BO Session I
Safe space in Healthy volunteers (HV) vs Patients

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

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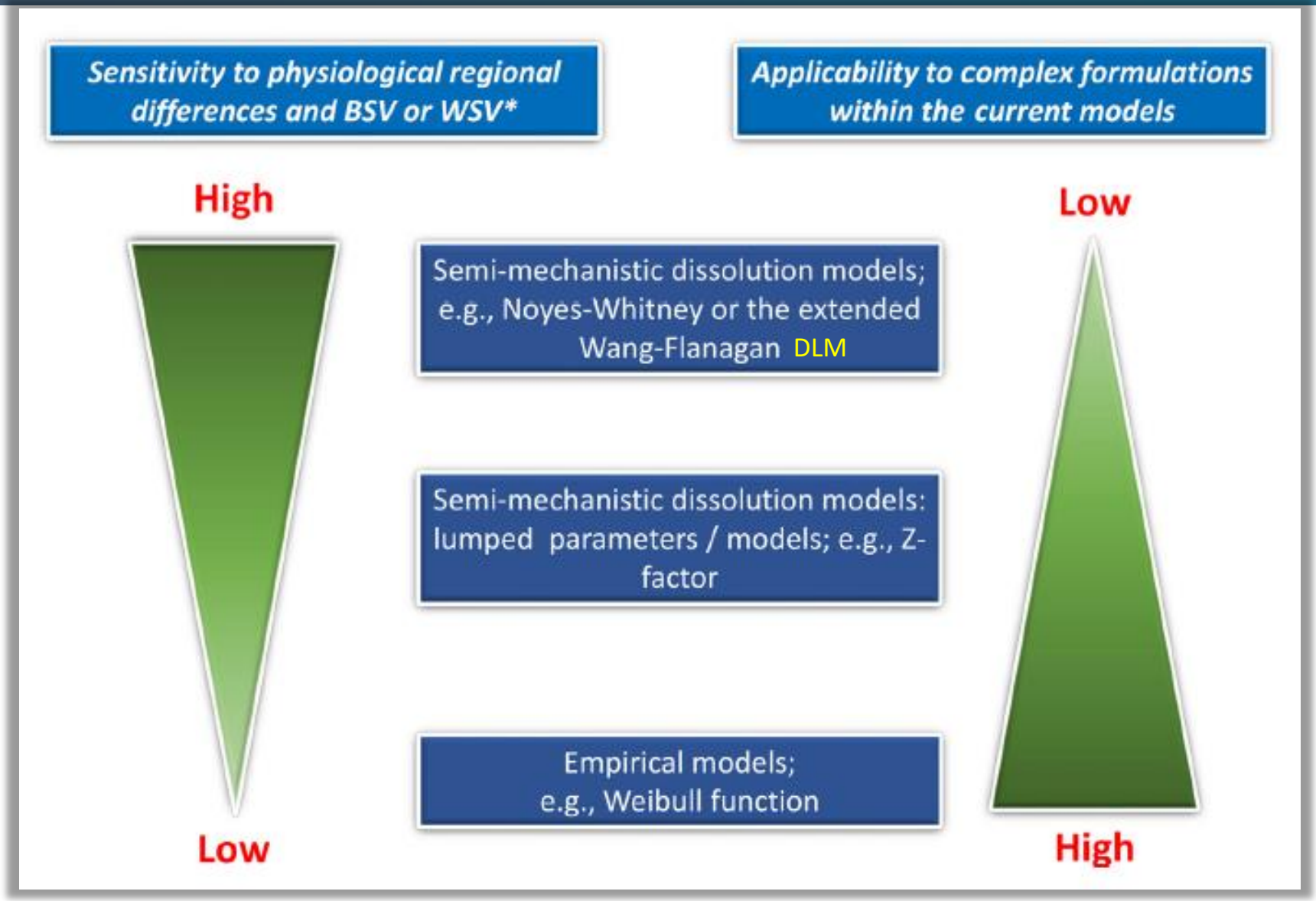
Empirical vs. (semi-)mechanistic modelling

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



(Jamei et al., 2020)

BSV = Between Subject Variability
WSV = Within Subject Variability

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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.

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pharmaceutics

MDPI

Article

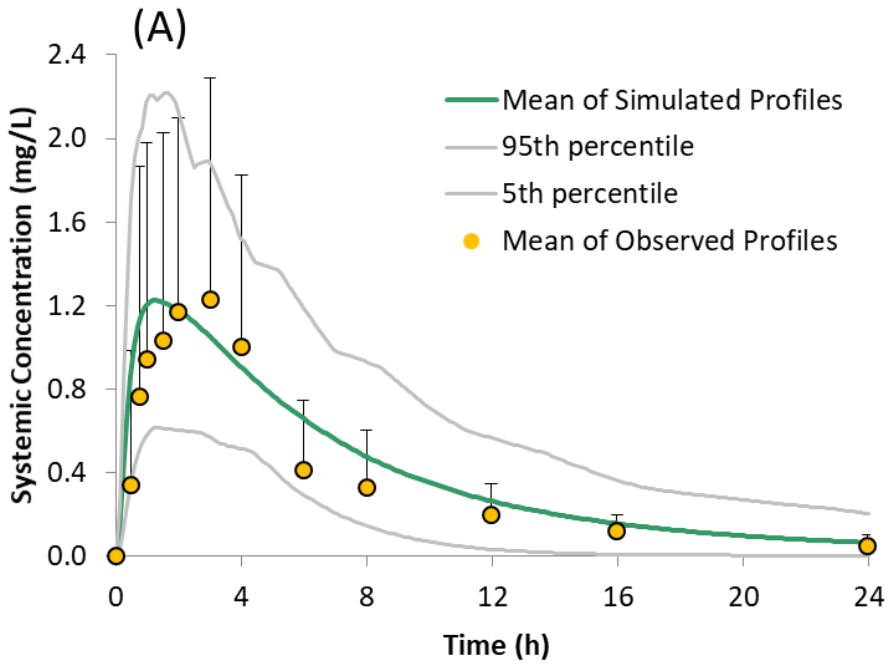
Mechanistic PBPK Modelling to Predict the Advantage of the Salt Form of a Drug When Dosed with Acid Reducing Agents

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

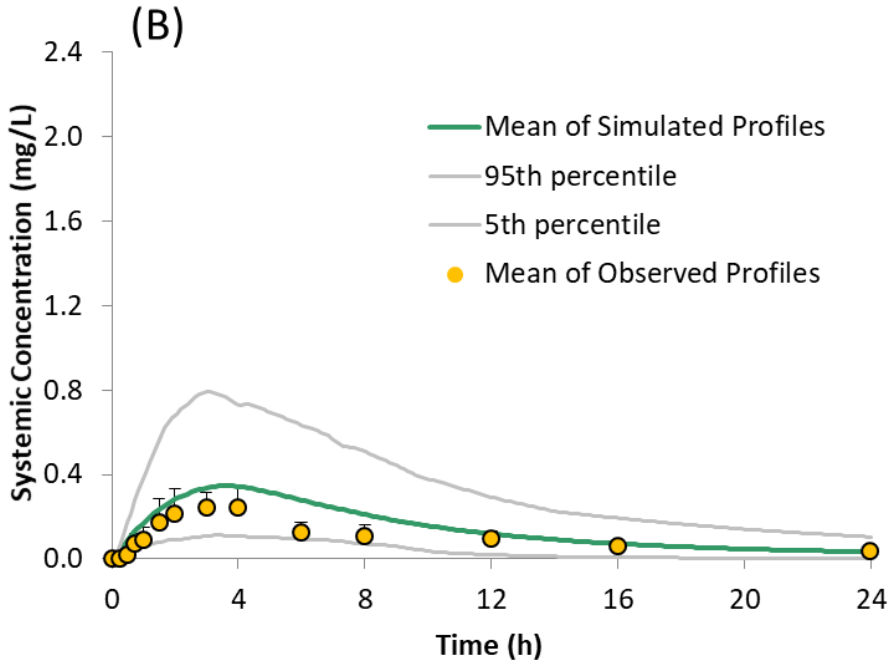
Free Form in Human HVs

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

Without Famotidine



With Famotidine



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

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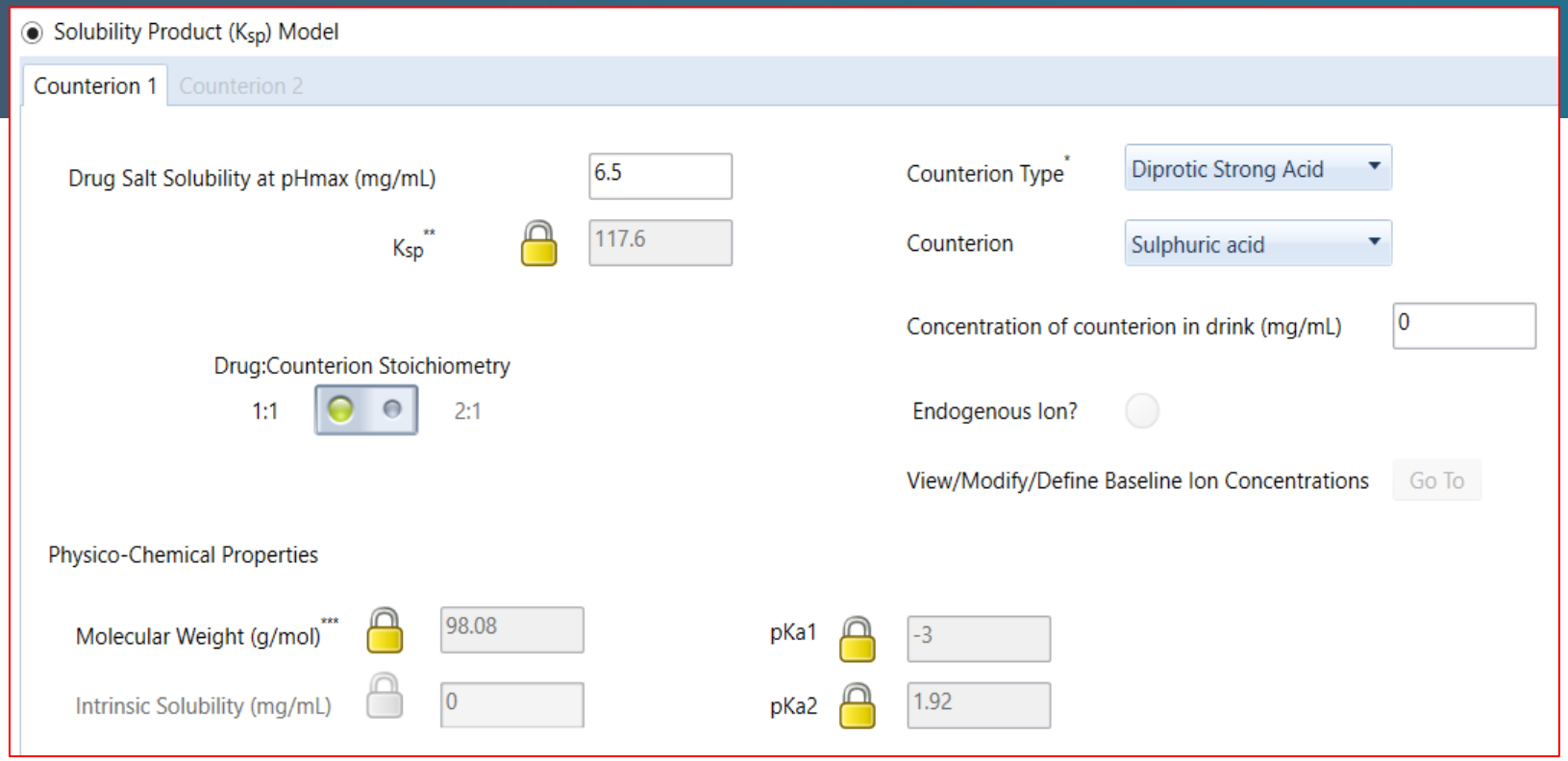
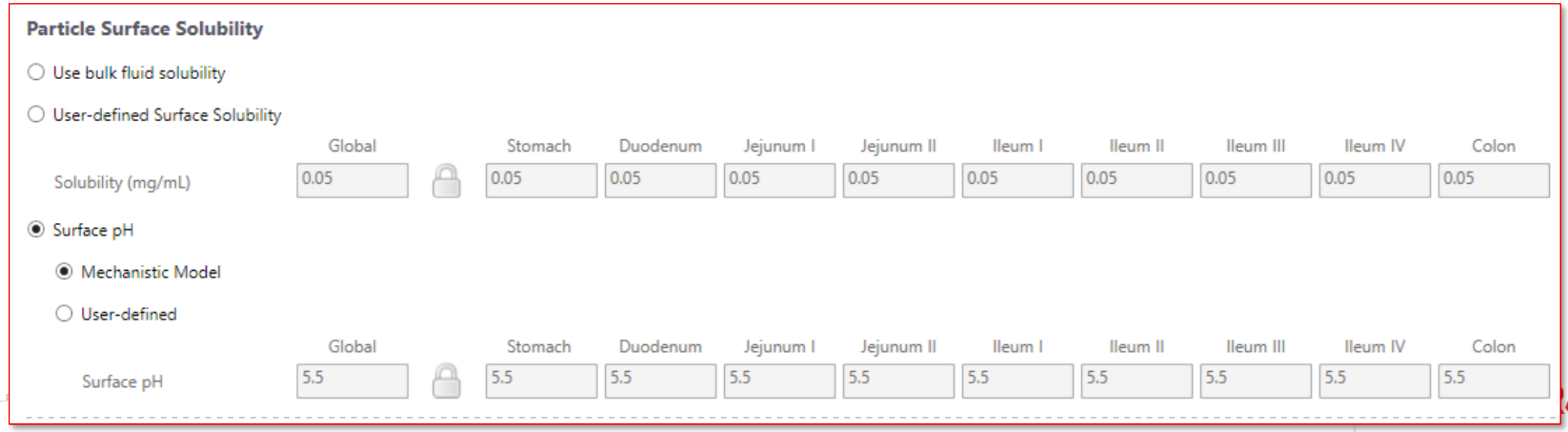
Modelling Salt Form

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.





VBE for risk assessment/safe space for salt disproportionation

Salts tend to disproportionate during manufacture or storage:

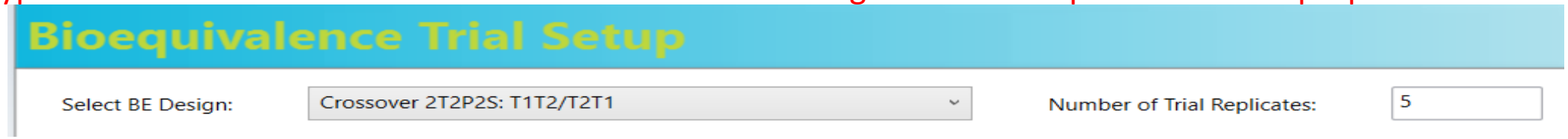
Basic drug salts
(e.g., HCL, Sulphate salts)

Basic excipients
(e.g., Mg Stearate)

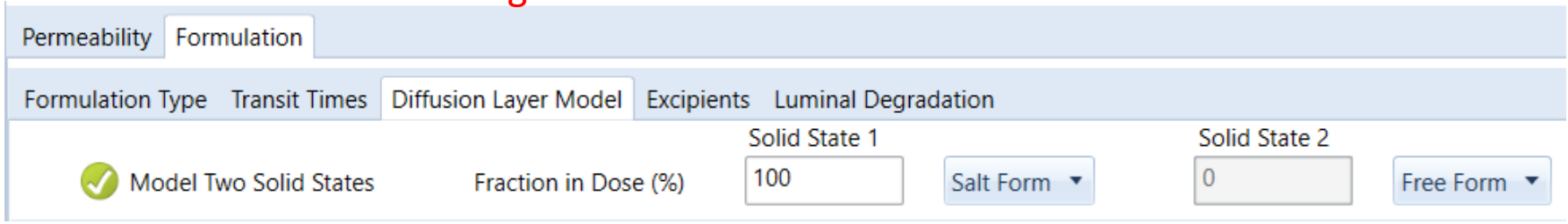
Manufacture/Storage

Basic drug (Free form)

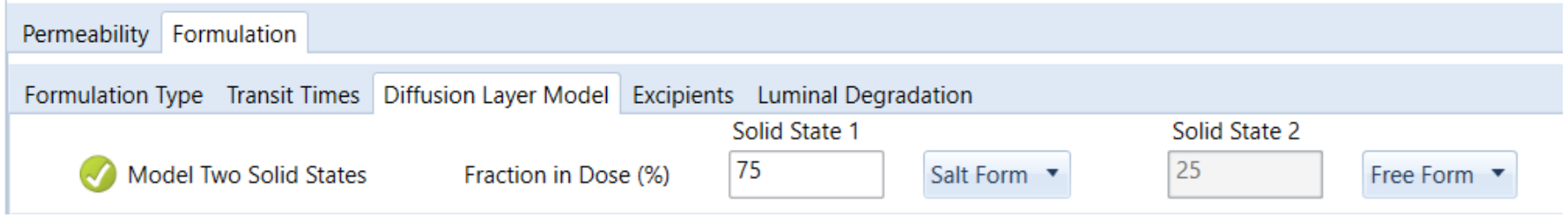
Simcyp VBE module and two solid state models can be used to generate safe space for salt disproportionation in dosage form:



Reference Formulation setting:



Test Formulation setting:



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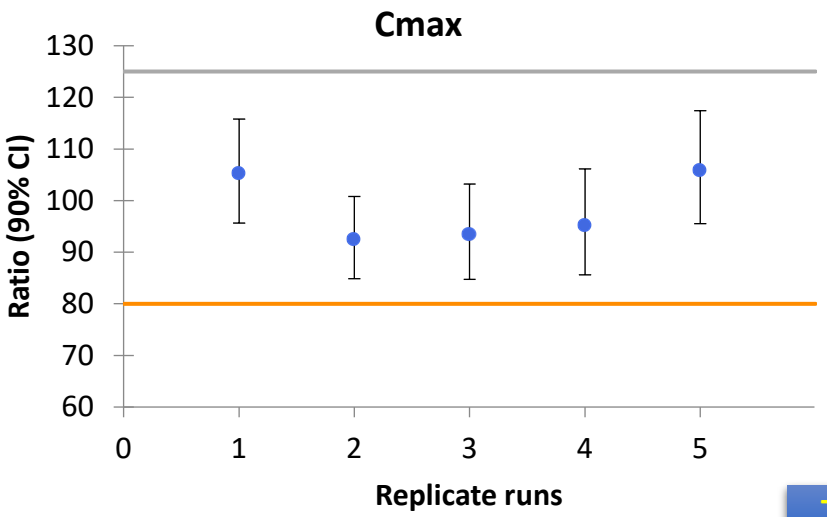
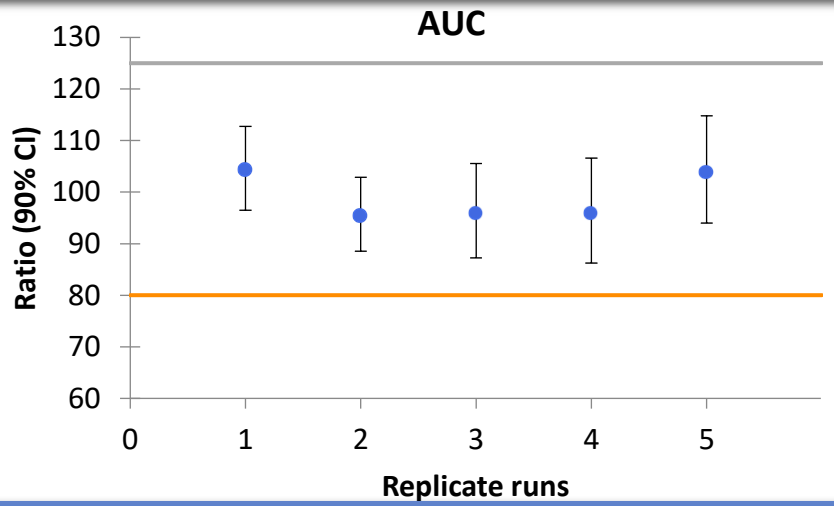
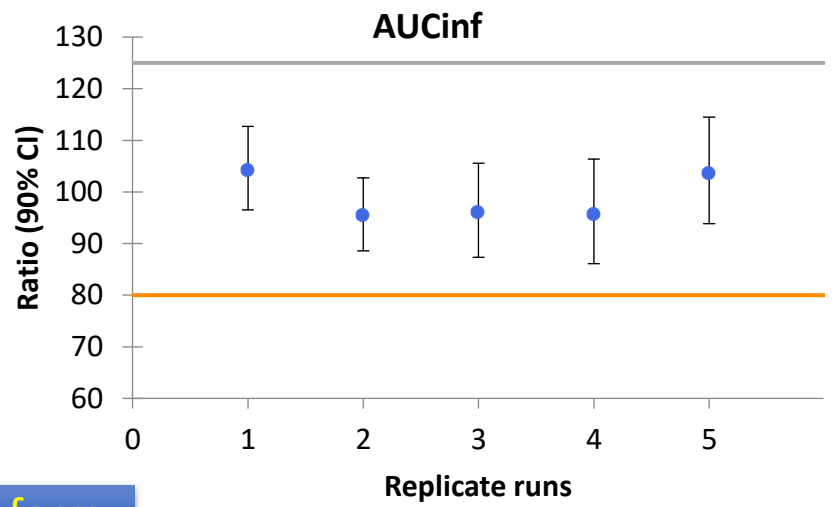
Safe space for salt disproportionation in HV (without ARA)

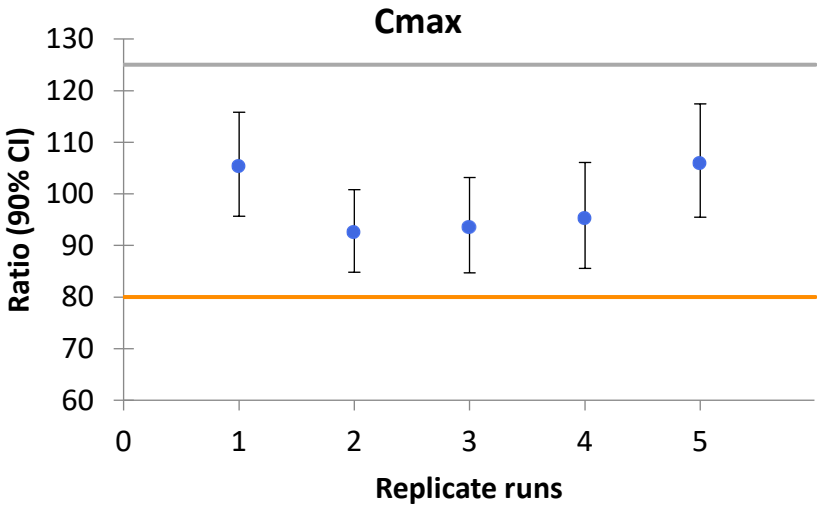
80% Salt and 20% Free form in the dosage form

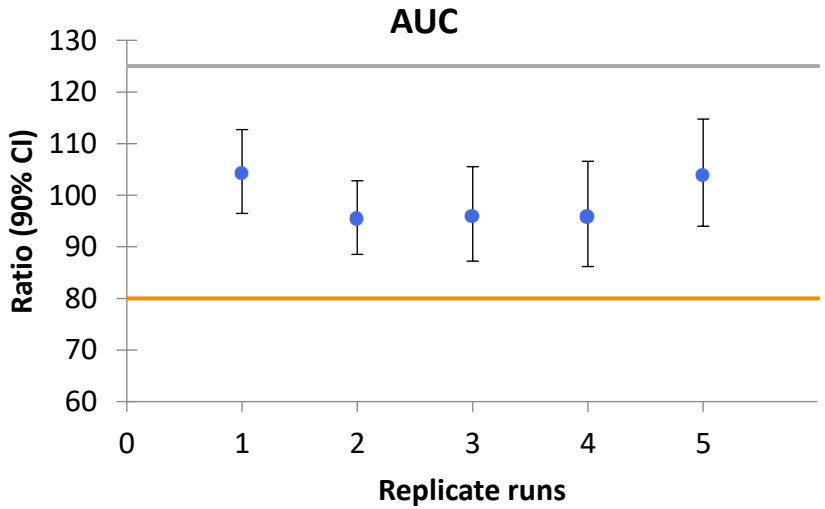


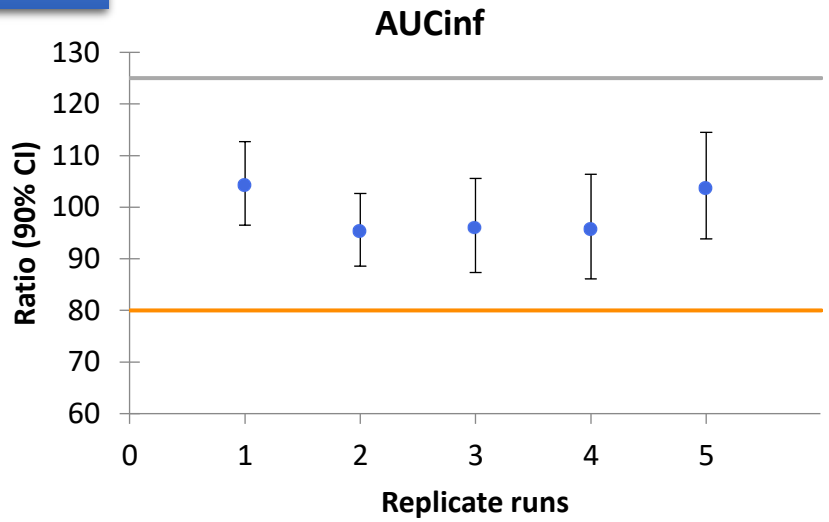




70% Salt and 30% Free form in the dosage form







30% of free form in the dosage form still passes BE in HV

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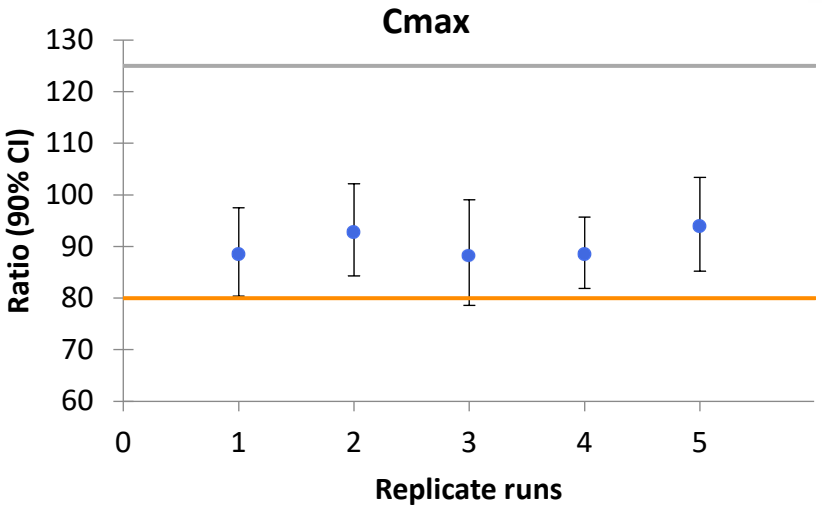
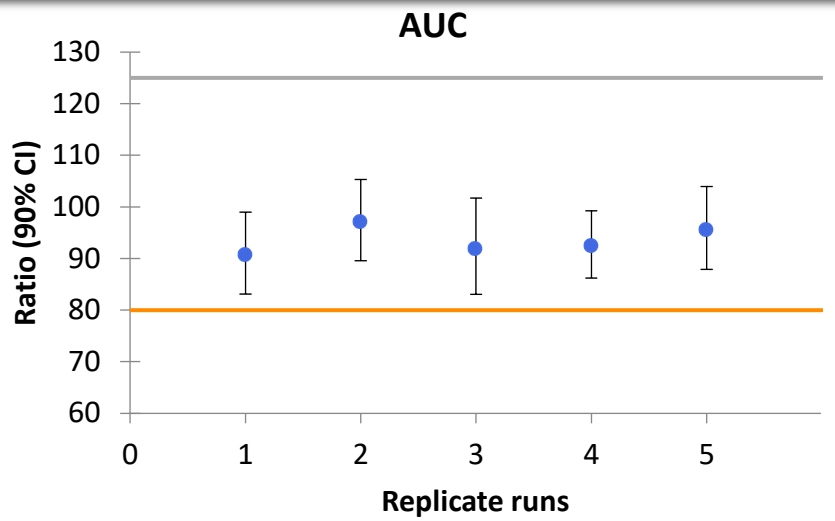
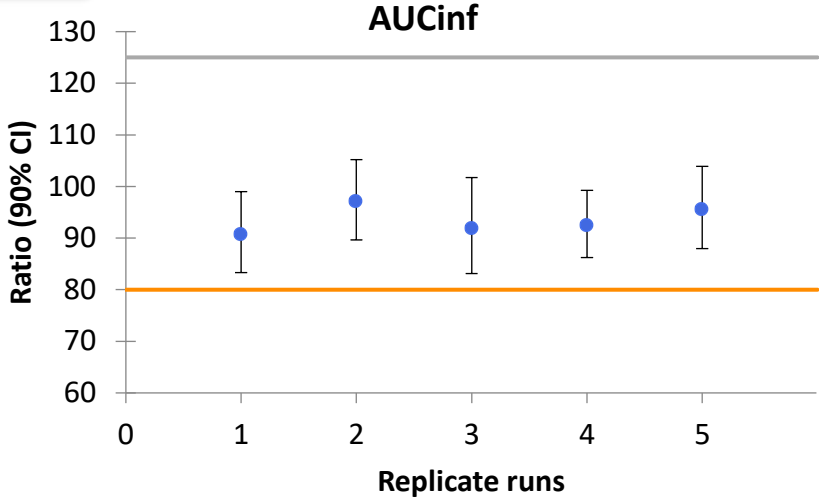
Safe space for salt disproportionation in Patients (with ARA)

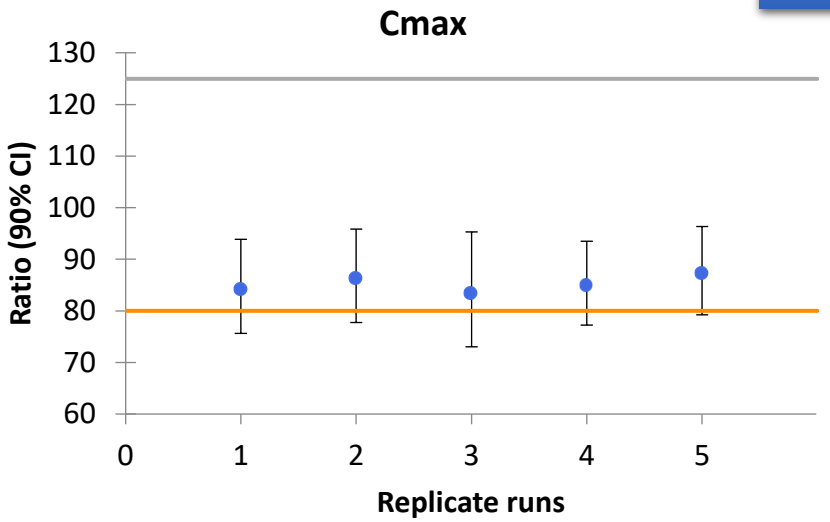
80% Salt and 20% Free form in the dosage form

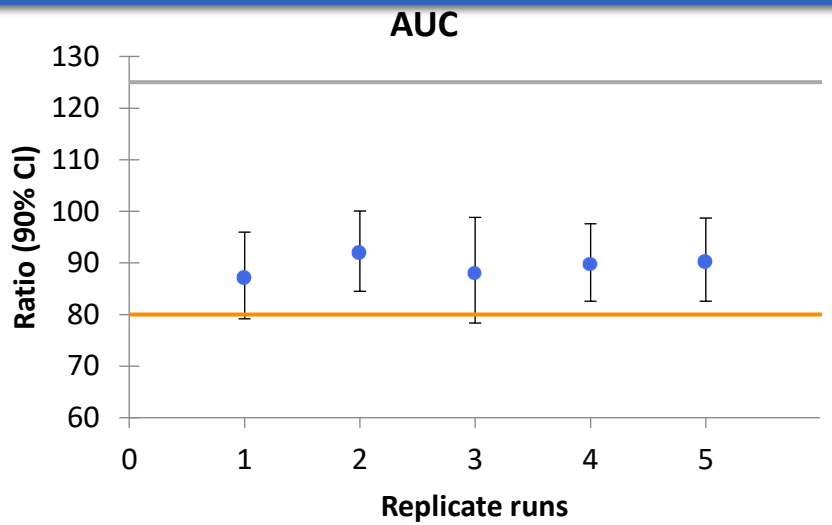


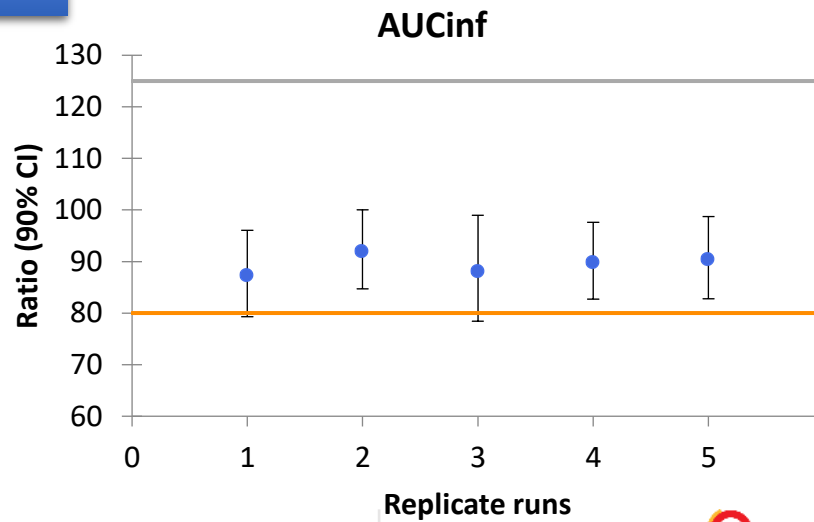




70% Salt and 30% Free form in the dosage form







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

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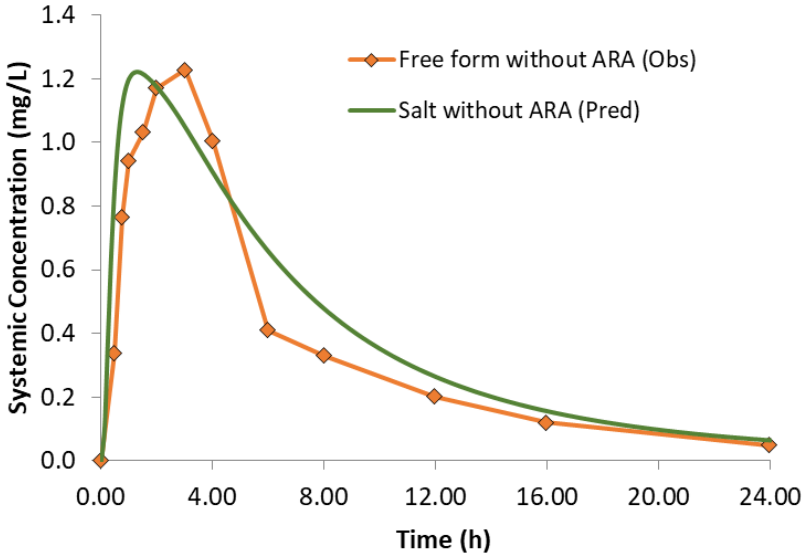
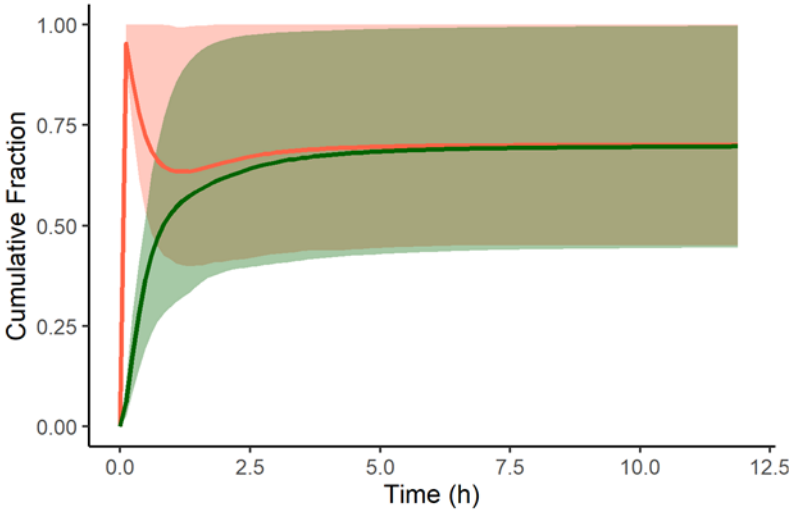
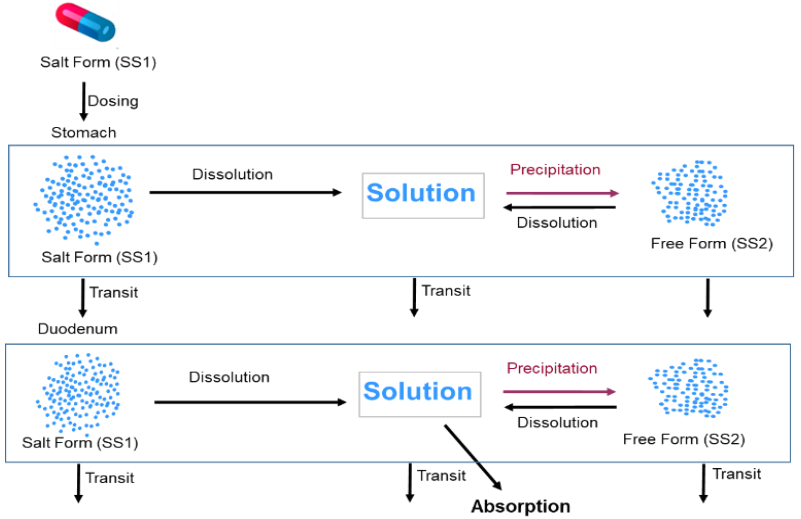
Reason for Wide Safe Space for Salt Disproportionation in HV (Without ARA)

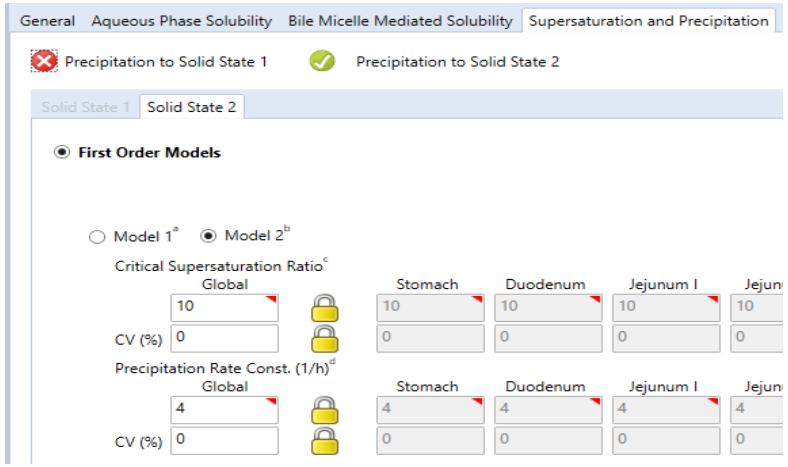


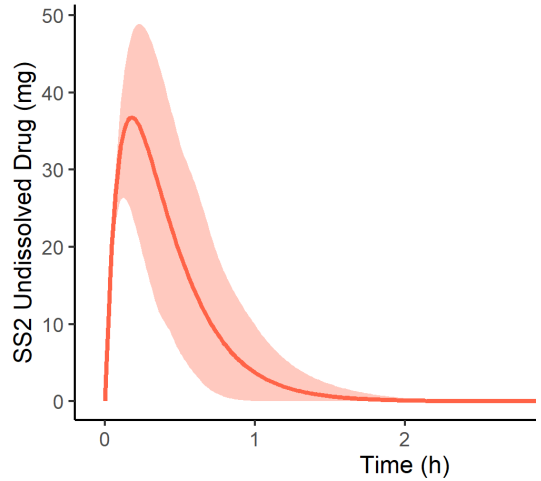
In the absence of ARA, salt form and Free form have same PK.





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 (SS2Precipitated free form of drug in stomach - will use free form surface pH and solubility

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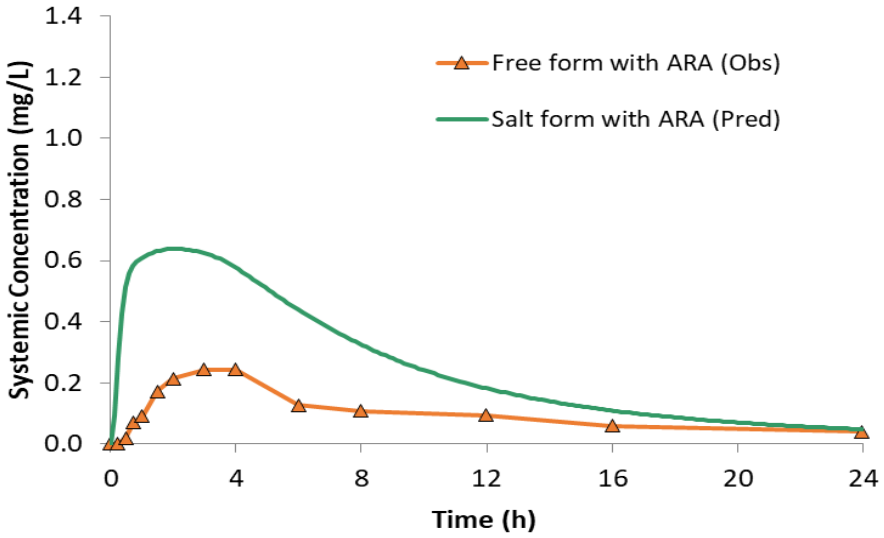
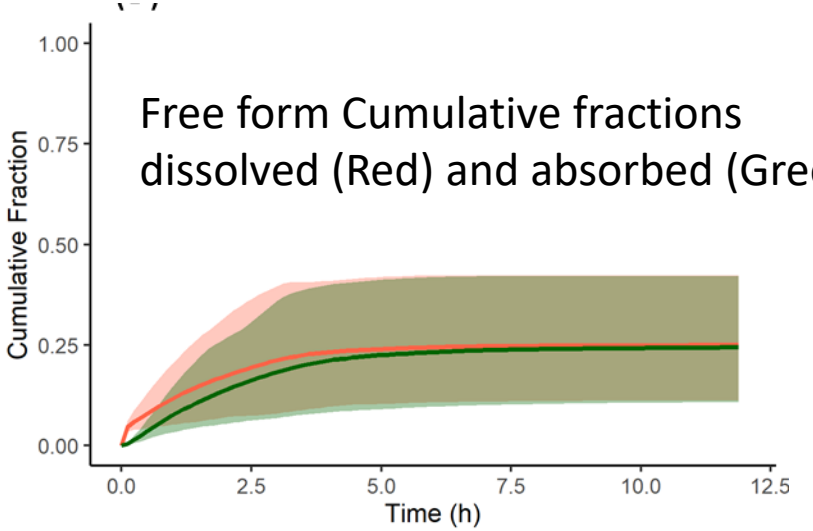
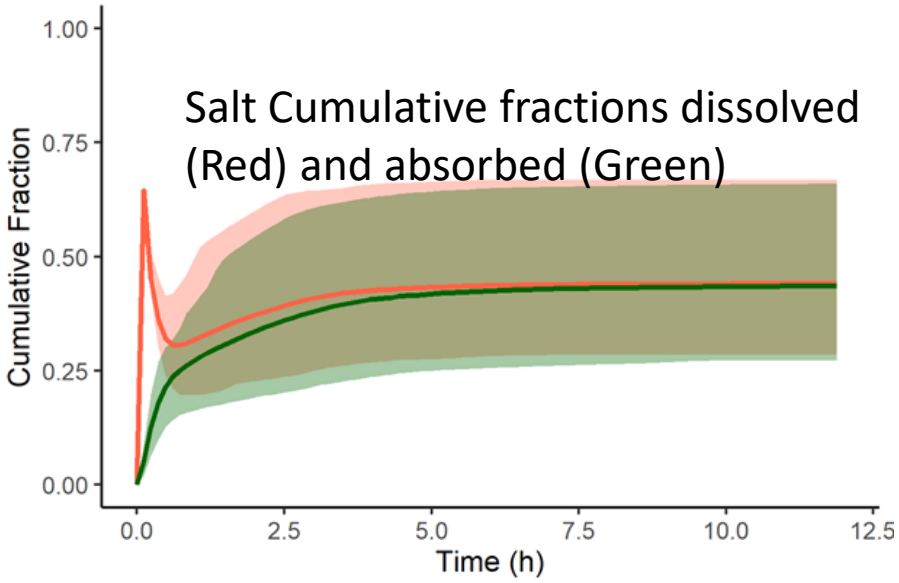
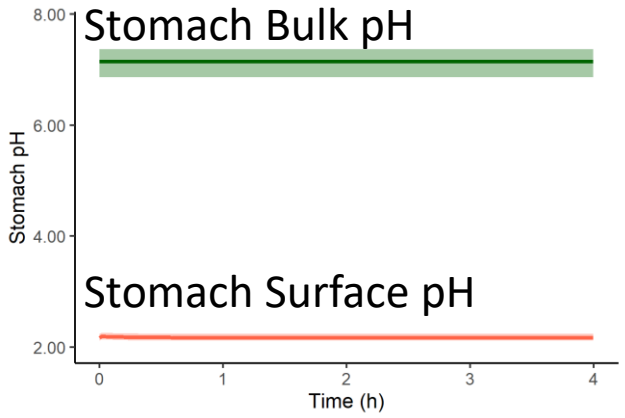
Reason for Narrow Safe Space for Salt Disproportionation in Patients (With ARA)









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 Fa than free form thereby being sensitive to disproportionation in presence of ARA (narrow safe space in patients)

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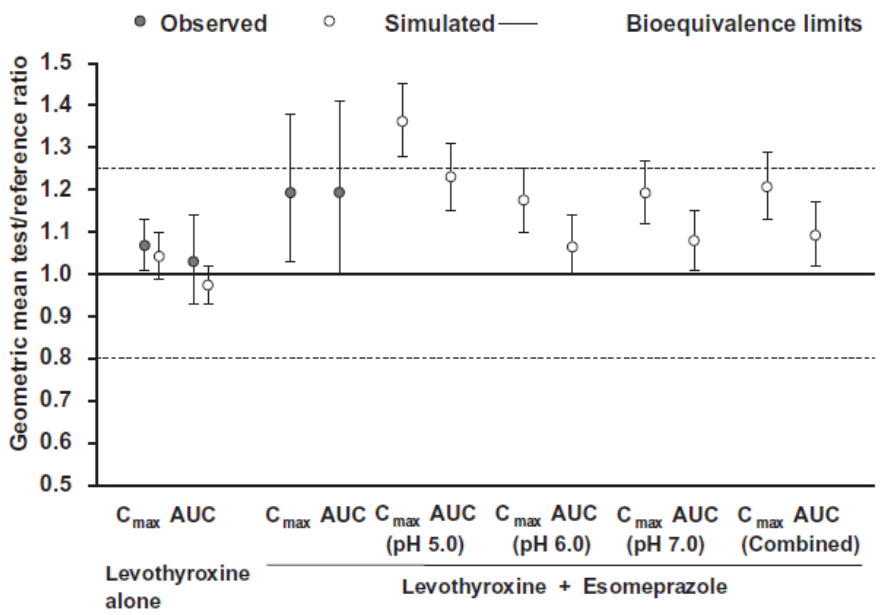
Case 2, 3:

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

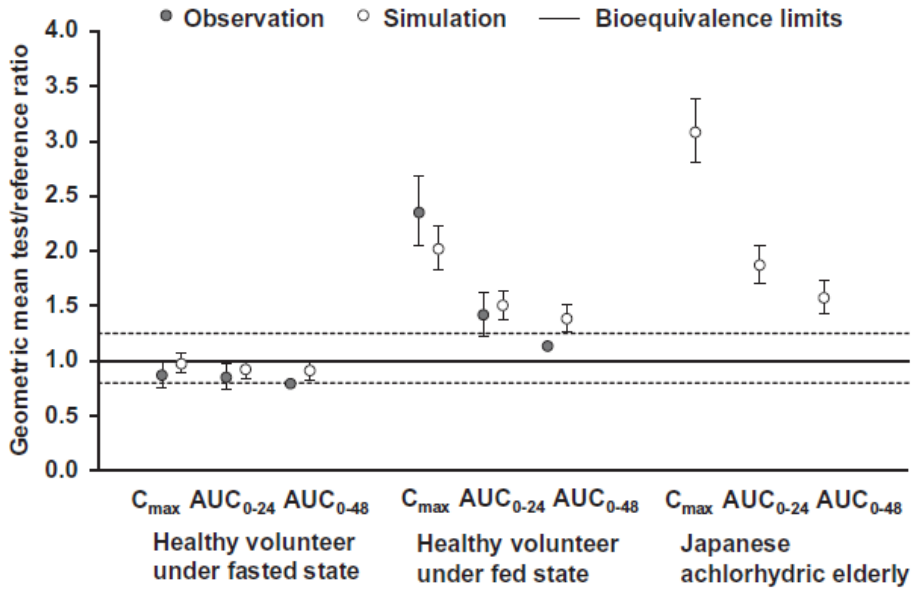
Kosuke Doki[a,b,*], Adam S. Darwich[a], Nikunjkumar Patel[c], Amin Rostami-Hodjegan[a,c]

[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

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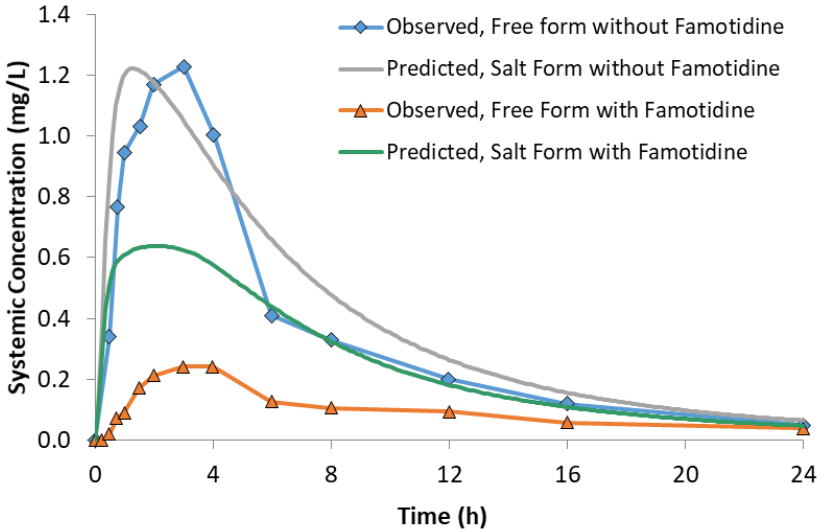
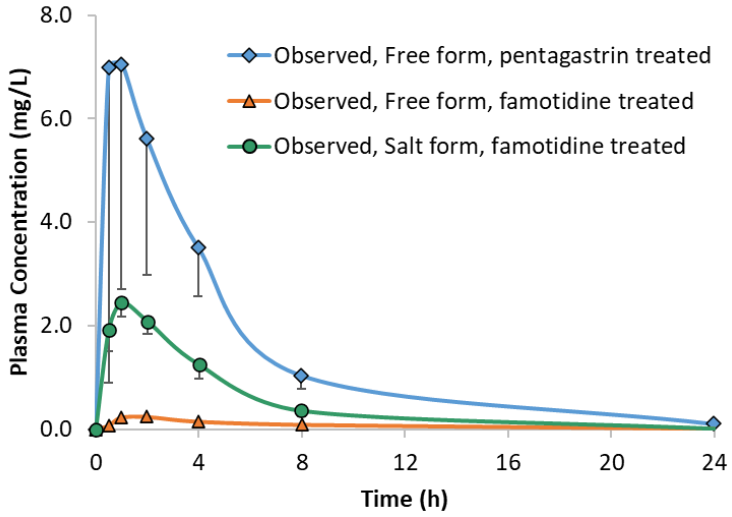
Back up

Simcyp Modelling Results – Salt Form

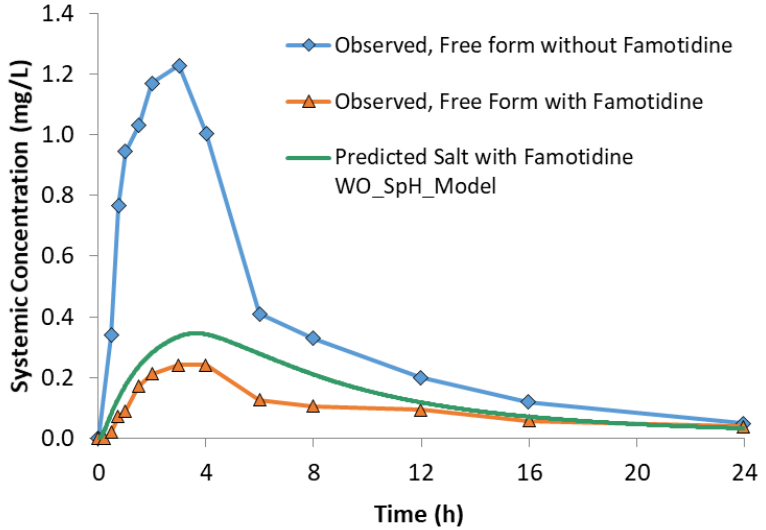
Humans with Surface pH model



Beagle Dogs



Humans without Surface pH Model



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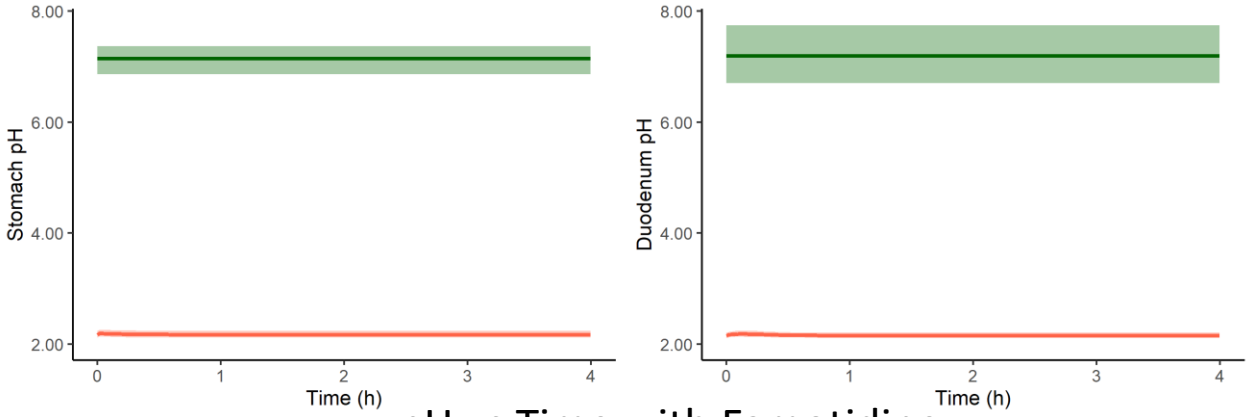
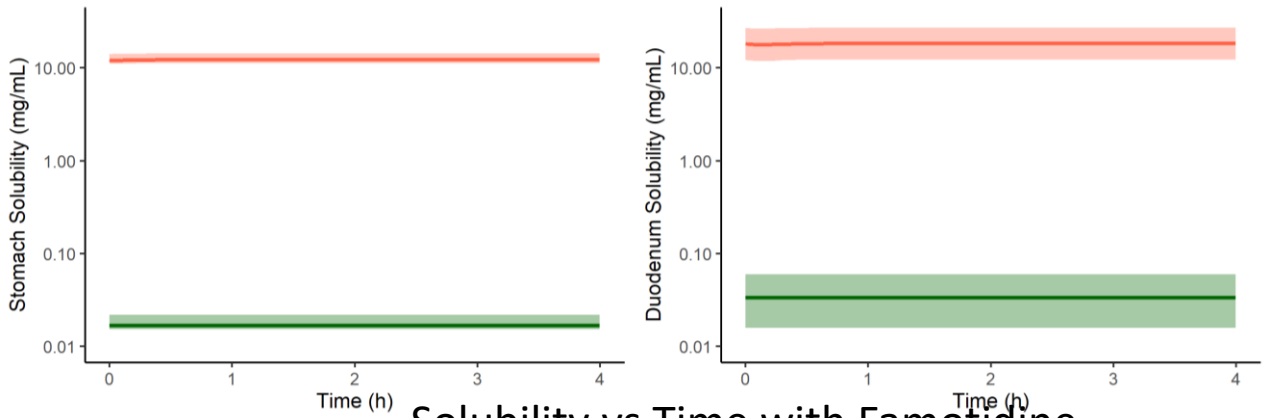


pH vs Time with Famotidine



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.