

USC School of Pharmacy

BPSI 403: Biopharmaceutics II

Coordinator: Hovhannes J. Gukasyan, PhD
Associate Professor, Department of Pharmacology and Pharmaceutical Sciences
University of Southern California
Email: gukasyan@usc.edu
Office Phone: (323) 442-1362
Office Location: HSC campus PSC 716
Office Hours: by appointment

Instructors: Daryl L. Davies, PhD
Professor, Department of Clinical Pharmacy
University of Southern California
Office: HSC campus PSC 506
Email: ddavies@usc.edu
Office Phone: (323) 442-1427
Office hours: by appointment

Course Weight: 4 Units (two weekly 1.5-hour sessions; plus computer simulations lab ad libitum complete three practice assignments and final exam case study)

Catalogue description: Comprehensive overview of early drug discovery and medicinal product development; *in vitro* and *in vivo* assays simulations/modeling, biopharmaceutical classification system, drug delivery science & technology

Day/Time/Location: M/W, 3:30-4:50pm, CPA 261

Introduction and Purpose

This introductory course will provide students with a comprehensive overview of tier-1 (early drug discovery and medicinal product development) *in vitro* and *in vivo* assays simulations and modeling, biopharmaceutical classification system, and drug delivery science & technology. Biopharmaceutical modeling has become integral to the design and development of new drugs. Influencing key aspects of the development process, including drug substance design, formulation design, and toxicological exposure assessment, biopharmaceutical modeling is now seen as the linchpin to any new medicinal products' future success. There are several commercially available software programs for drug modeling. Biopharmaceutics II is a multidisciplinary course encompassing areas of study that employ basics of general chemistry, biology (biosystems), and mathematics (calculus), addressing formulation and delivery of drugs. By applying concepts of Pharmaceutical Sciences various dosage forms, routes of administration,

and their interchangeability will be introduced to understand bioavailability and bioequivalence. Basic and applied chemistry, biology, mathematics, physics, and chemical engineering concepts as they relate to medicinal products will be applied to exemplify approaches in building physiologically based pharmacokinetic simulation models. Familiar topics to be enclosed in this course will include principals of pharmacokinetics, physical pharmacy, drug design and development, as well as pharmaceutical biotechnology. Applied mathematics in the quantitation of drug concentrations will be introduced (computer lab) to study absorption, distribution, metabolism, and elimination of drugs.

Advanced pharmacokinetic simulations, partly a computer-lab based course focusing on modeling and simulation of kinetic processes describing rates of Absorption, Distribution, Metabolism and Excretion (ADME) will be integrated into lecture topics. A bridge between dosage form characteristics (i.e., type solid vs liquid – pills and injections; route of administration – enteral and parenteral) with potential systemic exposure outcomes will be constructed to understand importance of matching specifications of a drug product to a ‘blood concentration vs time’ profile pattern. Students will have the opportunity of learning with literature data (using Gastroplus® software) and generating in vitro solubility/permeability and in vivo pharmacokinetic parameters applying information to absolute drug-dose determination and adjustment. Concepts of translation of these parameters from virtual pre-clinical research species to human will be introduced. Students’ understanding of basic biopharmaceutics and pharmacokinetic principles will be reinforced preparing them to apply knowledge gained in the design, implementation and management of drug therapy in a variety of real-world settings.

Principles introduced in this course will familiarize students with biopharmaceutical classification and formulation sciences terminology, including key concepts related to the processes of equivalence (generics and biosimilars) and will help set the stage for future, more sophisticated course work necessary for the student to gain a level of competency to be successful in the pharmaceutical drug discovery and development setting. Beginning with a focus on the oral absorption of drugs, BPSI 403 discusses the central dogma of oral drug absorption (the interplay of dissolution, solubility, and permeability of a drug), which forms the basis of the biopharmaceutical classification system (BCS), using in silico tools, i.e. virtual computer-software based, that are widely adapted by progressive drug development companies and global regulatory agencies. To help prepare the student for the ever-changing environment, this course will present foundational and newly advancing modeling and simulation technologies to provide knowledge regarding critical aspects of medicinal product development.

Objectives

This course a continuation of BPSI 402, Biopharmaceutics I. In BPSI 403, students will learn applications of physicochemical properties of drugs as they impact medicinal product development. Characteristics including kinetics of solubility, dissolution, and permeability, and the influence of compounding/formulation upon them will be systematically evaluated in solid or liquid drug dosage forms administered via common routes to the body. Modulation of dissolution kinetics will be studied in parallel to biological membrane diffusion/permeability to exemplify the effect these biopharmaceutical properties have on pharmacokinetics of drug products. Content presented in this course will enable students to acquire a strong understanding of the step-by-step processes involved in the role and importance of solid-state and ionizable/reactive

drug functional group properties on the dosing, efficiency, and delivery of pharmaceutical products. Translational aspects of biopharmaceutical developability will be introduced to facilitate understanding interspecies relationships in safety, efficacy, and allometric dose scaling. Importance of gastrointestinal physiological effects (fasted vs fed state) and physicochemical factors (solubility and permeability) that influence the availability of a drug from different dosage forms (immediate vs modified release), and the subsequent disposition of the drug in the body will be studied. Chapters from required textbooks will be supplemented with a variety of source materials, including articles from scientific journals and public websites. Case studies will be critically reviewed, and emerging “hot” topics discussed.

Upon successful completion of this course, the student should be able to:

- Understand physicochemical property descriptors of composite values of drug solubility and permeability.
- Understand principles of solubility, dissolution, and diffusion.
- Explain the differences between absolute bioavailability, relative bioavailability, and criteria of pharmaceutical bioequivalence.
- List reasons for incorporation of drugs into various dosage forms and describe the essentials of compounding practices by categorizing common excipients.
- Understand and be able to exemplify solid vs liquid dosage forms, and key biopharmaceutical blueprint attributes for oral vs intravenous administration of medicinal products.
- Define and comprehend basic pharmacokinetic principles modulated by dose, route of administration, and formulation of a medicinal product.
- Describe mechanisms of drug degradation and provide examples in vitro/in vivo settings of each.
- Describe various types of drug absorption from a pharmaceutical dosage form.
- Describe the physical and chemical characteristics of a drug that affect its dissolution from various dosage forms and explain how drug dissolution affects drug absorption.
- Perform pharmacokinetic analysis of given plasma drug concentration data and define the concept of oral bioavailability and bioequivalence.
- Compare and contrast advantages and disadvantages of the various types of tablet dosage forms.
- Define solubilization, list major factors affecting solubility, and perform calculations to determine appropriate parameters to establish maximum solubility.
- List physical and chemical characteristics of drugs that make them candidates for an extended-release, comparing/contrasting properties of common modified-release dosage forms.
- Explain the physical-chemical properties of drugs which determine their suitability to be incorporated into common dosage forms and differentiate between the various types of systems used for oral vs. intravenous delivery.
- Identify and explain physiologic factors which influence the drug absorption from oral administration and identify key rate limiting physicochemical factors.

Assignments and Grading:

Class participation: 10 pts (5 %)

5 quizzes @ 10 pts each	50 pts	(25%)
2 midterm exams @ 45 pts each:	90 pts	(45 %)
1 final exam (G+ Case study report):	50 pts	(25 %)
Total:	200 pts.	

Class Participation and Attendance (10 pts): On a scale of 10, 0-indicating no participation, 10-indicating best participation. You can therefore increase the probability of getting a higher mark by being proactive in terms of asking (relevant) questions in class and/or contributing to discussions.

Attendance at all classes is expected. Participation will include asking and answering questions and being actively involved in the discussion. It is expected that the students read the assigned papers prior to the lecture and be prepared to discuss background, current understanding, treatments, and gaps in knowledge for the topic in each lecture.

There will be 5 quizzes over the course of the semester that will primarily be based on questions pulled from the text book and lectures. The midterms (45 points each) will include multiple choice questions T/F questions fill-in the blank questions, and short answers.

Instead of a cumulative final exam, a 5-page double-spaced essay based on a G+ simulation case study (deliverable) will be due by **5pm PST on the day of the final** via posting on Blackboard and also via email to gukasyan@usc.edu by. The deliverable will focus on an applied pragmatic biopharmaceutical risk analysis of a putative medicinal product.

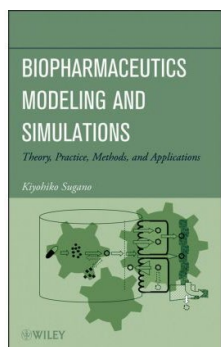
Additional details will be presented during week one of the class and included in the Week 1 PPT slides.

Notes, books, calculators, electronic dictionaries, regular dictionaries, cell phones or any other aids are not allowed during exams.

Students will be asked to complete an anonymous critical evaluation of the course at its completion.

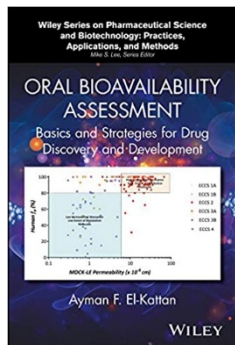
Course Readings

Required Readings



Biopharmaceutics Modeling and Simulations: Theory, Practice, Methods, and Applications. 1st Edition. Kiyohiko Sugano. ISBN-13: 978-1118028681

Additional text that students may find helpful:



Oral Bioavailability Assessment: Basics and Strategies for Drug Discovery and Development (Wiley Series on Pharmaceutical Science and Biotechnology: Practices, Applications and Methods) 1st Edition. Ayman F. El-Kattan (Author), Mike S. Lee (Series Editor). ISBN-13: 978-1118916698

Additional textbooks are not mandatory, however students interested in drug discovery process should consider their purchase to expand comprehension on BCS and drug delivery principles. The students will be able to use identified chapters in the text to support their learning process throughout the semester.

Other course materials including but not limited to the syllabus, supplemental reading assignments and additional handouts will be posted on <http://blackboard.usc.edu/>. The students will also be encouraged to use the online discussions among students via Blackboard.

Recommended Supplemental Readings

User manual to GastroPlus® (current version) (SimulationsPlus, Lancaster, CA)

Online learning Etiquette (if applicable)

- If it is not possible to have you webcam on during the entire class, do you best to have it on when speaking
- Turn off your microphone when not speaking
- If you need to step away from your computer during class (e.g. get a drink of water, use the bathroom, attend to a family member/pet) please do so quietly and without disturbing your classmates. Return to the class when you can.
- Be aware the contents of conversations typed into the chat box, even private conversations, are visible by the instructors

Course Outline

This course will be in the format of a directed seminar/lecture under the guidance of the instructor for the specific session. During each weekly session the instructor will engage the students with questions and draw comments or interpretations primarily based on the assigned reading. Students are expected to ask questions and participate in an interactive fashion.

Week & Date	Speakers	Subtopics to be Included	Assigned and Supplemental Reading
Introduction and Background			
Week 1 Jan 10, 12	Davies, DL Gukasyan, HJ	Introduction: expectations and goals of this class Career prospects in biopharmaceutics industry vs. regulatory agencies General overview of drug bioequivalence	Sugano, Ch.9 and El-Kattan Ch.1
Week 2 Jan 19	Davies, DL	History of the BCS. Bioequivalence and biowaivers Illustrative description of oral drug absorption: the whole story	Sugano, Ch.1 and El-Kattan Ch.1 Suppl. Amidon GL, et al. Pharm Res. 1995 Mar;12(3):413-20.
Physicochemical Properties and Biophysics			
Week 3 Jan 24, 26	Gukasyan, HJ	Solubility: concentration, acid/base/salt, thermodynamics, polymorphs, and solid form characterization	Sugano Ch. 2, 7.5, 7.6 and El-Kattan Ch. 4
Week 4 Jan 31, Feb 2	Gukasyan, HJ	Dissolution: particles, diffusion layer, 'nucleation'	Sugano Ch. 3, 7.7, 7.8 and El-Kattan Ch. 4
Week 5 Feb 7, 9	Gukasyan, HJ	Permeability: Fick's Law, mechanisms, unstirred layer, relationship physicochemical properties vs. fraction of a dose that is absorbed	Sugano Ch.4, 7.9 and El-Kattan Ch. 4, 9, 10
Weeks 3-5	Computer labwork	Identify software input modules for solubility, dissolution, and permeability parameters for 3 different existing drug molecules	GastroPlus® manual
Week 5 Midterm 1			
Advanced Gastrointestinal Absorption and Transit			
Week 6 Feb 14, 16	Gukasyan, HJ	Gastrointestinal transit: ACAT® model, compartments, integration	Sugano Ch. 5 and El Kattan Ch. 2
Week 7 Feb 21, 23	Gukasyan, HJ	Approximate fraction of a dose absorbed (analytical solutions to Fa% estimation, interpretations of Fa equations)	Sugano Ch. 5 and El Kattan Ch. 1, 2
Week 8 Feb 28, Mar 2	Gukasyan, HJ	In vivo Fa from pharmacokinetic data, PKPlus® IV dose deconvolution: absolute bioavailability, relative bioavailability (solid vs liquid dose, high vs low dose)	Sugano Ch. 5, 7.10 and El Kattan Ch. 1, 2, 4, 11
Week 9 March 7, 9	Gukasyan, HJ	Physiology of the gastrointestinal tract: stomach, intestines, pH, bile acids/food effect	Sugano Ch. 6 and El-Kattan Ch. 1, 2
Week 10 March 21, 23	Gukasyan, HJ	Physiology of the gastrointestinal tract: transporters (efflux vs uptake)	Sugano Ch. 6, 14 and El-Kattan Ch. 6, 7
Week 11 March 28, 30	Gukasyan, HJ	Drug Parameters: pKa, logP/D, micelles, size and shape distributions	Sugano Ch. 7 and El-Kattan Ch. 5
Weeks 6-11	Computer labwork	Identify software input modules for dose, dosage form, route of administration, drug physicochemical characteristics of logP and pH vs solubility relationship, efflux pump effect, and perform a Fa calculation at 3 doses for talinolol	GastroPlus® manual Bolger, M.B. et al. AAPS J. 2009 Jun; 11(2): 353–363.
Week 12 Midterm 2			
Applied Drug Delivery: BCS/Bioequivalence			
Week 12 Apr 4, 6	Gukasyan, HJ	Validation and reliability of mechanistic absorption models: case studies Permeability limited vs solubility limited (Caco-2, PAMPA, IVIVC) Salts?	Sugano Ch.8 and El-Kattan Ch. 4, 5

Week 13 Apr 11,13	Gukasyan, HJ (biopharma industry guest lecturer)	BCS and bioequivalence: case studies	Sugano Ch. 9 and El-Kattan Ch. 8, 13
Week 14 Apr 18, 20	Gukasyan, HJ (biopharma industry guest lecturer)	Changing drug dose and particle size Guidance in the Setting of Drug Particle Size Specifications to Minimize Variability in Absorption	Sugano Ch. 10 Suppl. Kevin C. Johnson & Archie C. Swindell Pharm Res v13, pgs 1795–1798 (1996)
Week 15 Apr 25, 27	Gukasyan, HJ	Food Effect: physiological and pharmacokinetic changes, predicting and applying to BCS, impact of medicinal product formulation	Sugano Ch. 12, 13 and El-Kattan Ch. 1, 2
Weeks 12-15	Computer labwork	Physiologically Based Absorption Modeling to Explore the Impact of Food and Gastric pH Changes on the Pharmacokinetics of Alectinib	GastroPlus® manual Parrott, N.J. AAPS J. 2016 Nov;18(6):1464-1474.
Final Exam: Exam Paper is due by 5:00 pm PST on .			

Statement on Academic Conduct and Support Systems

Academic Conduct:

Plagiarism – presenting someone else’s ideas as your own, either verbatim or recast in your own words – is a serious academic offense with serious consequences. Please familiarize yourself with the discussion of plagiarism in SCampus in Part B, Section 11, “Behavior Violating University Standards” policy.usc.edu/scampus-part-b. Other forms of academic dishonesty are equally unacceptable. See additional information in SCampus and university policies on [Research and Scholarship Misconduct](#).

Students and Disability Accommodations:

USC welcomes students with disabilities into all of the University’s educational programs. The Office of Student Accessibility Services (OSAS) is responsible for the determination of appropriate accommodations for students who encounter disability-related barriers. Once a student has completed the OSAS process (registration, initial appointment, and submitted documentation) and accommodations are determined to be reasonable and appropriate, a Letter of Accommodation (LOA) will be available to generate for each course. The LOA must be given to each course instructor by the student and followed up with a discussion. This should be done as early in the semester as possible as accommodations are not retroactive. More information can be found at osas.usc.edu. You may contact OSAS at (213) 740-0776 or via email at osasfrontdesk@usc.edu.

Support Systems:

Counseling and Mental Health - (213) 740-9355 – 24/7 on call
studenthealth.usc.edu/counseling

Free and confidential mental health treatment for students, including short-term psychotherapy, group counseling, stress fitness workshops, and crisis intervention.

National Suicide Prevention Lifeline - 1 (800) 273-8255 – 24/7 on call
suicidepreventionlifeline.org

Free and confidential emotional support to people in suicidal crisis or emotional distress 24 hours a day, 7 days a week.

Relationship and Sexual Violence Prevention Services (RSVP) - (213) 740-9355(WELL), press “0” after hours – 24/7 on call
studenthealth.usc.edu/sexual-assault

Free and confidential therapy services, workshops, and training for situations related to gender-based harm.

Office for Equity, Equal Opportunity, and Title IX (EEO-TIX) - (213) 740-5086
eeotix.usc.edu

Information about how to get help or help someone affected by harassment or discrimination, rights of protected classes, reporting options, and additional resources for students, faculty, staff, visitors, and applicants.

Reporting Incidents of Bias or Harassment - (213) 740-5086 or (213) 821-8298
usc-advocate.symplicity.com/care_report

Avenue to report incidents of bias, hate crimes, and microaggressions to the Office for Equity, Equal Opportunity, and Title for appropriate investigation, supportive measures, and response.

The Office of Student Accessibility Services (OSAS) - (213) 740-0776
osas.usc.edu

OSAS ensures equal access for students with disabilities through providing academic accommodations and auxiliary aids in accordance with federal laws and university policy.

USC Campus Support and Intervention - (213) 821-4710
campussupport.usc.edu

Assists students and families in resolving complex personal, financial, and academic issues adversely affecting their success as a student.

Diversity, Equity and Inclusion - (213) 740-2101
diversity.usc.edu

Information on events, programs and training, the Provost's Diversity and Inclusion Council, Diversity Liaisons for each academic school, chronology, participation, and various resources for students.

USC Emergency - UPC: (213) 740-4321, HSC: (323) 442-1000 – 24/7 on call
dps.usc.edu, emergency.usc.edu

Emergency assistance and avenue to report a crime. Latest updates regarding safety, including ways in which instruction will be continued if an officially declared emergency makes travel to campus infeasible.

USC Department of Public Safety - UPC: (213) 740-6000, HSC: (323) 442-120 – 24/7 on call
dps.usc.edu

Non-emergency assistance or information.

Office of the Ombuds - (213) 821-9556 (UPC) / (323-442-0382 (HSC)
ombuds.usc.edu

A safe and confidential place to share your USC-related issues with a University Ombuds who will work with you to explore options or paths to manage your concern.

Occupational Therapy Faculty Practice - (323) 442-3340 or otfp@med.usc.edu
chan.usc.edu/otfp

Confidential Lifestyle Redesign services for USC students to support health promoting habits and routines that enhance quality of life and academic performance.