An Integrated Approach to Mechanistically Model *In-Vitro* Experiments and Incorporate Drug-specific Parameter Estimates within a PBPK Framework to Simulate *In-Vivo* Drug Dissolution

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INTRODUCTION

In vitro dissolution testing is a critical component of drug product development programs and is often used as a surrogate for *in vivo* performance. Consequently, mechanistic modelling of *in vitro* dissolution studies and informed data interpretation early in the formulation development process is crucial. The Simcyp *In Vitro* (Data) Analysis (SIVA) toolkit is a standalone module that contains a pre-defined library of mechanistic models for analysing *in vitro* data generated from different dissolution techniques such as *USP* II, *USP* IV, transfer model, two phase dissolution model etc.[1] These modelling tools can be used to assess performance of models of *in vitro* experiments and, if required, re-visit input data (e.g., solubility, particle size), model assumptions and ultimately estimate unknown or uncertain parameters of the model.

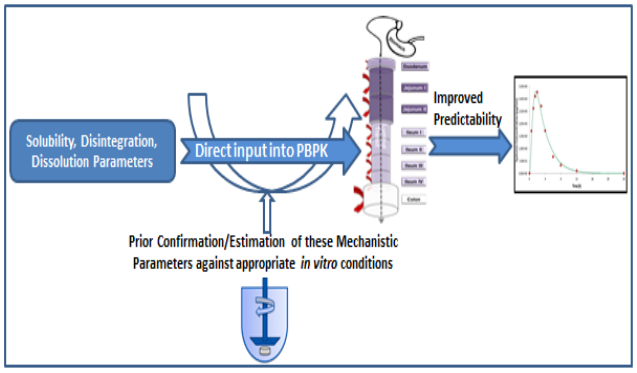

Figure 1. Integrated *in vitro* modelling approach

These mechanistic models thus enable the appropriate dissolution conditions (pH, fluid volume, Bile Salts, fluid velocity (hydrodynamics), stomach-duodenum transfer rates etc.) to be accounted for, enabling *in vitro* and *in vivo* differences (including population variability) to be considered. These models are directly compatible with those of the main PBPK simulator and hence the parameters confirmed/estimated against the appropriate *in vitro* system parameters can be used for *in vivo* extrapolation with enhanced confidence, thereby improving predictive performance of PBPK models (Fig. 1).

Herein a stepwise modelling approach (Fig. 2) is followed, confirming/estimating relevant physico-chemical parameters for ketoconazole (KTZ) against *in vitro* data before using them directly within a PBPK model. The usefulness of this modelling approach was then supported by predicting the dissolved and total (accounting precipitated fraction) concentration of KTZ in the duodenum of a simulated virtual population (Simcyp Simulator v15.1). The predicted concentrations were compared with previously reported luminal concentrations in duodenum of human volunteers[2].

METHODS

KTZ aqueous and biorelevant solubility data, the dissolution of Nizoral® (Ketoconazole) tablets in the USP-II apparatus & its precipitation attributes using transfer experiments were determined at Goethe-University. Human *in vivo* duodenal luminal KTZ (300 mg) concentrations were reported by Psachoulias et al. 2011.

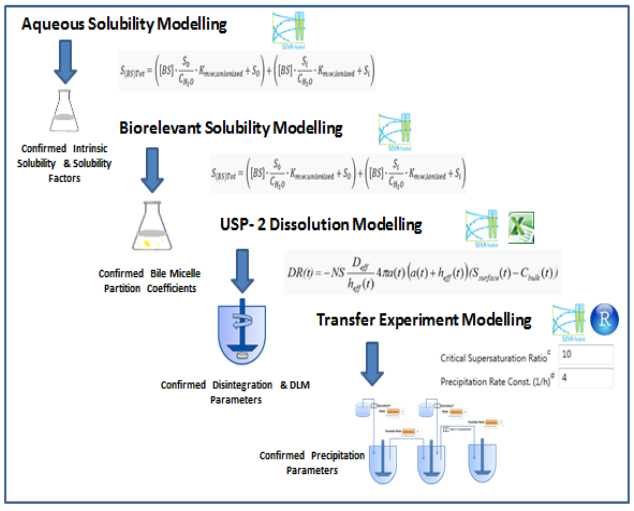

Figure 2. Sequential *in vitro* modelling workflow

As indicated in Figure 2 this *in vitro* dataset was then used for sequential fitting/verification of the physchem parameters starting from: Aqueous Solubility (for intrinsic solubility & Salt Solubility Factors (SFs) verification); Biorelevant Solubility (Bile-micelle partition coefficient estimation); USP-II pH 1.6 FaSSGF Dissolution Study

(for Disintegration modelling); and, finally, the transfer experiment (precipitation parameter estimation).
The parameters estimated at each stage were fixed in the subsequent modelling steps. The validity of the estimated parameters determined using a training dataset (Kostewicz et al.); was also tested for its external predictability using independent literature dataset.

RESULTS AND DISCUSSION

The physicochemical parameters were estimated using a sequential modelling approach and were able to satisfactorily reproduce the experimental data. The solubility of KTZ in pH 1.6 FaSSGF is very high (>10 mg/ml) and hence the USP II dissolution dataset was used to estimate disintegration parameters of the Nizoral® tablets. The transfer model experiment was used to estimate the precipitation model parameters: Critical Supersaturation Ratio (CSR) and Precipitation Rate Constants (PRC). A secondary PRC (sPRC) (Fig. 3) was found necessary to capture the peak region.

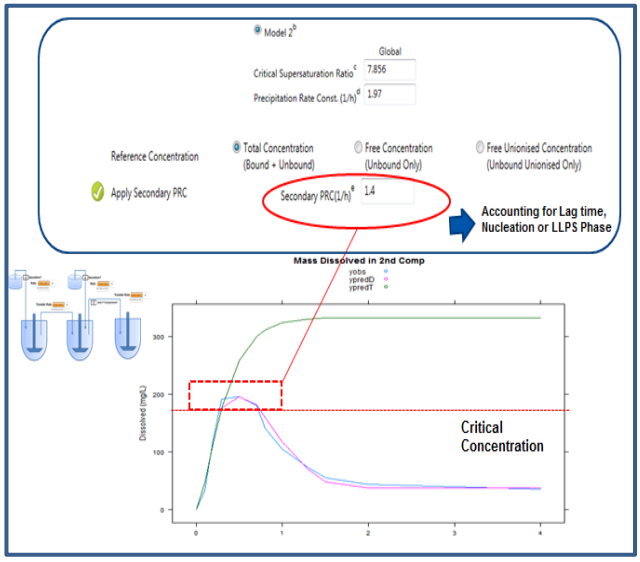

Figure 3. Precipitation Model Parameters

Mechanistically this region may correspond to a nucleation and sub-critical size growth phase or a Liquid-Liquid Phase Separation (LLPS). The model thus provides the means to estimate the CSR, the PRC and if required the sPRC.
The estimated parameters are then used to predict duodenal concentrations in 120 individuals (10 Trials with 12 volunteers each, with associated inter-individual variability of physiological parameters *viz.* pH, water volumes, bile salt concentration *etc.*) and found comparable with that of the reported dataset as shown in Fig. 4A and Fig. 4B.
Mechanistic analysis of *in vitro* data from the metabolic enzyme systems (*viz.* liver microsomes, hepatocytes, rCYP enzymes etc.) has been a well-known practice for successful *In Vitro-In Vivo* Extrapolation (IVIVE) of metabolic clearance and plays a key role in successful prediction of *in vivo* behaviour using PBPK models. Application of this concept to experimental solubility and dissolution data modelling for the estimation of mechanistic parameters required for *in vivo* simulation has not previously been reported as an integrated workflow with evidence of successful outcomes.

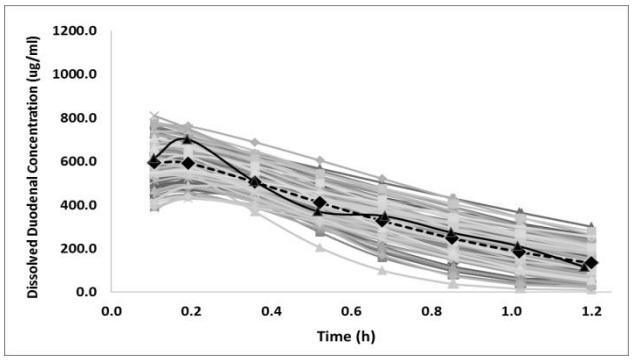

Figure 4A. Mean Predicted (Dotted Line) vs. Observed[2] (Solid Line) duodenal concentrations for dissolved ketoconazole concentration plots (Data for all 120 simulated virtual subjects also plotted for the reference).

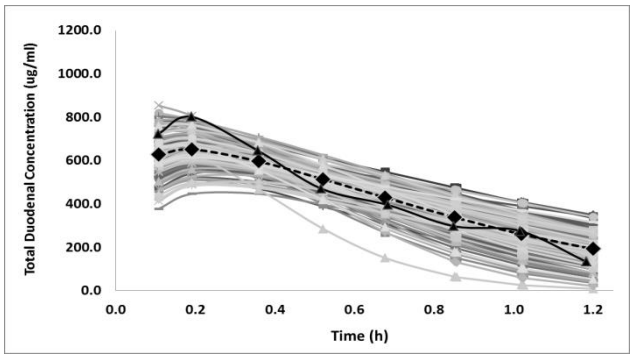

Figure 4B. Mean Predicted (Dotted Line) vs. Observed[2] (Solid Line) duodenal concentrations for the total ketoconazole concentration plots (Data for all 120 simulated virtual subjects also plotted for the reference).

The results herein demonstrate that this systematic *In Vitro-In Vivo* Extrapolation (IVIV_E) approach may help to build confidence in the quality of the input parameters and mechanistic models used for *in vivo* simulations, thereby improving predictability within a PBPK frame-work. Moreover, this approach streamlines designing informative *in vitro* experiments and helps avoiding unnecessary ones. More case studies with various drugs and different formulations are needed to spread awareness of this *in vitro* modelling approach and improve confidence in the methodology.

ACKNOWLEDGEMENT

This work was partially supported by funding from IMI OrBiTo Grant No. 115369 (http://www.imi.europa.eu).

REFERENCES

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