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International Journal of Pharmaceutics 167 (1998) 177–182

international journal of pharmaceutics

Comparison of models for describing multiple peaks in solubility profiles

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Received 22 August 1997; received in revised form 14 October 1997; accepted 30 January 1998

Abstract

A model derived from the combined nearly ideal binary solvent/Redlich-Kister equation (CNIBS/R-K) for reproducing the experimental solubility curve in mixed solvent systems showing two solubility maxima is presented. The model's ability to correlate experimental solubility data is compared with those of two previously published empirical models. Computations indicate that the descriptive capability of the CNIBS/R-K model is significantly better than that of both empirical models. The mathematical representation of solute solubility at different temperatures using the CNIBS/R-K model is also considered. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Solubility; Solvent mixtures; Chameleonic effect; Combined nearly ideal binary solvent/Redlich-Kister; Two solubility maxima

1. Introduction

The solubility profile versus the solvent's solubility parameters (δ_{1t}) for select drugs in certain solvent mixtures shows multiple solubility peaks—the chameleonic effect (Sunwoo and Eisen, 1971; Escalera et al., 1994; Bustamante et al., 1994; Romero et al., 1996). The chameleonic effect for complex molecules, including polymers, was reported by Hoy (1970). Such molecules seem to adjust their solubility characteristic in accordance with the solvent polarity. This effect for small drug molecules has been discussed in terms of the virtual solubility parameter (Λ_2) and the chameleonic solubility parameter of the solute (Γ_2) that changed depending upon the character of the environment (Martin et al., 1985). Such systems often contain strong specific interactions, as well as nonspecific van der Waals forces, and the Hildebrand solubility parameters do not satisfactorily explain the solubility of polar solutes in polar or semipolar mixed solvents. Moreover, the

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PII S0378-5173(98)00073-8

Hildebrand solubility equation (Hildebrand and Scott, 1950) or the extended Hildebrand approach (Martin et al., 1980) can not describe the chameleonic effect (Escalera et al., 1994; Romero et al., 1996).

Two empirical models which describe the chameleonic effect based upon Hildebrand (δ_{1t}), acidic (δ_{1a}), basic (δ_{1b}), dispersion (δ_{1d}) and polar (δ_{1p}) solubility parameters are available in the published literature (Escalera et al., 1994; Jouyban-Gharamaleki and Barzegar-Jalali, 1996). In the present paper the capability of the combined nearly ideal binary solvent/Redlich-Kister equation, CNIBS/R-K, (Acree, 1992) for the mathematical representation of the chameleonic effect is shown and the ability of this model to describe the observed solubility behavior is compared with that of the two previous equations.

Escalera et al. (1994) quantitatively described the chameleonic effect in terms of Lewis acid–base interactions using Eq. (1)

$$\ln X_m = C_0 + C_1\delta_{1t} + C_2\delta_{1t}^2 + C_3\delta_{1a} + C_4\delta_{1b} + C_5\delta_{1a}\delta_{1b} \quad (1)$$

where X_m is the mole fraction solubility of the solute in the mixed solvent and C_0–C_5 represent six curve-fit parameters. This model is empirical in nature and the variables used are related to the different solute–solute, solute–solvent and solvent–solvent interactions that may occur in solution. The term C_0 is related to the characteristics of the crystalline form of the solute, δ_{1t} for cavity formation, δ_{1t}^2 for van der Waals interactions, δ_{1a} and δ_{1b} for acidic and basic interactions, respectively, and the $\delta_{1a}\delta_{1b}$ term for self-association of the solvent (Escalera et al., 1994).

The second model to be considered is based upon statistical techniques as follows

$$\ln[-\ln X_m] = \sum J_i \cdot V_i \quad (2)$$

where J_i is the fitted coefficient for each variable and V_i denotes the model variables

$$V_1 = \delta_{1t}/\delta_{1d} \quad (3)$$

$$V_2 = \delta_{1t}/\delta_{1a} \quad (4)$$

$$V_3 = \delta_{1t}/\delta_{1b} \quad (5)$$

$$V_4 = (\delta_{1b}\delta_{1d})/\delta_{1t}^2 \quad (6)$$

$$V_5 = (\delta_{1a}\delta_{1p})/\delta_{1t}^2 \quad (7)$$

$$V_6 = (\delta_{1a}\delta_{1b}\delta_{1d}\delta_{1p})/\delta_{1t}^4 \quad (8)$$

which are defined by Eqs. (3)–(8).

The CNIBS/R-K equation was suggested for reproducing the solubility curves in binary solvent mixtures based upon the thermodynamic mixing proposed by Hwang et al. (1991). The mixing model includes contributions from two-body (A–A, B–B, C–C, A–B, A–C and B–C) and three-body interactions (A–A–A, B–B–B, C–C–C, A–A–B, etc.). It is assumed that some AAA, BBB and CCC clustering may occur along with the mixed collisions, and the apparent interactions are considered to be concentration dependent. By differentiating the Gibbs free energy expression of a ternary solution with respect to the number of moles of solute, the CNIBS/R-K equation was derived.

$$\ln X_m = f_a \ln X_a + f_b \ln X_b + f_a f_b \sum S_i (f_a - f_b)^i \quad (9)$$

In the above equation f_a and f_b refer to volume fractions of the solvents a and b, X_a and X_b denote mole fraction solubility of the solute in the neat solvents a and b, respectively, and S_i represent the model constants which are calculated via least square analysis (Acree et al., 1991). The values of i can be varied from 0–3. The various curve-fit parameters are functions of the interactional energies as described elsewhere (Acree, 1992). For convenience, the CNIBS/R-K equation is written in terms of the natural logarithms of the mole fraction solubilities of the solute, rather than as $RT \ln X_m$. The product RT is incorporated into the curve-fit constant at each temperature as $S_i = K_i/T$. As shown below, K_i is to a first approximation constant over a narrow range of solution temperatures.

The CNIBS/R-K model has been shown to provide very accurate mathematical representations of anthracene, pyrene and carbazole solubilities in a large number of both complexing and noncomplexing solvent mixtures (Acree, 1994, 1995a,b). The equation, however, has not been

tested on systems that exhibit the chameleonic effect, nor has the basic model been used to describe solubilities at different temperatures or solubility data in higher-order multicomponent mixtures. To date, all published applications using Eq. (9) has been limited to binary solvent mixtures and to isothermal solubility data.

2. Theoretical

One can extend the CNIBS/R-K model to solutes dissolved in a ternary solvent mixtures. The final descriptive equation takes the form

$$\ln X_m = f_a \ln X_a + f_b \ln X_b + f_c \ln X_c + f_a f_b \sum W_i (f_a - f_b)^i + f_a f_c \sum W'_i (f_a - f_c)^i + f_b f_c \sum W''_i (f_b - f_c)^i \quad (10)$$

where f_c is the volume fraction of solvent c, X_c denotes the mole fraction solubility of the solute in pure solvent c, and W_i , W'_i and W''_i stand for the model constants. As noted above, the CNIBS/R-K model was derived from a consideration of the Gibbs energy. Eq. (10) represents the thermodynamic extension of the basic mixing model to a quaternary solution (i.e. solute dissolved in a ternary solvent mixture).

In all solvent mixtures which show multiple solubility maxima (Escalera et al., 1994; Bustamante et al., 1994; Romero et al., 1996), the values of f_a and/or f_c is equal to zero, thus one can omit the terms $f_a f_c \Sigma W'_i (f_a - f_c)^i$ from Eq. (10) and obtain:

$$\ln X_m = f_a \ln X_a + f_b \ln X_b + f_c \ln X_c + f_a f_b \sum W_i (f_a - f_b)^i + f_b f_c \sum W''_i (f_b - f_c)^i \quad (11)$$

The value of $\ln X_m - f_a \ln X_a - f_b \ln X_b - f_c \ln X_c$ is regressed against $f_a f_b$, $f_a f_b (f_a - f_b)$, $f_a f_b (f_a - f_b)^2$, $f_b f_c$, $f_b f_c (f_b - f_c)$ and $f_b f_c (f_b - f_c)^2$ to obtain W_i and W''_i values. It is obvious that this model can be generalized for three, four or more binary systems which have common solvents, e.g. water–ethanol, ethanol–ethyl acetate and ethyl acetate–hexane mixtures.

The temperature dependence can be removed from the curve-fit parameters, allowing one to use the CNIBS/R-K equation to correlate the solubility of the solutes in a binary or two binary with a common solvent at different temperatures by means of Eq. (12):

$$\ln X_{m,T} = f_a \ln X_{a,T} + f_b \ln X_{b,T} + f_c \ln X_{c,T} + f_a f_b \sum (K_i/T)(f_a - f_b)^i + f_b f_c \sum (K''_i/T)(f_b - f_c)^i \quad (12)$$

where the 'T' subscripts denote that the mole fraction solubilities pertain to the specified temperature. Readers are cautioned not to give too much significance to the numerical values of the curve-fit coefficients in Eqs. (9)–(12). This is particularly true in the case of systems believed to exhibit complexation. The thermodynamic mixing model used in deriving Eqs. (9)–(12) does not take into account completely the contributions from hydrogen bond formation and molecular association. Model constants should be viewed as curve-fit coefficients that enable one to estimate solute solubilities at binary (ternary and higher-order) solvent compositions and temperatures for which actual experimental data do not exist. A more complete thermodynamic treatment of complexing systems would contain equilibrium constants to describe formation of the various hydrogen-bonded and molecular association complexes.

3. Computational results

The solubility data of four drug molecules in ethyl acetate–ethanol and ethanol–water mixtures which show two solubility maxima are summarized in Table 1. The accuracy and ability of the models to correlate the observed solubility

Table 1
Solubility data of drugs showing two solubility maxima and M.E.% for Eqs. (1) and (2)

No.	Solute	N[a]	M.E.% (Eq. (1))[b]	M.E.% (Eq. (2))	Data reference
1	Sulphamethoxypyridazine	26[c]	18.19	6.18	Escalera et al., 1994
2	Sulphanilamide	21	8.39	4.59	Bustamante et al., 1994
3	Sulphamethazine	24	11.29	5.27	Bustamante et al., 1994
4	Paracetamol	25	16.94	7.91	Romero et al., 1996
Average			13.70	5.99	

[a] N, number of experimental data points in each set.
[b] M.E.% is calculated based upon the predicted values reported in the references.
[c] Solubility data of ethyl acetate–hexane were excluded from calculation (entire 29 data points included in Eq. (14)).

data are assessed by the percent mean error, M.E.%, which is calculated using Eq. (13):

$$\text{M.E.\%} = \sum \left| 100\left[(X_m)^{calc} - (X_m)^{exp}\right](X_m)^{exp} \right| / N \quad (13)$$

where $(X_m)^{calc}$ is the calculated values of mole fraction solubility by the models.

Table 2 gives the model constants as well as M.E.% for Eq. (11) which were obtained by regressional analysis of the experimental solubility data. Comparison of the average M.E.% for Eqs. (1), (2) and (11) indicates that the later expression described the mole fraction solubility of the solute with less error and was better by factors of 3.68 and 1.61 from mathematical representation point-of-view than Eqs. (1) and (2), respectively.

Fitting the experimental data of sulphamethoxypyridazine in water–ethanol, ethanol–ethyl acetate and ethyl acetate–hexane mixtures (Escalera et al., 1994) to the extended form of Eq. (12) resulted in the following mathematical equation:

$$\begin{aligned}\ln X_m = {} & f_a \ln X_a + f_b \ln X_b + f_c \ln X_c + f_d \ln X_d \\ & + 6.096 f_a f_b - 3.912 f_a f_b (f_a - f_b) \\ & + 4.367 f_b f_c - 1.530 f_b f_c (f_b - f_c) \\ & + 3.887 f_c f_d + 4.450 f_c f_d (f_c - f_d) \qquad (14)\end{aligned}$$

$$r^2 = 0.9989, \quad \text{S.E.} = 0.0350, \quad N = 29,$$
$$F = 3627, \quad p < 0.00005, \quad \text{M.E.\%} = 2.18$$

in which f_d and X_d are the volume fraction of the solvent d and the solute mole fraction solubility in neat solvent d, respectively.

The solubility data of sulphamethoxypyridazine (Bustamante and Escalera, 1995) and paracetamol (Bustamante et al., 1995) in ethyl acetate–ethanol and ethanol–water systems obtained between 20–40°C were fitted to Eq. (12) and the corresponding equations were as follows

Paracetamol

$$\begin{aligned}\ln X_{m,T} = {} & f_a \ln X_{a,T} + f_b \ln X_{b,T} + f_c \ln X_{c,T} \\ & + 1223[f_a f_b]/T - 895.1[f_a f_b (f_a - f_b)]/T \\ & - 904.5[f_a f_b (f_a - f_b)^2]/T + 1306[f_b f_c]/T \\ & - 2256[f_b f_c (f_b - f_c)]/T \\ & + 2667[f_b f_c (f_b - f_c)^2]/T \qquad (15)\end{aligned}$$

Table 2
The model constants and M.E.% for Eq. (11)

No.	W_0	W_1	W_2	W_0''	W_1''	W_2''	M.E.%
1	6.108	−3.960	−0.1453	4.296	−1.479	0.4480	2.47
2	5.100	−1.656	0.2294	4.042	−1.266	0.08066	2.56
3	10.28	1.841	5.824	4.600	−1.379	1.556	4.53
4	4.590	−2.788	−0.1668	4.888	−2.152	4.691	5.32
Average							3.72

Table 3
Solubility data in binary mixtures at 20–40°C fitted to Eq. (12) and their statistical parameters

Solute and solvent system	K_0	K_1	K_2^d	M.E.%	N
Sulphamethoxypyridzine in water–ethanol[a]	1998	−1281	—	9.77	35
Sulphamethoxypyridzine in ethanol–ethyl acetate[a]	1340	−348.4	—	5.70	25
Paracetamol in water–ethanol[b]	1429	−971.5	—	7.68	35
Paracetamol in ethanol–ethyl acetate[b]	1528	−1827	2863	12.85	35
Phenacetin in water–dioxane[c]	2318	1563	1594	6.24	65

[a] Experimental data taken from Bustamante and Escalera (1995).
[b] Experimental data taken from Bustamante et al. (1995).
[c] Experimental data taken from Bustamante and Bustamante (1996).
[d] K_2 parameters were not needed for the first three systems.

$r^2 = 0.9710$, S.E. = 0.1808, $N = 65$, $F = 329$, $p < 0.00005$, M.E.% = 12.60

Sulphamethoxypyridazine

$$\ln X_{m,T} = f_a \ln X_{a,T} + f_b \ln X_{b,T} + f_c \ln X_{c,T} + 1868[f_a f_b]/T - 1053[f_a f_b (f_a - f_b)]/T - 1058[f_a f_b (f_a - f_b)^2]/T + 942.1[f_b f_c]/T - 620.6[f_b f_c (f_b - f_c)]/T + 683.9[f_b f_c (f_b - f_c)^2]/T \quad (16)$$

$r^2 = 0.9846$, S.E. = 0.1391, $N = 55$, $F = 522$, $p < 0.00005$, M.E.% = 9.17

The descriptive ability of Eq. (12) is comparable to an equation suggested in a recent paper (Jouyban-Gharamaleki and Barzegar-Jalali, 1996). Unlike the suggested equation, however, the CNIBS/R-K model does have a theoretical basis and can correlate solute solubility in binary solvent mixtures as a function of temperature. Table 3 lists the model constants and M.E.% for the various data sets studied.

The regressional analysis given above indicates that Eq. (12) can be considered as a general model of cosolvency in two binary mixtures showing single or multiple solubility peaks, solubility data sets without maximum, and a binary solvent at ambient or different temperatures. Application of Eq. (12) eliminates the need to obtain solubility parameter values for the solute and the solvents. The chameleonic effect, as well as other phenomena, in solvent mixtures can be described quantitatively.

Acknowledgements

The authors would like to thank Professor P. Bustamante, Departmento de Farmacia y Tenologia Famaceutica, Facultad de Famacia, Universidad de Alcala de Henares, Madrid, Spain for her suggestions.

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