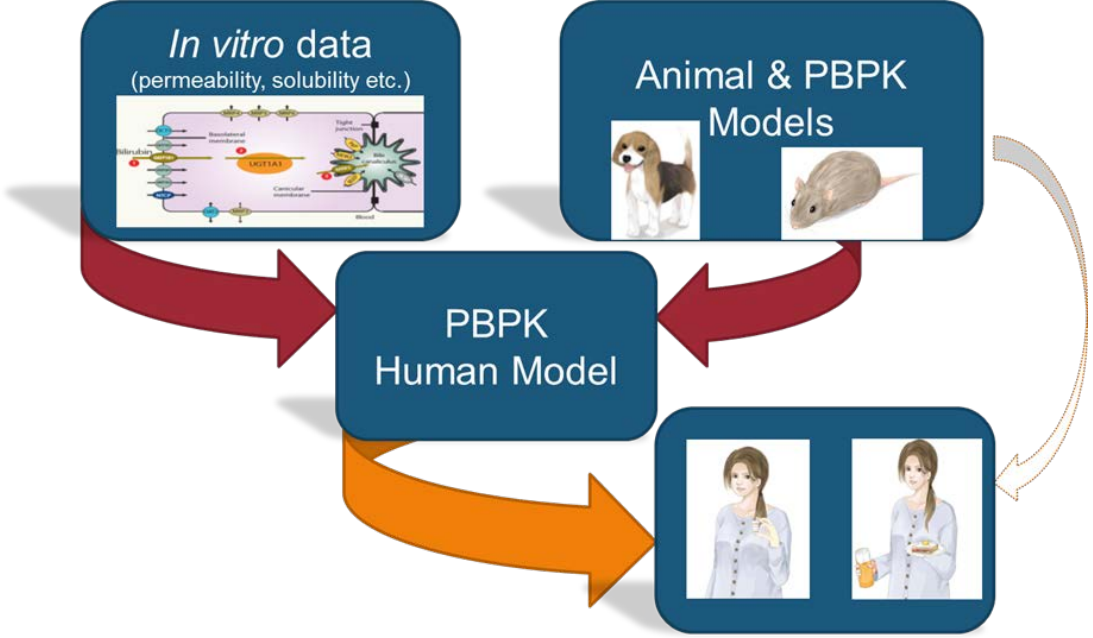

PBPK Modeling and Simulations of Oral Drug Absorption/Food Effect/PPI /PBIVIVC: Opportunities and Challenges

Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development
University of Maryland's Center of Excellence in Regulatory Science and Innovation (M-CERSI)
May 15th - May 17th 2017
www.pharmacy.umaryland.edu/dissolution2017

Tycho Heimbach, Marc Laisney, Tanay Samant, Mohamed Elmeliegy,
Fan Wu, Imad Hanna, Wen Lin, Jin Zhang, Stefanie Dodd, Anh-Thu Nguyen-Trung,
Hung Tian, Barbara Vogg, Stefania Beato, Sudhakar Garad, Somesh Choudhury, Xiao Ren,
Martin Mueller-Zsigmondy, Heidi Einolf, Kenichi Umehara,
Florence Hourcade-Potelleret, **Handan He**

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Outlines

- **Applications of PBPK absorption modeling tools**
- **Case examples:**
  - **Prediction on PPI effects**
  - **Formulation dependent PBPK**
  - **Food food effect predictions**
  - **Comparison of IVIVC vs PBIVIVC**
  - **Biorelevant Permeability Challenges**
- **Overall recommendations**

PBPK, Translational Biopharmaceutics

Fasted/Fed

Solubility
Bile salt conc.
In vivo solubility
Precipitation rate

Discovery
BCS/
BDDCS
Class

GI physiology:
Population
Stomach pH?
Stomach emptying time?
Intestinal pH
GI blood flow

Permeability:
Log P,
Inhibition of Efflux or Uptake Transporters

Drug Substance/ Formulation Solubility, pKa, etc.

Dissolution Profile Multiple pH?

Biorelevant Solubility

Precipitation Time

PBPK G+ Absorption Model Dog -> Human Human -> Human

Systemic PK (CL, V_d), PBPK Model

Biorelevant Permeability
Adsorption/Recovery

In vitro-In vivo Scaling

Caco-2 or MDCK P_{app}

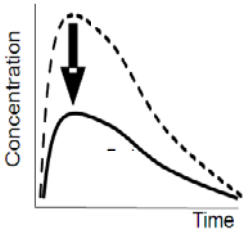
GI transporter J_{max}, K_m

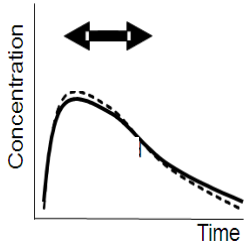
B(DD)CS II

B(DD)CS I

Low Confidence B(DD)CS IV

Predicted Effect





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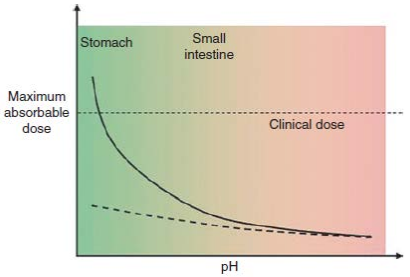
Theoretical PPI impacts for weak bases

Budha, Benet et. al, 2009, 2011 (mod)



High Solubility
Do<1 or ~1

Low Solub
Do >>1

High Permeability

Low Permeability

Class 1
F_{extent} ⟷

Class 2
F_{extent} ↓ ⟷

Class 3
F_{extent} ⟷

Class 4
F_{extent} ↓ ↑ ⟷

BCS

Class: according to BCS, BDDCS

Note: PPI Effects can be dose dependent!

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Successful PBPK models on PPI prediction and Label Impact

FARYDAK® (panobinostat) capsules
10mg/15mg/20mg

- **Farydak has pH dependent solubility (BCS II). However, solubility is relatively high.**
- **Q: Will Proton Pump Inhibitors (PPI) impact Farydak Exposure?**
- **Should a Clinical PPI study be run?**

Table 3-1 Solubility of (Panobinostat) lactate, anhydrous drug substance at 37.0°C (+/- 0.5°C), batch 0724011

Solution / buffer	Approximate solubility in mg/ml of solution at 37°C (± 0.5°C)	Corresponding maximum amount of drug soluble in 250ml of solution (in mg)
Water	4.775	1194
pH 1.2 (HCl)	1.017	254
pH 2.0 (HCl)	1.256	314
pH 4.5 (acetate)	4.771	1193
pH 6.0 (phosphate)	3.845	961
pH 6.8 (phosphate, simulated intestinal fluid)	0.261	65
pH 7.6 (phosphate)	0.064	16

(DSP5.2R5001203B)

Public domain:

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205353Orig1s000TOC.cfm

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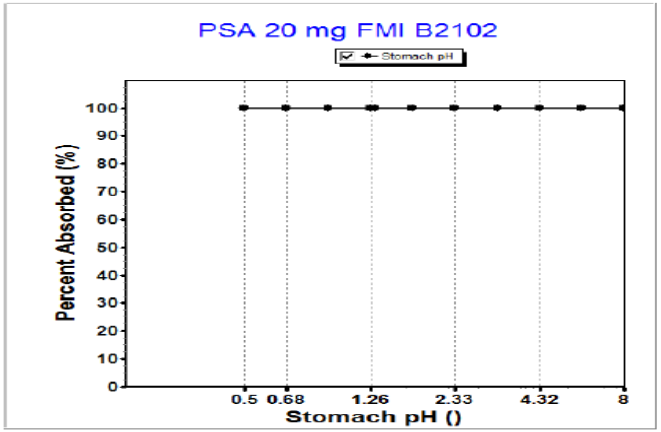
Clinical PPI study was waived based on PBPK modeling and simulations are used on labels

FARYDAK® (panobinostat) capsules 10mg/15mg/20mg

Figure 7-4 Projected absorption of 20 mg LBH589 vs. stomach pH in humans



Output figure from parameter sensitivity analysis using the ACAT absorption model of LBH589 within GastroPlus™

Absorption is not pH dependent over the pH range from 0.5 to 8.

- **12.3 Pharmacokinetics**
- ***Absorption***

The aqueous solubility of panobinostat is pH dependent, with higher pH resulting in lower solubility *[see Description (11)]*. Coadministration of FARYDAK with drugs that elevate the gastric pH was not evaluated in vitro or in a clinical trial; however, **altered panobinostat absorption was not observed in simulations using physiologically-based pharmacokinetic (PBPK) models.**

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205353Orig1s000TOC.cfm

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Outline

- **Applications of PBPK modeling of formulation dependent exposure and BCS/BDDCS**
- **Case examples:**
  - **Prediction on PPI effects**
  - **Formulation dependent PBPK**
  - **Food effect predictions**

  } Compound E

  - **Comparison of IVIVC vs PBIVIVC**
  - **Biorelevant Permeability Challenges**
- **Overall recommendations**

Compound E Absorption Modeling

- **Modeling objectives**

1. To assess BE equivalence/in-equivalence a priori knowing in vitro dissolution differences between early human CSF (capsule) and late development FMI (tablet)

   Q: Will FMI formulation be equivalent to CSF?

2. To assess impact of stomach pH on Compound E absorption (e.g. possible effect of co-administered PPI)

   Q: Will GI pH impact the extent of absorption?

In vitro data

No significant change in solubility with pH in bio-relevant media

- Slight pH-dependent solubility observed
  - High solubility at low pH (>2.4 mg/mL at pH 2 and 4.5)
  - ~3-fold decrease in solubility at pH 6.8 (0.8 mg/mL)
  - **Solubility in bio-relevant media (FaSSIF) at pH 6.5 is equivalent to solubility at lower pH**

Solvent	pH	Solubility at 37°C (mg/mL)[a]
HCl/KCl buffer	2.0	> 2.4 mg/mL
Acetate buffer	4.5	> 2.4 mg/mL
Phosphate buffer	6.8	0.8 mg/mL
Phosphate buffer	7.5	0.3 mg/mL
FaSSIF	6.5	> 2.4 mg/mL
FeSSIF	5.0	> 2.2 mg/mL

a

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pH-Dependent Solubility

Low Clinical Relevance of pH-Dependent Solubility based on Low Dose Number

Drug (Max Dose)	pKa	Solubility	pH-dependent solubility	BCS / BDDCS class	Dose number (max dose/250 mL / lowest solubility)	Clinical relevance (AUC / Cmax)
Dasatinib (100 mg)	3.1, 6.8, 10.8	18 mg/mL at pH 2.6 to <0.001 mg/mL at pH 7.0 at 24 °C	Yes	II	560	43% / 42%
Nilotinib (400 mg)	2.1, 5.4	Slightly soluble (1–10 mg/mL) at pH 1.0, very slightly soluble (0.1–1 mg/mL) in water, at pH 2.0 and pH 3.0, and practically insoluble (<0.1 mg/mL) in buffer solutions of pH ≥ 4.5	Yes	IV / II	160	34% / 27%
Axitinib (5 mg)	4.8	Solubility decreases from 1.8 mg/mL at pH 1.1 to 0.0002 mg/mL at 7.8	Probably not clinically applicable	II	100	15% / 40%
Imatinib (400 mg)	7.7	Freely soluble (100–1,000 mg/mL) up to pH 5.5, the solubility reduces at higher pH; lowest solubility 1 mg/mL	Yes	II	1.6	No effect
Everolimus (10 mg)	NA	Solubility in aqueous media is <0.01% (0.1 mg/mL) across the pH range 2–10	No	III / I	0.4	No study conducted
Ceritinib (750 mg)	4.1, 9.7	Highly soluble at pH 1 (11.9 mg/mL) and 2 (5.5 mg/mL); solubility decreases to 0.01 mg/mL at pH 6.0	Yes	IV	1000	76% / 79%
Palbociclib (125 mg)	NA	Slightly soluble (1.135 mg/mL) at pH 1 and 1.205 mg/mL at pH 4. Solubility decreases to 0.026 mg/mL at pH 6.8	Yes	NA	19.23	62% / 80% (Fasted) 13% / 41% (Fed)
Comp. E	5.5, 8.6	Highly soluble at pH 2.0 and 4.5; solubility decreases to 0.8 mg/mL at pH 6.8	Yes	IV	3-8	Unknown (Expected to be low based on dose number)

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Adapted from Budha et al., (2012) CPT 92(2):203-213. Palbociclib solubility data obtained from Sandoz.

PBPK Absorption Model

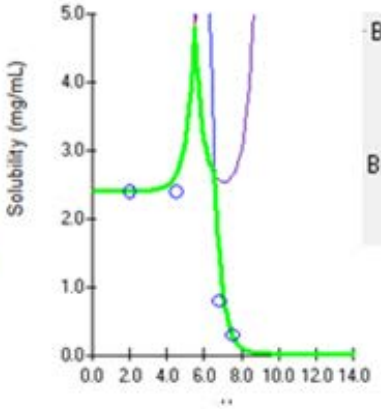
- Phys Chem / Permeability properties (incl. moderate perm)

Summary of input parameters for ACAT model in humans

Parameter	Used value	Source
Molecular Formula		-
Molecular Weight		-
logP	1.954	-
pH logP	-1 (indicating neutral species)	-
pK_a	pKa1: 8.6 (base); pKa2: 5.5 (base)	
		Adjusted to solubility vs pH profile
Reference solubility	0.3 mg/mL at pH 7.5	
Mean Precipitation Time	900 sec	Default value in G+
Diffusion Coefficient	0.6297 * 10^{-5} cm^2/sec	Calculated from molecular weight in GastroPlus™ v9.0
Drug Particle Density	1.2	Default value in G+
Particle Size radius [µm]	60 µm	
Caco-2 [10^{-6} cm/sec]	0.1833	
Human Peff [10^{-4} cm/sec]	0.9023	Converted from Permeability on Caco2

Table 3-2 pH-solubility curve

pH	Buffer substances	Solubility [mg/ml]	Bile Salt Concentration
pH 2	HCl/KCl	>2.4 [a]	
pH 4.5	Acetate	>2.4 [a]	-
pH 6.8	Phosphate	0.8	-
pH 7.5	Phosphate	0.3	-
pH 6.5	FaSSiF-V1 [b]	>2.4	3 mM
pH 5	FeSSiF-V1 [c]	>2.2	15 mM



Biorelevant In Vitro Solubilities

	SGF	FaSSIF	FeSSIF
pH:	1.2	6.5	5
Bile Salt Conc (mM):	0	3	15
Solubility (mg/mL):	0	2.4	2.2

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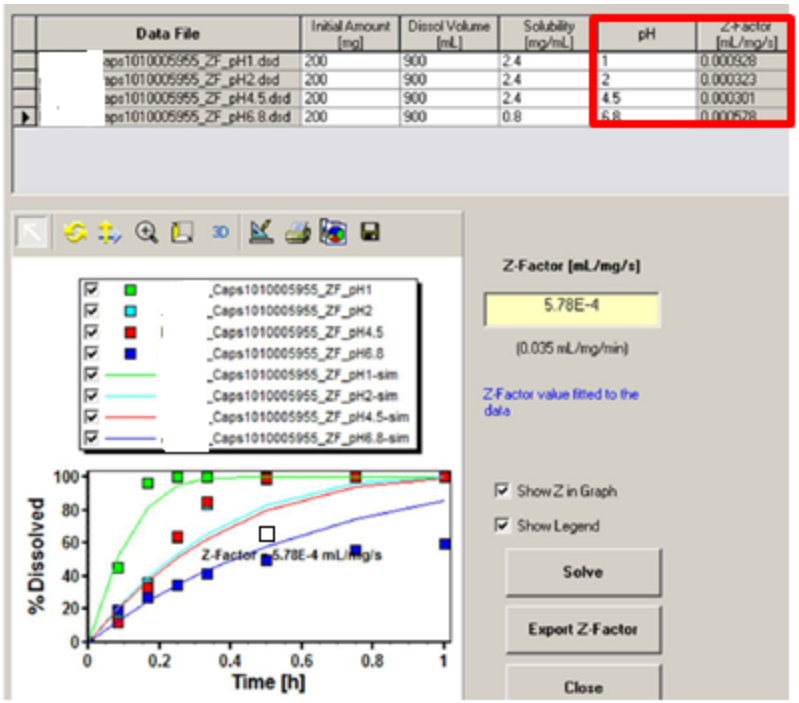
Z-factor dissolution (Takano)

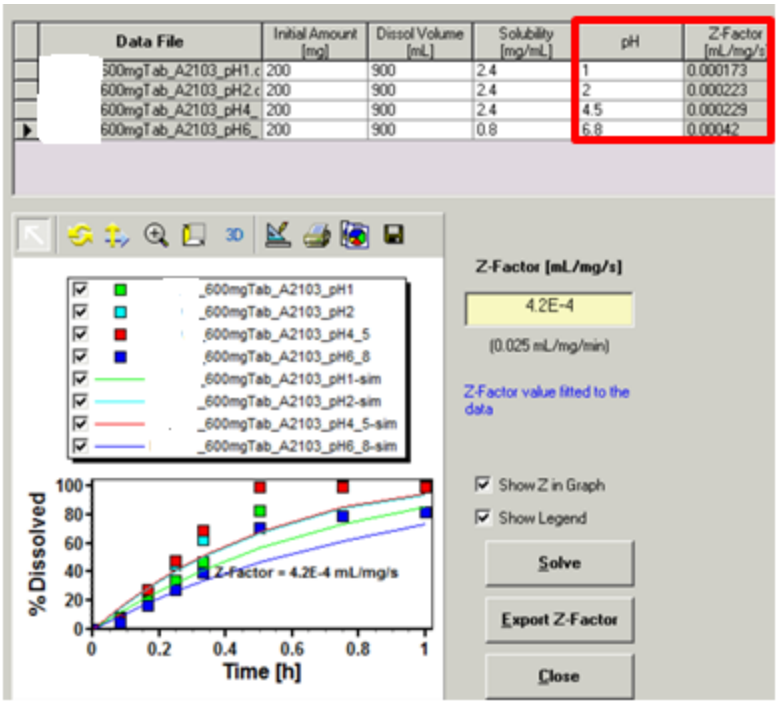
- Enable to consider the change of Compound E drug product dissolution rate vs pH during the drug transit in the gut

Z-factor vs pH for capsule



->pH dependent dissolution rate

Z-factor vs pH for tablets



->'slower' dissolution for the tablet

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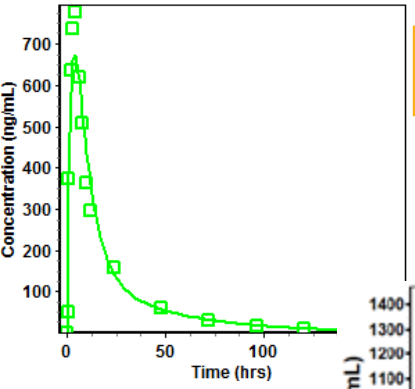
PBPK model built in GastroPlus™

- PK was fitted with a 2 comp model using PKPlus
  - default gut physiology for humans at fasted state (Human – Physiological – Fasted) and the Absorption Scaling Factors (ASF) model named OptlogD Model SA/V 6.1
  - Johnson dissolution model

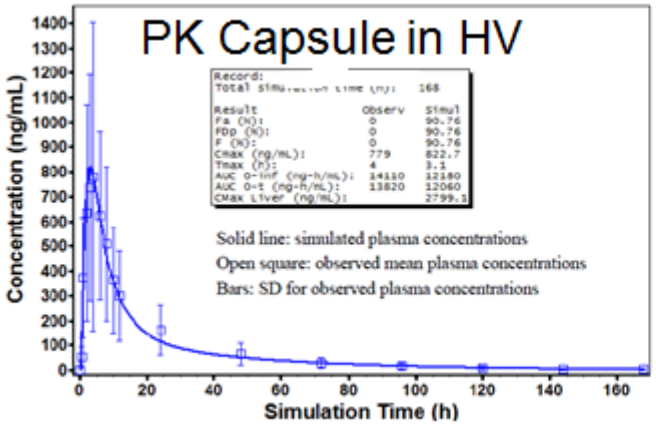
Fitting with
2 comp model

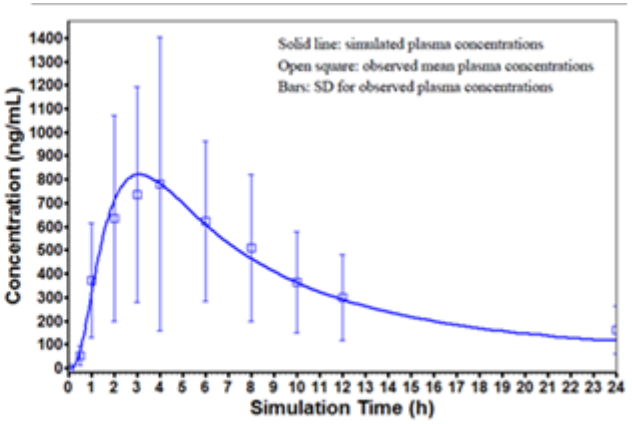


Optimization of Vc and K12 to improve the fit

Table 4-1 Estimated PK parameters in human

Parameters	Automatic estimation using PK Plus Module	Final 2 compartmental model
CL/F (L/h/kg)	0.596	0.596
Vc/F (L) central compartment	7.63	5 (optimized)
K12 (h^{-1})	0.041	0.07 (optimized)
K21 (h^{-1})	0.041	0.041





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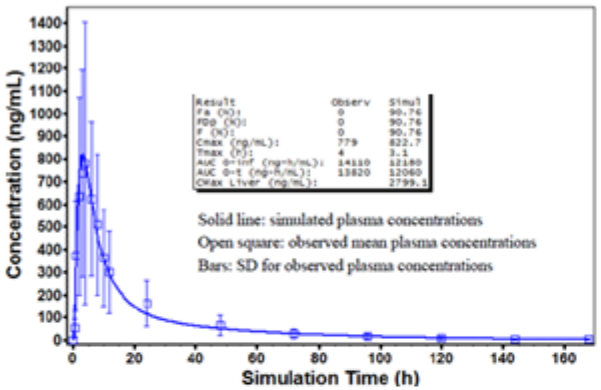
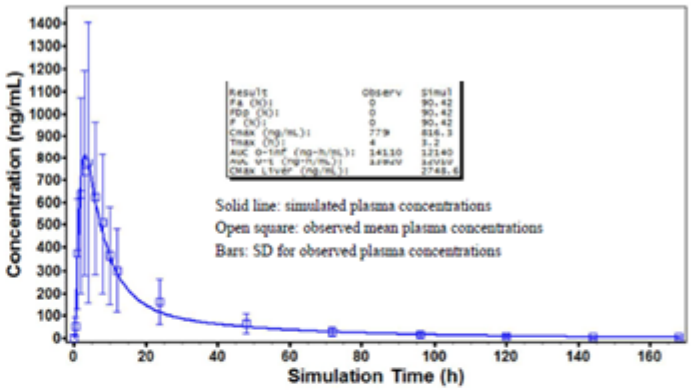
PK model qualification

- PK model established for Capsule in HV simulate correctly PK in Patients, PK with Tablets, using either Johnsson or Z-factor models

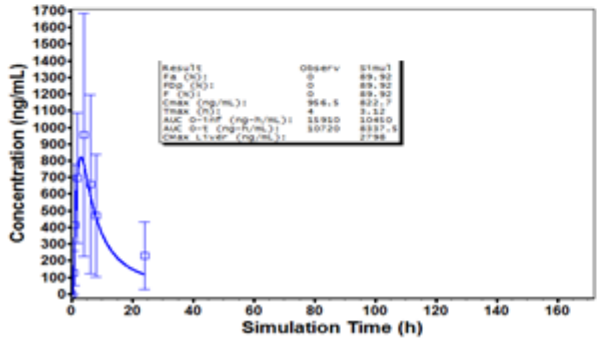
Capsule – HV – Johnson model



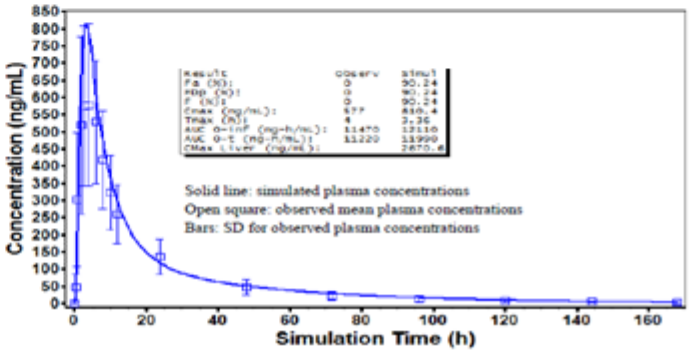
Capsule – HV – Z factor model



Capsule – Patients – Johnson model



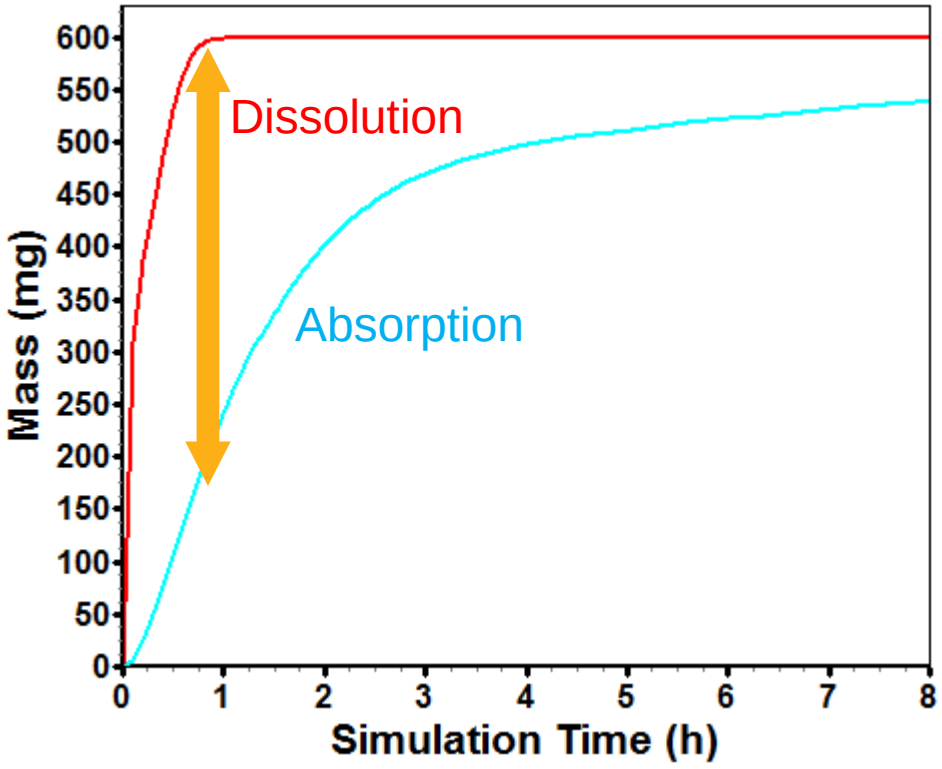
Tablet – HV – Z factor model



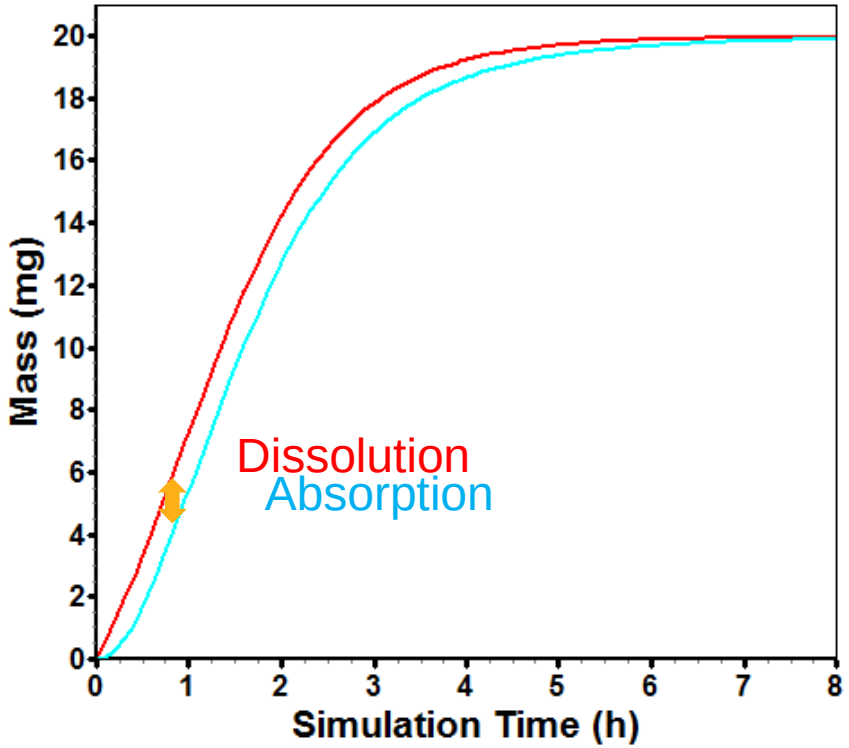
Absorption Kinetics – Diagnostic Plots

Dissolution controlled or permeability controlled?

- Compound E: permeability-controlled absorption



- Example: dissolution-controlled absorption



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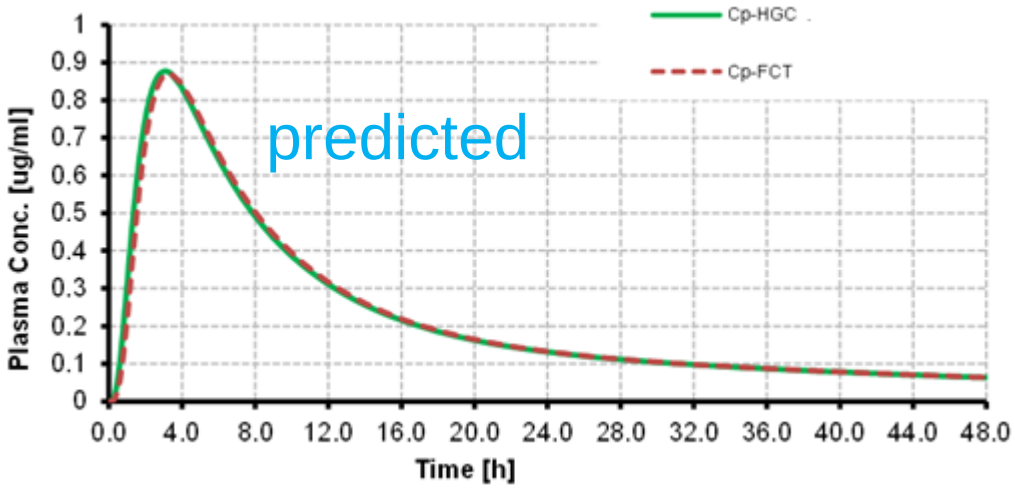
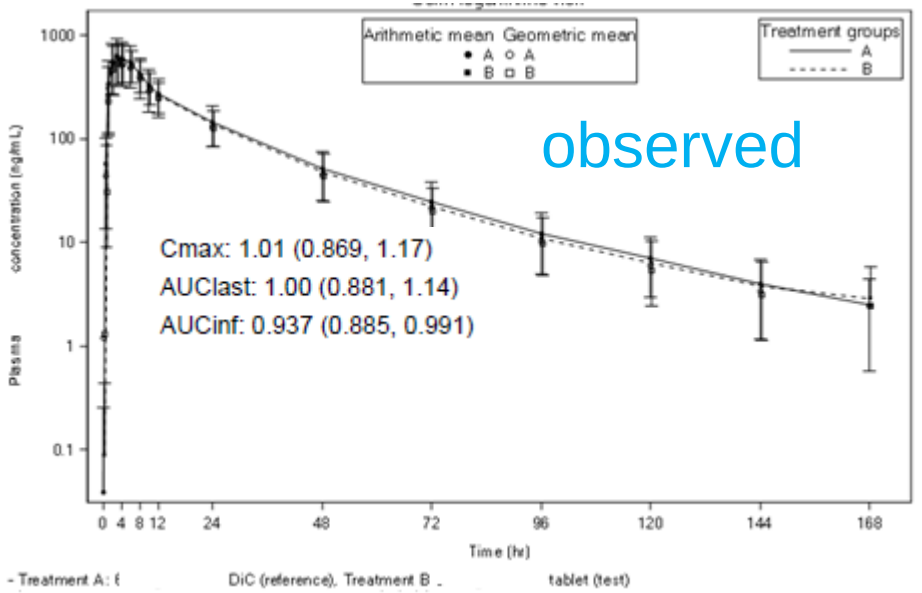
BE study outcome

Predicted versus observed plasma concentration profiles

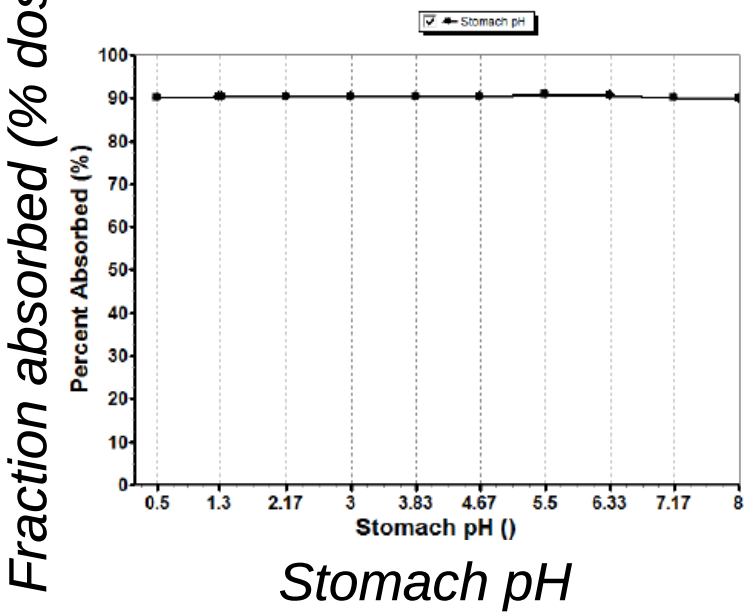




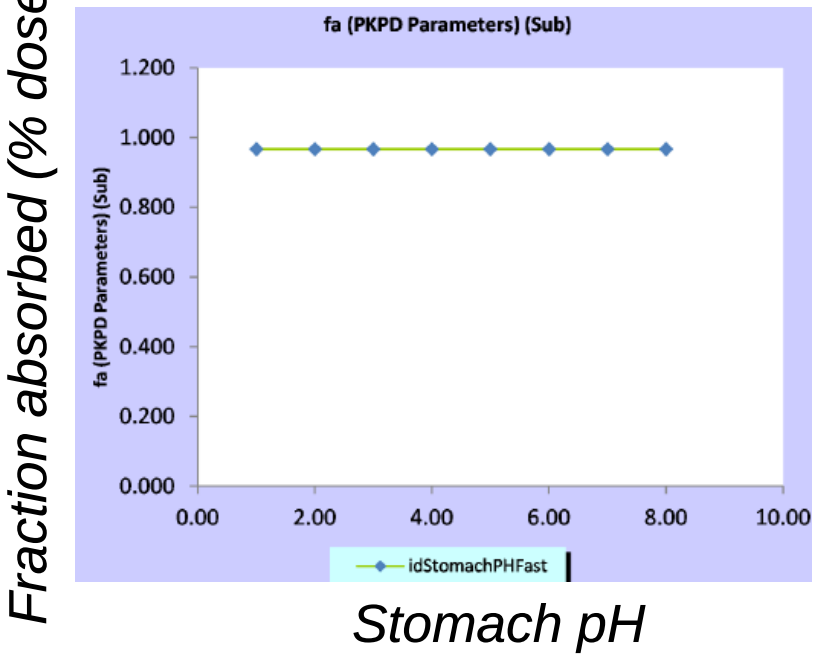
PBPK PSA
Influence of stomach pH on Compound E absorption

- Change of stomach pH has no impact on drug absorption (rate and extent)
- Consequently, no predicted effect on PK

GastroPlus



SimCYP



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PK model qualification

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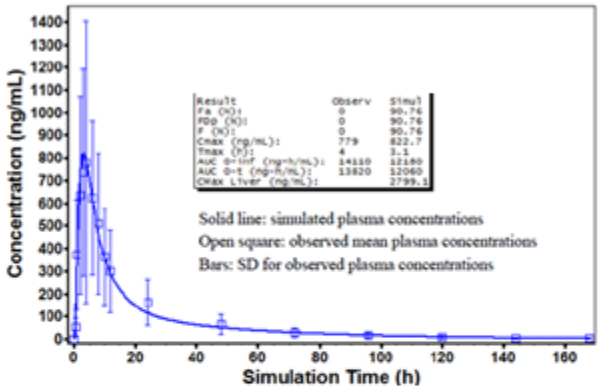
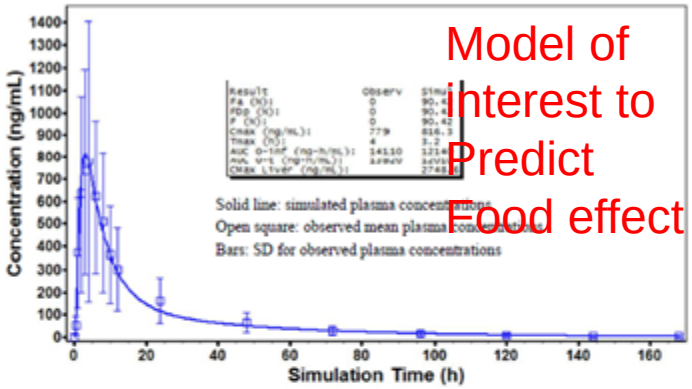
Capsule – HV – Johnson model

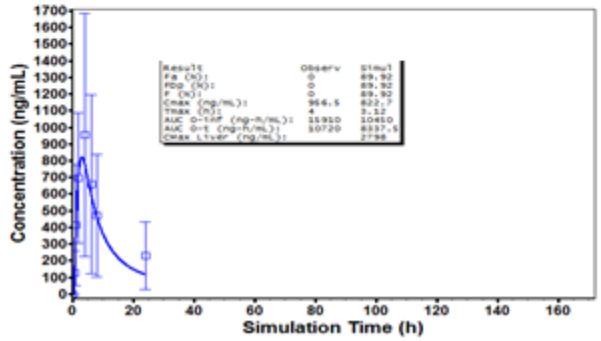


Capsule – HV – Z factor model

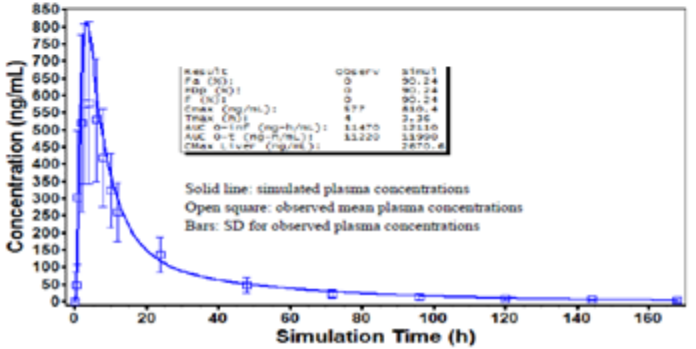


Model of interest to Predict Food effect

Capsule – Patients – Johnson model

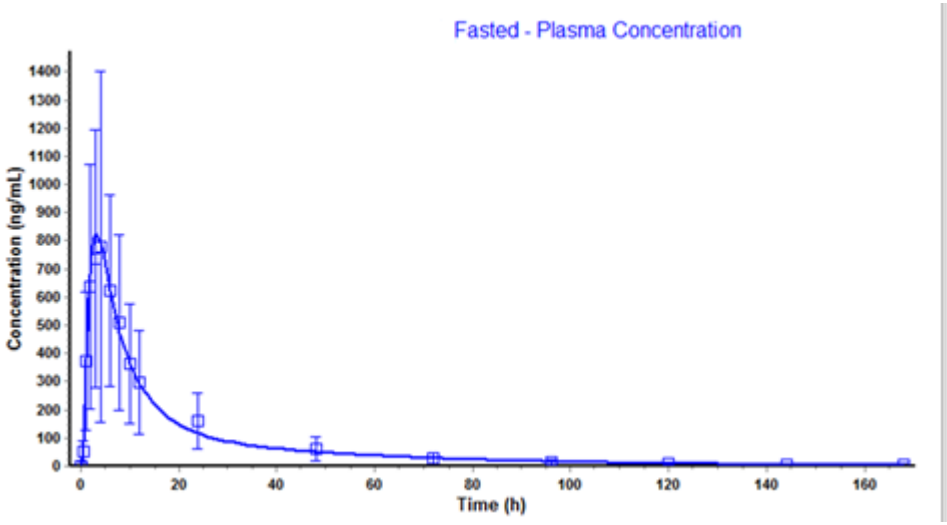


Tablet – HV – Z factor model

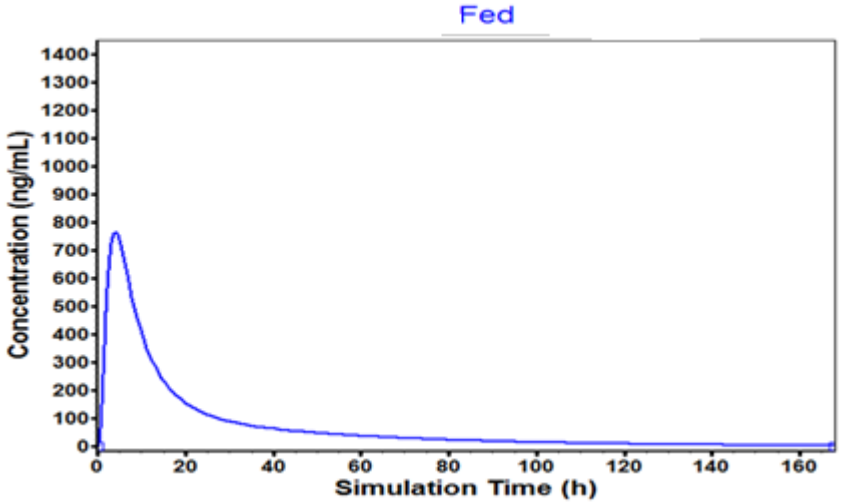


Prediction of Food effect, Compound E

Simulation Fasted State



Simulation Fed State



Biorelevant In Vitro Solubilities

	SGF	FaSSIF	FeSSIF
pH:	1.2	6.5	5
Bile Salt Conc (mM):	0	3	15
Solubility (mg/mL):	0	2.4	2.2

High and similar solubility measured in FaSSIFv1 and FeSSIFv1

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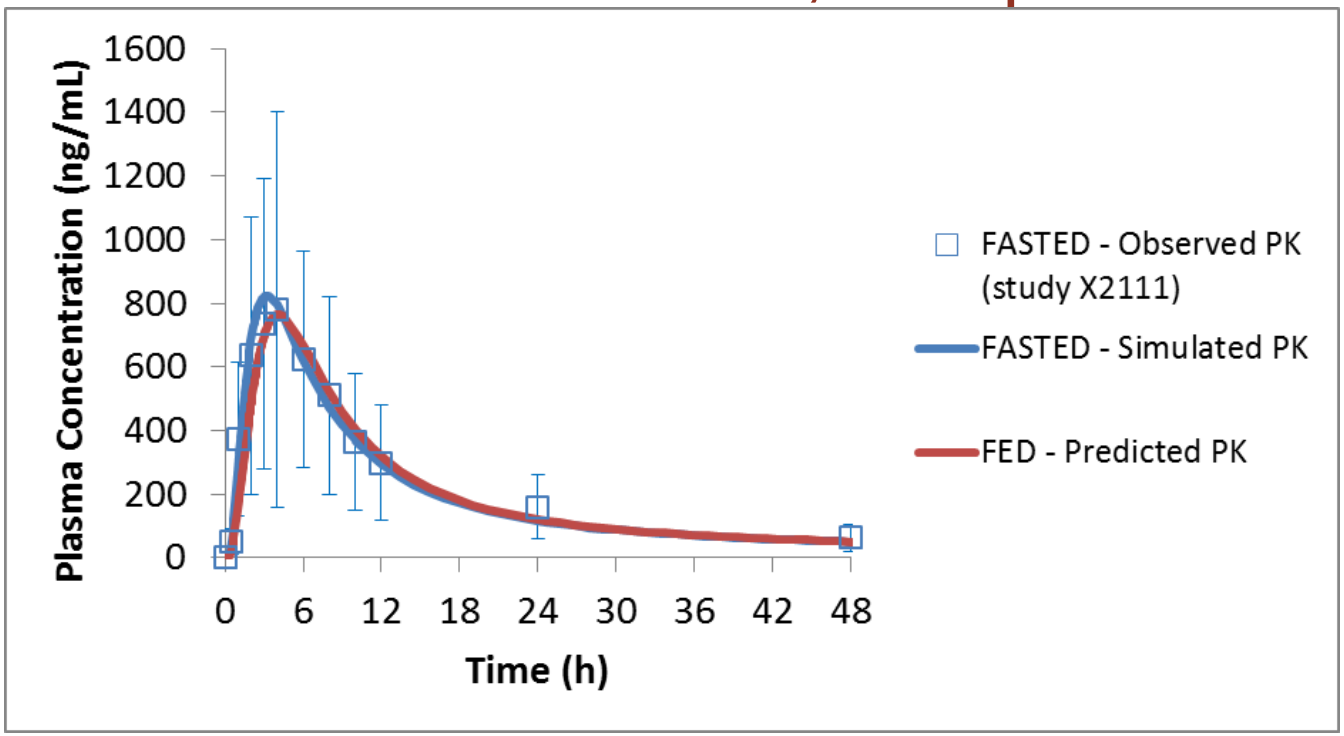
Prediction of Food effect, Compound E



Food Effect prediction	Cmax (ng/mL)	AUC0-168h (ng.h/mL)
Fasted	823.23	12090
Fed	764.29	12130
% change	**-7**	**0.3**

It was predicted that Food would not affect PK, with:

- Only slight decrease on Cmax
- No change in AUC0-168h

Compound E showed no clinically significant food effect

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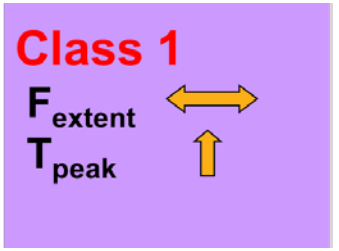
- **Applications of PBPK modeling of formulation dependent exposure and BCS/BDDCS**
- **Case examples:**
  - **Prediction on PPI effects**
  - **Formulation dependent PBPK**
  - **Food effect predictions**
  - **Comparison of IVIVC vs PBIVIVC**
  - **Biorelevant Permeability Challenges**

Compound F

- **Overall recommendations**

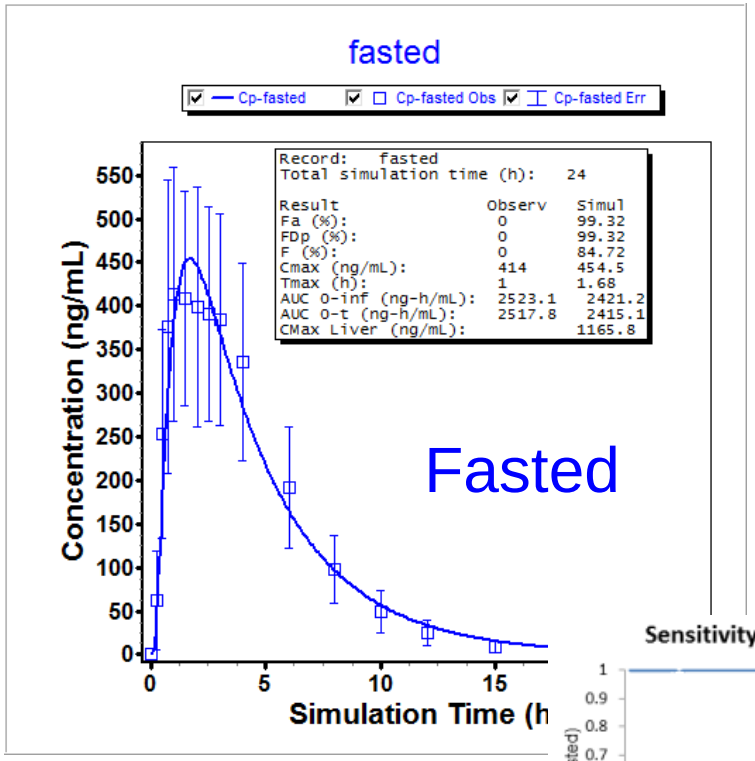
Compound F - Food Effect

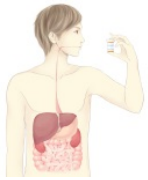


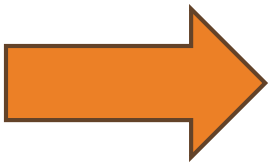
- **High Solubility,** > 10 mg/mL, Do < 1
- **High Absorption** > 80%, F > 80%, Fa > 80%
  - Caco-2 low, no pgp involvement
- **High Metabolism** – mainly metabolized
- Rat BDDCS I
  - No biliary excretion (Rat)
- No Adsorption/complexation issues
- **Q: Can Food effect be predicted?**
- No Food effect expected – Predictable Outcome!

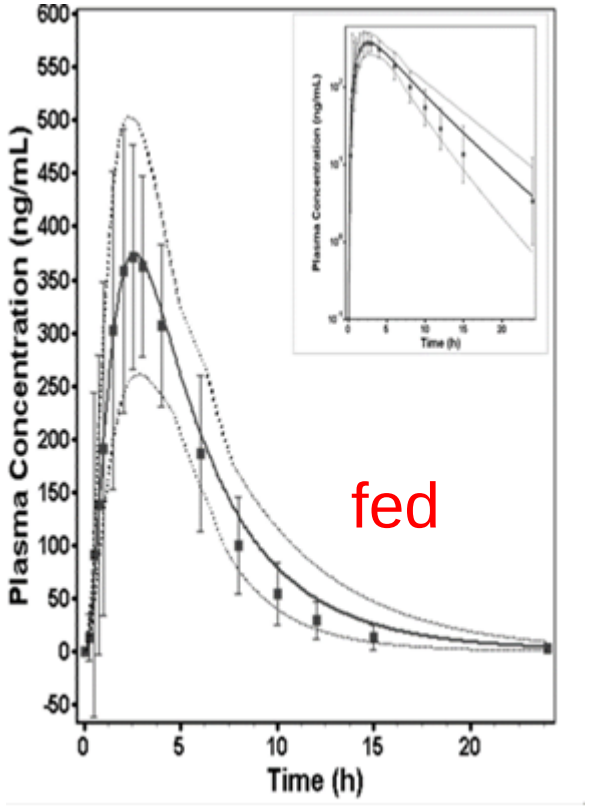
Class 1
F_{extent}
T_{peak}

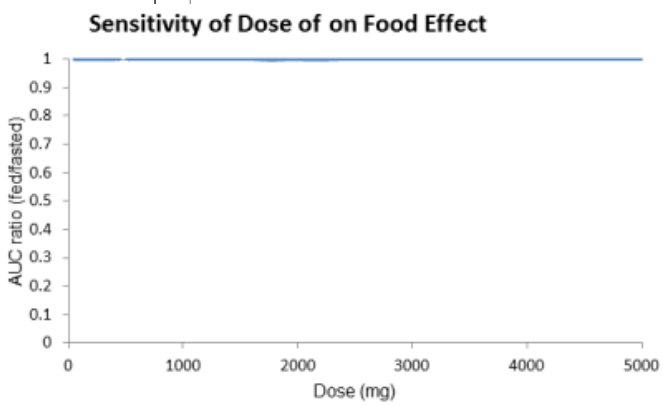
Predicted vs Observed Food Effect, BCS I Drug in Human











FaSSIF
pH 6.5 solubility
3.6 mg/ml

FeSSIF
pH 5 solubility
4.2 mg/ml

Food Effect Can be predicted via ACAT model

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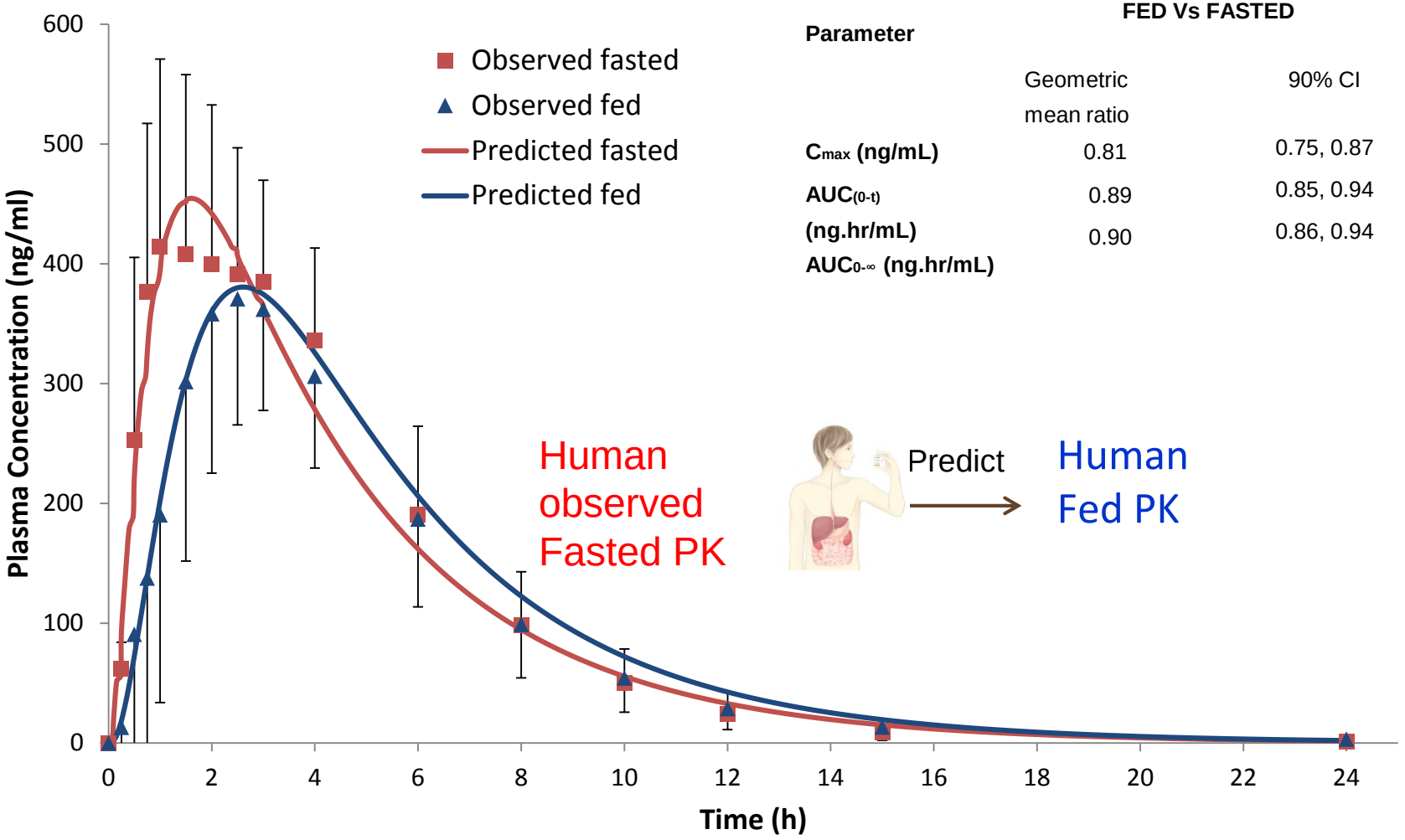
BCS I: Predicted vs Observed Food Effect in Human



Parameter	FED Vs FASTED Geometric mean ratio	90% CI
C_{max} (ng/mL)	0.81	0.75, 0.87
$AUC_{(0-t)}$ (ng.hr/mL)	0.89	0.85, 0.94
$AUC_{0-\infty}$ (ng.hr/mL)	0.90	0.86, 0.94

Journal of Pharmaceutical Sciences 105 (2016) 2723–2734

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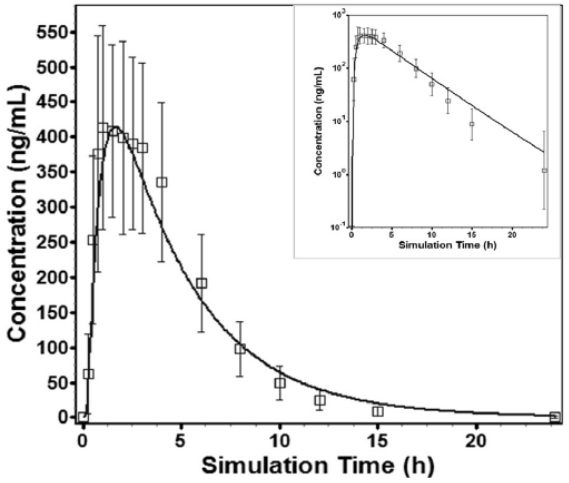
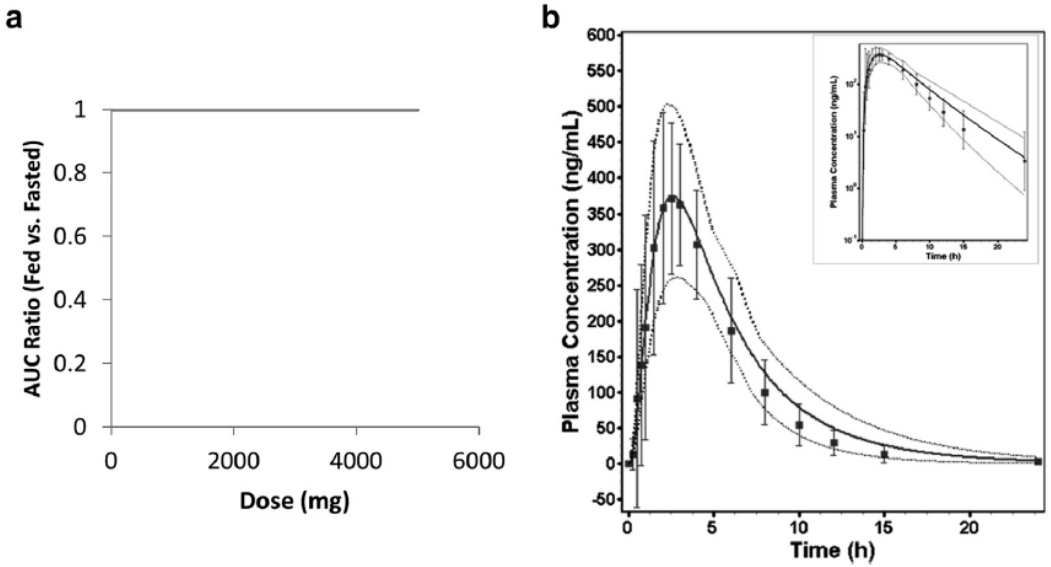
90% Probability

- Human PBPK model



Fasted

Figure 9. Clinically observed (squares) versus fitted PK for 100 mg for Compound X in the Fasted State. Percent prediction error for AUC_{0-t} (ng h/mL) = 5.28%; Predicted Fa = 98.3%; Predicted F = 83.5%. The inset shows the semilog plot.



Fed

Figure 10. (a) PSA demonstrating that the fed-to-fasted AUC ratio (FE ratio) is unity; thus, no significant food effect (exposure increase) is expected over a dose range of 0-5000 mg; (b) population simulation for Compound X PK profile following PO of 100 mg Compound X in fed state. The squares represent the mean observed data and the error bars represent the %CV associated with mean data. The mean simulated data is shown as solid black line. The 90% probability contour is represented by dashed black line. The inset shows the semilog plot.

Journal of Pharmaceutical Sciences 105 (2016) 2723–2734

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- **Applications of PBPK modeling of formulation dependent exposure and BCS/BDDCS**
- **Case examples:**
  - **Prediction on PPI effects**
  - **Formulation dependent PBPK**
  - **Food effect predictions**
  - **Comparison of IVIVC vs PBIVIVC**
  - **Biorelevant Permeability Challenges**

Compound NVS6

- **Overall recommendations**

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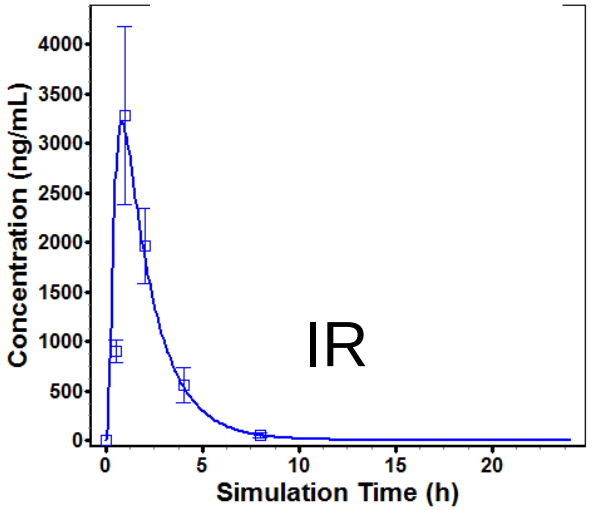
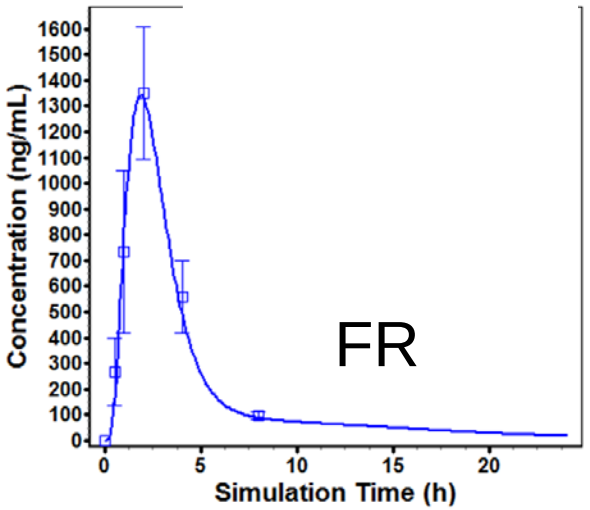
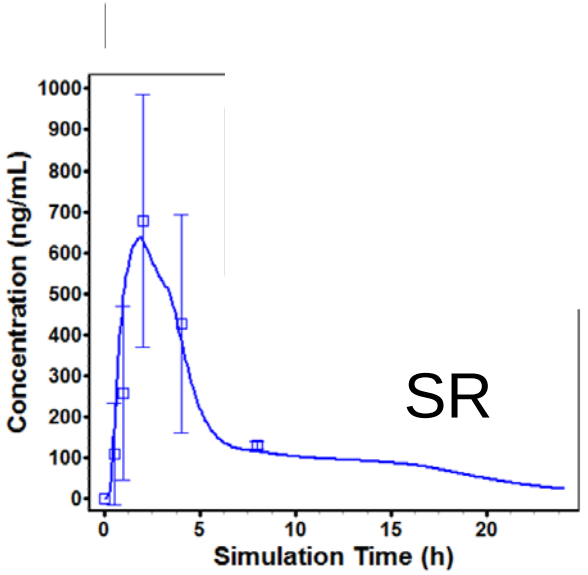
PB-IVIVC example NVS6 (BCS I): PK predictions in dogs by PB-IVIVC

PBPK model for immediately release vs. slow release vs. fast release







	Cmax ng/mL	AUC0-24h ng.h/mL	F %
IR	3280	8060	100
FR (fast ER)	1350	5340	66
SR (slow ER)	715	3860	46

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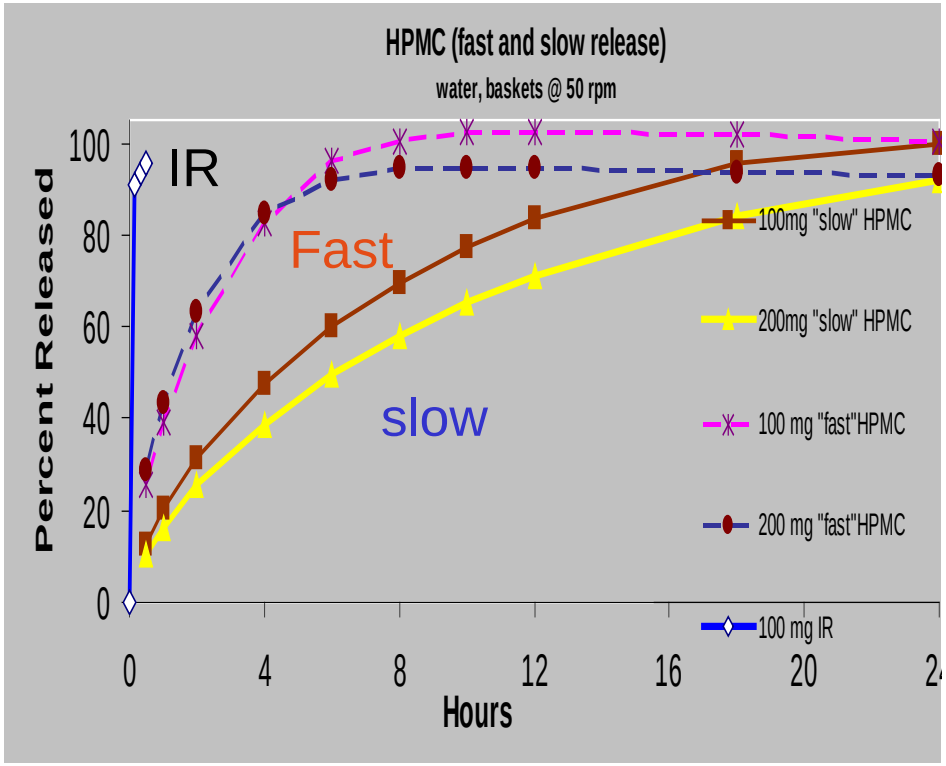
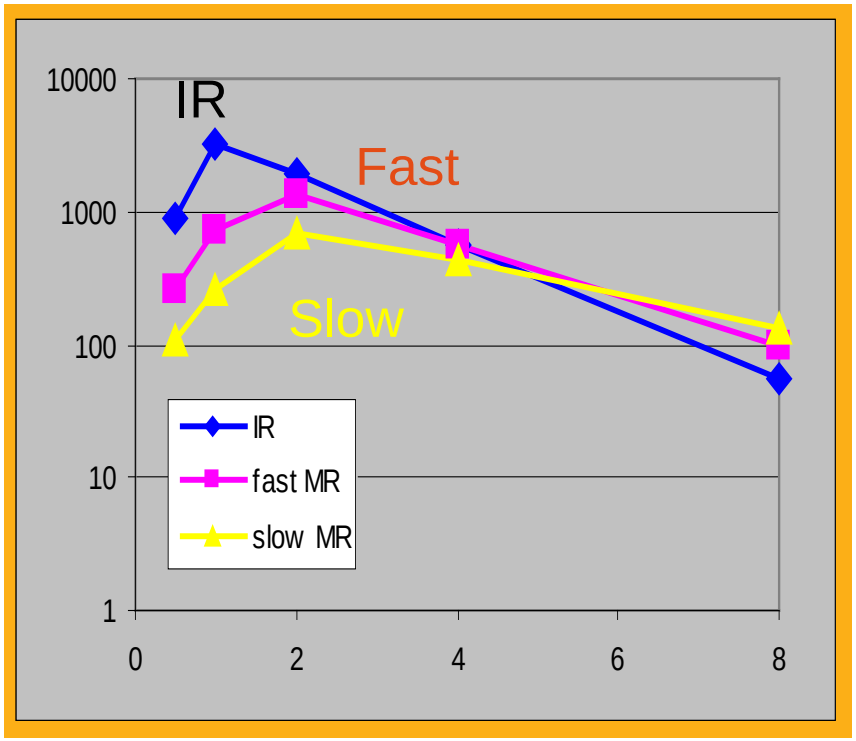
PB-IVIVC example NVS6: In vitro and in vivo dissolution profiles in dogs

■Dissolution



■In vivo Dog PK



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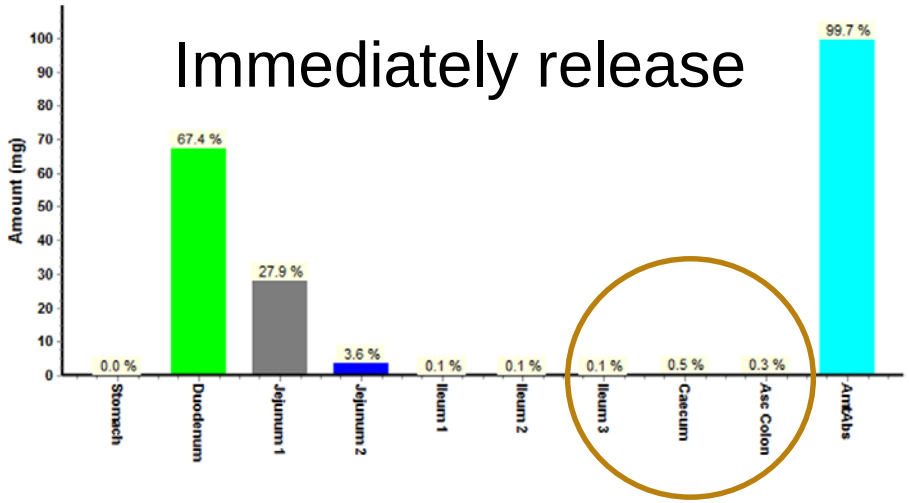
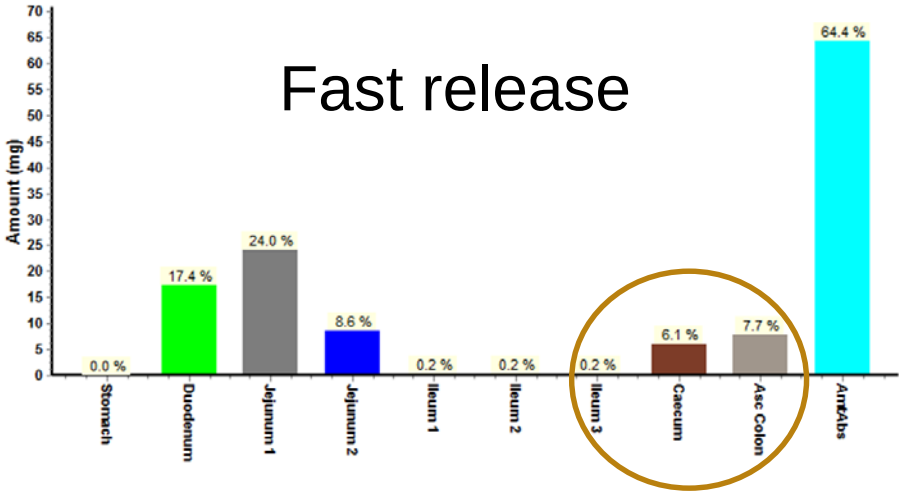
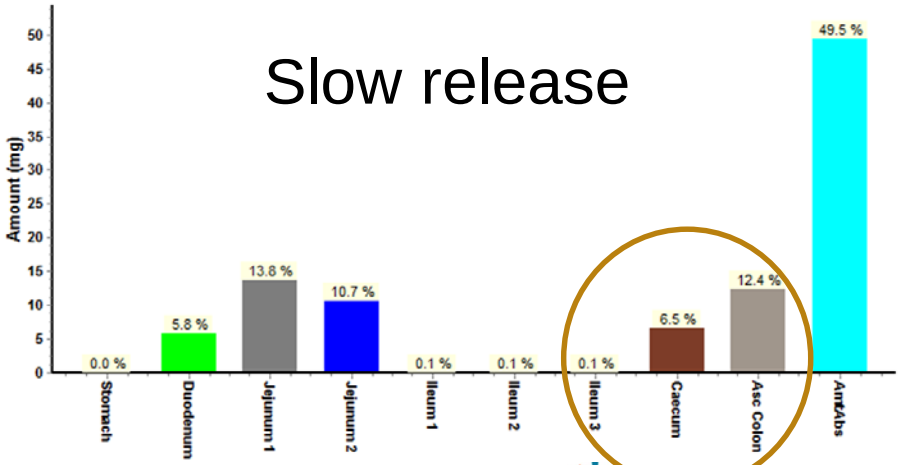
PB-IVIVC example NVS6: Regional absorption by PB-IVIVC

Reginal absorption: Immediately release vs. slow release vs. fast release





Upper GI absorption
vs.
Lower GI absorption



Conclusion: Slow release showed more colonic absorption

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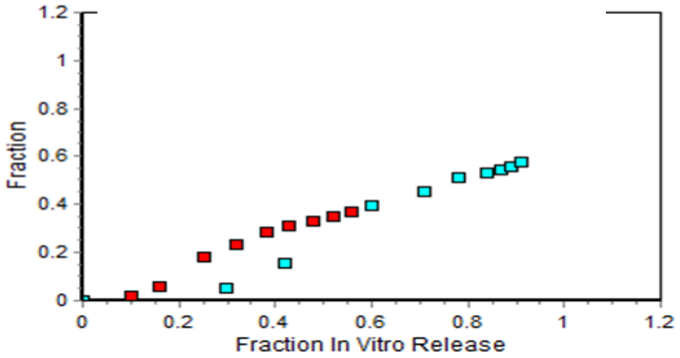
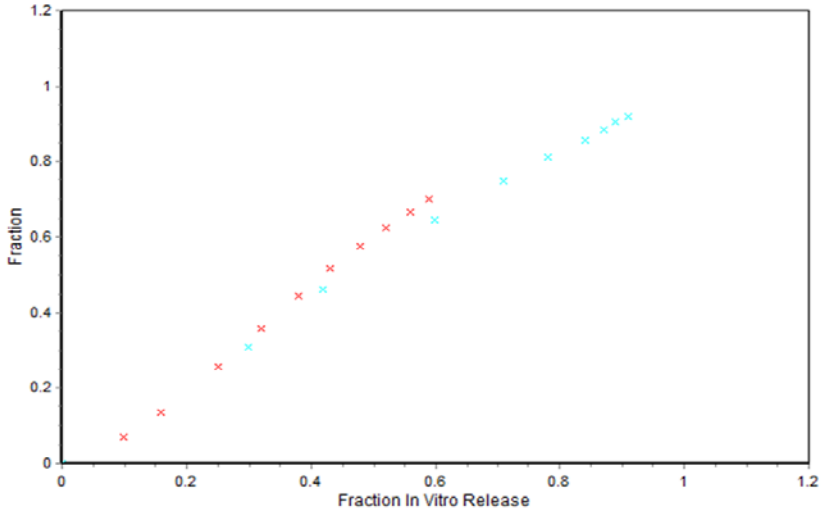
PB-IVIVC example NVS6: Comparisons of conventional IVIVC vs PB-IVIVC

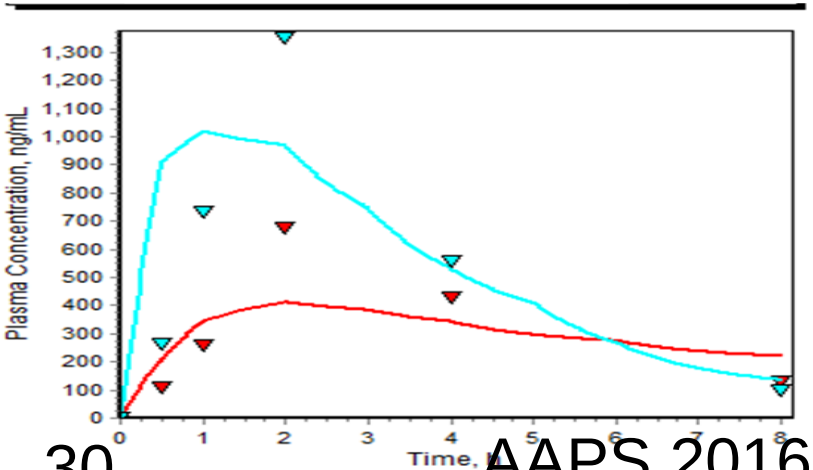
PB-IVIVC showed better prediction compared to conventional IVIVC

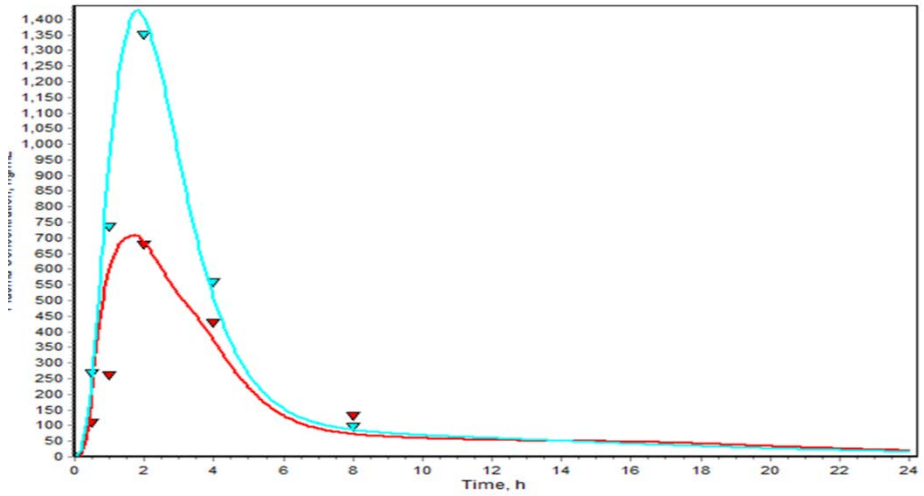
Conventional IVIVC



PB-IVIVC







Opportunities and challenges of modeling

A collective and multi-disciplinary paradigm

Applications of PBPK models:

Apply to selected compounds starting from CSP/sPOC

- Inform formulation – need for special formulations to optimize exposure
- Investigate knowledge gaps in disposition and absorption mechanisms (e.g. low F is due to low absorption or high first pass effects?)
- Translate PBPK models from animals to human/patients/special populations

For internal facilitation/informed decision making /bioequivalent (BE) evaluation

Applications of combining conventional IVIVC with PB-IVIVC

For **biowaiver**, if conventional IVIVC is challenging due to lack of data, it is suggested to also apply PB-IVIVC/virtual bioequivalence trial, e.g. MR development

- **Applications of PBPK modeling of formulation dependent exposure and BCS/BDDCS**
- **Case examples:**
  - **Prediction on PPI effects**
  - **Formulation dependent PBPK**
  - **Food effect predictions**
  - **Comparison of IVIVC vs PBIVIVC**
  - **Biorelevant Permeability Challenges**

Drug U, Compound X

- **Overall recommendations**

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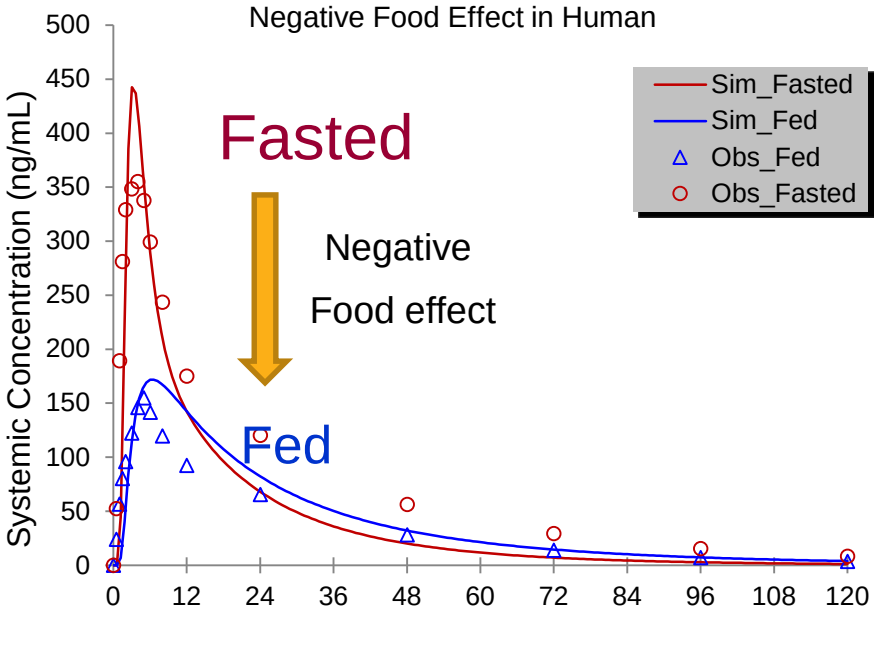
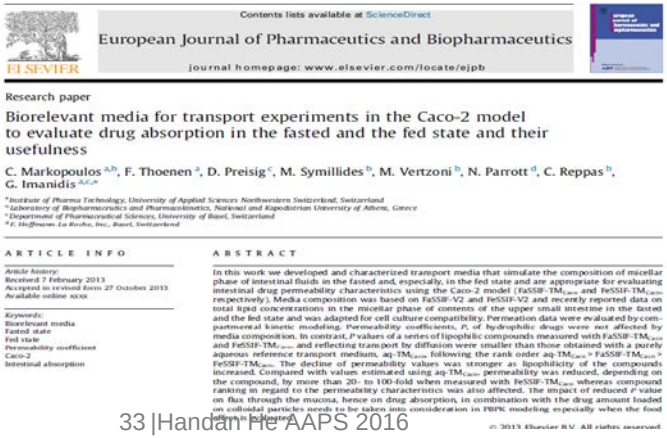
Biorelevant Permeability – Negative Food Effect Can Be Well Predicted Using PBPK Modeling



P_{app} x 10^{-5} cm/min ± SD			P_{app} FaSSIF/FeSSIF fold difference
HBSS	FaSSIF [a]	FeSSIF [b]	
2.93 ± 0.56	1.10 ± 0.12	0.132 ± 0.067	8.3

8 x lower Permeability

Custom Caco-2 assay


Contents lists available at ScienceDirect

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 [a,b], F. Thoenen [a], D. Preisig [c], M. Symillides [b], M. Vertzoni [b], N. Parrott [d], C. Reppas [b], G. Imanidis [a,c,*]

ARTICLE INFO

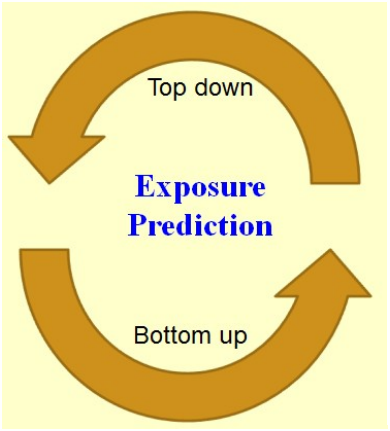
ABSTRACT

PBPK model:

Use Fed Papp

= 1/8 Fasted

=> Reduced Drug U exposure described!



Predicted No negative Food Effect For FIH with Conventional Caco2 Papp!

=> incorrect!

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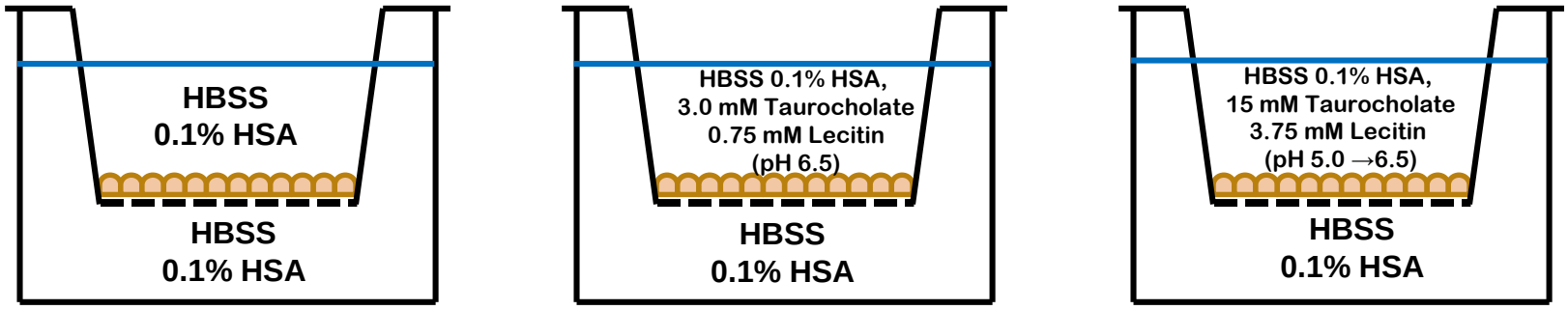
Biorelevant Permeability

Modified from Dressman et al., (2000) EJPS, 11: S73-80



Control	FaSSIF	FeSSIF
pH 6.5 Apical/pH 7.4 Basolateral		
Incubation at 37°C, 3 hours		
Absorptive permeability estimated as indicated below: $P_{app} = \Delta Q/(\Delta t \times C_0 \times Area)$		
HBSS: Hank's-buffered salt solution HSA: human serum albumin (non-specific binding reduction) SIF: simulated gastric fluid (lecitin, taurocholate, others)		

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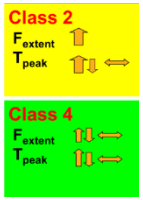
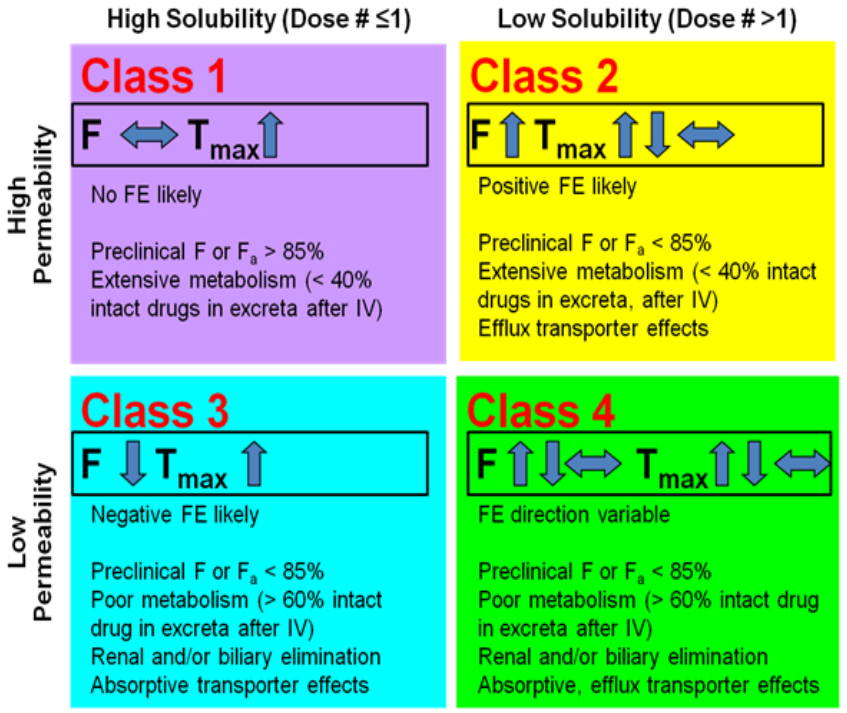
Compound X
Physicochemical and BDDCS data



Property	
Melting point	high
logP / logD6.8	> 4
Thermo. solubility [mg/mL]: pH 1 pH 6.8 pH 7.4	 0.003 n/a
Sim. fluids stability (8 h, 37°C) and solubility [mg/mL]: Fassif Fessif	 Stable 0.009 0.262
Permeability: (1) log PAMPA .	Mod Pred. FA = 40 %
BCS, BDDCS	Class II, IV



Compound X
Rat BDDCS 4

- ~60% intact
- Fabs < 65%

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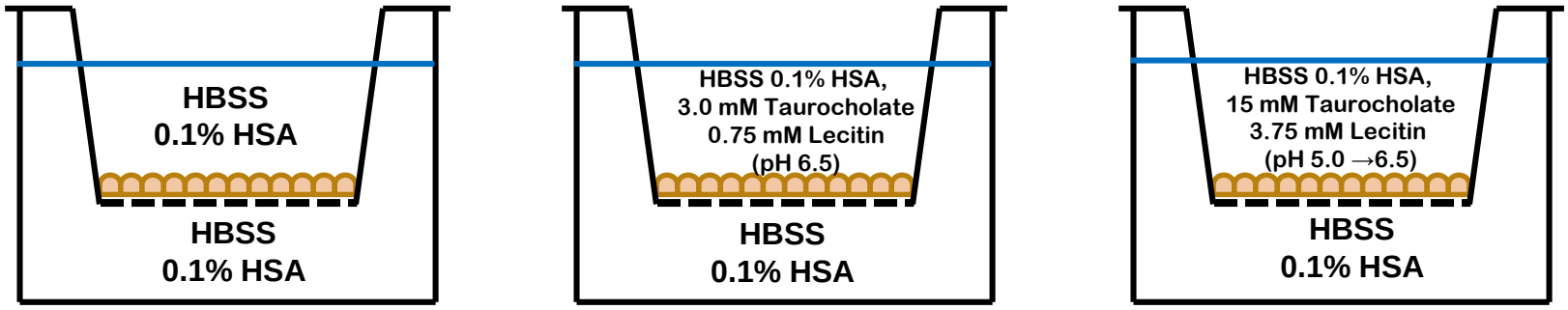
Biorelevant Permeability

Modified from Dressman et al., (2000) EJPS, 11: S73-80



Control	FaSSIF	FeSSIF
pH 6.5 Apical/pH 7.4 Basolateral		
Incubation at 37°C, 3 hours		
Absorptive permeability estimated as indicated below: $P_{app} = \Delta Q/(\Delta t \times C_0 \times Area)$		
HBSS: Hank's-buffered salt solution HSA: human serum albumin (non-specific binding reduction) SIF: simulated gastric fluid (lecitin, taurocholate, others)		

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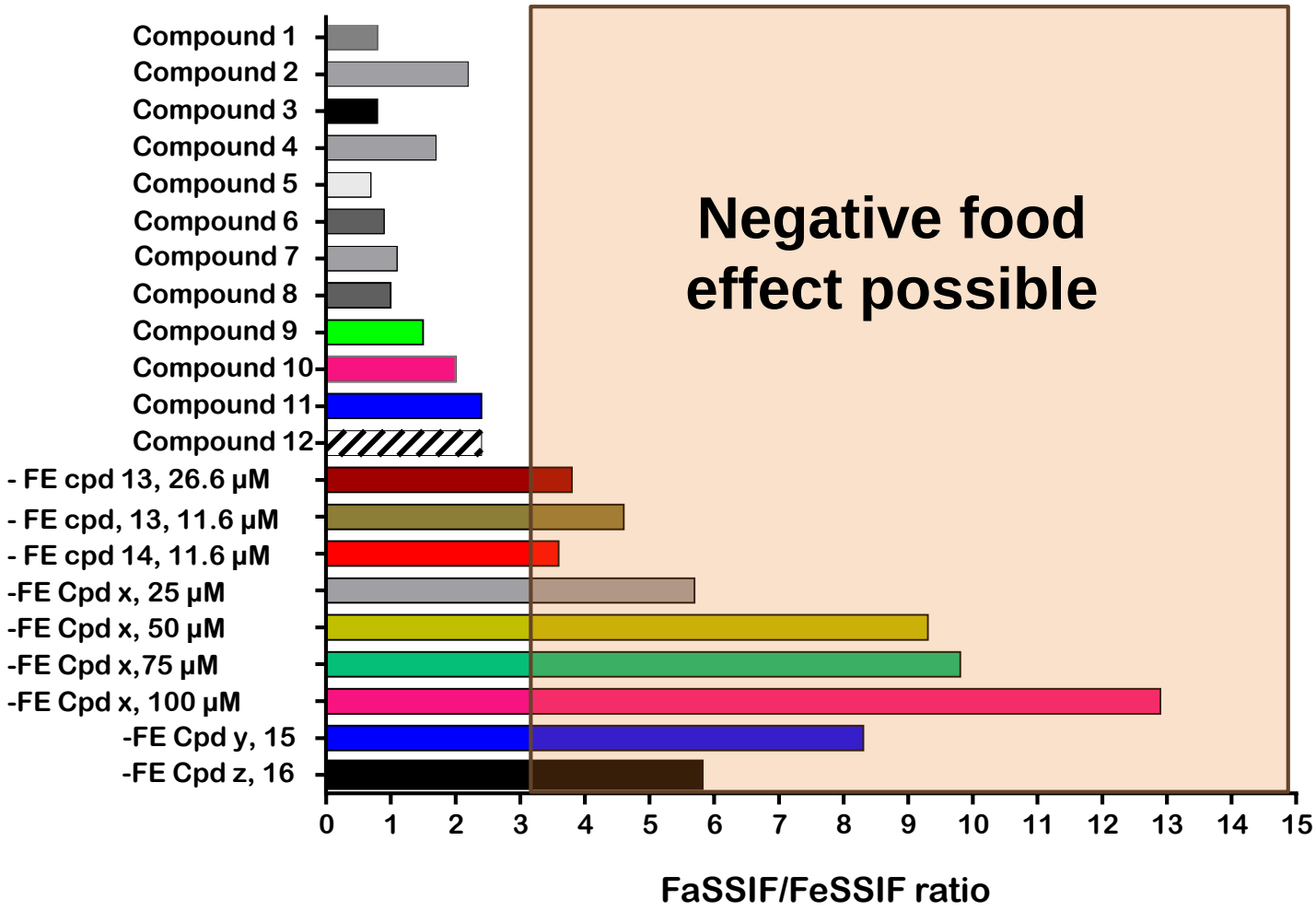
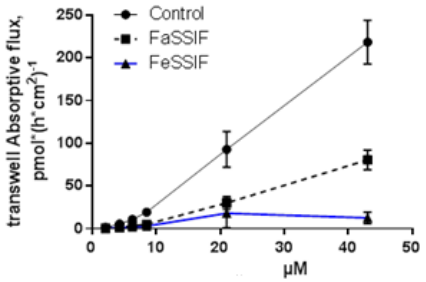
Compounds in Biorelevant Permeability Assay

Assessment for micellar complexation



- Class IV compounds were tested at concentrations in the soluble range as unformulated API
- An arbitrary cut-off value of ~3 for the FaSSIF/FeSSIF permeability ratio is proposed to differentiate compounds likely to experience negative food effects from non-susceptible ones



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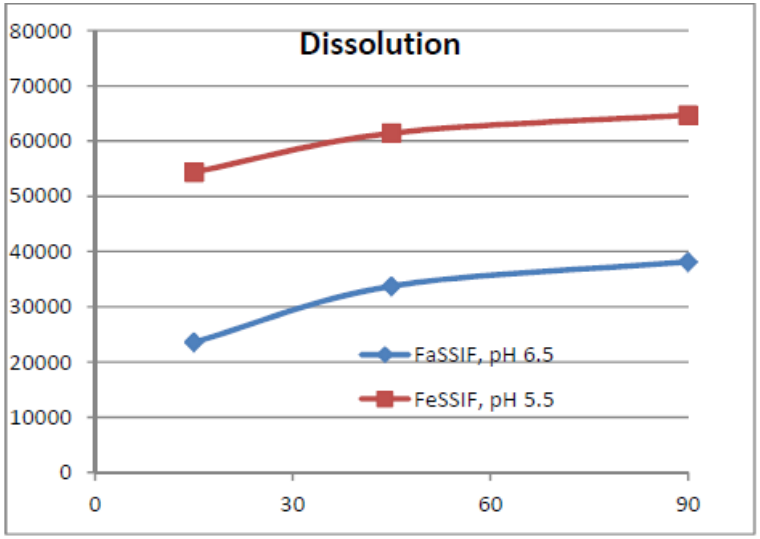
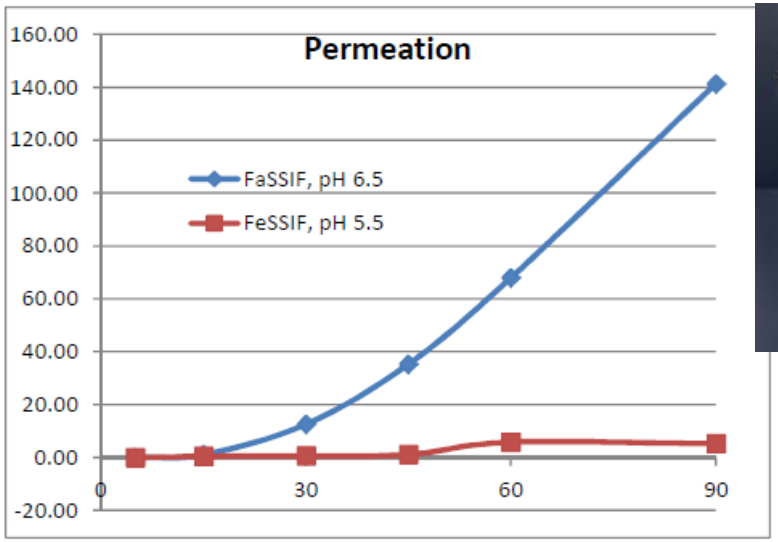
IDAS Biorelevant Flux Data, Compound X





Faster dissolution in fed state media, but permeation is low

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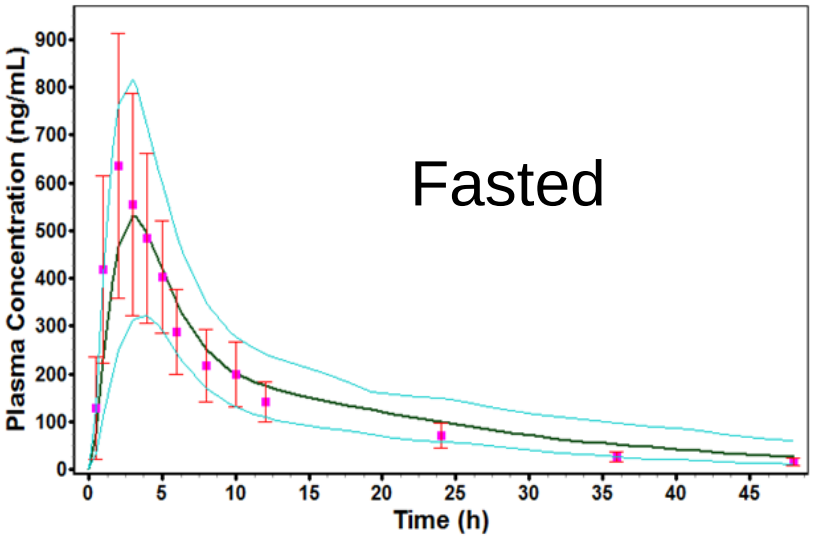
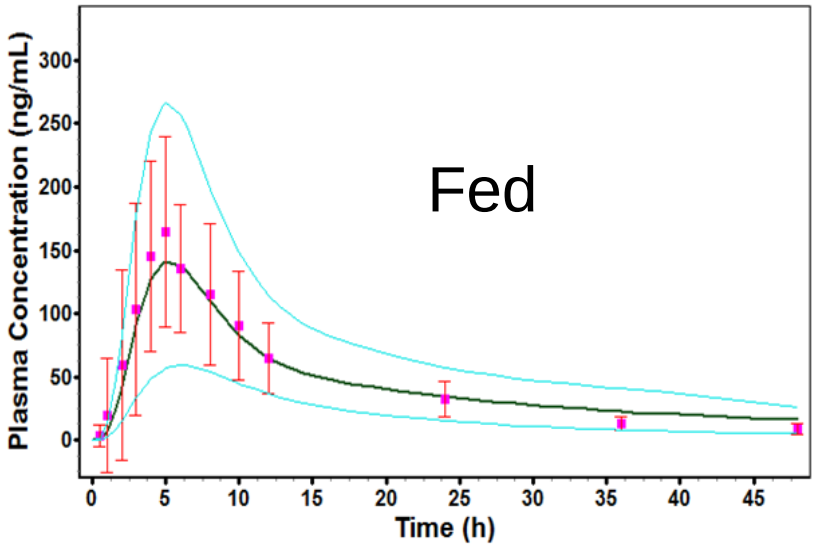
PBPK simulations food effect for Compound X

Using permeability difference of ~4-6 (FaSSIF vs. FeSSIF) in C2BBe1 cells





- PBPK model utilized in vitro biorelevent permeability data
- Negative food effect was simulated with reduced in vivo permeability input

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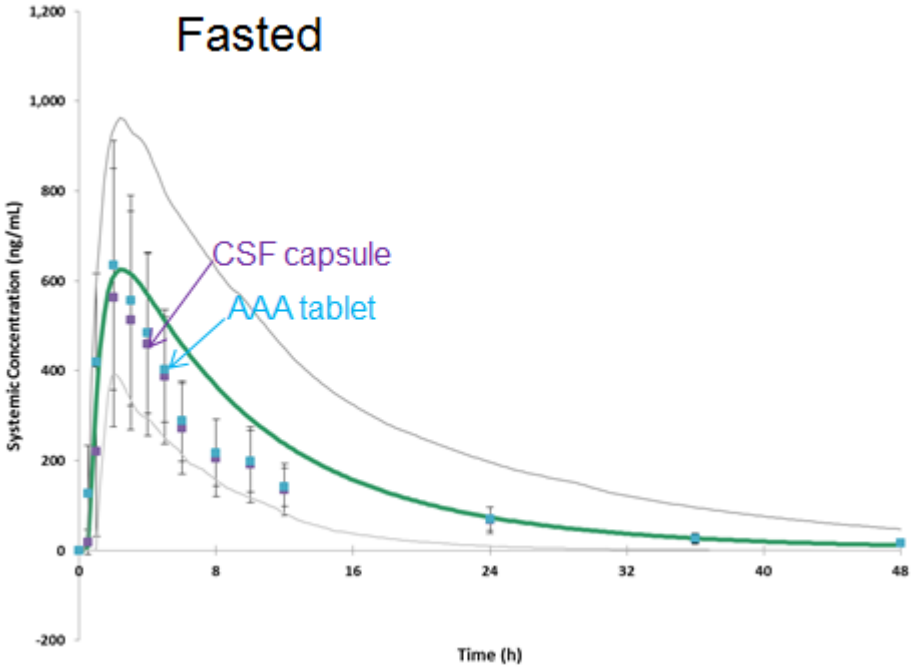
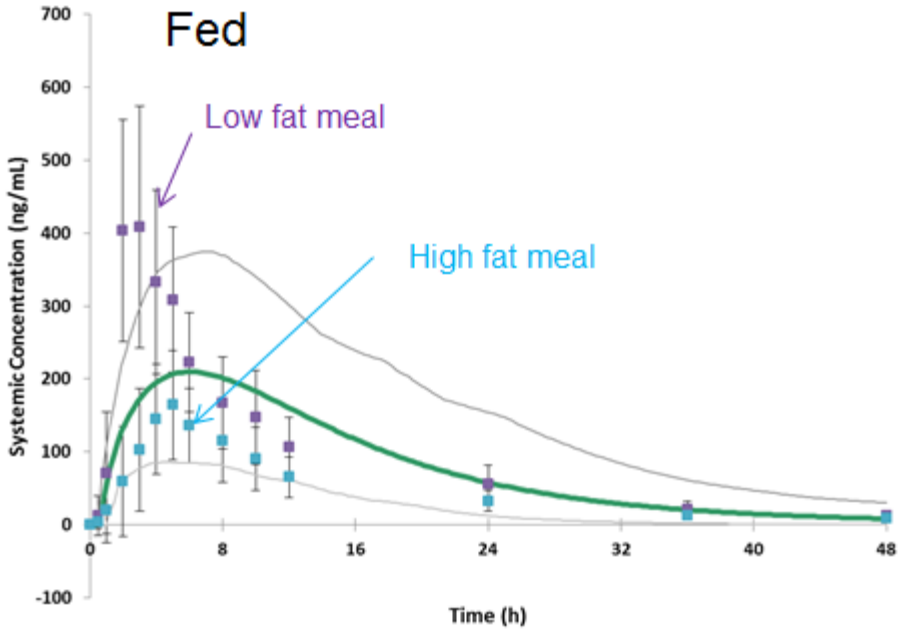
Compound X food effect assessments (Simcyp)

permeability difference (FaSSIF vs. FeSSIF) in C2BBe1 cells





The green line is the simulated data

The difference in permeability for compound X in the C2BBe1 cells can be used to predict the magnitude of reduced exposure change of the high fat meal (Fed/fasted ratios ~ 0.3).

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Discussions Points

- **For PBPK absorption models, conduct PSA for critical parameters**
- **Evaluate absorption kinetics diagnostic plots**
- **Takano z-factor model allows multiple pH dissolution profile data and can be included in exposure predictions, when profiles are available**
- **Food effect can be predicted for well characterized BCS/BDDCS I/II compounds, especially when human fasted date**
- **Biorelevant Permeability with Fassif/Fessif can identify potential for potential bile acid complexation**
- **Biorelevant Permeability, biorelevant solubility are important as PBPK inputs**

PPI: BCS II weak bases can show reduced AUC with high Dose number (>100)

Budha, Benet, Ware, 2012

Table 3 Effect of acid-reducing agents on the oral absorption of targeted anticancer agents

Drug (dose)	Acid-reducing agent	Mean change AUC	Mean change C_{max}	Dose Number, Do	Comments	Reference	BCS
Dasatinib (50 mg)	Famotidine (40 mg) 10 hours prior to dasatinib Famotidine (40 mg) 2 hours after dasatinib	↓61% ↔	↓63% ↔		UC_{0-12}	17	
Dasatinib (50 mg)	Maalox 30 ml 2 hours prior to dasatinib Maalox 30 ml coadministered with dasatinib	↔ ↓55%	↑26% ↓58%	200	UC_{0-12}	17	II
Dasatinib (100 mg)	Omeprazole (40 mg) daily for 5 days and on day 5 with dasatinib	↓43%	↓42%		AUC_{inf}	18	
Erlotinib (150 mg)	Omeprazole (40 mg) daily for 7 days	↓46% ↓58%[a]	↓61% ↓69%[a]	NC	rimary tabolite[a]	8,63	
Erlotinib (150 mg)	Ranitidine 300 mg daily for 5 days and erlotinib 150 mg single dose 2 hours after ranitidine dose on third day	↓33%	↓54%			8,63	
Erlotinib (150 mg)	Ranitidine 150 mg b.i.d. for 5 days and erlotinib 150 mg single dose 2 hours before and 10 hours after ranitidine on third day	↓15%	↓17%			8,63	II
Gefitinib (250 mg)	Two oral doses of 450 mg ranitidine (13 hours and 1 hour before 250 mg of gefitinib) followed by sodium bicarbonate to maintain gastric pH above 5 for 8 hours	↓44%	↓70%	1000		21	II
Imatinib (400 mg)	Omeprazole (40 mg) daily for 5 days and on day 5 with imatinib	↔	↔	1.6		23	II
Imatinib (400 mg)	Maalox Max (20 ml) 15 minutes before imatinib	↔	↔			24	
Lapatinib (1,250 mg)	Esomeprazole (40 mg) daily for 7 days at bedtime	↓26%	NA	>1000		27	
Nilotinib (400 mg)	Esomeprazole (40 mg) daily for 6 days and on day 6 with nilotinib	↓34%	↓27%	>300		29	II/IV
Axitinib (5 mg)	Rabeprazole (20 mg) q.d.	↓15%	↓40%	100		50	II

AUC, area under the curve, C_{max}, peak plasma concentration; NA, not applicable.

[a]Primary metabolite data.

The FDA does not require the use of a particular PBPK modeling software. Because of substantive differences in software models and versions, sponsors should include information on the PBPK modeling software. Table 1 below highlights the information that should be included regarding commercial PBPK modeling software (commercial PBPK platform) versus custom modeling software (e.g., commercial software that has been modified with custom codes or otherwise revised for the purpose of PBPK modeling).

Table 1. Software Information for PBPK Modeling

Suggested Software Information	PBPK Models	
	Custom Modeling Software	Commercial PBPK Platform
Name and version of the software	Yes	Yes
Schematic view of model structure and differential equations based on established theoretical or biological basis	Yes	Optional
Parameterization of system information and sources of parameter values	Yes	Optional
Table of drug-dependent parameters for the investigational drug of interest, including names, values, units, and sources of the parameters, prediction algorithms, and assumptions being made	Yes	Yes
Literature references and the sponsor's prior experience/knowledge in using the software for PBPK modeling (to help the reviewer understand how PBPK models are coded using the modeling software that was tested)	Yes	Yes
Manuals on model implementation of the software (to be provided as supporting documents)	Yes	Optional
Library system models (e.g., virtual population), including justifications for any modifications made to the model's physiological parameters by the sponsor	Not applicable	Yes
Library drug models, including justifications for any modifications to the model made by the sponsor and information on model verification	Not applicable	Yes