GastroPlus as an Educational Tool: Teaching Pharmacokinetics with University+

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SimulationsPlus MIDD+ Model Informed Drug Development + 2023

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Background

Drug disposition is increasingly studied using physiologically based pharmacokinetic (PBPK) modeling in both industry and academia

Students are interested in learning PBPK modeling, but this requires an in-depth understanding of biopharmaceutics and pharmacokinetics

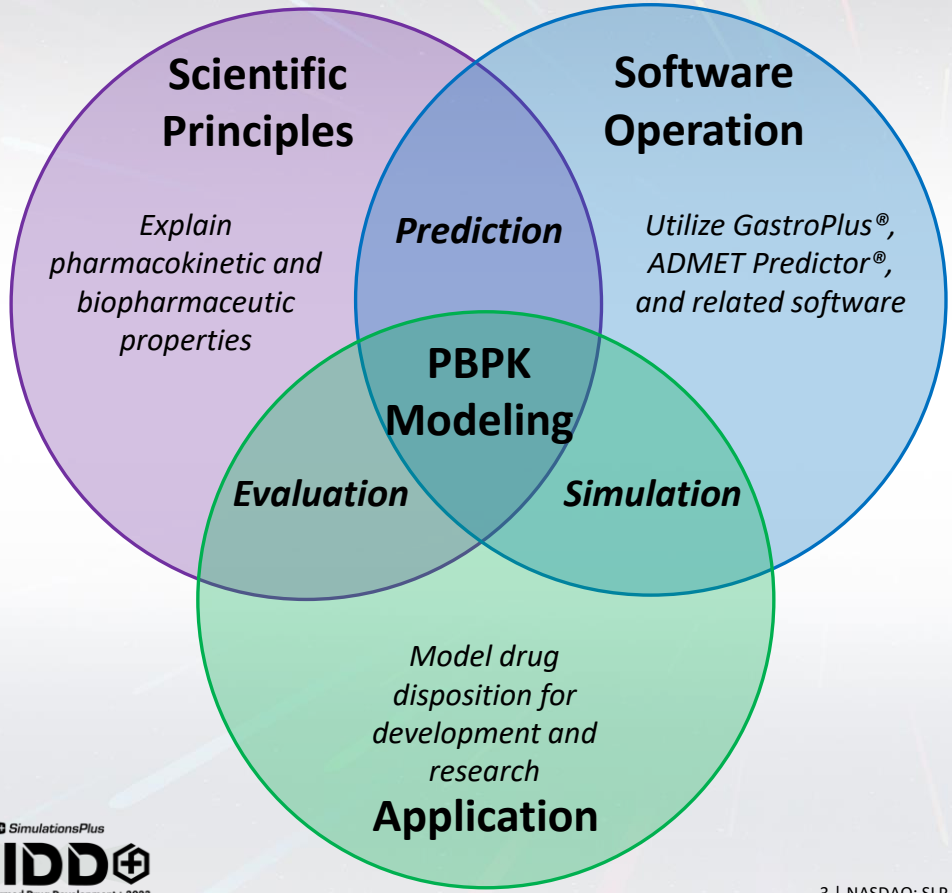
Understanding of pharmacokinetics and biopharmaceutics may be increased using teaching aids that provide practical application

Challenges:

Teaching interdependent scientific principles and software operation in parallel

Producing a course design and template that is transferrable to other teaching settings

Course Template: Principles of Course Design



Prediction: Understand scientific principles, and use software to generate parameter values that can be interpreted based on these principles

Simulation: Use software to simulate pharmacokinetic processes, based on an understanding of model building

Evaluation: Develop hypotheses for testing in a model application, based on understanding of scientific principles

PBPK Modeling: Combine all of the above to reach conclusions on drug disposition in a patient population

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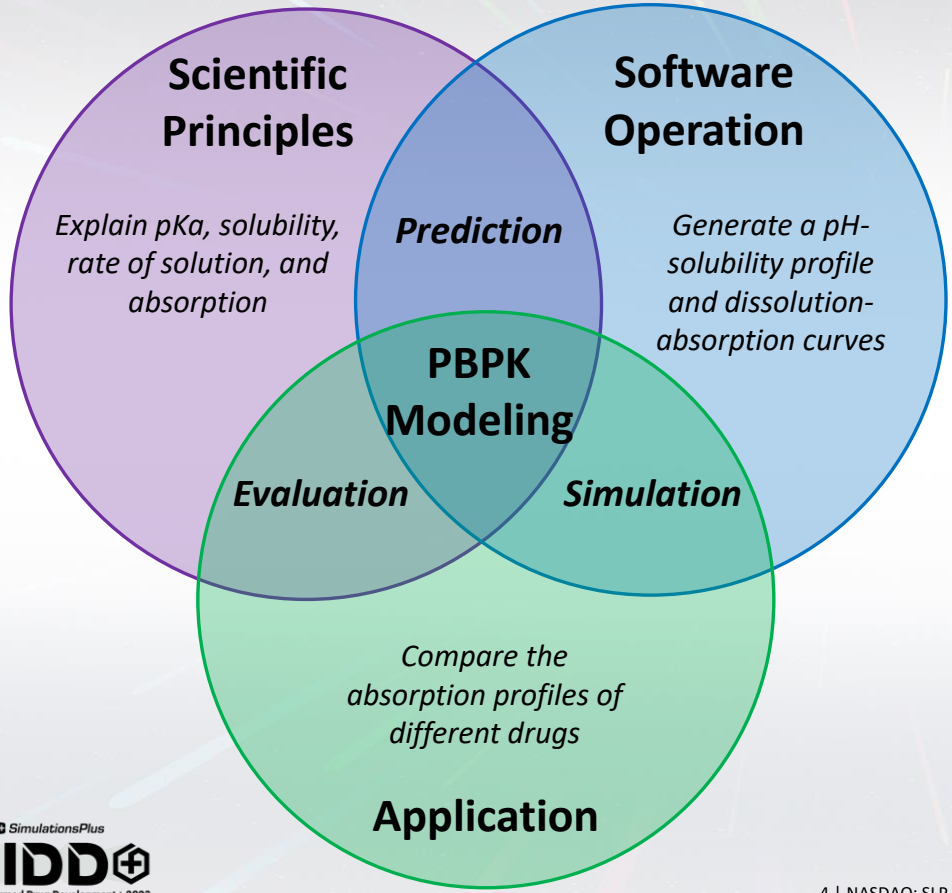
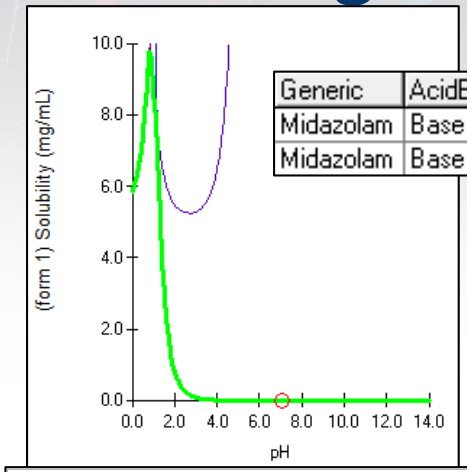
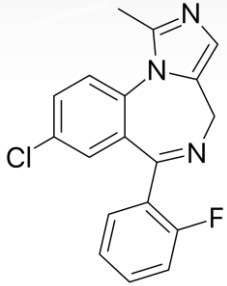
Course Template: An Example of Design



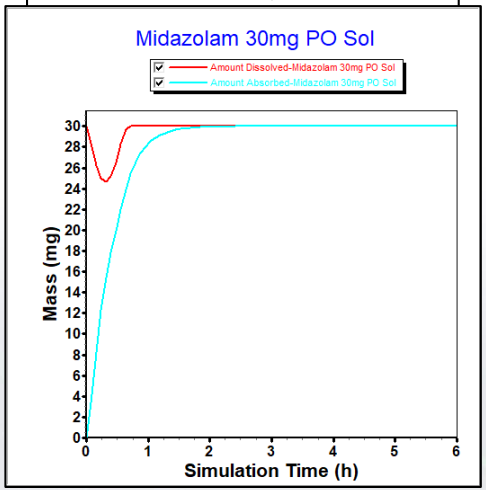


Generic	AcidBase	pKa	SolFactor
Midazolam	Base	4.57	2488.51
Midazolam	Base	0.84	2488.51

Data from ADMET Predictor



Midazolam



Course Template: Overview

Part	Science	Software	Project
I	Biopharmaceutics Compartmental Pharmacokinetics	Drug Properties (ADMET Predictor) Oral Absorption Model Compartmental model fitting (PK+)	Model Building
II	Physiologically Based Pharmacokinetics Metabolism and Transport	Whole Body PK models Enzyme and Transporter Kinetics	
III	Hypothesis Generation and Testing in Drug Development	Modeling Clinical Scenarios Analyzing Model Outputs	Model Application

Assessment: Pre- and post-course quiz to measure student understanding of physicochemical, biopharmaceutic, and pharmacokinetic principles

Current Implementation:
Semester-long (15 week) elective for MS, PhD, and PharmD Students

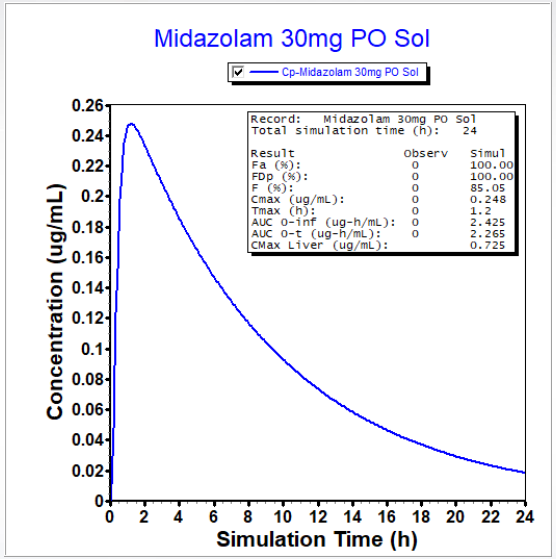
Course Template: Part I

Session	Topic	Didactic Science	GastroPlus Activity	Science Learning Objective	Software Learning Objective
1	Introduction	Principles of modeling and of pharmacokinetics (PK)	Search literature for data on drug	1. Describe the PK processes a drug undergoes in the body	1. Explain the principles of compartmental and PBPK modeling
2	Cheminformatics predictions	Advantages and limitations of predictions Parameterization of models	Use ADMET Predictor to predict physicochemical, biopharmaceutic, and pharmacokinetic properties	2. Explain how different chemical features relate to the physicochemical properties of a drug	2. Describe how PK models are parameterized using physicochemical properties & *in vitro d*ata
3	Dissolution and absorption	Relationships among pKa, ionization, solubility, LogD, and permeability and gut physiology	Describe dissolution-absorption profiles in terms of pKa, solubility, and permeability	3. Relate the physicochemical and biopharmaceutical properties of a drug to biological processes to explain dissolution and absorption, distribution, and clearance	3. Use predicted and experimental data to create a pharmacokinetic model for a drug (create initial model)
4	Compartmental pharmacokinetics	Concepts, strengths, and limitations of compartmental models	Fit compartmental PK parameters to observed Cp-time data		
5	Midpoint presentation	Description of molecular properties and implementation in model	Demonstration of effects of properties on PK, assessment of model		

Compartmental Pharmacokinetics

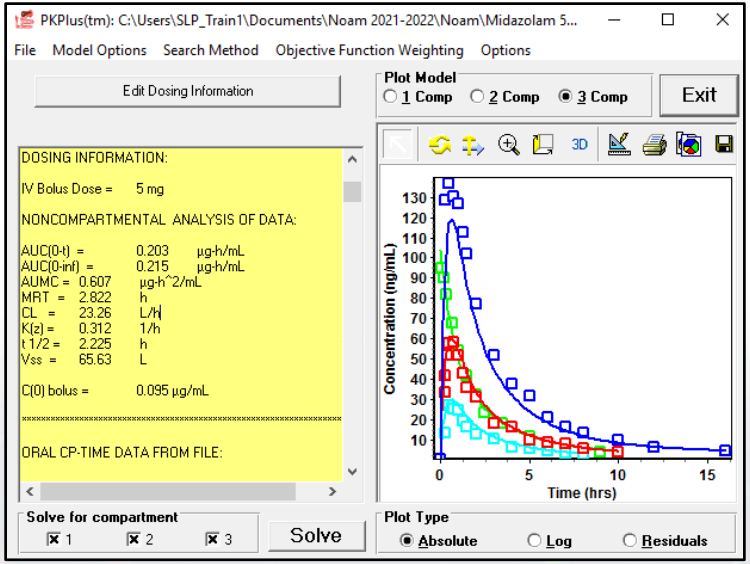
What is the relationship between absorption, distribution, and clearance?

1 Compartment

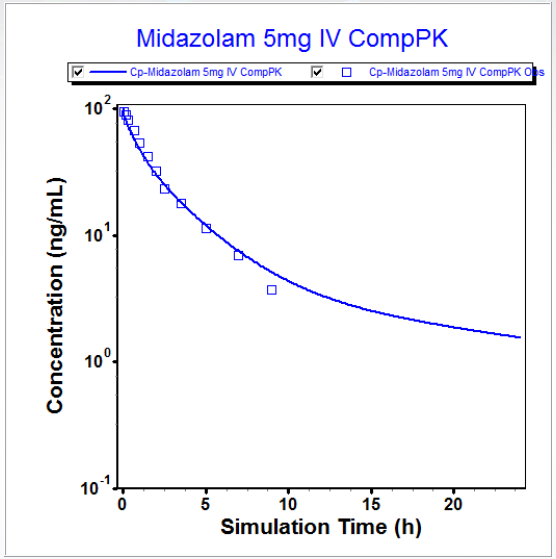


CL (L/h):	10.52	or (L/h/kg):	0
		Vc (L/kg):	1.27
		T 1/2 (h):	5.86
K12 (1/h):	0	K13 (1/h):	0
K21 (1/h):	0	K31 (1/h):	0
V2 (L/kg):	0	V3 (L/kg):	0

Fitting with PKPlus™



3 Compartment



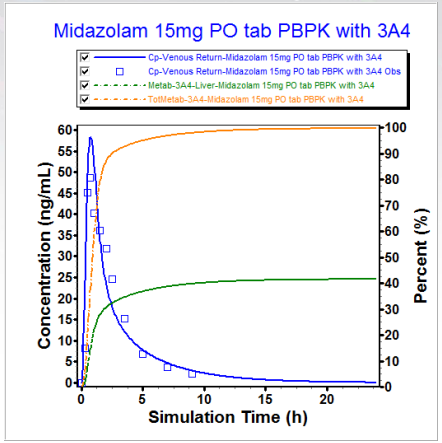
CL (L/h):	0	or (L/h/kg):	0.26454
		Vc (L/kg):	0.6936
		T 1/2 (h):	16.59
K12 (1/h):	0.32843	K13 (1/h):	0.1583
K21 (1/h):	0.8857	K31 (1/h):	0.06224
V2 (L/kg):	0.2572	V3 (L/kg):	1.7641

Course Template: Part II

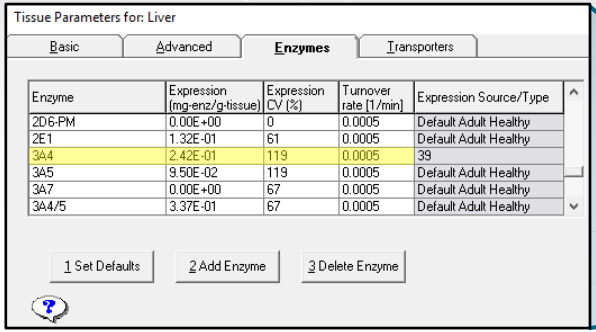
Session	Topic	Didactic Science	GastroPlus Activity	Science Learning Objective	Software Learning Objective
6, 7	PBPK models	Molecular and tissue properties affecting distribution	Create a PBPK model, compare to compartmental model	4. Characterize the contributions of drug-solvent, -lipid, and -protein interactions, and enzyme and transporter kinetics, to a drug's pharmacokinetics and biopharmaceutics	4. Compare and contrast inputs and outputs of different pharmacokinetic models and refine a model using observed data (improve model)
8, 9	Metabolism and transport	Enzyme and transporter kinetics	Incorporate nonlinear processes in model		
10	Model refinement	Model sensitivities and limitations	Refine model using observed data	5. Determine how chemical changes in the structure or formulation of a drug, or in the composition of body tissues, are expected to have an impact on pharmacokinetics	5. Use a PBPK model to evaluate how the features of a drug, a formulation, or a tissue have an impact on pharmacokinetics

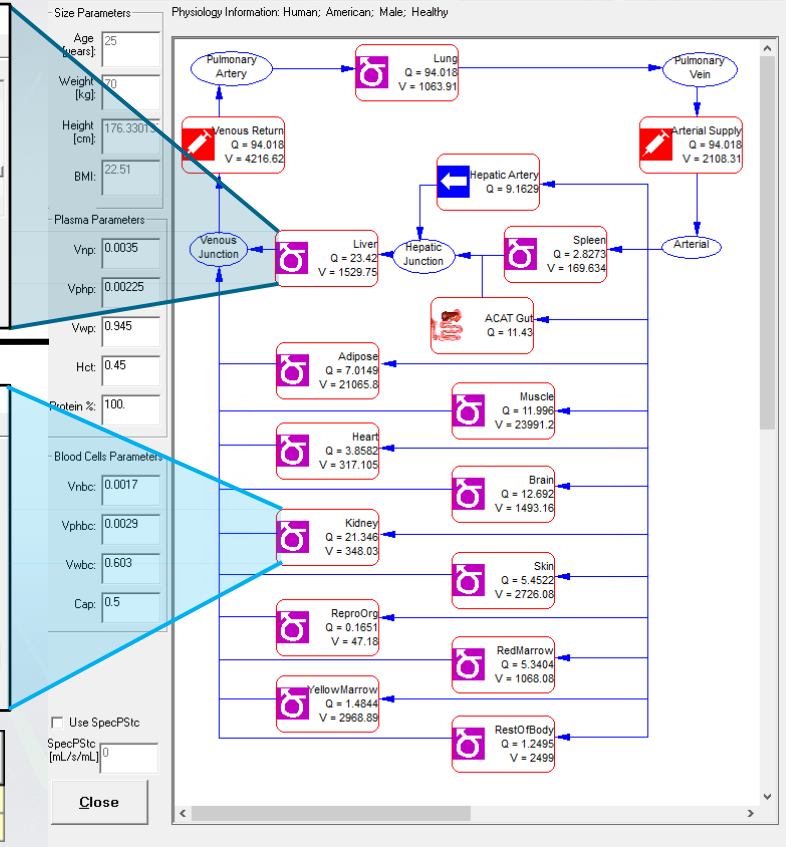
Metabolism & Transport

Generic	Enzyme	Location	Vmax (mg/s) or (mg/s/mg-enz)	Km (mg/L)
Midazolam	3A4	Gut	0.4	0.977
Midazolam	3A4	PBPK	0.000884	0.977

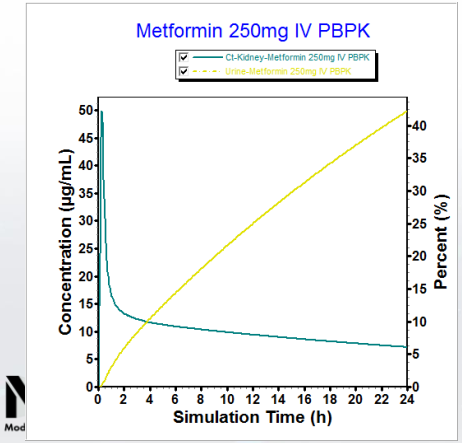


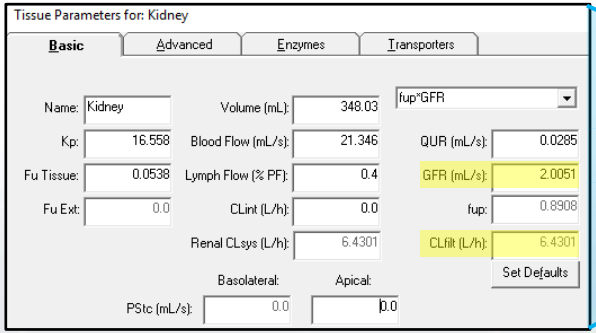
Midazolam





Metformin





Transporter	Type	Location	Vmax (mg/s) or (mg/s/mg-trans)	Km (mg/L)
MATE1	Efflux	PBPK	0.000467	27.39
OCT2	Influx	PBPK	0.000373	113.9

Course Template: Part III

Session	Topic	Didactic Science	GastroPlus Activity	Application Learning Objective
11	Research questions	Hypotheses on effects chemical, formulation, or physiological changes	Model setup for hypothesis testing	1. Define a research question and devise a corresponding modeling approach
12, 13	Prospective predictions	Pharmacokinetic changes	Run simulations to predict pharmacokinetics	2. Translate the approach into a PBPK model 3. Compare results of multiple models to test the hypothesis
14	Results interpretation	Underlying mechanisms and real-world significance	Interpret results to identify underlying mechanisms and judge significance of changes	4. Evaluate the significance of modeling results with regards to drug synthesis, formulation, manufacturing, or clinical application
15	Final presentation	Describe approach and discuss hypothesis testing	Use model to justify conclusions	5. Use a PBPK model to make and present prospective predictions of drug behavior with new formulations, dose regimens, and populations

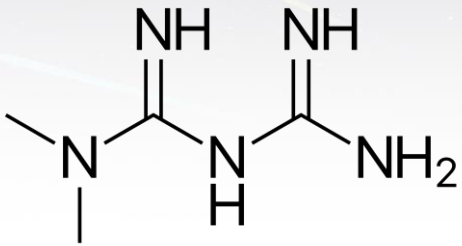
Course Template: Prompts for the Project

Prompt stem		[X]	
1.	Is your drug expected to be safe and effective in a special population of [X] patients:	A. B. C. D. E.	Elderly Pediatric Pregnant Renally impaired Pharmacogenetically diverse
2.	How would your drug's ADME be affected by changes in [X]:	A. B. C. D. E.	Formulation type Manufacturing processes Dose/dose schedule Food coadministration Enzyme/transporter inhibition

Drug	Prompts Chosen
Metformin	1D. **Is your drug expected to be safe and effective in a special population of renally impaired patients?** 1E. Is your drug expected to be safe and effective in a special population of MATE1 and/or OCT2 variant patients? 2C. How would your drug's ADME be affected by changes in dosing schedule (qDay vs BID vs TID)?
Ibuprofen	1B. Is your drug expected to be safe and effective in a special population of pediatric patients? 1E. **Is your drug expected to be safe and effective in a special population of CYP2C9 variant patients?** 2A. How would your drug's ADME be affected by changes in formulation type (tablet vs solution)? 2D. How would your drug's ADME be affected by changes in food coadministration (fasted vs fed)?

- How do we setup a patient physiology?
- How do we try different dosing regimens?
- What results are we looking for?
- How do we assess safety and efficacy?

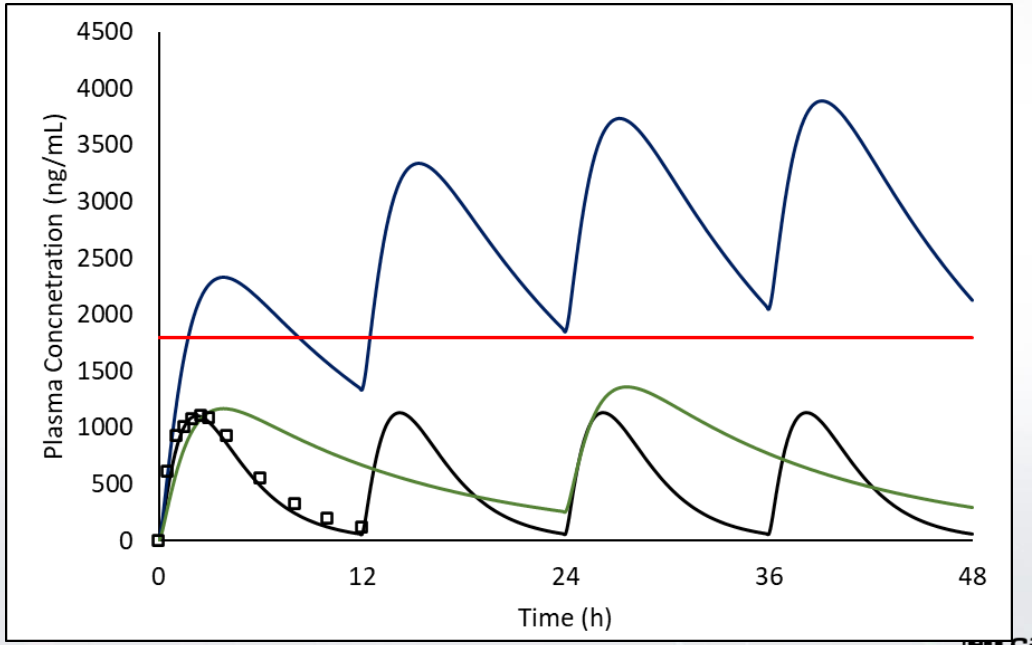
Metformin



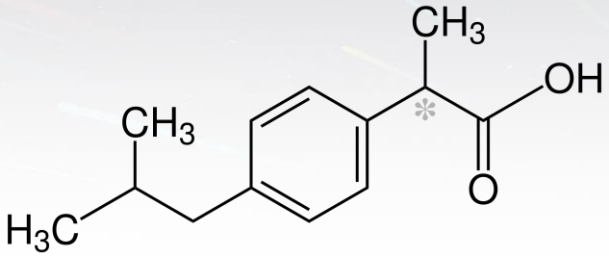
Drug Properties
- Low MW
- Hydrophilic
- Cationic
- Low protein binding
- Kidney transporter substrate

Is your drug expected to be safe and effective in a special population of renally impaired patients?

Physiologic Properties
- Decreased renal blood flow and GFR



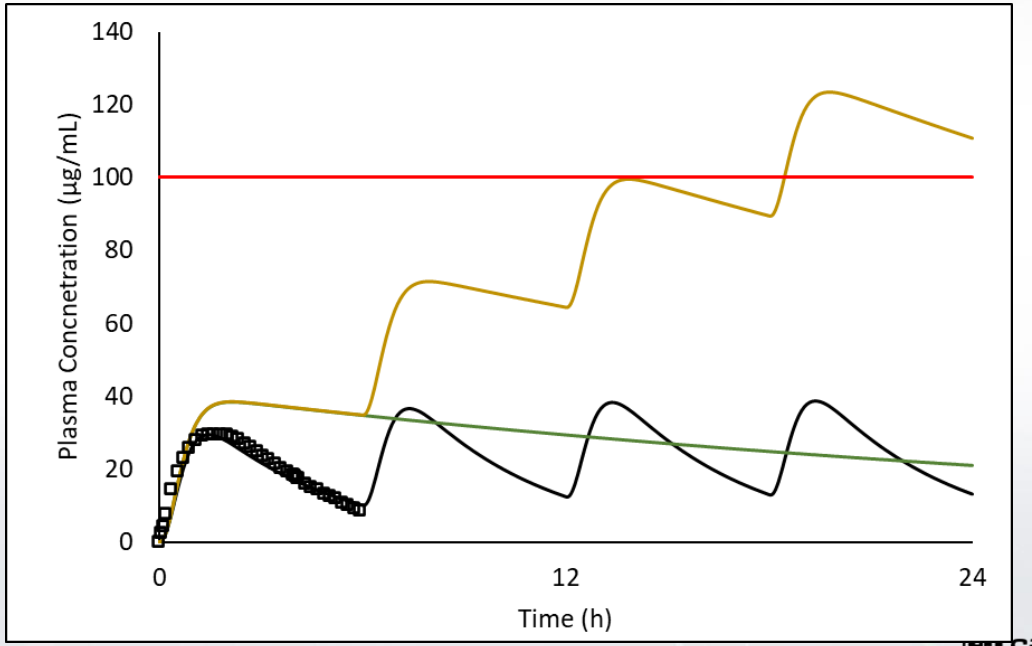
Ibuprofen



Is your drug expected to be safe and effective in a special population of CYP2C9 variant patients?

Physiologic Properties
- Decreased enzyme expression and/or activity

Drug Properties
- Highly protein bound
- Lipophilic
- Multiple enzymes
  - Major CYP2C9 contribution
- Variable dosing



Course Template: Pre-Post Assessment

Questions (Physicochemical, Biopharmaceutics, Pharmacokinetics)

1. What is the molecular basis for [drug] having a logP of [logP Value]?
2. Is [drug] ionizable? If so, is it an acid or a base? Justify your reasoning.
3. Where in the gastrointestinal tract does [drug] have the highest solubility and why?
4. What is the most likely mechanism of absorption for [drug], why do you reach this conclusion based on the molecular properties, and what is the charge of the species that crosses the gut wall?
5. What relationship do solubility and permeability have with the bioavailability of [drug]?
6. Based on the molecular properties of [drug], why is the F_{up} [F_{up} value]? What is the effect of [drug]'s F_{up} on volume of distribution and clearance?
7. What is the relationship between the pKa and LogP of [drug] and its distribution into [adipose/muscle] tissue, based on the nature of this tissue?
8. Will [drug] to be cleared primarily by the liver, the kidney, or both? Will [drug] be cleared mainly as the parent compound or as a metabolite?
9. What relationship do AUC and C_{max} have with dose, and why?
10. What are the differences in C_{max} and AUC profiles between a [dose/formulation 1] and a [dose/formulation 2], and what are possible reasons for any differences or lack thereof?
11. What is the effect of food on the pharmacokinetics of [drug] as compared to fasting conditions, and what is a likely explanation?
12. What is the reason for the effect of [interacting gene/interacting agent] on [drug] exposure, where in the body does this effect occur, and how does a comparison with other Cp-time data support your answer?

Data

Midazolam

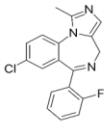


Table 1. Molecular properties of midazolam

MW (g/mol)	325.78
LogP	2.7
Permeability (10^{-4} cm/s)	4.57
pKa	6.04
Fup (Fraction unbound plasma)	4.4%
CYP3A4 Km (μM)	3.0
CYP3A4 Vmax (nmol/min/mg)	1.035

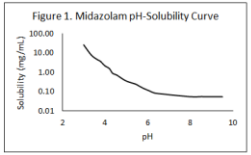


Figure 1. Aqueous solubility of midazolam across a range of pH values.

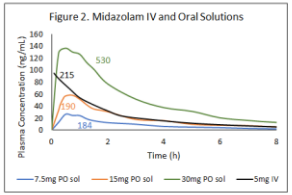


Figure 2. Plasma concentration-time profiles of midazolam after different doses of oral solution (PO) or intravenous formulation (IV). AUCs of each dose are provided next to the respective curve. Oral doses were given in fasted state.

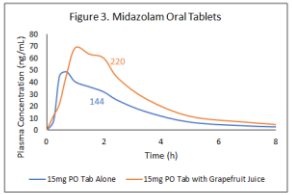


Figure 3. Plasma concentration-time profiles of midazolam after single oral administration of 15mg tablets alone (fasting) or in combination with grapefruit juice (otherwise fasting). AUCs of each dose are provided next to the respective curve.

Table 2. Effect of Food on Midazolam Pharmacokinetics

Cmax (ng/mL)	35.7
Tmax (h)	1.98
AUC (ng*h/mL)	177

Table 2. Pharmacokinetic parameters of midazolam for administration of a 15mg oral tablet one hour after a meal.

Process

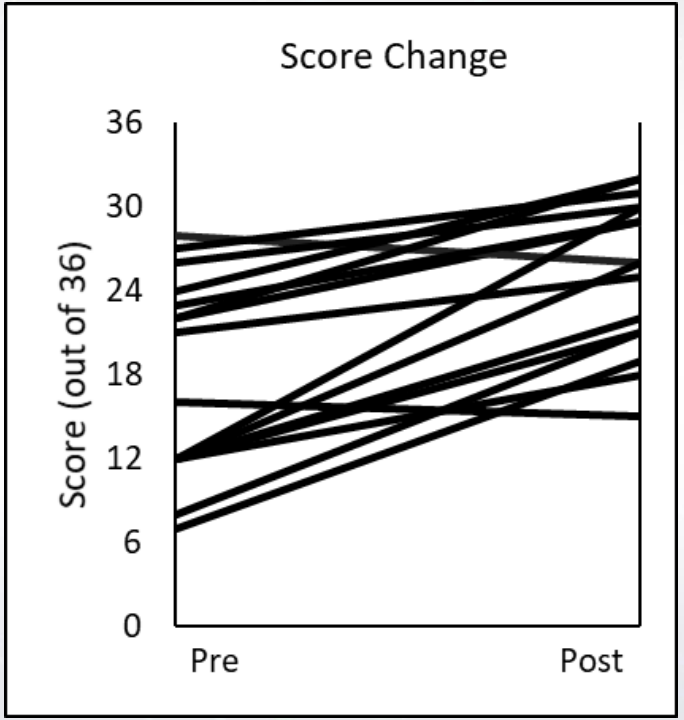
- Low stakes test: required and the students were asked to give their best answers, but the results were not used for grades
- Before the course: one hour (Midazolam)
- After the course: one hour (Loratidine)
- The pre- and post- questions are identical, but the drug is different
- Assessment focused on data interpretation in three sections: physicochemical, biopharmaceutics, pharmacokinetics
- Answers were free responses of one or two sentences
- Each question is worth three points: 1 – identify, 2 – describe, 3 - explain (a detailed rubric was used for grading)
- Each section worth 12 points, total possible score is 36 points

Results of the Pre-Post Assessment

Population Average

Section	Pre mean (range)	Post mean (range)	Mean Change (%)
Physicochemical	7.7 (1-12)	9.8 (5-11)	+2.1 (27.2%)
Biopharmaceutics	5.5 (2-10)	8.2 (4-12)	+2.7 (49.1%)
Pharmacokinetics	4.8 (0-10)	7.6 (4-11)	+2.8 (58.3%)
Total	18.0 (7-28)	25.6 (15-32)	+7.6 (42.2%)

Individual Differences



n=17 students

Conclusions

Use of GastroPlus through University+ as a teaching tool permits hands-on, practical application in a classroom setting

Active learning with GastroPlus promotes understanding of physicochemical properties, biopharmaceutics, and pharmacokinetics

By teaching scientific principles and software in parallel, students can start to utilize GastroPlus with an understanding of clinical and scientific context

The course template should assist instructors in teaching of this material

SimulationsPlus

MIDD+

Model Informed Drug Development + 2023

Q&A

Questions & Answers

Frequently Asked Questions

1) What have you learned after teaching this course multiple times?

2) What is the time commitment involved in this course?

3) How can I get more information about creating a course like this at my institution

More Information

University+:
simulations-plus.com/software/slp-university-program/

Simulations Plus:
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USC:
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Photo of the Month

RETURN TO CAMPUS: Students attend an in-person class outside of PSC, Tuesday, January 25. (Photo by Andrea Diaz).