NOV 9-12 2025

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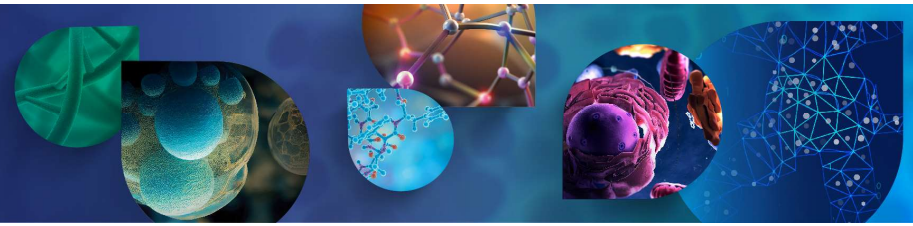

Derisking Formulation Strategies Using PBBM: Mechanistic Case Studies on Evaluating Food Effects and Guiding Dissolution Specifications

November 12, 2025

Deanna Mudie

Session Description

Physiologically based biopharmaceutics modeling (PBBM) is an increasingly valuable tool in drug development, enabling the prediction of in vivo performance based on in vitro data, drug properties, and physiological conditions. This presentation highlights two recent case studies that demonstrate the utility of PBBM in evaluating food effects and guiding dissolution specification development.

Session Objectives

Understand how PBBM mechanistically integrates formulation dependent processes—such as dissolution, precipitation, gastrointestinal transit, and metabolism—to simulate oral drug absorption under varying prandial conditions.

See how PBBM can support development of clinically relevant dissolution specifications, elucidate food effect mechanisms, and inform risk assessment across formulation types using salt and amorphous drug forms as examples.

Explore how PBBM can guide the selection and optimization of formulation parameters, establish safe and effective dissolution boundaries, and minimize the need for additional in vivo studies during late-stage development.

Biography and Contact Information

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- PBPK R&D scientist at Simulations Plus
- > 20 years experience in pharmaceutical solid oral dosage forms
  - Formulation & process development
  - Bioperformance prediction
  - Manufacturing
- BSE Chem Eng, PhD Pharm Sci

Outline

PBPK/PBBM background

PBBM for understanding food effects & setting dissolution specifications

PBPK/PBBM can enable smarter, faster decisions, reducing time & money

Acknowledgments

Xavier Pepin, Ph.D.

- Sandra Suarez-Sharp
- Andrea Ceja
- Christina Hendrickson
- Arlene Padron

What are PBPK and PBBM?

PBPK Modeling

- **P**hysiologically **B**ased **P**harmaco**k**inetic modeling

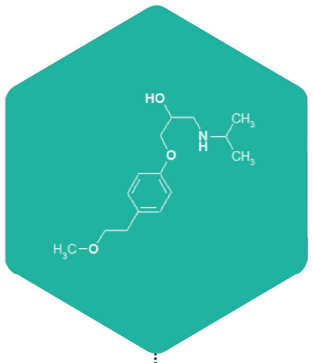
- Mathematical modeling integrating physiological and drug product properties to simulate and predict drug **Absorption, Distribution, Metabolism, Excretion**

PBBM

- **P**hysiologically **B**ased **B**iopharmaceutics **M**odeling

- PBPK for biopharmaceutics applications
- Includes more comprehensive representation of biopharmaceutics & absorption

PBPK/PBBM applications



Discovery

Discovery PK
- Screen compound libraries
- Identify toxic dose levels
- Predict FIH

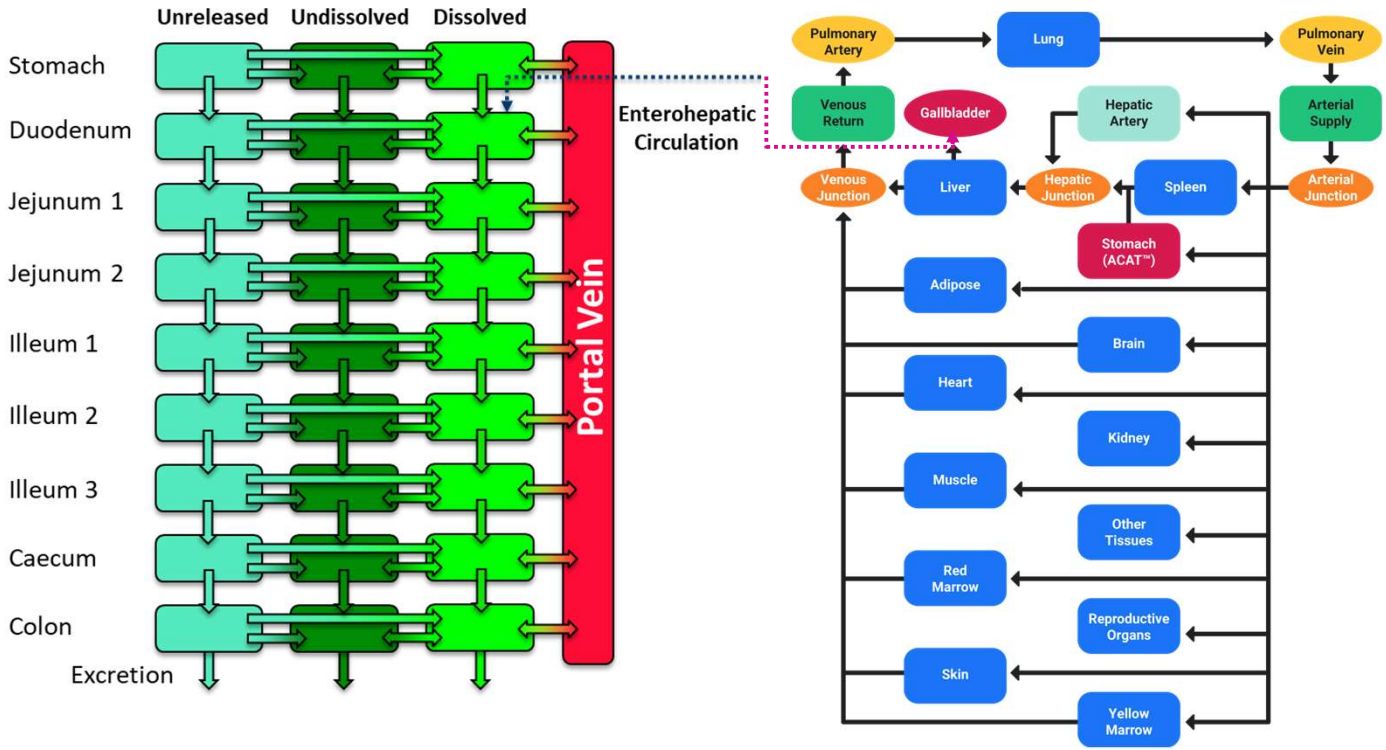
Preclinical

Pharmaceutical Development
- Develop IVIVCs
- Understand food effects
- Establish product specifications

Clinical

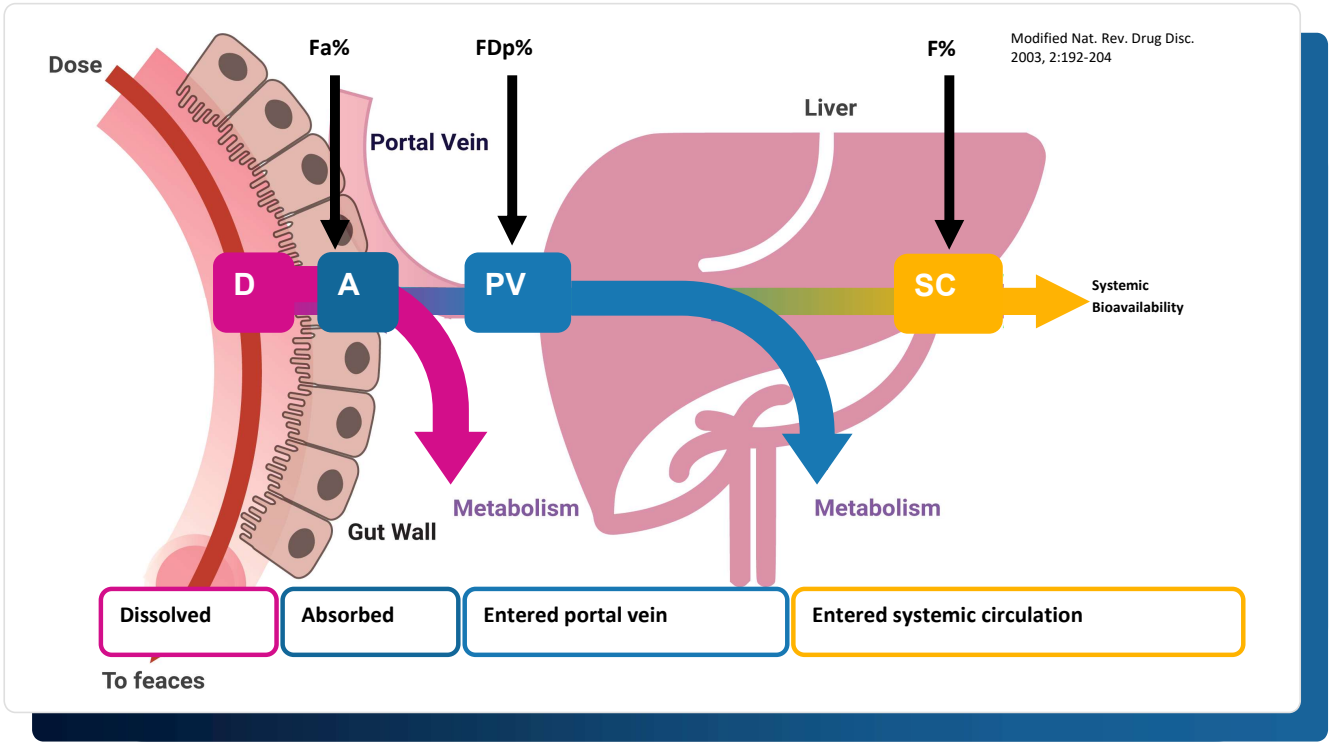
Clinical PK/Pharmacology
- Simulate special populations
- Link PK & PD
- Predict DDIs

GastroPlus® (GP) PBPK/PBBM Platform

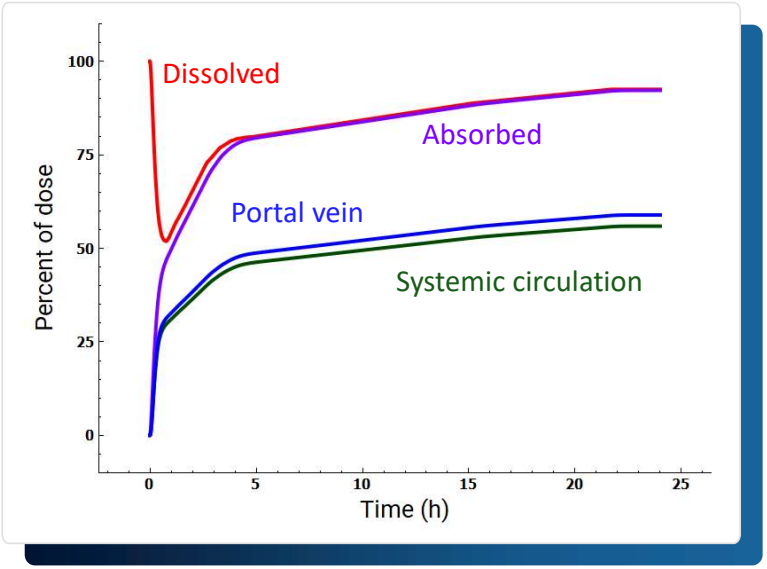


Advanced **C**ompartmental **A**bsorption and **T**ransit (**ACAT**™) Model

Key processes impacting oral bioavailability



Simulating key processes using PBBM



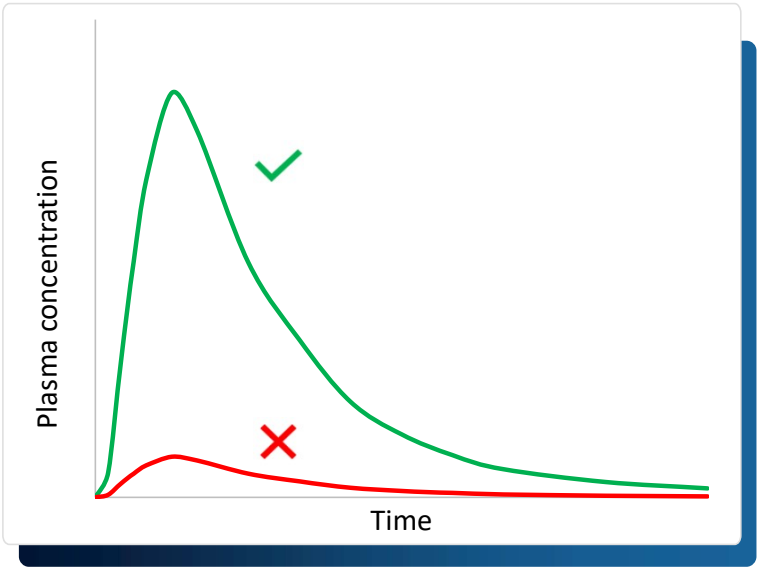
Elucidate

- Key performance mechanisms
- Rate determining steps

Use key performance mechanisms to inform development

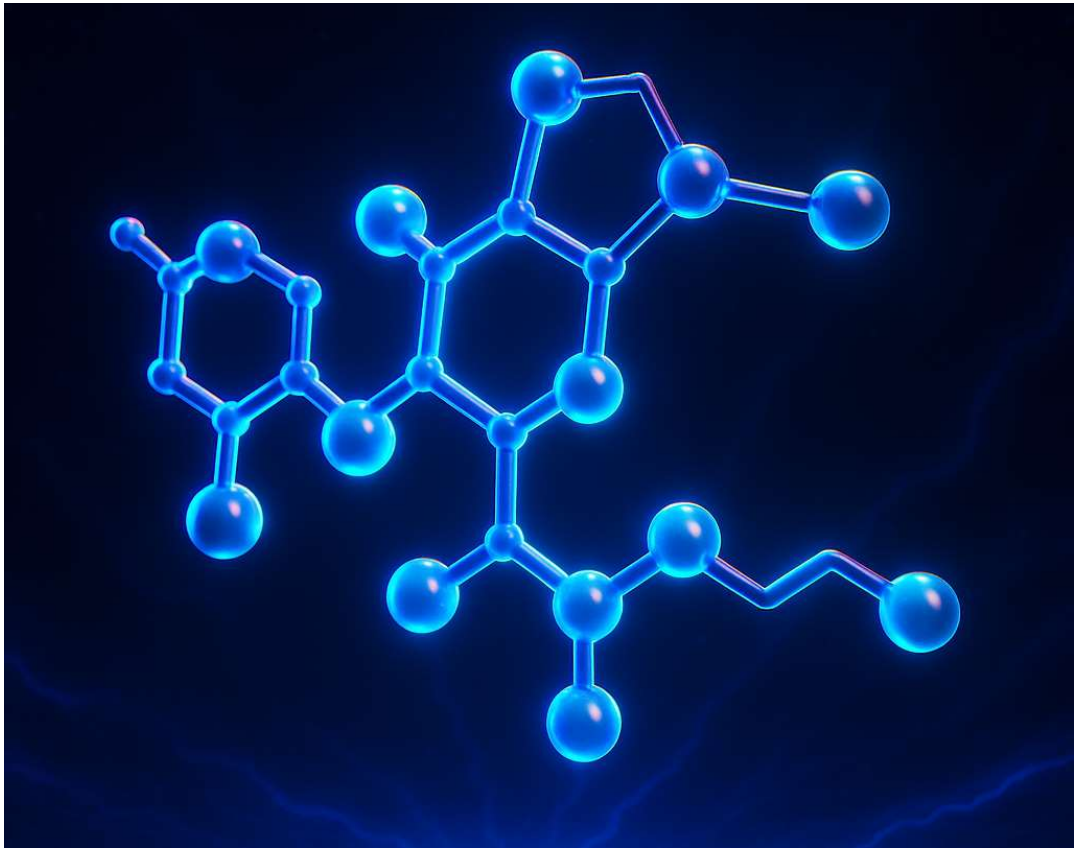
Inform formulation, e.g.

- Increase solubility
- Reduce particle size
- Tune release profile



Selumetinib case study

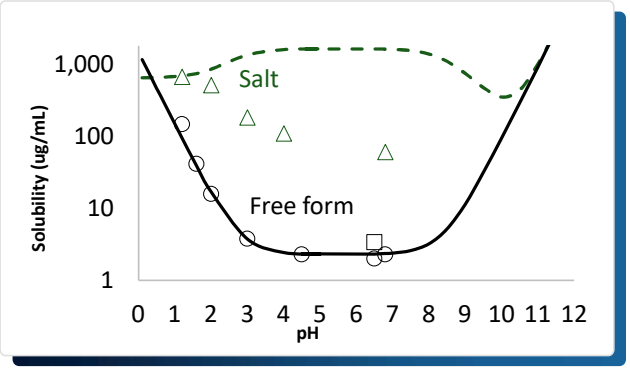
Use PBBM to elucidate food effect mechanisms and evaluate dissolution specifications

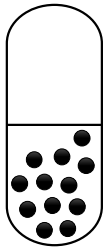


Salt of poorly soluble weak base

Selumetinib properties

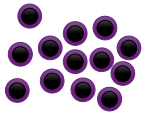
- Crystalline, hydrogen sulfate salt
- pK_a = 2.8 (b), 8.4 (a)
- log P = 2.4
- P_{eff} = 5.35 $X10^{-4}$ cm/s





Lipid matrix in capsule

- AUC ↓ 20% with food*
- Cmax ↓ 50% with food*



Enteric coated lipid granules

- AUC ↔ with food**
- Cmax ↓ 25% with food**

*High fat, high calorie
**Low fat, moderate calorie

Pepin XJH et al. Physiologically Based Biopharmaceutics Model for Selumetinib Food Effect Investigation and Capsule Dissolution Safe Space - Part I: Adults. Pharm Res. 2023 Feb;40(2):387-403.

Selumetinib modeling strategy & key inputs

Extract distribution & elimination from IV data

⬇

Develop & refine oral absorption model

⬇

Validate model

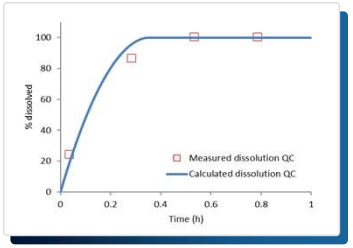
⬇

✓Clinically relevant dissolution method

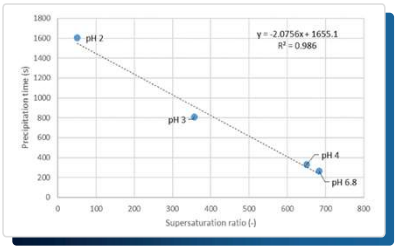
✓Dissolution safe space

✓Food effect mechanisms

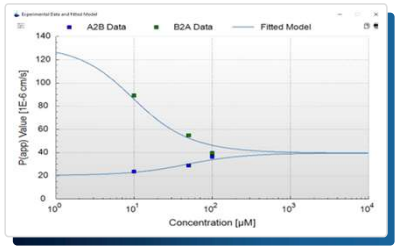
Dissolution



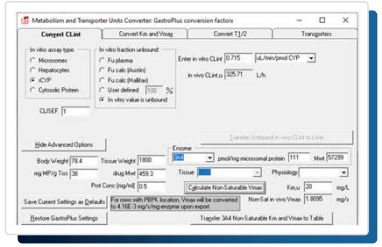
Precipitation



Permeability



First-pass gut extraction



Pepin XJH et al. Pharm Res. 2023 Feb;40(2):387-403.

In vitro dissolution & model parameterization

USP 2 apparatus

- 75 rpm
- 37 °C

Capsules (QC method)

- pH 6.5 phosphate + 0.5% (w/v) PS80

Granules

- pH 6.5 phosphate

Fit Product Particle Size Distribution (PPSD) equation to *in vitro* data

$$\frac{dm_{diss}}{dt} = A(t) \times \left[f_u \frac{D_u}{h_u} \left(C_{S,u} - C_u(t) \right) + \frac{D_b}{h_b} \left(C_{S,b} - C_b(t) \right) \right]$$

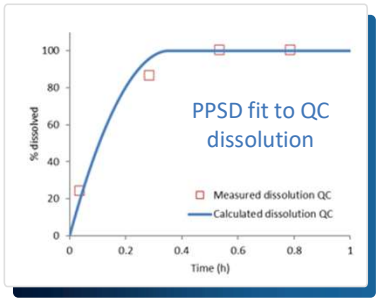
$$A(t) = n(r_i, 0) \cdot 4\pi (r_i(t))^2$$

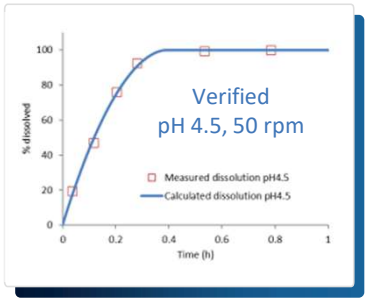
$$\frac{h_b}{h_u} = \sqrt[3]{\frac{D_b}{D_u}}$$

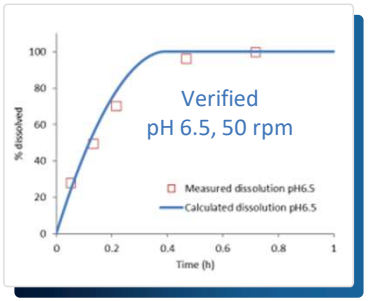
Pepin XJH et al. Pharm Res. 2023 Feb;40(2):387-403.

PPSD fitting results for capsule & granules

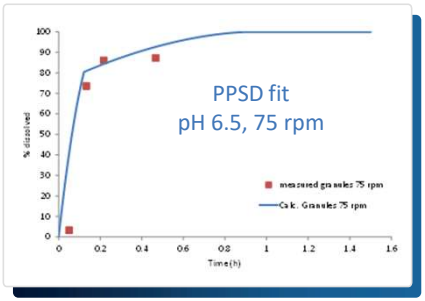
Capsule
(R = 80 µm, 1 bin)







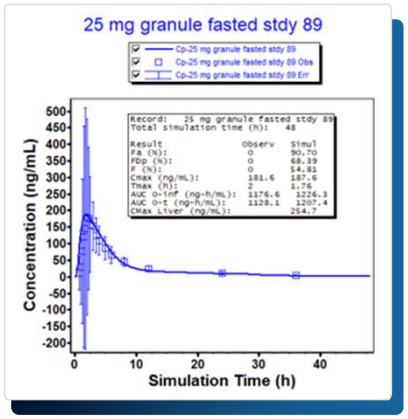
Granules
(R = 170 µm, 1 bin)

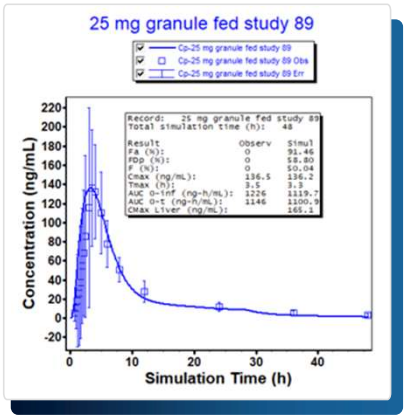


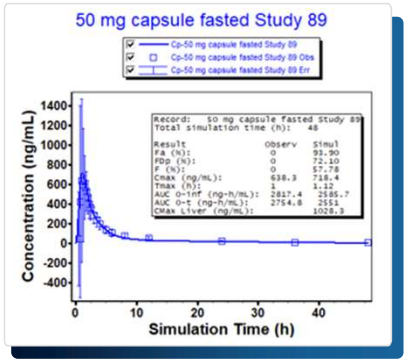
Pepin XJH et al. Pharm Res. 2023 Feb;40(2):387-403.

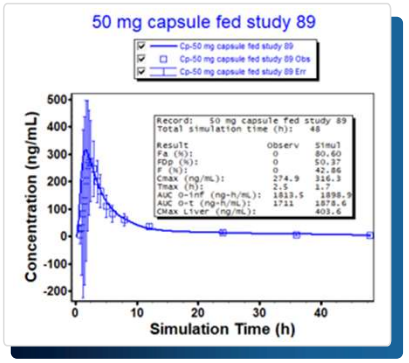
PBBM Validation

	Prandial state	Formulation	Dose (mg)	APE C_{max}	APE AUC_{0-t}
1	Fasted	Capsule	75 (3 × 25 mg)	14	0.1
2	Fed low fat	Granules	25	0.2	3.9
3	Fasted	Granules	25	3.3	7
4	Fasted	Capsule	75 (3 × 25 mg)	18.2	6.9
5	Fasted	Capsule	50 (2 × 25 mg)	12.6	7.4
6	Fed low fat	Capsule	50 (2 × 25 mg)	15.1	9.8
7	Fasted	Capsule	25	8.5	12.4
8	Fed high fat	Capsule	75 (3 × 25 mg)	4.3	15.3









APE = average absolute prediction error

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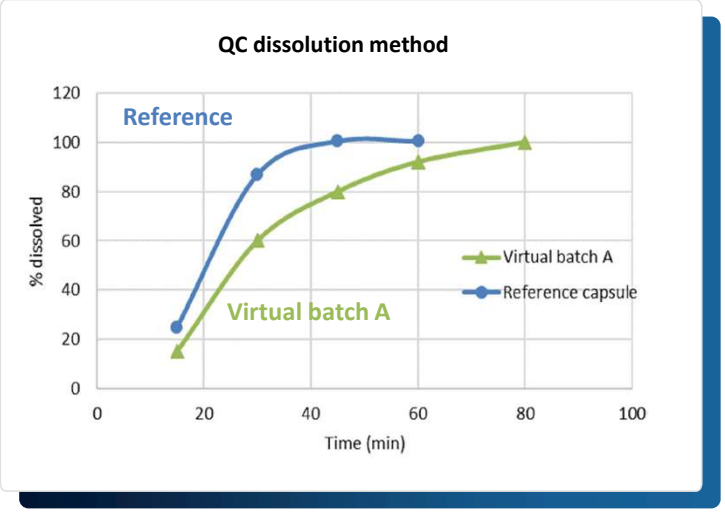
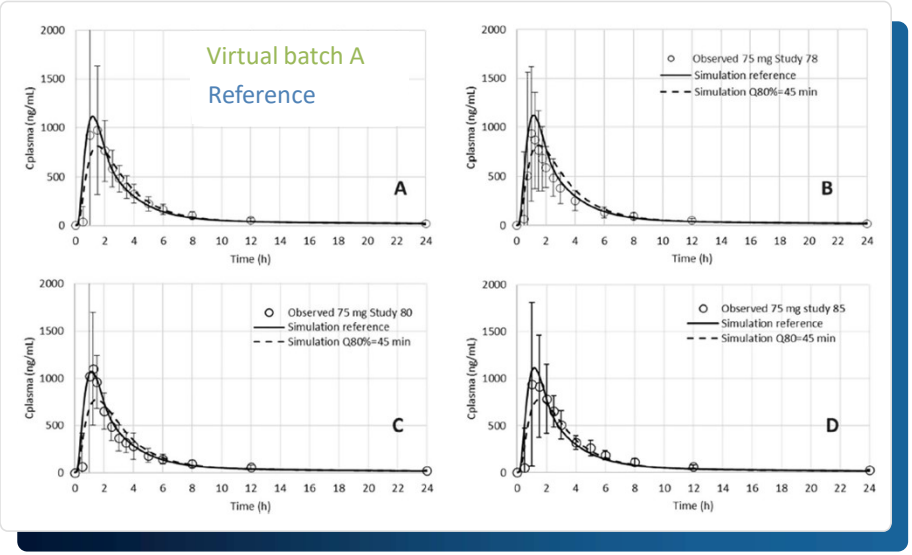
Selumetinib dissolution safe space

- Created slower releasing virtual batch



- Simulated virtual vs. reference capsule – 75 mg
- Virtual batch deemed as safe and effective
  - 4 – 7% ↓ AUC
  - 27 – 30% ↓ C_{max}



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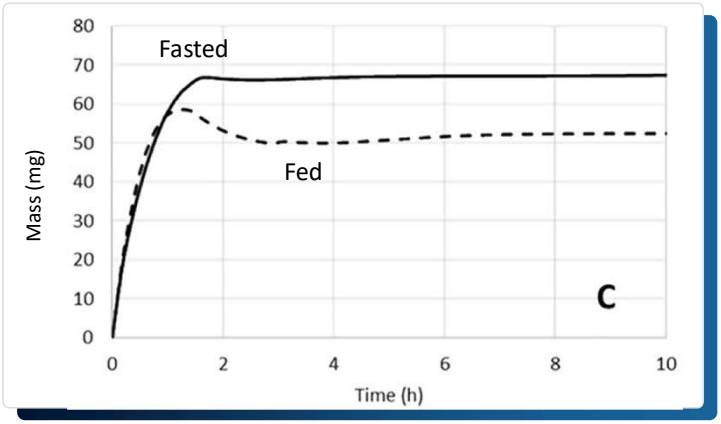
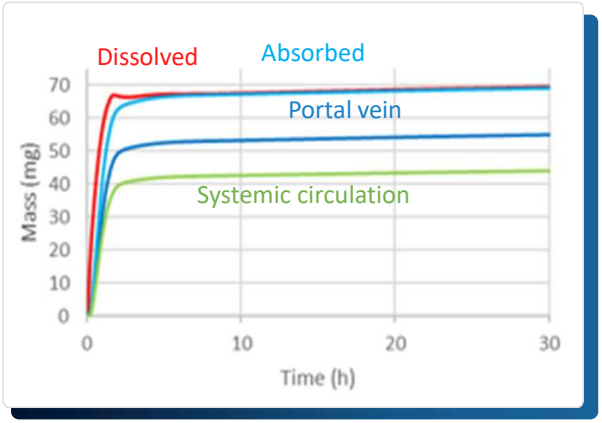
Food effect capsules: AUC↓ & C_{max}↓ w/food

Fasted vs. fed disso



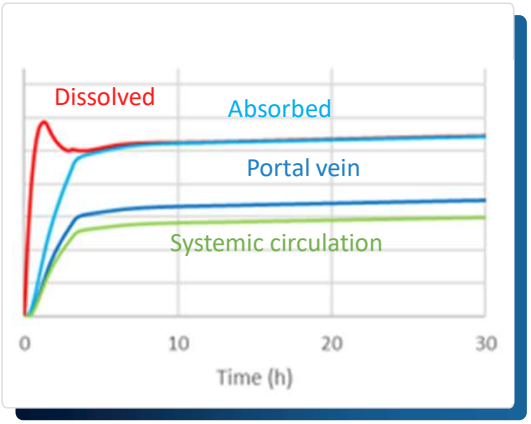
- 3 X 25 mg capsules
- w/o vs. w/ high fat, high calorie meal

Fasted



- 93% absorbed
- 74% portal vein
- 59% SC

Fed



- 74% absorbed
- 48% portal vein
- 41% SC

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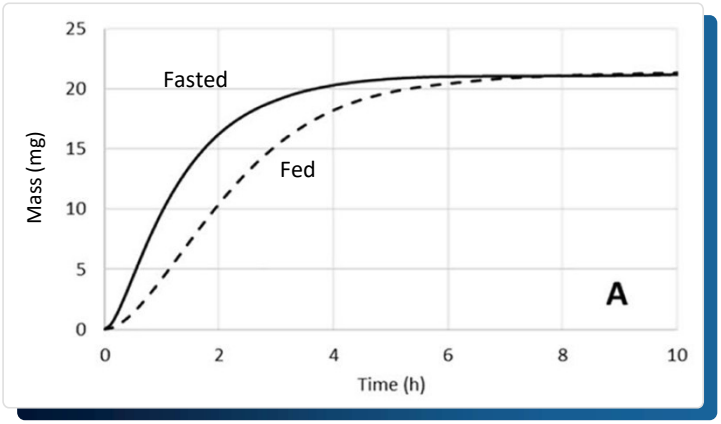
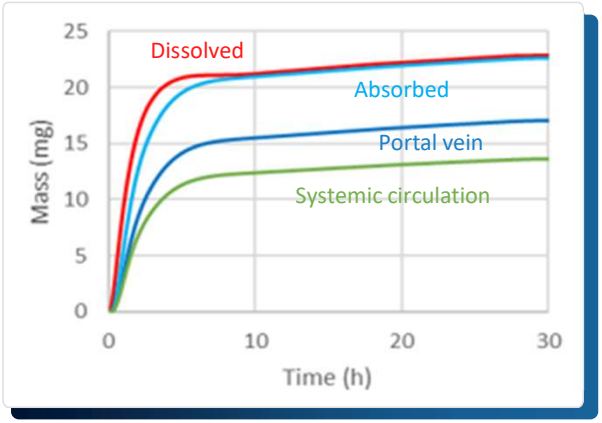
Food effect granules: AUC↔ & C_{max}↓ w/food

Fasted vs. fed disso



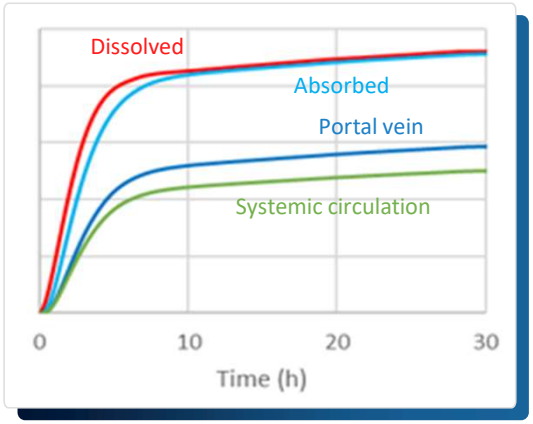
- 25 mg dose
- w/o vs. w/low fat, moderate calorie meal

Fasted



- 91% absorbed
- 68% portal vein
- 55% SC

Fed



- 91% absorbed
- 59% portal vein
- 50% SC

Pepin XJH et al. Pharm Res. 2023 Feb;40(2):387-403.

Omaveloxolone case study

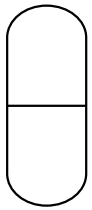
Use PBBM to elucidate food effect mechanisms

Highly lipophilic, amorphous drug

Omaveloxolone (Omav) properties

- Amorphous
- pK_a = 7.26 (a)
- log P = >5
- $P_{eff} \approx 3 \times 10^{-4}$ cm/s

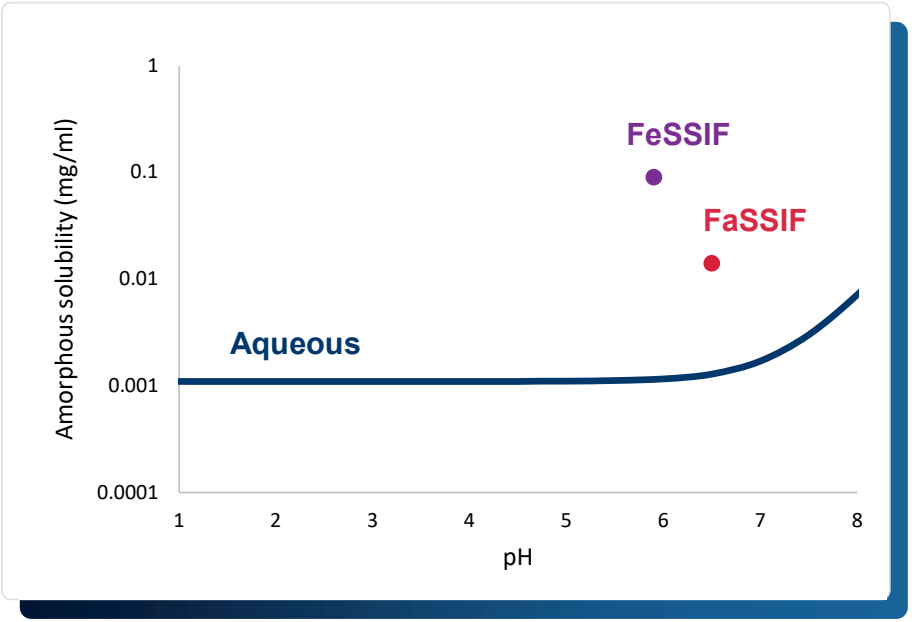
Dosage form



SDD solid blend in IR HPMC capsules

- C_{max} ↑ 350% with food*
- AUC ↑15% with food*

*High fat FDA standardized breakfast



Pepin XJH et al. CPT Pharmacometrics Syst Pharmacol. 2024 Oct;13(10):1771-1783

Omav modeling strategy & key inputs

Extract distribution from IV data

⬇

Base clearance on *in vitro* data

⬇

Develop & refine oral absorption model

⬇

Validate model

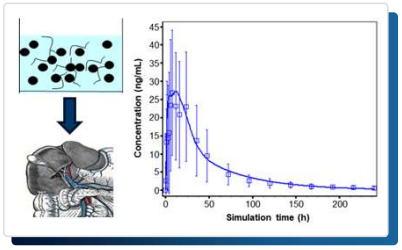
⬇

✓Model use

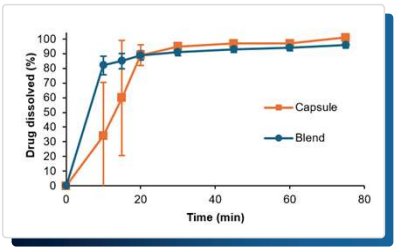
✓Parameter sensitivity analysis

✓Food effect mechanisms

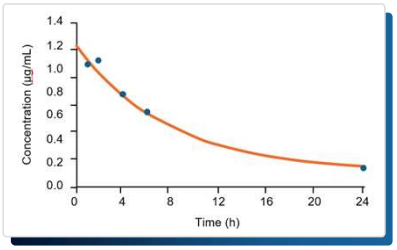
First-pass extraction



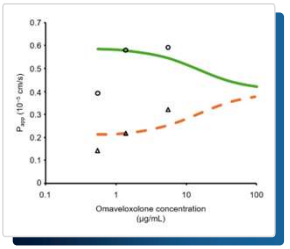
Dissolution



Precipitation



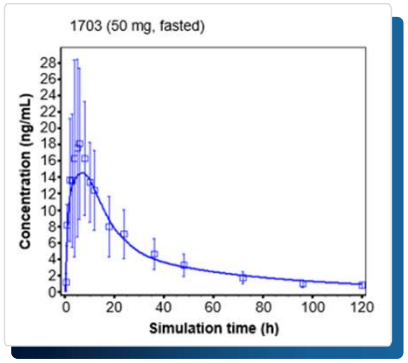
Permeability

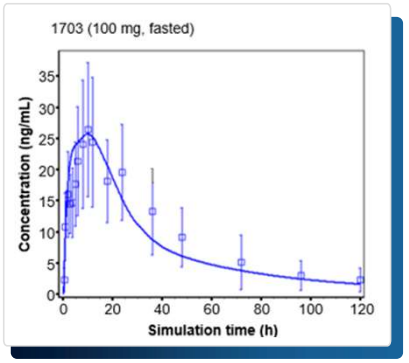


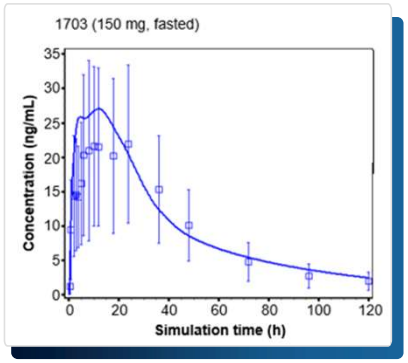
Pepin XJH et al. CPT Pharmacometrics Syst Pharmacol. 2024 Oct;13(10):1771-1783

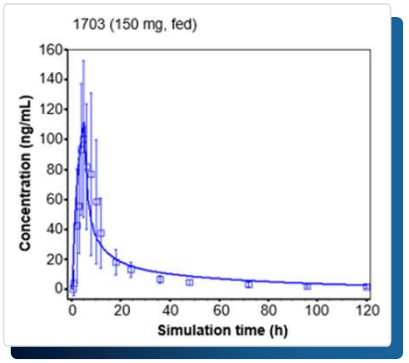
PBBM Validation

	Dose (mg)	Condition	APE C_{max}	APE AUC_{0-t}
1	150	Fasted +Itraconazole	11.6	2.2
2	150	Fasted	9.7	4
3	150	Fasted	1.2	4.4
4	50	Fasted	19.9	4.8
5	150	Fasted	23	5.7
6	150	Fasted +Verapamil	32.5	11.3
7	150	Fed	11.5	13.7
8	100	Fasted	2.8	15.1
9	150	Fasted	30.7	19.5









APE = average absolute prediction error

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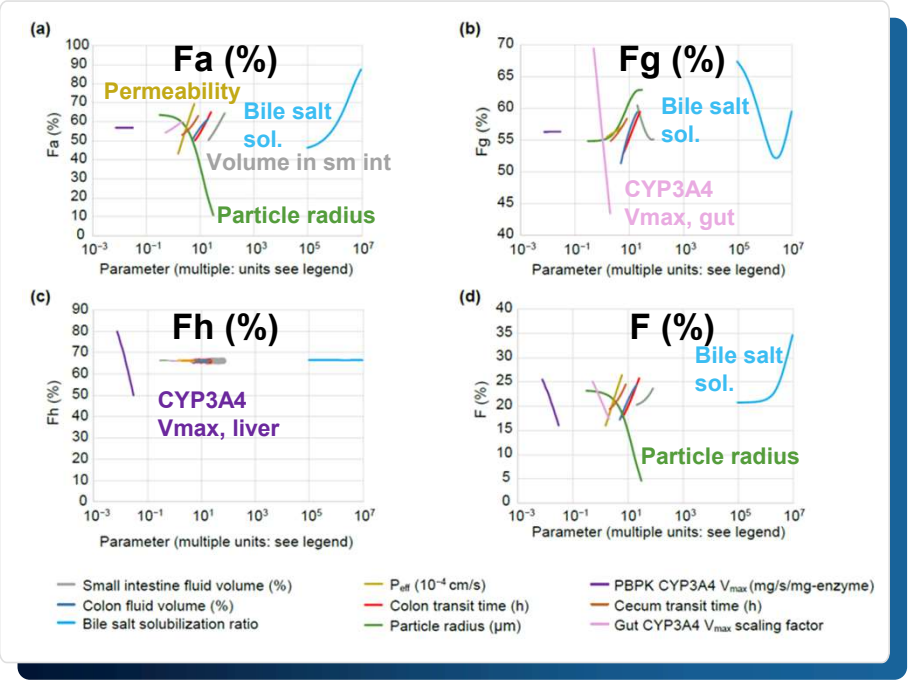
Omaveloxolone parameter sensitivity



Model & performance of Omav capsules (150 mg) most sensitive to:

- Bile salt solubilization
- Particle radius
- CYP3A4 Vmax (gut)
- CYP3A4 Vmax (liver)
- Permeability
- Volume fluid in small intestine

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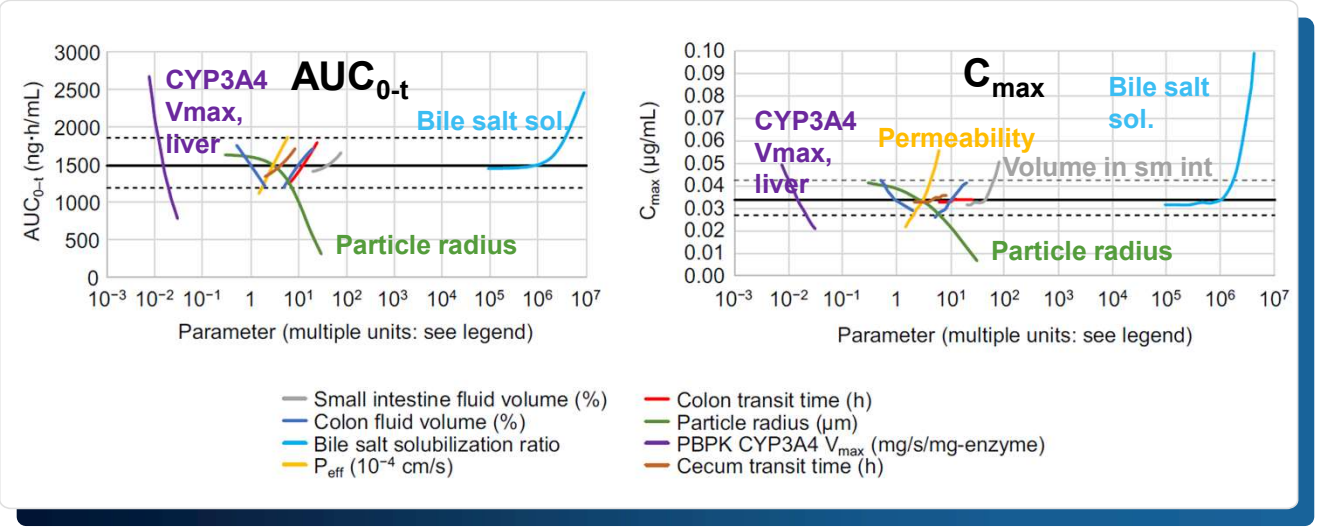
Omaveloxolone parameter sensitivity



Fasted state 150 mg

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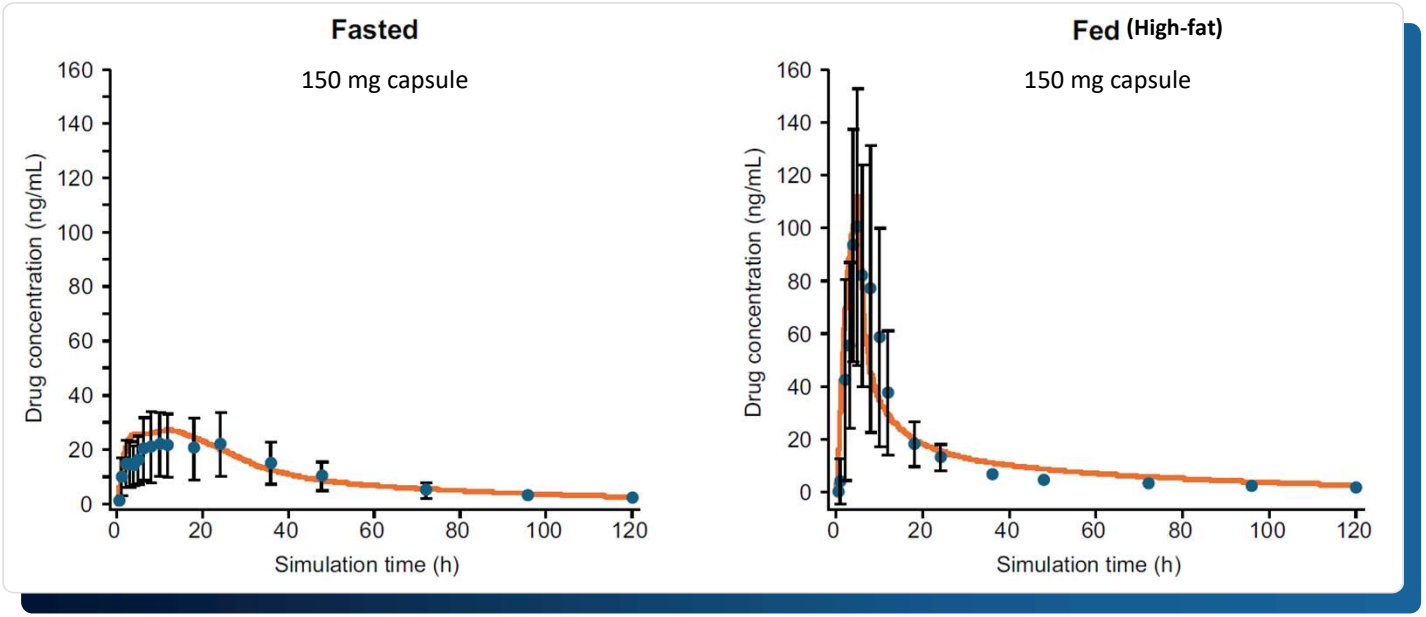
Food effect Omav: 350%↑C_{max}, 15%↑AUC



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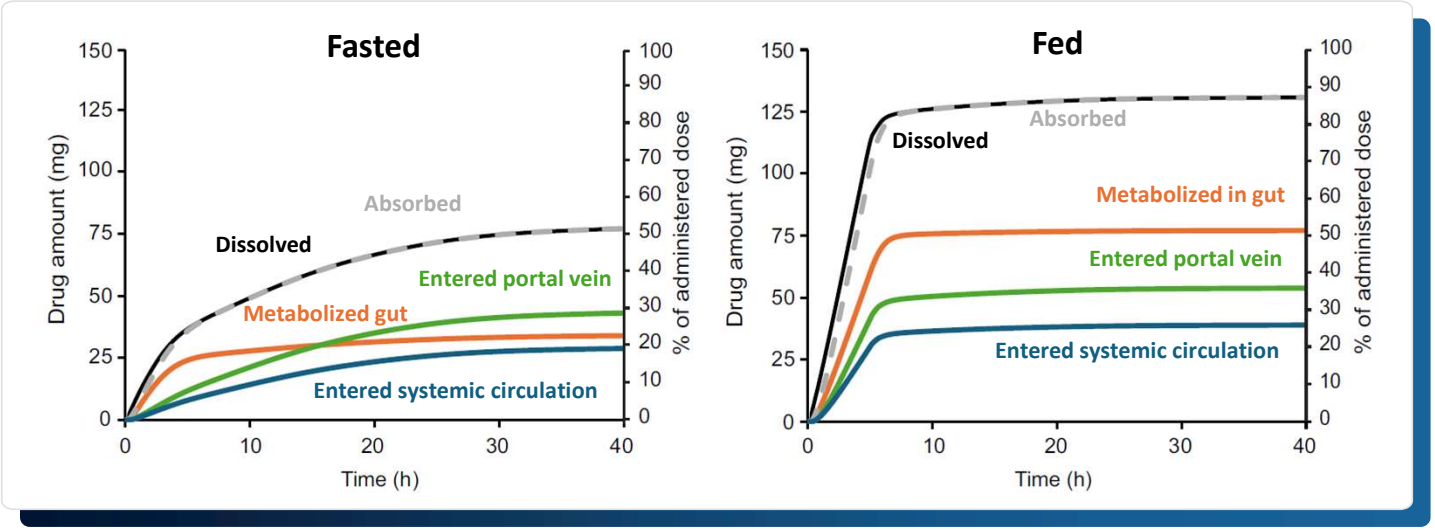
Omaveloxolone food effect mechanism



Fed state: ↑ dissolution, ↑ upper GI absorption, ↑ first pass gut extraction
Therefore, modest increase in amount entering portal vein (36% vs. 29%) and systemic circulation

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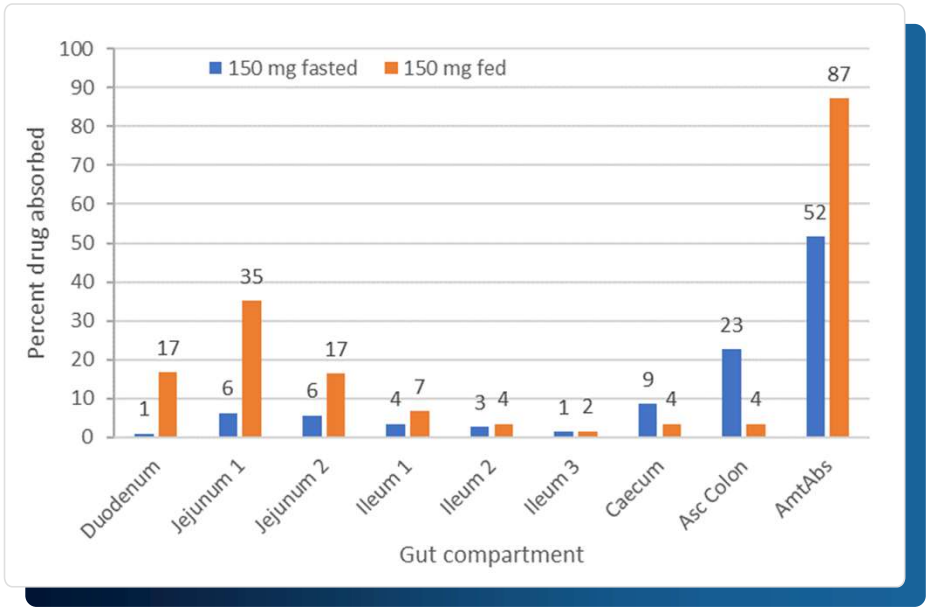
Fed vs. fasted regional absorption



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Case studies summary

PBBMs informed by DS and DP were successfully developed and validated:

- Selumetinib (IR capsule and enteric granules of salt of weakly basic drug)
- Omaveloxolone (IR capsule of highly lipophilic amorphous drug)

PBBMs used to:

- Show clinical relevance of QC dissolution method for selumetinib capsules
- Establish safe space for selumetinib capsule dissolution
- Elucidate mechanisms of negative food effect (selumetinib) and positive food effect (omaveloxolone)

PBBMs showed that first-pass gut extraction played a significant role in explaining food effects (in addition to solubility and dissolution)

- PBBMs enabled decoupling of first pass metabolism, dissolution, and absorption

Overall summary

PBPK/PBBM can enable smarter, faster decisions, reducing time & money

- Prioritize compounds
- Identify & mitigate risks
- Reduce cycle times

- Optimize formulations
- Elucidate performance mechanisms

- Justify release specifications
- Waive clinical studies

References

- Pepin XJH, Hammarberg M, Mattinson A, Moir A. Physiologically Based Biopharmaceutics Model for Selumetinib Food Effect Investigation and Capsule Dissolution Safe Space - Part I: Adults. Pharm Res. 2023 Feb;40(2):387-403. doi: 10.1007/s11095-022-03339-2

- Pepin XJH, Hynes SM, Zahir H, Walker D, Semmens LQ, Suarez-Sharp S. Understanding the mechanisms of food effect on omaveloxolone pharmacokinetics through physiologically based biopharmaceutics modeling. CPT Pharmacometrics Syst Pharmacol. 2024 Oct;13(10):1771-1783. doi: 10.1002/psp4.13221

Questions

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