An Integrated Experimental and Modelling Approach to Characterize the Precipitation Kinetics of Compounds with Poor Aqueous Solubility: From In Vitro to In Vivo Predictions

[1] Edward Close, [2] Robert Taylor, [1] Sean Bermingham, [3] Konstantin Tsinman, [2] Karl Box

[1] Process Systems Enterprise Ltd., London, UK [2] Pion Inc. (UK) Ltd., Forest Row, UK [3] Pion Inc., Billerica, USA

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CONTACT INFORMATION: K.Box@pion-inc.com and e.close@psenterprise.com

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 precipitation as a key risk to limiting absorption performance.

OBJECTIVE(S)

We describe **an integrated experimental and modelling approach** for developing a validated model of the precipitation kinetics of compounds with poor aqueous solubility and subsequent deployment of the validated model to predict in vivo performance.

METHOD(S)

In vitro solvent quench experiments on the Pion inForm (Pion Inc.) were used to generate supersaturation data in the presence of biorelevant media on 5 compounds at different supersaturation levels in triplicate. The data was used to **develop a calibrated mechanistic model of the precipitation kinetics** of the compounds in gPROMS FormulatedProducts™ (Process Systems Enterprise Ltd.) (Figure 1).
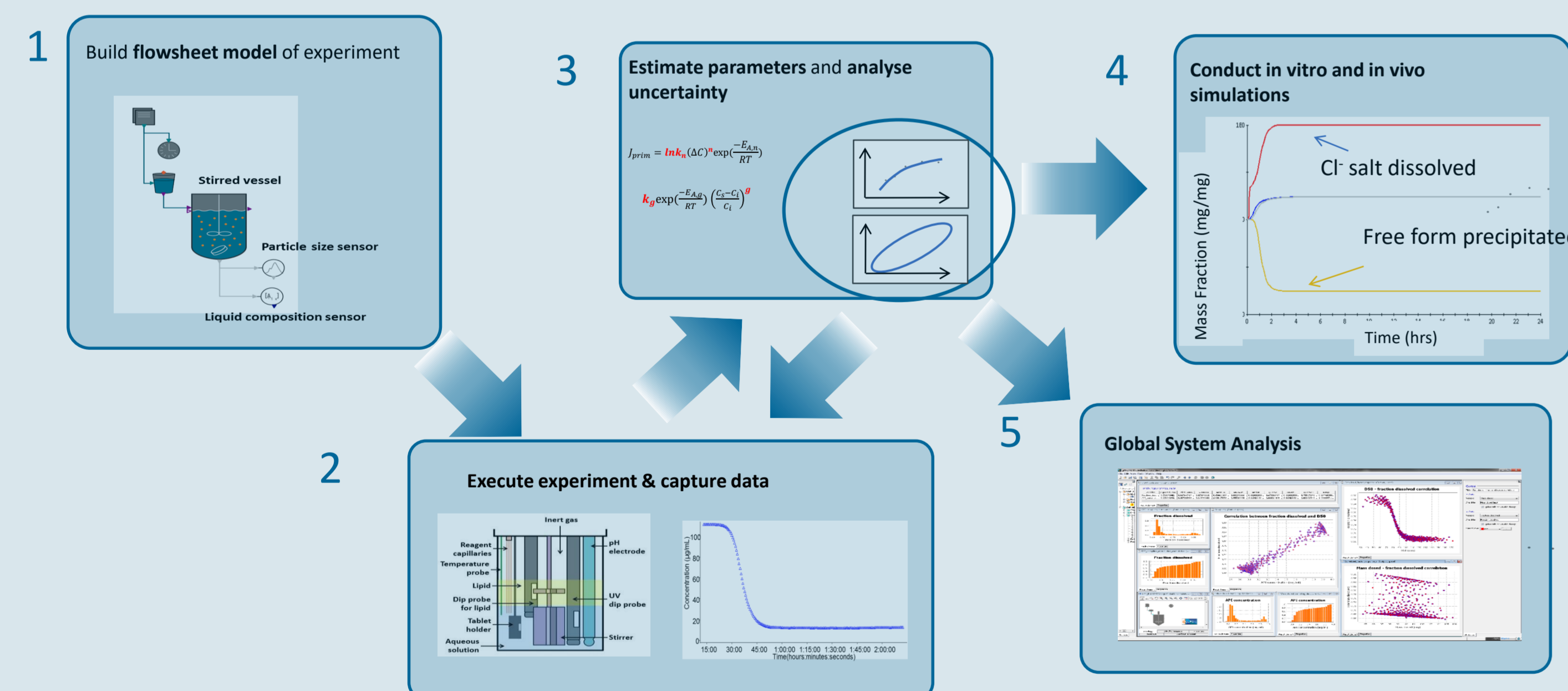

Figure 1. Integrated modelling and experimentation workflow

The in vitro vessel and solution dosage form models were used to build a 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. Automated 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. In addition, **the statistical significance** of the estimated parameter values were determined (e.g. confidence intervals, cross-correlation and 95% t-values).

In vivo oral absorption models were configured using the physiochemical properties of the molecules, dosing information, and the estimated nucleation and growth kinetic parameters. Then Global System Analysis was utilised to conduct an uncertainty analysis that determined the uncertainty in the predicted fraction absorbed due to the confidence intervals of the estimated precipitation model parameters.

RESULTS

The estimated precipitation parameters (shown in Table 1) 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. 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 (figure 2 – figure 6). 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.
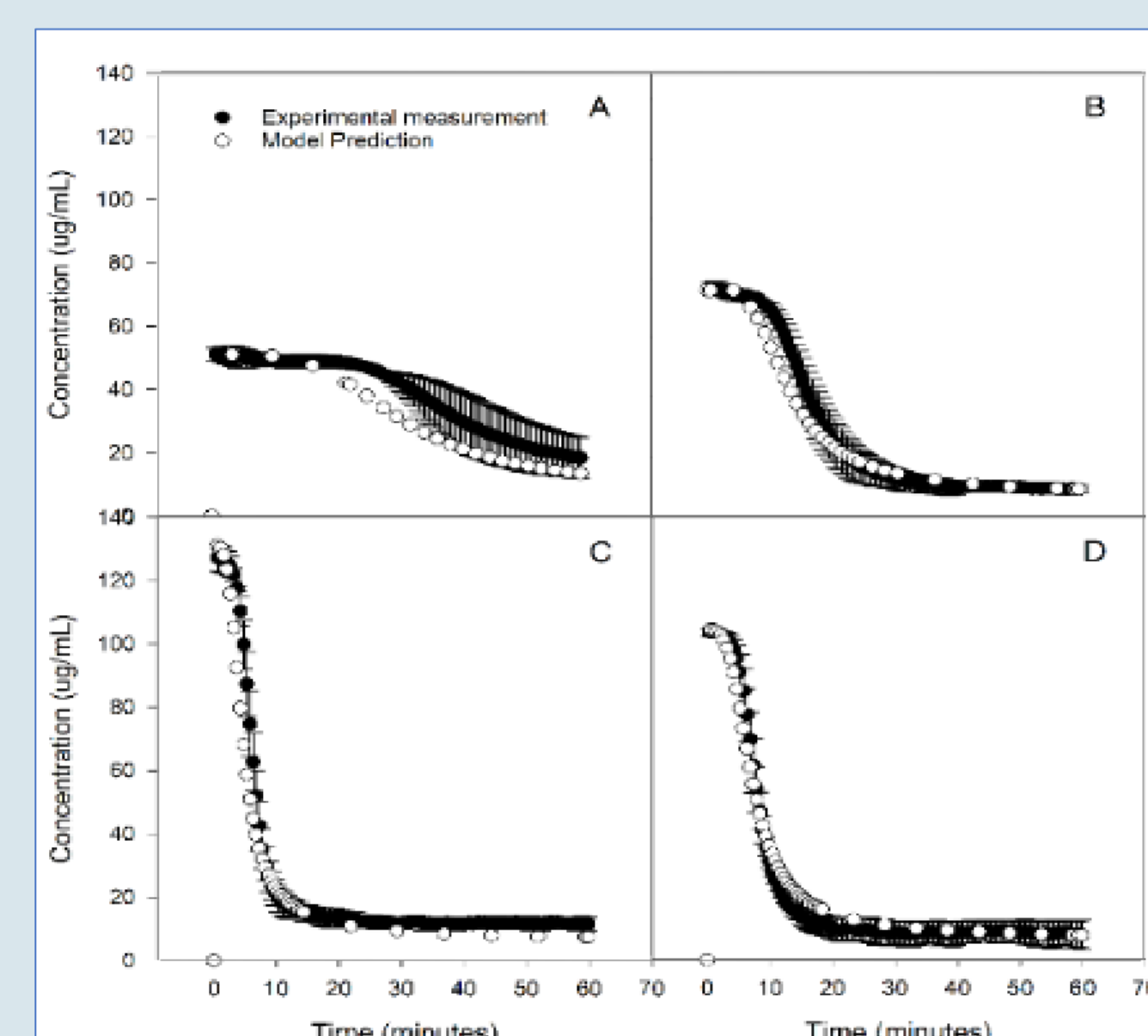

Figure 2. Concentration versus time profiles of aprepitant at A) 51, B) 77, C) 127 and D) 103 µg/mL (black). The error bars represent the standard deviation from triplicate experiments. The white data points represent the model superimposed on the experimental data
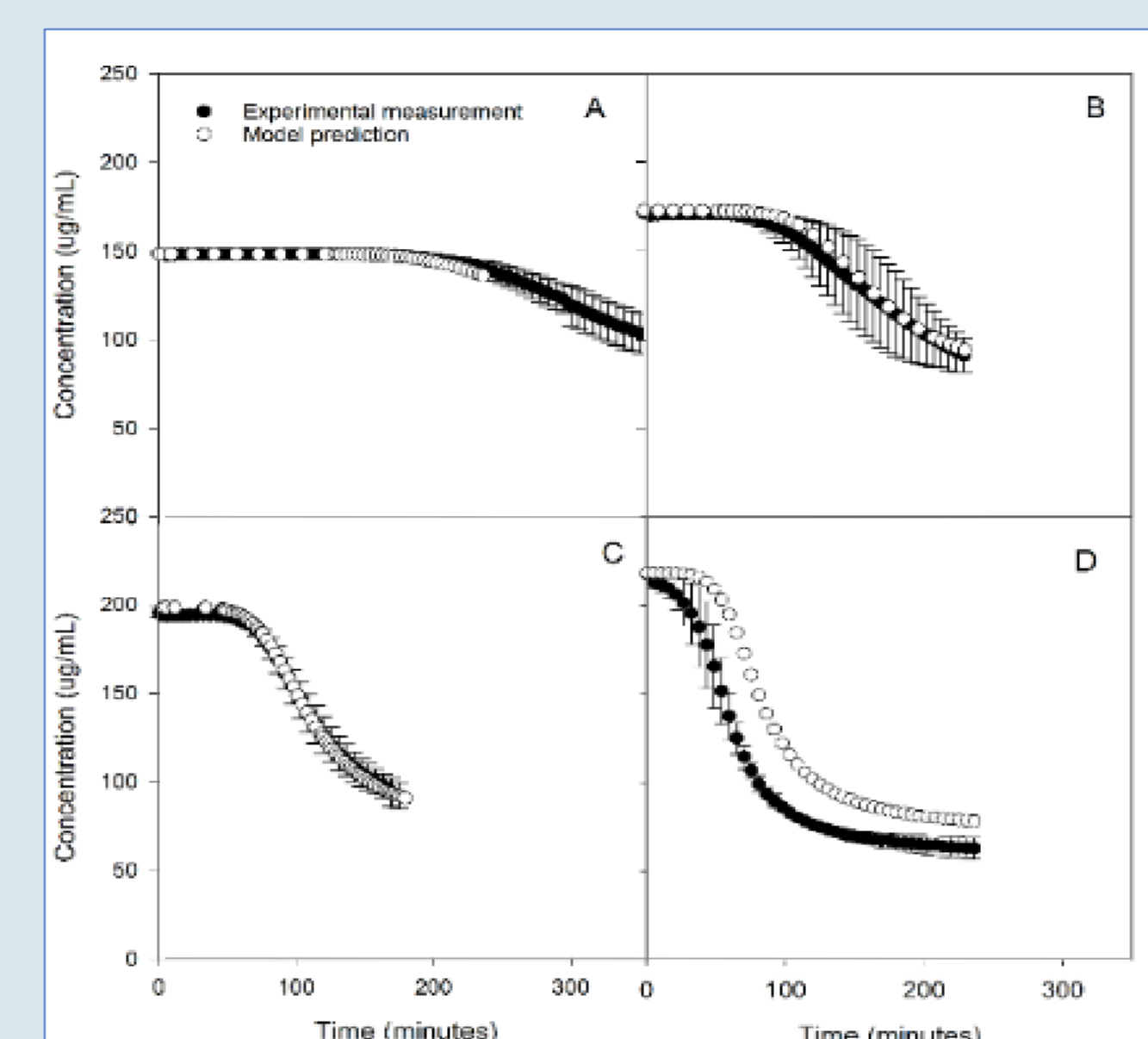

Figure 3. Concentration versus time profiles of felodipine at A) 148, B) 171, C) 195 and D) 214 µg/mL (black). The error bars represent the standard deviation from triplicate experiments. The white data points represent the model superimposed on the experimental data
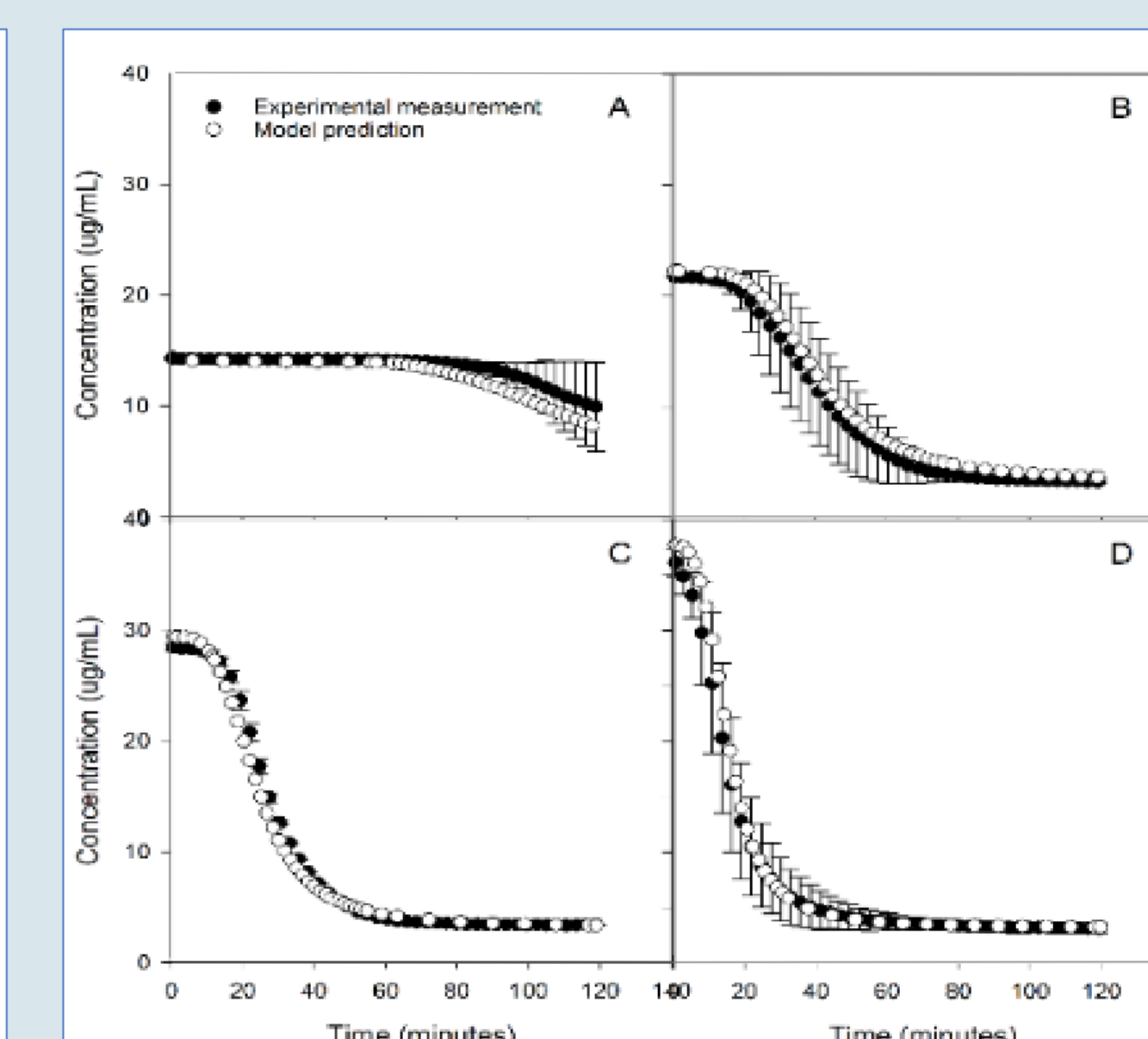

Figure 4. Concentration versus time profiles of indomethacin at A) 14, B) 22, C) 28 and D) 36 µg/mL (black). The error bars represent the standard deviation from triplicate experiments. The white data points represent the model superimposed on the experimental data
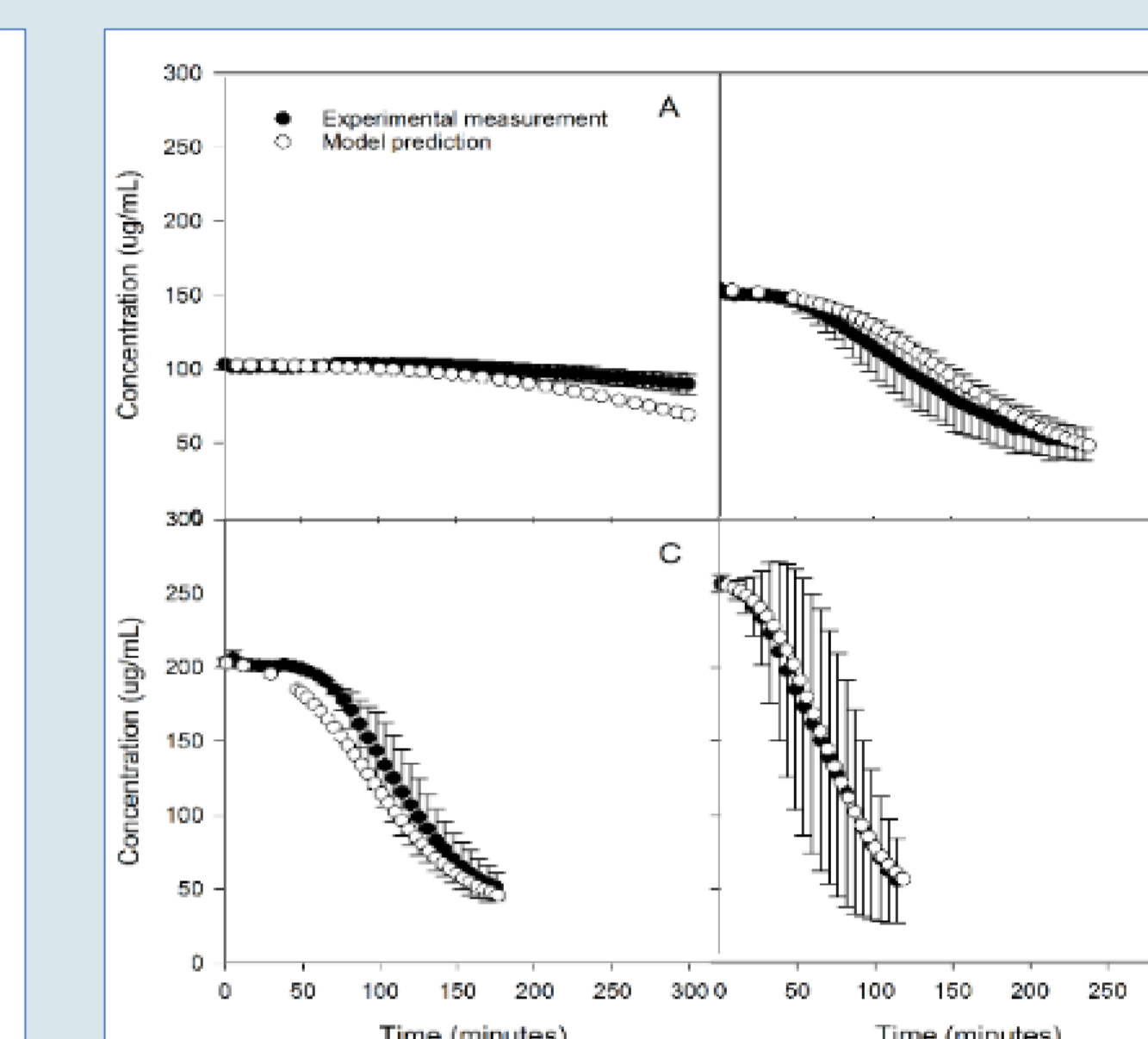

Figure 5. Concentration versus time profiles of ketoconazole at A) 103, B) 155, C) 203 and D) 256 µg/mL (black). The error bars represent the standard deviation from triplicate experiments. The white data points represent the model superimposed on the experimental data
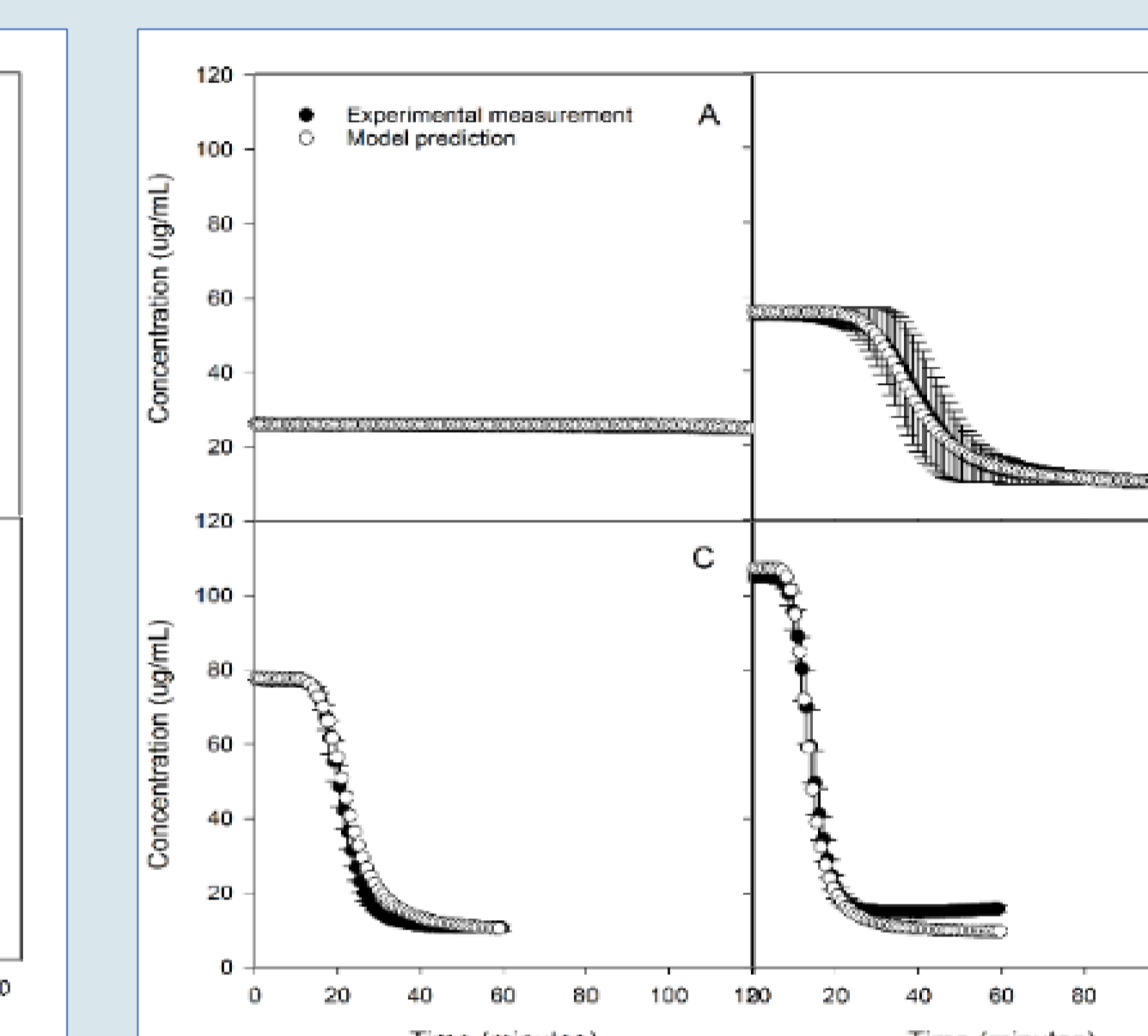

Figure 6. Concentration versus time profiles of tadalafil at A) 26, B) 57, C) 77 and D) 105 µg/mL (black). The error bars represent the standard deviation from triplicate experiments. The white data points represent the model superimposed on the experimental data

The uncertainty analysis was able to determine the impact of the uncertainty in the estimated precipitation model parameters on the in vivo performance. The estimated parameter values are. The 95% confidence intervals for the precipitation model parameters for tadalafil are shown in Table 2. In vivo predictions indicate that tadalafil in vivo behaviour is characterised by an initial rapid precipitation in the gastrointestinal tract, followed by permeation driven dissolution of the precipitated neutral drug (Figure 7). The uncertainty analysis results indicated that the fraction absorbed only varies between 0.97-0.99 due to uncertainty in the estimated parameters, and thus has minimal impact on the predicted in vivo performance (Table 3). These results increase the confidence that the model developed is sufficient for evaluating the risk of precipitation impacting drug product performance.

	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 values

	Tadalafil
Growth integration constant	0.035
Growth integration order	0.17
Primary nucleation rate constant	0.31
Primary nucleation order	0.16

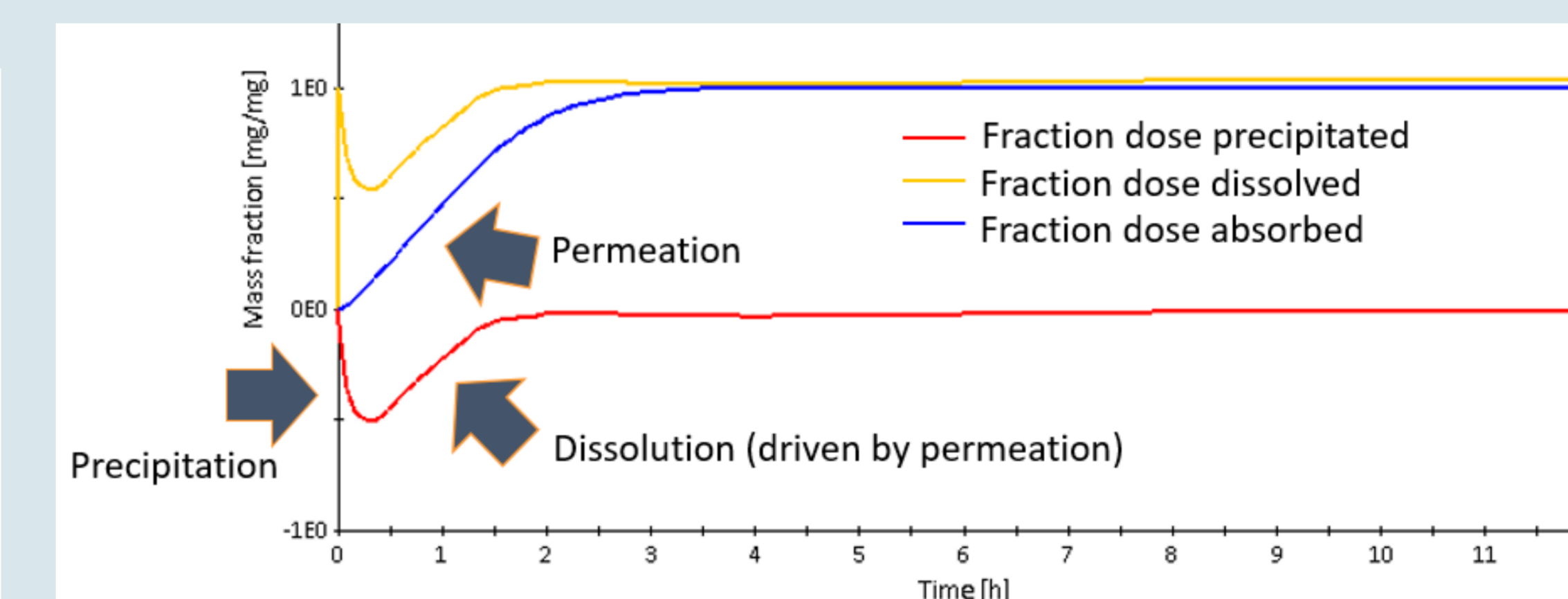Table 2. 95% confidence intervals

Figure 7. Fraction of tadalafil dosed that has precipitated, dissolved and absorbed in the gastrointestinal tract as a function of time (2.5. mg dose)

	Tadalafil fraction dose absorbed
Expected value (average)	0.98
Minimum value	0.97
Maximum value	0.99

Table 3. Uncertainty in predictions

CONCLUSION(S)

An in-vitro precipitation model was calibrated , validated to be able to extrapolate to other fluid conditions, and subsequently used to conduct in vivo oral absorption simulations. This allows formulators to evaluate the risk of in vivo precipitation impacting bioavailability, utilising uncertainty analysis to account for uncertainty in the estimated precipitation kinetics when conducting in vivo predictions. The uncertainty analysis can be extended to include effects of formulation and physiological factors.

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.