Incorporating Mechanistic Modeling & Simulation to Assist with Formulation Development and Regulatory Evaluations

Viera Lukacova

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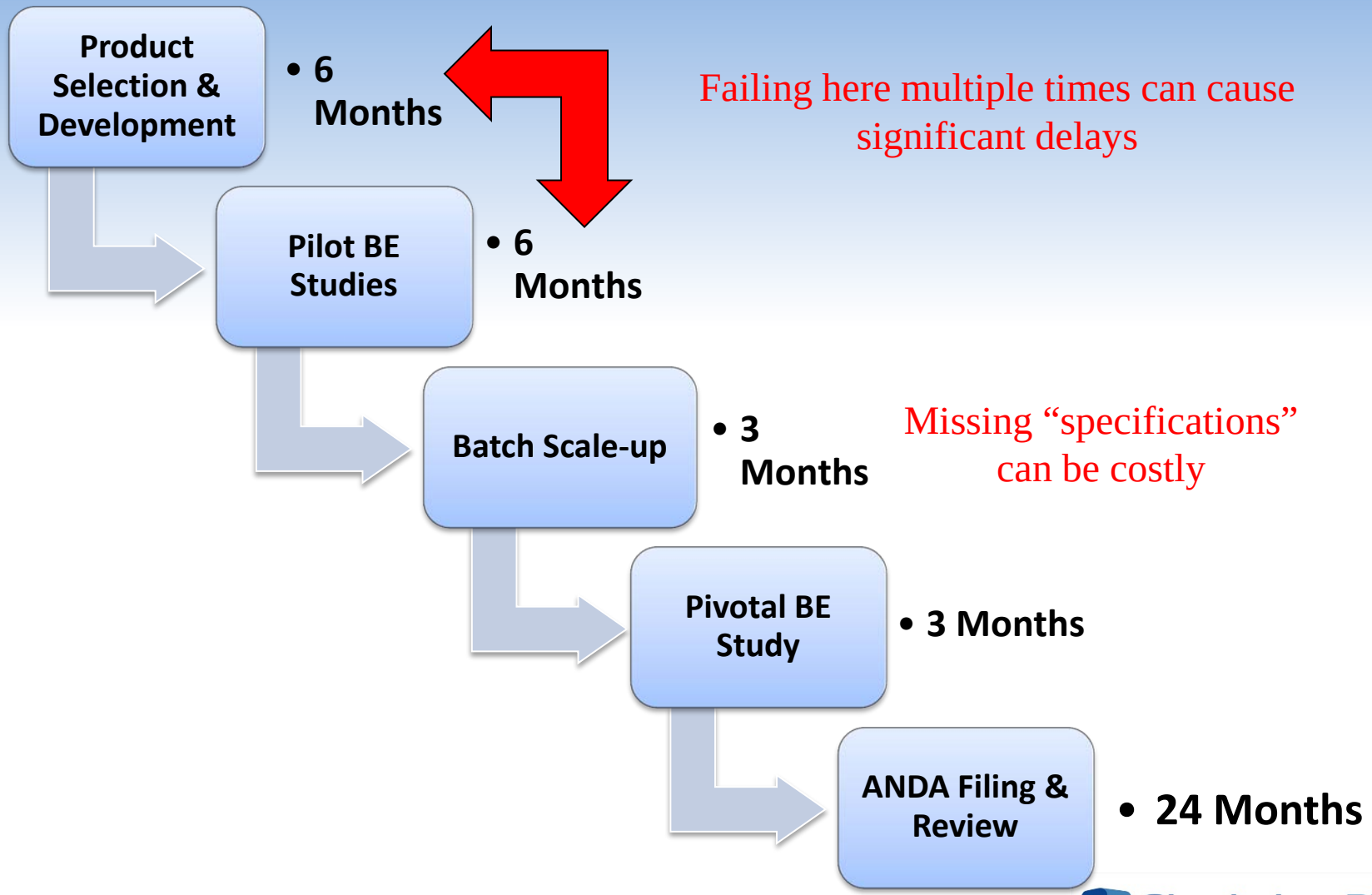
The Generic Product Development Process



Outline

- Why Modeling & Simulation?
- Overview of Mechanistic Simulation Models
  - Predicting *in vivo* absorption & PK
- Applications in Generic Product Development
  - Generating IVIVCs
  - Performing virtual bioequivalence trials and establishing dissolution specifications
  - Understanding food effects
- A successful biowaiver case study
- Conclusions

How can simulation software be used?

- Dissolution Method Development
  - Which *in vitro* method best correlates with an *in vivo* profile?
- Formulation Design
  - How do I design my formulation to achieve bioequivalence?
- Establish Dissolution Specifications
  - What is the acceptable variability in key parameters before we are no longer bioequivalent?

Flow Diagram for Simulation Studies

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Research Article

Utility of Physiologically Based Absorption Modeling in Implementing Quality by Design in Drug Development

Xinyuan Zhang,[1] Robert A. Lionberger,[1,2] Barbara M. Davit,[1] and Lawrence X. Yu[1]

Received 16 September 2010; accepted 14 December 2010; published online 5 January 2011

Abstract. To implement Quality by Design (QbD) in drug development, scientists need tools that link drug products properties to *in vivo* performance. Physiologically based absorption models are potentially useful tools; yet, their utility of QbD implementation has not been discussed or explored much in the literature. We simulated pharmacokinetics (PK) of carbamazepine (CBZ) after administration of four oral formulations, immediate-release (IR) suspension, IR tablet, extended-release (XR) tablet and capsule, under fasted and fed conditions and presented a general diagram of a modeling and simulation strategy integrated with pharmaceutical development. We obtained PK parameters and absorption scale factors (ASFs) by deconvolution of the PK data for IR suspension under fasted condition. The model was validated for other PK profiles of IR formulations and used to predict PK for XR formulations. We explored three key areas where a modeling and simulation approach impacts QbD. First, the model was used to help identify optimal *in vitro* dissolution conditions for XR formulations. Second, identification of critical formulations variables was illustrated by a parameter sensitivity analysis of mean particle radius for the IR tablet that showed a PK shift with decreased particle radius, C_{max} was increased and T_{max} was decreased. Finally, virtual trial simulations allowed incorporation of inter-subject variability in the model. Virtual bioequivalence studies performed for two test formulations suggested that an *in vitro* dissolution test may be a more sensitive discriminative method than *in vivo* PK studies. In summary, a well-validated predictive model is a potentially useful tool for QbD implementation in drug development.

KEY WORDS: advanced compartmental absorption and transit (ACAT) model; gastroplus™; modified release (MR); quality by design (QbD).

Flow Diagram for Simulation Studies

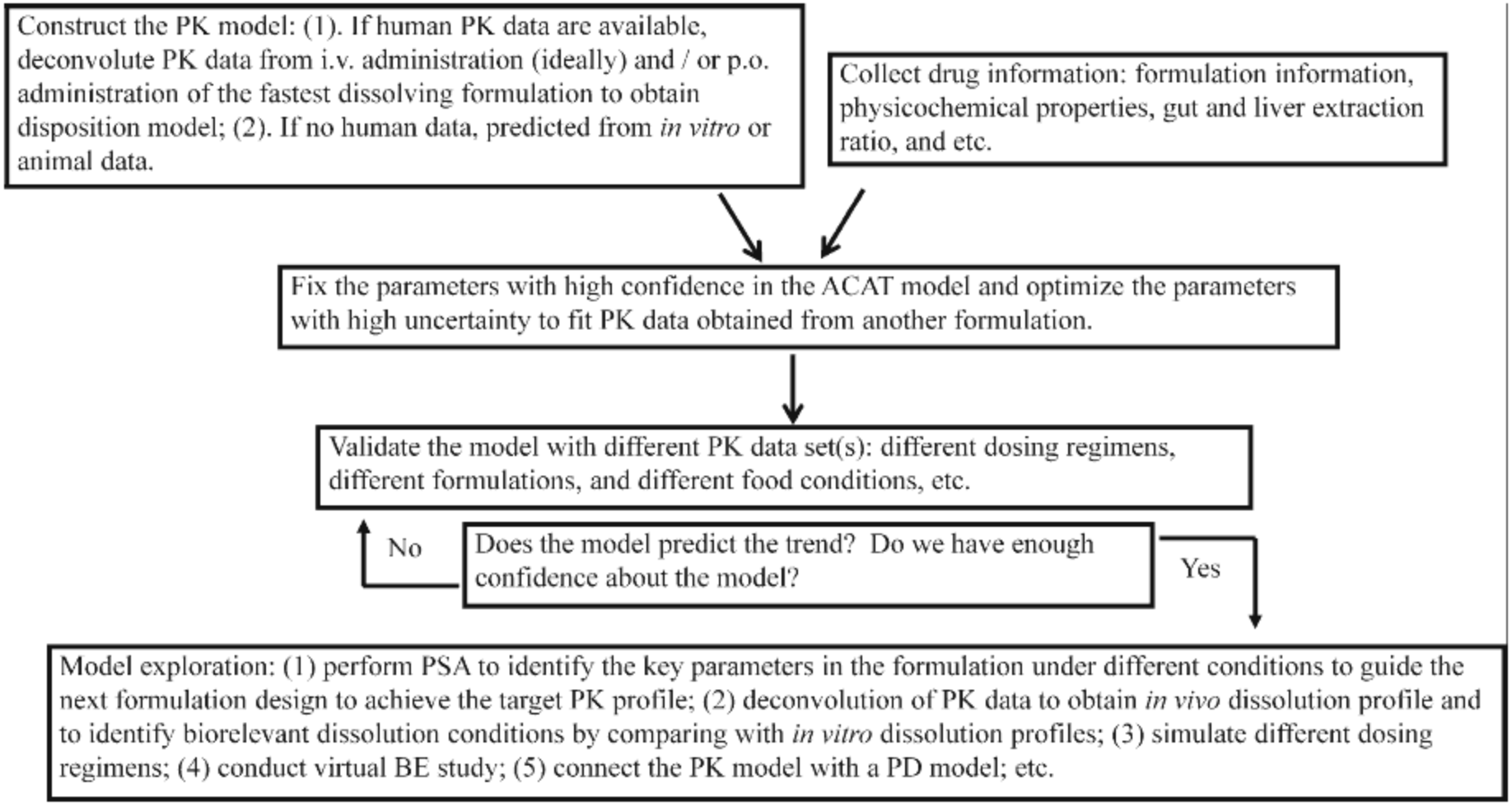
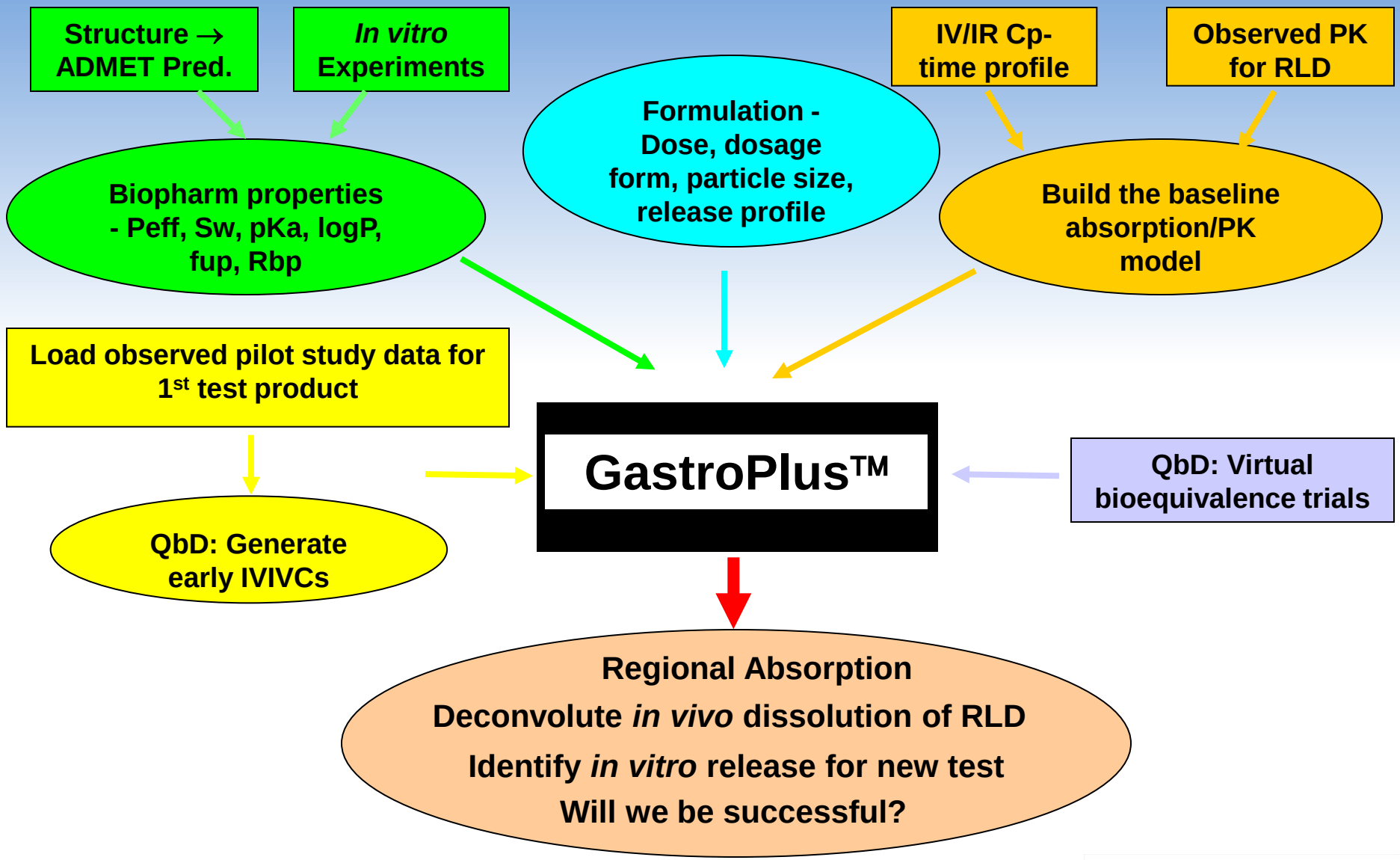


Fig. 1. The flow diagram shows a general process of using a physiologically based absorption model in QbD-based drug development

The Big Picture



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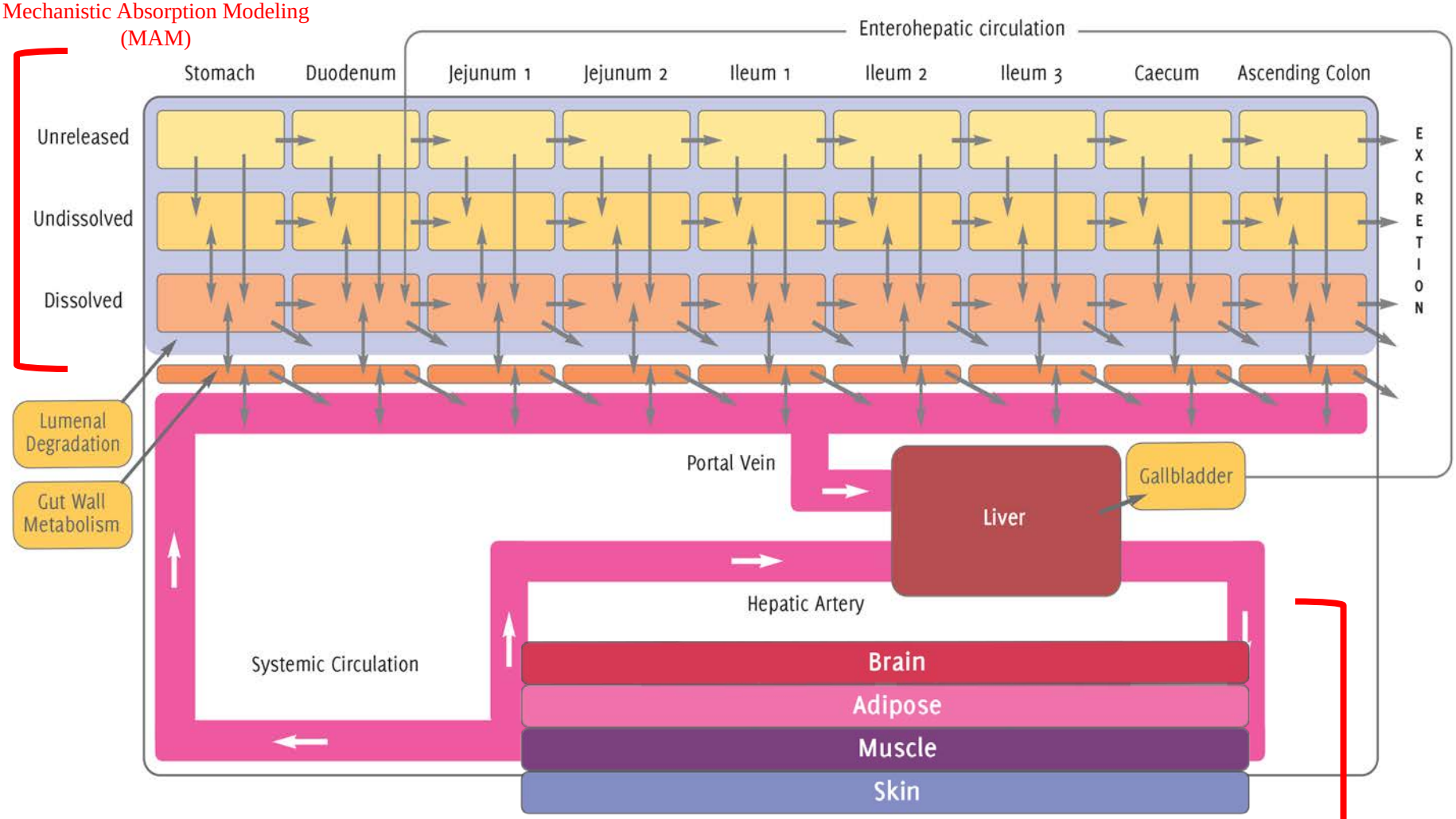
Advanced Compartmental Absorption and Transit Model (ACAT™)

Mechanistic Absorption Modeling (MAM)



Physiologically based Pharmacokinetics (PBPK)

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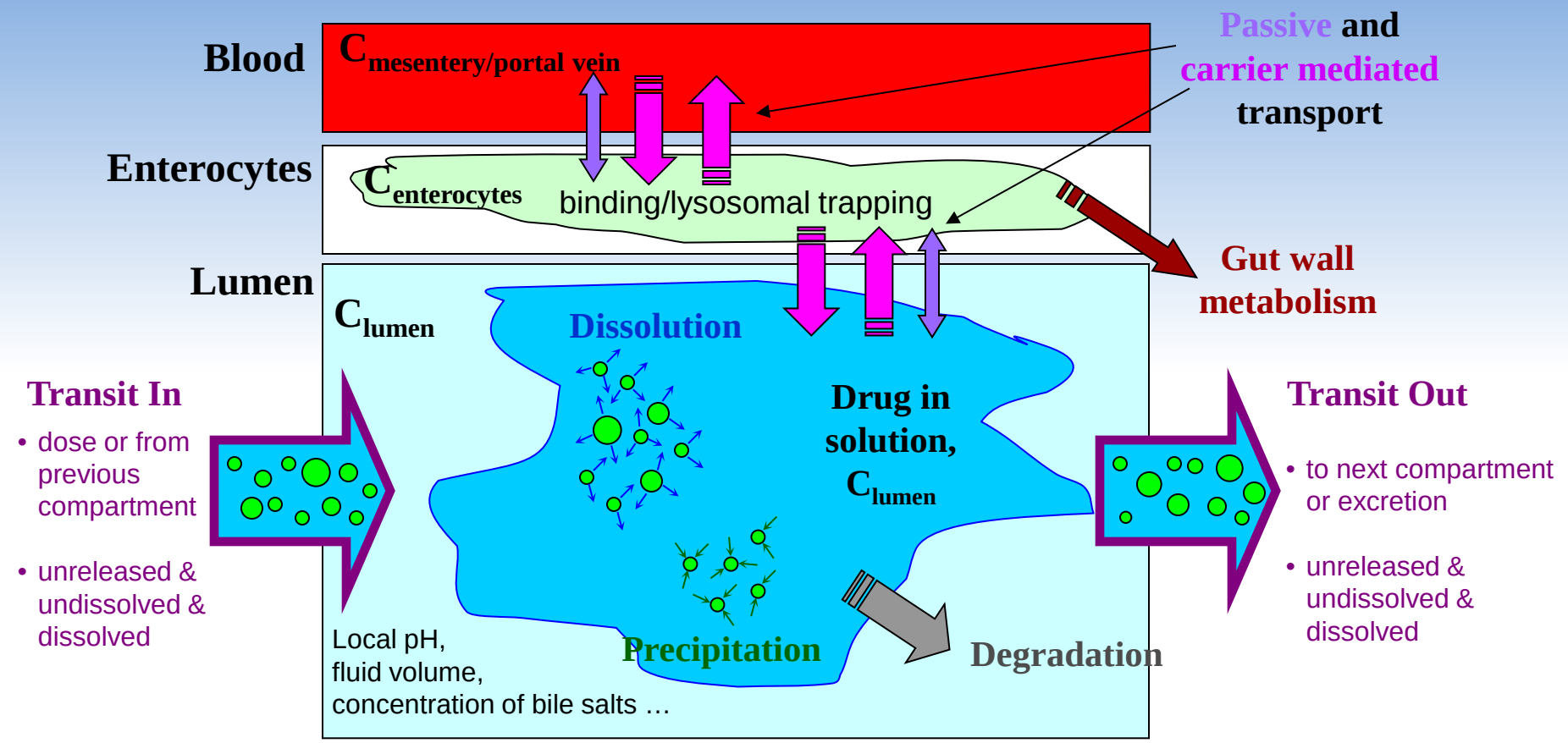
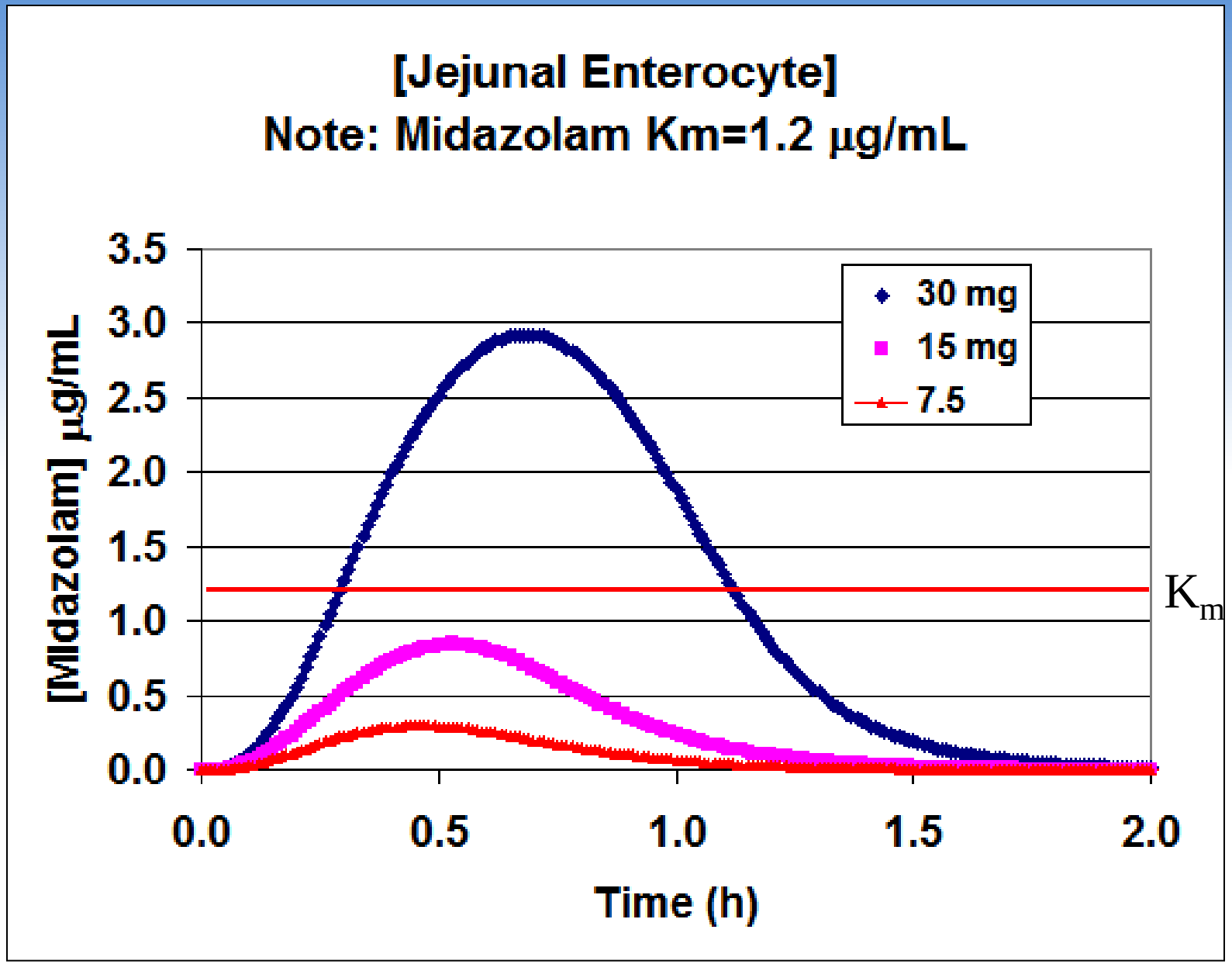
Processes Involved in Oral Absorption



These phenomena:

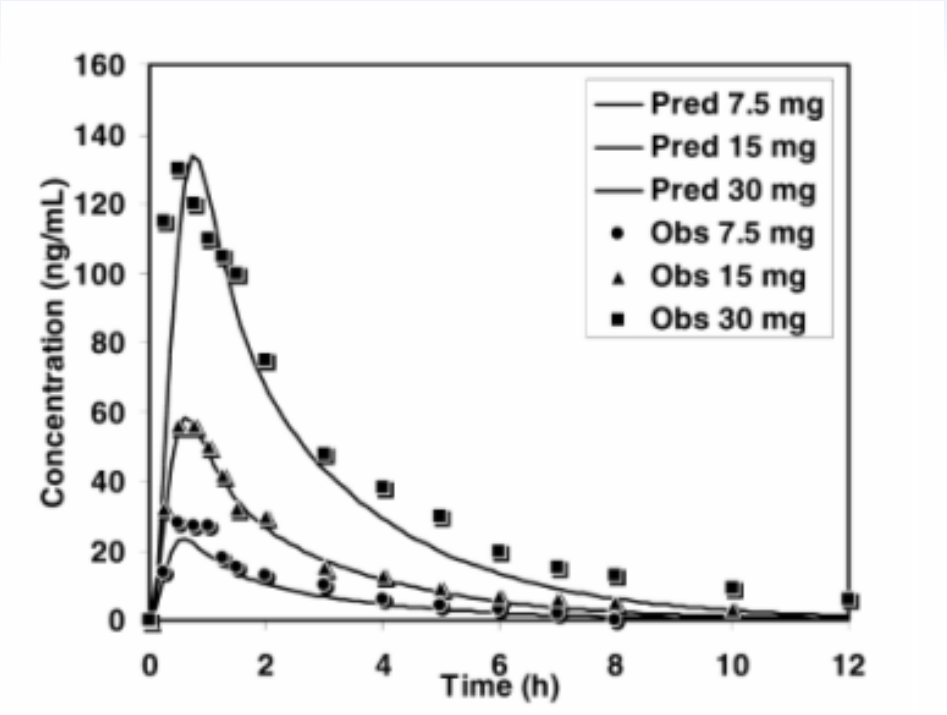
- **are happening simultaneously**
- **are repeated in each of the compartments of the gastrointestinal tract**



Nonlinear Dose Dependence of Midazolam Metabolism in Gut and Liver

Experimental			GastroPlus Compartmental Simulated				
Dose	Cmax	AUC	Cmax	AUC	Fa%	FDP%	Fb%
7.5	0.028	69	0.021	65	99	45	24
15	0.056	154	0.052	158	99	55	29
30	0.13	453	0.120	369	99	64	34

GastroPlus simulations of nonlinear dose dependence for midazolam using *in vitro* K_m and V_{max} and *iv* PK. (Agoram et al., 2001)



Observed nonlinear dose dependence for valacyclovir

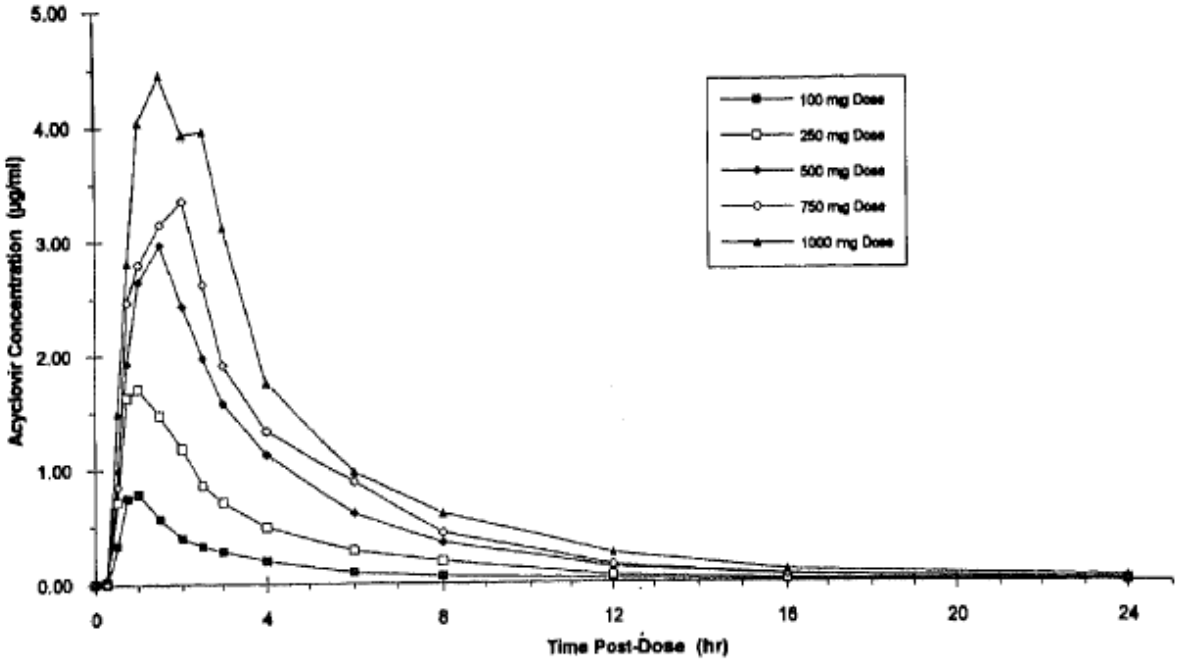


Fig. 1. Mean plasma acyclovir concentrations after single-dose administration of valaciclovir to normal volunteers. A single cohort of subjects received valaciclovir at each dose level ($n = 7$ except for the 100 mg dose, for which $n = 8$).

Weller, S. Clin. Pharm. Ther. 54(6):595 (1993)

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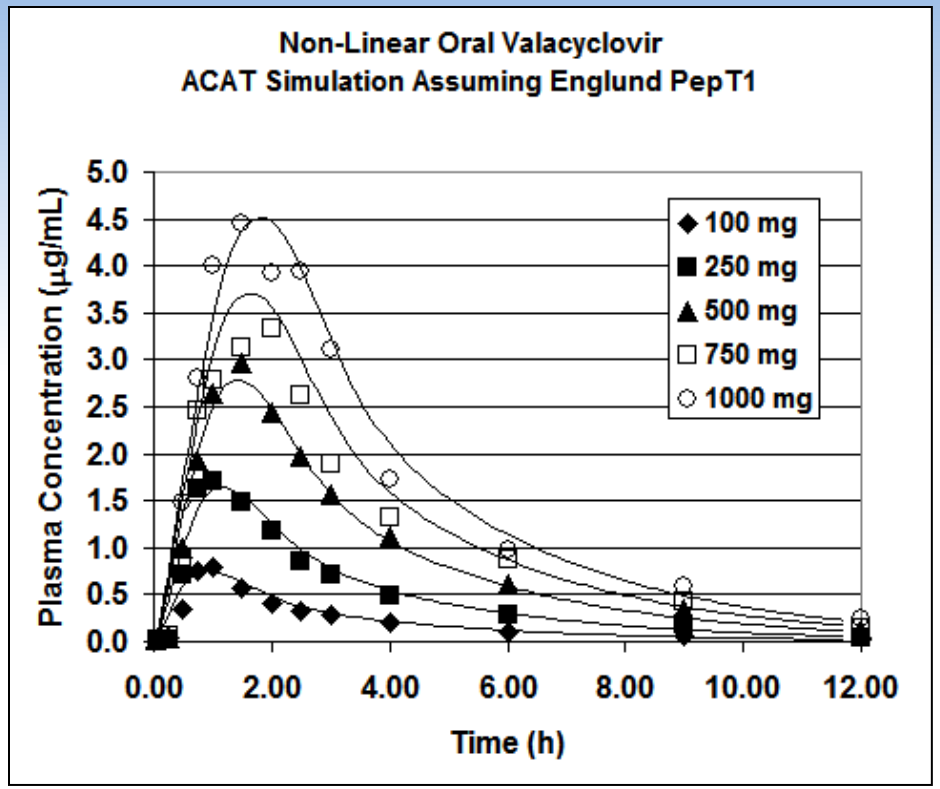
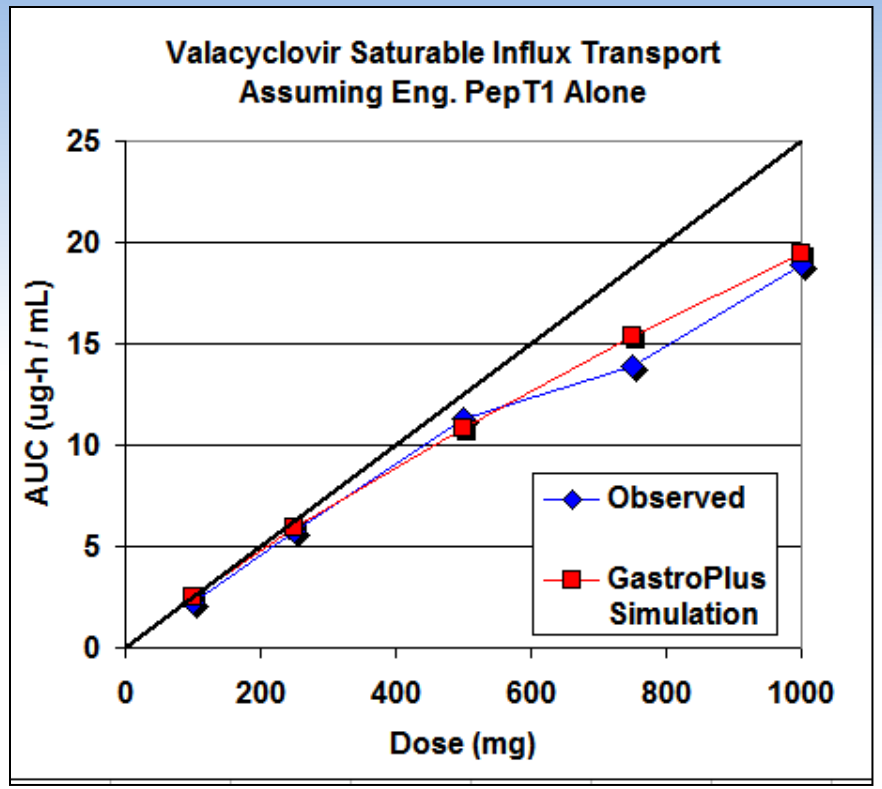
GastroPlus simulation of nonlinear dose dependence for influx transport of valacyclovir

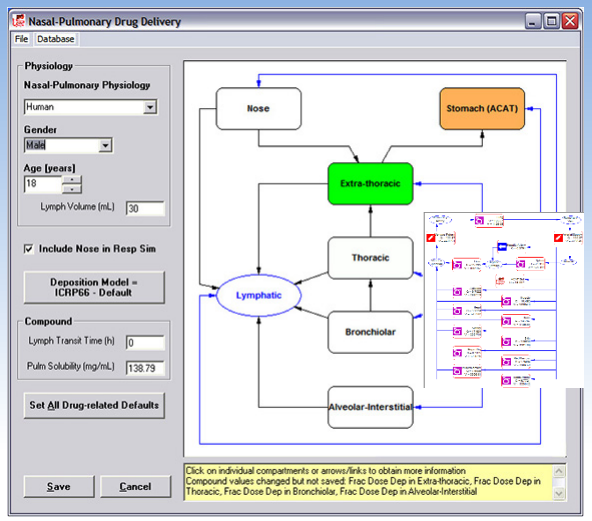




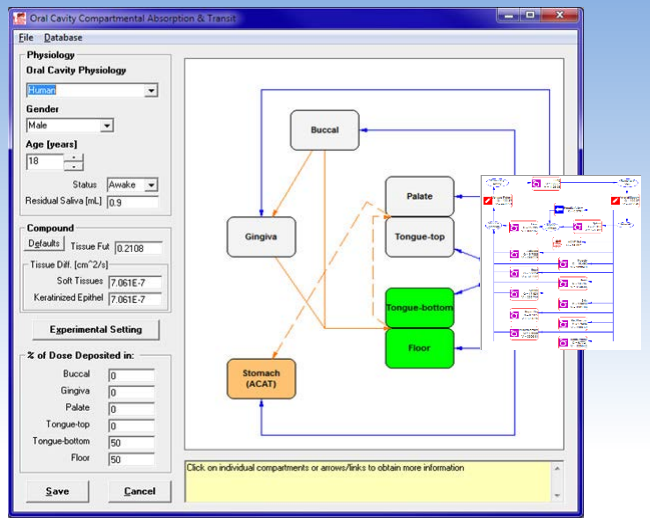
Bolger MB, et al. AAPS Journal 11(2):353 (2009)
GastroPlus results were first reported in Feb. 2003
at AAPS Drug Transport Workshop, Peachtree City, GA

QbD: Beyond mechanistic oral absorption

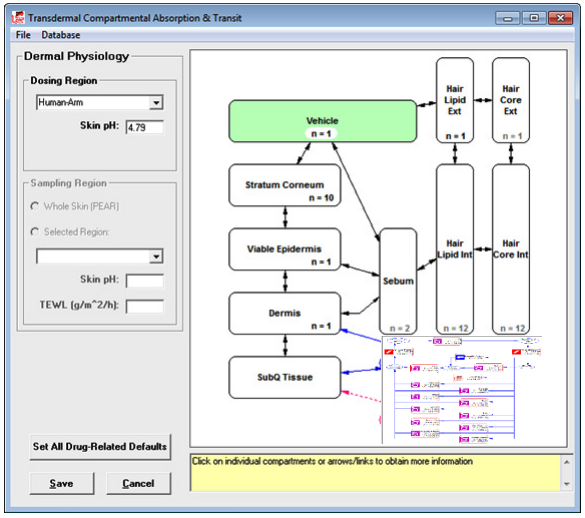
Pulmonary (PCAT™)



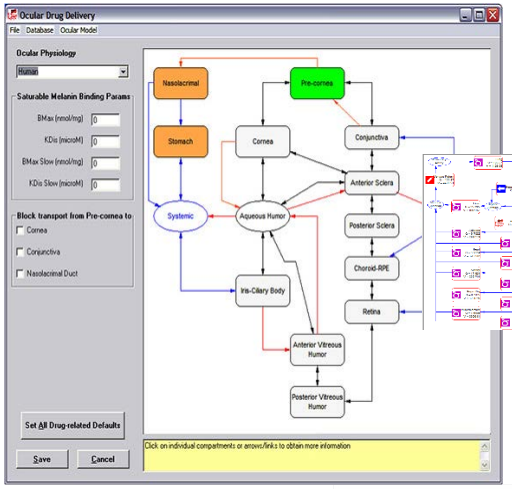
Oral Cavity (OCCAT™)



Dermal (TCAT™)



Ocular (OCAT™)



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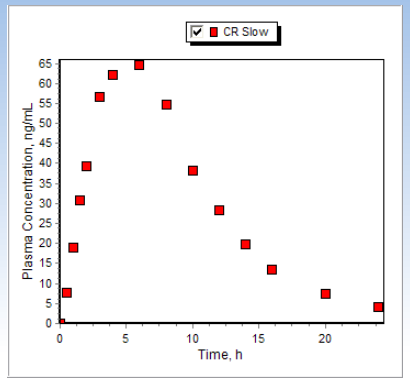
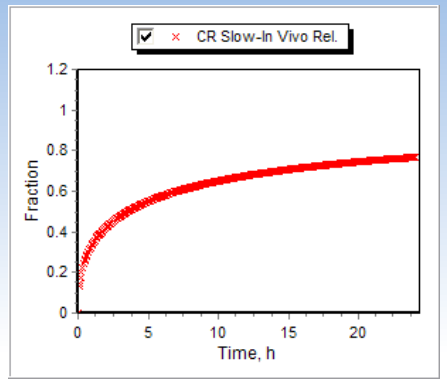
Developing a mechanistic in vitro-in vivo correlation (IVIVC)

Deconvolution (with GastroPlus™ Mechanistic Absorption method)



Deconvolution



in vivo dissolution vs. time along the gut– **NOT F%!**

- Inputs (in addition to the data required for the traditional methods):
  - Physiological parameters
  - Drug properties (solubility, Peff, logP, pKa, etc.)
- Outputs:

  A model that combines all available *in silico*, *in vitro* and *in vivo* information and provides:
  - *in vivo* dissolution, absorption and bioavailability vs. time profiles
  - Description of site dependent absorption
  - Description of tissue contributions to first pass extraction

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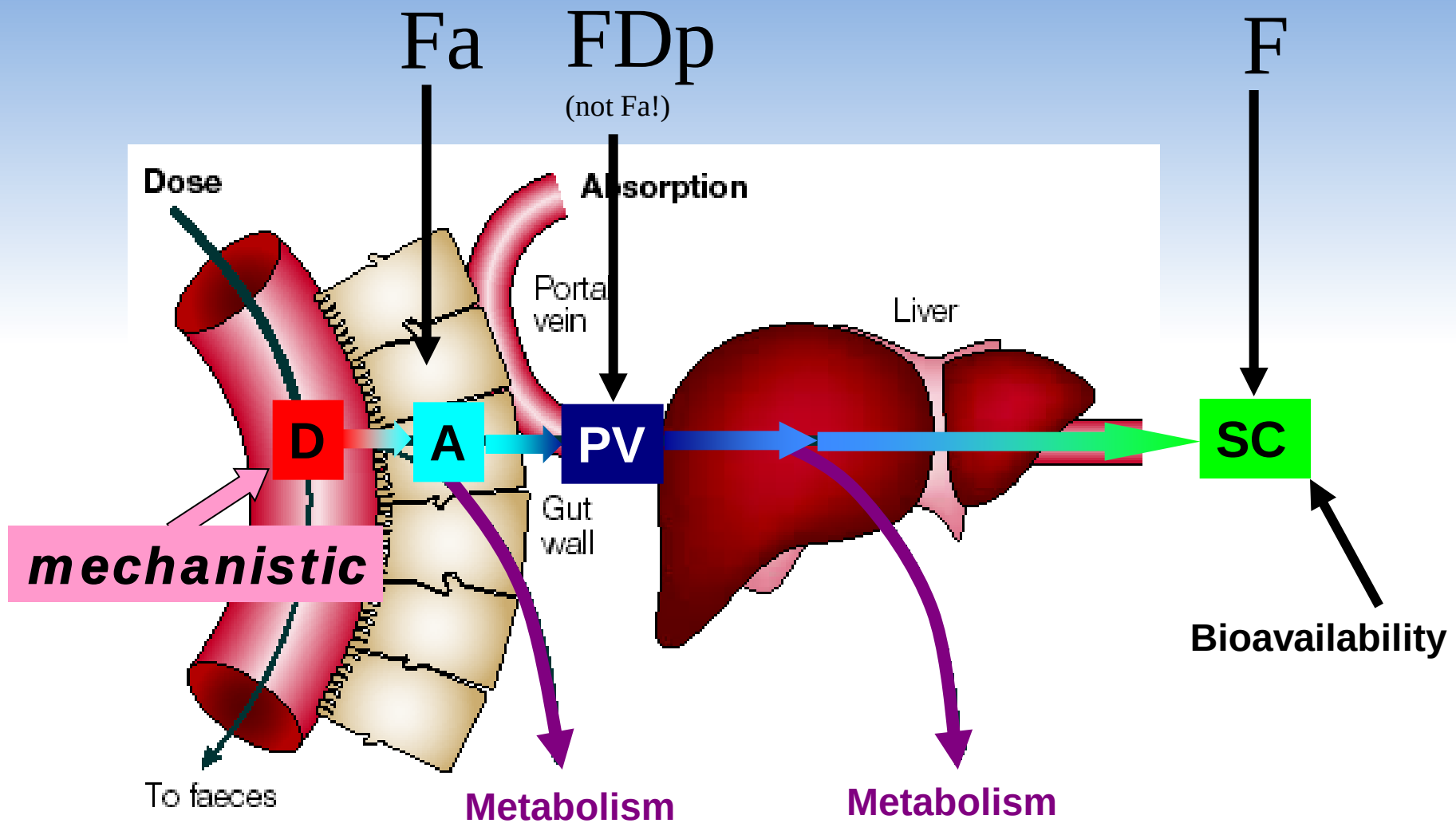
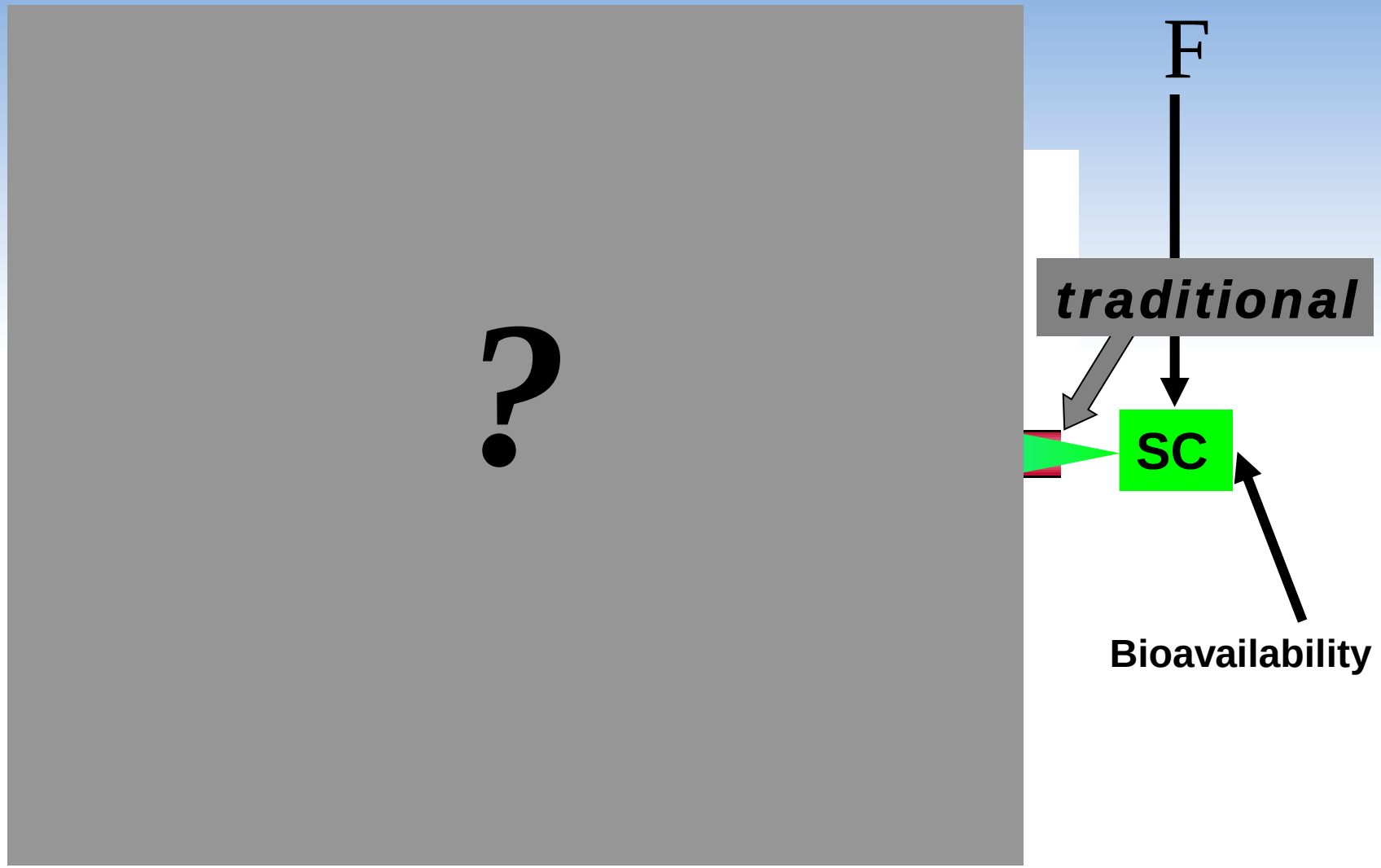
Difference between traditional and mechanistic deconvolution?



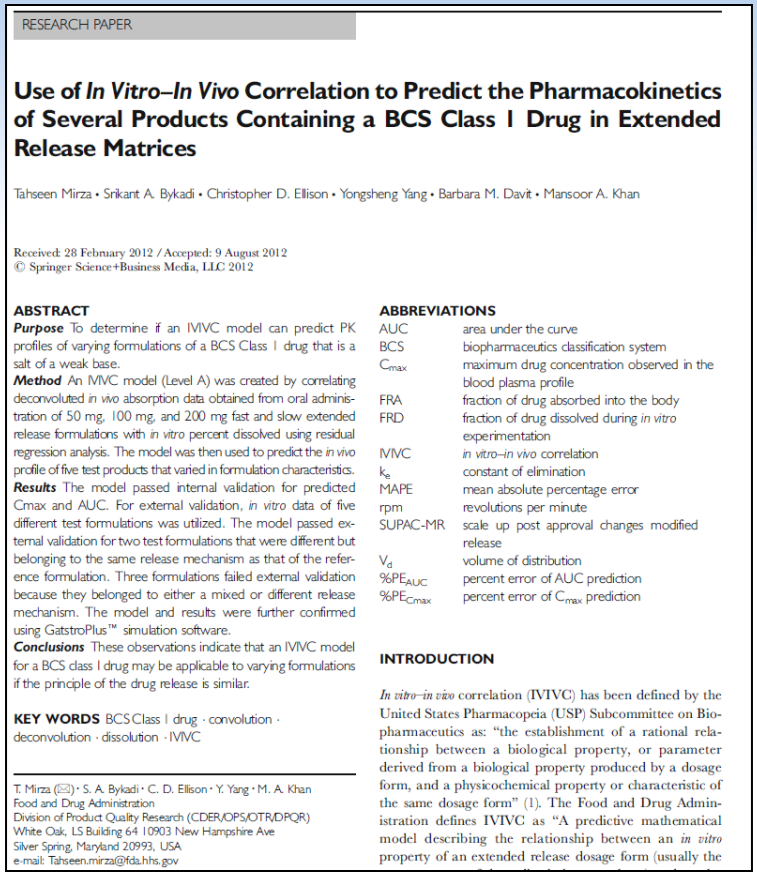
* Modified from van de Waterbeemd, H, and Gifford, E. ADMET In Silico Modelling: Towards Prediction Paradise? Nat. Rev. Drug Disc. 2003, 2:192-204

Difference between traditional and mechanistic deconvolution?



* Modified from van de Waterbeemd, H, and Gifford, E. *ADMET In Silico Modelling: Towards Prediction Paradise?* Nat. Rev. Drug Disc. 2003, 2:192-204

Comparison of IVIVC Methods: Predicting PK of new products



RESEARCH PAPER

Use of *In Vitro–In Vivo* Correlation to Predict the Pharmacokinetics of Several Products Containing a BCS Class I Drug in Extended Release Matrices

Tahseen Mirza • Srikant A. Bykadi • Christopher D. Ellison • Yongsheng Yang • Barbara M. Davit • Mansoor A. Khan

Received: 28 February 2012 / Accepted: 9 August 2012

ABSTRACT

Purpose To determine if an IVIVC model can predict PK profiles of varying formulations of a BCS Class I drug that is a salt of a weak base.

Method An IVIVC model (Level A) was created by correlating deconvoluted *in vivo* absorption data obtained from oral administration of 50 mg, 100 mg, and 200 mg fast and slow extended release formulations with *in vitro* percent dissolved using residual regression analysis. The model was then used to predict the *in vivo* profile of five test products that varied in formulation characteristics.

Results The model passed internal validation for predicted Cmax and AUC. For external validation, *in vitro* data of five different test formulations was utilized. The model passed external validation for two test formulations that were different but belonging to the same release mechanism as that of the reference formulation. Three formulations failed external validation because they belonged to either a mixed or different release mechanism. The model and results were further confirmed using GatstroPlus™ simulation software.

Conclusions These observations indicate that an IVIVC model for a BCS class I drug may be applicable to varying formulations if the principle of the drug release is similar.

KEY WORDS BCS Class I drug · convolution · deconvolution · dissolution · IVIVC

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ABBREVIATIONS

AUC	area under the curve
BCS	biopharmaceutics classification system
C_{max}	maximum drug concentration observed in the blood plasma profile
FRA	fraction of drug absorbed into the body
FRD	fraction of drug dissolved during *in vitro* experimentation
IVIVC	*in vitro–in vivo* correlation
k_e	constant of elimination
MAPE	mean absolute percentage error
rpm	revolutions per minute
SUPAC-MR	scale up post approval changes modified release
V_d	volume of distribution
$\%PE_{AUC}$	percent error of AUC prediction
$\%PE_{Cmax}$	percent error of C_{max} prediction

INTRODUCTION

In vitro–in vivo correlation (IVIVC) has been defined by the United States Pharmacopeia (USP) Subcommittee on Biopharmaceutics as: "the establishment of a rational relationship between a biological property, or parameter derived from a biological property produced by a dosage form, and a physicochemical property or characteristic of the same dosage form" (1). The Food and Drug Administration defines IVIVC as "A predictive mathematical model describing the relationship between an *in vitro* property of an extended release dosage form (usually the

Table I Formulations Used for *In Vitro* and *In Vivo* Testing

Product	Strength of dosage for *in vitro* testing	Strength of dosage for *in vivo* testing
Reference extended release	25 mg, 100 mg[a], 200 mg	50 mg, 100 mg[a], 200 mg
Reference fast release	100 mg	100 mg
Test A	50 mg	50 mg
Test B	200 mg	200 mg
Test C	200 mg	200 mg
Test D	200 mg	200 mg
Test E	200 mg	200 mg

[a] Only used for external validation

Table III Physiochemical Properties of Drug Compound Used in Creating the Gastroplus IVIVC Model

Parameters	Values
Log P	1.9
Molecular weight	261.36 g
Ph off or reference solubility fully saturated solution	5.48
Concentration of fully saturated solution	16.9 mg/ml
Mean precipitation time	5 s
Diffusion. coefficient ($cm^2/s \times 10^5$)	0.74081
Drug particle density	1.2 g/ml
Particle size (diameter)	50 μm
Human jejunal permeability (Peff) ($cm/s \times 10^4$)	1.34

Mirza et al., Pharm. Res. (2012)

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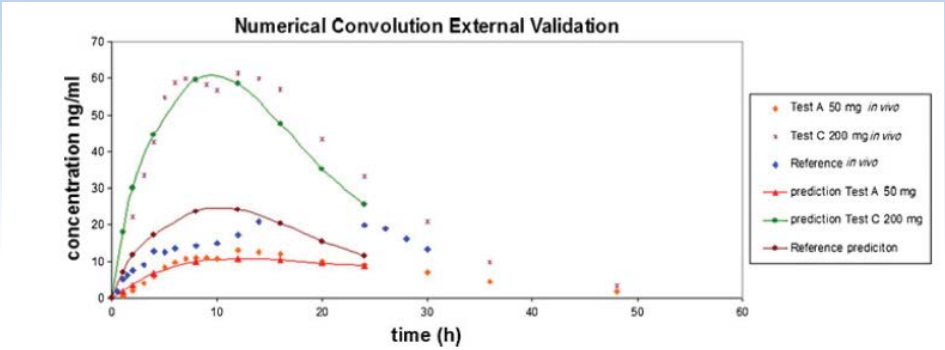
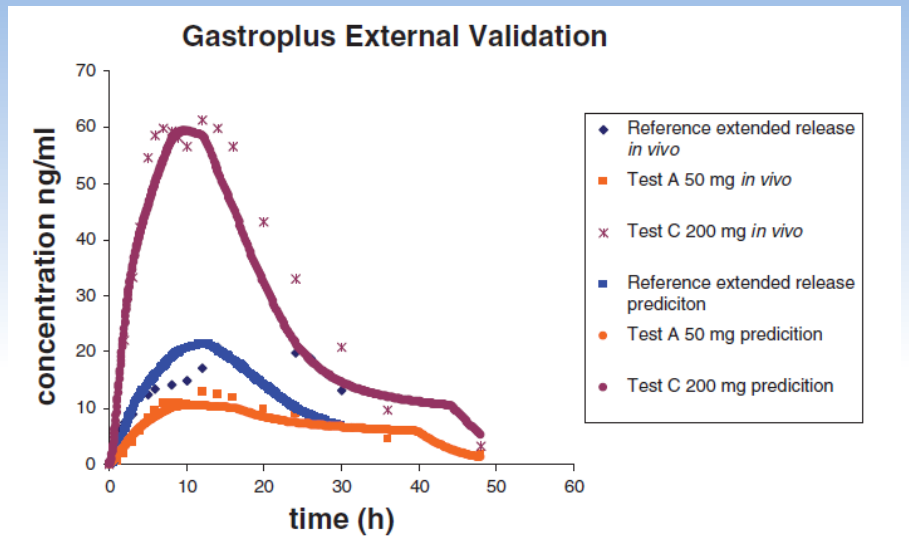
"External" Validation: Predicting PK of new products



Numerical Deconvolution



GastroPlus

- Internal validation of the IVIVC showed similar prediction accuracy
  - Internal validation = applying the same products used to build the IVIVC to test it
- GastroPlus showed "greater prediction accuracy" for the new products
  - External validation = predicting PK of new products with the IVIVC

Mirza et al., Pharm. Res. (2012)

IVIVC for BCS Class II (F = 66%)

AAPS PharmSciTech (© 2012)
DOI: 10.1208/s12249-012-9814-3

Research Article

Developing *In Vitro–In Vivo* Correlation of Risperidone Immediate Release Tablet

Yardi Saibi,[1,3] Hitoshi Sato,[1] and Hidehisa Tachiki[2]

Received 6 March 2012; accepted 30 May 2012

Abstract. The present study was aimed to predict the absorption profile of a risperidone immediate release tablet (IR) and to develop the level A *in vitro–in vivo* correlation (IVIVC) of the drug using the gastrointestinal simulation based on the advanced compartmental absorption and transit model implemented in GastroPlus™. Plasma concentration data, physicochemical, and pharmacokinetic properties of the drug were used in building its absorption profile in the gastrointestinal tract. Since the fraction absorbed of risperidone in simulation was more than 90% with low water solubility, the drug met the criteria of class II of the Biopharmaceutics Classification System. The IVIVC was developed based on the model built using the plasma data and the *in vitro* dissolution data in several dissolution media based on the Japanese Guideline for Bioequivalence Studies of Generic Products. The gastrointestinal absorption profile of risperidone was successfully predicted. A level A IVIVC was also successfully developed in all

IVIVC for Risperidone IR Tablet

Table IV. Percent Prediction Error (PE) for Cmax and AUC of Reference Tablet

Observed values : Cmax=9.648 (ng/ml), AUC=57.83 (ng h/mL)

Dissolution Media	Cmax (ng/ml)	PE (%)	AUC (ng h/mL)	PE (%)
Phosphate buffer pH 4 (50 rpm)	10.28	−6.55	60.77	−5.08
Phosphate buffer pH 1.2 (50 rpm)	10.27	−6.45	60.77	−5.08
Phosphate buffer pH 6.8 (50 rpm)	9.94	−3.01	60.74	−5.03
Water	10.33	−7.07	60.77	−5.08
Phosphate buffer pH 6.8 (100 rpm)	9.51	1.41	60.70	−4.96

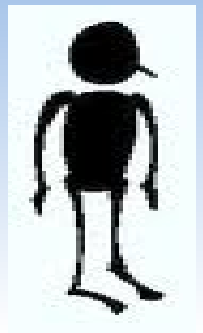
Table V. Percent Prediction Error (PE) for Cmax and AUC of Test Tablet

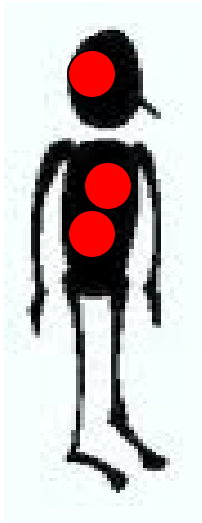
Observed values : Cmax=10.31 (ng/ml), AUC=62.80(ng h/mL)

Dissolution Media	Cmax (ng/ml)	PE (%)	AUC (ng/mL)	PE (%)
Phosphate buffer pH 4 (50 rpm)	10.26	0.48	60.77	3.23
Phosphate buffer pH 1.2 (50 rpm)	10.19	1.16	60.77	3.23
Phosphate buffer pH 6.8 (50 rpm)	10.09	2.13	60.75	3.26
Water	10.35	−0.39	60.77	3.23
Phosphate buffer pH 6.8 (100 rpm)	9.88	4.15	60.73	3.29

Virtual Bioequivalence Trials

A population has variability as function of age, gender, weight, height (BMI), disease state.





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Virtual Bioequivalence Trials

Bioequivalence trials are run to demonstrate bioequivalence between a test formulation and a reference formulation.

To demonstrate bioequivalence, the test product must duplicate the Cmax and AUC of the reference product within 80-125% at 90% confidence intervals under both fasted and fed conditions.

The number of subjects in the trial can affect the outcome. If the number of subjects is too small, the trial might fail when the product is actually bioequivalent. If the number is too large, time and money are wasted.

Failure of a bioequivalence trial is very expensive and time-consuming.

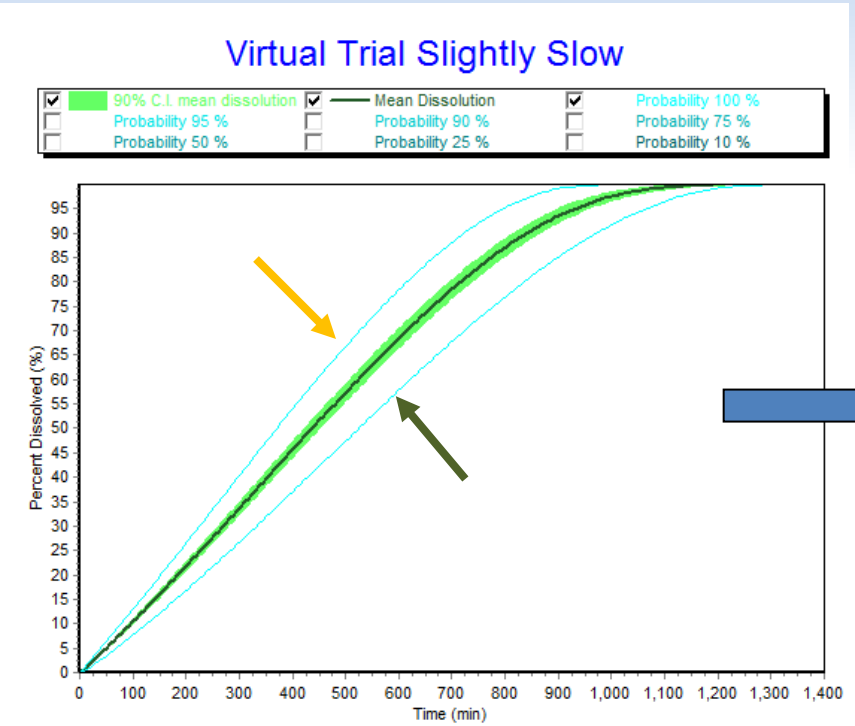
Virtual bioequivalence trials can help to predict whether a formulation is *likely* to pass or fail. They are not perfect, but they provide an important decision-making tool to use with all other information.

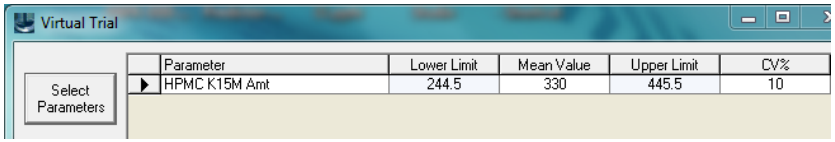
Establish dissolution specifications

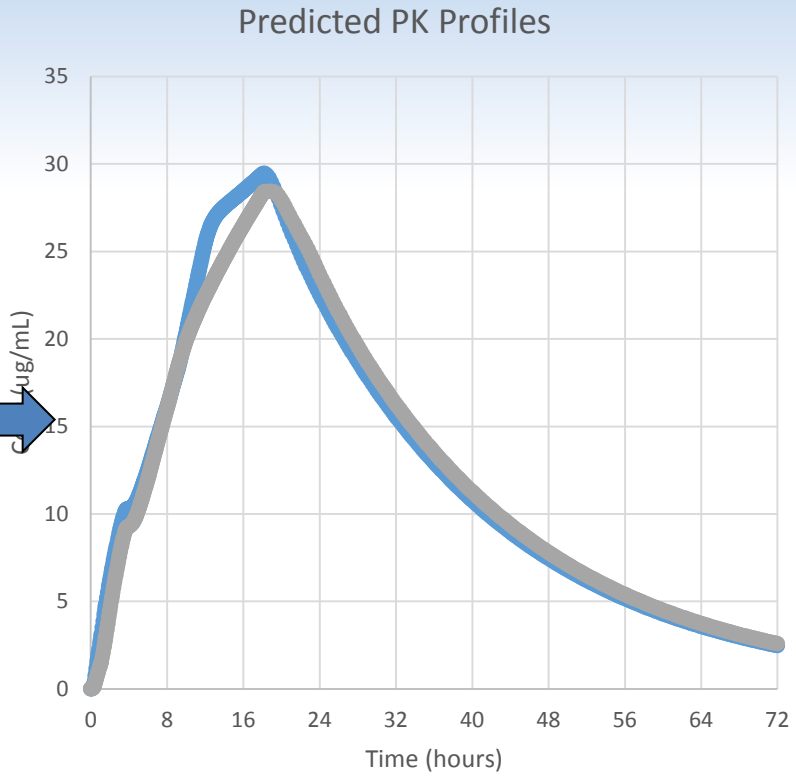
10% variability around HPMC content

25 virtual lots simulated in DDDPlus

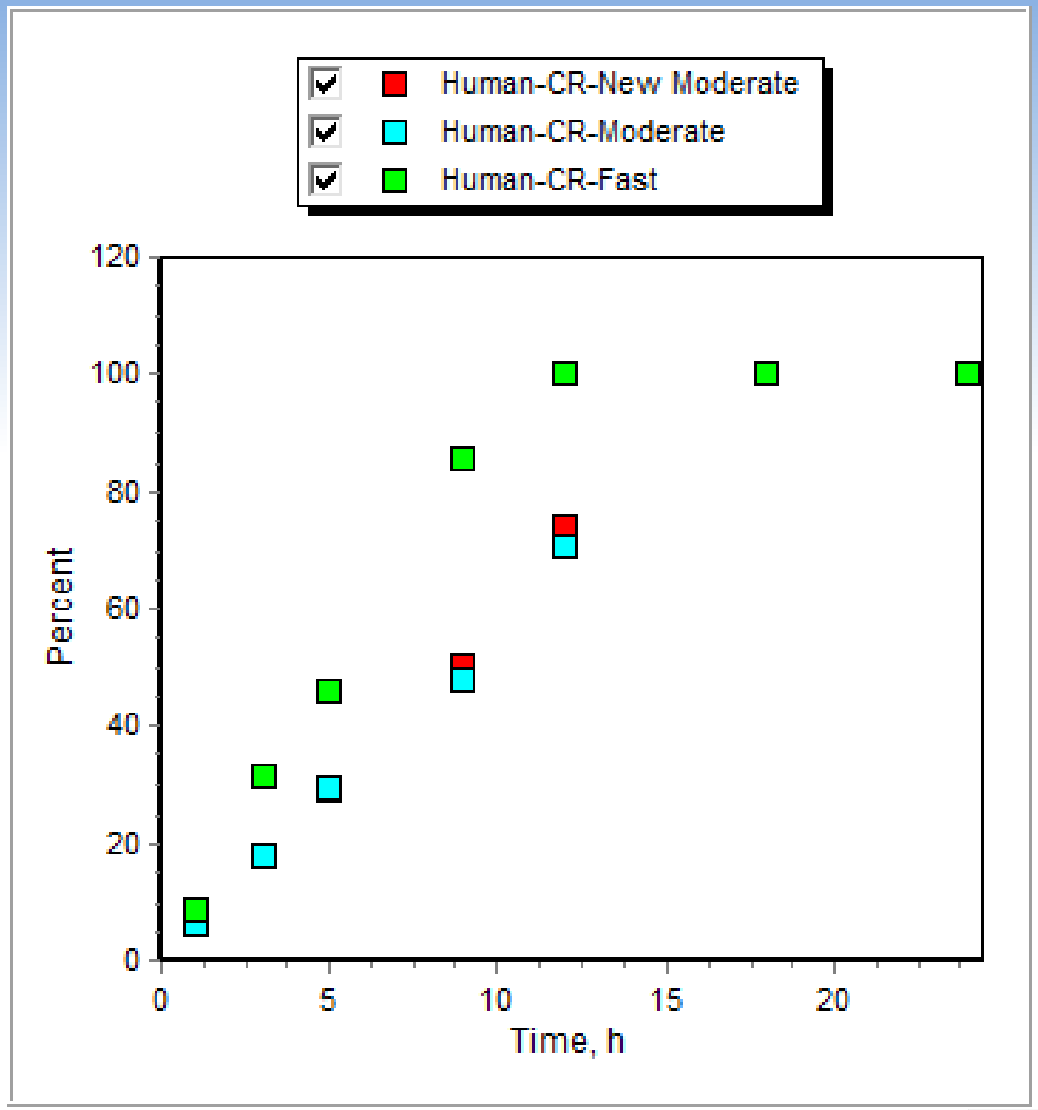
100th percentile ('extreme') dissolution profiles loaded into GastroPlus to predict PK







The Population Simulation



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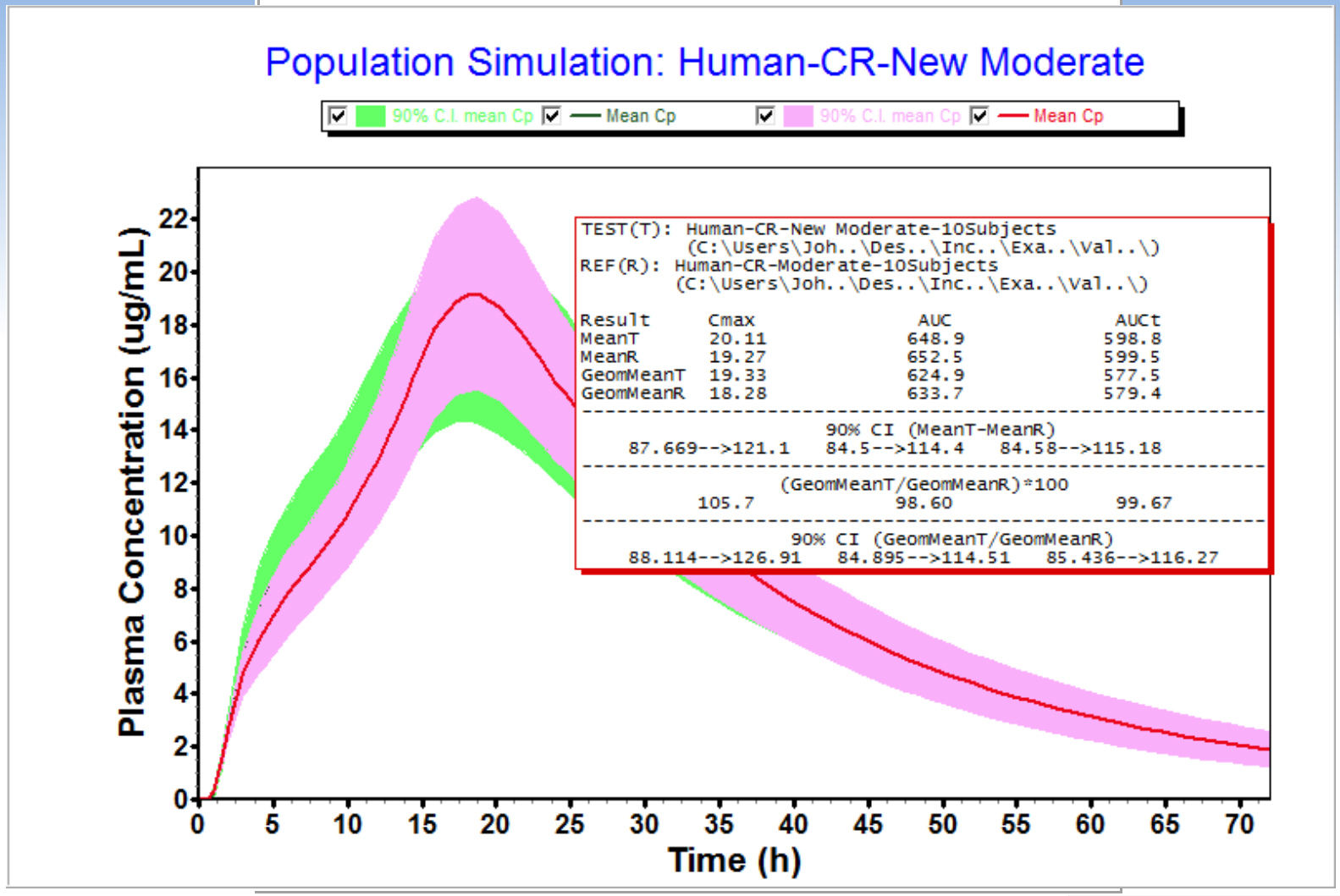
The Population Simulation



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Understanding food effects

BCS Predicts the likelihood and direction of a food effect 60 – 70% of the time.

Table I. Relationship Between Food Effect on the Extent of Absorption (AUC) and BCS Classification of Compounds

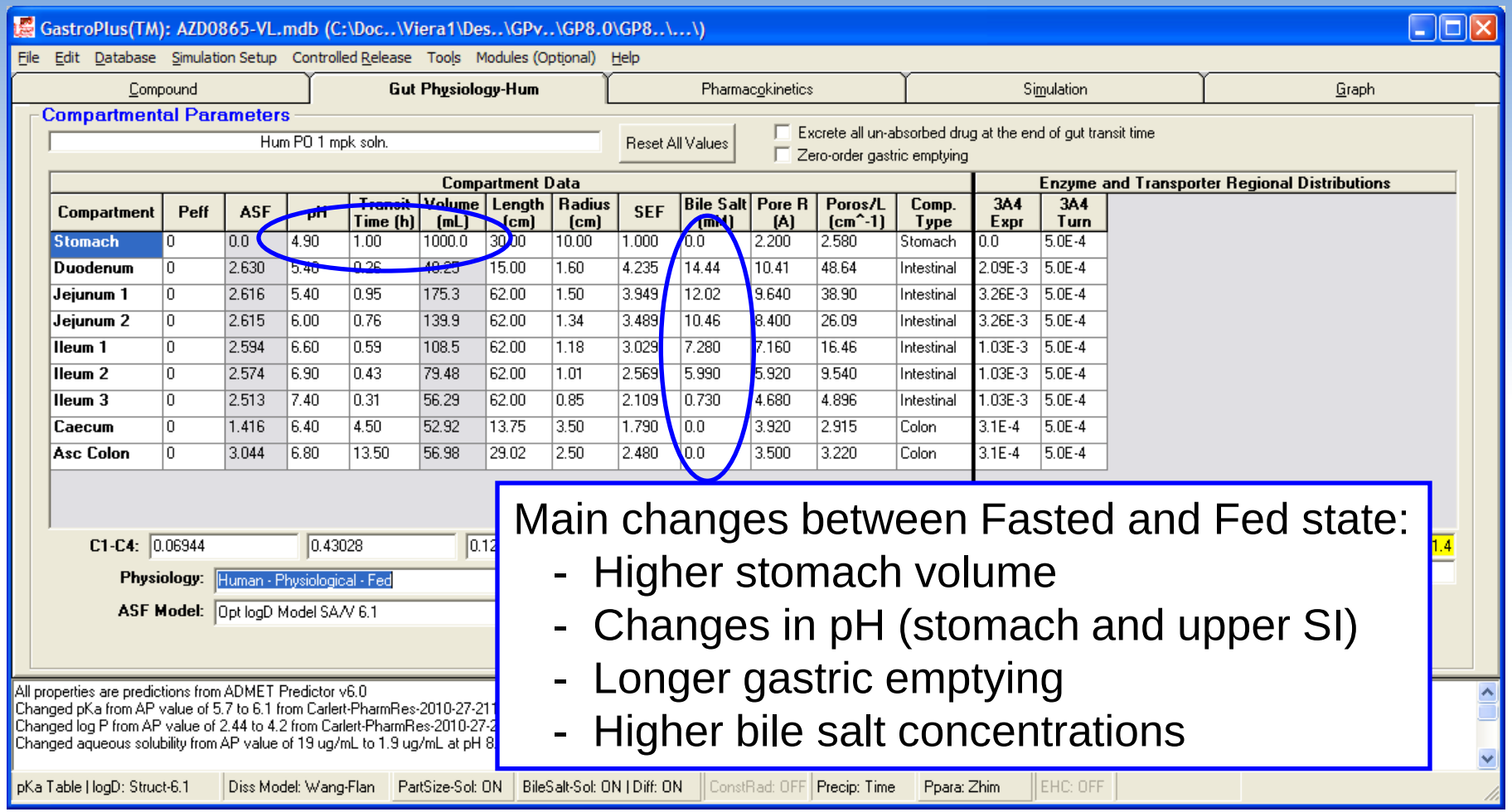
Food Effect/BCS	Class 1	Class 2	Class 3	Class 4	Total
Negative	9 (30%)	0 (0%)	14 (61%)	1 (9%)	24
No effect	20 (67%)	8 (29%)	7 (30%)	2 (18%)	37
Positive	1 (3%)	20 (71%)	2 (9%)	8 (73%)	31
Total	30	28	23	11	92

The number of compounds in each BCS class for a specific food effect category is listed and the percentage is provided in the parentheses.

- 67% of Class I drugs had **no** food effect.
- 71% of Class II drugs had a **positive** effect.
- 61% of Class III drugs had a **negative** effect.
- 73% of Class IV drugs had a **positive** effect.

Based on maximum absorbable dose (MAD), dose number, and log D.
Gu CH, Pharm. Res. 24 (6):1118 (2007)

Fed State – Light and High Fat Meal



Main changes between Fasted and Fed state:

- Higher stomach volume
- Changes in pH (stomach and upper SI)
- Longer gastric emptying
- Higher bile salt concentrations

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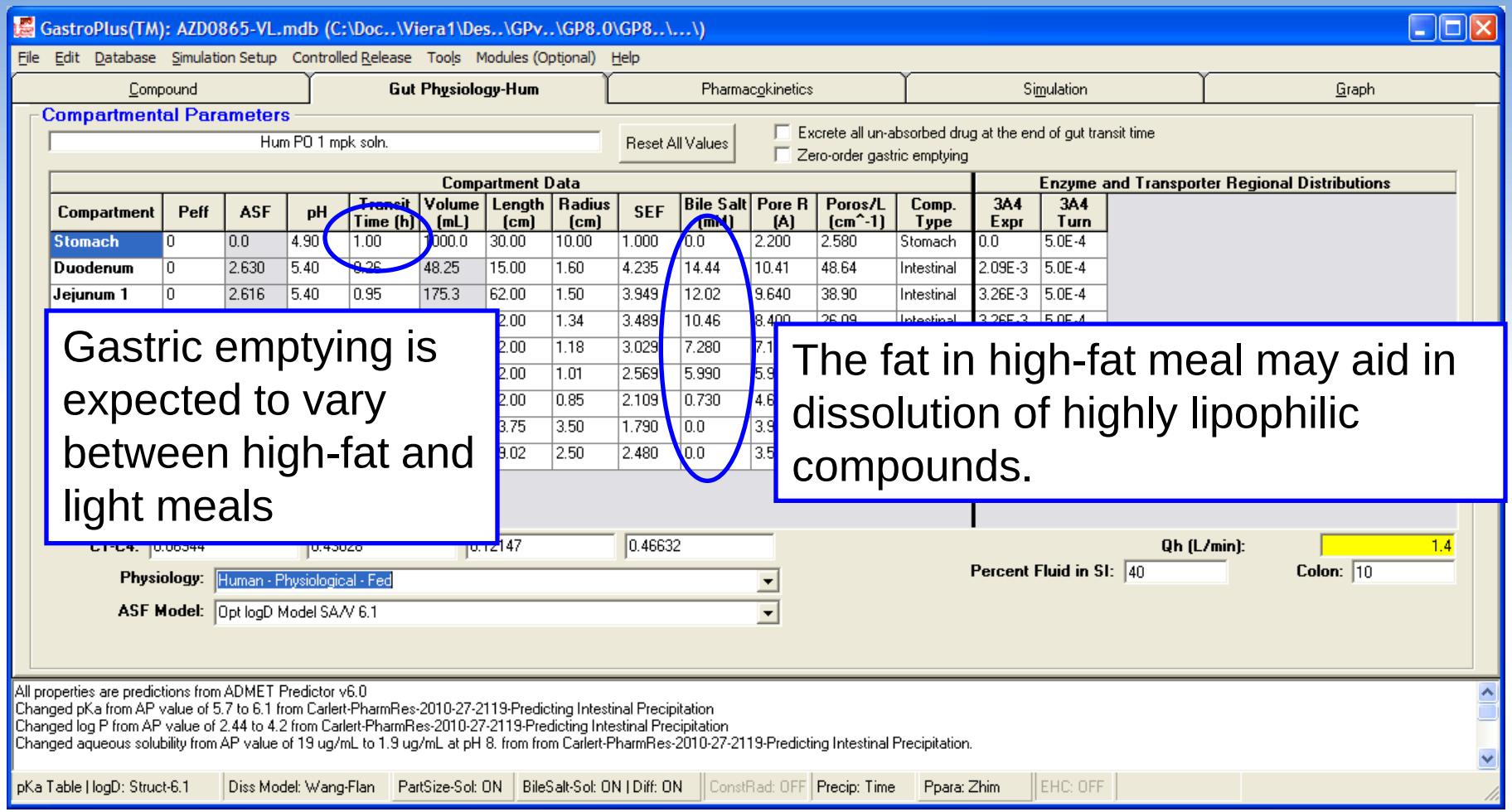
Fed State – Light and High Fat Meal



Gastric emptying is expected to vary between high-fat and light meals

The fat in high-fat meal may aid in dissolution of highly lipophilic compounds.

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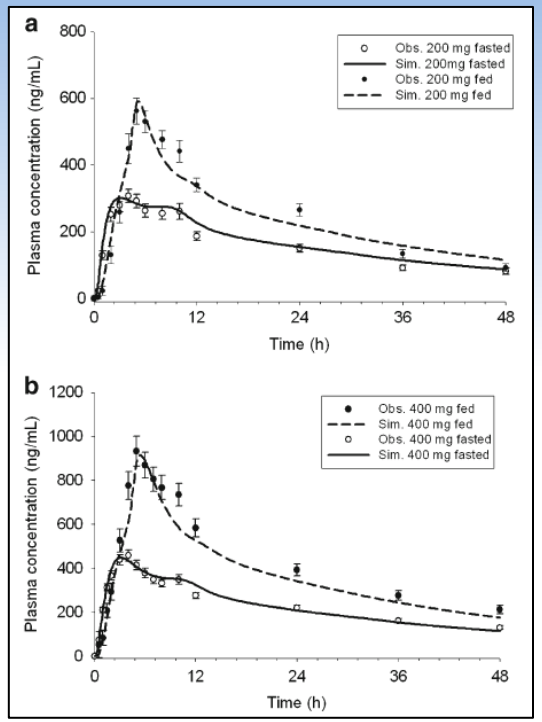
Analyzing multiple dimensions: Design of Experiments (DoE) Approach

Parameters	Value(s)
Compound parameters	
M_w: g/mol	>475
cLogP:	>4
pK_a (base):	3.2, 6.2
Dosage:	IR capsule
Solubility (mg/mL):	1.8 (pH 1), 0.3 (pH 2), 0.001 (pH 6.8)
Biorelevant solubility (mg/mL) :	0.023 (fasted); 0.190 (fed)
Mean precipitation time (s) :	450 s (fasted); 2,000 s (fed)
Effective permeability (cm/s):	1.48×10^{-4}
Particle radius of API (μm):	19
Physiological parameters	
Stomach pH	1.2 (Fasted); 1.2–4.9 (Fed)
Duodenum/jejunum pH	6.0–6.4 (Fasted); 5.4–6.0 (Fed)
Ileum pH	6.6–7.4 (Fasted); 6.6–7.4 (Fed)
Cecum–colon pH	6.4–6.8
Stomach transit time (h)	2.0 (Fasted); 5.4 (Fed)
Small intestine transit time (h)	3.3
Cecum transit time (h)	4.2
Ascending colon transit time (h)	12.6
Pharmacokinetics	
First pass extraction (%):	9.0
Blood/plasma ratio:	0.68
Plasma unbound (%):	1.6
Clearance (L/h/kg)	0.070
V_c (L/kg)	0.4
k_{12} (1/h)	0.64
k_{21} (1/h)	0.17
V_t (L/kg)	1.5



- Baseline models in GastroPlus were developed to predict the food effect for a weak base compound across different doses
- Is there an optimal combination of formulation parameters that allow us to reach our target endpoint (e.g., Fa%, Cmax, AUC)?

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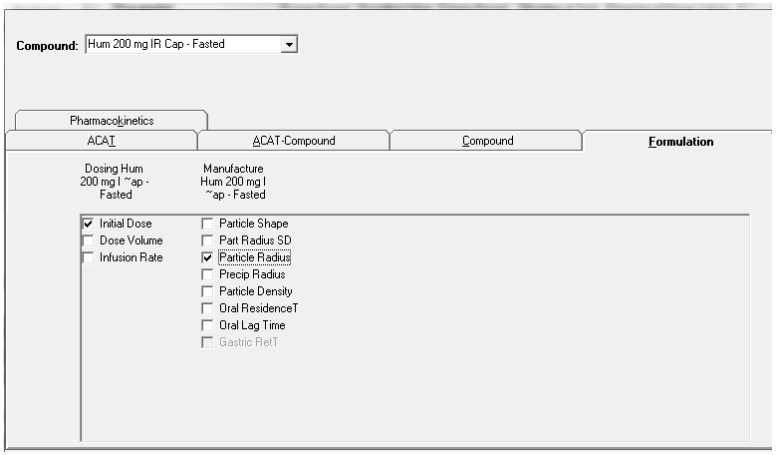
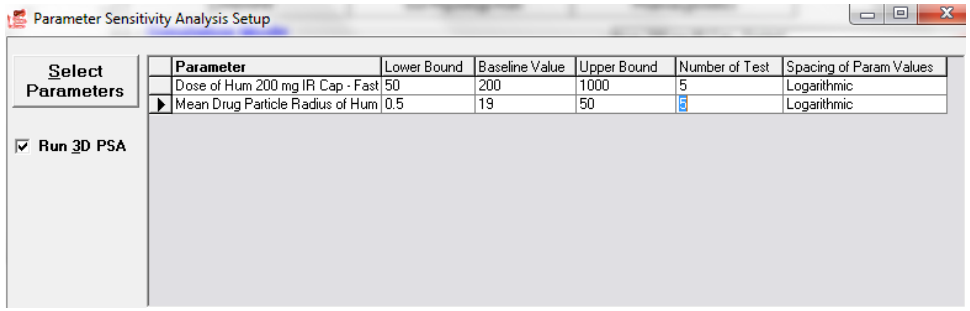
Analyzing multiple dimensions: Design of Experiments (DoE) Approach

- Is there an optimal combination of formulation parameters that allow us to reach our target endpoint (e.g., Fa%, Cmax, AUC)?
- Can we “design out” the food effect?





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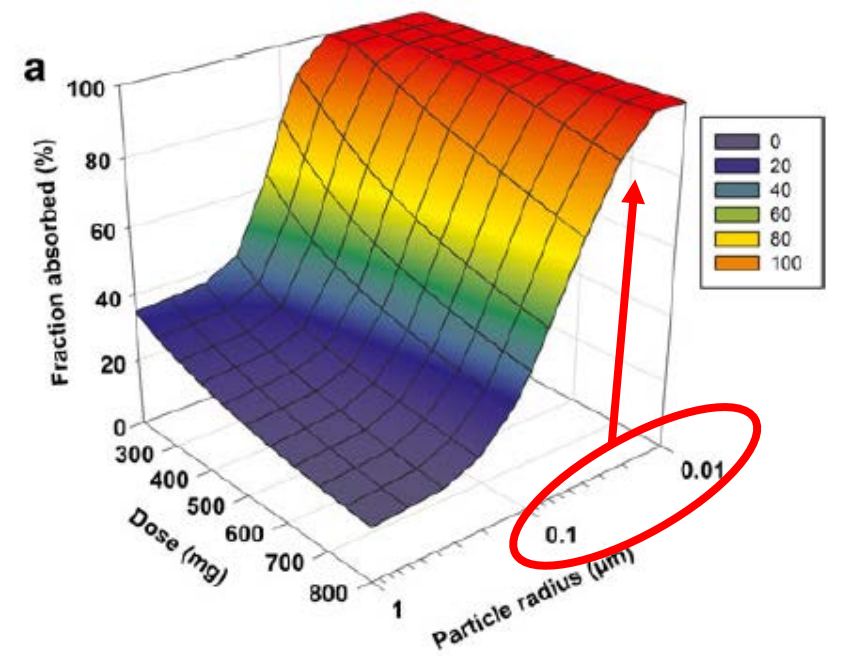
3D Parameter Sensitivity Analysis



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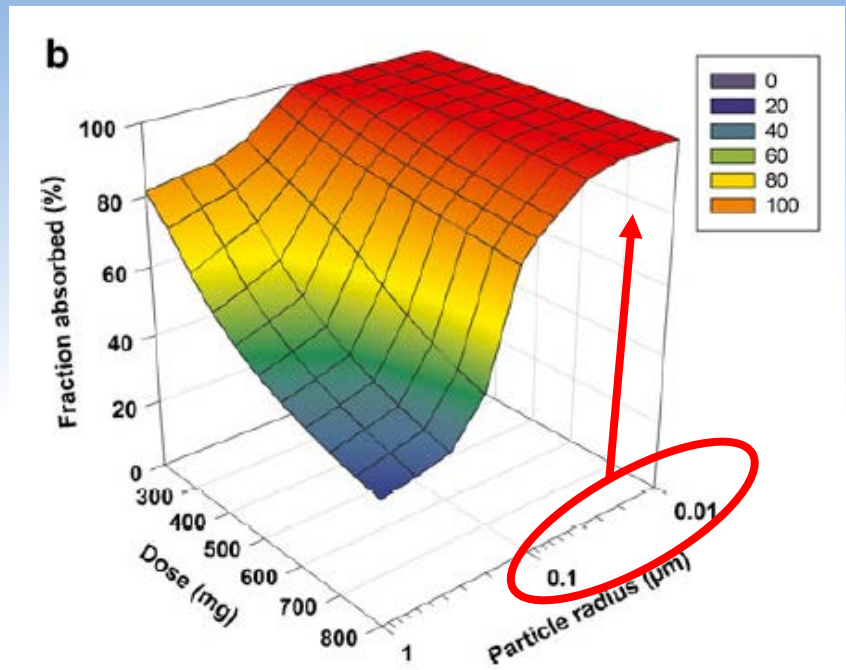

Fed

- Parameter sensitivity analysis was run across dose and particle size together
- API particle size reduction may be useful to mitigate the food effect

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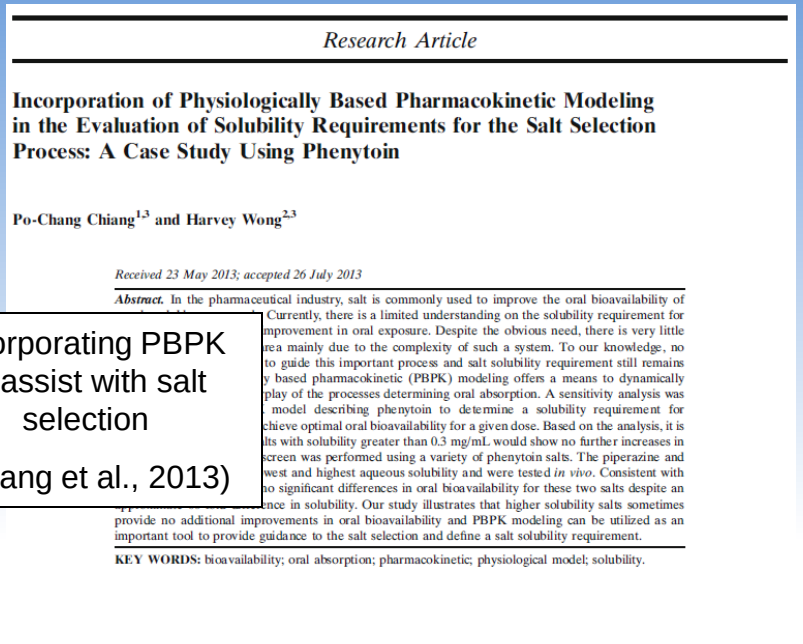
Pharmaceutical Development



Research Article

Incorporation of Physiologically Based Pharmacokinetic Modeling in the Evaluation of Solubility Requirements for the Salt Selection Process: A Case Study Using Phenytoin

Po-Chang Chiang[1,3] and Harvey Wong[2,3]

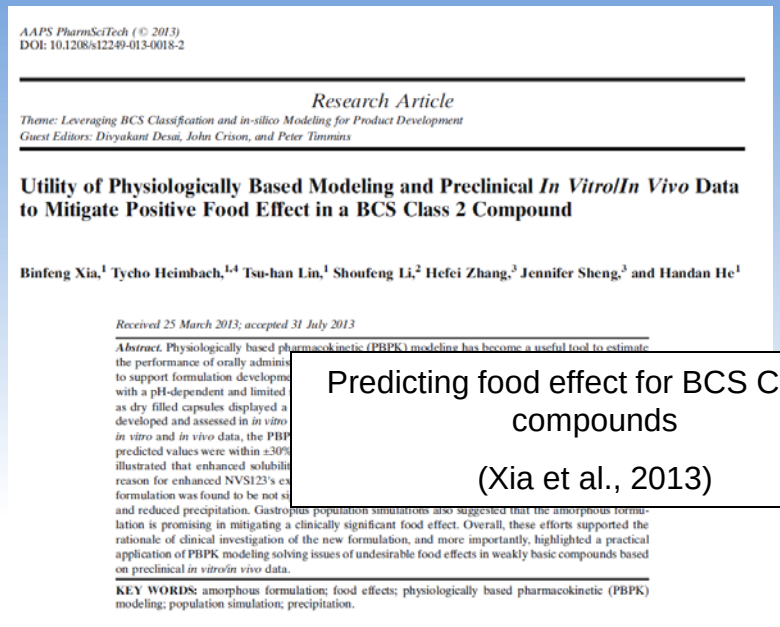
Received 23 May 2013; accepted 26 July 2013

Abstract. In the pharmaceutical industry, salt is commonly used to improve the oral bioavailability of … Currently, there is a limited understanding on the solubility requirement for … improvement in oral exposure. Despite the obvious need, there is very little … rea mainly due to the complexity of such a system. To our knowledge, no … to guide this important process and salt solubility requirement still remains … y based pharmacokinetic (PBPK) modeling offers a means to dynamically … play of the processes determining oral absorption. A sensitivity analysis was … model describing phenytoin to determine a solubility requirement for … chieve optimal oral bioavailability for a given dose. Based on the analysis, it is … lts with solubility greater than 0.3 mg/mL would show no further increases in … screen was performed using a variety of phenytoin salts. The piperazine and … west and highest aqueous solubility and were tested *in vivo*. Consistent with … o significant differences in oral bioavailability for these two salts despite an … nce in solubility. Our study illustrates that higher solubility salts sometimes provide no additional improvements in oral bioavailability and PBPK modeling can be utilized as an important tool to provide guidance to the salt selection and define a salt solubility requirement.

KEY WORDS: bioavailability; oral absorption; pharmacokinetic; physiological model; solubility.

Incorporating PBPK to assist with salt selection

(Chiang et al., 2013)



AAPS PharmSciTech (© 2013)
DOI: 10.1208/s12249-013-0018-2

Research Article

Theme: Leveraging BCS Classification and in-silico Modeling for Product Development
Guest Editors: Divyakant Desai, John Crison, and Peter Timmins

Utility of Physiologically Based Modeling and Preclinical *In Vitro*/*In Vivo* Data to Mitigate Positive Food Effect in a BCS Class 2 Compound

Binfeng Xia,[1] Tycho Heimbach,[1,4] Tsu-han Lin,[1] Shoufeng Li,[2] Hefei Zhang,[3] Jennifer Sheng,[3] and Handan He[1]

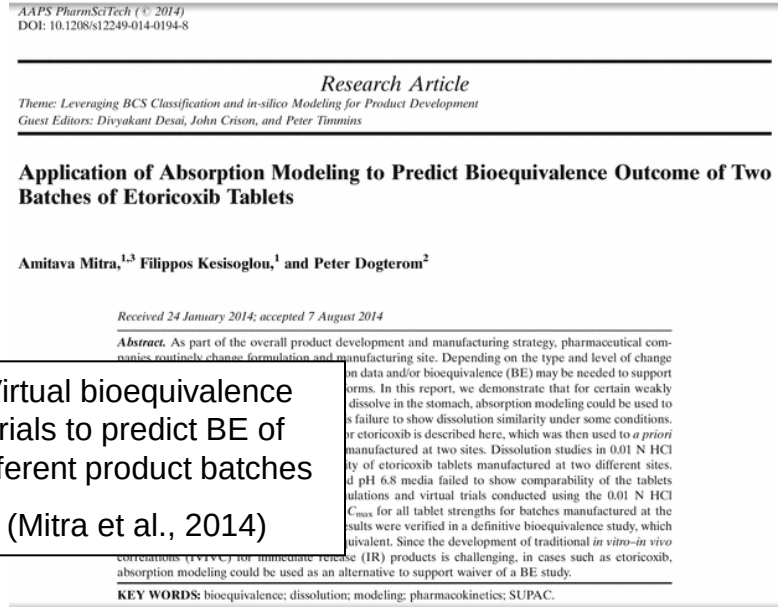
Received 25 March 2013; accepted 31 July 2013

Abstract. Physiologically based pharmacokinetic (PBPK) modeling has become a useful tool to estimate … the performance of orally admini… to support formulation develop… with a pH-dependent and limited … as dry filled capsules displayed a … developed and assessed in *in vitro* … *in vitro* and *in vivo* data, the PBP… predicted values were within ±30%… illustrated that enhanced solubili… reason for enhanced NVS123's e… formulation was found to be not si… and reduced precipitation. GastroPlus population simulations also suggested that the amorphous formulation is promising in mitigating a clinically significant food effect. Overall, these efforts supported the rationale of clinical investigation of the new formulation, and more importantly, highlighted a practical application of PBPK modeling solving issues of undesirable food effects in weakly basic compounds based on preclinical *in vitro*/*in vivo* data.

KEY WORDS: amorphous formulation; food effects; physiologically based pharmacokinetic (PBPK) modeling; population simulation; precipitation.

Predicting food effect for BCS Class II compounds

(Xia et al., 2013)



AAPS PharmSciTech (© 2014)
DOI: 10.1208/s12249-014-0194-8

Research Article

Theme: Leveraging BCS Classification and in-silico Modeling for Product Development
Guest Editors: Divyakant Desai, John Crison, and Peter Timmins

Application of Absorption Modeling to Predict Bioequivalence Outcome of Two Batches of Etoricoxib Tablets

Amitava Mitra,[1,3] Filippos Kesisoglou,[1] and Peter Dogterom[2]

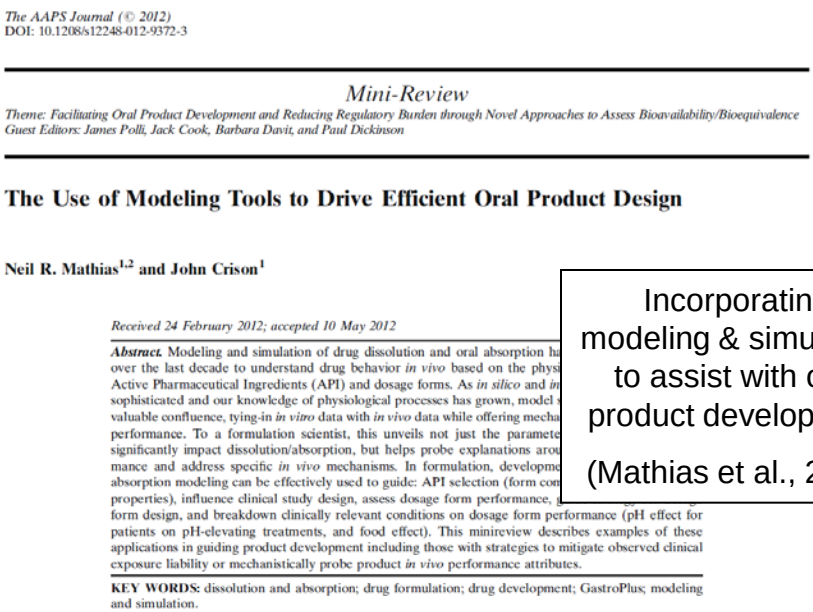
Received 24 January 2014; accepted 7 August 2014

Abstract. As part of the overall product development and manufacturing strategy, pharmaceutical companies routinely change formulation and manufacturing site. Depending on the type and level of change … n data and/or bioequivalence (BE) may be needed to support … orms. In this report, we demonstrate that for certain weakly … dissolve in the stomach, absorption modeling could be used to … s failure to show dissolution similarity under some conditions. … r etoricoxib is described here, which was then used to *a priori* … manufactured at two sites. Dissolution studies in 0.01 N HCl … ty of etoricoxib tablets manufactured at two different sites. … d pH 6.8 media failed to show comparability of the tablets … ulations and virtual trials conducted using the 0.01 N HCl … C_{max} for all tablet strengths for batches manufactured at the … sults were verified in a definitive bioequivalence study, which … uivalent. Since the development of traditional *in vitro–in vivo* correlations (IVIVC) for immediate release (IR) products is challenging, in cases such as etoricoxib, absorption modeling could be used as an alternative to support waiver of a BE study.

KEY WORDS: bioequivalence; dissolution; modeling; pharmacokinetics; SUPAC.

Virtual bioequivalence trials to predict BE of different product batches

(Mitra et al., 2014)



The AAPS Journal (© 2012)
DOI: 10.1208/s12248-012-9372-3

Mini-Review

Theme: Facilitating Oral Product Development and Reducing Regulatory Burden through Novel Approaches to Assess Bioavailability/Bioequivalence
Guest Editors: James Polli, Jack Cook, Barbara Davit, and Paul Dickinson

The Use of Modeling Tools to Drive Efficient Oral Product Design

Neil R. Mathias[1,2] and John Crison[1]

Received 24 February 2012; accepted 10 May 2012

Abstract. Modeling and simulation of drug dissolution and oral absorption ha… over the last decade to understand drug behavior *in vivo* based on the physi… Active Pharmaceutical Ingredients (API) and dosage forms. As *in silico* and *in*… sophisticated and our knowledge of physiological processes has grown, model … valuable confluence, tying-in *in vitro* data with *in vivo* data while offering mecha… performance. To a formulation scientist, this unveils not just the paramete… significantly impact dissolution/absorption, but helps probe explanations arou… mance and address specific *in vivo* mechanisms. In formulation, developme… absorption modeling can be effectively used to guide: API selection (form con… properties), influence clinical study design, assess dosage form performance, … form design, and breakdown clinically relevant conditions on dosage form performance (pH effect for patients on pH-elevating treatments, and food effect). This minireview describes examples of these applications in guiding product development including those with strategies to mitigate observed clinical exposure liability or mechanistically probe product *in vivo* performance attributes.

KEY WORDS: dissolution and absorption; drug formulation; drug development; GastroPlus; modeling and simulation.

Incorporating modeling & simulation to assist with oral product development

(Mathias et al., 2012)

Pharmaceutical Development

RESEARCH ARTICLE – *Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism*

Application of Physiologically Based Absorption Modeling for Amphetamine Salts Drug Products in Generic Drug Evaluation

ANDREW H. BABISKIN, XINYUAN ZHANG

Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland 20993

Received 30 January 2015; revised 8 April 2015; accepted 9 April 2015

library.com). DOI 10.1002/jps.24474

lease (ER) drug products are widely used for the treatment of attention deficit
d absorption models for mixed AMP salts ER capsules and dextroamphetamine
ring generic drug postmarketing surveillance and bioequivalence (BE) guidance
a sets. Virtual BE simulations were conducted to assess BE in various populations
generally conducted for approval. The models were also used to predict phar-
solution profiles falling within specification after the development of *in vitro–in*
odels to test sensitivity of PK metrics to the changes in formulation variables.
nd is in the public domain in the USA J Pharm Sci
nce; bioavailability; clinical trial simulation; modified release

Using M&S to predict virtual BE and assess dissolution specifications

(Babiskin et al., 2015)

Research Article

Utility of Physiologically Based Absorption Modeling in Implementing Quality by Design in Drug Development

Xinyuan Zhang,[1] Robert A. Lionberger,[1,2] Barbara M. Davit,[1] and Lawrence X. Yu[1]

Received 16 September 2010; accepted 14 December 2010; published online 5 January 2011

Abstract. To implement Quality by Design (QbD) in drug development, scientists need tools that link drug products properties to *in vivo* performance. Physiologically based absorption models are potentially useful tools; yet, their utility of QbD implementation has not been discussed or explored much in the literature. We simulated pharmacokinetics (PK) of carbamazepine (CBZ) after administration of four oral formulations, immediate-release (IR) suspension, IR tablet, extended-release (XR) tablet and capsule, under fasted and fed conditions and presented a general diagram of a modeling and simulation strategy integrated with pharmaceutical development. We obtained PK parameters and absorption scale factors (ASFs) by deconvo
validated for other PK pr
explored three key areas w
used to help identify optim
critical formulations variab
for the IR tablet that show
decreased. Finally, virtual t
Virtual bioequivalence stu
test may be a more sensitiv
predictive model is a poten

KEY WORDS: advanced compartmental absorption and transit (ACAT) model; gastroplus™; modified release (MR); quality by design (QbD).

Incorporating M&S to assist with Quality by Design (QbD)

(Zhang et al., 2011)

RESEARCH PAPER

Use of *In Vitro–In Vivo* Correlation to Predict the Pharmacokinetics of Several Products Containing a BCS Class I Drug in Extended Release Matrices

Tahseen Mirza • Srikant A. Bykadi • Christopher D. Ellison • Yongheng Yang • Barbara M. Davit • Mansoor A. Khan

Received: 28 February 2012 / Accepted: 9 August 2012

ABSTRACT

Purpose To determine if an IVIVC model can predict PK profiles of varying formulations of a BCS Class I drug that is a salt of a weak base.

Method An IVIVC model (Level A) was created by correlating deconvoluted *in vivo* absorption data obtained from oral administration of 50 mg, 100 mg, and 200 mg fast and slow extended release formulations with *in vitro* percent dissolved using residual regression analysis. The model was then used to predict the *in vivo* profile of five test products that varied in formulation characteristics.

Results The model passed internal validation for predicted Cmax and AUC. For external validation, *in vitro* data of five different test formulations was utilized. The model passed external validation for two test formulations that were different but belonging to the same release mechanism as that of the reference formulation. Three formulations failed external validation because they belonged to either a mixed or different release mechanism. The model and results were further confirmed
IVIVC model
formulations

ABBREVIATIONS

AUC	area under the curve
BCS	biopharmaceutics classification system
C_{max}	maximum drug concentration observed in the blood plasma profile
FRA	fraction of drug absorbed into the body
FRD	fraction of drug dissolved during *in vitro* experimentation
IVIVC	*in vitro–in vivo* correlation
k_e	constant of elimination
MAPE	mean absolute percentage error
rpm	revolutions per minute
SUPAC-MR	scale up post approval changes modified release
V_d	volume of distribution
$\%PE_{AUC}$	percent error of AUC prediction
$\%PE_{Cmax}$	percent error of C_{max} prediction

INTRODUCTION

In vitro–in vivo correlation (IVIVC) has been defined by the United States Pharmacopeia (USP) Subcommittee on Biopharmaceutics as "the establishment of a rational relationship between a biological property, or parameter derived from a biological property produced by a dosage form, and a physicochemical property or characteristic of the same dosage form" (1). The Food and Drug Administration defines IVIVC as "A predictive mathematical model describing the relationship between an *in vitro* property of an extended release dosage form (usually the rate or extent of drug dissolution or release) and a relevant *in vivo* response, e.g., plasma drug concentration or amount of drug absorbed" (2). In most cases, the *in vitro* property is the rate or extent of drug dissolution or release while the *in vivo* response is the plasma drug concentration

Khan
PQR)

Food and Drug Administration
Division of Bioequivalence II (CDER/OPS/OGD/DBII)
7520 Standish Place
Rockville, Maryland 20855, USA

Published online: 22 August 2012

Generating mechanistic IVIVCs to predict test formulations

(Mirza et al., 2012)

International Journal of Pharmaceutics 418 (2011) 151–160

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The role of predictive biopharmaceutical modeling and simulation in drug development and regulatory evaluation☆

Wenlei Jiang, Stephanie Kim, Xinyuan Zhang, Robert A. Lionberger*, Barbara M. Davit, Dale P. Conner, Lawrence X. Yu

Office of Generic Drugs, Food and Drug Administration, United States

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Quality-by-design
Bioequivalence
In vitro–in vivo correlation
Drug development and review

ABSTRACT

Advances in predicting *in vivo* performance of drug p
ucts are developed and reviewed. Modeling and sim
drug product development and regulatory drug revie
the development of biorelevant specifications, the de
release products with rapid therapeutic onset, the de
framework, and prediction of food effect. As new re
better application of biopharmaceutical modeling in drug product development, regulatory challenges in bioequivalence demonstration of complex drug products also present exciting opportunities for creative modeling and simulation approaches. A collaborative effort among academia, government and industry in modeling and simulation will result in improved safe and effective new/generic drugs to the American public.

Published by Elsevier B.V.

Role of M&S in drug development and regulatory evaluation

(Jiang et al., 2011)

Re-engineered formulations and "virtual" bioequivalence: A successful biowaiver case study

Objectives

- Post approval, sponsor's manufacturing process change resulted in different particle size distributions for new lots
- With GastroPlus, could they apply for a biowaiver by:
  - assessing the effects of changes in particle size distribution of the active pharmaceutical ingredient (API) on its oral bioavailability?
  - predicting the virtual bioequivalence between the "new" and "old" API lots?

Tasks

- Determine the most appropriate absorption/PBPK model for the API across several doses for the non-engineered lots
- Assess the effect of particle size on API exposure for the immediate release formulation
- Evaluate predicted bioequivalence of the tablets manufactured with particle-engineered (PE) API (narrower particle size distribution) versus the tablets manufactured with non particle-engineered (NPE) API (broader particle size distribution)

Formulation Specifications

Various Particle Size Used in Clinical Studies

NPE API Lot Number	d10 (µm)	d50 (µm)	d90 (µm)
NPE Lot 1	20	63	173
NPE Lot 2	8	179	512
NPE Lot 3	15	49	142
NPE Lot 4	31	86	348
NPE Lot 5	26	78	276
NPE Lot 6	9	29	101
NPE Lot 7	11	35	114
NPE Lot 8	12	37	124
NPE Lot 9	10	36	119
NPE Lot 10	13	45	138
NPE Lot 11	11	35	99

PE API Lot Number	d10 (µm)	d50 (µm)	d90 (µm)
PE Lot 1	16	40	88
PE Lot 2	20	49	102
PE Lot 3	22	53	108
PE Lot 4	19	39	71
PE Lot 5	17	35	67
PE Lot 6	23	48	93
PE Lot 7	21	44	87
PE Lot 8	21	45	90
PE Lot 9	24	50	94
PE Lot 10	21	45	89
PE Lot 11	19	42	88
PE Lot 12	22	47	95

API: active pharmaceutical ingredient; d10, d50, and d90: diameter for which 10%, 50%, and 90% (respectively) by volume of the particles are less than this value; NPE: non-particle-engineered; PE: particle-engineered

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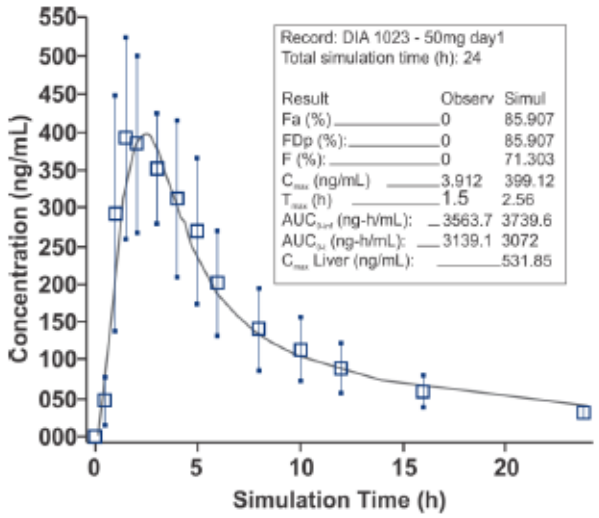
Part I: Model Validation

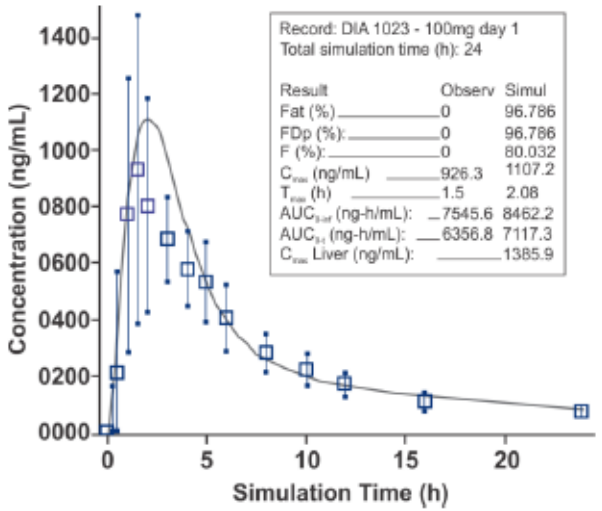
Model Validation

Simulated (lines) and experimental (points)

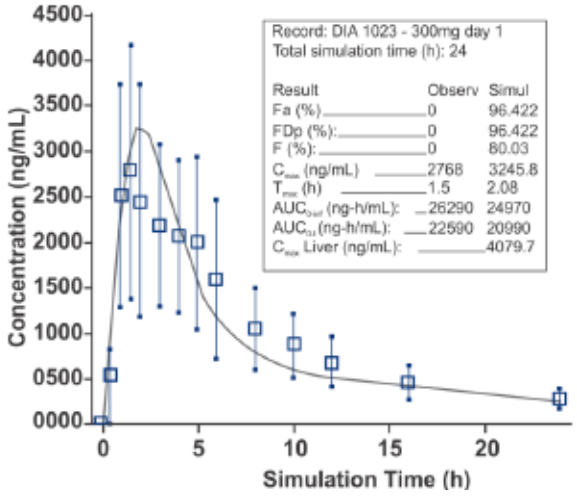
50 mg day 1



100 mg day 1



300 mg day 1



Excellent match between the measured and predicted Cp time profiles for 50, 100, and 300 mg doses

Cp-time: plasma concentration time

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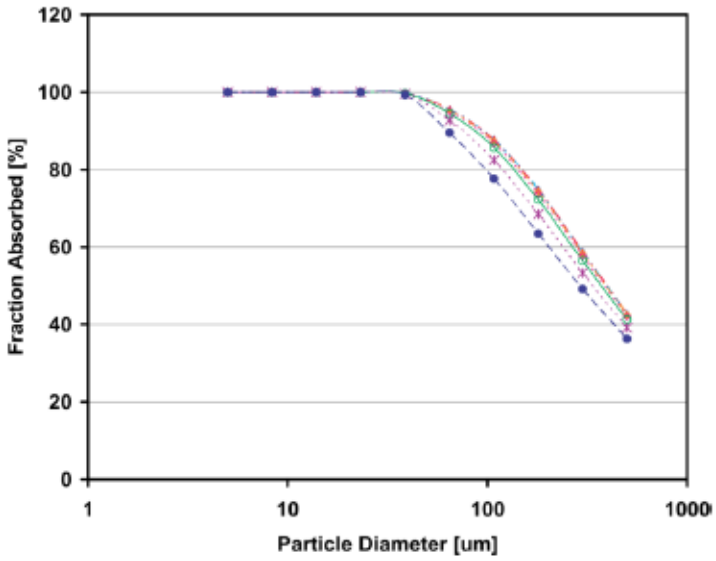
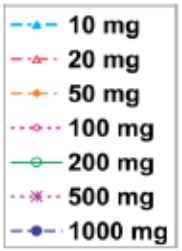
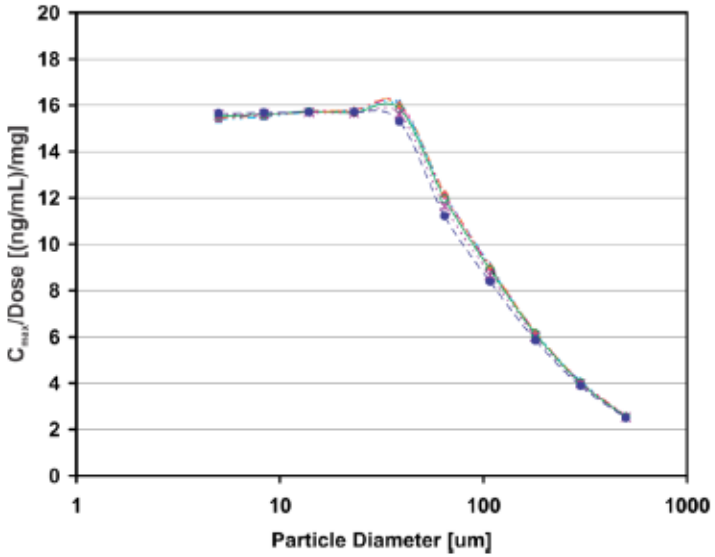
Part II: Parameter Sensitivity Analysis

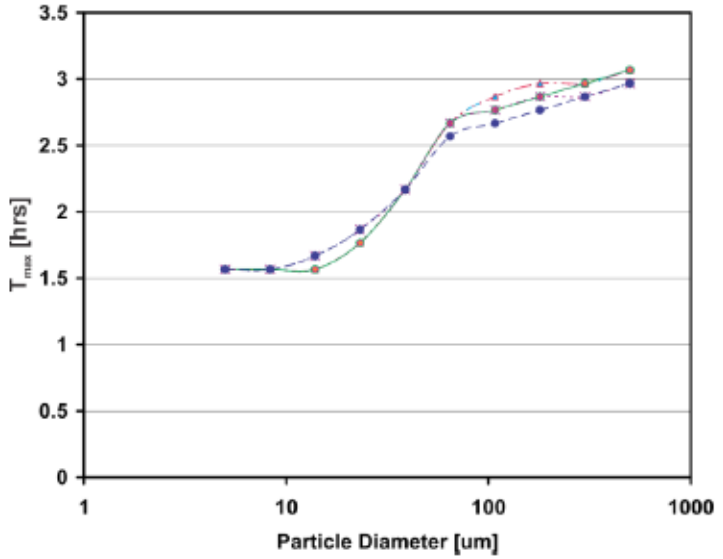
Parameter Sensitivity Analysis

Change in Fa%, C_{max}, T_{max} as a function of mean particle diameter









C_{max}: maximum observed plasma concentration; Fa%: fraction absorbed;
T_{max}: time to reach C_{max}

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Part III: Virtual BE Simulations

Virtual Bioequivalence Study Simulations

- Using crossover virtual trial simulation comparing different formulations (PK parameters: C_{max} and AUC)

API Lot	NPE or PE	d10 (µm)	d50 (µm)	d90 (µm)
Lot 1	NPE	26	78	276
Lot 2	NPE	11	35	99
Lot 3	NPE	14	43	116
Lot 4	NPE	11	32	91
Lot 5	PE	17	41	88

API: active pharmaceutical ingredient; AUC_{∞}: area under the plasma concentration-time curve; C_{max}: maximum observed plasma concentration; d10, d50, and d90: diameter for which 10%, 50%, and 90% (respectively) by volume of the particles are less than this value; NPE: non-particle-engineered; PE: particle-engineered; PK: pharmacokinetics

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Part III: Virtual BE Simulations

Virtual Bioequivalence Study Simulations

API Lot	PE/NPE	Dose (mg)	AUC_{∞} (ng.h/mL) (N=250)		C_{max} (ng/mL) (N=250)	
			GM	GMR (90% CI)	GM	GMR (90% CI)
Lot 5	PE	50	4180	113.3 (110.7, 116.1)	551	139.3 (136.0, 142.7)
Lot 1	NPE	50	3688		395	
Lot 5	PE	100	8242	103.0 (100.9, 105.1)	551	106.4 (104.3, 108.6)
Lot 3	NPE	100	8001		395	
Lot 5	PE	300	24998	102.2 (99.8, 104.6)	3118	100.0 (97.7, 102.4)
Lot 2	NPE	300	24460		3117	
Lot 5	PE	100	8242	98.2 (96.2, 100.2)	1068	95.1 (93.2, 97.0)
Lot 4	NPE	100	8395		1123	
Lot 5	PE	300	24998	101.9 (99.8, 104.1)	3118	98.3 (96.3, 100.4)
Lot 4	NPE	300	24525		3171	

API: active pharmaceutical ingredient; AUC_{∞}: area under the plasma concentration-time curve from time 0 to infinite time; CI: confidence interval; C_{max}: maximum observed plasma concentration; GM: geometric mean; GMR: geometric mean ration; NPE: non-particle-engineered; PE: particle-engineered

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Summary

- A mechanistic, physiologically-based absorption/PK model was constructed in GastroPlus and validated across three dose levels (50, 100, and 300 mg) using *in vivo* data collected from tablets manufactured with non-particle-engineered API.
- Parameter sensitivity analysis showed that mean particle size would be the main property that determines whether formulations are likely to be bioequivalent, regardless of dose.
- Virtual bioequivalence trial simulations showed that, for a sufficiently powered study, the population-derived C_{max} and AUC values would be bioequivalent between the tablets manufactured with non-particle-engineered (NPE) vs. new-particle-engineered (PE) API, regardless of the dose.
- Regulatory agencies approved the sponsor's biowaiver application

How Modeling & Simulation Can Save Resources in Generic R&D

- Understand the mechanisms that affect the absorption/PK of reference products earlier
  - Gain unique insight into the release kinetics & establish better targets
- Guide formulation & dissolution method design
  - Improve chances for success in follow-up pilot studies
- Estimate population behaviors before running clinical trials (*virtual bioequivalence trials*)
  - Separate formulation & physiological effects
- Ultimate goal:

Reduce “trial and error”