Automated Measurements of Precipitation, Supersaturation and Biphasic Dissolution

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Two aspects of precipitation

UNDERSTANDING PRECIPITATION

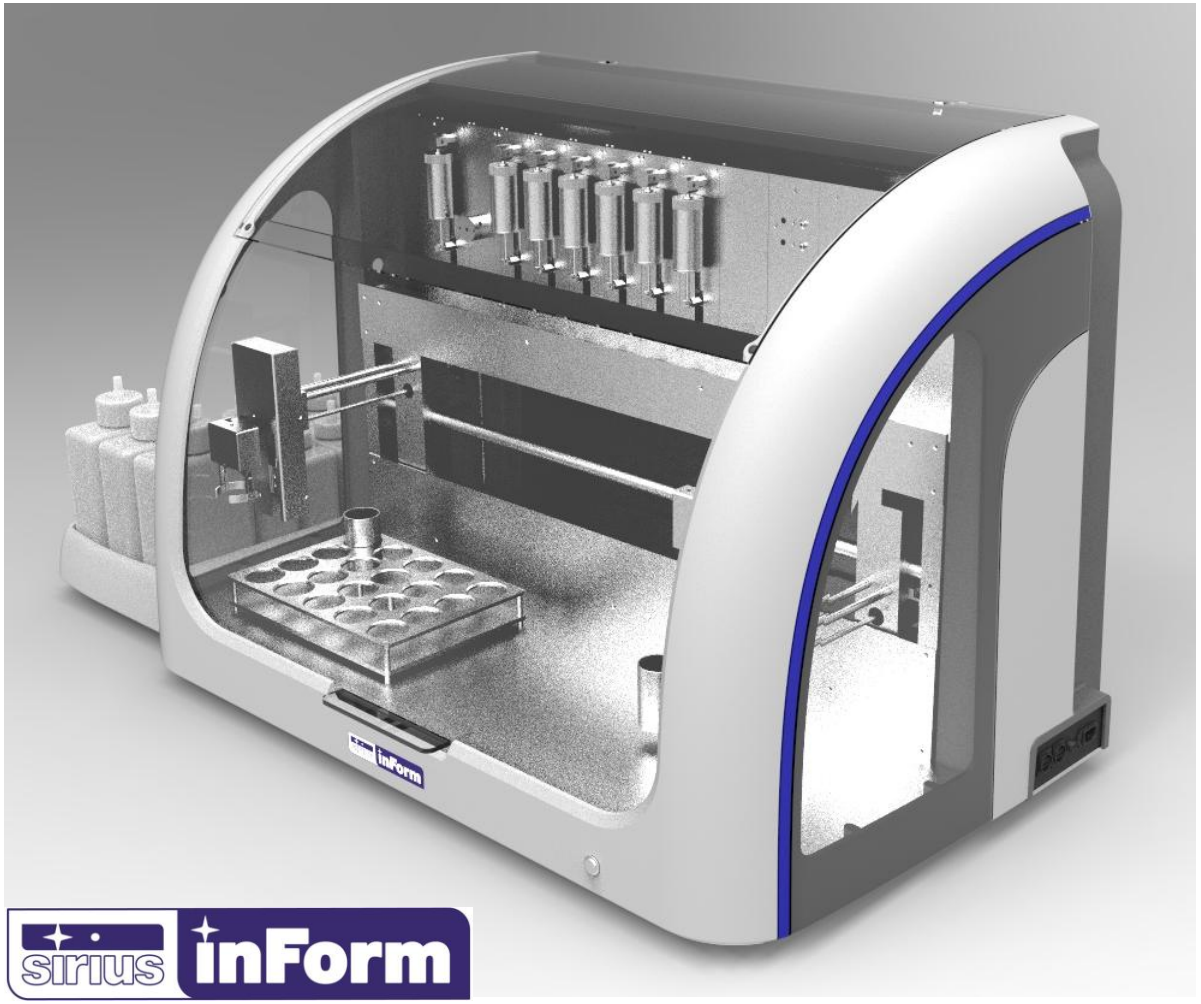
- Drugs may fall out of solution
- Other stuff may fall out of solution

DEALING WITH PRECIPITATION

- Can we measure concentration in the presence of suspended solids?

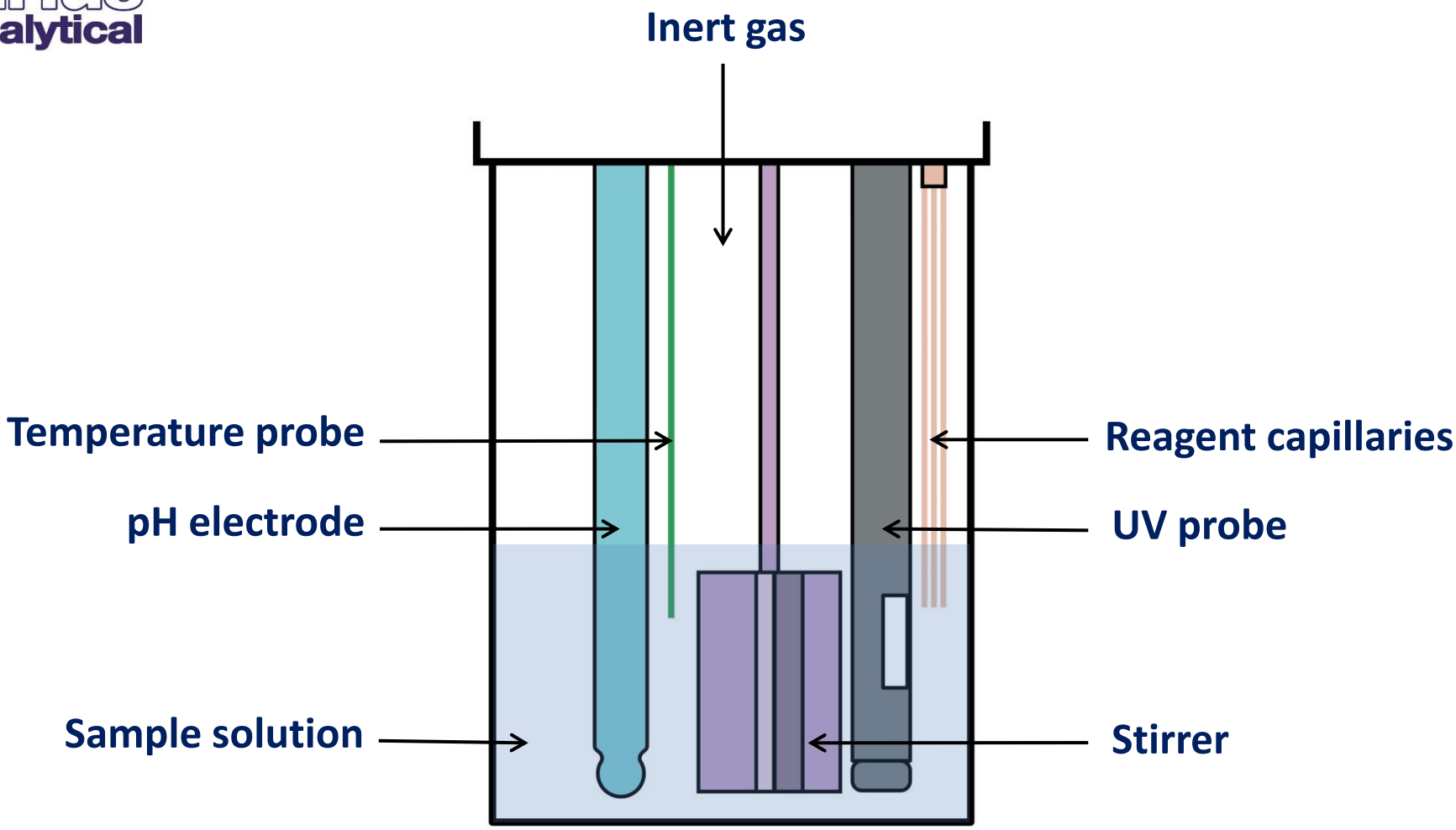
In this presentation …

1. Controlled supersaturation experiments
   - Concentration by pH. Concentration by UV.
2. Dealing with suspended solids
   - Baseline correction
3. Supersaturation examples: felodipine, ketoconazole
   - A clear understanding revealed
4. Biorelevant and Biphasic dissolution
   - Precipitation under aqueous conditions
   - No precipitation in presence of SIFs or lipid



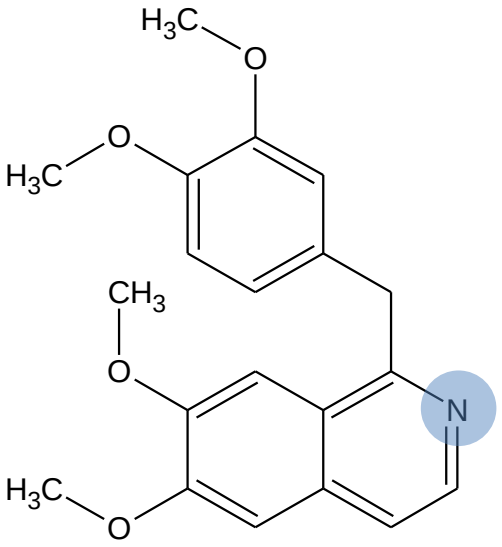
Sirius inForm
- new instrument for use in Formulation studies

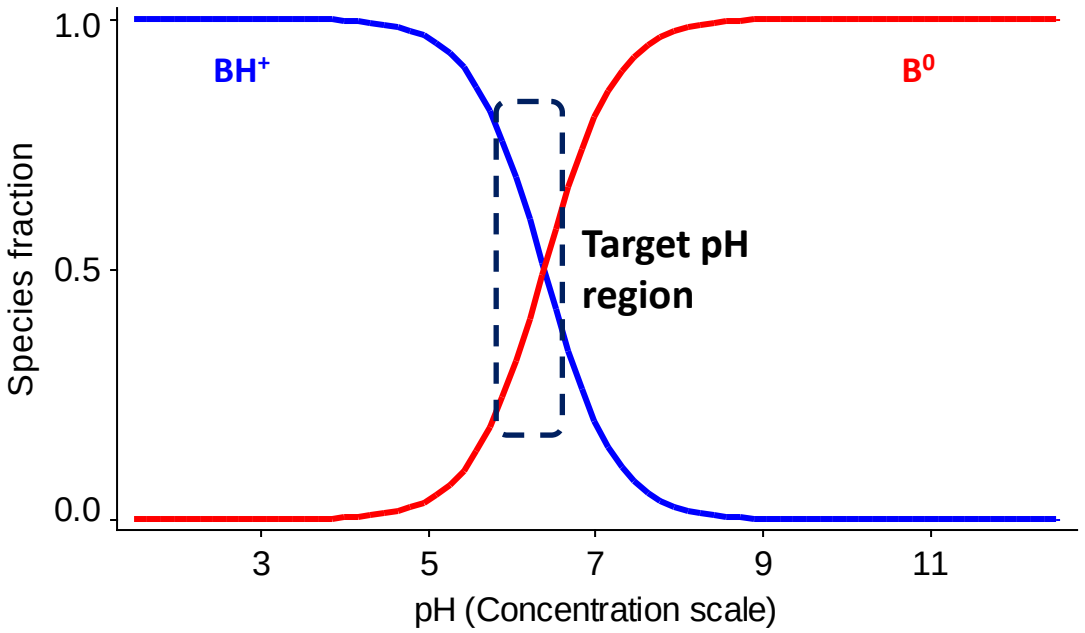
Controlled supersaturation by pH


Inert gas
Temperature probe
pH electrode
Sample solution
Reagent capillaries
UV probe
Stirrer

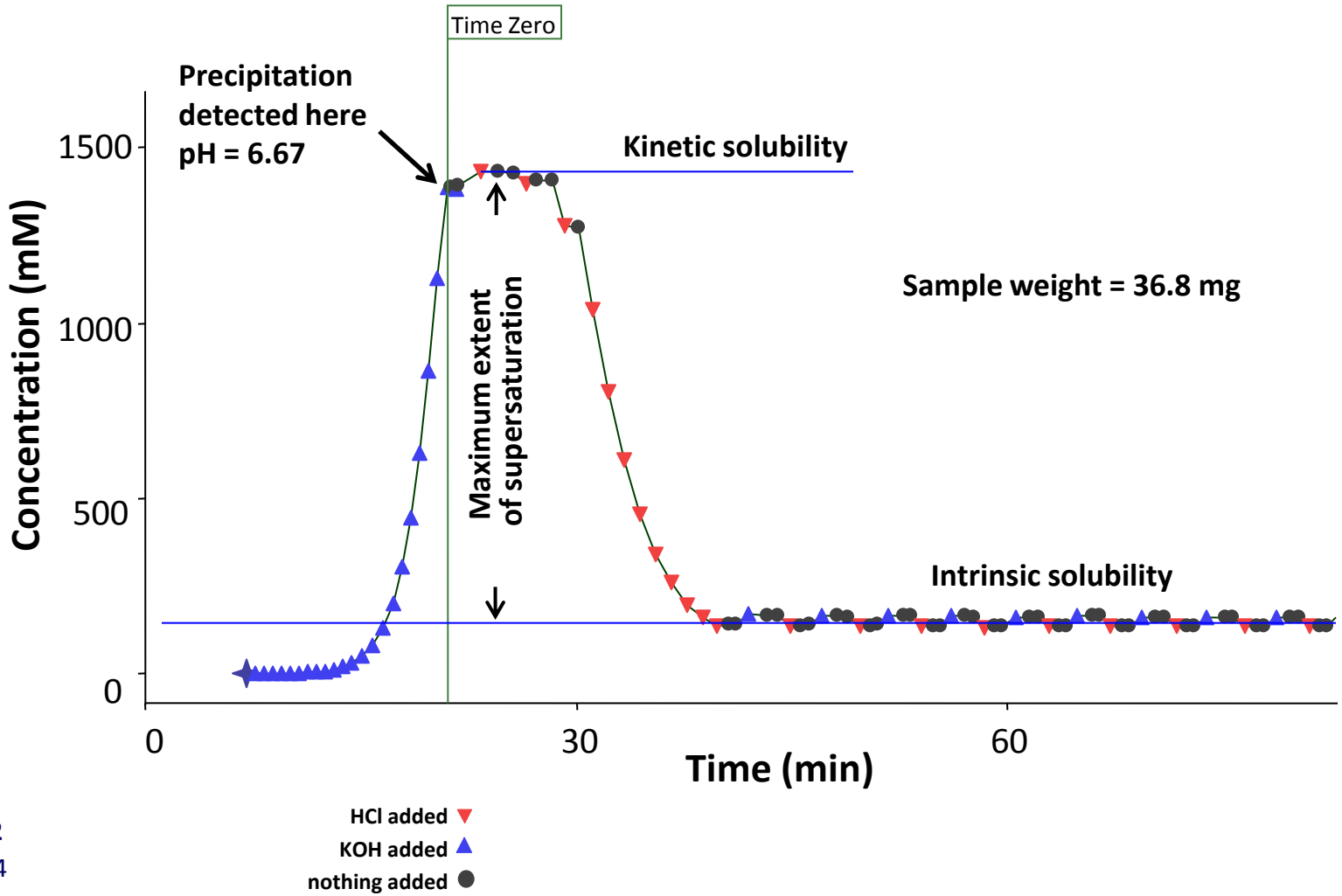
Controlled supersaturation by pH

- Papaverine: pK_a = 6.39. 17 – 37 mg of solid sample
- Sample dissolves at low pH
- Investigated by CheqSol

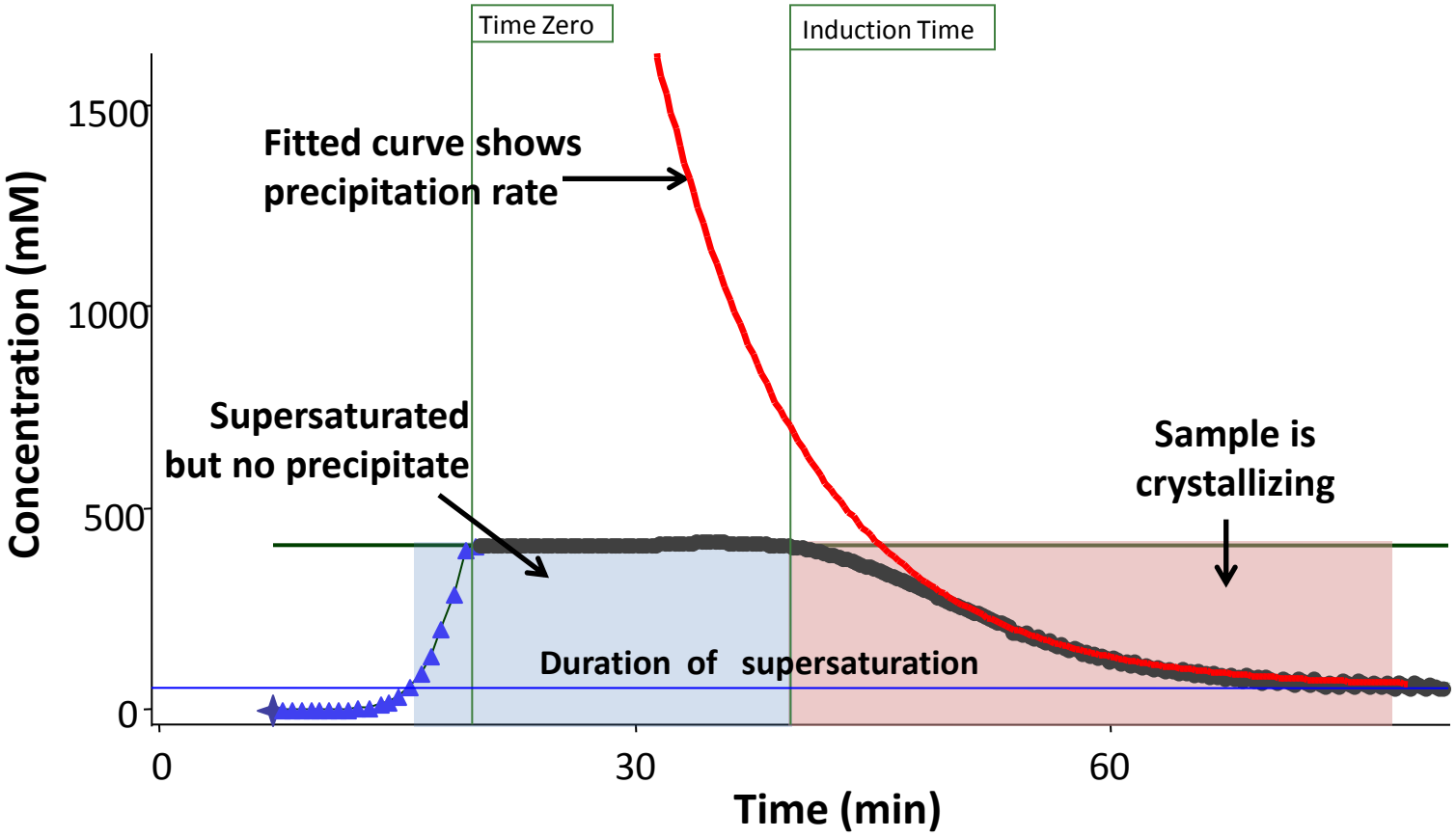




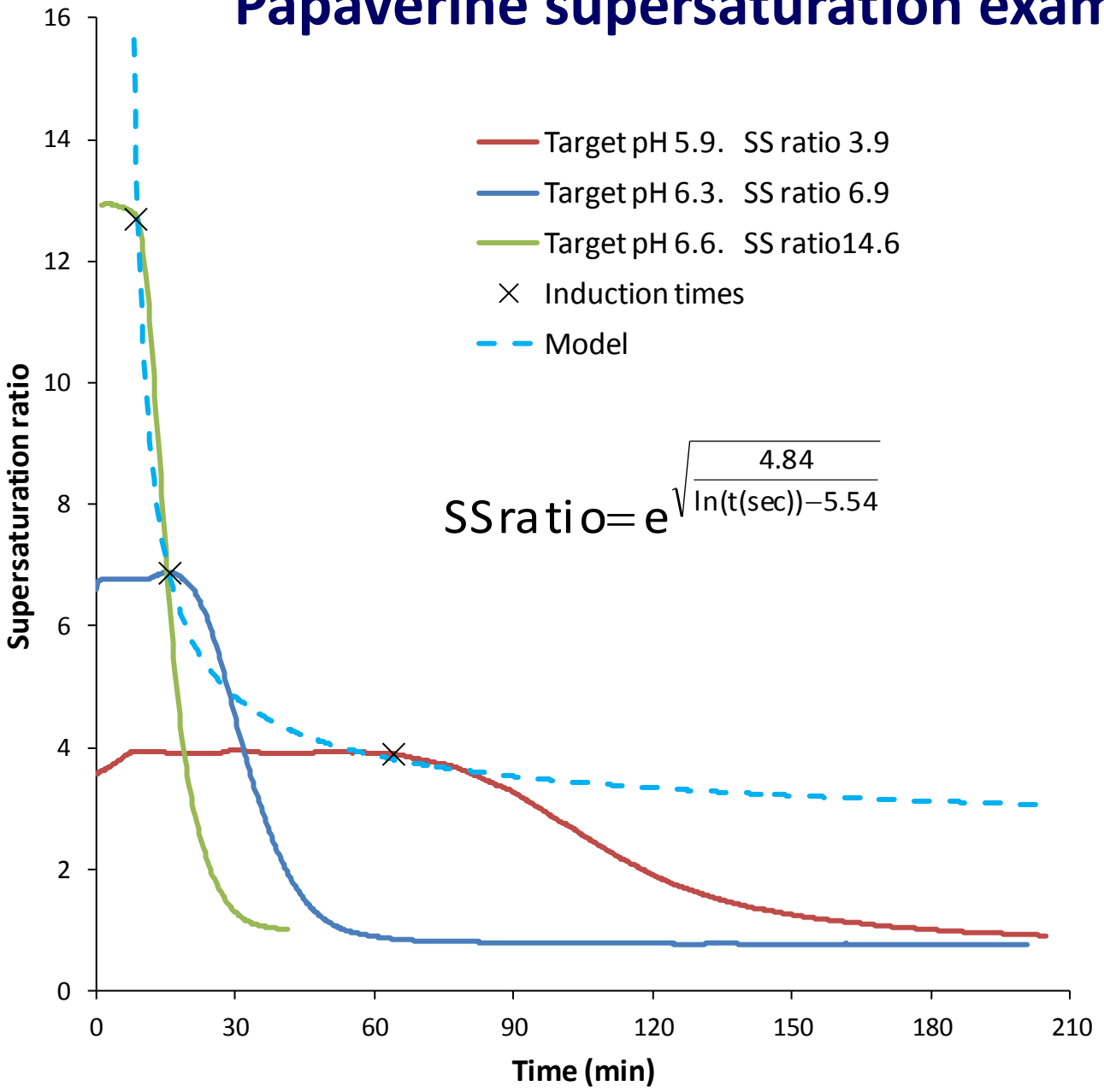
Forced precipitation to find the Target pH



Controlled supersaturation: Target pH 6.3



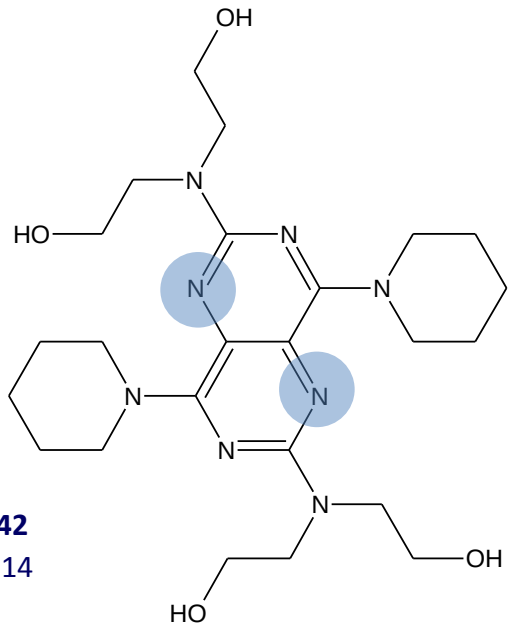
Papaverine supersaturation examples

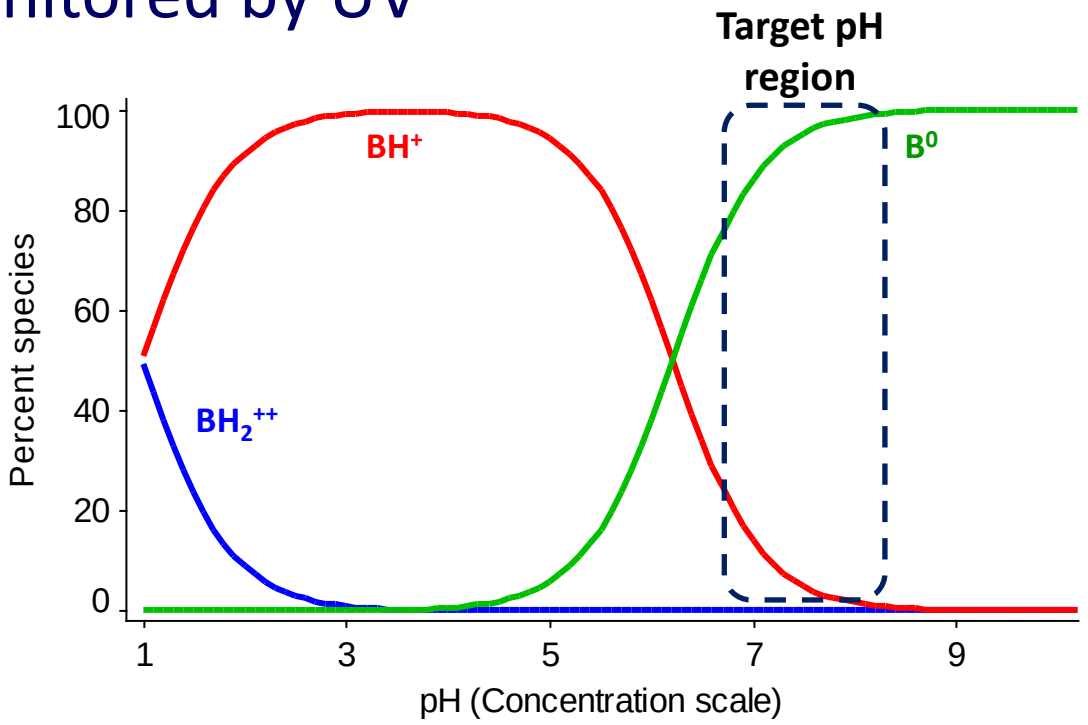


Controlled supersaturation by UV

Controlled supersaturation by UV

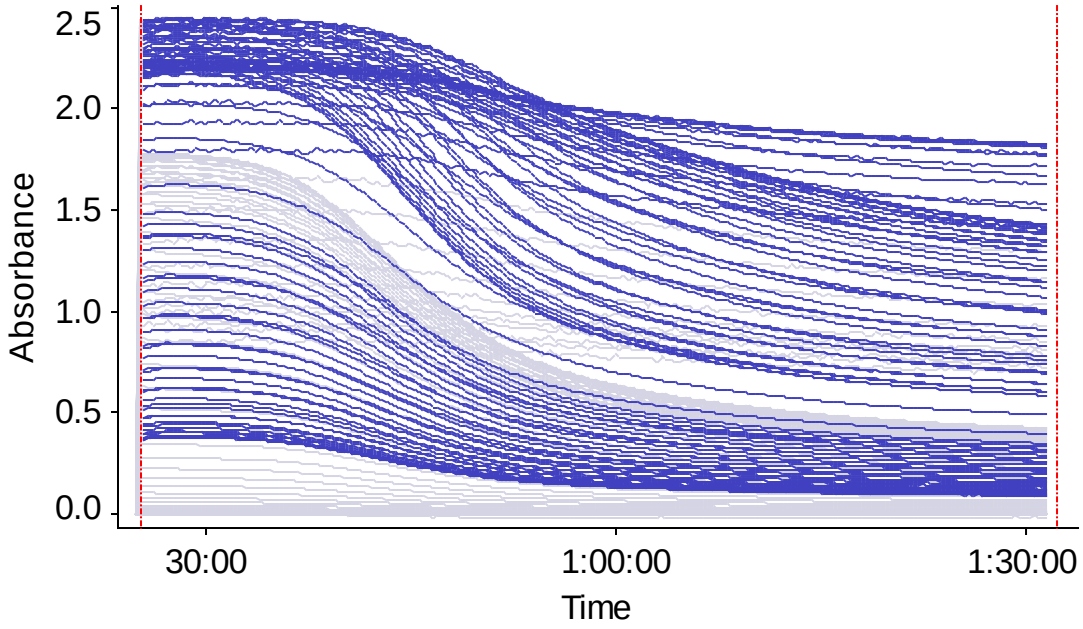
- Dipyridamole: pK_a = 6.17. 10mM in DMSO
- Aqueous solution prepared at “Target pH”
- Aliquot of DMSO stock injected in solution to create supersaturated solution (“solvent shift method”)
- Concentration monitored by UV





Target pH 6.89

0.515 mL of 10 mM stock injected into 40 mL of solution



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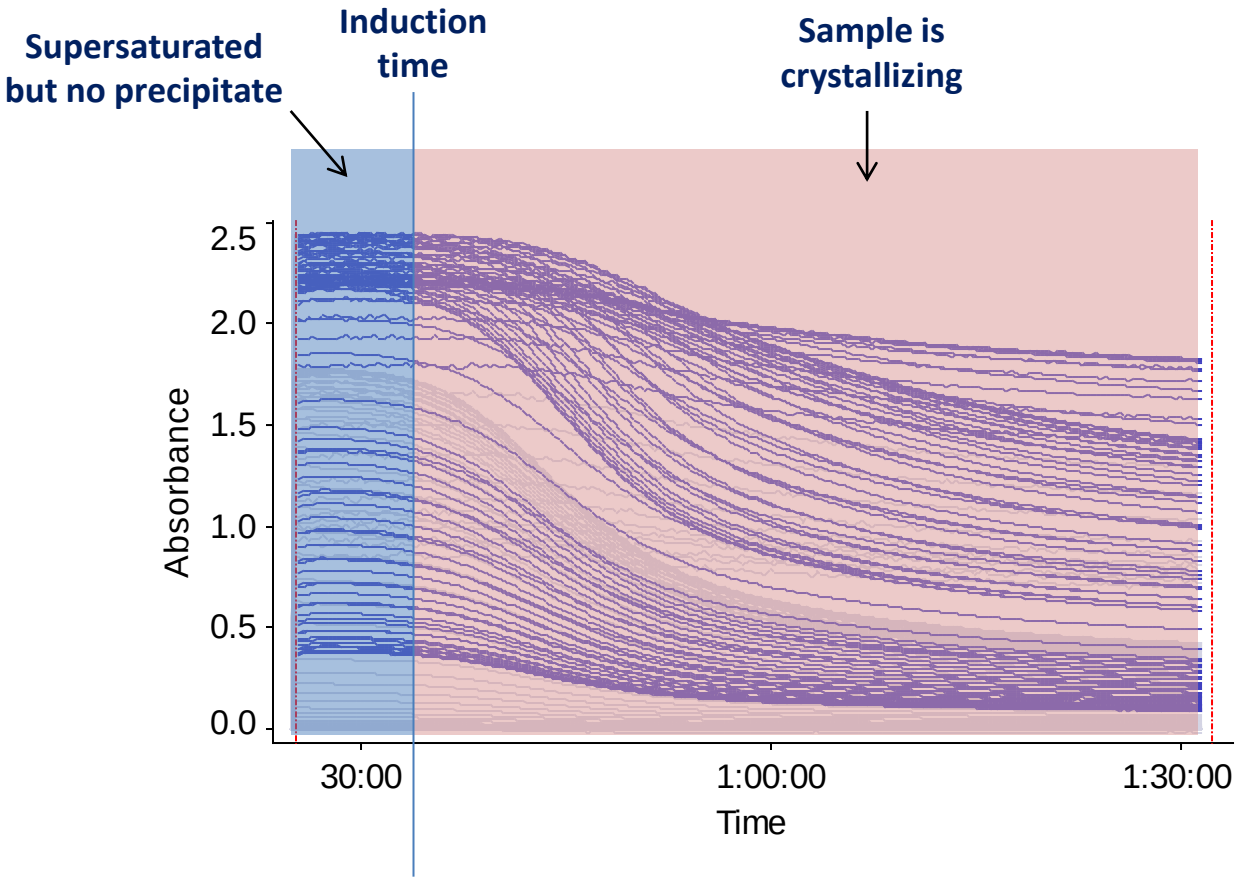
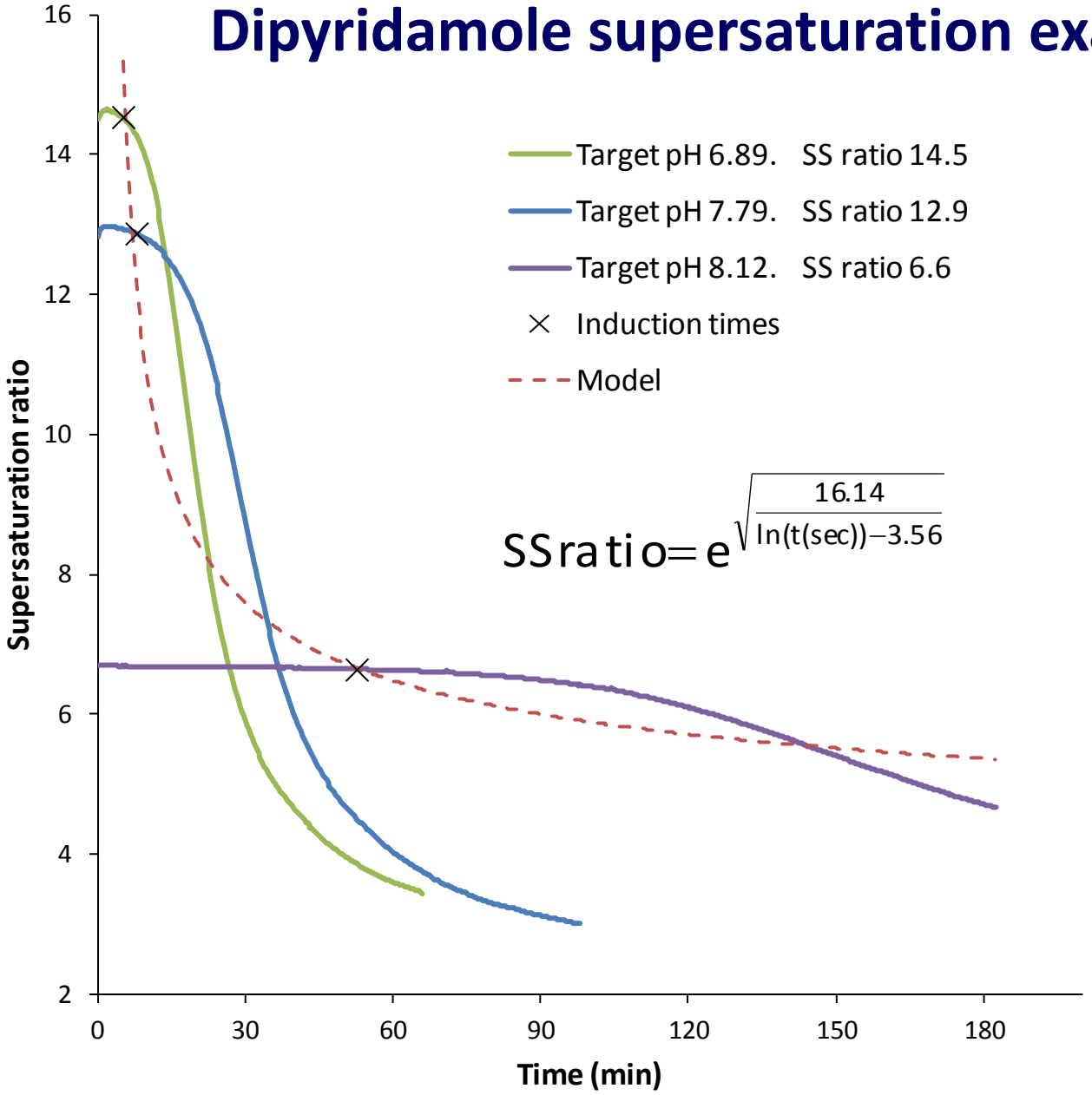


Dipyridamole supersaturation examples



Measuring concentration in the presence of solid

Measuring concentration in presence of solid

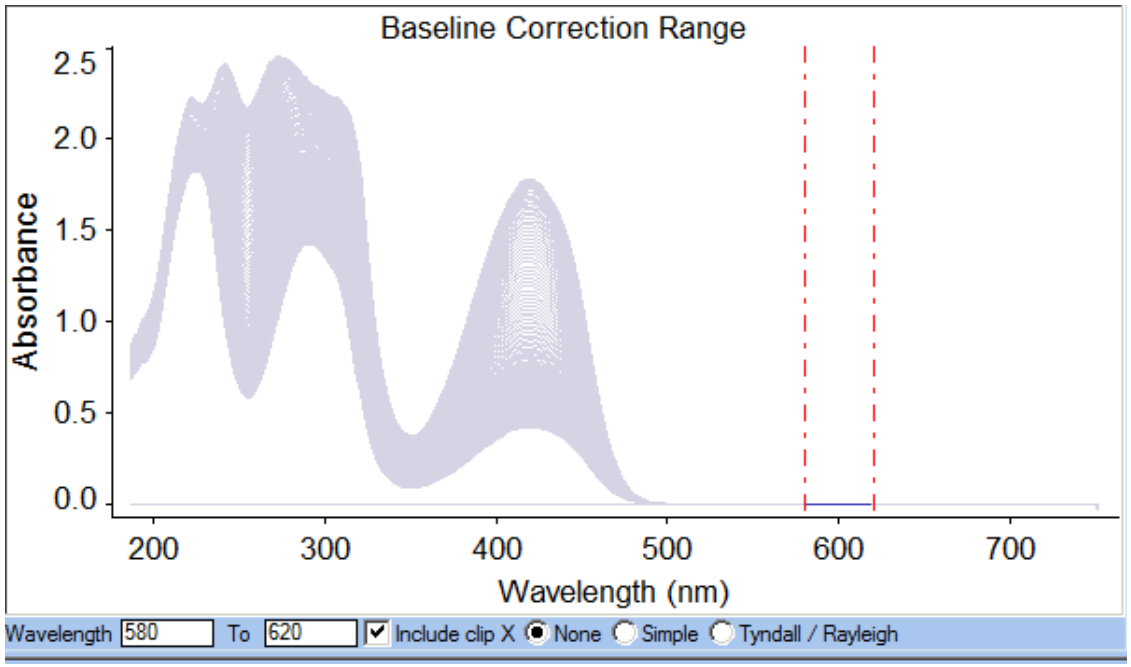
- By pH
  - Turbidity no problem.
  - Sample needs ionizable group
  - pH of solution must be $pK_a \pm 2$
  - Tricky for very poorly soluble samples
- Taking aliquots, measuring off-line
  - Sounds easy, but there are problems
- Using in-situ UV
  - Sample needs chromophore
  - Need to deal with turbidity

Problems with measuring off-line

- What we want: concentration vs. time while sample is precipitating
- Possible problems:
  - Sample may precipitate in needle
  - Sample is filtered but continues precipitating in filtrate
  - May need to dilute the filtrate to re-dissolve the precipitate
  - May need to evaporate the filtrate and then re-dissolve in solvent
  - Messy and a lot of work!

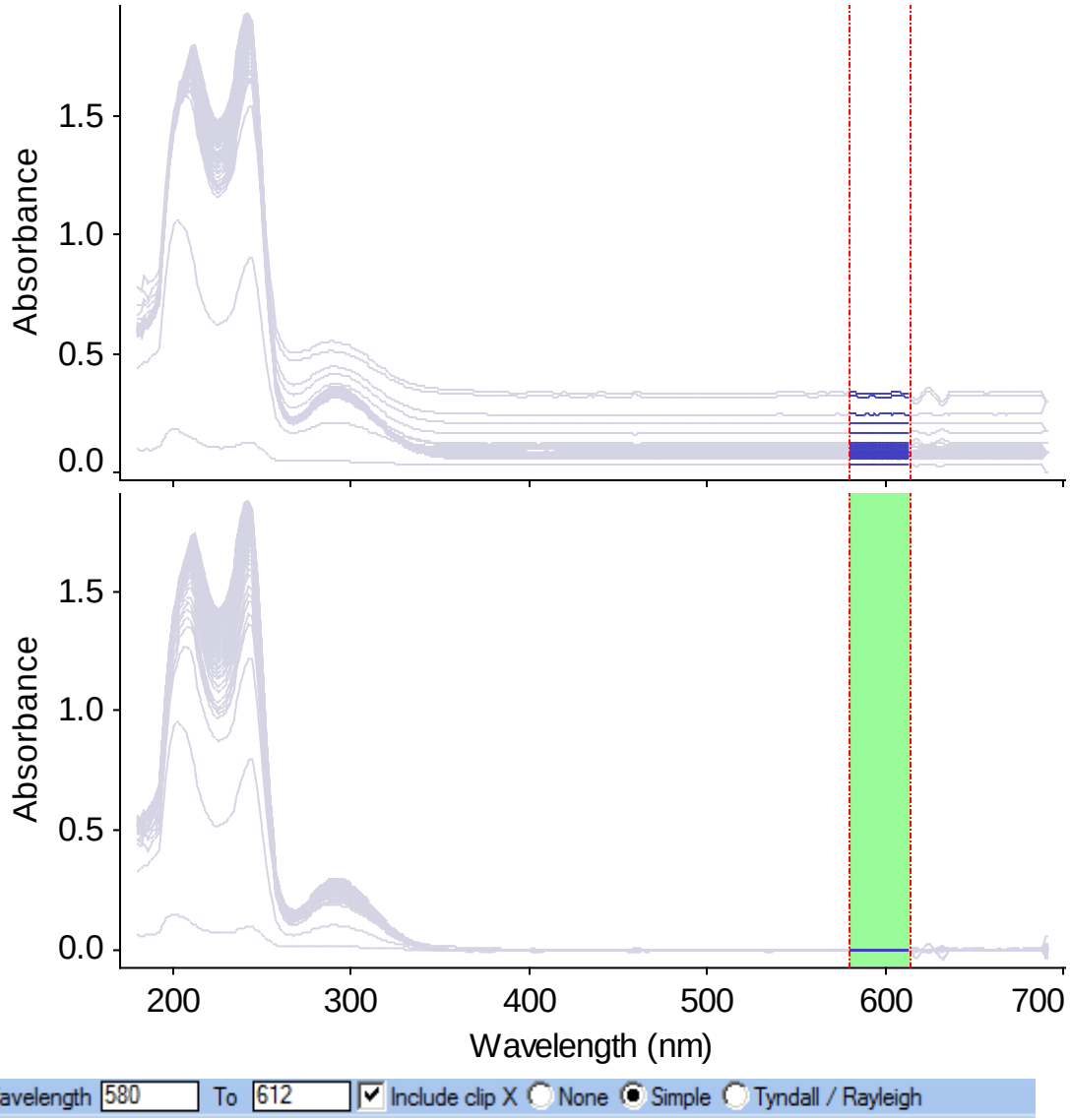
In situ UV, no base line correction

Data from dipyridamole controlled supersaturation
Sample was crystallizing



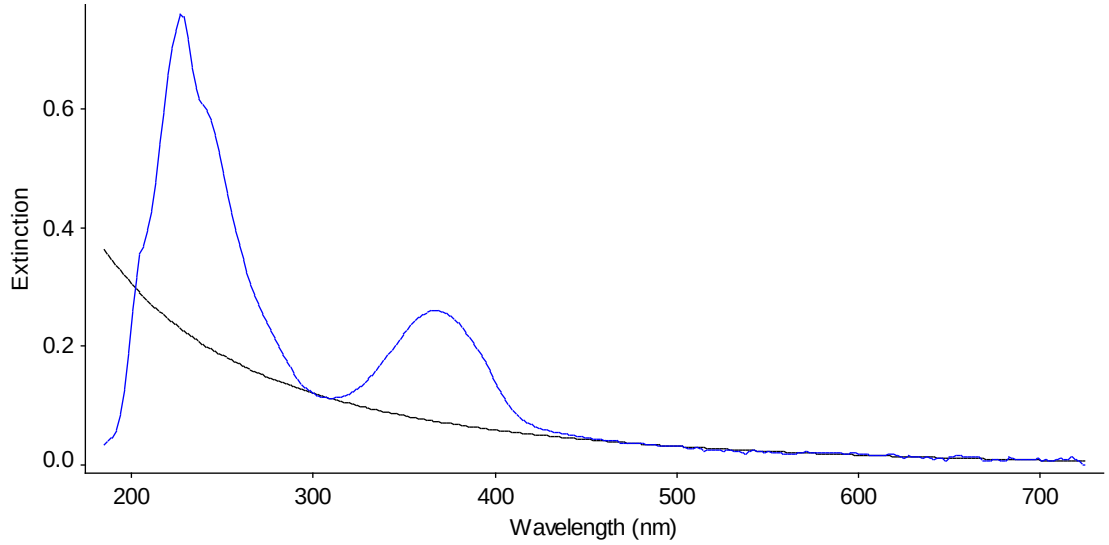
In situ UV, simple base line correction

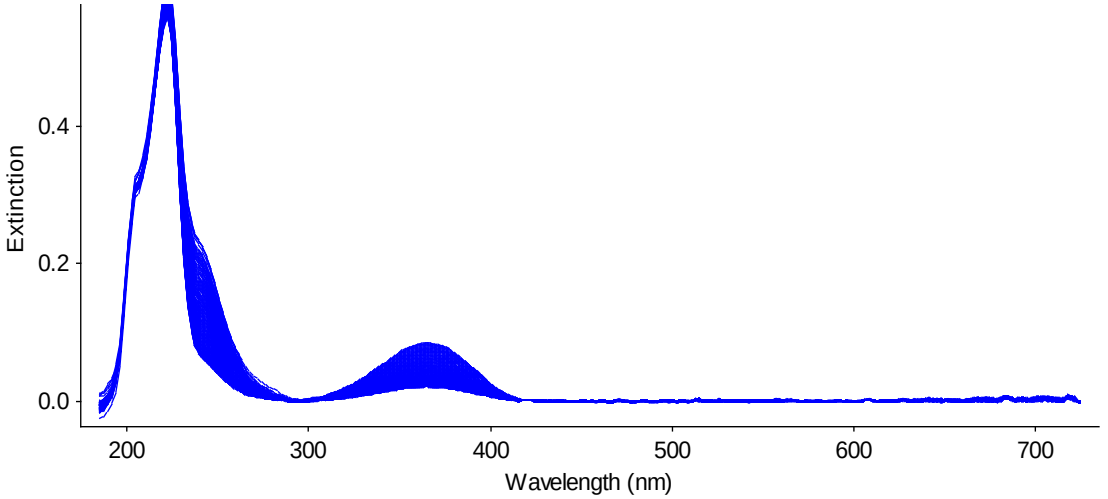
Dissolution of prochlorperazine tablet (5 mg) at pH 2.1: Excipient particles present

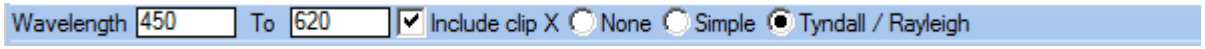


In situ UV, Tyndall-Rayleigh baseline correction

Data from felodipine supersaturation study: Amorphous suspension present



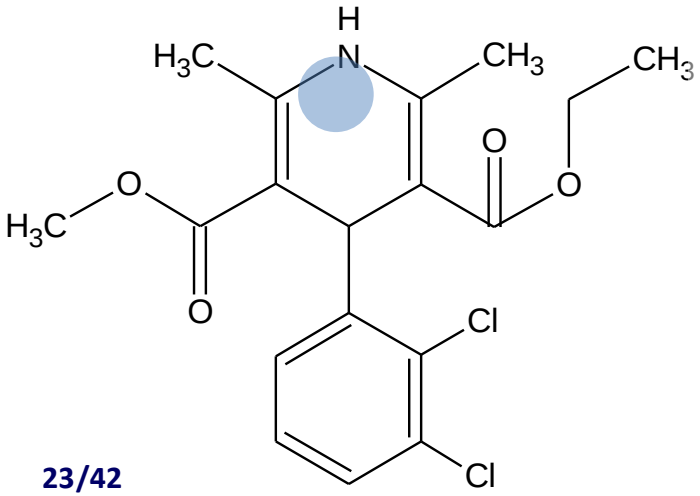


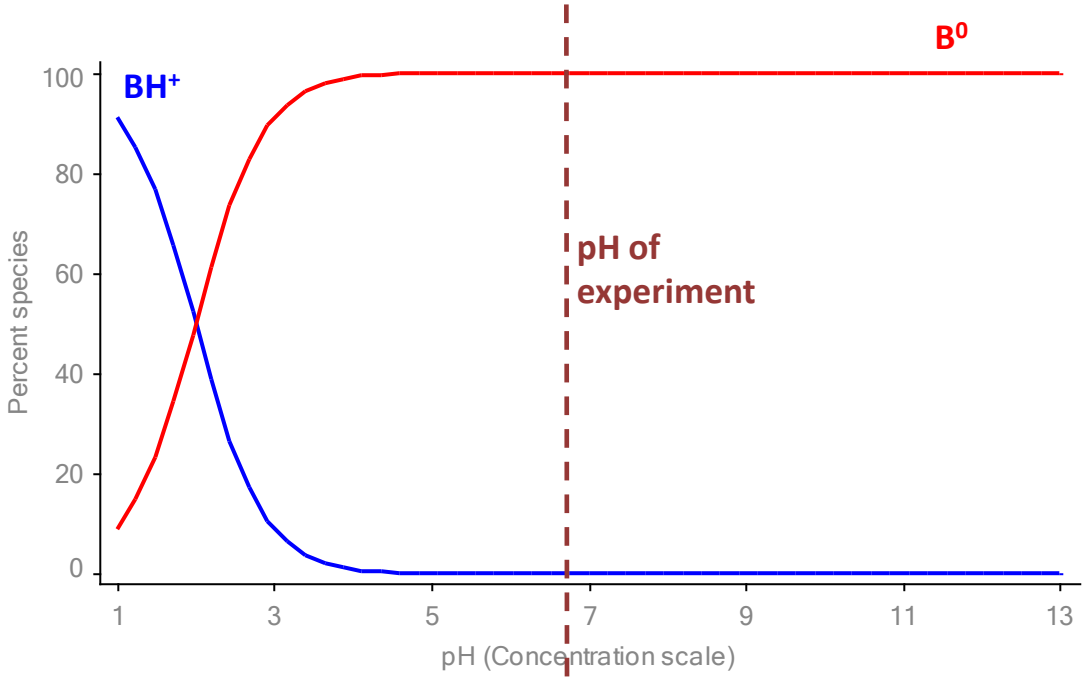


Felodipine supersaturation study

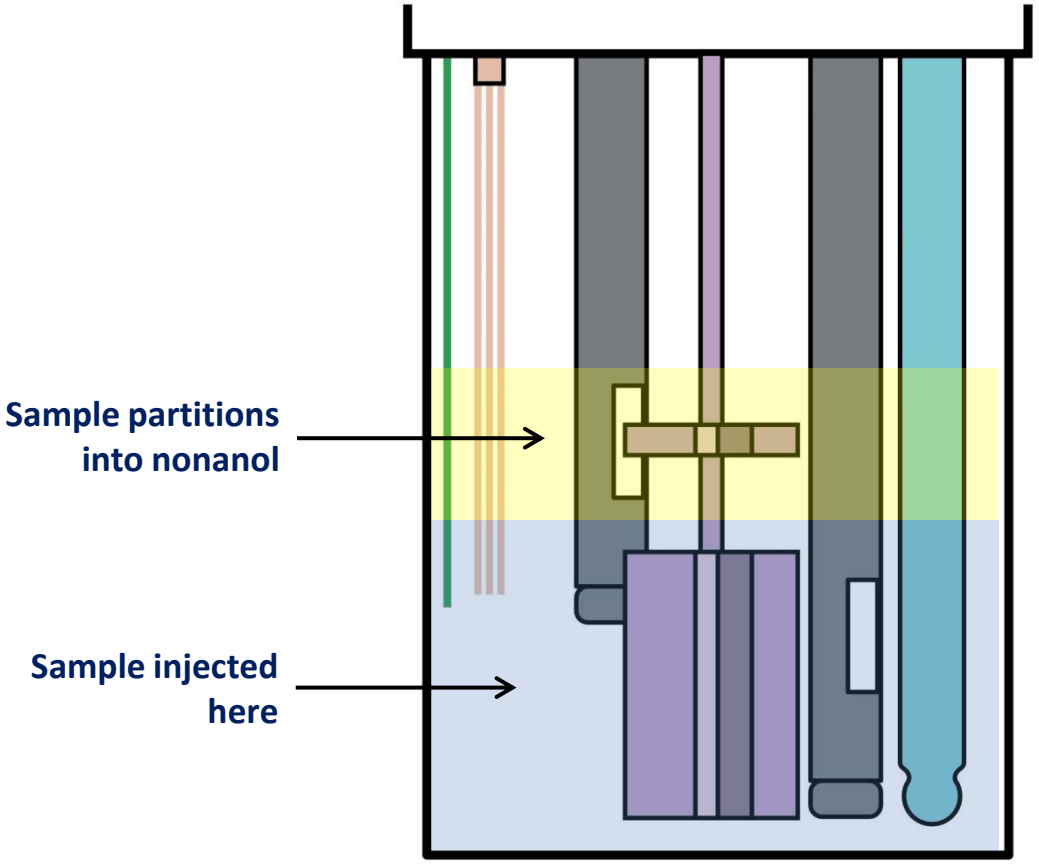
Felodipine supersaturation study

- Felodipine: very weak base (pK_a <2). 10mM in DMSO
- Aqueous solution prepared at pH 6. 8
- Aliquot of DMSO stock injected in solution to create supersaturated solution ("solvent shift method")
- We studied this in biphasic system

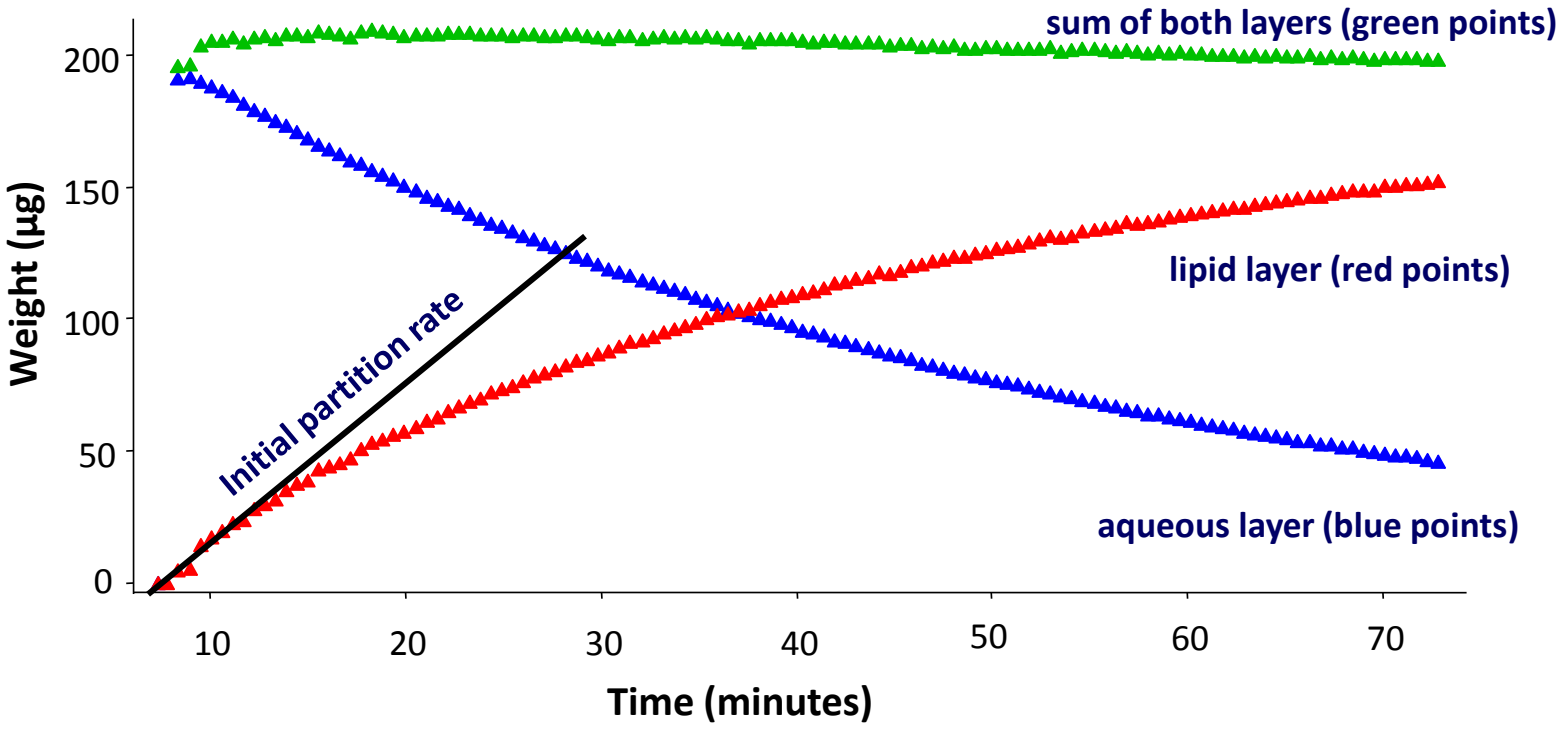




Cell used for biphasic solvent shift experiments

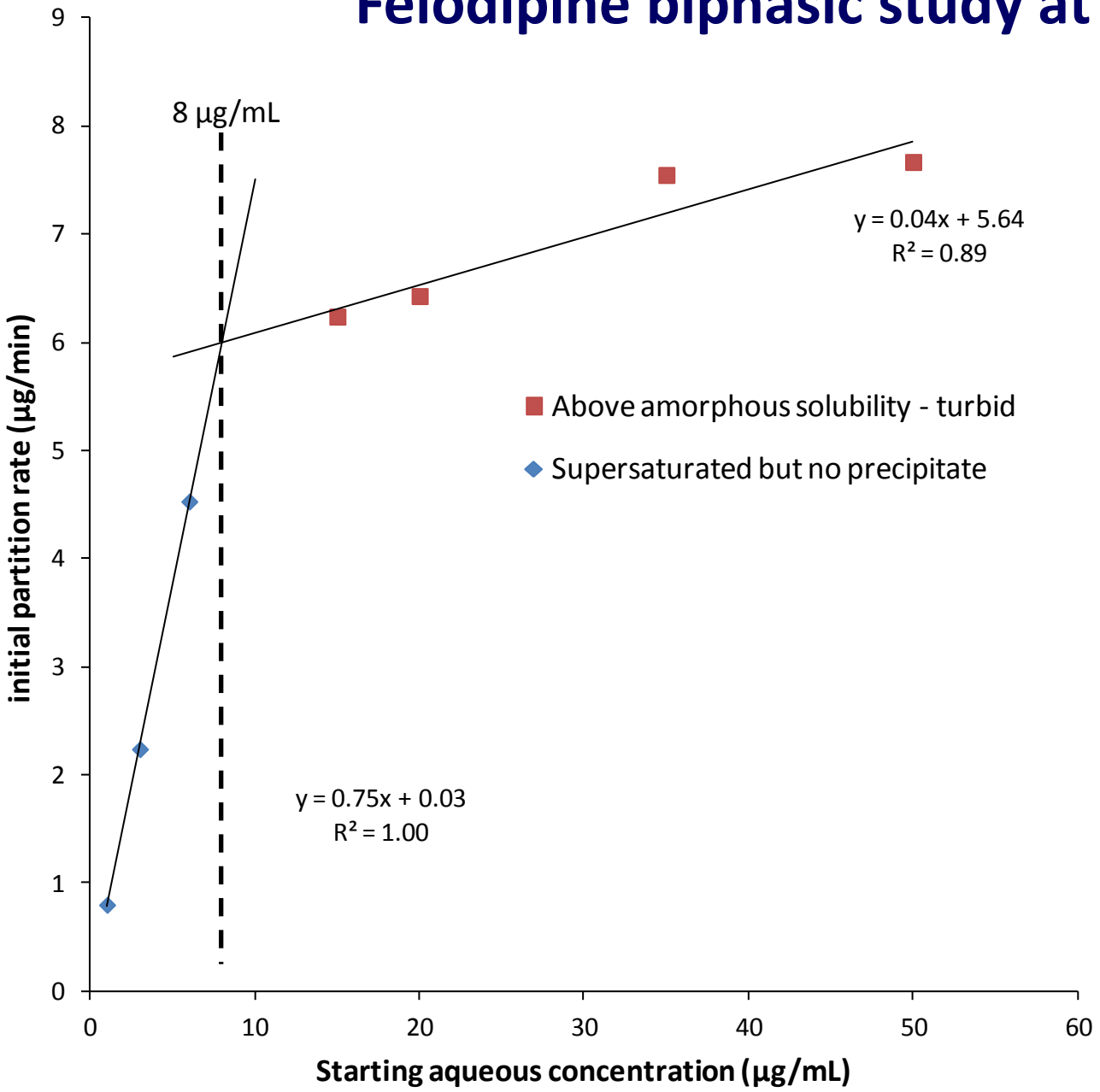


Felodipine - dissolved mass versus time

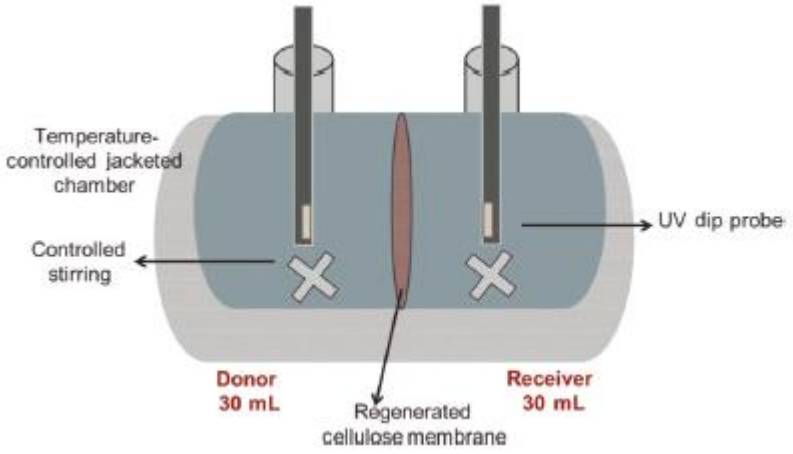


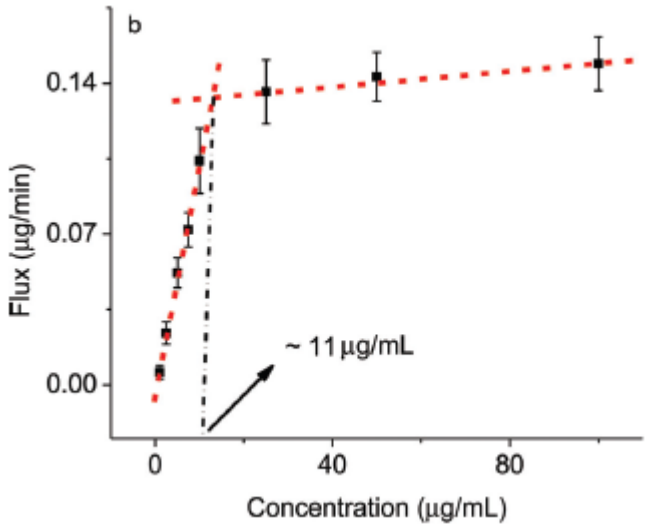
Box, K. et al.
Biphasic dissolution studies of Felodipine: understanding the effect of amorphous solubility on the rate of partition.
Poster, AAPS Annual Meeting 2013. Download from www.sirius-analytical.com

Felodipine biphasic study at 25°C



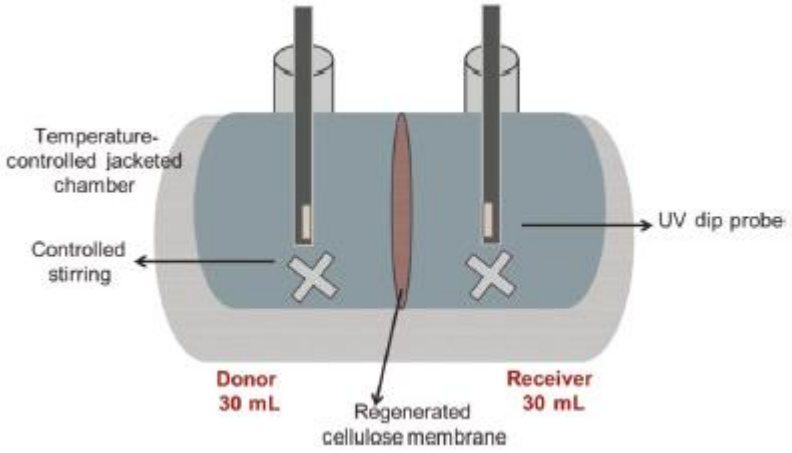
Felodipine permeation study at 37°C



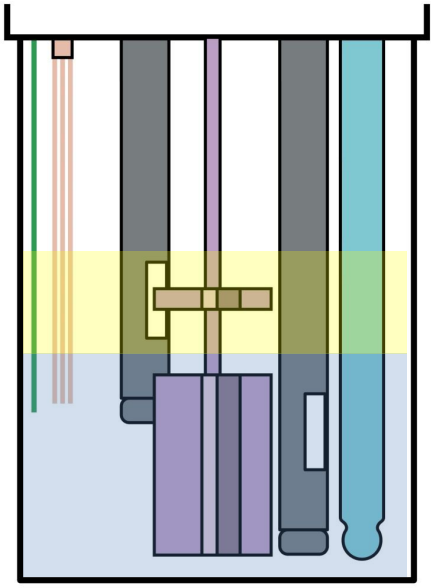


"Side-by-side diffusion cell"

Raina, S.A. et al.
Enhancements and Limits in Drug Membrane Transport Using Supersaturated Solutions of Poorly Water-Soluble Drugs.
J Pharm Sci 2014, DOI 10.1002/jps.23826



“Side-by-side diffusion cell”

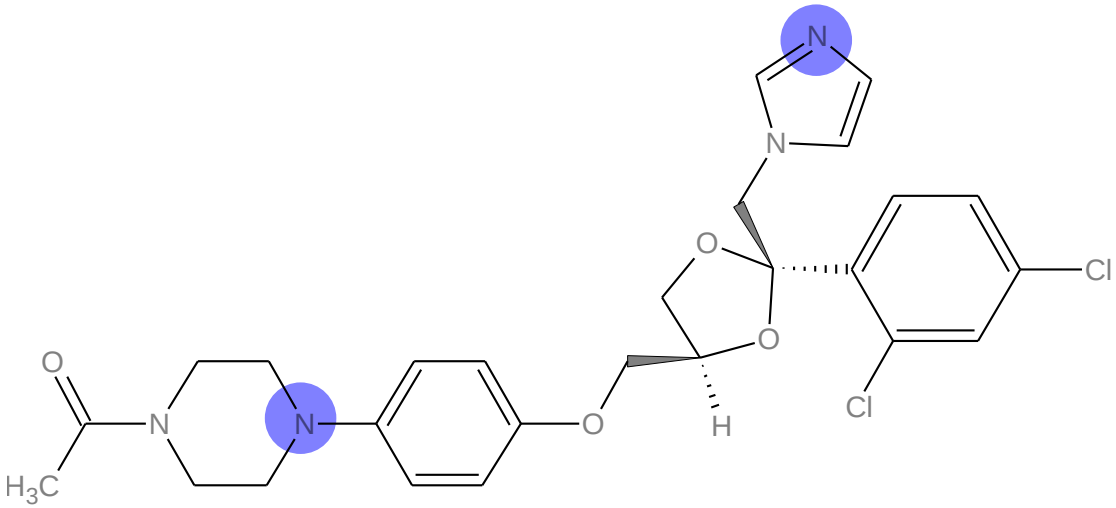


Biphasic cell

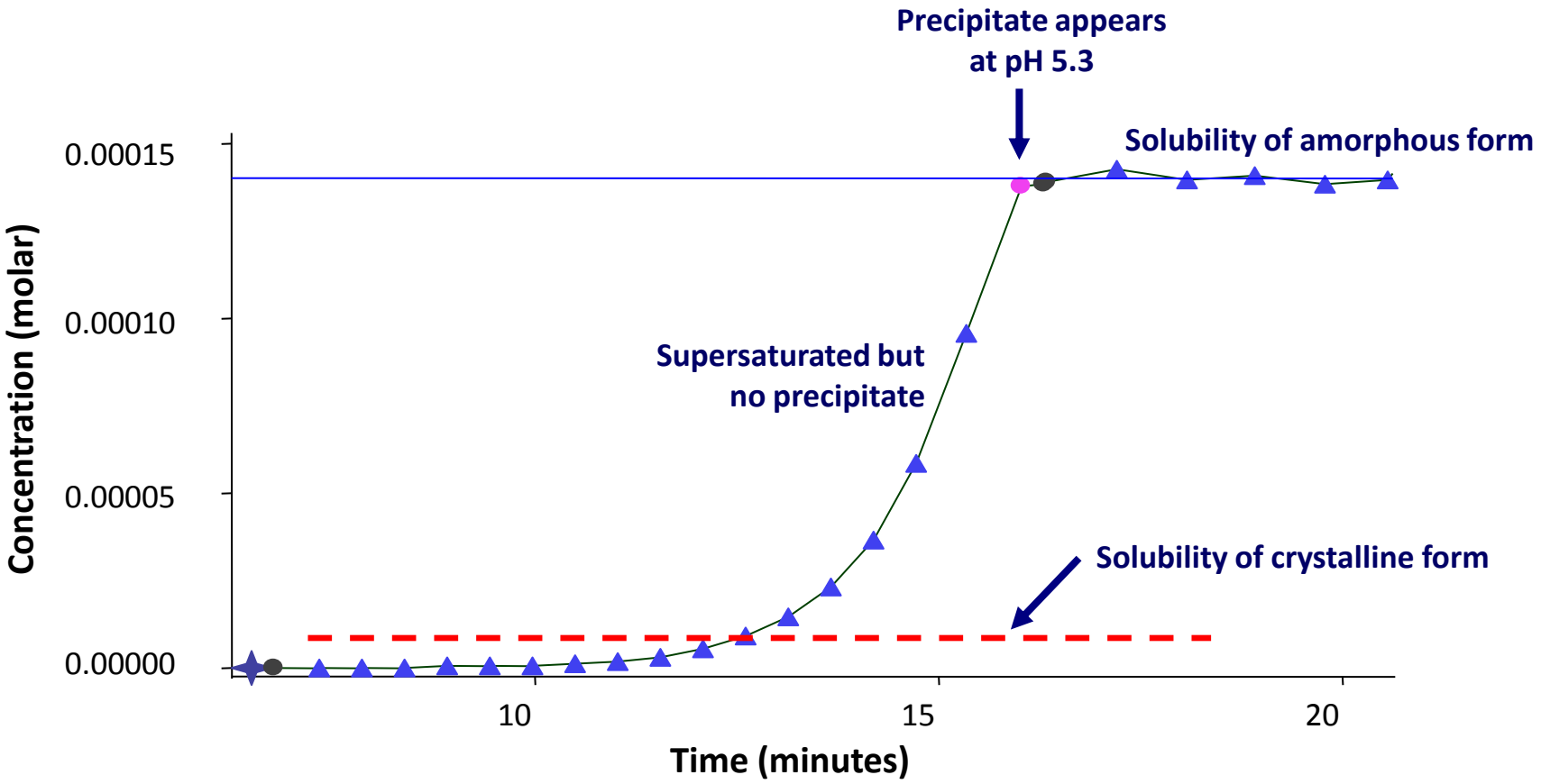
Robust, easy to automate

Active pH control

Ketoconazole supersaturation study



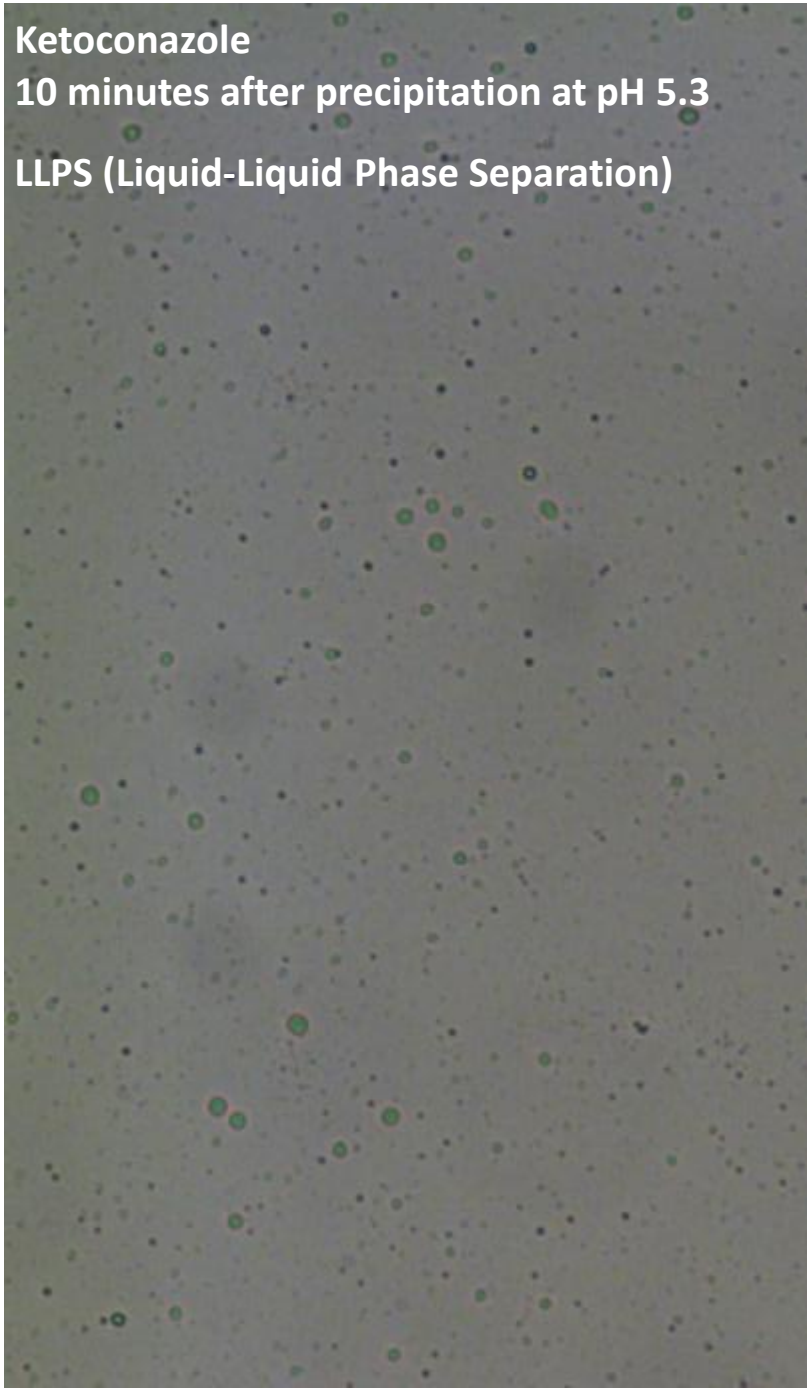
pK_as = 3.3, 6.3



Hsieh, Y. L. et al.
pH-Induced Precipitation Behavior of Weakly Basic Compounds: Determination of Extent and Duration of Supersaturation Using Potentiometric Titration and Correlation to Solid State Properties.
Pharm Res 2012, 29 (10), 2738-2753.

Ketoconazole
10 minutes after precipitation at pH 5.3

LLPS (Liquid-Liquid Phase Separation)



Ketoconazole
10 minutes after precipitation at pH 5.3

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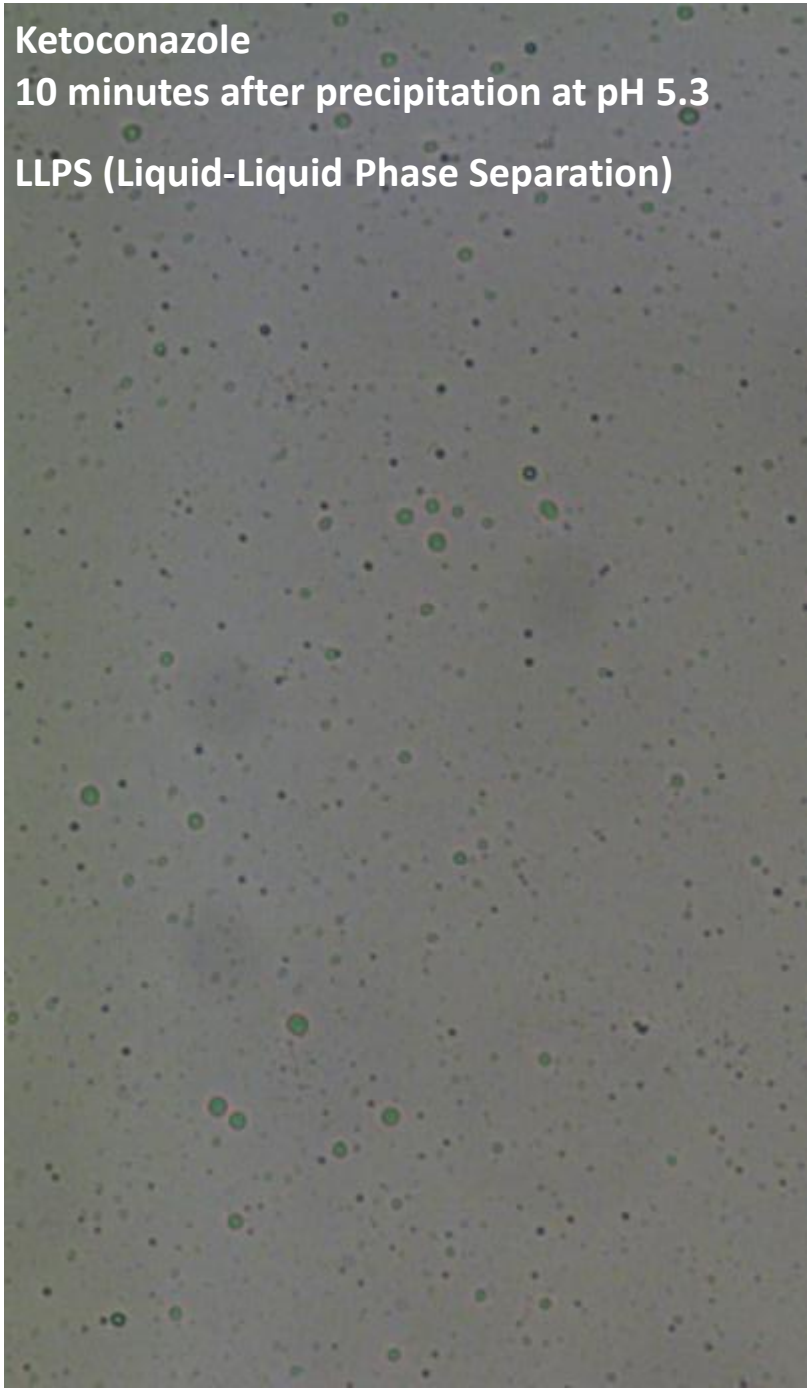
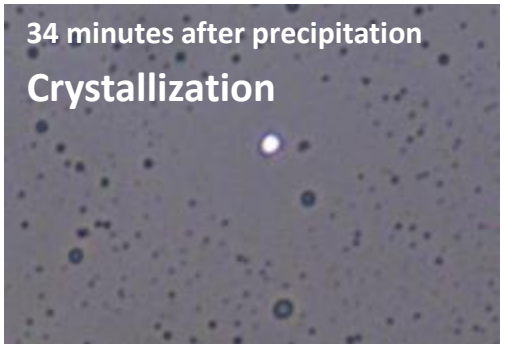
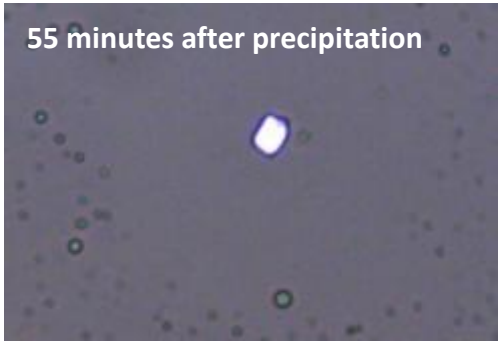


34 minutes after precipitation

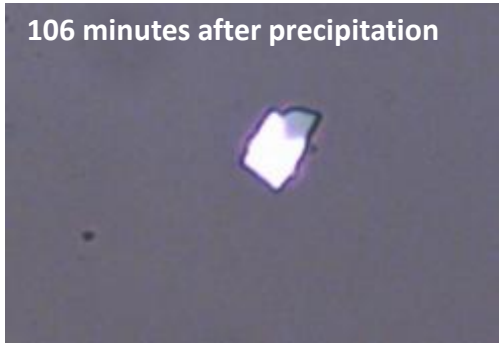
Crystallization



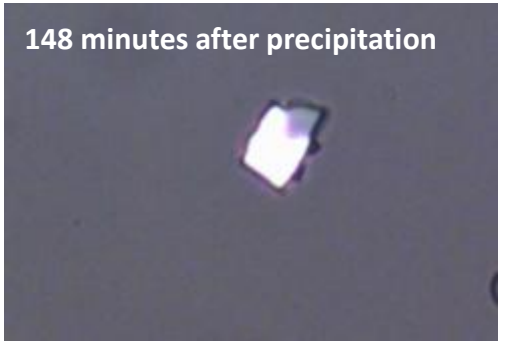
55 minutes after precipitation



106 minutes after precipitation



148 minutes after precipitation



Supersaturation – what can happen

Supersaturated but no precipitate

Supersaturation < amorphous solubility

It may crystallize (e.g. second papaverine example)

Excess of LLPS*

Supersaturation = amorphous solubility

Reservoir of LLPS, may help absorption

Dispersed in another phase, e.g. in lipid

Not crystalline

Initially dissolves at amorphous conc.

Crystallizes from LLPS

Quickly (e.g. first papaverine example)

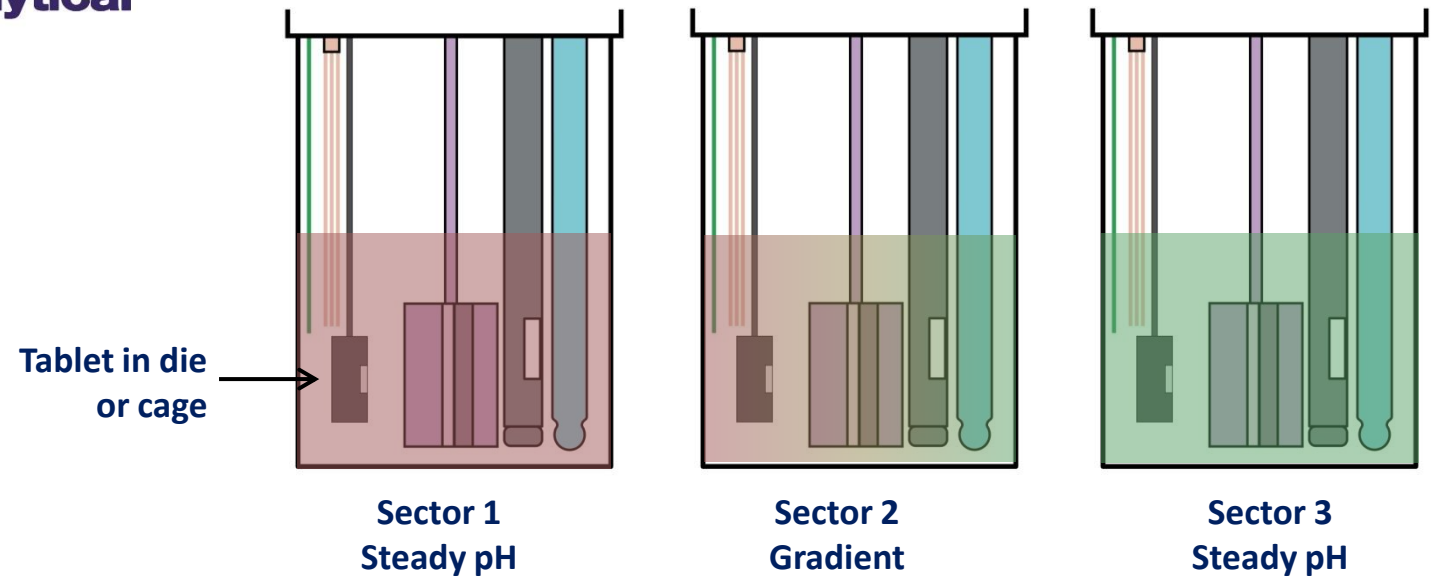
Eventually (e.g. ketoconazole)

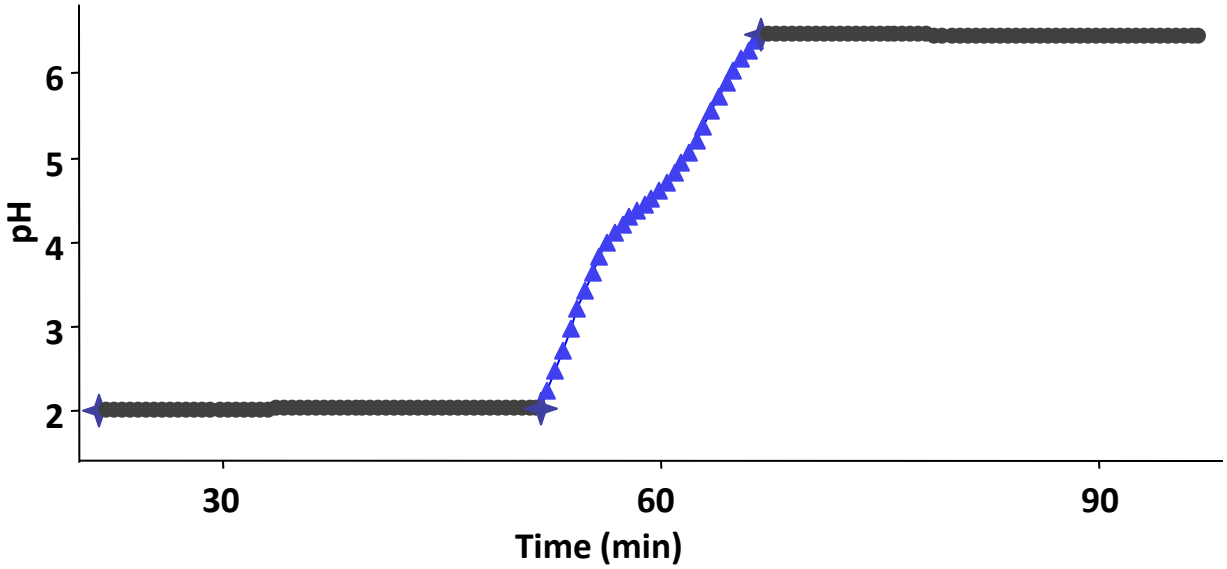
Inhibited (e.g. using HPMCAS)

* LLPS = Liquid-Liquid Phase Separation

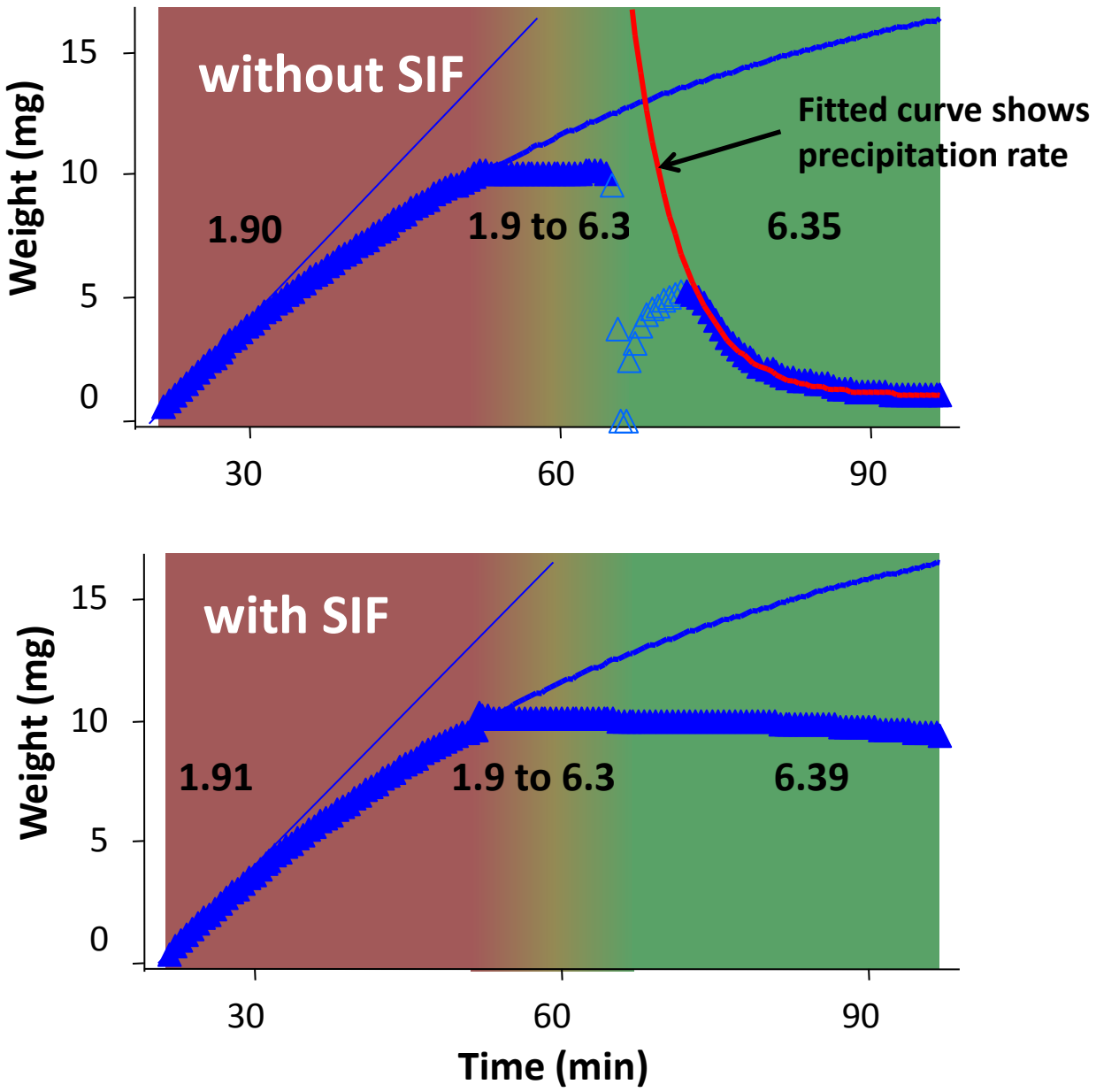
Biorelevant and Biphasic dissolution

Three-sector experiment with gradient pH

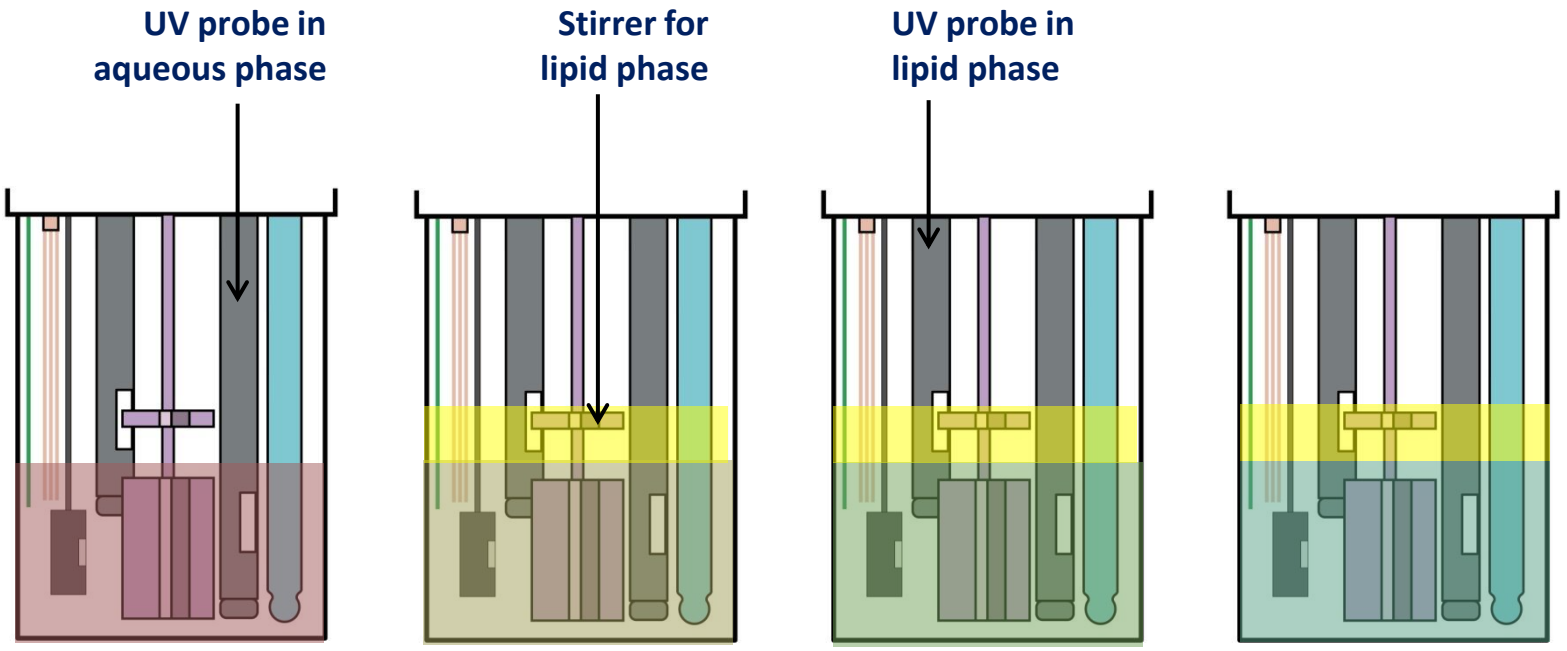




Dipyridamole GI Dissolution

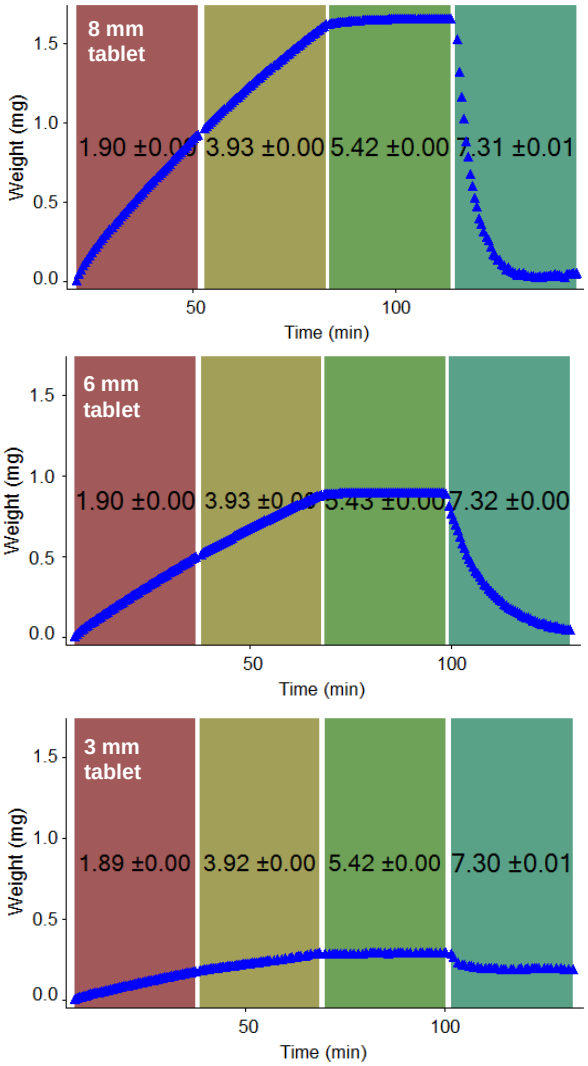


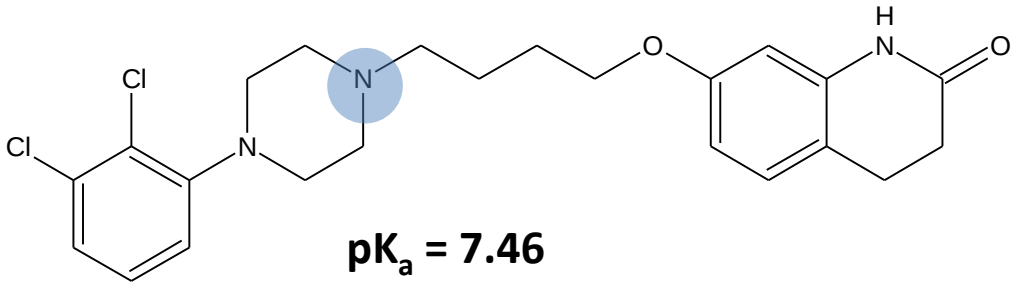
Four-sector biphasic dissolution



Sector 1	Sector 2	Sector 3	Sector 4
pH 1.9	Lipid added pH 3.9	pH 5.4	pH 7.3

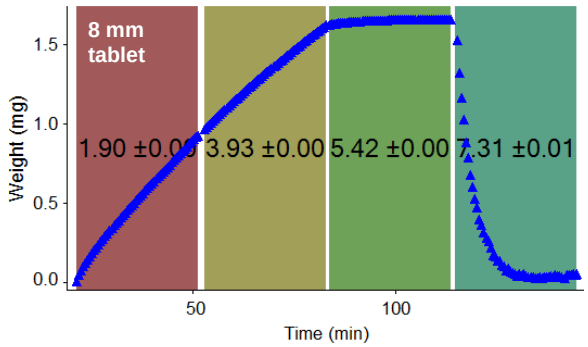
Aripiprazole aqueous Dissolution

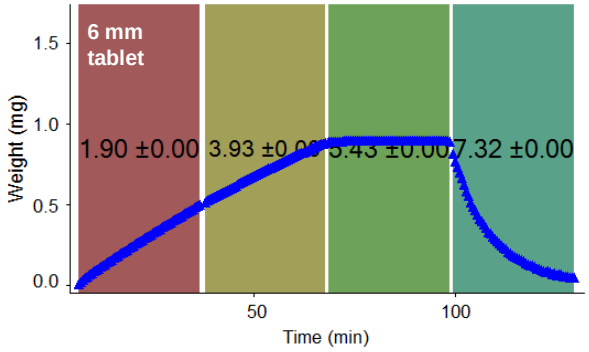


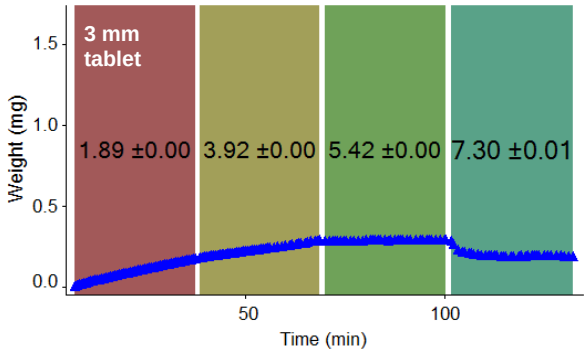


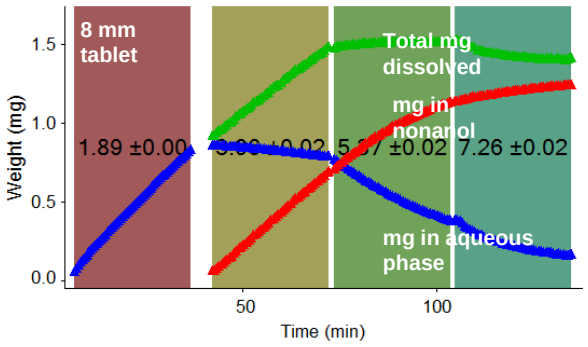
pK_a = 7.46

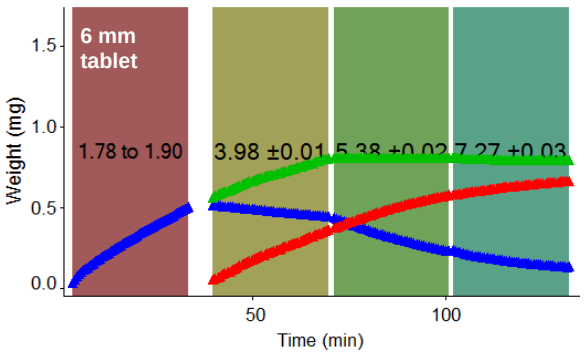
Aripiprazole Biphasic Dissolution

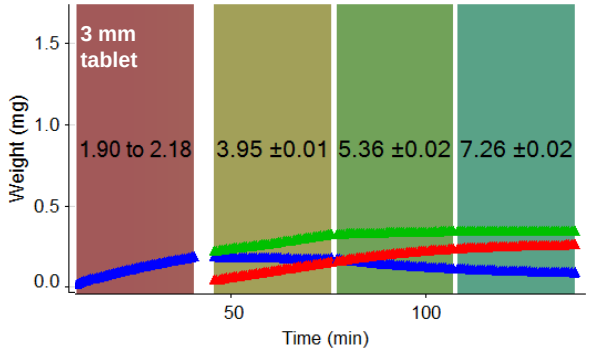












Summary

1. Controlled supersaturation experiments
2. Dealing with suspended solids
3. Supersaturation examples – the LLPS model
4. Biorelevant and Biphasic dissolution

Innovative tools for investigating drug behaviour to help develop better formulations

14th PhysChem Forum hosted by Sirius, 9-10 April

- **Richard Bickerton, University of Dundee**. Quantifying the Chemical Beauty of Drugs through informatics
- **Tim Potter, Cyprotex**. Compound Evaluation using Early Stage Screening Assays
- **Holger Fischer, Hoffman- La Roche**. Physical property screening and prediction in discovery
- **Richard Barker, Astra Zeneca**. Using the Tim-1 GI in-vitro model to understand drug absorption
- **James Butler, GSK**. The Developability Classification System (DCS); a tool for guiding drug development
- **Joachim Brouwers, University of Leuven**. Solubility in human gastric and intestinal fluids
- **Robert Taylor, Sirius Analytical**. Automated measurements of lipolysis, supersaturation and biphasic dissolution

Thanks to our Development Team

Chemists
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Robert Taylor
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Urszula Wnorowska

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Roger Allen
Richard Woodward
Norman Turrell
Ivo Reis
Craig Roberts

Project managers
Andy Latham
Rebecca Biloune

Thanks to collaborators

Lynne Taylor and colleagues, Purdue University

Sirius in the US

Office and lab in Beverly MA. Exhibiting here.