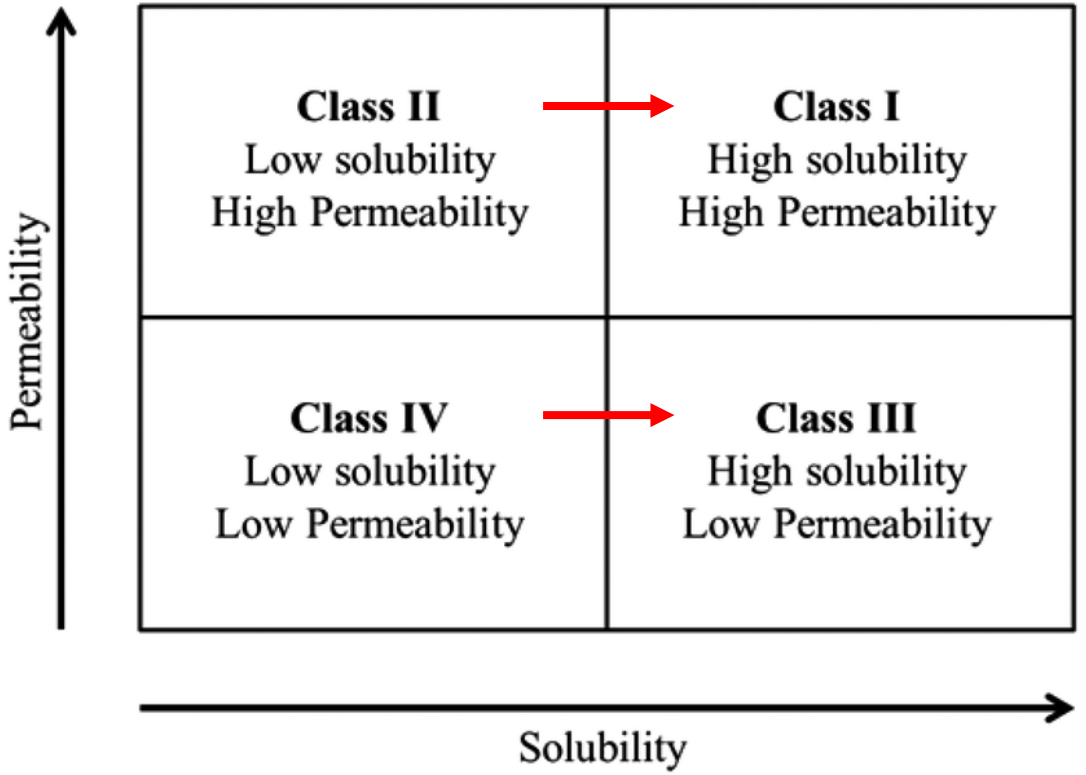
Supersaturation measurement and modelling

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*

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



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

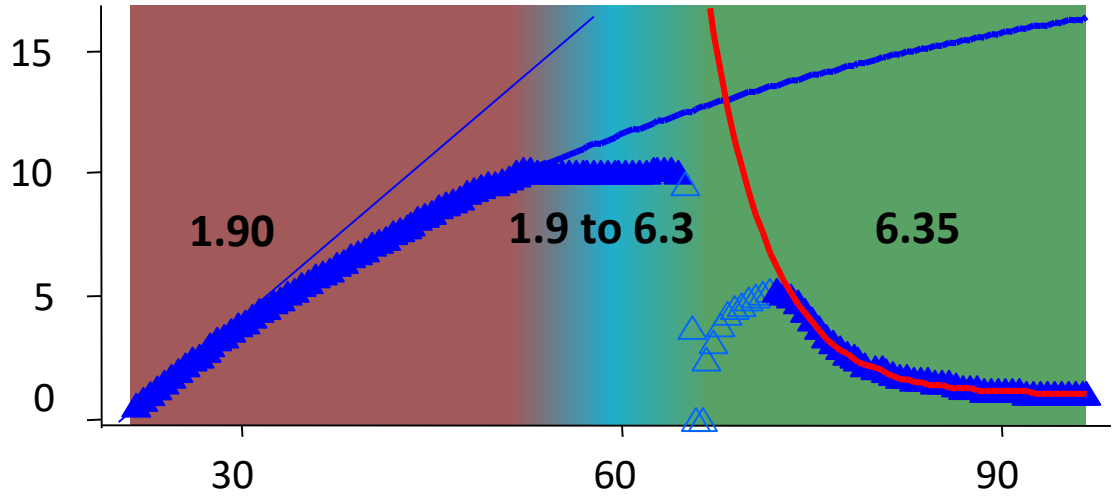
Property based study: Find the media conditions where the compound is supersaturated and precipitation is observed. Explore the supersaturation profile at different starting concentrations.

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

Typical data output

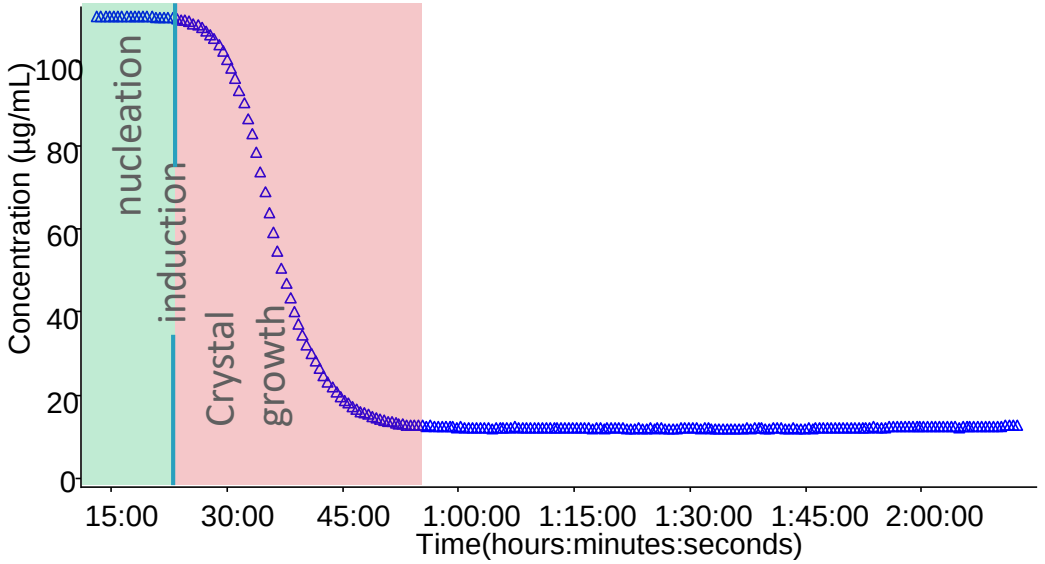
Biorelevant based study

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).

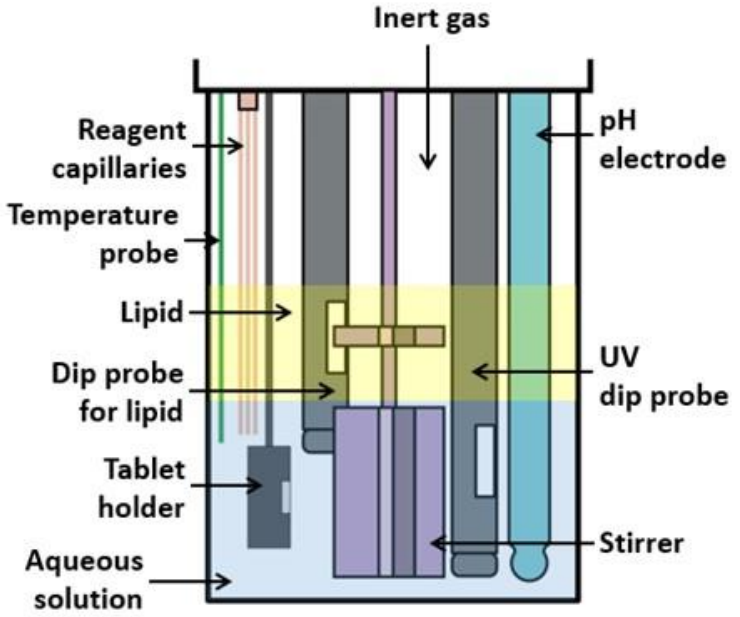


Property based study

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).



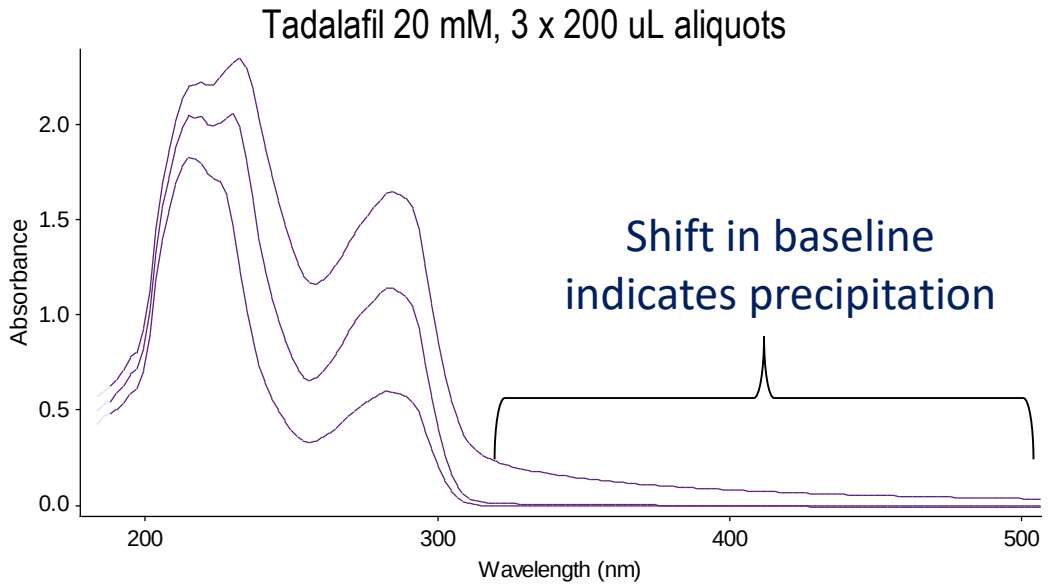
Hardware Features of the Sirius inForm

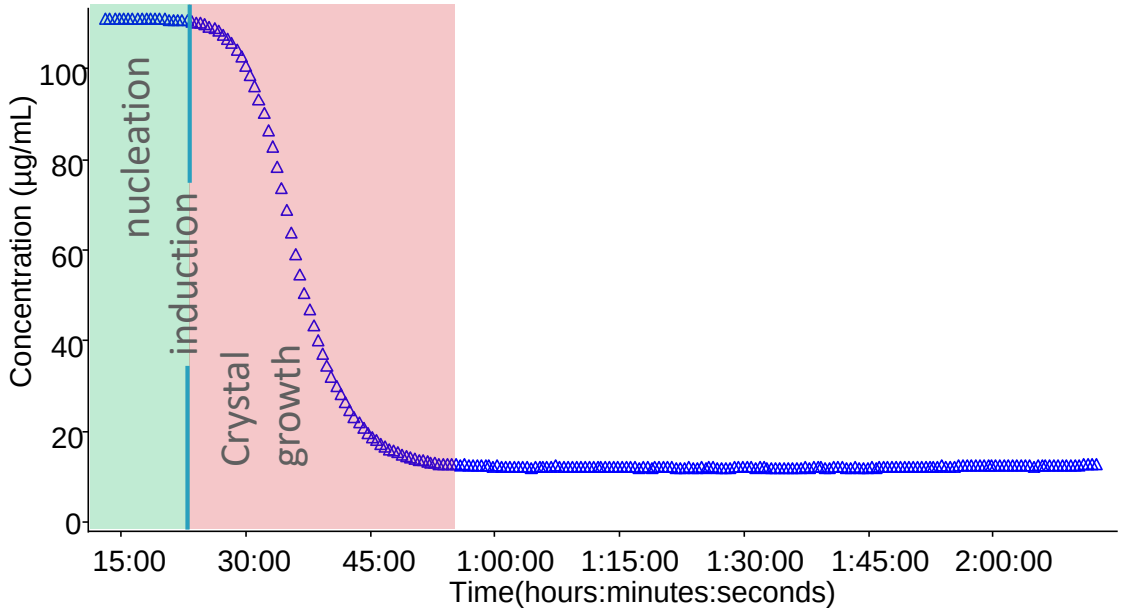


Solvent quench method

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.





Classic Nucleation Theory

Determining induction time, decay constant and extrapolated solubility

Induction time

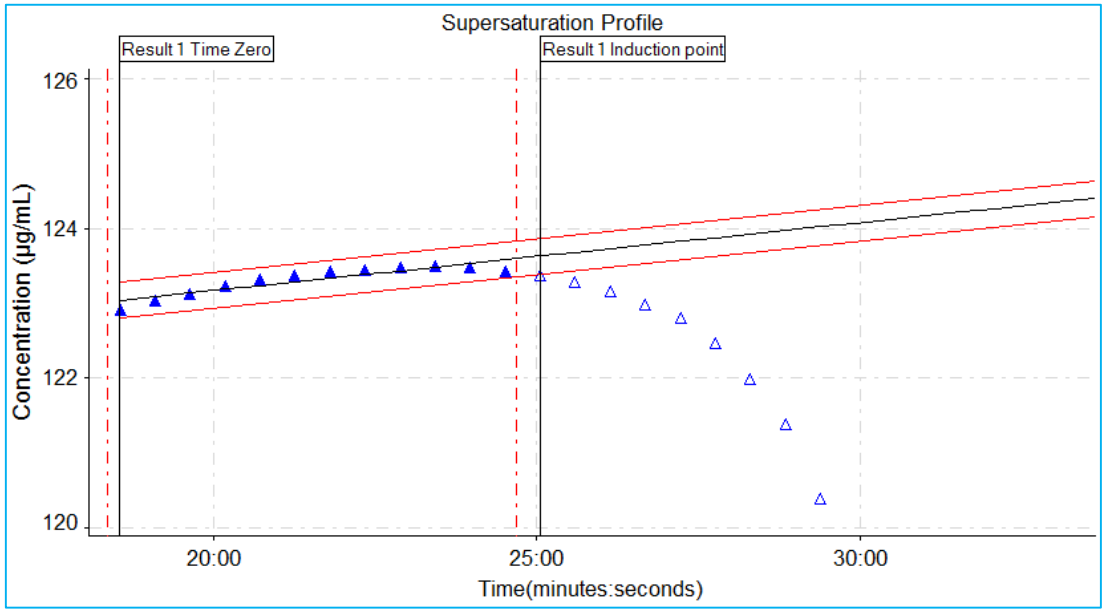
- Isolate data on the upper plateau (left graph)
- Fit straight line to plateau data (black line) and find the RMSD
- Assign induction point as the first point that exceeds 3 sigma (red lines)
- Induction time = induction point – time zero

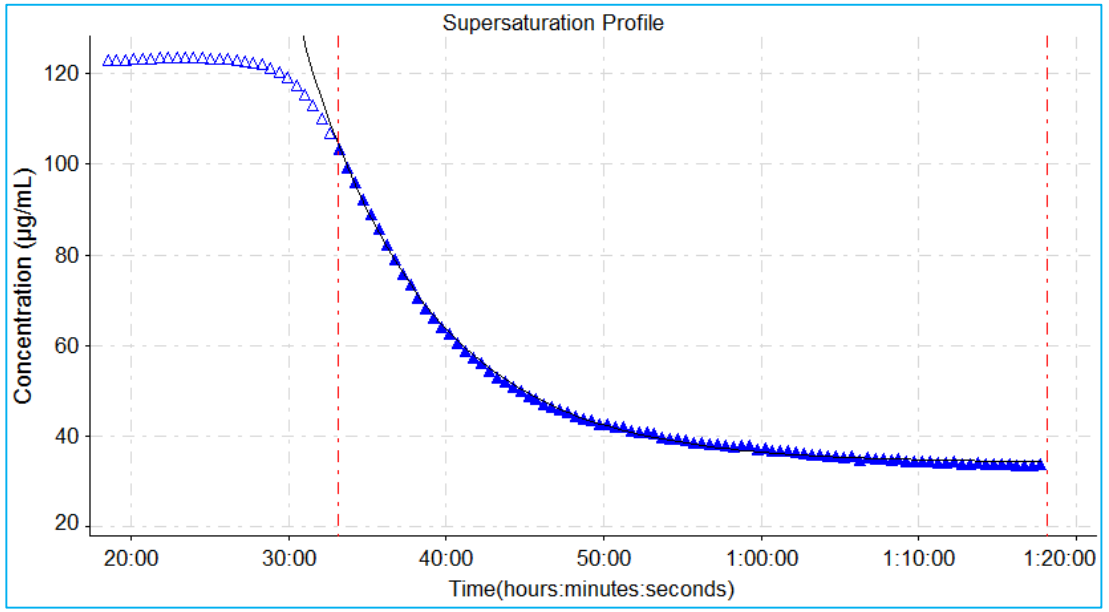
$$J = A \times \exp\left(\frac{16\pi v^2 \gamma^3}{3k^3T^3\ln(DS)^2}\right)$$

Decay constant and extrapolated solubility

- Isolate data in the decaying part and lower plateau of the curve (right graph)
- Fit a 1st order model and find the decay constant and extrapolated solubility

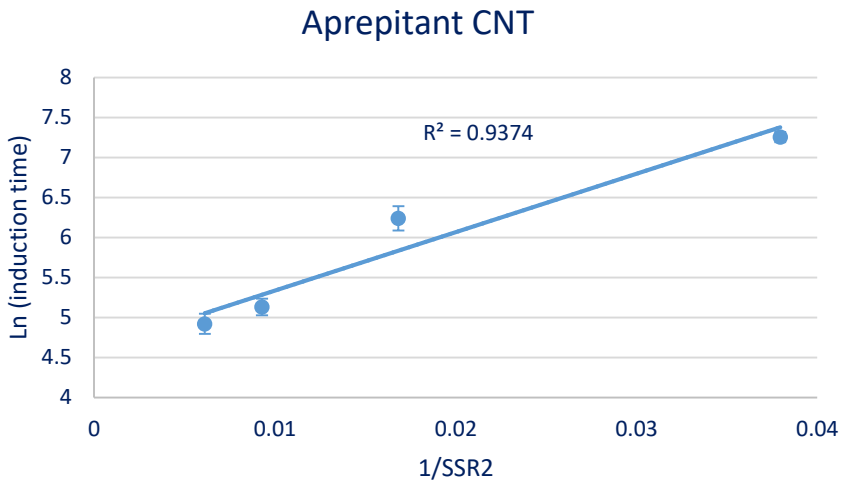
$$lnJ = lnA + ln\left(\frac{16\pi v^2 \gamma^3}{3k^3T^3}\right) \cdot 1/\ln(DS)^2$$

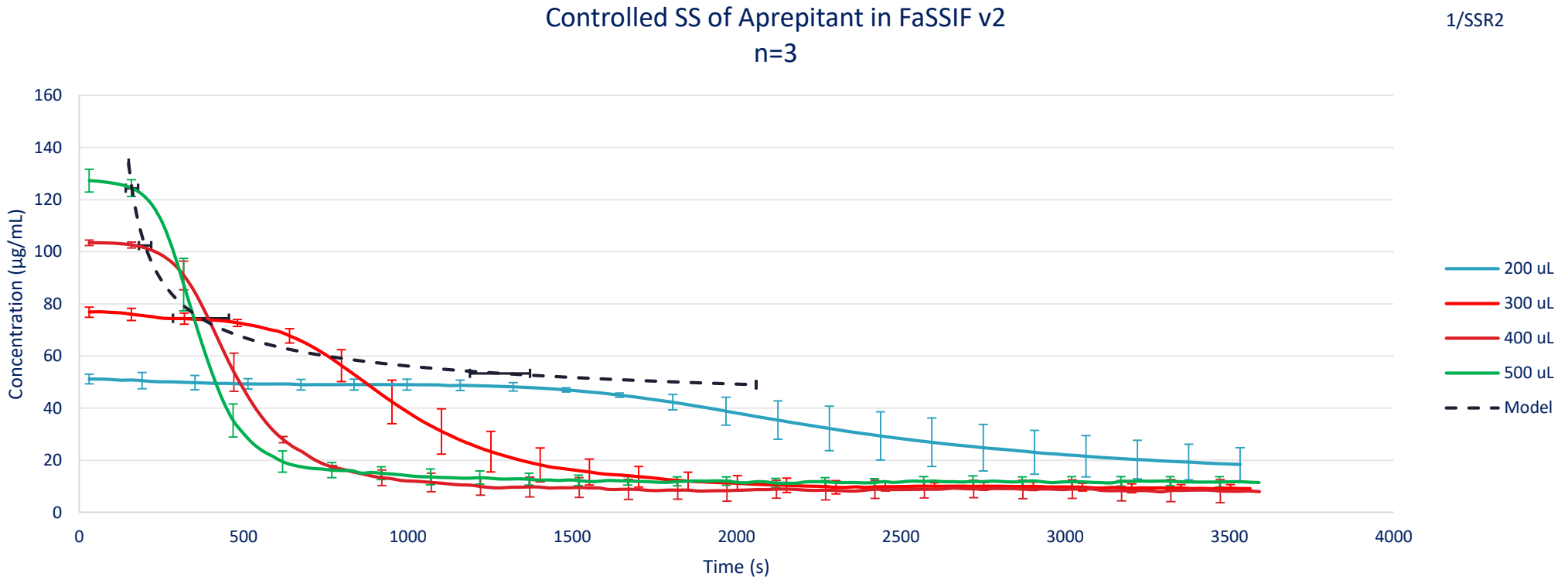




Aprepitant (n)

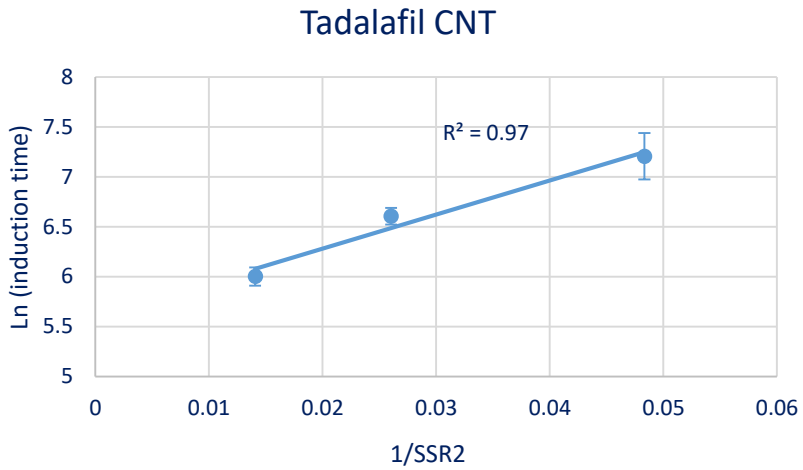
Injection Volume (µL)	Induction time		Decay constant		Extrapolated Solubility	
	Average (s)	%CV	Average (s^{-1})	%CV	Average (µg/mL)	%CV
500	137.3 ± 18.6	13.5	0.4490 ± 0.0613	13.7	12.10 ± 1.76	14.5
400	169.4 ± 18.5	10.9	0.3185 ± 0.0179	5.6	8.70 ± 3.79	43.6
300	513.1 ± 85.1	16.6	0.1715 ± 0.0401	23.4	9.13 ± 0.65	7.2
200	1417 ± 91.4	6.4	0.0649 ± 0.0441	68.0	9.93 ± 2.50	25.2

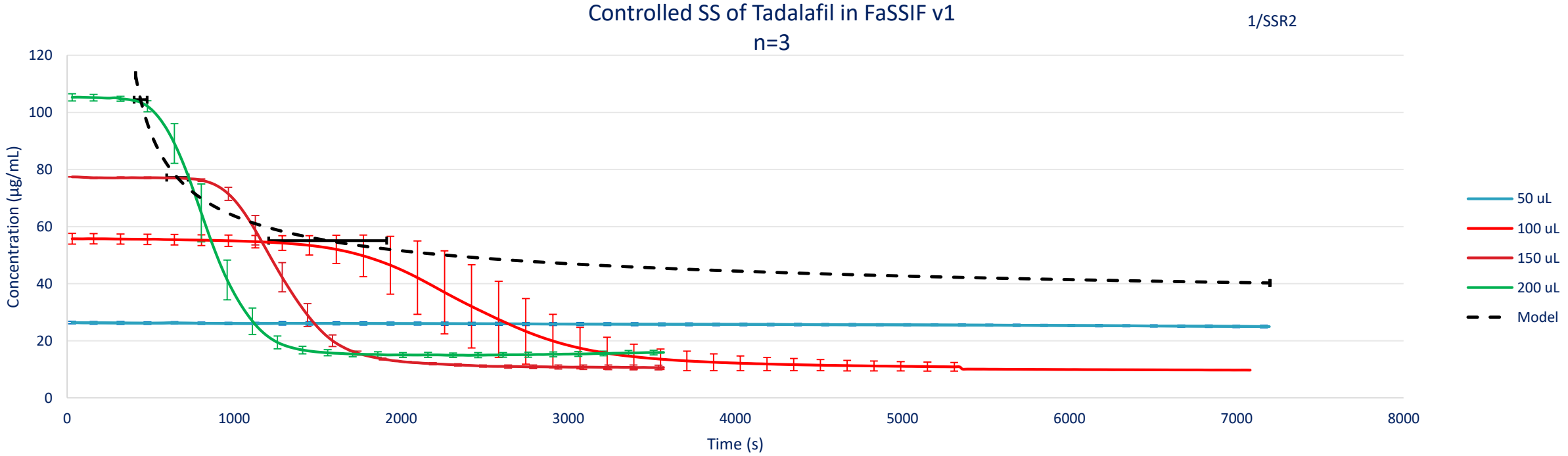




Tadalafil (n)

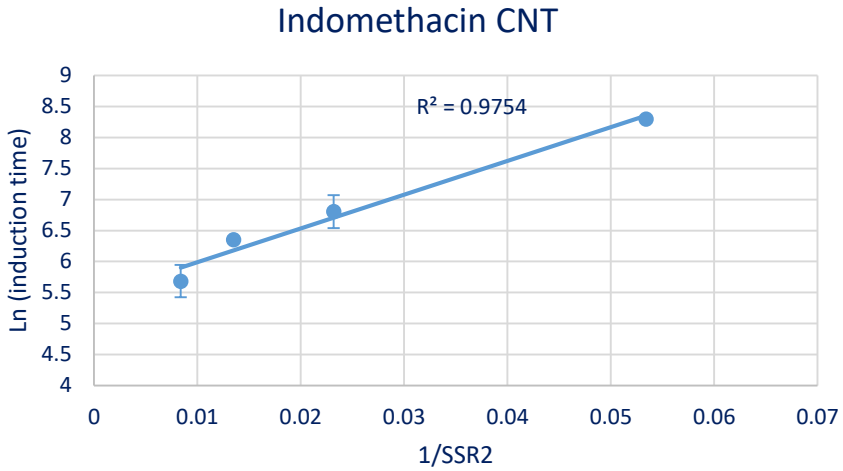
	Induction time		Decay constant		Extrapolated Solubility	
Injection Volume (µL)	Average (s)	%CV	Average (s^{-1})	%CV	Average (µg/mL)	%CV
200	404.3 ± 38.7	9.6	0.3421 ± 0.0231	6.7	15.17 ± 0.85	5.6
150	739.3 ± 64.4	8.7	0.2579 ± 0.0109	4.2	10.87 ± 0.7	6.4
100	1347 ± 353	26.2	0.1477 ± 0.0239	16.2	11.17 ± 1.40	12.6
50	No precipiatation over 2 hours					

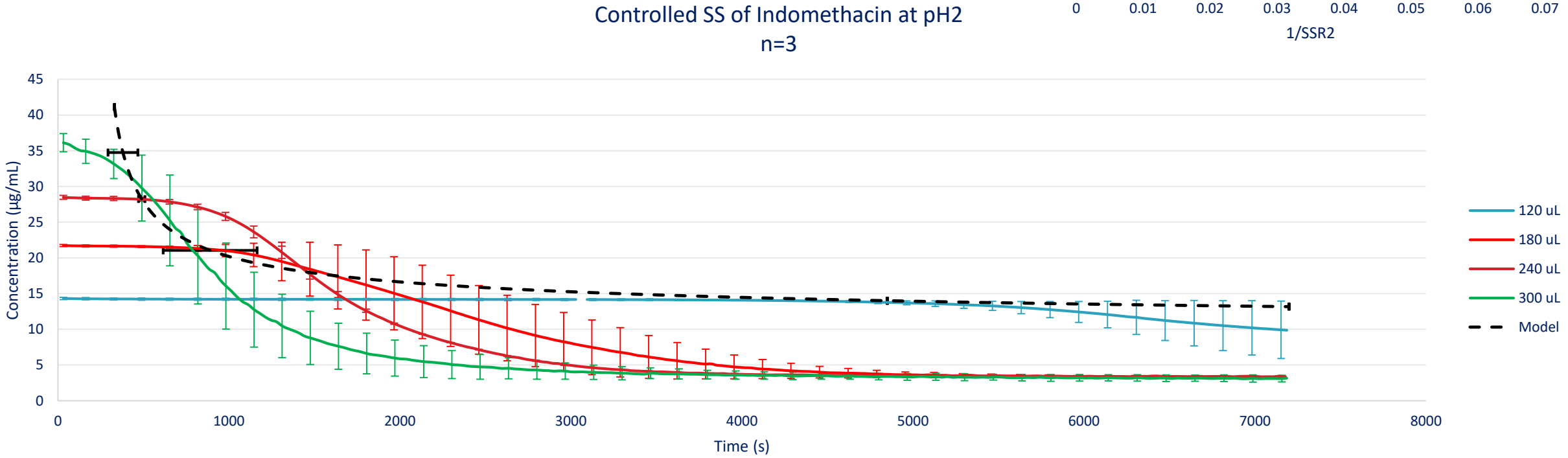




Indomethacin (a,4.2)

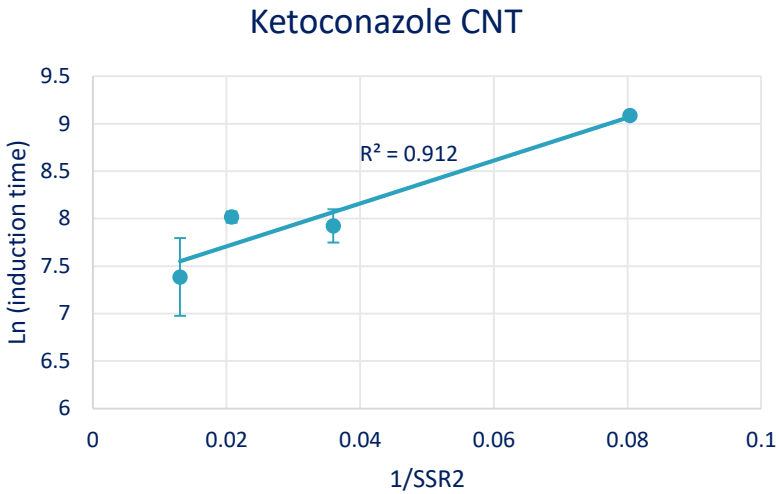
	Induction time		Decay constant		Extrapolated Solubility	
Injection Volume (µL)	Average (s)	%CV	Average (s^{-1})	%CV	Average (µg/mL)	%CV
300	294.0 ± 87.1	29.6	0.1123 ± 0.034	30.3	3.35 ± 0.41	12.2
240	575.7 ± 18.9	3.3	0.0835 ± 0.003	3.6	3.33 ± 0.06	1.8
180	904 ± 275.1	30.4	0.0866 ± 0.011	12.7	3.26 ± 0.17	5.2
120	4030 ± 1.9	0.05	0.0509	-	2.375	-

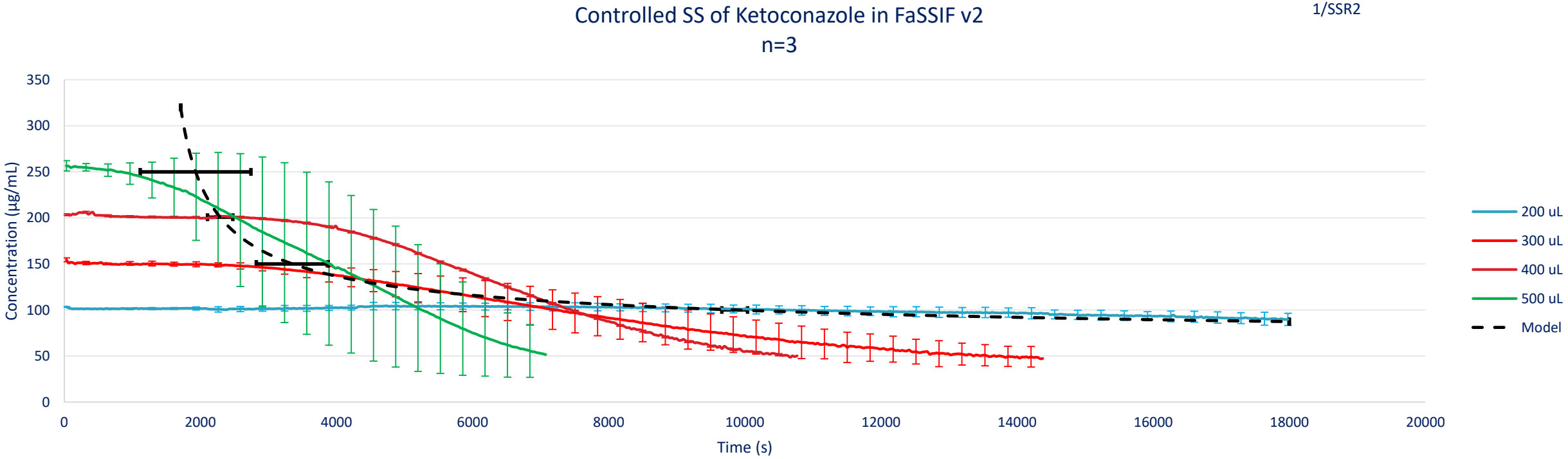




Ketoconazole (b)

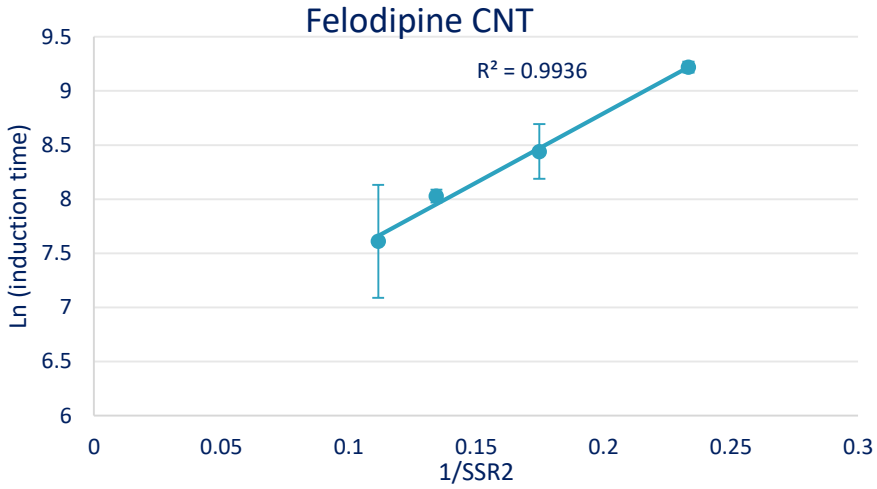
Injection Volume (µL)	Induction time		Decay constant		Extrapolated Solubility	
	Average (s)	%CV	Average (s^{-1})	%CV	Average (µg/mL)	%CV
500	1613 ± 812.7	50.4	0.0421 ± 0.0086	20.5	27.36 ± 1.93	7.0
400	3031 ± 185.4	6.1	0.0245 ± 0.0047	19.4	28.76 ± 10.87	37.8
300	2760 ± 528.4	19.1	0.0137 ± 0.0026	18.7	31.81 ± 3.23	10.2
200	8833 ± 190.2	2.2		-		-

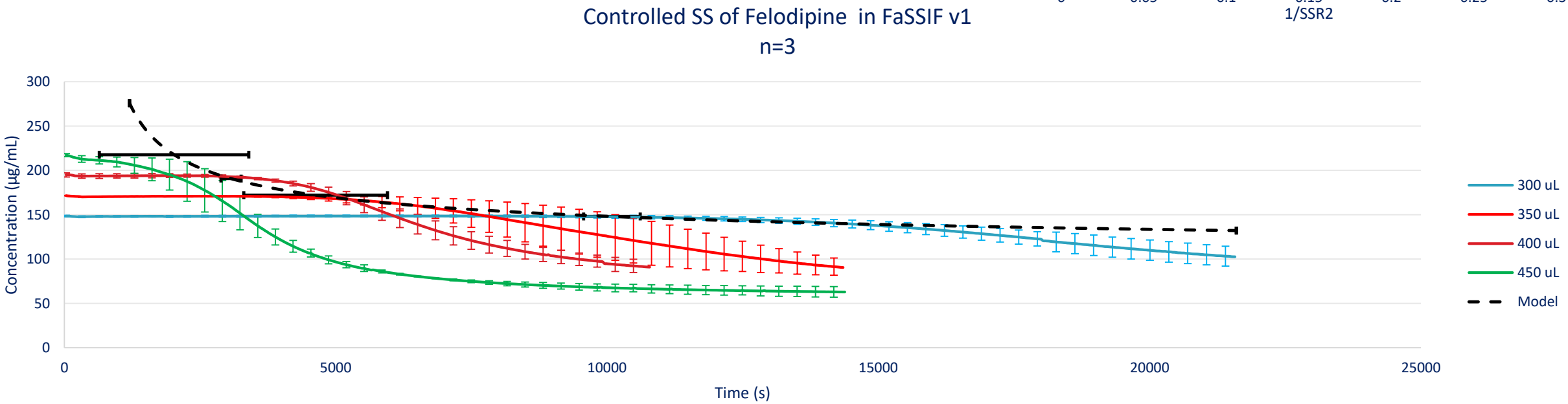




Felodipine (n)

Injection Volume (µL)	Induction time		Decay constant		Extrapolated Solubility	
	Average (s)	%CV	Average (s^{-1})	%CV	Average (µg/mL)	%CV
450	2019 ± 1379	68.3	0.0421 ± 0.0086	20.5	27.36 ± 1.93	7.0
400	3066 ± 185	6.0	0.0245 ± 0.0047	19.4	28.76 ± 10.87	37.8
350	4632 ± 1326	28.6	0.0137 ± 0.0026	18.7	31.81 ± 3.23	10.2
300	10086 ± 521	5.2	0.0075	-	61.45	-

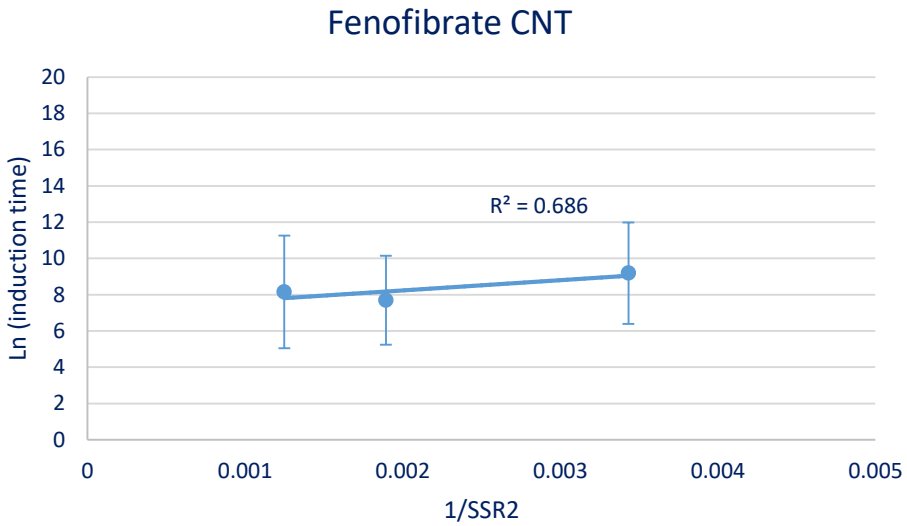


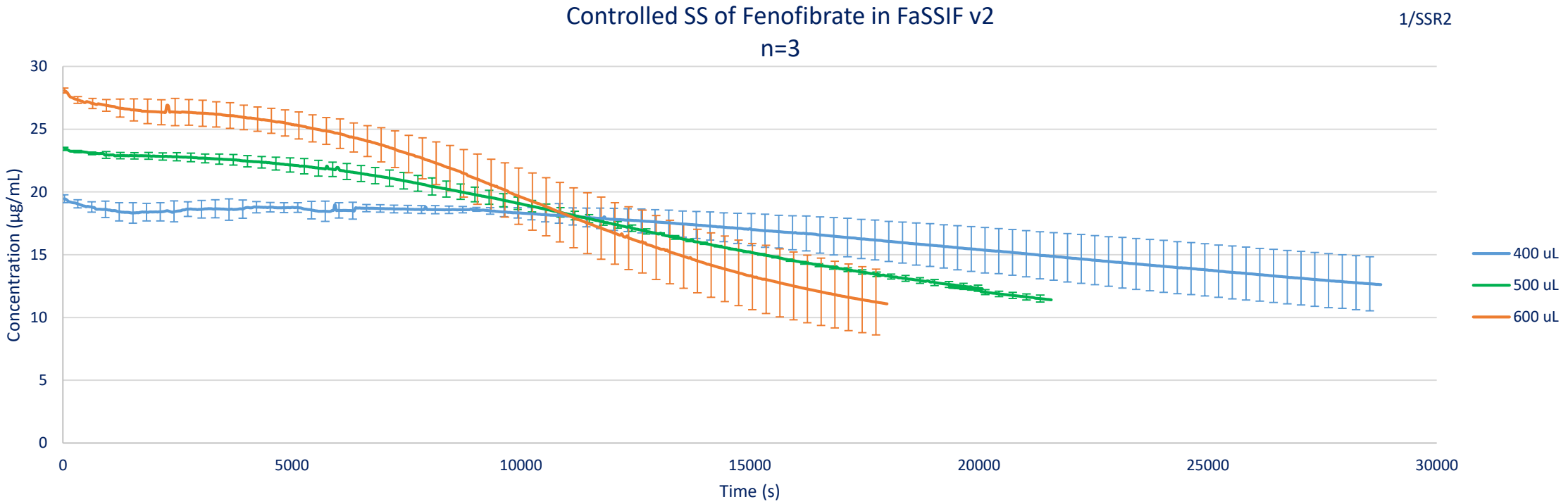


Not all compounds follow CNT!

Fenofibrate (n)

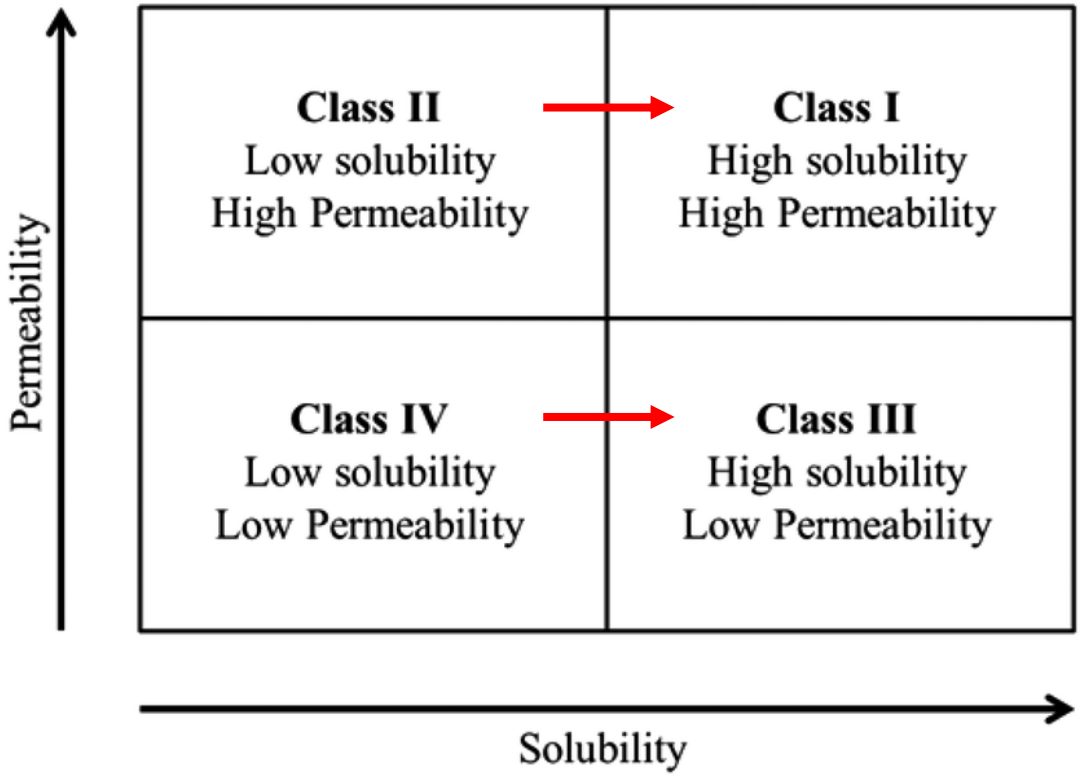
	Induction time		Decay constant		Extrapolated Solubility	
Injection Volume (µL)	Average (s)	%CV	Average (s^{-1})	%CV	Average (µg/mL)	%CV
600	3469 ± 732	21.1	0.007 ± 0.001	18.9	5.14 ± 1.57	30.6
500	2195 ± 918	41.8	0.004 ± 0.0003	8.7	5.06 ± 0.38	7.5
400	9780 ± 1518	15.5	0.0021 ± 0.0001	6.7	3.30 ± 0.6	18.2



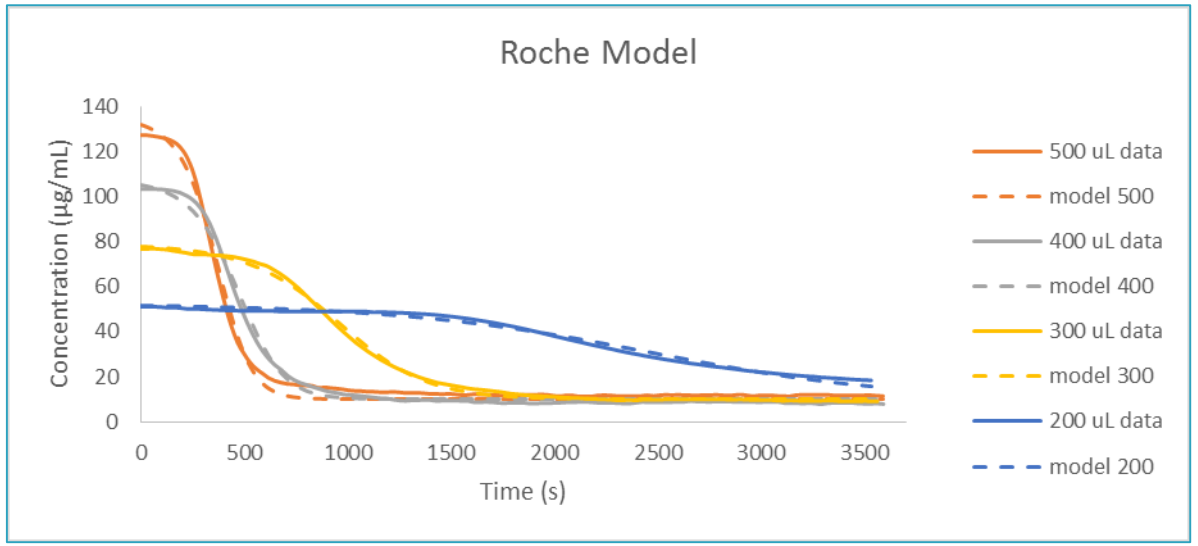


How can this data be used?

Rank	Compound	CNT slope
1	Indomethacin	54.4
2	Tadalafil	34.1
3	Ketoconazole	22.6
4	Aprepitant	20.4
5	Felodipine	12.8



Roche mechanistic model, aprepitant



	500 uL	400 uL	300 uL	200 uL	average	%error
concentration t0	132.0522205	105.0162274	77.91472	51.43376213		
kdiss	0.000926968	0.000929994	0.000671	0.000390711	0.000729635	30.4470692
knuc	2.33012E-06	2.95299E-06	2.61E-05	2.95967E-05	1.52484E-05	83.08251835
solubility	10	10	10	10		
volume	40	40	40	40		
alpha	1.959874051	1.876949727	1.192725	0.952142738	1.495422757	28.91834497
RMSD	2.882398065	1.879568244	1.100314	1.289490351		

P. Jakubiak et al**, Development of a Unified Dissolution and Precipitation Model and Its Use for the Prediction of Oral Drug Absorption** *Mol. Pharmaceutics*, **2016**, *13* (2), pp 586–598

Dissolution rate

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

Precipitation rate

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

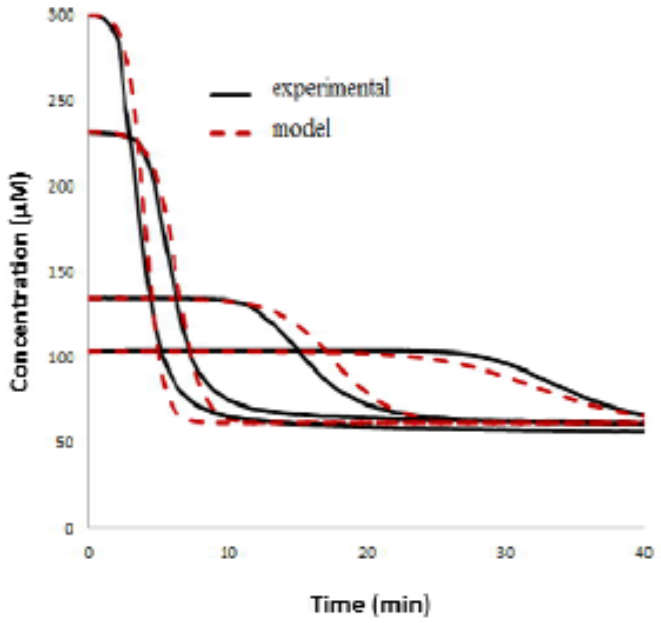
Evaluate dissolution rate and precipitation rate simultaneously to determine solution phase and solid phase quantities.

Use Excel Solver to vary concentration, kdiss, knuc and alpha and minimise RMSD.

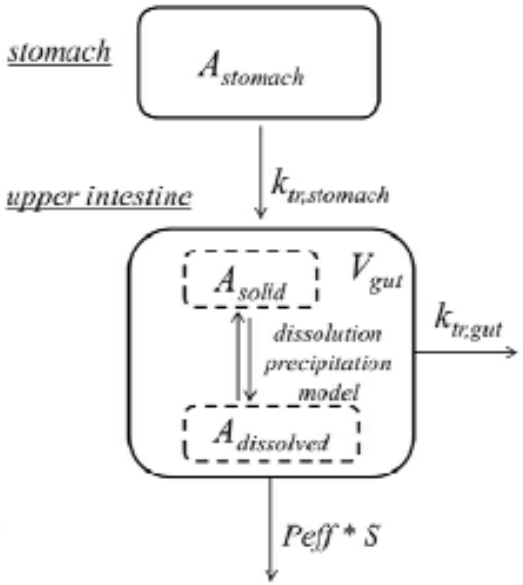
Low RMSDs indicate good model fit to the data and the rate constants and alpha were similar at 500 and 400 µL. But constants were different at 300 and 200 µL (high % error).

Roche mechanistic model, erlotinib

In vitro precipitation tests



In silico absorption model



In vivo PK extrapolation