

Purpose

Measurement of aqueous intrinsic solubility of ionizable drugs by potentiometric methods is a powerful, rapid method, providing information about the extent and duration of supersaturation as well as a solubility result; however, the method requires the sample to be in aqueous solution in ionized form at high or low pH at the start of the experiment. Although the Henderson Hasselbalch equation suggests that ionized forms can be orders of magnitude more soluble than neutral forms, compounds with low intrinsic solubility often form poorly soluble salts, and therefore aqueous solutions of the ionized form cannot be prepared. Solutions of the salt form can generally be prepared in the solvent-water mixtures. The purpose of this work was to validate the potentiometric determination of aqueous intrinsic solubility by extrapolation from measurements made in methanol-water mixtures.

Methods

The solubility of several poorly-soluble acidic and basic drugs was measured by potentiometric methods. Some of the compounds are known to be insoluble in salt form in aqueous solution. Solubility of each compound was measured in three cosolvent-water mixtures (e.g. 50%, 40%, 30% methanol by weight), and the aqueous intrinsic solubility was determined by extrapolation. The extrapolated results were compared with published results or with intrinsic solubility measured by saturation shake flask. The quality of the extrapolations was described by a calculated R² value.

Results

Compounds studied, and their measured intrinsic solubility and extrapolation R² include gliclazide (17 µg/mL, 0.99); glipizide (2 µg/mL, 0.96); glibenclamide (0.2 µg/mL, 0.99); prochlorperazine (9.7 µg/mL, 0.99); haloperidol (0.7 µg/mL, 0.99); and meclizine (0.1 µg/mL, 0.99). Data collection for most samples took 3 – 4 hours per extrapolated result; prochlorperazine (a maleate salt) took 6½ hours. Comparison with shake-flask values for intrinsic solubility showed R² of 0.93.

Conclusion

Intrinsic solubility measurement by extrapolation from solubility measured potentiometrically in various cosolvent-water mixtures is a valid method, and overcomes problems of salt solubility that impede measurement in aqueous solution.

References

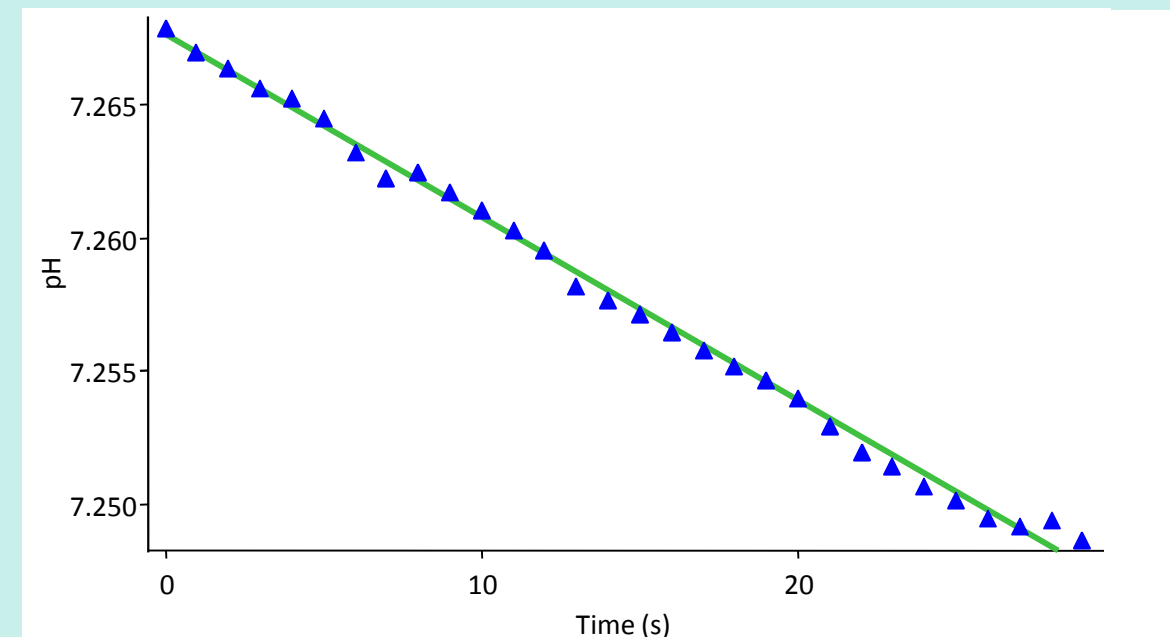
- [1] Box, K., Stuart, M., *Anal. Chem.* 2005, 77(4), 983 - 990
- [2] Baka, E., Box, K., Comer, J. Takács-Novák, K., Völgyi, G. *Anal. Chim. Acta.* 2010, 673, 40 - 46
- [3] Box, K., Comer, J., Gravestock, T., Stuart, M, *Chem. Biodivers.* 2009, 6(11), 1767 - 1788
- [4] Völgyi, G.; Ruiz, R.; Box, K.; Comer, J.; Bosch, E.; Takács-Novák, K. *Anal. Chim. Acta.* 2007, 583 (2), 418-428.



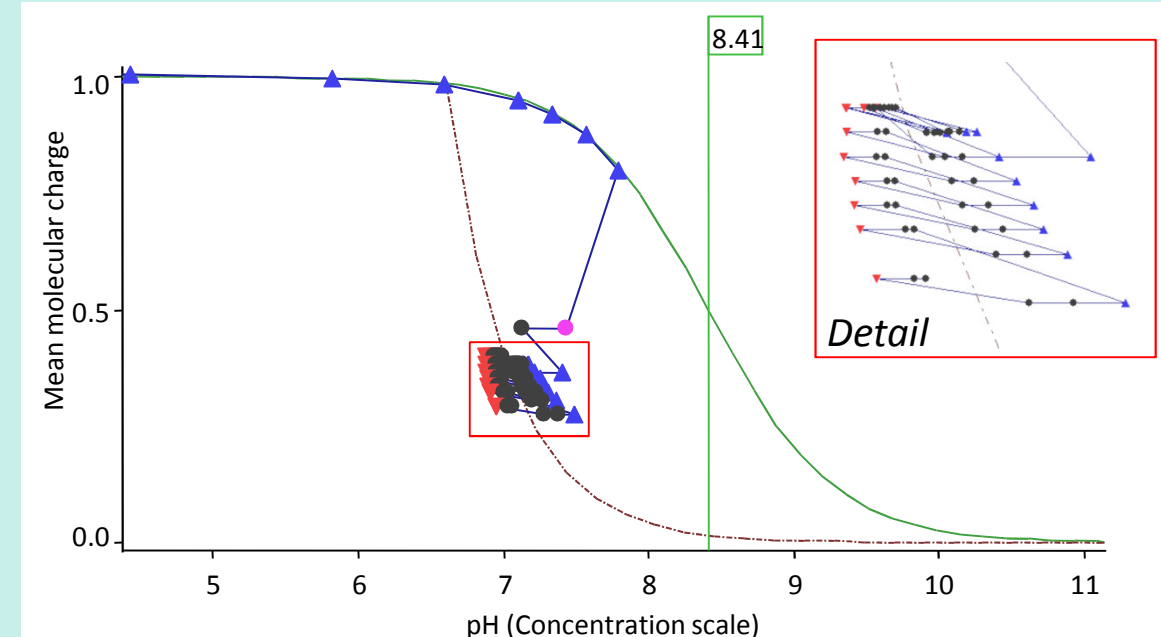
All measurements performed using the SiriusT3

Potentiometric Solubility Measurement

The fraction of a sample of an ionizable compound which exists in the neutral form can be controlled by varying the pH. If precipitate is formed during a titration of a weakly acidic or basic compound, the ionization equilibrium is perturbed and the observed pK_a is shifted relative to its true value. Precipitation or dissolution of an ionizable compound produces a measureable pH change with time. CheqSol [1] makes use of these effects to rapidly measure intrinsic solubility.



Example: haloperidol. A linear decrease in pH with time is observed as a weak base slowly precipitates from solution. Dissolution of a base causes an increase in pH. pH readings can be used to determine if the solution is subsaturated or supersaturated.

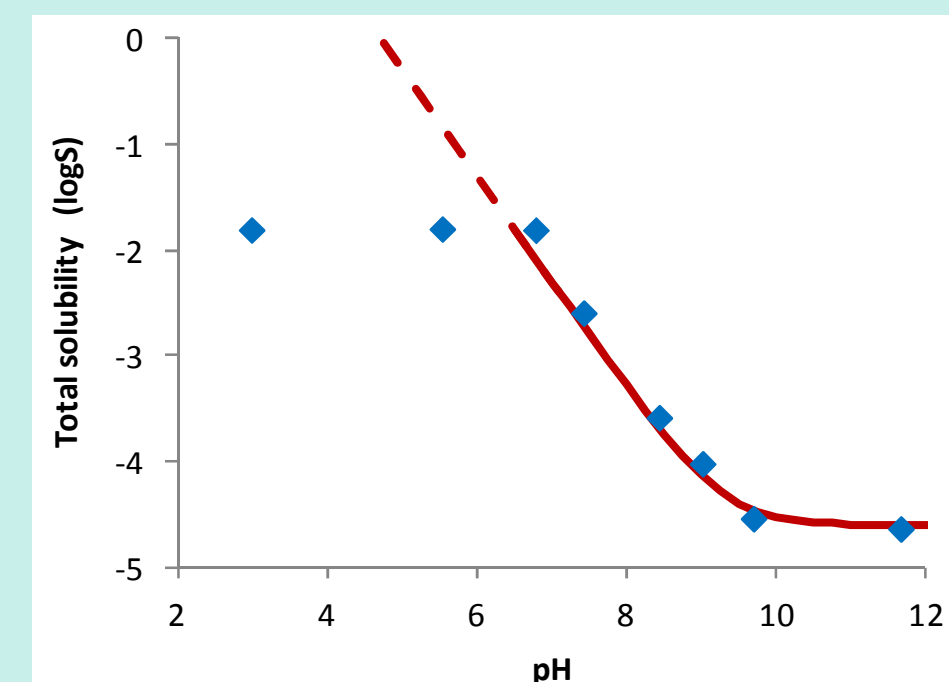


The presence of precipitate perturbs the ionization equilibrium and causes a shift in the apparent pK_a. By cycling between subsaturation and supersaturation states, this point can be found by interpolation, eliminating the need to wait for equilibration [3].

Solubility variation with pH

Ionized species are significantly more soluble than the corresponding neutral molecule, leading to variations in solubility with pH for ionizable compounds. The Henderson Hasselbalch equation can be used to calculate the total solubility of a compound at a given pH from its pK_a and intrinsic solubility. This equation assumes that the ionized form of the compound is infinitely soluble. In reality, a salt with a finite solubility will be formed if the concentration of ionized species is sufficiently high.

Before a CheqSol assay can be started, it is recommended that the sample is fully dissolved in its ionized form at a concentration of at least 3 mM. For very insoluble compounds, this may not be possible due to salt formation. Under these circumstances, a cosolvent may be needed to dissolve the sample.



Solubility/pH profile for a weak base with pK_a 9.32*. The red line is the predicted profile obtained using the Henderson Hasselbalch equation. The points were obtained from individual shake-flask measurements.

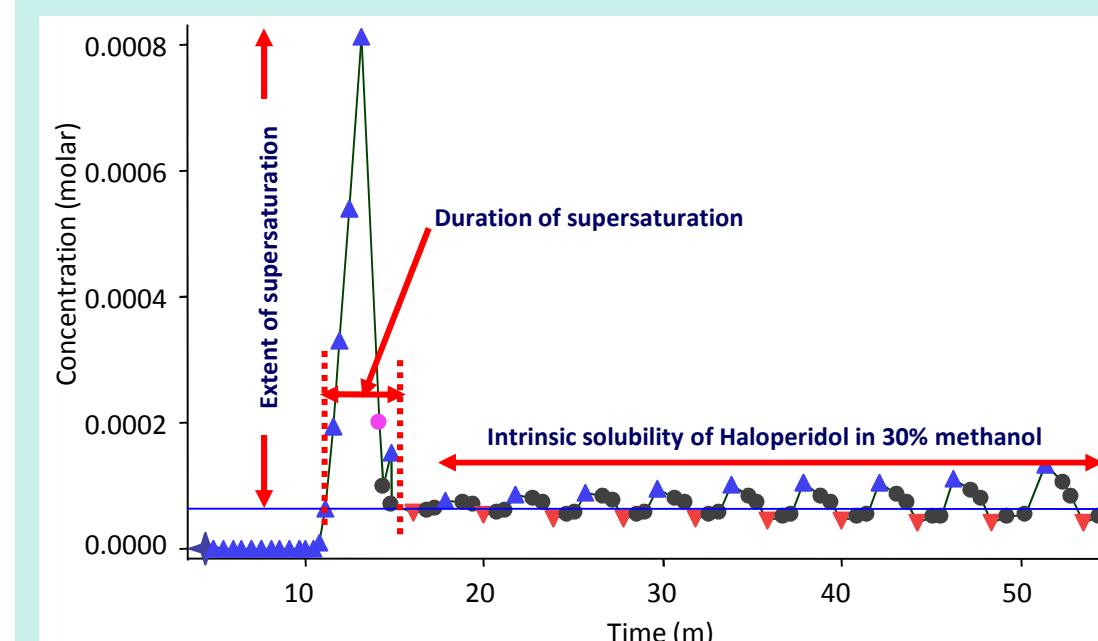
* Propafenone [2]

Experiment Design

Data collection is fully automated. There are three important points to consider when setting up an assay:

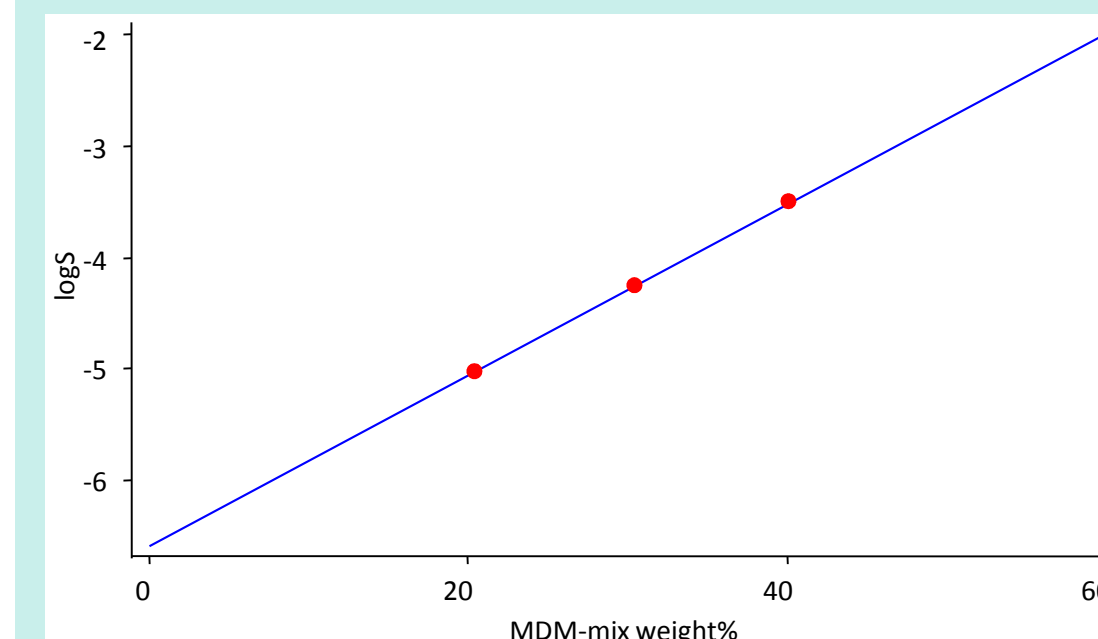
- The apparent pK_a in a cosolvent mixture (p_sK_a) will deviate from the aqueous value. It must be measured as it is essential for the solubility calculation.
- The sample weight must be high enough for precipitation to occur during the assay. Higher cosolvent ratios require larger sample weights.
- The sample must dissolve completely in its ionized form at the start of the experiment. An appropriate start pH must be chosen. Sonication may be needed.

Investigating Supersaturation Behaviour in Solvent Mixtures



CheqSol generates a profile of the neutral species concentration with time. The duration of supersaturation (width of the first peak) and extent (height of the first peak) are determined from a single, automated experiment. The intrinsic solubility (blue line) is the equilibrium point between subsaturation and supersaturation.

Results



Meclizine solubility determined by extrapolation from 3 cosolvent ratios. Meclizine is poorly soluble in methanol; experiments done in MDM, a mixture of cosolvents [4].

Compound	Shake-flask intrinsic solubility (logS)	Extrapolated Solubility (logS)	Linear fit R ²	Sample weight range / mg
ACIDS				
Gliclazide	-4.28	-4.28	0.99	4.5 – 6.5
Glipizide	-5.35	-5.35	0.96	4.6 – 6.5
Glibenclamide	-6.39	-6.39	0.99	5.1 – 6.5
BASES				
Prochlorperazine	-4.82	-4.59	0.99	2.9 – 8.5
Haloperidol	-5.14	-5.73	0.99	2.2 – 15.9
Meclizine	Below detection limit	-6.59	0.99	1.9 – 2.0

Extrapolated values showed good agreement with aqueous shake-flask results (R² = 0.93)

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For more information please contact:

sirius@sirius-analytical.com

Sirius Analytical
 Forest Row Business Park, Station Road
 Forest Row, East Sussex, RH18 5DW
 T +44 (0)1342 820720 F +44 (0)1342 820725