Development and application of PBBM to define clinically relevant dissolution safe space for a BCS IV zwitterionic lipophilic, IR drug product

Konstantinos (Kostas) Stamatopoulos

Presentation overview

Session date:

30/08/2023

Objectives

1. Understand the impact of meal type on the exposure of GSK3640254 (GSK254)
2. Understand the impact of biorelevant media composition and pH on the solubility of GSK3640254 (GSK254)
3. Understand the impact of mixed micelles on the permeability of GSK3640254 (GSK254)
4. Develop, qualify and verify a Physiologically Based Biopharmaceutics Model (PBBM) to define clinically relevant dissolution safe space

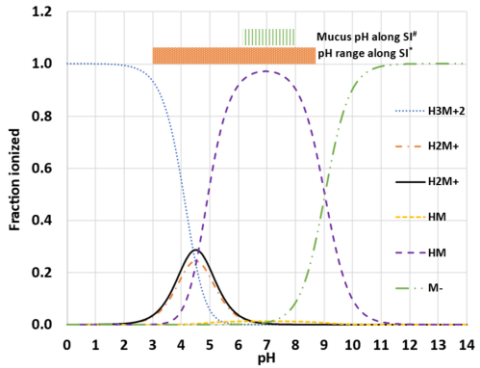
Key questions

1. Why GSK3640254 (GSK254) showed 20-25% higher Cmax after moderate-fat meal ingestion compared to high-fat meal?
2. What is the underlying mechanism of this difference observed in Cmax and is it clinically relevant?
3. What should be the stepwise approach to answer this question using in vitro and in silico tools?
4. What is the clinical relevance of the outcomes from this work conducted?
5. How can we integrate the knowledge/data obtained to a PBBM to define clinically relevant dissolution safe space?
6. What should be the criteria used to define the dissolution safe space?

Case study: GSK3640254 (GSK254)

Background

- BCS IV drug type: low solubility; low permeability
- Zwitterionic: can be positively or negatively charged, or neutral, depending on pH



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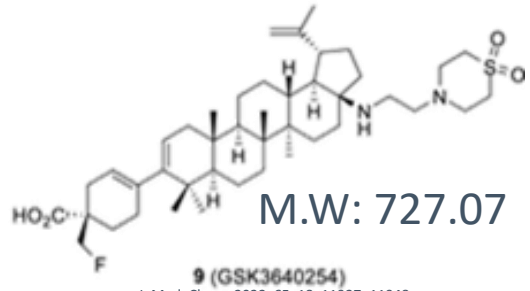
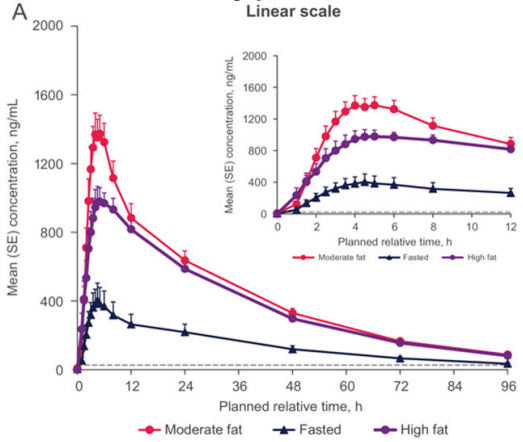


9 (GSK3640254)
J. Med. Chem. 2022, 65, 18, 11927–11948

- Impact on meal type on the PK of GSK3640254



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20-24% ↓ Cmax (with high- fat meal)

pharmaceutics

MDPI

Article

Integrating In Vitro Biopharmaceutics into Physiologically Based Biopharmaceutic Model (PBBM) to Predict Food Effect of BCS IV Zwitterionic Drug (GSK3640254)

Konstantinos Stamatopoulos [1,*], Paola Ferrini [2], Dung Nguyen [3], Ying Zhang [4], James M. Butler [1], Jon Hall [5] and Nena Mistry [1]

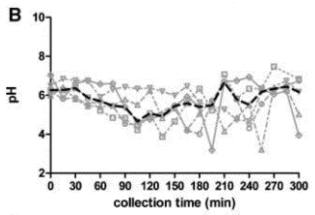
Case study: GSK3640254 (BSC IV, zwitterionic)

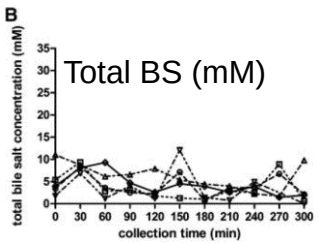
Question: Overall positive FE was observed, however, do we understand why moderate fat meal yield higher exposure than high fat meal?

Food Effect on human physiology

- **Changes in gastric emptying -> impacting Cmax and Tmax**
- **Changes in luminal composition and fluid volumes -> impacting solubility and dissolution**
- **Increasing blood flow rate -> impacting drug's absorption**
- **Increased viscosity -> impacting disintegration and dissolution**
- **Changes in Transit times in the gut -> impacting dissolution and absorption**

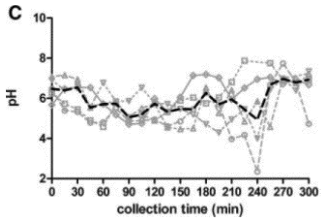
Moderate fat (Scandishake Mix)

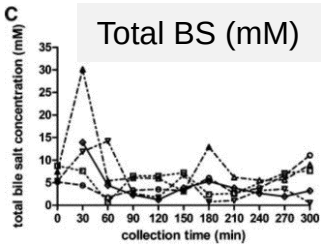




Total BS (mM)

High fat (Ensure Plus)

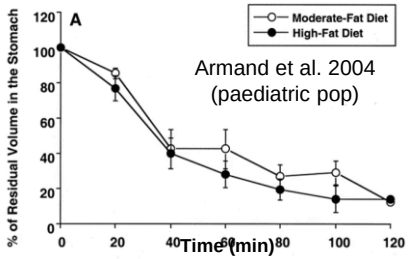




Total BS (mM)

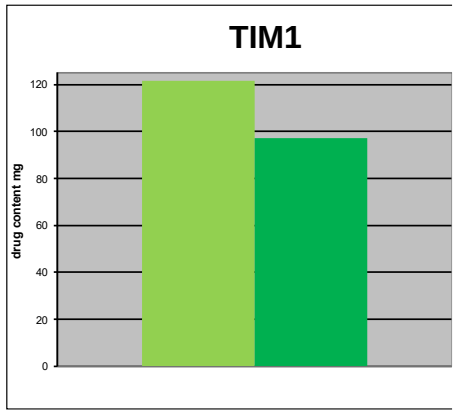
Clarysse et al 2009

Gastric emptying (true?)



Armand et al. 2004 (paediatric pop)

TIM1



Moderate – fat meal

High – fat meal

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…so where to look at?

…meal composition?

High fat

Whole milk: 26% palmitic, 20% oleic
Bacon: 25% palmitic, 45% oleic
Egg: 29% palmitic, 40% oleic
Butter: 28% palmitic, 22% oleic

Moderate fat

English muffin: palmitic acid (33.4%), oleic acid (37.4%)*

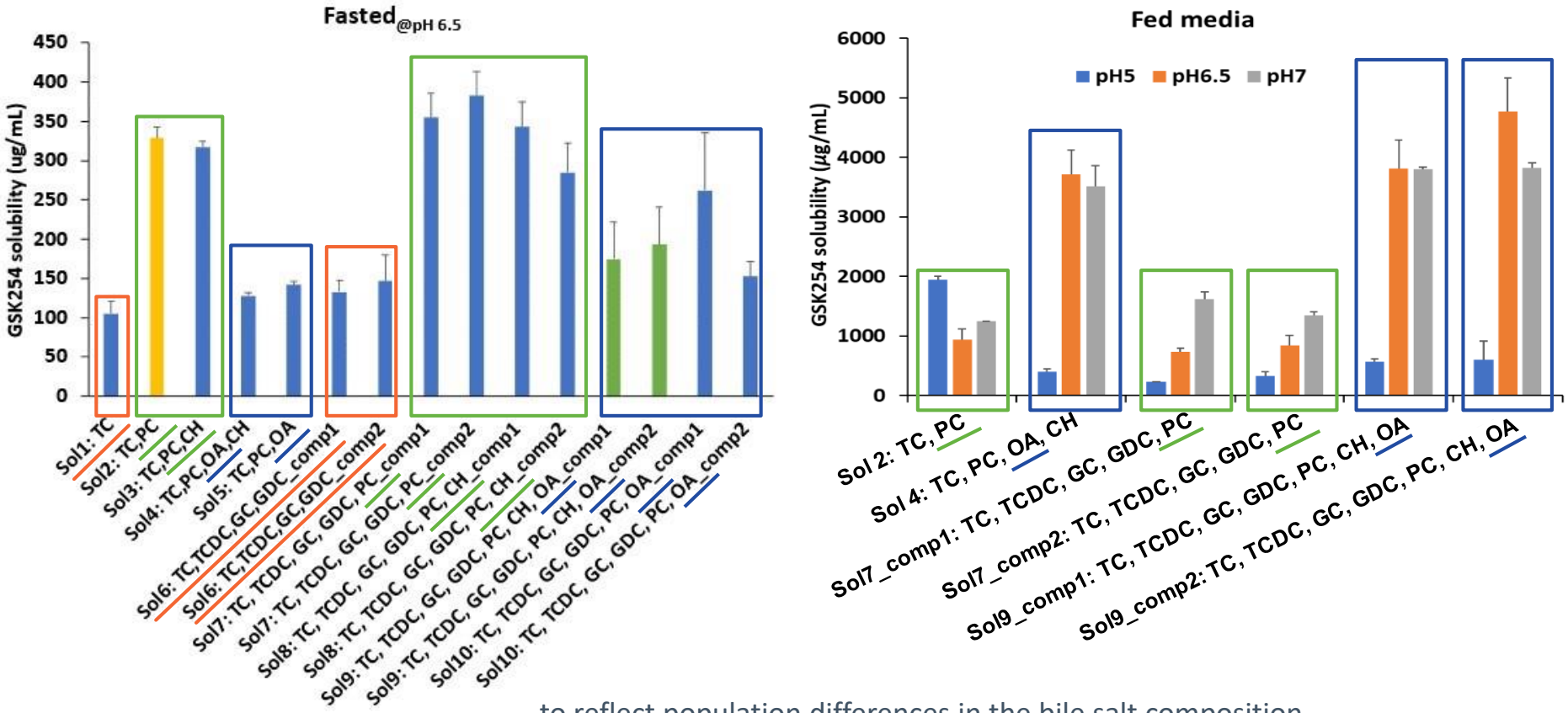
American cheese: Saturated 67.6, monounsaturated 27.3 (g/100 g of fatty acids in cheese)**

Sausage link: greatly depends on the type of meat(s) used. General high in saturated fatty acids

Cooked egg: see FDA high-fat meal

High-throughput automation in vitro platform

Understand impact of media composition and pH on the solubility of GSK254



…to reflect population differences in the bile salt composition

Comp1: 70% glycine- and 30% taurine- conjugated bile salts (Riethorst, D., et al.,. J Pharm Sci, 2016. 105(2): p. 673-681)

Comp2: 44% glycine- and 56% taurine- conjugated bile salts (Moreno, M., J Pharm Pharmacol, 2006. 58(8):1079–1089)

Each data point is obtained in triplicate; error bar = standard deviation across triplicates; data collected at 4 timepoints (1, 2, 4, and 24 h) and reported after 24 h screen

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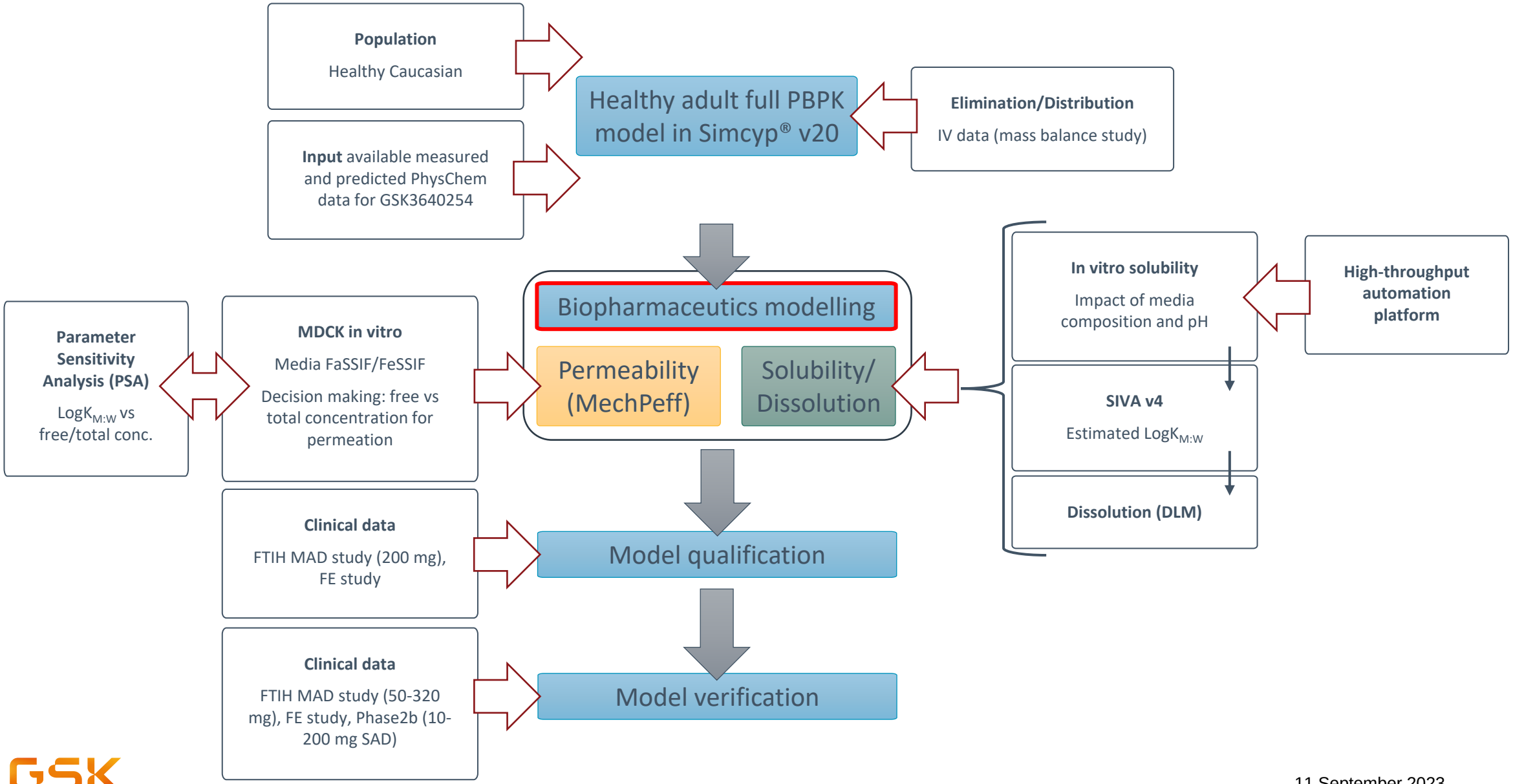
PBBM strategy - Overall modelling workflow



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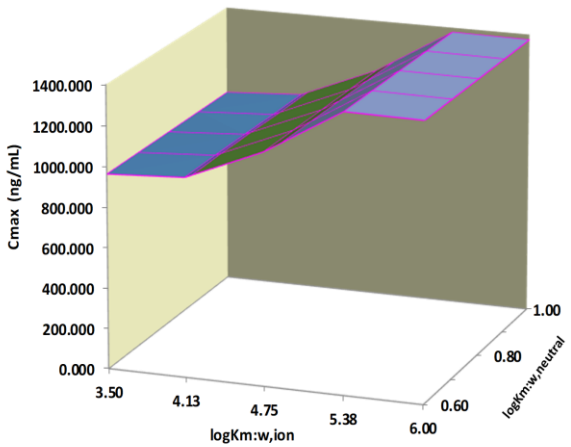
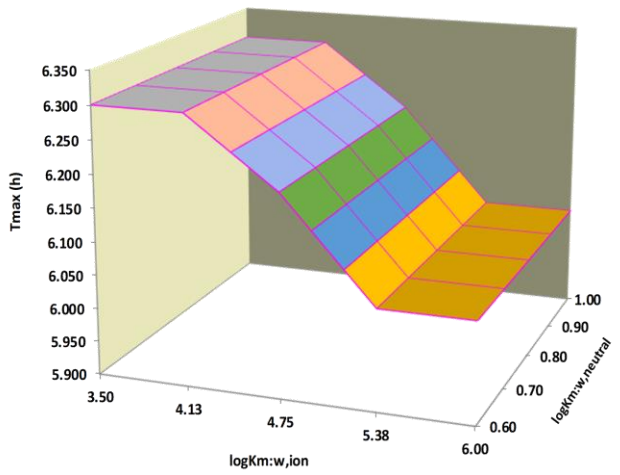
PBBM strategy - Permeability

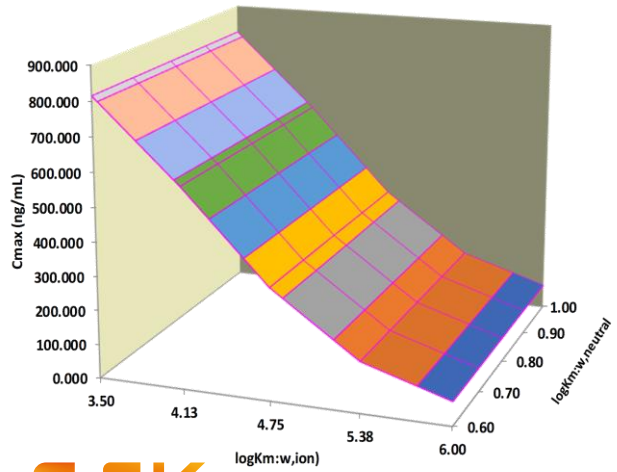
PSA – $LogK_{m:w}$

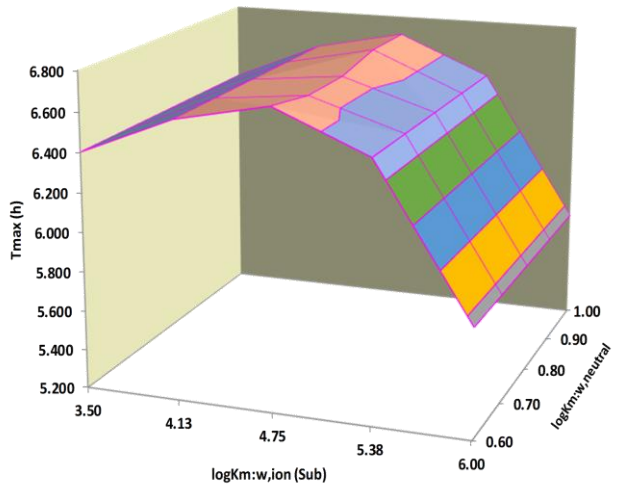
Total concentration





Free fraction





Apparent exact permeability of GSK254 in biorelevant media using MDCK cell lines

Compound	Drug (μM)	Rate A > B (nmoles/cm²/h)	s.d.	A > B M.B (%)	s.d.	P_{exact} (nm/s) A > B	s.d.
GSK254 + GF120918 (DMEM/DMEM)	2.67	0.00	0.0	74	8.3	0.0	0.0
GSK254 + GF120918 (FaSSIF pH7.4)	2.67	0.031	NA	109	NA	29	NA
GSK254 + GF120918 (FaSSIF pH6.5)	2.67	0.015	0.0041	97	2.4	16	4.5
GSK254 + GF120918 (FeSSIF pH7.4)	2.67	0.055	NA	87	NA	67	NA
GSK254 + GF120918 (FeSSIF pH5.8)	2.67	0.021	0.0068	96	9.7	23	6.9

Note: Apical to Basolateral (A > B); the data is presented in mean and standard deviation (s.d); %Mass Balance (%M.B). Permeability experiments were conducted in triplicates in each media (n = 3).

$LogK_{M:W}$ for ionized species is affecting model outputs

Total Conc: $LogK_{M:W}$ ↑ = Cmax↑ Tmax ↓

Free Conc: $LogK_{M:W}$ ↑ = Cmax↓ Tmax ↑↓

Total or free?

↓

Permeability data: Bile salt↑ →Free fract.↓ Papp↑

↓

- Clinical data showed increased Cmax in fed
- Permeability data showed increased Papp in FeSSIF beside the lower free fraction

↓

<u>Total concentration</u> should be used to describe the in vivo and in vitro findings

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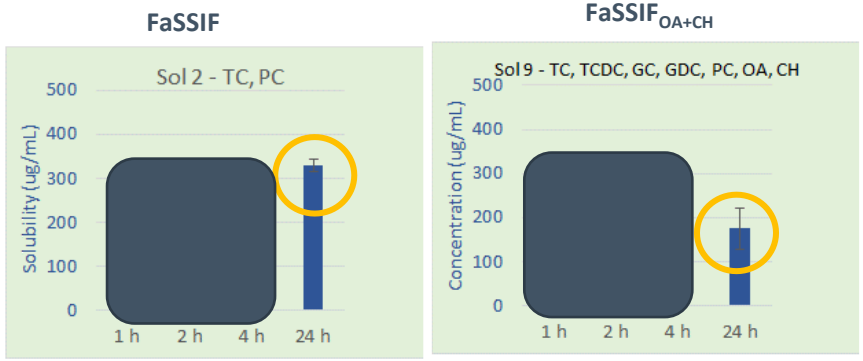
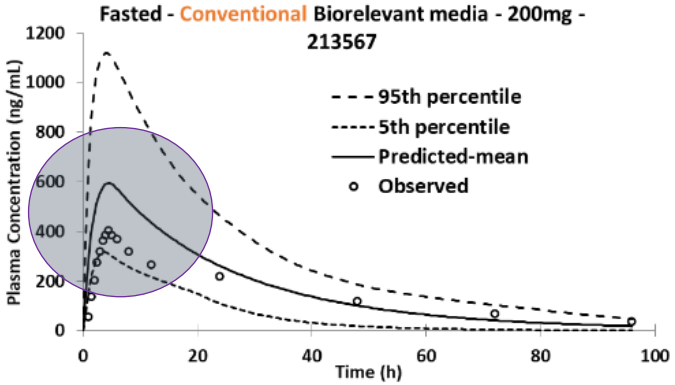
PBBM strategy - Log$K_{M:W}$ estimation and media composition

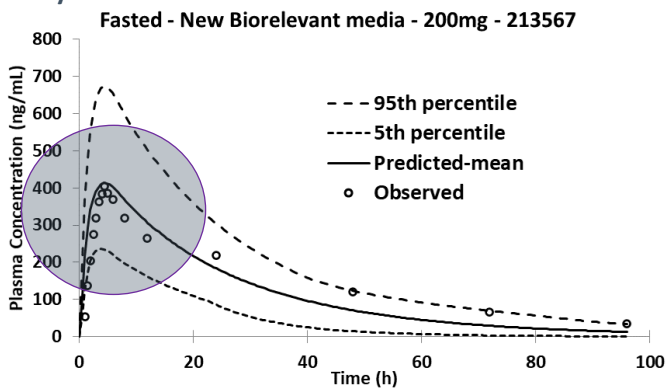


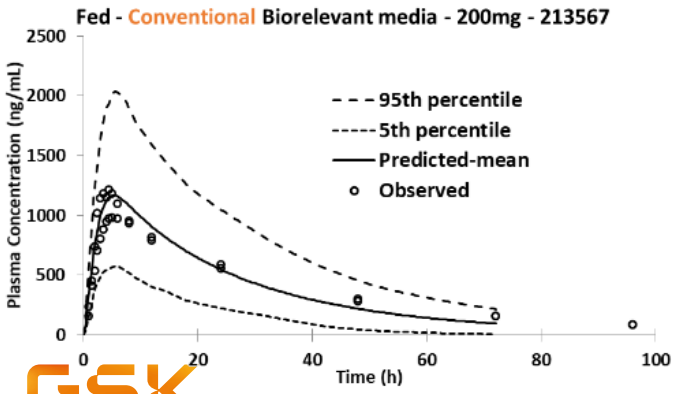
SIVA →

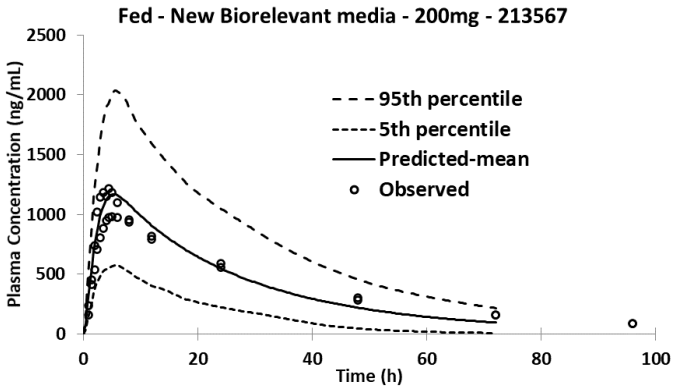
SIVA v4	Log$K_{M:W}$	Media set	Solubility (mg/mL)		
			Observed	Predicted	Pred/Obs
Neutral	1.05 × 10−6	FaSSIF$_{@pH6.5}$, FeSSIF$_{@pH4.8}$	0.36	0.65	1.81
Ion	**5.149**		1.94	1.84	0.95
Neutral	0.019	FaSSIF$_{+CH+OA@pH6.5}$, FeSSIF$_{+CH+OA@pH4.8}$	0.17	0.2	1.18
Ion	**4.559**		0.52	0.51	0.98

Food effect study









Limiting factor for absorption in vivo

Fasted →Solubility-limited
Media used to estimate total solubility affect model's predictions

Fed →permeability-limited
LogKm:w estimated using either set of media is high enough to hit the upper limit of absorption which is permeability

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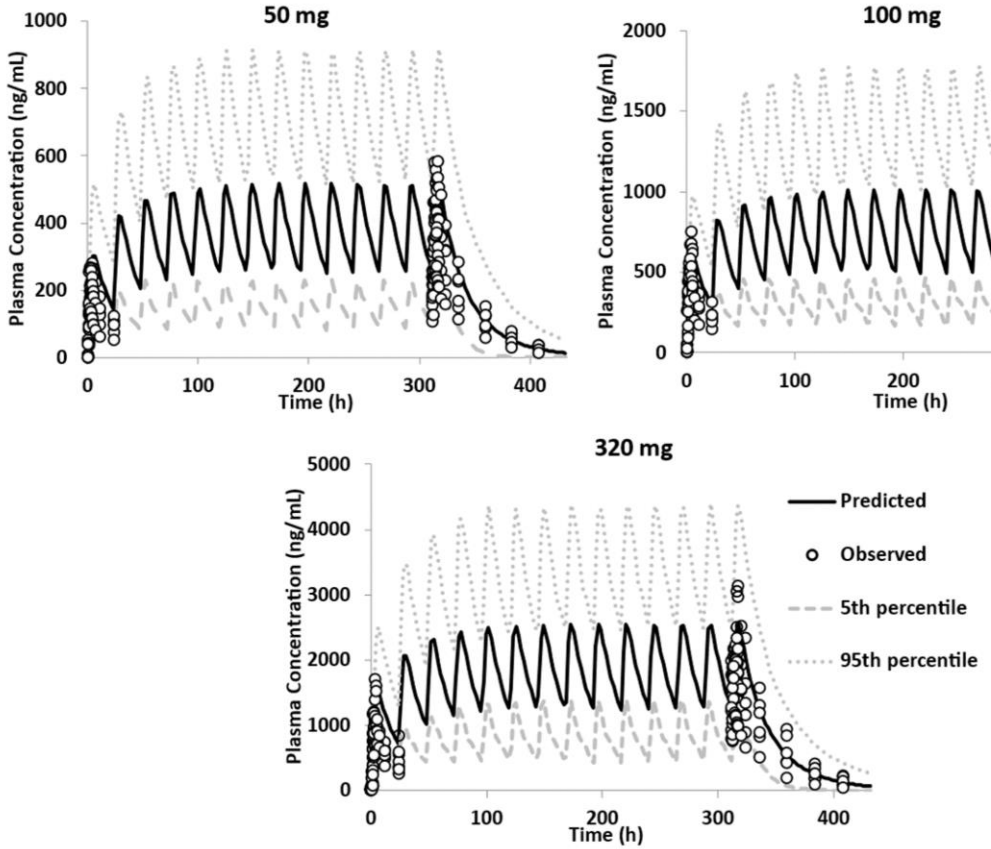
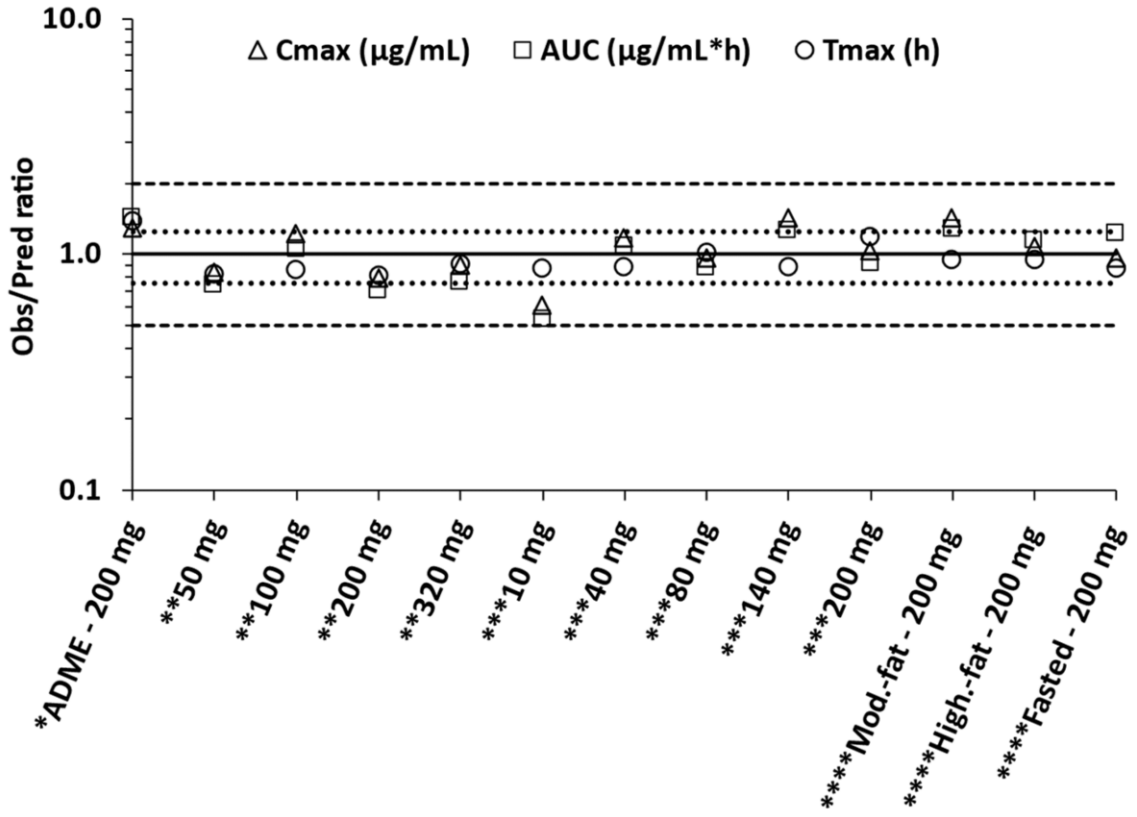
PBBM strategy - performance verification

FTIH MAD–50, 100 and 320 mg—tablet—single dose daily after a moderate- fat meal (clinical study Joshi et al. 2020)



Observed versus predicted ratio of pharmacokinetic parameters of GSK254



* Wen et al. 2022, ** Joshi et al. 2020, *** Spinner et al. 2022, **** Johnson et al. 2022.

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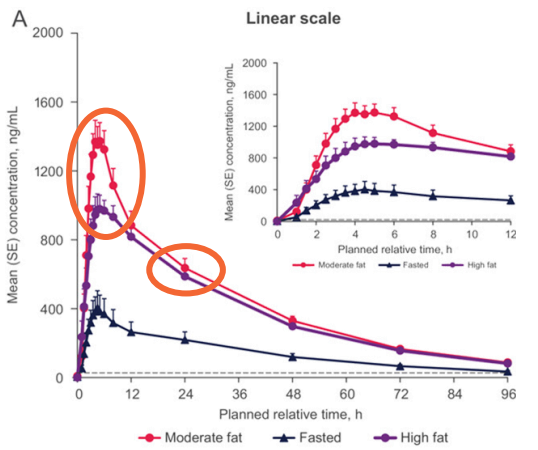
Application of PBBM to define clinically relevant dissolution safe space



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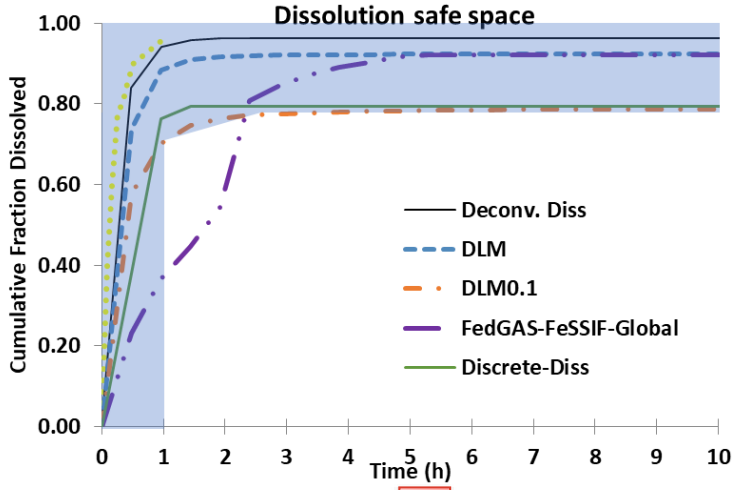
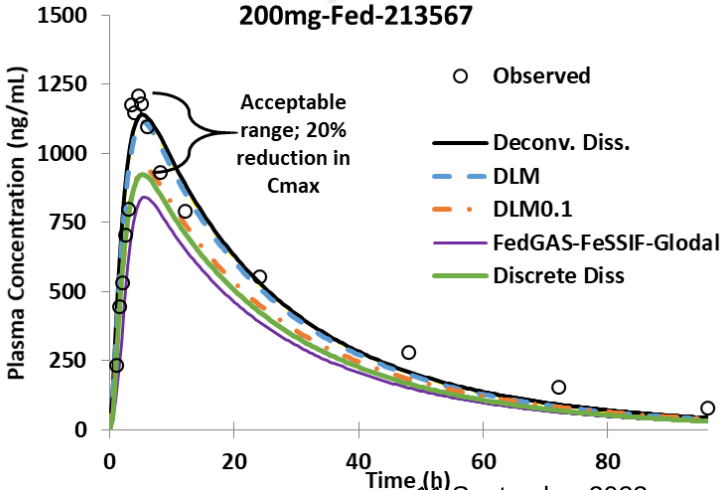
- Criteria: 20-24% ↕ Cmax is not clinically relevant with respect to the efficacy of GSK254 determined by C24h

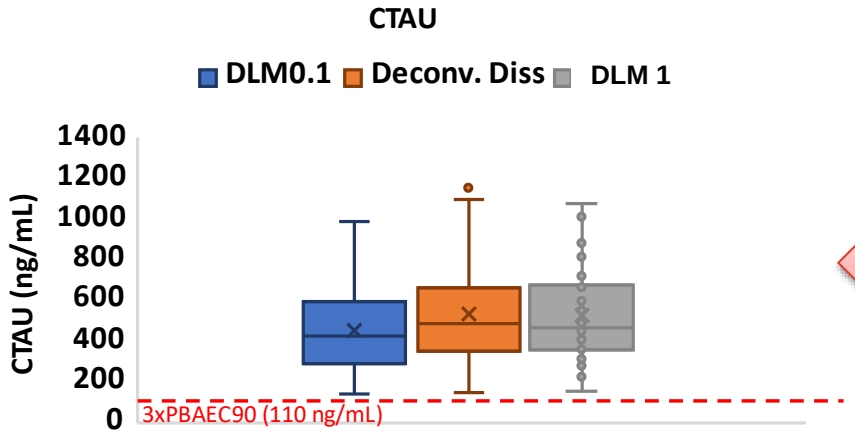


20% ↓ in max API dissolved

→ $Cmax_{avg}$ 20%↓

→ $CTAU_{avg}$ 11% ↓

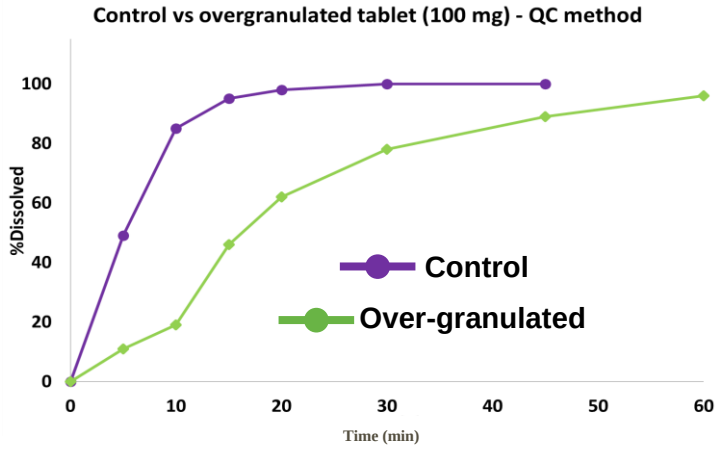


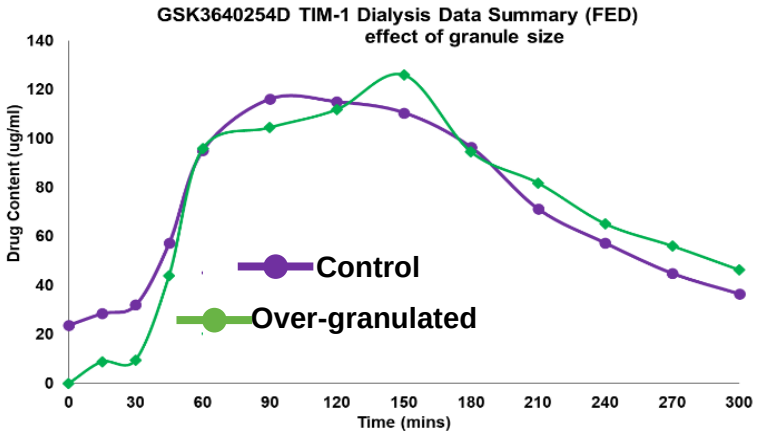


Target through concentration 3xPBAEC90 (110 ng/mL) – Spinner et al 2020 doi: 10.1093/cid/ciab1065

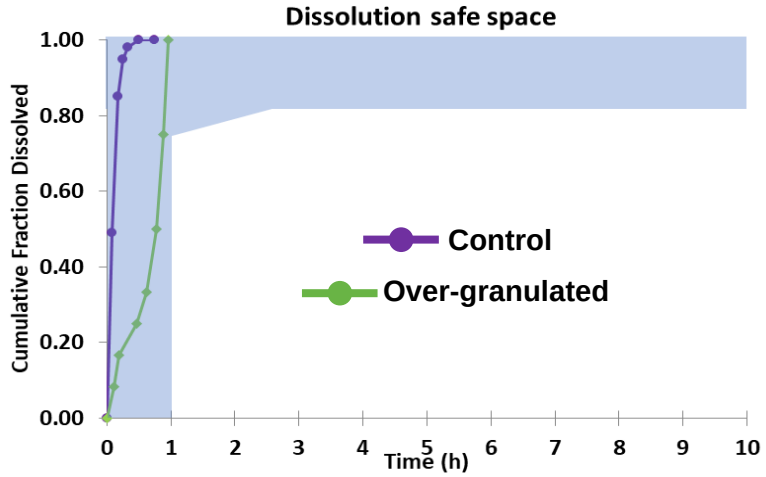
Test the hypothesis using stretched batches, PBBM and TIM-1

Control vs over-granulated dosage form





Note: Overgranulated batch had twice the granule size of the control batch



- Diss method showed significant differences in the dissolution profile (over-discriminating with respect to performance in vivo) between control and over-granulated dosage form
- TIM-1 showed no significant difference in the bio-accessibility of the drug between the two dosage forms
- Both dissolution profiles lying within the clinically relevant dissolution safe space suggested by the PBBM

Conclusion – final remarks

- A PBBM model was successfully developed and applied to predict the food effect of a BCS IV zwitterionic drug with complex interactions with mixed micelles. Predicted data were within a two-fold error with 70% being within 1.25-fold.

- In vitro data alongside PBBM modelling suggested that the positive food effect observed in the clinical studies was attributed to micelle-mediated enhanced solubility and permeability.

- This work showed that the predictive power of PBBM is improved when the understanding of the food effect goes beyond the typical approach (e.g., simply use of the typical FaSSIF and FeSSIF media) as well as when high quality in vitro data is integrated.

- The PBBM was applied to define clinically relevant dissolution safe space using criteria relevant to the target efficacious concentration of the drug (C24h).

- The PBBM suggested that ≥70% of the drug should be dissolved within 1 h to ensure no impact on the efficacy of the drug

- The developed model strategy can be effectively adopted to increase the confidence of using PBBM models to predict the food effect and define clinically relevant dissolution safe space clinically relevant dissolution safe space of BCS class IV drugs.

Acknowledgements

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