Mechanistic Absorption/PBPK Modeling to Predict Positive/Negative Food Effects: Approaches and Special Considerations

John DiBella
President – Lancaster Division
Simulations Plus, Inc.
john.dibella@simulations-plus.com

Presentation Outline

- Early examples and proposed approach
- Fasted vs. fed state model descriptions – where are we today?
- Case study: positive food effect predictions – input review
- Case study: negative food effect predictions – *in vitro* considerations
- Future directions and conclusions

EARLY EXAMPLES AND PROPOSED APPROACHES

BCS* Predicts Likelihood and Direction of 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 logD(7.4)

Gu CH et al. Pharm Res. 24(6):1118 (2007)

Early Mechanistic 'Food' Predictions – Grapefruit Juice

ELSEVIER

Advanced Drug Delivery Reviews 50 (2001) S41–S67

www.elsevier.com/locate/drugdeliv

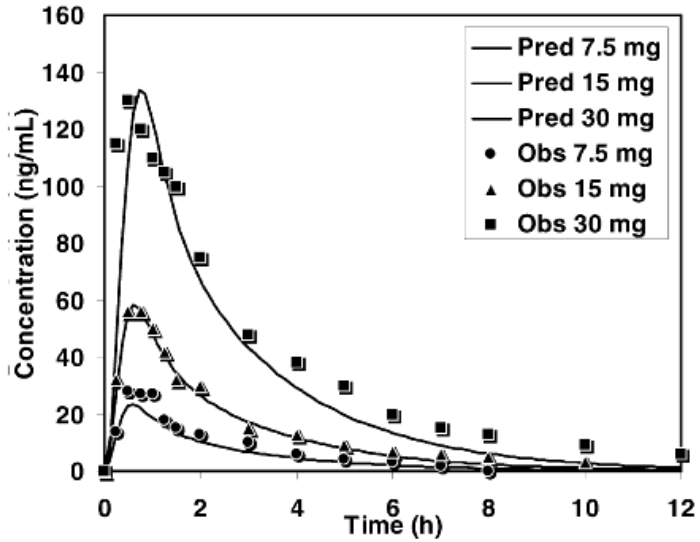
Predicting the impact of physiological and biochemical processes on oral drug bioavailability

Balaji Agoram[a], Walter S. Woltosz[a], Michael B. Bolger[a,b,*]

[a]*Simulations Plus, Inc. 1220 W. Avenue J, Lancaster, CA 93534-2902, USA*

[b]*Department of Pharmaceutical Sciences, USC School of Pharmacy, 1985 Zonal Ave. PSC 700, Los Angeles, CA 90089-9121, USA*

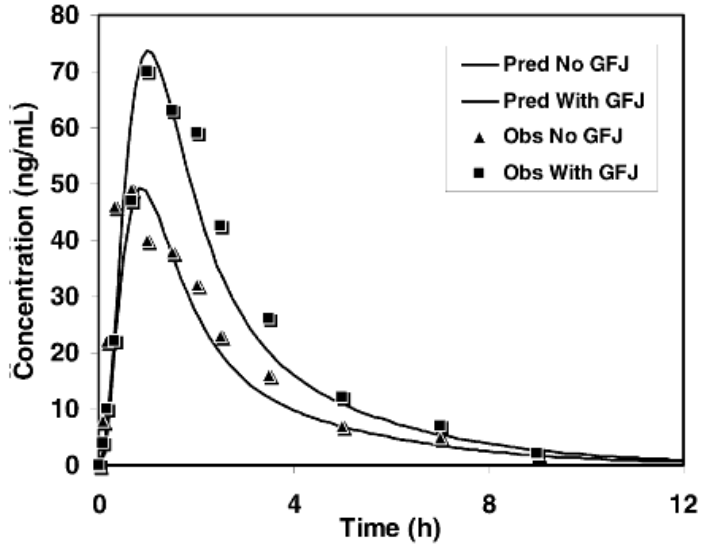
First ACAT™ model simulations of gut and liver first pass extraction & grapefruit (GFJ) effect



PO Midazolam: 7.5, 15, 30 mg solution

← Build/validate baseline models across several doses w/o GFJ

→ Predict PK w/ GFJ



PO Midazolam: 15 mg w/ and w/o GFJ

Agoram B et al. Adv. Drug Del. Reviews 50:S41 (2001)

Biorelevant Solubility Data – Inform Food Effect Predictions

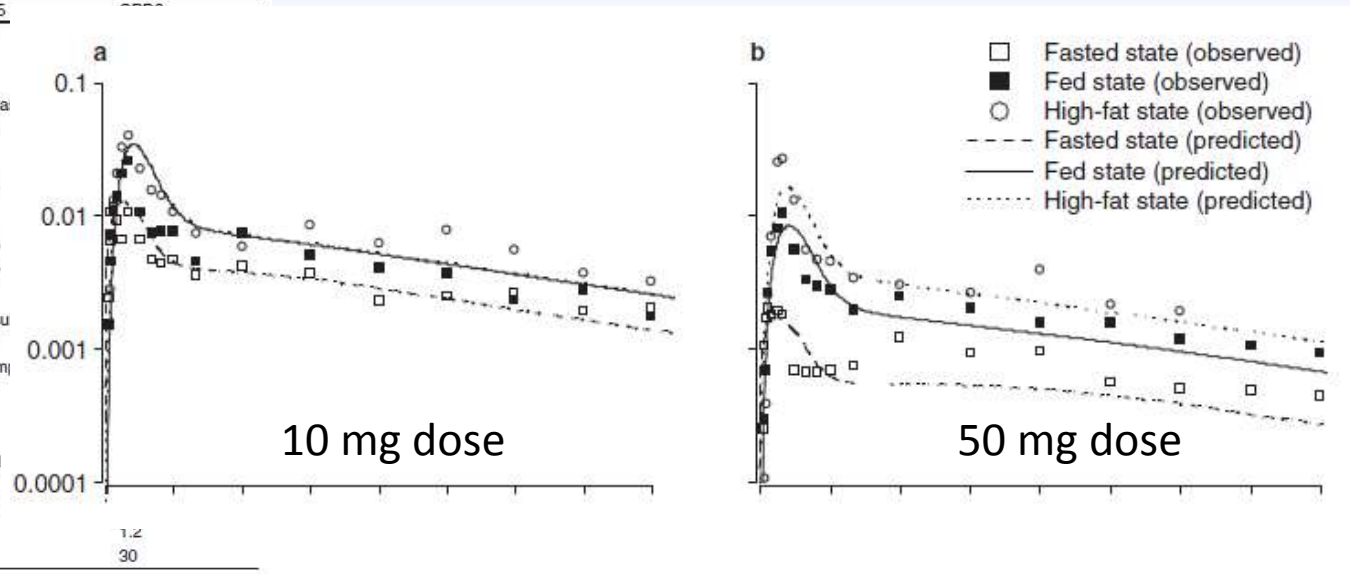
Predicting Pharmacokinetic Food Effects Using Biorelevant Solubility Media and Physiologically Based Modelling

Hannah M. Jones,[1] Neil Parrott,[1] Gerd Ohlenbusch[2] and Thierry Lavé[1]

1 Drug Metabolism and Pharmacokinetics, F. Hoffmann-La Roche Ltd, Basel, Switzerland
2 Pharmaceutical and Analytical R&D, F. Hoffmann-La Roche Ltd, Basel, Switzerland

Table II. Input data used for clinical food effect simulations

Parameter	CPD1	CPD2	CPD3	CPD4	CPD5
MW (g/mol)	566	579	632	393	605
Measured logD at pH 7.4	6.5	6.5	6.6	2.5[a]	2.7
LogP	6.5	6.5	6.6	2.7	3.9
Measured pKa	4.1 base	6.5, 2 base	4.2 base	5.7 base	8.6 ba
SGF(FA) solubility at pH 1.7 (mg/mL)	NA	NA	NA	0.0895	0.49
SGF(FE) solubility at pH 5 (mg/mL)	NA	NA	NA	0.0137	
FaSSIF solubility at pH 6.5 (mg/mL)	0.0062	1.03	0.0013	0.0085	0.26
FeSSIF solubility at pH 6.5 (mg/mL)	0.0375[b], 0.047	1.35	0.011	0.0533[c]	0.8[c]
FeSSIF(HF) solubility at pH 6.5 (mg/mL)	0.182	1.549	0.051	NA	NA
SCF I solubility at pH 5.2 (mg/mL)	<0.00005[d]	0.158	<0.00005[d]	0.0112	0.82[e]
SCF II solubility at pH 7.0 (mg/mL)	<0.00005[d]	<0.00005[d]	<0.00005[d]	0.005	0.45[e]
Particle radius (μm)	4.15	2.77	1.2	12.9	5.0
Formulation	Capsule	Capsule	Capsule	Tablet	Capsu
Effective human permeability (10^{-4} cm/s)	1.7	0.22	0.35	4.32	0.91
Disposition data	3-comp. fit[g]	2-comp. fit[g]	3-comp. fit[h]	2-comp. fit[g]	3-com
Human clearance (L/h)	15.4[i]	20.1[i]	5.39[i]	4.62[i]	19.6[i]
First-pass extraction in fasted state (%)	26	32	10	9	29
First-pass extraction in fed state (%)	20	24	7.5	7	22
Human f_u[k]	0.00095	0.0033	0.0007	0.075	0.021
Human B : P ratio[l]	0.65	0.69	0.6	0.55	0.75
Diffusion coefficient (cm^2/s)[m]	0.55	0.54	0.52	0.66	0.53
Particle density (g/mL)[n]	1.2	1.2	1.2	1.2	1.2
Diffusion layer thickness (μm)[n]	30	30	30	30	30



1.5- to 2.4-fold increase in AUC under fed conditions due to increased solubility at higher bile salt concentrations

Jones H, Clin. Pharmacokinet. 45(12):1213 (2006)

Mechanistic GI Physiology Changes to Predict Food Effects

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]

Table III. Comparison of Predicted *vs.* Observed Mean Plasma PK Parameters

Parameters		Suspension		IR tablet		XR tablet		XR capsule	
		Obs.	Pred.	Obs.	Pred.	Obs.	Pred.	Obs.	Pred.
Dose (mg)		200		400		400		300	
C_{max} (ng/mL)	Fasted	3066.7	2914.6	3610.1	3713.7	3005.2	3105.2	2066.1	2120.8
	Fed	2580.0	2506.9	5920.0	5501.2	3329.9	3786.6	2661.9	2798.5
AUC_t (μg×h/mL)	Fasted	166.6	163.3	279.8	301.6	270.4	263.7	194.3	190.2
	Fed	165.2	152.9	401.3	348.6	286.1	288.6	221.1	222.2
AUC_{inf} (μg×h/mL)	Fasted	179.8	177.3	298.6	330.0	285.8	272.2	226.4	203.8
	Fed	180.7	166.2	444.9	379.3	304.7	297.5	246.7	237.0
T_{max} (hr)	Fasted	1	1.45	24	16	24	28.9	26	20.98
	Fed	4	3.66	12	4.8	24	16.4	15	17.8
POT_{20} (hr)	Fasted	[0.6,8.5]	[0.8,10]	[3.7,41]	[2.9,40]	[10,42]	[13,44]	[8.2,54]	[8.9,48]
	Fed	[1.1,16]	[1.4,16]	[3.5,28]	[2.3,19]	[8.1,42]	[10,34]	[7.3,44]	[8.8, 39]
F_a (%)	Fasted	N.A.	99.9	N.A.	93.0	N.A.	71.6	N.A.	76.6
	Fed	N.A.	99.9	N.A.	99.8	N.A.	78.2	N.A.	89.0
Correlation coefficient (R^2)	Fasted	0.956		0.975		0.974		0.977	
	Fed	0.940		0.876		0.954		0.991	

POT_{20} peak occupancy time, time span over which the concentration is within 20% of C_{max}; F_a fraction absorbed; *N.A.* not available

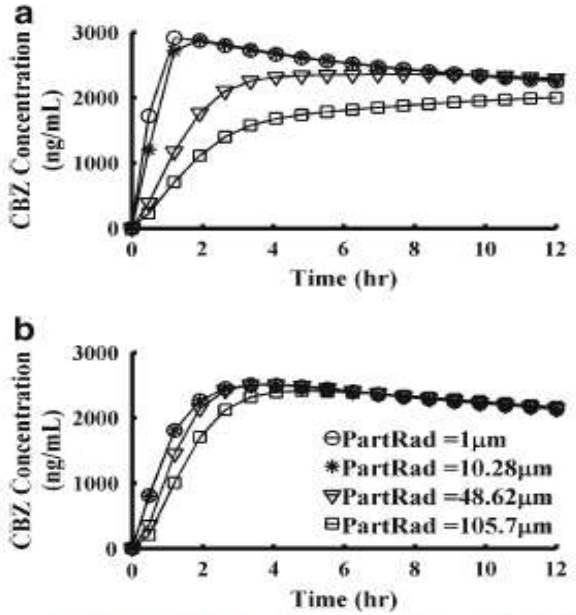


Fig. 7. PK profiles sensitivity to the mean particle radius is different under fasted and fed state. **a** IR suspension, fasted state; **b** IR suspension, fed state. Legend in (**b**) is also applied to (**a**)

Zhang et al. AAPS J. 13(1) (2011)

Proposed Flow Diagram for Simulation Studies in Quality by Design (QbD)

Build/validate models under **fasted** conditions

Predict absorption/PK exposure under **fed** conditions

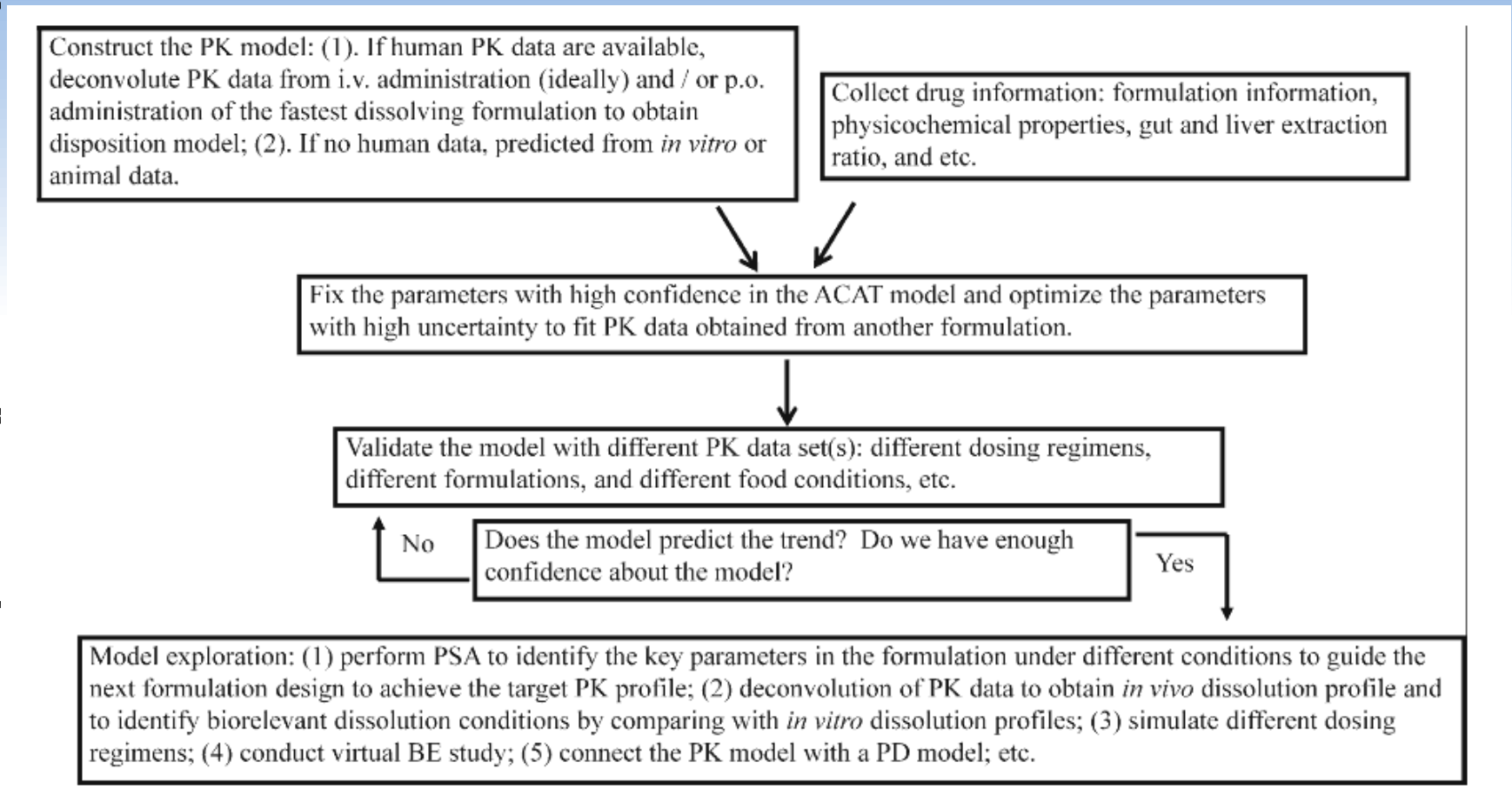


Fig. 1. The flow diagram shows a general process of using a physiologically based absorption model in QbD-based drug development

Zhang et al. AAPS J. 13(1) (2011)

FASTED VS. FED STATE MODEL DESCRIPTIONS – WHERE ARE WE TODAY?

What is ‘MAM’? What is ‘PBPK’?

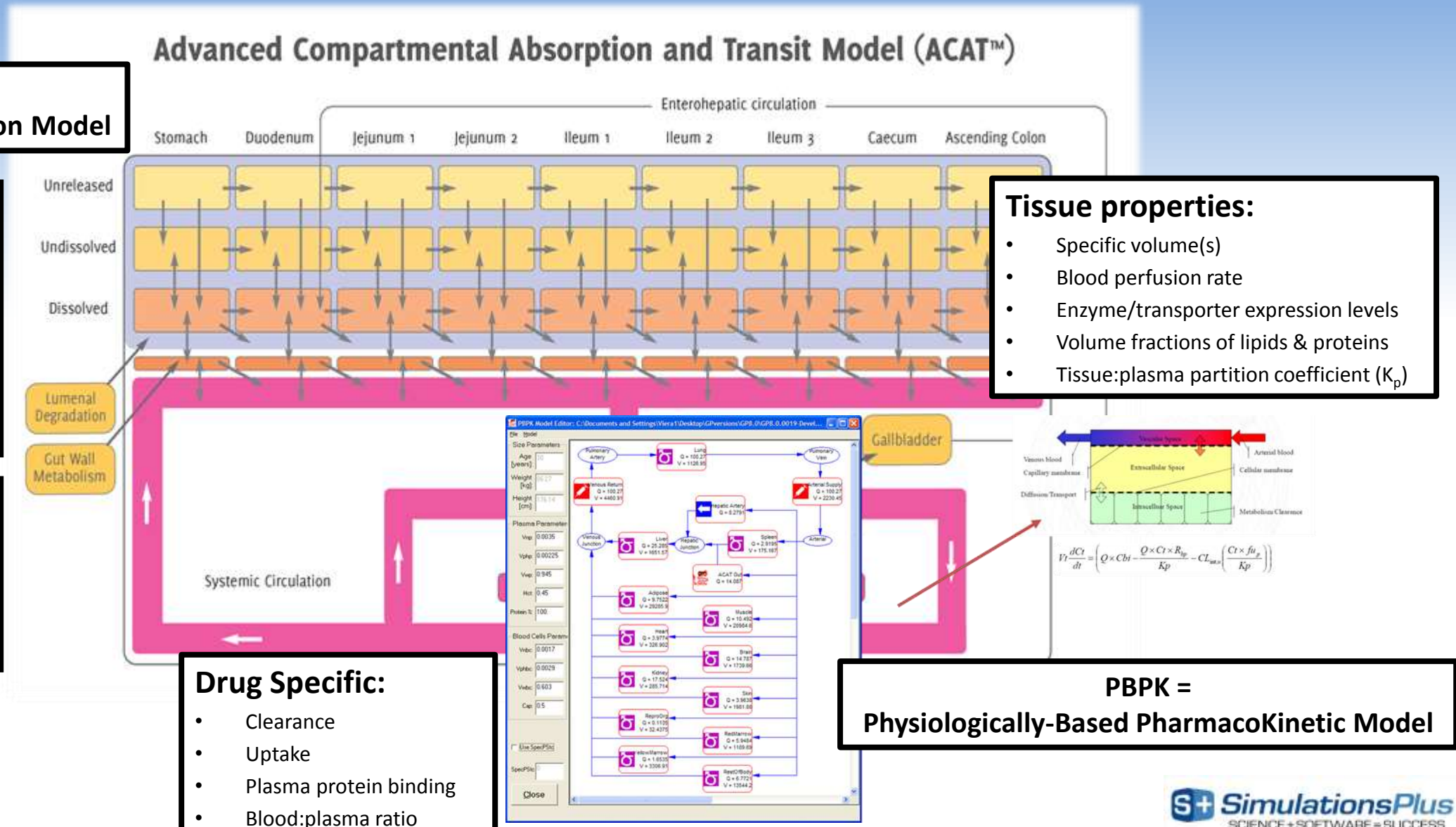
MAM =
Mechanistic Absorption Model

Physiological:

- pH gradients
- Dynamic fluid volumes
- Bile salt distributions
- Residence times
- Microvilli SAE
- Paracellular pore sizes
- Enzyme/transporter expressions

Drug Specific:

- pKa(s)
- Solubility vs. pH
- logD vs. pH
- Permeability
- Formulation properties



Tissue properties:

- Specific volume(s)
- Blood perfusion rate
- Enzyme/transporter expression levels
- Volume fractions of lipids & proteins
- Tissue:plasma partition coefficient (K_p)

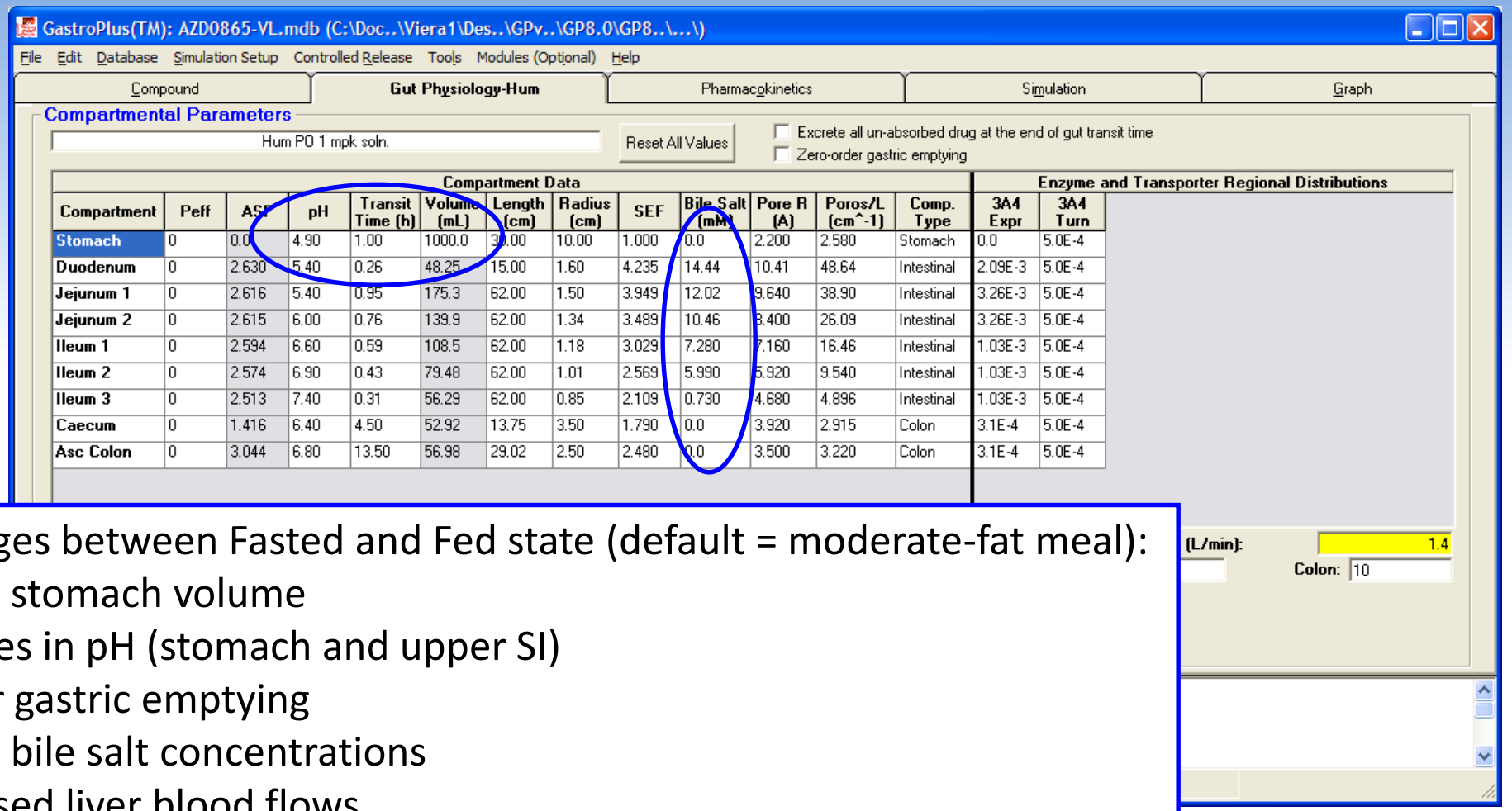
Drug Specific:

- Clearance
- Uptake
- Plasma protein binding
- Blood:plasma ratio

PBPK =
Physiologically-Based PharmacoKinetic Model

SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

Fed State – ACAT™ Model Changes



Compartment	Peff	ASF	pH	Transit Time (h)	Volume (mL)	Length (cm)	Radius (cm)	SEF	Bile Salt (mM)	Pore R (A)	Poros/L (cm^-1)	Comp. Type	3A4 Expr	3A4 Turn
Stomach	0	0.0	4.90	1.00	1000.0	30.00	10.00	1.000	0.0	2.200	2.580	Stomach	0.0	5.0E-4
Duodenum	0	2.630	5.40	0.26	48.25	15.00	1.60	4.235	14.44	10.41	48.64	Intestinal	2.09E-3	5.0E-4
Jejunum 1	0	2.616	5.40	0.95	175.3	62.00	1.50	3.949	12.02	9.640	38.90	Intestinal	3.26E-3	5.0E-4
Jejunum 2	0	2.615	6.00	0.76	139.9	62.00	1.34	3.489	10.46	8.400	26.09	Intestinal	3.26E-3	5.0E-4
Ileum 1	0	2.594	6.60	0.59	108.5	62.00	1.18	3.029	7.280	7.160	16.46	Intestinal	1.03E-3	5.0E-4
Ileum 2	0	2.574	6.90	0.43	79.48	62.00	1.01	2.569	5.990	5.920	9.540	Intestinal	1.03E-3	5.0E-4
Ileum 3	0	2.513	7.40	0.31	56.29	62.00	0.85	2.109	0.730	4.680	4.896	Intestinal	1.03E-3	5.0E-4
Caecum	0	1.416	6.40	4.50	52.92	13.75	3.50	1.790	0.0	3.920	2.915	Colon	3.1E-4	5.0E-4
Asc Colon	0	3.044	6.80	13.50	56.98	29.02	2.50	2.480	0.0	3.500	3.220	Colon	3.1E-4	5.0E-4

Main changes between Fasted and Fed state (default = moderate-fat meal):

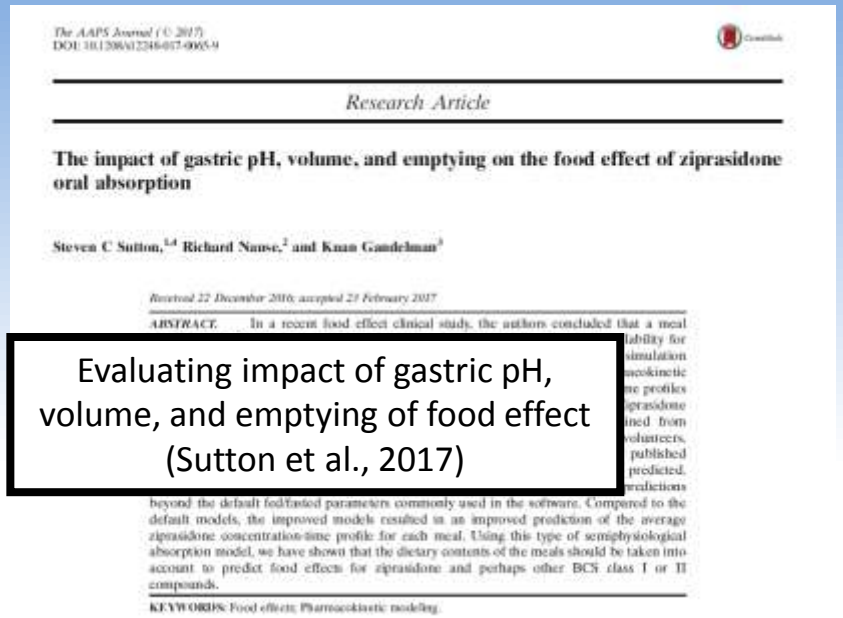
- Higher stomach volume
- Changes in pH (stomach and upper SI)
- Longer gastric emptying
- Higher bile salt concentrations
- Increased liver blood flows

Fed State – Light and High-Fat/Caloric Meals

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

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

Food Effect Predictions – Select References

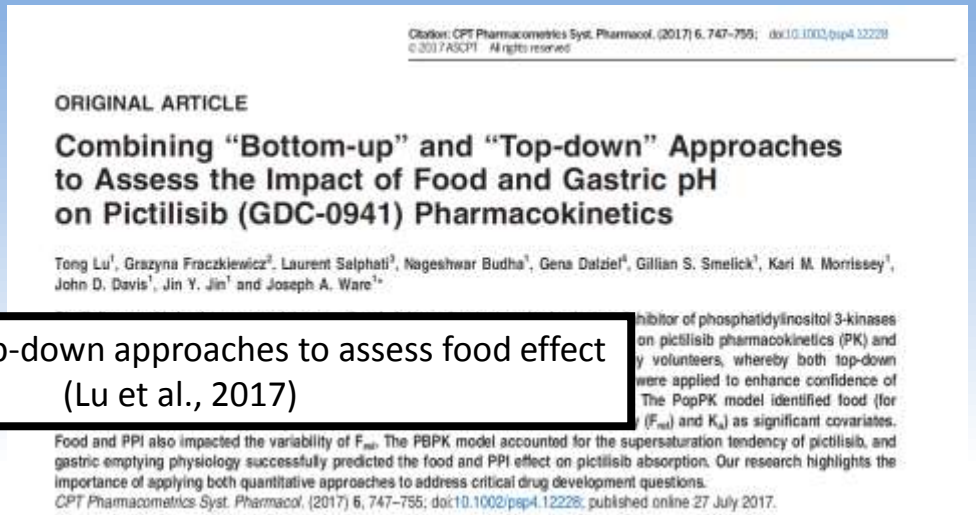


Research Article

The impact of gastric pH, volume, and emptying on the food effect of ziprasidone oral absorption

Steven C Sutton,[1,4] Richard Nause,[2] and Kuan Gandelman[3]

Evaluating impact of gastric pH, volume, and emptying of food effect (Sutton et al., 2017)



ORIGINAL ARTICLE

Combining "Bottom-up" and "Top-down" Approaches to Assess the Impact of Food and Gastric pH on Pictilisib (GDC-0941) Pharmacokinetics

Tong Lu[1], Grazyna Fraczkiewicz[2], Laurent Salphati[3], Nageshwar Budha[1], Gena Dalziel[4], Gillian S. Smelick[1], Kari M. Morrissey[1], John D. Davis[1], Jin Y. Jin[1] and Joseph A. Ware[1]*

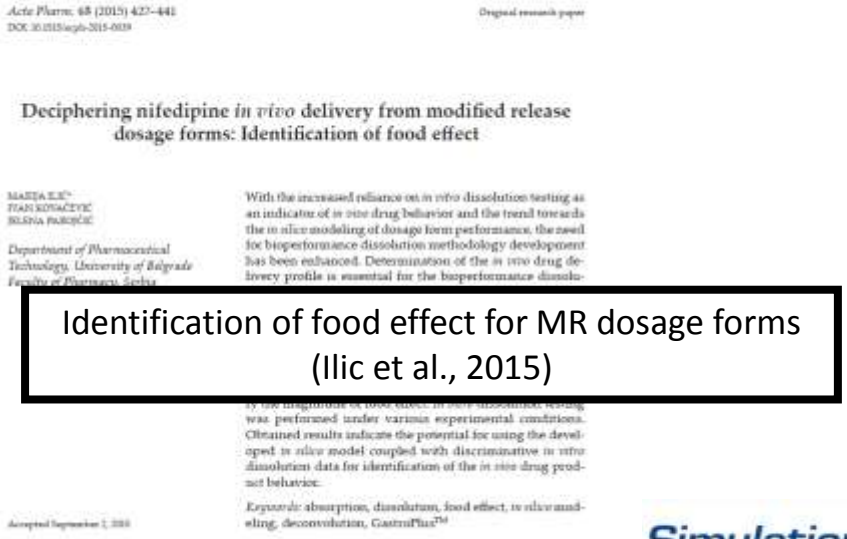
Bottom-up + Top-down approaches to assess food effect (Lu et al., 2017)

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

Utilizing Physiologically Based Pharmacokinetic Modeling to Inform Formulation and Clinical Development for a Compound with pH-Dependent Solubility

JOHN CHUNG,[1] FERNANDO ALVAREZ-NUNEZ,[1] VINCENT CHOW,[2] DOMINICK DAURIO,[1] JOHN DAVIS,[2] MICHAEL DODDS,[2] MAURICE EMERY,[3] KEVIN LITWILER,[4] ANNE PACCALY,[2] JOANNA PENG,[2] BROOKE ROCK,[2] LARRY WIENKERS,[2] CHARLES YANG,[1] ZHIGANG YU,[1] JAN WAHLSTROM[2]

Applying PBPK modeling to inform clinical development and assess food effects (Chung et al., 2015)



Deciphering nifedipine *in vivo* delivery from modified release dosage forms: Identification of food effect

Identification of food effect for MR dosage forms (Ilic et al., 2015)

SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

POSITIVE FOOD EFFECT PREDICTIONS – INPUT REVIEW

Food Effect Modeling – Class II/IV Compound 'X'

AAPS PharmSciTech (© 2014)
DOI: 10.1208/s12249-014-0075-1

Research Article

Application of Physiologically Based Absorption Modeling to Formulation Development of a Low Solubility, Low Permeability Weak Base: Mechanistic Investigation of Food Effect

Hefei Zhang,[1,2] Binfeng Xia,[1] Jennifer Sheng,[1] Tycho Heimbach,[1] Tsu-Han Lin,[1] Handan He,[1] Yunfeng Wang,[1] Steven Novick,[1] and Ann Comfort[1]

Received 2 October 2013; accepted 23 December 2013

- **Compound X (BCS Class II/IV)**
- Lipophilic (log P > 4) and moderate base (pKa 3.2 and 6.2)
- Low (0.001 mg/mL), pH dependent aqueous solubility
- Moderate intestinal permeability (1.48 x 10^{-4} cm/s)
- Estimated bioavailability of compound is ~30%

Table II. Physicochemical Parameters, Default Physiological Values, and Pharmacokinetic Parameter Used in the Simulation at Various Doses

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)
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

Are the different (fitted) precipitation and gastric emptying times under fasted & fed conditions masking something else in the model?

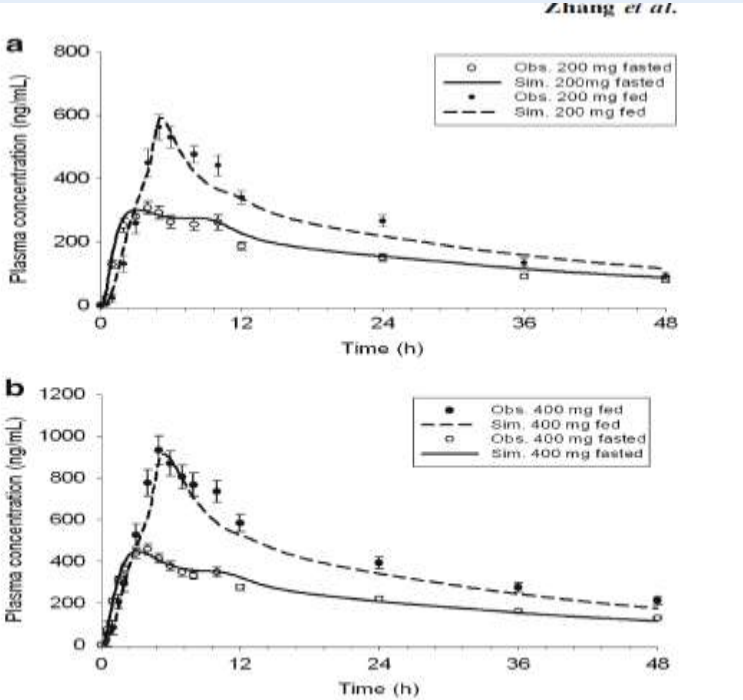


Fig. 1. Mean clinically observed (*solid circles* with standard error) and model-simulated plasma concentration *versus* time profiles of cpd X after a single oral dose of **a** 200 mg or **b** 400 mg cpd X under fasted and fed condition

Zhang et al. AAPS PharmSciTech 2014 January 17

SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

Lysosomal Trapping of Lipophilic Cations

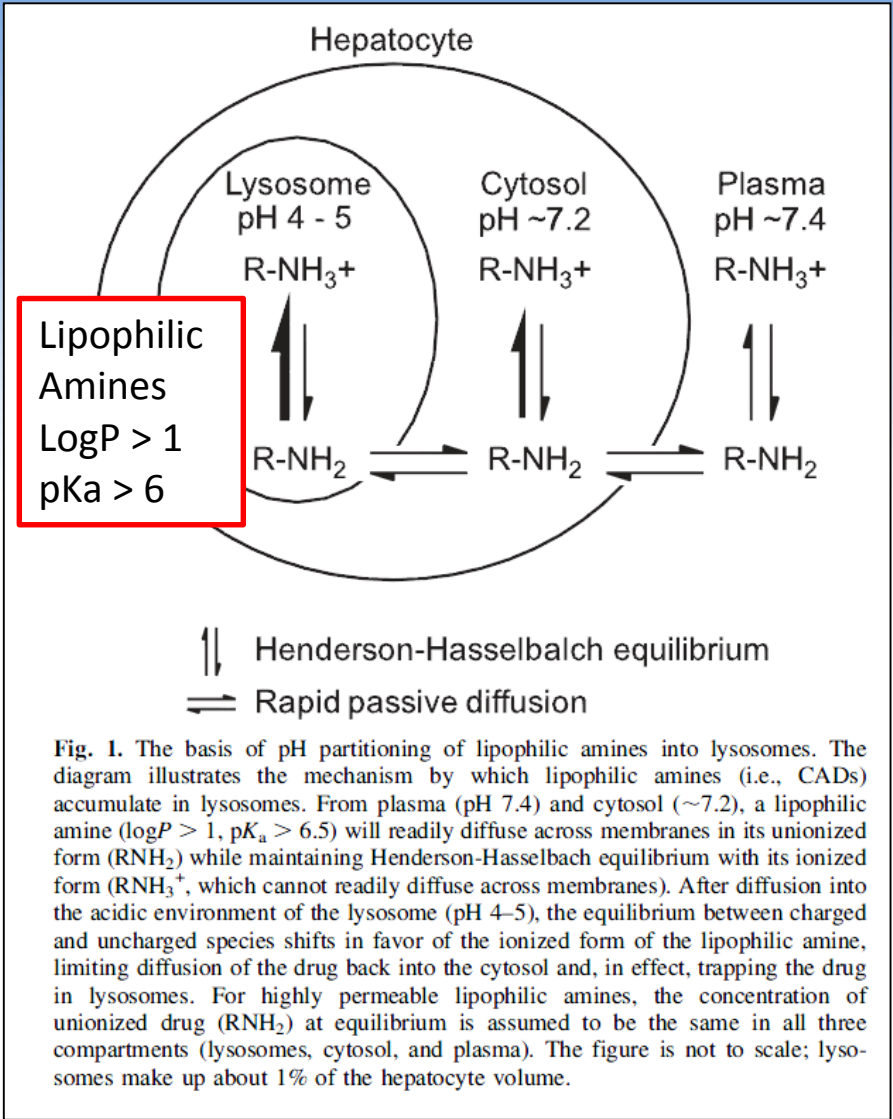
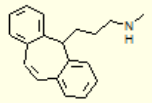
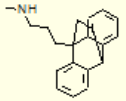
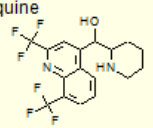
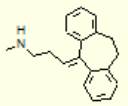
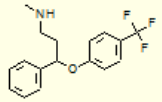
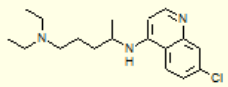


Fig. 1. The basis of pH partitioning of lipophilic amines into lysosomes. The diagram illustrates the mechanism by which lipophilic amines (i.e., CADs) accumulate in lysosomes. From plasma (pH 7.4) and cytosol (~7.2), a lipophilic amine ($\log P > 1$, $pK_a > 6.5$) will readily diffuse across membranes in its unionized form (RNH_2) while maintaining Henderson-Hasselbach equilibrium with its ionized form (RNH_3^+, which cannot readily diffuse across membranes). After diffusion into the acidic environment of the lysosome (pH 4–5), the equilibrium between charged and uncharged species shifts in favor of the ionized form of the lipophilic amine, limiting diffusion of the drug back into the cytosol and, in effect, trapping the drug in lysosomes. For highly permeable lipophilic amines, the concentration of unionized drug (RNH_2) at equilibrium is assumed to be the same in all three compartments (lysosomes, cytosol, and plasma). The figure is not to scale; lysosomes make up about 1% of the hepatocyte volume.

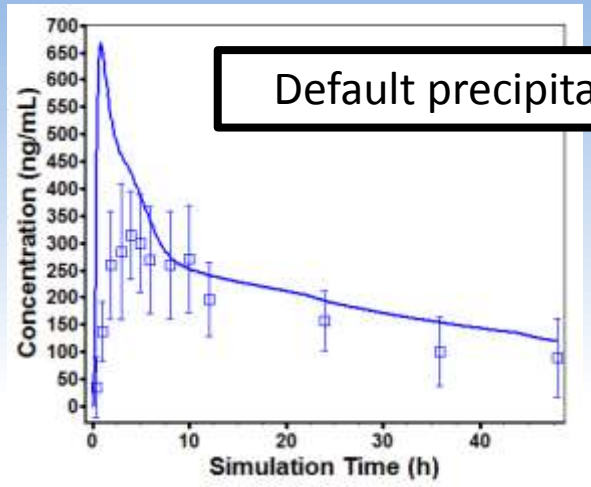
Drug	Log P	Basic pKa	T_{max} (h)
Protriptyline 	4.69	10.0	27
Maprotiline 	4.7	10.1	16
Mefloquine 	3.81	8.52	15
Nortriptyline 	4.46	9.65	7.8
Fluoxetine 	4.39	9.82	7
Chloroquine 	5.11	9.86	6

Kazmi F., Drug Metab. Disp. 41(3):897 (2013)

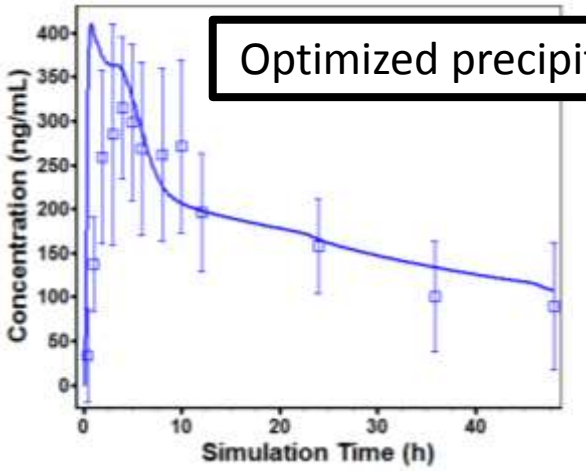
Compound ‘X’ – Fasted State Model Development

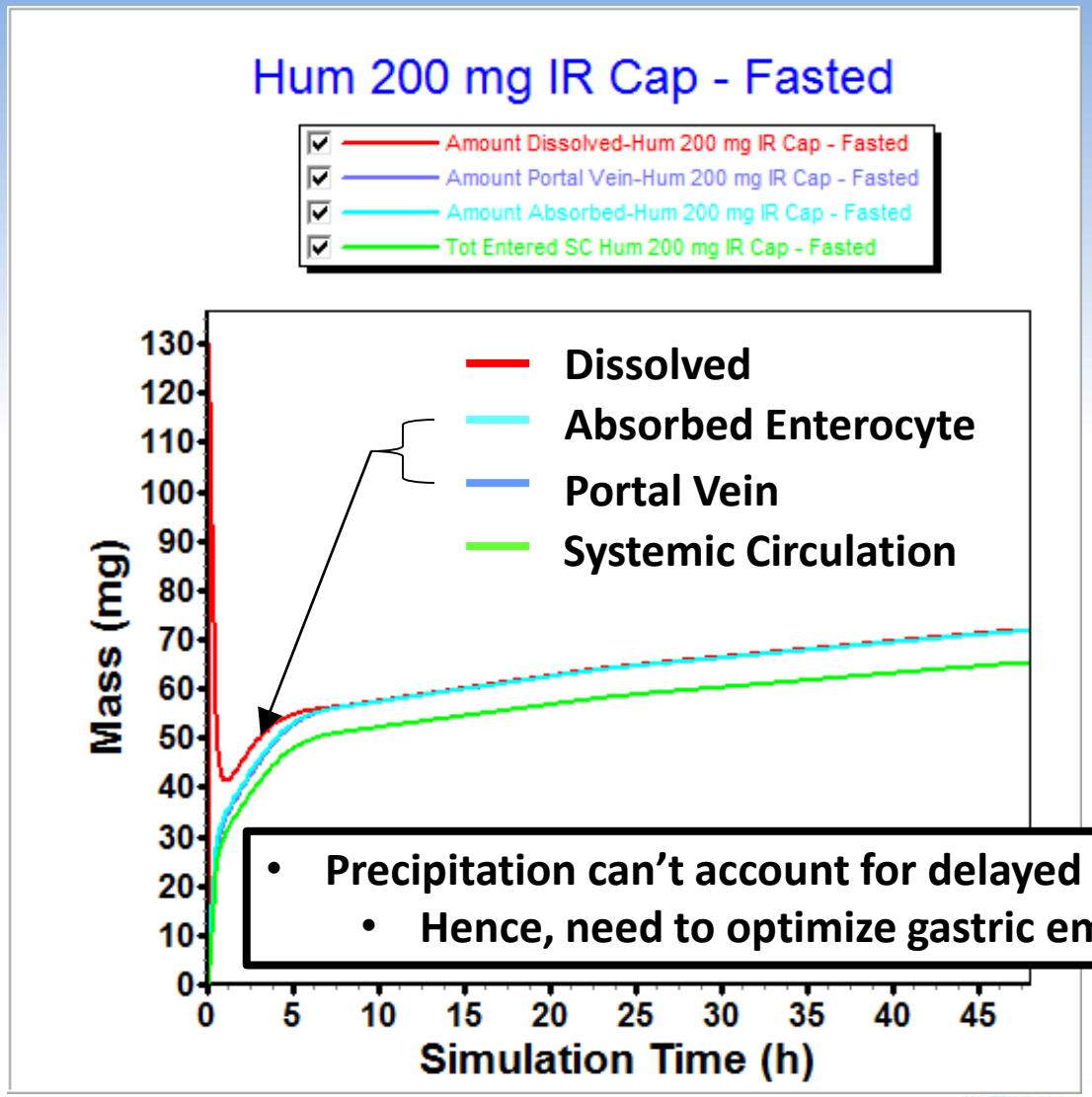
Measured & ACAT™ Default Model Parameters

Default precipitation



Optimized precipitation

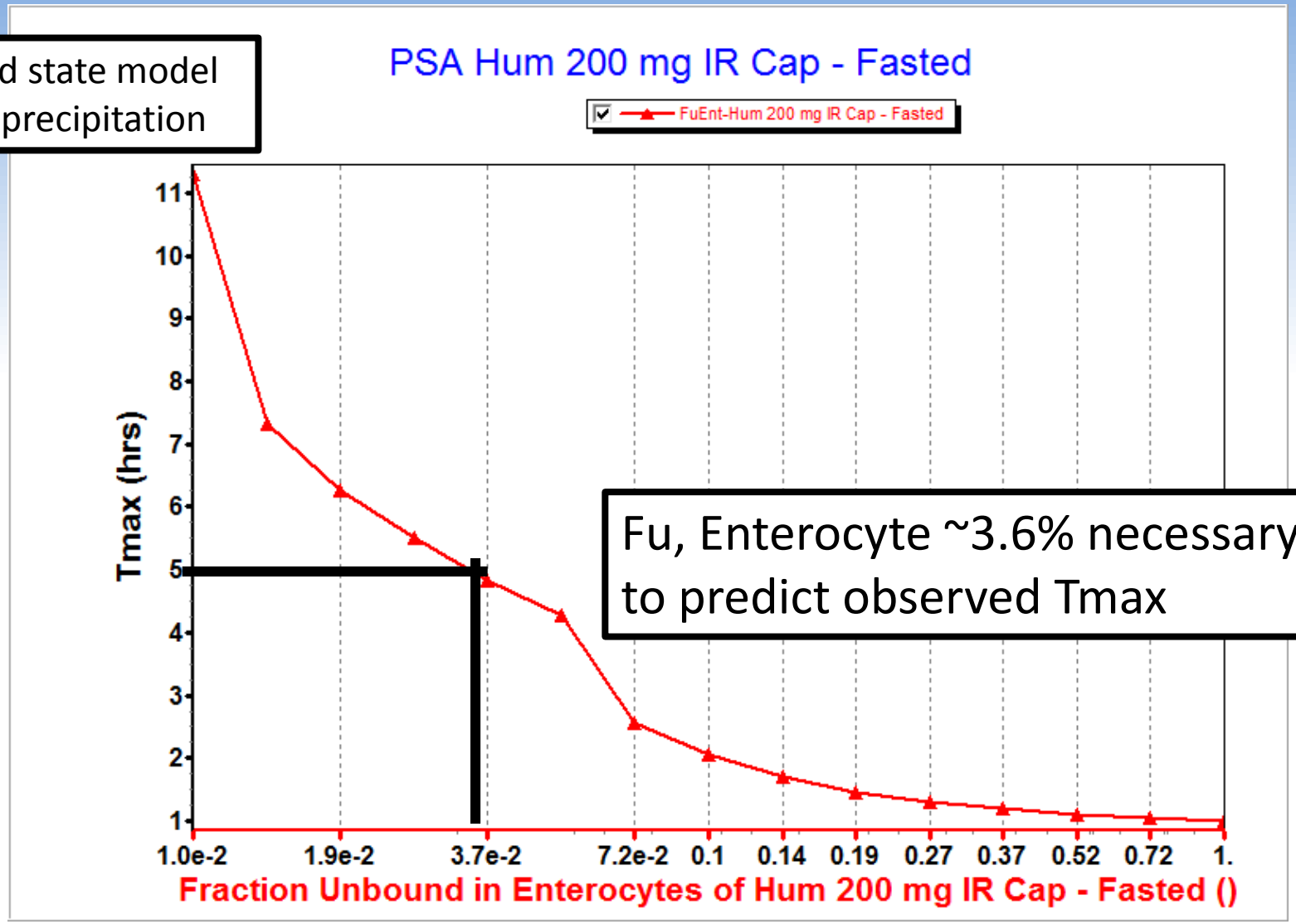




- Precipitation can’t account for delayed onset alone
- Hence, need to optimize gastric emptying time

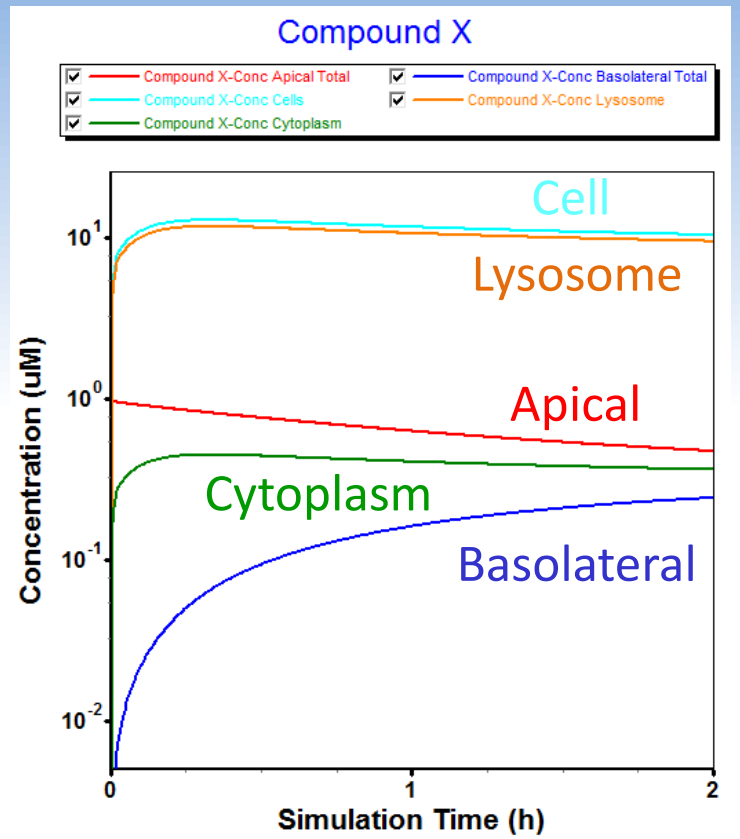
Compound ‘X’ – PSA Around Fu, Enterocyte

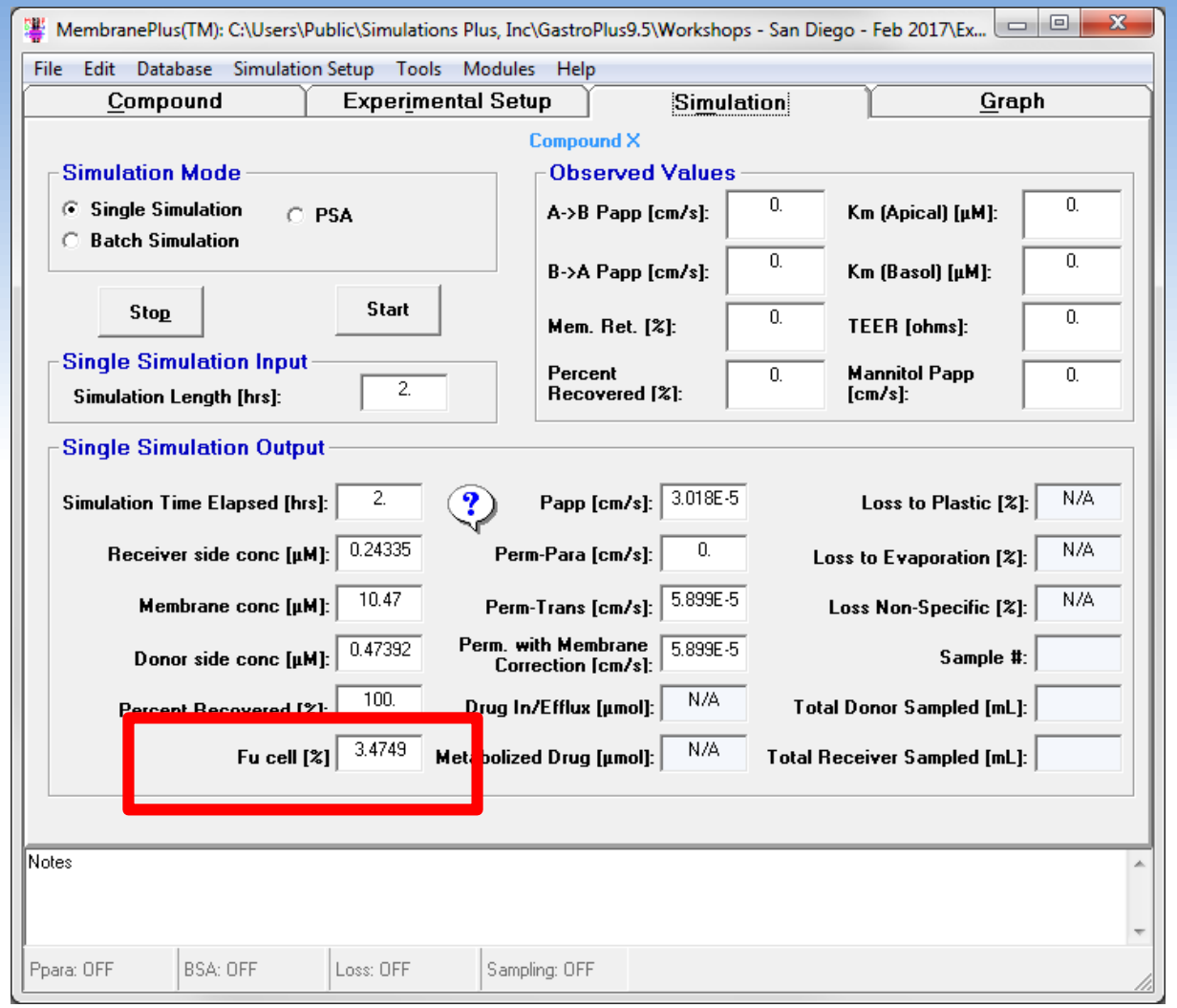
Baseline fasted state model w/optimized precipitation



Fu, Enterocyte ~3.6% necessary to predict observed Tmax

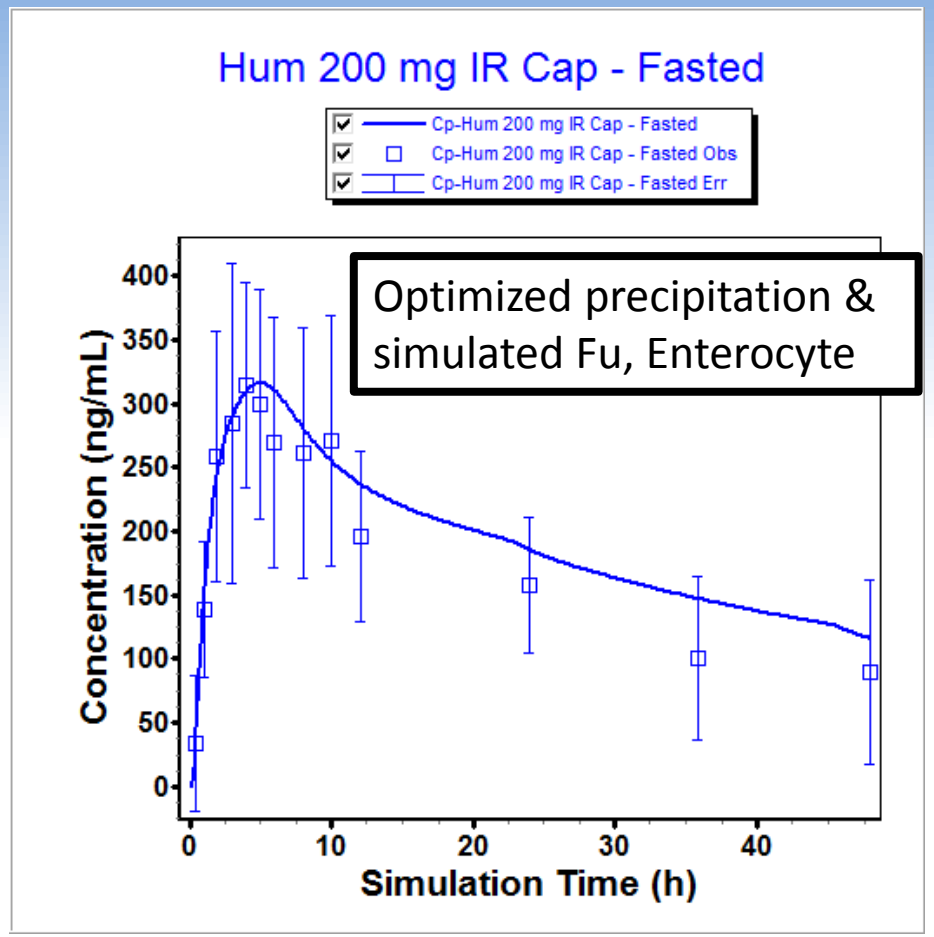
Compound X: MembranePlus™ Fu, Enterocyte Prediction

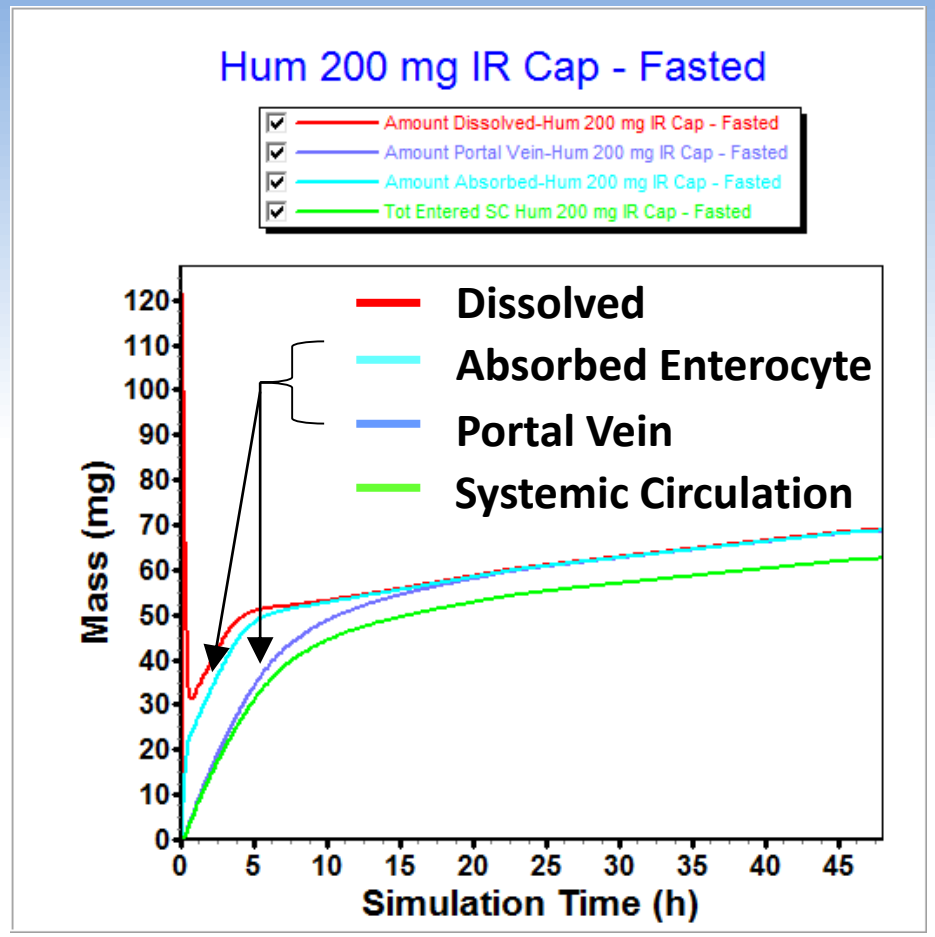




Mechanistic simulated Fu, Enterocyte = 3.47% matches close to the value determined from the GastroPlus™ PSA predictions

Compound ‘X’: GastroPlus™ Simulations with MembranePlus™ Fu, Enterocyte = 3.47%

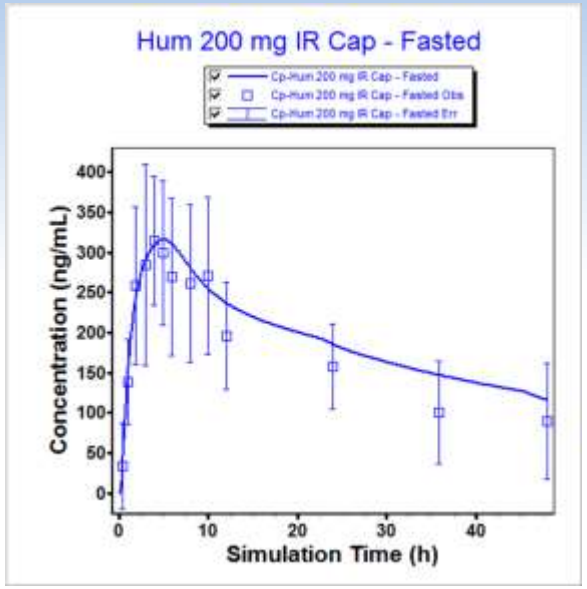


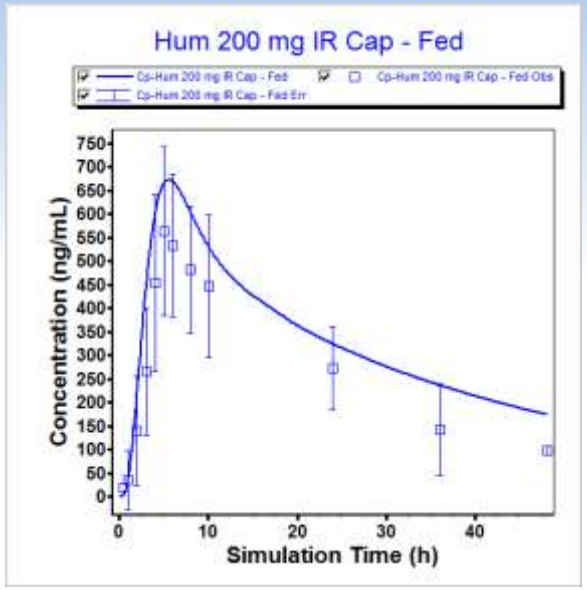


- The lag between absorption into enterocyte and basolateral clearance into portal vein captures the extended Tmax
- **No changes to default GI physiology required**

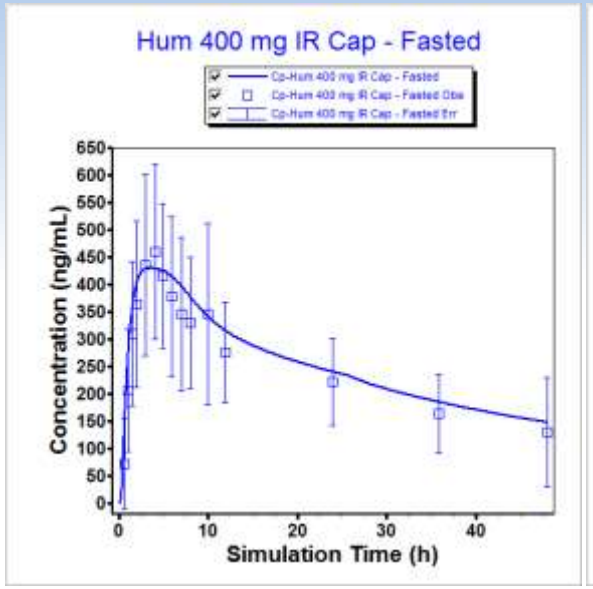
Compound ‘X’ – Food Effect Predictions Across Doses

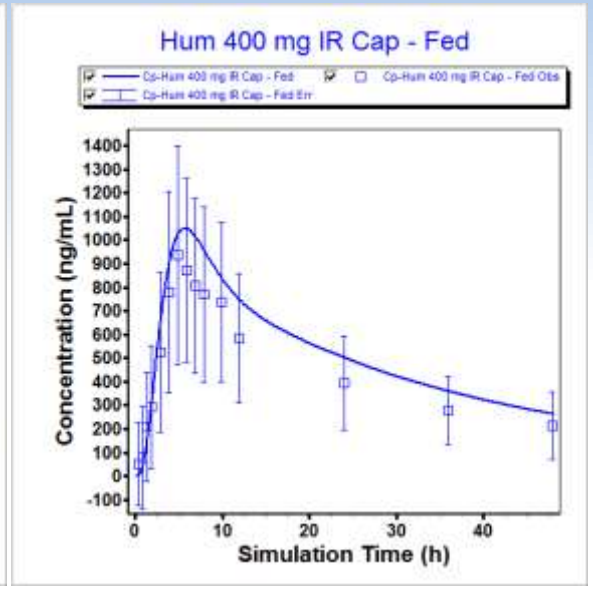
200 mg dose





400 mg dose

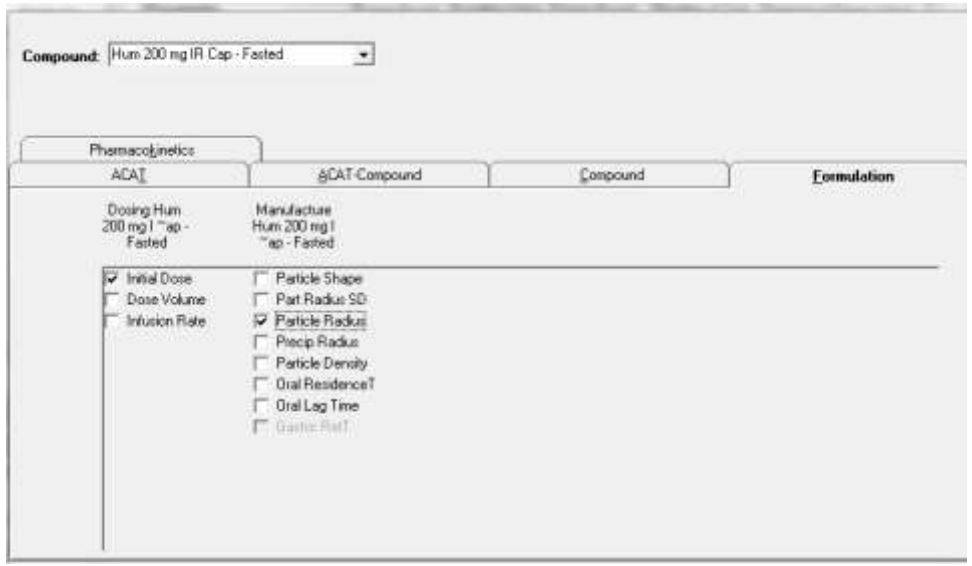


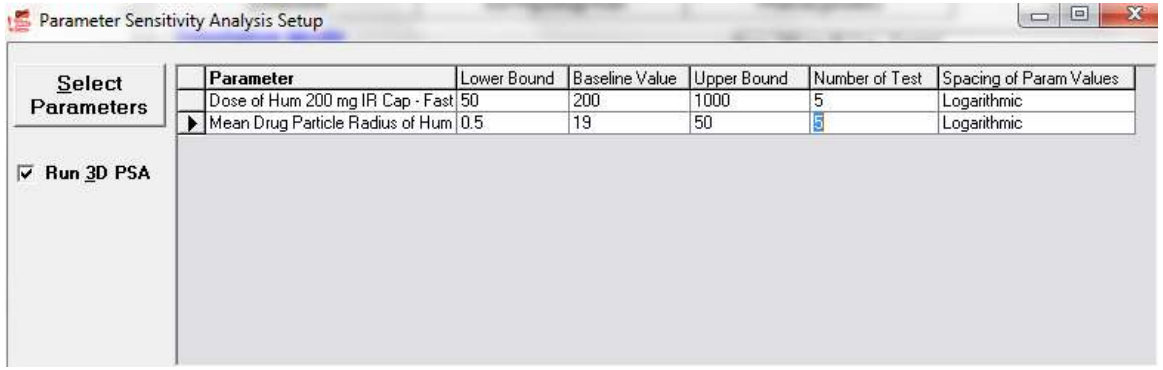


- Optimized precipitation from **low dose/fasted state PK data** + simulated MembranePlus™ Fu, Enterocyte input
- Default ACAT™ fasted/fed physiology parameters

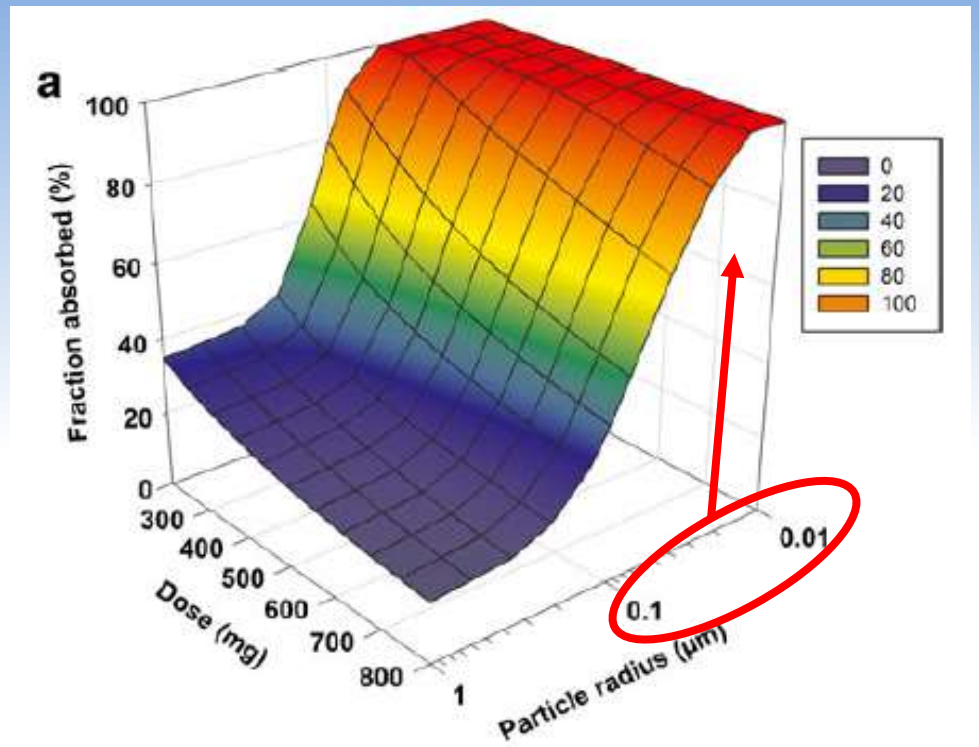
Mitigating Food Effect: Design of Experiments (DoE) Approach

- 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?

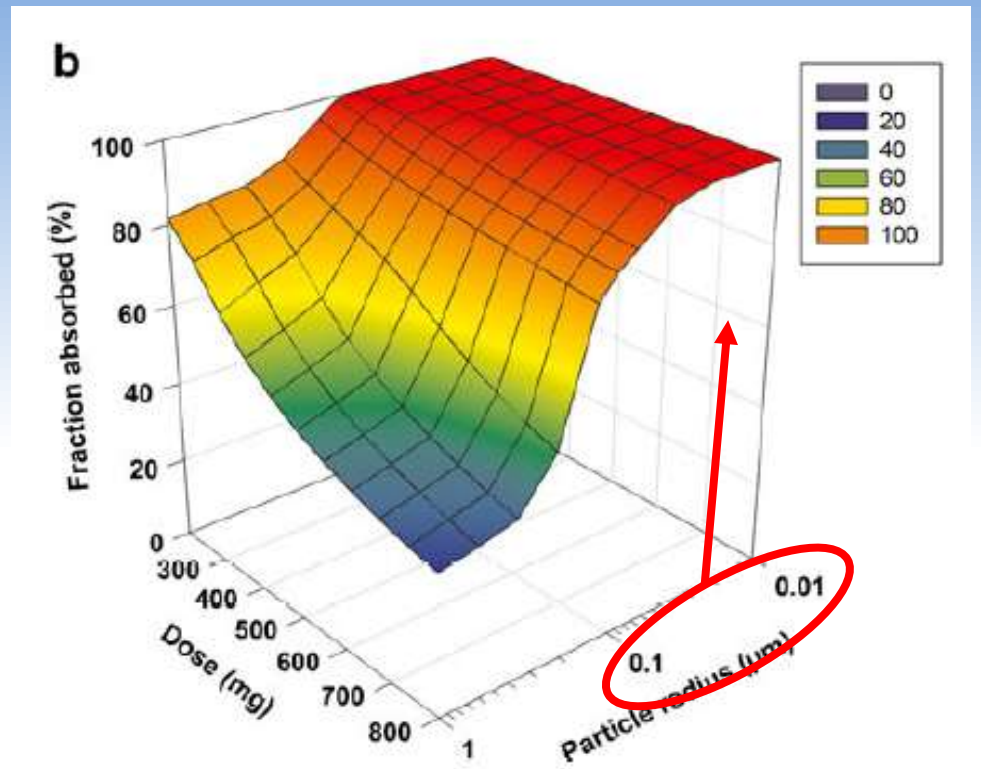




3D Parameter Sensitivity Analysis (PSA)



Fasted



Fed

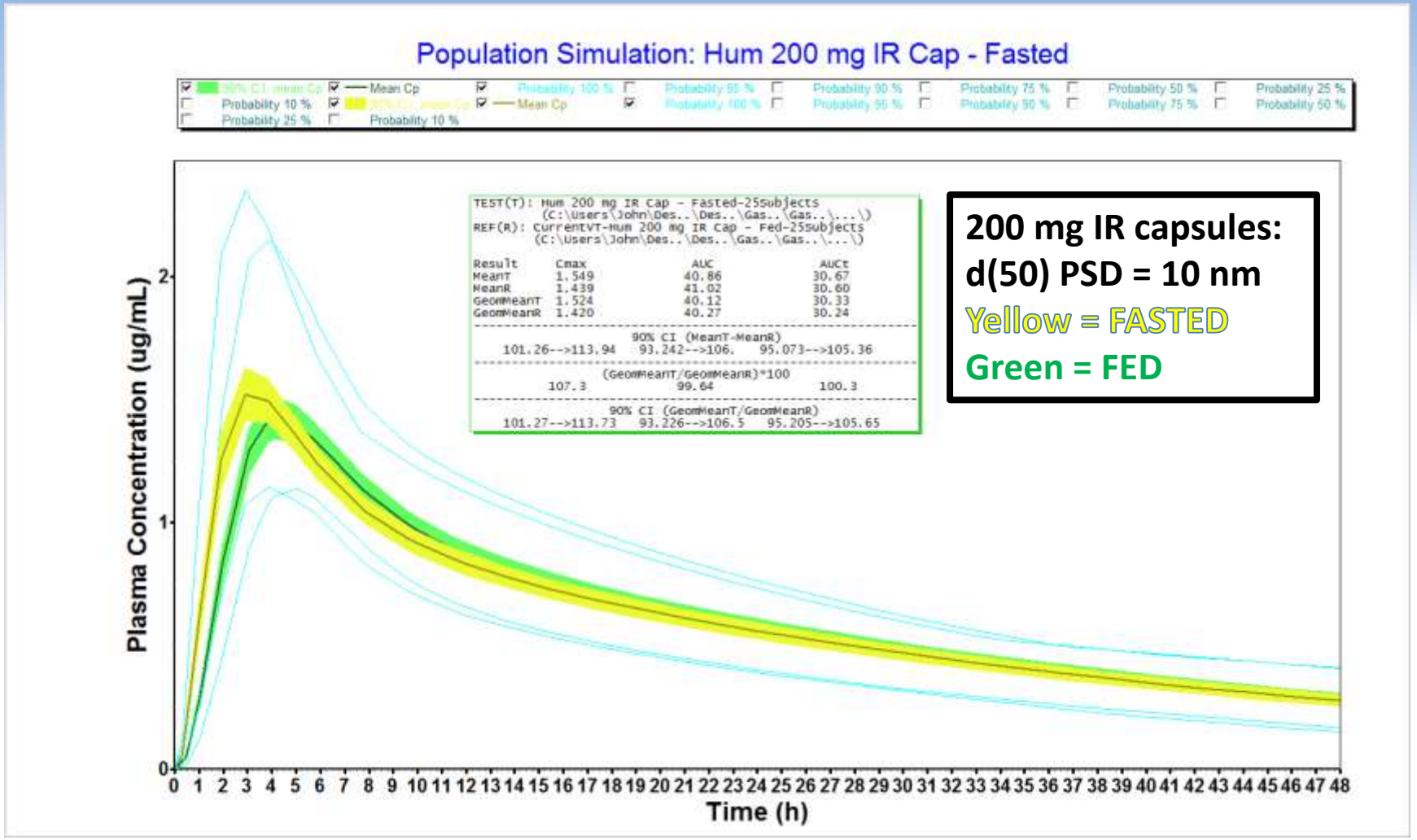
- Parameter sensitivity analysis was run across dose and particle size together
- API particle size reduction may be useful to mitigate the food effect
  - But, only if nanoparticle formulations are options

Zhang et al. AAPS PharmSciTech 2014 January 17

Virtual BE Trial Simulation: Fasted vs. Fed Crossover – 25 Subjects

PBPK Population Simulation Approach:

1. Run ‘x’ subject population simulation **applying systemic PK variability only**
2. Load subjects from trial #1 and **apply variability to fasted state ACAT™ model**
3. Load subjects from trial #1 and **apply variability to fed state ACAT™ model**
4. Calculate virtual BE



NEGATIVE FOOD EFFECT PREDICTIONS – *IN VITRO* CONSIDERATIONS

Food Effect Modeling – Class III Charged Compound

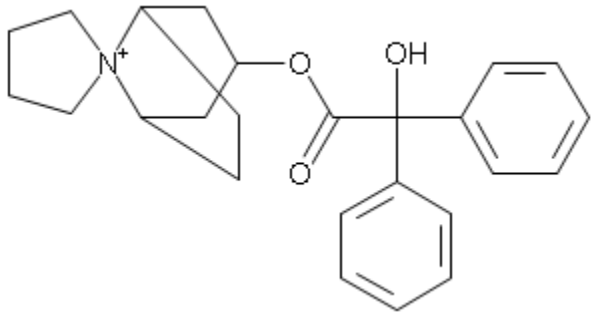
BIOPHARMACEUTICS & DRUG DISPOSITION
Biopharm. Drug Dispos. 33: 403–416 (2012)
Published online 11 August 2012 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/bdd.1798

Mechanistic investigation of food effect on disintegration and dissolution of BCS class III compound solid formulations: the importance of viscosity

Asma Radwan[a], Gordon L. Amidon[b], and Peter Langguth[a,*]
[a]*Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, Mainz, Germany*
[b]*College of Pharmacy, The University of Michigan, Ann Arbor, MI 48109-1065, USA*

Trospium HCl

- BCS Class III
- Hydrophilic (log P = -1.22)
- High (~700 mg/mL)
- Low intestinal permeability (0.07 x 10^{-4} cm/s)
- Not Metabolized
- Estimated bioavailability of compound is ~10%



Trospium Solution Viscosity

Table 2. Physicochemi
were performed once.

Media	
SIF	
0.1 N HCl	
0.5% HPMC (pH = 6.8)	
1% HPMC (pH = 6.8)	
2% HPMC (pH = 6.8)	
Acetate buffer	
0.5% HPMC (pH = 4.6)	
1% HPMC (pH = 4.6)	
2% HPMC (pH = 4.6)	
0.25% guar (pH = 6.8)	
0.5% guar (pH = 6.8)	
0.75% guar (pH = 6.8)	

lity, determinations
ns are reported

pressure (mmol/kg)

95
188
115
125
200
74
82
84
86
105
106
109

ND, not determined.

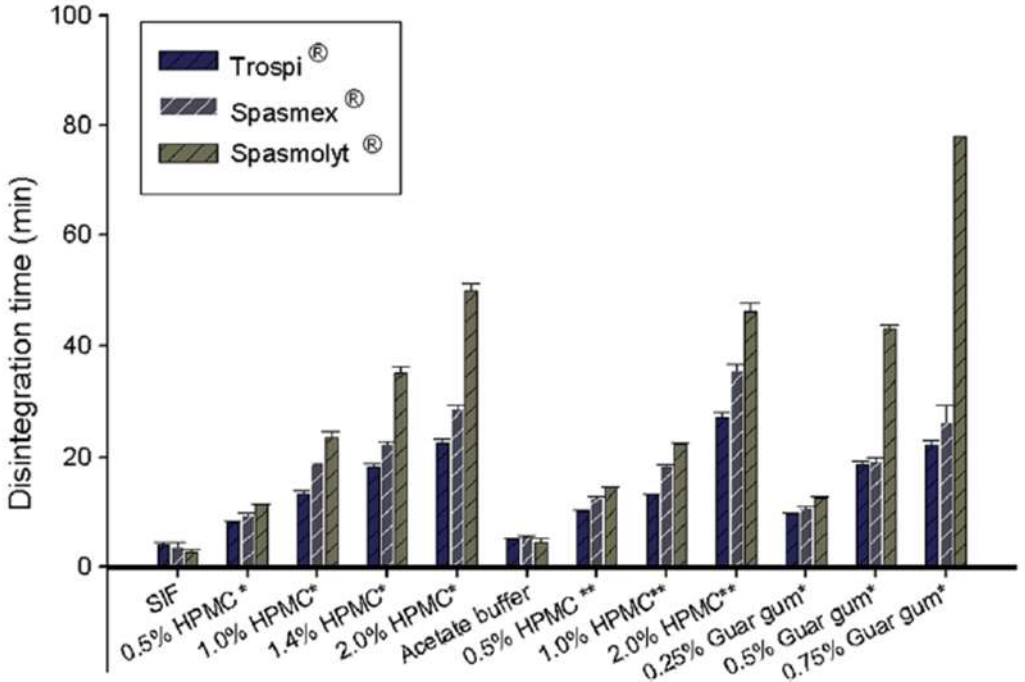


Figure 3. Disintegration times of various trospium chloride products in different disintegration media. The effects of increasing media viscosity on disintegration times were in all cases significant ($p < 0.05$), whereas the effect of change of pH for HPMC solutions at the same concentrations of VEA was insignificant ($p > 0.05$). *pH 6.8; **pH 4.6

os. 33: 403–416 (2012)
DOI: 10.1002/bdd

Trospium *in vitro* Dissolution

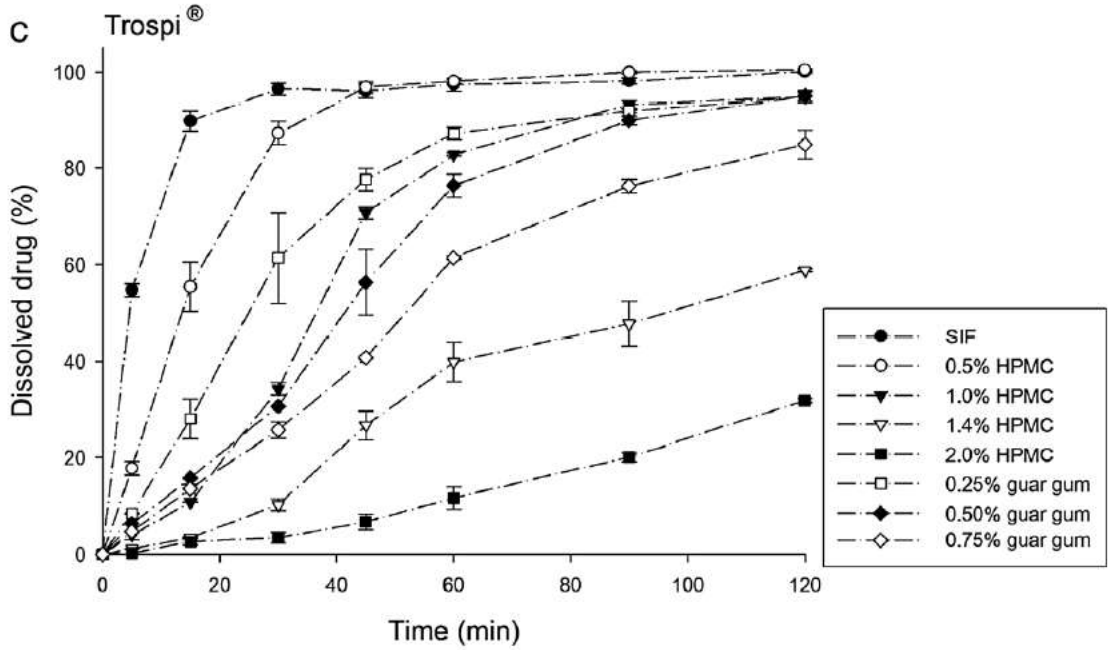


Figure 5. (a) Dissolution profiles for Spasmolyt® in viscous HPMC and guar solutions at pH 6.8, 50 rpm in USP-2 apparatus. In all cases values for f_2 were < 50. Mean ± SD, $n = 3$. (b) Dissolution profiles for Spasmex® in viscous HPMC and guar solutions at pH 6.8, 50 rpm in USP-2 apparatus. In all cases values for f_2 were < 50. Mean ± SD, $n = 3$. (c) Dissolution profiles for Trospi® in viscous HPMC and guar solution at pH 6.8, 50 rpm in USP-2 apparatus. In all cases values for f_2 were < 50. Mean ± SD, $n = 3$

Radwan et al. Biopharm. Drug Dispos. 33:403 (2012)

Negative Food Effect – Predictions

Model building steps:

1. Create virtual human physiology
2. Incorporate *in silico/in vitro* property data
3. Utilize *in vitro* dissolution data from 'fasted' method to fit Z-Factor
4. Build MAM/PBPK model under fasted conditions
5. Utilize *in vitro* dissolution data from 'fed' method (high viscosity) to fit Z-Factor
6. Apply baseline MAM/PBPK model to predict PK profiles under fed conditions

Model results:

1. Capture fasted state PK profile well
2. Predict trend, but not magnitude, of negative food effect

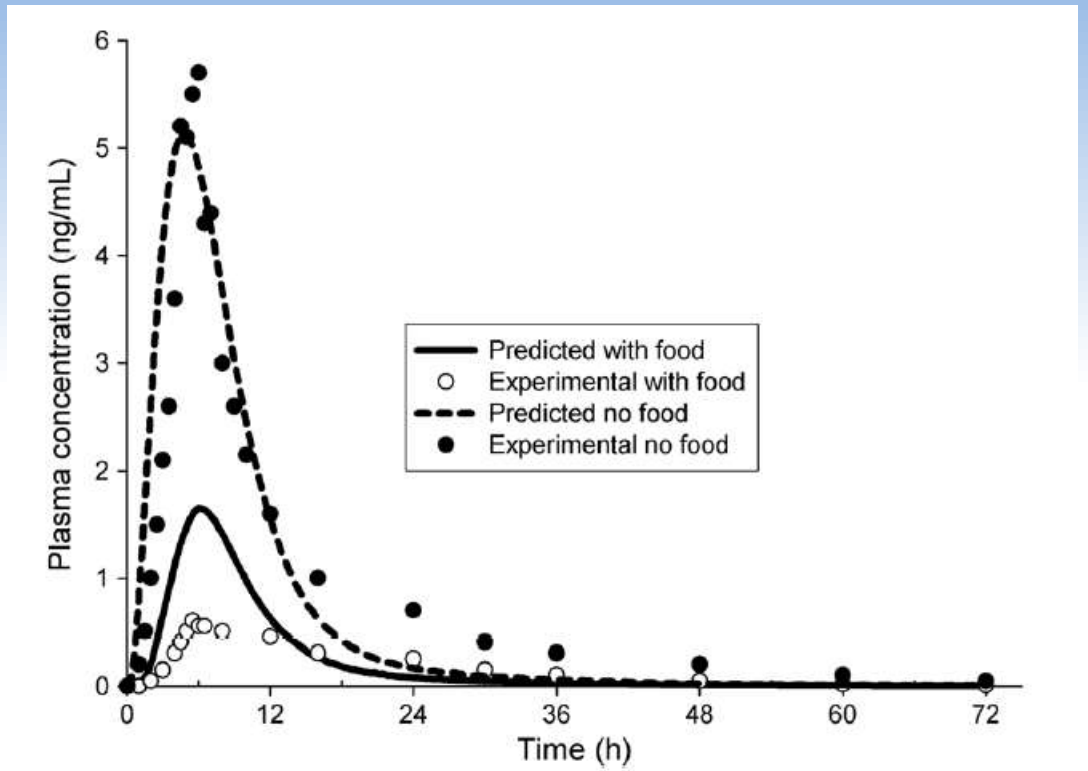
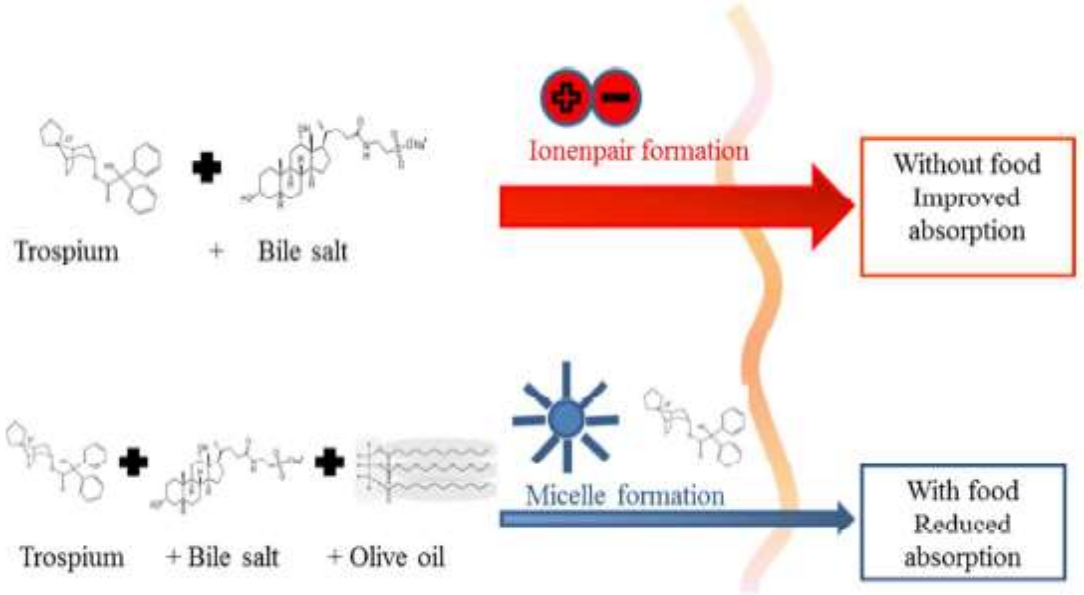


Figure 8. Simulated and predicted plasma concentration–time profiles for trospium in fasted and fed states in humans

Radwan et al. Biopharm. Drug Dispos. 33:403 (2012)

Ion pairing with bile salts modulates intestinal permeability and contributes to food-drug interaction of BCS class III compound trospium chloride



*Corresponding author:

Tel: +49 6131 39 24319

Fax: +49 6131 39 25021

E-mail address: langguth@uni-mainz.de

Novartis Negative Food Effect: Caco-2 Experiment in FeSSIF Buffer

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

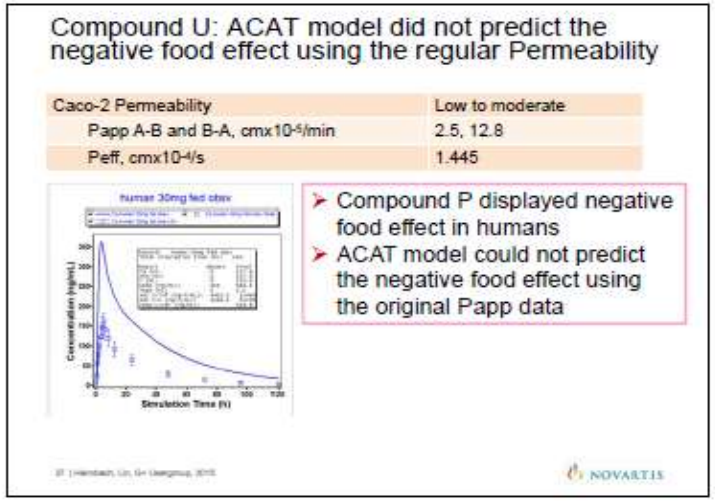
Research paper

Biorelevant media for transport experiments in the Caco-2 model to evaluate drug absorption in the fasted and the fed state and their usefulness

C. Mariospoulos, F. Thoenen, D. Preisig, M. Symillides, M. Vertzoni, N. Parrott, C. Reppas, G. Imanidis

ARTICLE INFO

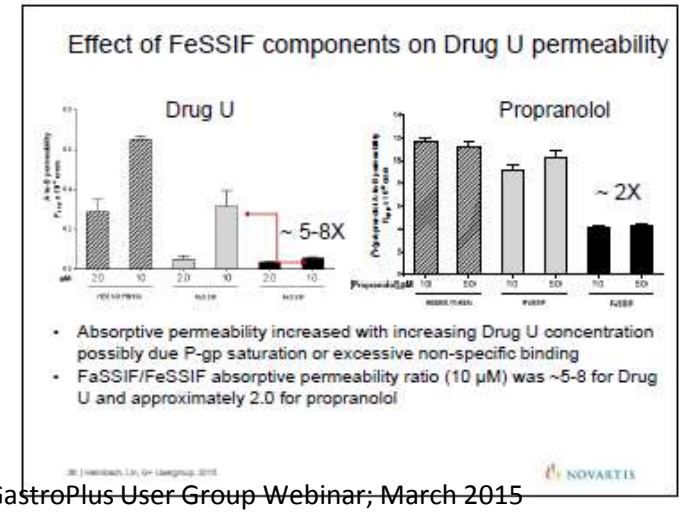
ABSTRACT



Compound U: ACAT model did not predict the negative food effect using the regular Permeability

Caco-2 Permeability	Low to moderate
Papp A-B and B-A, cmx10^{-5}/min	2.5, 12.8
Peff, cmx10^{-4}/s	1.445

- Compound P displayed negative food effect in humans
- ACAT model could not predict the negative food effect using the original Papp data



Effect of FeSSIF components on Drug U permeability

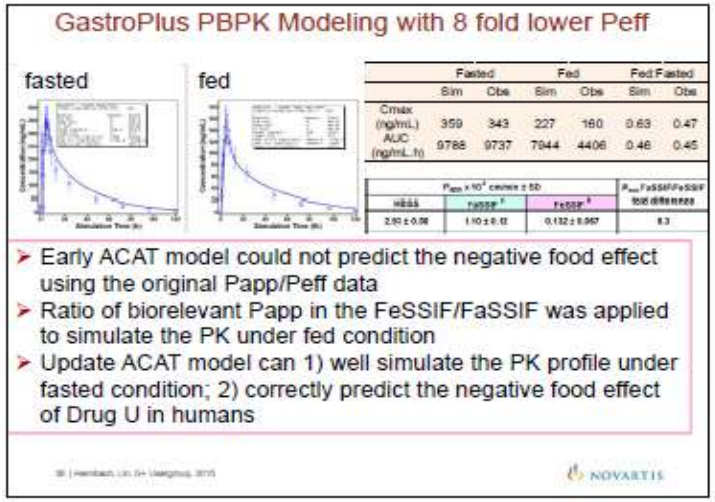
Drug U

Propranolol

~ 5-8X

~ 2X

- Absorptive permeability increased with increasing Drug U concentration possibly due P-gp saturation or excessive non-specific binding
- FaSSIF/FeSSIF absorptive permeability ratio (10 µM) was ~5-8 for Drug U and approximately 2.0 for propranolol



GastroPlus PBPK Modeling with 8 fold lower Peff

fasted

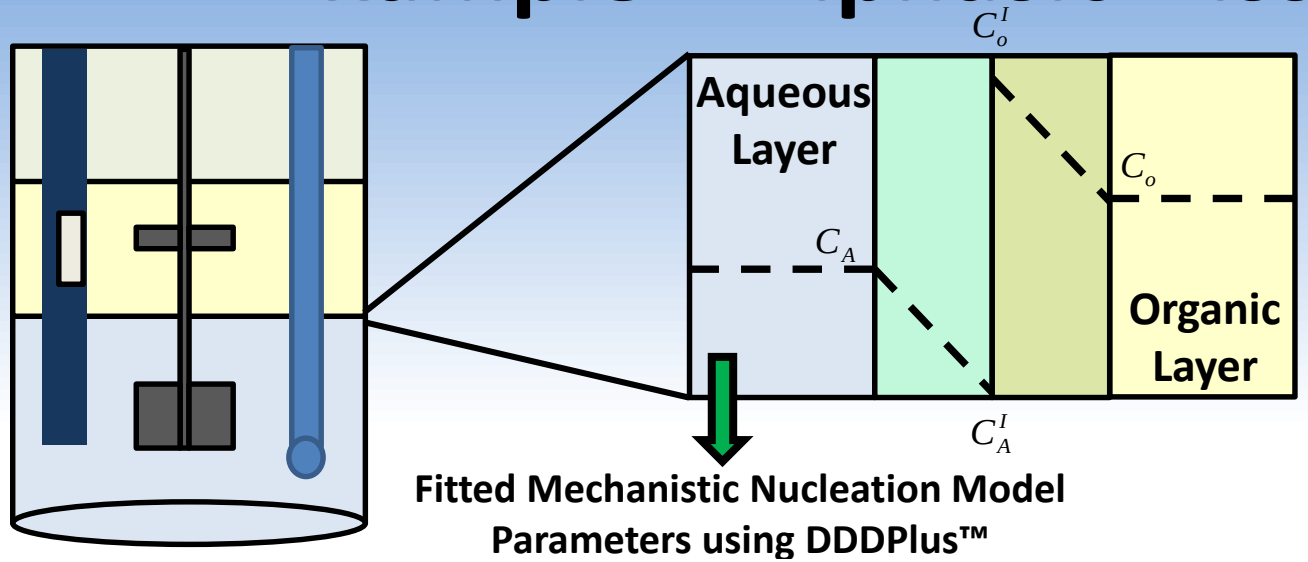
fed

	Fasted		Fed		Fed/Fasted	
	Sim	Obs	Sim	Obs	Sim	Obs
Cmax (ng/mL)	359	343	227	160	0.63	0.47
AUC (ng/mL·h)	9788	9737	7944	4406	0.46	0.45

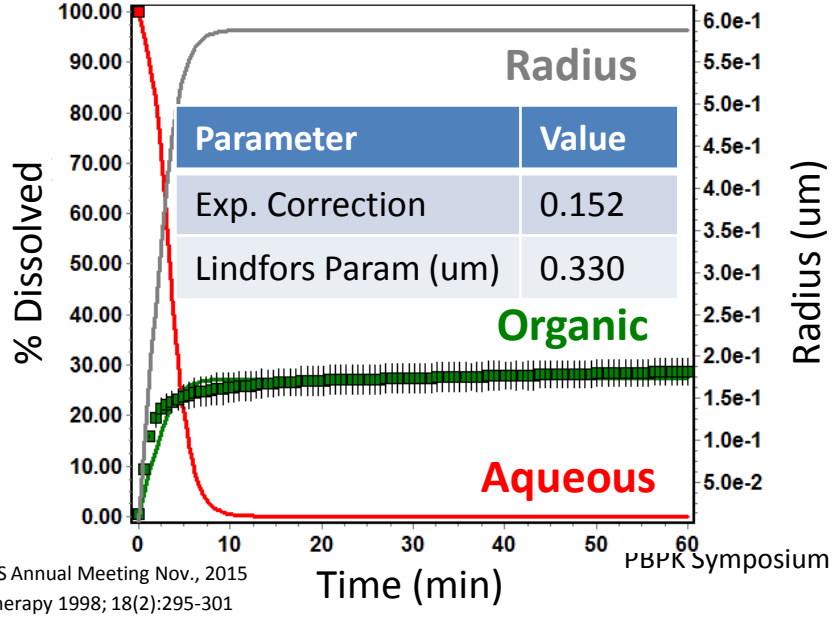
- Early ACAT model could not predict the negative food effect using the original Papp/Peff data
- Ratio of biorelevant Papp in the FeSSIF/FaSSIF was applied to simulate the PK under fed condition
- Update ACAT model can 1) well simulate the PK profile under fasted condition; 2) correctly predict the negative food effect of Drug U in humans

FUTURE DIRECTIONS AND CONCLUSIONS

Improved *In Vitro* Tools: Example – Biphasic Dissolution Experiment

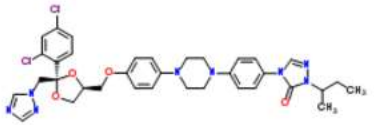


Fitted Mechanistic Nucleation Model Parameters using DDDPlus™

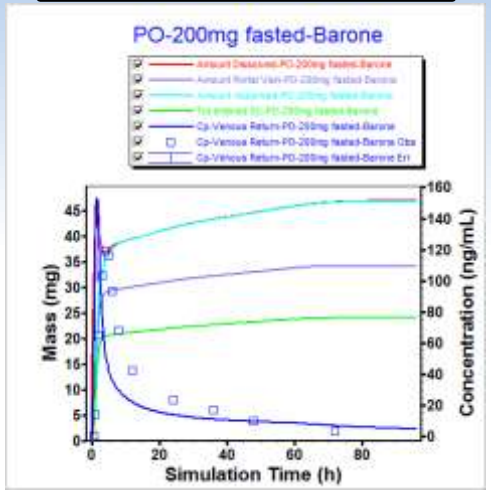


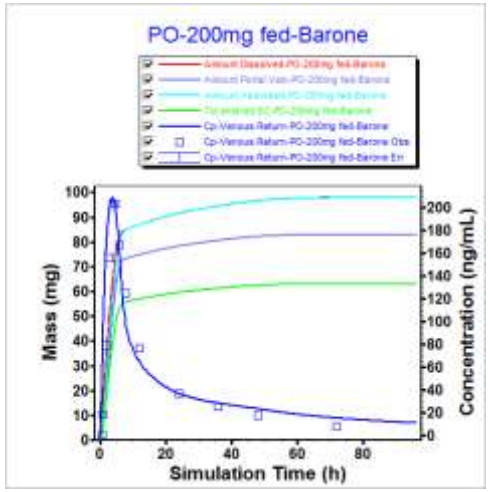
Parameter	Value
Exp. Correction	0.152
Lindfors Param (um)	0.330

Itraconazole

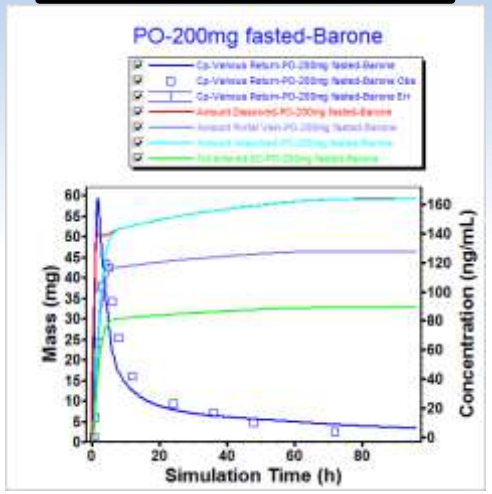


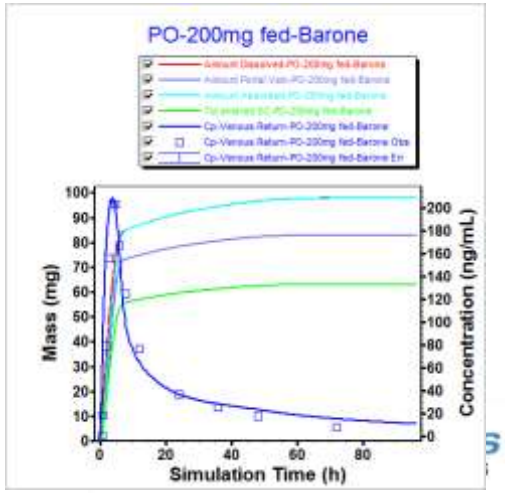
IVIVE for precipitation kinetics





***In vivo* fit for precipitation kinetics**

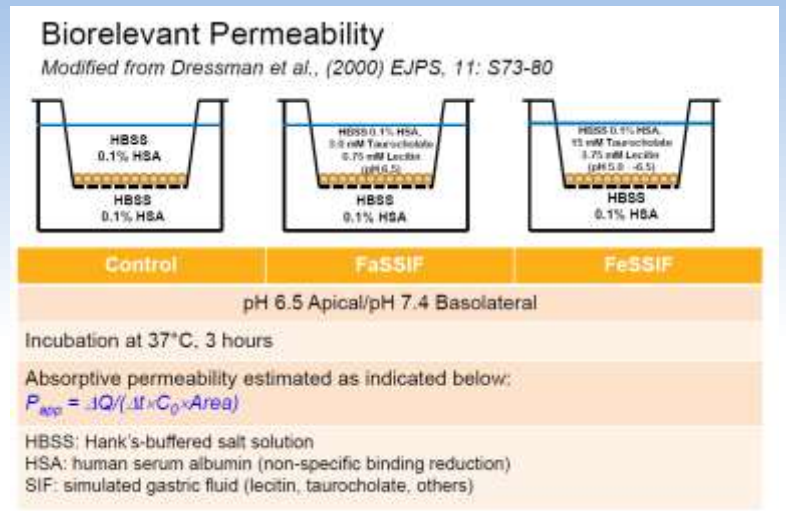


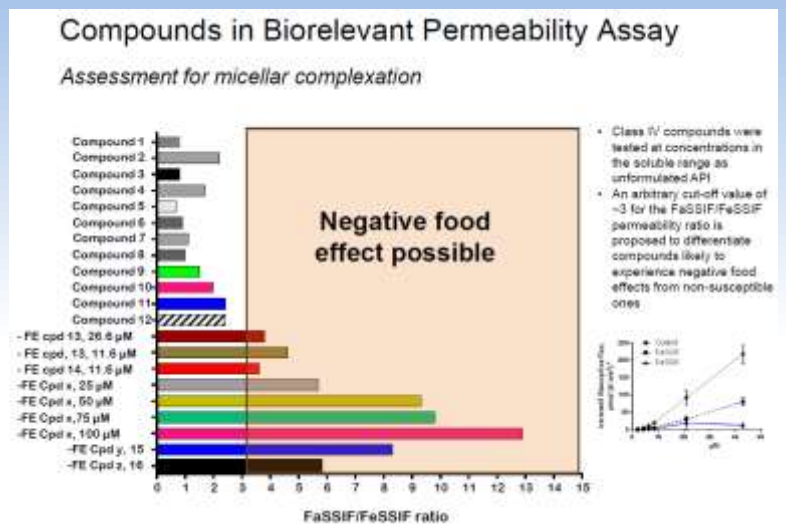


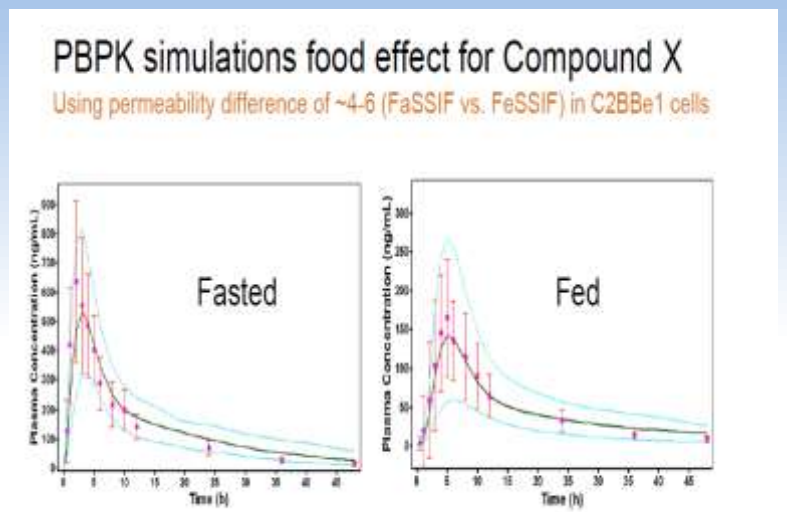
Modeling: Szeto, Poster W5237 AAPS Annual Meeting Nov., 2015

Clinical Data: Barone JA, Pharmacotherapy 1998; 18(2):295-301

Improved *In Vitro* Tools: Example – Biorelevant Permeability





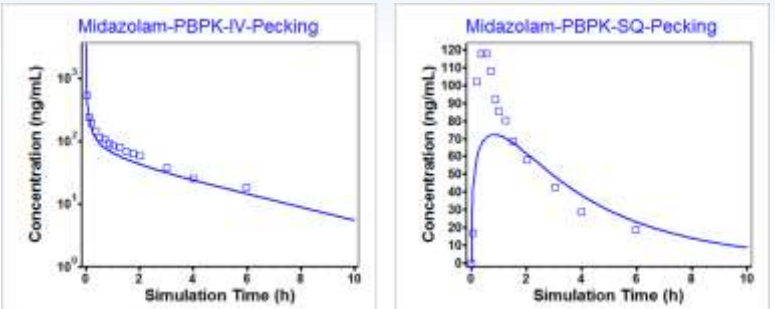


TODAY: Attempt to create absorptive flux vs. Peff correlations
FUTURE: Allow for flux input into models (dependent on method that combines system + drug-specific parameters)

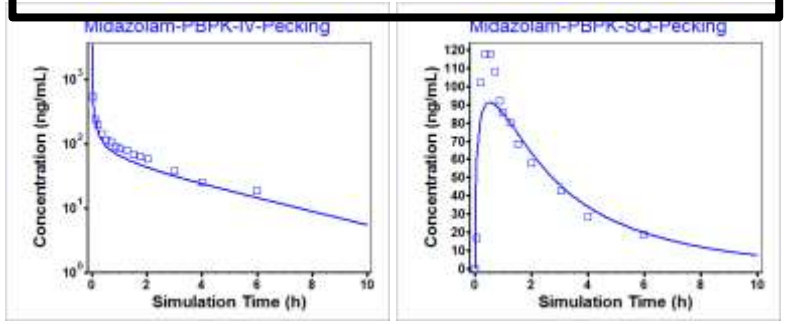
What About Non-Oral Administration Sites?

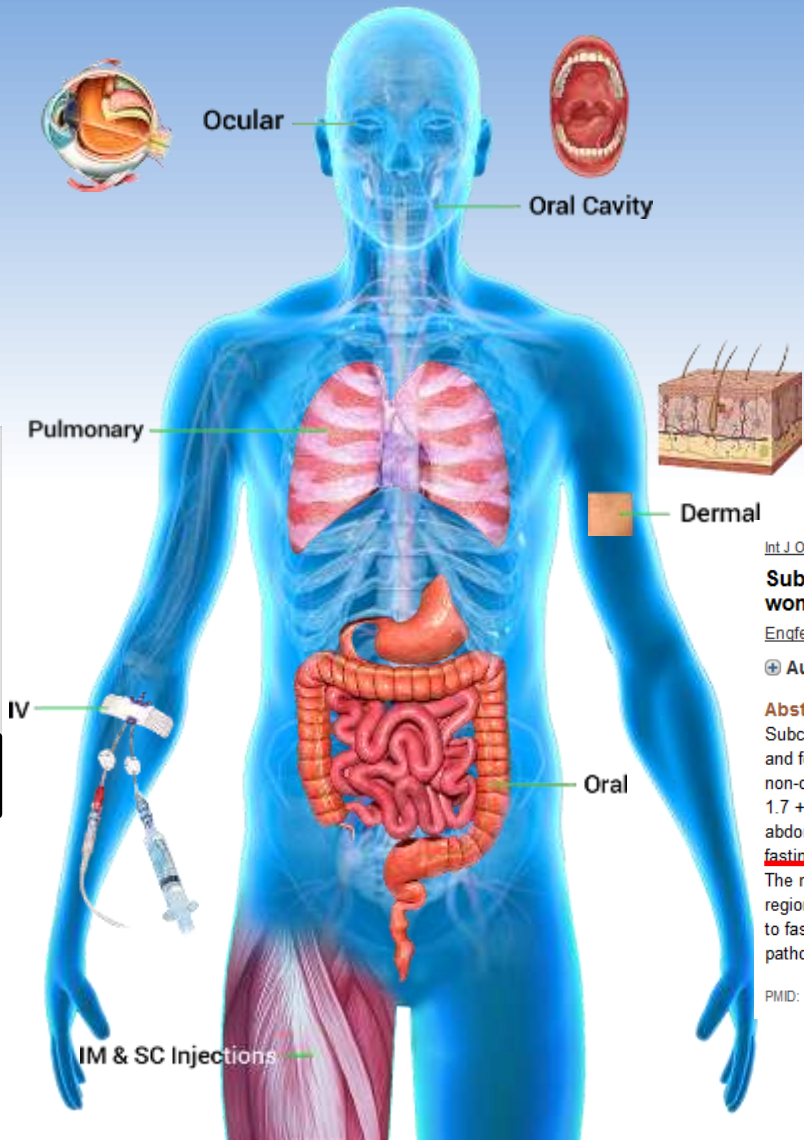
Midazolam SubQ Dosing

Default IVIVE



With 45% SubQ Blood Flow Increase





Int J Obes Relat Metab Disord. 1992 Nov;16(11):875-9.

Subcutaneous adipose tissue blood flow in the abdominal and femoral regions in obese women: effect of fasting.

Engfeldt P[1], Linde B.

⊕ Author information

Abstract

Subcutaneous adipose tissue blood flow (ATBF) was measured by the local clearance of 133Xe from the abdominal and femoral regions of nine individuals with non-endocrine obesity before and after seven days of fasting. Fifteen non-obese individuals served as controls. In the obese group ATBF was similar in the abdominal and femoral regions, 1.7 +/- 0.2 and 1.8 +/- 0.2 ml/min/100 g adipose tissue, respectively. In contrast, in the non-obese group the abdominal ATBF was higher, 4.1 +/- 0.6 and 2.4 +/- 0.2 ml/min/100 g adipose tissue, respectively ($P < 0.01$). During fasting, ATBF in the abdominal region increased by 45% ($P < 0.01$), but it remained unchanged in the femoral region. The mechanisms behind the differences in responses to fasting in the two regions are unsettled but may depend on regional differences in lipolytic activity and responses to vasoactive substances. Furthermore, the vasodilator response to fasting in the abdominal region in combination with the higher lipolytic rate in that region may be a pathophysiological factor behind the increased cardiovascular morbidity associated with abdominal obesity.

PMID: 1337342 [PubMed - indexed for MEDLINE]

 Experimental data from Pecking et al. Br J Clin Pharmacol 2002, 54:357

Conclusions & General Observations

- Mechanistic modeling and simulation approaches are predictive and play an important role in QbD for drug development and regulatory interactions
- Need to better understand impact of fruit juices/nutritional supplements on metabolic and transporter processes
- Focus on building baseline models under fasted conditions first
  - Important to consider all mechanisms of your drug before predicting food effect
- Continued collaborations will lead to:
  - Advanced understanding of GI (and other administration site) physiology
  - Improved *in vitro* methods for defining model inputs (e.g., precipitation kinetics)

Acknowledgements

- Simulations Plus, Inc.
  - Michael Bolger: Chief Scientist
  - Viera Lukacova: Director – Simulation Sciences
  - Jim Mullin: Team Leader – Simulation Technology
  - Grace Fraczkiewicz: Team Leader – Simulation Studies
  - Members of the Simulation Technologies team
  - Members of the Simulation Studies team
  - Members of the ADMET Cheminformatics team

Thank you for your kind attention!

Questions?