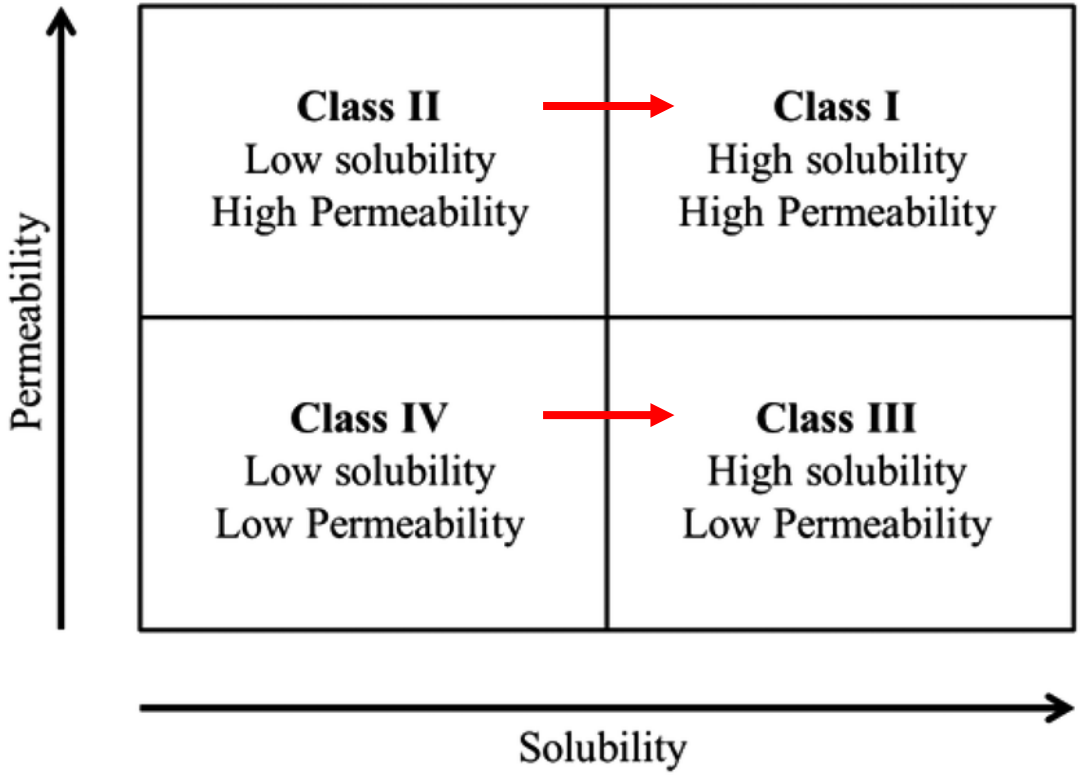
Supersaturation measurement and modelling

an application for pharmaceutical drug development

What is supersaturation and why is it interesting?

"an unstable system which has a greater concentration of a material in solution than would exist at equilibrium"
- *IUPAC*

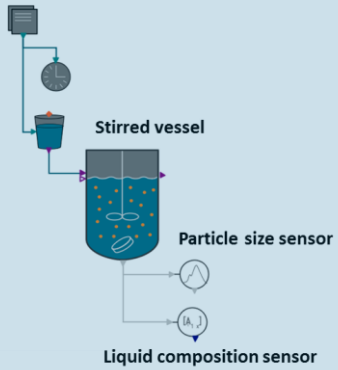
$$\frac{Solution\ concentration}{equilibrium\ solubility} > 1$$



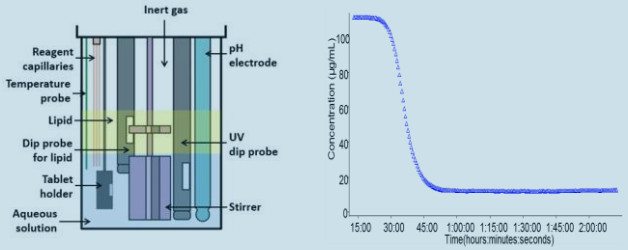
Advanced process modelling workflow

Introduction

1 Build **flowsheet model** of experiment



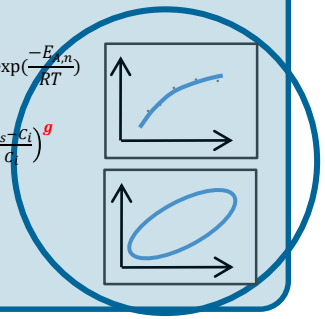
2 **Execute experiment & capture data**



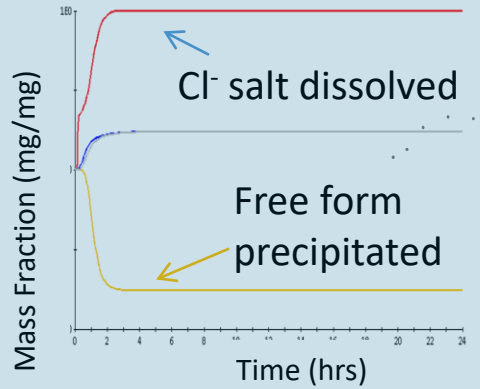
3 **Estimate parameters** and **analyse uncertainty**

$$J_{prim} = \boldsymbol{lnk_n}(\Delta C)^{\boldsymbol{n}}\exp(\frac{-E_{A,n}}{RT})$$

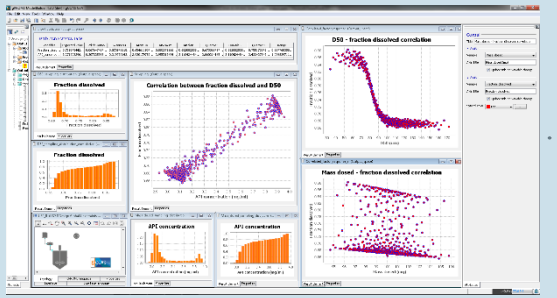
$$\boldsymbol{k_g}\exp(\frac{-E_{A,g}}{RT})\left(\frac{C_s - C_i}{C_s}\right)^{\boldsymbol{g}}$$



4 **Conduct in vitro and in vivo simulations**



5 **Global System Analysis**



Aims and objectives

- An approach that can characterise precipitation **over a range of conditions** with a **single set of parameters** is novel
- Workflow
  - Sirius Analytical: Experiments and data
  - Process Systems Enterprise: gCOAS In vitro models, parameter estimation and GSA capabilities
- Demonstrate applicability to a wide range of compounds

Compound	Intrinsic solubility (mg/ml)	pKa	logP
Dibase (ketoconazole)	0.0266	3.29, 6.24	3.7
Ordinary ampholyte (aprepitant)	0.0227	2.8, 8.5	4.5
Neutral (felodipine)	0.053	n/a	1.7
Base (tadalafil)	0.00389	5.39	3.86
Acid (indomethacin)	0.00201	4.2	4.3

Biorelevant or fundamental study?

Which approach to take?

Biorelevant based study: Design a method mimicking the solution state of a GI transit (pH, dilution, gastric residence and emptying, bile salts and phospholipids). Add the sample as a dosage form or similar**.** Measure the dissolution and precipitation rates.

- Possible correlation of in vitro supersaturation profile to in vivo data
- Evaluate propensity or risk of precipitation
- Don’t learn much about compound

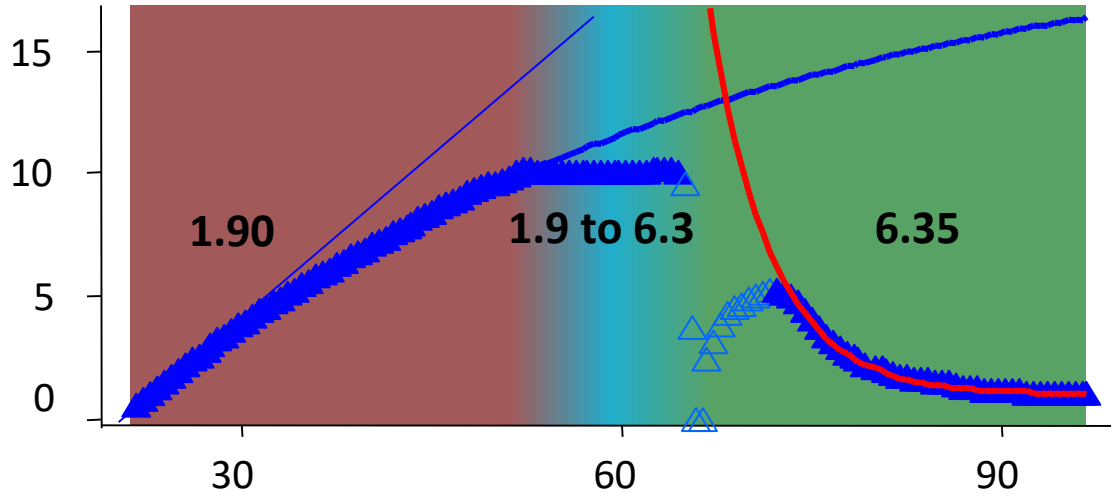
Property based study: Find the media conditions where the compound is supersaturated and precipitation is observed. Explore the supersaturation profile at different starting concentrations.

- Understand the fundamental aspects that govern nucleation, induction and crystal growth
- Include excipients and polymers for formulation development
- Not biopredictive

Typical data output

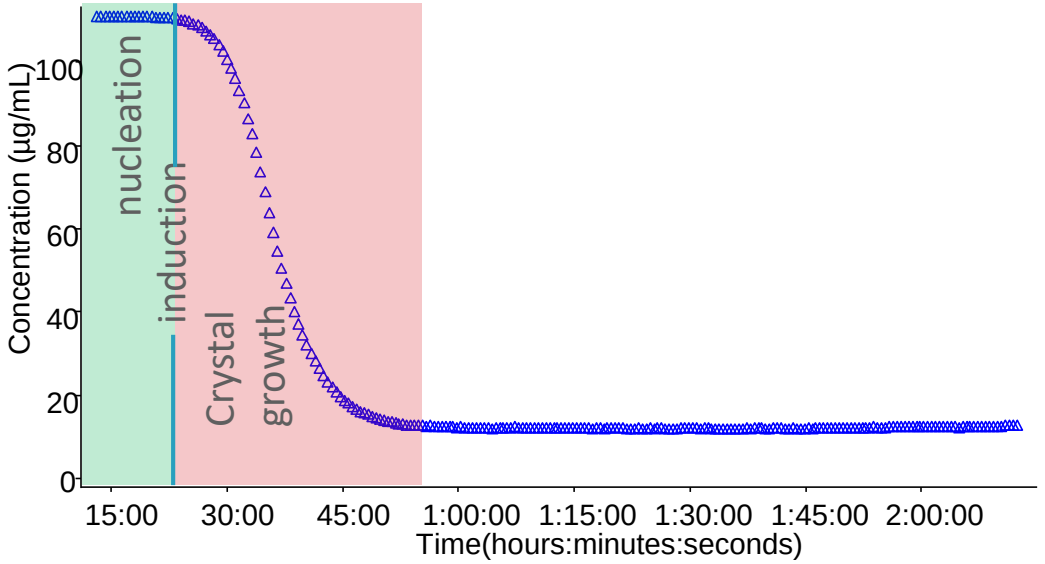
Biorelevant based study

pH shift: Sample may be either a stock solution or a solid, but must be fully dissolved at start pH. The pH is then shifted/titrated to a target value at a defined temperature (sample must ionisable).



Property based study

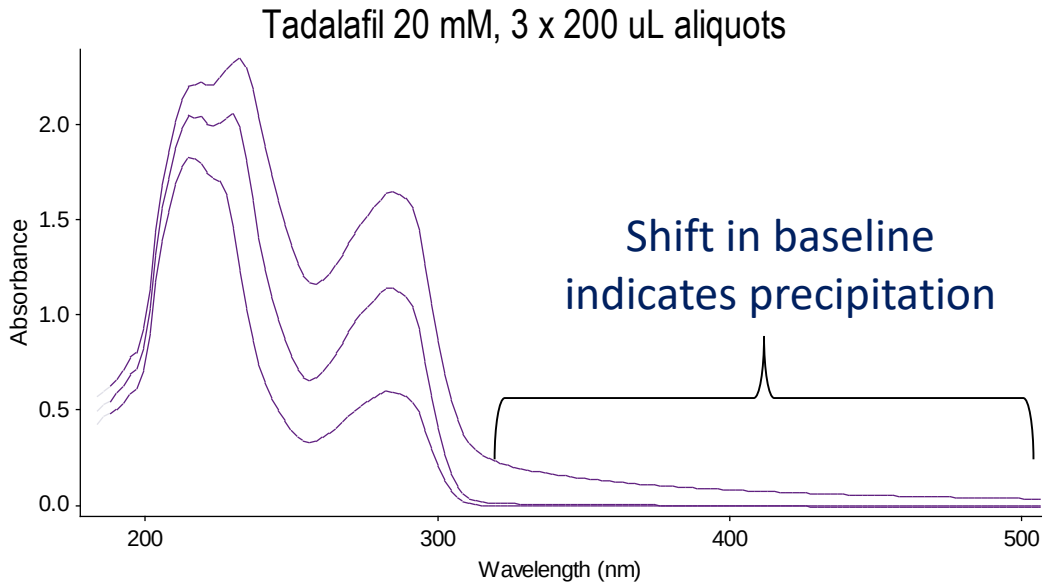
Solvent quench: Prepare sample as a stock solution and add a defined volume to the media at a defined temperature and pH (universal method for all sample types).

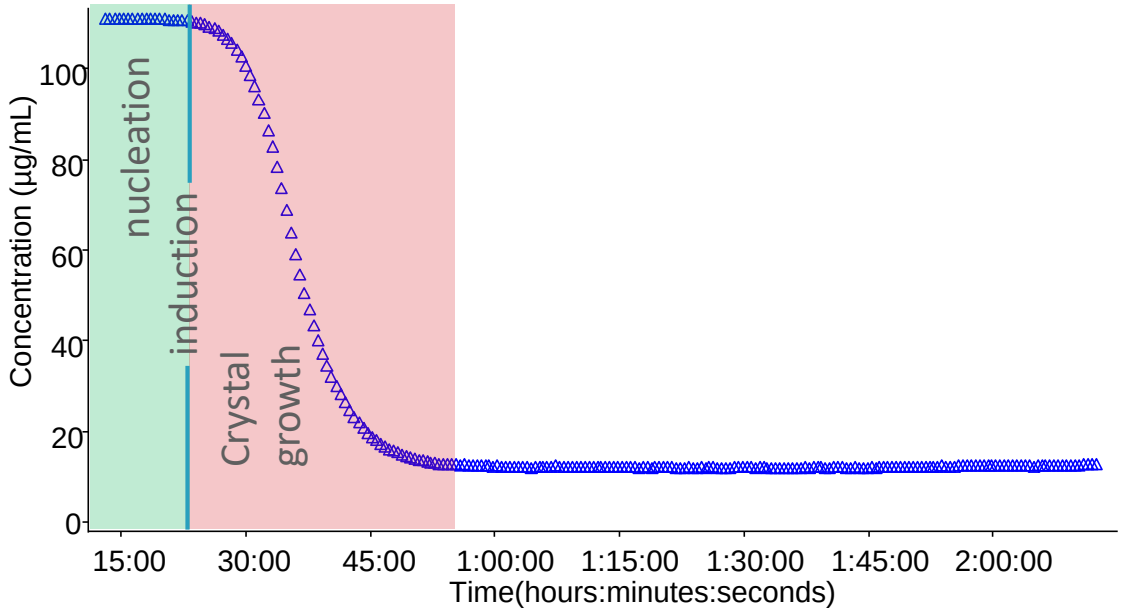


Solvent quench method

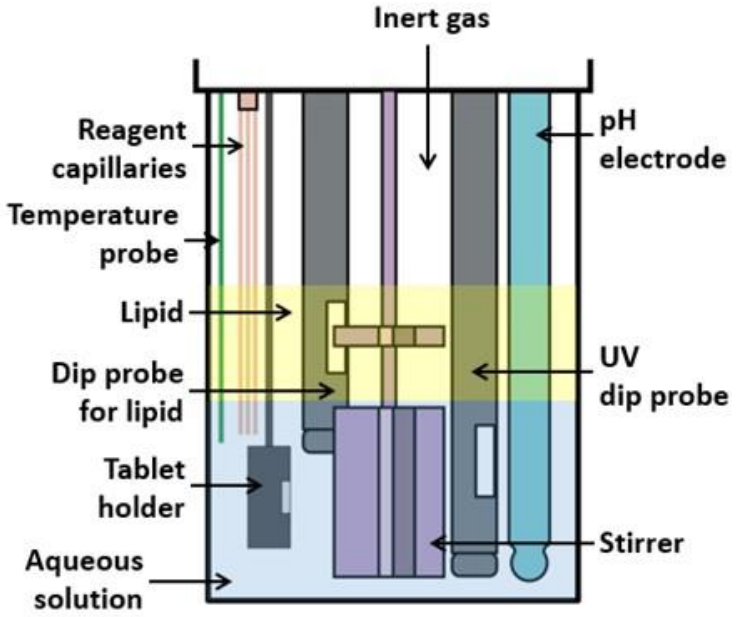
Method Overview

1. Use a fixed volume of FaSSIF v1 (40 mL on inForm) maintained at 37°C and find the concentration where instantaneous precipitation occurs (left graph). This is the maximum level of supersaturation.
2. Run some exploratory supersaturation assays below this concentration to observe a sigmoidal shape to the concentration vs. time profile (right graph)
3. Run supersaturation experiments using at least two different supersaturation levels.
4. Measure the induction time, decay constant and extrapolated solubility and fit to Classic Nucleation Theory (CNT).
5. Compare to other sites on selected compounds.

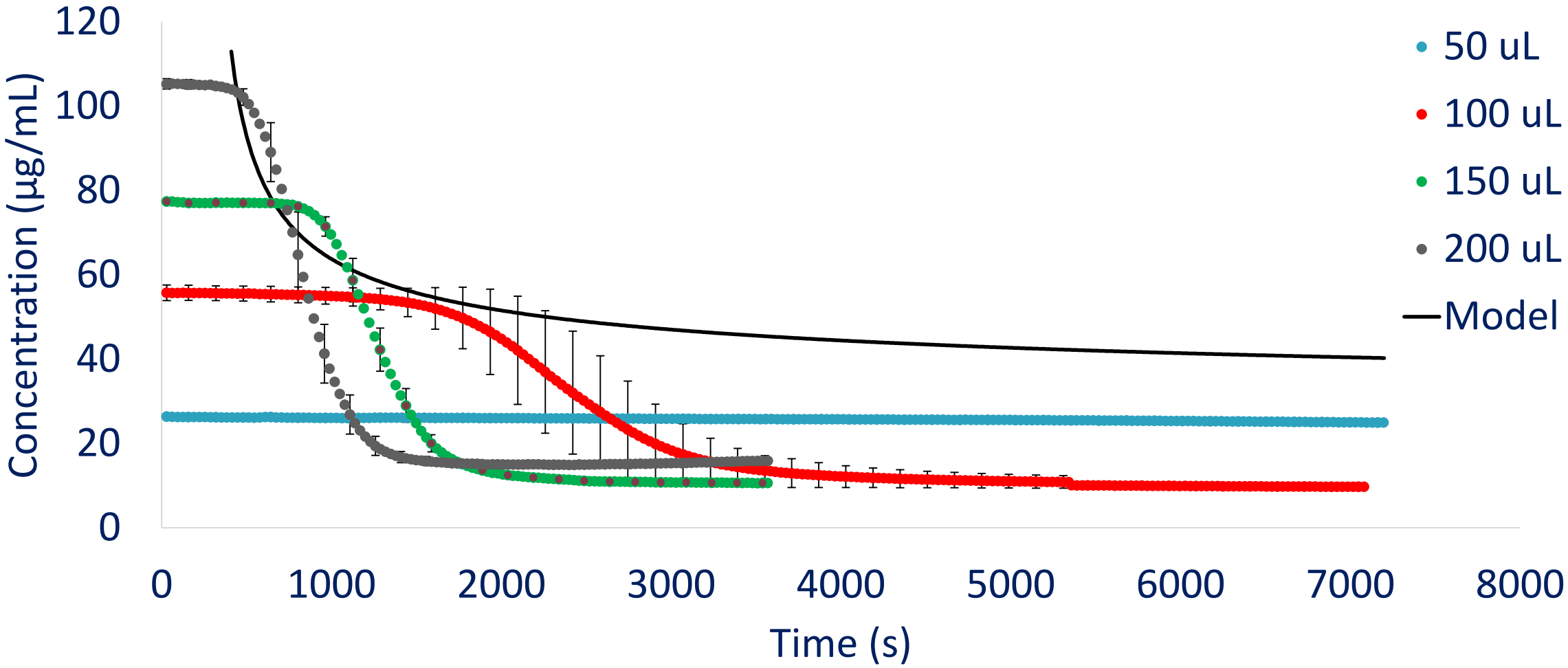




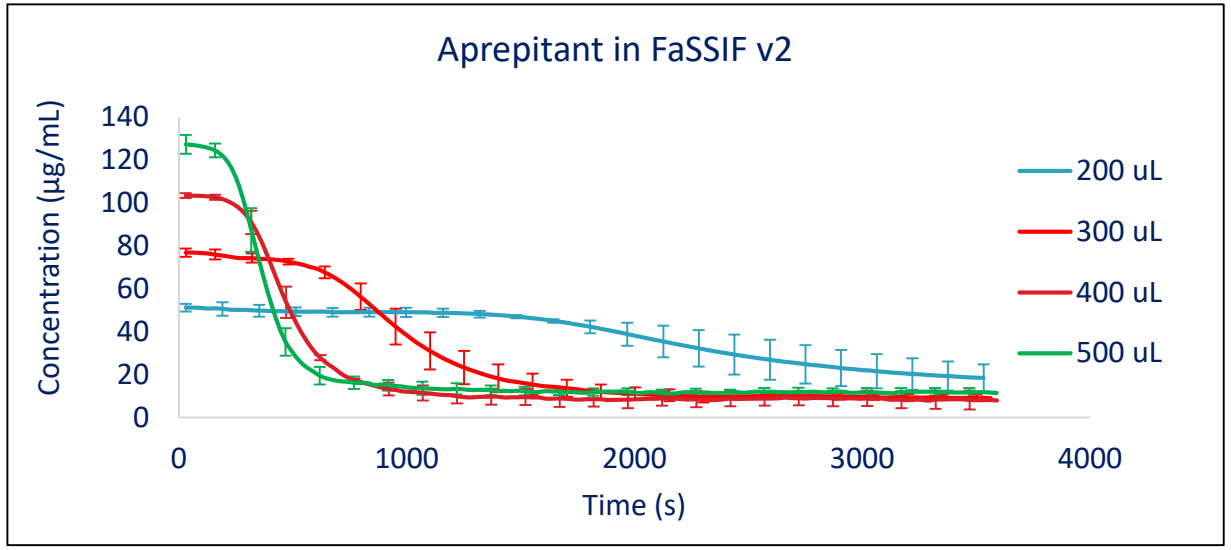
Hardware Features of the Sirius inForm

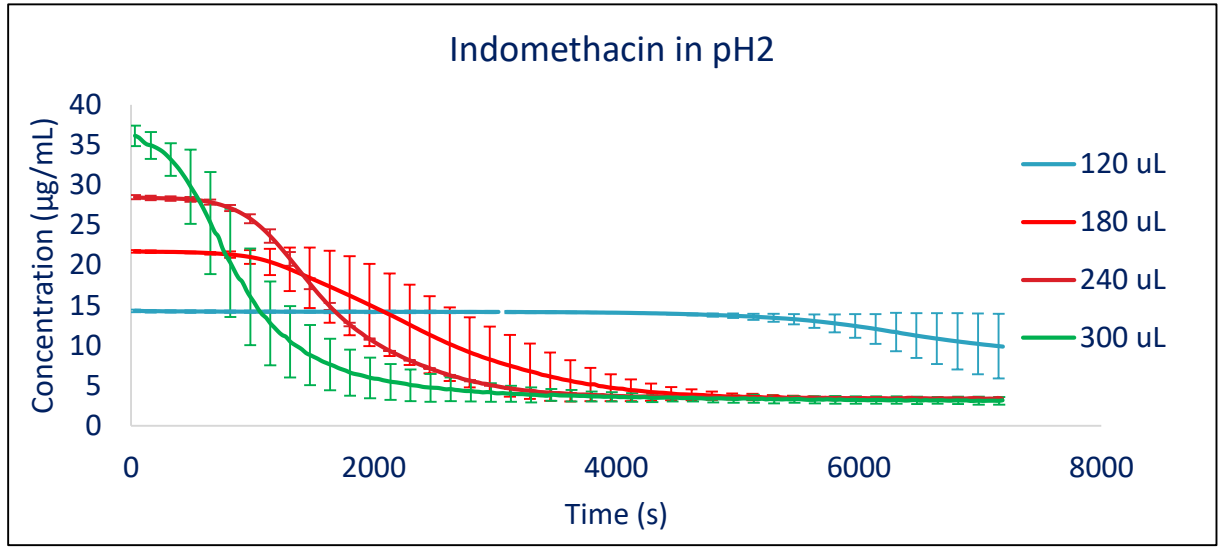


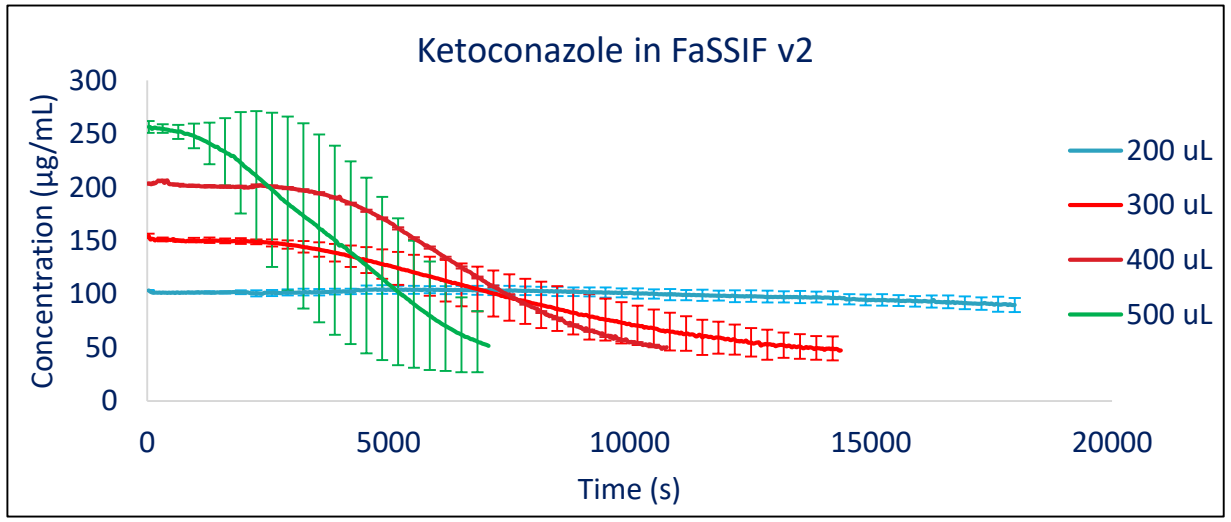
Supersaturation of tadalafil in FaSSIF v1

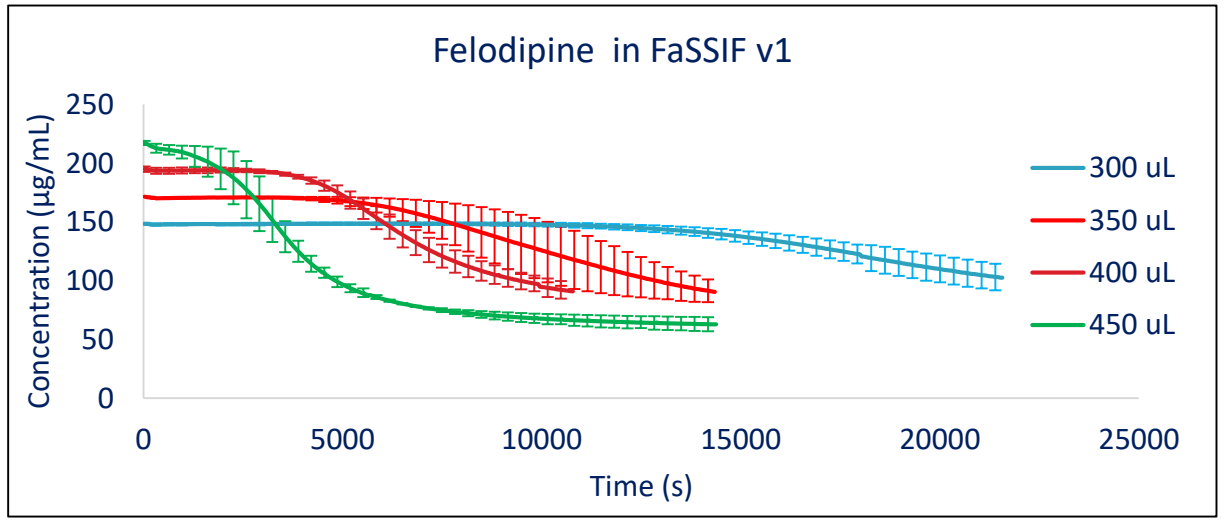


Other compounds in the study

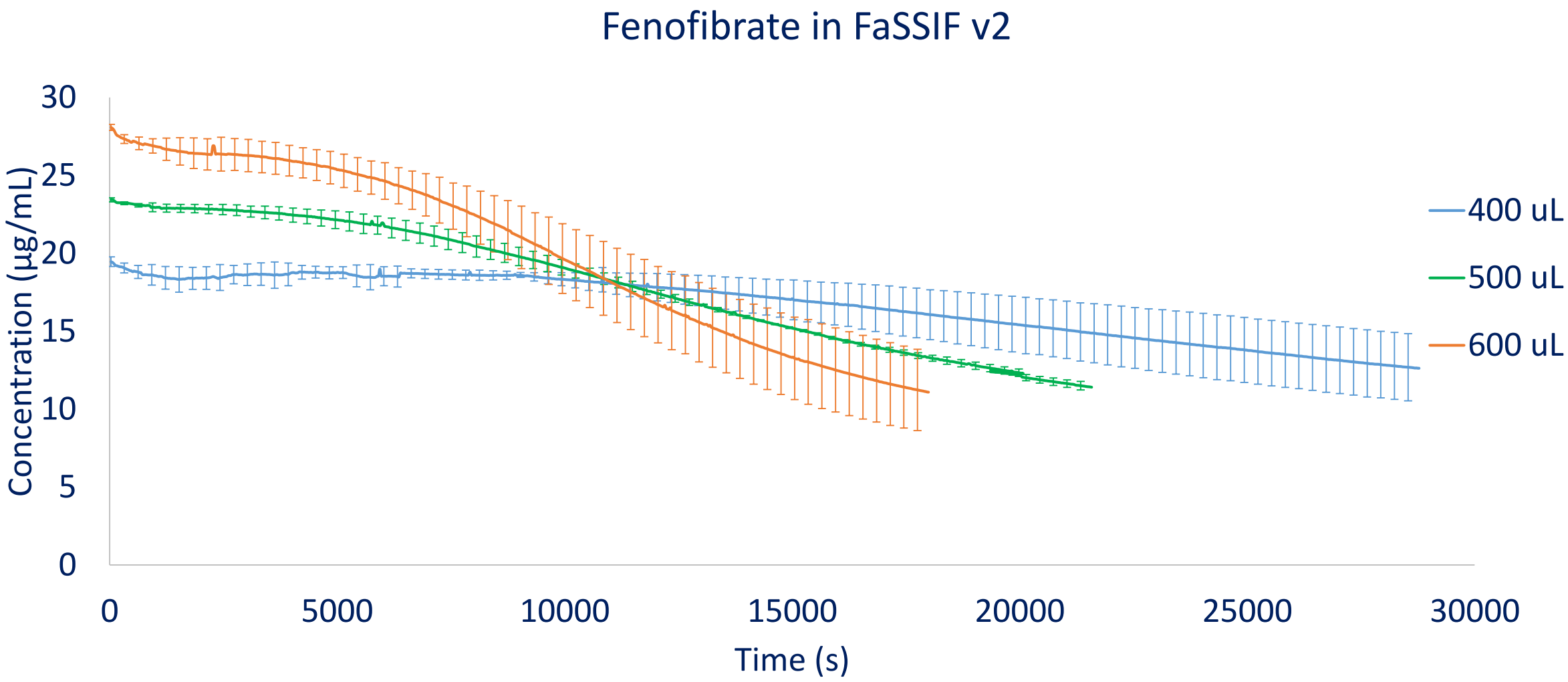








Not all compounds follow Classic nucleation theory!



Workflow recap

Advanced process modelling workflow

Introduction

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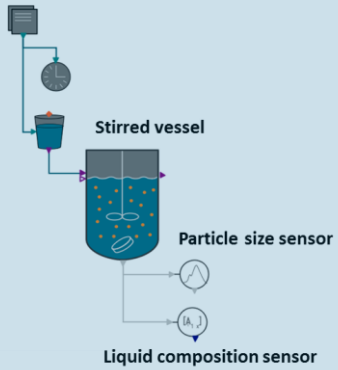

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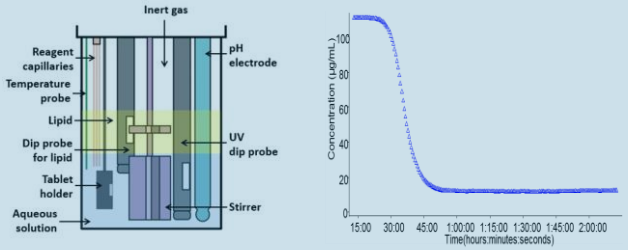

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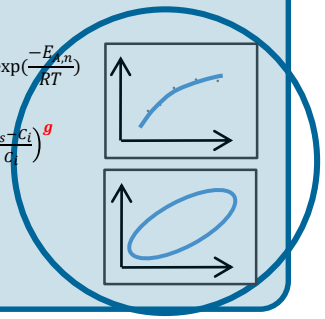
$$\boldsymbol{k_g}\exp(\frac{-E_{A,g}}{RT})\left(\frac{C_s - C_i}{C_s}\right)^{\boldsymbol{g}}$$



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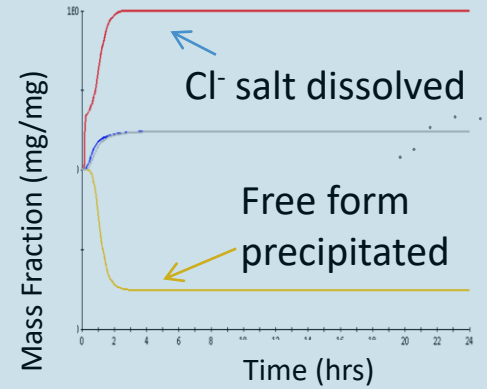

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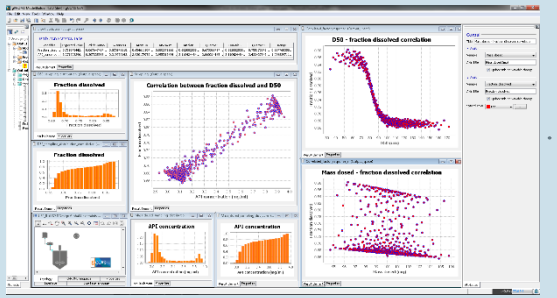
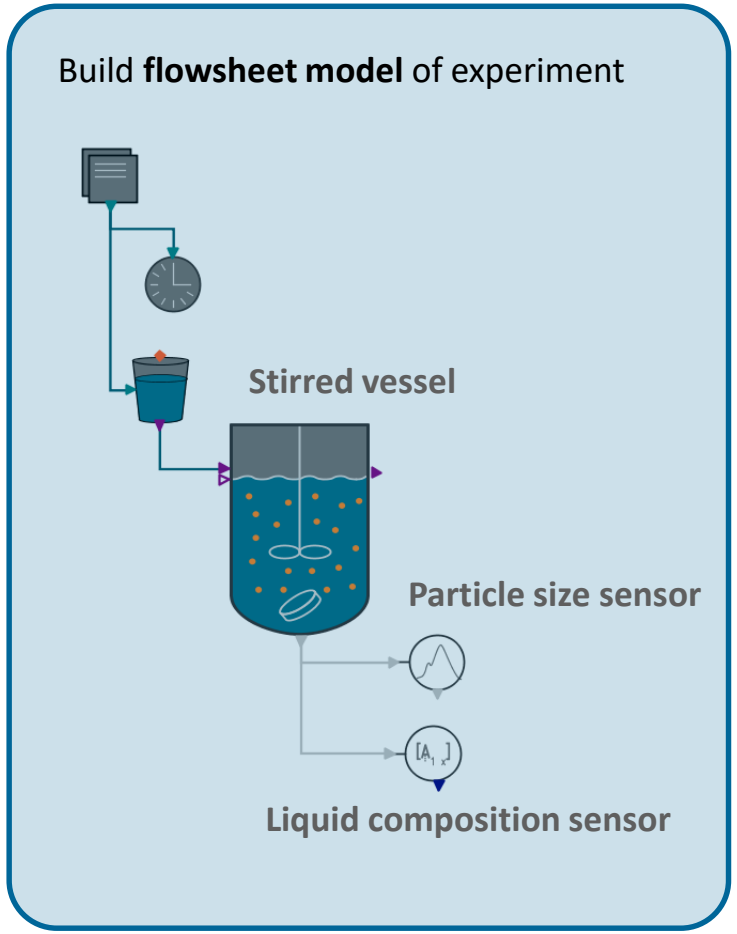


Model

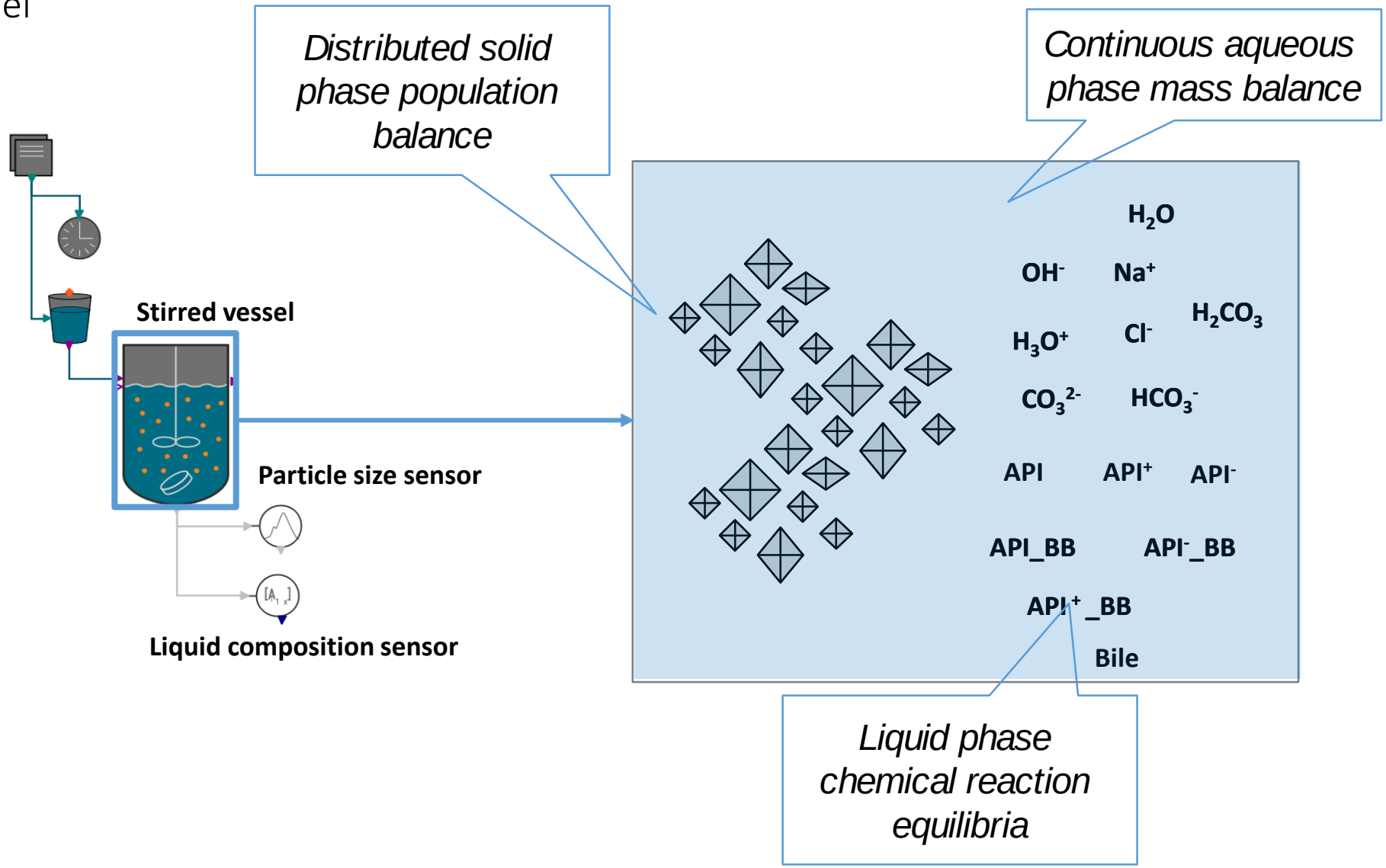
Building a flowsheet model of the experiment



- General system model
  - Solution
    - Contains highly concentrated API
  - In vitro vessel
  - Sensor models
    - Used for measured variables in parameter estimation
- Configured per compound
  - Physiochemical properties
  - Experimental operating procedure

Model equations (1)

gCOAS in vitro vessel



Model equations (2)

gCOAS in vitro vessel

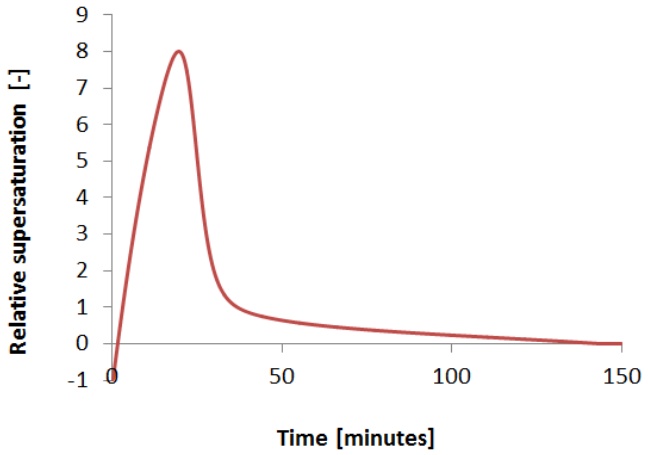
- Based on relative supersaturation
  - Freeform - based on intrinsic solubility
  - Salts - solubility product and counterion concentration

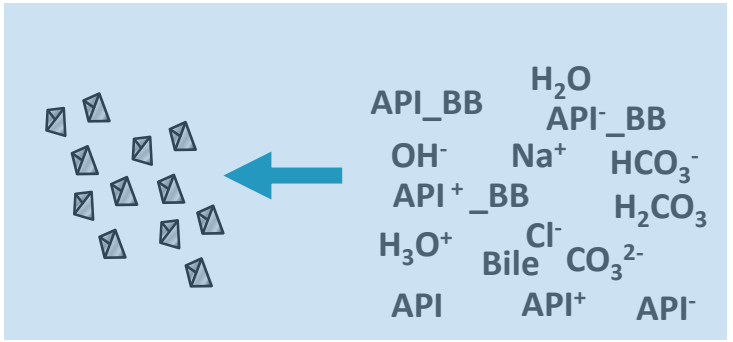
- Kinetic model options
  - Classical nucleation kinetics

$$J_{prim} = lnA_0\left(\frac{-16\pi(\alpha\sigma)^3 v^2{}_0}{3k^3T^3lnS^2}\right)$$

  - Power law nucleation kinetics

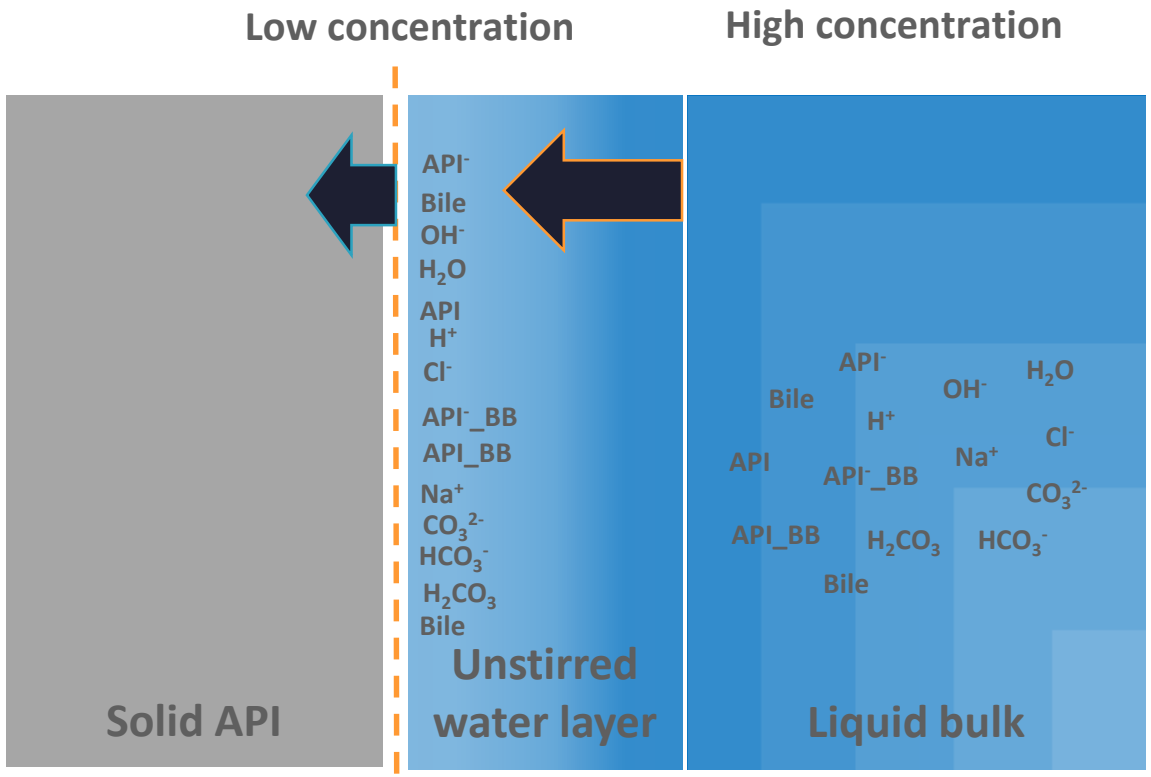
$$J_{prim} = lnk_n(\Delta C)^n \exp(\frac{-E_{A,n}}{RT})$$





Model equations (3)

gCOAS in vitro vessel



- Reaction

$$K_j = \prod_{i=1}^{NC} (C_i)^{\nu_{ij}},\ j = 1,..,NR$$

- Diffusion

$$\frac{D_i}{h}\left(C_i^s - C_i^b\right), i = 1, \ldots, NC$$

- Surface integration limited growth

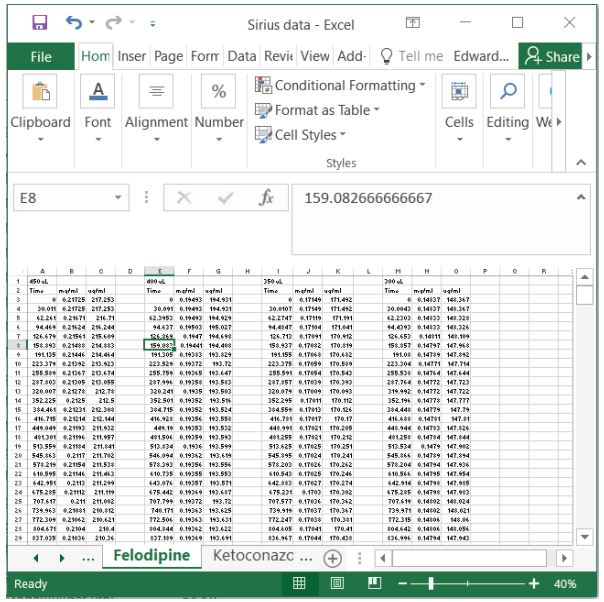
$$k_g \exp\left(\frac{-E_{A,g}}{RT}\right)\left(\frac{C_s - C_i}{C_i}\right)^g$$

Parameter estimation

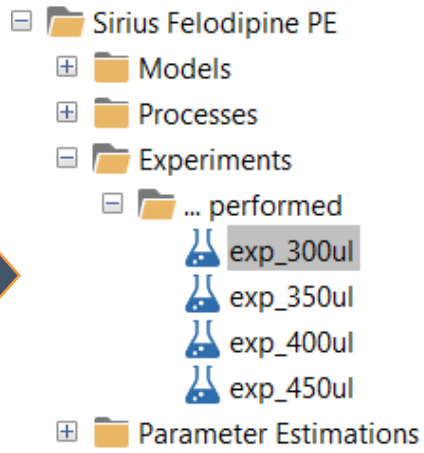
Importing experimental data

Parameter estimation

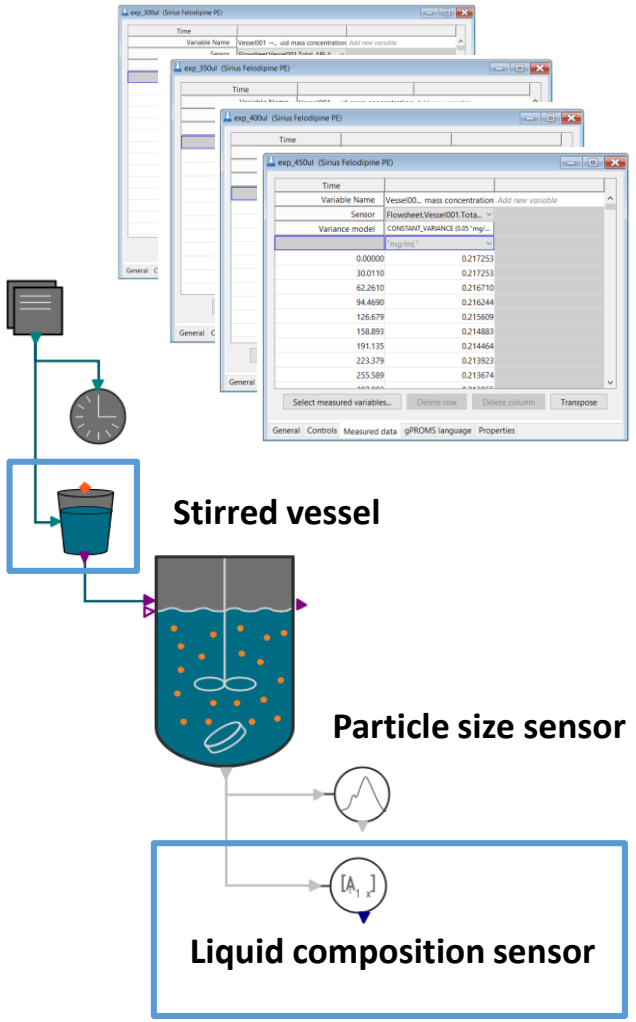
Experimental data



Performed experiments



Controls and measured variables



Set up (1)

Parameter estimation

- Maximum likelihood algorithm
  - Maximises the probability that the model will predict the measurement values obtained from the experiments
  - Simultaneous estimation of:
    - parameters in the physical model of the process (e.g. growth and primary nucleation parameters)
    - **and** the variance model of the measuring instruments

- Kinetic model parameters

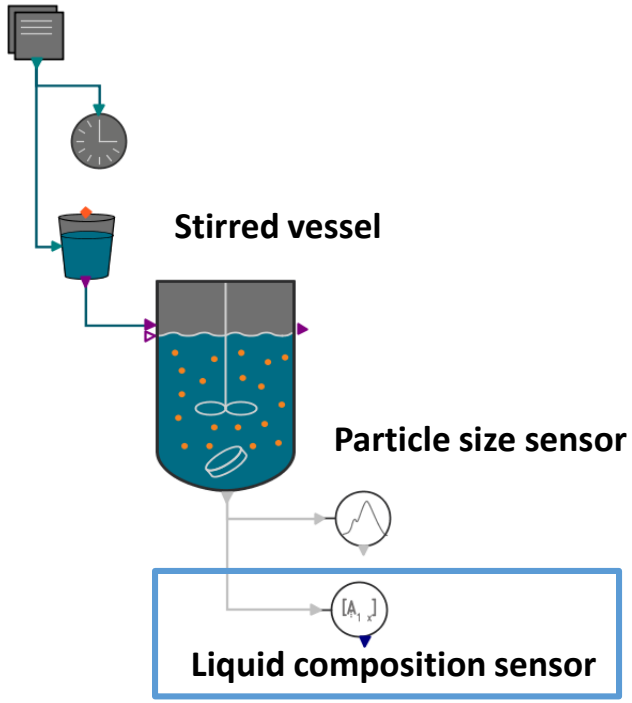
$$J_{prim} = \boldsymbol{k_n}(\Delta C)^{\boldsymbol{n}}$$

$$\boldsymbol{k_g}\left(\frac{C_s - C_i}{C_i}\right)^{\boldsymbol{g}}$$

- Linear variance model

$$\sigma^2 = (\alpha z + \beta)^2 + \varepsilon$$

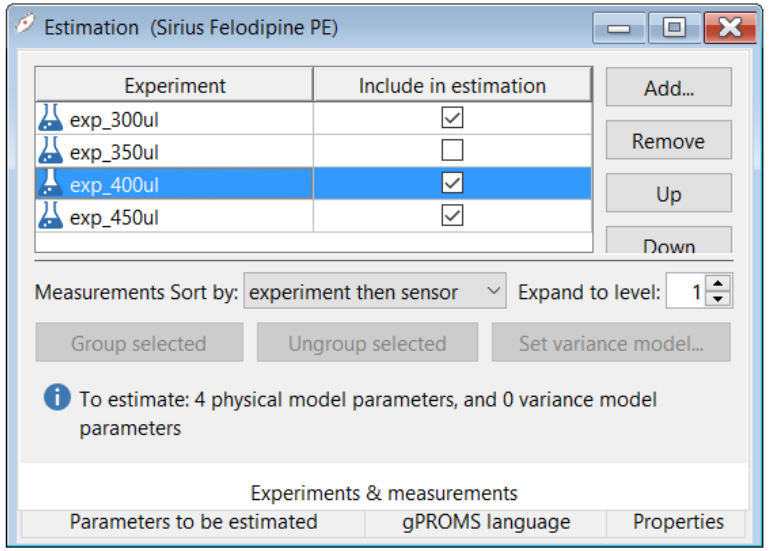
- σ is the variance, z is the measurement
- α and β are relative and constant terms, ε is a small non-zero constant

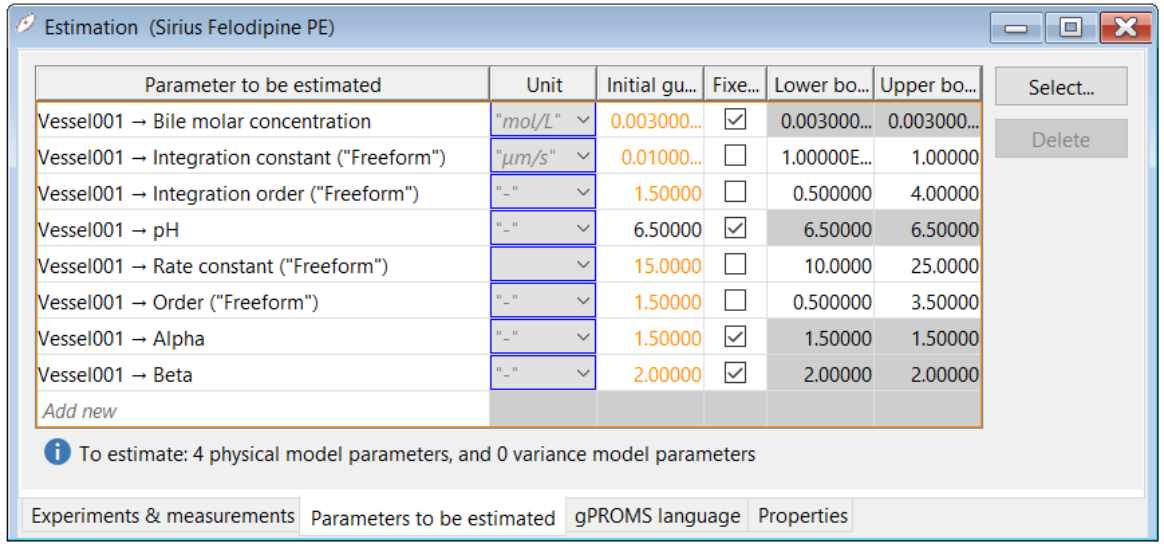


Set up (2)

Parameter estimation

- Experiments used in estimation: Hold experimental data back for external validation
- Experimental data: Concentration measurements were thinned based on the local gradient (high gradients contain more information)
- Initial guesses: Iterative procedure repeating the parameter estimation multiple times changing initial guesses
- Upper and lower bounds: Ensure these are reasonable
- Estimating uncertain experimental conditions

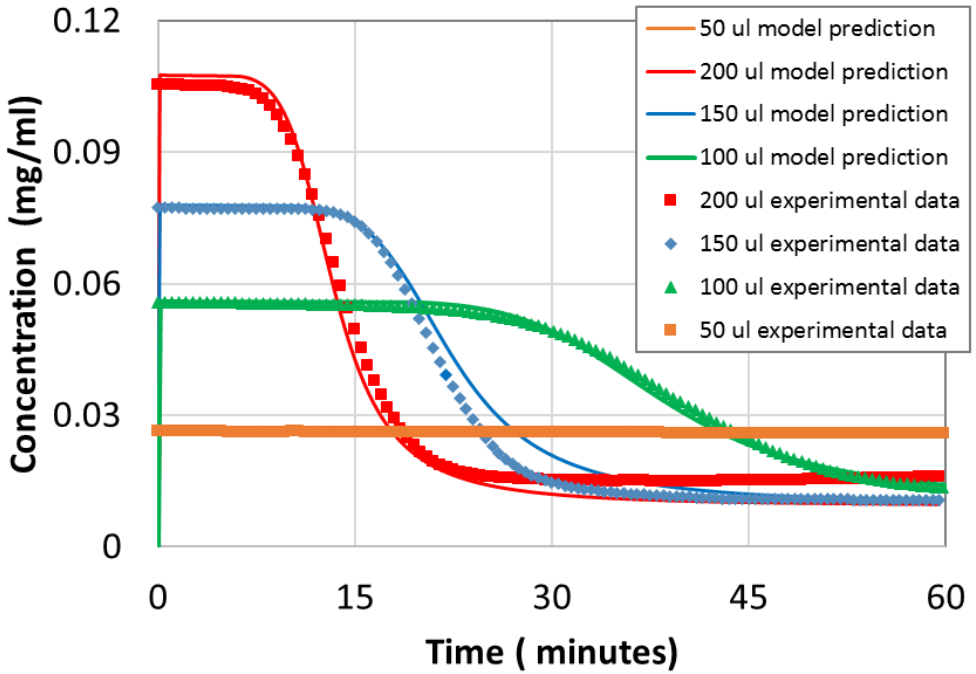




Results

Parameter estimation results

- **Single set of parameters** able to predict experimental measurements well
  - Were able to do this for a range of compounds
- 95% confidence intervals seem reasonable
  - Analyse with GSA

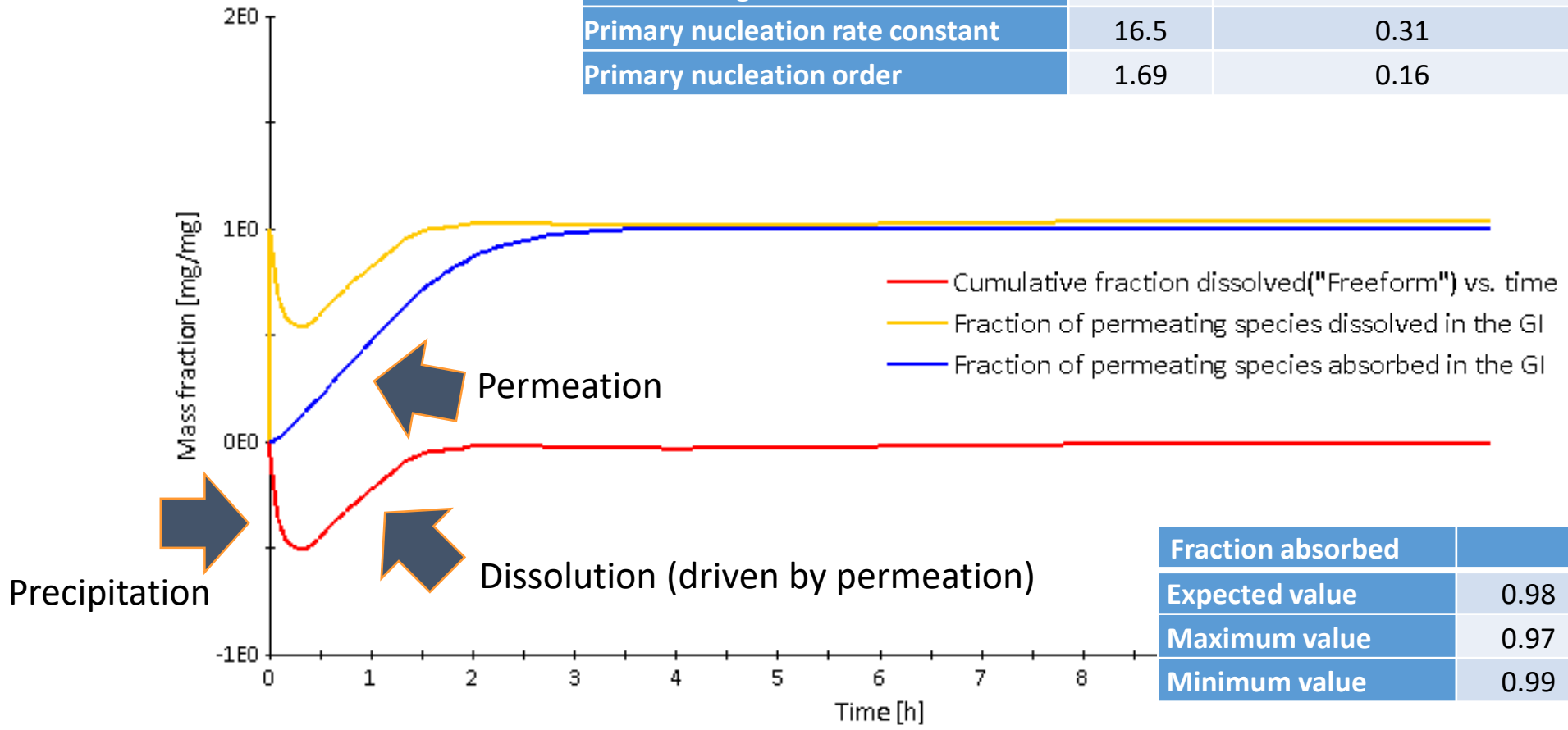


Compound	Ketoconazole	Aprepitant	Tadalalfil	Felodipine	Indomethacin
Type	Dibase	Ordinary ampholyte	Neutral	Base	Acid
Growth integration constant	0.00886	0.00903	0.0865	0.00501	0.019
Growth integration order	0.904	2.10	1.52	3.44	1.69
Primary nucleation rate constant	17.5	13.8	16.5	14.6	13.9
Primary nucleation order	2.93	2.70	1.69	2.81	2.77

Tadalafil *in vivo* performance

- 2.5 mg solution dose
- Using estimated parameters

Compound	Freeform	95% confidence interval
Growth integration constant	0.0865	0.035
Growth integration order	1.52	0.17
Primary nucleation rate constant	16.5	0.31
Primary nucleation order	1.69	0.16



Fraction absorbed	
Expected value	0.98
Maximum value	0.97
Minimum value	0.99

Future work

Future work

- Include pharmacokinetics *in vivo* simulations

- Application of Sirius Analytical experimental systems
  - Impact of excipients
  - Transfer experiments
  - Biphasic dissolution
  - Solubility

- gPROMS FormulatedProducts gCOAS libraries
  - Utilise new association reaction equilibria capabilities to model the impact of excipients on performance