Measuring supersaturation and enhanced solubility of a low solubility drug in the presence of excipients:

an opportunityto promote a compound's BCS class

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Abstract

Purpose: This poster describes rapid experiments that show how solubility may be increased by taking advantage of supersaturation and additives.

Methods: Solubilities were measured by pH-metric experiments, in which weighed samples were dissolved in ionized form in unbuffered aqueous solution at an appropriate pH, and then precipitated by pH adjustment with KOH or HCl. Kinetic solubility was determined from the pH at the onset of precipitation; intrinsic solubility was computed from near-equilibrium data [1],[2] with cyclic small additions of KOH and HCl, and supersaturation ratios were determined as (Kinetic ÷ Intrinsic solubility). Measurements were made in the presence of three additives: Cavasol, taurocholic acid and polyvinyl-pyrrolidone (PVP).

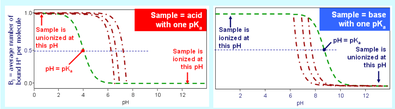
Results: The intrinsic solubility of isoxicam was measured as 0.5µg/mL and is sufficiently low to place the molecule into BCS Class II. However, isoxicam can form supersaturated solutions with a kinetic solubility over 60 times higher. Solubility was not significantly increased in the presence of 1% w/v taurocholic acid (0.7µg/mL) or 1% w/v Cavasol (0.9µg/mL) although supersaturation ratios were maintained. However, 1% w/v PVP increased solubility to 3.6µg/mL, although supersaturation ratios decreased to 30-fold. 1% w/v PVP also produced a more soluble precipitate with solubility of 98µg/mL and no supersaturation capability before transition to the less soluble 3.6µg/mL form. Further investigation showed that the more soluble precipitate could be stabilized for longer times at higher PVP content. In 8% w/v PVP, the precipitate was found to have a solubility of 281µg/mL before transitioning to a final solubility of 8.20µg/mL. Thus a formulation which could preserve this compound as the initial precipitate might be used to promote the compound to BCS Class I.

Conclusions: The kinetic and intrinsic solubilities of isoxicam were measured and compared to establish the effects of different additives on solubility and supersaturation, thereby illustrating a method to recognize potential opportunities for promoting molecules to BCS Class I by formulation.

Experimental

Measurements were made using a Sirius GLpKa titrator with D-PAS spectrometer. Measurements were performed in 0.15M KCl solution at a temperature of 25°C. The software was RefinementPro 2 and CheqSol. The acid and base titrants were 0.5M HCl and 0.5M KOH, delivered to the titration vessel through narrow bore capillaries by precision dispensers capable of delivering reproducible aliquots of known liquid volume. Deionised water of resistivity > 10^{14} Ω cm was used to prepare all the solutions.

Bjerrum graphs – a useful visualization



Solution Bjerrum Graph, depends on aqueous pK_a

Precipitation Bjerrum Graph. Greater shifts in pK_a caused by:
lower solubility (for a given concentration, shift increases as solubility decreases)
higher concentration (for a given solubility, shift increases with concentration)

Bjerrum Graphs are calculated from pH, pK_a and intrinsic solubility

The Solution Bjerrum Graph (green line) represents an ionizable sample that is in solution across the entire pH range.

The Precipitation Bjerrum Graph (brown line) represents a sample when precipitate is present, and *solution and precipitate are at equilibrium*

LogP vs. logS_0 graph for 84 drugs

We measured the aqueous intrinsic solubility (S_0) and logP(octanol-water) of 84 drugs, and coloured them according to their BCS class in Figure 1. LogS_0 is greater than -4 for most class I drugs, and below -4 for most class II drugs.

These results were shown in Poster T3104 at AAPS 2007 Annual Meeting in San Diego, and have recently been published [3].

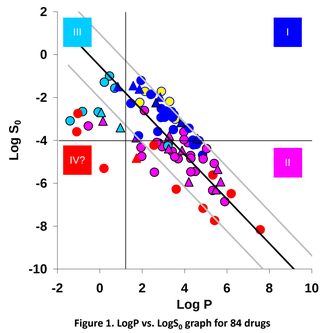


Figure 1. LogP vs. LogS_0 graph for 84 drugs

Promoting BCS Class

Warfarin, diclofenac, isoxicam and dicyclomine are in BCS Class II. Figure 2 shows their measured logP(octanol-water) values vs. kinetic and intrinsic solubilities with and without added PVP or Cavasol. Warfarin, diclofenac and isoxicam form supersaturated solutions before precipitation and their kinetic solubility (i.e. solubility at the time of precipitation) is higher than their intrinsic solubility. Dicyclomine did not supersaturate; its kinetic and equilibrium solubilities were equal.
Figure 2 shows that kinetic solubilities of isoxicam, diclofenac and warfarin are all in the region of the graph where neighbouring compounds are in class I. Moreover, the presence of PVP preserves warfarin and diclofenac in their more soluble kinetic (probably amorphous) form for the duration of the 2-hour experiments. Even the least soluble compound, isoxicam, remains in its kinetic form for 20 minutes in the presence of PVP.

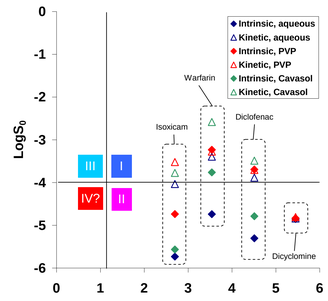


Figure 2. LogP vs. LogS_0 graph for drugs in this study

	Conditions	Kinetic solubility (µg/mL)	Kinetic solubility (-logS_0)	Intrinsic solubility (µg/mL)	Intrinsic solubility (-logS_0)
Warfarin	Aqueous	124.0	-3.40	5.6	-4.74
	0.3% PVP	180.2	-3.23	163.0	-3.28
	1% Cavasol	804.1	-2.58	53.4	-3.76
Diclofenac	Aqueous	38.5	-3.89	1.5	-5.31
	0.1% PVP	58.4	-3.70	59.8	-3.69
	1% Cavasol	96.3	-3.49	4.8	-4.79
Dicyclomine	Aqueous	4.5	-4.84	4.3	-4.86
	2% PVP	4.8	-4.81	4.5	-4.83
Isoxicam	Aqueous	30.9	-4.04	0.6	-5.73
	0.4% PVP	76.8	-3.64	3.1	-5.03
	1% Cavasol	56.3	-3.78	0.9	-5.57

Table 1. Solubility results for drugs in figure 2.

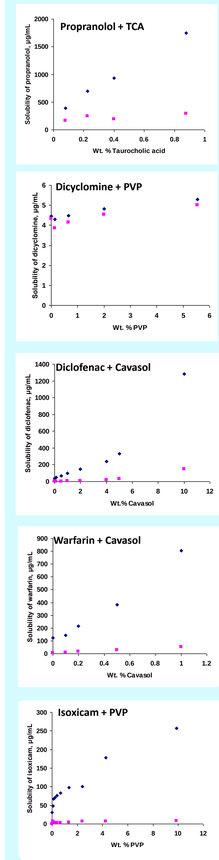
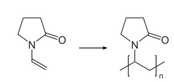
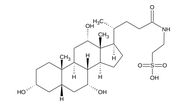


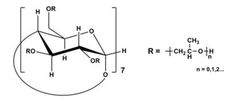
Figure 3. Kinetic (◆) and intrinsic (■) solubilities measured in increasing proportions of excipients.



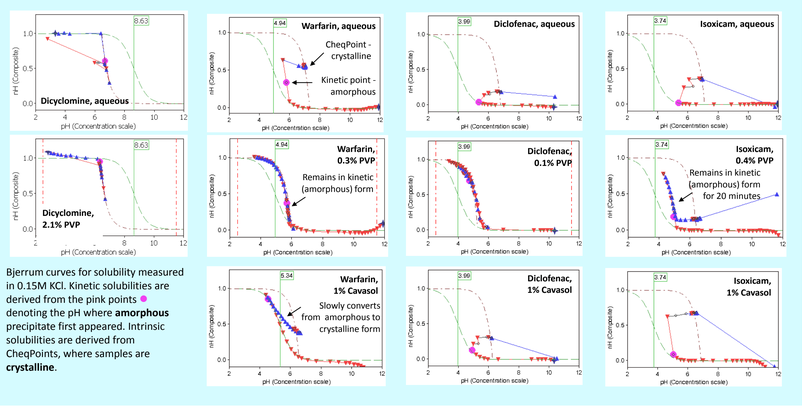
Polyvinyl-pyrrolidine (PVP) is an aid for increasing the solubility of drugs, and also inhibits recrystallization. PVP (MW 1,000,000) used in this study was purchased from Polysciences Inc., Warington PA 18976, USA



Taurocholic acid (TCA) is a bile acid, normally found in the human GI tract. Because of its powerful solubilizing ability, an example of solubility measurement in TCA was included here. Fluka sodium taurocholate hydrate was obtained from Sigma-Aldrich, Poole, UK.



CAVASOL® W7 HP is hydroxypropyl-beta-cyclodextrin, a highly water-soluble beta-cyclodextrin derivative, from Wacker Chemie AG., Burghausen, Germany.



Bjerrum curves for solubility measured in 0.15M KCl. Kinetic solubilities are derived from the pink points ● denoting the pH where **amorphous** precipitate first appeared. Intrinsic solubilities are derived from CheqPoints, where samples are **crystalline**.

Conclusion

Excipients provide a method for increasing kinetic and intrinsic solubilities. PVP preserved the acidic drugs in this study in their kinetic (and most likely amorphous) form, with huge observed increase in solubility. Dicyclomine showed no tendency for supersaturation and remained highly insoluble in the presence of these excipients.

Sirius instruments and software provide excellent tools for carrying out rapid, in-depth studies to investigate methods for solubility and supersaturation enhancement of ionizable drugs. Such experiments could be used to recognise opportunities for promoting a compound's BCS class through formulation.

References

[1] Stuart, M. Box, K. Anal. Chem. 2005, 77(4), 983-990

[2] Box, K J. Völgyi, G. Baka, E. Stuart, M. Takács-Novák, K. Comer, J E A. J. Pharm. Sci. 2006, 95, 1298-1307

[3] Box, K J. Comer, J E A. Current Drug Metabolism, 2008, 9(9), 869-878

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Surface Tension – CMC, TSA, K$_{AW}$

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