MEDICAL UNIVERSITY – PLOVDIV

FACULTY OF PHARMACY

DEPARTMENT OF PHARMACEUTICAL SCIENCES

SYLLABUS

in

BIOPHARMACY AND PHARMACOKINETICS

Approved by the Department Council - Protocol № 01/09.01.2023

Confirmed by the Faculty Council - Protocol № 01/25.01.2023

MEDICAL UNIVERSITY – PLOVDIV

FACULTY OF PHARMACY

Syllabus

Discipline	Final exam/ semester	According to the Faculty of Pharmacy curriculum of MU-Plovdiv Academic hours				ECTS	Academic hours in semester	
							IX semester	
		Aauditorium	Lectures	Practices	Non-auditorium		L	P
Biopharmacy and pharmacokinetics	**IX**	**120**	**45**	**75**	**156**	**11**	**45**	**75**

DISCIPLINE:
Biopharmacy and pharmacokinetics

TYPE OF DISCIPLINE ACCORDING TO THE UNIFORM STATE REQUIREMENTS:
Compulsory

LEVEL OF QUALIFICATION:
MPharm

FORMS OF TRAINING:
Lectures, seminars, practicals, self-training

YEAR OF TRAINING:
V course

DURATION OF TRAINING:
One semester

ACADEMIC HOURS:
45 hours lectures, 75 hours practicals

TECHNICAL EQUIPMENT APPLIED IN THE TRAINING:
Multimedia presentations, discussions, individual tasks, preparation of papers

FORMS OF EVALUATION:
Current assessment, individual problem-solving

EVALUATION CRITERIA:
A current average mark for the semester is formed

ASPECTS OF EVALUATION CRITERIA:
Participation in discussions, evaluation of the colloquiums, tests

SEMESTER EXAM:
Yes (theoretical exam – oral and written form)

STATE EXAM:
Yes (written and oral exam combined with Pharmaceutical technology I and Pharmaceutical technology II)

LECTURER:
Professor from the department of Pharmaceutical sciences

DEPARTMENT:
Pharmaceutical sciences

ANNOTATION

The discipline Biopharmacy and pharmacokinetics is one of the basic fields in the pharmaceutical science, which aims to build on the knowledge gained in Pharmaceutical technology, focusing on all processes and factors which influence the behavior of the drug in the body related to route of administration and type of the dosage form in order to optimize drug bioavailability.

Biopharmacy considers the interaction between the dosage form as a physicochemical system and the living organism as a complex biological macrostructure, mainly by studying the drug kinetics and drug metabolism in the biological environment. The basic concept of biopharmacy is that the therapeutic effect of drugs is determined not only by their specific molecular structure, but also by a number of additional factors (anatomical-physiological and biochemical characteristics of the organism, physicochemical and biopharmaceutical properties of the drug and the dosage form). Pharmacokinetics studies the processes of absorption, distribution and elimination of the drug and the factors that affect the interaction of the drug with the organism.

Biopharmaceutical evaluation and pharmacokinetic studies include both theoretical and experimental approaches. Theoretical training provides knowledge on the basic pharmacokinetic processes, the influence of physicochemical drug properties on the drug behaviour in the body, the main pharmacokinetic parameters and their determination depanding on the different routes of administration. The experimental aspects include *in vitro* study of the processes of drug release from different types of dosage forms, determination of the similarity factor, basic principles of biopharmaceutical control, pharmacokinetic modeling and optimization of the dosing regime for repeated drug administration.

EXPECTED RESULTS

After completing the course, students must have the following knowledge and skills:

- Identification of biopharmaceutical and pharmacokinetic relevant information from various sources and critical evaluation of dosing regimes.
- Knowing various pharmacokinetic models and application of relevant mathematical and statistical approaches and models for analysis of pharmacokinetic and biopharmaceutical data; comparing and reporting the differences between compartment and non-compartment analysis.
- Applying the knowledge in biopharmacy and pharmacokinetics according to the individual characteristics of the patient to create an appropriate dose regime (single or multiple dose) for personalized drug therapy, based on information from single dose studies or literature.
- Proposing an appropriate route/routes of administration based on prior biopharmaceutical or pharmacokinetic information; predicting the effects of changing the route of administration, dose and rate of administration on plasma concentration/time profiles.
- Knowing different pharmacokinetic parameters (AUC, K_{elim}, Cl, Vd), their determination, parameter variations comparing individual patients, patient populations, different dosage forms and different drugs.
- Understanding the difference between linear and nonlinear pharmacokinetics and its significance in drug administration; knowing mathematical approaches to work with nonlinear pharmacokinetics in the design or modification of the dosing regime; applying mathematical principles and concepts related to multiple dosing regimes.
- Predicting changes in drug pharmacokinetics resulting from drug-to-drug or food interactions, current health status (including functional status of key organs such as liver and kidneys), and their changes or genetic variations.
- Knowing pharmacokinetic principles of modified-release drugs and proposing therapeutically justified dosage changes by controlling the drug release process.
- Knowing main aspects of the experimental design for pharmacokinetics and bioavailability studies, in order to critically analyze their validity and limits of interpretation and actively participate in the design of such studies.

SYLLABUS FOR LECTURES

V course, IX semester

№	TOPIC	HOURS
1.	Stability of pharmaceutical products. Types of stability. Approaches for stabilization.	**3 h.**
2.	Stability assessment. Kinetics of degradation reactions.	**3 h.**
3.	Biopharmacy and pharmacokinetics – basic concepts. Behavior of the drug substance in the body (LADMER model). Pharmaceutical factors. Basic concepts.	**3 h.**
4.	Pharmacokinetic modeling. Compartment and non-compartment analysis. Linear and nonlinear pharmacokinetics. Basic pharmacokinetic parameters.	**3 h.**
5.	One-compartment and two-compartment models after intravenous drug administration. Determination of basic pharmacokinetic parameters.	**3 h.**
6.	Pharmacokinetic principles regarding intravenous infusion. Steady state. Kinetics after intravenous injection of the drug, followed by intravenous infusion. Kinetics of short-term infusion.	**3 h.**
7.	One-compartment model after extravascular administration of the drug. Determination of pharmacokinetic parameters. Pharmacokinetic principles of repeated administration of drugs. Cumulation of the drug. Cumulation index. Dosage regime selection based on pharmacokinetic behavior. Types of dosing regimes.	**3 h.**
8.	Nonlinear pharmacokinetics. Principles, problems. Processes with nonlinear kinetics.	**3 h.**
9.	Drug absorption in the body. Biopharmaceutical Classification System (BCS).	**3 h.**
10.	Distribution and protein binding of drugs. Elimination of drugs and hepatic clearance.	**3 h.**
11.	Biopharmaceutical control. Pharmacopoeial dissolution tests.	**3 h.**
12.	Biosubstitutes. *In vitro / in vivo* correlation.	**3 h.**
13.	Biopharmaceutical and pharmacokinetic evaluation of the transdermal route of administration – drug transdermal patches, controlled release drug systems. Biopharmaceutical and pharmacokinetic evaluation of the rectal and vaginal routes of administration.	**3 h.**
14.	Biopharmaceutical and pharmacokinetic evaluation of pulmonary and nasal formulations. Biopharmaceutical and pharmacokinetic evaluation of ophthalmic dosage forms.	**3 h.**
15.	Drug delivery systems for targeted drug delivery. Principles of targeted therapy. Biological drug products.	**3 h.**

TOTAL: 45 h.

SYLLABUS FOR PRACTICALS

V course, IX semester

№	TOPIC	HOURS
1.	Seminar. Stability. Stability tests. Predicting the shelf life of pharmaceutical products.	**5 h.**
2.	Studying the stability of easily oxidizable drugs in solution. Stability of ascorbic acid. Stabilization approaches. Investigating the influence of different approaches on chemical stability.	**5 h.**
3.	Studying the stability of easily hydrolyzable drugs in solution. Hydrolytic degradation of indomethacin under stress conditions. Predicting the shelf life.	**5 h.**
4.	One-compartment linear pharmacokinetic model for single dose intravenous injection – calculation of basic pharmacokinetic parameters using literature data on plasma and urinary concentrations. Solving tasks.	**5 h.**
5.	Two-compartment pharmacokinetic model for intravenous single dose injection – calculation of the main pharmacokinetic parameters using the method of residuals. Solving tasks.	**5 h.**
6.	One-compartment pharmacokinetic model after extravascular administration of a drug based on plasma concentrations. Solving tasks.	**5 h.**
7.	Two-compartment model after extravascular administration of a single drug dose. Solving tasks. Assessment of bioequivalence of drug products.	**5 h.**
8.	Pharmacokinetic aspects of different regimes for repeated administration of drugs. Solving tasks.	**5 h.**
9.	Determination of quantitative parameters of protein binding. Solving tasks.	**5 h.**
10.	Colloquium.	**5 h.**
11.	Seminar – *in vitro* tests for biopharmaceutical evaluation of the drug release process from dosage forms and processing the obtained results. Solving tasks.	**5 h.**
12.	*In vitro* dissolution tests. Comparative study of the dissolution behavior of two generic, pharmaceutically equivalent products (same type of formulation, same dose). Obtaining dissolution profiles. Determining the influence of the type and amount of excipients on *in vitro* release process.	**5 h.**
13.	*In vitro* dissolution tests. Comparative study of the biopharmaceutical behavior of two products, different type of dosage forms with the same drug dose (e.g. tablet and capsule). Processing the results and evaluating the influence of the biopharmaceutical factor – type of the dosage form.	**5 h.**
14.	*In vitro* dissolution tests for semisolid and rectal drug formulations. Studying the drug release profile from modified, controlled release formulations (tablets and transdermal patches).	**5 h.**
15.	Colloquium.	**5 h.**

TOTAL: 75 h.

LECTURES – THESES

LECTURE № 1 – 3 hours
STABILITY OF PHARMACEUTICAL PRODUCTS. TYPES OF STABILITY. APPROACHES FOR STABILIZATION
1. Stability of pharmaceutical products – definition.
2. Types of stability. Approaches for stabilization.
3. Chemical stability. Approaches for stabilization.
4. Physical stability. Approaches for stabilization.
5. Microbiological stability. Approaches for stabilization.

LECTURE № 2 – 3 hours
STABILITY ASSESSMENT. KINETICS OF DEGRADATION REACTIONS
1. Reasons for stability assessment.
2. Stability tests:
   - long term stability studies
   - accelerated stability studies
   - intermediate stability studies
   - stress testing
3. Application of chemical kinetics in stability tests.
4. Order of chemical reactions
5. Kinetic models.

LECTURE № 3 – 3 hours
BIOPHARMACY AND PHARMACOKINETICS – BASIC CONCEPTS. BEHAVIOR OF THE DRUG SUBSTANCE IN THE BODY (LADMER MODEL). PHARMACEUTICAL FACTORS. BASIC CONCEPTS
1. Biopharmacy and pharmacokinetics.
2. Prerequisites for their development.
3. Basic concepts.
4. Behavior of the drug substance in the body – processes of release/dissolution, absorption, distribution, metabolism and elimination of drugs (LADMER model).
5. Pharmaceutical factors.
6. Basic concepts:
   - pharmaceutical availability;
   - drug bioavailability.
7. Pharmaceutically equivalent, bioequivalent and therapeutically equivalent pharmaceutical products.

LECTURE № 4 – 3 hours
PHARMACOKINETIC MODELING. COMPARTMENT AND NON-COMPARTMENT ANALYSIS. LINEAR AND NONLINEAR PHARMACOKINETICS. BASIC PHARMACOKINETIC PARAMETERS
1. Pharmacokinetic modeling.
2. Compartment and non-compartment analysis.
3. Linear and nonlinear pharmacokinetics.
4. Basic pharmacokinetic parameters.

LECTURE № 5 – 3 hours

ONE-COMPARTMENT AND TWO-COMPARTMENT MODELS AFTER INTRAVENOUS DRUG ADMINISTRATION. DETERMINATION OF BASIC PHARMACOKINETIC PARAMETERS

1. One-compartment pharmacokinetic model.
2. Intravenous injection of a single drug dose.
3. Calculation of basic pharmacokinetic parameters.
4. Two-compartment pharmacokinetic model.
5. Intravenous injection of a single drug dose.
6. Calculation of basic pharmacokinetic parameters.

LECTURE № 6 – 3 hours

PHARMACOKINETIC PRINCIPLES REGARDING INTRAVENOUS INFUSION. STEADY STATE. KINETICS AFTER INTRAVENOUS INJECTION OF THE DRUG, FOLLOWED BY INTRAVENOUS INFUSION. KINETICS OF SHORT-TERM INFUSION

1. Intravenous infusion – one-compartment model.
2. Constant infusion rate (Zero order).
3. Steady state plasma concentration (Css).
4. Loading dose – a single intravenous dose in combination with an intravenous infusion.
5. Application of pharmacokinetic parameters to determine individual dose regime.

LECTURE № 7 – 3 hours

ONE-COMPARTMENT MODEL AFTER EXTRAVASCULAR ADMINISTRATION OF THE DRUG. DETERMINATION OF PHARMACOKINETIC PARAMETERS. PHARMACOKINETIC PRINCIPLES OF REPEATED ADMINISTRATION OF DRUGS. CUMULATION OF THE DRUG. CUMULATION INDEX. DOSAGE REGIME SELECTION BASED ON PHARMACOKINETIC BEHAVIOR. TYPES OF DOSING REGIMES

1. One-compartment model after extravascular administration of the drug.
2. Determination of pharmacokinetic parameters based on plasma concentration data.
3. Pharmacokinetic principles in repeated administration of drugs.
4. Cumulation. Cumulation index.
5. Dosage regime selection based on pharmacokinetic behavior. Types of dosing regimes.
6. Determination of average steady state concentration (Cssav), t1/2, Vd, Cl.
7. Loading dose, maintenance dose.
8. Prolonged and controlled release formulations.

LECTURE № 8 – 3 hours

NONLINEAR PHARMACOKINETICS. PRINCIPLES, PROBLEMS. PROCESSES WITH NONLINEAR KINETICS

1. Principles of nonlinear pharmacokinetics.
2. Basic differences between linear and nonlinear pharmacokinetics.
3. Reasons for nonlinear pharmacokinetic behavior.
4. Problems in determining dosing regimes of drugs with nonlinear pharmacokinetics.
5. Pharmacokinetic processes with nonlinear kinetics – absorption, distribution, metabolism, excretion.

LECTURE № 9 – 3 hours

DRUG ABSORPTION IN THE BODY. BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

1. Routes of drug administration.
2. Types of transmembrane transport.
3. Physicochemical and physiological factors affecting absorption.
4. Biopharmaceutical Classification System (BCS).

LECTURE № 10 – 3 hours

DISTRIBUTION AND PROTEIN BINDING OF DRUGS. ELIMINATION OF DRUGS AND HEPATIC CLEARANCE

1. Drug distribution.
2. Drug interactions with plasma proteins.
3. Drug elimination.
4. Clearance.
5. Hepatic elimination.
6. Renal excretion.

LECTURE № 11 – 3 hours

BIOPHARMACEUTICAL CONTROL. PHARMACOPOEIAL DISSOLUTION TESTS

1. Determination of the main biopharmaceutical indicators.
2. Pharmacopoeial tests for in vitro dissolution.
3. Evaluation of the results from in vitro dissolution test.
4. Linearization of dissolution profiles using mathematical models.
5. Demonstration of pharmaceutical equivalence.
6. Similarity factor.
7. Pharmaceutically equivalent drug products.

LECTURE № 12 – 3 hours

BIOSUBSTITUTES. IN VITRO / IN VIVO CORRELATION

1. *In vitro* tests to replace repeated bioavailability and bioequivalence studies.
2. Monographs on biosubstitutes.
3. Biosubstitutes based on the Biopharmaceutical Classification System. Application, regulatory aspects.
4. *In vitro* / *in vivo* correlation – nature, levels of correlation.

LECTURE № 13 – 3 hours

BIOPHARMACEUTICAL AND PHARMACOKINETIC EVALUATION OF THE TRANSDERMAL ROUTE OF ADMINISTRATION - DRUG TRANSDERMAL PATCHES, CONTROLLED RELEASE DRUG SYSTEMS. BIOPHARMACEUTICAL AND PHARMACOKINETIC EVALUATION OF THE RECTAL AND VAGINAL ROUTES OF ADMINISTRATION

1. Biopharmaceutical and pharmacokinetic aspects of dermal dosage forms.
2. Physiological and pharmaceutical factors.
3. Biopharmaceutical and pharmacokinetic aspects of vaginal dosage forms.
4. Physiological and pharmaceutical factors.
5. Biopharmaceutical and pharmacokinetic aspects of rectal dosage forms.
6. Physiological and pharmaceutical factors.

LECTURE № 14 – 3 hours

BIOPHARMACEUTICAL AND PHARMACOKINETIC EVALUATION OF PULMONARY AND NASAL FORMULATIONS. BIOPHARMACEUTICAL AND PHARMACOKINETIC EVALUATION OF OPHTHALMIC DOSAGE FORMS

1. Biopharmaceutical and pharmacokinetic aspects of nasal dosage forms.
2. Physiological and pharmaceutical factors.
3. Biopharmaceutical and pharmacokinetic aspects of formulations for pulmonary administration.
4. Physiological and pharmaceutical factors.
5. Biopharmaceutical and pharmacokinetic aspects of ophthalmic dosage forms.
6. Physiological and pharmaceutical factors.

LECTURE № 15 – 3 hours

DRUG DELIVERY SYSTEMS FOR TARGETED DRUG DELIVERY. PRINCIPLES OF TARGETED THERAPY. BIOLOGICAL DRUG PRODUCTS

1. Targeted drug delivery.
2. Principles of targeted therapy.
3. Passive targeting.
4. Active targeting.
5. Biological drug products.

PRACTICALS – THESES

PRACTICAL № 1 – 5 hours
SEMINAR – STABILITY
1. Stability tests.
2. Predicting the shelf life of drug products.

PRACTICAL № 2 – 5 hours
STUDYING THE STABILITY OF EASILY OXIDIZABLE DRUGS IN SOLUTION
1. Stabilization of ascorbic acid.
2. Stabilization approaches.
3. Investigating the influence of different approaches on the chemical stability.

PRACTICAL № 3 – 5 hours
STUDYING THE STABILITY OF EASILY HYDROLYZABLE DRUGS IN SOLUTION
1. Hydrolytic degradation of indomethacin under stress conditions.
2. Predicting the shelf life.

PRACTICAL № 4 – 5 hours
ONE-COMPARTMENT LINEAR PHARMACOKINETIC MODEL FOR SINGLE DOSE INTRAVENOUS INJECTION
1. Calculation of basic pharmaceutical parameters using literature data on plasm and urinary concentrations.
2. Solving tasks.

PRACTICAL № 5 – 5 hours
TWO-COMPARTMENT PHARMACOKINETIC MODEL FOR INTRAVENOUS SINGLE DOSE INJECTION
1. Calculation of the main pharmacokinetic parameters using the method of residuals.
2. Solving tasks.

PRACTICAL № 6 – 5 hours
ONE-COMPARTMENT PHARMACOKINETIC MODEL AFTER EXTRAVASCULAR ADMINISTRATION OF A DRUG
1. Calculation of the main pharmacokinetic parameters using plasma concentrations.
1. Solving tasks.

PRACTICAL № 7 – 5 hours
TWO-COMPARTMENT PHARMACOKINETIC MODEL AFTER EXTRAVASCULAR ADMINISTRATION OF A SINGLE DRUG DOSE
1. Solving tasks.
2. Assessment of bioequivalence of drug products.

PRACTICAL № 8 – 5 hours
PHARMACOKINETIC ASPECTS OF DIFFERENT REGIMES FOR REPEATED ADMINISTRATION OF DRUGS
1. Solving tasks.

PRACTICAL № 9 – 5 hours
DETERMINATION OF QUANTITATIVE PARAMETERS OF PROTEIN BINDING
1. Solving tasks.

PRACTICAL № 10 – 5 hours
COLLOQUIUM

PRACTICAL № 11 – 5 hours
SEMINAR – *IN VITRO* TESTS
1. Biopharmaceutical evaluation of the drug release process from dosage forms.
2. Processing the obtained results.
3. Solving tasks.

PRACTICAL № 12 – 5 hours
***IN VITRO* DISSOLUTION TESTS**
1. Comparative study of the dissolution behavior of two generic, pharmaceutically equivalent products (same type of formulation, same dose).
2. Obtaining dissolution profiles.
3. Determining the influence of the type and amount of excipients on *in vitro* release process.

PRACTICAL № 13 – 5 hours
***IN VITRO* DISSOLUTION TESTS**
1. Comparative study of the biopharmaceutical behavior of two products, different type of dosage forms with the same drug dose (e.g. tablet and capsule).
2. Processing the results.
3. Evaluating the influence of the biopharmaceutical factor – type of the dosage form.

PRACTICAL № 14 – 5 hours
***IN VITRO* DISSOLUTION TESTS**
1. *In vitro* dissolution tests for semisolid and rectal drug formulations.
2. Studying the drug release profile from modified, controlled release formulations (tablets and transdermal patches).

PRACTICAL № 15 – 5 hours
COLLOQUIUM

BIBLIOGRAPHY

1. L. Shargel, S. Wu-Pong, A.B.C. Yu. Applied Biopharmaceutics and Pharmacokinetics, 5th ed.McGraw-Hill, 2005

2. S. Rosenbaum. Basic Pharmacokinetics and Pharmacodynamics, John Wiley & Sons, Inc., Hoboken, NJ, 2011

3. M. Gibaldi, D. Perrier. Pharmacokinetics, 2nd edition, Informa healthcare USA Inc., 2007

4. S. Jambhekar, Ph. Breen, Basic Pharmacokinetics, Pharmaceutical Press, 2009

5. L. Bauer, Applied Clinical pharmacokinetics, 2nd edition, McGraw – Hill Companies, 2008

CONSPECTUS

1. Stability of pharmaceutical products. Types of stability. Approaches for stabilization.
2. Stability tests. Kinetics of degradation reactions.
3. Biopharmacy and pharmacokinetics – basic concepts. Behavior of the drug in the body (LADMER model). Pharmaceutical factors. Basic concepts.
4. Pharmacokinetic modeling. Compartment and non-compartment analysis. Linear and nonlinear pharmacokinetics. Basic pharmacokinetic parameters.
5. Pharmacokinetic principles of intravenous infusion. Steady state. Kinetics after intravenous injection of the drug, followed by intravenous infusion. Kinetics of short-term infusion.
6. One-compartment model after extravascular administration of the drug. Determination of pharmacokinetic parameters. Pharmacokinetic principles of repeated administration of drugs. Cumulation of the drug. Cumulation index.
7. Dosing regime based on pharmacokinetic drug behavior. Types of dosing regimes.
8. Nonlinear pharmacokinetics. Principles, problems. Processes with nonlinear kinetics.
9. Drug absorption in the body. Biopharmaceutical Classification System (BCS).
10. Routes of drug administration. Types of transmembrane transport. Physicochemical and physiological factors affecting absorption.
11. Drug distribution and protein binding.
12. Drug elimination and hepatic clearance. Renal excretion.
13. Biopharmaceutical control. Pharmacopoeial dissolution tests.
14. Biosubstitutes. *In vitro / in vivo* correlation.
15. Biopharmaceutical and pharmacokinetic evaluation of the transdermal route of administration – transdermal patches, controlled release drug systems.
16. Biopharmaceutical and pharmacokinetic evaluation of the rectal and vaginal route of administration.
17. Biopharmaceutical and pharmacokinetic evaluation of dosage forms for pulmonary and nasal administration.
18. Biopharmaceutical and pharmacokinetic evaluation of ophthalmic dosage forms.
19. Drug delivery systems for targeted delivery. Principles of targeted therapy.
20. Biological drug products.