

COURSE TITLE: Biopharmaceutics

COURSE NUMBER: 1130-424 **YEAR / SEMESTER:** 4/ 2

PRE-REQUISITE(S): 1130-423

COURSE COORDINATOR: A.A. Al-Khars

<u>STATUS</u>	THEORETICAL	<input checked="" type="checkbox"/>	THEORETICAL & PRACTICAL	<input type="checkbox"/>
	PRACTICAL	<input type="checkbox"/>		
	COMPULSORY	<input checked="" type="checkbox"/>	ELECTIVE	<input type="checkbox"/>
	CREDIT HOURS	<input type="checkbox" value="2"/>	COURSE HOURS PER WEEK	<input type="checkbox" value="2"/>
	LECTURES (H)	<input type="checkbox" value="25"/>	PRACTICALS (H)	<input type="checkbox"/>

TEACHING METHODS

DIADACTIC LECTURES	<input checked="" type="checkbox"/>	PRACTICALS	<input type="checkbox"/>
ASSIGNMENTS	<input type="checkbox"/>	STUDENT PRESENTATIONS	<input type="checkbox"/>
TUTORIALS	<input checked="" type="checkbox"/>	OTHER	<input type="checkbox"/>

EVALUATION (%)

MID-SEMESTER THEORY EXAM	<input type="checkbox" value="30"/>	FINAL THEORY EXAM	<input type="checkbox" value="60"/>
QUIZZES	<input type="checkbox" value="10"/>	LAB ASSIGNMENTS	<input type="checkbox"/>
STUDENT PRESENTATIONS	<input type="checkbox"/>	PROJECT REPORTS	<input type="checkbox"/>
MID-SEMESTER LAB EXAM	<input type="checkbox"/>	FINAL LAB EXAM	<input type="checkbox"/>
OTHER	<input type="checkbox"/>		

BRIEF COURSE DESCRIPTION

This course provides basic qualitative description of biopharmaceutics of drugs needed to understand the fundamental of pharmacokinetics, which is given as a co-requisite in the same semester. The major focus in biopharmaceutics will be concentrated on the various *in vitro* and *in vivo* factors that can affect drug performance in the body during the processes of liberation, absorption, distribution, metabolism, excretion and achievement of response.

COURSE OBJECTIVES / EXPECTED OUTCOMES

On completion this course, the students should be able to

1. Define the relative biopharmaceutic terminology,
2. Identify all biologic, physiologic, and pathologic factors, which influence drugs' absorption, disposition and response in the body,
3. Understand how physical and chemical drugs' properties, dosage form and route of administration can influence drug performance in the body,
4. Outline the complex and dynamic drugs' journey in the body during the processes of liberation, absorption, distribution, metabolism, excretion and achievement of response,
5. Understand how those factors may affect drugs' levels needed to reach site(s) of action, and
6. Use these qualitative concepts to understand the kinetics of drugs in the body in normal as well as pathologic conditions.

RECOMMENDED READING

1. Applied Biopharmaceutics and Pharmacokinetics by Leon Shargel and Andrew BC Yu, Appelton and Lang Stamford, Connecticut, 1999.
2. Handbook of Basic Pharmacokinetics by W.A. Ritschel and G.L. Kearns, 5th edition, Apha Publications, Washington DC. 1999.

COURSE OUTLINE (CONTENT OF EACH LECTURE)

1. Introduction to biopharmaceutics and its applications

Relationship and relevance of course to dosage form design, general overview of course contents, expectations. Description of the assessment system and marks distribution.

Physiological & physicochemical factors affecting absorption (3 lectures)

2. Definitions of commonly used terms

LADMER system, biopharmaceutics and pharmacokinetics, absorption, distribution, metabolism, excretion. Overall scheme for pharmacokinetics of drugs.

3. Physiological factors affecting drug absorption

Membrane physiology and examples for some membranes, e.g. blood brain barrier, renal tubules. Transport mechanisms across membranes; carrier and non carrier mediated transport, vesicular transport and ion-pair mechanisms. Factors affecting each type of drug transport mechanism along examples of drugs will be discussed.

4. Biopharmaceutic consideration of dosage forms

Physicochemical properties of the drugs affecting absorption; solubility, partition coefficient, particle size, polymorphs and solvates, and excipients. Formulation effect on drug absorption; solutions, suspensions, tablets, capsules and modified-release dosage forms. Testing methods of different dosage forms and relevance to evaluation of product characteristics, e.g. disintegration, dissolution, particle size analysis, etc.

Drug delivery systems (3 lectures)

5. Site specific drug delivery systems (DDS)

General concepts and reasons for using such products. Rationale of using new drug delivery systems; drug properties, biopharmaceutical-, pharmacokinetics- and clinical-related factors.

General requirements for drug delivery systems.

6. Liposomal and intranasal DDS

Liposomes as DDS, properties and advantages. Formulation of liposomal DDS, factors affecting half-life of the liposomes (particle size and mode of administration).

Intranasal DDS; advantages and requirements for drugs absorbed by intranasal route, use of enhancers.

7. Prodrugs and microparticles as DDS

Prodrugs as DDS. Requirements for prodrugs. Ideal properties for site specific DDS (adequate access to the receptors and availability of specific enzymes).

Microparticles as DDS; properties, effect of site of administration on drug targeting, particle size & surface characteristics and its effect on drug targeting and half-life. Formulation of microparticles, polymer type effect, mechanisms of drug release.

8-9 Absorption from gastrointestinal tract (GIT)

Factors affecting gastrointestinal absorption; gastric emptying, motility, enzymes and pH. First-pass effect and its influence on drug efficiency. Methods to avoid first-pass effect. Effect of diseases on absorption of orally administered drugs. Advantages and limitation of absorption by enteral routes other than oral; buccal, rectal.

10 Absorption from different sites

Characteristics and Advantages & limitation of different routes for administration of drugs; Intravenous, intramuscular, subcutaneous, intraarterial, intraspinal, oral, rectal, buccal, transdermal nasal and ocular routes.

11-12 Bioavailability and bioequivalence

Definition of bioavailability, absolute and relative bioavailability, pharmaceutical equivalents and bioequivalents, therapeutic equivalents and substitutes. Methods of determination and relevance to dosage form performance. Bioequivalence of dosage forms and method of determination. Regulatory status governing the products required for bioequivalence testing.

Drug Distribution (3 Lectures)**13 Circulatory System**

Central pump (heart), arteries, veins arterioles, venules, microcirculation, homeostasis, body fluids and the dynamic interchange between them.

14. Unequal Drug Distribution

Factor that contributes to an equality in drug distribution; physical and chemical nature of drug substance, pH of the region, existence of restrict membrane barriers, protein binding, sequestration into specific body sites.

15. Redistribution of drugs

Distribution in red blood cells, the central nervous system, mammary circulation, fatty tissues, liver, bones, thyroids and other specific tissues. Volume of distribution, concept and significance.

Drug Metabolism (6 lectures)**16. Role of drug metabolism as a part of overall elimination process**

Importance of lipid/water solubility of drugs, deactivation, activation and production of active metabolites from inert compounds (prodrugs). Metabolism is a complex process. Sites of drug metabolism.

17. Metabolic Pathways

Phase I or non-synthetic metabolic pathways; oxidation (microsomal and non-microsomal) reduction (nitro- and azo-), hydrolysis (ester and amide). The role of functional groups liberated as chemical active to be substrate for the next phase, some relevant examples. Phase II; synthetic phase, glucuronidation, glycine conjugation,

ethereal sulfate formation, glutathion conjugation, acetylation, methylation, abundance and relative solubility of final metabolites. Some relevant examples.

18. Metabolizing Enzymes

Cytochrome P450 superfamily and its major contribution, localization, distribution. Sensitivity to inducers and inhibitors. Relevant examples of drugs metabolized by the various members of the cytochrome P450 superfamily

19. Factors Affecting Drug Metabolism

Subject variability and its sources, induction and inhibition of metabolism; their significance and some relevant examples. Specific factors; stereoselectivity, chronopharmacokinetics, first-pass effect.

20. Extrahepatic Metabolism

Metabolism at absorption, distribution and excretion phases. Placental and fetal drug metabolism.

21. Prodrugs

Definition, significance and rationale for their production. Advantages with some relevant examples.

Drug Excretion (3 lectures)

22. Role and Pathways

Excretion is the final step in drug elimination from the body, importance of water solubility. Renal and non-renal excretion.

23. Renal excretion

The kidney and its unit of excretion, mechanisms; glomerular filtration, active tubular secretion, passive tubular re-absorption, urine pH dependency. Factors affecting renal excretion: age, gender, diseases

24. Non-renal excretion

Hepatic clearance; entero-hepatic recycling, intestinal excretion, salivary excretion, excretion with expired air, with sweat and milk.

LEARNING OBJECTIVES (EACH LECTURE)

Lecture 1 Introductory lecture

1. Understand the requirements of the course, its structure and its relevance.
2. Highlight the relationship of this course with dosage forms and biological Factors.
3. Explanation of method of students assessment and marks distribution

Lecture 2 Introduction and definitions

1. Explain the various terms employed in the field of biopharmaceutics and pharmacokinetics of drugs; LADMER system, bioavailability, biophase, pharmacodynamics, disposition, etc.
2. Describe the main physiological factors affecting absorption; membrane physiology, examples for membranes types (blood brain barrier, renal tubules, blood capillaries).

Lecture 3 Transport of drugs across membranes

1. Differentiate between the different absorption mechanisms of drugs; passive diffusion, carrier-mediated, vesicular transport and ion-pair transport.
2. Give examples for drugs absorbed by each mechanism.
3. Describe the effect of physicochemical nature of the drug on absorption; pK_a of the drug, particle size and distribution of powdered drugs, Formation of polymorphs/solvates, partition coefficient, the physicochemical properties of accompanying excipients.

Lecture 4 Biopharmaceutic considerations of dosage forms (DFs)

1. explain the effect of physicochemical nature of drug and excipients on absorption.
2. Describe the effect of formulation factors of different dosage forms on drug absorption:
 - a- Solution dosage forms compared to suspensions and solid DFs.
 - b- Suspensions; flocculated versus deflocculated suspensions, effect of particle size.
 - c- Capsules; soft and hard types and role of diluents.
 - d- Tablets; effect of compression force, effect type of additives and diluents.
 - e- Modified release DFs; types of products; benefits and problems associated with their administration.
3. Describe the quality control tests of DFs relevant to evaluation of absorption of drugs; disintegration & dissolution of solids DFs, viscosity of liquid dosage forms, particle size of suspensions and emulsions, etc.

Lecture 5 Drug delivery systems (DDS)

1. Define the site-specific DDS
2. Explain the rationale for targeted DDS and the main advantages in comparison with traditional DFs.
3. List the requirements of targeted DDS, regarding the drug molecules and biological systems (protection of drugs, effective treatment at low drug levels, etc.)
4. Describe the structure and composition of liposomes.
5. Discuss the advantages of liposomes as DDS.

Lecture 6 Liposomal and Intranasal DDS

1. Explain the effect of particle size of liposome on circulation time.
2. Discuss the surface properties of liposomes and method of administration on drug targeting and half-life of liposomes.
3. Discuss the issues of intranasal DDS and main advantages.
4. Explain the restriction in using nasal route as DDS.
5. Discuss the role of enhancers to improve drug nasal delivery.

Lecture 7 Prodrugs and microparticles as DDS

1. Describe the microparticles as DDS and the main routes of administration.
2. Explain the effect of size and way of injection on targeted drugs
3. Describe the different mechanisms for drug release from microparticles and the role of polymer nature and concentration in drug control
4. Discuss the effect of coating of microparticles on uptake of microparticles.
5. Describe how prodrugs can be used as targeted DDS.
6. Give examples of drugs which can be used as prodrug DDS

Lecture 8-9 Absorption from GIT

1. Outline the anatomical and physiologic considerations involved in oral drug absorption.
2. Discuss the different factors affecting drug absorption following oral administration; gastrointestinal motility, gastric emptying time, intestinal motility, perfusion of the GIT.
3. Explain the role of food type and co-administered drugs on absorption from GIT.
4. Discuss the effect of disease states on drug absorption through modification of blood flow, GIT motility, pH, bile secretion, enzyme secretion, GIT flora, etc.
5. Explain the requirements for drug absorption by the buccal routes and its advantages.
6. What are the main advantages and applications of the rectal route.

Lecture 10 Absorption from different sites

1. Discuss the common routes of drug administration other than enteral.
2. Outline the routes of drug administration; Intravenous, intramuscular, subcutaneous, intraarterial, intraspinal, transdermal nasal and ocular routes.
3. Discuss the advantages and limitation of each route of administration of drugs.

Lecture 11-12 Bioavailability and bioequivalence

1. Outline the definitions related to bioavailability and bioequivalence; bioequivalent drug products, chemical & brand names, generic name and generic substitute, pharmaceutical substitutes & equivalents, therapeutic alternatives, and therapeutic equivalents and substitutes.
2. Discuss the regulatory status related to performing bioavailability testing; approved drugs & therapeutic moieties pending approval, and unmarketed drugs which don't have full new drug application (NDA), change of drug form (salt, ester)
3. Discuss the requirements for performing bioequivalence studies; design, reference standard, evaluation of the data (analytical method, pharmacokinetic parameters, and statistical evaluation).
4. Describe the clinical significance and concerns about bioequivalence studies.

Drug Distribution**Lecture 13 The Circulatory System**

1. Revise the main components of the circulatory system involved in drug distribution.
2. Understand the impact of the anatomical structure of different blood vessels on the permeability of drug molecules.
3. Appreciate the concept of different body fluid compartment and its effect on drug exchange.

Lecture 14 Unequal Drug Distribution

1. Realize the concept of inequality in drug distribution and identify the factors that contribute in that unequal distribution.
2. Understand the effect of various drug characteristics, *pH*, blood flow, protein binding and existence of membrane barriers on drug distribution.
3. Understand why certain drugs are localized in specific sites

Lecture 15 Redistribution of Drugs

1. Identify the causes of redistribution of drugs outside the central circulation.
2. Appreciate the consequences of such redistribution specially that for drug that are redistributed into adipose tissue and leads to ultra-short action, or localized in deeper tissues which leads to large volume of distribution.
3. Able to define and understand the concept of volume of distribution.

Drug Metabolism

Lecture 16 Metabolism as a Part of Allover Elimination Process

1. Recognize the main roles of drug metabolism.
2. Appreciate the effect of parent drug and its metabolite lipid/water solubility.
3. Understand the various types of metabolites.
4. Realize that drug metabolism is a complex process.

Lecture 17 Metabolic Pathways

1. Able to identify the two metabolic phase and the individual metabolic pathways in each phase
2. Appreciate that the majority drug metabolism starts with phase I followed by phase II with some exceptions.
3. Understand the role of the liver as the main location for the majority of drug metabolism.
4. Be able to identify the metabolic pathway of a particular drug from the knowledge of the functioning groups it contains.

Lecture 18 Metabolizing Enzymes

1. Understand that most of metabolic pathways proceed through hepatic and non-hepatic metabolizing enzymes.
2. Appreciate the role of cytochrome P450 Super family in drug metabolism, and be able to identify certain drugs that are metabolized by specific member of that super family.
3. Realize that most of those metabolizing enzyme are subject to inhibition or induct by other drugs or exogenous chemicals

Lecture 19 Factors Affecting Metabolism

1. Understand the impacts of inter and intra-subject variability (genetics) and environmental factors on ability of enzyme in handling drug metabolism
2. Understand the concepts of inhibition and induction of metabolism; their mechanism and consequence on the fate and effect of drugs.
3. Appreciate the impact of specific factors such as the stereoselectivity of metabolism, effect on time on drug administration (chronopharmacokinetics) and first-pass effect on drug metabolism.

Lecture 20 Extra-hepatic Metabolism

1. Realize that metabolism may occur outside the liver; during absorption, during circulation with blood or even excretion.
2. Appreciate the role of certain organ such as the placenta on metabolism and its consequence on the fetus

Lecture 21 Prodrugs

1. Be able to define what is meant by a prodrug.
2. Understand the rationale for production of specific-acting drugs
3. Be familiarized with advantages of prodrugs production and able to give an example for each advantage.

Drug Excretion**Lecture 22 Role and Pathways of Excretion**

1. Understand the role of excretion event as a part of overall elimination process.
2. Understand that the main pathway for excretion is the kidney; other organs that may participate in excretion are the liver, large intestine, lung, salivary sweat and mammary glands.

Lecture 23 Renal Excretion

1. Revise the kidney's anatomy and physiology in relation to the process of drugs and/or metabolites excretion.
2. Understand the main mechanisms included in renal excretion; glomerular filtration, active tubular secretion and passive tubular re-absorption.
3. Understand the basic characteristics of filtration, tubular secretion and tubular re-absorption with some relevant examples.
4. Realize that renal excretion is a *pH* dependent.
5. Understand the main factors that affect renal excretion.

Lecture 24 Non-renal Excretion

1. Appreciate the role of liver as an important organ for drug elimination through secretion of metabolites with bile juice.
2. Understand the impact of the so-called enter-hepatic recycling.
3. Understand the role of large intestine, lungs, salivary, sweat and mammary glands in drug excretion.
4. Be able to give specific drugs secreted by such pathways.