M6018

An Integrated Experimental and Modelling Approach for Characterising the Precipitation Kinetics of Compounds with Poor Aqueous Solubility

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PURPOSE

Pharmaceutical drug development pipelines continue to produce drugs with the challenge of poor aqueous solubility. Enabling formulation technologies, e.g., amorphous solid dispersions, are used to overcome such limitations via the creation of supersaturated states. Depending on the crystal precipitation kinetics, the occurrence of supersaturation could be key to drug performance: higher soluble metastable states improving oral absorption outcome, or rapid crystallisation as a key risk to limiting absorption performance.

We describe an integrated experimental and modelling approach for characterising the precipitation kinetics of compounds with poor aqueous solubility.

METHOD(S).

In vitro solvent quench experiments on the Sirius inForm (Sirius Analytical Ltd.) are used to generate supersaturation data in the presence of biorelevant media on 5 compounds in triplicate. The data is used to develop a validated mechanistic model of the precipitation kinetics of the compounds in gPROMS Formulated Products™ (Process Systems Enterprise Ltd.).

The in vitro vessel and solution dosage form models were used to build a general system model of the solvent quench experimental process. The model was then configured per compound by entering the associated physiochemical properties (e.g. intrinsic solubility, logP etc.) and experimental operating procedure. Parameter estimation was used to calibrate the primary nucleation and growth parameters for each compound's precipitating solid form(s). This provides simultaneous estimation of parameters in the physical model of the process (i.e. the primary nucleation and growth parameters) and the variance model of the measuring instruments.

RESULT(S)

The estimated precipitation parameters were used to predict the precipitation in different experimental conditions to those used in the parameter estimation. The results obtained showed an excellent fit at various levels of supersaturation, achieved with a single set of precipitation parameters.

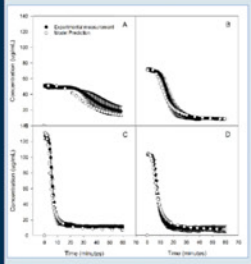

Figure 1. Concentration versus time profiles of aprepitant at A) 51, B) 77, C) 127 and D) 103 µg/mL (black). The error bars represent the standard deviation from triplicate experiments. The white data points represent the model superimposed on the experimental data

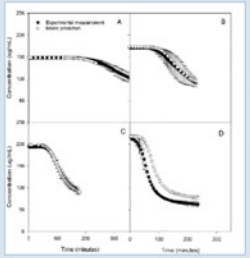

Figure 2. Concentration versus time profiles of felodipine at A) 148, B) 171, C) 195 and D) 214 µg/mL (black). The error bars represent the standard deviation from triplicate experiments. The white data points represent the model superimposed on the experimental data

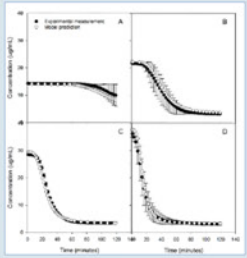

Figure 3. Concentration versus time profiles of indomethacin at A) 14, B) 22, C) 28 and D) 36 µg/mL (black). The error bars represent the standard deviation from triplicate experiments. The white data points represent the model superimposed on the experimental data

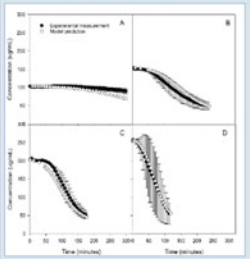

Figure 4. (left). Concentration versus time profiles of ketoconazole at A) 103, B) 155, C) 203 and D) 256 µg/mL (black). The error bars represent the standard deviation from triplicate experiments. The white data points represent the model superimposed on the experimental data

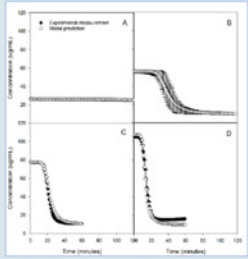

Figure 5. (right). Concentration versus time profiles of tadalafil at A) 26, B) 57, C) 77 and D) 105 µg/mL (black). The error bars represent the standard deviation from triplicate experiments. The white data points represent the model superimposed on the experimental data

	Ketoconazole	Aprepitant	Tadalafil	Felodipine	Indomethacin
Growth integration constant	0.00725	0.0146	0.0865	0.120	0.0422
Growth integration order	1.11	1.83	1.52	1.80	1.42
Primary nucleation rate constant	16.5	14.8	16.5	16.9	14.7
Primary nucleation order	2.88	2.81	1.69	2.91	2.81

Table 1. Estimated parameters derived from the mechanistic model

RESULTS(S)

Of the 20 supersaturation profiles generated in this work, the model was able to match the experimental data within the error bars for 18 of the profiles. The fit to the data may also be visualised in the parity plots in figure 6. Here, the experimental concentration data is plotted against the model concentration data at the same time point. A black line with a slope of 1 is used to represent the experimental data and an ideal model. Of the 2 profiles that did not fall within the error bars, the model under-predicted the induction time for the lowest concentration level for aprepitant and over-predicted the induction time for the highest concentration level for felodipine. Felodipine is known to readily form amorphous states [1], which could have interfered with the nucleation mechanism at high concentrations.

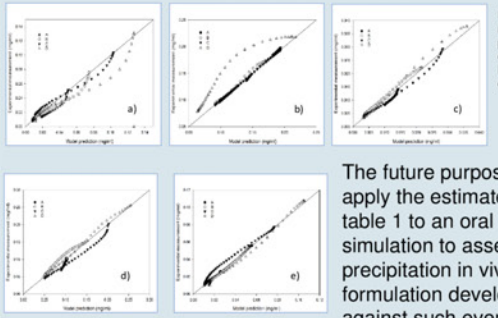

Figure 6. Parity plots of the measured concentration plotted against the modelled concentration of a) aprepitant, b) felodipine, c) indomethacin, d) ketoconazole and e) tadalafil

The future purpose of this work is to apply the estimated parameters in table 1 to an oral absorption simulation to assess the risk of precipitation in vivo and support formulation development to mitigate against such events.

CONCLUSION(S)

The validated precipitation models can subsequently be used to conduct in vivo oral absorption simulations in the same framework, using the same models, increasing confidence in model predictions, and supporting formulators evaluating the risk of in vivo precipitation impacting drug product performance.

REFERENCE

1. Raina, S.A. et al., 2014. Enhancements and limits in drug membrane transport using supersaturated solutions of poorly water soluble drugs. *Journal of Pharmaceutical Sciences*, 103(9), pp.2736–2748.