Kazan State Medical University
Ministry of Health of the Russian Federation

Institute of Pharmacy

BIOPHARMACY

Educational and methodical manual for students studying in the specialty "Pharmacy" in English

БИОФАРМАЦИЯ

Учебно-методическое пособие для студентов, обучающихся по специальности «Фармация» на английском языке

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Biopharmacy : educational and methodical manual for students studying in the specialty “Pharmacy” in English = Биофармация : учебно-методическое пособие для студентов, обучающихся по специальности «Фармация» на английском языке / A. V. Sitenkova, S. N. Egorova, E. S. Baltaeva ; Kazan State Medical University of the Ministry of Health of the Russian Federation. – Kazan, 2025. – 44 p., [1].

Educational and methodical manual of the discipline "Biopharmacy" for students studying in the specialty "Pharmacy" in English contains the purpose, tasks of studying the discipline, theses of lectures, exercises for practical lessons, a list of references.

UDC 615.011+615.015.4(075.8)

CONTENT

INTRODUCTION

Dear students!

You begin studying the discipline "Biopharmacy".

The object of study of this discipline is the influence of pharmaceutical, biological and other factors on the therapeutic efficacy of medicines.

You will listen to lectures and attend practical classes. You should come to practical classes prepared on a specific topic. You will take part in an oral interview on the topic of a practical lesson, answer test questions, and perform practical tasks under the guidance of a teacher.

This educational and methodical manual will allow you to navigate the work program of the discipline "Biopharmacy", as well as the distance course "Biopharmacy" of the educational portal of the Kazan State Medical University.

The discipline is studied in the 8^{th} semester, intermediate certification – offset.

1. PLANNED LEARNING OUTCOMES OF THE DISCIPLINE

The purpose of mastering the discipline is the formation of knowledge, skills and abilities in the field of manufacturing and quality control of medicines, taking into account biopharmaceutical properties.

Objectives of mastering the discipline:

1. To form knowledge, skills and abilities in order to assess the influence of pharmaceutical factors in the production of medicines.
2. To form knowledge, skills and abilities to conduct biopharmaceutical research in assessing the quality of medicines.

The study of the discipline is aimed at the formation of the following ***competencies***:

Code and name of the competence	Indicator code and name (indicator) of competence achievement	Learning outcomes		
		to know	**to be able to**	**to have**
General professional competencies				
GPC-2. Able to apply knowledge about morphofunctional features, physiological states and pathological processes in the human body to solve professional problems.	GPC-2 (IP-1). Analyzes the pharmacokinetics and pharmacodynamics of a medicine based on knowledge of morphofunctional features, physiological states and pathological processes in the human body.	the main aspects of the pharmacokinetics and pharmacodynamics of medicines based on knowledge of morphofunctional features, physiological states and pathological processes in the human body.	analyze the pharmacokinetics and pharmacodynamics of medicines based on knowledge of morphofunctional features, physiological states and pathological processes in the human body.	the main tools for analyzing the pharmacokinetics and pharmacodynamics of medicines based on knowledge of morphofunctional features, physiological states and pathological processes in the human body.
Professional and additional professional competencies				
PC-1. Capable to manufacture medicines and take part in the technology for the production of finished medicines.	PC-1 (IP-6). Carries out the selection of excipients for dosage forms of medicines, taking into account the influence of biopharmaceutical factors.	the main types of excipients in dosage forms of medicines, taking into account the influence of biopharmaceutical factors.	carry out the selection of excipients of dosage forms of medicines, taking into account the influence of biopharmaceutical factors.	the skills of selecting excipients for dosage forms of medicines, taking into account the influence of biopharmaceutical factors.
PC-3. Able to provide pharmaceutical informing and consultancy during the dispensing and realization of medicines for medical	PC-3 (IP-1). Provides informative and consultative assistance to visitors of the pharmacy organization when choosing medicines and other pharmacy products, as well as on their rational use, taking	biopharmaceutical features of various dosage forms for choosing a drug and justifying the issues of its rational use.	make a choice of a drug based on the biopharmaceutical features of the dosage form.	the skills of choosing medicine, based on the biopharmaceutical features of the dosage form.

use and other pharmacy products.	into account the biopharma-ceutical features of dosage forms of medicines.			
	PC-3 (IP-2). Informs medical professionals about medicines, their synonyms and analogues, possible side effects and interactions, taking into account the biopharmaceutical features of dosage forms.	biopharmaceutical features of various dosage forms to predict possible side effects and interactions with other drugs.	predict possible side effects and interactions with other medicines, taking into account the biopharmaceutical features of dosage forms.	the skills to predict possible side effects and interactions with other medicines, taking into account the biopharmaceutical features of dosage forms.
	PC-3 (IP-3). Makes a decision to replace the prescribed medicine with synonymous or similar drugs in the prescribed manner based on information about groups of drugs and synonyms within one international non-proprietary name and prices for them, taking into account the biopharmaceutical features of dosage forms.	biopharmaceutical features of various dosage forms for making a decision to replace a medicine.	make a decision to replace the medicine, based on the biopharmaceutical features of various dosage forms.	the skills of making decisions of the replacement of a medicinal product, based on the biopharmaceutical characteristics of various dosage forms.

2. ATTENDANCE REQUIREMENTS

It is expected that you will attend all training activities. The attendance will be recorded in the journals of lectures and practical lessons. In case of illness or other reasons why you will not be able to attend classes, you must notify the teacher and provide a medical certificate. Working off the missed lectures is carried out on the educational portal. Working off missed practical classes will require the fulfillment of all types of tasks performed according to the discipline program in these classes.

3. CURRENT CONTROL

Types of current control:

1. Testing is a tool using which the teacher assesses the degree of student's achievement the required knowledge, skills and abilities. Compiling a test includes the creation of a verified system of questions, the procedure of conducting the test and a method for assessment achieved results. The test consists of tasks with a choice of one answer from 5 proposed questions. The type of tasks – closed, the number of tasks in the test ticket – 10, the number of test ticket variants – 3, for a correct answer – 1 point, for an incorrect or unspecified answer – 0.

Testing is carried out on each practical lesson.

Description of the assessment scale of testing on the practical lesson:

- 9–10 points – a student correctly answered 90% of the test questions;
- 8 points – a student correctly answered from 80% to 90% of the test questions;
- less than 7 points – a student correctly answered less than 69% of the test questions.

2. Oral report on a practical lesson

The activity of work in the classroom, the level of preparation for classes are assessed.

Description of the assessment scale:

- 9–10 points – a student has revealed more than 90% of the content of the question of the topic of the lesson;
- 8 points – a student correctly disclosed from 80% to 90% of the questions of the topic of the lesson;
- less than 7 points – a student correctly disclosed less than 69% of the questions of the topic of the lesson.

3. Situational tasks on a practical lesson

The independence and correctness of performing practical tasks are assessed.

Description of the assessment scale:

- 9–10 points – a student correctly carried out more than 90% of the practical tasks;
- 8 points – a student correctly carried out from 80% to 90% of practical tasks;
- less than 7 points – a student correctly carried out less than 69% of practical tasks.

4. INTERMEDIATE CERTIFICATION

Intermediate certification is offset.

Lecture attendance, module results, current class grade (in the form of an arithmetic mean), final testing are taken into account when obtaining a student's rating.

5. STRUCTURE AND CONTENT OF THE DISCIPLINE

Sections / topics of the discipline	Total labor intensity, hours	Types of training lessons and labor intensity, hours			Forms of current progress control
		Classroom training lessons		Independent work of students	
		Lectures	Practical lessons		
Section 1. Introduction to biopharmacy. Pharmaceutical factors, bioavailability.	43	6	18	19	
Topic 1.1. Biopharmacy. Introduction. Biopharmaceutical Classification System (BCS) (LECTURE 1, PRACTICAL LESSON 1).	7	1	3	3	Interview, testing, oral questioning.
Topic 1.2. Pharmaceutical factors (LECTURE 2, PRACTICAL LESSON 2).	7	1	3	3	Interview, testing, oral questioning.
Topic 1.3. Bioavailability (LECTURE 3, PRACTICAL LESSON 3).	7	1	3	3	Case task, interview, testing, oral questioning.
Topic 1.4. Basic aspects of pharmacokinetics (LECTURE 4, PRACTICAL LESSON 4).	7	1	3	3	Interview, testing, oral questioning.
Topic 1.5. Equivalence of drugs (LECTURE 5, PRACTICAL LESSON 5).	8	2	3	3	Case task, interview, testing, oral questioning.
Control work on topics 1.1 – 1.5.	7	–	3	4	Control work
Section 2. Biopharmaceutical aspects of manufacturing and quality control of medicines.	65	10	27	28	
Topic 2.1. Excipients as a pharmaceutical factor (LECTURE 6, PRACTICAL LESSON 6).	8	2	3	3	Laboratory work, interview, testing.
Topic 2.2. Technological process of medicine manufacturing as a pharmaceutical factor (LECTURE 7, PRACTICAL LESSON 7).	8	2	3	3	Interview, testing, oral questioning.
Topic 2.3. Medicines with improved biopharmaceutical properties. Solid	8	2	3	3	Laboratory work, interview, testing.

dosage forms (LECTURE 8, PRACTICAL LESSON 8).					
Topic 2.4. Medicines with improved biopharmaceutical properties. Soft dosage forms and liquid dosage forms (LECTURE 9, PRACTICAL LESSON 9).	7	1	3	3	Laboratory work, testing, oral questioning.
Topic 2.5. Transdermal therapeutic systems (LECTURE 10, PRACTICAL LESSON 10).	7	1	3	3	Interview, testing, oral questioning.
Topic 2.6. Biopharmaceutical assessment of the quality of various dosage forms of medicines. Study of the release and absorption of medicines (LECTURE 11, PRACTICAL LESSONS 11, 12).	14	2	6	6	Laboratory work, interview, testing, oral questioning.
Control work on topics 2.1 – 2.6.	7	–	3	4	Control work
Offset lesson	6	–	3	3	Offset
Total	108	16	45	47	

6. PLANS OF LECTURES, PRACTICAL LESSONS AND INDEPENDENT WORK ORGANIZATION

SECTION 1. Introduction to biopharmacy. Pharmaceutical factors, bioavailability

Topic 1.1. Biopharmacy. Introduction. Biopharmaceutical Classification System (BCS)

Lecture 1 (1 hour)

Content: Biopharmacy. Introduction. Biopharmaceutical Classification System (BCS).

Abstracts

Biopharmacy is a science that studies the influence of pharmaceutical, biological and other factors on the therapeutic efficacy of drugs.

The task of biopharmacy is the theoretical substantiation and creation of an optimal dosage form that provides the maximum therapeutic effect of the active substance with minimal side effects on the body.

The content of biopharmacy is the study of the dependence of the therapeutic efficacy of drugs on pharmaceutical factors.

Biopharmaceutical Classification System (BCS) was adopted by the FDA in 2001 as industry recommendation for the development of the Dissolution Test, later used to predict the bioavailability of substances and conduct the Biowaiver procedure.

According to the BCS, all pharmaceutical substances are divided into 4 classes depending on their solubility in the biofluids of the gastrointestinal tract (GIT) and permeability:

- Class I – high solubility and high permeability;
- Class II – low solubility and high permeability;
- Class III – high solubility and low permeability;
- Class IV – low solubility and low permeability.

Solubility is determined in the pH range corresponding to the pH of biological fluids of the gastrointestinal tract – 1.2–6.8 (1.0–7.5). It is carried out by shaking in a thermostatted flask (Shake-flask method).

For 24 hours at a constant temperature of 37˚C in three replicates, preferably at pH 1.2; 6.8; 7.4. The characteristics of biopharmaceutical solubility that allow classifying drugs as drugs with "high solubility" or "low solubility" are the dose/solubility ratio (D/S) and the dose number (D_0).

Methods for determining permeability

In vivo methods:

- determination of bioavailability (absolute bioavailability greater than 85% - high permeability);
- determination of the permeability coefficient by the method of intestinal perfusion (Peff in vivo).

In vitro methods:

- determination of lipophilicity, distribution coefficient in the octanol-water system log P;
- determination of permeability on a monolayer of epithelial cells of colon carcinoma Caco-2.

Practical lesson 1 (3 hours)

The main issues for discussion. History of biopharmacy. Introduction to biopharmacy. Biopharmaceutical classification system.

The aim of the lesson is to study the history of the emergence and development of biopharmaceutical research, the biopharmaceutical classification system.

Table 1

The technological map of the lesson

№	Stages of the lesson	Duration, min
1.	Organizational moment (presence check)	5
2.	Analysis of the theoretical part of the questions that arose during the preparation. An oral interview	40
3.	Students perform tasks on the topic of the lesson	50
4.	Report to the teacher on the work done by the student and its results. General discussion of the results	30
5.	Teacher's explanations on the homework	10

The form of current control: interview, testing, oral questioning.

Examples of tasks

1. The solubility of Ibuprofen in an acetate buffer solution (pH 4.5) obtained by shaking in a full flask for 24 hours at 37°C is 0.084 mg/ml, and the maximum dose registered in the Russian Federation is 400 mg. How can the solubility of Ibuprofen in an acetate buffer be characterized?
2. There are data in the literature on the solubility of Ketoprofen in the water at room temperature (0.010 mg/ml), as well as at 37°C in solutions with a pH value of 1.2 (0.13 mg/ml), pH 4.6 (0.49 mg/ml) and pH 6.8 (40.76 mg/ml). The maximum dosage of Ketoprofen in immediate release dosage forms for internal use, registered for medical use in the Russian Federation, is 100 mg. Determine the solubility of Ketoprofen in the physiological pH range.
3. Distribute the API according to the BCS and BDDCS classification.

Amlodipine has high solubility in physiological environments of the gastrointestinal tract, high permeability and intensive metabolism, Lincomycin – low permeability, high solubility, weak metabolism, Warfarin – dose number 2.2, high permeability, intensive metabolism, Vancomycin – dose number 0.02, low permeability, weak metabolism, Theophylline – dose number 0.3, high permeability, intensive metabolism, Roxithromycin – dose number 12, low permeability, weak metabolism, Pilocarpine – high permeability, high solubility, intensive metabolism, Nystatin – dose number 0.2, low permeability, poor metabolism, Digoxin – dose number 0.001, low permeability, weak metabolism, Ampicillin – dose number 0.3, low permeability, low metabolism, Capsaicin – dose number 12, high permeability, intensive metabolism, Folic acid – dose number 13, high permeability, intensive metabolism, Melatonin – dose number 0.2, high permeability, intensive metabolism.

Independent work (3 hours)

Requirements for independent work: to study the literature on the topic of the lesson.

Questions for self-control:

1. Definition of biopharmacy.
2. Main tasks of biopharmacy.
3. Biopharmaceutical classification system.
4. Determination of solubility of pharmaceutical substances in gastrointestinal biofluids.
5. Methods for determining permeability.

Topic 1.2. Pharmaceutical factors

Lecture 2 (1 hour)

Content. Pharmaceutical factors: chemical modification of drugs; physicochemical state of drugs; excipients, technological processes, type of dosage form, routes of administration and method of use.

Abstracts

Pharmaceutical factors:

- simple chemical modification of active pharmaceutical ingredients (API);
- the physical state of the API;
- the nature and amount of excipients;
- technological operations, processes that take place when obtaining a medicinal product;
- dosage form.

A simple chemical modification of API is understood as the use of substances in the form of various salts, acids, bases and other compounds, in which the part of the substance molecule responsible for the pharmacological effect is completely preserved.

Physical state of API:

- Crystal shape;
- Particle sizes;
- Degree of crystallinity;
- Grinding degree;
- Polymorphism.

Polymorphism is the ability to form crystalline structures that are chemically identical but have different physical properties: solubility, specific heat capacity, melting point, etc.

Different polymorphic modifications of medicinal substances differ in the effectiveness of therapeutic action and stability.

The nature and amount of excipients can affect the localization of action, acceleration or deceleration of release, bioavailability.

Dosage form is the state of a medicinal product that corresponds to the methods of its administration and use and ensures the achievement of the necessary therapeutic effect. The most important task in the development and preparation of a dosage form is to ensure optimal conditions for the release and subsequent absorption of the API.

Practical lesson 2 (3 hours)

The main issues for discussion. Pharmaceutical factors: chemical modification of drugs; physicochemical state of drugs; excipients, technological processes, type of dosage form, routes of administration and method of use.

The aim of the lesson: to become familiar with the main pharmaceutical factors, to discuss the influence of pharmaceutical factors on the bioavailability of drugs.

Table 2

The technological map of the lesson

№	Stages of the lesson	Duration, min
1.	Organizational moment (presence check)	5
2.	Analysis of the theoretical part of the questions that arose during the preparation. An oral interview	40
3.	Students perform tasks on the topic of the lesson	50
4.	Report to the teacher on the work done by the student and its results. General discussion of the results	30
5.	Teacher's explanations on homework	10

The form of current control: interview, testing, oral questioning.

Task 1

1. Choose one of the dosage form:

1) Floracid® – film-coated tablets (API is Levofloxacin, excipients are crospovidone, magnesium stearate, sodium lauryl sulfate, povidone, microcrystalline cellulose. Shell composition – opadry, polyvinyl alcohol, titanium dioxide);
2) Ibuprofen oral suspension 100 mg/5 ml (API is ibuprofen 100 mg); excipients – polysorbate 80, glycerol, sorbitol, sodium saccharinate, citric acid monohydrate, xanthan gum, hydrochloric acid, sodium hydroxide, methyl parahydroxybenzoate, propyl parahydroxybenzoate, flavoring orange, purified water;
3) Oflomelide ointment (APIs are ofloxacin 10 mg; dioxomethyltetrahydropyrimidine (methyluracil) 40 mg; lidocaine hydrochloride (in the form of monohydrate) 30 mg.
   Excipients: macrogol 1500 (polyethylene oxide 1500, low molecular weight polyethylene glycol 1500), macrogol 400 (polyethylene oxide 400, low molecular weight polyethylene glycol 400), propylene glycol, methyl parahydroxybenzoate (nipagin or methyl paraben), propyl parahydroxybenzoate (nipazole or propyl paraben).
4) Cytoflavin solution for intravenous administration (Active substances in 1 ml of solution: succinic acid 100 mg, inosine (riboxin) 20 mg, nicotinamide 10 mg, riboflavin mononucleotide 2 mg).

2. Provide a technological scheme for this dosage form.

3. Look up the chemical properties of the pharmaceutical substance using the websites DrugBank, PubChem (pay attention to solubility, presence of isomers, polymorphic modifications, simple modification).

4. List all pharmaceutical factors that may affect the bioavailability of this drug.

Independent work (3 hours)

Requirements for independent work: to study the literature on the topic of the lesson.

Questions for self-control:

1. The concept of pharmaceutical factors.
2. The main pharmaceutical factors.
3. The effect of simple chemical modification of the API on the bioavailability of drugs.
4. The effect of the physical state of the API on the bioavailability of drugs.
5. The effect of excipients on the bioavailability of drugs.
6. The effect of the dosage form on the bioavailability of drugs.

Topic 1.3. Bioavailability

Lecture 3 (1 hour)

Content: Bioavailability. Absolute and relative bioavailability.

Abstracts

Bioavailability is the relative rate of absorption of a pharmaceutical substance (API) that has reached the degree of reaching the systemic circulation (degree of bioavailability) and the speed with which this process occurs (absorption rate), as well as the duration of its stay at the source of origin.

The degree of bioavailability is the ratio of the amount of unchanged API absorbed and detected in the blood after its administration in the form of an investigational dosage form to its amount in the blood after administration in the standard dosage form, expressed as a percentage:

Degree of BA= B/A x 100 %, where:

B – the amount of API in the blood after administration in the study dosage form, mg;

A – the amount of API in the blood after administration in the standard dosage form, mg.

Absolute bioavailability (F, %) is used to estimate the total amount of API from a given drug in the patient's blood, compared with a solution of the same substance administered intravenously.

$$F = \frac{[AUC]po \ .dose_{iv}}{[AUC]iv \ .dose_{po}}$$

[AUC] – area under the pharmacokinetic curve;
dose – API dosage;
po – orally;
iv – intravenously.

As a standard dosage form, when determining the absolute bioavailability, a solution for intravenous administration is used, which provides an immediate and complete supply of API to the systemic circulation. The annotations on the medicinal product indicate the absolute bioavailability. For oral drugs, it is considered optimal in the range of 40–60%.

Relative bioavailability (RF, %) is the ratio (in %) of the amount of API absorbed after extravascular administration in the studied dosage form to the amount of API that entered the systemic circulation after extravascular administration at the same dose.

$$\mathrm{R}F = \frac{[AUC]_A \ .dose_B}{[AUC]_B \ .dose_A}$$

Relative bioavailability is measured against a reference product by the same route of administration.

For drugs that are extensively metabolized by the liver when taken orally, the concept of total bioavailability is used.

Total bioavailability is the fraction of an ingested dose of a medicinal product that reaches the systemic circulation unchanged and in the form of metabolites formed during absorption as a result of first pass metabolyme ("First pass effect").

Methods for determining bioavailability

Pharmacodynamic method is based on the measurement of pharmacodynamic or biochemical reactions to a drug substance or its active metabolites (complicated, destructive).

Pharmacokinetic method – measuring the concentration of a drug or its metabolites in a biofluid (blood plasma, urine) over time. Based on the data obtained, graphs are built that reflect the kinetics of the content of the drug or active metabolite in the biofluid over time, and bioavailability is calculated using pharmacokinetic methods.

Practical lesson 3 (3 hours)

The main issues for discussion: Bioavailability. Absolute and relative bioavailability. Methods for determining bioavailability: pharmacodynamic and pharmacokinetic. Interview. Solution of situational problems.

The aim of the lesson: to become familiar with the main types of bioavailability and methods for determining it. Learn how to calculate absolute and relative bioavailability.

Table 3

The technological map of the lesson

№	Stages of the lesson	Duration, min
1.	Organizational moment (presence check)	5
2.	Analysis of the theoretical part of the questions that arose during the preparation. An oral interview	40
3.	Students perform tasks on the topic of the lesson	50
4.	Report to the teacher on the work done by the student and its results. General discussion of the results	30
5.	Teacher's explanations on homework	10

The form of current control: interview, testing, case task, oral questioning.

Task 1

Oral dosage form of indomethacin (25 mg dosage) has been evaluated. For a more complete assessment of the obtained picture, the calculation of the main pharmacokinetic parameters was carried out by a model-independent method using the Kinetica™ 5 program, the results of which are presented in the table 4.

Table 4

Main pharmacokinetic parameters of indomethacin tablet samples compared to the standard oral dosage form of indomethacin (25 mg)

№	Sample	C_{max}, mL	T	A U	M R
1.	S a	.		.	. 1
2.	S	.		.	.
3.	S a	. .		. .	. .
4.	S	.		.	.
5.	Standard dosage form of indomethacin	. .		. .	. .

Calculate the relative bioavailability for the test samples of indomethacin.

Task 2

Oral dosage form of sodium diclofenac (100 mg dosage) has been evaluated. For a more complete assessment of the obtained picture, the calculation of the main pharmacokinetic parameters was carried out by a model-independent method using the Kinetica™ 5 program, the results of which are presented in the table 5.

Table 5

The main pharmacokinetic parameters of the developed dosage forms of diclofenac sodium in comparison with the standard dosage form – Voltaren® retard

№	Sample	C_{max} (ug/mL)	t_{max}(h)	$AUC_{0-\tau}$(ug×h/mL)	MRT (h)
1.	Sample 1	0.98	2	16.83	9.231
2.	Sample 2	2.43	12	30.76	10.23
3.	Sample 3	3.26	4	38.84	13.99
4.	Sample 4	10.58	2	30.22	9.305
5.	Sample 5	7.56	1	39.38	10.029
6.	Sample 6	5.36	4	62.29	32.90
7.	Sample 7	8.40	8	56.05	9.78
8.	Sample 8	3.90	1	30.20	30.92
9.	Sample 9	7.17	2	87.49	11.58
10.	Voltaren® retard	2.96	8	39.9	13.6

Calculate the relative bioavailability for the test samples of diclofenac sodium.

Independent work (3 hours)

Requirements for independent work: to study the literature on the topic of the lesson.

Questions for self-control:

1. The concept of bioavailability.
2. Absolute bioavailability.
3. Relative bioavailability.
4. Total bioavailability.
5. Methods for determining bioavailability.
6. Pharmacokinetic method for determining bioavailability.

Topic 1.4. Basic aspects of pharmacokinetics

Lecture 4 (1 hour)

Content: Basic aspects of pharmacokinetics.

Abstracts

A pharmacokinetic curve is a graph of the dependence of the concentration of a drug in the blood plasma on time (Fig. 1).

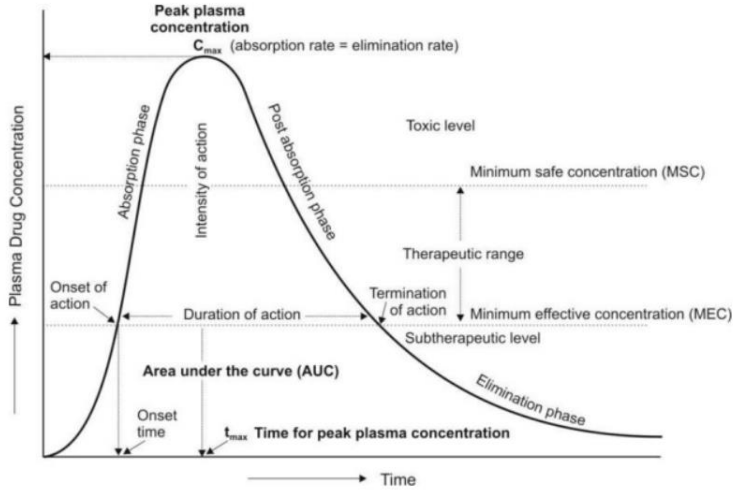

Fig. 1. Example of a pharmacokinetic curve

Main pharmacokinetic parameters

The half-elimination period ($T_{1/2}$) is the time it takes for the concentration of the drug in the blood plasma to decrease by 50%.

Maximum concentration (C_{max}). The use of a drug is safe only when the maximum concentration of the drug is within the therapeutic range – the range between the minimum and maximum effective concentrations.

Time of onset of maximum concentration (T_{max}). T_{max} often coincides with the maximum pharmacological effect of the drug after a single administration.

Area under the pharmacokinetic curve (AUC) is a value proportional to the total amount of the drug in the systemic circulation.

Average retention time of the drug in the body (MRT).

Total clearance (Cl) is the volume of plasma or blood that is completely cleared of the drug per unit of time.

Volume of distribution (Vd) is a hypothetical volume of body fluid required to evenly distribute the entire administered dose of the drug at a concentration similar to the concentration in the blood plasma.

Practical lesson 4 (3 hours)

The main issues for discussion: Basic aspects of pharmacokinetics. Pharmacokinetic parameters.

The aim of the lesson: to become familiar with the basic concepts of pharmacokinetics and the main pharmacokinetic parameters.

Table 6

The technological map of the lesson

№	Stages of the lesson	Duration, min
1.	Organizational moment (presence check)	5
2.	Analysis of the theoretical part of the questions that arose during the preparation. An oral interview	40
3.	Students perform tasks on the topic of the lesson	50
4.	Report to the teacher on the work done by the student and its results. General discussion of the results	30
5.	Teacher's explanations on homework	10

The form of current control: interview, testing, oral questioning.

Task 1

The table 7 shows the pharmacokinetic parameters in the form of a substance and an oral dosage form.

Table 7

The main pharmacokinetic parameters of dilept in plasma blood of rats after the introduction of the substance and tableted dosage form at a dose of 200 mg/kg

Parameter	Substance	Tablets
Cmax, ng/mL	8.5	20
Tmax, min	15	10
AUC0-∞, ng/mL × h	2.5	3.0
Clpo, L/h	8.0502	6.5786
Kel, h^{-1}	1.5	5.38
T1/2, min	27	8
MRTpo, h	0.7	0.3
Vzpo, L	5.297	12.23

Calculate relative bioavailability. Describe the obtained pharmacokinetic parameters. Make a conclusion about the absorption and elimination of the drug in different forms.

Independent work (3 hours)

Requirements for independent work: to study the literature on the topic of the lesson.

Questions for self-control:

1. Pharmacokinetic curve. Definition.
2. Main pharmacokinetic parameters.
3. The concept of first-order kinetics.
4. The concept of zero-order kinetics.
5. Therapeutic range of a drug.

Topic 1.5. Equivalence of drugs

Lecture 5 (2 hours)

Content: Equivalence of drugs.

Abstracts

Pharmaceutically equivalent and alternative medicinal products are considered bioequivalent if they have comparable bioavailability when tested under similar experimental conditions.

Methods for assessing the interchangeability of drugs:

- In vivo equivalence assessment;
- Comparative pharmacodynamic studies;
- Clinical researches;
- In vitro studies (study of comparative dissolution kinetics).

Biowaiver is a procedure in which the interchangeability determination and registration of generic medicines is carried out on the basis of an assessment of their biopharmaceutical properties and in vitro equivalence, as an alternative to in vivo studies.

Biowaiver procedure:

1) it is necessary to determine the biopharmaceutical properties of the active substance and carry out its reliable classification according to the BCS (if there are no literature data, it is necessary to experimentally determine the solubility and permeability);
2) conduct a comparative assessment of the composition of excipients and make sure that they do not affect the motility of the gastrointestinal tract, and other processes that affect the absorption of the active substance;
3) it is necessary to consider the risk of developing adverse drug reactions and data on the therapeutic index of the active substance under study (for substances with a low therapeutic index, the Biowaiver procedure is unacceptable);

4) in vitro equivalence assessment.

Comparative dissolution kinetics test is comparison of dissolution profiles in media with pH 1.2, 4.5, 6.8 of the study drug and the reference drug.

Conditions:

1) the number of time points taken into account *must be at least 3* (typical sampling times: 10, 15, 20, 30, 45 minutes, the last sampling time point corresponds to the moment when more than 90% of the active substance goes into solution or the saturation phase of the dissolution process);
2) for each time point for each drug, *at least 12 parallel determinations* are carried out.

The in vitro equivalence assessment is performed by calculating the difference factors (f_1) and convergence factors (f_2).

Calculation of the difference factor:

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100\%$$

n – number of time points (not counting 0);

R_t – the average value of the release of the pharmaceutical substance from the reference drug at a point in time t, %;

T_t – the average value of the release of the pharmaceutical substance from the study drug at a point in time t, %.

Dissolution profiles are considered equivalent if f1 is between 0 and 15.

Calculation of the convergence factor:

$$f_2 = 50 \times \log \left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} [(\overline{R(t)} - \overline{T(t)}]^2}{n}}} \right]$$

The value of the convergence factor f2 must be in the range from 50 to 100.

In the case when more than 85% of the drug substance goes into solution from both drugs within 15 minutes, the dissolution kinetics are considered equivalent without mathematical evaluation.

Practical lesson 5 (3 hours)

The main issues for discussion: Equivalence of drugs. Methods for determining the equivalence of drugs. Biowaiver procedure.

The aim of the lesson: to become familiar with the concept of equivalence of medicinal products, study the methods of assessing equivalence, become familiar with the principles of the biowaiver procedure.

Table 8

The technological map of the lesson

№	Stages of the lesson	Duration, min
1.	Organizational moment (presence check)	5
2.	Analysis of the theoretical part of the questions that arose during the preparation. An oral interview	40
3.	Students perform tasks on the topic of the lesson	50
4.	Report to the teacher on the work done by the student and its results. General discussion of the results	30
5.	Teacher's explanations on homework	10

The form of current control: case task, interview, testing, oral questioning.

Task 1

Evaluate the equivalence of the dissolution profiles of model tablets from different manufacturers. The table 9 shows the values of the release of the active substance from the dosage form.

Table 9

Drug release data from two model dosage forms

Sample	Time, min				
	3	5	15	30	45
Manufacturer 1 (standard)	48.75	78.75	97.5	103.3	102.6
Manufacturer 2 (investigated)	48.75	67.5	93.75	101.25	101.0

Assess the similarity of the resulting profiles by calculating the difference and convergence factors.

Task 2

The equivalence of the dissolution profiles of paracetamol tablets from different manufacturers was assessed: "Panadol, film-coated tablets, 500 mg" (GlaxoSmithKline, Switzerland) (standard drug) and "Paracetamol tablets, 500 mg" (JSC "Tatkhimfarmpreparaty").

Evaluate the feasibility of a biowaiver procedure for these medicinal products.

Evaluate the convergence factors; data on the release of API are given in the tables 10–11.

Table 10

The results of the release of paracetamol from the drug "Paracetamol tablets, 500 mg" JSC "Tatkhimfarmpreparaty"

	Q, % (pH 1.2)					
Time, min	1	2	3	4	5	6
10	81.4	83.4	83.0	81.5	81.0	82.8
15	82	85	83.4	83	82	85
30	85	87	89	89	87	89
45	88	90	96	97	90	96

	Q, % (pH 4.5)					
Time, min	1	2	3	4	5	6
10	85	87	83	88	87	82
15	87	89	87	90	92	85
30	90	95	98	98	93	89
45	99	99	100.5	100	99.7	96

	Q, % (pH 6.8)					
Time, min	1	2	3	4	5	6
10	75	76	77	75	77	79
15	80	80	87	80	82	85
30	90	95	98	98	93	89
45	99	99	100.5	100	99.7	96

Table 11

The results of the release of paracetamol from the drug "Paracetamol film-coated tablets, 500 mg" JSC "GlaxoSmithKline"

	Q, % (pH 1.2)					
Time, min	1	2	3	4	5	6
10	82.4	83	85	84	87	85
15	85	85	88	87	89	87
30	87	87	89	89	92	89
45	90	90	96	97	95	96

	Q, % (pH 4.5)					
Time, min	1	2	3	4	5	6
10	90	90	93	88	87	92
15	93	92	97	90	92	95
30	100	95	98	98	93	99
45	101	99	100.5	100	99.7	100

	Q, % (pH 6.8)					
Time, min	1	2	3	4	5	6
10	80	79	78	80	79	79

15	85	85	87	85	82	85
30	90	95	98	98	93	89
45	99	99	100.5	100	100.7	99

Independent work (3 hours)

Requirements for independent work: to study the literature on the topic of the lesson.

Questions for self-control:

1. The concept of bioequivalence of drugs.
2. Methods for assessing bioequivalence.
3. Assessing the bioequivalence of drugs in vivo.
4. The biowaiver procedure.
5. Comparative dissolution kinetics test.

SECTION 2. Biopharmaceutical aspects of manufacturing and quality control of medicines

Topic 2.1. Excipients as a pharmaceutical factor

Lecture 6 (2 hours)

Content: Modern ideas about excipients in the technology of dosage forms from the point of view of biopharmacy. The role of excipients in the creation of dosage forms with the required bioavailability.

Abstracts

Excipients are substances of inorganic or organic origin used in the production/manufacturing process of medicinal products to give them the necessary physical and chemical properties.

Modern requirements for excipients:

1. Should help to ensure the required therapeutic effect with a minimum dose of the drug.
2. Should not show toxic and allergenic effects on the body.
3. Should not interact with medicinal and other auxiliary components, packaging materials.
4. Should not impair the organoleptic properties of the medicinal product.
5. Should provide a given dosage form, its consistency, strength and degradation properties.
6. The quality of excipients must be stable and comply with regulatory documentation.

Classification of excipients

1. Depending on origin:
   - natural;
   - synthetic and semi-synthetic;

– microbiological synthesis.

2. Depending on destination:
   – form-building;
   – stabilizers;
   – prolongators;
   – flavors;
   – dyes improving the solubility and bioavailability of drugs.
3. Forming substances:
   – dispersed media in the technology of liquid dosage forms;
   – fillers for solid dosage forms;
   – bases for ointments;
   – bases for suppositories;
   – pushing dispersion media in the production of aerosols;
   – medicated patch bases and carriers for transdermal therapeutic systems

Purpose is the creation of a dosage form, its mass, volume, consistency. The nature of the excipient largely determines the stability of the drug and the rate of API release.

Stabilizers:

– chemical stability of the medicinal substance during storage and processing into a medicinal product;
– aggregative (consistent) stability of the dosage form;
– ensuring microbiological purity and sterility.

Prolongators:

1. For liquid dosage forms – increasing the viscosity of the dispersion medium by introducing thickeners – sugar syrup, glycerin, macromolecular compounds (gelatin, polyvinylpyrrolidone (PVP), cellulose derivatives, etc.).
2. For solid dosage forms –_materials used to create matrix dosage forms are introduced into dosage forms, they are classified into hydrophobic (synthetic, lipophilic), hydrophilic (forming hydrogels, soluble), biodegradable.

Substances that improve the solubility of pharmaceutical substances, increasing the bioavailability and therapeutic efficacy of drugs containing sparingly soluble APIs

Disintegrants

Disintegrating agents are introduced into tablets in order to improve their disintegration in the gastrointestinal tract, which is necessary for the release and subsequent absorption of active substances, as well as to prevent cementation of tablets during storage. All disintegrators ensure the destruction of the tablet into small particles upon contact with the liquid, resulting in a sharp increase in the total surface of the particles, which contributes to the release and absorption of active substances.

Practical lesson 6 (3 hours)

The main issues for discussion: to modern ideas about excipients in the technology of dosage forms from the point of view of biopharmacy. The role of excipients in the creation of dosage forms with the required bioavailability.

The aim of the lesson: to consider the use of excipients in drug technology from a biopharmaceutical point of view, to evaluate the influence of excipients on the bioavailability of drugs.

Table 12

The technological map of the lesson

№	Stages of the lesson	Duration, min
1.	Organizational moment (presence check)	5
2.	Analysis of the theoretical part of the questions that arose during the preparation. An oral interview	40
3.	Students perform tasks on the topic of the lesson	50
4.	Report to the teacher on the work done by the student and its results. General discussion of the results	30
5.	Teacher's explanations on homework	10

The form of current control: laboratory work, interview, testing, oral questioning.

Examples of test tasks

Choose one answer.

1. From a biopharmaceutical point of view, indifferent substances are:
   a) fillers;
   b) flavor corrigents;
   c) surfactants;
   d) preservatives;
   e) none of the above.

2. A factor that has a significant impact on the release of medicinal substances from ointments and suppositories is:
   a) type of base;
   b) type of packaging;
   c) storage method;
   d) method of analysis;
   e) method of introducing the medicinal substance into the base.

3. It is possible to increase the pharmaceutical availability of tablets containing a drug that is poorly soluble in water:
   a) introduction of solubilizers;
   b) introduction of the optimal amount of disintegrants;
   c) granulation;

d) introduction of antifriction substances;
e) change of pressing parameters.

4. Titanium dioxide in the composition of medicinal forms performs the function:
a) taste corrector;
b) odor corrector;
c) transparency corrector;
d) prolongator;
e) plasticizer.

5. Disintegrants are used in the technology of medicinal forms:
a) to obtain a certain mass of the dosage form;
b) to improve compressibility, increase the strength of dosage forms;
c) mechanical destruction of the dosage form in a liquid medium;
d) to improve the flowability of the powder mass;
e) to correct the organoleptic characteristics of the dosage form.

Laboratory work. Evaluation of technological and biopharmaceutical properties of ibuprofen tablets obtained using different technologies.

1. Obtain samples of ibuprofen tablets with different types of fillers using direct compression. The compositions are given in the table 13.
2. Determine the strength of the tablets, as well as ibuprofen tablets obtained using wet granulation technology, using the TBH 125 strength tester (ERWEKA, Germany).
3. Determine the disintegration of the tablets, as well as ibuprofen tablets obtained using wet granulation technology, using the ZT 121 light disintegration tester (ERWEKA, Germany).
4. Fill in the table 14, draw a conclusion about the effect of the composition of fillers and technology on the strength and disintegration of ibuprofen tablets.

Table 13

Composition of tablets

Composition	Amount, mg
Ibuprofen	200
Parteck® M	200
Calcium stearate	4
Ibuprofen	200
MCC	150
Potato starch	50
Talc	4
Calcium stearate	4
Ibuprofen	200
MCC	100
Hydroxypropyl methylcellulose	100
Calcium stearate	4

Table 14

Results of tablet quality assessment

Composition	Hardness, kgf	Diameter, mm	Thickness, mm	Disintegration, min

Independent work (3 hours)

Requirements for independent work: to study the literature on the topic of the lesson.

Questions for self-control:

1. Classification of excipients.
2. Fillers. Effect on biopharmaceutical properties of dosage forms.
3. Prolongators. Effect on biopharmaceutical properties of dosage forms.
4. Disintegrants. Effect on biopharmaceutical properties of dosage forms.
5. Methods for increasing the solubility of pharmaceutical substances.

Topic 2.2. Technological process of medicine manufacturing as a pharmaceutical factor

Lecture 7 (2 hours)

Content: factors of the technological impact of the main processes and devices on the bioavailability of drugs.

Abstracts

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

The method of preparation of drugs as a factor that affects the effectiveness of the drug, did not betray significant importance until the 60s, 20th century.

For a long time, the science of manufacturing medicines was considered as a branch of general commodity science.

Biopharmaceutical research has made it possible to give a scientific explanation of the role of technological processes, methods of obtaining drugs in the development of a therapeutic effect.

The method of obtaining a medicinal product largely determines the stability of the medicinal substance, the rate of its release from the dosage form, the intensity of absorption and, ultimately, its therapeutic efficacy.

Technological methods: grinding, dissolving, drying, filtering, sterilization, freezing, etc.

Technological stages have their own parameters and modes, which are specified in the technological regulations.

Failure to comply with these parameters can lead to a change in medicinal substances

Grinding is used to achieve homogeneity of mixing, elimination of large aggregates in clumping and adhesive materials, enhancement of technological and biological effects. The choice of the degree of grinding of the API should be scientifically substantiated. Often, a sharp decrease in the particle size of a substance causes either its rapid inactivation (for example, the antimicrobial activity of erythromycin, penicillin decreases), or rapid elimination from the body, or increases its undesirable effect on the body (for example, the toxic effect of furantoin on the mucous membranes of the gastrointestinal tract increases). For certain drugs (especially with a narrow therapeutic interval and a pronounced dependence of bioavailability on dispersion), pharmacopoeial articles determine the optimal particle size, compliance with which is part of the requirements for the finished dosage form.

Granulation is a targeted enlargement of particles, i.e. the process of converting a powdered material into grains of a certain size.

It is used to:

- improve the flowability of the tableted mass, which occurs due to a significant reduction in the total surface area of the particles when they stick together into granules;
- prevent stratification of a multi-component powder mixture (separation of the component with the highest specific density from the mixture and violation of the dosage);
- increase the strength of the granules (less susceptible to abrasion and have better flowability).

Wet granulation provides the necessary dynamic characteristics of the resulting mass and a uniform content of medicinal substances in solid dosage forms, and helps improve the quality of the manufactured dosage forms. The most widely used method for producing mixtures for capsules and tablets.

Dry granulation is chosen when wet granulation affects stability and when the physical characteristics of the drug substance do not allow direct compression.

Melt granulation is a process in which powder agglomeration is achieved by adding a binder that melts or softens at sufficiently low temperatures.

Extrusion granulation is a technology for producing granules by forcing a melt of material through a forming orifice.

Spray drying granulation is used in cases where prolonged contact of the granulated product with air is undesirable.

Pressing. The tableting process affects the strength and disintegration of tablets, their ability to dissolve upon contact with water in a certain period of time, which guarantees their bioavailability and the desired therapeutic effect. This depends on the amount of pressing pressure, pressing speed, condition and wear resistance of the pressing tool.

Practical lesson 7 (3 hours)

The main issues for discussion: Factors of the technological impact of the main processes and devices on the bioavailability of drugs.

The aim of the lesson: to consider the main technological processes from a biopharmaceutical point of view, to assess the impact of technological processes and equipment on the bioavailability of drugs.

Table 15

The technological map of the lesson

№	Stages of the lesson	Duration, min
1.	Organizational moment (presence check)	5
2.	Analysis of the theoretical part of the questions that arose during the preparation. An oral interview	40
3.	Students perform tasks on the topic of the lesson	50
4.	Report to the teacher on the work done by the student and its results. General discussion of the results	30
5.	Teacher's explanations on homework	10

The form of current control: interview, testing, oral questioning.

Examples of test tasks

Choose one answer.

1. Micronization is:
   a) the process of reducing the particle size of a medicinal substance to micron and submicron sizes;
   b) the process of reducing the particle size of a solid to the required size by mechanical action;
   c) colloidal dissolution, spontaneous and reversible penetration of any low-molecular substance, poorly soluble in a given liquid medium, into the surfactant micelles or molecular globules of a high-molecular compound located in it;
   d) the process of forced removal of liquid from substances and materials;
   t) squeezing a viscous melt of a material or thick paste through a forming hole.

2. Micronization methods:
   a) melt extrusion;
   b) milling, crushing;
   c) supercritical fluid technologies;
   d) drying in a fluidized bed apparatus;
   e) all of the above.

3. Spray drying is:
   a) the process of forced removal of water from substances and materials;
   b) forcing a viscous melt of material or thick paste through a forming hole;
   c) drying based on the ability of ice to evaporate under certain conditions, bypassing the liquid phase;

d) the process of removing organic solvents from materials using energy for evaporation and with the removal of the resulting vapors;
e) converting liquid raw materials into a dry product by spraying it in a hot drying agent.

4. Freeze drying is:
a) converting liquid raw materials into a dry product by spraying them in a hot drying agent;
b) the process of forced removal of water from substances and materials;
c) removing moisture from products by freezing them and then converting the ice into steam (bypassing the liquid phase) under vacuum;
d) forcing a viscous melt of material or thick paste through a forming hole;
e) the process of removing organic solvents from materials using energy for evaporation and with the removal of the resulting vapors.

5. Types of mills used for mechanical activation of solids:
a) colloidal;
b) hammer, ball, vibration, jet;
c) knife;
d) rotary-pulsation;
e) vibrocavitation

Interview questions:

1. The main stages of the technological process in the production of tablet dosage forms, their influence on the biopharmaceutical properties of drugs.
2. The main stages of the technological process in the production of solutions for internal and external use, their influence on the biopharmaceutical properties of drugs.
3. The main stages of the technological process in the production of ointments, their influence on the biopharmaceutical properties of drugs.
4. The main stages of the technological process in the production of suppositories, their influence on the biopharmaceutical properties of drugs.
5. The main stages of the technological process in the production of injectable dosage forms, their influence on the biopharmaceutical properties of drugs.
6. The main stages of the technological process in the production of aerosols, their influence on the biopharmaceutical properties of drugs.
7. The main stages of the technological process in the production of medical plasters, their influence on the biopharmaceutical properties of drugs.

Independent work (3 hours)

Requirements for independent work: to study the literature on the topic of the lesson.

Questions for self-control:

1. Grinding. Effect on bioavailability of drugs.
2. Types of granulation.

3. Wet granulation.
4. Dry granulation.
5. Granulation by extrusion.
6. Pressing. Effect on bioavailability of drugs.

Topic 2.3. Medicines with improved biopharmaceutical properties. Solid dosage forms

Lecture 8 (2 hours)

Content: Medicines with improved biopharmaceutical properties. Solid dosage forms.

Abstracts

Tablets is a solid dosage form obtained by pressing powders and granules containing one or more medicinal substances with or without the addition of excipients.

Modified release tablets are tablets with a modified, compared with the usual form, mechanism and nature of the release of medicinal substances.

They are coated or uncoated tablets containing special excipients or obtained by special technology, which allows you to change the speed or place of release of the drug.

Features to consider when designing modified release tablets:

- conditions for absorption of API in the gastrointestinal tract: place, rate and mechanism of absorption;
- solubility in the gastrointestinal tract;
- features of pharmacokinetics: the presence of first pass metabolism, the relationship between the absorption rate and the concentration of the drug in the blood plasma;
- features of pharmacodynamics: concentration-effect relationship, the likelihood of developing tolerance with a constant intake of APIs in the body.

Modification methods:

- physical: the use of substances that slow down the absorption, metabolism and excretion of a medicinal substance;
- chemical: obtaining sparingly soluble salts, replacing some functional groups with others, introducing new chemical groups into the composition of the molecule of the original substance;
- technological: incorporation into a matrix, coating with special shells.

Tablets with accelerated release (rapid) are tablets with a modified (accelerated) onset of the action of a medicinal substance.

Enteric-coated tablets (stomach-resistant, gastro-resistant, tablets soluble in intestinal juice, enteric-coated tablets, enterotablets) are tablets that are resistant to gastric juice and release medicinal substances in the intestine.

Multiphase tablets are prolonged-release tablets obtained by pressing a mixture of granules with different release rates of the same medicinal substance.

Rapid retard tablets are tablets with a two-phase release, containing a mixture of microgranules with fast and prolonged release of the medicinal substance. Provide a rapid onset of effect and long-term action of the medicinal substance.

Controlled-release tablets provide rapid achievement and long-term maintenance of a constant therapeutic concentration of the medicinal substance in the blood plasma, constancy of the pharmacological effect. They are characterized by an extension of the time of entry of the medicinal substance into the biophase and its release corresponding to the actual needs of the body.

Extended-release tablets are tablets from which the medicinal substance is released either in several portions or slowly and evenly, ensuring an increase in the duration of the medicinal substance's action by slowing its release.

Retard tablets are extended-release tablets that provide the body with a reserve of the medicinal substance and its subsequent slow release.

Matrix tablets are tablets with continuous, evenly extended release and supporting action of medicinal substances.

Intermittent-release tablets are extended-release tablets, during the use of which the medicinal substance is released in portions.

Continuous-release tablets are extended-release tablets, upon administration of which the initial dose of the medicinal substance is released, and the remaining (maintenance) doses are released at a constant rate corresponding to the rate of elimination and ensuring the constancy of the desired therapeutic concentration.

Delayed-release tablets are prolonged tablets, upon administration of which the release of the drug begins later and lasts longer than from a conventional dosage form.

Reservoir-type tablets are a core containing the drug and a polymer shell that determines the release rate.

Implantable tablets are sterile tablets with prolonged release in the form of a disk or cylinder for implantation under the skin.

Therapeutic drug delivery systems are dosage forms with controlled release of the drug at a rate set in advance, after a certain time, in a certain place, in accordance with the actual needs of the body. Basic elements: drug; element controlling the release of the drug; platform on which the system is placed; therapeutic program.

Practical lesson 8 (3 hours)

The main issues for discussion: Medicines with improved biopharmaceutical properties. Solid dosage forms.

The aim of the lesson: to become familiar with the main types of solid dosage forms with improved biopharmaceutical properties.

Table 16

The technological map of the lesson

№	Stages of the lesson	Duration, min
1.	Organizational moment (presence check)	5
2.	Analysis of the theoretical part of the questions that arose during the preparation. An oral interview	40
3.	Students perform tasks on the topic of the lesson	50
4.	Report to the teacher on the work done by the student and its results. General discussion of the results	30
5.	Teacher's explanations on homework	10

The form of current control: laboratory work, interview, testing, oral questioning.

Examples of test tasks

Choose one answer.

1. Specify which release is called prolonged:
   a) slow continuous;
   b) controlled;
   c) modified;
   d) delayed;
   e) all of the above.

2. Specify which release is called delayed intermittent:
   a) prolonged;
   b) controlled;
   c) modified;
   d) delayed;
   e) pulsating/phasic.

3. Provide an example of delayed release:
   a) rapid;
   b) enteric;
   c) retard;
   d) slow;
   e) osmotic.

4. Provide an example of delayed release technologies for modifying the release of solid dosage forms:
   a) coating;
   b) creation of a matrix structure;
   c) obtaining multimodular systems;
   d) creation of therapeutic systems;
   e) all of the above.

5. Specify materials suitable for modifying release from tablets:

a) shellac;

b) derivatives of polymethacrylic acid;

c) acetylphthalyl cellulose;

d) methyl cellulose;

e) all of the above.

Independent work (3 hours)

Requirements for independent work: to study the literature on the topic of the lesson.

Questions for self-control:

1. Types of modified-release tablets.
2. Extended-release tablets.
3. Controlled-release tablets.
4. Therapeutic drug delivery systems.
5. Gastroretentive dosage forms.
6. Microencapsulated dosage forms.

Topic 2.4. Medicines with improved biopharmaceutical properties. Soft dosage forms and liquid dosage forms

Lecture 9 (1 hour)

Content: Medicines with improved biopharmaceutical properties. Soft dosage forms and liquid dosage forms.

Abstracts

Ointments are soft dosage forms intended for application to the skin, wounds and mucous membranes.

Ointments – ointments proper – are soft dosage forms consisting of a single-phase base in which solid or liquid active substances are dissolved or dispersed.

Creams are soft dosage forms in the form of a multiphase system consisting of a lipophilic “water/oil” type and a hydrophilic “oil/water” type phase and a multiple emulsion.

Gels are soft dosage forms in the form of a colloidal dispersion obtained by gelation using special substances.

Pastes are soft dosage forms containing a significant amount (more than 25%) of finely ground solid substances.

Liniments are soft dosage forms for topical use that have the property of flowability at body temperature.

Ointment technology should ensure maximum dispersion and uniform distribution of active substances in the base. The consistency of the ointment should ensure ease of application and uniform distribution on the skin or mucous membrane. The stability of the ointment should guarantee the invariability of its composition during storage and use. The base for ointments should be selected taking into account the purpose of the drug, the effectiveness, safety and bioavailability of the active

ingredients, the compatibility of the components of the drug, the rheological properties, and stability during the shelf life.

Practical lesson 9 (3 hours)

The main issues for discussion: Medicines with improved biopharmaceutical properties. Soft dosage forms and liquid dosage forms.

The aim of the lesson: to get acquainted with the main types of soft and liquid dosage forms with improved biopharmaceutical properties.

Table 17

The technological map of the lesson

№	Stages of the lesson	Duration, min
1.	Organizational moment (presence check)	5
2.	Analysis of the theoretical part of the questions that arose during the preparation. An oral interview	40
3.	Students perform tasks on the topic of the lesson	50
4.	Report to the teacher on the work done by the student and its results. General discussion of the results	30
5.	Teacher's explanations on homework	10

The form of current control: interview, testing, oral questioning.

Task

1. Review literature reviews on the topic.
2. Answer the questions:
    1) How are soft dosage forms classified by route/method of administration?
    2) List the soft dosage forms.
    3) For which soft dosage forms can the Dissolution test be conducted?
    4) Name the models for assessing the release of drugs from Invitro soft dosage forms.
    5) Give examples of a rational choice of base for a soft dosage form.
    6) Give an example of an irrational choice of base for a soft dosage form.

Independent work (3 hours)

Requirements for independent work: to study the literature on the topic of the lesson.

Questions for self-control:

1. Types of soft dosage forms.
2. Types of liquid dosage forms.
3. Types of bases for soft dosage forms.
4. Ointments. Tests.
5. Suppositories. Tests.
6. Solutions. Tests.

7. Syrups. Tests.
8. Emulsions. Tests.
9. Suspensions. Tests.

Topic 2.5. Transdermal therapeutic systems

Lecture 10 (1 hour)

Content: Transdermal therapeutic systems.

Abstracts

Transdermal patches are a dosage form for external use, which is a medical patch consisting of a matrix or reservoir applied to a substrate, intended for controlled delivery of the active substance into the systemic bloodstream by passive diffusion through intact skin.

A transdermal patch is a multilayer patch. The outer covering layer (substrate) is impermeable to the active substance and serves to impart rigidity to the entire patch, as well as to protect it from external influences. On the side of the active substance release surface intended for application to the skin, there is a protective anti-adhesive coating that is removed immediately before use.

In *transdermal reservoir patches*, the active substance is in a sealed reservoir in the form of a solution, gel, suspension or emulsion. The outer cover layer of the reservoir is a polymer film impermeable to the contents of the reservoir, and the inner layer facing the skin is a polymer membrane that regulates the rate of release of the active substance from the reservoir to the skin through the adhesive layer.

In *matrix patches*, the outer cover layer is a flexible polymer film impermeable to the active substance, to which a polymer adhesive matrix containing active and auxiliary substances is attached. The area of the outer cover layer may be equal to the area of release of the active substance or be somewhat larger, for applying adhesive along the edges of the patch.

Practical lesson 10 (3 hours)

The main issues for discussion: Transdermal therapeutic systems.

The aim of the lesson: to become familiar with the main types of transdermal therapeutic systems, their properties and technological production parameters that affect biopharmaceutical properties.

Table 18

The technological map of the lesson

№	Stages of the lesson	Duration, min
1.	Organizational moment (presence check)	5
2.	Analysis of the theoretical part of the questions that arose during the preparation. An oral interview	40
3.	Students perform tasks on the topic of the lesson	50
4.	Report to the teacher on the work done by the student and its results. General discussion of the results	30
5.	Teacher's explanations on homework	10

The form of current control: interview, testing, oral questioning.

Interview questions:

1. Medical patches and transdermal patches.
2. Features of transdermal patch technology.
3. Excipients used in the technology of medical patches and transdermal patches.
4. Testing transdermal patches.
5. Dissolution test for transdermal patches.

Independent work (3 hours)

Requirements for independent work: to study the literature on the topic of the lesson.

Questions for self-control:

1. Transdermal patches. Definition.
2. Types of transdermal patches.
3. Diagram of a transdermal reservoir patch.
4. Diagram of a transdermal matrix patch.
5. Basic tests for transdermal patches.

Topic 2.6. Biopharmaceutical assessment of the quality of various dosage forms of medicines. Study of the release and absorption of medicines

Lecture 11 (2 hours)

Content: Biopharmaceutical evaluation of the quality of various dosage forms. The study of the release and absorption of medicinal substances. Dissolution test for drug analysis.

Abstracts

Dissolution testing measures the extent and rate of solution formation from a dosage form, such as tablet, capsule, ointment, etc. The dissolution of a drug is important for its bioavailability and therapeutic effectiveness. Dissolution and drug release are terms used interchangeably.

Table 19

Dissolution Testing Apparatus

Apparatus	USP 41-NF 36
Basket Apparatus (Rotate Basket)	A
Paddle Apparatus	A
Reciprocating Cylinder	Apparatus III
Flow-through Cell Apparatus	A
Paddle over disk	A
Rotate Cylinder	A
Reciprocating Holder	A

Dissolution Test for Solid Dosage Forms

USP <711> Chapter:

- Immediate-release dosage forms;
- Extended-release dosage forms;
- Delayed-release dosage forms.

Noted in individual monograph:

- Apparatus type;
- Dissolution medium (composition and volume);
- Rotation speed (apparatus I, II), medium flow rate (apparatus IV);
- Sampling time;
- Analytical method for quantitative determination;
- Requirements.

Dissolution media:

- water;
- 0,1 M HCl;
- buffer solutions with pH 6,8-7,8 (allowed deviation pH ±0,05);
- other solutions that indicated in individual monograph;
- dissolved gases should be removed before testing.

Biorelevant media contain bile salts and lecithin to replicate fluids from different regions of the gut. They also represent both 'fasted' and 'fed' states. And even simulate fluids of different animal species. They can help you determine biorelevant solubility: how much drug product dissolves in the gut.

Practical lesson 11 (3 hours)

The main issues for discussion: Biopharmaceutical evaluation of the quality of various dosage forms. The study of the release and absorption of medicinal substances. Dissolution test for drug analysis.

The aim of the lesson: to become familiar with the basic methods of conducting the dissolution test for solid dosage forms.

Table 20

The technological map of the lesson

№	Stages of the lesson	Duration, min
1.	Organizational moment (presence check)	5
2.	Analysis of the theoretical part of the questions that arose during the preparation. An oral interview	40
3.	Students perform tasks on the topic of the lesson	50
4.	Report to the teacher on the work done by the student and its results. General discussion of the results	30
5.	Teacher's explanations on homework	10

The form of current control: laboratory work, interview, testing, oral questioning.

Examples of test tasks

Choose one answer.

1. Dissolution test is used in pharmaceutical technology:

a) to study the bioavailability of drugs;
b) as an indicator of the quality of liquid dosage forms;
c) to study the pharmacodynamics of generic drugs;
d) to determine the solubility of drugs;
e) to conduct a comparative test of the dissolution kinetics of generic drugs.

2. Specify for which dosage forms the "Dissolution" test is carried out in two stages (acid and alkaline):

a) lozenges;
b) capsules;
c) enteric-coated tablets;
d) suppositories;
e) effervescent tablets.

3. Unless otherwise specified in the regulatory documentation, the stirrer rotation speed for a “rotating basket” apparatus should be:

a) 50 rpm;
b) 100 rpm;
c) 200 rpm;
d) 10 rpm;
e) 500 rpm.

4. Unless otherwise specified in the regulatory documentation, the rotation speed of the stirrer should be for the “paddle stirrer” apparatus:

a) 50 rpm;
b) 100 rpm;
c) 200 rpm;
d) 10 rpm;
e) 500 rpm.

5. A device is used to analyze the release of medicinal substances from suppositories:

a) paddle over the disk;
b) a flow-through cell;
c) a rotating basket;
d) a rotating cylinder;
e) a reciprocating holder.

Laboratory work. Comparative study of biopharmaceutical characteristics of tablets produced by different manufacturers.

1. Study the release of paracetamol from tablets of two different manufacturers under the conditions given in the table 21.
2. Fill in the table 22 with the release results and plot a graph of the dependence of paracetamol release from tablets of each sample on time.
3. Calculate the coefficients of difference and convergence for the release of paracetamol from tablets of two manufacturers. Conduct a comparative analysis of the obtained results. Draw a conclusion about the effect of excipients on the release of paracetamol from tablets.

Table 21

Conditions for the dissolution test for paracetamol tablets

Condition	Value
Apparatus	Paddle Apparatus
Rotation speed	50 rpm
Medium	0.1 M hydrochloric acid
Temperature	37±0.5˚C
Sampling time	5, 10, 20, 30, 45 min
Analytical method for determining the concentration of paracetamol	Spectrophotometry

Table 22

Results of the study of paracetamol release from tablets

Sample	Time, min				
	5	10	20	30	45
	Q, %	Q, %	Q, %	Q, %	Q, %
Manufacturer 1					
Manufacturer 2					

Practical lesson 12 (3 hours)

The main issues for discussion: Biopharmaceutical quality assessment of various dosage forms. Study of drug release and absorption. Work with scientific publications on the topic.

The aim of the lesson: to become familiar with the basic methods of conducting the “Dissolution” test for soft dosage forms and transdermal systems.

Table 23

The technological map of the lesson

№	Stages of the lesson	Duration, min
1.	Organizational moment (presence check)	5
2.	Analysis of the theoretical part of the questions that arose during the preparation. An oral interview	40
3.	Students perform tasks on the topic of the lesson	50
4.	Report to the teacher on the work done by the student and its results. General discussion of the results	30
5.	Teacher's explanations on homework	10

The form of current control: laboratory work, interview, testing, oral questioning.

Laboratory work. Study of the influence of the type of viscoplastic dosage form on the release of drugs.

1. Study the range and nomenclature of modern excipients for obtaining soft dosage forms: ointments, creams, gels.
2. Prepare 30 g of furacilin ointment, cream and gel. The compositions are given in the table 24.
3. Use the vertical diffusion cell method to study the release of furacilin. The conditions are given in the table 25.
4. Plot graphs of the dependence of the concentration of furacilin that has passed into solution from the dosage form to the dissolution medium on time for each sample.
5. Conduct a comparative analysis of the obtained results. Draw a conclusion about the influence of pharmaceutical factors (type of base, type of dosage form) on the release of furacilin from the dosage form.

Table 24

Compositions of soft dosage forms of furacilin

Dosage form	Composition, g
Furacilin ointment	Furacilin – 5 Vaseline medical – to 100
Furacilin cream	Furacilin – 5 Olive oil – 10 PEG-400 – 5 Distilled monoglycerides – 3 Oxyethylated alcohols – 3 Lanette® SX – 3 Purified water – to100
Furacilin gel	Furacilin – 5 Sodium carboxymethylcellulose – 6 Purified water – to100

Table 25

Conditions for assessing the release of furacilin from soft dosage forms

Condition	Value
Apparatus	Vertical diffusion cell
Medium	Phosphate buffer (pH 7.5)
Temperature	32±0.5˚C
Sampling time	0.5; 1; 1.5; 2 h
Analytical method for determining the concentration of paracetamol	Spectrophotometry

Independent work (6 hours)

Requirements for independent work: to study the literature on the topic of the lesson.

Questions for self-control:

1. Dissolution test for solid dosage forms. Methods and devices.
2. Dissolution medium for solid dosage forms.
3. Dissolution test for suppositories. Methods and devices.
4. Dissolution test for transdermal patches. Methods and devices.
5. Methods for assessing drug release from soft dosage forms.
6. Dissolution test. Interpretation of results.

7. THE LITERATURE FOR PREPARING FOR THE LESSONS

Basic literature

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Online resources

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2. Electronic library system of KSMU https://lib-kazangmu.ru/english
3. Student electronic library Student’s Konsultant, Books in English https://www.studentlibrary.ru/ru/catalogue/switch_kit/x2018-207.html
4. Electronic medical library Doctor’s Konsultant http://www.rosmedlib.ru
5. Electronic database "ClinicalKey" https://www.clinicalkey.com/#!/
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8. LIST OF SOURCES USED

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Educational and methodical manual

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