Experimental Methods for Investigating Drug Supersaturation Behavior: Promoting a Compound's BCS Class

Karl Box

AAPS Annual Meeting October 27th 2011

Overview

- About Sirius
- LogP/logS, BCS and DCS
- Supersaturation; spring and parachute
- CheqSol – studying supersaturation and precipitation
- Crystallization inhibition and excipient gain factors
- Oiling out and amorphous solubility
- GI-dissolution assay
- Questions

An introduction to Sirius

- Sirius was founded in 1990 in the United Kingdom. We are a **manufacturer** and **vendor** of instrumentation for measurement of physicochemical parameters.
- We provide an **Analytical Service**, and measure thousands of samples for hundreds of customers, worldwide, each year.

Sirius locations

- **Sirius Analytical Ltd.**
- Company headquarters in UK
  - Manufacturing
  - Engineering
  - Software
  - Chemistry R&D
  - Administration
- Located in Forest Row, East Sussex (30 minutes from London Gatwick Airport)
- Direct sales in some countries, distributors in others

- **Sirius Analytical Inc.**
- Support for North American customers
  - Instrument service
  - Installation
  - Training
  - Sales
  - Stock of parts
- Located in Beverly, MA

SiriusT3 PhysChem Platform

At Sirius, we make analytical instruments for measuring physchem properties of drugs.

The most important product for Sirius is the SiriusT3.

SiriusT3 will measure pK_a, logP, solubility and supersaturation of ionizable drugs.

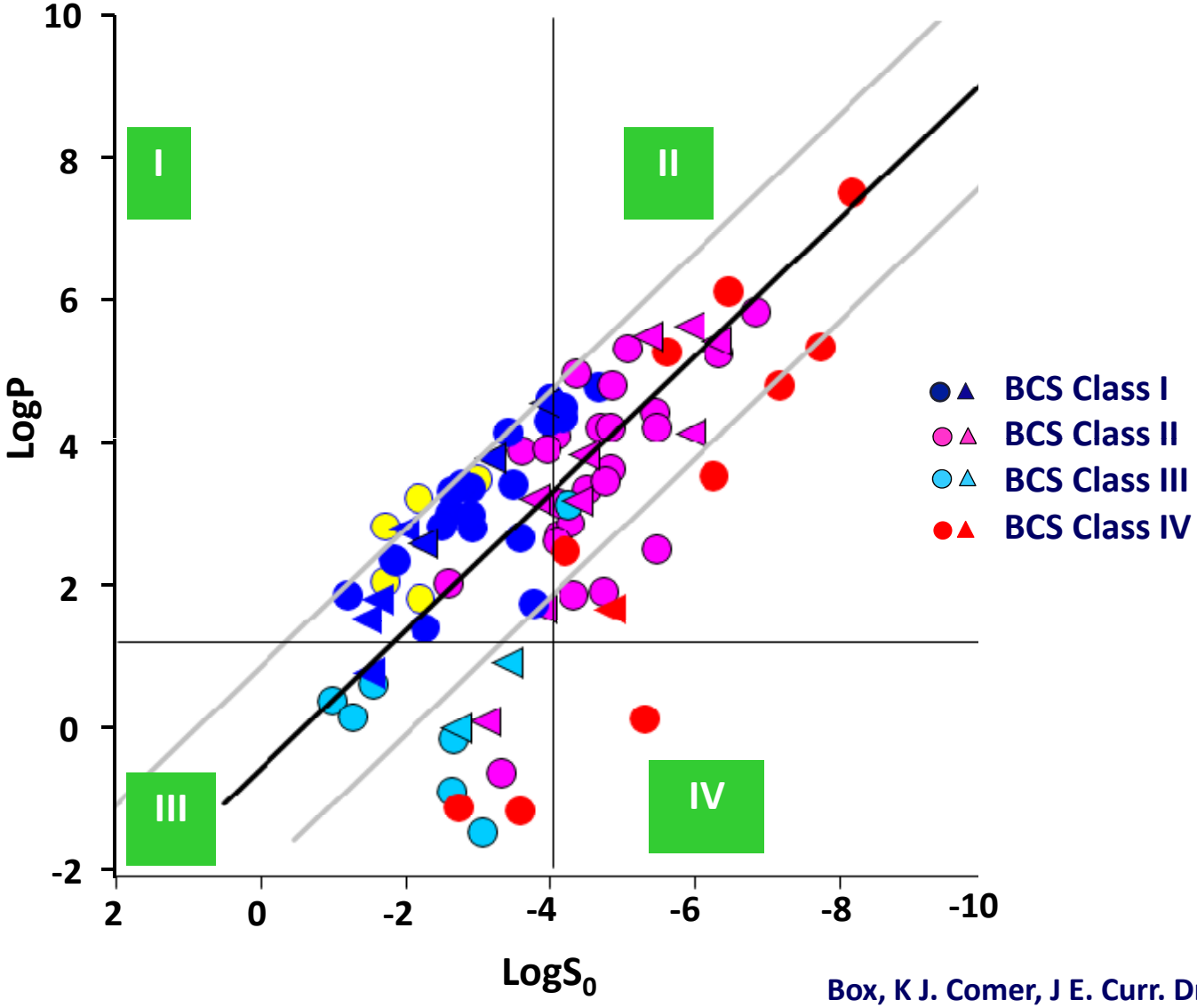
It will also measure dissolution rates of ionizable and neutral drugs

LogP and LogS

BCS

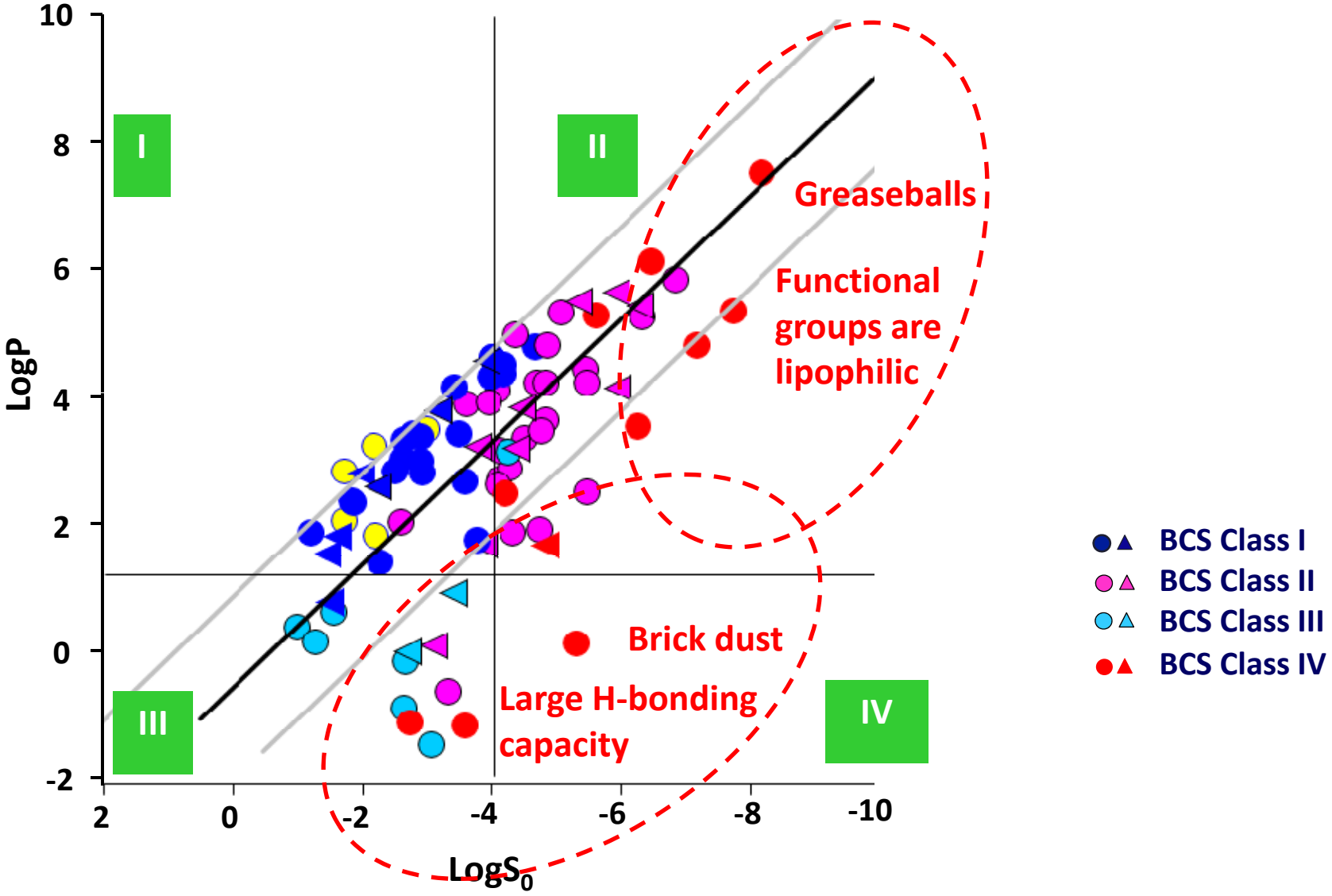
DCS

Sirius measured values for 84 drugs



Box, K J. Comer, J E. Curr. Drug Metab. 2008, 9(9), 868-878

Sirius measured values for 84 drugs



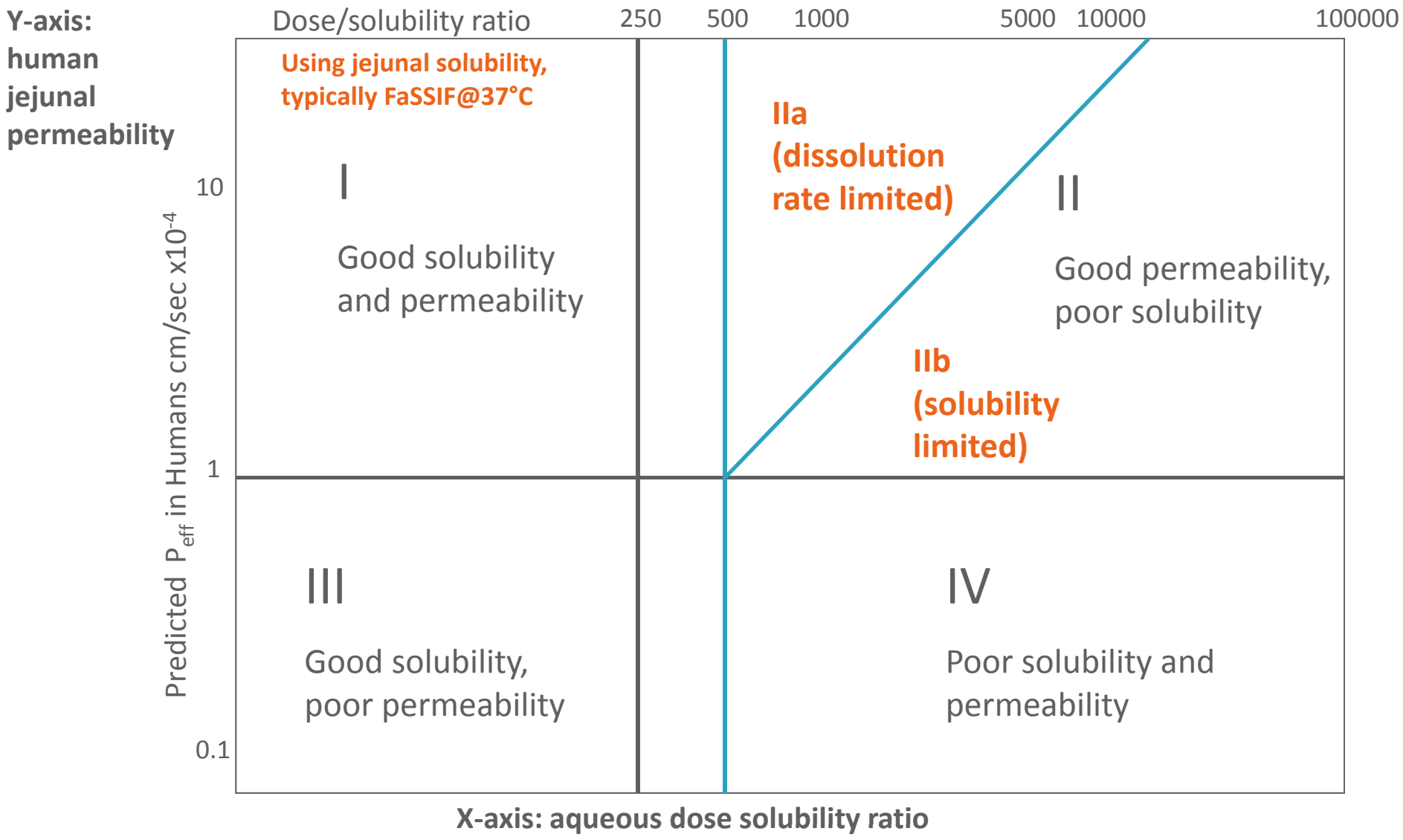
Drug classification systems

- Biopharmaceutics Classification System (BCS)
  - Regulatory tool
  - Conservative, efficacy and patient safety in mind

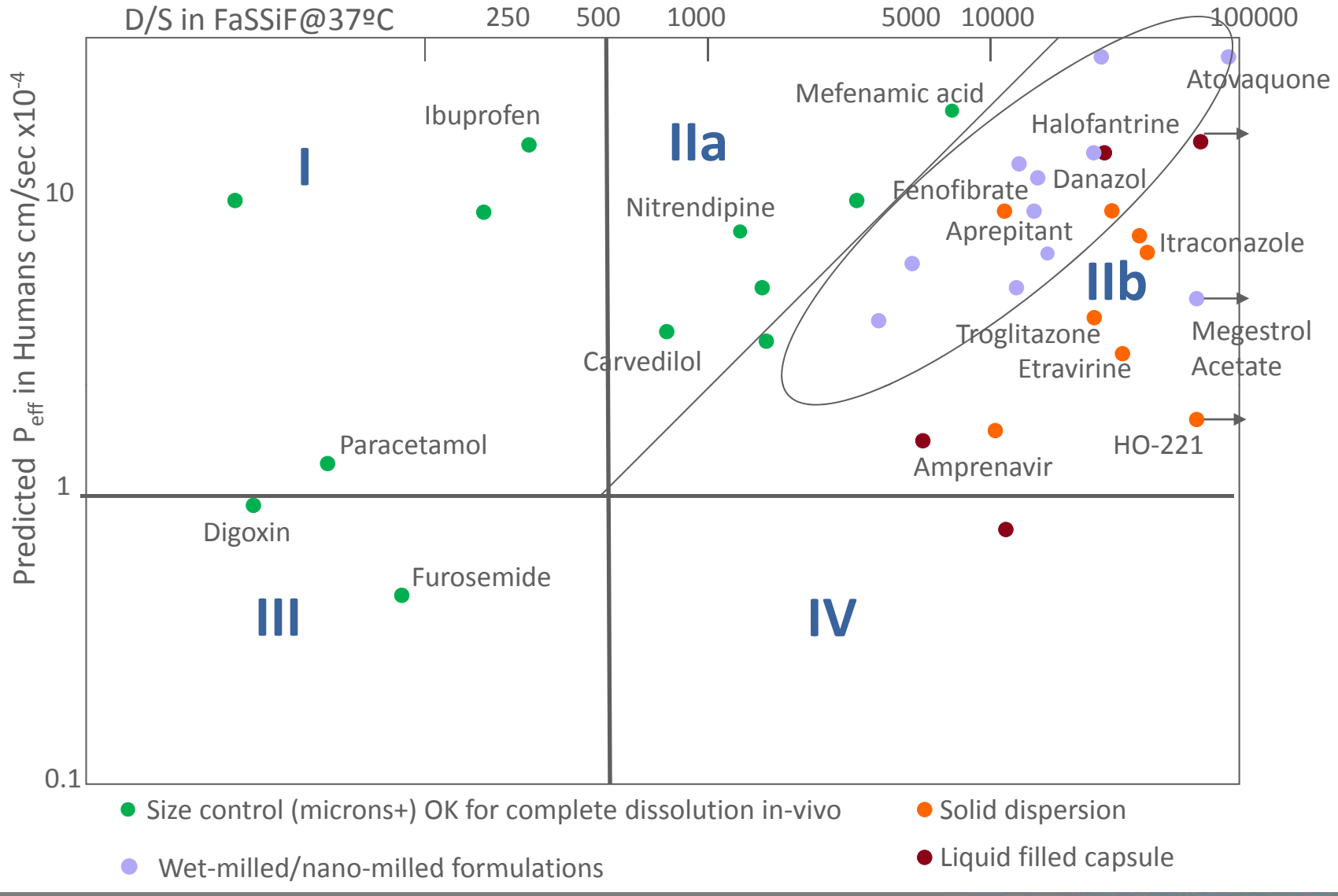
- Developability Classification System (DCS)
  - A tool to aid developability
  - Aim: realistic, product development issues in mind
    - > What factors are likely to control the extent of oral absorption?
      - Permeability, solubility, dissolution rate

Butler, J., Dressman, J. J. Pharm. Sci. 2010, 99 (12), 4940–4954

BCS and DCS


Y-axis: human jejunal permeability
Dose/solubility ratio
250
500
1000
5000
10000
100000
Using jejunal solubility, typically FaSSIF@37°C
I
Good solubility and permeability
IIa (dissolution rate limited)
II
Good permeability, poor solubility
IIb (solubility limited)
III
Good solubility, poor permeability
IV
Poor solubility and permeability
10
1
0.1
Predicted P_{eff} in Humans cm/sec x10^{-4}
X-axis: aqueous dose solubility ratio

DCS plot: Approximate position for selected drugs



Supersaturation – Spring and parachute

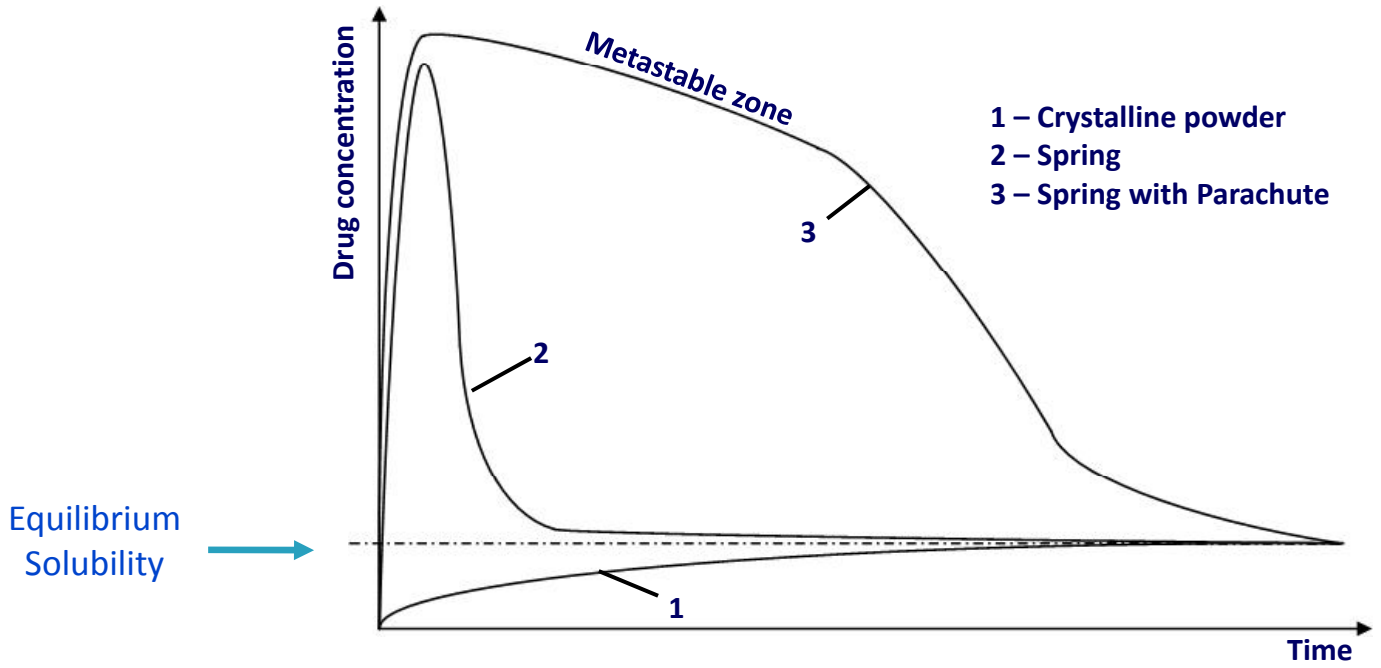


Figure adapted from Brouwers et al.

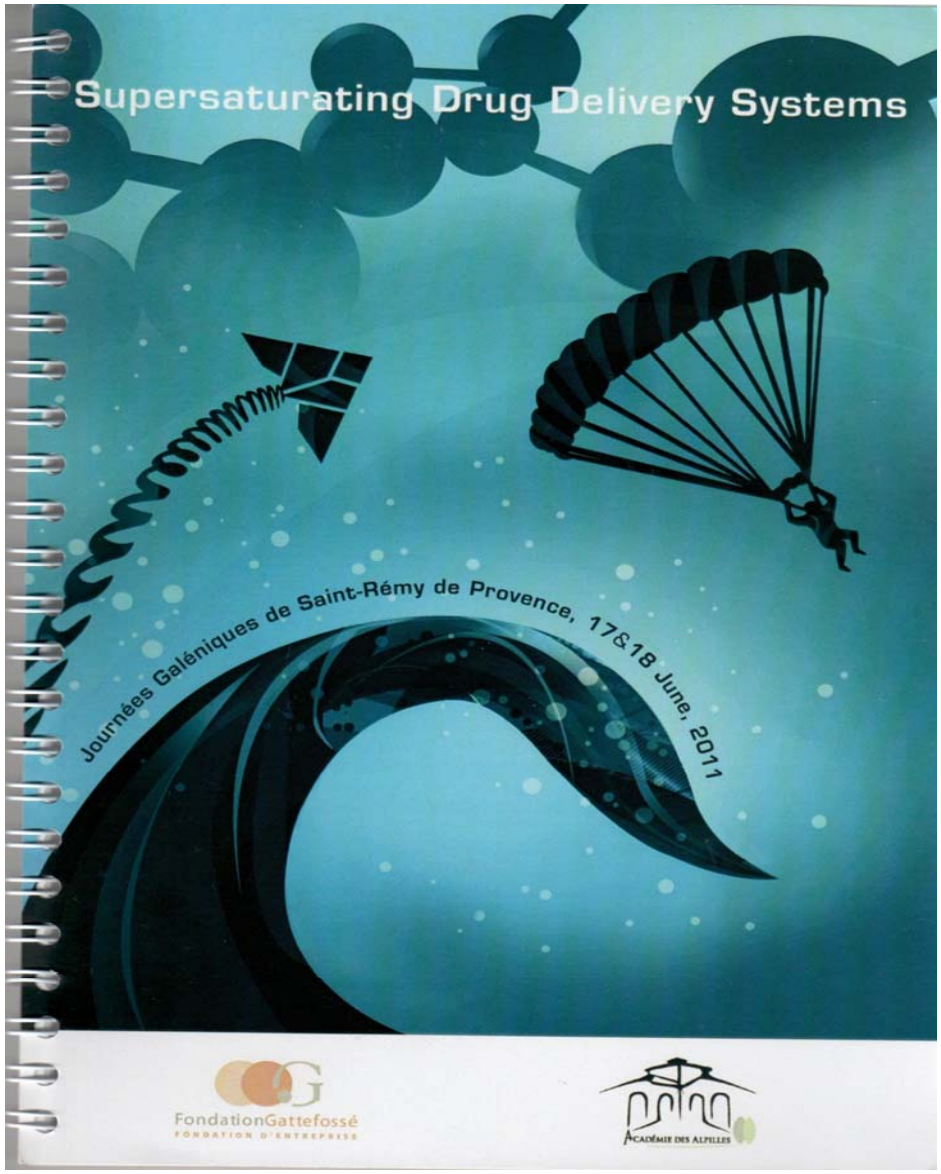
Schematic of drug concentration–time profile illustrating the spring and parachute approach

FIRST USE OF "SPRING AND PARACHUTE"

Guzmán, H. R. et al. **Combined use of crystalline salt forms and precipitation inhibitors to improve oral absorption of celecoxib from solid oral formulations.**
J Pharm Sci 2007, 96 (10), 2686-2702.

A DETAILED AND THOROUGH REVIEW

Brouwers, J. et al. **Supersaturating Drug Delivery Systems: The Answer to Solubility-Limited Oral Bioavailability?**
J. Pharm. Sci. 2009, 98 (8), 2549-2572.


Supersaturating Drug Delivery Systems
Journées Galéniques de Saint-Rémy de Provence, 17&18 June, 2011
FondationGattefossé
FONDATION D'ENTREPRISE
Académie des Alpilles

CheqSol

The Sirius method for measuring solubility is called CheqSol,
which stands for
"**Ch**asing **Eq**uilibrium **Sol**ubility"

It runs on the SiriusT3 instrument

HOW IT WORKS:
Box, K.; Comer, J. E.; Gravestock, T.; Stuart, M., **New ideas about the solubility of drugs.**
Chem Biodivers 2009, 6 (11), 1767-1788.

CALCULATION OF SOLUBILITY; MASS AND CHARGE BALANCE APPROACH:
Stuart, M. Box, K., **Chasing equilibrium: measuring the intrinsic solubility of weak acids and bases.**
Anal. Chem. 2005 (77(4)) pp 983-990

VALIDATION STUDY:
Box, K. J.; Völgyi, G.; Baka, E.; Stuart, M.; Takács-Novák, K.; Comer, J. E., **Equilibrium versus kinetic measurements of aqueous solubility, and the ability of compounds to supersaturate in solution - a validation study.**
J Pharm Sci 2006, 95 (6), 1298-1307.

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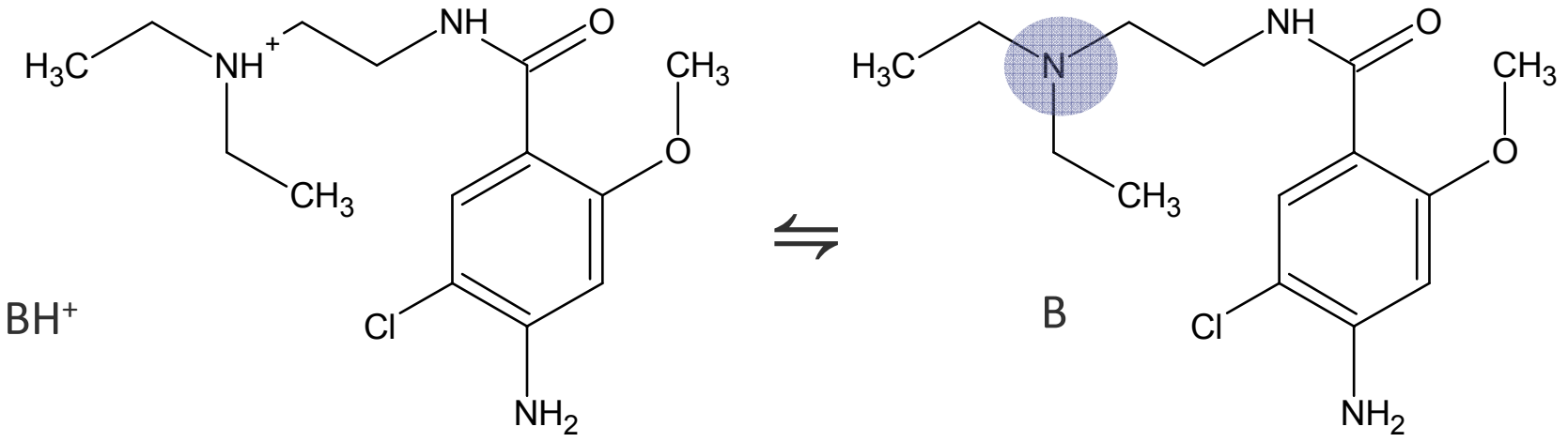
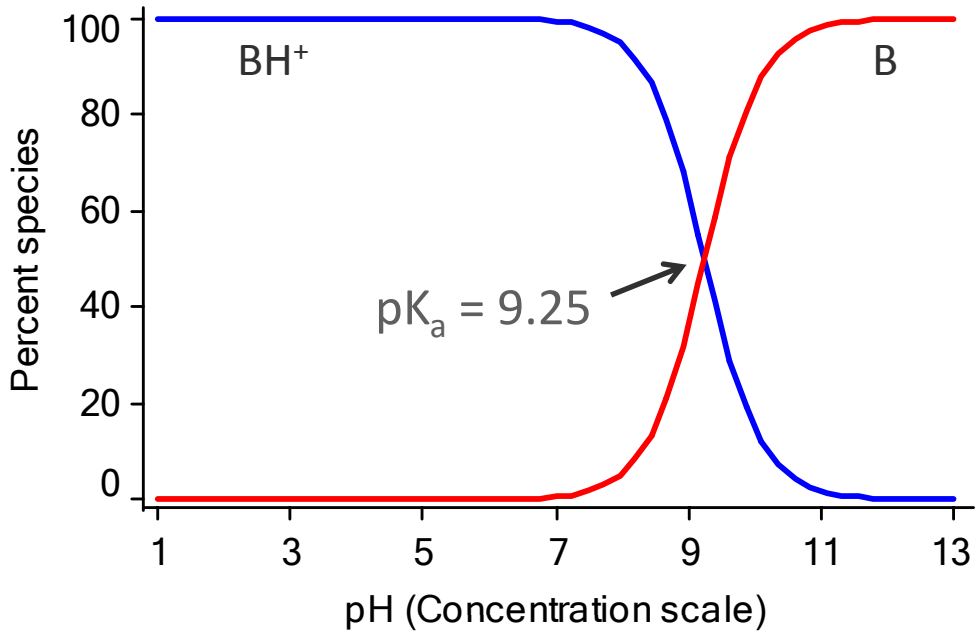
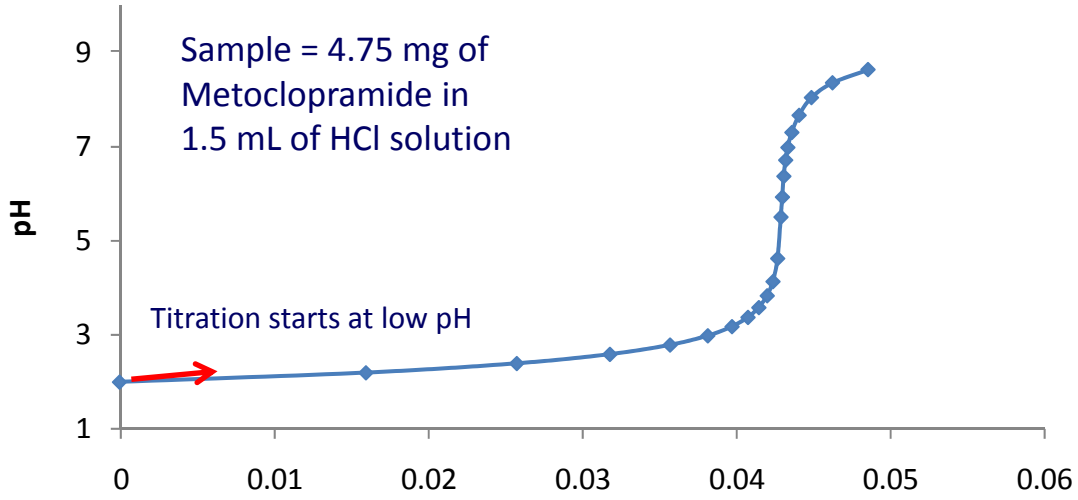
Making a supersaturated solution of an ionizable drug

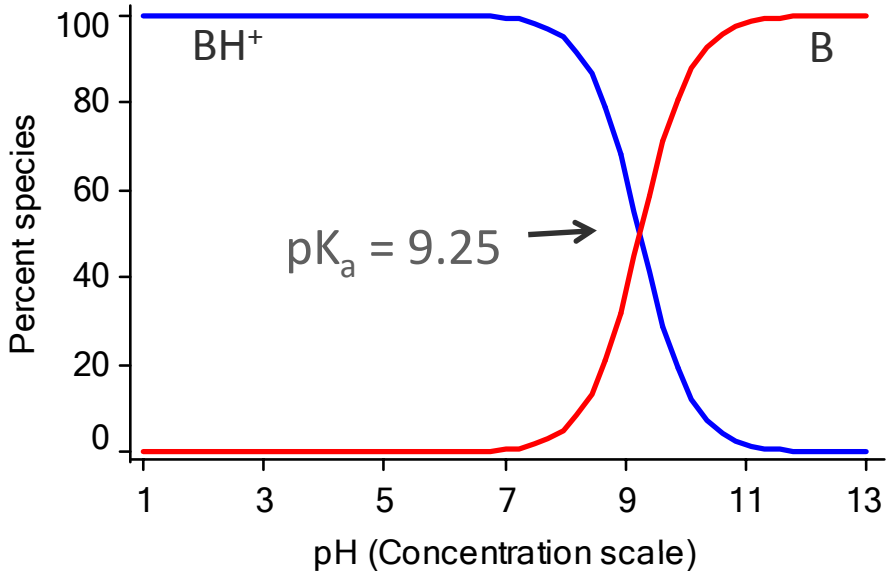




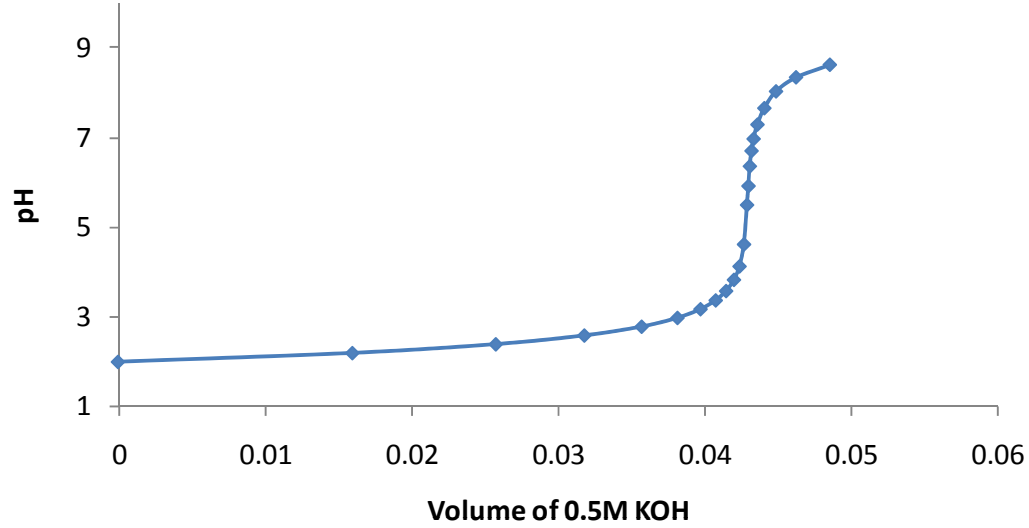
Metoclopramide

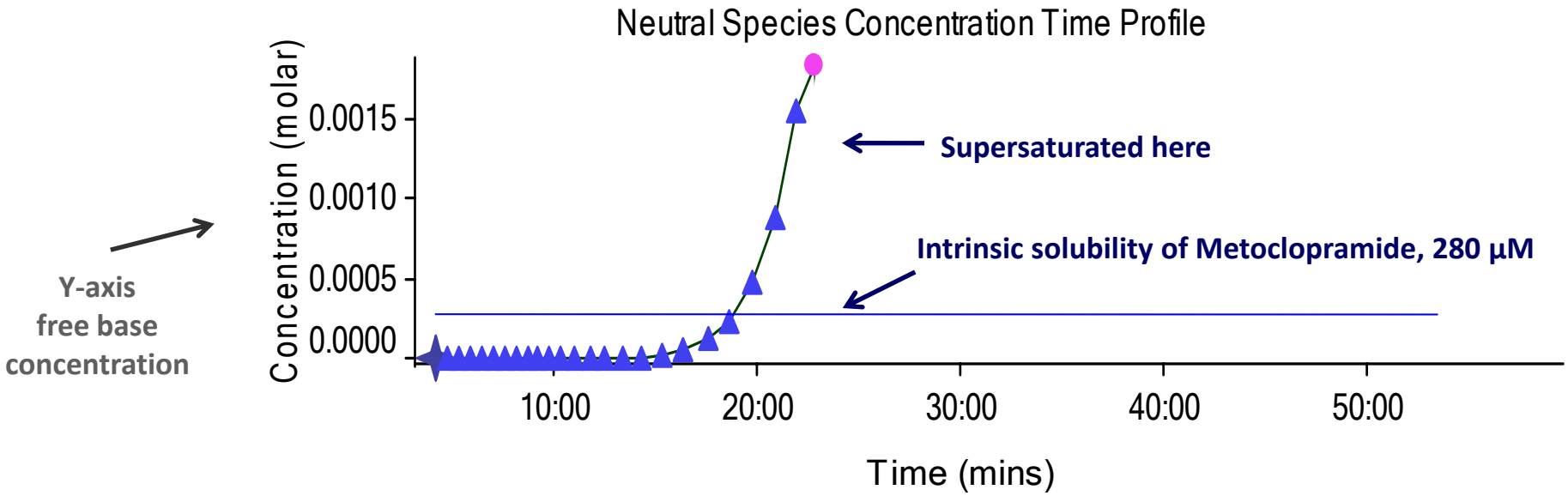
Making a supersaturated solution of an ionizable drug



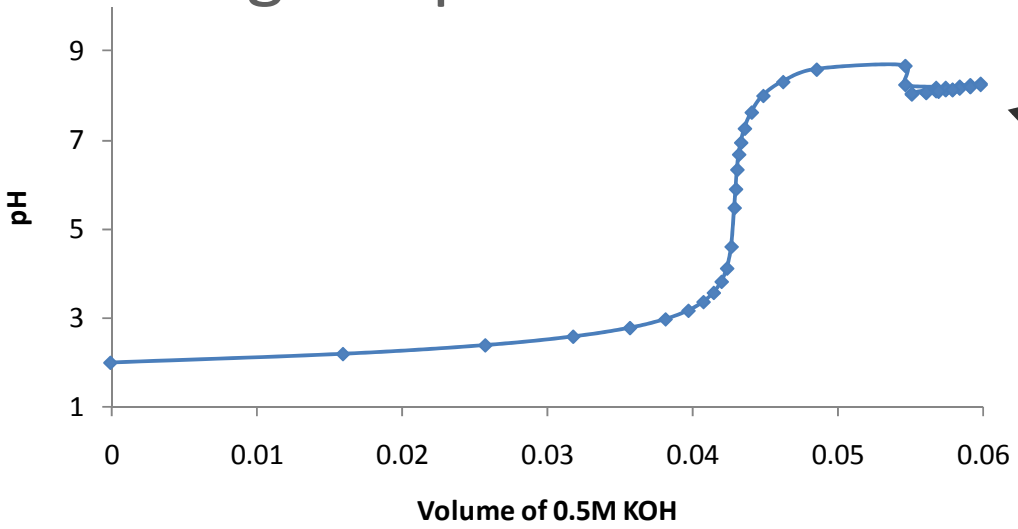


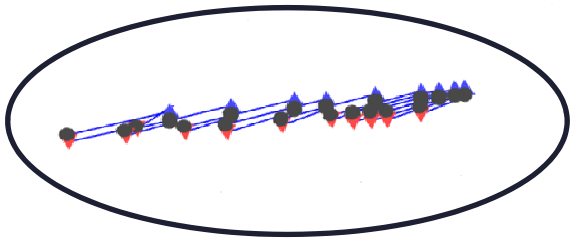
Making a supersaturated solution of an ionizable drug



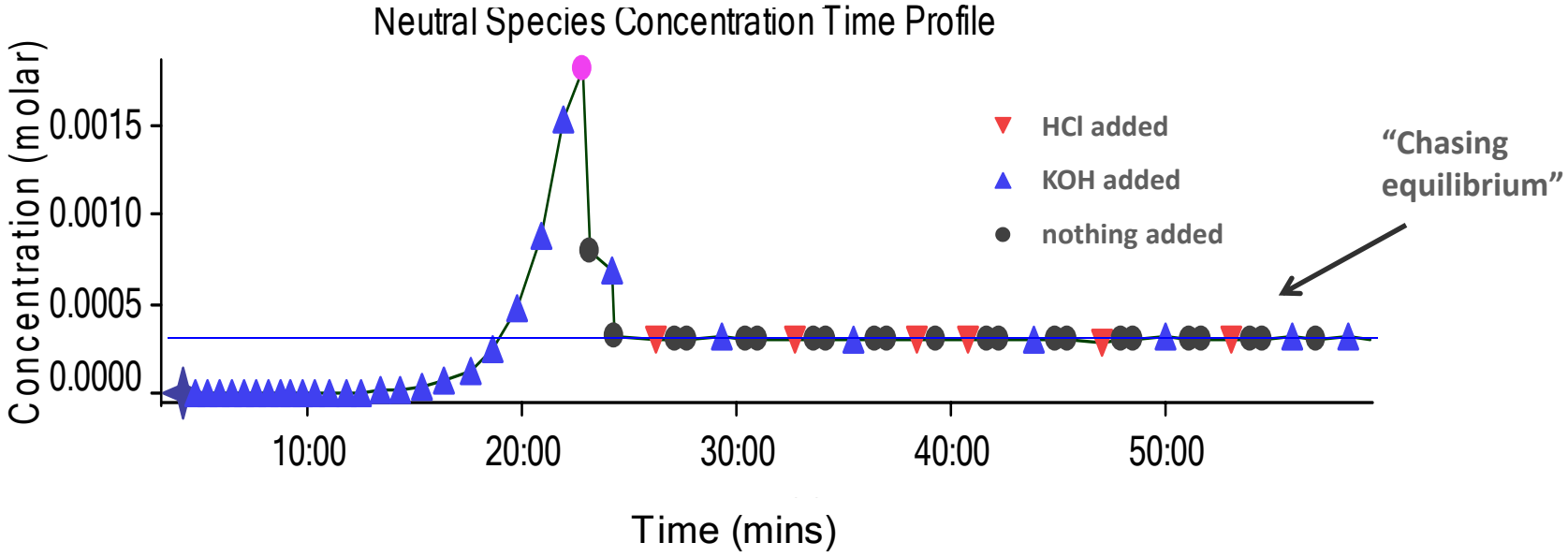


Making a supersaturated solution of an ionizable drug

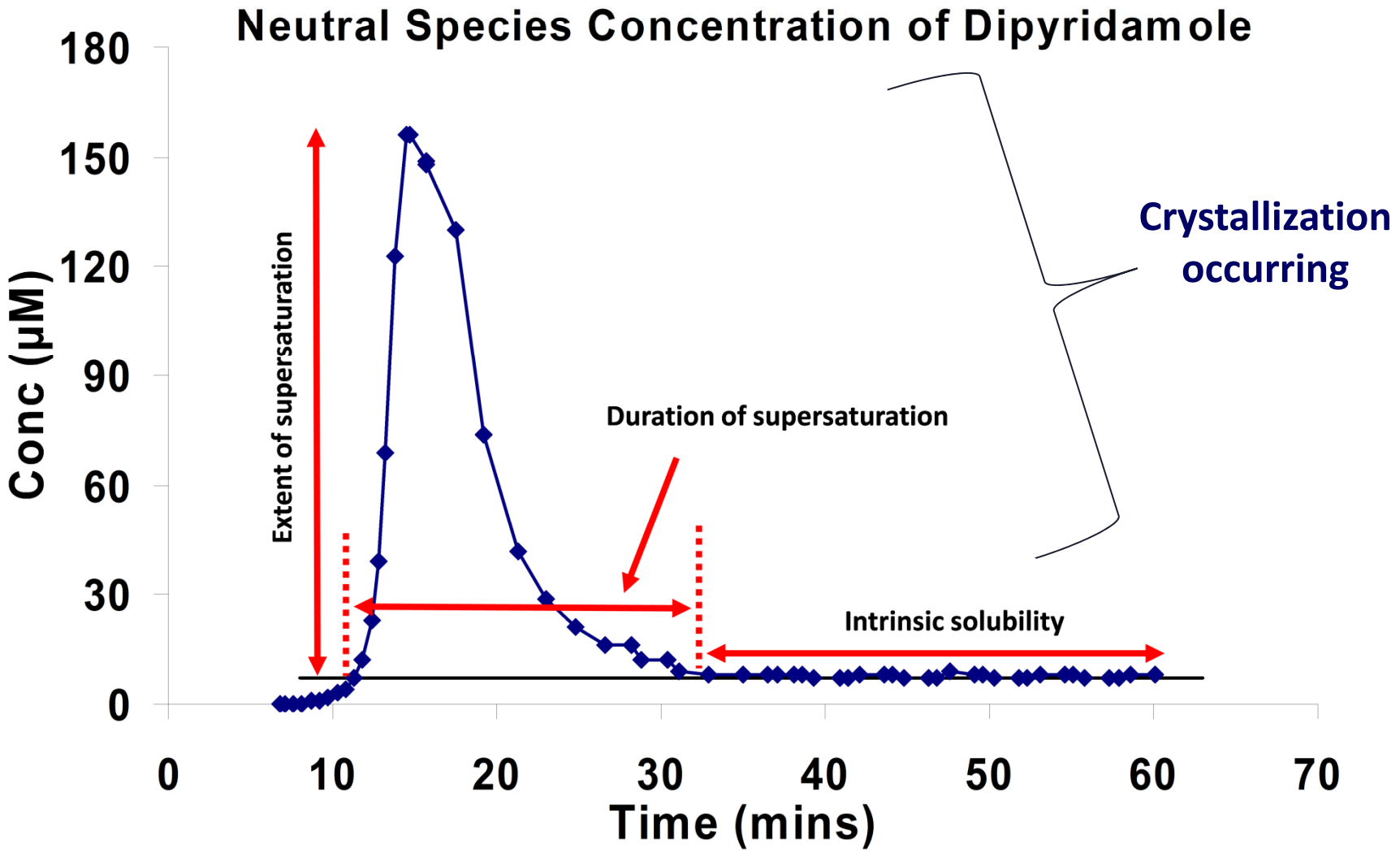




"Chasing equilibrium"

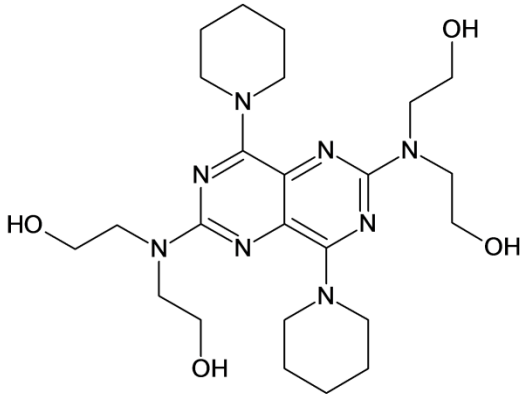


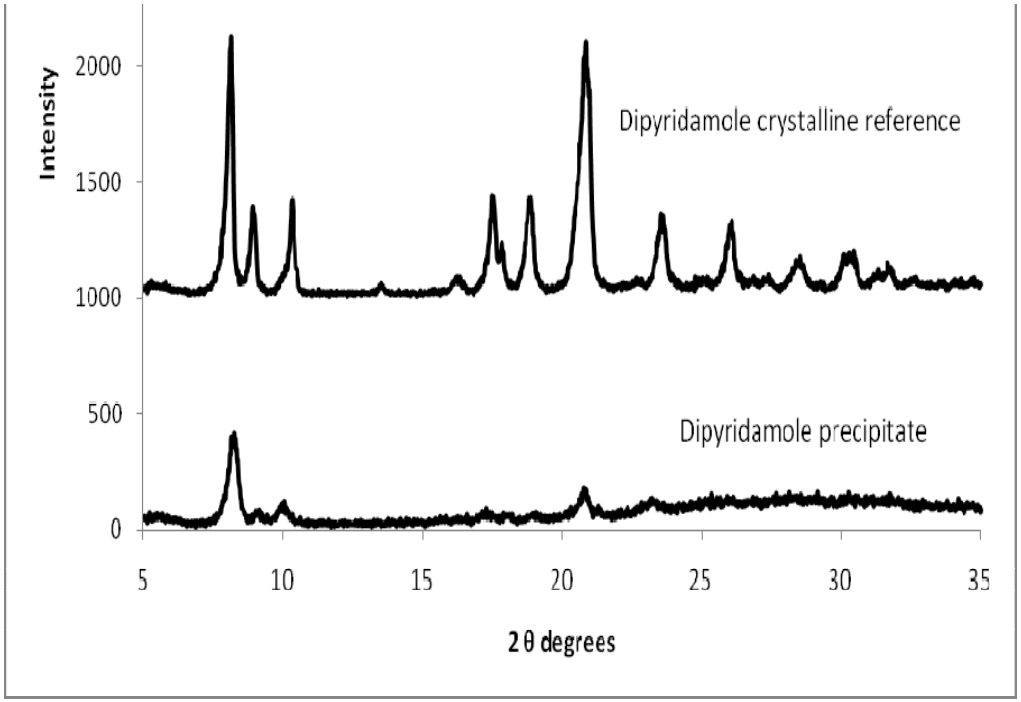
Supersaturation behaviour of dipyridamole in aqueous solution

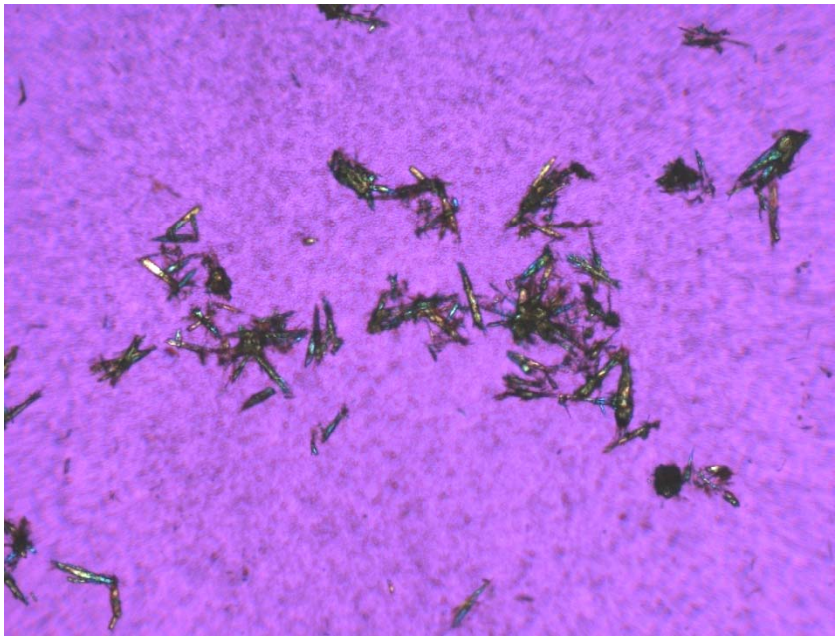


Crystalline precipitate of dipyridamole

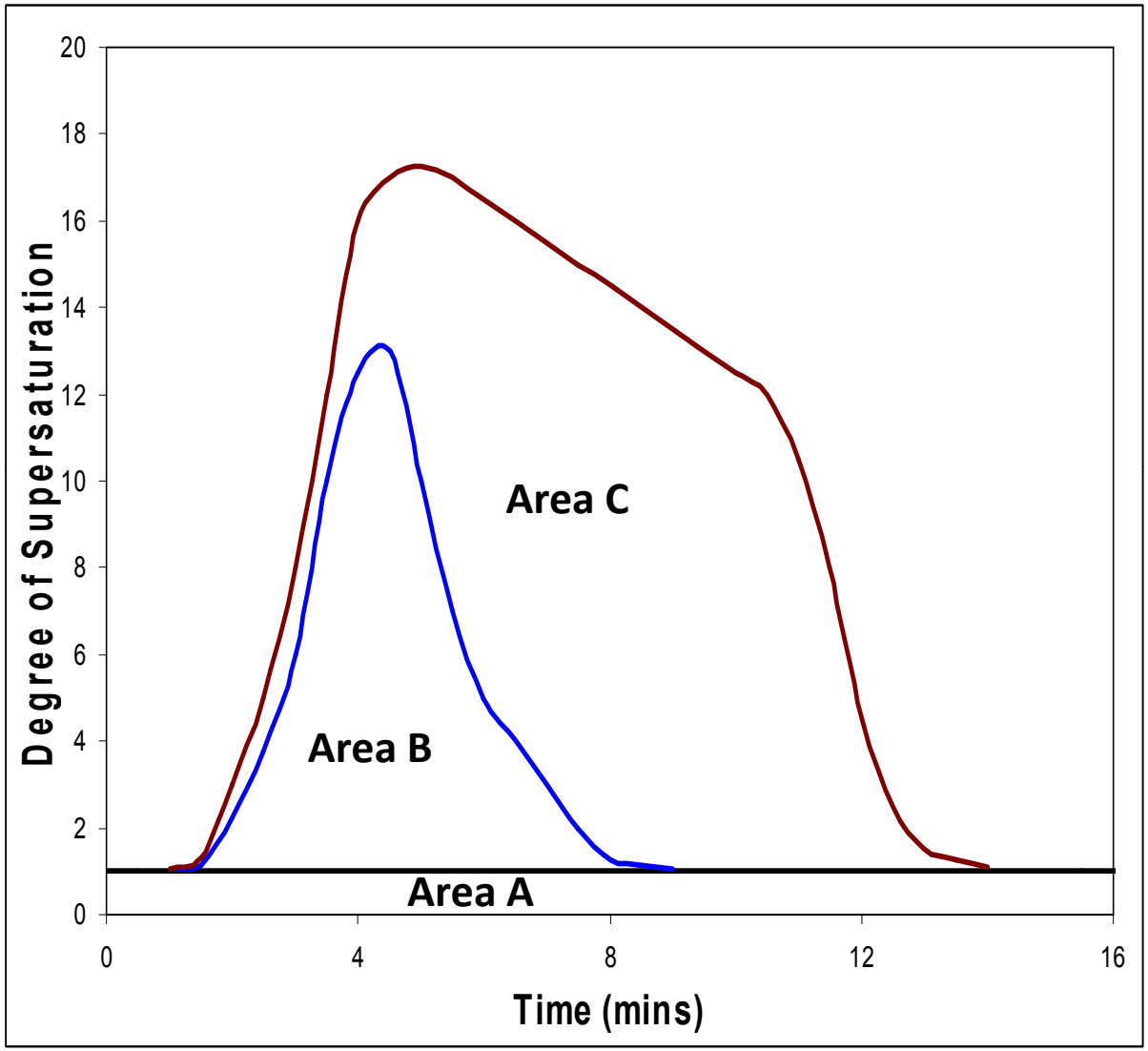
XRPD and polarising microscopy confirms crystalline nature of dipyridamole precipitate







Supersaturation Factor (SF) and Excipient Gain Factor (EGF)



$$SF = \frac{areaA + areaB}{areaA}$$

$$EGF = \frac{areaA + areaB + areaC}{areaA + areaB}$$

Saturation Solubility (Equilibrium)

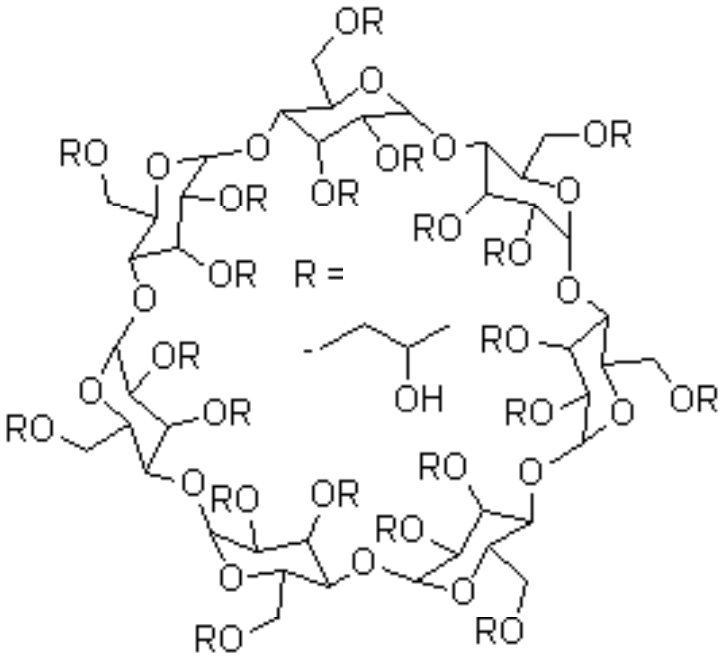
Supersaturation

Excipient Gain Supersaturation

Solubility enhancement using Cavasol

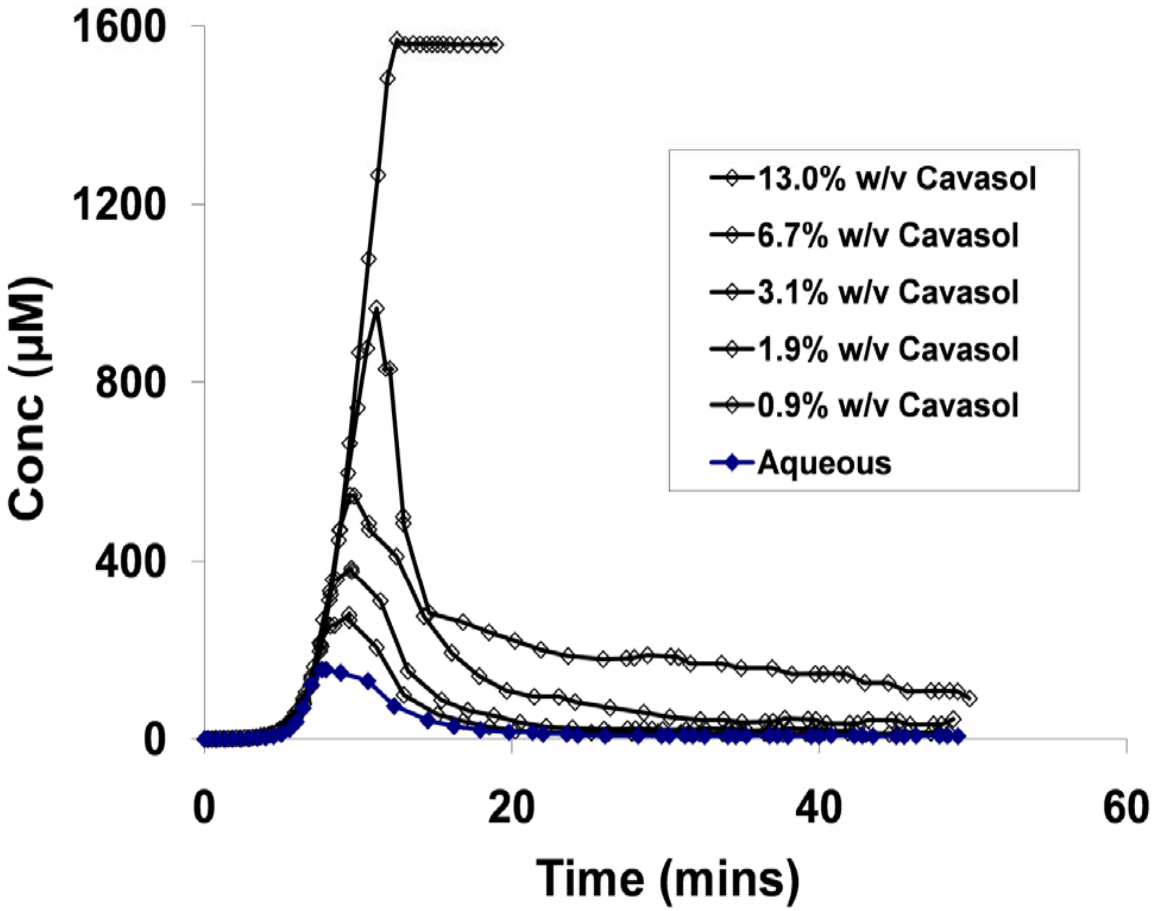
CAVASOL® W7 HP (hydroxypropyl-β-cyclodextrin) is a water-soluble cyclodextrin.

Inclusion complex formation of a poorly soluble, apolar hydrophobic guest with Cavasol in water results in an increase in the water solubility of the guest.



Cavasol supplied by Wacker Chimie AG

Effect of Cavasol on dipyridamole solubility



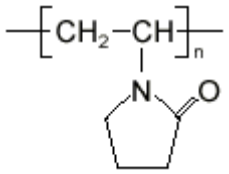
Expt	Supersaturation Factor (SF)
Aqueous	7.0

Excipient Expt	Excipient Gain Factor (EGF)	Total solubility enhancement (SF x EGF)
0.9% Cavasol	1.6	11.2
1.9% Cavasol	2.4	16.8
3.1% Cavasol	4.1	28.7
6.7% Cavasol	6.4	44.8
13.0% Cavasol	13.6	95.2

Solubility enhancement using Plasdone™ polymers

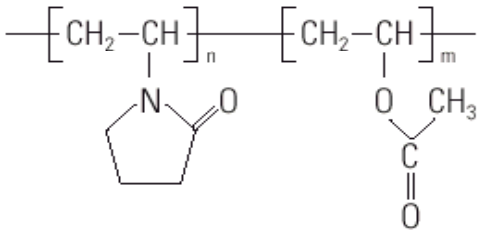
Plasdone PVP Polymers are synthetic, water-soluble homopolymers of N-vinyl-2-pyrrolidone (PVP).

They enhance solubility by inhibiting crystallization. We observe delayed precipitation and longer duration of supersaturation.



Product Name	K-Value	Average MW
Plasdone K-12	10.2-13.8	4,000
Plasdone K-17	16 -17.5	10,000
Plasdone K-25	24-26	34,000
Plasdone K-29/32	29-32	58,000
Plasdone K-90	85-95	1,300,000
Plasdone S-630	25-32	27,000

Plasdone S-630 is a synthetic, 60:40, linear, random copolymer of N-vinyl-2-pyrrolidone and vinyl acetate.

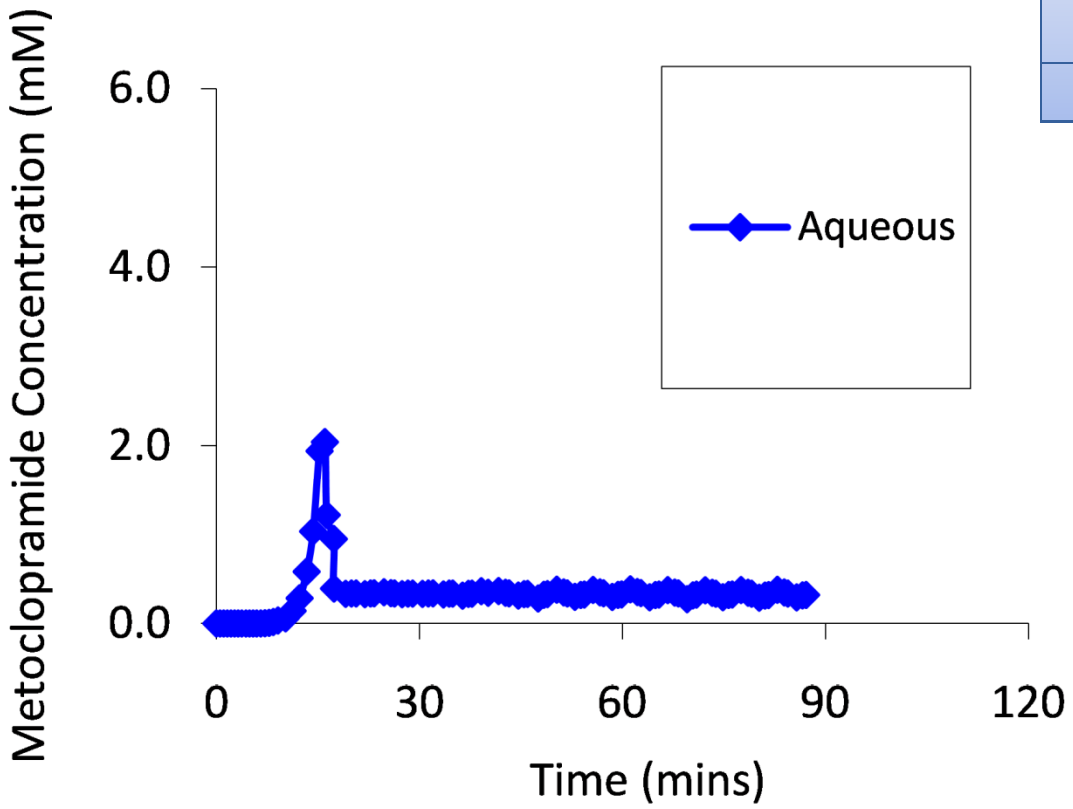


Plasdone polymers are supplied by Ashland Specialty Ingredients

sirius

Effect of Plasdone polymers on metoclopramide solubility

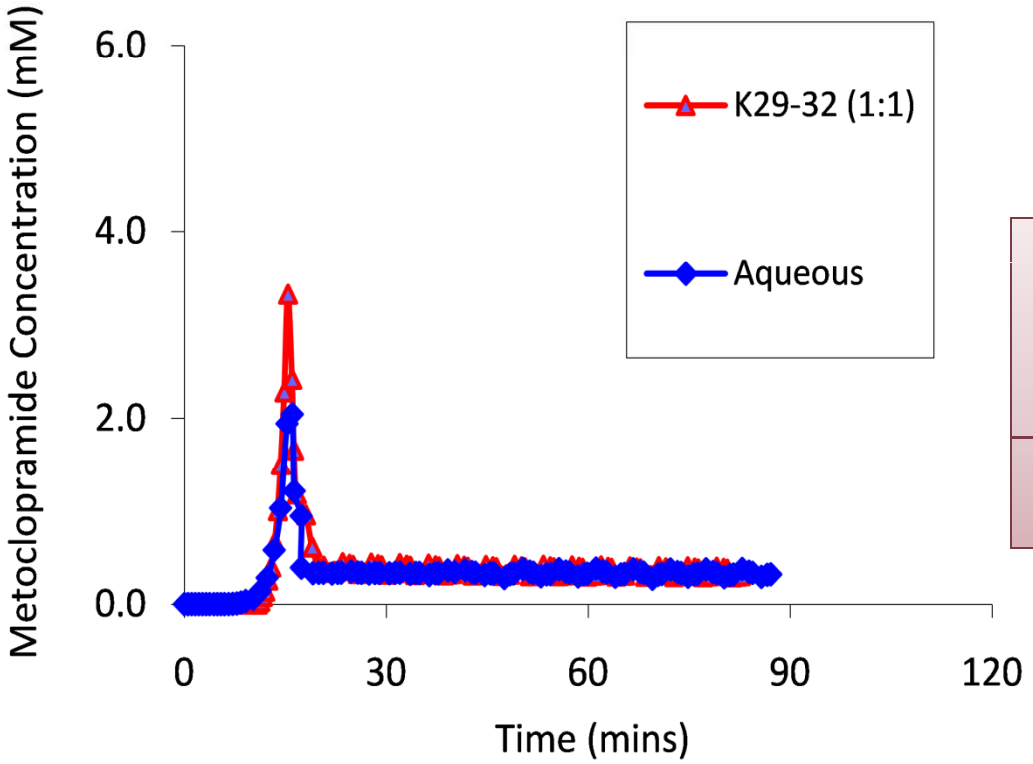
Weights of metoclopramide of around 5 mg were used in these experiments, in a starting volume of 1.5 mL of solution



Expt	Supersaturation Factor (SF)
Aqueous	4.0

Effect of Plasdone polymers on metoclopramide solubility

The ratio 1:1 denotes that equal weights of polymer and metoclopramide were used in this experiment.

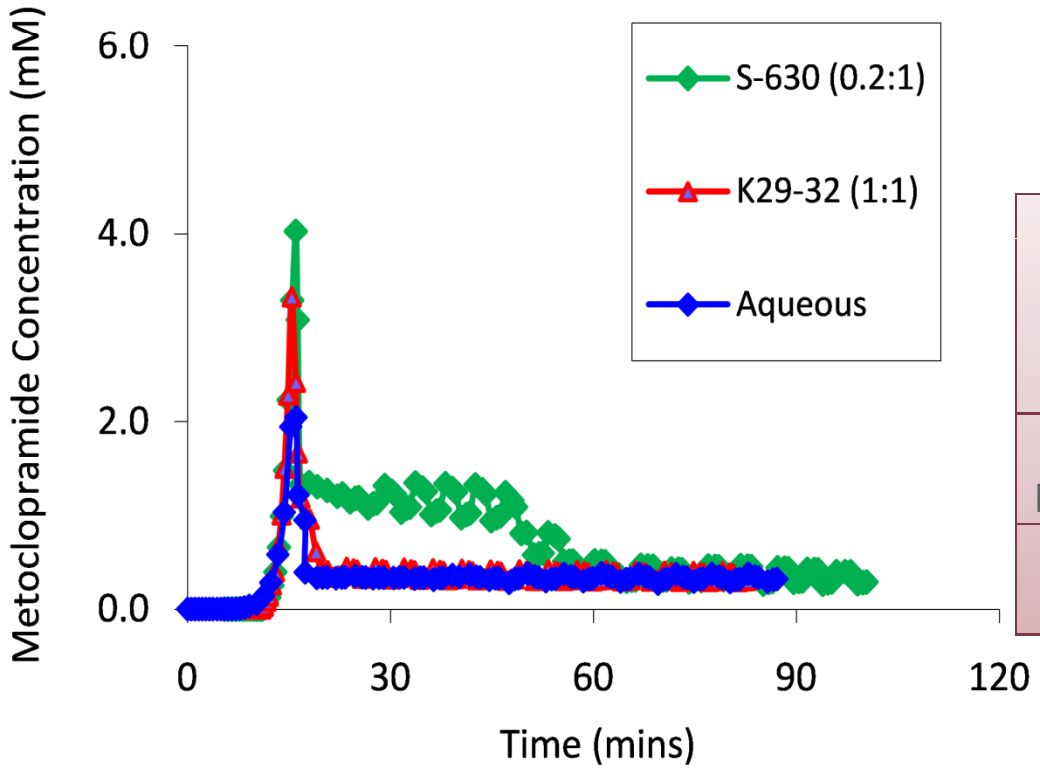


Expt	Supersaturation Factor (SF)
Aqueous	4.0

Excipient Expt	Excipient Gain Factor (EGF)	Total solubility enhancement (SF x EGF)
1:1w/w K29-32:drug	1.4	5.6

Effect of Plasdone polymers on metoclopramide solubility

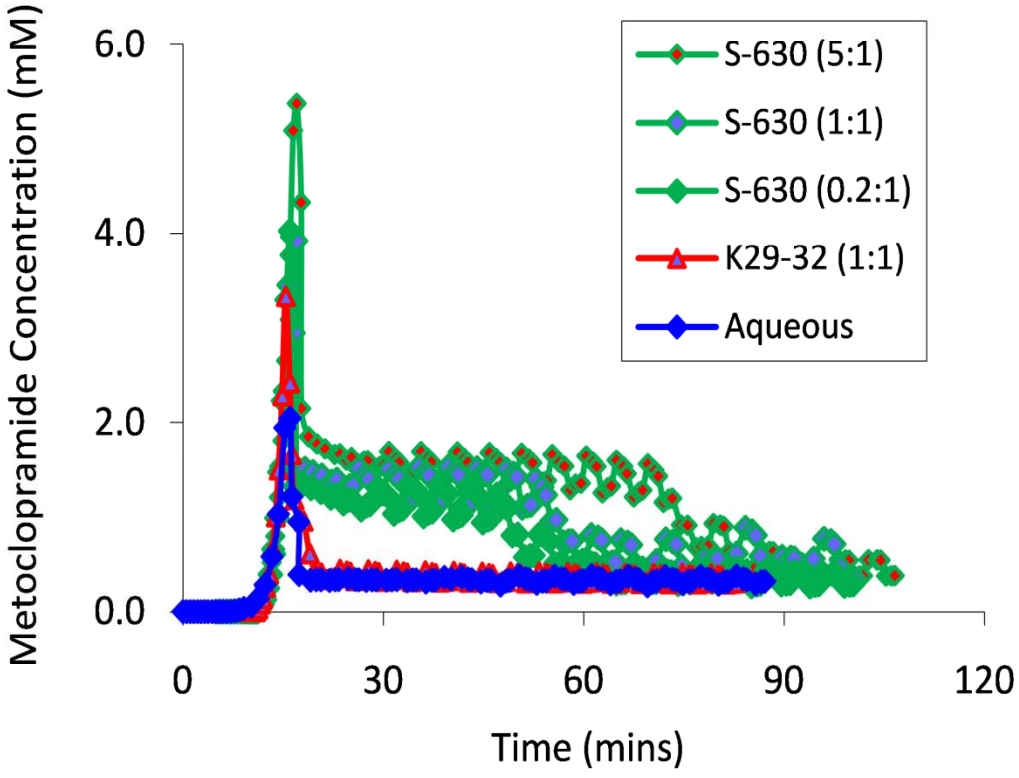
Copovidone S-630 leads to the formation of a relatively long-lived meta-stable form.



Expt	Supersaturation Factor (SF)
Aqueous	4.0

Excipient Expt	Excipient Gain Factor (EGF)	Total solubility enhancement (SF x EGF)
1:1w/w K29-32:drug	1.4	5.6
0.2:1w/w S-630:drug	2.7	10.8

Effect of Plasdone polymers on metoclopramide solubility



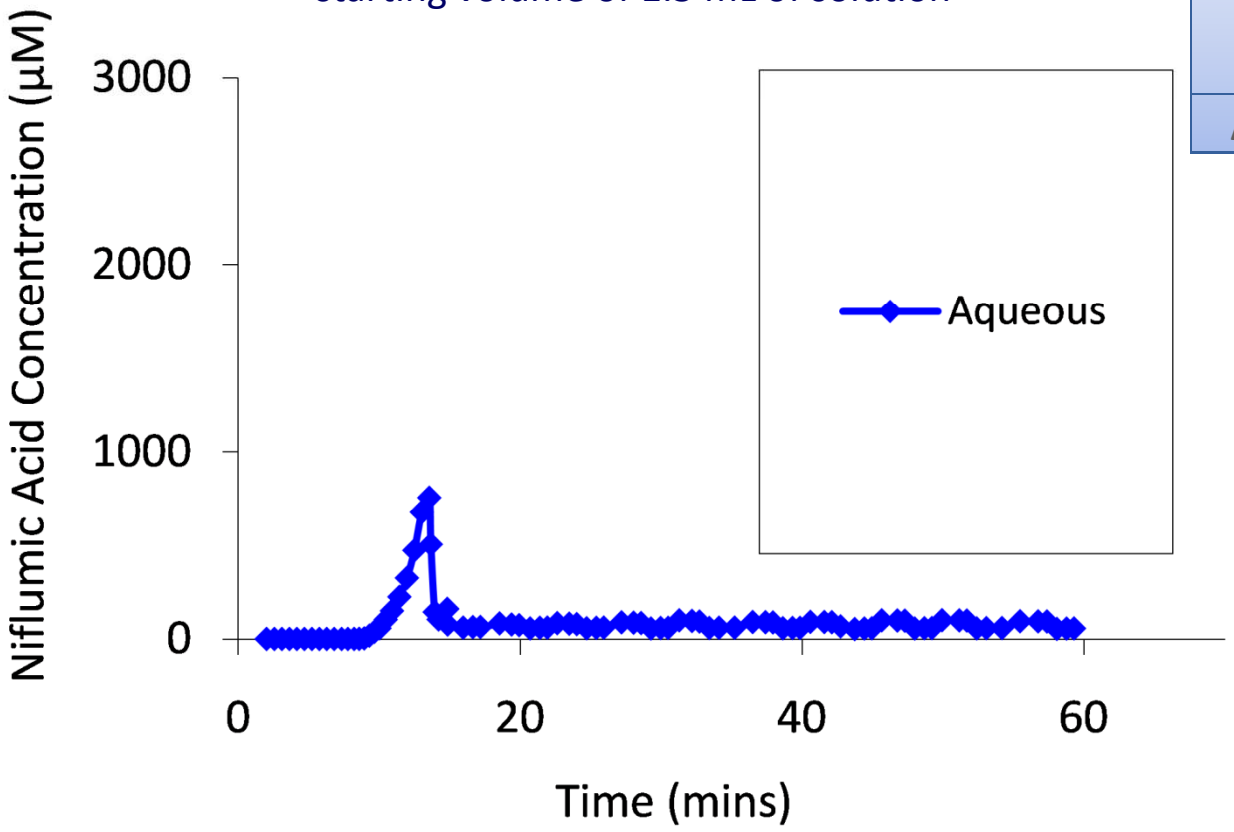
Expt	Supersaturation Factor (SF)
Aqueous	4.0

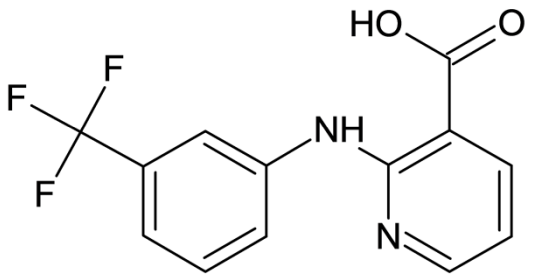
Excipient Expt	Excipient Gain Factor (EGF)	Total solubility enhancement (SF x EGF)
1:1w/w K29-32:drug	1.4	5.6
0.2:1w/w S-630:drug	2.7	10.8
1:1w/w S-630:drug	3.1	12.4
5:1w/w S-630:drug	3.8	15.2

Effect of Plasdone polymers on niflumic acid solubility

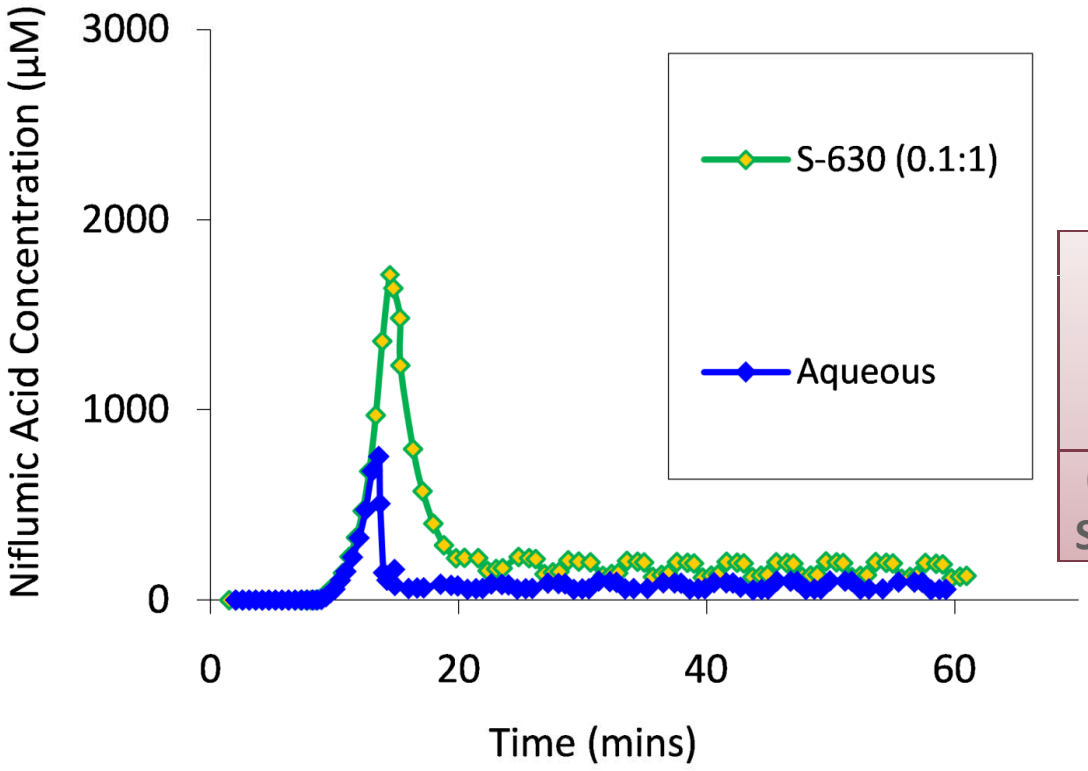
Weights of niflumic acid of around 5.0 mg were used in these experiments, in a starting volume of 1.5 mL of solution

Expt	Supersaturation Factor (SF)
Aqueous	5.1





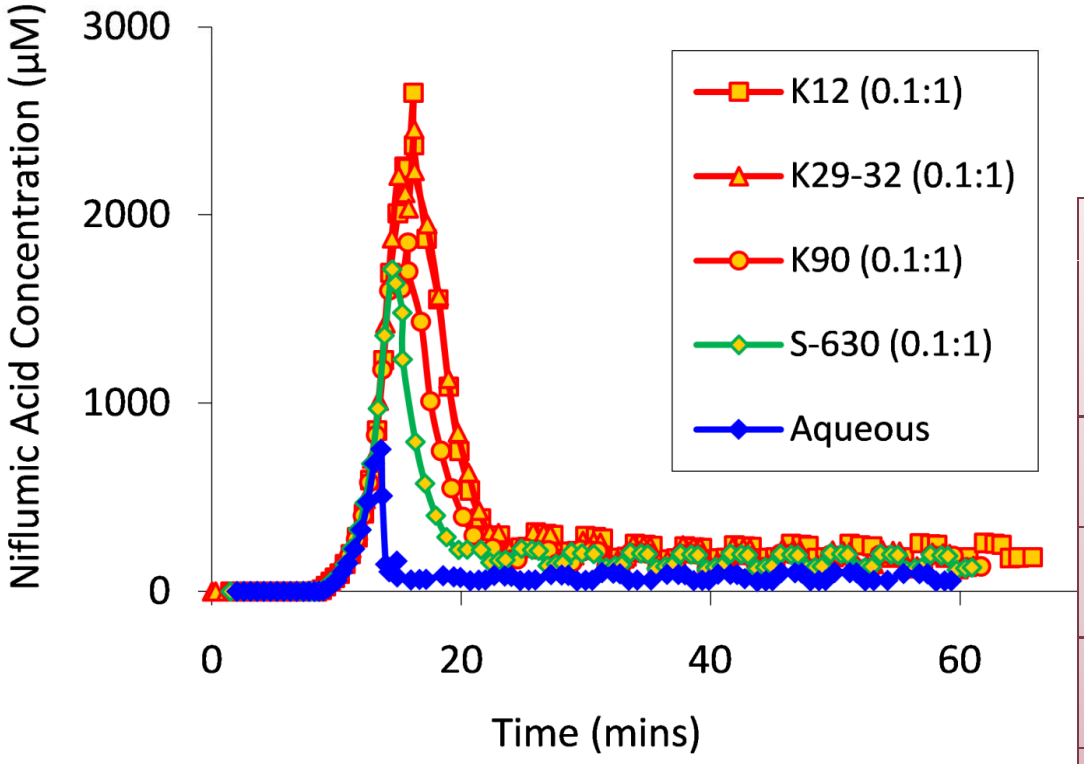
Effect of Plasdone polymers on niflumic acid solubility



Expt	Supersaturation Factor (SF)
Aqueous	5.1

Excipient Expt	Excipient Gain Factor (EGF)	Total solubility enhancement (SF x EGF)
0.1:1w/w S-630:drug	3.6	18.4

Effect of Plasdone polymers on niflumic acid solubility



Expt	Supersaturation Factor (SF)
Aqueous	5.1

Excipient Expt	Excipient Gain Factor (EGF)	Total solubility enhancement (SF x EGF)
0.1:1w/w S-630:drug	3.6	18.4
0.1:1w/w K90:drug	4.8	24.5
0.1:1w/w K29-32:drug	6.0	30.6
0.1:1w/w K12:drug	6.1	31.1

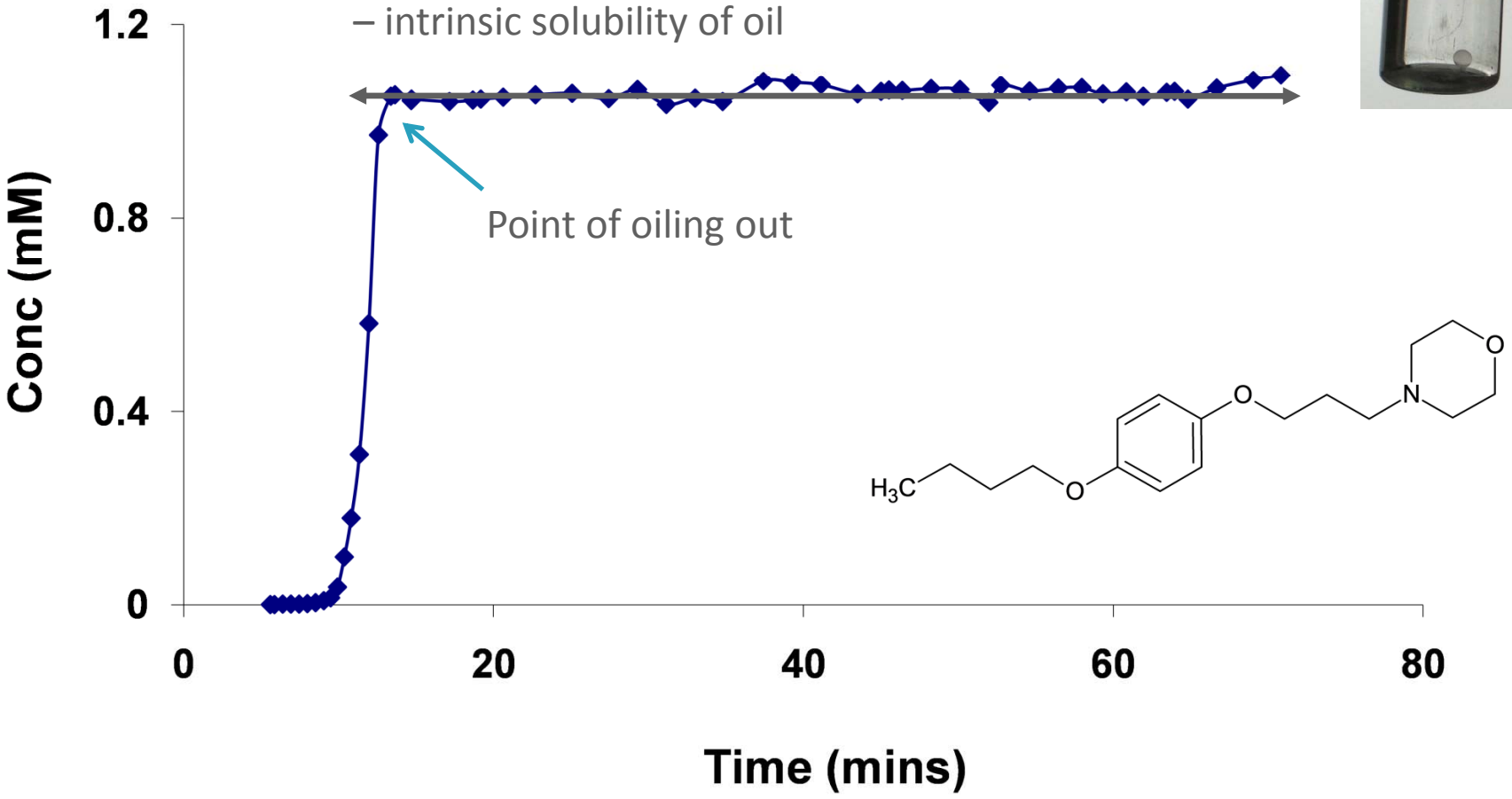
Other mechanisms of precipitation or phase separation

"Oiling out"

and

amorphous solubility

Oiling out – solubility of pramoxine



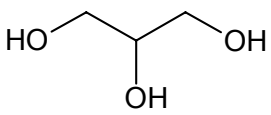
Solubility enhancement using Gattefossé Labrasol

Labrasol is a non-ionic water dispersible surfactant.

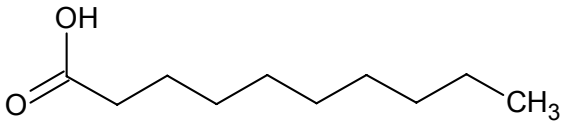
It's a mixture of polyethylene glycol (PEG) esters, a small glyceride fraction and free PEG, with mean MW between 200 and 400.

Labrasol can be used as a selfmicroemulsifying drug delivery system (SMEDDS). Other functions include a solubilizer and wetting agent and a bioavailability enhancer (associated with PgP inhibition).

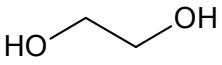
Glycerol



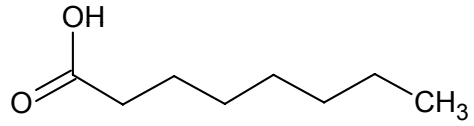
Capric acid



Macrogol



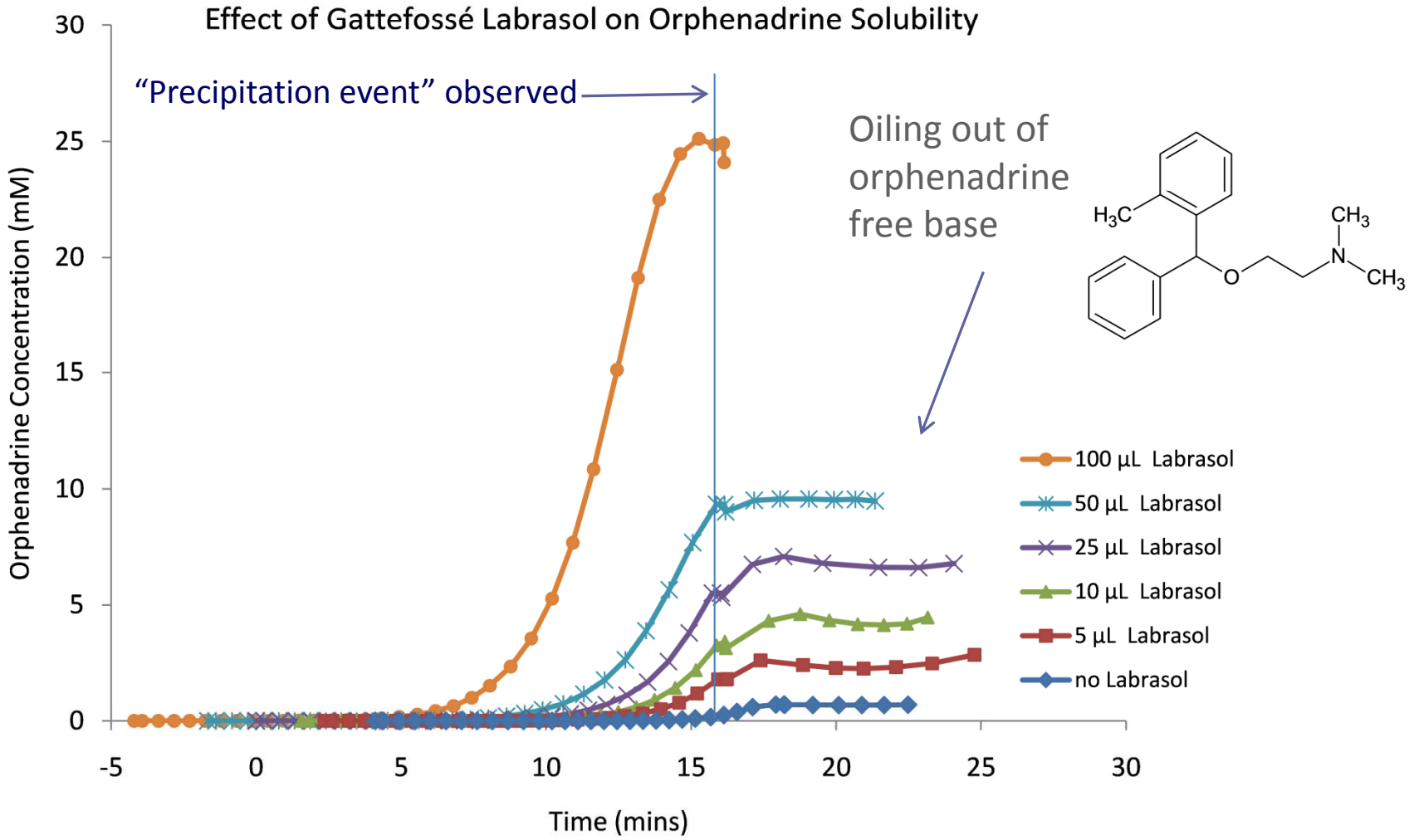
Caprylic acid



We determined a value of 5.9 for the "mean pK_a" of Labrasol. This value was used in the calculation of other results.

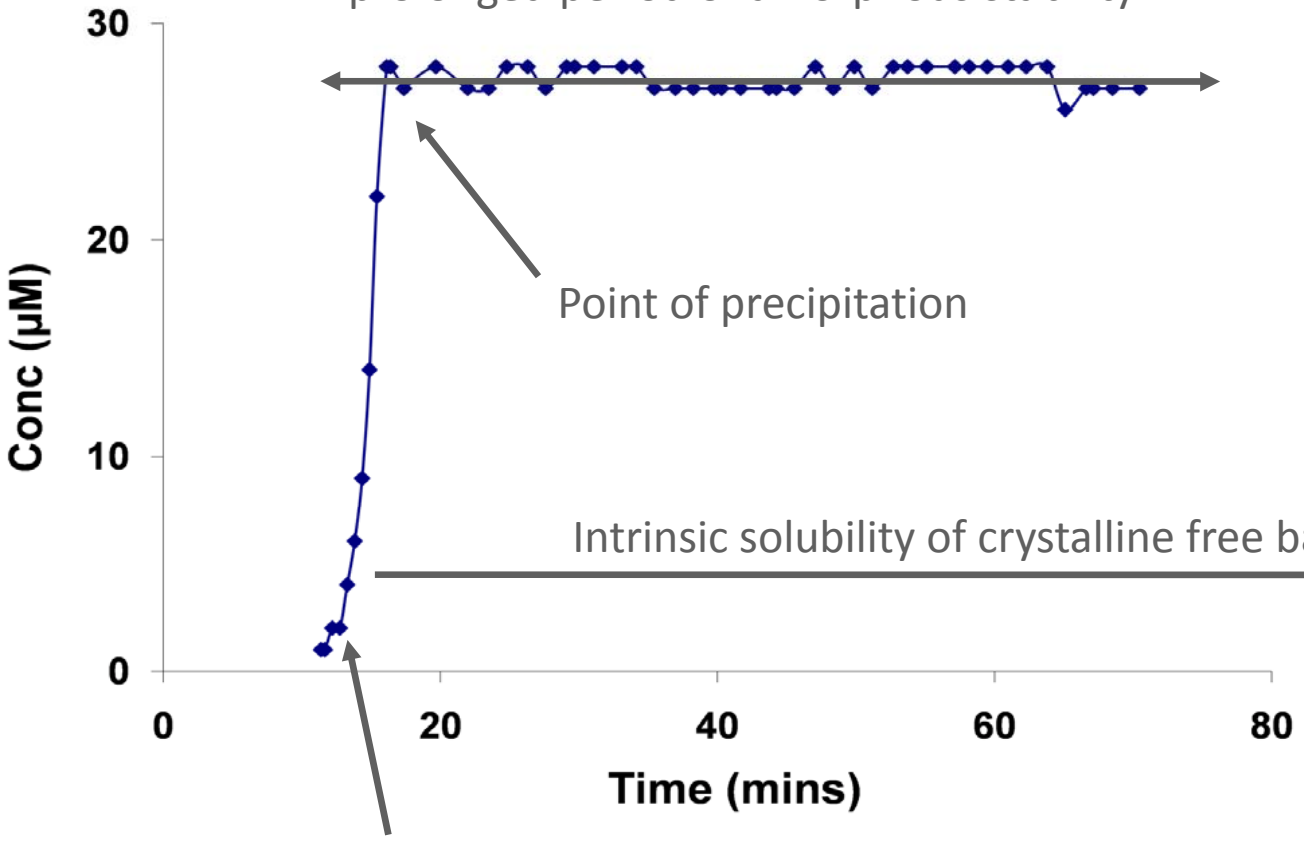
Labrasol was kindly donated by Gattefossé

Solubility enhancement of orphenadrine in Labrasol®

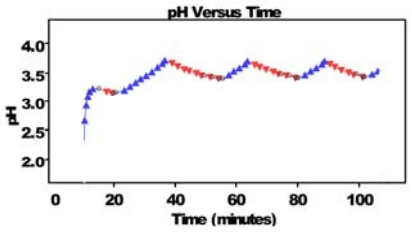


Amorphous solubility of loratadine

Concentration of neutral species after precipitation – amorphous solubility and prolonged period of amorphous stability



Compound is supplied as crystalline free base. However, no evidence for crystallization is observed for the duration of the solubility assay. The amorphous solubility can be determined very quickly for this class of behavior.



Precipitate responds rapidly to pH change

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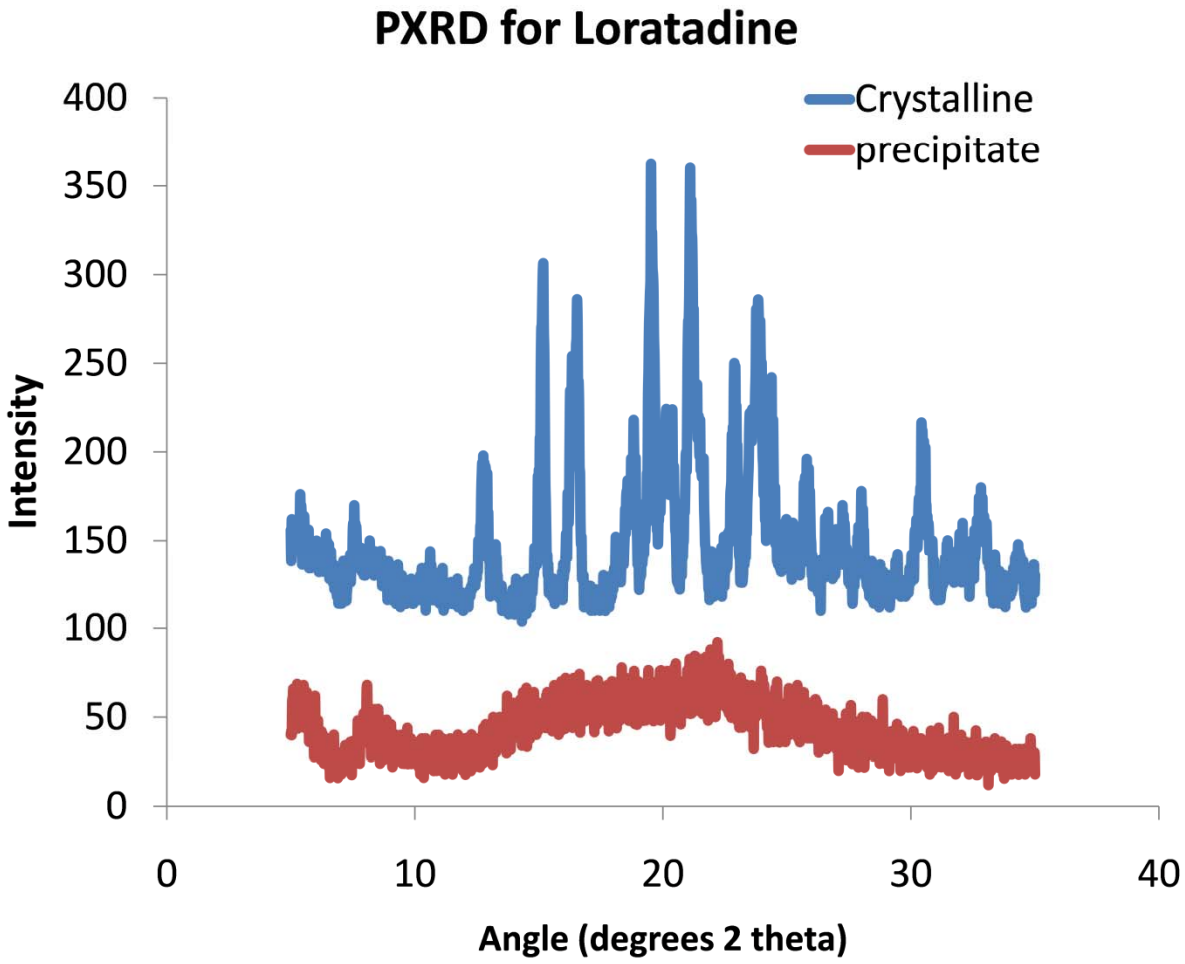
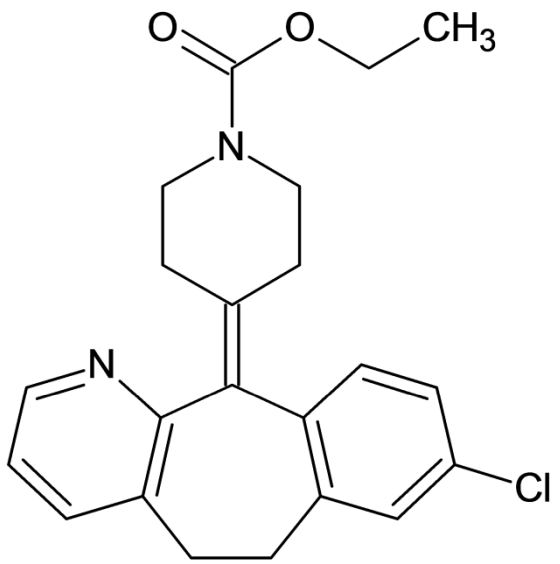
Amorphous precipitate of loratadine

XRPD confirms amorphous nature of loratadine precipitate





Amorphous tendency under aqueous conditions

Compound	pKa(s)	Solution Titration Behavior	Birefringence	Precipitate XRPD	Crystallization Tendency Classification (melt quench)[1]	Crystallization Tendency Classification (solvent evaporation)[2]
Carvedilol	7.75	Rapid precipitation, non-chasing	No	Amorphous	III	III
Clotrimazole	5.89	Rapid precipitation, non-chasing	No	Amorphous	III	III
Clozapine	3.83, 7.54	Rapid precipitation, non-chasing	No	Amorphous	III	III
Ketoconazole	3.16, 6.13	Rapid precipitation, non-chasing	No	Amorphous	III	III
Loratadine	5.26	Rapid precipitation, non-chasing	No	Amorphous	III	II/III

1. Baird, J.A., B. Van Eerdenbrugh, and L.S. Taylor, *A classification system to assess the crystallization tendency of organic molecules from undercooled melts.* Journal of Pharmaceutical Sciences, 2010. **99**(9): p. 3787-3806.

2. Van Eerdenbrugh, B., J.A. Baird, and L.S. Taylor, *Crystallization tendency of active pharmaceutical ingredients following rapid solvent evaporation—classification and comparison with crystallization tendency from undercooled melts.* Journal of Pharmaceutical Sciences, 2010. **99**(9): p. 3826-3838.

Amorphous tendency under aqueous conditions

Compounds	Crystalline Equilibrium solubility at 37°C (HPLC)	Predicted* amorphous solubility at 37°C	Measured amorphous solubility by pH titration (at 37°C)	Actual solubility advantage (amorphous/crystalline solubility ratio) at 37°C
Carvedilol	1.1 ± 0.1	24.4	19.4	17.6
Clotrimazole	0.4 ± 0.02	5.0	5.7	14.2
Clozapine	8.8 ± 0.1	179.5	170	19.3
Ketoconazole	3.7 ± 0.1	202	84.9	22.9
Loratadine	1.6 ± 0.1	11.0	9.9	6.2

All solubility values in µg/mL

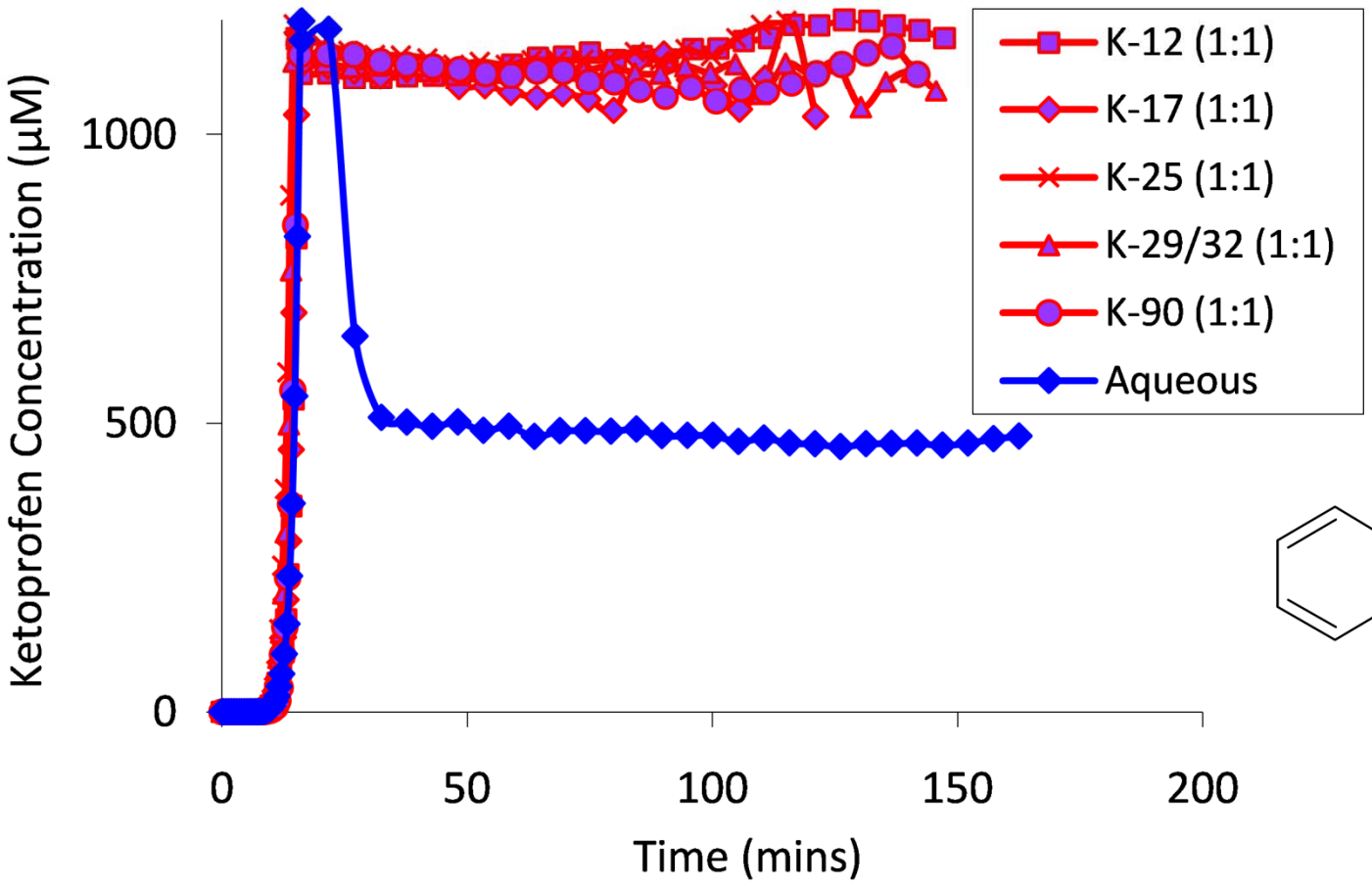
* Hoffman equation used with DSC data to estimate amorphous solubility and solubility advantage

$$\Delta G_c = \Delta H_f \frac{(T_m - T)T}{T_m^2}$$

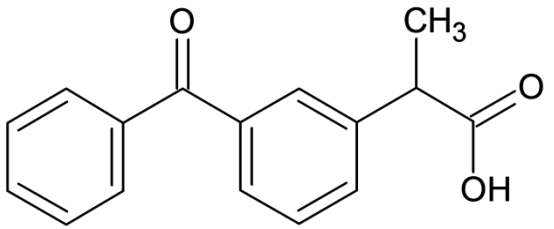
$$\frac{S_{amorphous}}{S_{crystalline}} \approx \exp\left(\frac{\Delta G_c}{RT}\right)$$

Realising the amorphous potential - ketoprofen

All K- grades of Plasdone PVP polymers are able to stabilize the amorphous form of ketoprofen

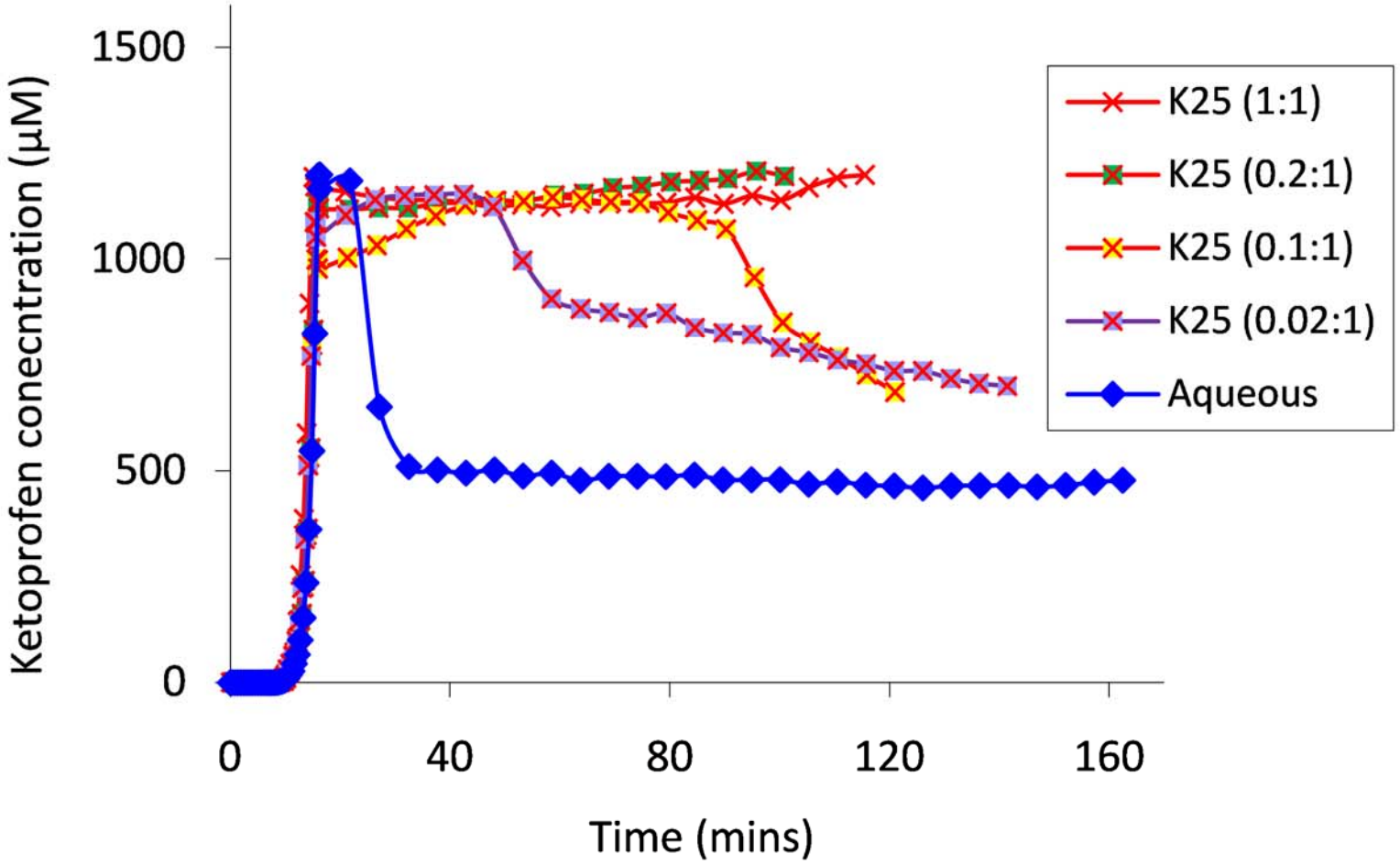


Weights of keto-profen of around 5.0 mg were used in these experiments, in a starting volume of 1.5 mL of solution



Amorphous ketoprofen stabilized at high drug loads

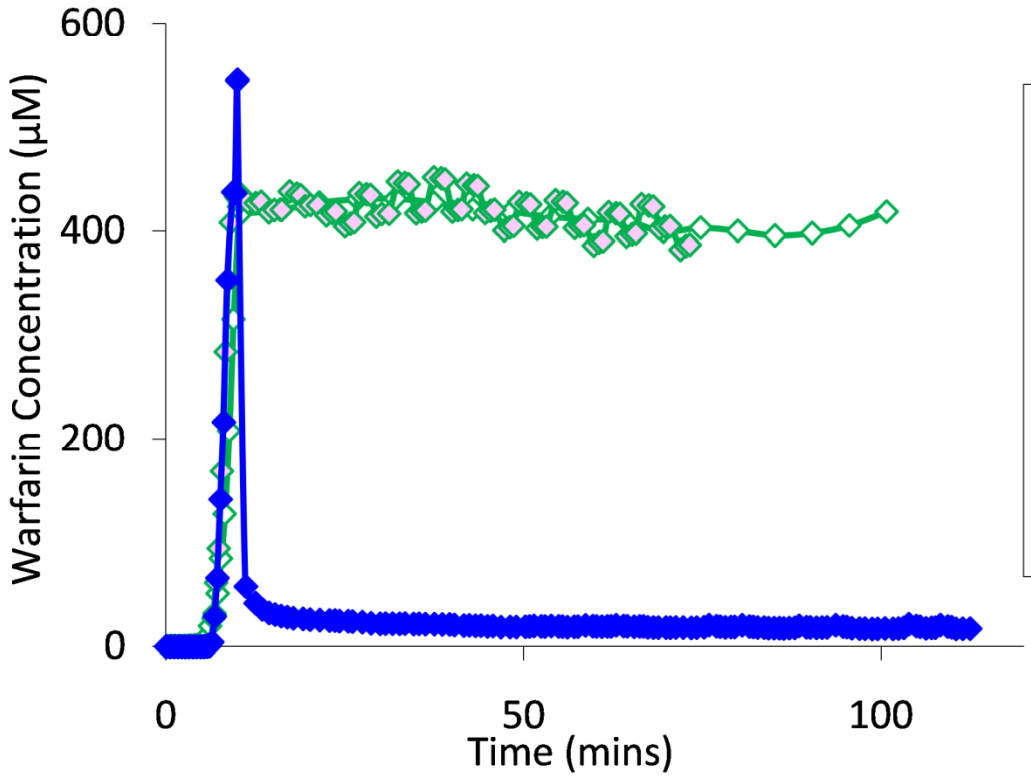
Crystallization occurs from 1:20 and 1:10 Plasdone PVP:drug levels.

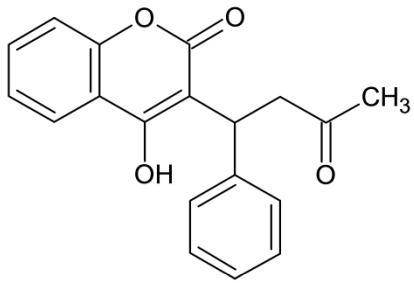


Realising the amorphous potential - warfarin

S-630 grade of Plasdone copovidone polymer is able to stabilize the amorphous form of warfarin

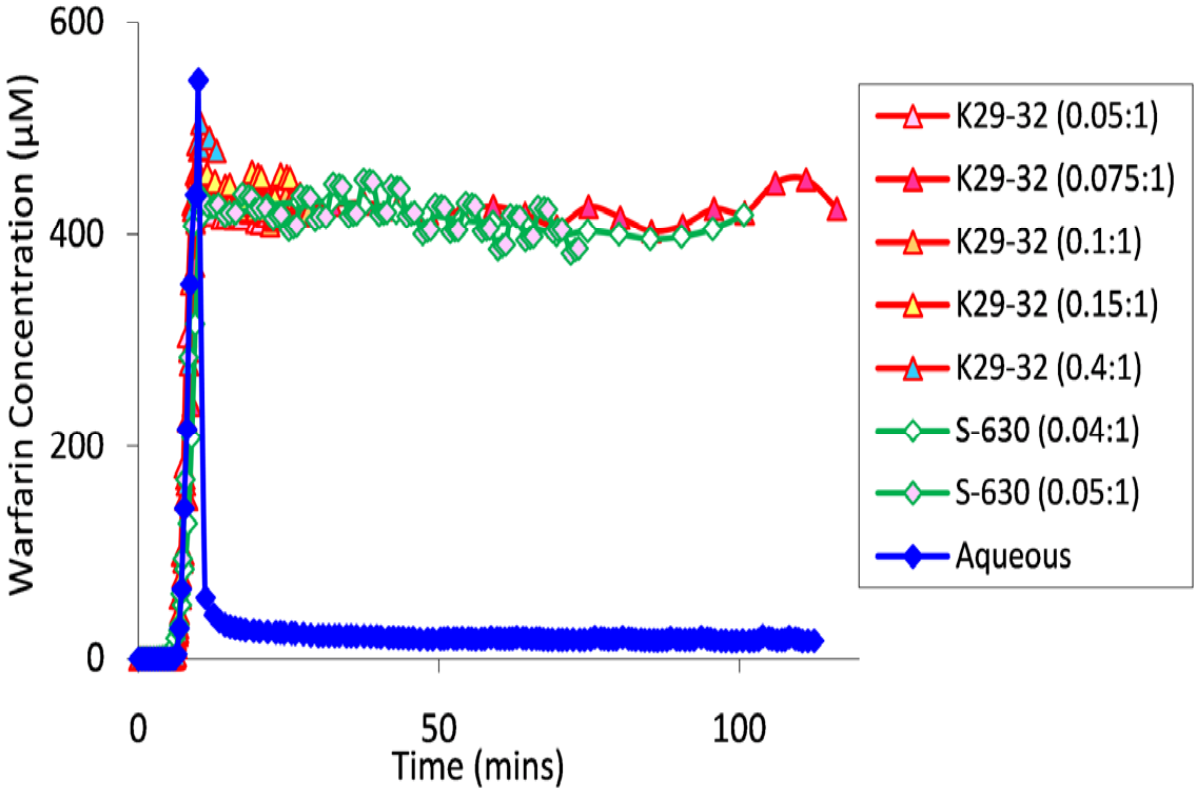
Weights of warfarin of around 5.0 mg were used in these experiments, in a starting volume of 1.5 mL of solution





Amorphous warfarin stabilized at high drug loads

K29-32 grade plasdone povidone PVP polymer also stabilizes the amorphous form of warfarin. Crystallization does not occur during these assays.



Expt	Supersaturation Factor (SF)
Aqueous	7.4

Excipient Expt	Excipient Gain Factor (EGF)	Total solubility enhancement (SF x EGF)
K29-32 (+10mins*)	2.3	17.0
K29-32 (+20mins)	4.6	34.0
K29-32 (+30mins)	6.6	48.8
K29-32 (+40mins)	8.6	63.6

* After precipitation

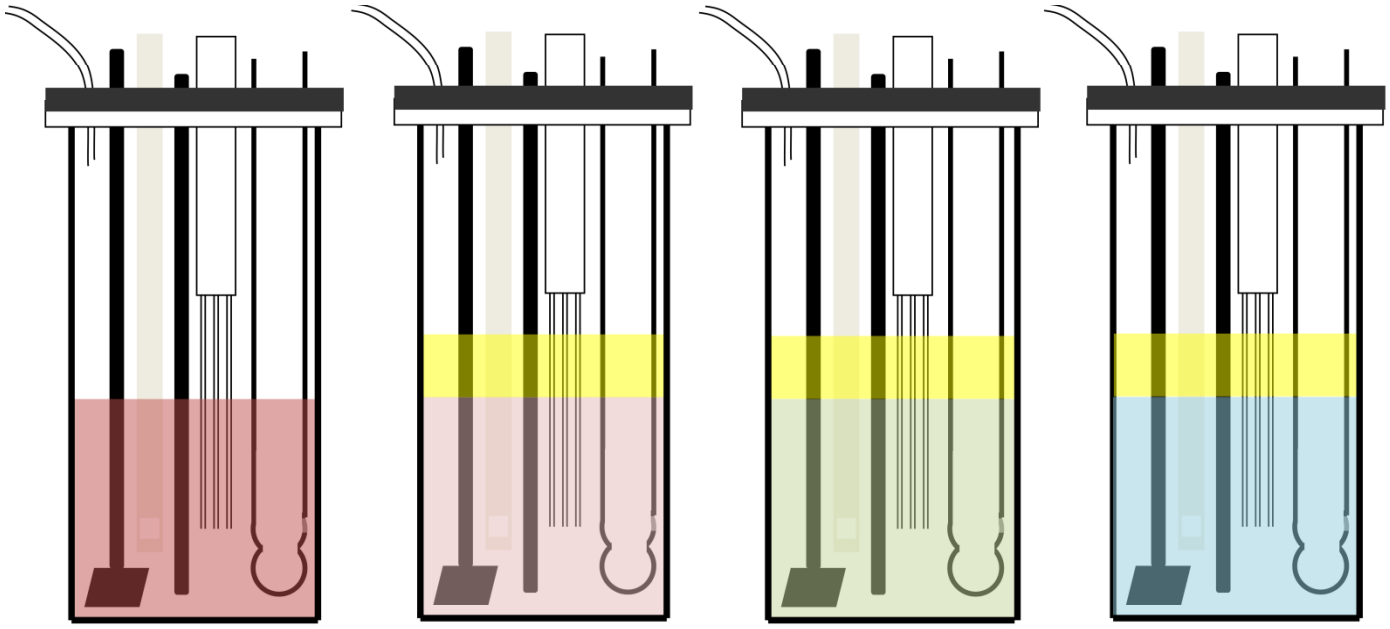
Summary of amorphous precipitation

- Rapidly precipitating form with enhanced solubility over crystalline form
- Rapid response to pH-change
- Readily dispersed and easily reabsorbed
- “Prolonged stability (or duration)” under aqueous conditions
- Identification of excipients for sustaining amorphous form
- Potential for long shelf-life stability

The Sirius GI-Dissolution Assay

- Studying dissolution, solubility and precipitation behavior
  - With simulated intestinal fluids
  - And the effects of formulation excipients

Schematic of GI-Dissolution Assay



"STOMACH" "DUODENUM" "JEJUNUM" "ILEUM"

1. 10 mg of API powder
20 mL of buffer added
Stirred for 30 min. at pH 2
UV recorded every 30 sec.

2. Lipid layer added
KOH solution added
Stirred for 30 min. at pH 3.8
UV recorded every 30 sec.

3. KOH solution added
Stirred for 30 min. at pH 5.4
UV recorded every 30 sec.

4. KOH solution added
Stirred for 30 min. at pH 7.1
UV recorded every 30 sec.

Experiments can be performed with tablet or powders, with or without solubility enhancing ingredients or in the presence of simulated intestinal fluids.

Optional use of lipid layer.

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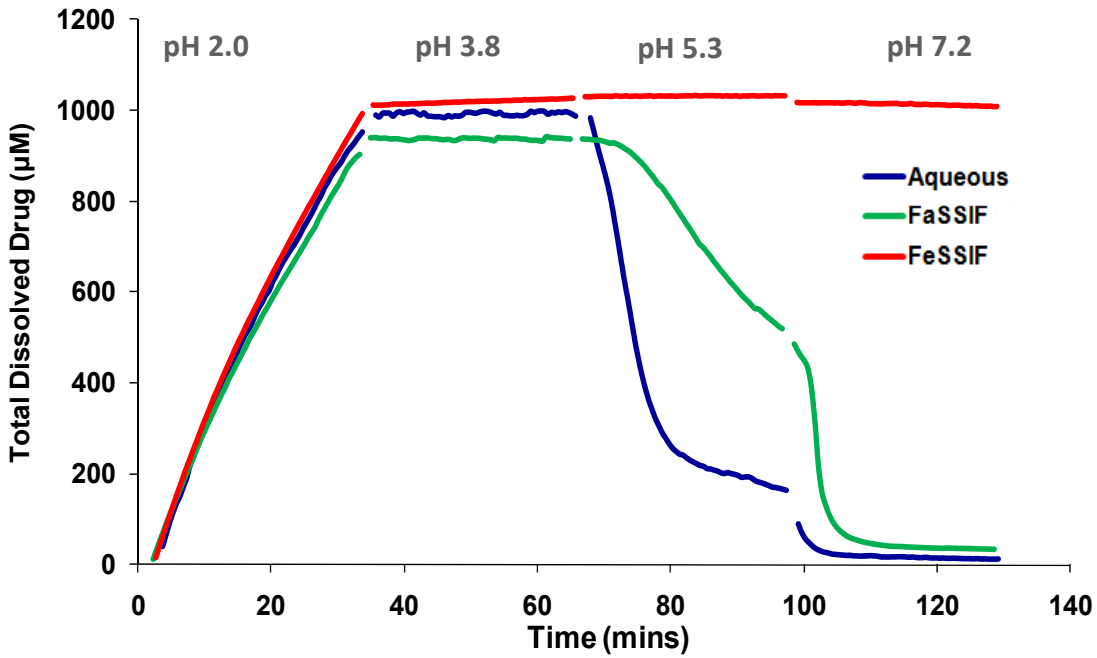
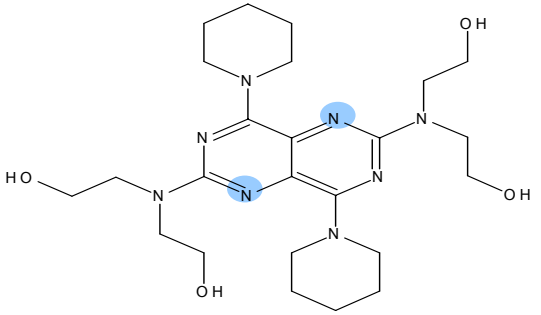
GI-Dissolution of Dipyridamole tablet in FaSSIF and FeSSIF





Two basic pK_as: 0.8, 6.2

* Prepared from Biorelevant.com SIF powder

FaSSIF (Fasted State Simulated Intestinal Fluid) = 3mM NaTC, 0.75mM lecithin
FeSSIF (Fed State Simulated Intestinal Fluid) = 15mM NaTC, 3.75mM lecithin
NaTC is sodium taurocholate

*** Formulae from Kostewicz, E.S., Brauns, U., Becker, R., Dressman, J.B. Pharm. Res. 2002, 19(3), 345-349.**

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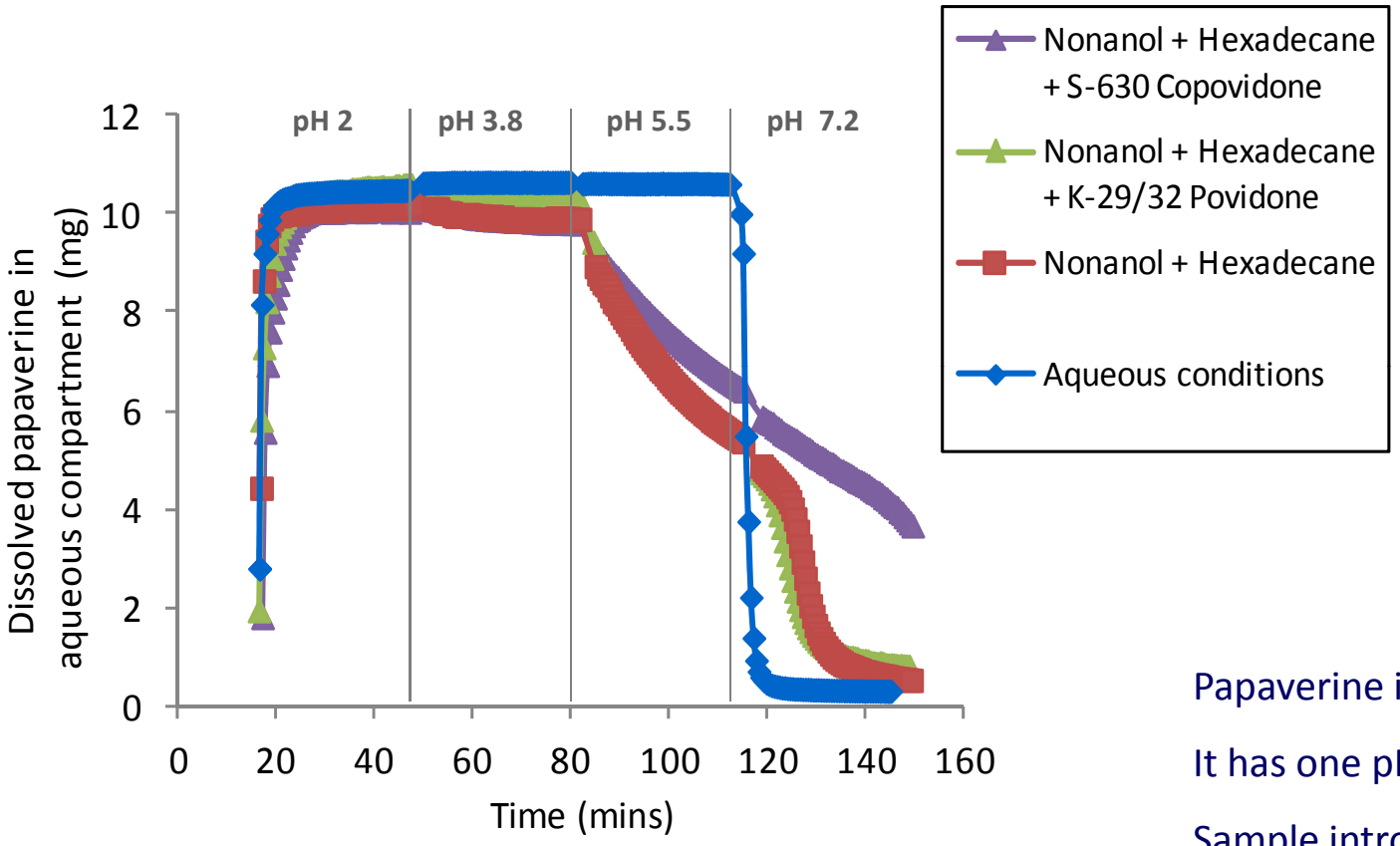
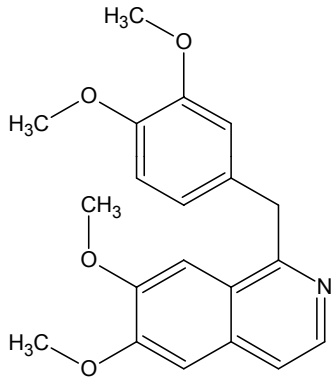
Dissolution lipid sink experiment with polymer - papaverine





Papaverine is a base

It has one pK_a: 6.47

Sample introduced as HCl salt, as powder

Final Summary

- pH-metric titration experiments (CheqSol) can reveal valuable information about drug supersaturation and solubility
- Mass balance and charge balance calculations can determine concentration in the presence of precipitate
- Amorphous behaviour can be recognised
- Dissolution experiments in presence of lipid can mimic GI tract

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- Thanks to colleagues, including
  - John Comer, Robert Taylor, Roger Allen, Brian Stockton, Sam Judge, Rebeca Ruiz, Liz Frake, Steve Evans, Jon Mole, Karen Osman
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  - Manuel Sanchez Felix (Eli Lilly)
  - Vivian Bi (Ashland Specialty Ingredients)
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