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International Journal of Pharmaceutics 260 (2003) 283–291

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Solubility of drugs in aqueous solutions
Part 2: Binary nonideal mixed solvent

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Received 27 February 2003; received in revised form 28 April 2003; accepted 28 April 2003

Abstract

As in a previous paper [Int. J. Pharm. 258 (2003) 193–201], the Kirkwood–Buff theory of solutions was employed to calculate the solubility of a solid in mixed solvents. Whereas in the former paper the binary solvent was assumed ideal, in the present one it was considered nonideal. A rigorous expression for the activity coefficient of a solute at infinite dilution in a mixed solvent [Int. J. Pharm. 258 (2003) 193–201] was used to obtain an equation for the solubility of a poorly soluble solid in a nonideal mixed solvent in terms of the solubilities of the solute in the individual solvents, the molar volumes of those solvents, and the activity coefficients of the components of the mixed solvent.

The Flory–Huggins and Wilson equations for the activity coefficients of the components of the mixed solvent were employed to correlate 32 experimental data sets regarding the solubility of drugs in aqueous mixed solvents. The results were compared with the models available in literature. It was found that the suggested equation can be used for an accurate and reliable correlation of the solubilities of drugs in aqueous mixed binary solvents. It provided slightly better results than the best literature models but has also the advantage of a theoretical basis.

Keywords: Solubility of drugs; Nonideal binary aqueous solvents; Fluctuation theory

1. Introduction

The solubility of drugs in aqueous mixed solvents often exhibits a maximum as a function of the mixed solvent composition. The higher solubility of a solid solute in a mixed solvent than in either of the pure solvents, was frequently observed (Acree, 1984; Prausnitz et al., 1986) and is not an exception as it seemed several decades ago.

Gordon and Scott (1952) observed an enhanced solubility of phenanthrene in the mixture of cyclohexane and methylene iodine, while Smith et al. (1959) noted such an enhancement in the solubility of iodine in the C_7F_{16}/CCl_4 mixture. In their book, Hildebrand and Scott (1962) pointed out that such enhancements can be predicted in the framework of the regular solution theory (the Scatchard–Hildebrand solubility parameter model), when the solubility parameter of the solid solute lies between those of the two solvents.

However, when the solute or either of the pure solvents is polar, the regular solution theory could no longer provide quantitative agreement regarding the solubility of a solid solute in a mixed solvent (Acree, 1984; Walas, 1985).

Many models, including various modifications of the Scatchard–Hildebrand solubility parameter model, were suggested for the correlation and prediction of

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doi:10.1016/S0378-5173(03)00273-4

the solubility of solids in mixed solvents. Details regarding these methods and their comparison with experiment have been summarized in books and recent publications (Acree, 1984; Prausnitz et al., 1986; Barzegar-Jalali and Jouyban-Gharamaleki, 1996; Jouyban-Gharamaleki and Acree, 1998; Jouyban-Gharamaleki et al., 1999).

In a previous paper (Ruckenstein and Shulgin, 2003), the Kirkwood–Buff theory of solutions (Kirkwood and Buff, 1951) was employed to obtain an expression for the solubility of a solid (particularly a drug) in binary mixed (mainly aqueous) solvents. A rigorous expression for the composition derivative of the activity coefficient of a solute in a ternary solution (Ruckenstein and Shulgin, 2001) was used to derive an equation for the activity coefficient of the solute at infinite dilution in an ideal binary mixed solvent and further for the solubility of a poorly soluble solid. By considering that the excess volume of the mixed solvent depends on composition, the above equation was modified empirically by including one adjustable parameter. The modified equation was compared with the other three-parameter equations available in the literature to conclude that it provided a better agreement.

In the present paper, an equation for the activity coefficient of a solute at infinite dilution in a nonideal mixed solvent is used to derive expressions for its solubility in a nonideal binary mixed solvent.

The paper is organized as follows: first, an equation for the activity coefficient of a solute at infinite dilution in a binary nonideal mixed solvent (Ruckenstein and Shulgin, 2003) is employed to derive an expression for its solubility in terms of the properties of the mixed solvent. Second, various expressions for the activity coefficients of the cosolvents are inserted into the above equation. Finally, the obtained equations are used to correlate the drug solubilities in binary aqueous mixed solvents and the results are compared with experimental data and other models available in the literature.

2. Theory and formulas

The following rigorous expression for the activity coefficient ($\gamma_2^{t,\infty}$) of a solid solute (the designation of the components in this paper is as follows: the solid solute is component 2, the water is component 3 and the other cosolvent component 1) in a binary mixed solvent at infinite dilution can be written as (Ruckenstein and Shulgin, 2003):

$$\ln \gamma_2^{t,\infty} = -\int \frac{B}{V}\left[1+x_3^{b,1-3}\left(\frac{\partial \ln \gamma_3^{b,1-3}}{\partial x_3^{b,1-3}}\right)_{P,T}\right]\mathrm{d}x_3^{b,1-3} + \frac{1}{2}\int \frac{(x_1^{b,1-3}-x_3^{b,1-3})}{x_1^{b,1-3}} \times \left(\frac{\partial \ln \gamma_3^{b,1-3}}{\partial x_3^{b,1-3}}\right)_{P,T}\mathrm{d}x_3^{b,1-3} + A \quad (1)$$

where P and T are the pressure and temperature, $x_i^{b,1-3}$ and $\gamma_i^{b,1-3}$ ($i = 1, 3$) are the mole fraction and the activity coefficient of component i in the binary solvent 1–3, V is the molar volume of the binary 1–3 solvent, $A(P, T)$ is a composition-independent constant of integration, and B is a function of the Kirkwood–Buff integrals (Ruckenstein and Shulgin, 2003). If B is considered independent of the composition of the binary mixed solvent 1–3, Eq. (1) can be rewritten in the form:

$$\ln \gamma_2^{t,\infty} = -BI_1 + \frac{I_2}{2} + A \quad (2)$$

where

$$I_1 = \int \frac{[1+x_3^{b,1-3}((\partial \ln \gamma_3^{b,1-3})/(\partial x_3^{b,1-3}))_{P,T}]}{V}\mathrm{d}x_3^{b,1-3} \quad (3)$$

and

$$I_2 = \int \frac{(x_1^{b,1-3}-x_3^{b,1-3})}{x_1^{b,1-3}}\left(\frac{\partial \ln \gamma_3^{b,1-3}}{\partial x_3^{b,1-3}}\right)_{P,T}\mathrm{d}x_3^{b,1-3} \quad (4)$$

On the other hand, the solubility of a poorly soluble solute in a mixed solvent is given by the expression (Prausnitz et al., 1986):

$$\frac{f_2^{\mathrm{S}}}{f_2^{\mathrm{L}}(T, P)} = x_2^t \gamma_2^{t,\infty} \quad (5)$$

where $f_2^{\mathrm{L}}(T, P)$ is a hypothetical fugacity of component 2 as a (subcooled) liquid at a given pressure (P) and temperature (T), f_2^{S} is the fugacity of the pure solid component 2 and x_2^t is the solubility of the solid solute. The combination of Eqs. (2) and (5) provides an expression for the solubility of a poorly soluble solid in a mixed binary solvent:

$$\ln x_2^t = BI_1 - \frac{I_2}{2} + \bar{A}(P,T) \tag{6}$$

where $\bar{A}(P,T) = -A(P,T) + \ln\left\lfloor f_2^{\mathrm{S}}/f_2^{\mathrm{L}}(T,P)\right\rfloor$.

The integrals I_1 and I_2 can be calculated if the composition dependencies of the activity coefficients and of the molar volume V of the binary mixed solvent 1–3 are known. The solubilities of the solute in the individual solvents are also needed for the calculation of the composition-independent constants $\bar{A}(P,T)$ and $B(P,T)$.

Because it contains the derivative of the activity coefficient and this gives rise to numerical errors, Eq. (6) is not entirely suitable for numerical calculations. Therefore, Eq. (6) was first modified by replacing the derivative of the activity coefficient with a less error-prone quantity.

The integral I_2 can be transformed by using the Gibbs–Duhem Eq. (7) for a binary system at constant temperature and pressure:

$$x_1^{b,1-3}\mathrm{d}\ln\gamma_1^{b,1-3} = -x_3^{b,1-3}\mathrm{d}\ln\gamma_3^{b,1-3} \tag{7}$$

Consequently,

$$\frac{(x_1^{b,1-3} - x_3^{b,1-3})}{x_1^{b,1-3}}\left(\frac{\partial\ln\gamma_3^{b,1-3}}{\partial x_3^{b,1-3}}\right)_{P,T} = \left(\frac{\partial\ln\gamma_1^{b,1-3}}{\partial x_3^{b,1-3}}\right)_{P,T} + \left(\frac{\partial\ln\gamma_3^{b,1-3}}{\partial x_3^{b,1-3}}\right)_{P,T} \tag{8}$$

and the integral I_2 becomes:

$$I_2 = \ln\gamma_1^{b,1-3} + \ln\gamma_3^{b,1-3} \tag{9}$$

The integral I_1 will be modified by assuming that V can be still considered as ideal:

$$V = x_1^{b,1-3}V_1^0 + x_3^{b,1-3}V_3^0 \tag{10}$$

where V_i^0 is the molar volume of the pure component $i (i = 1, 3)$.

Then,

$$I_1 = \frac{\ln(x_1^{b,1-3}V_1^0 + x_3^{b,1-3}V_3^0)}{V_3^0 - V_1^0} + \frac{\ln\gamma_3^{b,1-3}}{V_3^0 - V_1^0} - \frac{V_1^0}{V_3^0 - V_1^0} \times \int \frac{1}{x_1^{b,1-3}V_1^0 + x_3^{b,1-3}V_3^0}\mathrm{d}\ln\gamma_3^{b,1-3} \tag{11}$$

Integrating by parts, Eq. (11) becomes:

$$I_1 = \frac{\ln(x_1^{b,1-3}V_1^0 + x_3^{b,1-3}V_3^0)}{V_3^0 - V_1^0} + \frac{\ln\gamma_3^{b,1-3}}{V_3^0 - V_1^0} - \frac{V_1^0}{V_3^0 - V_1^0}\,\frac{\ln\gamma_3^{b,1-3}}{x_1^{b,1-3}V_1^0 + x_3^{b,1-3}V_3^0} - V_1^0\int\frac{\ln\gamma_3^{b,1-3}}{(x_1^{b,1-3}V_1^0 + x_3^{b,1-3}V_3^0)^2}\mathrm{d}x_3^{b,1-3} \tag{12}$$

Eqs. (9) and (12) for the integrals I_1 and I_2 no longer contain the derivative of the activity coefficient. The simplifying assumption that the molar volume can be treated as ideal (Eq. (10)) does not introduce major errors (see Appendix A).

Eq. (6) combined with Eqs. (9) and (12) allows one to calculate the solubility of a poorly soluble solid in a mixed solvent in terms of the solubilities in the individual solvents (which provide the values of $\bar{A}(P,T)$ and $B(P,T)$, their molar volumes and the activity coefficients of the components of the mixed solvent.

There are numerous expressions for the activity coefficients, which can be employed to calculate the solubility of a poorly soluble solid in a mixed binary solvent. In this paper two expressions for the activity coefficients will be used.

(1) The Flory–Huggins equation (Walas, 1985):

$$\ln\gamma_1^{b,1-3} = \ln\left[\frac{\varphi_1}{x_1^{b,1-3}}\right] + \left(1 - \frac{1}{r}\right)\varphi_3 + \chi\varphi_3^2 \tag{13}$$

and

$$\ln\gamma_3^{b,1-3} = \ln\left[\frac{\varphi_3}{x_3^{b,1-3}}\right] + (r-1)\varphi_1 + \chi\varphi_1^2 \tag{14}$$

(2) The Wilson equation (Wilson, 1964):

$$\ln\gamma_1^{b,1-3} = -\ln(x_1^{b,1-3} + x_3^{b,1-3}L_{13}) + x_3^{b,1-3} \times \left[\frac{L_{13}}{x_1^{b,1-3} + x_3^{b,1-3}L_{13}} - \frac{L_{31}}{x_3^{b,1-3} + x_1^{b,1-3}L_{31}}\right] \tag{15}$$

and

$$\ln \gamma_3^{b,1-3} = -\ln(x_3^{b,1-3} + x_1^{b,1-3}L_{31}) - x_1^{b,1-3} \times \left[\frac{L_{13}}{x_1^{b,1-3}+x_3^{b,1-3}L_{13}} - \frac{L_{31}}{x_3^{b,1-3}+x_1^{b,1-3}L_{31}}\right] \tag{16}$$

In Eqs. (13)–(16), $\varphi_i = (V_i^0 x_i^{b,1-3})/(V_1^0 x_1^{b,1-3} + V_3^0 x_3^{b,1-3})$ is the volume fraction of component $i (i = 1, 3)$ in the mixed solvent 1–3, $r = (V_3^0)/(V_1^0)$, χ is the Flory–Huggins interaction parameter and L_{13} and L_{31} are the Wilson parameters. All these parameters are assumed to be composition independent.

Eq. (6) combined with Eqs. (9) and (12) leads to a slightly cumbersome expression. The expression for the integral in Eq. (12) when the Wilson Eq. (16) is used for the activity coefficient $\gamma_3^{b,1-3}$ is given in Appendix B.

3. Calculations and results

For the sake of comparison, the same 32 sets of experimental data regarding the solubility of drugs in aqueous mixed solvents correlated in a previous paper (Ruckenstein and Shulgin, 2003) are used here.

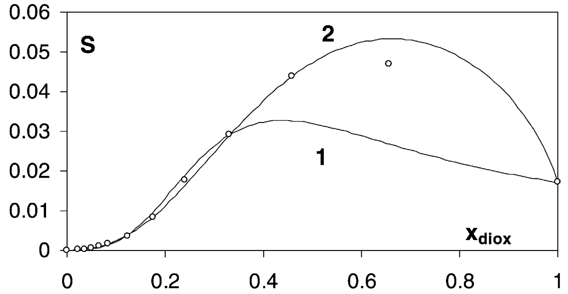

Fig. 1. Comparison between experimental (○) (Bustamante and Bustamante, 1996) and calculated (solid lines) solubilities of phenacetin (S is the mole fraction of phenacetin) in the mixed solvent water/dioxane (x_{diox} is the mole fraction of dioxane) at room temperature. The solubility was calculated using Eq. (6) combined with Eqs. (9) and (12): (1) the activity coefficients expressed via the Flory–Huggins equation; (2) the activity coefficients expressed via the Wilson equation.

Each data set is treated using Eq. (6) combined with Eqs. (9) and (12), with the activity coefficients expressed via the Flory–Huggins or Wilson equations.

The Flory–Huggins interaction parameter (χ) and the Wilson parameters (L_{13} and L_{31}) are considered here adjustable parameters and are calculated from the experimental data regarding the solubility of drugs in aqueous mixed solvents.

The results of the calculations are listed in Tables 1 and 2, and some details are provided for illustration in Figs. 1 and 2.

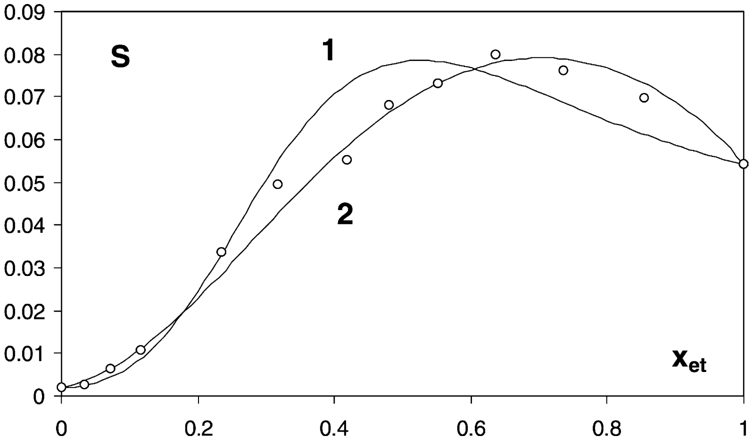

Fig. 2. Comparison between experimental (○) (Romero et al., 1996) and calculated (solid lines) solubilities of paracetamol (S is the mole fraction of paracetamol) in the mixed solvent water/ethanol (x_{et} is the mole fraction of ethanol) at room temperature. The solubility was calculated using Eq. (6) combined with Eqs. (9) and (12): (1) the activity coefficients expressed via the Flory–Huggins equation, (2) the activity coefficients expressed via the Wilson equation.

Table 1
The experimental data[a] regarding the solubilities (at room temperature) of drugs in aqueous mixed solvents and comparison with the predictions

System number	Cosolvent	Solute	Reference	Deviation from experimental data[b]	
				Flory–Huggins activity coefficients	Wilson activity coefficients
1	*N*,*N*-Dimethylformamide	Sulfadiazine	Martin et al. (1982)	30.5	13.7
2	*N*,*N*-Dimethylformamide	Theophyllene	Gonzalez et al. (1994)	13.4	7.8
3	*N*,*N*-Dimethylformamide	Caffeine	Herrador and Gonzalez (1997)	11.1	6.5
4	Dioxane	Caffeine	Adjei et al. (1980)	10.4	9.6
5	Dioxane	*p*-Hydroxybenzoic acid	Wu and Martin (1983)	15.3	3.5
6	Dioxane	Paracetamol	Romero et al. (1996)	16.5	8.6
7	Dioxane	Phenacetin	Bustamante and Bustamante (1996)	16.2	3.6
8	Dioxane	Sulfadiazine	Bustamante et al. (1993)	12.4	3.5
9	Dioxane	Sulfadimidine	Bustamante et al. (1993)	12.7	3.0
10	Dioxane	Sulfamethizole	Reillo et al. (1995a)	34.3	18.9
11	Dioxane	Sulfamethoxazole	Bustamante et al. (1993)	9.5	2.9
12	Dioxane	Sulfapyridine	Reillo et al. (1995b)	25.9	7.1
13	Dioxane	Sulfamethoxypyridazine	Bustamante et al. (1993)	10.6	2.6
14	Dioxane	Sulfanilamide	Reillo et al. (1993)	19.9	4.0
15	Dioxane	Sulfisomidine	Martin et al. (1985)	23.2	10.6
16	Dioxane	Theobromine	Martin et al. (1981)	3.2	8.4
17	Dioxane	Theophyllene	Martin et al. (1980)	15.5	6.3
18	Ethanol	Paracetamol	Romero et al. (1996)	11.4	6.2
19	Ethanol	Sulfamethazine	Bustamante et al. (1994)	12.3	5.8
20	Ethanol	Sulfanilamide	Bustamante et al. (1994)	14.6	3.2
21	Ethanol	Oxolinic acid	Jouyban et al. (2002)	14.6	5.2
22	Ethylene glycol	Naphthalene	Khossravi and Connors (1992)	13.9	9.8
23	Ethylene glycol	Theophyllene	Khossravi and Connors (1992)	4.8	3.4
24	Methanol	Theophyllene	Khossravi and Connors (1992)	5.2	8.9
25	Propylene glycol	Butyl *p*-aminobenzoate	Rubino and Obeng (1992)	10.2	9.0
26	Propylene glycol	Butyl *p*-hydroxybenzoate	Rubino and Obeng (1992)	17.1	24.0
27	Propylene glycol	Ethyl *p*-aminobenzoate	Rubino and Obeng (1992)	7.2	8.5
28	Propylene glycol	Ethyl *p*-hydroxybenzoate	Rubino and Obeng (1992)	17.9	2.3
29	Propylene glycol	Methyl *p*-aminobenzoate	Rubino and Obeng (1992)	4.3	6.6
30	Propylene glycol	Methyl *p*-hydroxybenzoate	Rubino and Obeng (1992)	7.2	12.4
31	Propylene glycol	Propyl *p*-aminobenzoate	Rubino and Obeng (1992)	10.3	9.7
32	Propylene glycol	Propyl *p*-hydroxybenzoate	Rubino and Obeng (1992)	5.2	16.1

[a] The same experimental data regarding the solubility of drugs in aqueous mixed solvents were used in a previous paper (Ruckenstein and Shulgin, 2003).

[b] Deviation from experimental data calculated as MPD (%) (the mean percentage deviation) defined as $(100\sum_{i=1}^{N_j}|(x_i^{\mathrm{exp}}-x_i^{\mathrm{calc}})/(x_i^{\mathrm{exp}})|)/(N_j)$, where x_i^{exp} and x_i^{calc} are experimental and calculated (using Eq. (6) combined with Eqs. (9) and (12)) solubilities (mole fractions), N_j is the number of experimental points in the data set j.

Table 2
Comparison between the results of calculation of the drug solubilities using the present method (Eq. (6)) combined with Eqs. (9) and (12) and various literature models

Number of parameters	MPD (%)[a]				
	Eq. (6) combined with Eqs. (9) and (12)		Literature models		
	Flory–Huggins activity coefficients	Wilson activity coefficients	MRS[b]	GSM[c]	CNIBS/R-K[d]
3	14.4	–	15.9	15.9	22.3
4	–	7.7	18.7	9.1	10.7

[a] MPD (%) is the mean percentage deviation defined as $(100\sum_{j=1}^{M}\sum_{i=1}^{N_j}|(x_i^{\mathrm{exp}}-x_i^{\mathrm{calc}})/x_i^{\mathrm{exp}}|)/(\sum_{j=1}^{M}N_j)$ where x_i^{exp} and x_i^{calc} are experimental and calculated solubilities (mole fractions), N_j is the number of experimental points in the data set (see Table 1) and M is the number of experimental data sets (here 32).

[b] MRS is the mixture response surface method (Ochsner et al., 1985). The value of MPD was taken from Table 2 of the Jouyban-Gharamaleki et al. (1999) paper.

[c] GSM is the general single model (Barzegar-Jalali and Jouyban-Gharamaleki, 1996). The value of MPD was taken from Table 2 of the Jouyban-Gharamaleki et al., 1999) paper.

[d] CNIBS/R-K is the combined nearly ideal binary solvent/Redlich–Kister equations (Acree et al., 1991). The value of MPD was taken from Table 2 of the Jouyban-Gharamaleki et al. (1999) paper.

When the activity coefficients are expressed via the Flory–Huggins equation, one adjustable parameter is introduced. When, however, the Wilson expressions are employed, two adjustable parameters are needed. The solubilities of the solute in the individual solvents are also necessary to calculate the composition-independent constants $\bar{A}(P,T)$ and $B(P, T)$. Therefore, our method can be considered a three-parameter method, when based on the Flory–Huggins equations, and a four-parameter one, when based on the Wilson equations (see Table 2).

4. Discussion

One can see from Tables 1 and 2 that our methods for the correlation of the solubility of drugs in aqueous mixed solvents provide accurate and reliable results. A comparison with the models available in the literature (Table 2) demonstrates that our Eq. (6) provides slightly better results than the best literature models with the same number of parameters.

Only one- and two-parameter activity coefficient expressions were employed in this paper. However,

Table 3
The Wilson parameters (L_{13} and L_{31}) determined from the solubilities of sulfadiazine, sulfadimidine, sulfamethizole, sulfamethoxazole, sulfapyridine, sulfamethoxypyridazine, sulfanilamide and sulfisomidine in water (1)/dioxane (3) mixtures

Solute	The Wilson parameters		Deviation (%) from experimental data, when the average values of the Wilson parameters are used
	L_{13}	L_{31}	
Sulfadiazine	0.11	0.10	19.4
Sulfadimidine	0.27	0.12	35.4
Sulfamethoxazole	0.19	0.12	31.1
Sulfamethoxypyridazine	0.19	0.10	22.0
Sulfamethizole	0.20	0.01	57.3
Sulfapyridine	0.31	0.04	20.7
Sulfanilamide	0.17	0.04	25.4
Sulfisomidine	0.12	0.02	48.6
Average	0.195	0.069	32.4

expressions for the activity coefficients with any number of parameters can be used.

It should be emphasized that the parameters involved in the activity coefficients are adjustable parameters which cannot be obtained easily from the properties of the mixed solvents, for instance the vapor–liquid equilibria. However, for the solubilities of structurally related caffeine and theophyllene in water/*N*,*N*-dimethylformamide, the values of the Wilson parameters are close to each other (1.96 and 0.12 for caffeine and 1.81 and 0.10 for theophyllene). If the Wilson parameters for theophyllene are used to predict the solubility of caffeine in water/*N*,*N*-dimethylformamide, a deviation of 8.8% from experimental data is obtained. The deviation was, however, 6.5% when the Wilson parameters were determined by fitting the experimental solubility data (Table 1). The values of the Wilson parameters determined from the solubilities of the structurally more different sulfonamides (sulfadiazine, sulfadimidine, sulfamethizole, sulfamethoxazole, sulfapyridine, sulfamethoxypyridazine, sulfanilamide and sulfisomidine) in water/dioxane mixtures are listed in Table 3. Even for such cases, the average values of the Wilson parameters can be used for a first estimation of the solubilities of the above group of drugs (Table 3).

Eq. (6) is a rigorous equation for the solubility of poorly soluble solids in a mixed solvent. The only approximation involved is that the solubilities of the solid in either of the pure solvents and in the mixed solvent are very small (infinite dilution approximation). It is not applicable when at least one of these solubilities has an appreciable value. Indeed (see Table 1), when the solubility of a solute in a nonaqueous solvent exceeds about 5 mol%, such as the solubilities of drugs in propylene glycol (Rubino and Obeng, 1992), the deviation from the experimental data is about 11.5% for the Wilson equation, whereas the average deviation for all 32 mixtures of Table 1 is only 7.7%.

5. Conclusion

In this paper, the fluctuation theory of solutions was applied to the solubility of drugs in aqueous mixed solvents. A rigorous expression for the activity coefficient of a solute at infinite dilution in a real mixed solvent was used to derive an equation for the solubility of poorly soluble solutes, such as drugs, in mixed solvents. The latter solubility is expressed in terms of the solubilities in the individual solvents, their molar volumes, and the activity coefficients of the constituents of the binary solvent. For illustration purposes, the one-parameter (Flory–Huggins) and the two-parameter (Wilson) expressions were employed for the activity coefficients of the constituents of the solvent.

Thirty-two experimental data sets were selected and used to test the equation suggested. The results were compared with the models available in literature. It was found that the suggested equation provides an accurate and reliable correlation of the solubility of drugs in aqueous mixed solvents with slightly better results than the best of the literature models.

Appendix A

The aim of this appendix is to evaluate the sensitivity of the integral in Eq. (12) to the ideality assumption of the molar volume. For this purpose, the composition dependence of $(\ln \gamma_3^{b,1-3})/(V^2)$ for the mixture water/1,4-dioxane at 25 °C was calculated for two cases: (1) $V^{\mathrm{E}} = 0$ (V^{E} being the excess molar volume); and (2) $V^{\mathrm{E}} \neq 0$ (the mixture water/1,4-dioxane was selected because it is the most frequently used mixed solvent considered in the present paper). The activity coefficient of water in water/1,4-dioxane mixture was calculated using the Wilson equation with the parameters provided by the Gmehling VLE compilation (Gmehling and Onken, 1977). The molar volume of the mixed solvent was calculated using the expression:

$$V = x_1^{b,1-3} V_1^0 + x_3^{b,1-3} V_3^0 \tag{A.1}$$

or

$$V = x_1^{b,1-3} V_1^0 + x_3^{b,1-3} V_3^0 + V^{\mathrm{E}} \tag{A.2}$$

The composition dependence of the excess molar volume of the mixture water/1,4-dioxane at 25 °C was found in a paper by Aminabhavi and Gopalakrishna (1995).

The composition dependence of the integrant $(\ln \gamma_3^{b,1-3})/(V^2)$ is presented in Fig. 3, which demonstrates that the numerical values of the integrand are

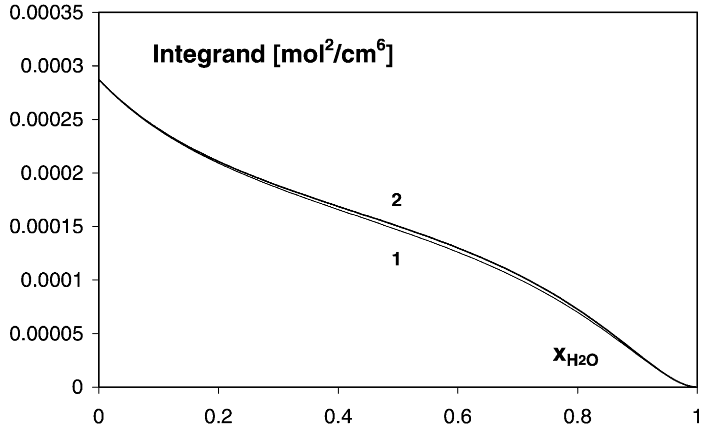

Fig. 3. The composition dependence of the integrand $(\ln \gamma_3^{b,1-3})/(V^2)$ of the integral in Eq. (12). (1) The molar volume of the mixed solvent was calculated using Eq. (A.1), (2) the molar volume of the mixed solvent was calculated using Eq. (A.2).

almost the same for the molar volumes expressed via both Eq. (A.1) or Eq. (A.2).

Appendix B

The aim of this appendix is to derive an analytical expression for the integral:

$$I = \int \frac{\ln \gamma_3^{b,1-3}}{(x_1^{b,1-3} V_1^0 + x_3^{b,1-3} V_3^0)^2} \mathrm{d}x_3^{b,1-3} \tag{B.1}$$

in Eq. (12), when the activity coefficient is expressed via the Wilson Eq. (16).

The integration leads to:

$$\begin{aligned} I = {} & \frac{L_{13}^2(\ln V - \ln(x_1^{b,1-3} + x_3^{b,1-3} L_{13}))}{(V_3^0 - L_{13} V_1^0)^2} + \frac{L_{31}^2(-\ln V + \ln(x_3^{b,1-3} + x_1^{b,1-3} L_{31}))}{(V_1^0 - L_{31} V_3^0)^2} \\ & + \frac{V_3^0(L_{13} L_{31} V_3^0 - L_{13} V_1^0 + L_{13} L_{31} V_1^0 - L_{31} V_3^0)}{(V_3^0 - L_{13} V_1^0)(L_{31} V_3^0 - V_1^0)(V_3^0 - V_1^0) V} + \frac{(-1 + L_{31})\ln((1 - L_{31}) V)}{(V_3^0 L_{31} - V_1^0)(V_3^0 - V_1^0)} \\ & - \frac{\ln[(x_3^{b,1-3} + x_1^{b,1-3} L_{31})(-x_3^{b,1-3} + 3L_{31} x_3^{b,1-3} - 2 + 2L_{31} - 3L_{31}^2 x_3^{b,1-3} + L_{31}^2 + L_{31}^3 x_3^{b,1-3})]}{(-1 + L_{31})(L_{31} V_3^0 - V_1^0)(L_{31} V - V)} \end{aligned} \tag{B.2}$$

where $V = x_1^{b,1-3} V_1^0 + x_3^{b,1-3} V_3^0$.

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