The effect of supersaturation on solubility measurements

Karl Box, John Comer, Martin Stuart, Sirius Analytical Instruments Ltd. Forest Row, East Sussex, RH18 5DW, UK

Summary

Some ionizable molecules form supersaturated solutions; others do not. We introduce the terms “chasers” and “non-chasers” to differentiate these two classes, and describe an experimental procedure [1] that distinguishes between molecules in each class, and rapidly measures equilibrium and kinetic solubility in about 30 minutes per sample.

When titrating solutions of samples in their ionized form towards a pH where they are unionized, precipitate of unionized species (detected by light scattering) will suddenly appear at a certain pH if the sample is poorly soluble. The concentration of unionized species at this pH is equivalent to the kinetic solubility. Samples that do not form supersaturated solutions (non-chasers) will precipitate rapidly and quantitatively in response to further additions of titrant. pH readings equilibrate quickly for non-chasers throughout the titration. The solubility may be derived from the shape of the precipitation Bjerrum curve. The kinetic solubility was found to be equal to the intrinsic solubility for nine of the molecules reported here.

When the method was used to investigate the solubility of samples that did form supersaturated solutions (chasers), the pH data followed a different pattern after precipitation, as illustrated for maprotiline. The CheqSol software assumes at the start of every assay that all samples are non-chasers. The Bjerrum curve is calculated during the experiment. If the precipitation point does not lie on the precipitation Bjerrum curve, the software changes the data collection method and assumes the sample is a chaser.

Definitions:

Kinetic solubility = the solubility at the time when an induced precipitate first appears in a solution

Equilibrium solubility (also called **Thermodynamic solubility**) = the concentration of compound in a saturated solution when excess solid is present, and solution and solid are at equilibrium. The equilibrium solubility of the free acid or base form of an ionisable compound at a pH where it is fully un-ionized is called the **Intrinsic solubility**

Supersaturation = the state of a solution containing more dissolved substance than would exist at equilibrium under the same conditions

Subsaturation = term introduced by Sirius to describe the state of a system containing precipitate that is dissolving in the surrounding solution.

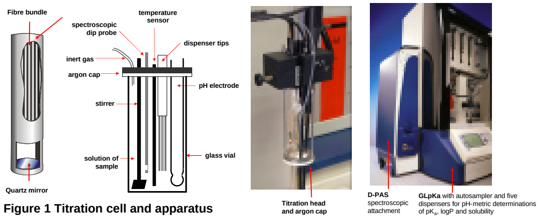


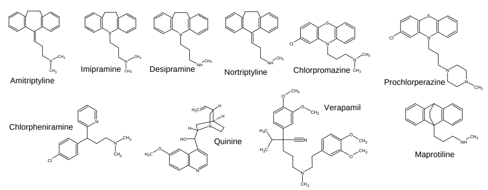
Figure 1 Titration cell and apparatus

Experimental

Solubility determinations were performed on a Sirius GLpKa titrator and D-PAS spectrometer, with RefinementPro 2 and CheqSol software. All titrations were performed in 0.15 M KCl solution. The UV absorption of the solution was continuously monitored in the titration vial by a fibre optic dip-probe. The sample quantity was selected to ensure that when fully neutral, the concentration would be above its intrinsic solubility and would precipitate. Before each experiment, accurate pK_a values were measured at 25°C on the GLpKa. The correct pK_a value is required, as an error of 1 unit in the pK_a will induce an error of 1 logarithmic unit on the solubility scale, log(1/S). The solubility assays are sensitive to carbon dioxide, therefore the measurements were performed in air-tight vessels with degassed reagents under argon atmosphere. A schematic titration head is shown in figure 1.

All results in μg/mL	pK_a	Kinetic solubility		Equilibrium solubility		
		chaser	non-chaser	this work	shake-flask	lit.
Amitryptiline	9.24		13.4	14.2		
Chlorpheniramine	9.28, 3.87		668.0	654.3		615.2
Chlorpromazine	9.24		2.7	2.7	2.4	1.7
Desipramine	10.08		99.4	103.9		
Imipramine	9.54		17.3	17.2	21.7	18.1
Maprotiline	10.33	77.0		5.8	8.1	3.5
Nortriptyline	9.90		27.3	27.0	49.3	20.0
Prochlorperazine*	8.08, 3.81			5.1		
Quinine	8.55, 4.24		391.0	363.0	201.0	491.0
Verapamil	8.72		47.8	48.5	48.5	9.7

*** Prochlorperazine value extrapolated from solubility measured in 4 water-methanol mixtures (12.2 – 29.2%)**
† Shake-Flask measurements were performed at Semmelweis University of Medicine, Budapest, Hungary



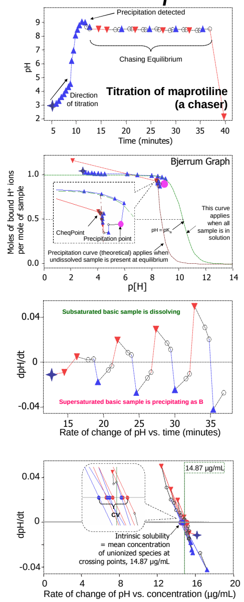
References

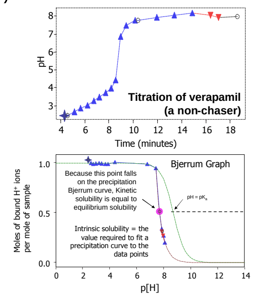
[1] Chasers and non-chasers introduced in *Box, K J. Völgyi, G. Baka, E. Stuart, M. Takács-Novák, K. Comer, J E A. Equilibrium vs. kinetic measurements of aqueous solubility, and the ability of compounds to supersaturate in solution - a validation study. J. Pharm. Sci. 2006, in press*

[2] Sirius first described Chasing Equilibrium in 2004. *Stuart, M. Box, K. Chasing equilibrium: measuring the intrinsic solubility of weak acids and bases. Anal. Chem. 2005, 77(4), 983-990*

[3] Bjerrum curve fitting to measure solubility was first described in 1998. *Avdeef, A. Solubility-pH profiles from Bjerrum plots. Gibbs buffer and pK_a in the solid state. Pharm. Pharmacol. Commun. 1998, 4, 165-178*

Chasers supersaturate; non-chasers don’t





The titration of verapamil (a base and non-chaser) is shown above. The neutral species of verapamil can’t form a supersaturated solution. It precipitates as soon as the solution reaches an appropriate pH. The precipitation point, as well as all pH points after precipitation fall on the precipitation Bjerrum curve. The kinetic solubility of non-chasers is equal to their intrinsic solubility.

The titration of maprotiline (a base and chaser) is shown on the left. The neutral species B of maprotiline can form a supersaturated solution. After precipitation, it can be forced to cycle between being supersaturated and subsaturated by adding small volumes of HCl or KOH titrants. When the rate of pH change with time (dpH/dt) is negative, the sample is precipitating as the neutral species B. The conversion of BH^+ to B releases H^+ ions, so the pH goes down. When dpH/dt is positive, the sample is dissolving as the ionized species BH^+. The conversion of B to BH^+ consumes H^+ ions, so the pH goes up. The rate of pH change would be zero at the crossing points, and the sample would be at equilibrium. The kinetic solubility of chasers is higher than their intrinsic solubility.

Discussion

Supersaturation impacts on drug bioavailability and must be considered during formulation and manufacturing. For example, a weak base might dissolve fully in the stomach but precipitate on entering the high pH environment of the upper intestinal tract. A better understanding of this would enable better adsorption models to be constructed. Do non-chasers fall out of solution as amorphous material whereas chasers produce crystalline precipitate? Conversely, do the non-chasers have some kind of structured or ordered solution phase (liquid crystals, micelles, aggregates) that prevents supersaturation? Is it possible to formulate supersaturated solutions that stay in solution long enough such that absorption is enhanced? Conversely, if a compound is administered in supersaturated solution, could it crash out of solution with unpleasant side effects? Maprotiline supersaturates, but the other molecules in this study do not. While the similarities between some structures are obvious, we have yet to develop rules for predicting this behaviour from structure. Since introducing CheqSol in March 2004 [2], we have found only one non-chasing acid, but about 20% of bases have been non-chasers.

www.sirius-analytical.com