**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.

**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.)

**Results**

- POSA plasma concentrations, measured simultaneously in the same study subjects to quantify the effect of luminal supersaturation/precipitation on systemic exposure, were also compared to the PBPK simulated plasma profiles.
- The developed model reasonably well characterised the intraluminal dissolution, supersaturation, and precipitation behaviour of POSA.

**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**