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Mechanistic Model-Based Analysis of Biopharmaceutics Experiments- Application of In Vitro in Vivo Extrapolation (*IVIV_E*) Techniques Within A PBPK Modelling Framework

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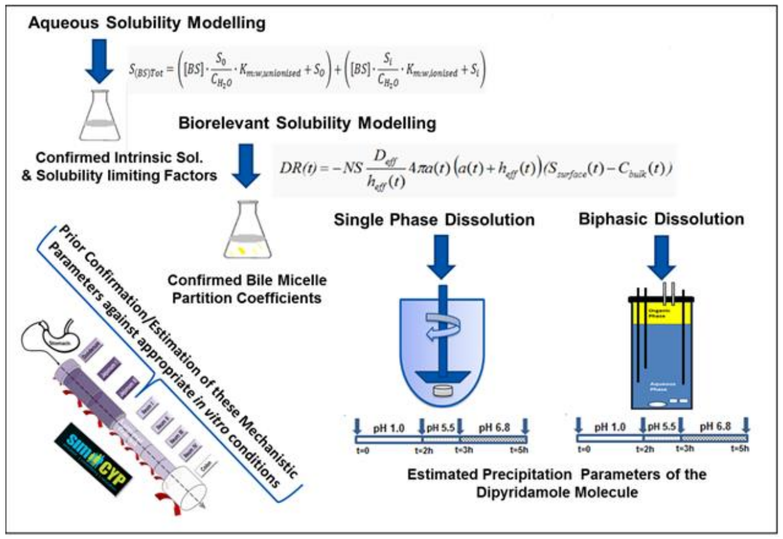
PURPOSE

- *In vitro* dissolution testing is a critical component of drug product development and is often used as a surrogate for *in vivo* performance.
- While the range of (USP) standard methods have been developed and tested for many years, no single dissolution test or apparatus comprehensively maps the *in vivo* behaviour of the range of compound classes and sub-classes therein.
- Moreover, in the case of poorly soluble, low pKa basic drugs, handling supersaturation and precipitation related attributes, mainly relevant upon transfer of the drug from the low pH stomach into unfavourable elevated pH in the small intestine, is very important and needs to be accounted for during *in vitro* testing.
- Recently, advances have been made in *in vitro* experimental designs to better mimic the complex drug dissolution and precipitation kinetics in the GI lumen.
- The two-phase dissolution setup is one such attempt, undertaken to simulate drug dissolution in the near sink conditions expected *in vivo* for poorly soluble, highly permeable BCS II compounds .
- The purpose of this work was to demonstrate how mechanistic modelling of dissolution experiments can help to assess effectively the physiological relevance of these methods for extrapolating to *in vivo* simulations via a PBPK modelling approach.

METHODS



- As shown in the Fig. 1 above, we followed a sequential, stepwise *in vitro* modelling approach, estimating or confirming relevant biopharmaceutical parameters of the weakly basic drug-dipyridamole from *in vitro* experiments before using them directly within the Simcyp simulator[2] (Version 15.1).
- In a systematic comparative study, the dissolution of dipyridamole (**DIP**) in 2 independent *in vitro* experiments was evaluated, namely:
  a) A small scale, single phase dissolution apparatus, where the pH of the medium was changed (pH 1.0, pH 5.5, pH 6.8) during the experiment;
  b) A small scale two-phase dissolution set up that contained an aqueous phase medium (with the same pH changes during the experiment as above) with an octanol phase as a separate layer[1] (Fig 1.).
- These two *in vitro* experiments were modelled mechanistically to estimate supersaturation and precipitation parameters for dipyridamole using Simcyp's standalone in vitro modelling toolkit - SIVA (Simcyp, UK).

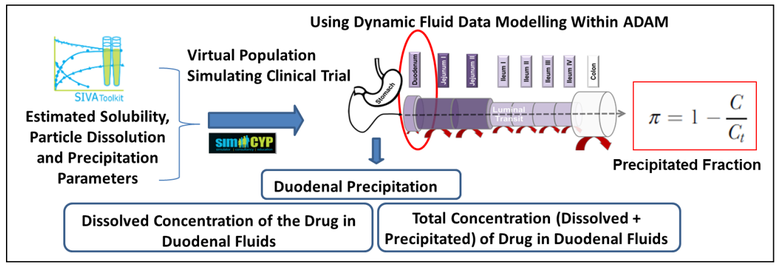


Fig. 2. *The Model was assessed by predicting the dissolved concentration & precipitate mass of DIP in the in vivo duodenal fluids using the ADAM model.*

- The effectiveness of the systematic modelling approach was assessed by predicting the in vivo luminal concentration of DPI in duodenal fluids of a simulated virtual population (10 Trails X 12 Volunteers) and compared to the previously reported luminal concentrations in healthy volunteers[3].

RESULTS

- The model reasonably well characterised the in vivo intraluminal dissolution, supersaturation, and precipitation behaviour of DPI.

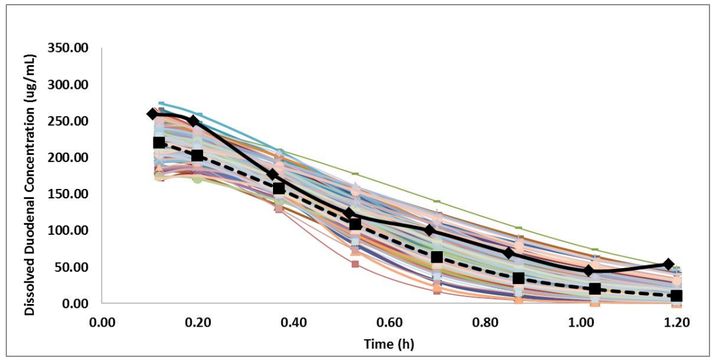


Fig. 3. Mean Predicted (Dotted Line) vs. Obs.[2] (Solid Line) Duodenal Dissolved DPI Concentration Plots (All 120 simulated subjects plotted for reference).

- The simulation results confirm that the single phase dissolution model with pH change estimated the maximum precipitated fraction (π) to be 37%, much higher than the two-phase dissolution experiments (π = 10%).
- The precipitation model parameters estimated from the two-phase dissolution study coupled with the PBPK disposition model predicted a low level of precipitation which correlated well with *in vivo* luminal measurements (via fluid aspiration using luminal intubation)[3] with a maximum precipitated fraction of about 7% (Figs. 3 and 4).

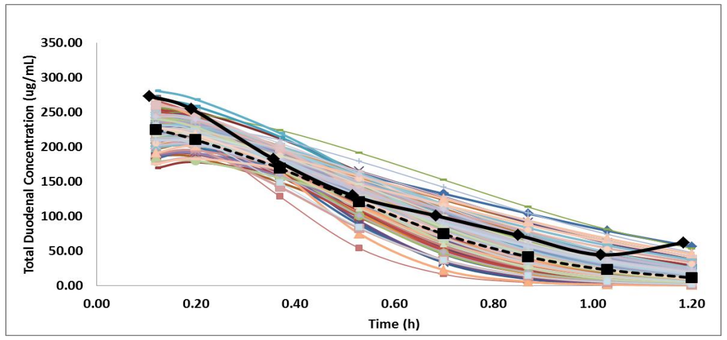
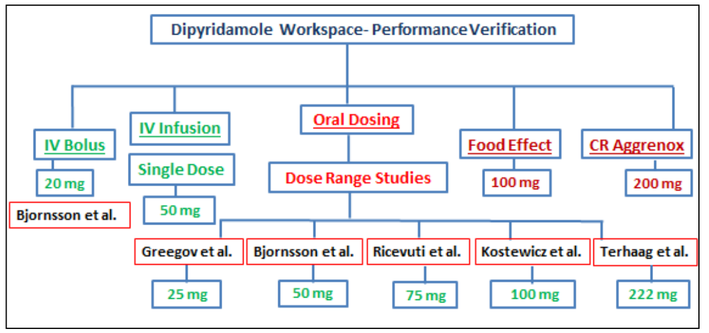


Fig. 4. *Mean Predicted (dashed line) vs. Obs[2] (black solid line) duodenal total (Dissolved + Precipitated) DPI Conc. (All 120 simulated virtual subjects plotted for reference).*

- The predictive performance of model was also verified against observed clinical PK studies with different doses to further strengthen the evaluation.



- The parameters derived from the two-phase model also closely reproduced the systemic exposure to DPI with significantly lower % prediction errors for C_{max} and $AUC_{0\text{-}t}$ compared to the model parameterised from the single phase dissolution experiment.

CONCLUSION

Mechanistic modelling of *in vitro* experiments to estimate and/or confirm drug-specific parameters and apply them within a PBPK framework is not a new concept to the modelling fraternity. For example, mechanistic analysis of *in vitro* data obtained from cell-based enzyme systems for the estimation of enzyme kinetic parameters (CL_{int}, V_{max} and K_m) is an established practice for successful *IVIV_E* of drug metabolic clearance. However, application of this approach to biopharmaceutical experiments for the estimation of mechanistic parameters required in drug absorption modelling has not been explored widely. The bottom up, stepwise, sequential, mechanistic modelling approach described herein was reasonably successful at reproducing clinically obtained luminal and plasma concentrations of dipyridamole. This *IVIV_E* approach can help formulation scientists to streamline the design of informative biorelevant *in vitro* experiments during drug development.

REFERENCES

1. Frank KJ, et al. (2014) Eur J Pharm Sci.; **2.** Jamei M, et al. (2013) In Silico Pharmacology. **3**. Psachoulias D, et al. (2011) Pharm Res.