GastroPlus®

Part I: Basic model considerations & food effect predictions

Jim Mullin

Ke Szeto

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)

The AAPS Journal, Vol. 13, No. 1, March 2011 (© 2010)
DOI: 10.1208/s12248-010-9250-9

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]

GastroPlus simulations of fed and fasted: PO 200, 300, & 400 mg Carbamazepine

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

Example: Class II Drug – impact of particle size changes under fasted vs. fed conditions

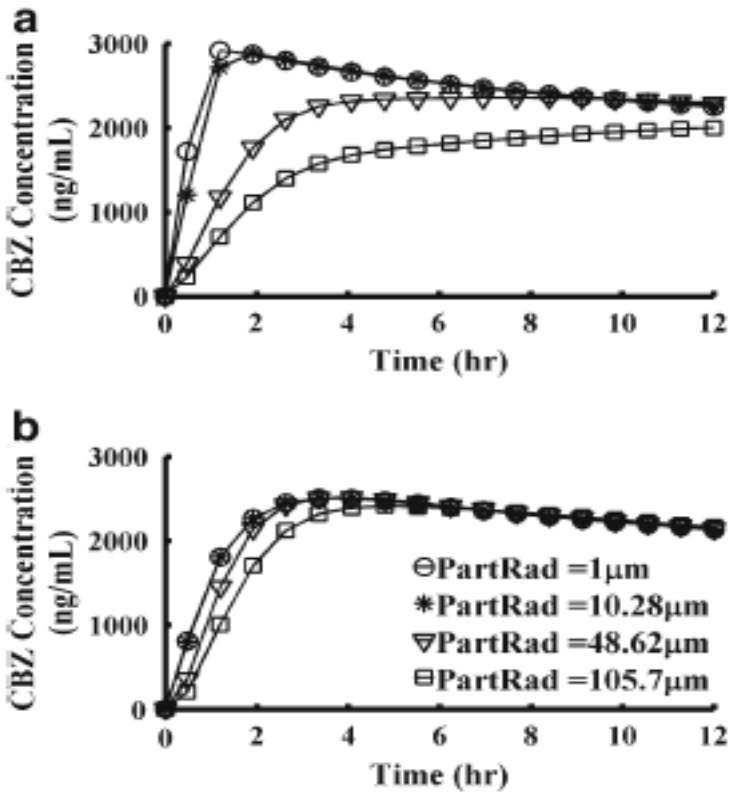
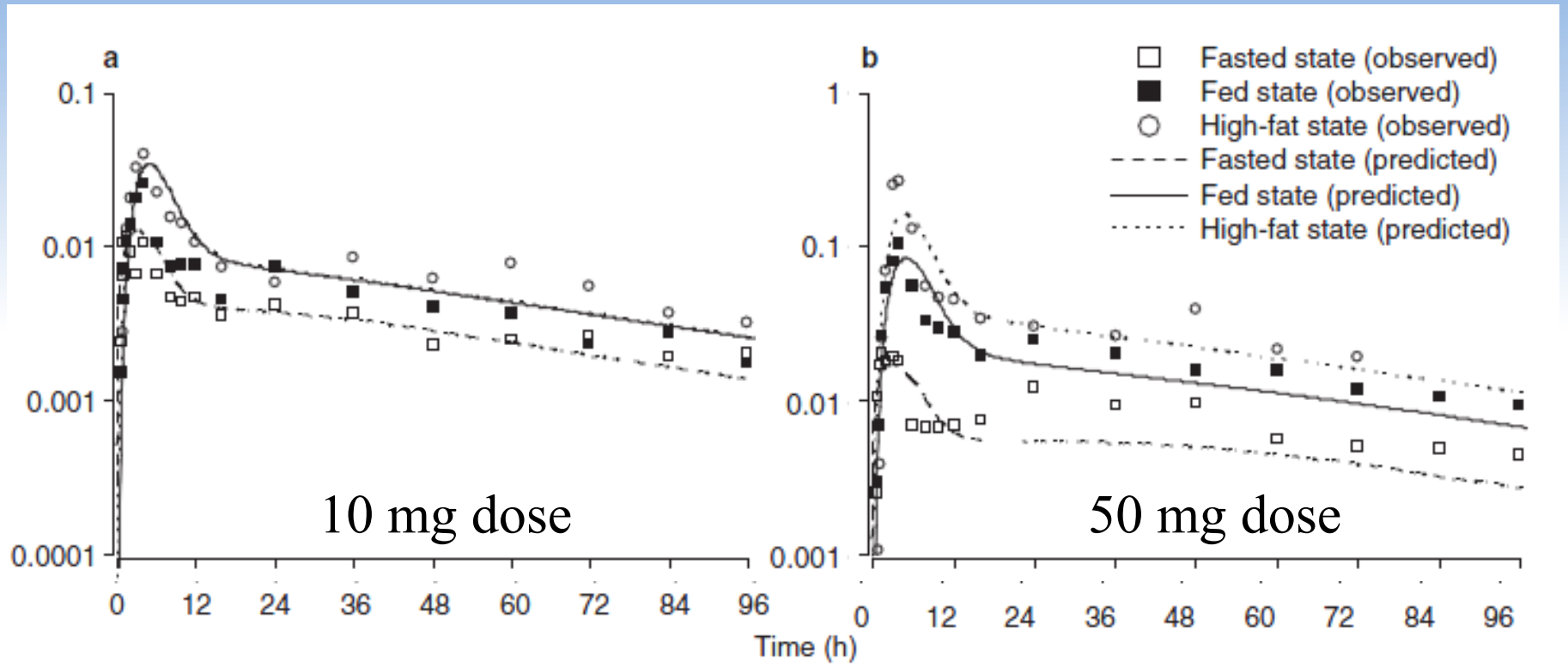


Fig. 7. PK profiles sensitivity to the mean particle radius is different under fasted and fed state. **a** IR suspension, fasted state; **b** IR suspension, fed state. Legend in (**b**) is also applied to (**a**)

Zhang et al., AAPS J. 2011

Cmd3
(basic pKa = 4.2, log P = 6.6, FaSSIF = 1.3 mg/mL)

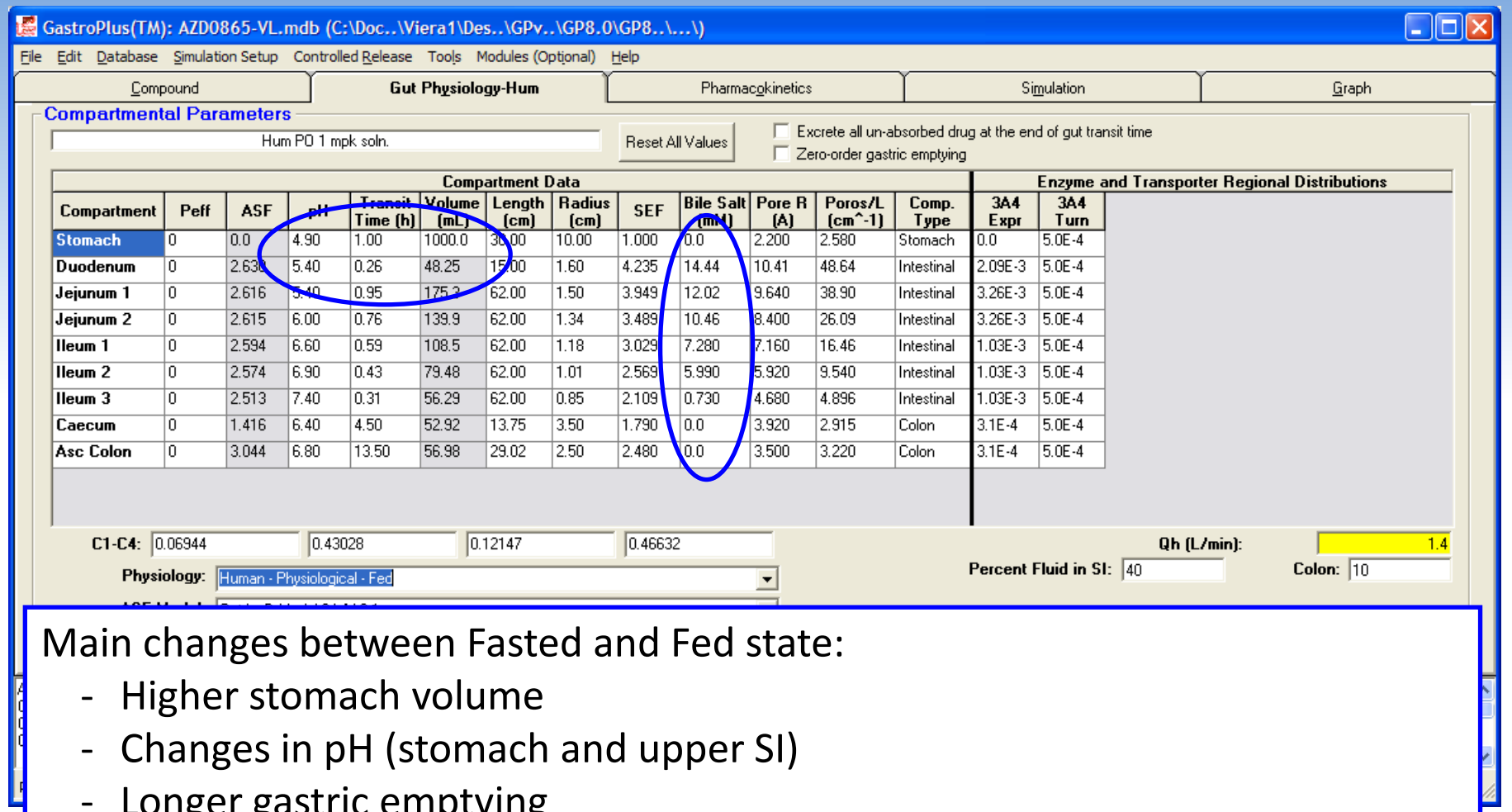


1.5- to 2.4-fold increase in AUC under fed conditions due to increased solubility at higher bile salt concentrations

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

What changes are accounted for between fasted and fed state models in GastroPlus?

Fed State – GI Physiology



Main changes between Fasted and Fed state:

- Higher stomach volume
- Changes in pH (stomach and upper SI)
- Longer gastric emptying
- Higher bile salt concentrations
- Higher liver blood flow (needs to be manually changed with PBPK models)

Solubility – Bile Salt

To account for physiological 'distribution' of bile salts, GastroPlus uses published equation based on concentration of bile salts in media and compound's affinity to bile salt micelles

$$Sol_{bile,pH} = Sol_{aq,pH}\left(1 + \frac{Mwt_{H_2O}}{\rho_{H_2O}} \times SR \times C_{bile}\right)$$

in vivo solubility in compartment with specific pH and bile salt concentration

Buffer solubility at given pH
calc from reference solubility, pKa(s) and solubility factor(s)

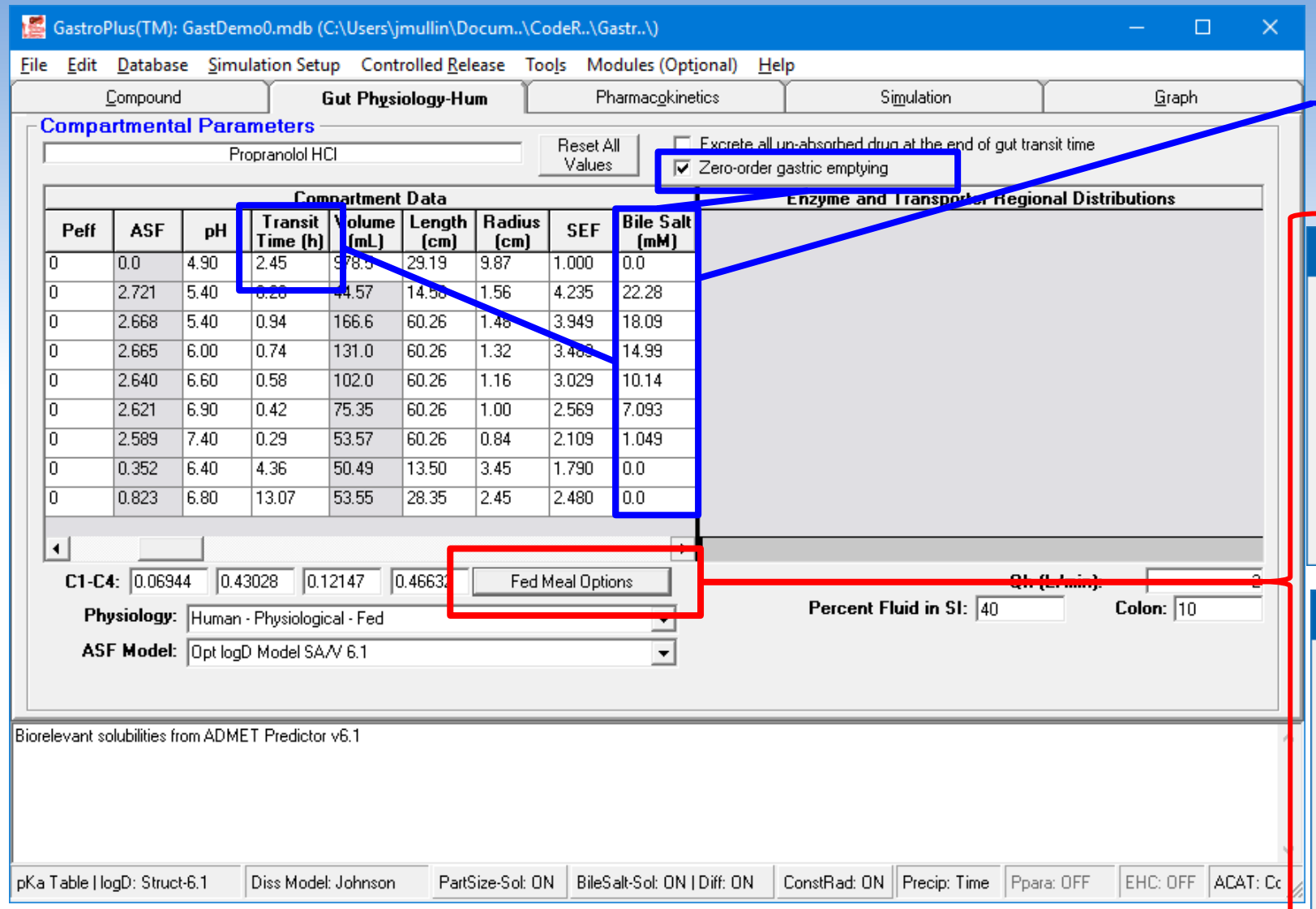
Molecular weight and density of water

Bile salt solubilization ratio – represents drug's affinity to bile salt micelles
This parameter is required to account for physiological effect of bile salts on solubility and dissolution rate

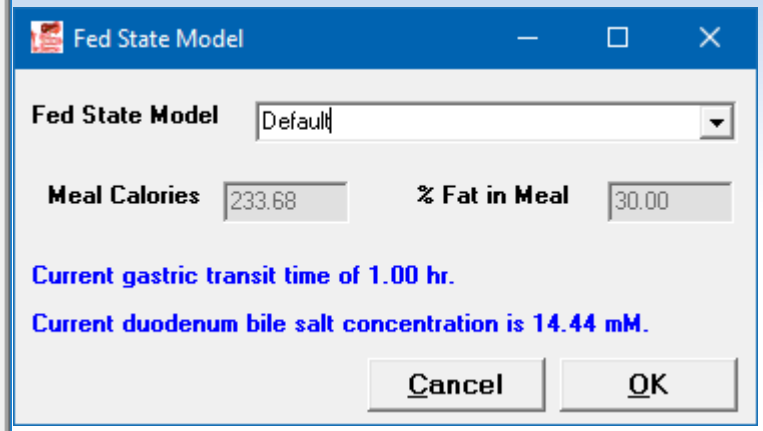
in vivo concentration of bile salts in given compartment
(physiological parameter)

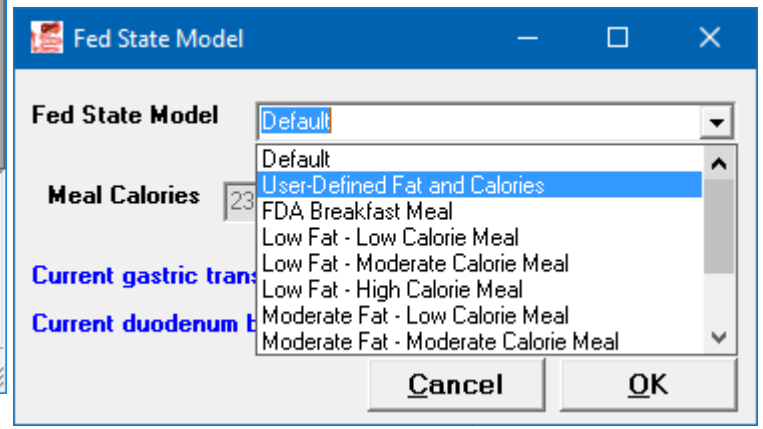
Mithani, Pharm Res 1996, 13:163-167

Built-in Fed Physiologies for Different Meal Types



- Link gastric emptying time to meal calories
- Account for effect of fat content on bile salt concentration





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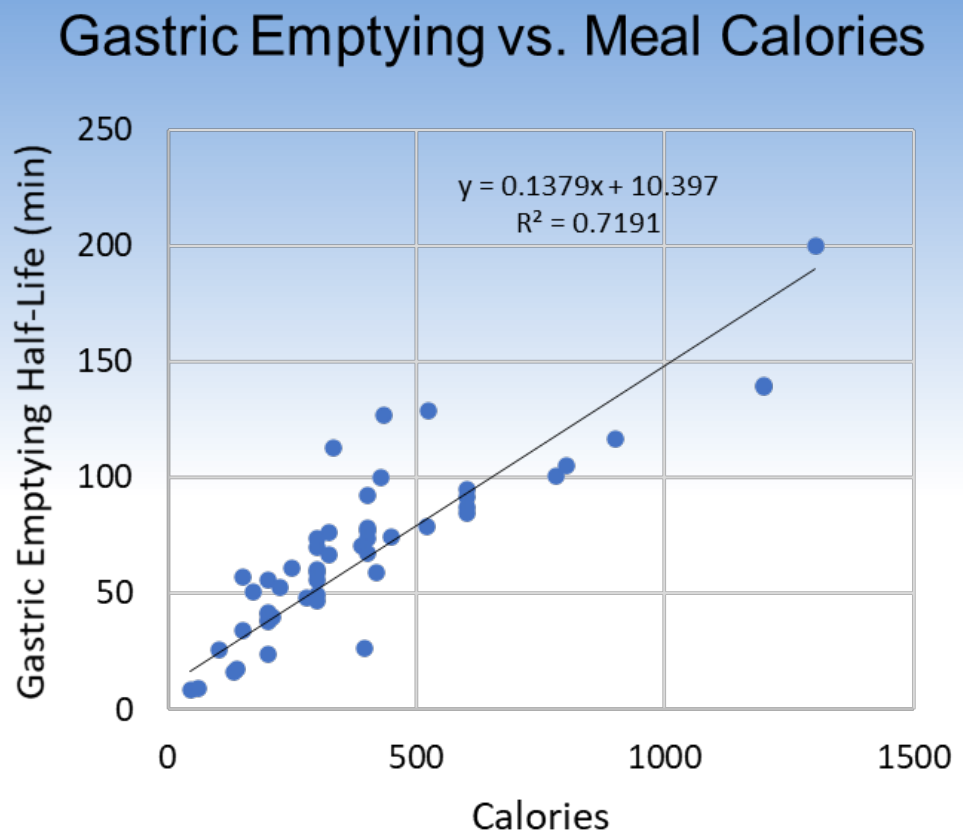
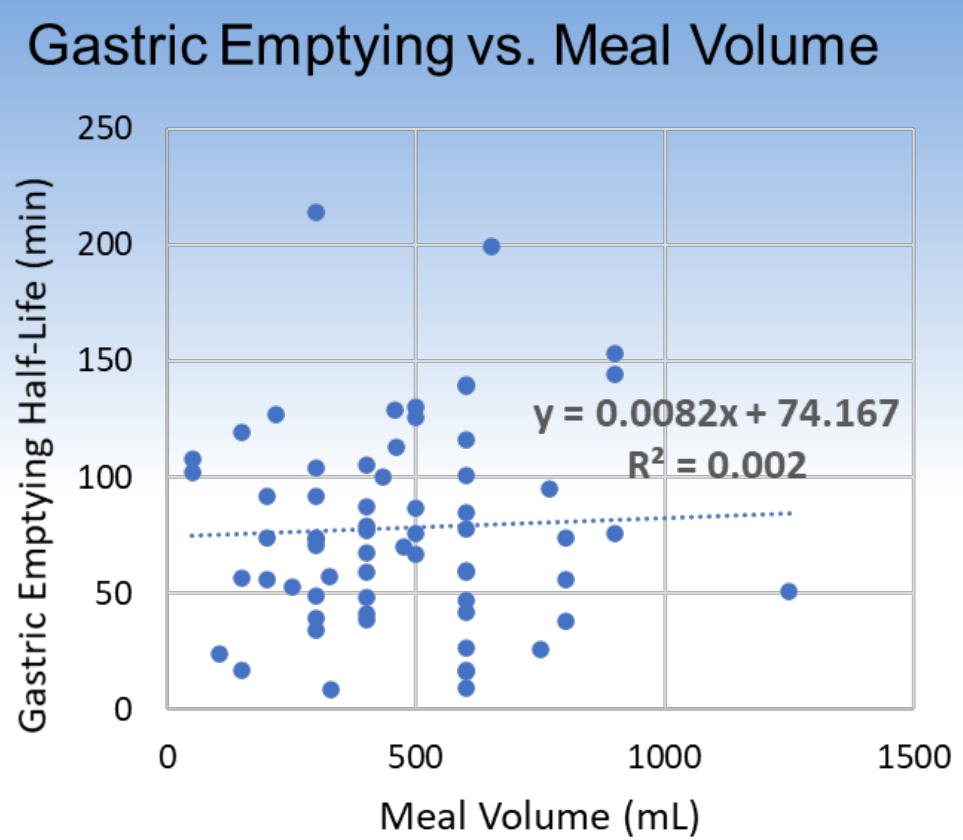
Adjusting Fed State Based on Calories and Meal Volume





- Meal value is not well correlated with emptying time
- Gastric Emptying is linearly related to calories and can be slightly modified by meal type (fat, protein, carbohydrates)
  - Smaller impact and not currently considered due to lack of data

Adjusting Fed State for Biliary concentration

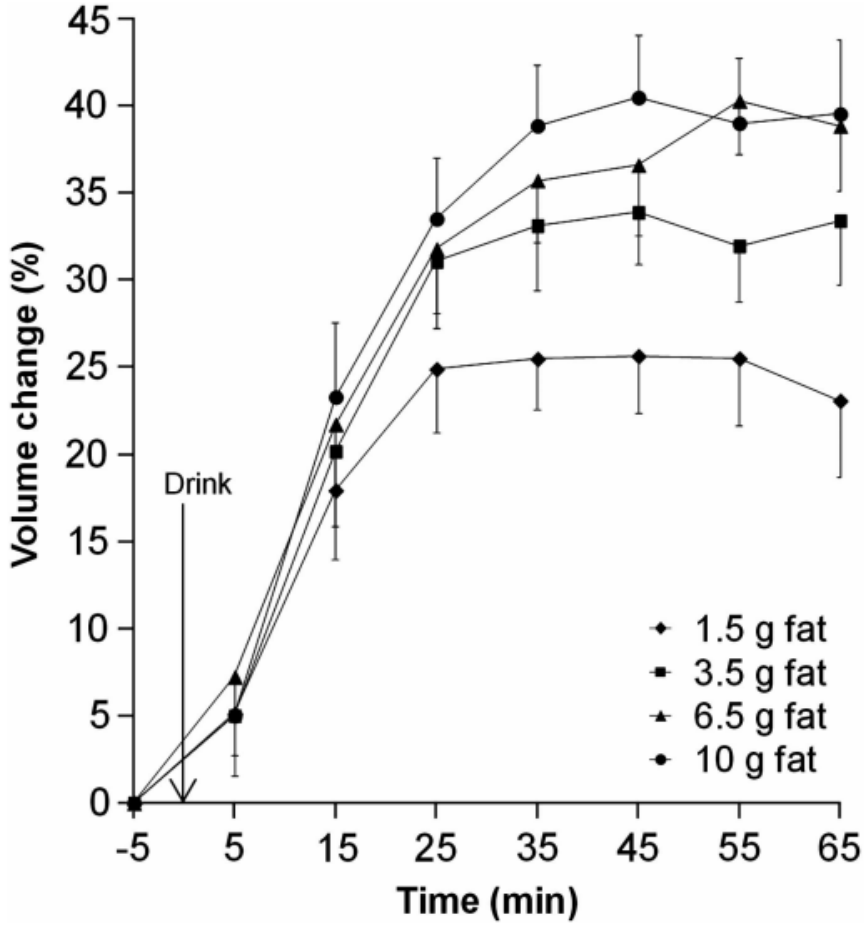


Figure 3. Plot of the % gall bladder volume change with time for healthy volunteers after they consumed each of the four milk-based beverages of increasing fat content in Study 2. Values are mean ± s.e.m., $n = 21$.

- With increasing fat, gall bladder excretion volume increases
- Gall bladder secretion is mediated by hormone cholecystokinin CCK

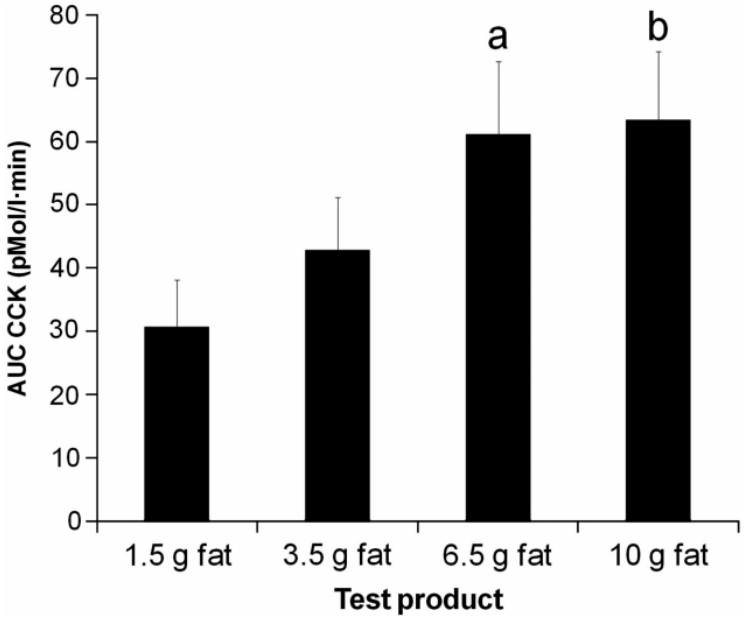


Figure 4. Area under the curve (AUC) for plasma cholecystokinin (CCK) for healthy volunteers after they consumed each of the four milk-based beverages of increasing fat content in Study 2. Values are mean ± s.e.m., $n = 17$. [a]Significant difference versus 1.5g fat drink ($P < 0.05$); [b]Significant difference versus 1.5g fat drink ($P < 0.01$).

L Marciani et al. Eur J of Clin Nutr (2013) 67, 1182-1187

Results of Dynamic Bile-Salt Model

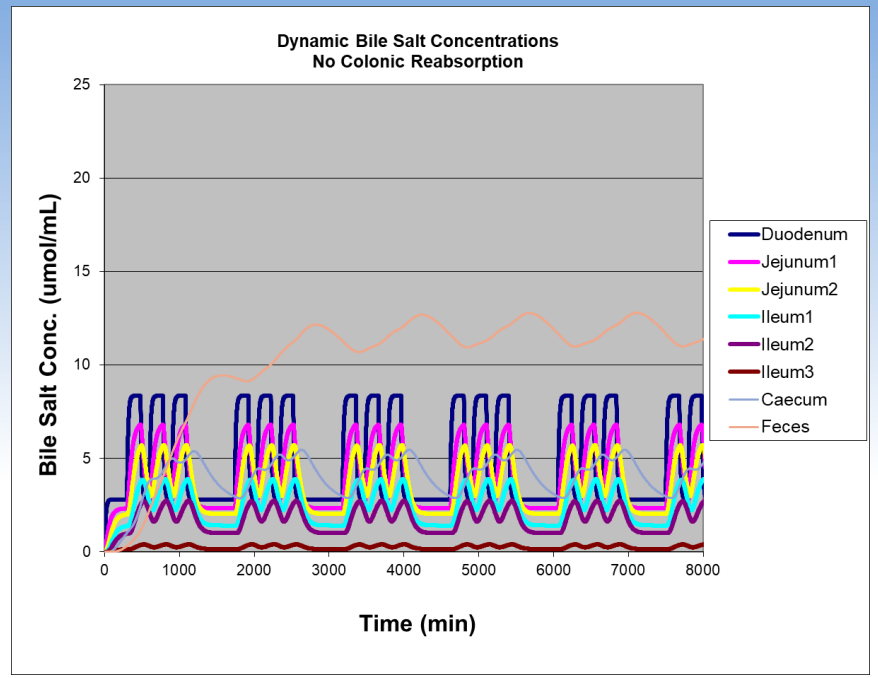
Bile Salt Concentration Spreadsheet Model:

- A caecum and feces (large intestine) compartment were added using same volumes and transit times as G+
- No bile reabsorption assumed for caecum and colon

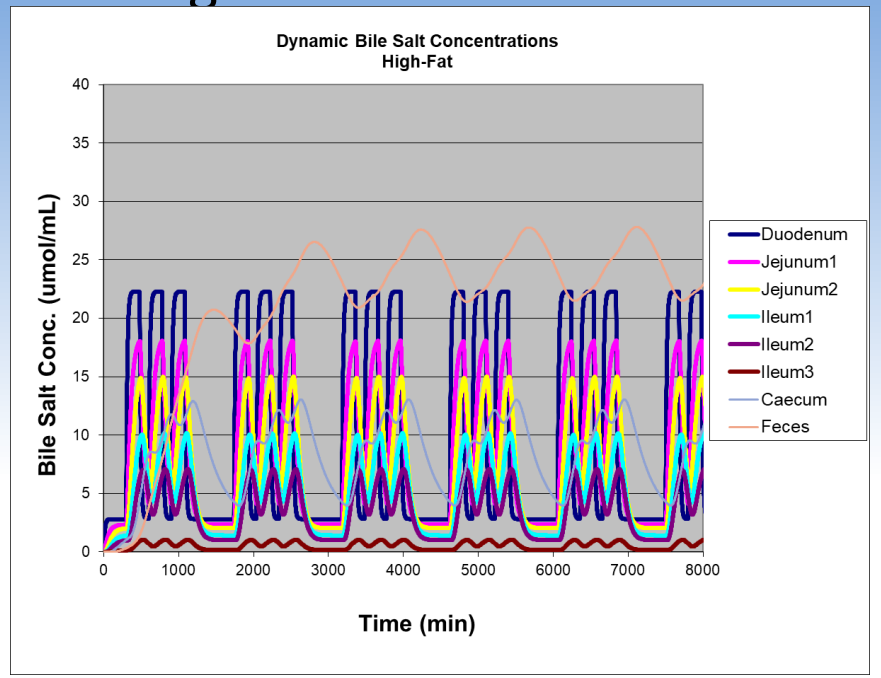
Feces Bile Concentration Reference:

Reddy, CANCER RESEARCH, 1981, 41, 3766-3768

Low-Fat Bile Prediction



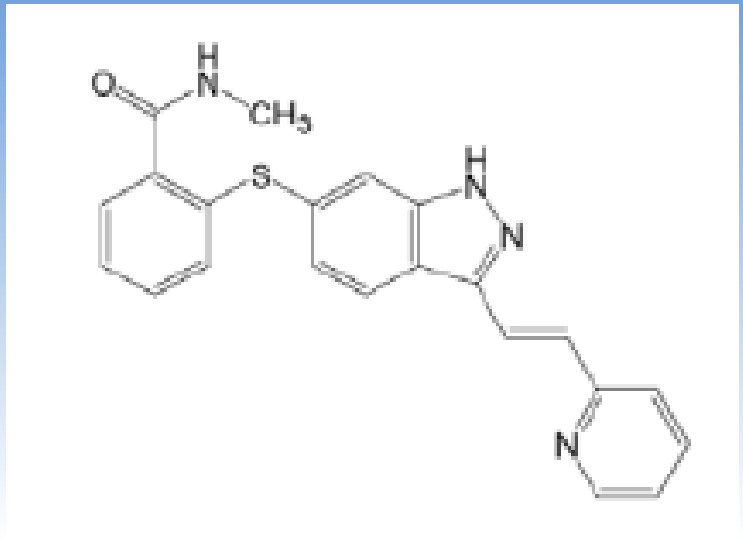
High-Fat Bile Prediction



- Assumptions, 3 meals and fed-state occurs for 3 hours duration
- Then the bile production rate was fit to make fold change in bile in feces the same as literature data

			Bile Concentration in Each Compartment (mM)					
	% Fat	**Fold Change Bile in Feces**	**Duodenum**	**Jejunum1**	**Jejunum2**	**Ileum1**	**Ileum2**	**Ileum3**
Low Fat	10	1.000	*8.36*	*6.83*	*5.72*	*3.90*	*2.74*	*0.41*
Normal	30	1.476	*14.55*	*11.83*	*9.84*	*6.67*	*4.67*	*0.69*
Bile High Fat	55	2.072	*22.28*	*18.09*	*14.99*	*10.14*	*7.09*	*1.05*

Case Study: Axitinib



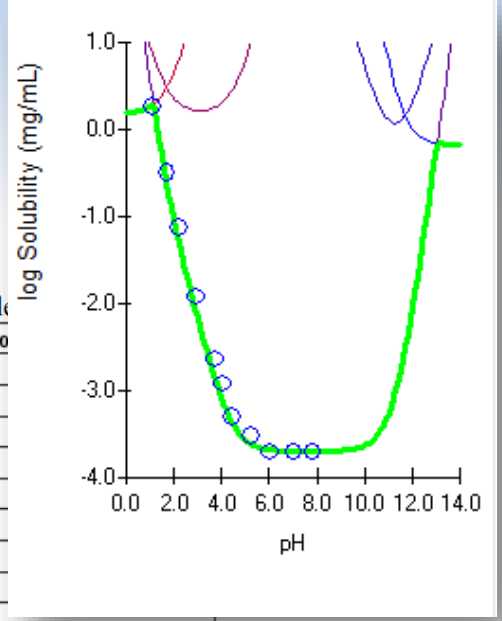


Table 21. Solubility of Axitinib in Aqueous Media as a Function of pH at 20°C for at l

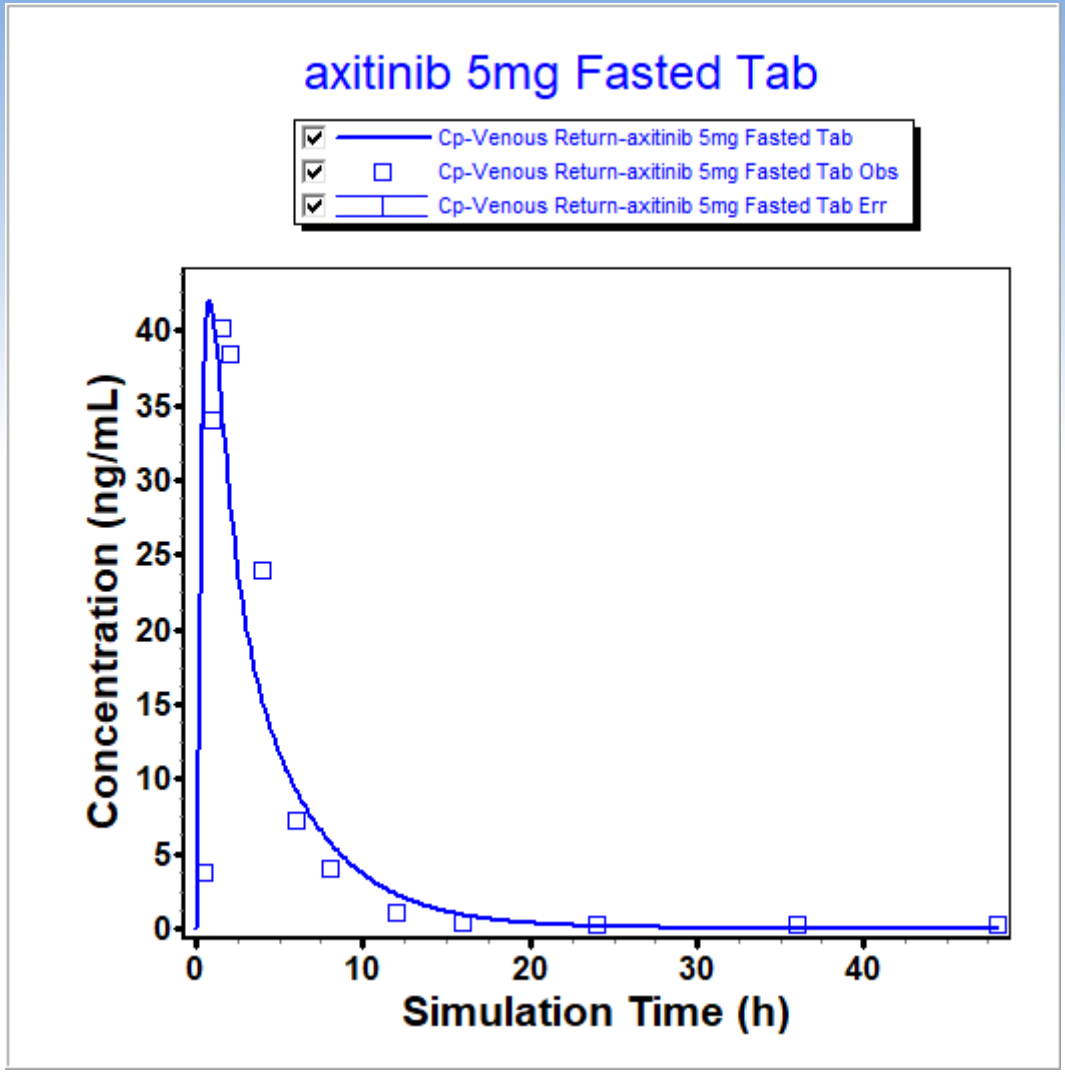
Aqueous Solution	Solubility (micro
Water pH 7.5	0.2
0.1N HCl, pH 1.1	1841
0.06N HCl pH 1.7	320
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 2.2	75
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 2.9	12
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 3.7	2.3
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 4.0	1.2
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 4.4	0.5
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 5.2	0.3
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 6.0	0.2
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 7.0	0.2
0.02M Sodium Phosphate/0.02M Sodium Acetate pH 7.8	0.2

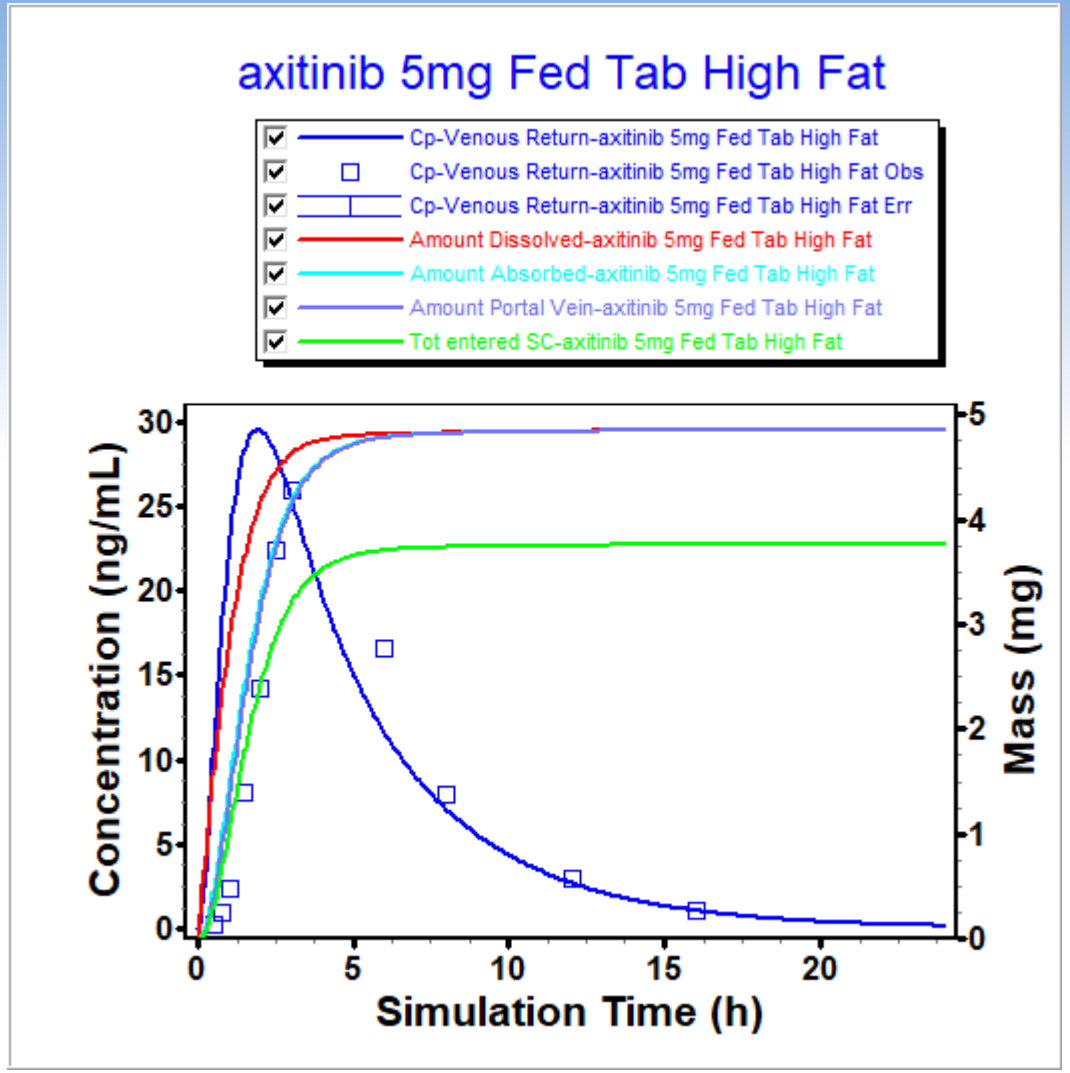
Property	Value	Ref
LogP	3.91	AP
pKa	1.71, 4.5 (Base) 11.68, 10.84 (Acid)	AP
Reference solubility Exp Sol.	1.48E-3 @ pH 7.02 1.841 mg/mL @ pH 1.1 0.0002 mg/mL @ pH 7.8	AP [1] [1]
Solubility Factor	3332.93 (AP) 7600(Exp)	AP, [1]
FaSSIF Sol. FeSSIF Sol.	0.001 0.114	[2] [2]
Human Peff (from Pampa)	2.89	[2]
Blood:plasma concentration ratio (R_{bp})	0.8	[1]
Plasma protein binding (Fup)	1	[1]
Particle Size	4 um (SD = 3)	[3]
Metabolism		
CL (3A4)	21 L/hr	[1]
Vd	68 L	[1]

[1] FDA application 202324 Clin Pharm and Biopharm. Review
[2] Dodd, Journal of Pharmaceutical Sciences,2019,108,87-101
[3] Reynor, Drug Metabolism and Disposition (2013): dmd-113.

Axitinib is a case study for gastric emptying because of high permeability and high solubility in gastric. Precipitation doesn't occur even though Axitinib is a low solubility weak base.

Case Study: Axitinib Fasted State and Baseline Fed Model



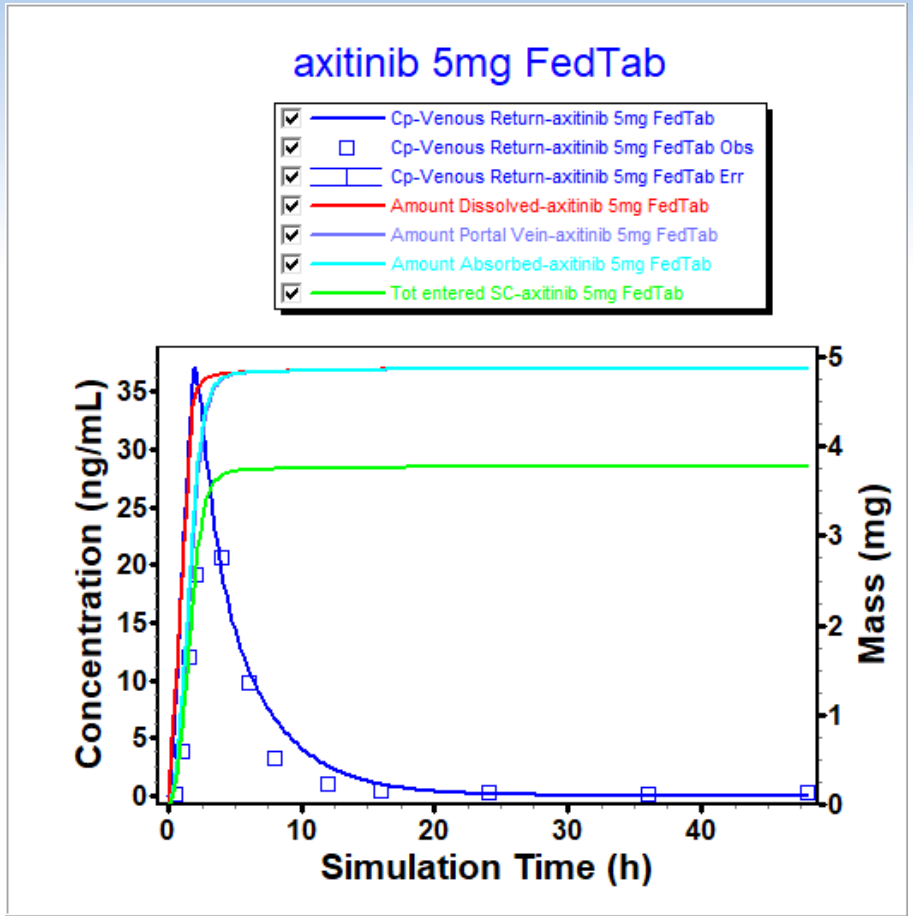


Pithavala, Cancer Chemother Pharmacol (2012) 70:103–112

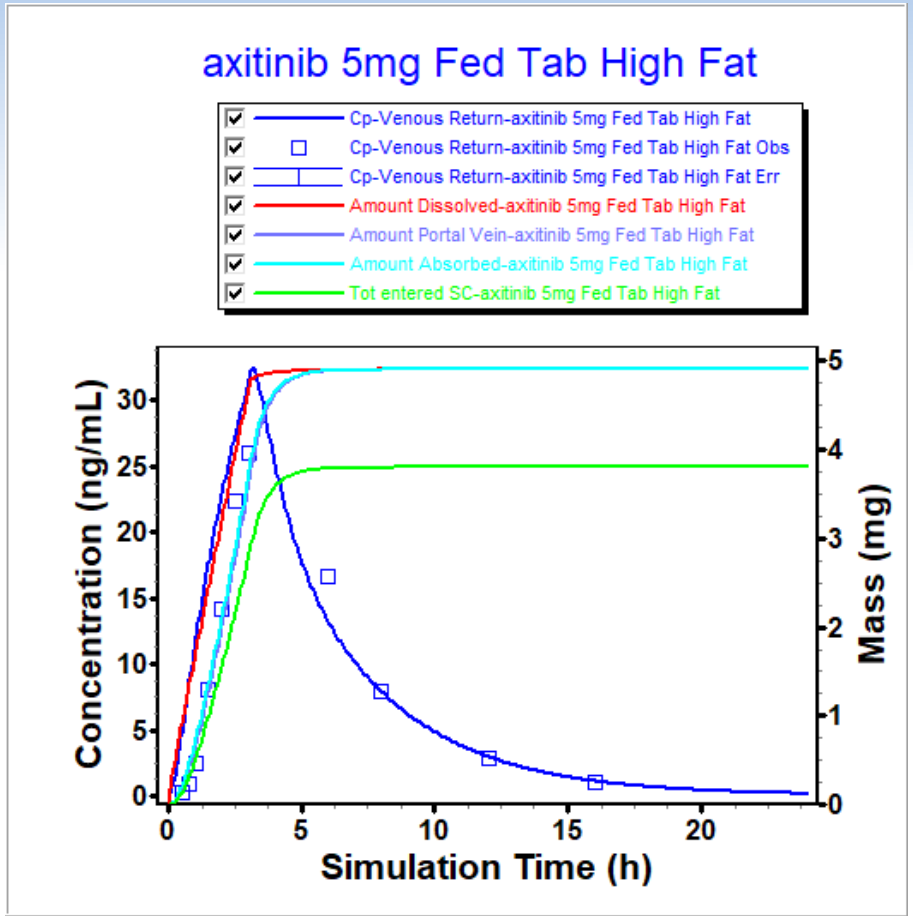
Gastric emptying is too fast using default values

Case Study: Axitinib Fed State Zero Order Emptying

Normal Meal (500 cal)
Gastric Emptying = 1.84 hr



Fed High-Fat (900 cal) Bile Salt Increased
Gastric Emptying = 3.11 hr

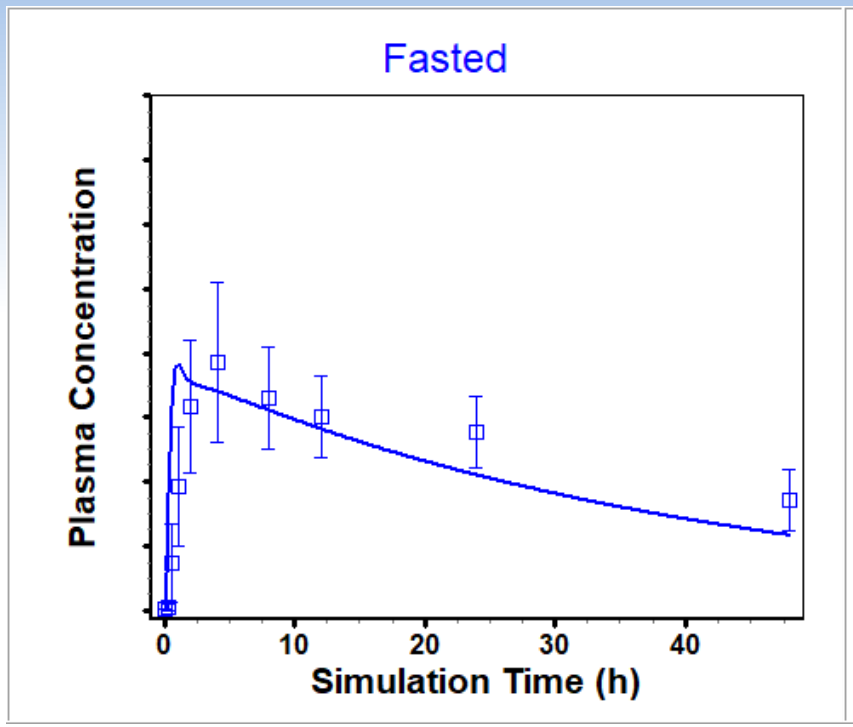


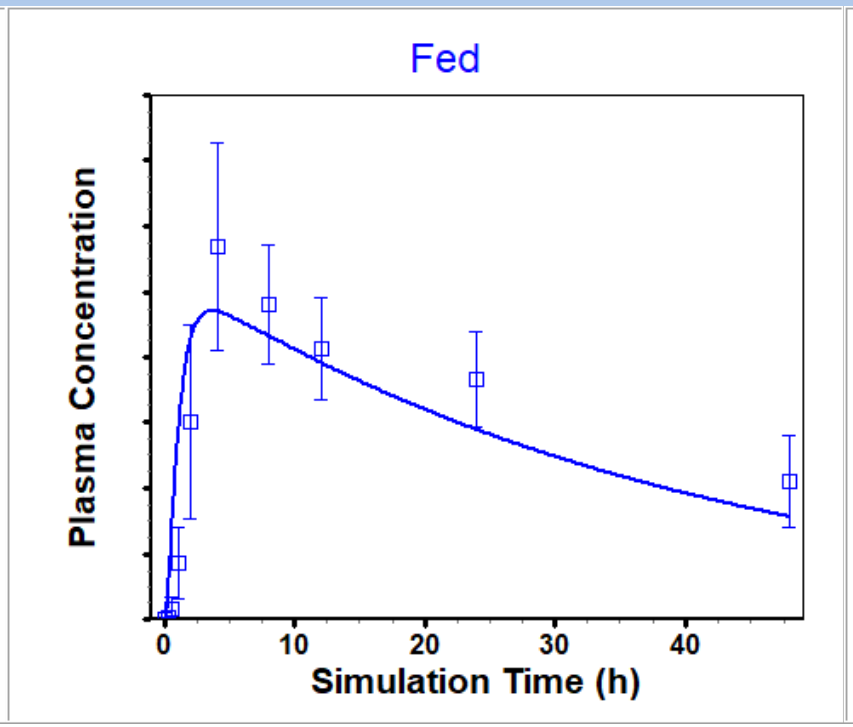
Pithavala, Cancer Chemother Pharmacol (2012) 70:103–112

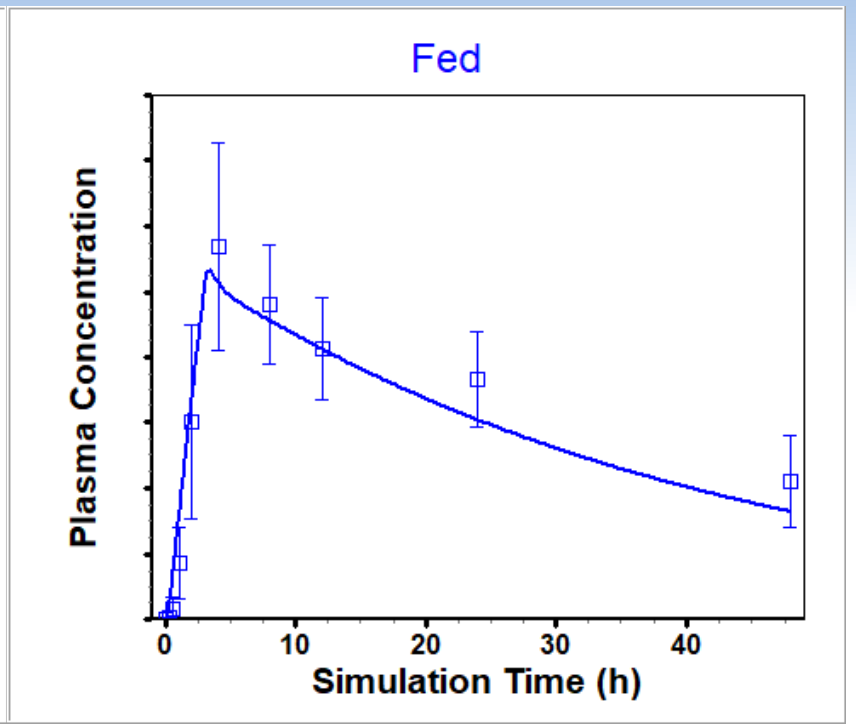
Case Study: High Fat Meal Prediction

Default Fed in GP9.6

Default for FDA standard breakfast







New Fed State Meal Option Validation Summary

	Meal Type	Best Fed Model Setting
Dolutegravir	High Fat / High Calorie	Zero Order GP 9.7
	Mod. Fat / Mod. Calorie	Zero Order GP 9.7
	Low Fat / Low Calorie	Zero Order GP 9.7
Lapatinib	Low Fat / Low Calorie	Default Gastroplus 9.6
	High Fat / High Calorie	Default Gastroplus 9.6
Ixazomib	High Fat / High Calorie	Exponential GP 9.7
Axitinib	Normal Meal	Exponential GP 9.7
	High Fat / High Calorie	Zero Order GP 9.7
Internal Study 1	Low Fat / Low Calorie	Zero Order GP 9.7
	High Fat / High Calorie	Zero Order GP 9.7
Internal Study 2	FDA High Fat Breakfast	Zero Order GP 9.7
Internal Study 3	High Fat / FDA Breakfast	Zero Order GP 9.7
Internal Study 4	High Fat / FDA Breakfast	Zero Order GP 9.7

- Validation studies indicate zero-order emptying is most predictive of plasma concentration in fed-state

Q&A

Questions & Answers

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GastroPlus® Demo – Compound X Positive Food Effect

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

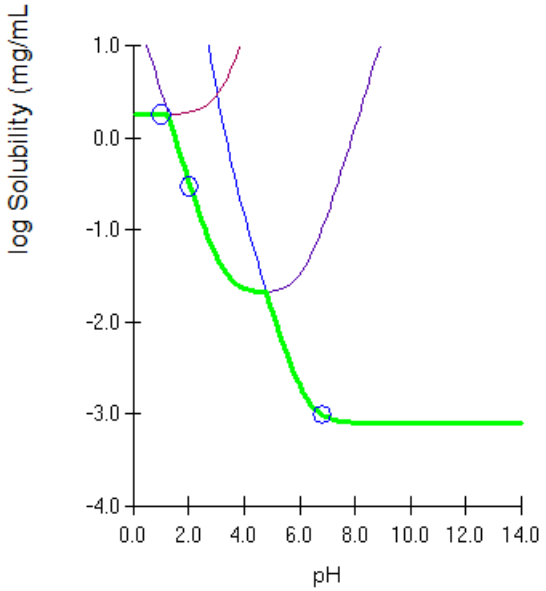
Research Article

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] Yanfeng 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)
- Class II (or IV)
- 70% dose recovered in feces as parent
- Estimated bioavailability of compound is ~30%



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Physicochemical and pharmacokinetic parameters for Compound X

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)
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

Lysosomal Trapping of Lipophilic Cations

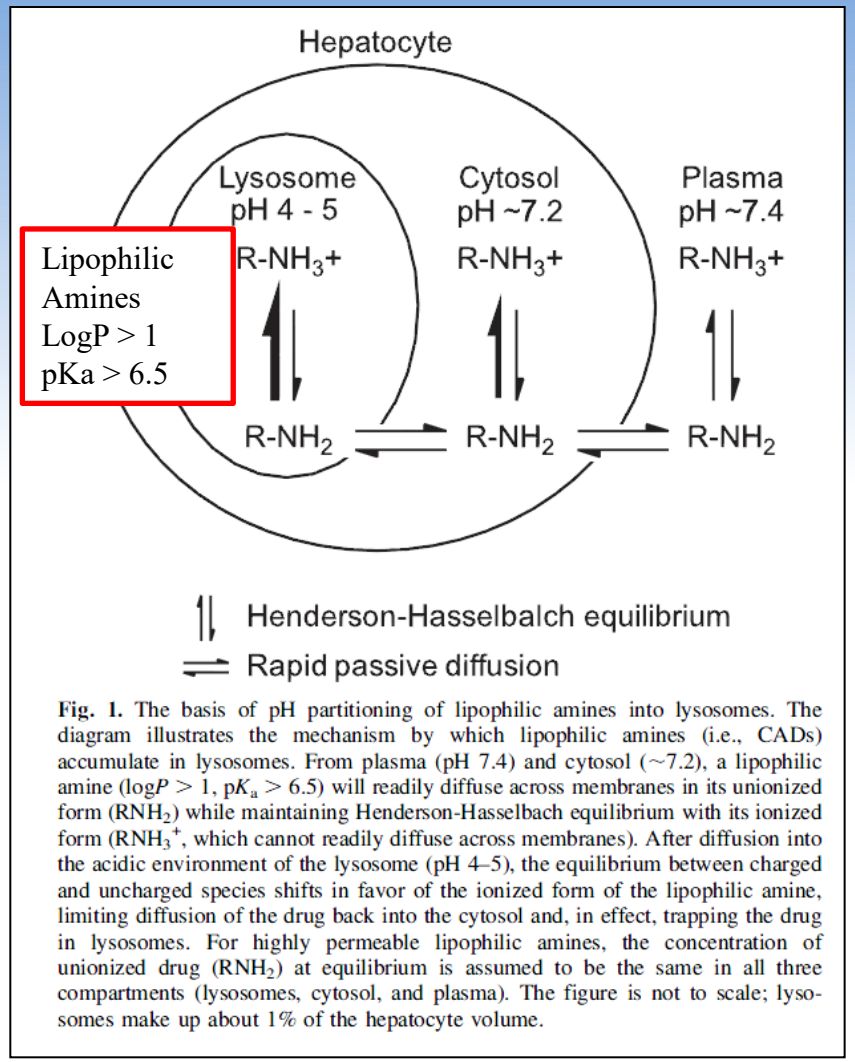
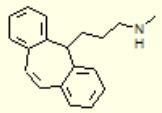
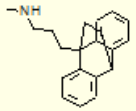
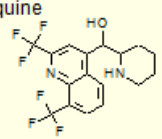
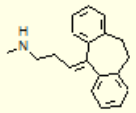
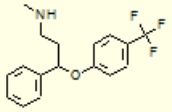
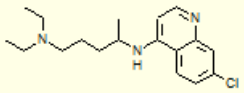


Fig. 1. The basis of pH partitioning of lipophilic amines into lysosomes. The diagram illustrates the mechanism by which lipophilic amines (i.e., CADs) accumulate in lysosomes. From plasma (pH 7.4) and cytosol (~7.2), a lipophilic amine ($\log P > 1$, $pK_a > 6.5$) will readily diffuse across membranes 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.

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

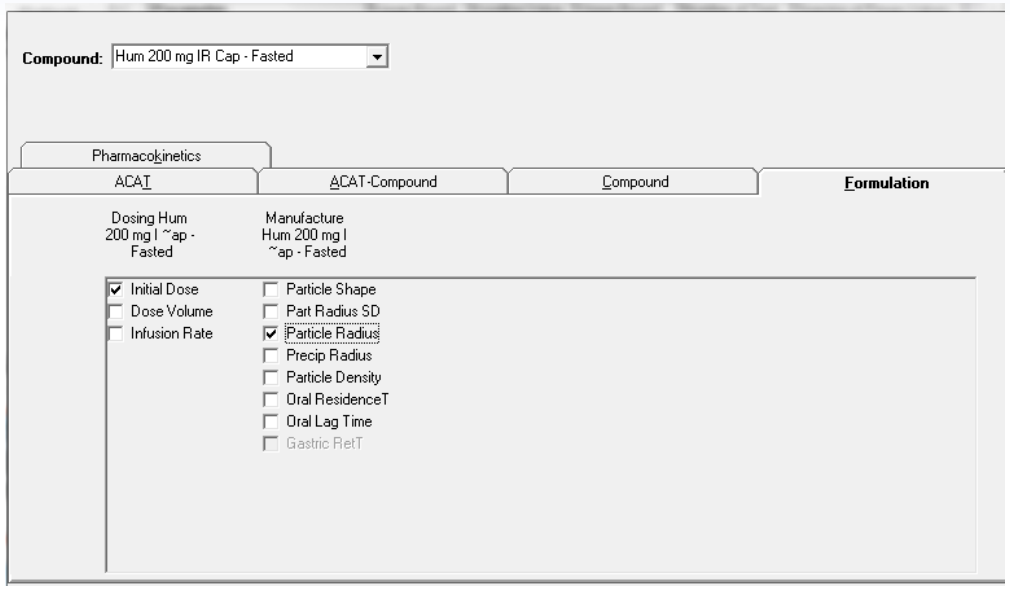
Drug	Log P	Basic pKa	T_{max} (h)
Protriptyline 	4.69	10.0	27
Maprotiline 	4.7	10.1	16
Mefloquine 	3.81	8.52	15
Nortriptyline 	4.46	9.65	7.8
Fluoxetine 	4.39	9.82	7
Chloroquine 	5.11	9.86	6

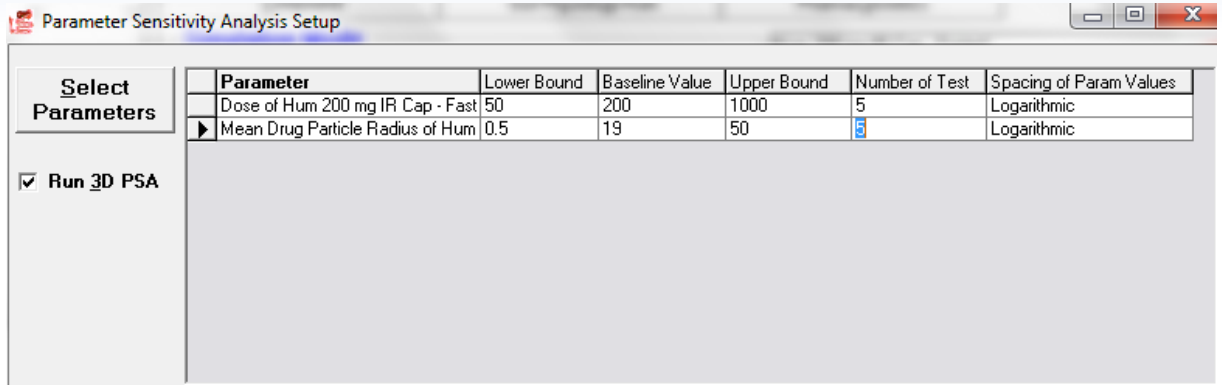
Activity: Compound X

1. **Open** the **“Compound X”** database in your **Examples\Compound X** folder
2. Navigate to the **Hum 200 mg IR Cap – Fasted** record and review the model parameters. *What is unique about this compound?*
3. Let’s run a PSA around the fraction unbound in enterocytes. **Click** on the “PSA” button on the **simulation tab** and select “FuEnt” on the **pharmacokinetics tab**
4. Need to change **Fu,ent** to ~3% by going to the **Database→4 View/Edit Tables→ 1 View/Edit Drugs** Table menu
5. Let’s modify the **mean precipitation time** in the model to match better with the observed PK data
6. Navigate to the **Hum 200 mg IR Cap – Fed** record and enter this new **Mean Precipitation Time**

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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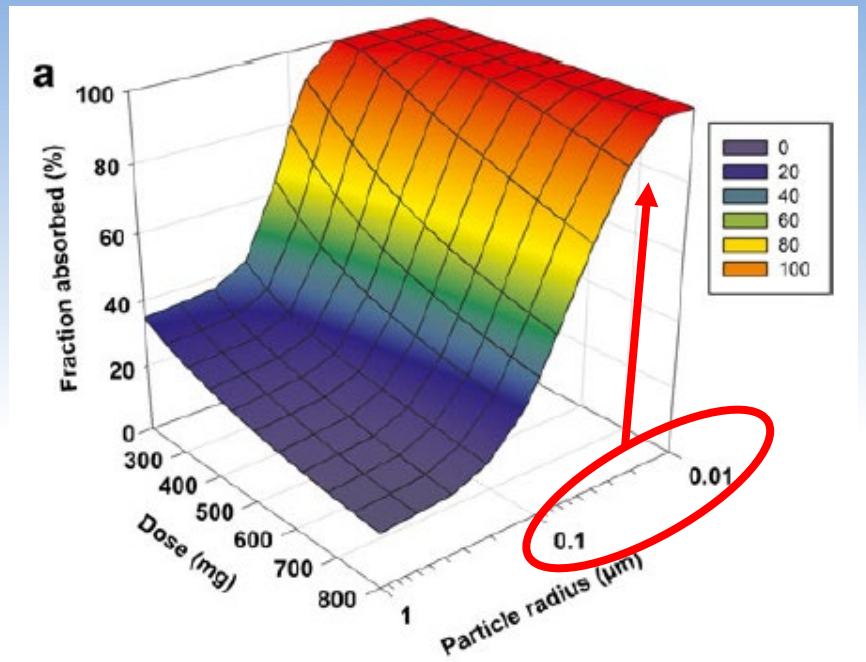
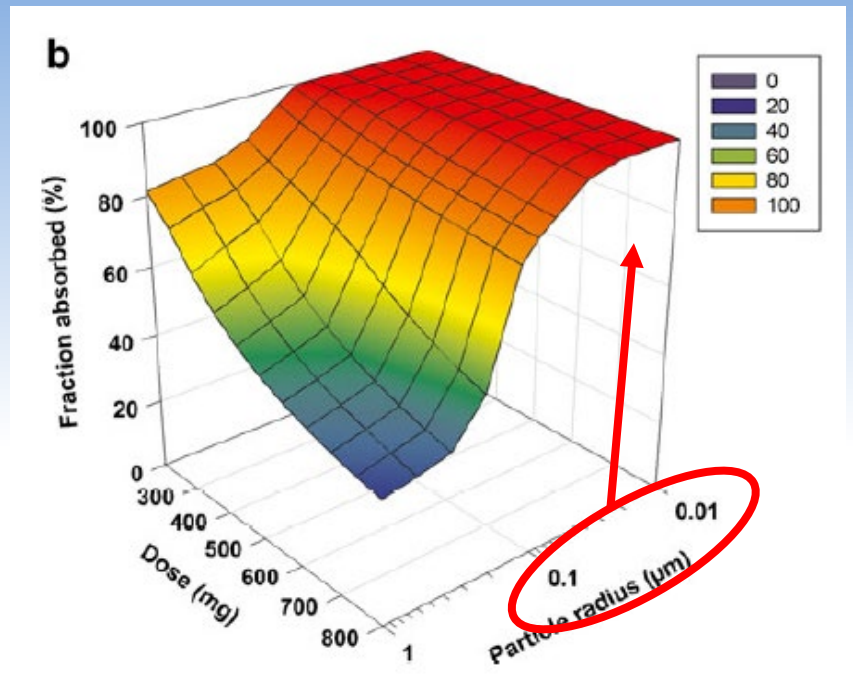
3D Parameter Sensitivity Analysis



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

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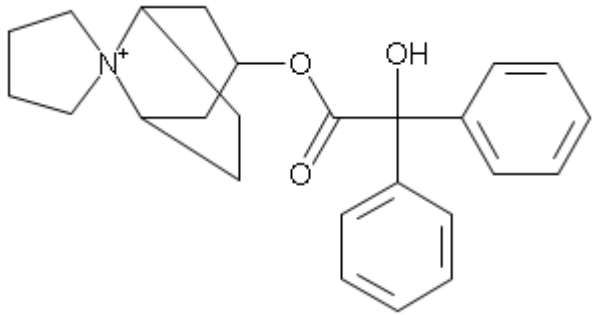
Negative food effects

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)
- Class III
- Not metabolized
- Estimated bioavailability of compound is ~10%



Trospium Solution Viscosity

Table 2. Physicochemical characteristics of trospium chloride solutions in different media. Except for solubility, determinations were performed once. For solubility, the means of $n = 2–3$ and the individual values or the standard deviations are reported

Media	Viscosity η(cP) at 1.29 s^{-1}	Density (g/ml)	Solubility (g/ml)	Osmotic pressure (mmol/kg)
SIF	1	0.997	0.786 ± 0.021	95
0.1 N HCl	1	0.991	0.696 (0.703, 0.689)	188
0.5% HPMC (pH = 6.8)	20	0.993	0.667 ± 0.029	115
1% HPMC (pH = 6.8)	100	0.998	0.537 (0.540, 0.533)	125
2% HPMC (pH = 6.8)	1300	1.004	0.415 (0.420, 0.410)	200
Acetate buffer	1	0.990	0.765 (0.759, 0.770)	74
0.5% HPMC (pH = 4.6)	ND	0.991	0.658 (0.624, 0.693)	82
1% HPMC (pH = 4.6)	ND	0.994	0.559 (0.568, 0.550)	84
2% HPMC (pH = 4.6)	900	0.997	ND	86
0.25% guar (pH = 6.8)	15	0.998	0.787 (0.770, 0.803)	105
0.5% guar (pH = 6.8)	140	0.998	0.636 (0.643, 0.628)	106
0.75% guar (pH = 6.8)	1350	0.998	0.515 (0.520, 0.510)	109

ND, not determined.

Biopharm. Drug Dispos. 33: 403–416 (2012)
DOI: 10.1002/bdd

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)	

ND, not determined.

lity, determinations
ns are reported

pressure (mmol/kg)
95
188
115
125
200
74
82
84
86
105
106
109

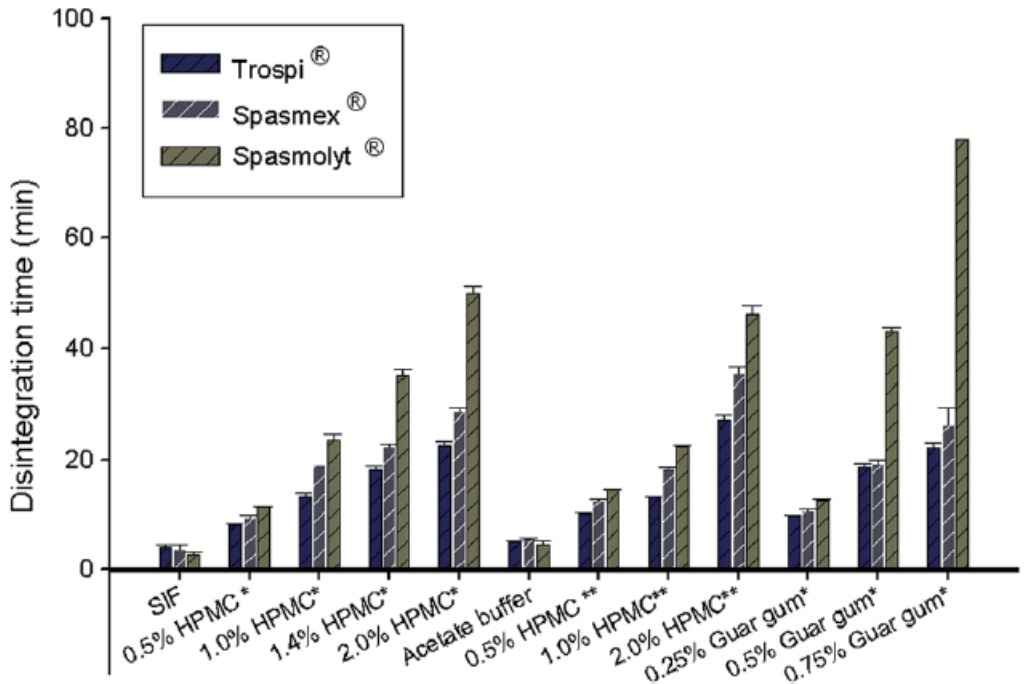


Figure 3. Disintegration times of various trospium chloride products in different disintegration media. The effects of increasing media viscosity on disintegration times were in all cases significant ($p < 0.05$), whereas the effect of change of pH for HPMC solutions at the same concentrations of VEA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

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

Trospium *in vitro* dissolution

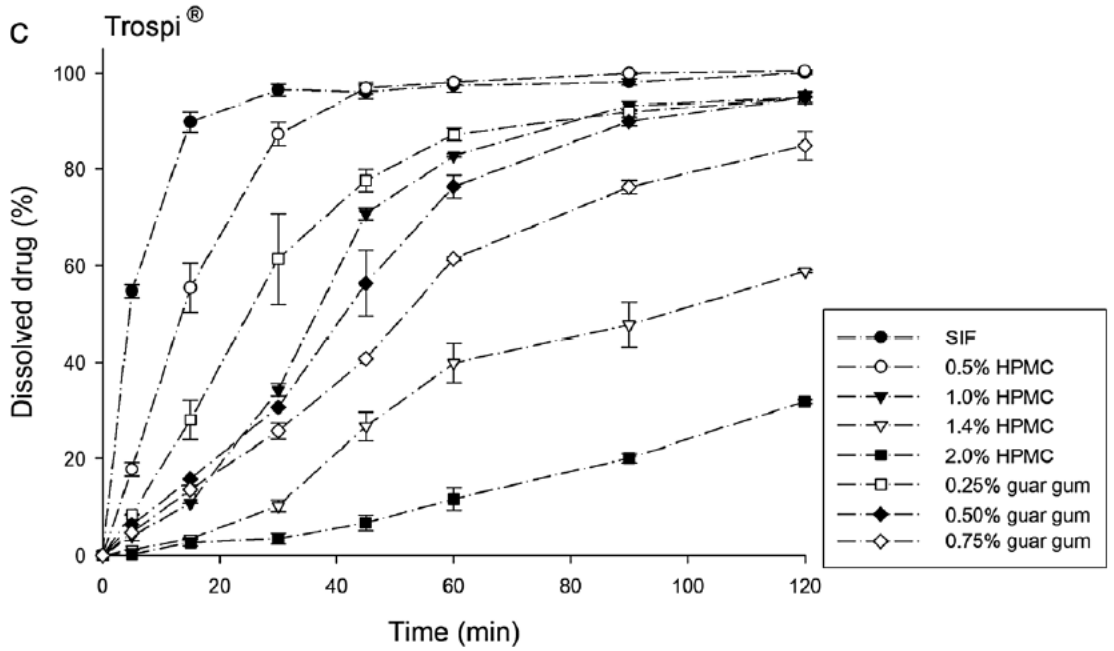


Figure 5. (a) Dissolution profiles for Spasmolyt® in viscous HPMC and guar solutions at pH 6.8, 50 rpm in USP-2 apparatus. In all cases values for f_2 were < 50. Mean ± SD, $n = 3$. (b) Dissolution profiles for Spasmex® in viscous HPMC and guar solutions at pH 6.8, 50 rpm in USP-2 apparatus. In all cases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

Activity: Trospium

1. **Open** the **“Trospium”** database in your **Examples\Trospium folder**
2. Navigate to the **Human 60 mg Tablet Fasted** record and review the model parameters. **Run PSA** around select parameters to identify the key properties impacting absorption
3. Transfer the adjusted Peff to the **Human 60 mg Tab 0.5 pct HPMC – Fasted** record. With the *in vitro* dissolution data, use the **Z-Factor** model to **simulate** the PK
4. Transfer the adjusted Peff to the **Human 60 mg Tab 2 pct HPMC – Fed** record and **switch** the gut physiology to the **Fed model**. With the *in vitro* dissolution data, use the **Z-Factor** model to **simulate PK**
5. Investigate possible reasons for the slight overprediction of the PK under fed conditions

Negative Food Effect

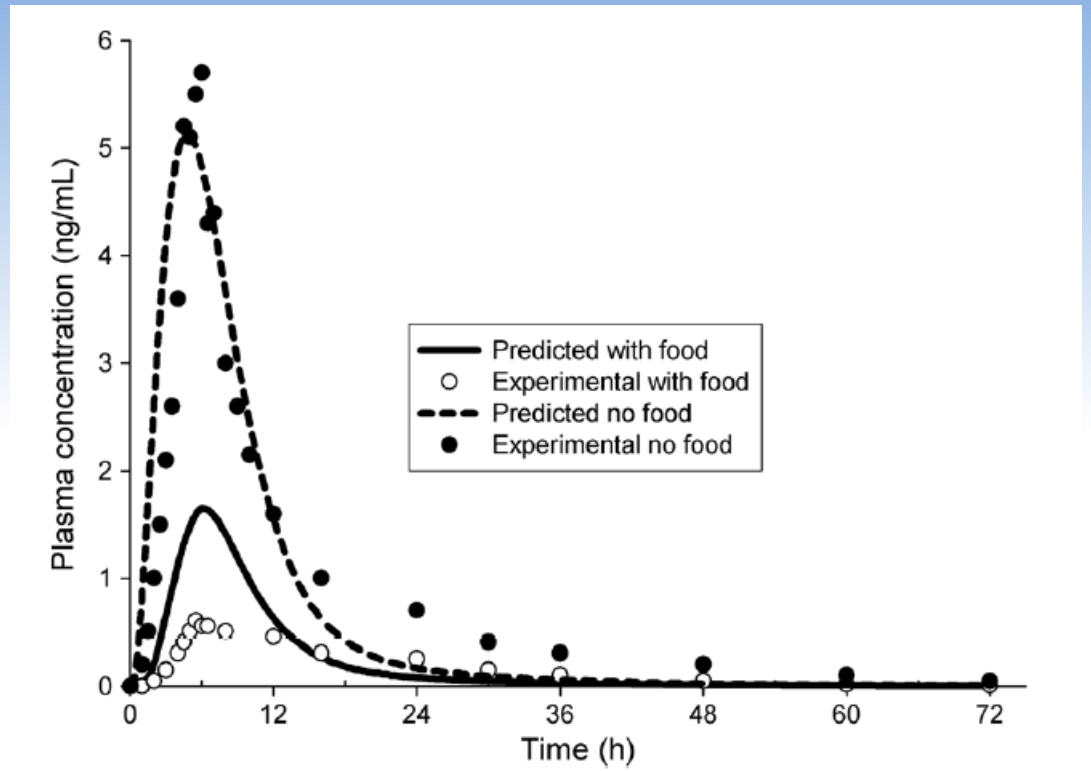
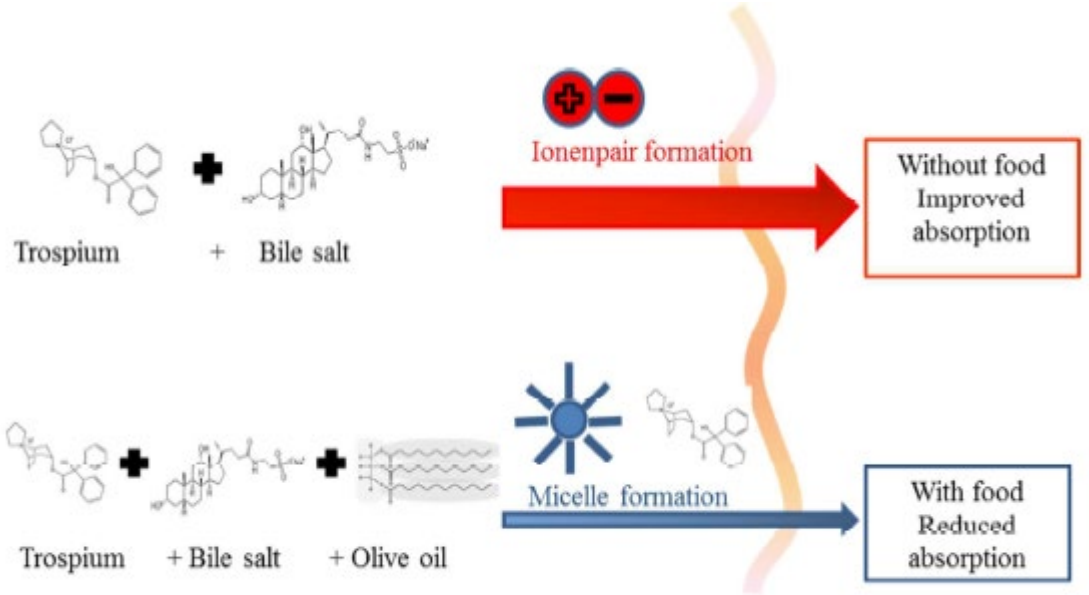


Figure 8. Simulated and predicted plasma concentration–time profiles for trospium in fasted and fed states in humans

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



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Heinen CA et al. Mol Pharm. 2013 Nov 4;10(11):3989-96

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

European Journal of Pharmaceutics and Biopharmaceutics

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

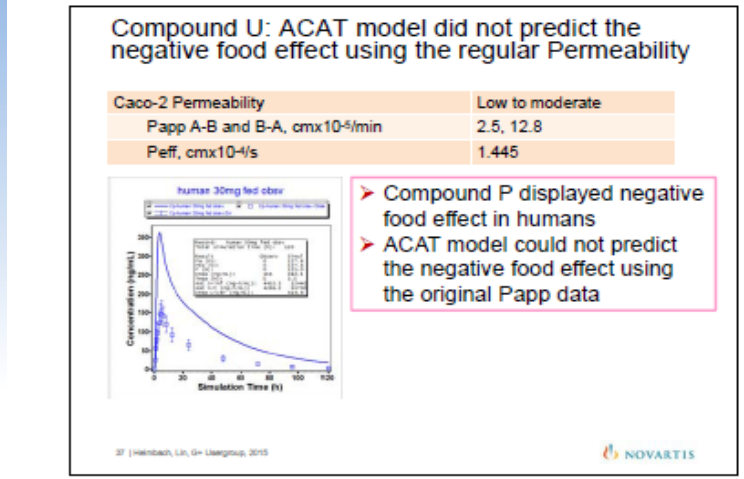
Research paper

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. Markopoulos, P. 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, cmx10-6/min	2.5, 12.8
Peff, cmx10-4/s	1.445

human 30mg fed obsv

Concentration (ng/mL)

Simulation Time (h)

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

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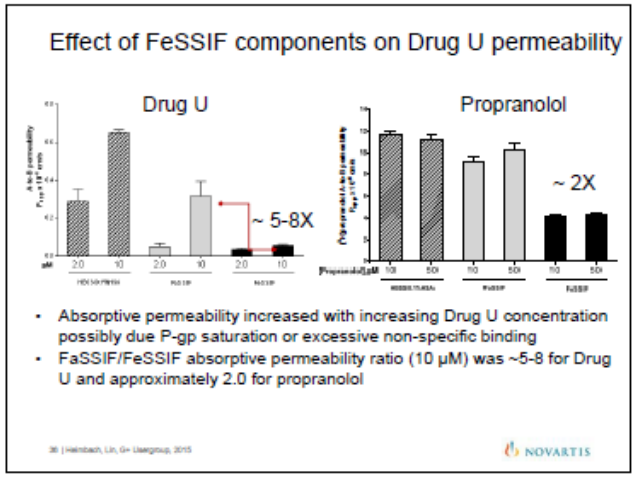


Effect of FeSSIF components on Drug U permeability

Drug U

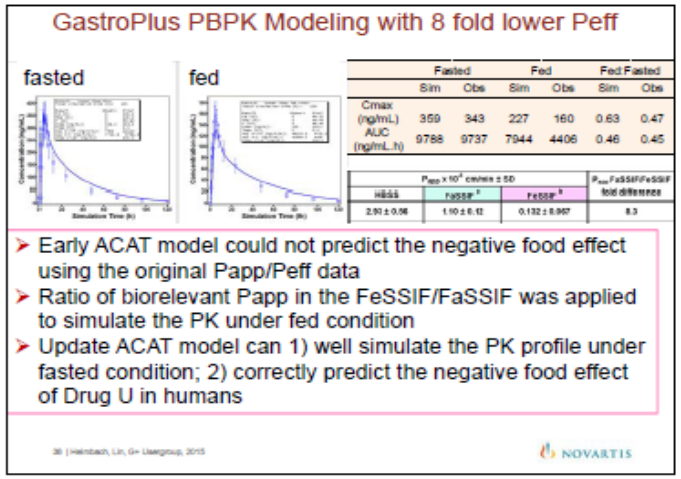
Propranolol

~ 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

NOVARTIS



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

P_{app} x 10^{-6} cm/min ± SD			P_{app} FaSSIF/FeSSIF fold difference
HBSS	FaSSIF	FeSSIF	
2.90 ± 0.06	1.10 ± 0.12	0.132 ± 0.007	8.3

- 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

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Q&A

Questions & Answers

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