05W1200

Controlled supersaturation experiments in SGIM and models

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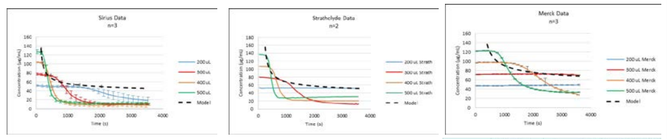
PURPOSE

To develop and validate a novel, low volume experiment for the assessment of API supersaturation, nucleation and precipitation in simulated gastrointestinal media (SGIM). Using Classic Nucleation Theory (CNT) and a new mechanistic approach, the data could be modelled allowing for prediction of the nucleation and precipitation at different supersaturation levels.



Injection Volume (µL)	Induction time Average (s)	%CV	Decay constant Average (s^{-1})	%CV	Extrapolated Solubility Average (µg/mL)	%CV
500	137.3	13.5	0.4490	13.7	12.10	14.5
400	169.4	10.9	0.3185	5.6	8.70	43.6
300	513.1	16.6	0.1755	23.4	9.13	7.2
200	1417	6.4	0.0649	68.0	9.93	25.2

Injection Volume (µL)	Induction time Average (s)	Decay constant Average (s^{-1})	Extrapolated Solubility Average (µg/mL)
500	275.3	0.657	29.28
400	374.3	0.338	20.95
300	880.7	0.1	32.2
200	N/A	N/A	N/A

Injection Volume (µL)	Induction time Average (s)	%CV	Decay constant Average (s^{-1})	%CV	Extrapolated Solubility Average (µg/mL)	%CV
500	390.67	0.12	0.13	6.28	31.81	3.27
400	1117.00	9.06	0.07	6.43	19.90	4.94
300	2406.33	3.45	N/A	N/A	N/A	N/A
200	N/A	N/A	N/A	N/A	N/A	N/A

Figure 1. The supersaturation profiles and data tables of aprepitant collected on the Sirius inForm from Sirius (left), Strathclyde (middle) and Merck (right). The green, orange, red and blue graphs show the supersaturation profiles at different levels of supersaturation and the black dotted line shows the CNT model for nucleation determined from figure 2.

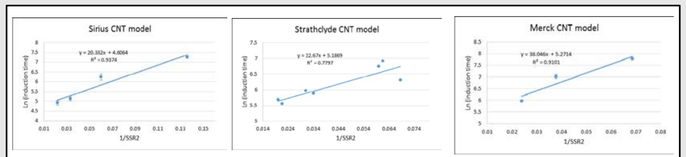


Figure 2. The classic nucleation theory models of the induction times derived from the supersaturation profiles (above).

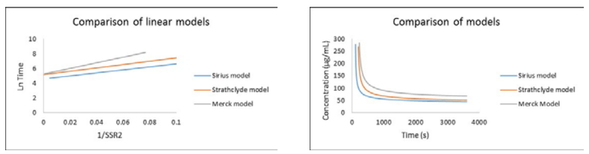


Figure 3. Comparison of the linear CNT models (left) and when transformed to concentration versus time (right).

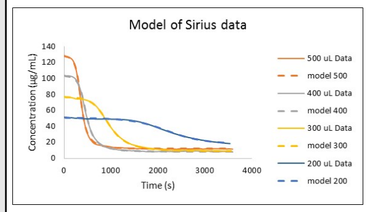
The supersaturation ratio (SSR) was found by dividing the initial concentration by the average extrapolated solubility of all datasets (18.86 µg/mL). The induction times were plotted against supersaturation ratio and transformed by the classic nucleation equation to give a straight line for homogeneous nucleation mechanisms (Figure 2).

METHOD

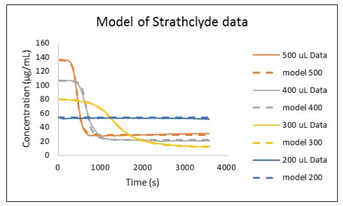
The supersaturation experiments were conducted at Sirius, the University of Strathclyde and Merck & Co., Inc. on a Sirius inForm using the Controlled Supersaturation assay. Here, 40 mL of the medium was dispensed into the vessel, the temperature was controlled to 37°C and the pH adjusted to 6.5. A volume of a concentrated stock solution of the API in solvent was then added to the medium. UV spectra were collected by an immersion probe for a specified duration. Experiments at the same volume were repeated in triplicate, except for the Strathclyde data where duplicates were only available.

The medium was prepared from FaSSIF v2 powder supplied by Biorelevant.com and NaCl, but the maleic acid buffer system was replaced with the v1 phosphate buffer system to enable in situ UV quantitation.

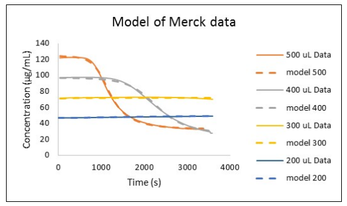
Microsoft Excel and the Solver add-in was used to model the data and minimise the errors of the model fit.



	500 uL	400 uL	300 uL	200 uL	average	%error
concentration t0	127.3	103.4	76.8	51.2		
kdiss	0.0027	0.0020	0.0016	0.0059	0.0030	56
knuc	0.0010	0.0011	0.0016	0.0051	0.0022	77
solubility	18.86	18.86	18.86	18.86		
nuc power	1.82	1.75	1.47	1.23	1.57	15
disso power	0.71	0.74	0.92	0.95	0.83	13
RMSD	0.55	0.53	0.35	0.47		



	500 uL	400 uL	300 uL	200 uL	average	%error
concentration t0	137.1	107.2	80.4	53.5		
kdiss	0.0074	0.0071	0.0010	0.0020	0.0044	66
knuc	0.0011	0.0012	0.0010	0.0000	0.0008	58
solubility	18.86	18.86	18.86	18.86		
nuc power	1.90	1.98	1.50	1.56	1.73	12
disso power	0.68	0.63	0.94	0.39	0.66	30
RMSD	1.48	2.08	0.52	0.89		



	500 uL	400 uL	300 uL	200 uL	average	%error
concentration t0	121.9	96.9	71.5	46.7		
kdiss	0.0011	0.0020	0.0007	0.00075	0.0011	48
knuc	0.0002	0.0014	0.0006	0.00108	0.0008	54
solubility	18.86	18.86	18.86	18.86		
nuc power	2.12	1.33	1.54	0.00	1.25	62
disso power	0.79	0.94	0.05	0.39	0.54	64
RMSD	1.47	1.44	0.59	0.10		

Figure 4. The mechanistic models fitted to the supersaturation profiles and the tables of parameters and their values.

Dissolution Rate

$$\frac{dC}{dt} = k_{diss} \cdot \frac{A_s \cdot (1 - SR)}{V} - k_{nuc} \cdot C^{\alpha}$$

Precipitation Rate

$$\frac{dA_s}{dt} = -k_{diss} \cdot A_s \cdot (1 - SR) + k_{nuc} \cdot C^{\alpha} \cdot V$$

Equation 1. The Roche model. C: concentration, t: time, kdiss: dissolution rate constant, knuc: nucleation constant, As: mass undissolved, SR: supersaturation ratio, α: molecularity index, V: volume

Net rate of change = dissolution rate - precipitation rate

$$\frac{dC}{dt} = (k_{diss} \cdot A_s^{\beta} \cdot SR) - (k_{nuc} \cdot A_s \cdot SR^{\alpha})$$

Equation 2. The adapted model. C: concentration, t: time, kdiss: dissolution rate constant, knuc: nucleation constant, As: mass undissolved, SR: supersaturation ratio, α: nucleation power, β: dissolution power.

For the mechanistic approach, the group at Roche Pharmaceuticals in Basel, Switzerland[1], developed a model that accurately described the precipitation curve of a supersaturated compound in a fixed volume experiment, using dissolution and nucleation rate constants and a power function to account for nucleation cluster size (equation 1). This model was adapted to include a second power function for dissolution and exclude volume (equation 2).

RESULTS

The resulting data had a sigmoidal shape to the profile with upper and lower plateaux and a decaying slope. The data on the upper plateau was used to determine induction time. Here, the RMSD of the data on the plateau was determined and the induction time was found from the first data point that exceeded 2 standard deviations from the mean. A first order model was fitted to the decaying slope and lower plateau to find the decay constant and extrapolated solubility (Figure 1).

CONCLUSION

The supersaturation experiments conducted on aprepitant at three different sites (Sirius, Strathclyde and Merck) showed good reproducibility. It is our intention to collect data on a wider range of compounds to better evaluate the consistency of this experiment. The adaptations to the Roche model[1] improved the fit to the data, but we are yet to see the effect on the in silico prediction of PK.

FUNDING / GRANTS / ENCORE / REFERENCE or other use

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1. Jakubiak, P. *et al.* Development of a Unified Dissolution and Precipitation Model and Its Use for the Prediction of Oral Drug Absorption. *Mol. Pharm.* **13,** 586–598 (2016).