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Note

Model for solubility estimation in mixed solvent systems

M. Barzegar-Jalali [a,*], J. Hanaee [b]

Divisions of [a] Pharmaceutics and [b] Pharmaceutical Chemistry, School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

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Abstract

A simple and rapid method referred to as the double log-log model for linearizing solubility data obtained from mixed solvent systems is presented. The model was able to linearize data which could not be linearized by means of the log-linear solubility equation. Also, the accuracy and prediction capability of the model were greater than those of the excess free energy equation of solubility estimation.

Key words: Solubility estimation; Cosolvency; Mixed solvent system; Double log-log model; Solubility data linearization

The phenomenon of cosolvency, through solvent blending, has been widely used to increase the water solubility of poorly water-soluble drugs in order to formulate solution dosage forms of the drugs. In cosolvency, a permissible water-miscible organic liquid designated as the cosolvent is mixed with water to bring about drug solubilization.

The first quantitative expression of solubility in mixed solvent systems known as the log-linear solubility equation was provided by Yalkowsky and Roseman (1981). According to this expression, the log ratio of drug solubility in mixed solvent systems to its water solubility is linearly related to the volume of the fraction of cosolvent in a water : cosolvent mixture. However, several cases of deviation from linearity have been reported (Rubino and Yalkowsky, 1987; Rubino and Obeng, 1991). Other expressions, based on the excess free energy in an attempt to take into account different interactions involved in solubilization, have been presented (Williams and Amidon, 1984a–c).

In this report, we present a new approach referred to as the double log-log model which can be used for the estimation and prediction of solubility as well as the linearization of experimental data that cannot be linearized by means of the log-linear solubility equation. A method of linearization of the excess free energy equation is provided from which one can readily linearize the solubility data. Also, the accuracy and prediction capability of the double log-log model have been compared with those of the excess free energy equation using some experimental data.

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[*] Corresponding author.

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Double log-log model: The proposed double log-log model for linearizing the solubility data is expressed as:

$$\ln[\ln(x_m/x_w)] = \ln\{\ln[(x_m)_{0.5}/x_w]\} + B\,\ln(f_c/f_w) \qquad (1)$$

when $0 < f_c \leq 0.5$

$$\ln[\ln(x_c/x_m)] = \ln\{\ln[x_c/(x_m)_{0.5}]\} + b\,\ln(f_w/0.5) \qquad (2)$$

when $0 < f_w \leq 0.5$

where x_m, x_w, $(x_m)_{0.5}$ and x_c are the drug solubilities in the mixed solvent system, water, a system containing 0.5 fraction of organic solvent (and/or water) and neat organic solvent, respectively, and f_c and f_w denote the volume fractions of organic solvent and water in the solvent system

These equations can be obtained from the log-linear equation by making some assumptions as follows;

The log-linear equation is written in the form of Eq. 3

$$(x_m/x_w) = (x_c/x_w)^{f_c} \qquad (3)$$

Recognizing $f_c = 1 - f_w$, Eq. 3 becomes:

$$(x_c/x_m) = (x_c/x_w)^{f_w} \qquad (4)$$

As mentioned above, several cases of deviation from the log-linear plot have been reported. At f_c values less than 0.5, the plots were concave upward and at $f_c > 0.5$ the plots became concave downward. We assume that at f_c values below 0.5 the organic solvent acts as a cosolvent and since the degree of breakdown in the three-dimensional water structure is dependent on f_c (Rubino and Obeng, 1991), the solubility should therefore depend on the ratio (f_c/f_w) rather than f_c alone and on introducing the interaction parameter, B, Eq. 3 will become:

$$(x_m/x_w) = [(x_m)_{0.5}/x_w]^{(f_c/f_w)^B} \qquad (5)$$

Eq. 5 is valid between the limits $0 < (f_c/f_w) \leq 1$ or $0 < f_c \leq 0.5$ and its linear form is Eq. 1. At f_c greater than 0.5, water acts as a cosolvent and its three-dimensional structure is lost (Rubino and Obeng, 1991), thus, the solubility depends on $f_w/0.5$ rather than on f_w/f_c.

Taking into account an interaction parameter, b, Eq. 4 becomes:

$$(x_c/x_m) = [x_c/(x_m)_{0.5}]^{(f_w/0.5)^b} \qquad (6)$$

The linear form of Eq. 6 is Eq. 2. Eq. 6 is valid for $0 < (f_w/0.5) \leq 1$ or $0 < f_w \leq 0.5$.

Linearization of the excess free energy equation: The reduced three-suffix solubility equation based on the excess free energy which has been used successfully as a general method for characterizing and estimating solubility in mixed solvent systems (Williams and Amidon, 1984b) is:

$$\ln(x_m/x_w) = f_c\,\ln(x_c/x_w) - A_{1-3} f_c f_w (2f_c - 1) q_2/q_1 + A_{3-1} 2 f_c^2 f_w q_2/q_3 + C_2 f_c f_w \qquad (7)$$

The A, q and C_2 were described in the original paper (Williams and Amidon, 1984a) and the other symbols have been defined in this report. Eq. 7 can be rearranged to give:

$$\frac{\ln\left(\frac{x_m}{x_w}\right)}{f_c \cdot f_w} = \frac{\ln\left(\frac{x_c}{x_w}\right)}{f_w} + 2f_c \cdot \left(\frac{A_{3-1} \cdot q_2}{q_3} - \frac{A_{1-3} \cdot q_2}{q_1}\right) + C_2 + \frac{A_{1-3} q_2}{q_1} \qquad (8)$$

If the corresponding expressions of Eq. 8 for two successive $[\ln(x_m/x_w)]/f_c f_w$, i.e., terms i and $i+1$ are subtracted from each other, then Eq. 9 can be obtained:

$$\frac{\left[\dfrac{\ln\left(\frac{x_m}{x_w}\right)}{f_c \cdot f_w}\right]_{i+1} - \left[\dfrac{\ln\left(\frac{x_m}{x_w}\right)}{f_c \cdot f_w}\right]_{i}}{f_{c_{i+1}} - f_{c_i}} = \left[\frac{\dfrac{1}{f_{w_{i+1}}} - \dfrac{1}{f_{w_i}}}{f_{c_{i+1}} - f_{c_i}}\right] \ln\left(\frac{x_c}{x_w}\right) + 2\left[\left(A_{3-1} \cdot \frac{q_2}{q_3}\right) - \left(A_{1-3} \cdot \frac{q_2}{q_1}\right)\right] \qquad (9)$$

Table 1
Fitness of solubility data of alkyl *p*-hydroxybenzoates and alkyl *p*-aminobenzoates to Eq. 1, 2, 9 and 8

Solute	Double log-log model							Excess free energy model						
	Eq. 1 [a]			Eq. 2 [b]			$\Sigma(\%D)^2$	Eq. 9 [c]			Eq. 8 [c]			$\Sigma(\%D)^2$
	I	*S*	*r*	*I*	*S*	*r*		*I*	*S*	*r*	*I*	*S*	*r*	
MPHB	1.0787 (1.0543) [d]	0.9400	0.9996	1.0173 (1.0543) [e]	1.3180	0.9994	288.8	6.1864	5.7048	0.9992	−3.2387	1.0078	1.0000	505.2
EPHB	1.2054 (1.1600)	0.9744	0.9953	1.2109 (1.2384)	1.2126	0.9994	568.3	7.0088	6.6207	0.9988	−4.0263	0.9973	0.9998	629.2
PPHB	1.2750 (1.2837)	0.9635	0.9996	1.4358 (1.3813)	1.3984	0.9981	1011.7	5.6741	7.9018	0.9991	−4.9799	1.0472	0.9998	4346.1
BPHB	1.3858 (1.3913)	0.9578	0.9995	1.6606 (1.5411)	2.2117	0.9981	6284.1	12.6799	8.9213	0.9973	−7.8528	1.0501	0.9993	5995.4
MPAB	0.9780 (0.9516)	0.8973	0.9995	0.9940 (0.9969)	1.0799	0.9998	151.5	3.4351	5.2533	0.9994	−2.7491	1.0503	0.9994	852.1
EPAB	1.1427 (1.1282)	0.8932	0.9999	1.1458 (1.1569)	1.0742	0.9994	104.7	4.5399	6.1666	0.9994	−2.7039	0.9909	0.9999	363.6
PPAB	1.2884 (1.2470)	0.9401	0.9993	1.3831 (1.3838)	1.0559	0.9986	610.5	5.9770	7.2995	0.9994	−3.7475	0.9837	0.9993	1976.5
BPAB	1.3781 (1.3635)	0.8882	0.9996	1.6007 (1.5476)	1.2698	0.9976	1806.3	2.8802	9.0282	0.9995	−4.3878	1.0532	0.9999	5392.2

[a] Data points at f_c values of 0.1, 0.2, 0.3, 0.4 and 0.5 were used.

[b] Data points at f_w values of 0.1, 0.2, 0.3, 0.4 and 0.5 were employed.

[c] Data points at f_c values of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 and 0.9 were used.

[d,e] Values between parentheses are the experimental values of $\ln[\ln((x_m)_{0.5}/x_w)]$ and $\ln[\ln(x_c/(x_m)_{0.5})]$, respectively.

I, intercept; *S*, slope; *r*, correlation coefficient; MPHB, methyl *p*-hydroxybenzoate; EPHB, ethyl *p*-hydroxybenzoate; PPHB, propyl *p*-hydroxybenzoate; BPHB, butyl *p*-hydroxybenzoate; MPAB, methyl *p*-aminobenzoate; EPAB, ethyl *p*-aminobenzoate; PPAB, propyl *p*-aminobenzoate; BPAB, butyl *p*-aminobenzoate.

Solubility data were taken from Rubino and Obeng (1991).

Table 2
Fit of phenytoin solubility data in different solvent systems to double log-log model

Solvent system	Eq. 1 [a]			Eq. 2 [b]		
	I	S	r	I	S	r
Propylene glycol : water	1.2324 (1.2317) [c]	0.8258	0.9964	1.1776 (1.2053) [d]	1.1217	0.9996
1,3-Butandiol : water	1.3502 (1.3238)	0.7215	0.9989	0.9298 (0.9484)	1.3357	0.9998
Polyethylene glycol 200 : water	1.5585 (1.5150)	0.7219	0.9982	1.3171 (1.2948)	1.5351	0.9999

[a] Data points at f_c values of 0.1, 0.2, 0.3, 0.4 and 0.5 were used.
[b] Data points at f_w values of 0.1, 0.2, 0.3, 0.4 and 0.5 were employed.
[c,d] Values between parentheses are the experimental values of $\ln[\ln((x_m)_{0.5}/x_w)]$ and $\ln[\ln(x_c/(x_m)_{0.5})]$, respectively.
I, intercept; S, slope; r, correlation coefficient.
Solubility data were taken from Rubino et al., (1984).

It is obvious that a plot of the left-hand side of Eq. 9 vs $(1/f_{w_{i+1}} - 1/f_{w_i})/(f_{c_{i+1}} - f_{c_i})$ gives a line whose ordinate intercept is equal to $2[(A_{3-1} \cdot q_2/q_3) - (A_{1-3} \cdot q_2/q_1)]$. After inserting the numerical value of this term into Eq. 8, from the plot of $[\ln(x_m/x_w)]/(f_c f_w)$ vs $\{[\ln(x_c/x_w)]/f_w + 2f_c[(A_{3-1} \cdot q_2/q_3) - (A_{1-3} \cdot q_2/q_1)]\}$, the value of $[C_2 + (A_{1-3} \cdot q_2/q_1)]$ is obtained which is the ordinate intercept of the resulting line.

The double log-log model and linearized forms of the excess free energy equation were applied to the data obtained from solubility studies of alkyl *p*-hydroxybenzoates and alkyl *p*-aminobenzoates in propylene glycol : water mixtures reported by Rubino and Obeng (1991). The data which had not been linearized by the log-linear model were linearized by both methods, as became evident from the high correlation coefficients (Table 1).

Plots of the left-hand sides of Eq. 1 and 2 vs the corresponding independent variables should produce lines with the ordinate intercepts of $\ln[\ln((x_m)_{0.5}/x_w)]$ and $\ln[\ln(x_c/(x_m)_{0.5})]$, respectively. There was an excellent agreement between the intercepts and experimental values of the $\ln[\ln(x_m)_{0.5}/x_w)]$ and $\ln[\ln(x_c/(x_m)_{0.5})]$ terms, indicating the suitability of the double log-log model.

The accuracy and prediction capability of the double log-log and the excess free energy models have been assessed using Eq. 10:

$$\sum(\%D)^2 = \sum\left\{\left[\left[(x_m)_{cal} - (x_m)_{exp}\right]/(x_m)_{exp}\right] \times 100\right\}^2 \quad (10)$$

where $\Sigma(\%D)^2$ is the sum of squares of the percent difference between the calculated and experimentally obtained values of x_m relative to its experimental value at each f_c, and $(x_m)_{cal}$ and $(x_m)_{exp}$ denote the calculated and experimental values of x_m at f_c. The value of $(x_m)_{cal}$ is calculated by inserting numerical values of B, b and the ordinate intercepts of Eq. 9 and 8 together with the experimental values of x_w, x_c and $(x_m)_{0.5}$ into the appropriate equation (Eq. 5, 6 and 8). As can be seen from the $\Sigma(\%D)^2$ values in Table 1, in general, the accuracy and prediction capability of the double log-log model are greater than those of the excess free energy model. The lower the $\Sigma(\%D)^2$, the more accurate is the model.

The double log-log model was also applied to solubility data of phenytoin in different solvent systems given by Rubino et al. (1984) and the goodness of fit of data to the model is evident from the high correlation coefficients as demonstrated in Table 2.

In conclusion, the double log-log model offers a simple and practical way of linearizing data for the cases which cannot be linearized by the log-linear method as well as a more accurate method of predicting and estimating drug solubility in mixed solvent systems as compared with the excess free energy model.

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