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Physiologically-Based Pharmacokinetic (PBPK) Modelling Approach for the Prediction of Small Intestinal Precipitation of Poorly Soluble Drugs - A Simulation Study of Posaconazole Using the Simcyp ADAM Model

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PURPOSE

- Weakly basic poorly soluble drug compounds, such as posaconazole (POSA), may dissolve completely at fasted gastric pH but precipitate upon transit to higher small intestinal pH.
- A number of *in vitro* and *in vivo* methods have been used to study intestinal precipitation of poorly soluble drug compounds with a varying degree of complexity.
- This research work investigates the predictive capability of PBPK models to explore gastrointestinal (GI) luminal dissolution, supersaturation, and precipitation behaviour of POSA after oral administration of two suspension formulations (pH 7.1 and pH 1.6) in healthy volunteers.

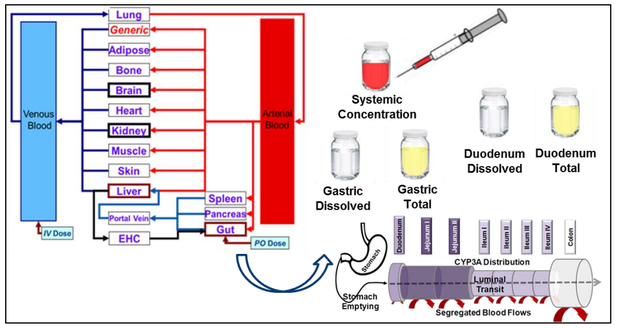

Figure 1. A PBPK Model was developed to simulate 5 different sample concentrations:- Gastric & Duodenal dissolved and total and plasma concentrations of 2 POSA suspension formulations.

METHODS

- Prior physicochemical and disposition parameters of posaconazole were entered into the Advanced Dissolution Absorption and Metabolism (ADAM) model, implemented within the Simcyp simulator (V15.1).
- Intragastric administration of two suspension formulations - 1) pH 7.1 suspension of 40 mg POSA (2.3% POSA in solution), and 2) pH 1.6 suspension of 40 mg POSA (70.0% POSA in solution) - were simulated.
- Simulations were run using 100 individuals (20 virtual trials with 5 volunteers each, with associated inter-individual variability of physiological parameters *viz*. pH, water volumes, bile salt concentration etc.)
- Virtual trials were simulated to closely match clinical study design[1] in terms of dose/dosage form administered, proportion of males and females, age range of the population, fluid intake with administered dose & luminal sampling time points.
- The predictive performance of this approach was assessed by predicting the dissolved and total (*i.e.*, including precipitated fraction) concentrations of POSA in both stomach and duodenal compartments and comparing these to *in vivo* results[1].

$$S_{(BS)_{tot}} = \left([BS] \bullet \frac{S_0}{C_{H_2O}} \bullet 10^{\log Km:w\_unionised} + S_0\right) + \left([BS] \bullet \frac{S_{ionised}}{C_{H_2O}} \bullet 10^{\log Km:w\_ionised} + S_{ionised}\right)$$

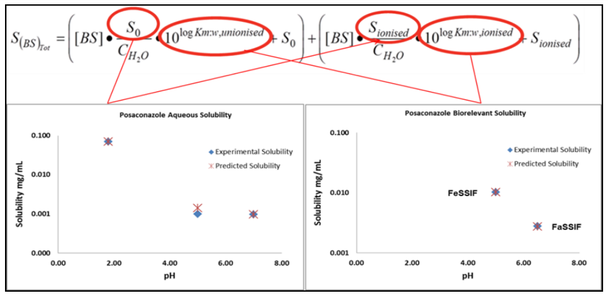

Figure 2. Solubility modelling using the SIVA Toolkit. Aq. Solubility was used to estimate/confirm intrinsic solubility (S_0); Solubility Factor (SF) & biorelevant solubility for estimation of bile micelle partition coefficients ($logK_{m:w}$).

Media Used	Experimental Solubility (mg/ml)	Predicted Solubility (mg/ml)	Model Parameter Optimised
pH 1.8 SGF Media	0.07000	0.07000	Salt Limiting Factor (SF1)= 71.347
pH 5.0 Buffer Media	0.00100	0.00143	
pH 7.0 Buffer Media	0.00098	0.00099	
pH 6.5 FaSSIF Media	0.00280	0.00275	logKm:w (Neutral)= 4.52
pH 5.0 FeSSIF Media	0.01020	0.01021	logKm:w (Ionised)= 1.00

- POSA plasma concentrations, measured simultaneously in the same study subjects to quantitate the effect of luminal supersaturation/ precipitation on systemic exposure, were also compared to the PBPK simulated plasma profiles.

RESULTS

- The developed model reasonably well characterised the intraluminal dissolution, supersaturation, and precipitation behaviour of POSA.

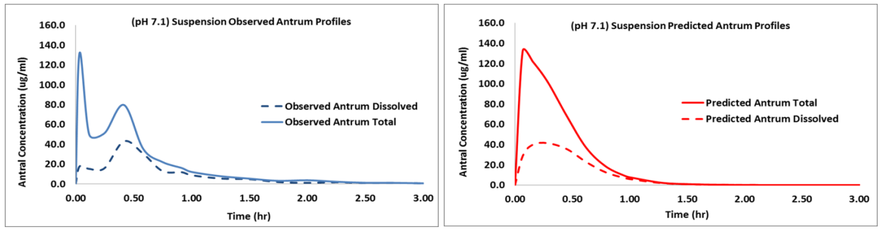

Figure 3A. Mean Dissolved (Dotted Line) and Total (Solid Line) Antral Concs. of POSA (Suspension pH 7.1) Observed (—) *vs.* Predicted by PBPK Model (—).

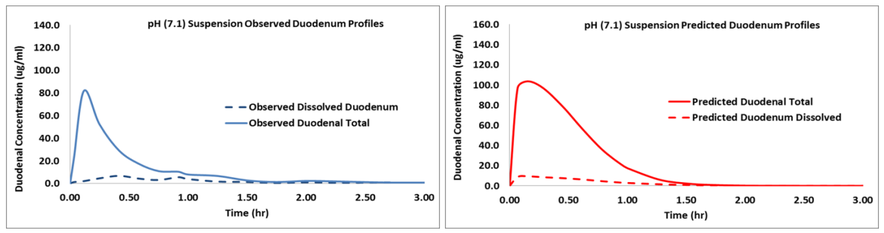

Figure 3B. Mean Dissolved (Dotted Line) and Total (Solid Line) Duodenal Concs. of POSA (Suspension pH 7.1) Observed (—) *vs.* Predicted by PBPK Model (—).

Parameter	Antrum Dissolved Observed	Antrum Dissolved Predicted	Duodenum Dissolved Observed	Duodenum Dissolved Predicted
Cmax (ug/ml)	52.10 ± 30.09	42.46 ± 25.29	9.09 ± 3.80	10.30 ± 5.99
AUC (ug-h/ml)	26.10 ± 15.14	28.83 ± 16.73	6.14 ± 2.64	8.71 ± 4.12

Parameter	Antrum Total Observed	Antrum Total Predicted	Duodenum Total Observed	Duodenum Total Predicted
Cmax (ug/ml)	150.68 ± 152.73	137.55 ± 7.61	83.76 ± 26.83	107.73 ± 8.96
AUC (ug-h/ml)	53.64 ± 29.44	67.82 ± 16.12	33.70 ± 17.60	66.23 ± 12.58

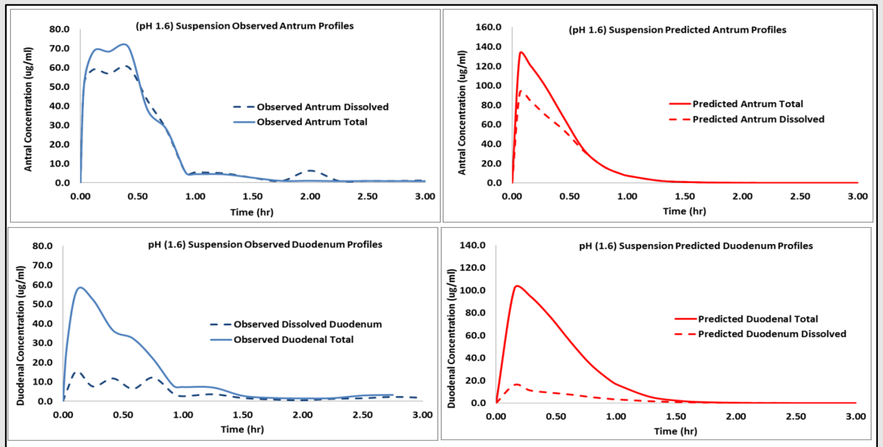

Figure 4. Mean Dissolved (Dotted Line) and Total (Solid Line) Gastric (Upper plots) and Duodenal (Lower plots) Concs. of POSA (Suspension pH 1.6) Observed (—) *vs.* Predicted by PBPK Model (—).

Parameter	Antrum Dissolved Observed	Antrum Dissolved Predicted	Duodenum Dissolved Observed	Duodenum Dissolved Predicted
Cmax (ug/ml)	67.42 ± 40.31	96.29 ± 5.32	17.95 ± 6.55	29.89 ± 5.54
AUC (ug-h/ml)	44.89 ± 24.18	53.07 ± 12.90	12.07 ± 2.98	12.53 ± 4.30

Parameter	Antrum Total Observed	Antrum Total Predicted	Duodenum Total Observed	Duodenum Total Predicted
Cmax (ug/ml)	79.77 ± 37.91	137.55 ± 7.61	56.29 ± 21.67	105.14 ± 8.83
AUC (ug-h/ml)	47.47 ± 25.21	67.81 ± 16.03	37.66 ± 17.70	67.41 ± 11.71

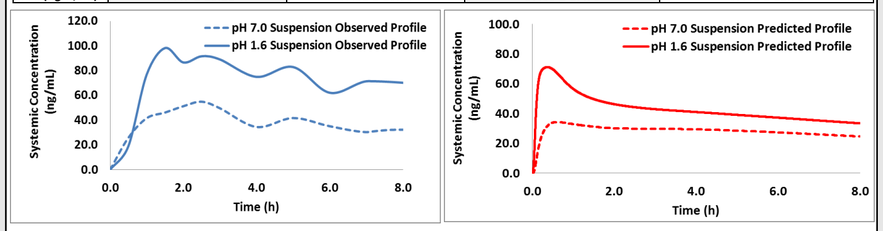

Fig. 5. Compared to the Neutral Suspension (Dispersed in pH 7.1), the Acidified Suspension (pH 1.6 Dispersion) was significantly more absorbed.

CONCLUSION

Mechanistic modelling of *in vitro* experiments, as described here, builds confidence in the quality of the input parameters and mechanistic models used for the *in vivo* PBPK simulations. The results also support the application of population-based PBPK modelling techniques for predicting the luminal supersaturation and precipitation characteristics of poorly soluble weak bases and thereby characterising their systemic absorption profiles in humans. Generally, in clinical studies luminal contents are not characterised and PBPK model performance is only compared against observed clinical PK profiles. Therefore the ability of a model to accurately simulate luminal drug dissolution and also precipitation kinetics is usually not directly assessed. More case studies with a range of drug compounds and dosage forms are required to build further confidence in this predictive approach.

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REFERENCES Hens B et al. (2014) J Pharm Sci. (doi: 10.1002/jps.24690).