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Solubility correlation of structurally related drugs in binary solvent mixtures

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Abstract

Applicability of the well-established cosolvency equation, i.e. combined nearly ideal binary solvent/Redlich-Kister, CNIBS/R-K, model for calculating the solubility of structurally related drugs in a given cosolvent and water mixtures is presented. The accuracy and predictability of the model are also compared with those of two other models. Computational results show that the CNIBS/R-K model provides very reasonable solubility predictions for the solutes considered, and the CNIBS/R-K model is superior to the other two models.

Keywords: Cosolvency; Structurally related drugs; Solubility; Combined nearly ideal binary solvent/Redlich-Kister equation

1. Introduction

Solubilization of a poorly water-soluble drug is important in the formulation of liquid dosage forms. One of the most effective methods to increase the solubility is by adding a cosolvent. Several equations have been published for mathematical representation of the solubility of solutes in binary solvent mixtures (Martin et al., 1980; Williams and Amidon, 1984; Ochsner et al., 1985; Acree et al., 1991; Acree, 1992; Barzegar-Jalali and Jouyban-Gharamaleki, 1996a,b; Barzegar-Jalali et al., 1996; Barzegar-Jalali and Jouyban-Gharamaleki, 1997). Solubility predictions are valuable for obtaining the optimum concentration of the cosolvent in preparing a liquid dosage form of a drug especially in preformulation studies where a small amount of the drug is available.

The aim of this communication is to show the accuracy and applicability of the theoretically based cosolvency model, i.e. the combined nearly

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ideal binary solvent/Redlich-Kister, CNIBS/R-K, for calculating the solubility of similar drugs in binary solvent mixtures. Also, the limitations and application of the CNIBS/R-K model will be compared with that of two previously published solubility correlational models (Bustamante et al., 1993; Barzegar-Jalali and Jouyban-Gharamaleki, 1996a,b).

2. Theoretical treatment

Bustamante et al. (1993) proposed the modified form of the extended Hildebrand solubility approach, M-EHS, for calculating the solubility of structurally related drugs in a given binary solvent mixture. The M-EHS model is as follows:

$$\log X_M = B_0 + B_1 \log X_C + B_2 \log X_W + B_3\delta_1\delta_2 + B_4\delta_1^2 + B_5\delta_1^3 + B_6\delta_{1b} \quad (1)$$

where X_M denotes the solute mole fraction solubility in mixed solvent. B_0–B_6 are the model constants, X_C and X_W represent the mole fraction solubility of the solute in the neat cosolvent and water, respectively, δ_1 and δ_2 stand for the solubility parameter of the solvent and solute, and δ_{1b} is the basic solubility parameter of the solvent. The values of δ_1 and δ_{1b} for the mixed solvent are calculated by means of $\delta_{mixture} = \Sigma\, \delta_i f_i$, where δ_i denotes the solubility parameter or basic solubility parameter of pure solvent i and f_i is the volume fraction of solvent i in mixture in the absence of the solute (Bustamante et al., 1993). Employing the given model constants and the known values of X_C, X_W and δ_2, one can calculate the solubility of the other members of a group of structurally related drugs in the mixed solvent. The authors have shown the predictability of Eq. (1) for estimating the solubilities of select sulfonamides and *p*-hydroxybenzoic acid in water–dioxane mixtures.

The second model to be considered calculates X_M is follows:

$$\log X_M = A_1 q^{-3fc} + A_2 q^{-fc} + A_3 q^{fc} + A_4 q^{3fc} + A_5 f_C[\log(-\log X_C)] + A_6 f_W[\log(-\log X_W)] + A_7[\log(X_C/X_M)]^{fc} \quad 0 < f_C < 1 \quad (2)$$

where A_1–A_7 are curve-fitting parameters of the model, q is equal to $\log X_C \cdot \log X_W$, f_C and f_W represent the volume fractions of cosolvent and water in the absence of the solute. Eq. (2) predicted the values X_M of the sulfonamides and the benzoates for $0 < f_C < 1$ using the corresponding values of X_C and X_W (Barzegar-Jalali and Jouyban-Gharamaleki, 1996b).

The CNIBS/R-K model (Acree, 1992) is a theoretical model derived for the mathematical representation of solubility data in solvent mixtures. To date, it has been shown that this model provided accurate back-calculations of the observed solubility data in binary solvent mixtures (Acree, 1994, 1995a,b; Barzegar-Jalali and Jouyban-Gharamaleki, 1996a), as well as in two binary solvent systems with a common solvent at ambient and different temperatures (Jouyban-Gharamaleki and Acree, 1998). The CNIBS/R-K model is expressed by Eq. (3)

$$\log X_M = f_C \log X_C + f_W \log X_W + J_0 f_C f_W + J_1 f_C f_W (f_C - f_W) + J_2 f_C f_W (f_C - f_W)^2 + J_3 f_C f_W (f_C - f_W)^3 \quad (3)$$

where J_0–J_3 are the model constants calculated via a new method of least square analysis, i.e. repressing $\log X_M - f_C \log X_C - f_W \log X_W$ versus $f_C f_W$, $f_C f_W (f_C - f_W)$, $f_C f_W (f_C - f_W)^2$ and $f_C f_W (f_C - f_W)^3$ (Jouyban-Gharamaleki and Hanaee, 1997). Eq. (3) is derived from a two- and three-body interactional model and the four Js are thus functions of various interactional energies between molecules present in the fluid solution. Numerical values of J are expected to be nearly constant for structurally related drugs in a given binary solvent mixture. This expectation has not been discussed in our previous papers. In the present communication, we examine this idea using experimental data on the cosolvency of two sets of structurally related drugs, i.e. sulfonamides and benzoates.

Table 1
Sulfonamides in water–dioxane[a] systems used for comparison of Eqs. (1)–(3)

Set no.	Solute	N^b	δ_2	Reference
1	Sulfisomidine	21	12.60	Martin et al., 1985a
2	Sulfanilamide	16	12.03	Reillo et al., 1993
3	Sulfapyridine	17	13.05[c]	Reillo et al., 1995a
4	Sulfamethizole	19	13.59	Reillo et al., 1995b
5	Sulphamethoxypyridazine	18	11.89	Bustamante et al., 1993
6	Sulfadimidine	19	12.58	Bustamante et al., 1993
7	Sulfadizine	17	13.20	Bustamante et al., 1993
8	Sulfamethoxazole	15	11.60	Bustamante et al., 1993

[a] The values of $\delta_{1(\text{Water})} = 23.40$, $\delta_{1(\text{Dioxane})} = 10.01$, $\delta_{1b(\text{Water})} = 32.00$ and $\delta_{1b(\text{Dioxane})} = 6.50$ (cal ml^{-1})$^{1/2}$ were taken from Beerbower et al. (1984). Dioxane is a toxic solvent and is not used in pharmaceutical formulation. However, because of its low polarity and miscibility with water, the different mixtures of dioxane and water provide solvent systems with various polarities which can be used as model system in cosolvency studies.
[b] N is the number of experimental data points in each set.
[c] The value of δ_2 was taken from Regosz et al. (1992) and the other δ_2 values were taken from the corresponding references.

3. Computational results and discussion

Eight experimental data sets of sulfonamides in water–dioxane mixtures as well as eight sets of benzoates in water–propylene glycol mixtures were employed to compare the accuracy and predictability of the models. Tables 1 and (2) show the details of the sets studied. The comparison criterion was percent mean error, P.M.E., calculated using Eq. (4)

$$\text{P.M.E.} = 100/N \,\Sigma\, \left|(X_M^{\text{calc}} - X_M^{\text{exp}})/X_M^{\text{exp}}\right| \qquad (4)$$

where N is the number of data points in each set of structurally related drugs.

For evaluating the accuracy of the models, the two sets of structurally related drugs were fitted to the three models:

For sulfonamides in water–dioxane mixtures:

$$\begin{aligned}\log X_M = {} & 1.74331 + 0.89685 \log X_C \\ & + 0.26958 \log X_W + 0.02290\delta_1\delta_2 \\ & - 0.10263\delta_1^2 + 0.00166\delta_1^3 + 0.79491\delta_{1b} \\ & (\text{P.M.E.} = 33.4,\ N = 142)\end{aligned} \qquad (5)$$

$$\begin{aligned}\log X_M = {} & -0.58584q^{-3fc} + 1.97668q^{-fc} \\ & - 0.28267q^{fc} + 0.00013q^{3fc} \\ & + 1.08209f_C[\log(-\log X_C)] \\ & - 8.69420f_W[\log(-\log X_W)] \\ & + 0.21209[\log(X_C/X_W)]^{fc} \\ & (\text{P.M.E.} = 70.8,\ N = 126)\end{aligned} \qquad (6)$$

$$\begin{aligned}\log X_M = {} & f_C \log X_C + f_W \log X_W + 3.66144 f_C f_W \\ & + 0.55729 f_C f_W (f_C - f_W) \\ & + 2.89845 f_C f_W (f_C - f_W)^2 \\ & + 4.26370 f_C f_W (f_C - f_W)^3 \\ & (\text{P.M.E.} = 23.2,\ N = 142)\end{aligned} \qquad (7)$$

and for benzoates in water–propylene glycol mixtures

$$\begin{aligned}\log X_M = {} & 43.44062 + 0.52007 \log X_C \\ & + 0.53754 \log X_W + 0.00111\delta_1\delta_2 \\ & - 0.30820\delta_1^2 + 0.00547\delta_1^3 + 1.68331\delta_{1b} \\ & (\text{P.M.E.} = 36.7,\ N = 88)\end{aligned} \qquad (8)$$

$$\begin{aligned}\log X_M = {} & 0.71766q^{-3fc} + 1.30804q^{-fc} \\ & - 0.88851q^{fc} + 0.00207q^{3fc} \\ & + 4.98608f_C[\log(-\log X_C)] \\ & - 9.80939f_W[\log(-\log X_W)] \\ & + 0.79362[\log(X_C/X_W)]^{fc} \\ & (\text{P.M.E.} = 11.1,\ N = 72)\end{aligned} \qquad (9)$$

Table 2
Benzoates in water–propylene glycol[a] systems used for comparison of Eqs. (1)–(3)

Set no.	Solute	N[b]	δ_2	Reference
1	Methyl-*p*-hydroxybenzoate	11	13.31[c]	Rubino and Obeng, 1991
2	Ethyl-*p*-hydroxybenzoate	11	12.82	Rubino and Obeng, 1991
3	Propyl-*p*-hydroxybenzoate	11	12.42	Rubino and Obeng, 1991
4	Butyl-*p*-hydroxybenzoate	11	12.09	Rubino and Obeng, 1991
5	Methyl-*p*-aminobenzoate	11	11.42	Rubino and Obeng, 1991
6	Ethyl-*p*-aminobenzoate	11	11.13	Rubino and Obeng, 1991
7	Propyl-*p*-aminobenzoate	11	10.89	Rubino and Obeng, 1991
8	Butyl-*p*-aminobenzoate	11	10.69	Rubino and Obeng, 1991

[a] The values of $\delta_{1(\text{Water})} = 23.40$, $\delta_{1(\text{Propylene glycol})} = 14.77$, $\delta_{1b(\text{Water})} = 32.00$ and $\delta_{1b(\text{Propylene glycol})} = 4.6$ (cal ml^{-1})$^{1/2}$ were taken from Beerbower et al. (1984).
[b] N is the number of experimental data points in each set.
[c] The values of δ_2 were calculated using a group contribution method (Fedors, 1974).

$$\log X_M = f_C \log X_C + f_W \log X_W - 0.39914 f_C f_W + 1.99894 f_C f_W (f_C - f_W) + 0.36137 f_C f_W (f_C - f_W)^2 - 0.82267 f_C f_W (f_C - f_W)^3 \quad (\text{P.M.E.} = 12.0,\ N = 88) \quad (10)$$

The overall mean values of P.M.E. for Eqs. (1)–(3) were 35.1, 41.0 and 17.6, respectively. The results showed that the CNIBS/R-K model was generally superior to the other models from the point of view correlational accuracy.

Eq. (1) was also applied to calculate the solubility of *p*-hydroxybenzoic acid in water–dioxane mixtures (Wu and Martin, 1983) using $\delta_2 = 12$ of Bustamante et al. (1993). It should be noted that different values of δ_2 for any given solute may be reported in the literature, e.g. for *p*-hydroxybenzoic acid, one may take $\delta_2 = 15.30$ (Martin et al., 1985b), $\delta_2 = 10.10$ (Wu and Martin, 1983) or $\delta_2 = 12.00$ (Bustamante et al., 1993). Since the calculated X_M values were influenced by the values of δ_2, the corresponding P.M.E. for the above mentioned δ_2 values were found to be 30915, 58 and 291, respectively. Furthermore, the value of $\delta_{1b(\text{dioxane})}$ was different in various references, for example, 7.6 (Bustamante et al., 1993; Bustamante and Bustamante, 1996) and 6.5 (Beerbower et al., 1984). Taking $\delta_{1b(\text{dioxane})} = 6.5$, the P.M.E. values were 16830, 86.5 and 45 for the mentioned δ_2 values, respectively. The dependence of the calculated solubility by M-EHS model on the δ_1, δ_{1b} and δ_2 values was a disadvantage for the model. The P.M.E. for *p*-hydroxybenzoic acid in water–dioxane mixture employing Eq. (7) was 61 bearing in mind that this solute was not strictly a closely-related drug to sulfonamides.

In closing, we note that correlational expressions such as Eqs. (1)–(3) do play an important role in drug design, particularly in the selection of a solubilizing cosolvent. Very small quantities of the drug are usually available in the initial development stages, and researchers must propose an appropriate liquid formulation using a minimum number of experimental determinations. Of the three equations considered in the present study, the CNIBS/R-K model provided the more accurate set of back-calculated values for structurally related drugs in binary solvent mixtures. Jouyban-Gharamaleki and Acree (1998) recently showed that the model best described solubility data in two binary solvents containing a common solvent at ambient or different temperatures. Moreover, the model predicted the experimental solubility of paracetamol in dioxane–water at 25°C (Romero et al., 1996) using curve-fit coefficients obtained by regressing experimental data of phenacetin in dioxane–water mixtures at 25–40°C. Eqs. (1) and (2), on the other hand, can not correlate solubilities as a function temperature. Based upon the comparisons presented here, and in our earlier papers (Acree, 1994, 1995a,b; Barzegar-Jalali and Jouyban-Gharamaleki, 1996a; Jouyban-Gharamaleki and Acree, 1998), we conclude that the

CNIBS/R-K model is a useful cosolvency model for correlating/predicting solubilities for pharmaceutical applications.

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