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Note

Estimation of the aqueous solubility of weak electrolytes

Neera Jain [b], Gang Yang [c], Stephen G. Machatha [a,*], Samuel H. Yalkowsky [a]

[a] *Department of Pharmacy Practice and Science, College of Pharmacy, The University of Arizona, 1703 E. Mabel Street, Tucson, AZ 85721-0207, United States*
[b] *Wyeth-Ayerst Research, Pearl River, NY 10965, United States*
[c] *Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, NJ 08869, United States*

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Abstract

Jain and Yalkowsky [Jain, N., Yalkowsky, S.H., 2001. Estimation of the aqueous solubility. I. Application to organic non-electrolytes. J. Pharm. Sci. 90, 234–252.] demonstrated that the general solubility equation (GSE) can be used to estimate the aqueous solubility of organic non-electrolytes. In this study the applicability of the GSE was extended to weak electrolytes. It is demonstrated that the GSE estimates the aqueous solubility of 949 compounds, including 367 weak electrolytes with an AAE of 0.58. It is also shown that the intrinsic solubilities of weak acids for which the $\mathrm{p}K_\mathrm{a} + \log S_\mathrm{w} \leq 0$ and for weak bases for which $\mathrm{p}K_\mathrm{a} - \log S_\mathrm{w} \leq 14$ are within a factor of 2 of the total solubilities.

Keywords: Solubility; GSE; Weak electrolytes; pKa

1. Introduction

The estimation of aqueous solubility is of importance in pharmacy because of its implications in the formulation of drugs and in drug absorption. A large number of methods have been reported in the literature for predicting the aqueous solubility of non-electrolytes using various physical attributes of the compound. One of the simplest models used to determine the water solubility is the general solubility equation (GSE). The derivation of the GSE is reported in detail by Ran and Yalkowsky (2001). In a previous study by Jain and Yalkowsky (2001), it was also shown that the water solubility of non-electrolytes can be calculated simply and accurately from its melting point (m.p.) and its octanol–water partition coefficient ($C\log P$) by the general solubility equation (GSE):

$$\log S_\mathrm{w} = -0.01(\mathrm{m.p.} - 25\,^\circ\mathrm{C}) - C\log P + 0.50 \qquad (1)$$

where S_w is the solubility of a non-electrolyte solute in mol/L.

The GSE also assumes that the drug/compound is miscible with octanol. The constant 0.5 is the logarithm of 3.15, half the molar concentration of pure octanol.

In this study the GSE is applied to organic weak electrolytes. The pH of the aqueous solution is determined by the concentration of the ionizable solute at saturation. Therefore for calculations of the total solubility, it is necessary to incorporate the ionization constant(s) of the solute, the pH of the resulting solution and the intrinsic solubility.

2. Theoretical

Weak electrolytes can be categorized into three categories, monoprotic acids, bases and ampholytes. Equations for determining the total solubilities of each group will be derived from sound thermodynamic relationships with no fitted parameters.

2.1. Weak monoprotic acid

When a weak acid is saturated in water the following charge balance equilibrium exists:

$$[\mathrm{A}^-] = [\mathrm{H}^+] - [\mathrm{OH}^-] \qquad (2)$$

And the dissociation constant is described by:

$$K_\mathrm{a} = \frac{[\mathrm{H}^+][\mathrm{A}^-]}{[\mathrm{HA}]} \qquad (3)$$

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* Corresponding author. Tel.: +1 520 626 4308; fax: +1 520 626 4063.
E-mail address: machatha@pharmacy.arizona.edu (S.G. Machatha).

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Table 1
$[A^-]/[HA]$ for a weak acid and $[BH^+]/[B]$ for a weak base as a function of pK_a and intrinsic solubility in mol/L

Acid pK_a	2	3	4	5	6	7	8	9	10	11	12
Base pK_a	12	11	10	9	8	7	6	5	4	3	2
$\log S_w$											
−1	**0.3**	**0.1**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
−2	**1.0**	**0.3**	**0.1**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
−3	3.1	**1.0**	**0.3**	**0.1**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
−4	10.0	3.1	**1.0**	**0.3**	**0.1**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
−5	31.6	10.0	3.1	**1.0**	**0.3**	**0.1**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
−6	100.0	31.6	10.0	3.1	**1.0**	**0.3**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**
−7	316.2	100.0	31.6	10.0	3.3	1.4	1.1	**1.0**	**1.0**	**1.0**	**1.0**

Substituting the value of $[A^-]$ from Eq. (2) into (3), gives:

$$K_a = \frac{[H^+]([H^+] - [OH^-])}{[HA]} \tag{4}$$

For a saturated solution of a weak acid $[HA] = S_w$, and on substitution and rearranging in Eq. (4) we get:

$$\mathrm{pH} = -\log(\sqrt{K_a S_w + K_w}) \tag{5}$$

which can be used to calculate the pH of a saturated solution of a weak acid.

For a monoprotic acid $[A^-] = [H^+]$, therefore the total solubility can be described using Eq. (6):

$$S_{\mathrm{total}} = S_w + \sqrt{K_a S_w + K_w} \tag{6}$$

Thus, the total solubility of a weak monoprotic acid in a saturated aqueous solution can be calculated from Eq. (6) where the value of S_w obtained from Eq. (1). When $K_w \ll K_a S_w$ Eq. (6) is simplified to:

$$S_{\mathrm{total}} = S_w + \sqrt{K_a S_w}. \tag{7}$$

2.2. Weak monoprotic base

Applying the same theory to a weak monoprotic base, the total solubility can be estimated from:

$$S_{\mathrm{total}} = S_w + \sqrt{\frac{K_w}{K_a^{\mathrm{base}}} S_w + K_w} \tag{8}$$

When $S_w \gg K_a$ Eq. (8) simplifies to:

$$S_{\mathrm{total}} = S_w + \sqrt{\frac{K_w}{K_a^{\mathrm{base}}} S_w}. \tag{9}$$

2.3. Ampholytes

Ampholytes have an acid (K_a) and a base (K_a^{base}) ionization constant. Using the same principal as that used for the monoprotic acids and bases, both the ionization constants are incorporated in the calculation of the total solubility:

$$S_{\mathrm{total}} = S_w + \sqrt{S_w \left(\frac{K_w}{K_a^{\mathrm{base}}} + K_a \right)} \tag{10}$$

The total solubilities for polyprotic acids and bases can also be estimated using the same reasoning.

3. Methods

The reported melting temperature (m.p.), octanol ionization constants (pK_a), and intrinsic aqueous solubility (S_w) of 949 non-electrolytes and weak electrolytes are obtained from literature. The $\log K_{ow}$ values are obtained from the $C \log P$ (ClogP, 1999) program.

The ratio of ionized concentration to total solute concentration was calculated using Microsoft Excel® for a weak monoprotic acid, weak monoprotic base, and a zwitterion.

The average absolute error (AAE) was determined by:

$$\mathrm{AAE} = \frac{\sum |\log S_{\mathrm{cal}} - \log S_{\mathrm{obs}}|}{N} \tag{11}$$

where $\log S_{\mathrm{cal}}$ and $\log S_{\mathrm{obs}}$ are the logarithms of calculated and experimental molar solubilities and N is the number of compounds used.

4. Results and discussion

4.1. Relating the extent of dissociation to the intrinsic solubility

The ratio of the ionized to non-ionized form of weak acids and bases that are listed in Table 1 were calculated using Eqs. (7) and (9). The pK_a values range from 2 to 13 and intrinsic solubilities of 10^{-1} to 10^{-7} mol/L.

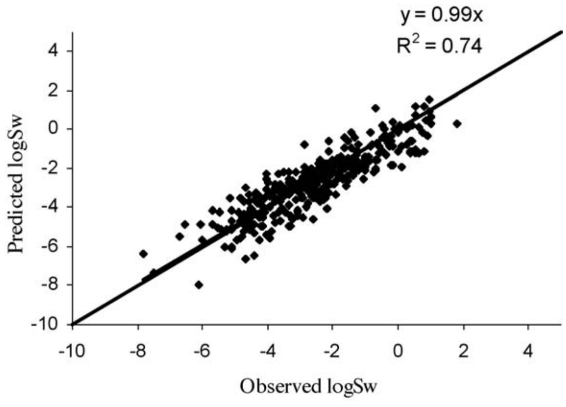

Fig. 1. Experimental aqueous solubility vs. calculated solubility using the GSE.

Table 2
Average absolute errors (AAE) of the data sets

Data set	*n*	AAE (log units)
Non-electrolytes	582	0.43
Weak electrolytes (acids and bases)	367	0.64
All compounds	949	0.58

The region that is bold represents an error of 50% or less in the calculation of the total solubility if ionization is ignored. Therefore the intrinsic solubilities are approximately a factor of two of the total solubilities for weak acids if the $\mathrm{p}K_\mathrm{a} + \log S_\mathrm{w} \geq 0$ and for weak bases if $\mathrm{p}K_\mathrm{a} - \log S_\mathrm{w} \geq 14$. The Eqs. (7), (9) and (10) are accurate for all but strong acids and bases having very low intrinsic solubilities.

Table 1 can also be used to calculate the total solubilities of an amphiphile provided that it can exist as a non-electrolyte. However since zwitterions cannot exist as uncharged then the aqueous solubility cannot be calculated using the GSE.

4.2. Aqueous solubility

The solubilities of 367 weak electrolytes were calculated using the GSE (Eq. (1)) and are plotted versus the reported values in Fig. 1.

The plot shows that the predicted values correlate reasonably well ($R^2 = 0.74$) with the experimental values. The average absolute error (AAE) is shown in Table 2. The AAE using no correction for the ionization is 0.64 log units. The table also includes the AAE of 582 organic electrolytes from a previous study done by Jain and Yalkowsky (2001).

It would be expected that the $\mathrm{p}K_\mathrm{a}$ would be necessary to determine the aqueous solubility. The GSE which does not apply the $\mathrm{p}K_\mathrm{a}$ and assumes miscibility with octanol, has been demonstrated to reasonably estimate the solubility of weak electrolytes, the fit is better for non-electrolytes.

5. Conclusions

The general solubility equation (GSE) has previously been demonstrated that it is applicable to organic non-electrolytes. As has been shown the GSE is simple and versatile and is also applicable to organic electrolytes without the use of the $\mathrm{p}K_\mathrm{a}$.

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