

A complex network diagram on the left side of the slide. It consists of numerous nodes of varying sizes and colors (black, grey, yellow, red) connected by thin black lines. A prominent feature is a dense, blue, funnel-shaped structure that narrows from left to right, with many lines converging towards a central point. This structure appears to be a visualization of a specific network or data flow.

BO Session I

Safe space in Healthy volunteers (HV) vs Patients

FDA / M-CERSI Workshop (30th Aug 2023)

Siri Kalyan Chirumamilla

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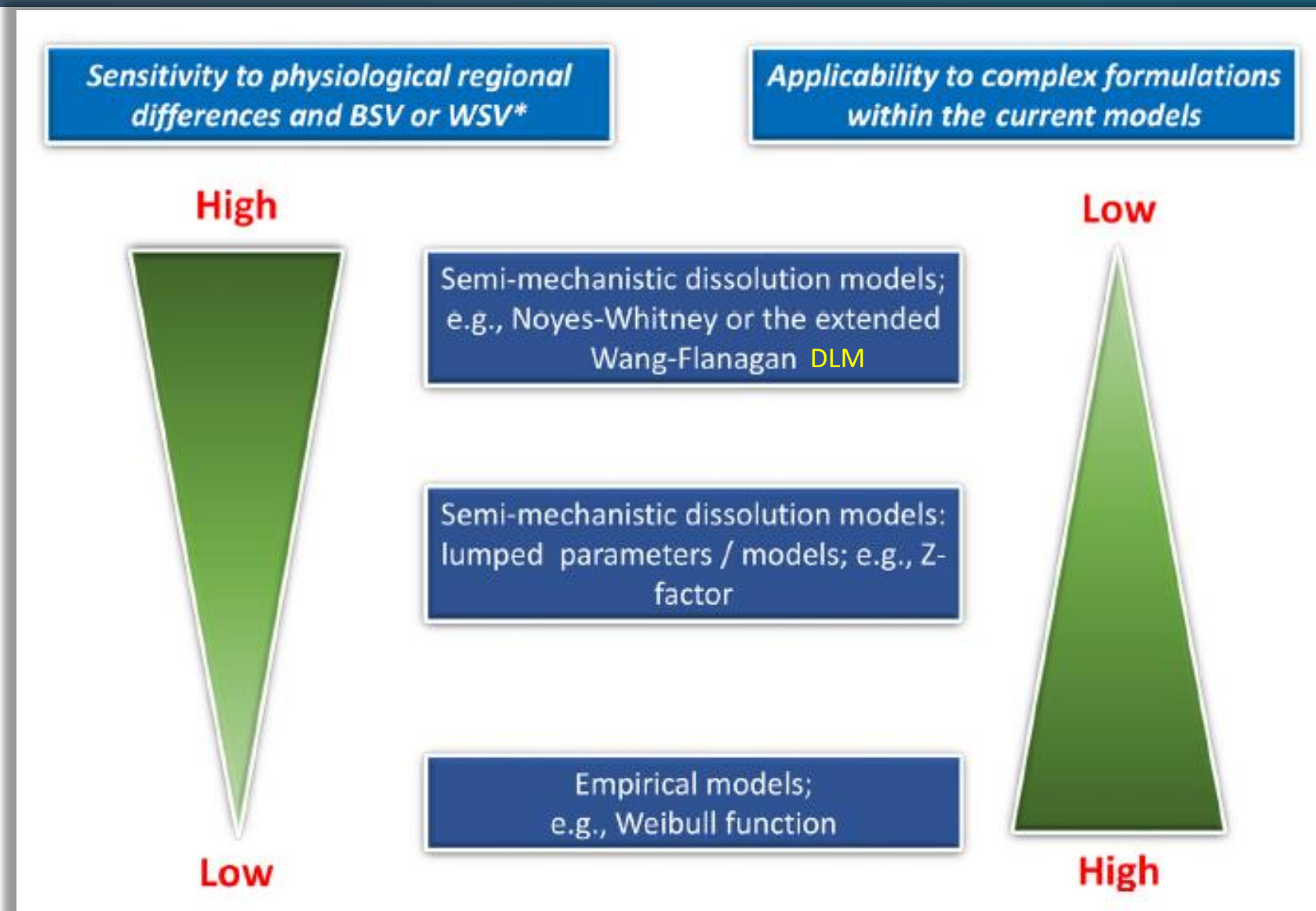
Empirical vs. (semi-)mechanistic modelling

Elevated gastric pH:

Cancer patients
Japanese elderly (Achlorhydria)
Co-medications

Mechanistic models should be used to make the model sensitive to change in physiological parameters

BSV = Between Subject Variability
WSV = Within Subject Variability



(Jamei et al., 2020)

Case 1: Salts

BMS developed Salt form to overcome the poor performance of free form when dosed with ARA.
Preclinical dog PK study showed higher Fa of salt form compared to free form in presence of ARA.

BCS Class II BMS Diprotic Base
Free form has a significant reduction in fa in the presence of ARAs



In-vitro Salt screening



Sulphate Salt



Preclinical: Salt performs better than Free form with ARA

Gesenberg et al. (2019) *Pharm Res* 36:164.



Article

Mechanistic PBPK Modelling to Predict the Advantage of the Salt Form of a Drug When Dosed with Acid Reducing Agents

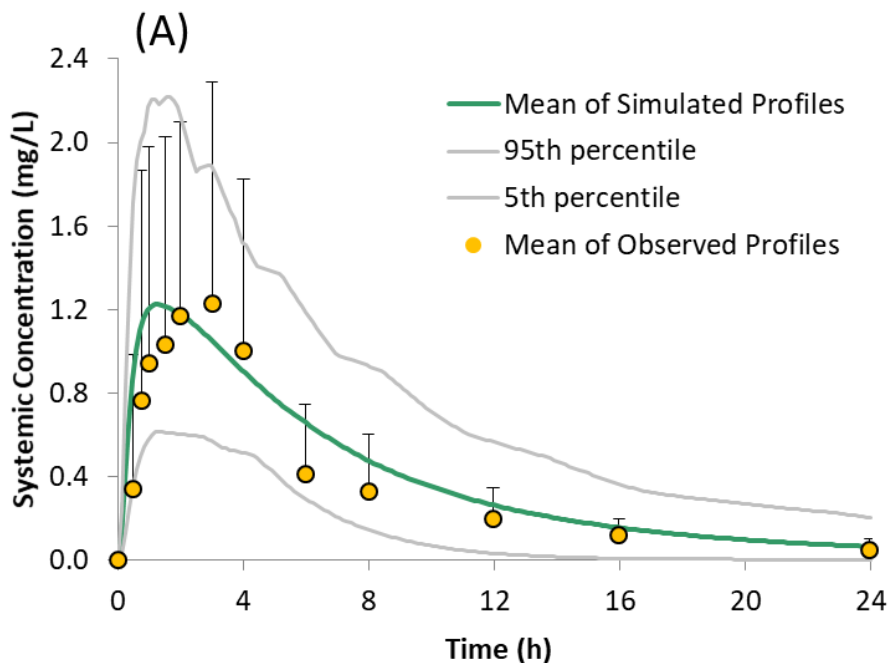
Siri Kalyan Chirumamilla *¹, Venkatesh Teja Banala ², Masoud Jamei ³ and David B. Turner



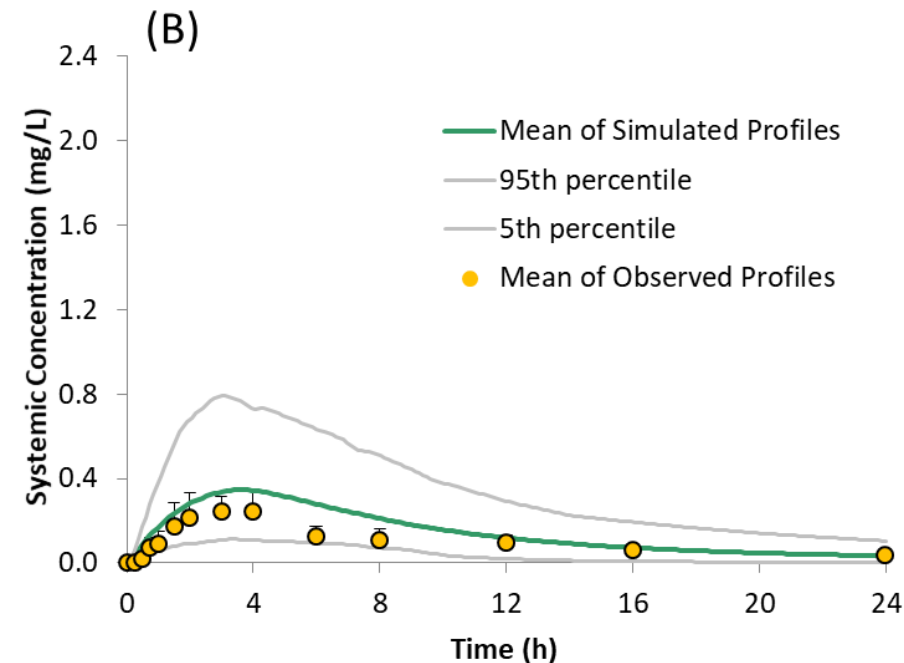
Simcyp Simulator was used to develop model for Free form by using the PK data without ARA, then verified the model by predicting PK with ARA

Free Form in Human HVs

Without Famotidine



With Famotidine



Clinical data: Gesenberg et al. (2019) *Pharm Res* 36:164.

Modelling Salt Form

The free form model was extended to predict Salt form PK by using the Ksp Salt model, Mechanistic surface pH and Two Solid States Model of the Simulator. The developed model predicted higher Fa for Salt form compared to free form in presence of ARA, similar to what was observed in dog PK study.

Solubility Product (K_{sp}) Model

Counterion 1 Counterion 2

Drug Salt Solubility at pHmax (mg/mL)

K_{sp}

Counterion Type*

Counterion

Concentration of counterion in drink (mg/mL)

Endogenous Ion?

View/Modify/Define Baseline Ion Concentrations

Drug:Counterion Stoichiometry

1:1 2:1

Physico-Chemical Properties

Molecular Weight (g/mol)***

Intrinsic Solubility (mg/mL)

pKa1

pKa2

Particle Surface Solubility

Use bulk fluid solubility

User-defined Surface Solubility

	Global	Stomach	Duodenum	Jejunum I	Jejunum II	Ileum I	Ileum II	Ileum III	Ileum IV	Colon
Solubility (mg/mL)	<input type="text" value="0.05"/>	<input type="text" value="0.05"/>	<input type="text" value="0.05"/>	<input type="text" value="0.05"/>	<input type="text" value="0.05"/>	<input type="text" value="0.05"/>	<input type="text" value="0.05"/>	<input type="text" value="0.05"/>	<input type="text" value="0.05"/>	<input type="text" value="0.05"/>

Surface pH

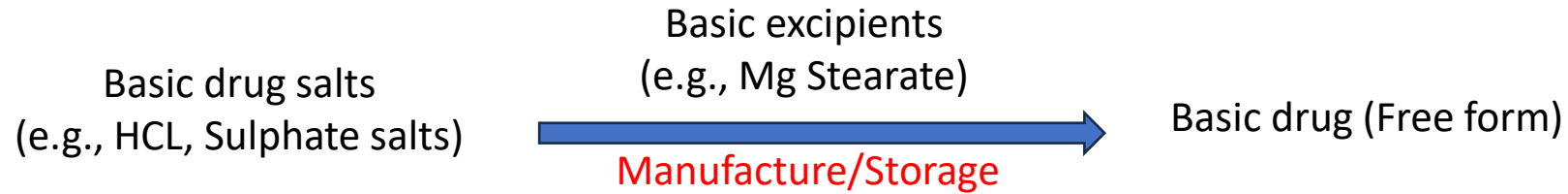
Mechanistic Model

User-defined

	Global	Stomach	Duodenum	Jejunum I	Jejunum II	Ileum I	Ileum II	Ileum III	Ileum IV	Colon
Surface pH	<input type="text" value="5.5"/>	<input type="text" value="5.5"/>	<input type="text" value="5.5"/>	<input type="text" value="5.5"/>	<input type="text" value="5.5"/>	<input type="text" value="5.5"/>	<input type="text" value="5.5"/>	<input type="text" value="5.5"/>	<input type="text" value="5.5"/>	<input type="text" value="5.5"/>

VBE for risk assessment/safe space for salt disproportionation

Salts tend to disproportionate during manufacture or storage:



Simcyp VBE module and two solid state models can be used to generate safe space for salt disproportionation in dosage form:

Bioequivalence Trial Setup

Select BE Design: Crossover 2T2P2S: T1T2/T2T1 Number of Trial Replicates: 5

Reference Formulation setting:

Permeability Formulation

Formulation Type Transit Times Diffusion Layer Model Excipients Luminal Degradation

Model Two Solid States Fraction in Dose (%) Solid State 1 Salt Form Solid State 2 Free Form

100 0

Test Formulation setting:

Permeability Formulation

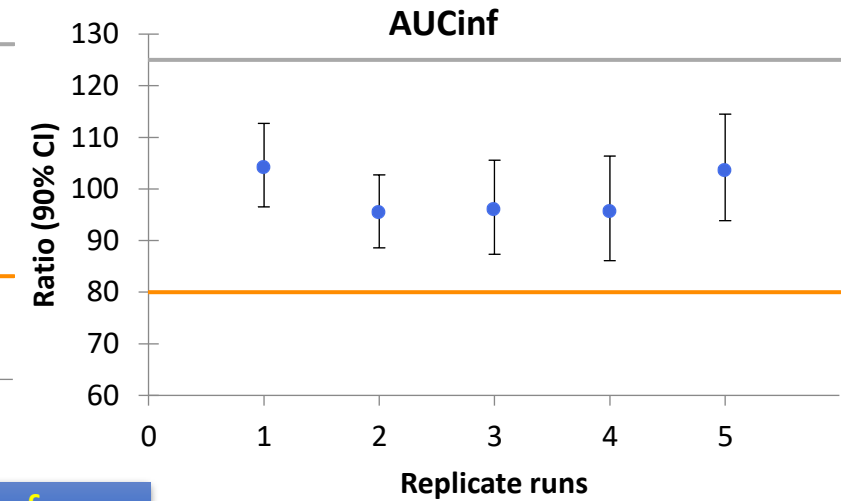
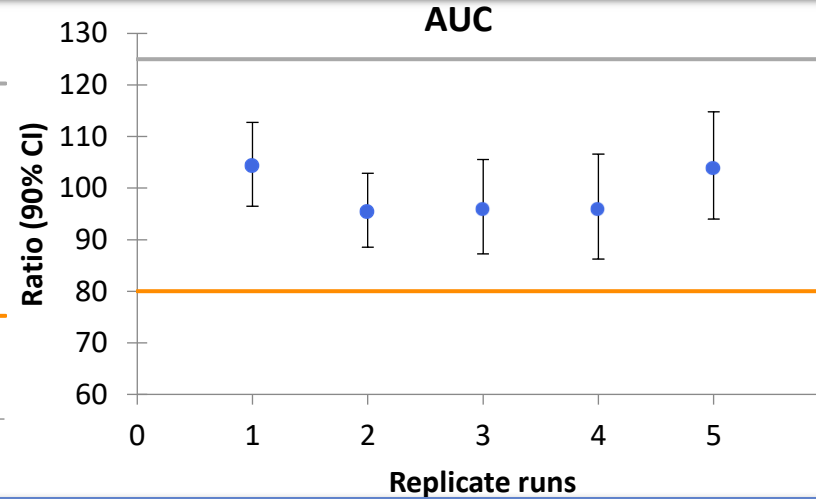
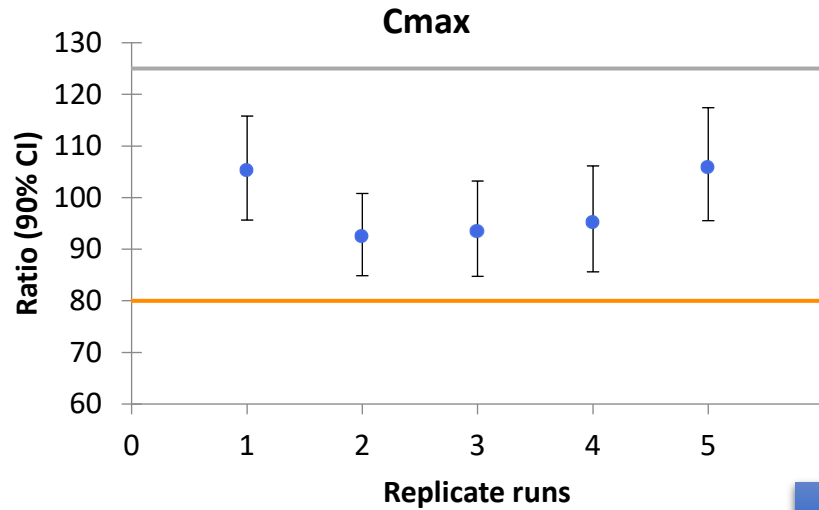
Formulation Type Transit Times Diffusion Layer Model Excipients Luminal Degradation

Model Two Solid States Fraction in Dose (%) Solid State 1 Salt Form Solid State 2 Free Form

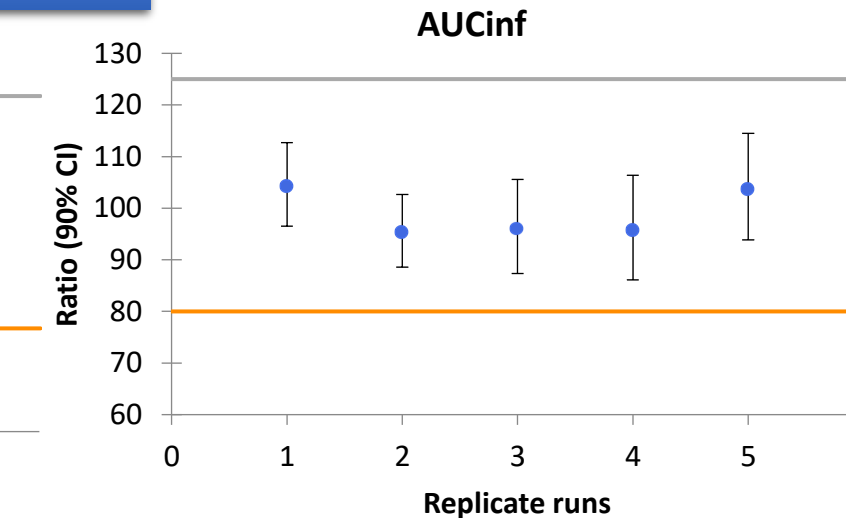
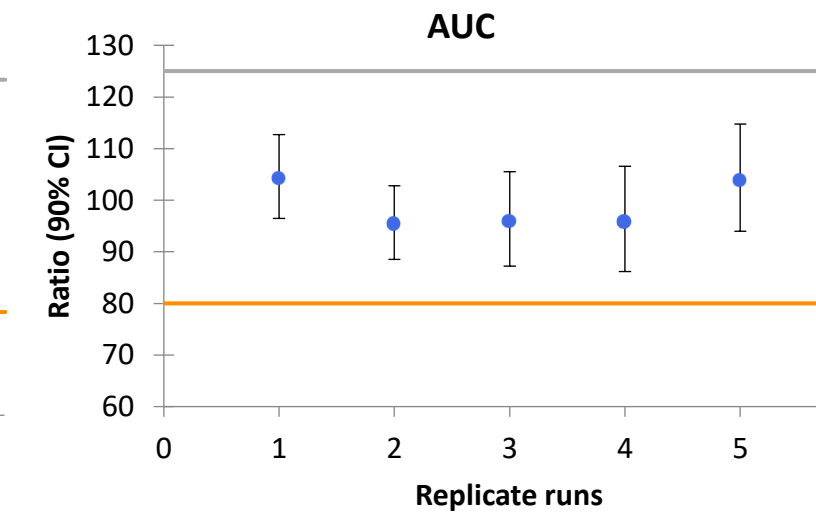
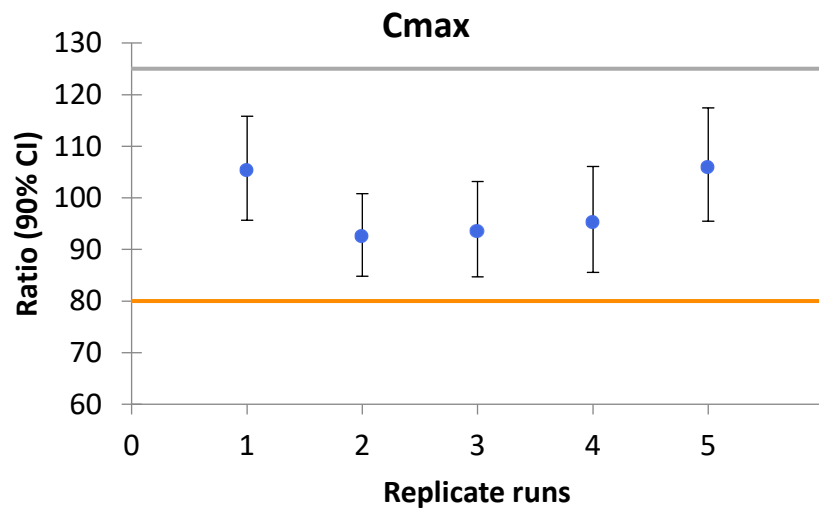
75 25

Safe space for salt disproportionation in HV (without ARA)

80% Salt and 20% Free form in the dosage form

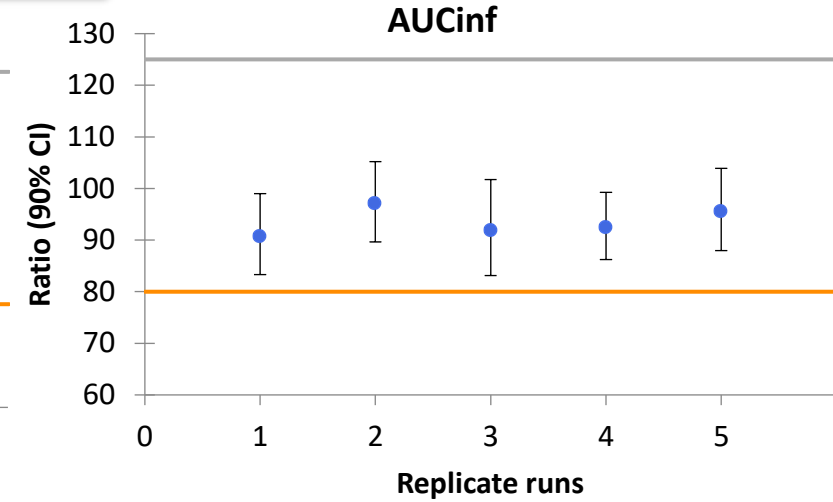
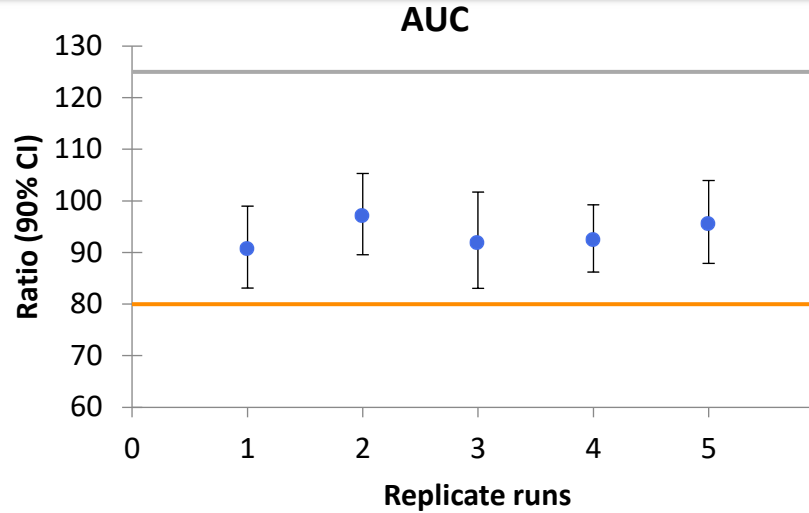
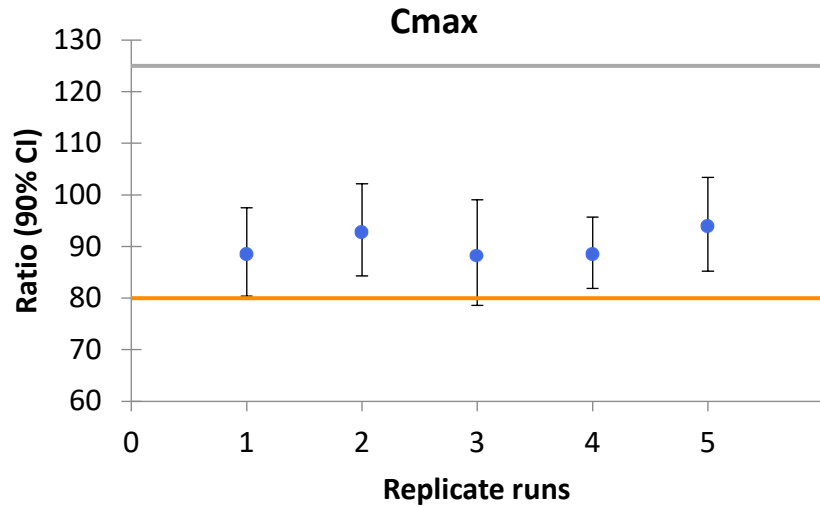


70% Salt and 30% Free form in the dosage form

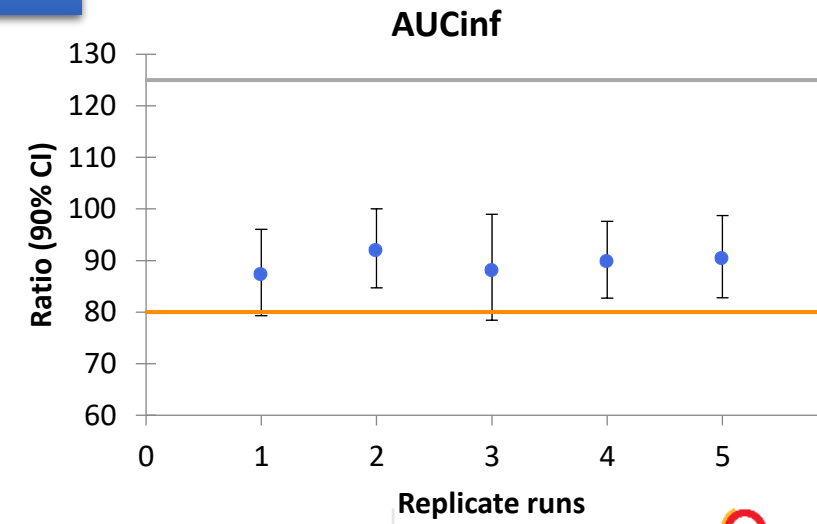
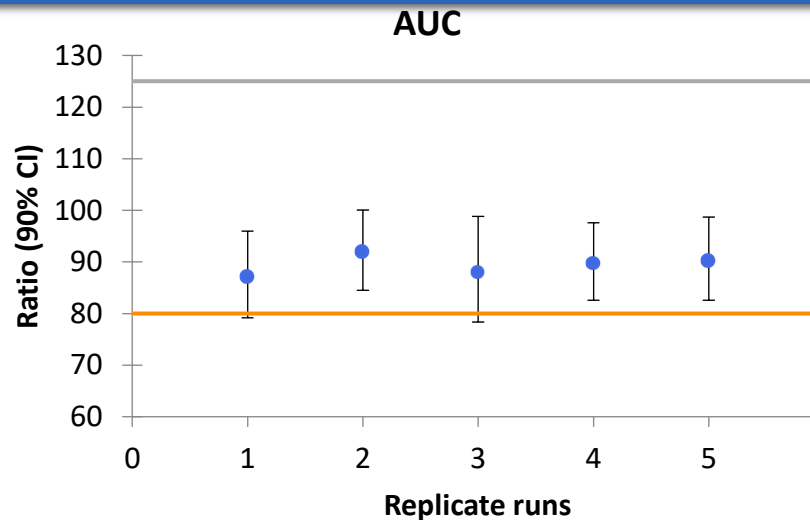
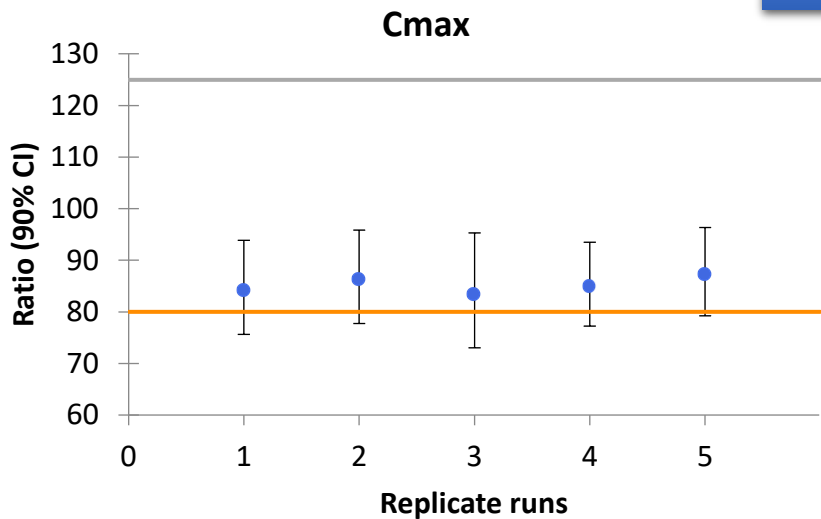


Safe space for salt disproportionation in Patients (with ARA)

80% Salt and 20% Free form in the dosage form

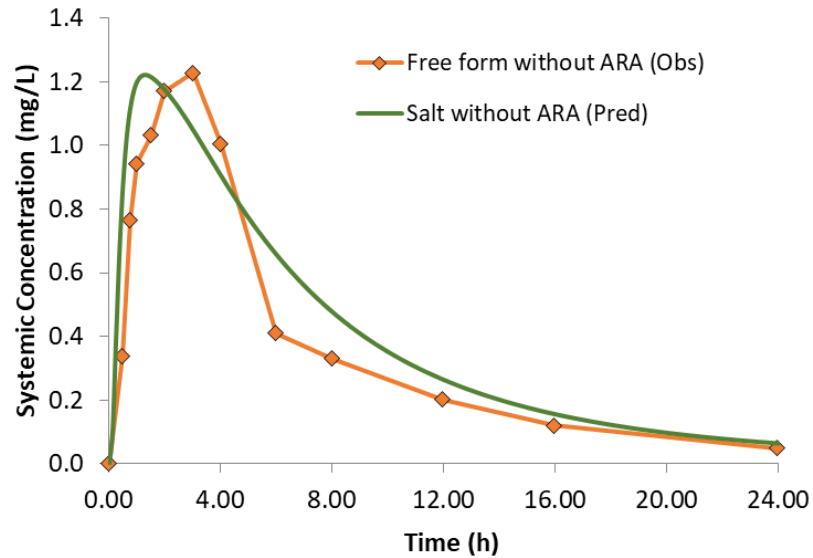


70% Salt and 30% Free form in the dosage form

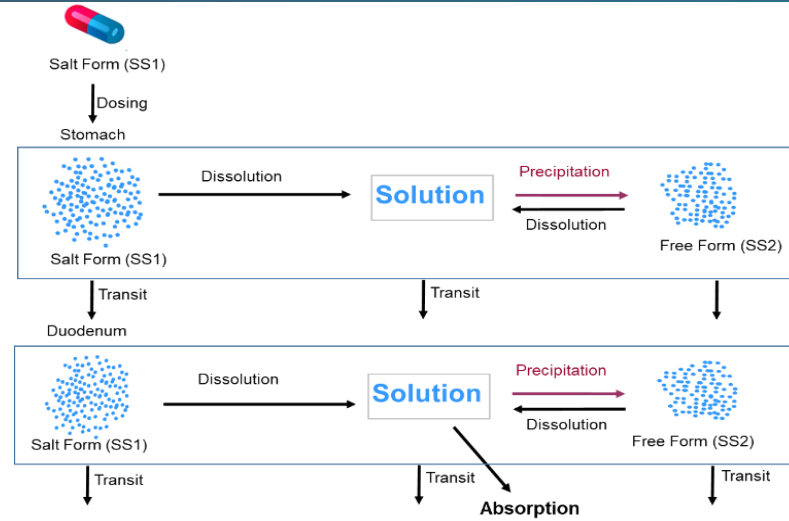
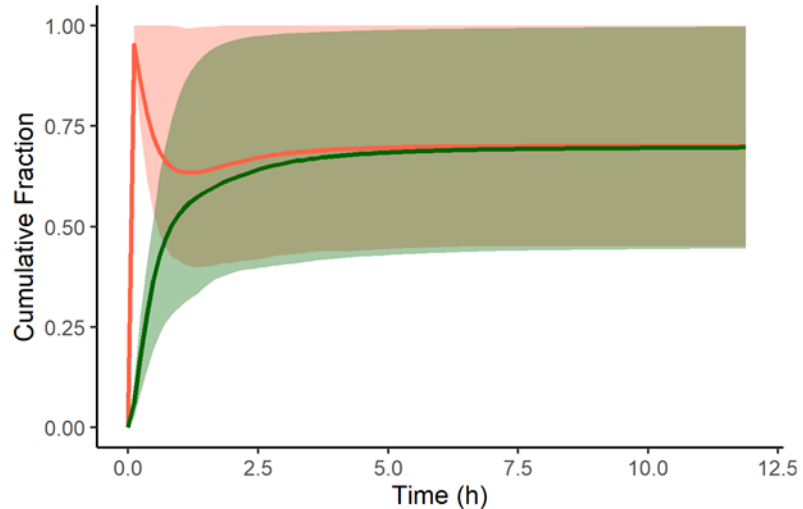


30% of free form in the dosage form fails BE in Patients (with ARA)

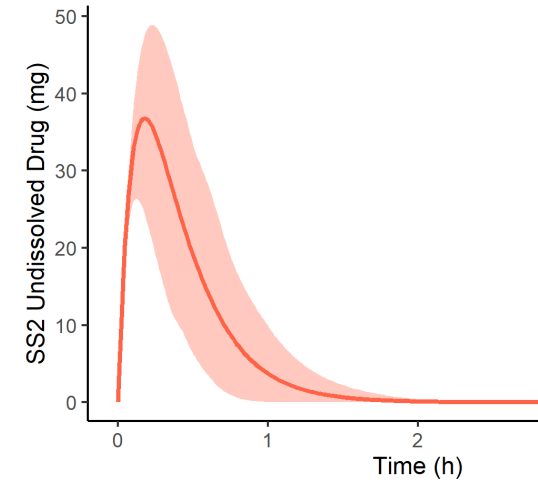
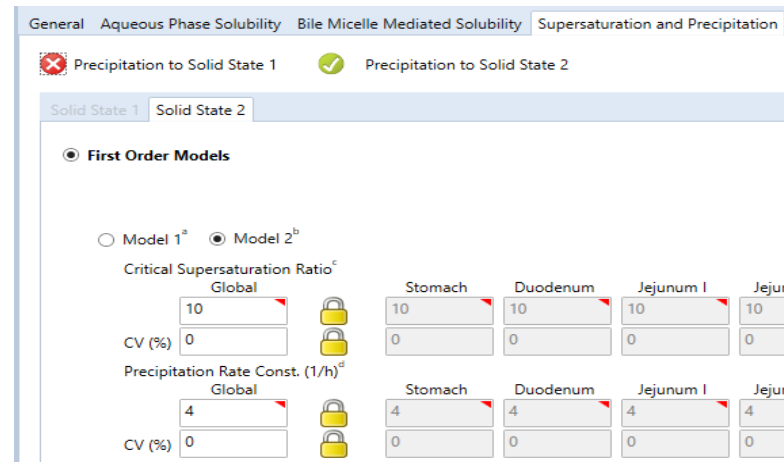
Reason for Wide Safe Space for Salt Disproportionation in HV (Without ARA)



In the absence of ARA, salt form and Free form have same PK.

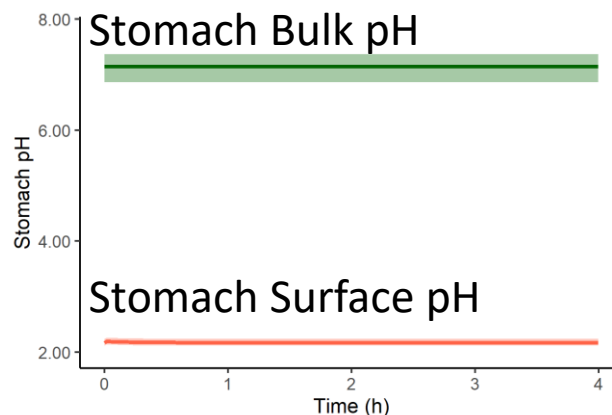
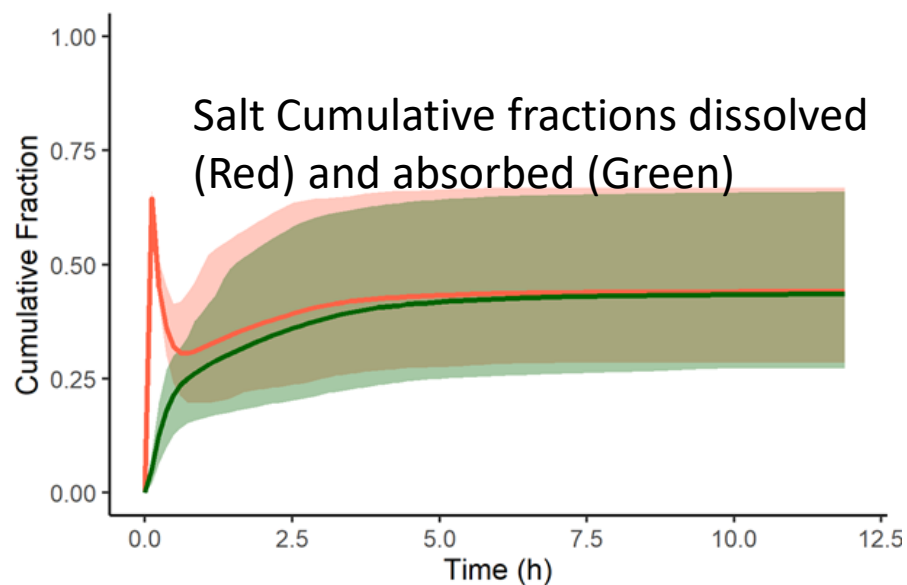
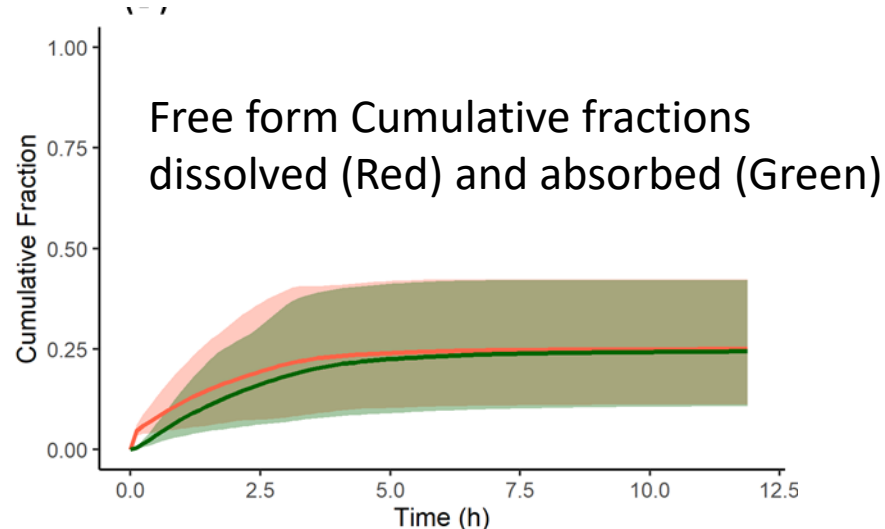
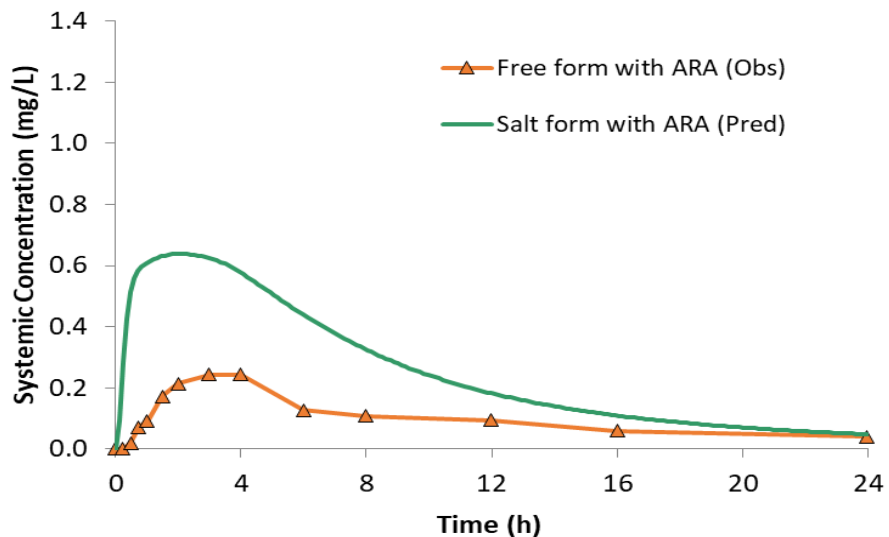


This is due to the precipitation of dissolved salt form as free form inside the GIT. Which is modelled using Two Solid State model of Simcyp



Precipitation of free form (SS2) of drug in stomach - will use free form surface pH and solubility

Reason for Narrow Safe Space for Salt Disproportionation in Patients (With ARA)



Salt form driving supersaturation in stomach, due to favorable surface pH leading to difference b/n salt and free form in presence of ARA. Salt has higher F_a than free form thereby being sensitive to disproportionation in presence of ARA (narrow safe space in patients)

Case 2, 3:

Virtual bioequivalence for achlorhydric subjects: The use of PBPK modelling to assess the formulation-dependent effect of achlorhydria

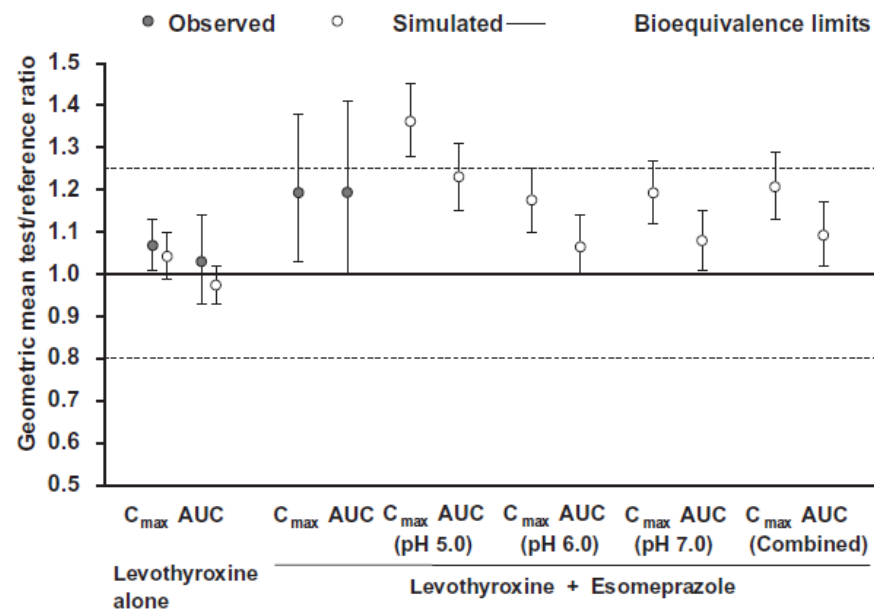
Kosuke Doki^{a,b,*}, Adam S. Darwich^a, Nikunj Kumar Patel^c, Amin Rostami-Hodjegan^{a,c}

^a Centre for Applied Pharmacokinetic Research, Division of Pharmacy & Optometry, University of Manchester, Manchester, UK

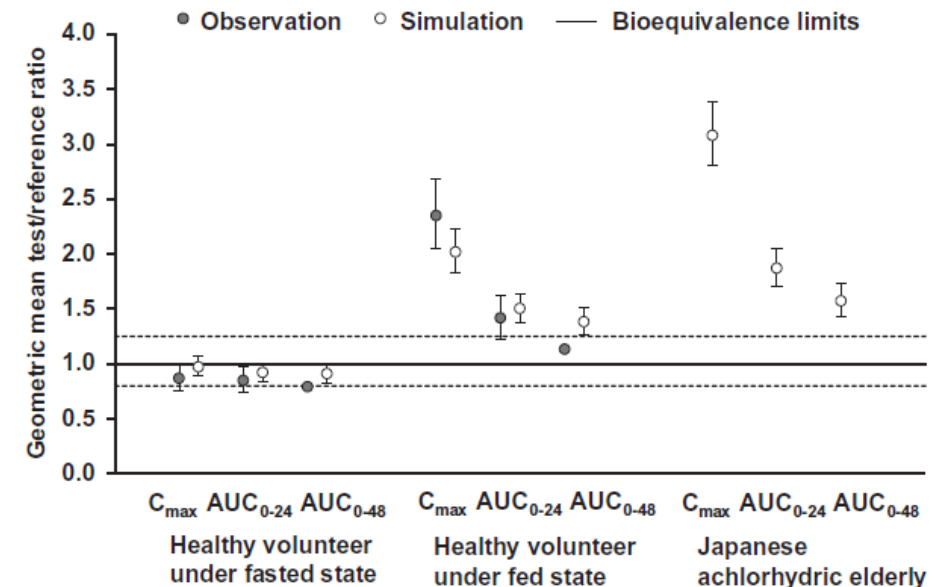
^b Department of Pharmaceutical Sciences, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

^c Simcyp Limited (A Certara Company), Sheffield, UK

EJPS: Nov 2017



Levothyroxine - pH dependent solubility



Nifedipine CR - pH dependent polymer

Similar to Case study I where Safespace is different between HV and Patients, the BE could also be different between healthy volunteers and patients as described in this article.

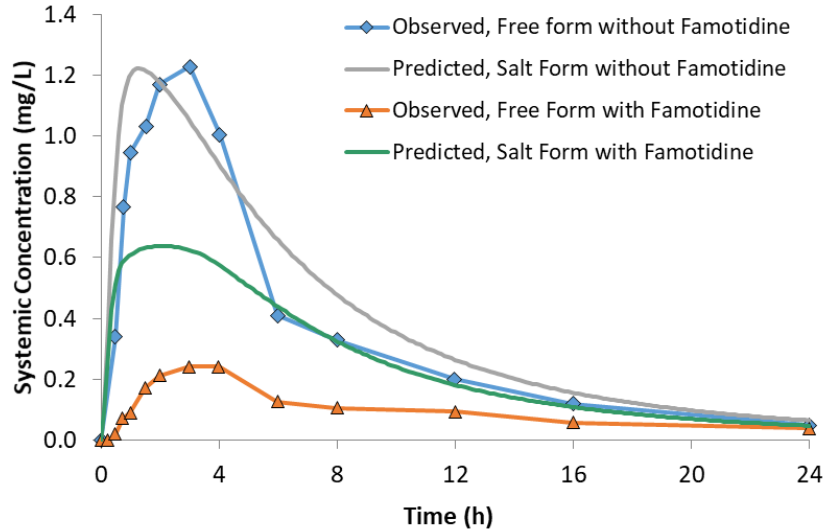
Conclusion

- Patient characteristics might influence the Safe space
- Mechanistic models can help understanding the effect of these perturbations

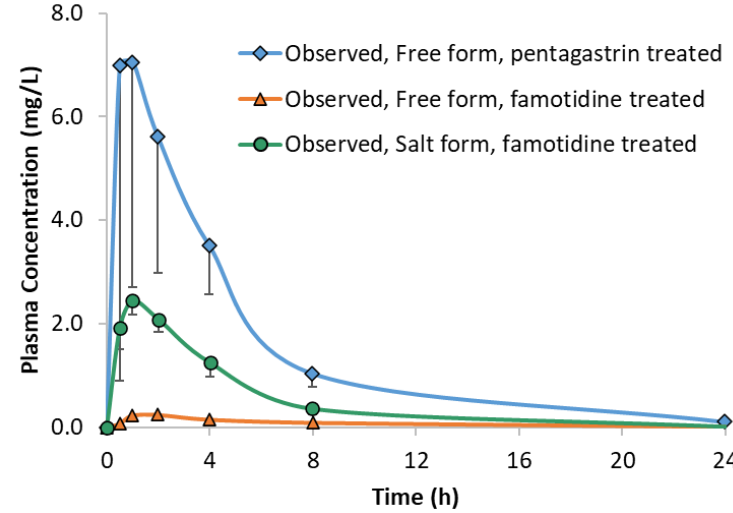
Back up

Simcyp Modelling Results – Salt Form

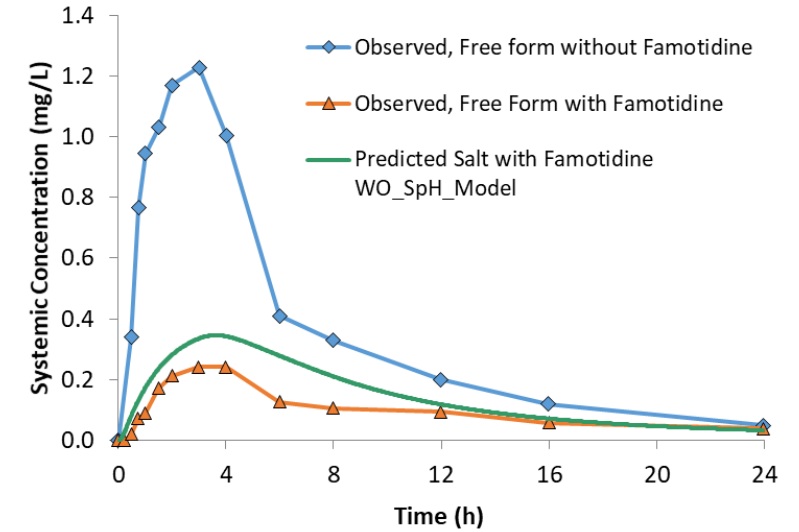
Humans with Surface pH model



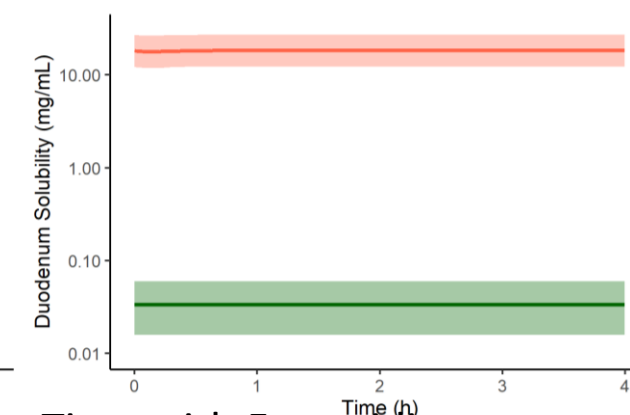
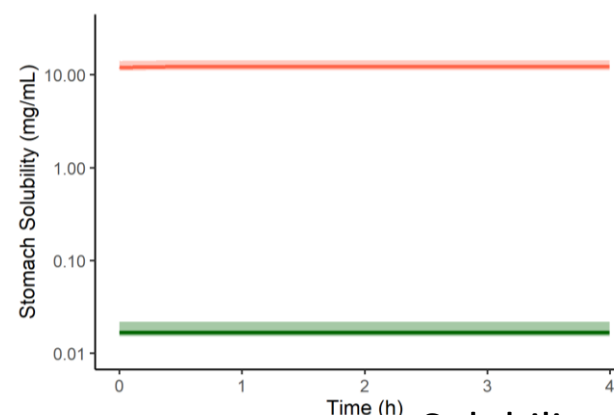
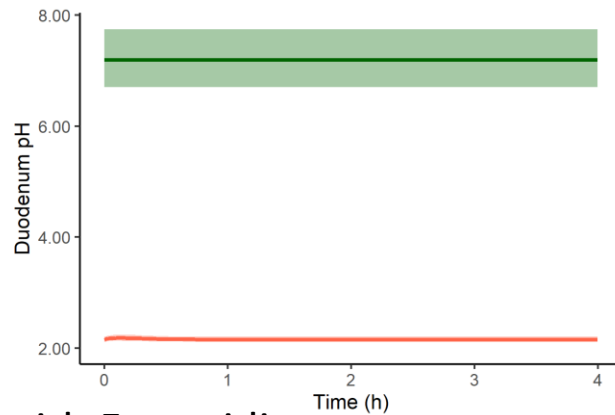
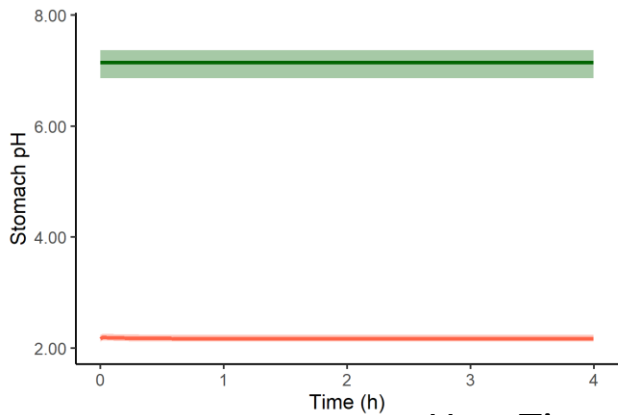
Beagle Dogs



Humans without Surface pH Model



Clinical data: Gesenberg et al. (2019) *Pharm Res* 36:164.



pH vs Time with Famotidine

Solubility vs Time with Famotidine

■ Bulk ■ Surface

Simcyp Simulator predicted similar advantage of salt form compared to free form in presence of ARA, which was observed in dog preclinical PK study.

