Universidad de Alcalá

# COURSE GUIDE

# BIOPHARMACEUTICS AND PHARMACOKINETICS

(Revisada en CD el 27-05-2021)

## Degree in PHARMACY
## University of Alcalá

**Academic year 2021/2022**
**3rd Year 1st Season**

# COURSE DESCRIPTION

| | |
|---|---|
| **Title:** | **Biopharmaceutics and Pharmacokinetics** |
| **Code:** | **570014** |
| **Degree:** | **PHARMACY** |
| **Department:** | **Biomedical Sciences** |
| **Field of Knowledge:** | **Pharmacy and Pharmaceutical Technology** |
| **Type:** | **Compulsory** |
| **ECTS credits:** | **6 ECTS (4.5 Theory + 1.5 Experimental Work)** |
| **Year:** | **Third / first season** |
| **Teacher:** | Dr. Jesús Molpeceres García del Pozo |
| **Coordinator:** | **Dr. Jesús Molpeceres García del Pozo** |
| **Schedule for tutorials:** | **appointment with the teacher** |
| **Language:** | **English** |

## 1. INTRODUCTION

This subject aims to characterize, from a qualitative and quantitative standpoint, all the processes and factors affecting a drug once it has been given a particular dosage form by a particular administration route, in order to optimize its bioavailability. Biopharmaceutics and Pharmacokinetics are complementary disciplines; the former is focused on the study of the interaction between the dosage form and the biological substrate and the latter more oriented towards evaluating drug and metabolite kinetics through analysis of concentration/time curves in biological fluids.

The learning outcomes pursued with this course can be summarized thus:

1. Awareness of the mechanisms for drug passage through biological barriers.
2. Understand basic procedures for the study of drug transfer kinetics in the body.
3. Recognize the relevance of pharmacokinetic parameters.
4. Understand the influence of physiological, pathological, environmental, etc… factors on drug transit within the body.
5. Identify the influence of dosage form design on both the drug incorporation into the systemic circulation and the therapeutic effect.
6. Understand drug bioavailability and bioequivalence as related to drug product safety.
7. Knowledge and implementation of the basis for the establishment of drug dosing regimens.

## Prerequisites and Recommendations

It is highly recommended that the students have previously passed the courses on Mathematics, and principles of Physics, Biophysics and Physical Chemistry.

# 2. COMPETENCES AND ABILITIES

### Generic competences (Orden CIN/2137/2008, 3 de julio) provided by this course:

1. Knowledge of the ADME process and the factors influencing drug absorption and disposition as related to each administration route.
2. Knowledge of the physical-chemical and biopharmaceutical properties of drugs and excipients and their potential relationships.
3. Drug dosing and drug dosing adjustment by pharmacokinetic parameters.
4. Determination of bioavailability, evaluation of bioequivalence and conditioning factors.

### Specific competences:

1. Ability to analyze the passage of drugs through the body: LADME.
2. Knowledge of the biopharmaceutical factors associated with each administration route.
3. Evaluation and estimation of drug changes in the body by using pharmacokinetic models.
4. Knowledge of drug clearance and ability to estimate drug clearance.
5. Ability to analyze the influence of dosage form design and formulation on drug release and absorption.
6. Capacity to evaluate drug bioavailability and bioequivalence.
7. Ability to analyze the pharmacokinetic parameters influencing drug dosing.

# 3. CONTENTS

### Lectures:

**I. INTRODUCTION TO BIOPHARMACEUTICS and PHARMACOKINETICS**

**- Chapter 1.-** INTRODUCTION.

Concepts and relevance of biopharmaceutics and pharmacokinetics.
Sources of information.
The passage of drugs through the body.
The LADME process: Overview and basic concepts of drug release, absorption, distribution, metabolism and excretion.

**Chapter 2.-** PHARMACOKINETICS.

Data for the study of LADME.
Drug plasma level curves and urinary excretion curves.
Kinetics of the LADME steps: Zero order, first order and Michaelis-Menten kinetics.
Usual kinetics in LADME.

**II. DRUG INCORPORATION AND DISPOSITION INTO THE BODY**

**Chapter 3.-** DRUG RELEASE.
Mechanisms and effect on bioavailability.
Immediate release drug dosage forms: Disintegration and dissolution as limiting factors for drug absorption.

**Chapter 4.**
Factors influencing drug dissolution.
Mechanisms and drug release kinetics in modified release dosage forms.
Relevance of diffusion on the global process.

**Chapter 5.-** DRUG ABSORPTION**.**
Administation routes and absorption sites.
Drug access to the blood stream.
Pre-systemic metabolism and first pass effect.
Recycling processes.
Kinetic study of absorption mechanisms.
Drug transporters.
The BCS and other classification systems.

**Chapter 6.-** DRUG DISTRIBUTION.
Body fluid compartments and volume of distribution.
Extent and rate of distribution.
Factors affecting drug distribution.
Drug protein binding: factors and binding parameters (Klotz and Scatchard methods). Competitive binding and effects on drug distribution and elimination.

**Chapter 7.-** DRUG BIOTRANSFORMATION.
Overview. Hepatic biotransformation and first-pass effect.
Non-hepatic metabolism.
Kinetics and factors affecting drug metabolism.
*In vitro* characterization of drug metabolism.

**Chapter 8.-** DRUG EXCRETION.
Sites and mechanisms.
Renal excretion and conditioning factors.
Excretion by other routes: biliary excretion.
Enterohepatic recycling.
Salivary excretion.
Pulmonary excretion.
Milk-breast excretion.
Secondary excretion routes.
Influence of non-renal excretion of drugs on therapy.

**Chapter 9-** CLEARANCE.
Concept. Extraction rate.
Hepatic clearance.
Renal clearance.

Factors influencing drug clearance.
Determination of drug clearance.

**Chapter 10.-** PARENTERAL ADMINISTRATION.
Intravascular and extra-vascular administration: injection sites, advantages, disadvantages and uses.
Drug release as a limiting factor in parenteral absorption.
Factors influencing parenteral absorption.
Modified release dosage forms for parenteral administration: mechanisms and kinetics of parenteral absorption.

**Chapter 11.-** ORAL ADMINISTRATION**.**
Absorption sites.
Buccal and sublingual administration.
Anatomy and physiological factors influencing drug absorption in the GI tract.
Drug stability in the lumen.
Recycling

**Chapter 12.-**
Theories and models to explain GI drug absorption: pH-partition, Wagner-Sedman, Higuchi-Ho, Pla-Moreno*. In vitro-in vivo* correlations.

**Chapter 13.-** RECTAL AND VAGINAL ADMINISTRATION.
Characteristics, therapeutic goals and factors affecting drug absorption and bioavailability.
Therapeutic systems for the vaginal route: Mechanisms and drug release kinetics.

**Chapter 14.-** NASAL AND PULMONARY ADMINISTRATION.
Characteristics of the airway epithelium.
Advantages and disadvantages of airway delivery.
Factors affecting drug absorption.
Absorption mechanisms.

**Chapter 15.-** PERCUTANEOUS ADMINISTRATION.
Absorption sites and mechanisms for drug absorption through the skin.
Factors affecting drug permeability.
Absorption enhancers.
Biopharmaceutics of skin permeation.
*In vitro* and *in vivo* methods.

**III. KINETIC STUDIES OF DRUG CHANGES WITHIN THE BODY**
**Chapter 16.-** PHARMACOKINETIC MODELS.
Compartmental pharmacokinetics: Concepts of compartment, simple models, linear and non-linear pharmacokinetics.
Non-compartmental pharmacokinetics.
Physiological modelling.
Population pharmacokinetics.
*In silico* prediction of pharmacokinetics.

**Chapter 17.-** ONE-COMPARTMENT OPEN MODEL. INTRAVENOUS BOLUS ADMINISTRATION.
Interpretation of plasma concentration/time profiles.
Elimination phase: concept and determination of the elimination rate constant.
Elimination half-life, area under the curve, volume of distribution and plasma clearance. Relationships and their influence on drug plasma concentration/time curves.

**Chapter 18.** ONE-COMPARTMENT OPEN MODEL. EXTRA-VASCULAR ADMINISTRATION WITH FIRST ORDER ABSORPTION.
Overview and interpretation of plasma concentration/time profiles.
Lag time and its determination.
Determination of area under the curve, $C_{max}$ and $t_{max}$.
Estimation of the absorption rate constant by using direct and indirect methodologies: method of residuals, cumulative absorption method (Wagner-Nelson), The Dost method.

**Chapter 19.**
Mathematical equation for single extra-vascular dosing in the one-compartment open model. The Bateman equation.
Characteristics of drug plasma concentration/time curves.
Influence of administration route and dosage form.
The Flip-flop model.
Effect of changes in the absorption and disposition parameters.
Mass balance: drug amounts in the body, eliminated or in the absorption site.

**Chapter 20.-** ONE-COMPARTMENT OPEN MODEL: ZERO ORDER INCORPORATION KINETICS.
Determining factors.
Intravenous infusion.
Drug plasma concentration/time curves in one- and two-compartment open models.
Plateau or steady-state concentration.
Incorporation and disposition phases.
Calculation of pharmacokinetic rate constants.
Immediate steady-state concentration.

**Chapter 21.-** ONE-COMPARTMENT OPEN MODEL: URINARY EXCRETION CURVES.
Drug plasma concentrations and excretion rates in urine.
Distributive and cumulative curves.
Determination of pharmacokinetic rate constants in the one- and two-compartment open models.
*Pros* and *cons* of urinary excretion curves.

**Chapter 22.-** ONE-COMPARTMENT OPEN MODEL: MULTIPLE DOSE KINETICS.
Overview and basic parameters.
Calculation of steady-state concentrations.
Cumulative index.
Cumulative factor.
One-compartment open models.

**Chapter 23.-** TWO-COMPARTMENT OPEN MODEL. INTRAVENOUS BOLUS ADMINISTRATION.
Bolus intravenous dosing: why this model?
Central and peripheral compartments.
Overview and interpretation of drug plasma concentration/time curves.
Model equations.
Determination of hybrid (macro-constants) and individual disposition rate constants (micro-constants), area under the curve and volumes of distribution.
Relationships between disposition and elimination rate constants.
Mass balance: drug amounts in the body and eliminated.

**Chapter 24.-** TWO-COMPARTMENT OPEN MODEL. EXTRAVASCULAR ADMINISTRATION.
Extra-vascular administration with first order absorption.
Pharmacokinetic model and equations.
Characteristics of the drug plasma concentration/time curves.
Calculation of $C_{max}$, $t_{max}$ and area under the curve.
Estimation of the absorption rate constant by different methodologies: Residuals or retro-projection method.
The Loo-Riegelman method. Lag phase.
Mass balance: drug amounts in the body, eliminated or in the absorption site.

**Chapter 25.-** NON-COMPARTMENTAL PHARMACOKINETICS.
Disadvantages of compartmental analysis.
The theory of statistical moments.
Estimated pharmacokinetic parameters.
Mean residence time and its calculation.
Area under the curve.
Volume of distribution.
Clearance.

**Chapter 26.-** NON-LINEAR PHARMACOKINETICS.
Concept and causes for non-linear kinetics.
Michaelis-Menten kinetics.
Dose-dependent pharmacokinetics.
Chronopharmacokinetics.
Factors that change pharmacokinetic parameters.

**IV. BIOAVAILABILITY AND BIOEQUIVALENCE**
**Chapter 27.-** OVERVIEW OF BIOAVAILABILITY AND BIOEQUIVALENCE.
Definition and factors influencing drug bioavailability.
Determination of rate and extent of bioavailability from single dose and multiple dose administration.
Bioequivalence.
Concept, definition and regulatory aspects.
Methods to determine drug product bioequivalence.

**Chapter 28.-** Bioavailability and Bioequivalence studies.
Goals, experimental design and ethical issues.
Methodology, pharmacokinetic analysis and significant parameters to compare.

**V. DRUG DOSING**
**Chapter 29.-** CLINICAL PHARMACOKINETICS.
Concept and goals.
Pharmacologic response in pharmacokinetics.
Drug dosing: administration regimens.
Therapeutic margin.
Strategies to establish a dosing regimen.

**Chapter 30.-** Therapeutic drug monitoring.
Concept, methodology and pharmacokinetic significance.

**Chapter 31.-** DRUG DOSING IN ADULTS.
Sex differences. Drug dosing in pregnancy.
Transplacentary exchanges.
Drug teratogenicity.
Drug dosing in breastfeeding women.
Drug excretion in milk and factors affecting the process.
Use of drugs during breastfeeding.

**Chapter 32.-** DRUG DOSING IN NEONATOLOGY AND PEDIATRICS.
Factors affecting drug absorption, distribution and elimination.
Dose adjustment on a weight basis or a body surface basis.
Drug dosing in the elderly.

**Chapter 33.-** DRUG DOSING IN ORGAN DYSFUNCTION.
Renal insufficiency.
Liver dysfunction.
Heart failure.
Function indexes.
Dose calculations.

## Laboratory:

- "In vitro" simulation of the one-compartment open model by means of a hydraulic device. Pharmacokinetic analysis of simulated blood and urine data.

**Exercise 1.-** Single dose bolus IV administration.

**Exercise 2.-** Single dose EV administration.

**Exercise 3.-** Multiple dose bolus IV administration.

**Exercise 4.-** Constant rate IV administration.

- Influence of the physical chemical characteristics of a drug and the dosage form on the ADME process.

**Exercise 5.-** Drug dissolution testing in accordance to the RFE. Influence of the dosage form and kinetic analysis.

**Exercise 6.-** Comparative “in vitro” study of drug release from semisolid products through a semipermeable membrane. Influence of vehicle viscosity.

**Exercise 7.-** Protein binding drug displacement interaction study.

### Other activities: Seminars

Seminar 1, Dissolution studies.
Seminars 2, 3, 4 and 5.- One-compartment open model.
Seminars 6 and 7.- Two-compartment open model.
Seminar 8.- Non-compartmental pharmacokinetics.
Seminar 9.- Bioavailability and bioequivalence.
Seminar 10.- Drug dosing.

## 3.1. Distribution of contents

| Thematic Units | Chapters | Time |
|---|---|---|
| **Introduction** | 1 and 2 | 2h L, |
| **Drug incorporation and disposition** | 3 to 15 | 11h L,<br>1h S,<br>8h Lab |
| **Kinetic study of drug changes within the body** | 16 to 26 | 10h L,<br>5h S,<br>10h Lab |
| **Bioavailability and Bioequivalence** | 27 and 28 | 2h L,<br>1h S, |
| **Drug dosing** | 29 to 33 | 3h L,<br>1h S, |

# 4. Teaching-Learning Methodologies. Activities

## 4.1. Distribution of ECTS credits (specify in hours)

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|---|---|
| **Classroom:** | • Lecture hours: 28 h<br>• Seminars: 8 h<br>• Laboratory work: 18 h<br>• Tutorials: 4,5 h |
| **Independent study:** | • Laboratory-related calculations: 17,5 h<br>• Independent study: 74 h |
| **Total** | 150 h |

## 4.2. Materials, methodological strategies and teaching resources

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|---|---|
| **In the classroom or laboratory** | Lectures will be based on presentations made by the teacher and discussions about the main items included in each chapter. In some cases, computer programs or videos will be used for comprehensive purposes.<br><br>Seminars will be focused to problem solving and discussion of topics. Group activities can be designed in order to facilitate the active participation of students.<br><br>Laboratory work will consist on the development and setting of different experimental approaches to mimic compartmental models and real systems to identify basic concepts exposed during the lectures.<br><br>Materials and teaching resources: blackboard, powerpoint presentations, printed material provided by the teacher, a laboratory notebook and web resources. |
| **Independent work** | Students will analyze and assimilate the information provided in classroom and laboratory activities on their own. They can use all available information such as books and literature search tools to complete this information.<br><br>Use of ICTs to facilitate the contact between the students and the teacher during independent work outside of the classroom. |

## 5. EVALUATION: Procedures, criteria and rating

Every academic year the student has two calls for assessment, regular and extraordinary. The regular call can be undertaken in two different formats, continuous assessment or final evaluation. Continuous assessment is strongly recommended but there are a few exceptional cases considered in UAH regulatory documents allowing the students to do a final exam. The student can leave this course and join the corresponding Spanish version within the first two weeks.

### REGULAR CALL

**Continuous assessment:**

Continuous assessment is the default option associated to the regular call. Attendance of all classroom activities is mandatory. In accordance to UAH regulations students will have two formal tests to evaluate their progress with regards to their knowledge of the subject including theoretical concepts and problem solving abilities. The first one will take place at the middle of the teaching period and the second one at the end. The assessment of those skills and knowledge acquired through laboratory work will also be carried out with a formal examination. Students who have not performed the laboratory work and passed the exam will not pass the subject in this call.

Students must show a minimum level in the achievement of the corresponding competences for the gathering of partial marks to obtain the global score.

Students that do not pass the subject in a regular call will follow a second final evaluation as extraordinary call within the same academic year.

**Final examination:**

It will evaluate theoretical concepts and problem solving abilities focused to assess the acquisition of specific competences detailed previously. The assessment of those skills and knowledge acquired through laboratory work will also be carried out with a formal examination.

### EXTRAORDINARY CALL

It will evaluate theoretical concepts and problem solving abilities focused to assess the acquisition of specific competences detailed previously. Students who have completed the laboratory work but failed must pass a specific exam.

### Assessment criteria:

- Assimilation and understanding of course content.
- Attendance and participation in seminars.
- Ability to apply acquired knowledge.
- Interpretation of results and resolution of numerical problems or questions.
- Critical and coherent thinking.
- Compliance with laboratory safety rules.
- Skills for laboratory work.
- Integration and communication of knowledge.

**Rating criteria:**

As the subject holds a high experimental degree, laboratory work is mandatory and must be passed by doing the corresponding exam, regardless of the course assessment format selected by the student.

**REGULAR CALL**

**Continuous assessment**:

- Laboratory work: 20%.
- Partial exam: 40%.
- Final exam: 40%

Additionally, the student can participate in a voluntary team work activity weighing 5% to the final score. In this case the scores obtained in the previous evaluations will be pro-rated to a maximum of 10 including the team work.

**Final Examination:**

This assessment will be based on a test including questions, problems and exercises focused to assess the acquisition of specific competences detailed previously. In order to pass the course, a score higher than or equal to 5 is needed. Students who have completed the laboratory work but failed must pass a specific exam with scores higher than or equal to 5. Laboratory work will contribute 20% to the final score.

**EXTRAORDINARY CALL:**

This assessment will be based on a test including questions, problems and exercises focused to assess the acquisition of specific competences detailed previously. In order to pass the course, a score higher than or equal to 5 is needed. Students who have completed the laboratory work but failed must pass a specific exam with scores higher than or equal to 5. Laboratory work will contribute 20% to the final score.

If Health Authorities decide to suspend classroom teaching or the circumstances of the course make it necessary, the teaching or part of it, would continue with the on-line methodology until the suspension was lifted, at which point it would return to face-to-face delivery again.

## 6. BIBLIOGRAPHY


[1] Ritschel, W, Kearns G. "Handbook of basic pharmacokinetics including clinical applications". Ritschel, W, Kearns G. Ed. American Pharm.l Assoc. Washintong. 2004. (Reference: BAF615.03RIT)

[2] Rosenbaum, S. "Basic pharmacokinetics & pharmacodynamics an integrated textbook & comp. simulation". Ed. John Wiley & Sons. 2011. (Reference: D615.03ROS).

[3] Washington N.,Washington C, Wilson C. "Physiological pharmaceutics biological barriers to drug absorption". Taylor & Francis, London 2001. (Reference: BAF615WAS).

[4] L. Shargel y A. Yu. "Applied Biopharmaceutics and Pharmacokinetics". Prentice-Hall International Inc., 2004. (Reference: BAF615.03SHA)

[5] Rowland M, Tozer T.N “Clinical pharmacokinetics and pharmacodynamics concepts and applications”. Ed. Lippincott & Wilkins,2011. (Reference: BAF615.03ROW)

[6] Van de Waterbeemd H, Lennernäs H, Arturson P. "Drug Bioavailability estimation of solubility, permeability, absorption and bioavailability". Wiley-Vch 2005. (Reference: BAF615-032WAT)

[7] Software available at the computer classroom in the Faculty of Pharmacy :
   a. Biofarmacia Moderna. Amidon G.M. Ed. TSRL. Inc. 5.04.
   b. Pharmacokinetics Simulations. University of Bath. C.O.A.C.S. Ed. PCCAL, 1999.
   c. Introductory Pharmacokinetics Workshop.University of Bath. COACS. Ed. PCCAL,1999.
   d. JANA. Dunne A.P. Ed. SCI Software,1993.