly, are absorbed faster.

Didactic units:

- The degree of grinding or dispersion
- Polymorphism of medicinal substances;
- Physical state
- Physico-chemical properties
- Surface properties of the drug substance
- Degree of purity

2.2. Questions (tests, tasks, clinical situations) to test basic knowledge on the topic of the lesson:

Answer the question:

1. Biopharmacy as a scientific discipline and its importance in the development of the composition and technology of dosage forms.
2. History of biopharmacy development.
3. Basic concepts and terms of biopharmacy.
4. The main tasks of biopharmacy at the present stage and their role for practical health care.
5. Pharmaceutical factors influencing the therapeutic efficacy of drugs.
6. Physical state of medicinal and excipients in dosage forms and their effect
7. The concept of physical condition. What parameters are understood by physical condition.
8. Grinding of medicinal substances.
9. Influence of particle size on therapeutic activity.
10. Polymorphism and polymorphic modifications.
11. Ways to increase the solubility of sparingly soluble substances and thus bioavailability.

Solve tests:

1. The patient needs to prepare an ointment. Specify the substance that must be introduced into the ointment base in the form of an aqueous solution:
   A. Diphenhydramine
   B. Vaseline
   C. Spermacet
   D. Menthol oil
   E. Sulfur
2. The sequence of alloying the components of ointment bases is carried out:
   A. in ascending order of melting point;
   B. in descending order of melting point;
   C. first hydrocarbon bases, then fat;
   D. first fat, then hydrocarbon bases;
   E. the components of the base are dissolved by heating in fatty or mineral oils.
3. In the manufacture of ointments with protargol, the pharmacist made a mistake when introducing the ingredient into the base. How to introduce protargol in the base?
   A. Rub with glycerin, then with water
   B. Grind in a mortar with Vaseline
   C. Rub with Vaseline oil
   D. Grind in a mortar with ether
   E. Rub with lanolin
4. In the manufacture of powder, the pharmacist crushed this substance with alcohol. Specify the substance that is difficult to grind:
   A. Streptocide
   B. Copper sulfate
   C. Sugar
   D. White clay
   E. Talc

5. When preparing powders with this substance, the pharmacist used separate scales, a separate mortar and a separate workplace. Specify the substance for which the following technology is characteristic:
   A. Sulfur
   B. Diamond green
   C. Copper sulfate
   D. White clay
   E. Talc
6. How much Vaseline should be taken to prepare 40.0 10% streptocidal ointment?
   A. 10.0
   B. 20.0
   C. 36.0
   D. 35.0
   E. 40.0
7. How much Vaseline should be taken to prepare 50.0 10% streptocidal ointment?
   A. 10.0
   B. 20.0
   C. 35.0
   D. 30.0
   E. 45.0
8. The pharmaceutical factors include everything except:
   A. pharmaceutical technology;
   B. physicochemical properties;
   C. the degree of dispersion and polymorphism of the drug substance;
   D. the type of dosage form and method of administration;
   E. flowability.
9. How much water should be taken to purify 50.0 2% agar gel?
   A. 50ml
   B. 45ml
   C. 49ml
   D. 40ml
   E. 48ml
10. How much emulsifier I need to take to prepare a 100.0 emulsion base?
   A. 1.0
   B. 2.0
   C. 5.0
   D. 7.0
   E. 10.0

III. Formation of professional skills, abilities:

3.1. content of tasks:

Task1

To establish the influence of the degree of dispersion of streptocide on the process of its release from ointments by the method of "agar plates".

3.2. recommendations (instructions) for performing tasks

Task1

The study of the influence of the degree of grinding of the substance on the absorption process is convenient to determine for ointments or suppositories prepared on the same basis, using fractions of the drug substance, the particle size of which differs markedly.

The method of direct diffusion into agar gel, known as "agar plates", is based on the formation of colored products of drugs with reagents.

The objects of the study are 10% streptocidal ointments with varying degrees of grinding of streptocide:

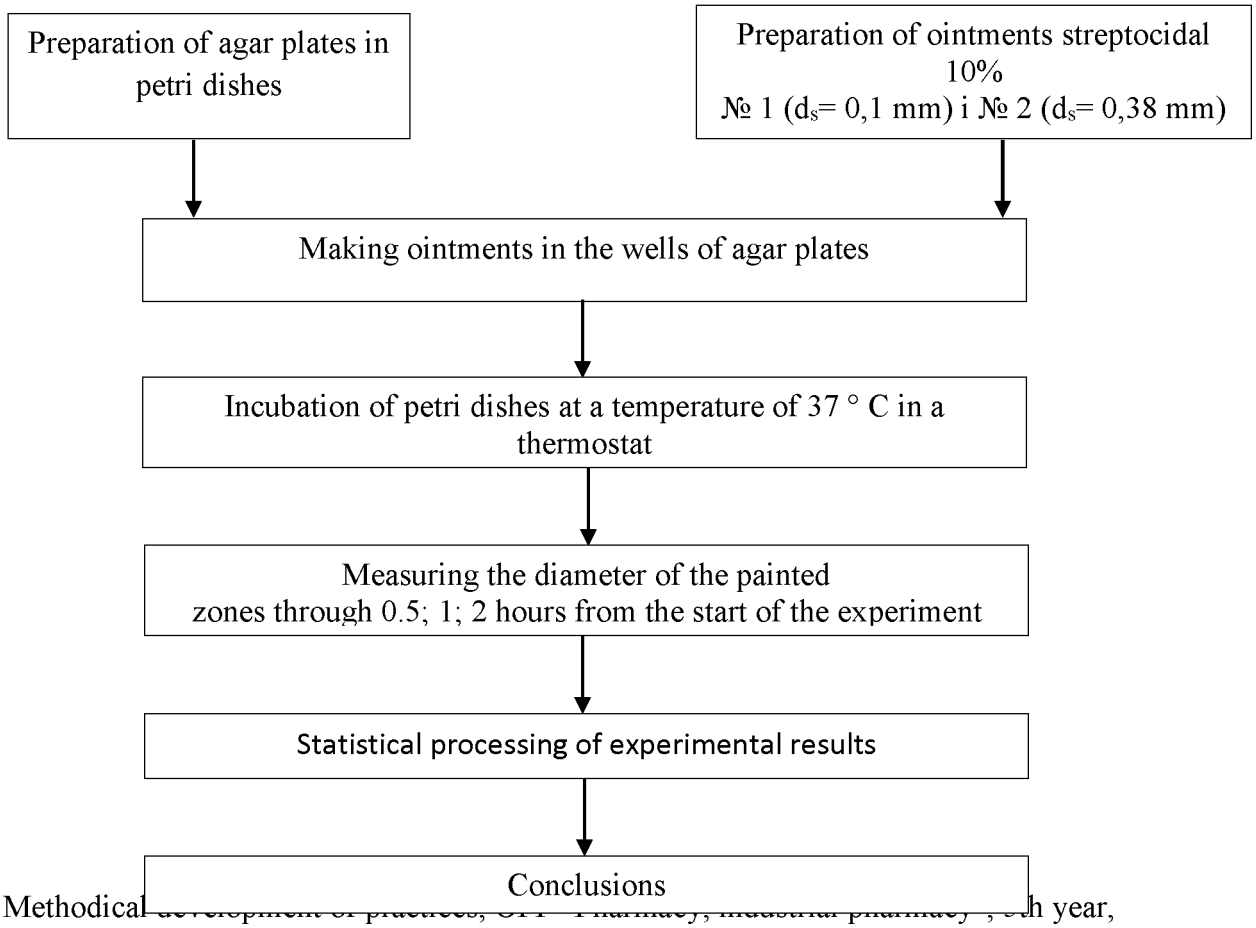
ointment № 1 - particle diameter of streptocide (d_s) = 0.1 mm;

ointment № 2 - particle diameter of streptocide (d_s) = 0.38 mm.

Before completing the task, get acquainted with the algorithm of experimental work for task № 1 (Appendix 1).

Appendix 1

ALGORITHM OF EXPERIMENTAL WORK ON DETERMINATION OF THE INFLUENCE OF THE DEGREE OF STREPTOCIDE DISPERSITY ON THE PROCESS OF ITS RELEASE FROM OINTMENTS BY THE AGATHOH METHOD



Preparation of gel and agar plates

The agar gel is prepared at 2% concentration in a pre-aged glass beaker tightly closed with a lid. The crushed agar (GOST 6470 - 53) is drained with purified water and left for 30 minutes to swell.

The swollen agar is heated to boiling, brought to the required mass and 5% of Ehrlich's reagent is added to the warm gel. The composition of the Ehrlich reagent: p-dimethylaminobenzaldehyde 0.5 g, concentrated hydrochloric acid and ethanol 95% in 15 ml, n-butanol 90 ml.

The prepared agar gel is poured into Petri dishes (diameter 98-100 mm, height 20 mm), which are placed on the table, pre-calibrated horizontally with a spirit level. Agar is poured into cups in two portions of 10 and 15 ml. After solidification of the first portion of agar on its surface in each cup is placed three cylinders of stainless steel or glass (outer diameter 8 mm, height up to 10 mm) and pour the second layer of agar. After the agar solidifies, the cylinders are carefully removed.

Ointment technology

To obtain fractions of varying degrees of dispersion, 50 g of streptocide are sieved through a set of sieves, separating particles with a size of 0.38 mm Streptocide with particles less than 0.38 mm is further ground in a mortar with 95% alcohol for 10 min and sieved through a sieve, selecting a fraction with a particle size of 0.1 mm

Ointments are prepared at 10% concentration using any available ointment base (eg, Vaseline), part of which is pre-melted and mixed with a certain fraction of streptocide. To avoid undesired further grinding of the particles of the dispersed phase, the ointment base is melted and mixed with the substance using a propeller stirrer (1500 rpm).

In the absence of a propeller stirrer, the ointment can be prepared as follows: a streptocide with a certain particle size is placed in a mortar and mixed according to Deryagin's rule with half the amount of molten base, and then add the remaining unmelted base and mix.

Determination of the rate of release of drugs from ointments

Ointments containing the drug substance with varying degrees of dispersion are placed in the wells of two cups of agar. Cups are numbered or indicate the degree of grinding. Ointment is added to the wells with a glass rod, making sure that there was good contact with the agar. The cups are placed in a thermostat with temperatures of 37 ° C.

The drug substance, releasing from the ointment, diffuses into the agar gel, interacting with Ehrlich's reagent and forming a colored area. After 0.5; 1; 2 hours using a ruler to measure the diameter of the painted area. In the case of the formation of an ellipse, measure the larger and smaller diameter and determine the average diameter of the painted area.

Statistical processing of the obtained results is carried out by the method of Montsevichyute-Eringen.

The arithmetic mean error is calculated by the formula:

$m = \pm \Sigma a \cdot k$,
where *t is the* error of the arithmetic mean of the diameters of the painted areas;
Σ - amount;
a - numerical values of deviations of diameters of zones from arithmetic mean with a sign "plus" or "minus";
k is a value that depends on the number of options, ie the number of experiments (*n*) for each sample of ointment (Table 1).

Example of calculation

Ointment №1 ($d_{ср}$ = 0.1 мм).
1 час
$d_1 = 20$ mm
$d_2 = 20$ mm $d_{ср} = \frac{20+20+21}{3} = 20.3$ (mm)
$d_3 = 21$ mm

№	a
1	20,3 – 20 = +0,3
2	20,3 – 20 = +0,3
3	20,3 – 21 = – 0,7

a = | + 0.3 | + | +0.3 | + | - 0.7 | = 1.3 (values of «*a*» are summed without algebraic signs);
m = 1.3 * 0.29004 = 0.38;
d = 20.3 ± 0.38 (mm).
Enter the obtained data in table. № 1.

Table 1

DIFFUSION OF STREPTOCIDE WITH DIFFERENT DEGREES OF DISPERSION WITH OINTMENTS

Ointment	Diameter of the painted zone, mm		
	0.5 hours	1:00	2 hours
№1 №2			

After completing the task, draw conclusions about the influence of the degree of dispersion of streptocide on its release.

3.3. requirements for work results, including before registration
In accordance with the recommendations (instructions) for the tasks.
3.4. control materials for the final stage of the lesson: tasks, tasks, tests, etc .:
1. In what year were polymorphic modifications of carbon discovered?
A. 1756 p
B. 1801 p
C. 1809 p
D. 1811 p
E. 1821
2. Indicate which term corresponds to the following statement: "It is the property of a chemical to form crystals in different crystallization conditions that differ

from each other by a class of symmetry or shape, physical and sometimes chemical properties."

A. optical activity
B. polymorphism
C. degree of purity
D. crystallinity
E. amorphous

3. The pharmacist prepares a suspension-type ointment. What substance is well soluble in water, but in the composition of dermatological ointments is introduced by type of suspension:

A. Novocaine
B. Silver nitrate
C. Resorcinol
D. Potassium iodide
E. Sodium benzoate

4. The pharmacist prepares a suspension-type ointment. What substance is well soluble in water, but in the composition of dermatological ointments is introduced by type of suspension:

A. Zinc sulfate
B. Potassium iodide
C. Furacillin
D. Caffeine benzoate
E. Magnesium sulfate

5. Indicate which term corresponds to the following statement: "This is the process of spontaneous transition to a stable solution using surfactants insoluble or sparingly soluble in this solvent."

A. hydrotopy
B. solubilization
C. recrystallization
D. hydration
E. hydrolysis

6. Indicate which term corresponds to the following statement: "This is a factor when the same substance can be used as a drug in various chemical compounds (salt, base, acid, ether, etc.), in which part of the drug molecule is completely preserved. , which is responsible for the pharmacological effect.

A. polymorphism
B. simple chemical modification
C. the degree of ionization of the substance
D. solubilization
E. hydrotopy

7. The patient needs to prepare a protective cream. Which substance most protects the skin from the effects of harmful environmental factors?

A. Zinc oxide.

B. Potassium bromide.
C. Magnesium sulfate.
D. Calcium chloride.
E. Sodium chloride.

8. The patient needs to prepare an ointment. Specify the substance that must be introduced into the ointment base in the form of an aqueous solution:
A. Vaseline
B. Spermacet
C. Menthol oil
D. potassium chlorine
E. Sulfur

9. The patient needs to prepare an ointment. Specify the substance that must be introduced into the ointment base in the form of an aqueous solution:
A. Vaseline
B. Spermacet
C. Menthol oil
D. Analgin
E. Sulfur

10. The patient needs to prepare an ointment. Specify the substance that must be introduced into the ointment base in the form of an aqueous solution:
A. Vaseline
B. Spermacet
C. Menthol oil
D. Novocaine
E. Sulfur

IV. Summing up

List of recommended reading

Main:

1. .Biopharmaceutics. Збірник текстів лекцій./ Tikhonov A.I., Yarnykh T.G., Yuryeva A.B., Podorozhna L.N., Zuykina S.S., НФаУ Оригінал, 2011. – 140 с.

2. Biopharmaceutics. Практикум / Tikhonov A.I., Bogutskaya Ye.Ye., Yarnykh T.G., Kotenko A.M., Garkavtseva O.A., НФаУ Оригінал, 2011. – 80 с.

3. Janicki S., Sznitowska M., Zielinski W. Dostepnosc farmaceutyczna I dostepnosc biologiczna lekow. – Warshawa, 2001.–242 s.

4. Biopharmaceuticals: Biochemistry and Biotechnology, 2nd Edition. – 2013. – 544 p

ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF DRUGS TECHNOLOGY

APPROVE
Head of Department

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

METHODICAL DEVELOPMENT OF PRACTICAL LESSON

Course: 5 Faculty: Pharmaceutical

Course: Biopharmacy

Practical lesson №3 Topic: **«The influence of the nature of excipients on the process of releasing drugs from dosage forms.»**

The practical lesson was developed by:
Ph.D., Assoc.

_____ (Fizor. N.S.)
signature
The practical lesson was discussed at the methodical meeting of the department
«29» august 2022 y.
Protocol № 1

Odesa – 2022

The purpose of the lesson: the formation of knowledge, skills, practical skills to study the influence of the nature of excipients on the process of releasing drugs from dosage forms.

Basic concepts: Excipients, solubilizers, surfactants, emulsifiers, stabilizers, correctors.

Equipment: according to the requirements of Good Pharmacy Practice (GPP).

Study time: 2.0

Plan

I. Organizational moment.

II. Control of basic knowledge

2.1. Requirements for theoretical readiness of students to perform practical classes (knowledge requirements, list of didactic units):

Requirements for theoretical knowledge:

According to the literature, no pharmaceutical factor has such an effect on the biological activity of drugs as excipients. Excipients - a huge group of compounds of natural and synthetic origin, used in the preparation of drugs in various dosage forms with appropriate physicochemical and medicinal properties. In pharmacy, excipients are used as a shaping agent, fillers, solvents, solubilizers, emulsifiers, stabilizers, leavening agents, preservatives. Biopharmacy for the first time in the 60s of the XX century gave a scientific justification for the use of excipients, showed the complete failure of the empirical attitude to them.

With the development of biopharmacy, the concept of "indifference" of excipients has lost its meaning. When creating new and improving existing drugs, it is necessary to take into account the influence of excipients.

There are no completely indifferent substances. Excipients may increase or decrease the pharmacological action, increase or eliminate side effects. The variety of properties of excipients and a wide range oblige scientists to abandon attempts to convert the excipient into a universal, used with any drug.

Consider the effect of excipients on the example of such a common dosage form as an ointment. The variety of ointment bases contributes to the need to study their effect on the pharmacological action of drugs.

3. Objectives of the lesson:

Formation of knowledge, skills, practical skills to study the influence of the nature of excipients on the process of releasing drugs from dosage forms.

3.1. General objectives: to get acquainted with the modern definition of bioavailability of drugs, the factors that affect it.

3.2. Educational goals: to get acquainted with the contribution of domestic scientists in studying the problem of the influence of excipients on the bioavailability of drugs; be able to explain to the patient the need to take drugs in accordance with the doctor's instructions in compliance with the time frame and dietary conditions.

3.3. Specific goals:

- Know:
- Physico-chemical properties are included in the prescription of ingredients and be able to find them in the AND and reference literature.
- Physico-chemical properties of drugs and be able to find them in the analytical regulations (AND) and reference literature;
- Influence of physical and technological factors on the rate of release of substances from the dosage form.
- Causes of polymorphic modifications of drugs.
- Classification of excipients and their role in the preparation of dosage forms.
- The influence of the nature of excipients on the rate of absorption of drugs and their therapeutic efficacy.
- Modern methods for determining the effectiveness of drugs.
- Methods "in vitro" (direct diffusion through the membrane, "agar plates", chromatographic, solubility test, etc.).
- "In vivo" methods, which are performed on laboratory animals, healthy human volunteers, isolated organs with single and multiple injections.
- Modern methods for determining the concentration of drugs in biological fluids (blood, urine, excretion).
- Microbiological and acanthosis tests.
- Graphical method of calculating the area of the pharmacokinetic curve and the degree of drug absorption, determination of the absorption and elimination constants, radioisotope method.
- Correlation of methods.

3.4. Based on theoretical knowledge on the topic:

- master the techniques / be able /:

be able:

- Prepare different ointments taking into account the physicochemical properties of drugs and the nature of the ointment base.
- Use in vitro methods ("agar plates" and dialysis) to assess the release of drugs from ointments.
- Be able to use "in vivo" methods to determine the influence of the nature of the ointment base on the process of releasing streptocide.
- Apply ointments on the skin of laboratory animals and draws blood from the ear vein of rabbits.
- To generalize the obtained results, to carry out statistical processing of results of experiment.
- To build curves of dynamics of release of streptocide from ointments depending on the nature of an ointment basis and to draw conclusions.
- Have different methods of analysis of sulfonamide drugs - prepare trituration ointments, taking into account the quantities and physicochemical properties of drugs;
- Summarize the obtained data and perform statistical processing of the obtained results.

Didactic units:

- Excipients
- Methods "in vitro" (direct diffusion through the membrane, "agar plates", chromatographic, solubility test, etc.).
- "In vivo" methods, which are performed on laboratory animals, healthy human volunteers, isolated organs with single and multiple injections.

2.2. Questions (tests, tasks, clinical situations) to test basic knowledge on the topic of the lesson:

Answer the 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. Origin and functions of excipients.
4. Mechanisms of influence of excipients on bioavailability.
5. Compounds that form excipients and are characterized by a high degree of dissolution and bioavailability.
6. The main role of excipients.
7. How is the choice of excipients.
8. Modern methods for determining the effectiveness of drugs.
9. Graphic method of calculating the area of the pharmacokinetic curve and the degree of absorption of drugs. Determination of absorption and elimination constants.

Solve the test

1. The recipe prescribes eye ointment with norsulfazole sodium. Specify the optimal ointment base?
   A. Alloy of vaseline with lanolin (9: 1)
   B. Emulsion base type o / v
   C. Alloy of Vaseline with paraffin (6: 4)
   D. Alloy of vaseline with lanolin (6: 4)
   E. Vaseline alloy with paraffin (8: 2)
2. Important factors influencing the release of drugs from ointments and suppositories are:
   A. structural and mechanical properties of the base;
   B. type of bases;
   C. type of packaging;
   D. method of storage;
   E. introduction of suction activators.
3. For suppositories made on a lipophilic basis, determine the melting point, which should not exceed
   A. 60 C
   B. 120 C
   C. 25 C
   D. 50 C

E. 37 C

4. The pharmacist prepares an ointment on a hydrophobic basis. What substance does he use to increase the melting point and viscosity of the base?
   A. Lanolin anhydrous
   B. Vaseline
   C. Paraffin
   D. Naphthalene oil
   E. Lard
2. For suppositories made on a hydrophilic basis, determine the dissolution time. According to HFCs, the suppository should dissolve:
   A. for 10 minutes
   B. not less than 60 minutes
   C. no more than 60 minutes
   D. for 25 minutes
   E. 40 min
3. The pharmacist prepares an ointment on a hydrophobic basis. What substance does he use to reduce the melting point of the base?
   A. Glycerin
   B. Vaseline oil
   C. PEG-400
   D. Dimexid
   E. Ethanol
4. The patient must prepare an ointment with ephedrine hydrochloride (up to 5%) on an emulsion basis. How to introduce this substance into a dermatological ointment:
   A. Dissolution in a small amount of water
   B. In the form of a fine powder of the suspension type
   C. Dissolution in a submerged base
   D. Dissolution in a liquid suitable for the base
   E. Fusion with the base
5. A patient who needs to prepare a hydrophilic ointment applied to the pharmacy. What basis should a pharmacist use to prepare such an ointment:
   A. Polyethylene oxide base
   B. Goose fat
   C. Vaseline-lanolin base
   D. Vaseline
   E. Paraffin
6. Which of the following factors applies to pharmaceuticals?
   A. concomitant pathologies
   B. become ill
   C. simple chemical modification
   D. time of taking the drug
   E. age of the patient
7. Which of the following factors applies to pharmaceuticals?

A. excipients
B. become ill
C. concomitant pathologies
D. time of taking the drug
E. age of the patient

8. A patient who needs to prepare zinc paste went to the pharmacy. What is the peculiarity of the introduction of zinc oxide?
A. Grind with starch and glycerin
B. Grind with ether.
C. Grind with alcohol.
D. Grind with part of the molten base.
E. Grind with starch and melted base.

9. The pharmacist prepares a topical ointment. What basis should he use?
A. Polyethylene oxide base
B. Soap-glycerin base
C. Vaseline
D. The basis of Kutumova
E. Gelatin-glycerin base

10. The pharmacist prepared a dermatological ointment with resorcinol (up to 5%) on a hydrophobic basis. How to introduce this substance into a dermatological ointment:
A. Dissolution in a small amount of water
B. In the form of a fine powder of the suspension type
C. Dissolution in a submerged base
D. Dissolution in a liquid suitable for the base
E. Fusion with the base

III. Formation of professional skills, abilities:

3.1. content of tasks:

Task № 1

To establish the influence of the nature of the ointment base on the rate of release of streptocide from ointments by the method of "agar plates".

Task № 2

To establish the influence of the nature of the ointment base on the process of releasing streptocide from ointments by dialysis.

3.2. recommendations (instructions) for performing tasks

Task № 1

Methodical recommendations for the task

For better visibility of the experimental results, ointment bases with pronounced and weakly expressed diffusion properties can be used.

The objects of the study are 10% streptocide ointments prepared on different bases (Table 1).

Table 1

OBJECTS OF RESEARCH

№ p / p	Ointment base	Base components and their concentration, g	
1	Vaseline	Vaseline	100
2	Vaseline-lanolin	Vaseline Lanolin anhydrous	70.0 30.0
3	Vaseline-lanolin with DMSO	Vaseline Lanolin anhydrous Dimethyl sulfoxide	65.0 30.0 5.0
4	The basis of Kutumova	Vaseline Purified water Emulsifier T_2	60.0 30.0 10.0
5	Methylcellulose gel	Methylcellulose Glycerin Purified water	5.0 10.0 85.0
6	Polyethylene oxide	Polyethylene oxide-400 Polyethylene oxide-1500	70.0 30.0

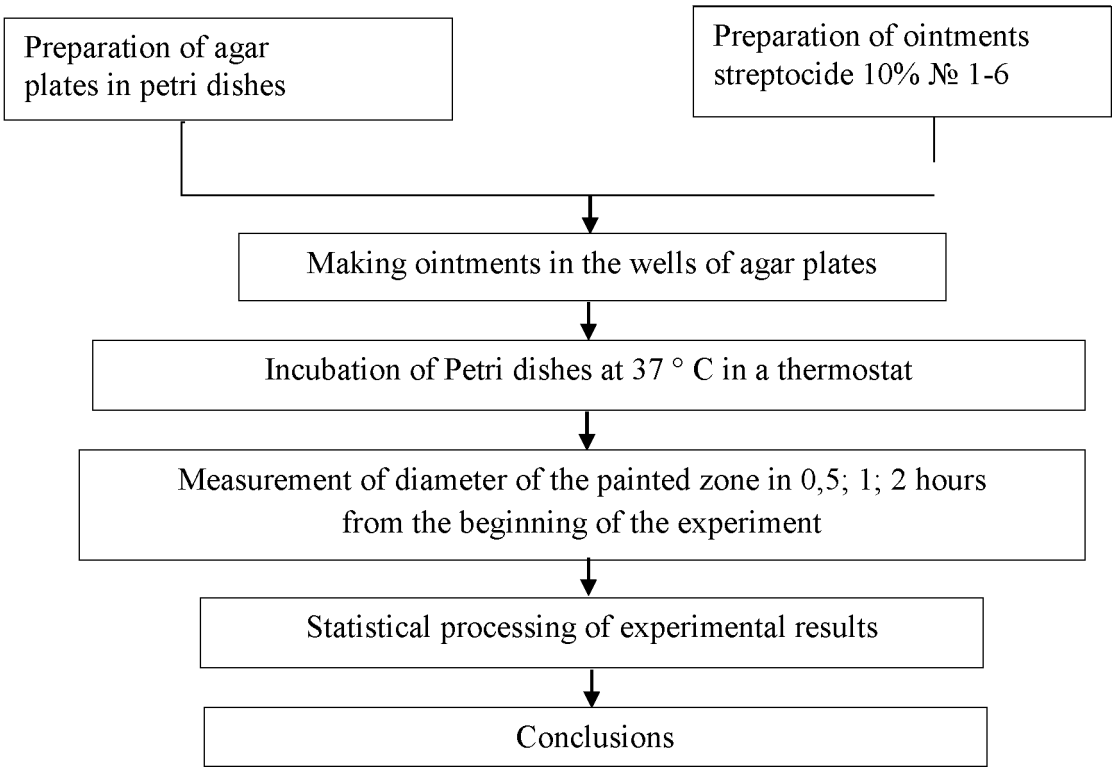
Before completing the task, get acquainted with the algorithm of experimental work for task № 1 (Appendix 1).

Ointment technology

Test samples of ointments are prepared in accordance with technical regulations. The particle size of 0.1 mm promotes a more complete release of streptocide.

Appendix 1

ALGORITHM OF EXPERIMENTAL WORK ON DETERMINATION OF THE INFLUENCE OF NATURAL OINTMENT BASE ON THE PROCESS OF RELEASE OF STREPTOCIDE FROM OINTMENT BY THE AGAR PLATE METHOD



Ointment technology. Streptocide is placed in a mortar and crushed as a powdered substance with 95% ethyl alcohol at the rate of 5 drops per 1.0 substance.

Ointments № 1 - 2. In a porcelain cup melt about 5.0 Vaseline, grind with it streptocide according to the rules of Deryagin, add the remaining amount of Vaseline or Vaseline and Lanolin anhydrous.

Ointment № 3. In a mortar grind streptocide according to Deryagin's rule with dimethyl sulfoxide and mix with vaseline and anhydrous lanolin.

Ointment № 4. Emulsion base (water - Vaseline) according to Kutumov, consisting of 10 parts of emulsifier T-2, 30 parts of water and 60 parts of Vaseline, is prepared as follows: in a beaker in a water bath melt emulsifier T-2 and alloy it with Vaseline. Then purified to 60-70 ° C purified water is added in a thin stream with constant stirring. The beaker with the emulsion is placed in a plastic container of a micro-shredder of tissues RT-2, which contains cold water (17-18 ° C). The emulsion is cooled with stirring at a speed of 3000 rpm until it acquires an oily consistency.

Ointment № 5. Prepare on methylcellulose glycerogels. 5.0 methylcellulose is filled with half the amount of purified hot water (temperature 80-90 ° C), left to swell, after 2 hours add the remaining water and leave for 12 hours. Streptocide is ground in a mortar with 95% ethyl alcohol, add according to Deryagin's rule (1/2 of the amount of drug substance) glycerin, methylcellulose gel and mix with the remaining glycerin.

Ointment № 6. In a water bath alloy polyethylene oxide-1500 with polyethylene oxide-400. Streptocide is added to the semi-solidified base in the form of crushed powder.

When preparing the ointment, part of the base, approximately equal to half the mass of the substance, is melted in a porcelain cup in a water bath and thoroughly mixed in a mortar with streptocide, pre-crushed with alcohol to a particle size of 0.1 mm Then add the remaining base in portions and mix until smooth.

Ointments № 1-5 - suspension. From VEO streptocide forms an ointment-solution, as it dissolves well in it.

Determination of the rate of release of streptocide from ointments by the method of "agar plates" is carried out according to the method described in lesson № 1 (task № 1).

The measurement results are subjected to statistical processing (see lesson № 1). Enter the obtained data in table. № 2.

Table 2

DIFFUSION OF STREPTOCIDES FROM OINTMENTS, PREPARATION ON DIFFERENT OINTMENT BASE

№ p / p	The name of the ointment	Diameter of the painted zone, mm		
		0.5 years	1:00	2 hours
1	10% streptocide ointment on Vaseline			
2	10% streptocide ointment on vaseline-lanolin basis			
3	10% streptocide ointment on vaseline-lanolin basis with dimethyl sulfoxide			
4	10% streptocide ointment based on Kutumov			
5	10% streptocide ointment on a methylcellulose gel			
6	10% streptocide ointment on a polyethylene oxide basis			

Example of calculation

10% streptocidal ointment based on polyethylene oxide.

1hour

№ experiment	
1	19.3-19.0 = -0.3
2	19.3-20.0 = -0.7
3	19.3-20.0 = -0.7

d 1 = 19 mm

d 2 = 20 mm

d 3 = 20 mm

a = | +0.3 | + | -0.7 | + | -0.7 | = 1.7 (the value of " a " is summed without algebraic signs)

$m = 1.3 \cdot 0.29004 = 0.49$

$d = 19.3 \pm 0.49$ (mm)

Thus, statistical processing of the obtained results is performed.

After completing the task, draw conclusions about the effect of ointment bases on the release of streptocide from ointments

Task № 2

Methodical recommendations for the task

To assess the degree of release of drugs from ointments depending on the nature of the ointment base using the dialysis method (direct diffusion through the membrane) followed by determination of the substance diffused into the solution by various physicochemical methods (photocolorimetric, spectrophotometric).

Before completing the task, get acquainted with the algorithm of experimental work for task № 2 (Appendix 2).

Determination of the degree of release of streptocide from ointments

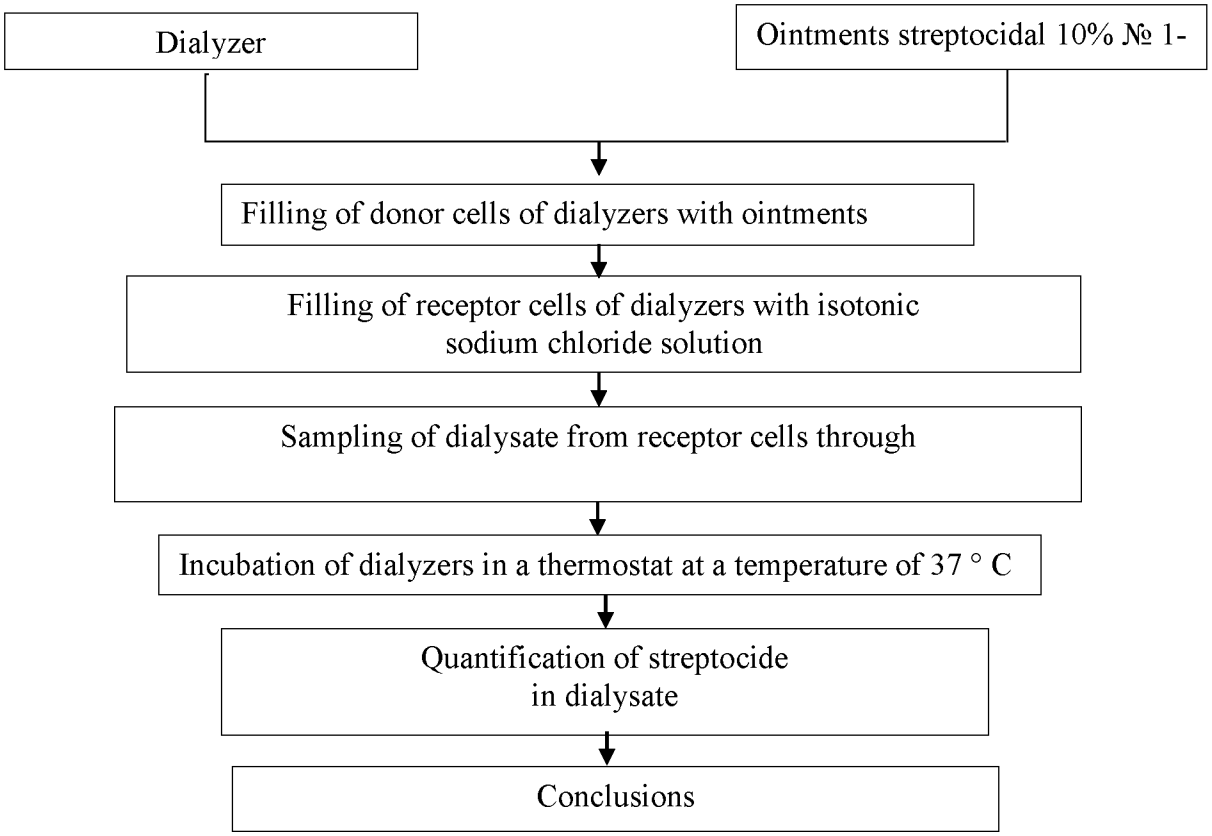
The degree of release of streptocide from ointments prepared using different bases is carried out by dialysis through a cellophane membrane similar to that described in lesson № 1 (task № 2), filling the receptor cells of the dialysis chamber with 15 ml of 0.9% sodium chloride solution.

Sampling from receptor cells is performed after 0.5; 1; 1.5 hours from the start of dialysis, filling the selected volume of dialysate with saline.

Dialysate samples are analyzed for streptocide content.

Annex 2

ALGORITHM OF EXPERIMENTAL WORK ON DETERMINATION OF INFLUENCE OF OINTMENT BASES ON THE PROCESS OF STREPTOCIDE RELEASE BY DIALYSIS METHOD



Quantitative determination of streptocide

In a chemical tube make 1 ml of the analyzed dialysate and add 9 ml of 0.9% sodium chloride solution. The optical density of the solutions is measured on a spectrophotometer SF-26 in a cuvette with a layer thickness of 10 mm at a wavelength of 250 nm. Dialysate obtained by passing an isotonic solution through drug-free ointment bases is used as a reference solution. The concentration of streptocide (M kg / ml) is determined using a calibrated graph of the found value of optical density.

Construction of the calibration schedule

0.1 g (exact portion) of streptocide is placed in a volumetric flask with a capacity of 100 ml, add 20 ml of isotonic solution and 1 ml of saturated sodium carbonate solution. After dissolving the substance, the volume is adjusted to the mark with isotonic solution. 1 ml of the obtained solution A contains 1 mg (1000 μg) of streptocide. 1 ml of solution A is diluted with saline in a volumetric flask to 50 ml (solution B). Then prepare working standard ra?? creatures. For 0.5; 1; 1.5; 2; 2.5; 3 ml of solution B is placed in Pycnometers with a capacity of 10 ml and adjusted with saline to the mark. Get a series of solutions containing streptocide 1, 2, 3, 4, 5, 6 m kg / ml. measure the optical density of the solutions.

On the basis of the received data build the calibration schedule (fig. 1).

The received data on quantity of the released streptocide for certain intervals of time (in 0,5; 1; 1,5 hours) bring in tab. № 3.

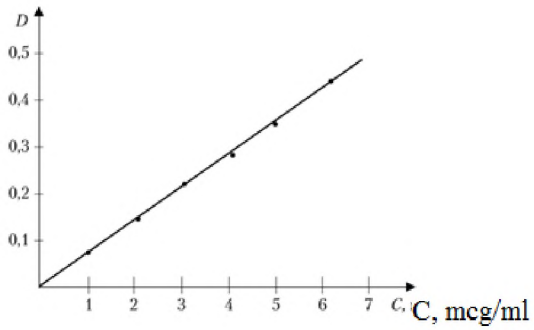


Fig. 1. Calibration graph for quantitative determination of streptocide

Table 3

DIFFUSION OF STREPTOCIDE FROM OINTMENTS, PREPARED ON DIFFERENT OINTMENT BASES

№ p / p	The name of the ointment	Diameter of the painted zone, mm		
		0.5 years	1:00	2 hours
1	10% streptocide ointment on Vaseline			
2	10% streptocide ointment on vaseline-lanolin basis			
3	10% streptocide ointment on vaseline-lanolin basis with dimethyl sulfoxide			

4	10% streptocide ointment based on Kutumov			
5	10% streptocide ointment on a methylcellulose gel			
6	10% streptocide ointment on a polyethylene oxide basis			

Based on the obtained data, construct a graph showing the degree of release of the drug from ointments in the coordinates: the concentration of the substance (mg) on the y-axis, and on the abscissa - time (t , h).

The calculation of the amount of streptocide (X , mg) released from the ointment for a certain period of time, is carried out according to the formula:

$$X_n = \frac{C_n \cdot V \cdot 10}{1000 \cdot V_1} + Y_n,$$

where *Cn* is the concentration of streptocide found according to the calibration graph (m kg / ml);

V is the volume of dialysate in the cell (ml);

V 1- volume of dialysate selected for analysis (ml);

Y is the amount of streptocide contained in the previously selected dialysate (mg):

$$Y_{0,5} = 0;$$

$$Y_1 = \frac{C_{0,5} \cdot 10 \cdot V_1}{1000};$$

$$Y_{1,5} = \frac{(C_{0,5} + C_{1,5}) \cdot 10 \cdot V_1}{1000}.$$

Example of calculation

Ointment № 1. 10% streptocidal ointment (on Vaseline).

0,5 hours $\frac{0,\ 30 * 15 * 10}{1000 * 1} = 0,045\ (\text{mg})$

1 hour $\frac{0,40 + 15 * 10}{1000 * 1} + \frac{0,3 * 10}{1000} = 0,063\ (\text{mg})$

1,5 hours $\frac{0,45 * 15 * 10}{1000 * 1} + \frac{(0,3 + 0,4) * 10}{1000} = 0,075\ (\text{mg})$

After completing the task, formulate conclusions about the influence of the nature of the ointment base on the process of releasing streptocide from ointments by dialysis, reflecting the importance of this method in the technology of ointments.

Task № 3

Methodical recommendations for the task

The influence of excipients (nature of the ointment base) on the process of release and absorption kinetics of drugs can also be established in model experiments on animals. To determine the excipients for the absorption of streptocide can be used different types of dosage forms: ointments, suppositories, tablets, etc. The choice as

the object of study of sulfonamide drug in this case is due to the simplicity of its determination in the blood of experimental animals. According to the principle of the described method, you can also use dosage forms containing other drugs. The number of animals and study factors may also vary. To simplify the experiment (for educational purposes only), you can limit yourself to one animal for each sample of the drug.

The object of the study are 10% streptocidal ointments prepared using different bases.

Before performing the task, get acquainted with the algorithm of experimental work for task № 3 (Appendix 3).

The experiment is performed on two rabbits of the chinchilla breed of approximately the same weight and age. Animals are pre-weighed and the data recorded in a diary.

The animal on the freed from the fur area of skin measuring 5 × 5 cm in the back of the back is applied ointment at the rate of 0.5 g / kg. The ointment is rubbed with a glass shelf or plastic spatula. Blood sampling is performed after applying the ointment in 0.5; 1; 1.5 years.

Quantitative determination of sulfonamides in the blood is carried out by photocolorimetric method VN Prebsting, VI Gavrilov (1939) in the modification of IM Перцева, Д.П. Salo and VF Desenko (1975).

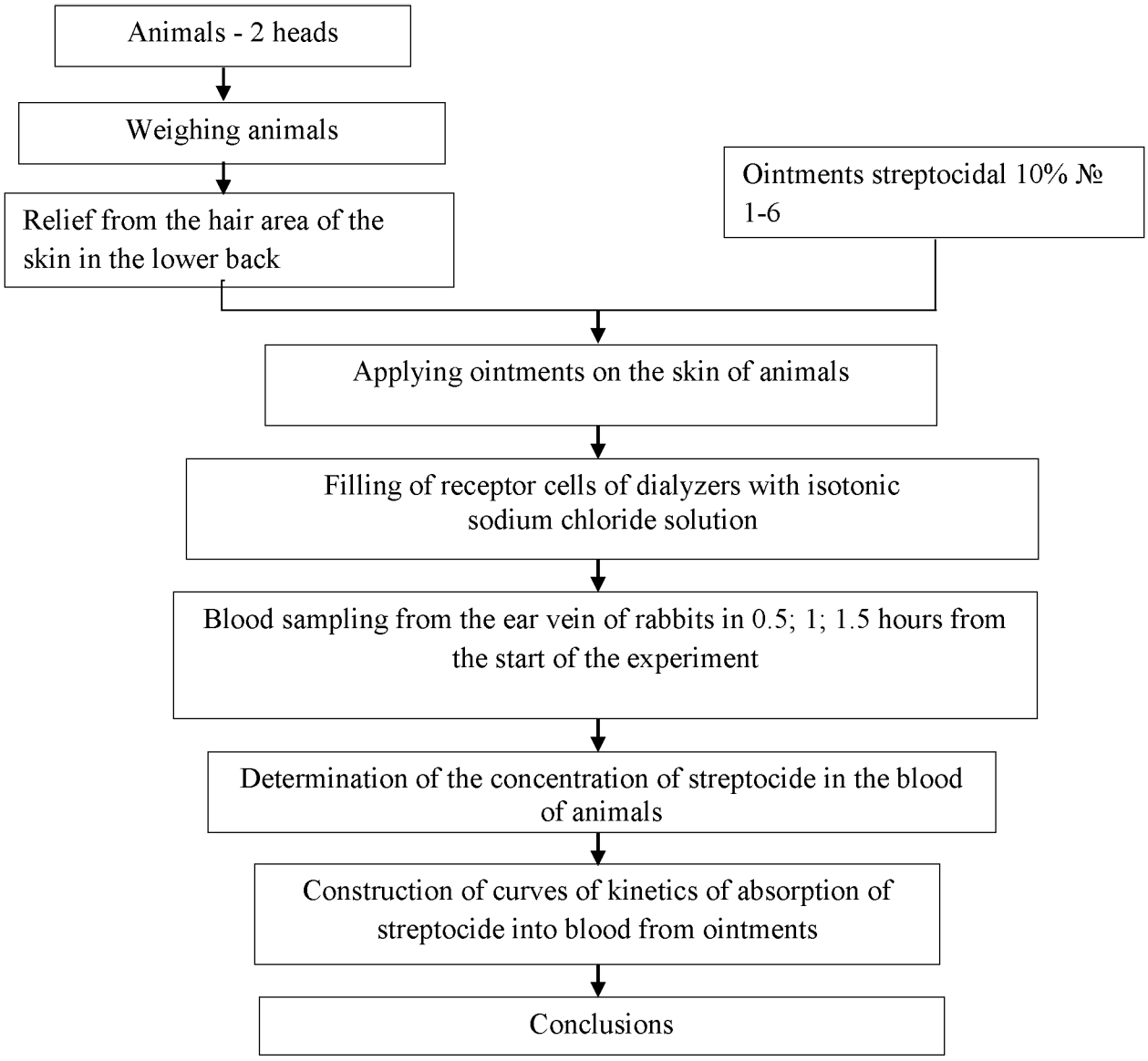
The method is based on obtaining a colored compound by combining diazotized sulfonamide with resorcinol.

Construction of the calibration schedule

0.03 g (exact portion) of streptocide is quantitatively transferred to a dry volumetric flask of 200 ml, dissolved in frequent purified water and adjusted to the mark. 1 ml of solution A contains 150 μg of streptocide. From the initial solution A prepare a working solution B. To do this, 10 ml of solution A is made in a volumetric flask per 100 ml and add water.

Annex 3

ALGORITHM OF EXPERIMENTAL WORK ON DETERMINATION OF THE INFLUENCE OF NATURE OF OINTMENT BASES ON THE SPEED OF SUCTION OF STREPTOCIDES FROM OINTMENTS IN ANIMAL BLOOD



cleaned to the mark with constant stirring. 1 ml of this solution B contains 15 μg of streptocide. To build a calibration graph in a series of tubes make 0.5; 1.0; 1.5; 2.0; 2.5; 3 ml of solution B and adding purified water 3.5; 3; 2.5; 2; 1.5; 1 ml, respectively, to lead solutions to a total volume of 4 ml. The contents of all tubes are mixed and add 1 ml of 15% solution of trichloroacetic acid. From each tube take 2.5 ml of solution, transfer to clean dry numbered tubes, to each sample add with vigorous shaking 0.1 ml of 0.5% sodium nitrite solution and after 10 minutes 0.1 ml of 40% urea solution. All subsequent operations are performed similarly to those described in the determination of streptocide in the blood.

After measuring the optical density of the solutions, build a calibration graph (Fig. 2). On the abscissa axis are deposited known concentrations of streptocide in solution (M kg / ml), and on the ordinate axis - the corresponding indicators of the optical density of the solution.

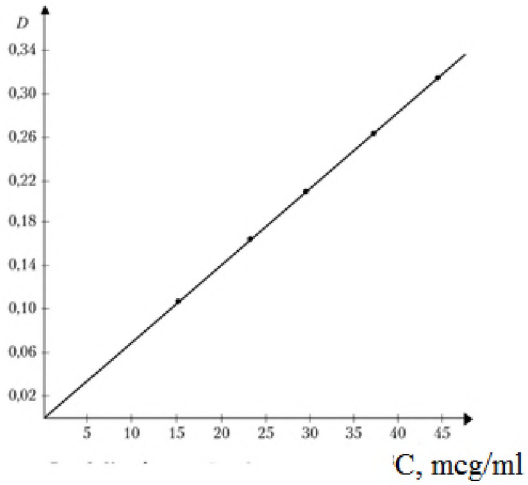


Fig. 2. Calibration graph for quantitative determination of streptocide in the blood

Determination of streptocide in the blood

4.8 ml of a 5% solution of trichloroacetic acid are added to centrifuge tubes for protein precipitation, 0.2 ml of blood taken from a rabbit's ear vein is added by micropipette, mixed by rinsing the micropipette with the contents of the tube 2-3 times, and left for a few minutes until complete hemolysis. The tubes are centrifuged for 10 minutes at 6000 rpm. Pour 2.5 ml of centrifugate, 0.1 ml of 0.5% sodium nitrite solution into chemical tubes and mix thoroughly. At the end of 10 min add 0.1 ml of 40% urea solution and mix again.

After 10 minutes, 1.5 ml of saturated sodium acetate solution and 0.25 ml of 0.5% resorcinol solution are added to the samples and left for 15 minutes, the contents are mixed thoroughly with a glass rod or shaken. The optical density of the solution is measured using a device FEK-56 PM (blue light filter № 4, cuvettes with a layer thickness of 10 mm). In parallel, perform photocolorimetry of a control sample that does not contain streptocide, treated similarly to test samples.

The concentration of streptocide (X, μg / ml) in the blood of experimental animals is determined by the formula:

$$X = \frac{C \cdot V \cdot K}{V_1 \cdot a},$$

where C *is the* concentration of the substance determined according to the calibration schedule (m kg / ml);

V *is the* total volume of the centrifuge (ml);

V_1 *- the* amount of centrifuge taken to determine streptocide (ml);

a *- the* amount of blood taken for analysis (ml);

K *is the* amount of blood that is calculated

(Usually 1 or 100 ml, in our experience 1 ml).

Example of calculation

Ointment № 2. 10% streptocidal ointment (vaseline-lanolin-based).

0,5 hours $\frac{2,5 * 5 * 1}{2,5 * 2} = 25 \ (\text{m}\frac{\text{kg}}{\text{ml}})$

1 hours $\frac{4,7 * 5 * 1}{2,5 * 2} = 47 \ (\text{m}\frac{\text{kg}}{\text{ml}})$

1,5 hours $\frac{3,6 * 5 * 1}{2,5 * 2} = 36 \ (\text{m}\frac{\text{kg}}{\text{ml}})$

Enter the results in table. № 4.

Table 4

INFLUENCE OF EXCIPIENTS ON THE SUCTION OF STREPTOCIDE IN THE BLOOD FROM OINTMENTS

№ p / p	The name of the ointment	Diameter of the painted zone, mm		
		0.5 years	1:00	2 hours
1	10% streptocidal ointment on Vaseline			
2	10% streptocidal ointment on vaseline-lanolin basis			
3	10% streptocidal ointment on vaseline-lanolin basis with dimethyl sulfoxide			
4	10% streptocidal ointment based on Kutumov			
5	10% streptocidal ointment on a methylcellulose gel			
6	10% streptocidal ointment on a polyethylene oxide basis			

Using the data in Table № 4, construct the kinetics of streptocide absorption into the blood depending on the nature of the base used in the coordinates: the concentration of the substance (m kg / ml) along the abscissa and the ordinate - time (*t* , h).

After completing the task, draw conclusions about the influence of the nature of the ointment base on the rate of absorption of streptocide into the blood of animals. Compare the experimental data obtained by the methods "in vivo" and "in vitro".

Draw a conclusion about the correlation of these methods.

IV. Summing up

List of recommended reading

Main:

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

ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF DRUGS TECHNOLOGY

APPROVE
Head of Department

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signature
«29» august 2022 y.

METHODICAL DEVELOPMENT OF PRACTICAL LESSON

Course: 5 Faculty: Pharmaceutical

Course: Biopharmacy

Practical lesson №4 Topic: «**Influence of dosage form on the process of drug release from drugs.»**

The practical lesson was developed by:
Ph.D., Assoc.

_____ (Fizor. N.S.)
signature
The practical lesson was discussed at the methodical meeting of the department
«29» august 2022 y.
Protocol № 1

Odesa – 2022

The purpose of the lesson: the formation of knowledge, skills, practical skills to study the impact of the dosage form on the process of release of drugs from drugs.
General goal: to get acquainted with the modern definition of bioavailability of drugs, the factors that affect it.
Educational purpose: to get acquainted with the contribution of domestic scientists in studying the problem of the influence of the dosage form on the process of drug release; be able to explain to the patient the need to take drugs in accordance with the doctor's instructions in compliance with the time frame and dietary conditions.
Basic concepts: Dosage form, pharmacokinetic curve, elimination constant.
Equipment: according to the requirements of Good Pharmacy Practice (GPP).
Study time: 2.0

Plan

I. Organizational moment.
II. Control of basic knowledge
2.1. Requirements for theoretical readiness of students to perform practical classes (knowledge requirements, list of didactic units):
Requirements for theoretical knowledge:

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

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

The creation of a dosage form in almost all cases requires the use of an excipient. The excipients are not indifferent and in all cases they affect the release of the drug in one way or another. Milk sugar is most often used for these purposes. However, in its presence, for example, increases the absorption of testosterone, reduces the activity of isoniazid. Therefore, in each case, the choice of excipient must be individual to the particular drug substance. For example, ointments with antibiotics (particularly penicillin) made with Vaseline are ineffective due to poor resorption. In this case, you need a base that includes 6 parts of Vaseline and 4 parts of lanolin, which is now used for the manufacture of many ointments with antibiotics.

Boric acid does not have a bacteriostatic effect in the manufacture of ointments based on fat, but is effective in ointments based on hydrophilic bases, which contain large amounts of water. Iodine, on the other hand, is inactive in ointments based on large amounts of water. Thus, the introduction of substances into different types of emulsion bases makes it possible to obtain ointments with different degrees of absorption.

The rate of diffusion of drugs from ointment bases is influenced by the structural and mechanical properties of the bases. For example, the introduction of aerosil in the amount of 5-8% in hydrocarbon bases leads to an increase in the viscosity of ointment bases, resulting in a decrease in the release of salicylic acid. This confirms the need for an individual approach in the choice of excipients.

Dimethyl sulfoxide is able to easily penetrate intact skin, transport, deposit and prolong the flow of drugs into the body. Thus, the addition of DMSO in eye drops accelerates the penetration of antibiotics into the tissues of the eye, the use of MC allows you to keep drugs in the tissues for a long time, thus exerting a prolonged effect, which is important in the treatment of many chronic diseases.

A large number of LRs with molecules of complex configuration easily enter into the complexation reaction. The resulting complexes can be very strong and weaken the basic pharmacological properties of the drug. The intensity of technological processes that take place in the production of drugs can significantly affect the complexation reaction, accelerating or directing it in the appropriate direction. Particularly responsible in this respect are the stages of dissolution, filtration, recrystallization, melting, mixing, etc., in which there is a change in the physical state of drugs and excipients, the intensity and growth of the number of contacts between them.

Dosage form is a structural unit of both pharmacotherapy and industrial production.

The most important task in the development and preparation of the dosage form is to ensure optimal conditions for the release and subsequent absorption of the substance. All other requirements to which the dosage form must meet are subject to these conditions.

The pharmacy considered the dosage form as a means of transporting the drug into the body. In this regard, the convenience of administration of drugs through natural routes was mainly taken into account, and therefore 70-80% of all drugs are administered orally. Comparative studies of one or another dosage form have not been conducted, and the current practice has shown that of all dosage forms, the most popular are tablets (50% of all GLZ). In pediatric practice, up to 70% are liquid drugs. This can be explained by the fact that the oral route is the most convenient, although not always effective. With the introduction of "per os" many drugs are enzymatically broken down, lose activity, irritate the mucous membrane of the gastrointestinal tract, enter into chemical interactions at different pH from 2 to 8. The decomposition products cause various complications.

Resorption processes due to the individuality of each drug and the patient's pathology are different, so the drugs have different bioavailability. The degree of influence of the dosage form on the processes of absorption is determined by the ability to release the active substance from the oral dosage form and the possibility of contact with the mucous membranes of the stomach, intestines and interaction with their secretions. According to the degree of release and, accordingly, better bioavailability, all oral drugs can be arranged in the following order: solutions — emulsions — suspensions — powders — granules — tablets. The dosage form affects the therapeutic activity in combination with other pharmaceutical factors. This can be seen in the example of tablets and capsules "Propoltina".

№ p / p	The name of the drug	Time of complete dissolution, min	Sampling time, min	Release of active substance,%

1	Propoltin tablets (0.05 PHPP)	30.5 ± 2.4	6	16.2 * 3.1
			30	76.0 ± 4.2
2	Propoltin capsules (0.05 PHPP)	6.5 ± 0.64	6	78.4 ± 2.4

The maximum content of the sum of phenolic compounds in Propoltin capsules was observed in the studied samples after their complete dissolution, ie after 6 to 8 minutes. The content of the sum of phenolic compounds in tablets "Propoltin" in this period of time was 1b, 2 ± 3.1%, reaching a peak concentration in the samples after 30 min (average dissolution time of tablets).

The discrepancy in the obtained results is due to the presence of enteric-coated tablets. The shell itself dissolved under visual observation after 3 to 5 minutes In addition, the excipients in Propoltin tablets (sugar, starch, calcium stearate, magnesium carbonate basic) and in Propoltin capsules, which contain magnesium basic carbonate and Aerosil, have a significant effect on the bioavailability of PHPP. The tablets dissolve in the intestines, the capsules - in the stomach.

On the basis of numerous biopharmaceutical studies and scientific substantiation of the influence of this factor, it is possible to create drugs with specified pharmacokinetic properties, which have a certain pharmacological effect: synergism, potentiation, antagonism, prolongation, differentiated or directed action, broadening and antibacterial spectrum. Thus the set therapeutic effect is provided not only by structure of a dosage form, but also an opportunity to involve physiological features of an organism. Therefore, among modern dosage forms are widespread tablets: retard, duruli, sandwiches, duplex, enteric, perlingual, sublingual, buccal, implantation, and others. Depending on the situation, you can use different rectal forms: suppositories layered, swollen, rectioles, syringes, tampons, enemas, etc.

New dosage forms based on micro- and monocapsulation, spansulas, depot preparations, pseudopowders and pseudosuspensions, as well as liposomes, ionixens, collagen, etc. have appeared in medical practice and are successfully used in pharmacotherapy.

The choice of a rational dosage form has a positive effect on the therapeutic effect of drugs. Thus, the replacement of tablet forms of theophylline, euphylline, diprophylline, digoxin with rectal suppositories significantly increases their bioavailability. The use of rectal forms of these drugs can reduce their dose. According to VV Nagorny, VO Golovkin, IL Kechinov, suppositories can replace the introduction of these drugs in the form of injections, as the rectal route of administration is bioavailable to injectable and allows not to injure the patient. In addition, when administered intravenously, the drugs are rapidly excreted from the body, and after rectal administration of some drugs in the form of suppositories and microenemas (eg, Xan-tiverine) there is a prolongation of their action. To achieve a prolonged effect of nitroglycerin, it is recommended to use the patch "Nit-Roderm" instead of tablets. The well-known anti-ischemic drug "trinitrolong" is better to enter in the form of plates. This dosage form allows you to individually dose the drugs, providing uninterrupted and maximum therapeutic effect. According to statistics, approximately 30% of

patients have difficulty taking tablets and capsules, so they grind the tablets and open the capsules. 23% of patients prefer soluble dosage forms. With this in mind, the industry is setting up the production of the latter. Thus, instead of the usual amocillin capsules (bioavailability of 75%) the drug "Flemoxina solutab" (bioavailability of 95%) is produced.

The choice of dosage form simultaneously determines the method (path) of administration of the drug into the body. Each route of administration has its advantages, but not all of them are effective. For one reason or another, sometimes even intravenous administration of the drug does not provide bioavailability. For example, in the treatment of choriogonin in the form of injections there were changes in the emotional state of the patient, allergic reactions, and the introduction of the drug in the form of suppositories did not cause side effects. In the case of cardiac decompensation, injections and rectal forms should be considered rational dosage forms of cardiac glycosides, as oral administration causes intestinal irritation (ulcer, bleeding, pain), which is associated with impaired absorption of mucous membranes in such patients. Long-term therapy of methindol in suppositories proceeds without complications with a good therapeutic effect, while the use of the drug in tablets is accompanied by dyspeptic symptoms, disorders of the central nervous system and other complications.

Thus, the dosage form should be convenient to use, advantageous and rational only in economic, aesthetic terms, but primarily in terms of pharmacodynamics of the drug and the provision of modern requirements for pharmacotherapy.

Didactic units:

Dosage form

2.2. Questions (tests, tasks, clinical situations) to test basic knowledge on the topic of the lesson:

Answer the question:

1. The concept of dosage form
2. Basics used in manufactured dosage forms.
3. The rate of diffusion of drugs from ointment bases.
4. Among modern dosage forms are widespread tablets…
5. The influence of the choice of a rational dosage form on the therapeutic effect of drugs.
6. Methods of obtaining tablets. The influence of pharmaceutical factors on the therapeutic efficacy of tablets.
7. Gelatin capsules, preparation and methods of filling. Influence of pharmaceutical factors on their therapeutic activity.
8. The concept of solubility of drugs. Pharmacopoeial test to determine solubility.
9. The influence of the dosage form on the rate of absorption of the drug, its concentration in biological fluids and the stability of drugs.

10. Calculation of the area under the pharmacokinetic curve. Absorption and elimination constants.

11. Correlation of methods "in vitro" and "in vivo" in determining the release and bioavailability of drugs.

Solve the test:

1. In what order it is necessary to arrange oral dosage forms on degree of absorption
   A. solutions-powders-suspensions-emulsions-granules-tablets
   B. emulsions-suspensions-solutions-powders-granules-tablets
   C. suspensions-emulsions-granules, solutions-powders-tablets
   D. solutions-emulsions-suspensions-powders-granules-tablets
   E. suspensions-emulsions-granules-tablets-solutions-powders
2. Indicate which term corresponds to the following statement: "The process of transition of the drug from the place of reception to the bloodstream."
   A. bioavailability
   B. equivalence
   C. system availability
   D. biotransformation
   E. absorption
3. Indicate which term corresponds to the following statement: "The process by which a drug is excreted from the circulatory system through the kidneys, urine, bile and saliva into the intestines and feces, through the skin, mammary glands and sweat glands.
   A. selection
   B. resorption
   C. biotransformation
   D. distribution
   E. does not have the correct answer
4. Indicate which term corresponds to the following statement: "The process by which a drug substance is distributed or dispersed from the blood into one or more parts, into tissues and organs of the body."
   A. distribution
   B. purity
   C. purity of the whole body
   D. resorption
   E. biotransformation
5. Indicate which processes are directly related to the study of pharmacodynamics?
   A. derivation, effect
   B. release of the substance from the dosage form, absorption
   C. metabolism, excretion
   D. absorption, distribution, metabolism, excretion
   E. LADMER
6. Indicate which processes are directly related to the study of pharmacokinetics?
   A. derivation, effect

B. release of the substance from the dosage form, absorption
C. metabolism, excretion
D. absorption, distribution, metabolism, excretion
E. LADMER

7. The maximum allowable ratio when mixing powders
A. 1: 1
B. 1: 5
C. 1:20
D. 1: 2
E. 1: 7

8. Some types of capsules have their own names. Select the definition that corresponds to the medulla:
A. soft gelatin capsules with an elongated neck
B. hard gelatin capsule with film-coated microcapsules
C. hard gelatin capsules with microdraggering with a fatty shell
D. individual particles of LR with a thin shell, the size of which is 1 - 5000 microns .;
E. soft elastic capsule

9. Some types of capsules have their own names. Select the definition that corresponds to the nanocapsules:
A. soft gelatin capsules with an elongated neck
B. individual particles of LR with a thin shell, the size of which is less than 1 μm
C. hard gelatin capsules with microdraggering with a fatty shell
D. hard gelatin capsule with film-coated microcapsules
E. soft and elastic capsule of various shapes

10. Some types of capsules have their own names. Select the definition that corresponds to the microcapsules:
A. soft gelatin capsules with an elongated neck
B. individual particles of LR with a thin shell, the size of which is 1 - 5000 microns
C. individual particles of LR with a thin shell, the size of which is less than 1 μm
D. hard gelatin capsule with film-coated microcapsules
E. soft and elastic capsule of various shapes

III. Formation of professional skills, abilities:

3.1. content of tasks:

Task № 1

To establish the influence of the dosage form on the process of releasing the phenolic hydrophilic preparation of propolis by the "in vitro" method.

Task № 2

To establish the influence of the type of dosage form on the process of absorption of streptocide into the blood of animals by the method of "In vivo".

Task № 3

Calculate the area under the pharmacokinetic curve, the elimination constant and the absorption constant of streptocide in the blood from ointments and suppositories.

3.2. recommendations (instructions) for performing tasks

Task № 1

The effect of the dosage form on the process of drug release can be traced on various dosage forms: tablets, capsules, potions, ointments, suppositories, injectable solutions, and others. For comparison, you can use 2 or more dosage forms of the same drug substance.

The object of the study are coated tablets and capsules "Propoltin" 0.05.

Preparation of tablets:

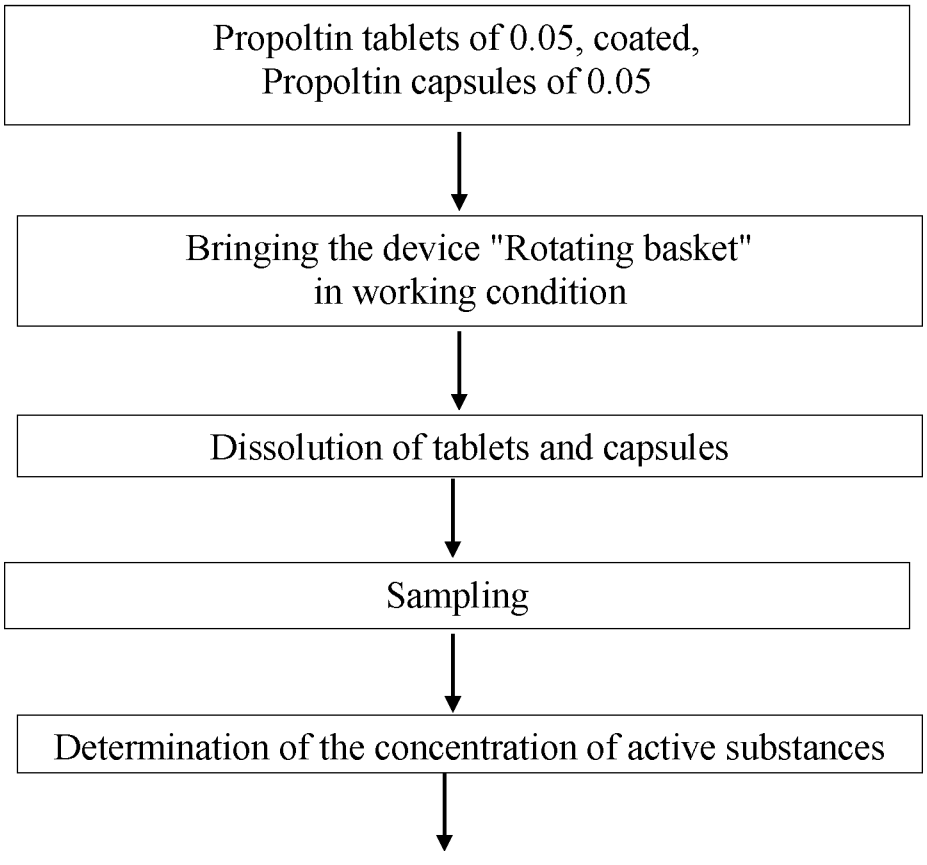
Propoltin coated tablets are used ready-made. Their prototypes were obtained on the DNCLZ by direct pressing.

Preparation of Propoltin capsules

To fill, use gelatin capsules № 4, also obtained by pressing in the factory. Capsules are filled manually with 0.1 mixture of phenolic hydrophilic preparation of propolis with excipients. The mixture contains the same excipients as in tablets. Before completing the task, get acquainted with the algorithm of experimental work for task № 1 (Appendix 1).

Appendix 1

ALGORITHM OF EXPERIMENTAL WORK FOR DETERMINATION OF SOLUBILITY OF THE TESTED TABLETS AND CAPSULES "PROPOLTIN"



Statistical processing of the obtained results

↓

Conclusions

Determination of the dissolution rate of tablets and capsules "Propoltin"

For the experiment using the device "Rotating basket", where the dissolution medium is purified water (0.5 l) with a temperature of 37 ± 1 ° C, the speed of rotation of the basket is equal to 100 rpm The test tablet is placed in a dry basket, to which is immersed in the dissolution medium so that the distance to the bottom of the vessel was 20 ± 2 mm the vessel is closed with a lid and the basket is rotated for a long time until the tablet is completely dissolved.

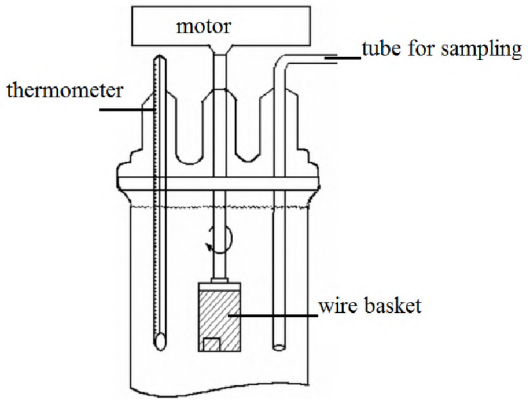


Fig.1. Diagram of the device for determining the dissolution rate

Quantitative determination of phenolic hydrophilic preparation of propolis

Propoltin tablets and capsules contain 0.05 phenolic hydrophilic drug propolis (FGPP). It consists of the sum of phenolic acids, oxycoumarins, flavones and traces of polysaccharides. When determining the amount of phenolic compounds in the selected samples using the method of determining FGPP, set out in VFS 42-2024-90.

5 ml of the resulting solution is placed in a volumetric flask of 25 ml, bring the volume of the solution with 95% ethyl alcohol to the mark and mix. Measure the optical density of the obtained filtrate on a spectrophotometer SF-46 at a wavelength of 290 nm in a cuvette with a layer thickness of 10 mm, using as a reference solution 95% ethyl alcohol.

In parallel, measure the optical density of the working standard sample (PCR) of potassium dichromate, using purified water as a reference solution.

Preparation of a solution of RCC potassium dichromate .

About 0.06 g (exact portion) of potassium dichromate is placed in a volumetric flask with a capacity of 1000 ml, dissolved in a small amount of water, add 5 ml of 1 M solution of sulfuric acid, make the volume of the solution with water to the mark and mix.

The content of phenolic compounds (X) in one capsule in grams is calculated by the formula:

$$X = \frac{D_1 \cdot a_0 \cdot 500 \cdot 25 \cdot 0{,}1715 \cdot 100}{D_0 \cdot V \cdot 1000 \cdot a},$$

where D_1 is the optical density of the test solution;

D_0 - optical density of the solution of RCC potassium dichromate (in this case was 0.58);

a_0 is the weight of the sample of the standard sample, g;

0.1715 - conversion factor of potassium dichromate absorption by the sum of phenolic compounds at λ = 290 nm;

V is the volume of solution taken for analysis, ml;

a - the content of active substances in one capsule or tablet;

500, 25 - dilution of the drug, ml;

$$X = \frac{D_1 \cdot 0{,}06 \cdot 500 \cdot 25 \cdot 0{,}1715 \cdot 100}{D_0 \cdot 5 \cdot 1000 \cdot 0{,}0075}.$$

Carry out statistical processing of the results of 5 samples. To calculate the error of the average measurement result use the formula:

$$\varepsilon_\alpha = S_{\bar{X}} \cdot t_\alpha,$$

where ***- the*** error of the arithmetic mean of the measurements;

S_X - standard deviation of the arithmetic result of measurements, which, in turn, dorvin

$$\sqrt{\frac{\Sigma a^2}{n \cdot (n-1)}},$$

where a is the numerical value of the deviation of the measurements from the arithmetic mean;

n is the number of observations;

ta - Student's ratio at $k = n - 1$ is found in table 1;

α- "confidence probability", which characterizes the reliability of the magnitude of the error.

Table 1

RATIO DEVIATION COEFFICIENT (WITH A SMALL NUMBER OF OBSERVATIONS) A **;**

$k = n - 1$	α		
	0,95	0,99	0,999
1	12,706	63,657	636,619
2	4,303	9,925	31,598
3	3,182	5,841	12,941
4	2,776	4,604	8,610
5	2,571	4,032	6,859
6	2,447	3,707	5,959
7	2,365	3,499	5,405
8	2,306	3,355	5,041

Example of calculation for tablets "Propoltin".

Time of complete dissolution (min)

$X_1 = 30$
$X_2 = 30$
$X_3 = 31$
$X_4 = 31$
$X_5 = 30$

$$\bar{X} = \frac{30+30+31+30+30}{5} = 30,2$$

№ посеву	α	α_2	$\Sigma\alpha^2$
1	30,0 – 30 = 0,2	0,4	2,24
2	30,0 – 30 = 0,2	0,4	
3	30,0 – 31 = –0,8	0,64	
4	30,0 – 30 = 0,2	0,4	
5	30,0 – 30 = 0,2	0,4	

$$S_{\bar{X}} = \sqrt{\frac{\Sigma\alpha^2}{n\cdot(n-1)}} = \sqrt{\frac{2,24}{5\cdot(5-1)}} = 0,335$$

$$\varepsilon_\alpha = S_{\bar{X}} \cdot t_\alpha;\ \ \varepsilon_\alpha = 0,335 \cdot 2,776 \approx 0,93$$

$$\bar{X} \pm \varepsilon_\alpha = 30,2 \pm 0,93$$

The dissolution time of solid dosage forms and the percentage of release of active substances make in table. 2.

Table 2

DYNAMICS OF DISSOLUTION OF COATED TABLETS SHELL, AND PROPOLTIN CAPSULES

№ p / p	Name preparation	Time of complete dissolution, min	Sampling time, min	Release of active substance,%
1.	Propoltin tablets (0.05 PHPP)			
2.	Propoltin capsules (0.05 PHPP)			

After completing the task, draw conclusions about the effect of the dosage form on the release of phenolic hydrophilic drug propolis.

Task № 2

Methodical recommendations for the task

The effect of the dosage form on the degree and nature of absorption of drugs from ointments and suppositories can be traced by determining their concentration in the blood.

The investigated dosage forms are prepared on the same chemical basis and administered to rabbits in equal doses.

The object of study are streptocidal ointment and suppositories with streptocide on polyethylene oxide bases.

Preparation of ointments

Ointment is prepared at 10% concentration. In the molten base, consisting of 80% PEO 400, and 20% PEO 1500, dissolve the streptocide with stirring with a glass rod, then the mixture is transferred into a mortar and stirred to cool.

Preparation of suppositories

Suppositories are prepared weighing 1.5 g by pouring. The dose of streptocide in suppositories is calculated based on the fact that 1 kg of rabbit weight should be administered

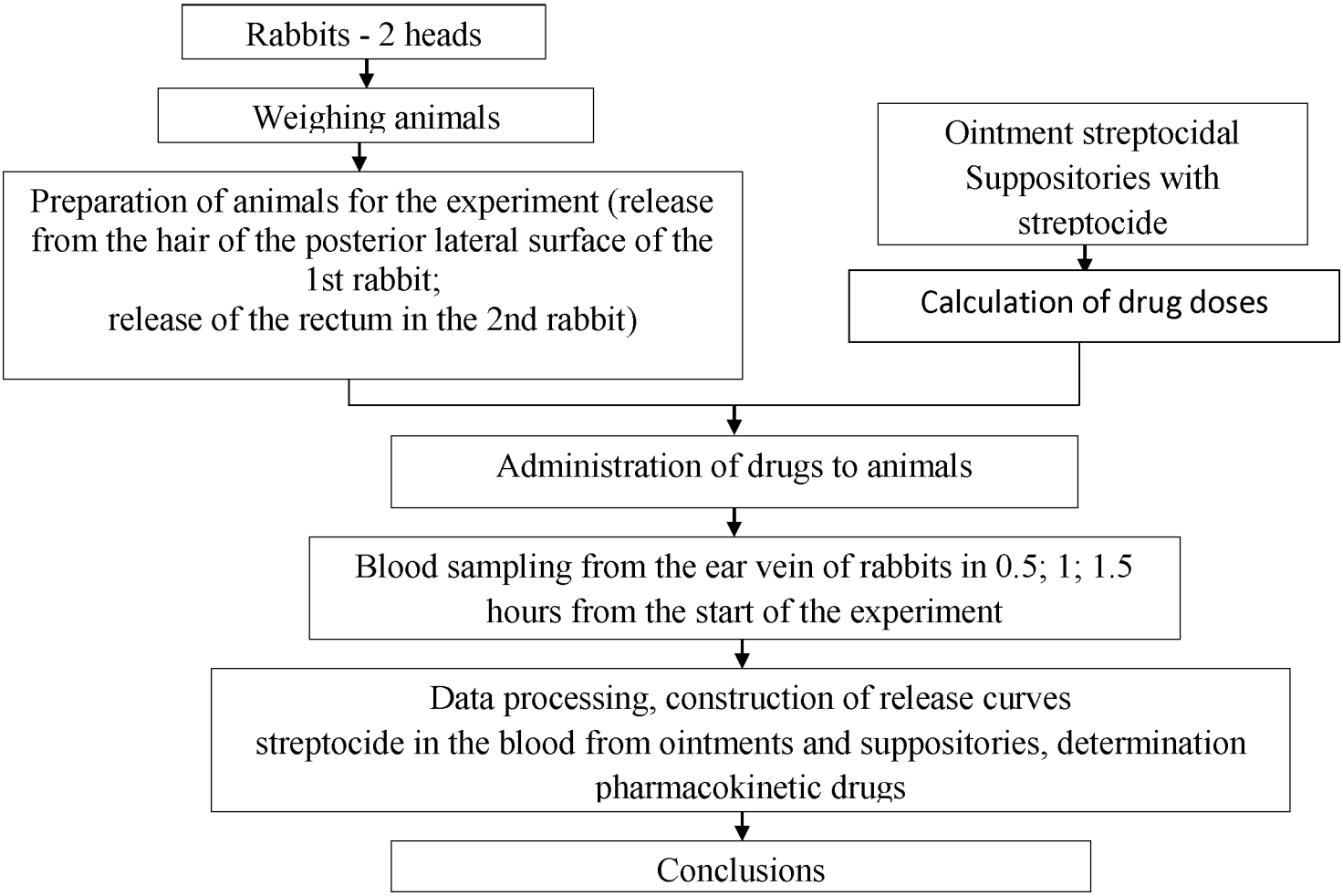
0.05 substance. Calculate the amount of base, the substitution rate of streptocide on a polyethylene oxide base is 1.26. Streptocide is dissolved in a molten base consisting of

80% PEO 1500 and 20% POE 400, and poured into a mold lubricated with Vaseline oil. Propoltin capsules
(0.05 FGPP). The machine is placed in the refrigerator. After cooling, the candle is wrapped in a scarf and placed in a box.

Before completing the task, get acquainted with the algorithm of experimental work for task № 2 (Appendix 2).

Annex 2

ALGORITHM OF EXPERIMENTAL WORK ON DETERMINATION OF THE INFLUENCE OF THE DOCUMENT ON THE ABSORPTION OF STREPTOCIDE BY THE "IN VIVO" METHOD



The experiment is performed on 2 rabbits weighing 2.5-3 kg.

One rabbit is injected with a suppository, and the other on the freed from the area of 5 × 5 cm back of the back is applied ointment with a glass rod or a plastic spatula at a rate of 0.5 g / kg.

Blood sampling is performed after 0.5; 1; 1.5 hours after administration of drugs.

Quantitative determination of streptocide in the blood is carried out according to the method described in lesson № 2 (task № 3). Enter the results in table. 10 and use to plot the concentration of streptocide in the blood of rabbits (m kg / ml) from time (hours) (Fig. 2).

After completing the task, draw conclusions about the influence of the dosage form on the process of absorption of streptocide into the blood.

Table 3

DATA FOR DETERMINATION OF PHARMACOKINETIC PARAMETERS OF STREPTOCIDE FROM DIFFERENT PHARMACEUTICAL FORMS

Dosage form	0.5 years	1:00	1.5 years
Ointment streptocidal 10% Suppository with streptocide			

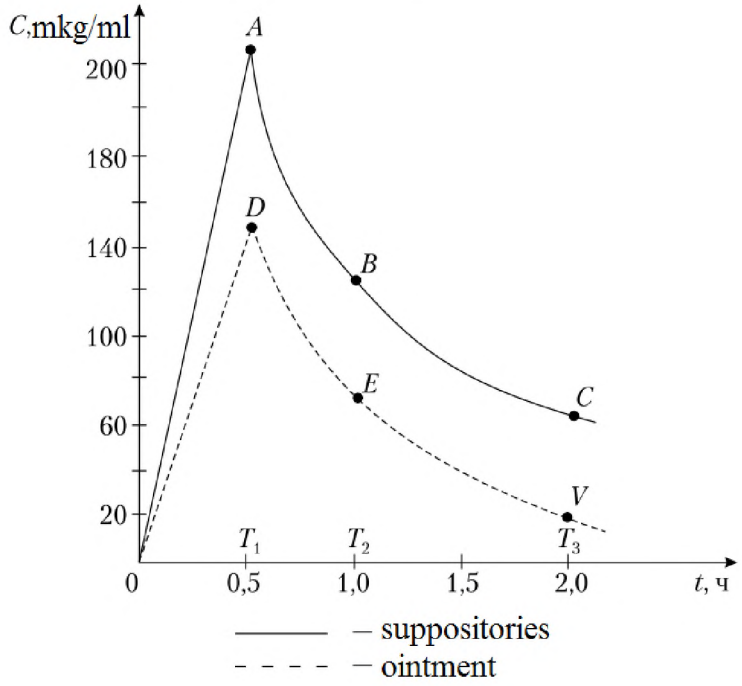


Fig. 2. Dependence of concentrations of streptocide absorbed into the blood from different dosage forms on time

Task № 3

Calculate the area under the pharmacokinetic curve, the elimination constant and the absorption constant of streptocide in the blood from ointments and suppositories.

Methodical recommendations for the task

In cases where a complete analysis of pharmacokinetic data is not possible, the degree of bioavailability of the drug in the blood can be determined by the ratio of the areas under the pharmacokinetic curves obtained by drug administration in the studied forms. Determination of bioavailability is carried out by a linear method, which involves the approximation of individual sections of the pharmacokinetic curve by segments of lines. The area under the pharmacokinetic curve (S) is expressed by the sum of the areas of triangles and trapezoids.

The elimination constant (K_{el}) is defined graphically as the tg of the angle (angular coefficient) formed by the intersection of the abscissa axis and the pharmacokinetic curve of the concentration of streptocide in the blood in semi-logarithmic coordinates. One way to determine the absorption constant is the Dosta method, which is based on the method of sequential logarithm, according to which to determine the absorption constant it is enough to know the value of the elimination constant and the time to reach the maximum concentration of the drug in the blood.

Using the table Enough by the product of elimination and the time to achieve the maximum concentration of the drug in the blood find the value of, and then calculate the value of the absorption constant.

1. Determination of the area under the pharmacokinetic curve

Based on the results of determining the concentration of streptocide in the blood of rabbits for 1.5 hours when applying the ointment and the introduction of the suppository, construct curves of the concentration of streptocide in the blood over time (Fig. 3).

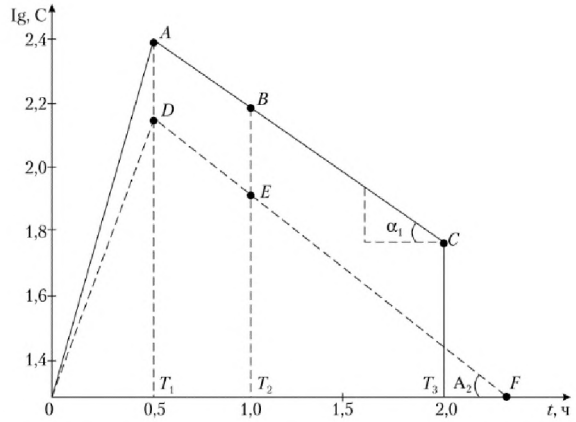


Fig . 3. The dependence of the concentration of streptocide absorbed into the blood from different dosage forms, from time to time in semi-logarithmic coordinates

The area under the pharmacokinetic curve (S) is determined by the sum of the areas ($S_1 + S_2 + S_n$) into which it can be divided.

According to the linear trapezoidal method, the *ABC* curve can be replaced by two straight lines *AB* , *BC* , and the *DEF* curve - straight lines *DE* and *EF* .

The area under the curve of the corresponding suppository, ie. under the curve *OAVS (S)* will consist of the areas of a right triangle OAT_1 *(S)* and two AT_1T_2V *(S)* and VT_2T_3C *(S)* . The area of a right triangle is equal to the sum of the legs. The area of the trapezoid is equal to the sum of the bases of the trapezoid multiplied by the height.

Example of calculation for a suppository

$$S = \frac{OT_1 \cdot T_1A}{2} + \frac{AT_1 + T_2B}{2} \cdot T_1T_2 + \frac{BT_2 + CT_3}{2} \cdot T_2T_3$$

$$S = \frac{0,5 \cdot 240}{2} + \frac{240 + 130}{2} \cdot 0,5 + \frac{130 + 52,2}{2} \cdot 1 =$$

$$= 60 + 92,5 + 91,1 = 243,6 \ \frac{\text{mcg hours}}{\text{ml}}$$

For ointments, the area of the *ODEF* curve *is* determined to be similar.

2. Determination of the elimination constant

To determine the elimination constant on the segments of the lines *ABC* and *DEF* construct right triangles. The elimination constant is determined by the ratio of the length of the opposite leg to the adjacent leg of the triangle.

For the suppository:

$$K_{el} = \text{tg}_{\alpha 1} \frac{16\ \text{mm}}{20\ \text{mm}} = 0{,}8\ (\text{hours}^{-1})$$

For ointment K_{el} is determined similarly.

3. Determination of the suction constant

The suction constant (K_{01}) is equal to the product of ξ and the elimination constant K_{el}:

$$K_{01} = \xi \cdot K_{el}.$$

ξ is found by the value of the product of the elimination constant and the time to reach the maximum concentration of the drug in the blood (Table 4).

For the suppository:

$$K_{el} \cdot t_{\max} = 0{,}8 \cdot 0{,}5 = 0{,}4\ (\text{hours}^{-1})$$

ξ = 5.0 (according to the table Enough)

K_{01} = 0.8-5.0 = 4.0 (hours $^{-1}$)

For ointment K_{01} is determined similarly.

Table 4

DETERMINATION OF SUCTION CONSTANT BY METHOD

ξ	$K_{el} \cdot t_{\max}$	ξ	$K_{el} \cdot t_{\max}$	ξ	$K_{el} \cdot t_{\max}$
0,01	4,652	1,6	0,784	4,0	0,462
0,02	3,992	1,7	0,759	4,1	0,455
0,03	3,615	1,8	0,736	4,2	0,448
0,04	3,353	1,9	0,715	4,3	0,442
0,05	3,153	2,0	0,695	4,4	0,436
0,06	2,980	2,1	0,676	4,5	0,430
0,07	2,859	2,2	0,658	4,6	0,424
0,08	2,745	2,3	0,641	4,7	0,418
0,09	2,646	2,4	0,625	4,8	0,412
0,1	2,558	2,5	0,610	4,9	0,407
0,2	2,012	2,6	0,596	5,0	0,402
0,3	1,720	2,7	0,583	5,1	0,397
0,4	1,526	2,8	0,571	5,2	0,392
0,5	1,386	2,9	0,560	5,3	0,388
0,6	1,276	3,0	0,549	5,4	0,383
0,7	1,188	3,1	0,539	5,5	0,379
0,8	1,115	3,2	0,529	5,6	0,374
0,9	1,054	3,3	0,519	5,7	0,370
1,0	1,000	3,4	0,510	5,8	0,366
1,1	0,953	3,5	0,501	5,9	0,362
1,2	0,912	3,6	0,493	6,0	0,358
1,3	0,872	3,7	0,487	6.1	0,354
1,4	0,841	3,8	0,477	6,2	0,351
1,5	0,811	3,9	0,469	6,3	0,347

After completing the task, formulate a conclusion about the dependence of the therapeutic effect on the type of dosage form.

3.3. requirements for work results, including before registration

In accordance with the recommendations (instructions) for the tasks.

3.4. control materials for the final stage of the lesson: tasks, tasks, tests, etc .:

4. In order to prolong the action of nitroglycerin it is used in the form
   A. patch
   B. capsules
   C. suppository
   D. injections
   E. infusions
5. A patient who needs to prepare camphor ointment went to the pharmacy. What concentration of ointment should be prepared by a pharmacist, guided by the requirements of regulatory documents?
   A. 10%
   B. 1%
   C. 15%
   D. 20%
   E. 5%
6. The patient must undergo treatment with methindol (indomethacin). Which dosage form will be rational:
   A. tablets
   B. capsules
   C. suppositories
   D. ointment
   E. gel
7. When the influence of the type of dosage form on the process of analgin release by the method of "in vitro", as the medium used:
   A. water
   B. acid
   C. meadow
   D. formalin
   E. acetone
8. How will the quality of gelatin capsules change if the temperature of the mass specified in the regulations is reduced during their formation by the immersion method?
   A. the walls of gelatin capsules will be thick
   B. the walls of gelatin capsules will be thin and brittle
   C. the walls of the gelatin capsules will be with the inclusion of air
   D. the walls of gelatin capsules do not dissolve
   E. the walls of gelatin capsules will be very hard
9. What are the acid-resistant coatings used in the manufacture of tablets and capsules:

A. plasticizers
B. enteric
C. disintegrating
D. thixotropic
E. insoluble

10. What are the substances that promote deaggregation of encapsulated powder mass:
A. thixotropics
B. slippery substances
C. disintegrators
D. anti-fractional substances
E. fillers

11. Excipients in the dosage form do not affect:
A. pharmacokinetic parameters
B. appearance, stability, storage
C. conditions of technological operations
D. homogeneity by weight of packaging units
E. therapeutic equivalence

12. The patient needs to prepare a non-fat cream. What substances can be used as a basis for such a cream?
A. Sunflower or cottonseed oil.
B. Vaseline oil
C. Methylcellulose base
D. Vaseline-lanolin base.
E. Vaseline

13. The patient needs to prepare a non-fat cream. What substances can be used as a basis for such a cream?
A. Sunflower or cottonseed oil.
B. Vaseline oil
C. Gelatin-glycerin base.
D. Vaseline-lanolin base.
E. Vaseline

IV. Summing up

List of recommended reading

Main:

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

4. Biopharmaceuticals: Biochemistry and Biotechnology, 2nd Edition. – 2013. – 544 p

ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF DRUGS TECHNOLOGY

APPROVE
Head of Department

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

METHODICAL DEVELOPMENT OF PRACTICAL LESSON

Course: 5 Faculty: Pharmaceutical

Course Biopharmacy

Practical lesson №5 Topic: **«The influence of the route of administration and simple chemical modification of drugs on the process of their absorption.»**

The practical lesson was developed by:
Ph.D., Assoc.

_____ (Fizor. N.S.)
signature
The practical lesson was discussed at the methodical meeting of the department
«29» august 2022 y.
Protocol № 1

Odesa – 2022

The purpose of the lesson: the formation of knowledge, skills, practical skills to study the effect of the route of administration and simple chemical modification of drugs on the process of absorption.
Basic concepts: simple chemical modification
Equipment: according to the requirements of Good Pharmacy Practice (GPP).
Study time: 2.0

Plan

I. Organizational moment.
II. Control of basic knowledge
2.1. Requirements for theoretical readiness of students to perform practical classes (knowledge requirements, list of didactic units):
Requirements for theoretical knowledge:

Simple chemical modification

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

For example: novocaine - base and salt of novocaine hydrochloride; codeine - base and codeine phosphate - salt; caffeine - base and caffeine-sodium benzoate - salt; alginic acid and sodium and calcium salts of alginic acid.

From the point of view of official standards, the replacement of some substances by others is valid and should not cause objections and affect the therapeutic efficacy, because the substances have a similar pharmacological action. However, the clinical application of simple modifications of the drug substance shows different results due to their pharmacokinetics. Thus, the alkaloid quinine - base can be used in medical practice in the form of various salts: quinine sulfate (solubility 1: 800) quinine chloride (solubility 1:34), quinine bromide (solubility 1:16). These substances have different pharmacokinetics, retaining the main effect. When replacing the hydrogen ion in ascorbic acid with sodium ion, the drug acquires the ability to change the electrolyte balance of the body to a greater extent and to detect non-characteristic ascorbic acid properties - to suppress the function of the insular apparatus in patients with diabetes. Solutions of etmosin, amphotericin B and partusistene can not be prepared on saline, as there is a phenomenon of salting. It is not recommended to use glucose solution as a solvent when preparing solutions of alkaline substances. It reduces the activity of euphyllin, hexamethylenetetramine, caffeine-sodium benzoate and other drugs due to changes in pH. Cardiac glycosides should also not be diluted with glucose solution, as they are easily hydrolyzed. Essence for injection (opalescence) should not be combined with glucose and sodium chloride solution.

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

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

Oral route of administration of drugs

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

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

Many drugs taken after a meal can lose or significantly reduce activity by interacting with digestive juices.

Erythromycin, benzylpenicillin, pancreatin, pituitrin, insulin and a number of other drugs are inactivated under the influence of acidic environment and gastric enzymes. Hexamethylenetetramine is completely decomposed into ammonia and formaldehyde. Preparations of cardiac glycosides (lily of the valley, strophanthus, sea onion) are completely destroyed, and the most stable of them - preparations of foxglove - significantly reduced activity under the action of enzymes of the gastrointestinal tract. However, in the presence of proteolytic enzymes, tetracycline and isoniazid are absorbed more rapidly. Gastric juice stimulates the absorption and acetylation (transition to an inactive form) of sulfonamide drugs.

A serious obstacle to the absorption of many drugs is mucin, which is released after a meal and covers a thin, highly viscous film of the mucous membranes of the mouth, stomach and intestines. Streptomycin sulfate, atropine sulfate, belladonna preparations, scopolamine hydrobromide, platyphylline hydrotartrate, antispasmodic, aprofen, metacin form poorly absorbed complexes with mucin.

Bile increases the solubility of some fat-soluble substances (vitamins) and at the same time is able to form sparingly soluble and non-absorbable complexes with neomycin sulfate, polymyxin B sulfate. Bile acids can bind to sodium paraaminosalicylate, activated charcoal, white clay, and so on, and their deficiency leads to impaired absorption of other drugs (diphenine, rifampicin, butadione, etc.).

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

Influence of composition and temperature of food

The composition and temperature of food have a great influence on the effectiveness of drugs.

Ordinary mixed food contains substances of plant, animal and mineral origin: proteins, fats, carbohydrates, amino acids, fatty acids, glycerin, tannins (in tea, persimmons), caffeine (in tea, coffee), serotonin (in nettles, peanuts, bananas). , pineapples), tyramine (in cheese, bananas, beans, herring, coffee, beer, wine, chicken liver), oxalates (in rhubarb, celery, sorrel, spinach), sterols, phytosterols, heavy metal ions and other chemically and pharmacologically active substances. In addition, various food additives are introduced into food: preservatives (sorbic, acetic, citric acid), antioxidants, emulsifiers, sweeteners, substances that can actively interact with drugs and affect their bioavailability: in some cases increase the solubility and absorption drug, in others, to form insoluble or sparingly soluble complexes (eg, proteins, tannins, dipeptides) with food components, reduce their absorption.

Depending on the composition of food affects the peristalsis and secretory function of the digestive tract, which affects the degree and rate of absorption of the drug.

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 gastric motility, which leads to delayed digestive processes and transportation of food mass. Under the influence of foods rich in fat, significantly increases the absorption of many drugs, especially fat-soluble, such as anthelmintics, anticoagulants, sulfonamides, griseofulvin, anaprilin, diphenine, fat-soluble vitamins A, D, E, K, carbamazepine, methadone and seduda etc. Deficiency in the diet of fats slows down the metabolism of ethylmorphine hydrochloride. Pre-eating fatty foods reduces the activity of salol and besalol.

The presence of a large amount of carbohydrates in food (sugar, candy, jam) slows down the motility of the stomach, delays the absorption in the intestine of isoniazid, calcium chloride. The effect of food carbohydrates can be indirect - through intermediate metabolism.

Food slows down the absorption of phenoxymethylpenicillin, oxacillin sodium, ampicillin, rifampicin, lincomycin hydrochloride, acetylsalicylic acid, glibenclamide, isoniazid, etc. Medicinal substances containing sulfur, when interacting with heavy metal ions that are constantly in the food, form insoluble compounds with low bioavailability. The absorption of drugs from the digestive tract is delayed by low molecular weight products of hydrolysis of nutrients: glucose, amino acids, fatty acids, glycerin, as well as sterols contained in food.

Foods rich in vitamins and minerals affect the metabolism of drugs. Foods containing ascorbic acid stimulate the function of oxidases, accelerating the metabolism of drugs, and sometimes reduce their toxicity; containing folic acid, accelerates the metabolism of pyridoxine hydrochloride, reduces the effectiveness of levodopa. In patients who eat foods rich in vitamin K (spinach, white cabbage),

significantly changes the prothrombin time, as well as the metabolism of anticoagulants, barbiturates, nozepam, phenacetin. In some cases, food increases the bioavailability of drugs such as verospirone, dicoumarin, beta-blockers, and others.

The temperature of food also has a certain effect. Very cold (below 7 ° C), as well as excessively hot (above 70 ° C) food and drinks cause digestive disorders. Cold food increases the excretory function and acidity of the stomach contents, followed by a decrease and weakening of the ability of gastric juice to digest. Excessively hot food leads to atrophy of the gastric mucosa, accompanied by a sharp decrease in the secretion of gastrointestinal enzymes. These changes in gastrointestinal secretion in turn affect the bioavailability of the drug.

Influence of the nature of the liquid used to wash down the drug

A certain role in the bioavailability of drugs is played by the nature of the liquid that the drug drinks. Often, to mask the unpleasant taste and smell of drugs, use a variety of fruit or vegetable juices, tonic drinks, syrups, milk. Most fruit and vegetable juices are acidic and can destroy acid-labile compounds, such as ampicillin sodium, cycloserine, erythromycin (base), potassium salt of benzylpenicillin. Juices can slow down the absorption of ibuprofen, furosemide, enhance the pharmacological effect of adebit, barbiturates, diacarb, nevigramon, nitrofurans, salicylates. Fruit juices and beverages contain tannins that precipitate digitoxin, caffeine-sodium benzoate.

The tonic drinks "Baikal", "Pepsi-Cola" include iron ions, which in the gastrointestinal tract form insoluble complexes with lincomycin hydrochloride, oleandomethacin phosphate, tetracycline hydrochloride, sodium thiosulfate, unithiol, slowing down.

Widely used for these purposes, tea and coffee contain, in addition to caffeine and theophylline, tannin and various tannins and can potentiate the pharmacological effect of paracetamol, acetylsalicylic acid, form insoluble compounds with aminazine, atropine sulfate, haloperidol, coderohydrin, hydrochloride morphine . Therefore, they are not recommended to drink the medication, except for hypnotic barbiturates, which drink 1/2 cup of warm, weak and unsweetened tea.

When sweetening the drug with syrups or milk sugar, the absorption of isoniazid, ibuprofen, calcium chloride, tetracycline hydrochloride, furosemide is sharply slowed down. Some drugs that have an irritating effect on the gastrointestinal mucosa, washed down with milk. Medicines for their infants are mixed with milk and dairy products. Milk can change the drug substance and reduce the bioavailability of, for example, benzylpenicillin, cephalexin. A glass of whole milk reduces by 50-60% the concentration in the blood of tetracycline hydrochloride, oxytetracycline and metacycline hydrochloride, having a slightly smaller effect on the absorption of doxycycline hydrochloride. It is not recommended to drink with milk drugs that have an acid-resistant coating (enteric), such as bisacodyl, pancreatin, pancurman, because of the risk of premature dissolution of the protective shell. For the same reason, it is impractical to drink these drugs with alkaline mineral waters (Borjomi, Luzhansk, Svalyava, Smirnovsk). On the contrary, alkaline mineral waters should be washed down with pancreatin, PAS, salicylates, citramon, phthazine, novocephalgin and

sulfonamides. The latter are acetylated in the body, and acetyl compounds in a neutral and acidic environment do not dissolve and precipitate in the form of stones. In the alkaline environment of acetylation sulfanilamides are in a dissolved state and are easily excreted from the body.

Taking the drug in a mixture with milk by children can lead to a violation of the accuracy of their dosage. Drink milk those drugs that irritate the surface of the gastrointestinal mucosa, do not change their activity at milk pH (6, 4), do not bind to milk proteins and calcium (butadione, indomethacin, prednisolone, reserpine, trichopol, potassium salts, nitrofurans, vibramycin, ethoxide, mefenamic acid, iodine preparations, etc.).

Some patients, taking the drug, do not drink it at all, which is not recommended, because the capsules, tablets, pills, sticking to certain parts of the inner surface of the esophagus and gastrointestinal tract, are destroyed before reaching the site of absorption. In addition, they cause irritation at the site of adhesion, and the lack of sufficient fluid delays their absorption.

Rectal route of administration of the drug

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

At a rectal way of introduction bioavailability can be influenced by individual features (blood supply of a rectum, a condition of its mucous membrane (with age, at systematic use of laxatives, at a thematic lack of vegetable fiber in food, the functional condition of a mucous membrane worsens).

The glands of the mucous membrane of the colon secrete a liquid alkaline secretion (pH sometimes exceeds 9). Changes in intestinal pH, as well as changes in gastric pH, significantly affect the degree of ionization and absorption of drugs.

The process of intestinal absorption is influenced by the autonomic nervous system (2 and (-adrenergic agonists stimulate absorption, and cholinergic agonists - secretion), endocrine system, biologically active peptides. Endocrine, autonomic nervous and neuropeptide systems regulate in turn, determines the length of stay of the drug in the intestine.

A number of diseases of the rectum (hemorrhoids, cracks in the anorectal region, proctitis) also impair the bioavailability of drugs administered rectally.

Inhalation route of drug administration

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

Didactic units:

-simple chemical modification;
-oral route of administration of the drug;
-rectal route of administration of the drug;
-inhalation route of drug administration;

2.2. Questions (tests, tasks, clinical situations) to test basic knowledge on the topic of the lesson:

Answer the question:

1. The concept of simple chemical modification of drugs and its impact on the bioavailability and stability of drugs.
2. Ways of introduction of drugs into an organism and their influence on therapeutic activity.
3. The main biological factors affecting the absorption of drugs.
4. The influence of the physiological state of the patient on the pharmacodynamics and pharmacokinetics of drugs.
5. Variable biochemical factors. Drug metabolism.
6. Influence of exogenous factors on pharmacotherapy.
7. Interaction of drugs with food.
8. Modern methods of analysis of drugs in biological fluids.

Solve tests:

1. Indicate which term corresponds to the following statement: "Part of the total absorbed dose of the drug that enters the circulatory system after oral administration."

A. therapeutic inequality
B. equivalence
C. pharmaceutical inequality
D. relative bioavailability
E. system availability

2. The fastest pharmacological effect develops with the introduction of drugs:

A. Subcutaneously
B. Rectally
C. Orally

D. Intravenously
E. Intramuscularly

3. Patient P., 45 years old, has had angina pectoris for a long time. Nitrate intake is not always regular due to the nature of work. The doctor advised long-acting nitrate, which does not require control during the day. What form of drug allows you to do this?

A. Granule.
B. Tablet.
C. Plaster.
D. Capsule
E. Solution

4. Who first discovered the phenomenon of polymorphism?

A. Boucher
B. Halabala
C. Dewey
D. Fat
E. Hajj

5. The dissolution time for suppositories on a hydrophilic basis should not exceed:

A. 20 min
B. 30 min.
C. 45 min
D. 1 hour
E. 2 years

6. Is it permissible to arbitrarily replace any ion in the drug molecule, based on purely technological or economic considerations:

A. inadmissible
B. admissible
C. is permissible only for technological reasons
D. is permissible only for economic reasons
E. is permissible only with the permission of the head of the enterprise

7. What is meant by the term aggregate state of drugs?

A. electrical conductivity
B. solubility
C. amorphous

D. polymorphism
E. pH

8. What is meant by the term aggregate state of drugs?

A. electrical conductivity
B. solubility
C. crystallinity
D. polymorphism
E. pH

9. What is meant by the term physicochemical properties of drugs?

A. pH
B. polymorphism
C. physicochemical properties
D. degree of purity
E. all the answers are correct

10. Which of the following compounds does not belong to the polymorphic modifications of carbon?

A. coal
B. diamond
C. graphite
D. granite
E. Gravel

III. Formation of professional skills, abilities:

3.1. content of tasks:

Task № 1

To establish the effect of a simple chemical, medicinal formula, modification and route of administration on the pharmacological action of barbital and sodium barbital.

Task № 2

To establish the effect of a simple chemical modification of the dosage form of furosemide on the rate of onset and the amount of diuresis when administered intraperitoneally in rats.

3.2. recommendations (instructions) for performing tasks

Task №1

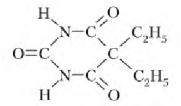
Methodical recommendations for the task

The effect of the route of administration and simple chemical modification on the therapeutic activity of drugs can be traced on 2 drugs of barbital: barbital and barbital sodium. Both drugs have a hypnotic effect and are derivatives of barbituric acid.

The choice of barbital as an object of study is due to the simplicity of control of the therapeutic effect of the drug. To simplify the experiment (for educational purposes only), you can limit yourself to one animal for each route of administration.

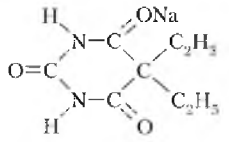
The object of study is: 1% suspension of barbital, 1% solution of sodium barbital, barbital sodium tablets.

Barbital
Barbitalum



5,5-Diethylbarbituric acid

Barbital
Barbitalum



5,5-Diethylbarbiturate-sodium

Before completing the task, get acquainted with the algorithm of experimental work for task № 1 (Appendix 1).

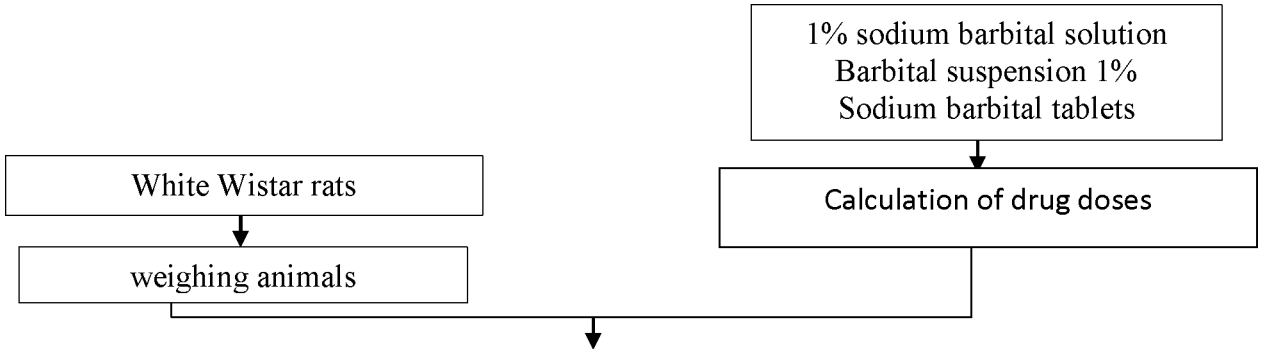
Technology. Under aseptic conditions on BP-1 weigh 1.0 barbital, grind in a mortar with 10 drops of water for injections (according to Deryagin's rule), then add the remaining water, transfer to a vial, make out.

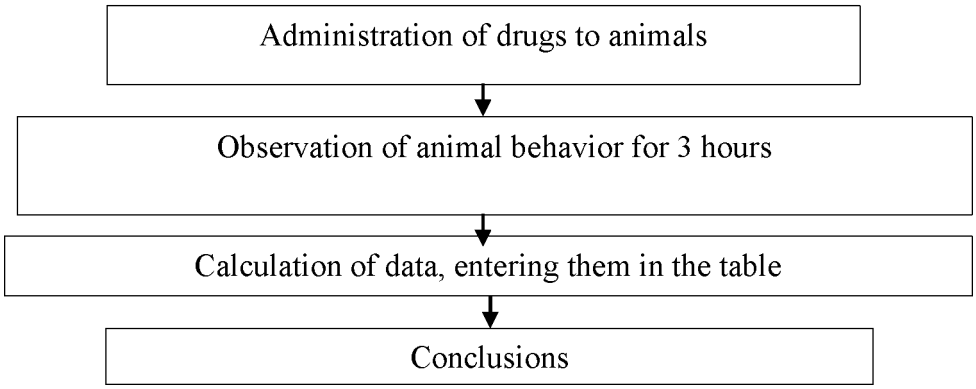
The barbital-sodium solution is prepared in a volumetric flask, first weighed dry matter, and then dissolved in a portion of water for injection and brought to the mark, filtered into a vial, the first portions are returned to the filter, then proceed similarly. Prepared drugs are not sterilized. According to the literature, they are prepared under aseptic conditions.

Preparation of 1% suspension of barbital sodium tablets. The tablets are crushed in a mortar. The exact weight of the tablets in terms of the content of the active substance is weighed on BP-1 and placed in a mortar, add first a small amount of purified water, and then the remaining water.

Appendix 1

ALGORITHM FOR DETERMINING THE INFLUENCE OF THE ROUTE OF INTRODUCTION, DOSAGE AND SIMPLE CHEMICAL MODIFICATION OF BARBITAL AND BARBITAL-SODIUM ON HIGH SPEED AND HIGH SPEED





Determination of the hypnotic effect of barbital and barbital sodium

The hypnotic effect of the obtained drugs is studied in rats. In experiments using white Wistar rats weighing 200-220 g. The animals are weighed and the dose of drugs is calculated.

The drugs are administered at a rate of 10 mg / 100 g of animal weight, in terms of volume - 1 ml per 100 g

One rat is injected "per os" 1% suspension of barbital intramuscularly (in the back muscle). Another animal is administered a similar dose of 1% sodium barbital solution by intraperitoneal administration. The third rat - a tablet of barbital sodium - ground with water - "per os". The fourth rat is used as a control.

Experimental animals are placed under glass caps, providing free access of air. For three hours, observe the behavior of rats, recording the time of onset of muscle relaxation of the hind limbs, drowsiness, sleep (lateral position), the beginning of movements, full activity. The duration of sleep is determined by the difference between the time of onset of movement and the onset of sleep. Enter the obtained data in table. 1.

Table 1

DURATION AND DEPTH OF SNOIDING ACTION OF BARBITAL AND SODIUM BARBITAL IN DIFFERENT WAYS INTRODUCTION OF DIFFERENT PHARMACEUTICAL FORMS

The name of the drug	Mass of animal, g	Dose, mg / 100 g	Input path	Time of onset effect, min			
				Muscle relaxation of the hind limbs	Drowsiness without movement	Sleep duration	Full activity
Barbital suspension 1%							

Barbital sodium solution 1%							
Sodium barbital tablets							

After completing the task, draw conclusions about the rate of onset and depth of hypnotic action of barbital and barbital sodium at different routes of administration, as well as the effect of simple chemical modification of the dosage form.

Task № 2

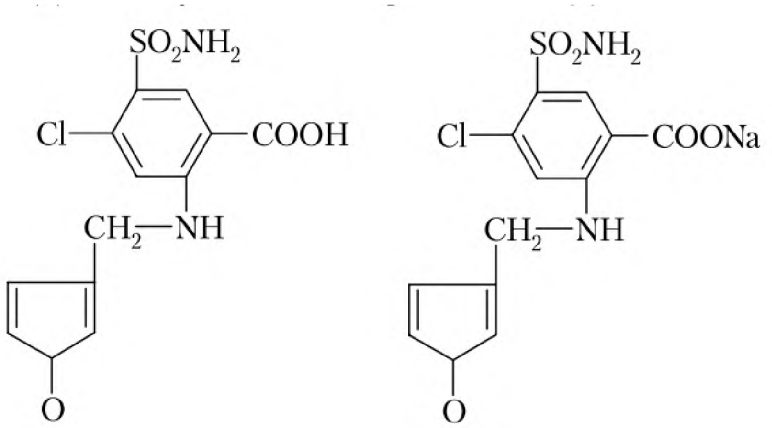
Methodical recommendations for the task

Furosemide (4-chloro-N- (2-furylmethyl) -5-sulfomoilanthronilic acid) is available in the form of tablets for oral administration and ampoule solution for parenteral administration (Lasix).

Storage:

Tablets		Ampouled solution	
Furosemide Milk sugar Wheat starch Talca Magnesium stearate	0.04 0.02 0.036 th most common 0.003 0.001	Furosemide 1n district of caustic soda Sodium chloride Water (saturated CO_2) to	0.02 0.064 0.015 2 ml
1 tablet	0.100	1 ampoule	2 ml

In tablets, furosemide is contained in acid form (1), and in ampoules in the form of sodium salt (2).

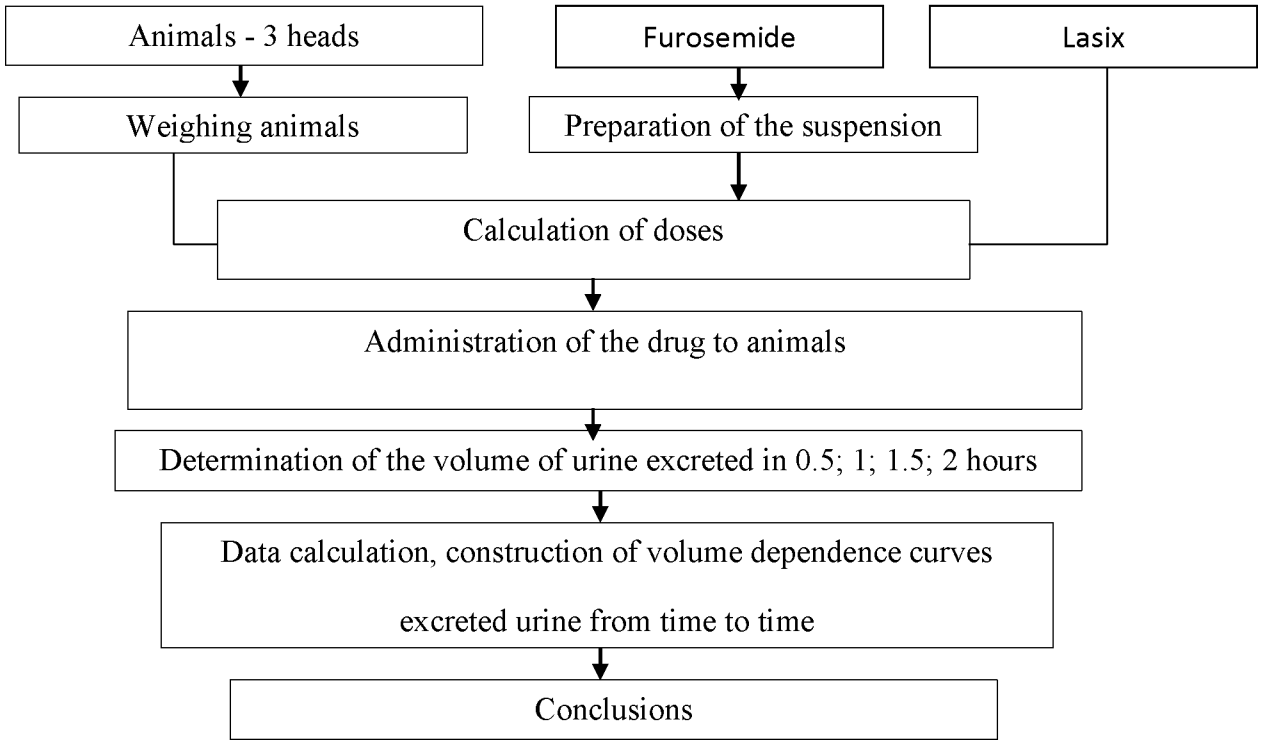


The sodium salt of furosemide is easily soluble in water, the acid form is insoluble, so they are administered to animals in the form of an aqueous solution and suspension, respectively. To simplify the experiment (for educational purposes only), you can limit yourself to one animal for each determination.

Before completing the task, get acquainted with the algorithm of experimental work for task № 2 (Appendix 2).

Annex 2

ALGORITHM
OF EXPERIMENTAL WORK ON DETERMINATION OF THE INFLUENCE OF SIMPLE CHEMICAL MODIFICATION AND DOCUMENT FORM OF FUROSEMIDE ON THE RATE OF OCCURRENCE AND SIZE INTRODUCTION TO RATS



The experiment is performed on three white rats of approximately the same weight and age. Animals are pre-weighed and injected "per os" with a cannula of 1 ml of purified water per 100 g of mass.

Weigh 0.05 g of powder of crushed tablets of furosemide (furosemide content of 0.02 g) and gradually disperse in a mortar with 2 ml of purified water. The resulting suspension is administered intraperitoneally to the first rat. The second animal is administered intraperitoneally 2 ml of lasix, corresponding to 0.02 g of sodium salt of furosemide. The control animal is injected intraperitoneally with 2 ml of purified water.

Rats are placed in plastic funnels and covered with metal nets. Measuring cylinders with a capacity of 25 ml are placed under the funnels. Note the beginning of diuresis and the volume of urine excreted every 30 minutes for 2 hours. At the end of the experiment, the animals are injected "per os" with a cannula 1-2 ml of water.

Enter the data in table 2. Based on the results obtained, plot the dependence of the volume of urine on time in coordinates: on the y-axis - the volume of urine excreted every 0.5 hours during the experiment (V , ml).

Table 2

SPEED OF OCCURRENCE AND SIZE OF DIURETIC EFFECT OF SODIUM AND ACID FORMS OF FUROSEMIDE AT INTRODUCTION TO RATS

№ p / p	Mass of animal, g	The dose of furosemide, g	The chemical formula of furosemide	Input time	Time of the beginning of diuresis, h, min	Time from the moment of drug administration, min	The total amount stood out urine (*v*), ml			
							The amount of urine that is excreted for the last 0.5 h (Δv), ml			
							after 0.5 hours	in 1 hour	in 1.5 hours	in 2 hours

After completing the task, draw conclusions about the effect of chemical modification of furosemide on the rate and magnitude of diuretic action during intra-abdominal administration.

3.3. requirements for work results, including before registration

In accordance with the recommendations (instructions) for the tasks.

3.4. control materials for the final stage of the lesson: tasks, tasks, tests, etc .:

1. Which of the following indicators affects the size of the colored area during the study of streptocide ointment by agar plates?

   A. the physical state of streptocide
   B. the degree of grinding of streptocide
   C. the phenomenon of polymorphism in the ointment
   D. quantitative content of streptocide
   E. purity of the substance

2. Which of the following factors applies to pharmaceuticals?

   A. physical condition of the drug
   B. become ill
   C. concomitant pathologies
   D. time of taking the drug
   E. pregnancy

3. Which of the following factors applies to pharmaceuticals?

A. technological process
B. become ill
C. concomitant pathologies
D. time of taking the drug
E. age of the patient

4. Which of the following factors does not apply to pharmaceuticals?

A. excipients
B. simple chemical modification
C. dosage form and ways of its introduction into an organism
D. to become ill
E. technological process

5. When making a solution of novocaine 0.5% it is stabilized with a solution of:

A. 0.1 N HCl solution
B. 0.1 N NaOH solution
C. 0.1 N KOH solution
D. 0.1 N Na2SO4 solution
E. do not stabilize

6. How much ethylene glycol should be taken to prepare 100.0 proxanol base?

A. 14.0
B. 21.0
C. 28.0
D. 30.0
E. 44.0

7. Patient [U1] needs to prepare a non-fat cream. What substances can be used as a basis for such a cream?

A. Sunflower or cottonseed oil
B. Vaseline oil
C. Carbopol basis
D. Vaseline-lanolin base
E. Vaseline

8. Stirring the dissolution medium provides:

A. uniform concentration of the drug substance;
B. reproducibility of the results of the experience;

C. increased diffusion;
D. the ability to change the dissolution rate and type of kinetics;
E. pharmacological activity.

9. At what stage of the study by the method of agar plates is used reagent iron (III) chloride?

A. is added to agar during cooking
B. is introduced into the agar after it hardens
C. introduced into the ointment before use
D. apply to the ointment after filling the agar wells
E. add simultaneously to the ointment and agar

IV. Summing up

List of recommended reading

Main:

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

ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF DRUGS TECHNOLOGY

APPROVE
Head of Department

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

METHODICAL DEVELOPMENT OF PRACTICAL LESSON

Course: 5 Faculty: Pharmaceutical

Course Biopharmacy

Practical lesson №6 Topic: « **The influence of technological factors on the dissolution rate of tablets and the stability of injectable solutions. Therapeutic non-equivalence of drugs.»**

The practical lesson was developed by:
Ph.D., Assoc.

_____ (Fizor. N.S.)
signature
The practical lesson was discussed at the methodical meeting of the department
«29» august 2022 y.
Protocol № 1

Odesa – 2022

The purpose of the lesson: To study the influence of technological factors on the dissolution rate of tablets and the stability of injectable solutions, as well as the therapeutic equivalence of drugs.
Basic concepts: polymorphism, optical properties, degree of ionization of matter.
Equipment: according to the requirements of Good Pharmacy Practice (GPP).
Study time: 2.0

Plan

I. Organizational moment.
II. Control of basic knowledge
2.1. Requirements for theoretical readiness of students to perform practical classes (knowledge requirements, list of didactic units):
Requirements for theoretical knowledge:

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

All pharmaceutical factors that affect the biological action of drugs can be divided into 5 groups:

- Physical condition of the drug substance;
- Simple chemical modification of the drug;
- Excipients (their nature, physical condition and quantity);
- Dosage form and ways of its introduction into the body;
- Technological process.

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

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

From the point of view of biopharmacy and pharmacokinetics, the drug will have the necessary bioavailability only if the drug is presented in the most favorable condition for the resorptive process (ionic or molecularly dispersed form).

Physical state of the drug

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

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

Grinding of medicinal substances is the simplest, but at the same time one of the most important technological operations performed by the pharmacist in the preparation of various dosage forms. The dispersion of the drug affects not only the flowability of powdered materials, bulk, homogeneity of mixing, dosing accuracy. It is especially important that the particle size depends on the speed and completeness of

absorption of the drug, as well as its concentration in biological fluids, mainly in the blood, in any way of its appointment in the form of various dosage forms.

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

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

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

It is known that polymorphic modifications form many chemicals and, including drugs. Since the discovery of the Devi carbon polymorphism (1809) (graphite, coal, and diamond), the transitions of some polymorphic modifications to others have been studied in detail. It is emphasized that the *chemical composition remains unchanged,* which is taken mainly for quality assessment. A review of works on the study of polymorphism in medicinal substances is given in the works of AI Tentsova, Halebleyne, Bush, Halabala.

Particles of drugs in the form of a powder in the solid state have a different structure (crystalline or amorphous), which depends on the molecular structure of a substance. Electron microscopic studies have shown that drugs in most cases have a crystalline structure, due to the fixed location of atoms in the molecule and the directional growth of crystals under certain conditions during crystallization. The amorphous state is less common. Any drug 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 particle size, etc.). conditions, the substance crystallizes in another system and has other physicochemical characteristics, and hence other indicators of bioavailability. Such physical characteristics of powders in the existing AND as "crystalline", "fine crystalline", "amorphous", "light powder" are sufficient for the technological process, but to identify their impact on therapeutic activity requires more accurate definitions given by crystal chemistry.

There are seven crystallographic systems (syngony): monoclinic, diclinal, trigonal, tetragonal, hexagonal, rhombic, cubic, they are used to identify drugs. Andronik I. Ya. And Babil FV published an atlas of diffractograms of crystalline drugs and developed an information retrieval system for the identification of crystalline

drugs by their diffraction spectra. The use of an atlas and an automated system can speed up the identification of drugs.

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

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

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

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

The dissolution process also affects the effectiveness of drugs.

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

Usually more soluble substances are released faster from dosage forms, are absorbed faster, have a faster therapeutic effect. At the same time, for the prolongation of action are more suitable sparingly soluble drugs to create such drugs, sometimes creating an environment in which the drug does not dissolve. For example, when prescribing a solution of estradiol benzoate in oil, the drug has a therapeutic effect for 3 days, and when administered as an aqueous suspension - about 3 weeks.

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

The choice of excipients - Solubilizer, co-solvents, surfactants, which in turn can increase the effectiveness of the drug, has a particularly significant effect on the solubility of drugs. This confirms the need for targeted use of both excipients and the choice of technological method of obtaining dosage forms.

The therapeutic activity of drugs is also significantly influenced by their *optical properties.* There is no chemical difference between optical isomers, but each of them rotates the plane of the polarizing beam in a certain direction. Although chemical

analysis fully confirms the presence of the same substance in drugs with different isomers, they will not be therapeutically equivalent.

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

Anhydrous drugs or crystal hydrates have different solubilities, which leads to a change in their pharmacological action. For example, anhydrous forms of caffeine, ampicillin, theophylline dissolve faster than their crystal hydrates, and therefore are absorbed faster.

Excipients

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

Such substances include: starch, glucose, purified water, ethyl alcohol, Vaseline, cocoa butter, talc, bentonites, Aerosil, paraffin, wheat flour, polyethylene oxides, various cellulose derivatives, etc.

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

However, no pharmaceutical factor has such a significant and complex effect on the action of the drug as excipients. Biopharmacy for the first time gave a scientific justification for the use of excipients and showed the complete failure of the empirical attitude to them, inherited by pharmacy from the distant past. Research on excipients has been so extensive and revolutionary that it has led some scientists to define biopharmacy as the science that studies the effects of excipients on the therapeutic efficacy of drugs.

Based on work biopharmaceutical found that *adjuvants - is not indifferent* mass used in purely technological terms. They have certain physicochemical properties and depending on the nature of the substance *can enhance, reduce, change the nature of the action of drugs* under the influence of various causes and combinations (complexation and adsorption, molecular reactions, etc.), which can dramatically change the rate and complete absorption of the drug. The interaction between drugs and excipients can occur both in the process of preparation of drugs and in the process of their storage.

It is known that the degree of interaction is determined by the energy of the physico-chemical or chemical bond. If the *bond is fragile* (vanderwaals forces - 1 kcal / mol (4.10 ^{3} J) or hydrogen bond 7-10 kcal / mol), the process can be reversed, because the body can cope with this bond, can split, modify and the drug will be disposed of.

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

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

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

Excipients may not only reduce the pharmacological action of drugs, but also form compounds which, in contrast, are characterized by a high degree of dissolution and bioavailability (eg, polyvinylpyrrolidone-prednisolone; polyvinylpyrrolidone-griseofulvin; polyvinylpyrrolidone-salicylavimide; . Saponins enhance the absorption of glucose in the gastrointestinal tract. Sodium lauryl sulfate accelerates the absorption of penicillin, griseofulvin, etc.

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

The biological membranes through which the drug is absorbed must be considered as a complex receptor mechanism through which resorption is performed according to Fick's law based on the law of diffusion, but in strict order and at different rates.

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

Among these factors it is necessary to consider the latter, all other things being equal. It is known from the literature that the best resorptive ability have dissociating low molecular weight compounds, substances having a diphilic structure with methyl, ethyl, phenyl and other radicals, substances with greater affinity for the environment.

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

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

Examples of the effect of excipients on therapeutic efficacy are known in the literature. For example, lactose minimizes the action of isoniazid, but enhances the action of testosterone, slows down the action of barbital. Twin-80 enhances the adsorption of vitamins A, D, E.

Excipients can not only enhance but also reduce the therapeutic effect, mechanically blocking the path to resorption of drugs.

Among the works devoted to the study of the effects of excipients, special attention is paid to ointment and suppository bases. Thus, Professor IS Azhgikhin studied the effect of the type of bases on the pharmacokinetics of drugs in suppositories with sodium salicylate, acetylsalicylic acid, norsulfazole, ephedrine hydrochloride, teturam, isoniazid, PAS, ftivazide, furazolidone, intataledone. The introduction of even a small amount of dimethyl sulfoxide led to a sharp increase in the rate of adsorption of active substances.

Ointments prepared on Vaseline have a superficial effect, as Vaseline does not penetrate the skin well and blocks the access of the drug to tissues (ointments of sulfonamides, phenols, antibiotics, etc.).

Replacement of vaseline-lanolin base on polyethylene glycol in the combined ointment "Levosin" allowed to increase its antimicrobial action 20-80 times. This ointment used the potentiating effect of PEG-400 on chloramphenicol, discovered by PS Bashura and VI Bogdanova. It turned out that when chloramphenicol is dissolved in VEO-400, the sensitivity of various microorganisms to it increases 62 times (Wood's staphylococci and Escherichia coli; typhoid, pathogenic Escherichia coli and Grigoriev-Shiga dysentery bacteria - 8 times).

The antimicrobial spectrum of other antibiotics with the use of similar bases also increases, with the exception of penicillin.

The choice of excipients is made on a scientific and rational basis (economic, aesthetic, etc.), which provides for their functional purpose, ensuring bioavailability, technological characteristics, technological properties, cost-effectiveness and affordability. Thus, the variety of properties of drugs and excipients and the rapid growth of their range obliges the specialist to abandon attempts to convert any excipient into a universal, used with any drug.

Technological (production) processes are methods that consist of certain technological techniques and operations.

The behavior of drugs in the body may depend on pharmaceutical technology. In pharmacies and factories, drugs were prepared in strict accordance with the provisions of general technology and were evaluated on the basis of commodity principles in terms of weight, consistency, geometric shape, and content of active substances.

The discovery in the clinic of the dependence of the therapeutic efficacy of drugs on the methods of their preparation meant a fundamentally new understanding of the processes of pharmaceutical technology. Often changes in the substance can be determined by chemical methods, and only a biological assessment is reliable in determining the benignity of the drug.

Biopharmaceutical research has provided a scientific explanation of the role of technological processes, methods of obtaining drugs in the development of the effect. Until the formation of biopharmacy, this issue was given almost no attention.

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

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

Among the variety of technological operations of the production process of preparation of dosage forms, not all operations are equivalent in terms of physicomechanical properties of drugs, and in terms of their impact on the pharmacokinetics of drugs. The importance of dosage forms in pharmacotherapy, and their prevalence, and the degree of study of their production processes are unequal.

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

Didactic units:

- Physical state of the drug
- Polymorphism
- Excipients
- Technological (production) processes

2.2. Questions (tests, tasks, clinical situations) to test basic knowledge on the topic of the lesson:

Answer the question:

1. The influence of technological factors on pharmacotherapy.
2. The concept of drug stability. The role of stabilizers in drug technology.
3. The influence of drug storage conditions on their stability.
4. Methods for determining the stability of injectable solutions.
5. The concept of therapeutic inequivalence of drugs and the causes of its occurrence.
6. Brands and generics. Replacement of drugs by their analogues.

Solve the test:

1. The recipe prescribes a powder, which includes glucose, boric acid and analgin in equal amounts. Specify the ingredient to be crushed first:

A. Boric acid
B. Analgin
C. A mixture of boric acid and glucose
D. A mixture of analgin and boric acid
E. Glucose

2. The teacher in the laboratory asked the students: "Which substances from the list are colored?" Enter the correct answer:

A. Etacredine lactate, protargol, furacillin;
B. Furacillin, protargol, sulfur, copper sulfate;
C. Sulfur, copper sulfate, protargol, kolargol;
D. Riboflavin, protargol, sulfur, copper sulfate;
E. Furacillin, ethacredine lactate, acridine

3. The teacher asked the students to list the basic requirements for powders. From the following properties, enter the incorrect answer:

A. Homogeneity of mixing
B. Optimal dispersion
C. Looseness
D. Optimal solubility
E. Stability

4. Specify the method of obtaining tablets that provides the fastest release of the drug:

A. through the formation of solid dispersions;
B. due to wet granulation;
C. direct pressing;
D. formation;
E. through structural granulation.

5. Specify the main requirements that apply to powders:

A. Looseness, mixing uniformity, dosing accuracy, stability, optimal dispersion
B. Looseness, dosing accuracy, optimal solubility, uniform distribution of the substance throughout the mass of the powder
C. Looseness, homogeneity of mixing, stability, optimal solubility
D. Homogeneity of mixing, flowability, optimal solubility, stability
E. Stability, sterility, optimal solubility.

6. For introduction of medicinal substances in a basis at homogenization of ointments in factory production use:

A. magnetostrictive emitter;
B. steam coil;
C. reactor with RPA;
D. grinder mills;
E. ultrasonic installation

7. Vials are used to release injectable solutions:

A. Alkaline glass
B. Neutral glass brand NS-1, NS-2
C. Perfume bottles
D. Sour glass
E. Borne glass

8. To intensify the processes occurring in the manufacture of emulsion, suspension and combined ointments, use

A. RPA
B. disk mazeterka
C. dismembler
D. Unitron faucet,
E. suction filter.

9. The pharmacist additionally used paraffin to prepare the ointment. Indicate the role of paraffin in technology?

A. sealant
B. basis
C. preservative
D. for dispersing powders
E. emulsifier

10. To prepare eye lotion from ethacridine lactate, the pharmacist-technologist used as an excipient to create an isotonic concentration of sodium chloride. Evaluate the actions of the pharmacist.

A. Sodium sulfate should be used for isotoning
B. Boric acid must be used for isotoning
C. Glucose solution should be used for isotoning
D. Sodium nitrate should be used for isotoning
E. Etacridine eye lotions are not lactated with lactate

In . *Tasks for self-control with answers.*

III. Formation of professional skills, abilities:

3.1. content of tasks:

Task № 1

To establish the influence of technological factors on the dissolution rate of "Propolin" tablets and the release of FGPP (phenolic hydrophobic preparation of propolis) by the "in vitro" method.

Task № 2

To study the effect of hydrochloric acid on the stability of novocaine solution for injection by the "invivo" method.

Task № 3

To study the effect of hydrochloric acid on the stability of novocaine solution for injection by quantitative rapid analysis.

Task № 4

To establish the therapeutic equivalence of tablets produced by different manufacturers by the method of "In vitro".

Task № 5

To establish the antipyretic effect of acetylsalicylic acid tablets produced by different manufacturers by the "in vitro" method.

3.2. recommendations (instructions) for performing tasks

Task № 1

Methodical recommendations for the task

When developing solid dosage forms, a solubility test is mandatory.

To assess the dissolution rate of tablets using the device "Rotating basket". Along with the dissolution of the tablets, which is determined visually, also study the release of the drug substance from the dosage form.

The objects of the study are tablets "Propoltin", obtained by direct compression and wet granulation.

The composition of the tablets includes:

Phenolic hydrophobic preparation of propolis 0.010;
Glucose 0.015;
Lactose 0.040;
Powdered sugar 0.006;
Starch 0.038;
Calcium stearate 0.001;
In total - 0,110.

Preparation of tablets by direct compression *(technology № 1)*

The resulting tablet mass is compressed into tablets with a core weight of 0.11 g, with a diameter of 7 mm on a rotary press "Kellian".

Technology of tablets "Propolin" by granulation method *(technology № 2)*

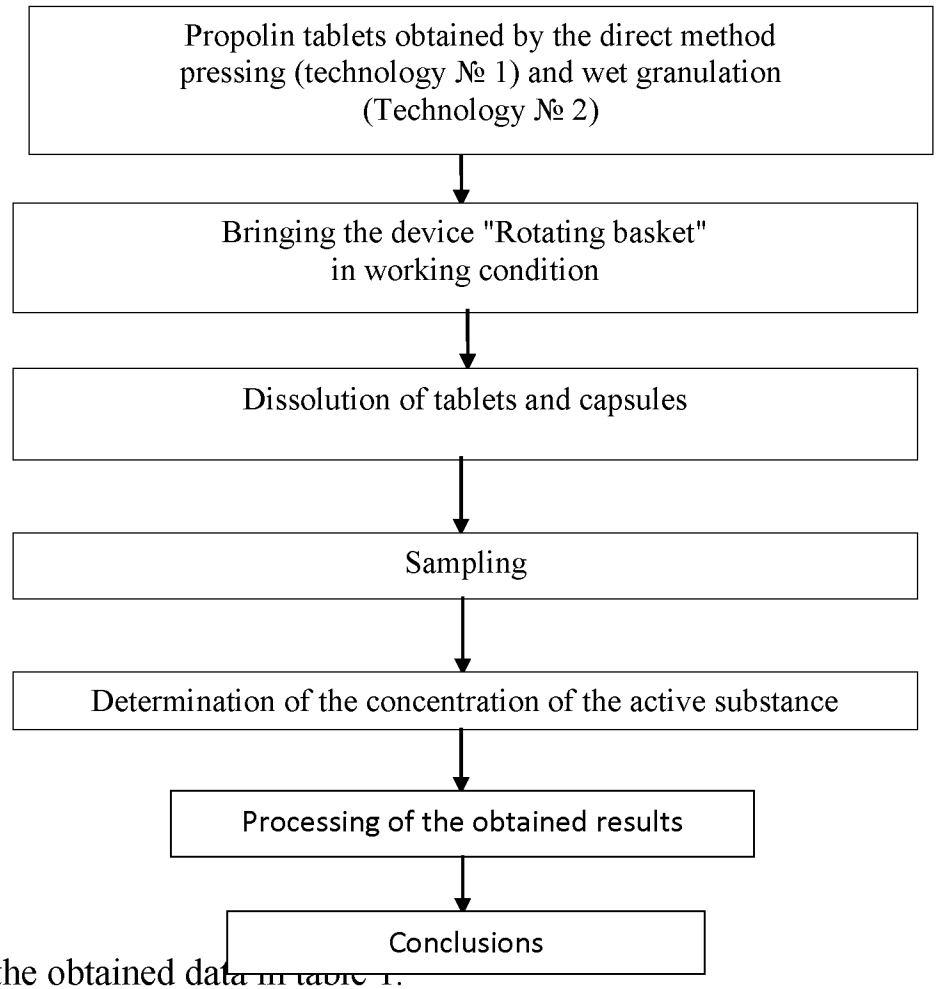
Sifting of components is performed manually through a silk sieve № 32 GOST 4403-67. The starch is pre-dried to a residual moisture content of 2.5-3%. Mixing of ingredients is carried out manually in a special container for 20 min to a homogeneous mass. Moisten with a 5% solution of starch paste in an amount of 10% by weight of the pill mass. The wet granulate is dried to a residual humidity of 2.5% at a temperature of 40 ± 1 ° C.

Dry granulation is carried out by rubbing through a sieve with a hole diameter of 2 mm. Dust with calcium stearate and table with a punch with a diameter of 7 mm.

Before completing the task, get acquainted with the algorithm of experimental work for task № 1 (Appendix 1).

Appendix 1

ALGORITHM OF EXPERIMENTAL WORK ON DETERMINATION OF SOLUBILITY OF PROPOLINE TABLETS



Enter the obtained data in table 1.

Table 1

DYNAMICS OF DISSOLUTION OF PROPOLINE TABLETS AND HIS RELEASE

№ p / p	Name preparation	Time of complete dissolution, min	Optical density solution (*D*)	Release FGPP, %
1.	Propolin tablets by technology № 1			
2.	Propolin capsules by technology № 2			

3.	Standard solution			

Draw conclusions about the influence of methods of obtaining tablets "Propolin" on the rate of their dissolution and the degree of release of FGPP.

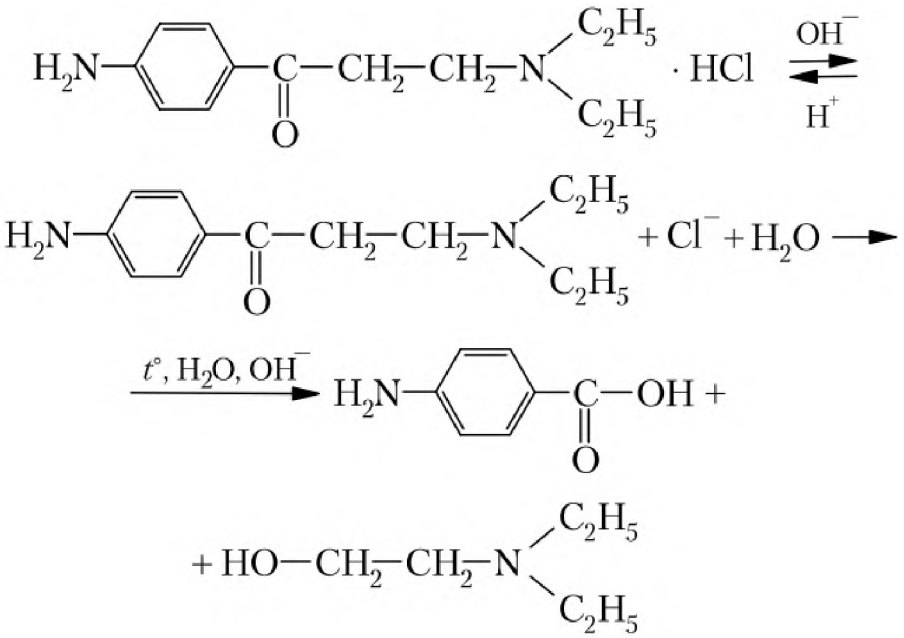
Task № 2

Methodical recommendations for the task

Solutions of novocaine are most stable at pH 3.8-4.5. In an alkaline environment, they decompose easily with the release of novocaine-based, which hydrolyzes to form pharmacologically inactive and toxic products (*p*- aminobenzoic acid, aniline, etc.).

A 0.1 N hydrochloric acid solution is used to stabilize novocaine solutions.

The role of 0.1 N hydrochloric acid as a stabilizer of novocaine solutions is studied by the method of "In vivo" in experiments on guinea pigs, as it is the most sensitive species of laboratory animals.



The object of the study are 0.5% solutions of novocaine for injection: solution № 1, prepared in accordance with the requirements of the analytical regulations, solution № 2, prepared without a stabilizer. As a comparison drug using 0.5% solution of novocaine factory production.

Technology of 0.5% solutions of novocaine for injection

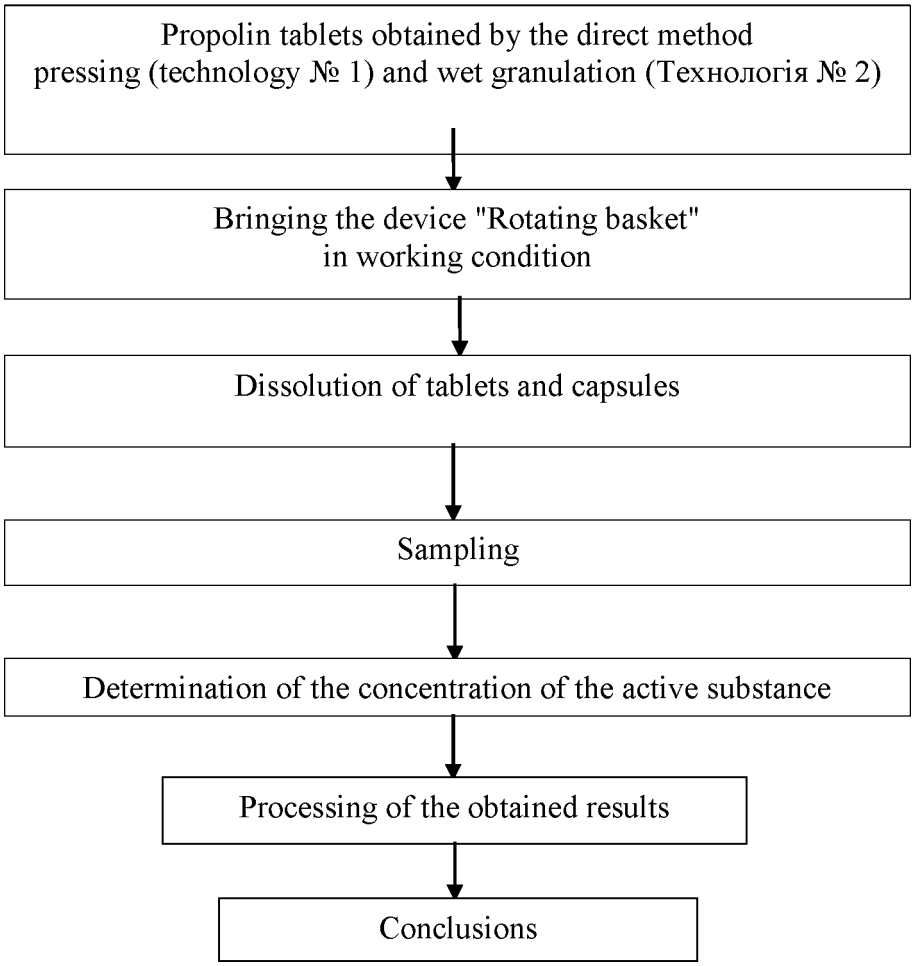
Solution № 1. Under aseptic conditions in a sterile volumetric flask with a capacity of 100 ml is placed 0.5 g of novocaine, dissolved in part of water for injection, add 0.4 ml of 0.1 N hydrochloric acid solution and make up to the mark with water for injection . The pH of the solution is 3.8-4.5, the value of which is determined using the universal ionomer EV-74.

The solution is filtered, dosed into vials of 50 ml, closed with rubber stoppers under running, control the quality of solutions according to TND, then sterilized at a temperature of 100 ° C for 30 minutes

Solution №2 is prepared analogously to solution № 1 without adding 0.1 N hydrochloric acid solution. Solutions №№ 1, 2 after their preparation are subjected to artificial aging at a temperature of 100 ° C for 95 hours. Before completing the task, get acquainted with the algorithm of experimental work for task № 2 (Appendix 2).

Annex 2

ALGORITHM OF EXPERIMENTAL WORK ON THE STUDY OF THE ROLE OF HYDROCHLORIC ACID IN 0.5% SOLUTION OF NOVOCAINE BY THE "IN VIVO" METHOD



Determination of local anesthetic action of 0.5% solutions of novocaine

The experiment is performed on four guinea pigs, which at the beginning of the experiment release the area of skin from the fur (2.5 × 2.5 cm) in the posterior surface of the back. Two animals are injected under the skin with 0.25 ml of test solutions №№ 1, 2, the third animal - the comparison drug, the fourth - the same amount of water for injection.

The presence of anesthesia in animals is detected by six injections of a needle into the injection site every 5 minutes for half an hour.

A positive response is considered to be the contraction of the skin around the injection, which is accompanied by a motor reaction and squeaking of the animal. One

hundred percent anesthesia is noted if no response to any of the six injections is observed.

Enter the results of the experiment in table 2 and on their basis construct curves of local anesthetic action on time for each drug (effect in% - on the y-axis, time in min - on the abscissa).

Table 2

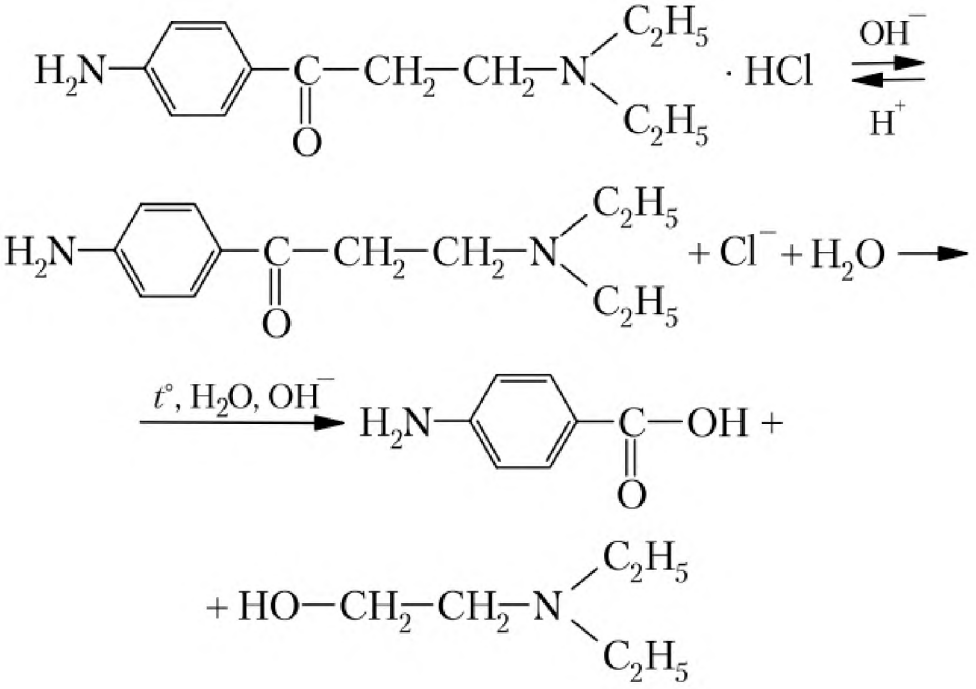
LOCAL ANESTHESIA ACTION
0.5% NOVOCAIN SOLUTIONS FOR INJECTION

№ p / p	The name of the drug	Marking of an animal	Number of negative reactions (*n*)					
			Effect (%)					
			5 min	10 min	15 min	20 min	25 min	30 min
			n	*n*	*n*	*n*	*n*	*n*
			%	%	%	%	%	%

Based on the data obtained, draw conclusions about the effect of hydrochloric acid on the stability of novocaine solutions for injection and the manifestation of local anesthetic action.

Methodical recommendations for the task

Quantitative determination of novocaine solutions is carried out by the method of rapid analysis, which is based on the neutralization reaction.



The sodium chloride formed as a result of the neutralization reaction is determined mercurimetrically:

Objects of research see lesson № 5 (task № 2).

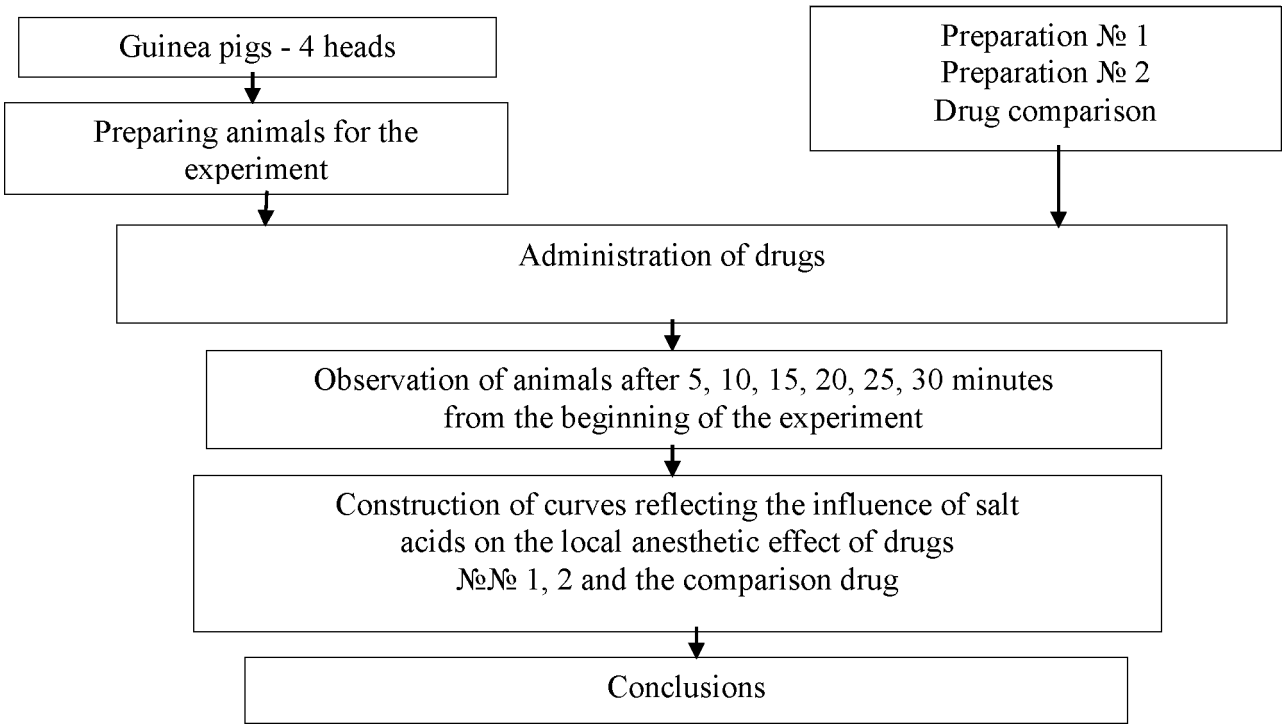
Before completing the task, get acquainted with the algorithm of experimental work for task № 3 (Appendix 3).

Quantitative determination of the hydrochloride salt of novocaine is carried out by titration. Initially, using the ionomer EV-74 determine the pH of all analytical drugs. This requires at least 30 ml of test solutions. In conical flasks with a capacity of 30 ml measure 5 ml of solutions and titrate with freshly prepared 0.01 N sodium hydroxide solution in the presence of 1 drop of methylene red indicator to change color from pink to yellow. Then add 1 drop of diphenylcarbazone and titrate with 0.1 N mercury nitrate solution to blue-violet staining.

In parallel, conduct a control experiment. 0.4 ml of 0.1 N hydrochloric acid solution is added to a 100 ml volumetric flask and made up to the mark with water for injections.

Annex 3

ALGORITHM OF EXPERIMENTAL WORK ON STUDY OF THE ROLE OF HYDROCHLORIC ACID IN 0.5% NOVOCAIN SOLUTION FOR INJECTIONS BY EXPRESS ANALYSIS



The content of novocaine *(X,* %) is calculated by the formula:

$$V = \frac{\left|V_n - \left(V_c + V_k\right)\right| \cdot T \cdot K\Pi \cdot 100}{5},$$

where *V **n*** is the amount of 0.1 N solution of mercury nitrate, passed for titration of the analyzed drug (ml);

*V **c*** is the amount of 0.01 n sodium hydroxide solution passed for titration of the analyzed drug (ml);

*V **k*** is the amount of 0.01 n sodium hydroxide solution passed for titration of the control sample (ml);

T is the titer of 0.1 n solution of mercury nitrate:

1 ml of 0.1 N mercury nitrate solution corresponds to 0.02728 g of novocaine hydrochloride;

KP - correction factor.

Enter the obtained data in table 3.

Table 3

NOVOKAIN CONTENT
IN THE ANALYZED SOLUTION

№ п / п	The name of the drug	pN	Novocaine content (%)

Based on the data obtained, draw conclusions about the effect of hydrochloric acid on the stability of the solution of novocaine for injection.

Task№4

Methodical recommendations for the task

The effect of some pharmaceutical factors on the therapeutic equivalence of drugs can be detected using the most common drugs, such as tablets of analgin, streptocide, acetylsalicylic acid, manufactured by different manufacturers.

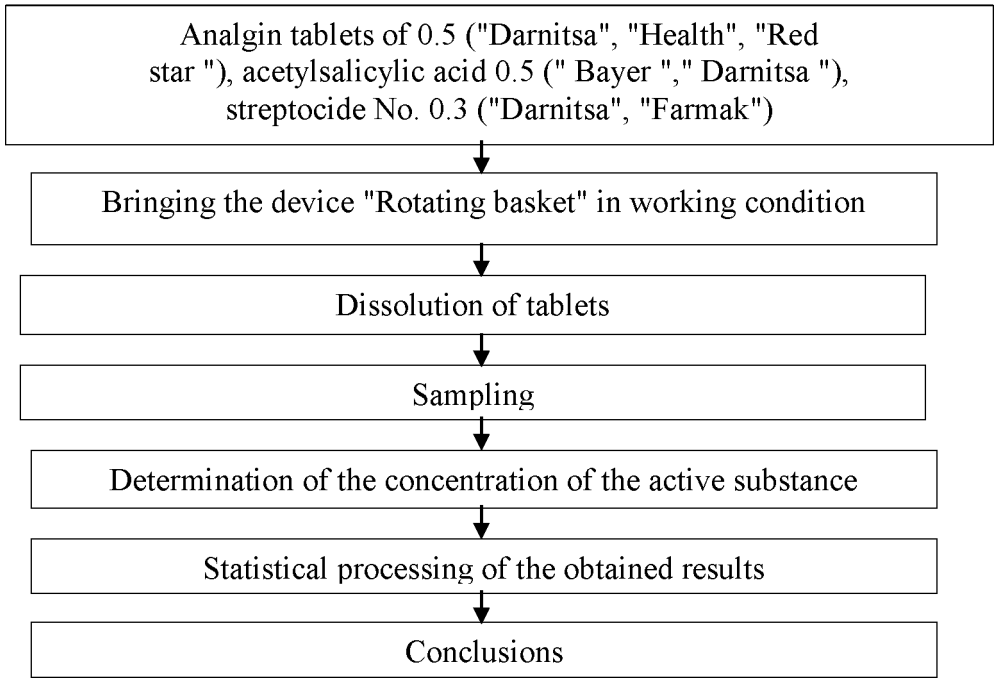
The object of the study are analgin tablets of 0.5, manufactured by "Darnitsa", "Health", "Red Star", acetylsalicylic acid tablets of "Wauer", "Darnitsa" 0.5, streptocide 0.3 - "Darnitsa" and "Farmak". In experiments it is possible to use tablets which are issued also by other firms.

Before performing the task, get acquainted with the algorithm of experimental work for task № 4 (Appendix 14).

The method of experimental work is described in lesson № 3 (task № 1).

Annex 4

ALGORITHM
EXPERIMENTAL WORK ON DEFINITION
SOLUBILITIES OF THE TABLETS STUDIED



Study of dissolution and release of the active substance from analgin tablets produced by different manufacturers
Quantitative determination of analgin

The solutions obtained by determining the "dissolution" test are filtered, measured with 2.5 ml of filtrate, placed in a volumetric flask of 25 ml, adjusted to volume with 95% ethyl alcohol, transferred to a conical flask with a capacity of 100 ml and titrated with 0.1 N iodine solution until a yellow color of iodine appears, which does not disappear within 30 seconds.

The content of analgin (X,%) is calculated by the formula:

$$X = \frac{V \cdot T \cdot KП \cdot 100}{5},$$

where V is the amount of 0.1 N iodine solution spent on the titration of the analyzed drug (ml);

T is the titer of 0.1 N iodine solution, 1 ml of 0.1 N iodine solution corresponds to 0.01667 analgin;

KP - correction factor.

The dissolution time of solid dosage forms and the percentage of release of active substances enter in table. 17.

Example of calculation

1. Time of complete dissolution, in min:

(25 + 26 + 26 + 26 + 27): 5 = 26 (min).

Experiment error calculation:

№ досліду	α	α^2	$\Sigma\alpha^2$
1	26 – 25 = 1	1	
2	26 – 26 = 0	0	
3	26 – 26 = 0	0	2
4	26 – 26 = 0	0	
5	26 – 27 = –1	1	

$$S_{\bar{X}} = \sqrt{\frac{\sum \alpha^2}{n(n-1)}} = \sqrt{\frac{2}{5(5-1)}} = 0{,}32$$

$\varepsilon_\alpha = S_{\bar{X}} \cdot t_\alpha$

$\varepsilon_\alpha = 0{,}32 \cdot 2{,}776 = 0{,}889 \approx 0{,}89$

$k = n - 1$; 1 5 – 1 = 4; при $k = 4$, $t_\alpha = 2{,}776$

$\bar{X} \pm \varepsilon_\alpha = 26{,}0 \pm 0.89$

2. Release of analgin after complete dissolution, in%

(80.2 + 84.0 + 78.1 + 83.0 + 78.0): 5 = 80.7 min.

Experiment error calculation:

№ досліду	α	α^2	$\Sigma\alpha^2$
1	80,7 – 80,2 = 0.5	0,25	
2	80,7 – 84,0 = –3,3	10,83	
3	80,7 – 78,1 = 2,6	6.76	30,42
4	80,7 – 83,0 = –2,3	5,29	
5	80,7 – 78,0 = 2,7	7,29	

$$S_{\bar{X}} = \sqrt{\frac{30{,}42}{5\,(5-1)}} = 1{,}23$$

$\varepsilon_\alpha = 1{,}23 \cdot 2{,}776 = 3{,}41$

$\bar{X} \pm \varepsilon_\alpha = 80{,}7 \pm 3{,}41$

Quantitative determination of acetylsalicylic acid

5 ml of the filtrate is shaken with 10 ml of phenolphthalein-neutralized 95% ethyl alcohol for 10 minutes The liquid is cooled at a temperature of 8-10 ° C and titrated with the same indicator with 0.1 N sodium hydroxide solution until pink. The acetylsalicylic acid content is calculated by the formula described above. Titer of 0.1 N sodium hydroxide solution 0.01802 g

Quantitative determination of streptocide

In a volumetric flask per 100 ml make 10 ml of the analyzed filtrate and 2.5 ml of 10% hydrochloric acid solution. The flask is placed for 10 min in an ice bath, then add

5 ml of 0.5% freshly prepared sodium nitrate solution. After 5 min add 1 g of urea and shake. After 15 min add 1 ml of 0.5% freshly prepared solution of thymol in 10% sodium hydroxide solution and 5 ml of 10% sodium hydroxide solution. After 10 minutes, bring the water to the mark. The content of streptocide is determined on a photoelectrocolorimeter KFM-C-2 with a blue filter (maximum transmittance 400 nm) in a cuvette with a layer thickness of 10 mm. As a control, use a mixture of all reagents, treated similarly.

Photoelectrocolorimeter KFM-Ts-2 pre-calibrated on a standard solution.

Preparation of standard solution

In a volumetric flask of 1000 ml make 0.05 g (exact portion) of streptocide, dissolve in 10 ml of alcohol and make up to the mark with water. 1 ml of solution contains 0.05 mg of streptocide.

In a volumetric flask per 100 ml make 6 ml Preparation of the th solution of streptocide, add 4 ml of purified water and then come, as indicated in the method of quantitative determination of streptocide.

The prepared standard solution is used to calibrate the photoelectrocolorimeter KFM-C-2, setting the scale so that the readings of the device coincide numerically with the concentration of the substance within ± 2 units (0.3 ± 0.02). Calculation of the amount of streptocide (X , mg) released from the tablets for a certain period of time, is carried out according to the formula:

$$X_n = \frac{C_n \cdot V_1}{V} + Y_n,$$

where *Cn* is the content of streptocide in 2 ml of dialysate found by the device (mg);

V is the volume of dialysate selected for analysis (ml);

V_1 - volume of dialysate in the cell (ml);

Yn - the amount of streptocide contained in the previously selected dialysate (mg)

$Y_1 = 0$; $Y_2 = C_1$; $Y_3 = C_1 + C_2$.

Enter the obtained data in table. 4.

After completing the task, formulate conclusions about the presence of therapeutic inequality in drugs manufactured by different manufacturers.

Table 4

DYNAMICS OF DISSOLUTION OF ANALGIN TABLETS, ACETYLSALICYLIC ACID, STREPTOCIDE OF THEIR RELEASE

№ p / p	Name preparation	Time of complete dissolution, p	Sampling time. with	Release of active substance,%
1. Analgin tablets of 0.5 from Darnytsia				
2. 2. Analgin tablets of 0.5 company "Health"				

3. Aspirin tablets of 0.5 firm "Red Star"				
4. Aspirin tablets of 0.5 from Bayer				
5. Tablets of acetyl salicylic acid 0.5 company "Darnitsa"				
6. Tablets of streptocide 0.3 OJSC "Farmak"				
7. Tablets of streptocide 0.3 of the company "Darnitsa"				

Task №5

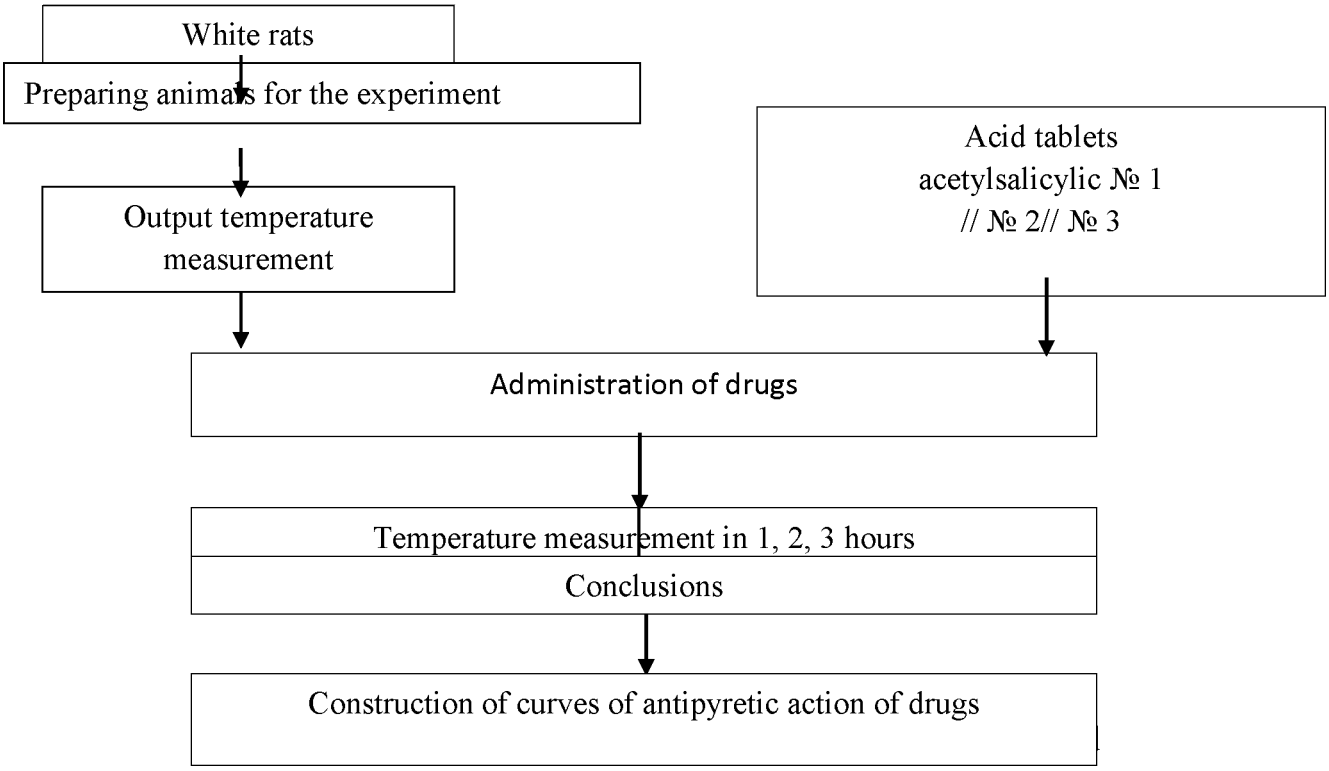
Methodical recommendations for the task

The presence of therapeutic non-equivalence in drugs can be established by the method of "in vitro" in laboratory animals. As objects of research it is possible to use analogues of antipyretic drugs let out by various manufacturers.

The object of the study are acetylsyl salicylic acid tablets produced by various factories. Before performing the task, get acquainted with the algorithm of experimental work for task № 5 (Appendix 5).

Annex 5

ALGORITHM OF EXPERIMENTAL WORK ON STUDY OF ANTHYDRATING ACTION OF AETHYLSALICYLIC ACID



The antipyretic properties of drugs are evaluated for their ability to provide a hypothermic effect. The fever is caused by intravenous administration of 50 mpd of pyrogenal per 100 g of animal weight. Against the background of the maximum increase in temperature (after 2 hours), the test drugs are administered at a dose of 98 mg / kg (OD_{50} of the drug) in the form of a suspension with purified water (2 ml per animal).

The temperature is measured in the rectum every hour for 3 hours using a thermometer TPEM-1. Record the results in table 5.

Table 5

HEAT-REDUCING EFFECT OF ACETYLSALICYLIC ACID ON THE MODEL OF PYROGENIC FEVER IN RATS

Name preparation	Dose, mg / kg	Way introduction	Body temperature of rats, ° C			
			Entrance.	1 year	2 years	3 years

On the basis of the received data construct curves of dependence of antipyretic action of drug (° C) on time (*t* , h).

After completing the task, draw conclusions about the therapeutic equivalence of acetylsalicylic acid tablets and its dependence on variable pharmaceutical factors.

3.3. requirements for work results, including before registration

In accordance with the recommendations (instructions) for the tasks.

3.4. control materials for the final stage of the lesson: tasks, tasks, tests, etc .:

1. To prepare the powder with sodium tetraborate, this substance was ground in the presence of an excipient. Specify it:
   A. Water
   B. Glycerin
   C. Ethyl alcohol
   D. Dimexi
   E. Vaseline oil
2. A suction filter with an iron tank was used to filter the alcoholic iodine solution at the plant. What technological violations of the production of alcoholic iodine solution were committed?
   A. The technology is correct
   B. no contact of iron with iodine in production
   C. the use of a suction filter is not permitted
   D. the use of a suction filter and contact of iron with iodine in production is not allowed
   E. iodine solution is not filtered at all at the factory
3. For which drugs use freezing technology

A. vitamins
B. enzymes
C. hormones,
D. antibiotics,
E. sulfonamides.

4. To what temperature should the thermostat be heated so that agar cups can be placed in it?
   A. 35 ° C
   B. 36 ° C
   C. 37 ° C
   D. 39 ° C
   E. 38 ° C
5. The plant for the production of oil injectable solutions received ampoules marked: IP-2V, USP-1, IP-2, AB-1, BB-2. Which of them should be used in production?
   A. IP-2B
   B. USP-1
   C. BB-2
   D. AB-1
   E. SP-2
6. To increase the pharmaceutical availability of tablets containing sparingly water-soluble drug, it is possible:
   A. reducing the degree of dispersion of the substance;
   B. introducing the optimal amount of surfactants;
   C. introducing the optimal amount of excipients;
   D. using granulation;
   E. changing the shape of crystals.
7. According to the Vant-Goff rule, when the temperature rises by 10 0C, the physicochemical processes occurring in the drug are accelerated in:
   A. 2-4 times
   B. 8-10 times
   C. 4-8 times
   D. 2 times
   E. 10 or more times
8. The time interval from the start of manufacturing the solution for injection to sterilization should not exceed:
   A. 1 year
   B. 2 hours
   C. 3 years
   D. 4 years
   E. 24 years
9. By direct compression, tablets are obtained from the following medicinal substances that meet the following requirements:

A. good elasticity, isodiametric shape of crystals, bulk, good compressibility

B. porosity, good solubility

C. good flowability, compressibility, isodiametric shape of crystals, low adhesion to the press tool

D. low adhesion to the press tool, porosity, elasticity, isodiametric shape of the crystals

E. good elasticity, isodiametric shape of crystals, bulk mass, good compressibility

10. Dissolution at room temperature was performed in the production of 10% calcium gluconate solution for injection. Point out the shortcomings in the technology and their likely consequences

A. Preparation of 10% solution of calcium gluconate is carried out by heating for 3 hours

B. The technologist did everything right

C. Preparation of 10% solution of calcium gluconate is carried out by heating for 1 hour

D. Preparation of 10% calcium gluconate solution is carried out under cooling for 1 hour

E. Preparation of 10% calcium gluconate solution is carried out in homogenizers

IV. Summing up

List of recommended reading

Main:

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

ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF DRUGS TECHNOLOGY

APPROVE
Head of Department

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

METHODICAL DEVELOPMENT OF PRACTICAL LESSON

Course: 5 Faculty: Pharmaceutical

Course Biopharmacy

Practical lesson №7 Topic: «**Pharmaco-technological methods for assessing the decomposition, solubility and release of drugs from drugs.»**

The practical lesson was developed by:
Ph.D., Assoc.

_____ (Fizor. N.S.)
signature
The practical lesson was discussed at the methodical meeting of the department
«29» august 2022 y.
Protocol № 1

Odesa – 2022

The purpose of the lesson: to study pharmaco-technological methods for assessing the decomposition, solubility and release of drugs from drugs.
Basic concepts: kinetics, disk method, device with a basket.
Equipment: according to the requirements of Good Pharmacy Practice (GPP).
Study time: 2.0

Plan

I. Organizational moment.
II. Control of basic knowledge
2.1. Requirements for theoretical readiness of students to perform practical classes (knowledge requirements, list of didactic units):
Requirements for theoretical knowledge:

Dissolution and its kinetics

Determination of the disintegration of solid dosage forms does not allow to fully conclude about the release of drugs from disintegrated dosage forms and, consequently, are unsuitable for assessing the bioavailability of drugs.

Among the more reliable methods of assessing the quality of drugs, which eliminates their therapeutic inadequacy, are methods for determining the dissolution rate of drugs.

The degree of dissolution of the solid dosage form means the amount (proportion) of active substance in percent, which must pass into solution over a period of time.

Methods for assessing the dissolution of drugs are indispensable in comparing different dosage forms of the same substance and in quality control in the industrial process.

During dissolution, two processes occur: the release of molecules from crystal bonds and their diffusion into the solvent. The dissolution rate is represented by the time required to release the molecule from the crystalline bond, and the time required for diffusion. It can be calculated by the following equation:

$$\frac{dm}{dt} = \frac{K \cdot D}{D + K + h} \cdot O \cdot (C_s - C),$$

where dm / dt - the amount of substance that enters the solution per unit time;
K is the rate constant;
O is the surface of the solute;
Cs - saturated concentration of this substance;
C is the concentration of this substance at a certain time;
D is the diffusion coefficient;
h is the thickness of the diffusion layer.

During dissolution, surface and diffusion processes are not in equilibrium. The dissolution equation allows you to display and determine the parameters on which the dissolution rate depends. Such parameters include temperature, solubility, surface, viscosity.

The effect of temperature in determining the dissolution rate is manifested in the fact that all tests are performed at the same temperature (37 ° C).

Solubility means the concentration of solute in saturated solutions at a certain temperature. The solubility of drugs is given in pharmacopoeias and textbooks.

The solubility of weak electrolytes changes with pH. For weak acids, the dissolution rate increases with increasing pH, and for weak bases - decreases. The solubility of salts differs from the solubility of the corresponding acids or bases. For example, sodium and potassium salts of weak acids, as well as salts of strong acids with weak bases, dissolve better than free acids or bases. This is due to the buffer power of the diffusion layer.

Dissolution is directly proportional to the size of the crystal surface. It is established that the diffusion layer formed near the crystals has approximately the same value as their radius.

Dissolution begins with wetting the surface of the crystals. Wettability is represented by the difference between the surface tension of the crystals and the surface tension of the solvent, which is a function of the angle of contact that compresses the solvent between the crystal and air. If this angle is less than 50 °, then the wetting is positive, and it is greater the smaller the angle. If the surface is easily wetted, dissolution occurs faster. If the solvent has the same charge as the surface of the crystals, they repel each other, so the dissolution rate decreases. In addition to wettability, the factor of crystal surface formation is also manifested here. Wet crystals of the correct structure will dissolve more slowly than non-wet crystals with lattice deviations. However, if the crystals with lattice deformation are well wetted, they will dissolve significantly faster than wettable crystals with the correct lattice, which only confirms the value of surface tension.

Changes in the size of the surface of the crystals in the control of the dissolution rate is used in practice very often (with micronized drugs, good absorption is achieved, and the dose can be reduced without reducing the therapeutic concentration in the blood).

Dissolution proceeds the faster, the lower the viscosity of the diffusion layer.

The above equation of dissolution neglects the effect of mixing, and proceeds from the assumption of constant wetting. It is impossible to accurately determine the effect of the stirring rate, as it is necessary to take into account the density, size and type of solid crystals, viscosity, number and temperature of the liquid phase, type of stirrer and mixer, circulation method and other factors. That is, the mixing speed and its dependent parameters must be maintained constantly.

In addition, it is assumed that the dissolution occurs on the surface; the effect of mixing the solvent in each region of the crystals is the same, the crystals when dissolved retain their appearance; and the shape of the crystals is spherical.

Methods and devices

Many methods and devices have been developed to determine the dissolution rate (devices for determining the disintegration can also be used for this purpose).

Devices and methods for dissolution studies must meet the following conditions:

- the type, dimensions and position of each individual part of the device must be precisely determined;

- the device should be relatively simple, not difficult to maintain, adaptable to the changed conditions of the experiment, and when repeated experiment should give reproducible results;
- the dissolution process occurring in the device must correlate with the process of absorption in vivo;
- the device must be controlled, provide a change in speed, uniform non-turbulent mixing;
- the design of the instrument must allow the embedding of the samples in the solvent while the device is operating and maintaining them in a constant position in which the samples are completely immersed in the solution. In the process of dissolution, the sample must be subjected to only minimal mechanical impact to maintain the standard conditions of its microenvironment;
- the dissolution vessel should be closed so that the solvent does not evaporate, and transparent, which simplifies the observation of the dissolution process. The solvent must have a standard composition;
- the device must be suitable for disintegrating, non-disintegrating, flotation, as well as finely ground solid dosage forms.

Disk method . This method is suitable for determining the actual dissolution rate. The method has been modified many times, and the proposed changes relate to the speed, the type of handle for attaching the sample and the regulation of the movement of the solvent.

In this method, the tablet is attached with paraffin to the acrylic handle (disk), and only one surface of the tablet comes into contact with the solvent. The handle with the breakdown rotates in a vessel containing 200 ml of solvent at a temperature of 37 ° C. The number of revolutions is 300 or 400 per minute.

Method using a laboratory beaker . This method uses 250 ml of solvent heated to a temperature of 37 ° C. Mixing is provided by a propeller stirrer located in the center. The number of revolutions is 60 rpm. This method critically evaluates the method of mixing the sample (the relative position of the sample and the stirrer). To prevent a change in the position of the sample, it was proposed to use a cylindrical vessel with a hemispherical bottom. Thus, it was possible to fix the position of the sample, but the change in the geometric shape of the vessel caused a change in the dissolution process.

A modification that has solved the same problem is to put the sample in the handle or in the basket. The invariability of the position of the basket mounted on a metal stand is provided by a magnet, which is located under the bottom of the test basket. In another embodiment of these devices, the fixation of the sample is carried out by plates adapted for mounting a tablet or capsule. The plates are made of organic glass or Teflon and allow you to attach many (usually six) capsules or tablets. When using such a device, the difficulties associated with the evaluation of capsules, which tend to float on the solvent or stick to the wall, disappear. The circulation of the solvent near the sample also becomes more regular.

Rotating basket method . Determination of dissolution is carried out in a device consisting of a test vessel and a basket made of stainless steel.

The advantages of this method are often substantiated in the literature, but it should be noted some of its disadvantages:

- Particles of the disintegrated sample clog the holes of the basket and distort the dissolution conditions, mainly with capsules;
- Particles accumulate in different parts of the container and fall unevenly into the solvent stream, ie the solute is distributed unevenly in the total volume of solvent;
- Air bubbles remain on the basket, which interfere with the dissolution process;
- Improper location of the handle of the basket or its small deformation causes incorrect oscillations, and thus changes the general nature of the circulation around the sample;
- Hydrochloric acid causes corrosion of the basket mesh and limits its service life;
- The method does not register changes in excipients;
- The speed and intensity of mixing are high, and therefore the time allotted for determining the dissolution is significantly reduced compared to the time set for absorption in vivo.

This method has been repeatedly modified and automated. A simple modification was the processing of the basket, which consisted in fixing the hangers to the stirrer to the bottom of the basket to prevent the formation of a fixed layer of decomposed particles deposited on the bottom of the container under the basket. As a result, the distribution of solute in the solvent improved , but at the same time increased the intensity of circulation.

Another processing was to replace the frequent sieve with a rare one, which improved the circulation of the solvent. It was proposed to place the basket on a horizontal axis, because in this way the tablet was at the same distance from the center of rotation, regardless of the speed of rotation of the basket. Mixing has also become more uniform.

A remote modification of the basket method can be considered a device in which the basket is in a horizontal position, with a low speed close to the peristaltic movement of the gastrointestinal tract. Sampling to determine the drug substance occurs at specified intervals automatically. The advantage of the device is that it is suitable for the evaluation of drugs with controlled release of the drug.

The solubility test with a description of the appearance of the tank and basket is given in the SPU (Article 2.9.3, p. 153).

A device with a stirrer blade, a basket or, in special cases, a flow cell, may be used to perform the solubility test, unless otherwise specified in the AND. In each case, the use of the "Dissolution" test should indicate the following:

- the device used, and in cases where a device with a flow cell is used, the type of flow cell must also be indicated;
- The composition, volume and temperature of the solvent medium;
- Speed of rotation or flow rate of the dissolution medium;

- Time, method and volume of the selected test solution or conditions for continuous monitoring;
- Method of analysis;
- The amount or quantities of active substances that must dissolve within the specified time.
- The choice of the device used depends on the physicochemical characteristics of the dosage form.

The device with a basket (Fig. 1) includes:

- cylindrical vessel 1 of borosilicate glass or other suitable transparent material with a hemispherical bottom and a nominal capacity of 1000 ml with a lid 2, which slows evaporation; the lid must have a central hole for the axis of the stirrer and other holes for the thermometer 3 and the devices used to obtain the liquid;

- stirrer 4, consisting of a vertical shaft 5, to the lower part of which is attached a cylindrical basket. The basket (Fig. 1, b) consists of two parts: the upper part A with a hole of 2 mm welded to the shaft and equipped with three elastic clamps 6, allowing you to remove the lower part of the basket for administration of the study drug and hold it concentrically with the vessel axis during rotation; the lower part B of the basket, which is a welded in the form of a cylinder shell 7 of wire with a diameter of 0.254 mm and a hole area of 0.381 mm 2; a basket with a gold coating with a thickness of 2.5 μm can be used for testing in dilute acidic environment; the bottom of the basket must be at a height of 25 ± 2 mm from the inner surface of the bottom of the vessel; the upper part of the shaft must be connected to the motor equipped with a speed regulator; the stirrer should rotate smoothly, without noticeable oscillations;

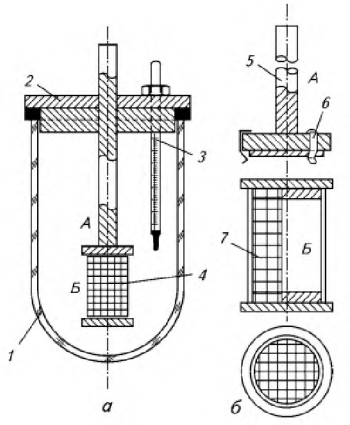


Fig. 1 Equipment with basket (for SFU):
and - the scheme of the general look of the device assembled;
b - elements of the basket (bottom - top view)

- water bath, which maintains a constant temperature of the dissolution medium of 37.0 ± 0.5 ° C.

The device with a shovel (Fig. 2) includes:

- vessel 1 with lid 2 identical to those described above for the device with a basket;

- stirrer 4, consisting of a vertical shaft 5, to the end of which is attached a blade 6 having the shape of a part of a circle cut off by two parallel chords; the stirrer should rotate smoothly, without noticeable oscillations;

- water bath, which maintains a constant temperature of the dissolution medium of 37.0 ± 0.5 ° C.

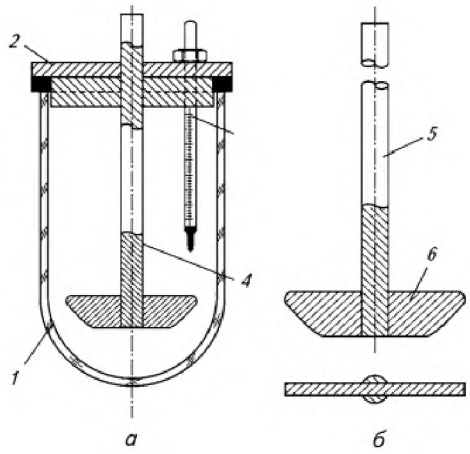


Fig. 2. Equipment with a shovel-stirrer (according to SPU):
and - the scheme of the general look of the device;
b - shovel-doll (below - top view in section)

Dissolution medium . If the dissolution medium is a buffer solution, its pH is set to within 0.05 of the specified value.

Dissolved gases are removed from the dissolution medium before the test, as they may cause bubbles to form which significantly affect the results.

Methodology (according to SFU, p. 155). Place the specified volume of dissolution medium in the vessel, collect the device, heat the dissolution medium to a temperature of 37.0 ± 0.5 ° C and remove the thermometer.

Place one unit of the test drug in the device. For the device with a shovel before the beginning of rotation of a shovel place preparation on a vessel bottom; solid dosage forms, which can emerge, are placed on the bottom of the vessel horizontally using a suitable device, such as wire or glass spiral.

For the device with a basket, the drug is placed in a dry basket, which is lowered to the appropriate position before rotation.

Measures should be taken to prevent the presence of air bubbles on the surface of the drug. The rotation of the blade or basket at the specified speed (± 4%) begins immediately.

Sampling and evaluation of results. At this time or at these intervals, or continuously carry out sampling of 1 ml of the specified volume or volumes from the area between the surface of the dissolution medium and the top of the basket or shovel at a distance of not less than 10 mm from the vessel wall. Except in cases where continuous measurements are used (the selected liquid is returned to the vessel) or when only one portion of the liquid is taken, the selected volume of liquid should be compensated by adding an equal volume of dissolution medium or appropriate changes in calculations.

The selected liquid is filtered using an inert filter with an appropriate pore size, which does not cause significant adsorption of the active ingredient from the solution and does not contain substances that are extracted with a dissolving medium that would

affect the results of this analytical method. The analysis of the filtrate is carried out by the method specified in private articles. The amount of active substance dissolved at the specified time is expressed as a percentage of the content specified in the "Composition" section.

To conduct this test, manufacturers produce modern equipment. For example, RägschaTev1 (Germany) manufactures more than 20 types of devices for testing the dissolution of tablets and capsules. In fig. 3 shows a seven-position model PTWS 3CE, which contains seven round-bottomed vessels with lids, plexiglass water bath with lid, electric lifting device, Teflon-coated paddle stirrers and baskets. The set includes a set of devices for setting the depth and centering of the stirrers. The electronic controller of speed of rotation of mixers allows to regulate frequency of rotation from 20 to 250 rpm. The built-in thermostat-circulator maintains temperature in the range from 25 to 45 ° C with an accuracy of ± 0,2 ° C. Some models are completed with the removable temperature sensor with a possibility of definition of temperature in each of vessels.

Fig. 3 Installation for testing for dissolution of tablets and capsules manufactured by Pharmatest (Germany) model PTWS 3CE

Modern solubility testing devices provide convenient electronic or liquid crystal displays to display the set and current mixing speed and temperature, testing time, pH value, etc.

There are fully automatic high-performance solubility test systems that allow you to not stop the experiment even at night and on weekends. They are automated filling the vessels with test medium, introducing samples, selecting the medium and measuring, as well as washing the vessels after testing. Concentration analysis can be performed using a connected spectrophotometer.

Flow method. The disadvantages of the basket method and the method using a laboratory beaker prompted researchers to develop a flow method, while they sought to improve circulation during mixing, which depends on the size and type of tank, solvent volume, position and type of stirrer, etc. These effects are difficult to standardize , a large volume of solvent (almost 2000 ml) used in these methods is not suitable in vivo.

In addition, in all beaker methods, the concentration of the drug increases from zero to the saturation limit or to a concentration corresponding to complete dissolution. This increase in concentration does not correspond to the increase in concentration in vivo, because in the latter case, the dissolved and absorbed substance is removed from the site of absorption.

In the flow device, the material is placed in a flask located vertically on a sieve through which the solvent passes. Passing through the sieve forms an evenly distributed laminar flow. At a certain height, the flask is covered with another sieve, which prevents the passage of dissolved particles. The filtered liquid is suitable for analytical determination of dissolved drug substance. The solvent in the device moves by pumping; when passing through the heat exchanger, it is heated to a given temperature. By improving the flow of the solvent, you can simulate the conditions of passage of the dissolved drug through the biological membrane. In other devices, this type of mixing is provided by the flow of liquid created by the peristaltic pump. The resulting stream is a series of unidirectional pulses without stirring the liquid of the solution passing to the flask near the sample. The flask has the form of a separating funnel, which contributes to the fact that the flow rate decreases with increasing distance from the mixing zone. The liquid is fed in a flat horizontal plane, and no dead spots are formed in the flask, which was experimentally confirmed by stained solutions.

In the development of flow methods, in addition to the vertical flask, used a flask oriented horizontally.

We can say that all flow methods have much in common. The devices have the same main parts, such as a tank, pump, heat exchanger, flask (column), tablet handle, filter system for determining the solute.

The solvent is stored in the tank and either circulates in the system or passes through it. The movement of the solution-calf is carried out by a pump: oscillating, pulsating or centrifugal.

The flask is usually cylindrical, arranged vertically or horizontally. Horizontally located flasks did not justify themselves, the flow of solvent in them is non-kelp, and around the sample there is turbulence. In the experiment with tablets containing the dye, it was found that in a horizontal flask, the solution of the substance is retained at the bottom, in the upper layers is almost one solvent.

The solvent flow can be ascending or descending. The downstream flow is advantageous in that there is no backflow under the influence of the separation of the density of the solution and the solvent, but difficulties arise when the experiment begins. Preferably the method with upward flow. The flow of fluid should be laminar. The formation of this type of flow is facilitated by balls of glass wool or a filter made of sintered glass, gauze.

Embedding the sample is a critical point of these experiments. The tablet should not change its position during the experiment, it should remain in the center of the solvent stream. Typically, the tablet is fixed in gauze, glass wool or glass beads. Glass beads are not the best way because they affect the tablet mechanically.

The flow method from the point of view of further development is considered perspective. Compared with the rotating basket method, it has the advantage of less intensive mixing, which brings it closer to in vivo conditions.

The flowing device (on SPU, fig. 4) includes:

- tank 1 for the dissolution medium;
- pump 2, which pumps the dissolution medium up through the flow cell;

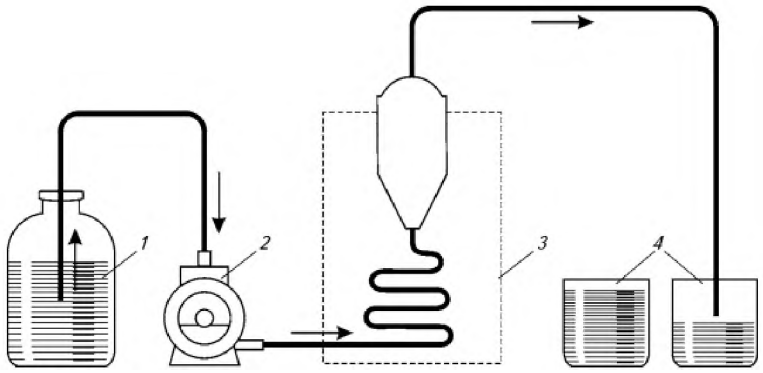


Fig. 4 Flowing device (according to HFC)

- flow cell 3 (Fig. 5) made of transparent material, installed vertically, which consists of a filter system that prevents the loss of undissolved particles and a water bath that maintains a constant temperature of the dissolution medium of 37.0 ± 0.5 ° C;

- tank 4 for collecting the analyzed sample.

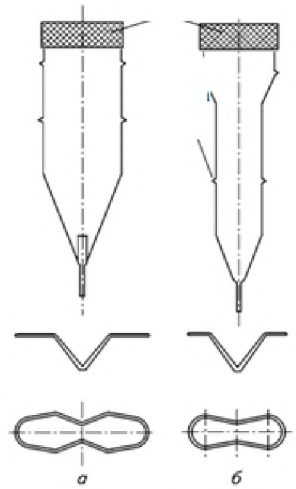


Fig.5 Flowing cuvettes on (HFC): a - cell 22.6 mm; b - cell 12.0 mm

Dissolution medium (see "Rotating basket method"). *Methodology* (according to SFU, p. 155). To protect the entrance to the chamber intended for the liquid, at the bottom of the cone is placed one ball with a diameter of 5 ± 0.5 mm, then glass balls of appropriate size, preferably with a diameter of 1 ± 0.1 mm Using a special holder, place one unit of the test drug in a cuvette on the surface (or inside) of the resulting layer of glass beads. Assemble the filter head.

Heat the dissolution medium to a temperature of 37.0 ± 0.5 ° C. Using a suitable pump, pass at the specified speed (± 5%) the dissolution medium through the bottom of the cuvette to obtain a suitable continuous flow.

Sampling and evaluation of results. Sampling is always performed at the outlet of the cuvette, regardless of whether the circuit is open or closed. Except in cases where continuous measurements are used (the selected liquid is returned to the vessel) or when only one portion of the liquid is taken, the selected volume of liquid should be compensated by adding an equal volume of dissolution medium or appropriate changes in calculations.

The selected liquid is filtered using an inert filter with an appropriate pore size, which does not cause significant adsorption of the active ingredient from the solution and does not contain substances that are extracted with a dissolving medium that would affect the results of this analytical method. The analysis of the filtrate is carried out by the method specified in the AND. The amount of active substance dissolved at the specified time is expressed as a percentage of the content specified in the "Composition" section.

Passage of drugs through membranes

While in single-chamber models the rate of solid dissolution in water or in buffer solutions simulating gastrointestinal juices is investigated, when measuring the passage of drugs in two- and three-chamber models, dissolution is determined together with the transition of the solute into the fatty medium (ratio balance and transfer), which corresponds to the passage of the drug through the lipoid intestinal barrier or the passage of the drug from the aqueous medium of the digestive tract through the intestinal membrane into the aqueous medium of blood plasma.

From a physical point of view, the essence of this method is to determine the partition coefficient between water and fatty medium and to determine the constant rate of penetration.

The formation of equilibrium in the system of two miscible liquids depends on the stirring rate, surface, viscosity of the solvent, the solubility of the substance in the non-aqueous phase and the pH.

Membrane systems are used to obtain systems whose transport characteristics would be correlated with passive absorption in the human body. Such systems allow the study of many variables operating in vivo, as well as used to assess the ability of new drugs to pass through the digestive membranes.

Membrane models for studying the penetration of drugs should have the following properties:

a) the membrane must be thin so that the amount of drugs remaining in it is minimal;

b) the transport of the drug substance through the membrane should be based on the solubility of the drug substance in the membrane (membranes in which it is possible to pass through the pores, not suitable for this purpose);

c) the membrane must be sufficiently resistant to mechanical loads so that its sensitivity is not violated during the experiment;

d) the membrane must allow to prove the correlation between the rate of penetration and absorption in vivo.

Membrane models are divided into two groups: the first consists of membranes of bioexperimental models, which are used for biochemical and biophysical studies of the role and function of the membrane and are designed at the molecular level; the second group consists of biotransporting membranes, which are used to study transportation. It is a penetration in which sorption occurs on one side of the membrane and desorption of the drug on the other.

Artificial lipoid membranes can be obtained in three ways.

The first method is to dry a dilute solution containing lipoid and its carrier.

The stability of the thus formed membrane depends on the filtered substance (carrier), which can usually be collodion, alginans or synthetic polymers. It is not easy to form a membrane with the same pore size in this way, because there are many influencing factors: the composition of the starting material and its concentration, water content in the substance used, quality and properties of the surface on which the membrane is formed, temperature and drying time, humidity, swelling ability. dried membrane, etc.

An example of membranes of this type is a membrane consisting of ethylcellulose, liquid paraffin and a biological element (lecithin and cholesterol), which very well mimics in vivo conditions. Lecithin is a necessary part of the membrane, because it is the main element of biological membranes. With its hydrophilic groups, lecithin affects the solubility of the drug in the membrane. It is important to note that the solubility of the drug in lecithin differs significantly from the solubility in other lipoid substances, such as liquid paraffin, oils, fatty acids, etc.

The second method is to impregnate (impregnate) the appropriate carrier (fabric, film) with lipoid. As a carrier used linen, silk fabric, polyamide, filter paper, film of acetylcellulose, polyethylene, polyvinyl chloride, etc., as impregnating lipoid substances - liquid paraffin, natural and synthetic phospholipids, vegetable oils, triaphylates, fatty acids and fatty acids. and others. In the manufacture of these membranes, it is important that they include an impregnating substance, because the pores of the carrier must be larger than the size of the molecules of the penetrating substance. The disadvantage of this method is that for impregnation are often used substances foreign to the body (liquid paraffin, vegetable oils, tributyl phosphate). There is a known example of such membranes - membranes in the resorption model of Sartorius.

The third way is to use a film that independently performs the function of a lipoid barrier. Dimethylpolysilicone serves as a non-polar membrane of this type.

The penetration rate depends on the properties of the diffusion layer on the surface of the membrane, on the condition of slow mixing, which corresponds to the slow mixing of gastric and intestinal contents. The significant effect of the diffusion layer on the penetration partially refutes the theory of distribution of the substance depending on the pH, because in the diffusion layer also move ionized and non-ionized forms of the drug.

Methods and devices (two- and three-chamber). Methods and devices for determining the release of drugs from drugs are divided into two groups. The first is formed by two- and three-chamber models without a solid membrane, the second - devices and methods that use one of the above-described solid membranes.

Methods and devices without a solid membrane. The main representative of the two-chamber model is a device called a resomat. The design of the device is based on the statement that the absorption of the drug depends on the dissolution in the digestive juices and the partition coefficient of this substance between the lipoid and aqueous phase.

In a two-chamber device, a substance dissolved in an aqueous medium comes into contact with the lipoid phase. Due to mixing, the solute is relatively quickly distributed between the water and the lipoid phase. The content of the drug in the lipoid phase is discretely analyzed. This model allows us to study the effect of excipients, drug structure, pH, viscosity.

The most well-known representatives of three-chamber models without a solid membrane include a tube in the shape of an inverted letter epsilon with aqueous phases in both arms and a lipoid phase connecting both phases. When the drug substance is soluble in one of the phases, then with slow stirring by the oscillating motion of the device, the drug substance is distributed in all three phases. The process of drug transport can be quantified in any of the three phases.

Methods and devices with a solid membrane. The core of all devices that use solid membranes are permeable cells, which must ensure the integrity of the membrane, a constant temperature, to allow mixing and extraction.

Many permeable cells have been described and constructed, which are quite different from each other. The main distinguishing features can be called their size and shape.

There are three main types of permeable cells. A relatively simple system is horizontal, in which the membrane is located between two chambers. The upper chamber is open or closed. The lower chamber is equipped with magnetic stirrers.

The second type of permeable cells has a membrane mounted on the end of the cylinder, immersed in a container with a large capacity.

The third type of permeable cells has a vertical membrane. Among the devices of this group, the most famous is the so-called resorption model from Sartorius, which is manufactured in industrial conditions.

Drug dissolution and absorption are two interrelated steps that depend on each other to a greater or lesser extent and affect each other: on the one hand, the amount of absorbed substance is added in proportion to the amount of drug substance in solution; on the other hand, dissolution, especially in sparingly soluble substances, may depend, inter alia, on the rate of transport in the medium. Both processes determine the rate of drug invasion in the environment, and only one of them is crucial, resulting from the ratio of dissolution rate and absorption rate. In contrast to dissolution, which on the basis of complex dependencies (for example, variable data on the form of application) only rarely follows simple patterns.

Diffusion of solutes in the digestive tract is more or less inhibited by food. With complete starvation, this empirical factor has a value equal to 1, after a light breakfast - about 0.8, in the afternoon - about 0.3.

Several types of membranes were prepared for this device by Sartorius, and in most cases the nitrocellulose membrane filter was impregnated with lauryl alcohol, lamino oil, caprylic, linoleic acid or a mixture of these substances in different volume ratios. Penetration through these membranes was compared with the results obtained in those experiments in vivo. The most acceptable results were achieved with a

membrane filter impregnated with a mixture of caprylic acid with lauryl alcohol. Two permeable cells were used for measurements.

In the first of them an aqueous solution of the drug is in one chamber, the second chamber is filled with artificial plasma. During the experiment, the cell rotates around the axis of the drug substance in the plane of the membrane, which is provided by the movement of the metal disk, which mixes their contents.

In the other - both aqueous phases (drug solution and artificial plasma) are in two heated containers, the contents of which are mixed. With the help of a pump, both of these chambers enter the permeable cell, and penetration occurs. The amount of drug that has passed through the membrane is fixed at certain intervals.

These cells and membranes were used in the construction of the resorption model Sartorius, which is used to determine the rate constants of drugs. The obtained results are correlated with the values obtained in vivo.

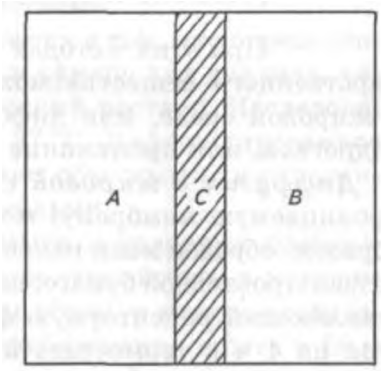


Fig. 6 Device for studying the penetration of medicinal substances from ointments into the liquid medium

A- chamber filled with a sample of ointment

B-receptor phase

C-cellophane

The chamber can be equipped with a stirrer

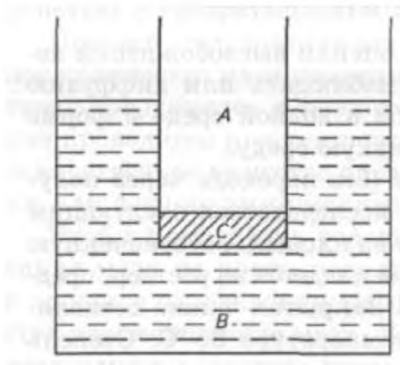


Fig. 7 Device for studying the penetration of a medicinal substance from ointments into a liquid medium

A-tube with ointment sample

B-receptor phase

C-cellophane

The experiment is carried out at a temperature of 37C. Receptor phase - Ringer's solution, ointment contains dyes, such as methylene blue

Release of drugs from soft dosage forms

Evaluation of the release of drugs from soft dosage forms (MLF), such as ointments, is determined by the ability of the base to release drugs.

Currently, many different methods have been developed and proposed to determine the release of drugs with ointment bases. All these methods can be divided into:

> In vitro model experiments based on physicochemical and microbiological studies;

> Biological methods in vivo performed on living organisms or isolated organs.

The results of biological methods are not always reproducible, so in vitro experiments are used for comparative studies.

To obtain comparable results it is necessary to maintain a constant temperature, the same composition of the test medium, the same concentrations of the drug substance, use samples of similar size with the same degree of dispersion of the suspended or emulsified substance.

Didactic units:

1. Dissolution and its kinetics
2. Devices and methods of dissolution research must meet the following conditions:
3. Methods and devices:

-Disc method.
-Method using a laboratory beaker
-The method of a rotating basket
-Device with a basket
-Device with a shovel
-Flowing method and flowing device

4. The passage of drugs through membranes
5. Release of drugs from soft dosage forms

Answer the question

1. The concept of simple chemical modification of drugs and its impact on the bioavailability and stability of drugs.
2. Classification of excipients and their role in the preparation of dosage forms. The influence of the nature of excipients on the rate of absorption of drugs and their therapeutic efficacy.
3. The influence of the dosage form on the rate of absorption of the drug, its concentration in biological fluids and the stability of drugs.
4. Ways of introduction of drugs into an organism and their influence on therapeutic activity.
5. Influence of technological factor on pharmacotherapy.
6. The concept of drug stability. The role of stabilizers in drug technology.

7. Influence of drug storage conditions on their stability.
8. The concept of pharmacodynamics and pharmacokinetics of drugs.
9. The main biological factors influencing the absorption of drugs.
10. The influence of the physiological state of the patient on the pharmacodynamics and pharmacokinetics of drugs.
11. Variable biochemical factors. Metabolism and elimination of drugs.

Take the test:

1. Choose the most commonly used methods of drug analysis in biological samples:
A. microbiological;
B. chromatographic;
C. chromatomass-spectroscopic;
D. spectro- and photocolorimetric;
E. chronopharmacological.

2. Indicate which term corresponds to the following statement: "A hypothetical volume of a part of the body that has been deprived of the corresponding substance per unit time".
A. distribution
B. purity
C. purity of the whole body
D. resorption
E. biotransformation

3. To determine the dissolution of the drug substance from the tablets DF recommends devices such as:
A. «hit basket»;
B. "Rhezomat";
C. "Sartorius";
D. "rotating basket";
E. stirrer over the disk.

4. To disperse the drug substance and homogenize ointments used:
A. disintegrator;
B. RPA;
C. excelsior.
D. dismembers;
E. ball mill

5. The pharmaceutical availability of ointments is determined by the following methods:
A. passive diffusion;
B. diffusion into the gel;
C. microscopy;
D. colored complexes;
E. dialysis through a semipermeable membrane.

6. To perform a pharmacopoeial test to determine the "dissolution" we need to use the following device:

A. device with a blade
B. RPA
C. homogenizer
D. reactor
E. friabilizer

7. To standardize suppositories that are made on a lipophilic basis, determine:
A. organoleptically
B. dissolution time
C. melting point
D. changes in pH
E. viscosity

8. The single-phase models of drug release from solid dosed LF include the device:
A. "Rotating basket";
B. Simax device;
C. Varian VK - 700;
D. Rhezomat II;
E. Sartorius.

9. For what purpose are laboratory samples placed in a thermostat?
A. to activate the reagent
B. for better release of the active substance
C. to undergo the process of polymorphism
D. to change the consistency of the ointment
E. to change the consistency of agar

10. For what purpose are laboratory samples placed in a thermostat?
A. to activate the reagent of iron (III) chloride
B. for better release of propolis
C. to undergo the process of polymorphism
D. to change the consistency of the ointment
E. to change the consistency of agar

III. Formation of professional skills, abilities:

3.1. content of tasks:

Task № 1

To establish the influence of the degree of dispersion of streptocide on the process of its release from ointments by dialysis through a semipermeable membrane.

3.2. recommendations (instructions) for performing tasks

Task № 1

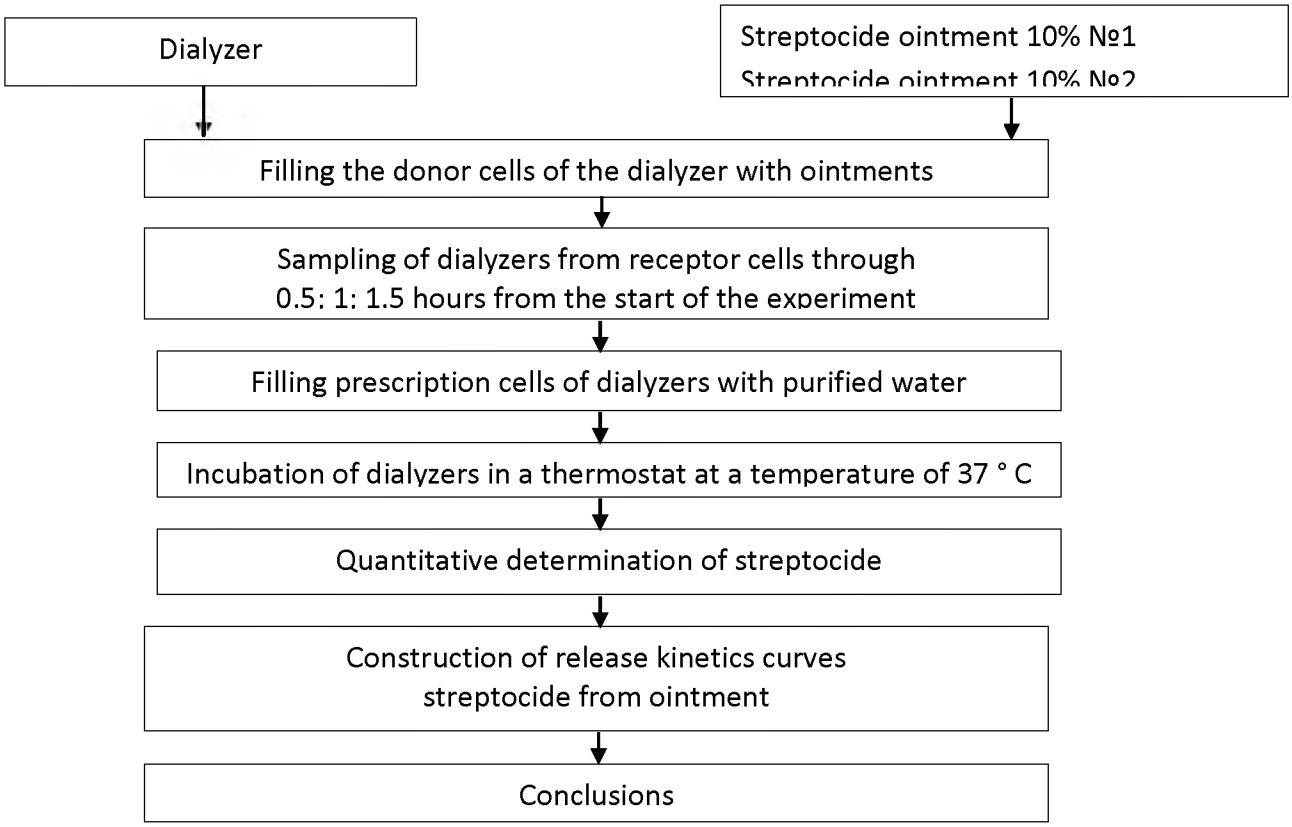
Methodical recommendations for the task

To assess the degree of release of drugs from ointments using the method of direct diffusion, in which the drug substance from the ointment base diffuses into the medium separated from the ointment by a semipermeable membrane. Cellophane with a thickness of 45 μm is used as a membrane. The environment is purified water.

Before completing the task, get acquainted with the algorithm of experimental work for task № 2 (Appendix 2).

Annex 2

ALGORITHM OF EXPERIMENTAL WORK ON DETERMINATION OF THE INFLUENCE OF THE DEGREE OF STREPTOCIDE DISPERSITY ON THE PROCESS OF ITS RELEASE FROM OINTMENTS BY DIALYSIS



For the experiment use a dialysis chamber with two cells, consisting of two parts. Cells are numbered, in the 1st donor cell is placed streptocidal ointment with a particle diameter of 0.1 mm, in the 2nd - with a particle diameter of 0.38 mm. Cells must be filled to the brim.

Cellophane is applied to the surface and the dialyzer is collected (Fig. 1). Using a pipette with a thin end or a syringe with a needle in the receptor cells make 15 ml of purified water. The dialyzer is placed in a thermostat at a temperature of 37 ° C.

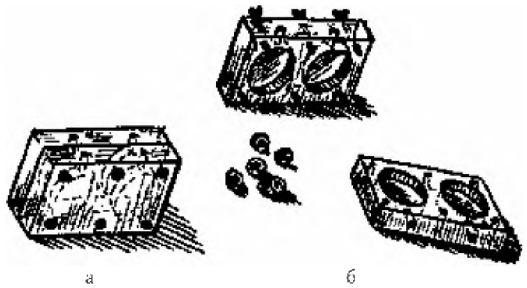


Fig. 1 Dialyzer in assembled form (a) and disassembled (b)

Sampling of dialysate from receptor cells is performed after 0.5; 1; 1.5 hours from the beginning of the experiment, filling the selected amount of solution with purified water. A sample of the dialysate sample is analyzed for streptocide content.

Quantitative determination of streptocide

In a volumetric flask per 100 ml make 2 ml of the analyzed dialysate containing 0.05-0.5 mg of streptocide, add 8 ml of purified water and 2.5 ml of 10% hydrochloric acid solution. The flask is placed for 10 minutes in an ice bath, then add 5 ml of 0.5% freshly prepared sodium nitrite solution. After 5 min add 1 g of urea and shake. After 15 minutes, add 1 ml of freshly prepared 0.5% solution of thymol in 10% sodium hydroxide solution and 5 ml of 10% sodium hydroxide solution. After 10 min, the contents of the flask are taken up with water to the mark. The content of streptocide is determined on a photoelectrocolorimeter KFM-C-2 with a blue light filter (maximum transmittance 400 nm) in a cuvette with a layer thickness of 10 mm. As a control, use a mixture of all reagents, treated similarly.

Photoelectrocolorimeter KFM-Ts-2 pre-calibrated on a standard solution.

Preparation of standard solution

In a volumetric flask per 1000 ml make 0.05 g (accurate to significant) of streptocide, dissolved in 10 ml of ethyl alcohol and make up to the mark with purified water. 1 ml of solution contains 0.05 mg of streptocide.

In a volumetric flask per 100 ml make 6 ml of the prepared solution of streptocide, add 4 ml of purified water.

Then come, as indicated in the section on the quantitative determination of streptocide.

The prepared standard solution is used to calibrate the photoelectrocolorimeter KFM-C-2, adjusting the scale so that the readings of the device numerically coincide with the concentration of the substance within ± 2 units (0.3 ± 0.02).

The calculation of the amount of streptocide (X, mg) released from the ointment for a certain period of time, is carried out according to the formula:

$$X_n = \frac{C \cdot V}{V_1} + Y_n,$$

where C is the content of streptocide in 2 ml of dialysate, found by the device (mg);

V is the volume of dialysate in the cell (ml);

V_1 - volume of dialysate selected for analysis (ml);

Y_n - the amount of streptocide contained in the previously selected dialysate (mg)

$Y_1 = 0$; $Y_2 = C_1$; $Y_3 = C_1 + C_2$.

The received data on quantity of the released streptocide for certain intervals of time bring in tab. 2, and then on their basis to construct the schedule in coordinates: on an ordinate axis postpone concentration of the released streptocide (C, mg); on the abscissa - time (t, h).

Table 2

DIFFUSION OF STREPTOCIDES WITH VARIOUS DEGREES OF DISPERSED OINTMENTS

Ointment	The amount of streptocide released, mg		
	0.5 hours	1:00	2 hours
№1 №2			

After completing the task, formulate conclusions about the influence of the degree of dispersion of streptocide on its release and compare the results obtained by the method of "agar plates" and dialysis.

3.3. requirements for work results, including before registration

In accordance with the recommendations (instructions) for the tasks.

3.4. control materials for the final stage of the lesson: tasks, tasks, tests, etc .:

1. The method of dialysis through a semipermeable membrane is used to assess the quality of dosage forms:
   A. ointments;
   B. soft capsules;
   C. prolonged-release tablets;
   D. powders insoluble in water;
   E. tablets with a well-soluble drug substance.
2. The method of dialysis through a semipermeable membrane is used to assess the quality of dosage forms:
   A. liniments;
   B. hard capsules;
   C. prolonged-release tablets;
   D. powders insoluble in water;
   E. tablets with a well-soluble drug substance.
3. At what stage of the study by the method of agar plates is used Ehrlich's reagent?
   A. is added to the agar during cooking
   B. is introduced into the agar after it hardens
   C. introduced into the ointment before use
   D. apply to the ointment after filling the agar wells
4. What is used as a comparison solution in the spectrophotometric method for determining the content of phenolic compounds of propolis in the dialysate?
   A. purified water
   B. distilled water
   C. ethyl alcohol
   D. standard solution of phenolic compounds
   E. propolis solution
5. Which of the following indicators is determined by the analysis of colored areas in the method of agar plates?
   A. color of the painted area
   B. color intensity
   C. the diameter of the colored area
   D. depth of the colored area

E. change the color of the zone

6. What concentration of iron (III) chloride reagent should be taken, which is added to agar?
   A. 1%
   B. 2%
   C. 5%
   D. 10%
   E. 20%
7. What concentration of alcohol should be taken to grind streptocide?
   A. 40%
   B. 60%
   C. 70%
   D. 90%
8. What concentration should be taken of ethyl alcohol as a reference solution in the spectrophotometric method for the determination of phenolic compounds?
   A. 60%
   B. 70%
   C. 90%
   D. 96%
   E. 40%
9. At what stage of the study by the method of agar plates is used reagent iron (III) chloride?
   A. is added to agar during cooking
   B. is introduced into the agar after it hardens
   C. introduced into the ointment before use
   D. apply to the ointment after filling the agar wells
   E. add simultaneously to the ointment and agar
10. The company produces oil solutions. Vaseline oil was used as a solvent in the production of oil solution for injection, and ampoules made of HC-3 glass were used as ampoules. Evaluate the actions of the technologist.
    A. The technologist did the right thing
    B. For ampoules of oil solutions it is expedient to use ampoules from clear glass of the AB - 1 brand
    C. To ampoule oil solutions, it is advisable to use ampoules made of clear glass brand NS - 1
    D. To ampoule oil solutions, it is advisable to use ampoules made of clear glass brand NS - 2
    E. For ampoule of oil solutions it is expedient to use ampoules from clear glass of the NS-5 brand

IV. Summing up

List of recommended reading

Main:

Methodical development of practices, OPP «Pharmacy, industrial pharmacy», 5th year, Faculty of Pharmacy, Discipline: «Biopharmacy» p. 21

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

ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF DRUGS TECHNOLOGY

APPROVE
Head of Department

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

METHODICAL DEVELOPMENT OF PRACTICAL LESSON

Course: 5 Faculty: Pharmaceutical

Course Biopharmacy

Practical lesson №8 Topic: «**Bioequivalence of drugs. Bioequivalence assessment.»**

The practical lesson was developed by:
Ph.D., Assoc.

_____ (Fizor. N.S.)
signature
The practical lesson was discussed at the methodical meeting of the department
«29» august 2022 y.
Protocol № 1

Odesa – 2022

The purpose of the lesson: to study the influence of technological factors on the dissolution rate of tablets and the stability of injectable solutions, as well as the therapeutic equivalence of drugs.
Basic concepts: bioequivalence
Equipment: according to the requirements of Good Pharmacy Practice (GPP).
Study time: 2.0

Plan

I. Organizational moment.
II. Control of basic knowledge
2.1. Requirements for theoretical readiness of students to perform practical classes (knowledge requirements, list of didactic units):
Requirements for theoretical knowledge:

The concept of bioequivalence is closely related to the concept of bioequivalence. Two drugs are considered bioequivalent if they provide the same bioavailability of the drug after administration in the same dose and the same dosage form. According to the WHO regulations (1994, 1996) and the EU (1992), the differences in pharmacokinetic parameters for bioequivalent drugs should not exceed 20%.

Currently, the study of bioequivalence is the main type of medical and biological quality control of generic drugs. The introduction of the definition of bioequivalence as a method allows to make a reasonable conclusion about the quality, efficacy and safety of comparable drugs on the basis of a smaller amount of primary information and in a shorter time than in clinical trials.

To date, there are regulations for studying the bioequivalence of the WHO (1996), the EU (1992), the Russian Federation (1995, 2000). They set out the main rationale for the need for bioequivalence studies. These studies must be performed if there is a risk of lack of bioequivalence or a risk of reduced pharmacotherapeutic action and clinical safety of the drug.

For example, drugs for the treatment of conditions that require a guaranteed therapeutic effect must be evaluated; drugs with a small therapeutic breadth; drugs whose pharmacokinetics are complicated by a decrease in absorption of less than 70% or with high elimination (more than 79%); drugs with unsatisfactory physicochemical properties (low solubility, instability, polymorphism); drugs with documented evidence of a bioavailability problem.

Bioequivalence studies (pharmacokinetic equivalence) should in no way be considered as an alternative to pharmaceutical equivalence testing - the equivalence of generic drugs in terms of qualitative and quantitative composition of drugs assessed by pharmacopoeial tests, as pharmaceutical equivalence does not guarantee equivalence. However, bioequivalence studies suggest that the bioequivalence of the original generic drugs provide the same efficacy and safety of pharmacotherapy, ie are therapeutic equivalents.

Assessment of bioequivalence is based on the results of studying the relative bioavailability of the drug in the compared drugs. In essence, bioequivalence studies are a special type of pharmacokinetic study. First of all, it should be emphasized that the study of bioequivalence is a clinical trial where the subject of the study is a person. Therefore, such studies are subject to all the official requirements and regulations as for all other clinical trials. A team of specialists of various profiles should plan and conduct research to determine bioequivalence: clinical pharmacologists, clinicians, biochemists, chemists-analysts. The study of bioequivalence should be conducted in full compliance with the principles of "Good Clinical Practice" (GLP) in order to guarantee the quality of data presented and protect the rights, health and well-being of subjects.

Animal bioequivalence studies have not been widely accepted and are practically not used. They are used only at the stage of preclinical studies or in the case of the study of drugs intended for use in veterinary medicine. Typically, the term "bioequivalence" in this case is replaced by the term "pharmacokinetic equivalence".

In determining the equivalence of antimicrobial drugs, it is possible to use in vitro methods, but in this case the term "bioequivalence" should not be used.

Currently in Ukraine there is a sufficient material and technical base, highly effective methods are used to determine pharmacokinetic parameters, training in the field of bioequivalence research, which allows to solve the urgent problem of assessing the effectiveness and safety of generic drugs of domestic and foreign production.

Objects of bioequivalence research

The objects of bioequivalence studies are generic drugs intended for extravascular administration (oral, sublingual, etc.), provided that the action of these drugs indirectly appears drug in the systemic circulation. As a reference drug, the corresponding original drug or its analogue, which has found wide medical application (preferably one produced under the license of the authors of the original drug), should be used.

In some cases, equivalent confirmation is not required. For example, for pharmaceutical analogues of permitted means of systemic action in the form of solutions - injectable solutions, solutions for external use, eye drops.

For drugs to which the concept of bioavailability cannot be applied (drugs of non-systemic action - external, ocular, vaginal, etc.), it is recommended to conduct comparative clinical or pharmacodynamic studies.

Contingent of subjects in the study of bioequivalence

Given the fact that the parameters of bioavailability can be significantly influenced by individual anatomical and physiological features, the contingent of subjects in the study of bioequivalence should be as homogeneous as possible. To reduce the scatter of the data obtained, drug trials are performed on healthy volunteers. Persons of both sexes between the ages of 18 and 55 may be involved. The body weight of the subjects should not exceed 20% of the age physiological norm for this sex. Preferably, the subjects were non-smokers. Before the start of the study, it is necessary to conduct a thorough history, as well as examine the subjects with standard laboratory tests to exclude persons with dysfunction of the elimination organs (liver,

kidneys) and the cardiovascular system. Before and during the tests, you can perform special medical examinations, the need for which is due to the peculiarities of the pharmacological properties of the study drug.

In some cases, patients with certain diseases are included in the study group instead of healthy volunteers. This situation can occur if the study drug has known side effects and the health of volunteers can be seriously damaged (for example, the study of drugs used in oncology, in the treatment of HIV, etc.).

The minimum number of subjects required to study bioequivalence is 12 people. The bank of volunteers that meet the above criteria is formed taking into account the participation of candidates in other studies and donations. The minimum interval between participation in other studies and donation is 3 months. All volunteers must be informed of the objectives and test procedure, which is documented in a special "informed consent".

The planning and conduct of the study should be based on knowledge of the pharmacokinetics and pharmacodynamics of the investigational drug substance.

2 weeks before the start of the test, volunteers are invited to re-collect medical history. If in the period preceding the interview, the volunteer has suffered any diseases that may affect the results of the study, he is not included in the group of subjects.

In preparation for the study is carried out so ¬ selection of backups in case of unforeseen replacement of the study of volunteers. The number of backups is 25% of the number of volunteers.

Standard conditions must be created for all subjects, namely:

- Food and water regime (standard diet for 1 day before the study and throughout its implementation);
- Complete exclusion of any other drugs within 2 days before taking the study drugs and during the pharmacokinetic study;
- Exclusion of alcohol, caffeine, drugs, concentrated juices;
- Standard motor mode and day mode. The state of health of volunteers, their compliance with the regime,
- The organization of nutrition, the correctness of blood sampling and their processing are controlled by researchers-clinicians.

Bioequivalence studies are performed with a single dosage (preferably the largest) of this generic drug in this dosage form, even if it is declared for registration in several dosages. In cases of prolonged-release dosage forms, bioequivalence should be checked for each dose separately. Assessment of bioequivalence can be based both on the data obtained with a single injection of drugs, and with their repeated (course) use. In the latter case, it is necessary that the subjects received the drugs in the same single dose with the same dosage interval (according to the instructions for medical use of this drug) until steady state.

The peculiarity of the design of bioequivalence studies is that each of the subjects receives both the study drug and the comparison drug. When selecting volunteers for groups, the cross-method with a randomized distribution of volunteers is preferred.

The time interval between administration of the study drug and the comparison drug depends on the duration of circulation of the drug in the body and should be at least half-life (T 1/2). Volunteers spend time at home after the first period of the study before the start of the second period, but must adhere to the established regime during this period.

Blood sampling in the study of bioequivalence

The biomaterial in which the drug concentration should be determined in bioequivalence studies is plasma, serum or whole blood. The sampling scheme, as in any pharmacokinetic study, is determined by the shape of the curve "drug concentration - time". The more complex the form, the more often samples should be taken. The sampling time should provide for obtaining for each fragment a pharmacokinetic curve of several points - at least two for the phase of the initial increase in concentration and at least five - for the phase of its decrease. The total duration of monitoring the concentration of the drug should be at least 4 times longer than the half-life.

The following conditions must be strictly adhered to when taking blood samples:

- blood is taken from the ulnar vein through a special cubital catheter;
- the first portion of blood (initial, ie before taking the drug) is taken in the morning on an empty stomach 5-10 minutes after installation of the catheter in the ulnar vein;
- the time of sampling corresponds to the study program and depends on the pharmacokinetics of the study drug;
- blood samples are carefully labeled (test code, sample number and drug name);
- the time interval between blood sampling and treatment should not exceed 5 minutes;
- plasma or serum samples should be stored at a temperature not exceeding -20 ° C;
- the first meal is allowed no earlier than 4 hours after taking the drug;
- in the event of unforeseen situations, excluding the possibility of blood sampling in the prescribed interval, work with the data of the subject pro-continued, but the encrypted test tube remains empty.

Methods for determining the concentration of drugs in a blood sample in the study of bioequivalence

Different methods (physicochemical, immunological, microbiological and others) can be used to determine the concentration of drugs in plasma, serum or whole blood, provides the ability to reliably monitor the concentration of the drug under selected conditions of pharmacokinetic studies, including its duration, and meets the general requirements. selectivity, accuracy, reproducibility.

If due to presystemic elimination of drugs it is not detected in the blood in an unchanged state and (or) does not have biological activity (prodrug), it is necessary to determine the concentration of the biologically active metabolite, not the prodrug.

Analysis of pharmacokinetic data. Bioequivalence assessment

Assessment of the bioavailability of the drug or its main biologically active metabolite (if the studied drugs are a prodrug) is based on a comparison of the values of pharmacokinetic parameters obtained by analyzing the curves "concentration C - time t" for the study drug and the comparison drug.

Individual values of the area under the curves "concentration - time" - AUC (both within the duration of monitoring the concentration of the drug - AUC t, and in the range from 0 to ∞-AUC∞, the maximum concentration Cmax and time to reach tmax should be calculated according to The values of the parameters AUCt, Cmax and t max can be estimated both by model methods (by describing the data "drug concentration - time" by a mathematical model) and by extramodel methods (the highest of the measured values of concentration - Cmax and the corresponding time of the observed maximum - tmax) .The value of AUC is calculated using the method of ordinary or logarithmic trapezoids. the concentration of the drug in the last sample and the elimination constant, respectively. non-linear curve is described by nonlinear regression analysis or a straight line equation in the coordinates ln C - t, using the method of linear regression.

With a sufficient follow-up period, when AUCt ≥ 80% AUC∞, the AUCt value should be used to assess the completeness of absorption of the study drug, and under conditions that AUCt <80% AUC∞, the AUC∞ value should be used.

Further analysis of pharmacokinetic data involves the calculation of individual ratios of AUCt or AUC∞ (respectively f'i f - estimates of compliance with the degree of absorption) and Cmax (f") for any dosage form, the ratio of Cmax / AUCt or Cmax / AUC∞ as characteristics absorption rates - for conventional forms, and for forms of prolonged action - the differences between the values of Cmax and the minimum concentration Cmin relative to the integral mean concentration Css = AUCt, where t is the duration of monitoring the concentration of the drug substance.

Bioequivalence is assessed by the parameters AUCt or AUC∞, as well as Cmax - for any dosage form, the parameters Cmax / AUCt or Cmax / AUC∞ - for the usual forms and the parameter (Cmax - Cmin) / Css - for forms prolonged action.

Drugs are considered equivalent if the 90% confidence interval for the geometric mean, calculated for individual relationships logarithmically converted values of each of these pharmacokinetic parameters (except Cmax), for the study drug to those for the comparison drug, is within 0.80 .. 1.25. For Cmax, the corresponding limits are 0.70 ... 1.43. The limits of the above confidence interval are calculated using the strength of two one-sided tests (mainly by the method of Schuirmann) after logarithmic transformation of the values of pharmacokinetic parameters. If the specified confidence interval in the case of AUCt or AUC∞ parameters exceeds the established limits, the drugs are considered non-bioequivalent.

Combined drugs and principles of their use

The phenomenon of drug interaction in practice is used in the appointment of combined drugs.

Combined drugs are dosage forms containing two or more active pharmacological substances. A similar concept - combination therapy involves the simultaneous use of two or more monocomponent drugs.

The main goal is to increase efficiency and, in some cases, improve portability.

The share of combined drugs in the range of pharmacies is about 20% of the names. They are characterized by both advantages and disadvantages. The "subjective" advantages include: ease of use for the patient (eliminates the need to make complex combinations of different tablets); psychological and social comfort (it is much easier to swallow one pill than several, at work, in a public place, etc.); in most cases, the price of combined drugs is lower than the total price of single drugs.

The objective advantages of combined drugs include potentiation of action due to the unidirectional effect of the ingredients, and by reducing the inactivation of the drug in the body and creating conditions for one ingredient to show the effect of another (combination of antibiotics and lactamase inhibitors). Also, when taking such drugs there is a reduction in the risk of side effects.

The disadvantages of combined drugs are the fixed ratio of active pharmacological substances (does not allow, if necessary, to change the dose of one ingredient); impossibility of multidirectional combination with food (before, after or during food).

Currently, the manufacture of finished combination drugs is a complex process that includes multifaceted pharmacological, toxicological, pharmacokinetic, technological and other studies.

Pharmacological studies should prove the feasibility of introducing into the combined drug of each of its components; determine whether and in which direction the action of the main component changes. It is taken into account that the pharmacological interaction may have the character of synergism and antagonism, and synergism can result in a simple summation of effects (additive action) or potentiation, when the total effect exceeds the simple addition of the effects of each of the components.

In some cases, there may be a synergy-antagonism, in which some effects of the components are enhanced and others are weakened. All this should be detected during a pharmacological study.

The mechanism of pharmacological interaction may be related to the effect of individual components on the respective receptors. However, in some cases, the modification of the pharmacological effect may be associated with other factors: improved bioavailability, increased resistance of the main component to the destructive effects of enzymes, various components on metabolic processes, and others. Thus, in modern antiparkinsonian drugs nacom and madopar the action of the main component of levodopa is enhanced by the addition of decarboxylation inhibitors and prevent inactivation of the active substance in peripheral tissues.

Modern ready-made combination drugs are an important contribution to the arsenal of drugs. In some cases, combined drugs facilitate pharmacotherapy, expand its boundaries, eliminate the need for extemporaneous preparation of prescriptions.

When prescribing any combination drug, it is necessary to know its full composition and take into account the pharmacological properties of each of its components, even if its properties are well known. Some combination drugs with analgesic and anti-inflammatory properties (pentalgin, solpadein), often used for colds, contain codeine, which not only suppresses cough, but also inhibits intestinal motility and can cause constipation with prolonged use. Combined drugs citramon, solpadein contain caffeine and with hypersensitivity and prolonged use can cause irritability, sleep disturbances, and in large doses - convulsive reactions, the development of arrhythmias. Combination preparations containing sympathomimetic amines and may cause an increase in blood pressure.

All the above allows us to formulate the principles of rational combination therapy.

1. Prescribe only those drugs for which the patient has a clear indication.
2. Combination drugs should be prescribed only in case of clear indications for combination therapy.
3. Use combination drugs only in the case of "typical" course of the disease.
4. Use combination drugs only at the stage of maintenance therapy (not in the acute period of the disease at the stage of selection of adequate doses).
5. Give the patient clear instructions about possible interactions of oral medications with food and other medications.
6. Prefer combined drugs if necessary long-term (lifelong) treatment of "undisciplined" patients.

Didactic units:

1. Objects of bioequivalence research
2. The contingent of subjects in the study of bioequivalence
3. Sampling of blood in the study of bioequivalence
4. Methods for determining the concentration of drugs in a blood sample in the study of bioequivalence
5. Analysis of pharmacokinetic data. Bioequivalence assessment

Answer the question:

1. Influence of environmental factors on pharmacotherapy.
2. Interaction of drugs with food.
3. The concept of therapeutic non-equivalence of drugs and the causes of its occurrence.
4. Brands and generics. Replacement of drugs by their analogues.
5. Types of bioavailability of drugs. Determination of absolute and relative bioavailability of drugs.
6. Methods "in vivo", which are carried out on living organisms of laboratory animals, healthy human volunteers and on isolated organs with single and multiple injections.
7. Distinctive features in the reactivity of different species of animals to the introduction of biologically active substances.

8. "In vitro" methods used in biopharmacy (direct diffusion through the membrane, "agar plates", chromatographic, solubility test, etc.).
9. Modern methods for determining the concentration of drugs in biological fluids (blood, urine, and other body secretions).
10. Graphical method of calculating the area of the pharmacokinetic curve and the relative degree of absorption depending on pharmaceutical factors. Determination of absorption and elimination constants

Solve the test:

1. Which drugs should be selected to determine bioequivalence?
   A. drugs from different manufacturers
   B. drugs from different manufacturers
   C. drugs that are manufactured by one plant, but different series
   D. drugs that are manufactured by one factory, but one series
   E. drugs from different manufacturers; drugs that are manufactured by one plant, but different series.
2. Indicate which term corresponds to the following statement: "A condition that allows a drug substance, when administered into the body, to reach the site of exposure."
   A. relative bioavailability
   B. bioavailability
   C. absolute bioavailability
   D. therapeutic inequality
   E. bioequivalence
3. Indicate which term corresponds to the following statement: "Correspondence of the amount of drug substance (drug) or drug to the analytical regulatory documentation or the identity of the effect of the studied drug to the drug comparison".
   A. bioavailability
   B. equivalence
   C. system availability
   D. biotransformation
   E. resorption
4. Indicate which term corresponds to the following statement: "The equivalent of a drug that, after administration of the same doses, gives the same therapeutic effect, tested on any symptom or treatment of the disease."
   A. clinical equivalent
   B. equivalence
   C. bioequivalence
   D. bioavailability
   E. pharmaceutical equivalent
5. Indicate which term corresponds to the following statement: "Total constant that determines the rate of penetration of the drug from the site of introduction into the body through the biological membrane."

A. biotransformation
B. elimination constant
C. the release rate constant
D. equivalence
E. LADMER

6. Indicate which term corresponds to the following statement: "Inequality of therapeutic action of the same drugs in the same doses, prepared by different manufacturers or the same plant, but different series."
A. clinical equivalent
B. equivalence
C. bioequivalence
D. bioavailability
E. pharmaceutical equivalent
7. Indicate which term corresponds to the following statement: "Inequality of therapeutic action of the same drugs in the same doses, prepared by different manufacturers or the same plant, but different series."
A. therapeutic inequality
B. equivalence
C. pharmaceutical inequality
D. bioavailability
E. pharmaceutical equivalent
8. Indicate which term corresponds to the following statement: "It is a drug that contains the same amount of therapeutically similar substance in a certain dosage form that meets the requirements defined by technological standards."
A. clinical equivalent
B. equivalence
C. bioequivalence
D. bioavailability
E. pharmaceutical equivalent
9. Indicate which term corresponds to the following statement: "The purity of the hypothetical volume of plasma per mole (volume of distribution) by which the body is released from the drug, releasing it through the kidneys, bile, lungs, skin, etc.
A. distribution
B. purity
C. purity of the whole body
D. resorption
E. biotransformation
10. From a biopharmaceutical point of view, indifferent substances are:
A. sugar;
B. correctors;
C. South Africa;
D. preservatives;
E. none of the above.

III. Formation of professional skills, abilities:

3.1. content of tasks:

Task №1

To establish the effect of polymorphic modifications of insulin preparations on the rate of its release by the "in vivo" method.

3.2. recommendations (instructions) for performing tasks

Task №1

Methodical recommendations for the task

The objects of study are amorphous and crystalline zinc insulin, widely used in medical practice in diabetes.

During the experiment, three animals (white rats or rabbits) of the same weight after 18 hours of fasting were used for training purposes.

In animals, determine the initial concentration of glucose in the blood. After that, two animals are injected subcutaneously, respectively, drugs: amorphous zinc insulin and crystalline zinc insulin at a dose of 1.0 IU / kg. Taking into account the small body weight of experimental animals (white rats), use drugs in a dilution of 1: 100. The third animal is a control.

Determination of the concentration of glucose in the blood of animals is carried out after 1; 1.5; 2 hours from the start of the experiment. Before completing the task, get acquainted with the algorithm of experimental work for task № 3 (Appendix 3).

Determination of blood glucose

1.5 ml of 3% trichloroacetic acid solution is placed in four centrifuge tubes. In three of them make 0.1 ml of blood taken from the retroorbital venous plexus or tail vein of the animal, and in the fourth - 0.4 ml of standard glucose solution. The mixture is shaken and centrifuged for 10 min at 3000 rpm, then placed in 4 chemical tubes of 1.5 ml of orthotoluidine reagent and added per 1 ml of centrifugate. The tubes with the mixture are shaken and placed in a boiling water bath for 10 minutes. After that, they are cooled under a stream of cold water. The optical density of the solution is measured using a photoelectrocolorimeter (FEC 56 PM) with a red light filter (№ 8) with a wavelength of 600-650 nm in a cuvette with a liquid layer thickness of 5 mm. Purified water is used as a reference solution.

The concentration of glucose in the blood (m mol / l) is calculated by the formula:

$$C_{on} = \frac{C_{cm} \cdot E_{on}}{E_{cm}},$$

where *Cop* is the concentration of glucose in the test sample (M mol / l);

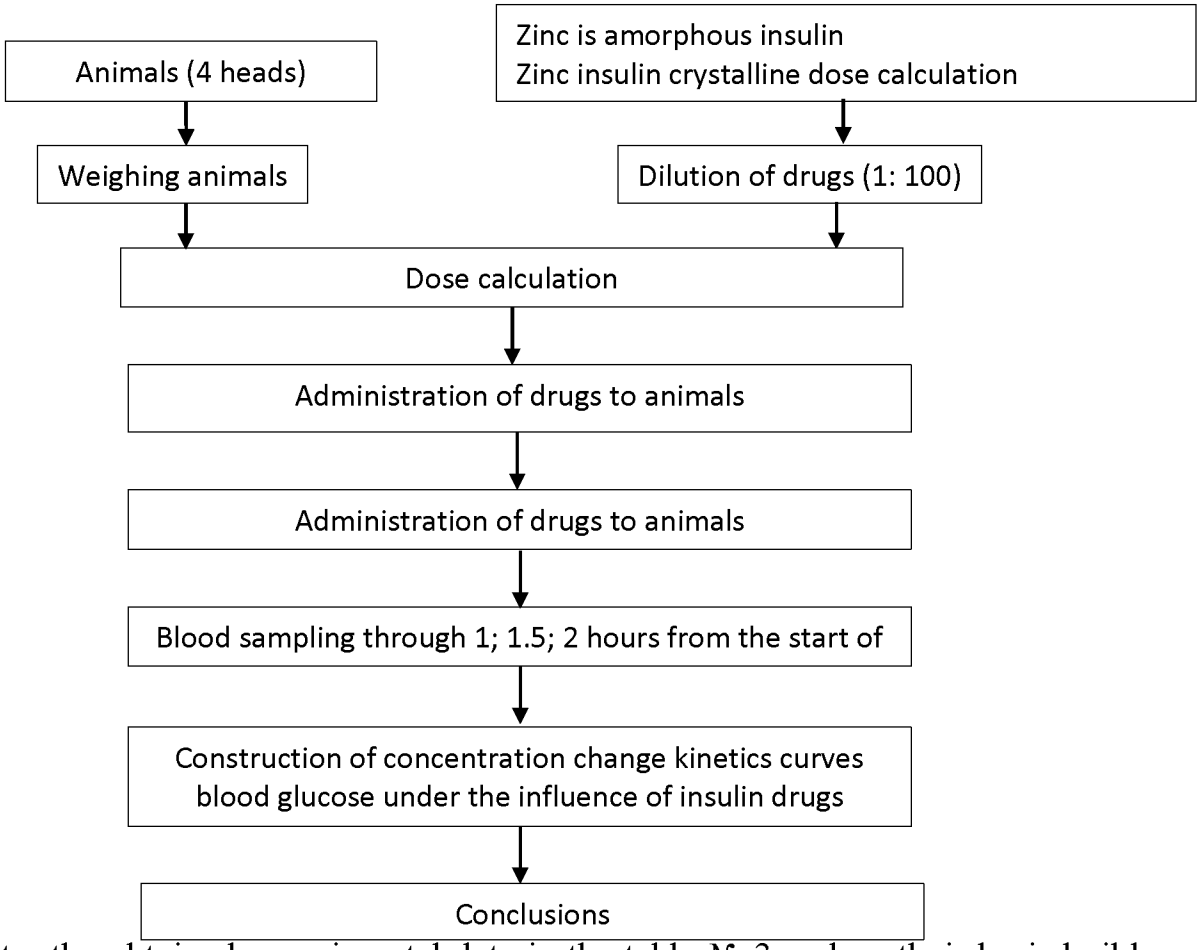
CC - glucose concentration in a standard sample (M mol / l);

Eop - optical density of the test sample;

Est is the optical density of the standard solution.

Annex 3

ALGORITHM OF EXPERIMENTAL WORK ON STUDY OF INFLUENCE OF POLYMORPHIC MODIFICATIONS OF INSULIN DRUGS FOR THE RATE OF ITS RELEASE



Enter the obtained experimental data in the table № 3 and on their basis build a graph in the coordinates: on the y-axis - the concentration of glucose in the blood (C , m mol / l); on the abscissa - time (t , h).

Table 3

CONCENTRATION OF GLUCOSE IN THE BLOOD OF WHITE RATS UNDER THE INFLUENCE OF INSULIN DRUGS AT A DOSE OF 1 UNIT / kg

Marking	Animal weight, kg	Preparation	Blood glucose concentration, m mol / l			
			day off	1:00	1.5 years	2 hours

After completing the task, draw conclusions about the effect of polymorphic modifications of zinc insulin on blood sugar.

3.3. requirements for work results, including before registration

In accordance with the recommendations (instructions) for the tasks.

3.4. control materials for the final stage of the lesson: tasks, tasks, tests, etc .:

1. Possible causes of therapeutic inadequacy of drugs produced by different plants:
   A. technology;
   B. dose of drug substance;
   C. sex and age of the patient;
   D. routes of administration;
   E. dosage form.
2. The fastest pharmacological effect develops with the introduction of drugs:
   A. Subcutaneously
   B. Rectally
   C. Orally
   D. Intravenously
   E. Intramuscularly
3. In which way of drug management, the number of factors that will affect the bioavailability of the drug will be the largest:
   A. rectal
   B. inhalation
   C. oral
   D. parenteral
   E. sublingual
4. The rectal route of administration of drugs provides their fast absorption. In which disease the bioavailability of drugs will deteriorate:
   A. flu
   B. GRVZ
   C. hemorrhoids
   D. sore throat
   E. gout
5. Patient D., 37 years old, was given a parenteral antibiotic. But due to the high price of the drug, the patient refused it. The doctor suggested a lower-priced generic drug that was bioequivalent to the brand. What did the doctor mean by bioequivalence in the first place?
   A. Has no side effects.
   B. Manufactured by the same company.
   C. Reaches the same concentration in the blood at the same dose.
   D. Has the same number of dosage forms.
   E. Has the same country of origin.
6. The pharmaceutical availability of ointments is determined by the following methods:
   A. passive diffusion;
   B. diffusion into the gel;
   C. microscopy;
   D. colored complexes;
   E. dialysis through a semipermeable membrane.

7. Patient D., 67 years old, suffering from chronic hepatitis, the doctor prescribed the drug in half dose. What effect does the doctor want to avoid with such an appointment?
   A. Tachyphylaxis.
   B. Cumulation.
   C. Addiction.
   D. Idiosyncrasy.
   E. Sensitization
8. Sometimes changes in drugs can not be determined by chemical methods, then use:
   A. pharmacological methods
   B. biological methods
   C. pharmaceutical methods
   D. clinical methods
   E. hygienic methods
9. What should be the temperature of the environment for the pharmacopoeial test to determine the "dissolution":
   A. 37 0C
   B. 36 0C
   C. 38 0C
   D. 25 0C
   E. 21 0C
10. Which drug manufacturer has the right to produce a drug under the trade name "Aspirin":
   A. Darnytsia
   B. Pharmac
   C. Styrene
   D. Astellas
   E. Bayer

IV. Summing up

List of recommended reading

Main:

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