Solubility measurement of crystalline and LLPS forms by extrapolation from values measured in water-methanol mixtures

Kyoowon Baek [1], John Comer [1], Karl Box [1], Jon Mole [2], Jaechun Woo [3]

[1] Sirius Analytical Ltd. Forest Row, RH18 5DW, UK. [2] Sirius Analytical Inc. Sirius Analytical Inc., Beverly, MA, USA. [3] Korea Research Institute of Chemical Technology, Daejeon, Korea

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Purpose

To verify that solubility of ionizable drugs measured in aqueous solution is correctly predicted from solubility measured in water-methanol mixtures.

Methods

Four ionizable drugs were chosen for this study: bendroflumethiazide (acid) and cinnarizine, loratidine and clotrimazole (bases). Their aqueous pK_a values were determined by Yasuda-Shedlovsky extrapolation from p_sK_a values measured in water-methanol mixtures. Their aqueous solubilities were measured by pH-metric techniques (CheqSol or Curve Fitting) in which the aqueous pK_a was used in the calculation of results from the experimental data. Their solubilities were also measured in water-methanol mixtures, in which p_sK_a values interpolated from the Yasuda-Shedlovsky graphs were used in the calculation of results from the experimental data. The pH-metric solubility experiments lasted typically for 1 – 2 hours.

Results

Bendroflumethiazide crystallizes soon after precipitation. Cinnarizine initially precipitates in a non-crystalline form but converts within minutes to a crystalline form. It was the solubility of the crystalline forms of cinnarizine and bendroflumethiazide that the pH-metric experiments measured. Loratidine and clotrimazole are known to undergo Liquid-Liquid Phase Separation (LLPS) and to precipitate initially in a glassy, non-crystalline form that can persist for several hours, and it was the solubility of this non-crystalline form that the pH-metric experiments measured. Measured aqueous solubilities agreed well with results obtained by extrapolation. For all four compounds the graphs of log (pH-metric solubility) vs. methanol weight % were linear with R^2 of 0.986 or better

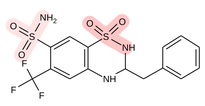
Results at 25 °C	pK_a (1)	pK_a (2)	Extrapolated solubility			Crystalline solubility		
			M	log S (M)	µg/mL	M	log S (M)	µg/mL
Bendroflumethiazide	**8.33**	**9.86**	**0.000029**	**-4.54**	**12.0**			
Cinnarizine	**2.41**	**7.53**	**0.000001**	**-6.09**	**0.3**			
Clotrimazole	**5.80**		**0.000039**	**-4.41**	**13.4**	**0.000001**	**-5.93**	**0.4 [1]**
Loratidine	**5.26**		**0.000036**	**-4.44**	**13.7**	**0.000004**	**-5.38**	**1.6 [1]**

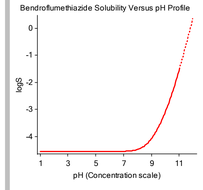
Conclusion

Solubilities for the four compounds measured in aqueous solution were predicted by extrapolation from solubilities measured in water-methanol mixtures. The pH-metric experiments revealed information about the transition of precipitated compounds between solid state forms.

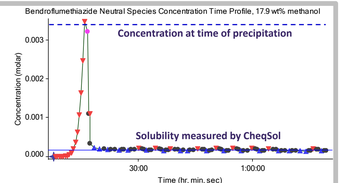
Reference

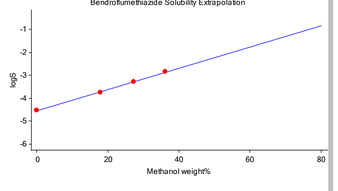
[1] Hsieh, Y. L.; Ilevbare, G. A.; Van Eerdenbrugh, B.; Box, K. J.; Sanchez-Felix, M. V.; Taylor, L. S., pH-Induced Precipitation Behavior of Weakly Basic Compounds: Determination of Extent and Duration of Supersaturation Using Potentiometric Titration and Correlation to Solid State Properties. Pharm Res 2012, 29 (10), 2738-2753.

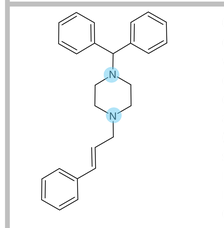


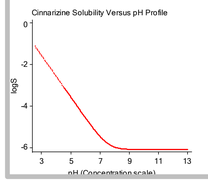


Bendroflumethiazide is a thiazide diuretic. It is an acid with two pK_as (8.33 and 9.86). The graph on the right shows a CheqSol experiment to measure solubility. A basic solution of bendroflumethiazide is acidified (red points). It becomes supersaturated, precipitates and then quickly crystallizes and chases equilibrium. Similar behavior was observed at all methanol percentages, and indicates a tendency to crystallize rapidly after precipitation. It would be hard to devise a formulation to preserve this compound at the concentration seen at the time of precipitation.
Solubility was measured at several ratios of water to methanol. Results extrapolate to an aqueous solubility of -4.54 (as logS (M)).

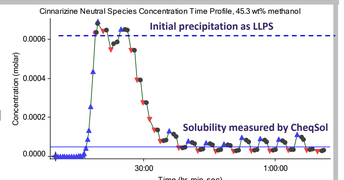


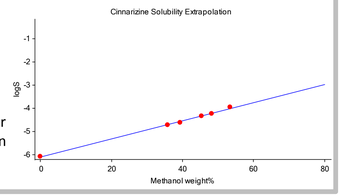




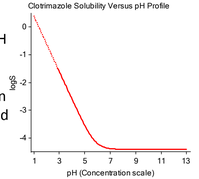


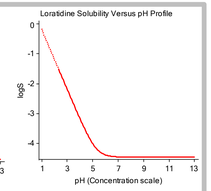
Cinnarizine is an anti-histamine and calcium channel blocker. It is a base with two pK_as (2.41, 7.53). The graph on the right shows a CheqSol experiment to measure solubility. An acidic solution of cinnarizine is basified (blue points). It becomes supersaturated and precipitates, but remains supersaturated for about 10 minutes and then crystallizes and chases equilibrium. Similar behaviour was observed at all methanol percentages, and indicates that initial precipitation was in fact a LLPS event. The onset of crystallization was much slower than was seen for bendroflumethiazide. The LLPS solubility of compounds with behaviour similar to that seen for clotrimazole can often be preserved by means of amorphous solid dispersions.

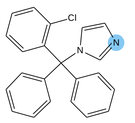


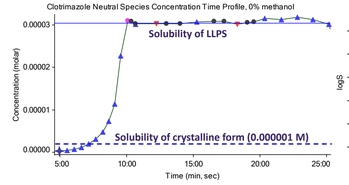


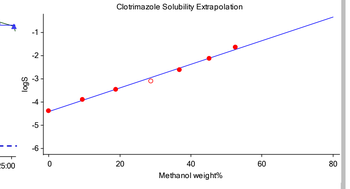
Clotrimazole is an antifungal, and **loratadine** is an H1 histamine antagonist. When they precipitate in response to pH change, they undergo Liquid-Liquid Phase Separation (LLPS). The LLPS form comprises non-crystalline droplets of supercooled liquid. It is the solubility of the LLPS that has been measured here. Shake-flask measurements of the original solid indicate a much lower solubility corresponding to the crystalline form [1]. Further work will focus on the determination of the time taken to convert from LLPS to crystals using controlled supersaturation experiments

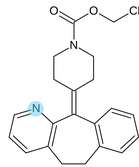


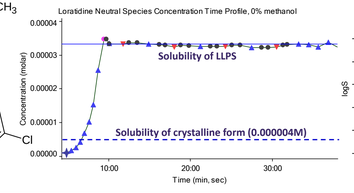


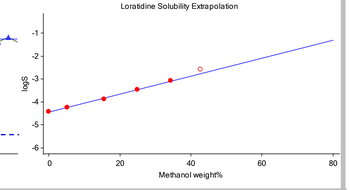












The pK_a values and solubilities of these samples were measured on SiriusT3 instruments. Bendroflumethiazide and cinnarizine were measured by Karl Box and co-workers at Sirius UK, and clotrimazole and loratidine were measured by Kyoowon Baek using an instrument in Dr. Jaechun Woo's laboratory at KRICT.

Photo: SiriusT3.

For more information please contact:
Sirius Analytical, Forest Row Business Park, Station Road, Forest Row, East Sussex, RH18 5DW, UK
T +44 (0)1342 820720 **F** +44 (0)1342 820725 **E** sales@sirius-analytical.com

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