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Oral Absorption Modeling and Simulation for Formulation Development and Bioequivalence Evaluation

An Industry Perspective

Filippos Kesisoglou, PhD
Biopharmaceutics,
Pharmaceutical Sciences and Clinical Supply
Merck Research Laboratories
Merck & Co., Inc., Kenilworth, NJ, USA

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Outline

- Introduction and current status of absorption modeling in formulation development
- Case studies
  - Formulation development and achlorhydric simulations
  - Dissolution impact on PK and BE projections
  - Multimedia dissolution and BE projections
  - Projection of API form change and population simulations
  - Food effect projection for a BCS I compound
  - Absorption modeling-based IVIVC for IR tablet
- Conclusions and future directions

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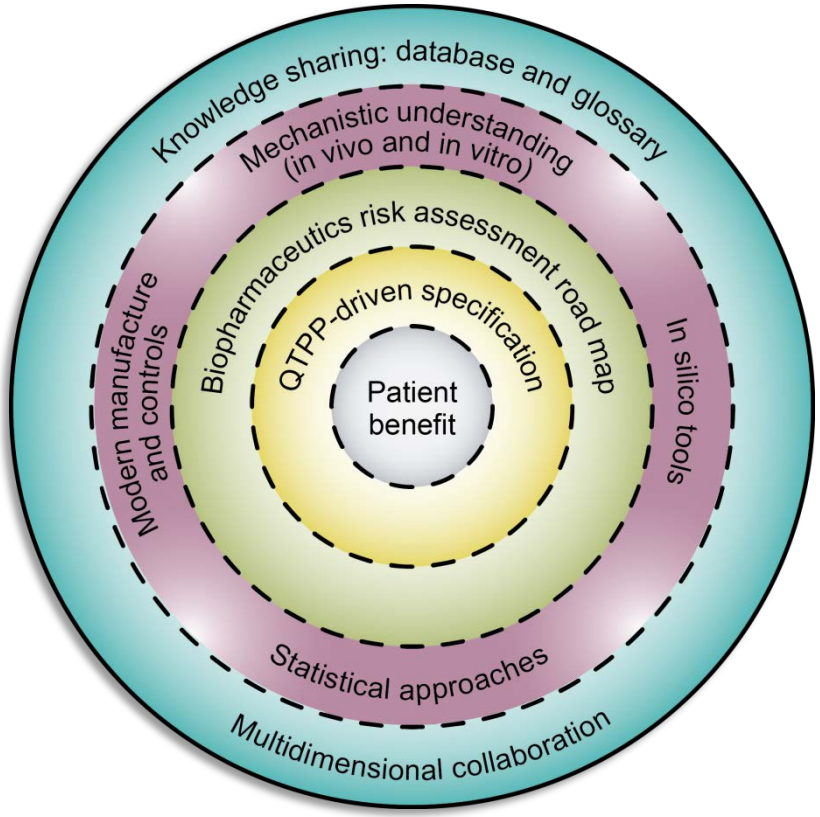
Quality by Design and Biopharmaceutics



- Understanding of the formulation dissolution/ release **in vivo** (and the factors affecting that) that ensures the anticipated dose response
- Link the **in vivo** dissolution/release to an *in vitro* assay to ensure consistency of product administered to patients

Biopharmaceutics Risk Assessment Roadmap
Selen A, et al. *AAPS J*. 2010;12(3):465-472.
Selen A, et al, JPharmSci, 2014 Nov;103(11):3377-97.

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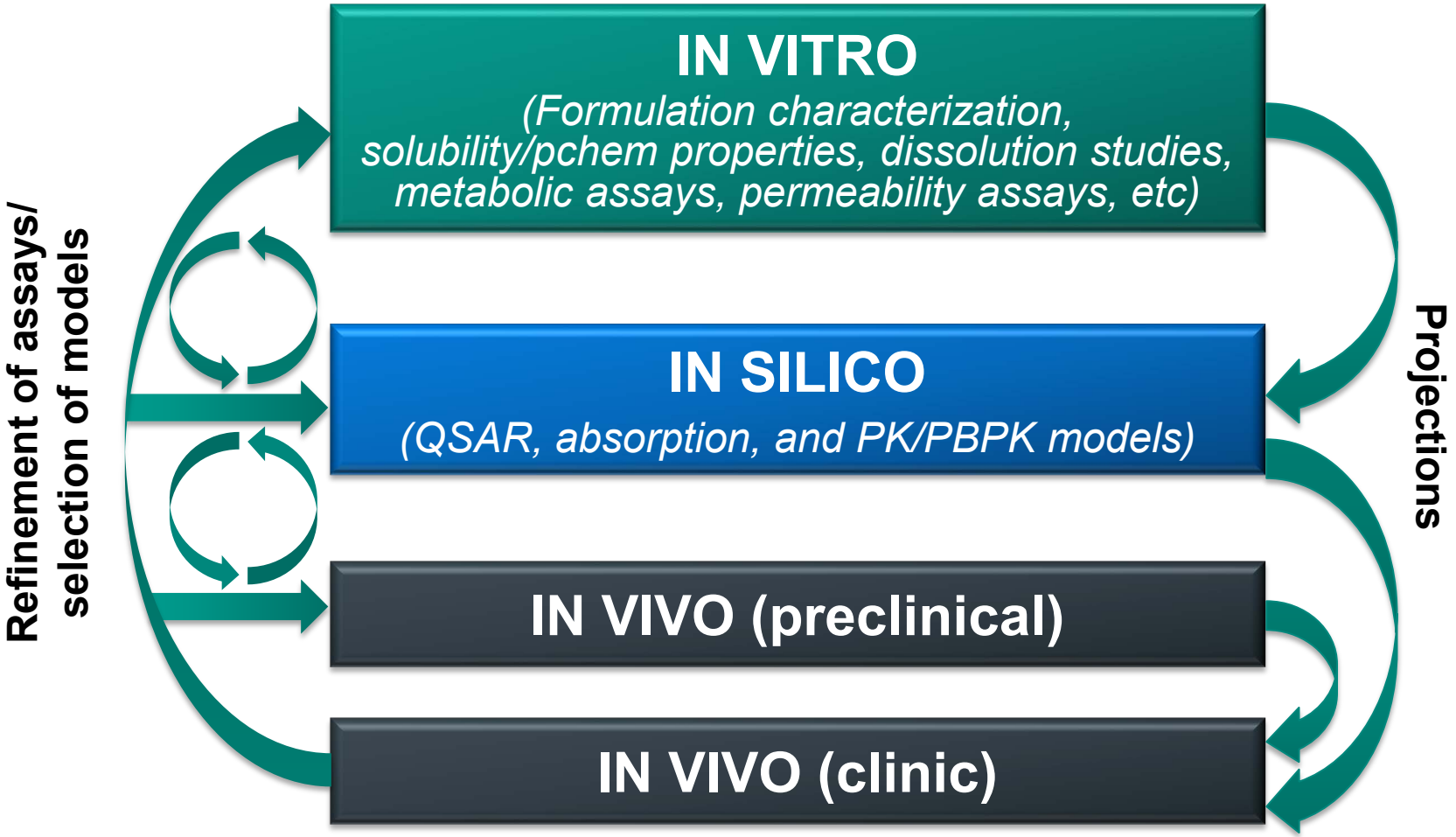
Integrate Knowledge to Optimize Outcome – Adopt Model to Question at Hand



Current Status of Absorption Modeling

Application	Current Status
Guide FIH formulation/dose	**Relatively well established** Supplements formulation decision trees
Guide formulation development past FIH	**Relatively well established** Guide formulation decisions (eg, API PSD, MR development); helps with replacement/reduction of preclinical studies (3Rs)
Projection of bioequivalence	**Occasional application, mostly for "well-behaved" compounds** Inform bioequivalence POS/"internal" biowaivers
Food effect projections and projections of DDI with pH-altering agents	**Relatively well established** More for risk assessment and to inform formulation direction. Relatively small impact on clinical practice as studies typically conducted
Input to other models (eg, DDIs)	Potential for impact if DDI is at gut level and sensitive to formulation (not very common scenario)
Link dissolution and PK to drive IVIVCs and clinically relevant specifications	**Starting to gain increased attention**

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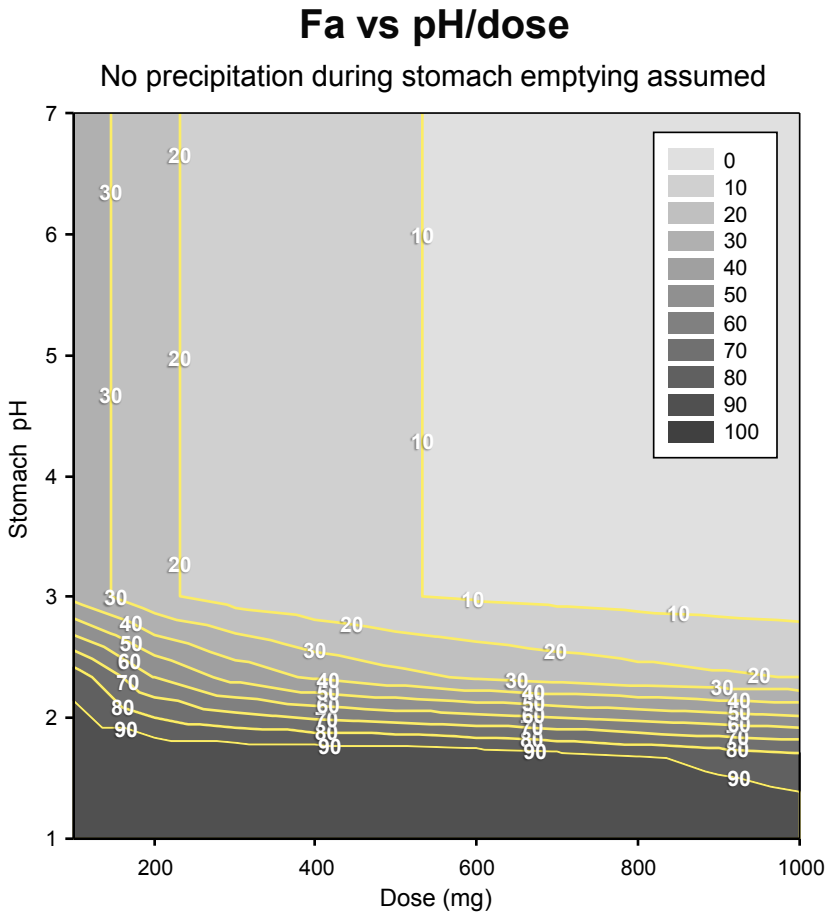
Case Study 1: Guide Early Formulation Development



Adequate bioavailability under normal fasted conditions

FIH formulation decision; free base – defer antacid mitigation post-FIH (decision may differ for other programs)

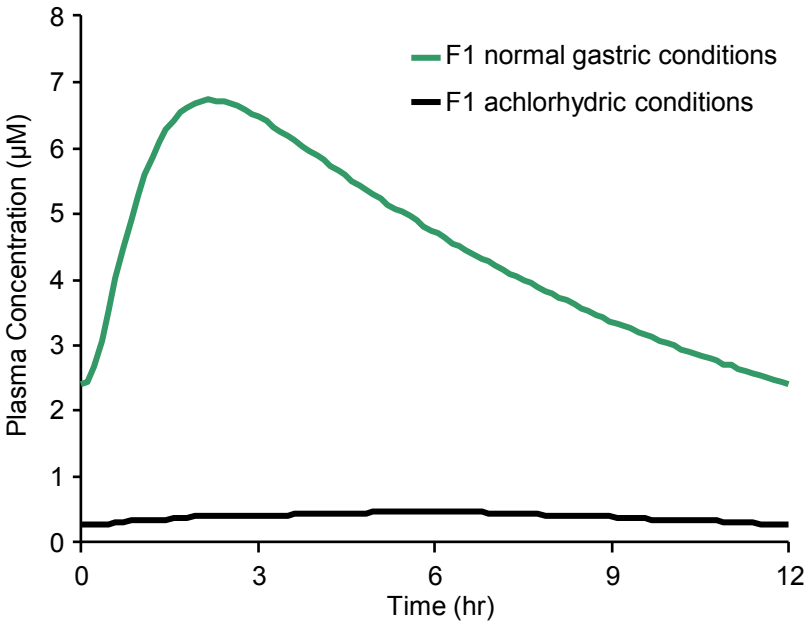
Parameter sensitivity analysis is a common tool in early formulation stage

Mitra A, Kesisoglou F, Beauchamp M, et al. *Mol Pharm*. 2011;8(6):2216-2223.

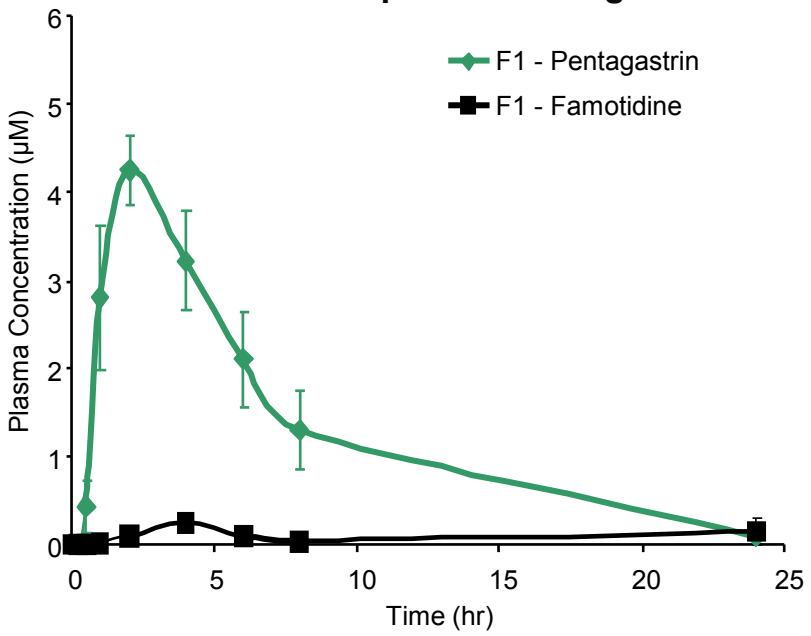
Modeling to Develop a pH-Resistant Formulation

Adequate exposures obtained in Phase I PK –
Formulation development to mitigate acid-reducing interactions as a follow-up

Model-based steady-state predicted exposures



Comparison of F1 formulation in pentagastrin- and famotidine-pretreated dogs



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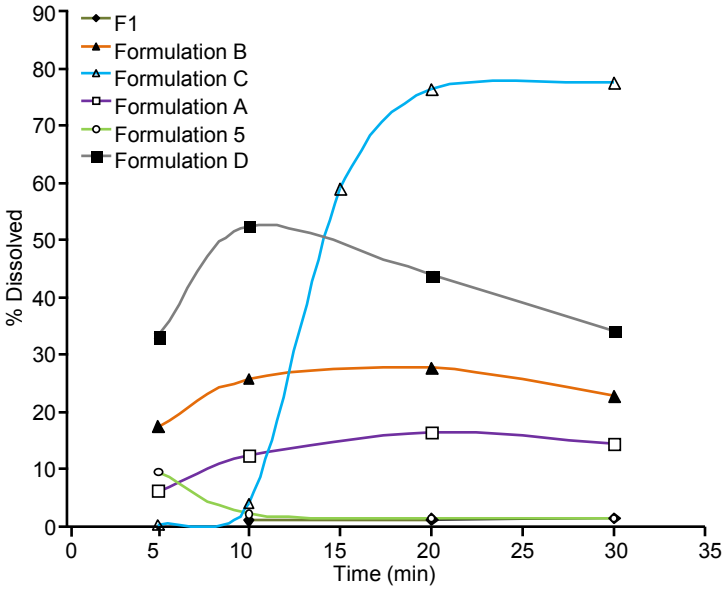
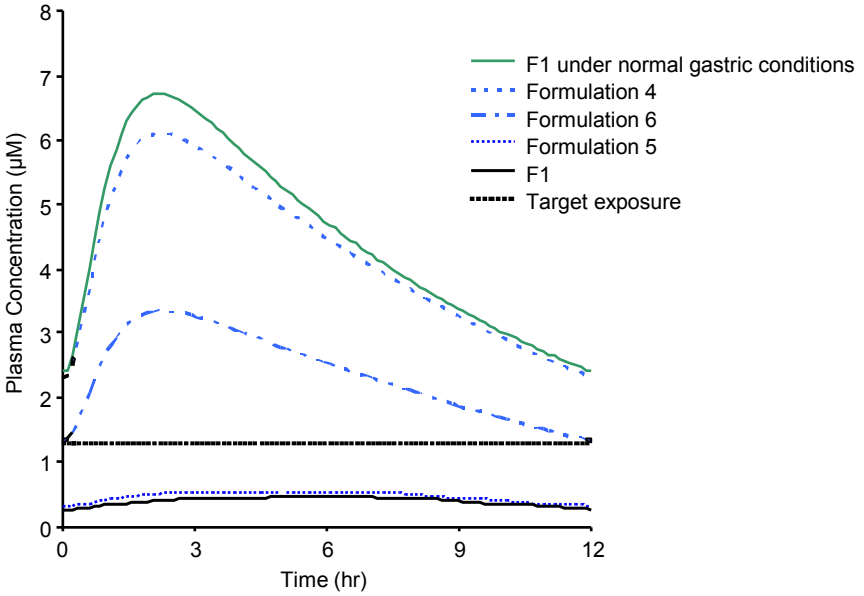
Translate Dissolution Data to Clinical Exposures

Dissolution at "PPI-simulating" pH 3.0 media, USP II





Formulation	M&S Predicted AUC Impact	Observed AUC Impact Preclinically
F1	91% reduction	95% reduction
F4	6% reduction	5% increase
F5	90% reduction	85% reduction

Conclusion: Formulation 4 high POS to mitigate stomach pH sensitivity (confirmed in subsequent clinical study)

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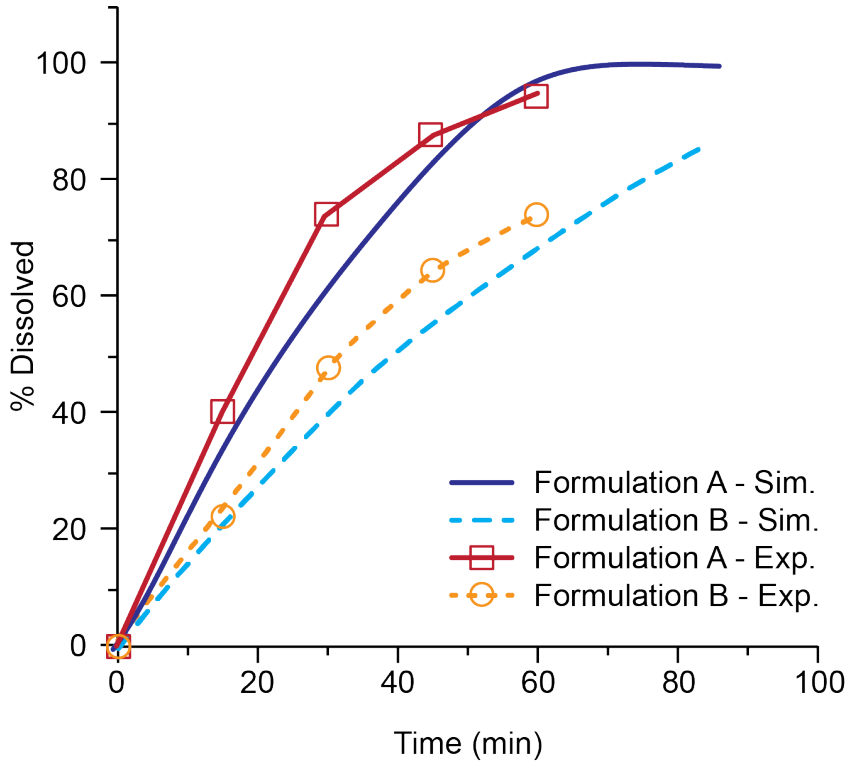
Case Study 2: Mechanistic Modeling of Dissolution Data

- BCS I compound
- Enteric-coated beads to protect from stomach acid instability
- Standard USP 2-stage acid-challenge dissolution method



$$-\frac{dX_s}{dt} = \frac{DS}{h}\left(C_s - \frac{X_d}{V}\right) \Rightarrow -\frac{dX_s}{dt} = \frac{3DX_0}{pfh(r_0{}^3 - rc^3)}\left[\frac{X_s}{X_0}(r_0{}^3 - rc^3) + rc^3\right]^{2/3}\left(C_s - \frac{X_d}{V}\right)$$

Sperry DC, Thomas SJ, Lobo E. *Mol Pharm*. 2010;7(5):1450-1457.

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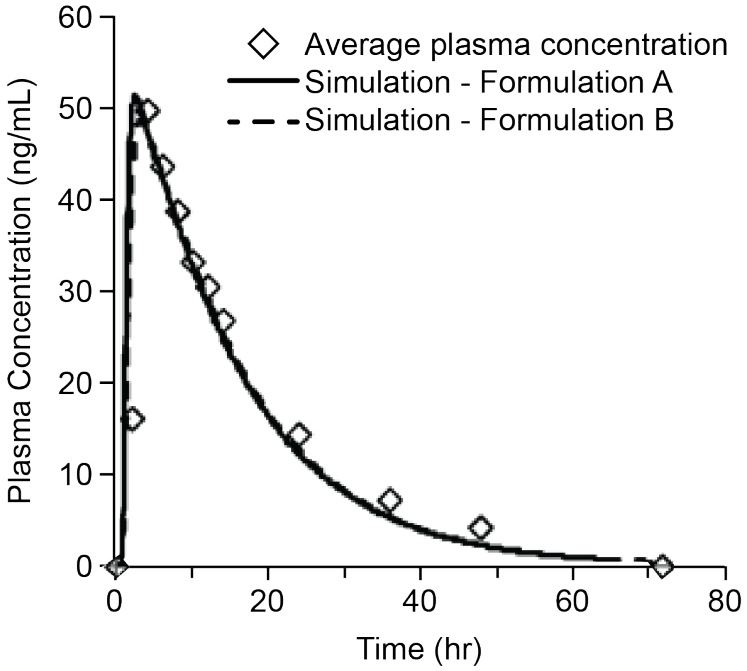
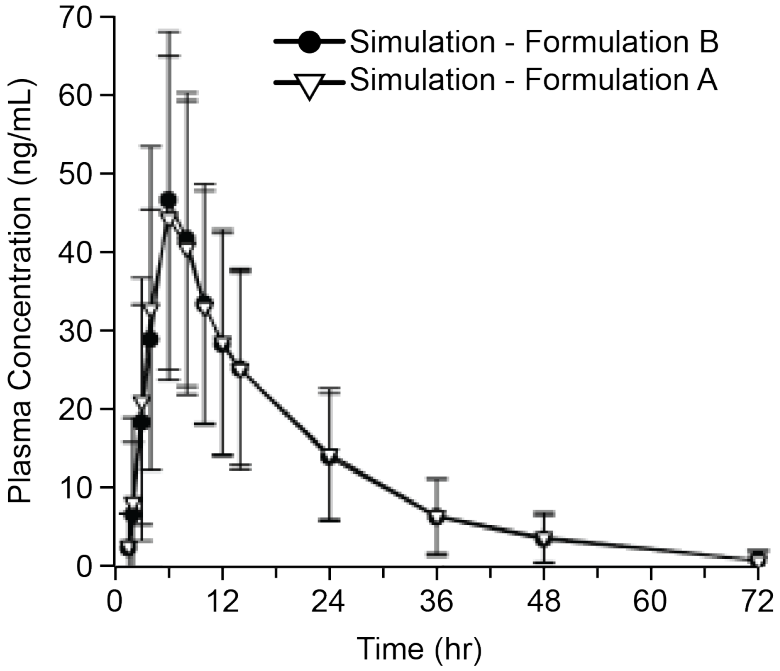
Projection of BE Based on Mechanistic Dissolution Model

Simulated A vs B



Observed A vs B



Parameter sensitivity analysis indicated that even a T80 of ~2 hours would result in no impact on AUC and minimal impact on C_{max}

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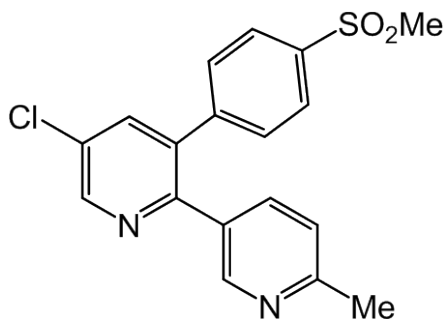
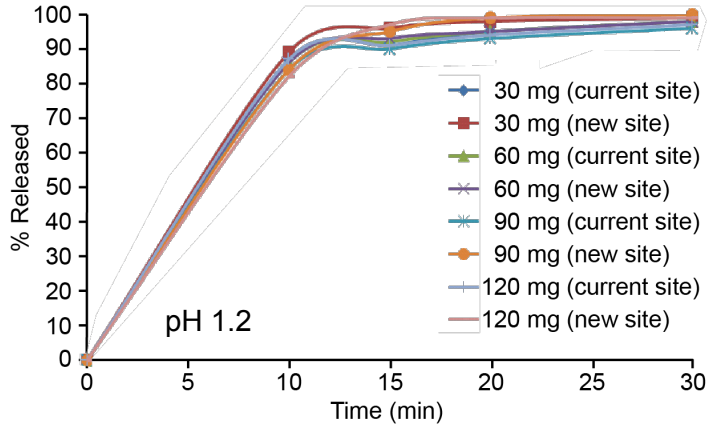
Case Study 3: Multimedia Dissolution and BE

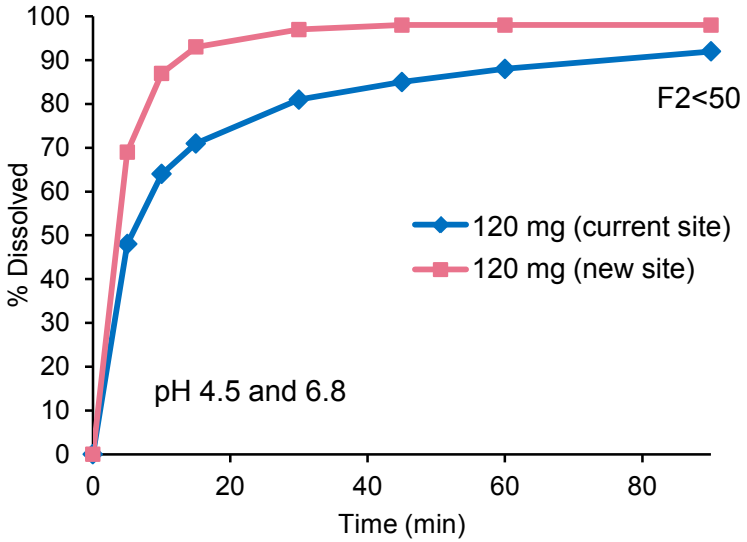
Etoricoxib





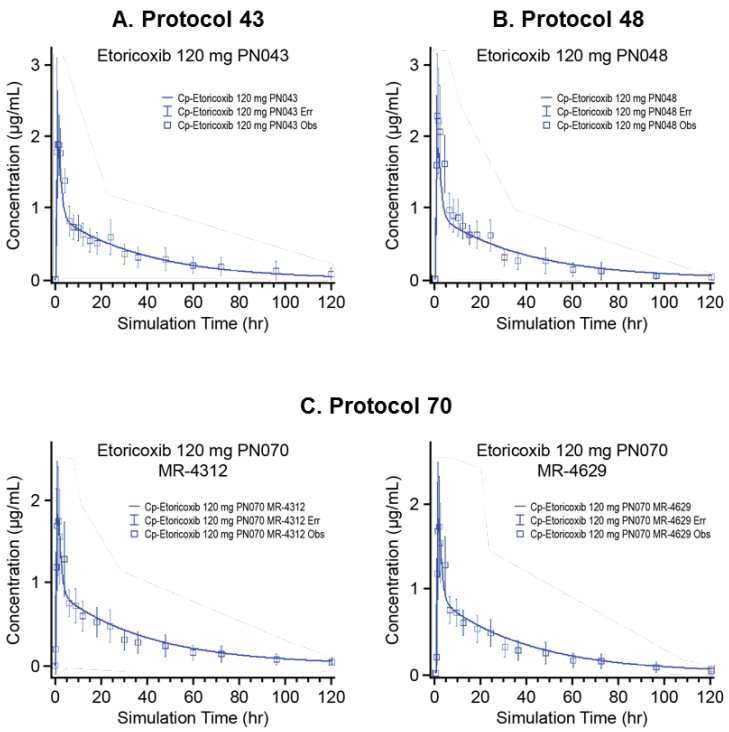
BCS II
Log D = 2.28 (pH 7.0)
pKa = 4.5
Caco-2 Permeability = 5.23 x 10^{-5} cm/sec

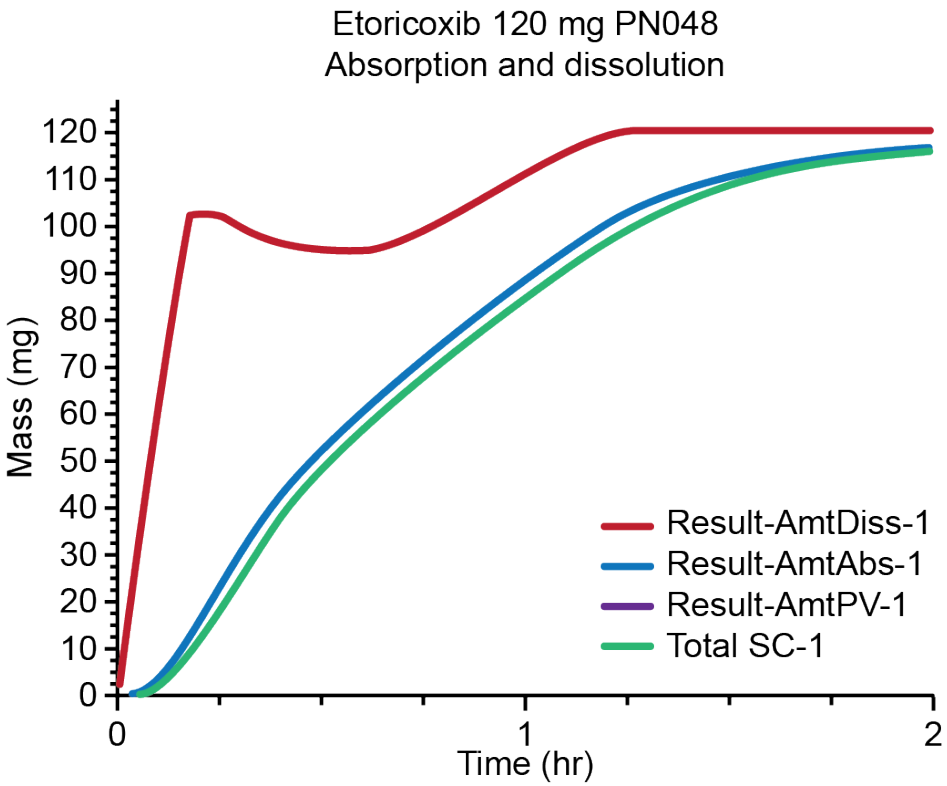
pH 2.0 (0.01N hydrochloric acid) = 25.1 mg/mL
pH 3.07 (0.1M glycine buffer) = 2.01 mg/mL
pH 4.01 (0.1M sodium acetate buffer) = 0.3 mg/mL
pH 5.03 (0.1M sodium acetate buffer) = 0.09 mg/mL
pH 6.9 (water) = 0.05 mg/mL



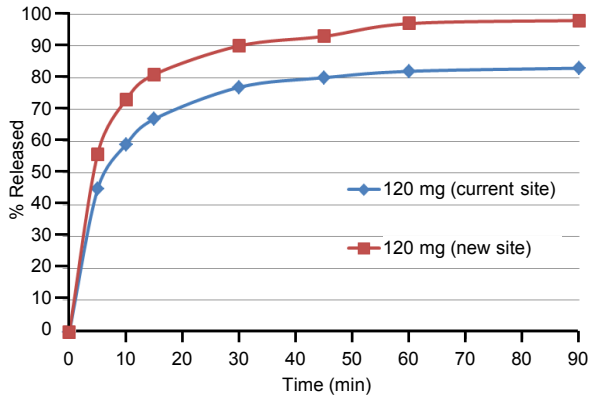
Mitra A, Kesisoglou F, Dogterom P. *AAPS PharmSciTech*. 2015;16(1):76-84.

Validation of Model Against Clinical Data for the Reference Formulation





Predictions vs Experimental Data – Identification of Clinically Relevant Dissolution



Dissolution at pH 4.5 and 6.8 overpredicts differences relative to clinical BE study. Dissolution at pH 1.2 most clinically relevant

M&S projections

	$AUC_{0\text{-}120hr}$ (%CV)	C_{max} (%CV)	Relative $AUC_{0\text{-}120hr}$	Relative C_{max}
Dissolution in pH 4.5				
120 mg (current site)	34.4 (16.3%)	1.65 (15.3%)	—	—
120 mg (new site)	35.8 (15.3%)	1.82 (14.4%)	1.04	**1.10**
Dissolution in pH 6.8				
120 mg (current site)	30.8 (17.2%)	1.50 (18.6%)	—	—
120 mg (new site)	34.1 (15.1%)	1.71 (19.1%)	**1.11**	**1.14**

Clinical BE data

PK Parameters	Treatment		Geometric Mean Ratio (A vs B)	90% Confidence Interval (A vs B)
	A	B		
$AUC_{0\text{-}\infty}$ (µg*hr/mL)[1]	32.3 ± 13.1	32.1 ± 14.6	**1.01**	0.97, 1.06
C_{max} (µg/mL)[1]	1.94 ± 0.47	1.98 ± 0.41	**0.97**	0.89, 1.06
T_{max} (hr)[2]	1.25 (0.5 – 2.0)	1.00 (0.5 – 4.0)	—	—

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Case Study 4: Impact of API Form

- Weak base/BCS II
- **Dosed as HCl salt**
- SGF solubility (pH 1.2) = 2.4 mg/mL
- FaSSIF solubility (pH 6.5) <1 µg/mL
- HCl salt dissolves fast and provides high bioavailability regardless of stomach pH

Simulation approach

Goal: Assess potential risks from conversion of HCl salt to free base in the formulation (eg, due to excipient interaction)

Simulated exposures in virtual HV population

HCl salt was simulated as nonprecipitating solution and free base absorption simulated based on pH solubility curve

Kesisoglou F, Mitra A. *AAPS J*. 2015;17(5):1224-1236.

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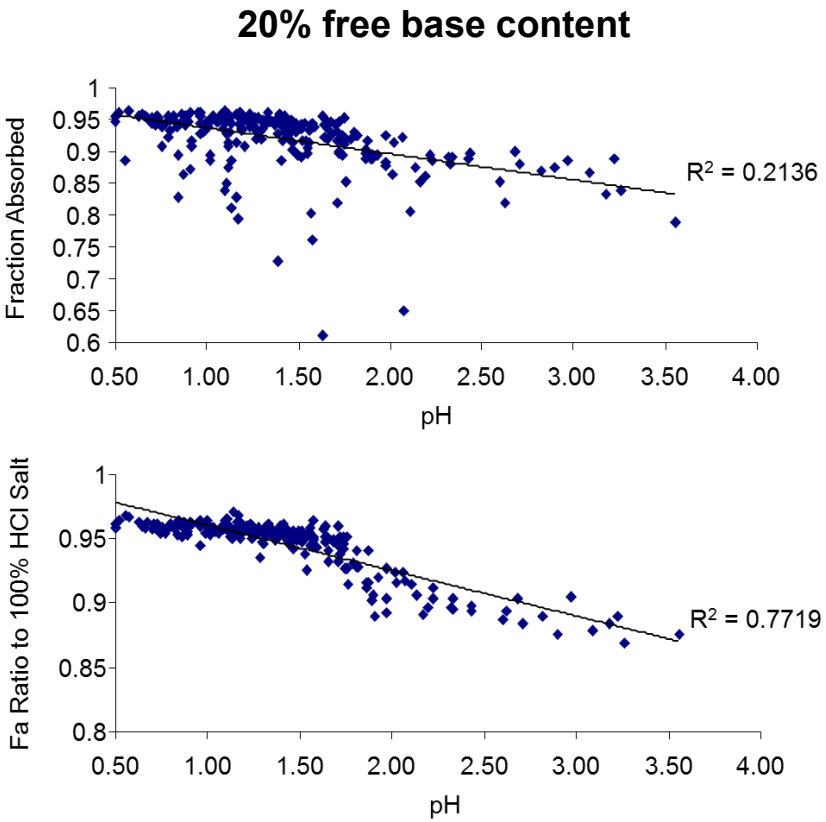
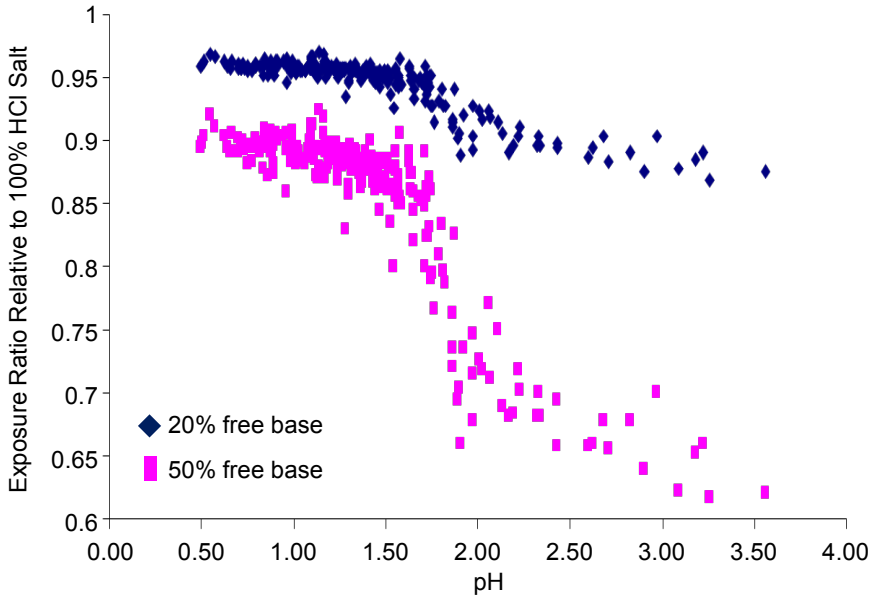
Projected Effect of pH on Exposure





At 20% free base, a small effect on total exposure is predicted (GMR to HCl salt is predicted at 0.95)
At 50% free base, the predicted mean relative Fa is 85%

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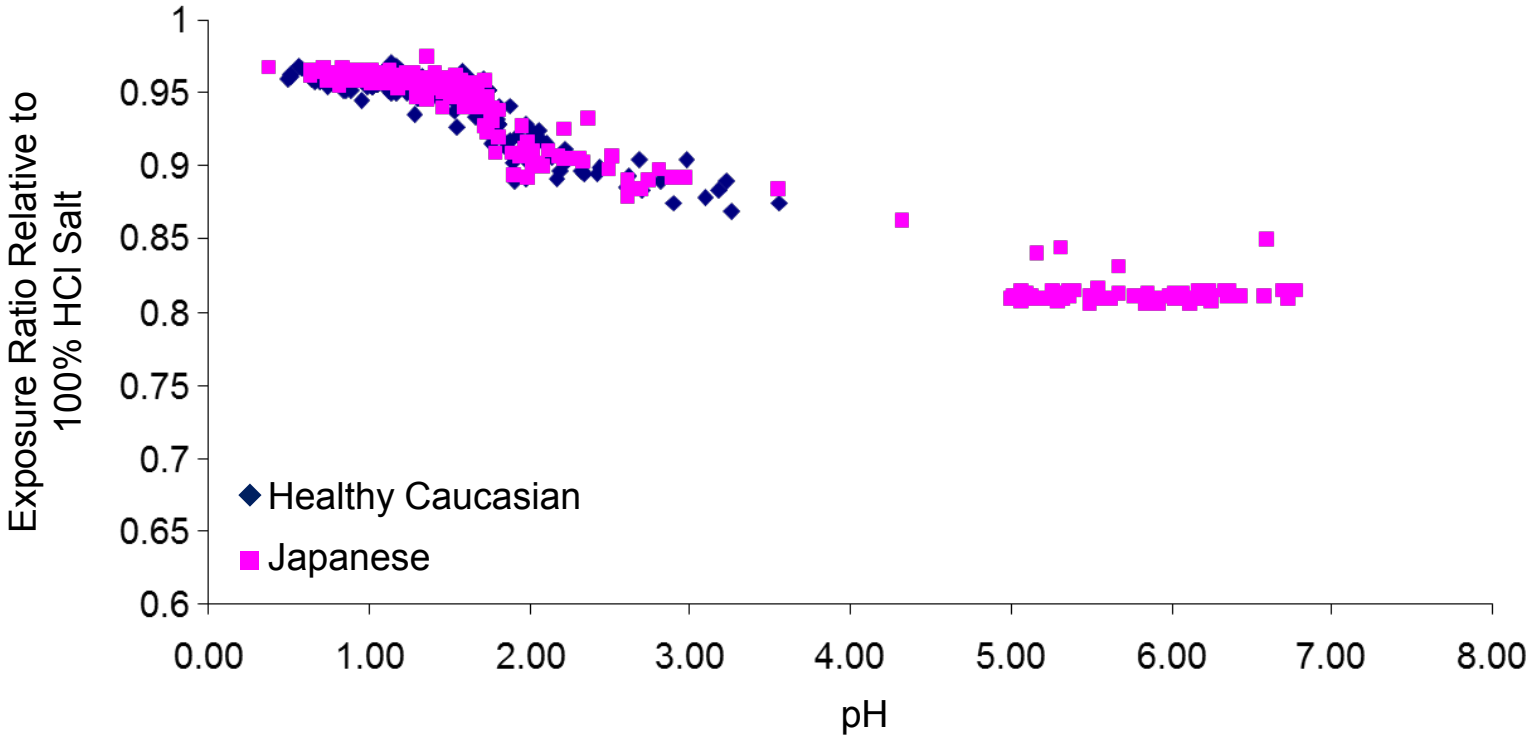
Impact in Different Populations



In a simulated Japanese population (larger percentage of patients with stomach pH >4), more differentiation of the formulations due to 20% free base (although GMR still 0.90)

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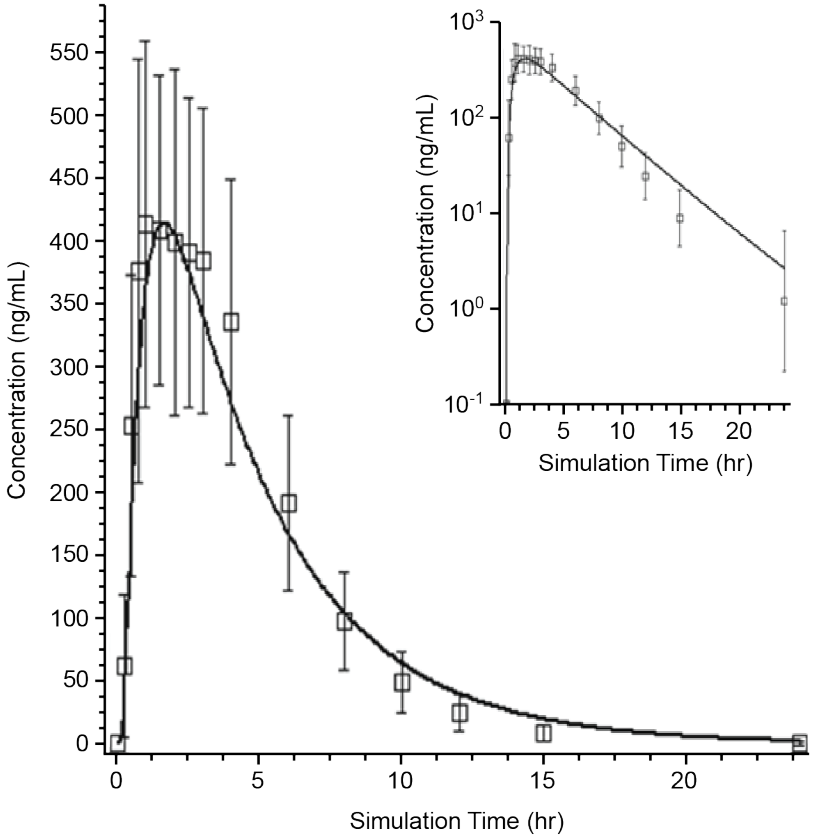
Beyond Formulation BE – Case Study 5: Food Effect Projections for BCS I

- Weak base
- pKa 7.9, LogD (7.4) -0.5
- Highly soluble (~ 4 mg/mL)
- Highly permeable
- Small first-pass effect

Fasted-state simulations



Kesisoglou F, Chung J, van Asperen J, Heimbach T. *J Pharm Sci*. 2016.

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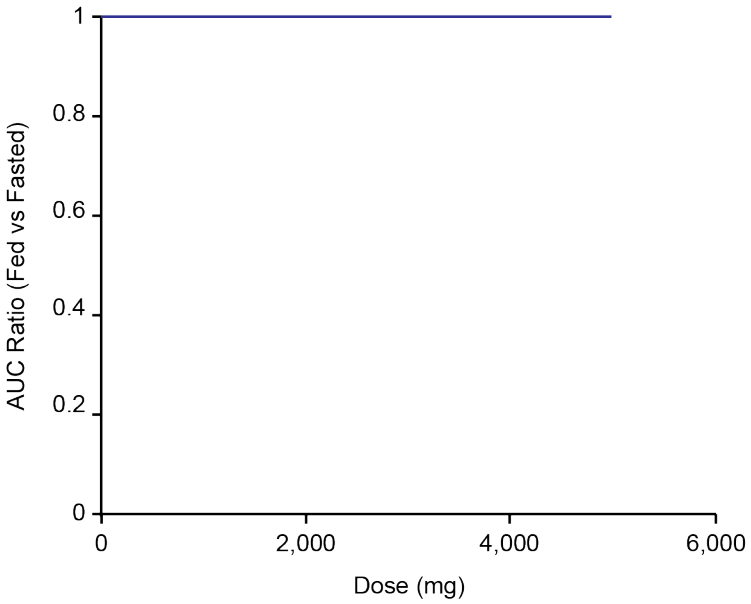
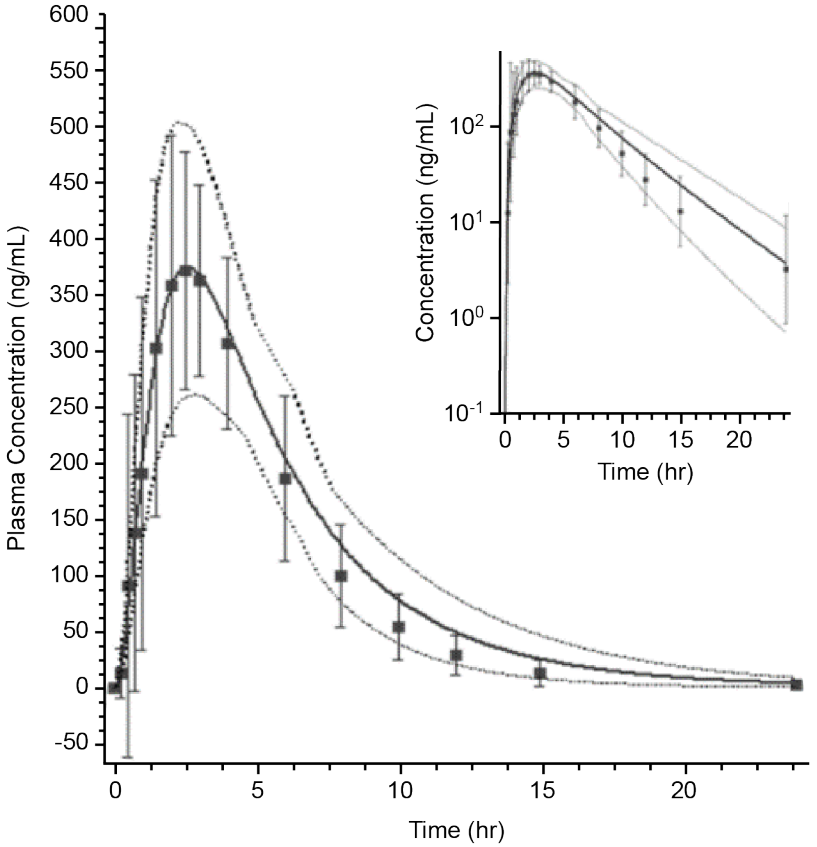
Successful Prediction of Food Effect

A. FE sensitivity to dose



B. Observed vs predicted (fed state)



Food effect for well-behaved BCS I compounds where fasted-state model is established can be predicted via M&S in lieu of a clinical study

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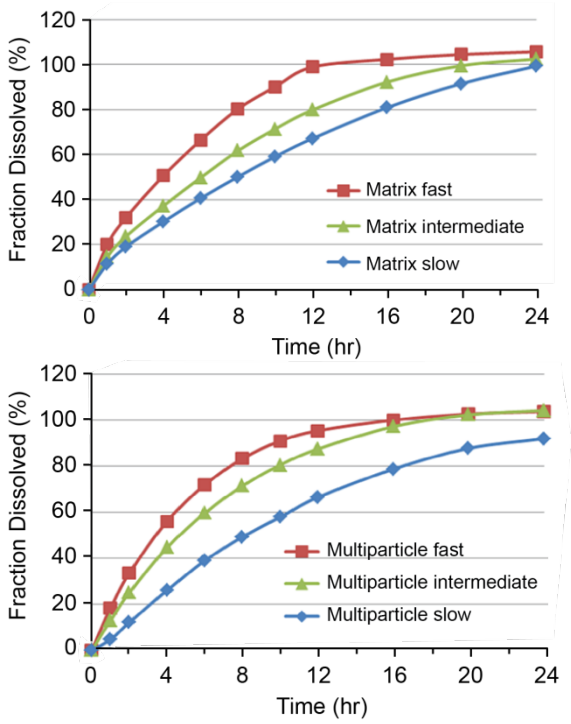
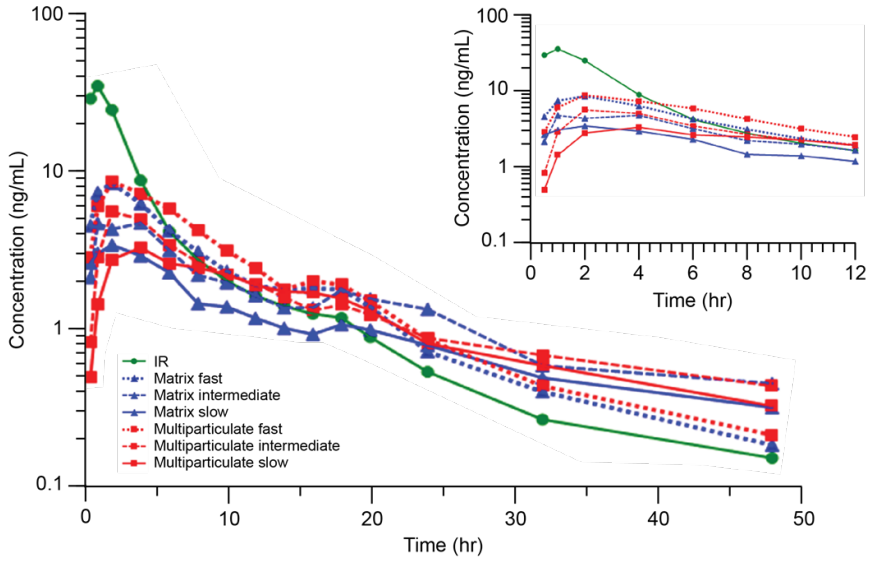
Case Study 6: Absorption Modeling-Based IVIVC

BCS III
Dose: 4 mg
pKa: 1.75 (base), 10.95 (acid)
Solubility: ~ 0.8 – 2 mg/mL (pH 1 – 10)
LLC-PK1 P_{app}: ~ 9 X 10^{-6} cm/sec
Regiodependent absorption (~30% colonic bioavailability)





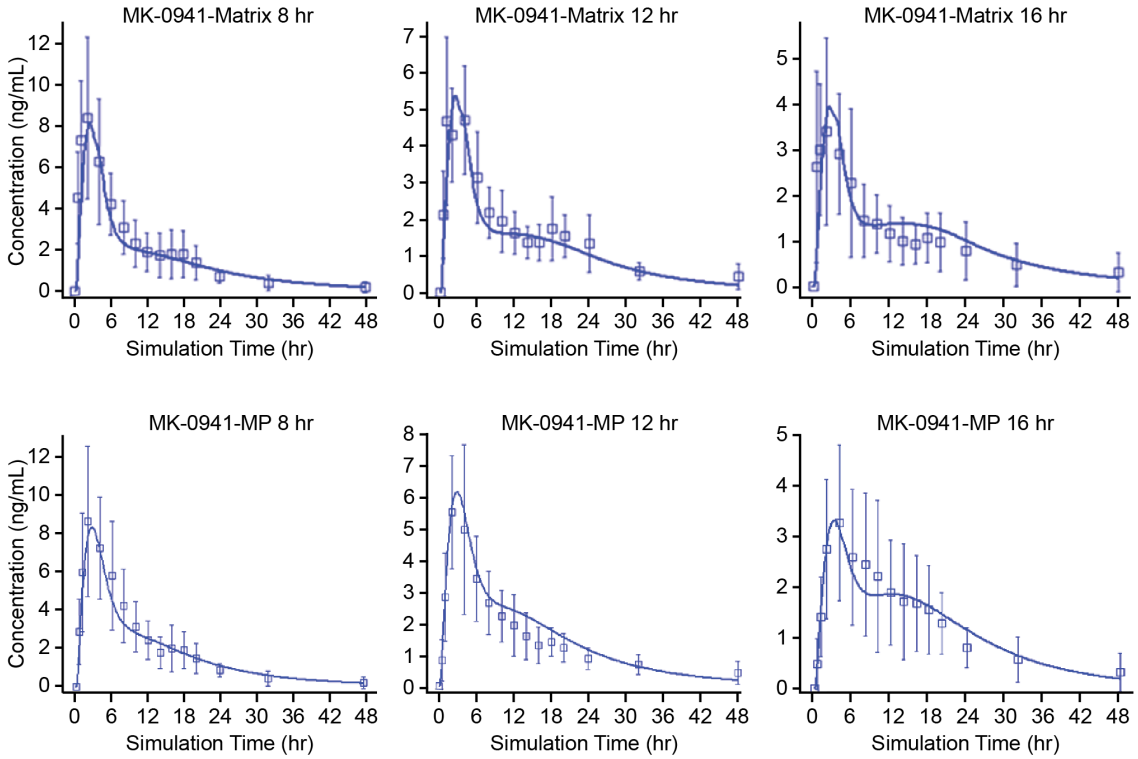
Kesisoglou F, Xia B, Agrawal NG. *AAPS J*. 2015;17(6):1492-1500.

Incorporation of Regional Absorption in PBPK Model Allows for Successful Predictions

Regional absorption incorporated in model

Compartment	Compartment Data			
	Peff	ASF	pH	Transit Time (hr)
Stomach	0	0.0	1.30	0.25
Duodenum	0	9.100	6.00	0.26
Jejunum 1	0	5.200	6.20	0.93
Jejunum 2	0	2.600	6.40	0.74
Ileum 1	0	0.600	6.60	0.58
Ileum 2	0	0.600	6.90	0.42
Ileum 3	0	0.600	7.40	0.29
Caecum	0	0.026	6.40	4.19
Asc Colon	0	0.026	6.80	12.57

Absorption modeling IVIVC projected vs observed



Looking Forward

- Increased application of absorption models to understand fundamental biopharmaceutics questions (eg, food effect, stomach pH) and inform clinical study designs
- Increased utilization of absorption modeling in CMC filing sections
  - Supportive arguments for formulation development and Quality by Design, when relevant to final market image
- Increased utilization of absorption modeling and IVIVC to inform specifications (clinically relevant specifications)

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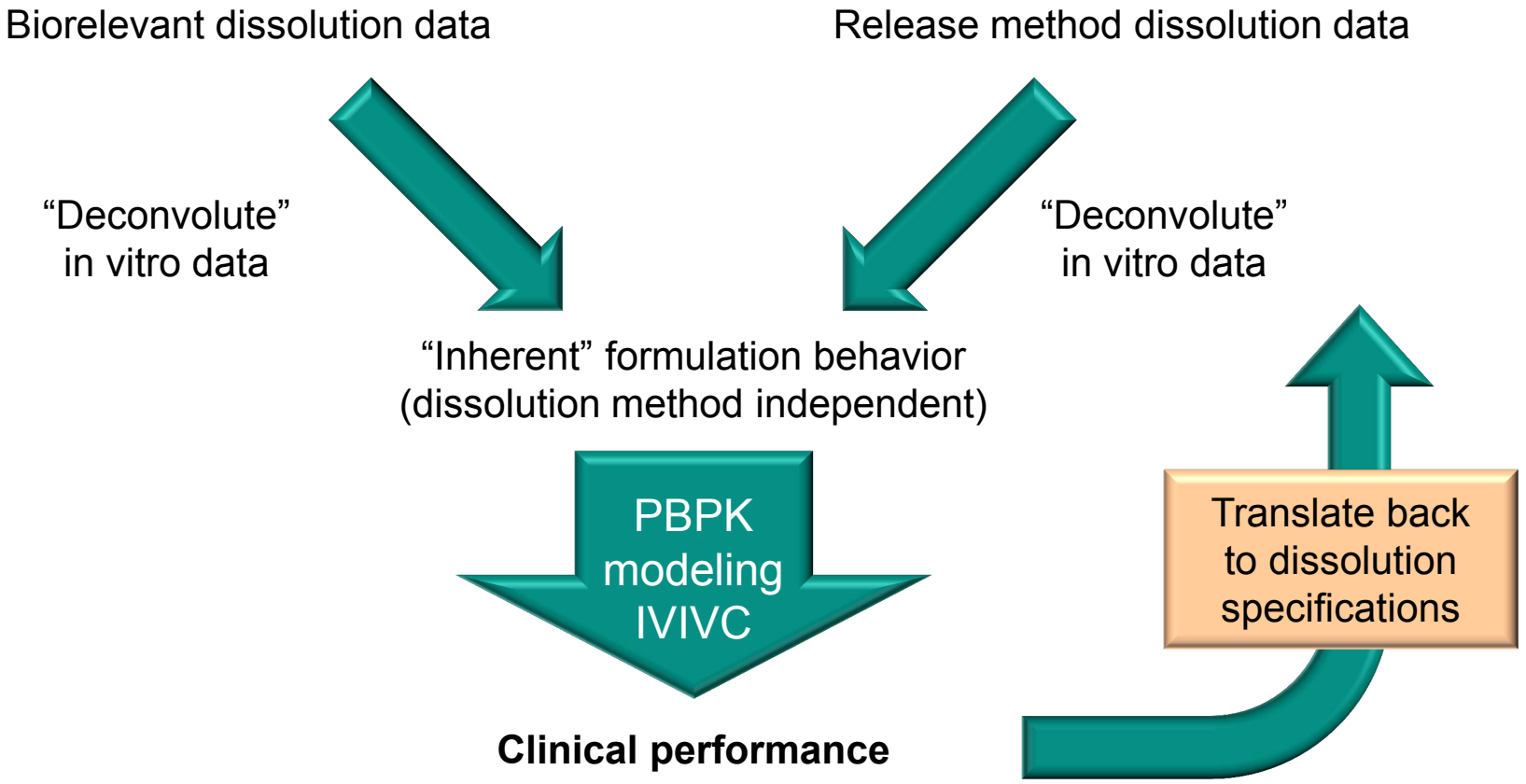
Informing Clinically Relevant Specifications



Current focus is mostly in this space for IR formulations

Area of future focus for IR – currently mostly applied to MR formulations

Opportunity Areas for Regulatory Guidance

- Modeling acceptance/qualification criteria for IVIVC/BE questions
- Regulatory framework for clinically relevant specifications and absorption modeling/IVIVC for IR products
  - Including global harmonization
- Use of absorption modeling as surrogate for clinical studies (eg, food effect biowaivers, acid-reducing agents)

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Acknowledgements

- PQRI BTC
- AAPS Quality by Design and Product Performance Focus Group
- Amitava Mitra, Binfeng Xia, and other Merck colleagues

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