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# Usefulness of Small Scale Biphasic Dissolution Experiments in Estimating Precipitation Rates for Input in PBPK modelling

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## PURPOSE

Inclusion of the dynamic dissolution process of a formulation into physiologically based pharmacokinetic (PBPK) modelling software allows the potential impact of any supersaturation and precipitation in the gastrointestinal tract to be evaluated. Many current *in vitro* setups fail to adequately capture this precipitation of drug.

## OBJECTIVE(S)

In this study, precipitation data obtained from the biphasic dissolution experiments for two weakly basic drugs (dipyridamole and ketoconazole) were inputted into the Simcyp (Certara UK, Sheffield) PBPK modelling software.

## METHOD(S)

- The biphasic dissolution experiments were carried out using the inForm instrument (Pion Inc.), with the setup shown in Figure 1.
- Drug precipitated upon transition from gastric to intestinal conditions.
- An empirical first-order precipitation rate constant (PRC) can be calculated from the drug concentration profile in the aqueous layer (Figure 2). Precipitation was deemed to have finished when drug reached its equilibrium solubility in the aqueous phase.
- To calculate the critical supersaturation concentration (CSC) aliquots of stock solution were injected into FaSSIF V2 at 37°C. The CSC was determined as the lowest concentration at which precipitation occurs, detected by light scattering in the UV/Vis spectrum.
- PRC and CSC values estimated using the *in vitro* experiments were inputted into the Simcyp PBPK modelling software and the plasma profile was simulated under dosing conditions replicating publications for dipyridamole [1] and ketoconazole [2].
- These were compared to the profiles modelled using the default simulators values of PRC and critical supersaturation ratio (CSR) of 4 $hr^{-1}$ and 10 respectively. $\mathrm{CSR} = \frac{\mathrm{CSC}}{\mathrm{Equilibrium\ Solubility}}$
- The elimination kinetics were modelled from relevant IV studies. Other absorption and distribution properties were estimated using the physiochemical properties and results from *in vitro* experiments.

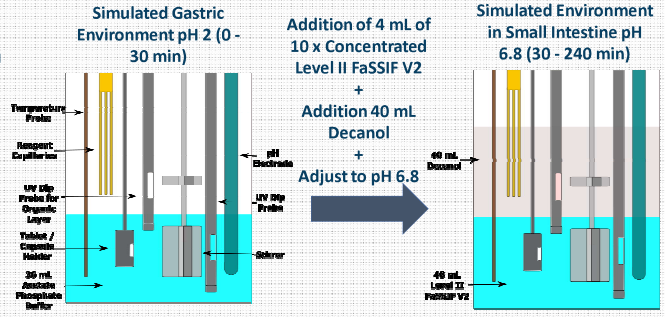


*Fig.1: Schematic of the biphasic dissolution test using the inForm platform.*

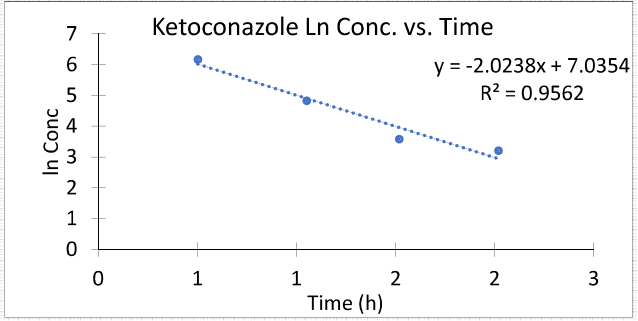


*Fig. 2: Modelling first order PRC using the natural log vs. time profile for ketoconazole using the aqueous phase data.*

## RESULT(S)

- The AUC and $C_{max}$ obtained from the PBPK modelling using biphasic dissolution data for both dipyridamole and ketoconazole were within a 20% percentage error (PE) when compared to the *in vivo* values.
- Using simulator default values for PRC and CSR led to a significant underestimation and a greater PE of both AUC and $C_{max}$ in each case relative to the *in vivo* profiles.

*Table 1: Observed and Modelled Drug Exposure Pharmacokinetic Parameters*

| | Dipyridamole | | | Ketoconazole | | |
|---|---|---|---|---|---|---|
| | Ricevuti et al. ± SD [1] | PBPK using experimental biphasic PRC value ± SD (%PE) | PBPK Default Simulator Values ± SD (%PE) | Daneshmend et al. ± SD [2] | PBPK using biphasic experimental PRC value ± SD (%PE) | PBPK Default Simulator Values ± SD (%PE) |
| AUC (mg/L.hr) | 4.13 ± 0.52 | 4.12 ± 1.49 (0.24%) | 2.81 ± 1.13 (31.96%) | 12.9 ± 1.50 | 10.49 ± 4.37 (18.68%) | 7.44 ± 3.41 (42.33%) |
| $C_{max}$ (mg/L) | 0.93 ± 0.13 | 0.83 ± 0.21 (10.75%) | 0.49 ± 0.15 (47.31%) | 4.36 ± 0.54 | 4.01 ± 1.23 (8.03%) | 2.80 ± 1.00 (35.78%) |

## CONCLUSION(S)

- Despite using an empirical first order precipitation model, reasonably accurate models of plasma profiles were obtained.
- While a more mechanistic precipitation model would be useful, it can be difficult to adequately parameterise such a model.
- This empirical first order model is a simple and pragmatic approach to early stage precipitation modelling.

## REFERENCE

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