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International Journal of Pharmaceutics 278 (2004) 221–229

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Solubility of drugs in aqueous solutions
Part 4. Drug solubility by the dilute approximation

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Received 20 October 2003; received in revised form 13 February 2004; accepted 2 March 2004

Abstract

As in our previous publications in this journal [Int. J. Pharm. 258 (2003a) 193; Int. J. Pharm. 260 (2003b) 283; Int. J. Pharm. 267 (2003c) 121], this paper is concerned with the solubility of poorly soluble drugs in aqueous mixed solvents. In the previous publications, the solubilities of drugs were assumed to be low enough for the so-called infinite dilution approximation to be applicable. In contrast, in the present paper, the solubilities are considered to be finite and the dilute solution approximation is employed. As before, the fluctuation theory of solutions is used to express the derivatives of the activity coefficient of a solute in a ternary solution (dilute solute concentrations in a binary solvent) with respect to the concentrations of the solvent and cosolvent. The expressions obtained are combined with a theoretical equation for the activity coefficient of the solute. As a result, the activity coefficient of the solute was expressed through the activity coefficients of the solute at infinite dilution, solute mole fraction, some properties of the binary solvent (composition, molar volume and activity coefficients of the components) and parameters reflecting the nonidealities of binary species. The expression thus obtained was used to derive an equation for the solubility of poorly soluble drugs in aqueous binary solvents which was applied in two different ways. First, the nonideality parameters were considered as adjustable parameters, determined from experimental solubility data. Second, the obtained equation was used to correct the solubilities of drugs calculated via the infinite dilution approximation. It was shown that both procedures provide accurate correlations for the drug solubility.

Keywords: Solubility; Drugs; Dilute approximation

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1. Introduction

In our previous papers regarding the solubility of poorly soluble drugs in aqueous mixed solvents (Ruckenstein and Shulgin, 2003a–c), the fluctuation theory of solutions (Kirkwood and Buff, 1951) was used for their correlation and prediction. Such information is useful because poor aqueous solubility can often affect the drug efficiency.

Whereas the first two publications of this series (Ruckenstein and Shulgin, 2003a,b) were concerned with binary mixed solvents, the third one (Ruckenstein and Shulgin, 2003c) was devoted to the solubility of drugs in multicomponent solvents.

In the above papers, the solubility of drugs in mixed solvents was assumed to be low enough for the infinite dilution approximation to be applicable. Let us examine this approximation in more detail. The solubility of solid substances in pure and mixed solvents

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doi:10.1016/j.ijpharm.2004.03.007

can be described by the classical solid–liquid equilibrium equations (Acree, 1984; Prausnitz et al., 1986). For the solubilities of a solid solute (component 2) in water (component 3), cosolvent (component 1), and their mixture (mixed solvents 1–3), one can write the following equations

$$\frac{f_2^{\mathrm{S}}}{f_2^{\mathrm{L}}(T,P)} = y_2^{b_1}\gamma_2^{b_1}(T,P,\{y\}) \tag{1}$$

$$\frac{f_2^{\mathrm{S}}}{f_2^{\mathrm{L}}(T,P)} = y_2^{b_3}\gamma_2^{b_3}(T,P,\{y\}) \tag{2}$$

$$\frac{f_2^{\mathrm{S}}}{f_2^{\mathrm{L}}(T,P)} = y_2^{t}\gamma_2^{t}(T,P,\{y\}) \tag{3}$$

where $y_2^{b_1}$, $y_2^{b_3}$, and y_2^t are the solubilities (mole fractions) of the solid component 2 in the cosolvent, water, and their mixture, respectively; $\gamma_2^{b_1}$, $\gamma_2^{b_3}$, and γ_2^t are the activity coefficients of the solid solute in its saturated solutions in the cosolvent, water, and mixed solvent, respectively; $f_2^{\mathrm{L}}(T,P)$ is the hypothetical fugacity of a solid 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 $\{y\}$ indicates that the activity coefficients of the solute depend on composition. If the solubilities of the pure and mixed solvents in the solid phase are negligible, then the left hand sides of Eqs. (1)–(3) depend only on the properties of the solute.

The infinite dilution approximation implies that the activity coefficients in Eqs. (1)–(3) can be replaced by their values at infinite dilution of the solute ($\gamma_2^{b_1,\infty}$, $\gamma_2^{b_3,\infty}$, and $\gamma_2^{t,\infty}$). However, the solubilities of drugs in aqueous mixed solvents are not always very low. While the solubilities of various drugs in water (only poorly soluble drugs are considered in the present paper) do not exceed 1–2 mol%, the solubilities of the same drugs in the popular cosolvents ethanol and 1,4-dioxane can reach 5–20 mol%, and the solubilities in the water/1,4-dioxane and water/ethanol mixtures are often appreciable and can reach 8–30 mol%. Therefore, the effect of the infinite dilution approximation on the accuracy of the predictions of the solubilities of poorly soluble drugs deserves to be examined.

In the present paper, dilute binary and ternary solutions (drug + water, drug + cosolvent, and drug + water + cosolvent) will be considered, hence the infinite dilution approximation will be replaced by the dilute solution approximation. The range in which the infinite dilution approximation is valid and the range in which the dilute approximation can be used were discussed by Kojima et al. (1997). They pointed out that the above composition ranges depend on the nature of the solute and solvent and on the types of intermolecular interactions in the mixtures involved. For example, mixtures with self-association of one of the components have a narrower range in which the dilute approximation is valid.

As for infinite dilution, the main difficulty in predicting the solid solute solubility in a mixed solvent for a dilute solution is provided by the calculation of the activity coefficient of the solute in a ternary mixture. To obtain an expression for the activity coefficient of a low concentration solute in a ternary mixture, the fluctuation theory of solution will be combined with the assumption that the system is dilute with respect to the solute.

The paper is organized as follows: first, an equation for the activity coefficient of a low concentration solute in individual and binary solvents will be written. This equation will be combined with the fluctuation theory of solutions and with Eqs. (1)–(3) to derive an expression for the drug solubility. Further, the expression obtained will be compared with experimental data and with the infinite dilution approximation (Ruckenstein and Shulgin, 2003a,b).

2. Theory

2.1. *The activity coefficient of a solute in its dilute range in binary solvents*

For a binary dilute mixture, Debenedetti and Kumar (1986) suggested the following series expansion for the fugacity coefficient of a solute (ϕ_2^b)

$$\ln\phi_2^b = \ln\phi_2^{b,\infty} - k_{22}x_2^b \tag{4}$$

where $\phi_2^{b,\infty}$ is the fugacity coefficient at infinite dilution, x_2^b is the mole fraction of the solute, and

$$k_{22} = -\left(\frac{\partial \ln\gamma_2^b}{\partial x_2^b}\right)_{P,T,x_2^b\to 0} = -\left(\frac{\partial \ln\phi_2^b}{\partial x_2^b}\right)_{P,T,x_2^b\to 0} \tag{5}$$

γ_2^b being the activity coefficient of the solute in the binary mixture.

The above expression was extended to ternary mixtures, containing a solute and a cosolvent in low concentrations by Chialvo (1993), Jonah and Cochran (1994), and Munoz et al. (1995).

In this paper we consider the case in which only the solute concentration is small (Ruckenstein and Shulgin, 2002). Let us consider those compositions (mole fraction) of the ternary mixture (x_1^t, x_2^t, x_3^t) which are located on the line connecting the points ($x_1^t = 0$, $x_2^t = 1$, $x_3^t = 0$) and ($x_1^t = x_1^0$, $x_2^t = 0$, $x_3^t = x_3^0$) in the Gibbs triangle (Fig. 1). This line connects the pure component 2 (a solute) and the binary mixtures 1–3 (cosolvent + solvent) with a mole fraction of component 1 equal to x_1^0. Physically speaking, this line represents the locus of the compositions of ternary mixtures formed by adding a solute (2) to a binary mixture of a solvent (3) and a cosolvent (1).

On the above line, the following relation holds

$$\left(\frac{x_1^t}{x_3^t}\right) = \left(\frac{x_1^0}{x_3^0}\right) = \alpha \tag{6}$$

Because $x_1^t + x_2^t + x_3^t = 1$, one can write that

$$x_1^t = \alpha \frac{1 - x_2^t}{1 + \alpha} \tag{7}$$

and

$$x_3^t = \frac{1 - x_2^t}{1 + \alpha} \tag{8}$$

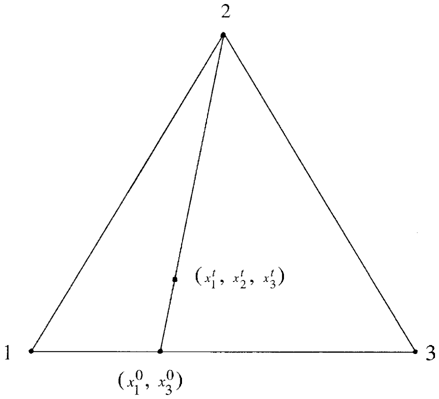

Fig. 1. The change of composition in a ternary mixture solute + binary solvent, when a solute (2) is added to a binary solvents (1–3) of composition (mole fractions) (x_1^0, x_3^0).

For the fugacity coefficient of a solute in a ternary dilute solution, one can write, at constant temperature and pressure, near the composition $x_1^t = x_1^0$, $x_2^t = 0$, $x_3^t = x_3^0$, the following expression

$$\ln \phi_2^t = \ln \phi_2^t(x_1^0, 0, x_3^0) + x_2^t \left(\frac{\partial \ln \phi_2^t}{\partial x_2^t}\right)_{P,T,\alpha,(x_1^0,0,x_3^0)} \tag{9}$$

where ϕ_2^t is the fugacity coefficient of the solute in a ternary mixture and $\phi_2^t(x_1^0, 0, x_3^0) = \phi_2^{t,\infty}$ is its value at infinite dilution of the solute.

If, at a given pressure and temperature, the mole fractions of components 1 and 3 are taken as independent variables, one can rewrite Eq. (9) under the form

$$\begin{aligned}\ln \phi_2^t = {} & \ln \phi_2^t(x_1^0, 0, x_3^0) \\ & + x_2^t \left[\left(\frac{\partial \ln \phi_2^t}{\partial x_1^t}\right)_{P,T,x_3^t,(x_1^0,0,x_3^0)} \left(\frac{\partial x_1^t}{\partial x_2^t}\right)_{\alpha} \right. \\ & \left. + \left(\frac{\partial \ln \phi_2^t}{\partial x_3^t}\right)_{P,T,x_1^t,(x_1^0,0,x_3^0)} \left(\frac{\partial x_3^t}{\partial x_2^t}\right)_{\alpha}\right]\end{aligned} \tag{10}$$

which, taking into account Eqs. (7) and (8), becomes

$$\begin{aligned}\ln \phi_2^t = {} & \ln \phi_2^t(x_1^0, 0, x_3^0) \\ & - \frac{x_2^t}{1+\alpha}\left[\alpha \left(\frac{\partial \ln \phi_2^t}{\partial x_1^t}\right)_{P,T,x_3^t,(x_1^0,0,x_3^0)} \right. \\ & \left. + \left(\frac{\partial \ln \phi_2^t}{\partial x_3^t}\right)_{P,T,x_1^t,(x_1^0,0,x_3^0)}\right]\end{aligned} \tag{11}$$

or equivalently,

$$\begin{aligned}\ln \phi_2^t = {} & \ln \phi_2^t(x_1^0, 0, x_3^0) \\ & - x_2^t \left[x_1^0 \left(\frac{\partial \ln \phi_2^t}{\partial x_1^t}\right)_{P,T,x_3^t,(x_1^0,0,x_3^0)} \right. \\ & \left. + x_3^0 \left(\frac{\partial \ln \phi_2^t}{\partial x_3^t}\right)_{P,T,x_1^t,(x_1^0,0,x_3^0)}\right]\end{aligned} \tag{12}$$

A similar equation can be written for the activity coefficient of a low concentration solute in a ternary mixture

$$\begin{aligned}\ln\gamma_2^t = \ln\gamma_2^t(x_1^0, 0, x_3^0) &- x_2^t\left[x_1^0\left(\frac{\partial\ln\gamma_2^t}{\partial x_1^t}\right)_{P,T,x_3^t,(x_1^0,0,x_3^0)}\right.\\ &\left. + x_3^0\left(\frac{\partial\ln\gamma_2^t}{\partial x_3^t}\right)_{P,T,x_1^t,(x_1^0,0,x_3^0)}\right]\end{aligned} \quad (13)$$

Eq. (13) will be used for the drug solubility when its saturated solution in a binary solvent can be considered dilute. First, expressions for the two partial derivatives in Eq. (13) will be derived on the basis of the fluctuation theory of solutions (Kirkwood and Buff, 1951).

2.2. *Expressions for the derivatives* $(\partial\ln\gamma_2^t/\partial x_1^t)_{P,T,x_3^t}$ *and* $(\partial\ln\gamma_2^t/\partial x_3^t)_{P,T,x_1^t}$

It was shown previously, that, for the derivatives of the activity coefficient (γ_2^t) one can write the following relations (Ruckenstein and Shulgin, 2001)

$$\left(\frac{\partial\ln\gamma_2^t}{\partial x_1^t}\right)_{T,P,x_3^t} = \frac{-c_2c_3(G_{12}+G_{33}-G_{13}-G_{23}) + c_1c_2\Delta_{12}+c_2c_3\Delta_{23}+c_1c_2c_3\Delta_{123}}{x_2^t(c_1+c_2+c_3+c_1c_2\Delta_{12}+c_1c_3\Delta_{13} + c_2c_3\Delta_{23}+c_1c_2c_3\Delta_{123})} \quad (14)$$

and

$$\left(\frac{\partial\ln\gamma_2^t}{\partial x_3^t}\right)_{T,P,x_1^t} = \frac{-c_1c_2(G_{11}+G_{23}-G_{12}-G_{13}) + c_1c_2\Delta_{12}+c_2c_3\Delta_{23}+c_1c_2c_3\Delta_{123}}{x_2^t(c_1+c_2+c_3+c_1c_2\Delta_{12}+c_1c_3\Delta_{13} + c_2c_3\Delta_{23}+c_1c_2c_3\Delta_{123})} \quad (15)$$

where c_k is the bulk molecular concentration of component k and $G_{\alpha\beta}$ is the Kirkwood–Buff integral given by

$$G_{\alpha\beta} = \int_0^\infty (g_{\alpha\beta}-1)4\pi r^2\,\mathrm{d}r \quad (16)$$

In the above expressions, $g_{\alpha\beta}$ is the radial distribution function between species α and β, r is the distance between the centers of molecules α and β, and $\Delta_{\alpha\beta}$ and Δ_{123} are defined as follows

$$\Delta_{\alpha\beta} = G_{\alpha\alpha}+G_{\beta\beta}-2G_{\alpha\beta}, \qquad \alpha\neq\beta \quad (17)$$

and

$$\begin{aligned}\Delta_{123} = {} & G_{11}G_{22}+G_{11}G_{33}+G_{22}G_{33}+2G_{12}G_{13}\\ & +2G_{12}G_{23}+2G_{13}G_{23}-G_{12}^2-G_{13}^2-G_{23}^2\\ & -2G_{11}G_{23}-2G_{22}G_{13}-2G_{33}G_{12}\end{aligned} \quad (18)$$

It was shown that the expressions in the brackets in the numerators of Eqs. (14) and (15) and Δ_{123} can be expressed in terms of $\Delta_{\alpha\beta}$ as follows (Ruckenstein and Shulgin, 2001)

$$G_{12}+G_{33}-G_{13}-G_{23} = \frac{\Delta_{13}+\Delta_{23}-\Delta_{12}}{2} \quad (19)$$

$$G_{11}+G_{23}-G_{12}-G_{13} = \frac{\Delta_{12}+\Delta_{13}-\Delta_{23}}{2} \quad (20)$$

and

$$\Delta_{123} = -\frac{(\Delta_{12})^2+(\Delta_{13})^2+(\Delta_{23})^2-2\Delta_{12}\Delta_{13} -2\Delta_{12}\Delta_{23}-2\Delta_{13}\Delta_{23}}{4} \quad (21)$$

The insertion of Eqs. (19)–(21) into Eqs. (14) and (15) provides the following expressions for the derivatives $(\partial\ln\gamma_2^t/\partial x_1^t)_{P,T,x_3^t}$ and $(\partial\ln\gamma_2^t/\partial x_3^t)_{P,T,x_1^t}$ in terms of $\Delta_{\alpha\beta}$ and the concentrations of the solute-free mixed solvent

$$\begin{aligned}\lim_{x_2\to 0}\left(\frac{\partial\ln\gamma_2^t}{\partial x_1^t}\right)_{T,P,x_3^t} = {} & \frac{(c_1^0+c_3^0)\{(c_1^0+0.5c_3^0)\Delta_{12}+0.5c_3^0\Delta_{23} -0.5c_3^0\Delta_{13}\}_{x_2^t=0}}{c_1^0+c_3^0+c_1^0c_3^0\Delta_{13}}\\ & -\frac{c_1^0c_3^0(c_1^0+c_3^0)((\Delta_{12})^2+(\Delta_{13})^2+(\Delta_{23})^2 -2\Delta_{12}\Delta_{13}-2\Delta_{12}\Delta_{23}-2\Delta_{13}\Delta_{23})_{x_2^t=0}}{4(c_1^0+c_3^0+c_1^0c_3^0\Delta_{13})}\end{aligned} \quad (22)$$

and

$$\lim_{x_2\to 0}\left(\frac{\partial \ln \gamma_2^t}{\partial x_3^t}\right)_{T,P,x_1^t} = \frac{(c_1^0+c_3^0)\{0.5c_1^0\Delta_{12}+(0.5c_1^0+c_3^0)\Delta_{23} - 0.5c_1^0\Delta_{13}\}_{x_2^t=0}}{c_1^0+c_3^0+c_1^0c_3^0\Delta_{13}} - \frac{c_1^0c_3^0(c_1^0+c_3^0)((\Delta_{12})^2+(\Delta_{13})^2+(\Delta_{23})^2 - 2\Delta_{12}\Delta_{13}-2\Delta_{12}\Delta_{23}-2\Delta_{13}\Delta_{23})_{x_2^t=0}}{4(c_1^0+c_3^0+c_1^0c_3^0\Delta_{13})} \qquad (23)$$

where c_1^0 and c_3^0 are the bulk molecular concentrations of components 1 and 3 in the solute-free binary 1–3 solvent.

The derivatives $(\partial \ln \gamma_2^t/\partial x_1^t)_{P,T,x_3^t}$ and $(\partial \ln \gamma_2^t/\partial x_3^t)_{P,T,x_1^t}$ are expressed in Eqs. (22) and (23) in terms of $\Delta_{\alpha\beta}$ and the concentrations of the solute-free mixed solvent. It is worth noting that $\Delta_{\alpha\beta}$ is a measure of nonideality (Ben-Naim, 1977) of the binary mixture $\alpha - \beta$, because for an ideal mixture $\Delta_{\alpha\beta} = 0$. Furthermore, being measures of nonideality, the parameters $\Delta_{\alpha\beta}$ have a clear physical meaning and this fact is useful in the thermodynamic analysis of multicomponent mixtures.

2.3. Equations for the solubility of a solid in a binary solvent

Insertion of Eqs. (22)–(23) into Eq. (12) leads to

$$\ln \gamma_2^t = \ln \gamma_2^t(x_1^0, 0, x_3^0) - x_2^t\frac{(x_1^0\Delta_{12}+x_3^0\Delta_{23}-x_1^0x_3^0\Delta_{13})_{x_2^t=0}}{V+x_1^0x_3^0\Delta_{13}} + \frac{x_1^0x_3^0x_2^t((\Delta_{12})^2+(\Delta_{13})^2+(\Delta_{23})^2 - 2\Delta_{12}\Delta_{13}-2\Delta_{12}\Delta_{23}-2\Delta_{13}\Delta_{23})_{x_2^t=0}}{4V(V+x_1^0x_3^0\Delta_{13})} \qquad (24)$$

where V is the molar volume of the solute-free binary solvent.

An expression for the activity coefficient of a solute at infinite dilution in a ternary mixture $\gamma_2^t(x_1^0, 0, x_3^0)$ was obtained elsewhere (Ruckenstein and Shulgin, 2003b) and has the form

$$\ln \gamma_2^{t,\infty} = \ln \gamma_2^t(x_1^0, 0, x_3^0) = -(\Delta_{12}-\Delta_{23})_{x_2^t=0}\left(\frac{I_1}{2}\right) + \left(\frac{I_2}{2}\right) + A \qquad (25)$$

where A is a composition independent constant

$$I_1 = \int \frac{1 + x_3^0(\partial \ln \gamma_3^b/\partial x_3^0)_{P,T}}{V}\,\mathrm{d}x_3^0 \qquad (26)$$

and

$$I_2 = \ln \gamma_1^b + \ln \gamma_3^b \qquad (27)$$

In Eqs. (26) and (27), γ_1^b and γ_3^b are the activity coefficients of the cosolvent and solvent in a solute-free binary solvent.

The combination of Eqs. (24)–(27) with the equation for the solid–liquid equilibrium provides a relation for the solubility of a solute forming a dilute solution in a ternary mixture.

$$\ln y_2^t = (\Delta_{12}-\Delta_{23})_{x_2^t=0}\left(\frac{I_1}{2}\right) - \left(\frac{I_2}{2}\right) + y_2^t\frac{(x_1^0\Delta_{12}+x_3^0\Delta_{23}-x_1^0x_3^0\Delta_{13})_{x_2^t=0}}{V+x_1^0x_3^0\Delta_{13}} + \bar{A} - y_2^t\frac{x_1^0x_3^0((\Delta_{12})^2+(\Delta_{13})^2+(\Delta_{23})^2 - 2\Delta_{12}\Delta_{13}-2\Delta_{12}\Delta_{23} - 2\Delta_{13}\Delta_{23})_{x_2^t=0}}{4V(V+x_1^0x_3^0\Delta_{13})} \qquad (28)$$

where $\bar{A}(P, T) = -A(P, T) + \ln[f_2^{\mathrm{S}}/f_2^{\mathrm{L}}(T, P)]$ is a composition-independent constant.

Eq. (28) allows one to calculate the solubility of a solute in a binary mixed solvent if the composition dependence of the activity coefficients, the molar volume V, the nonideality parameters Δ_{12}, Δ_{23} and the constant $\bar{A}$ are known. The nonideality parameters $\Delta_{\alpha\beta}$ for a binary mixture $\alpha - \beta$ can be obtained from the composition dependence of the activity coefficients in the above mixture using the expression (Kirkwood and Buff, 1951)

$$\Delta_{\alpha\beta} = -\frac{V(\partial \ln \gamma_\beta^b/\partial x_\beta^0)_{P,T}}{x_\alpha^0 - x_\alpha^0x_\beta^0(\partial \ln \gamma_\beta^b/\partial x_\beta^0)_{P,T}} \qquad (29)$$

Table 1
The solubility of drugs in binary solvents calculated with Eq. (28)

Drug	Mixed solvent	Deviation from experimental data[a]	
		Eq. (28) combined with Wilson's equation	Infinite dilution approximation combined with Wilson's equation[b]
Caffeine	Water/*N*,*N*-dimethylformamide	2.8	6.5
Caffeine	Water/1,4-dioxane	5.3	9.6
Sulfamethizole	Water/1,4-dioxane	16.8	18.9
Methyl *p*-hydroxybenzoate	Water/propylene glycol	12.8	12.4
Methyl *p*-aminobenzoate	Water/propylene glycol	6.5	6.6
Ethyl *p*-aminobenzoate	Water/propylene glycol	8.1	8.5
Propyl *p*-hydroxybenzoate	Water/propylene glycol	13.5	16.1
Butyl *p*-hydroxybenzoate	Water/propylene glycol	22.4	24.0

[a] Deviation from experimental data calculated as MPD (%) (the mean percentage deviation) defined as $100 \times \sum_{i=1}^{N} |(x_i^{\mathrm{exp}} - x_i^{\mathrm{calc}})/x_i^{\mathrm{exp}}|/N$, where x_i^{exp} and x_i^{calc} are the experimental and calculated solubilities, and N is the number of experimental points.

[b] These results were taken from our previous publication (Ruckenstein and Shulgin, 2003b).

Eq. (29) can be used to calculate the parameter $\Delta_{\alpha\beta}$ from vapor–liquid equilibrium data for mixed binary solvents. Unfortunately, for most solute + individual solvent pairs such data are not available.

3. Application of Eq. (28) to the solubility of drugs in a binary solvent

Being a transcendent equation, Eq. (28) cannot provide an explicit expression for the solubility of a drug (y_2^t), but has to be solved numerically for every set of parameters.

In order to check Eq. (28), the solubilities of caffeine in the water/*N*,*N*-dimethylformamide (Herrador and Gonzalez, 1997) and water/1,4-dioxane mixtures (Adjei et al., 1980), as well as the solubilities of sulfamethizole in the mixture water/1,4-dioxane (Reillo et al., 1995) and of five solutes in water/propylene glycol (Rubino and Obeng, 1991) were employed.

First, Δ_{12}, Δ_{23}, and $\bar{A}$ were considered adjustable parameters which were determined by fitting Eq. (28) to the experimental solubility data. The activity coefficients of the components in binary solvents were expressed via the Wilson equation (Wilson, 1964) (of course, any other expressions for the activity coefficients can be used)

$$\ln \gamma_1^b = -\ln(x_1^0 + x_3^0 L_{13}) + x_3^0 \left(\frac{L_{13}}{x_1^0 + x_3^0 L_{13}} - \frac{L_{31}}{x_3^0 + x_1^0 L_{31}} \right) \tag{30}$$

and

$$\ln \gamma_3^b = -\ln(x_3^0 + x_1^0 L_{31}) - x_1^0 \left(\frac{L_{13}}{x_1^0 + x_3^0 L_{13}} - \frac{L_{31}}{x_3^0 + x_1^0 L_{31}} \right) \tag{31}$$

where L_{13} and L_{31} are the Wilson parameters.

The parameters L_{13} and L_{31} were also determined from the experimental solubility data. Therefore, Eq. (28) can be considered as a five parameters equation. The results of the calculations as well as a comparison with those obtained under the infinite dilution approximation are listed in Table 1.

Table 1 shows that Eq. (28) provides slightly better results that the correlation based on the infinite dilution approximation. However, it is not clear whether this improvement was caused by the use of the more realistic dilute approximation, or of a larger number of adjustable parameters (five in the present case instead of four in the equation based on the infinite dilution approximation).

The new equation can be consider as a correction to the infinite dilution approximation. Indeed, combining Eq. (24) with Eq. (3) and with the following equation involving the infinite dilution approximation

$$\frac{f_2^{\mathrm{S}}}{f_2^{\mathrm{L}}(T, P)} = z_2^t \gamma_2^t (x_1^0, 0, x_3^0) \tag{32}$$

Table 2
Comparison between the drug solubilities in aqueous binary solvents calculated using Eq. (34) and the infinite dilution approximation (Ruckenstein and Shulgin, 2003a)

System number	Cosolvent	Solute	MPD (%)[a]	
			Eq. (34)[b]	The infinite dilution approximation (Ruckenstein and Shulgin, 2003a)[c]
1	*N*,*N*-dimethylformamide	Sulfadiazine	11.8	11.4
2	*N*,*N*-dimethylformamide	Theophyllene	14.1	14.1
3	*N*,*N*-dimethylformamide	Caffeine	11.9	11.9
4	Dioxane	Caffeine	10.2	12.8
5	Dioxane	*p*-Hydroxybenzoic acid	21.7	28.1
6	Dioxane	Paracetamol	7.3	15.4
7	Dioxane	Phenacetin	6.2	6.9
8	Dioxane	Sulfadiazine	5.0	7.6
9	Dioxane	Sulfadimidine	7.4	5.4
10	Dioxane	Sulfamethizole	12.0	12.7
11	Dioxane	Sulfamethoxazole	9.1	10.3
12	Dioxane	Sulfapyridine	7.6	9.0
13	Dioxane	Sulfamethoxypyridazine	6.6	7.8
14	Dioxane	Sulfanilamide	9.1	14.6
15	Dioxane	Sulfisomidine	12.0	13.0
16	Dioxane	Theobromine	23.6	23.7
17	Dioxane	Theophyllene	13.7	16.6
18	Ethanol	Paracetamol	7.3	15.4
19	Ethanol	Sulfamethazine	7.5	7.6
20	Ethanol	Sulfanilamide	22.2	22.5
21	Ethanol	Oxolinic acid	9.5	9.5
22	Ethylene glycol	Naphthalene	9.1	9.3
23	Ethylene glycol	Theophyllene	4.6	4.6
24	Methanol	Theophyllene	11.1	11.1
25	Propylene glycol	Butyl *p*-aminobenzoate	19.6	19.7
26	Propylene glycol	Butyl *p*-hydroxybenzoate	36.3	36.4
27	Propylene glycol	Ethyl *p*-aminobenzoate	10.7	10.7
28	Propylene glycol	Ethyl *p*-hydroxybenzoate	4.0	4.6
29	Propylene glycol	Methyl *p*-aminobenzoate	9.3	9.3
30	Propylene glycol	Methyl *p*-hydroxybenzoate	17.8	18.4
31	Propylene glycol	Propyl *p*-aminobenzoate	13.9	14.2
32	Propylene glycol	Propyl *p*-hydroxybenzoate	26.8	27.1
Average[d]			11.8	13.3

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

[b] The parameter Δ_{13} was calculated from vapor–liquid equilibrium data for binary solvents using Eq. (29). The activity coefficients of the components in the binary solvents were expressed via the Wilson equation (Wilson, 1964) and the Wilson parameters L_{13} and L_{31} were taken from Gmehling's vapor–liquid equilibrium data compilation (Gmehling et al., 1977–2003).

[c] The values of MPD were calculated in a previous paper (Ruckenstein and Shulgin, 2003a).

[d] The average was calculated as $100\times\sum_{j=1}^{M}\sum_{i=1}^{N_j}|(x_i^{\mathrm{exp}}-x_i^{\mathrm{calc}})/x_i^{\mathrm{exp}}|/\sum_{j=1}^{M}N_j$ where x_i^{exp} and x_i^{calc} are the experimental and calculated solubilities (mole fractions), N_j is the number of experimental points in the data set *j*, and *M* is the number of experimental data sets (here 32).

one obtains

$$\ln y_2^t = \ln z_2^t + y_2^t \frac{\{x_1^0\Delta_{12} + x_3^0\Delta_{23} - x_1^0 x_3^0 \Delta_{13}\}_{x_2^t=0}}{V + x_1^0 x_3^0 \Delta_{13}} - y_2^t \frac{\begin{array}{c} x_1^0 x_3^0((\Delta_{12})^2 + (\Delta_{13})^2 + (\Delta_{23})^2 \\ - 2\Delta_{12}\Delta_{13} - 2\Delta_{12}\Delta_{23} \\ - 2\Delta_{13}\Delta_{23})_{x_2^t=0} \end{array}}{4V(V + x_1^0 x_3^0 \Delta_{13})} \qquad (33)$$

where z_2^t is the solubility of the solute under the infinite dilution approximation.

Because the infinite dilution approximation provides in many cases accurate results (Ruckenstein and Shulgin, 2003a), the difference between y_2^t and z_2^t is expected to be small. Consequently, one can expand $\ln(y_2^t/z_2^t)$ in a Taylor series to obtain for the solute solubility in the dilute approximation, the expression

$$y_2^t = \frac{z_2^t}{1 - z_2^t \Phi} \qquad (34)$$

where

$$\Phi = \frac{(x_1^0\Delta_{12} + x_3^0\Delta_{23} - x_1^0 x_3^0 \Delta_{13})_{x_2^t=0}}{V + x_1^0 x_3^0 \Delta_{13}} - \frac{\begin{array}{c} x_1^0 x_3^0((\Delta_{12})^2 + (\Delta_{13})^2 + (\Delta_{23})^2 - 2\Delta_{12}\Delta_{13} \\ - 2\Delta_{12}\Delta_{23} - 2\Delta_{13}\Delta_{23})_{x_2^t=0} \end{array}}{4V(V + x_1^0 x_3^0 \Delta_{13})}$$

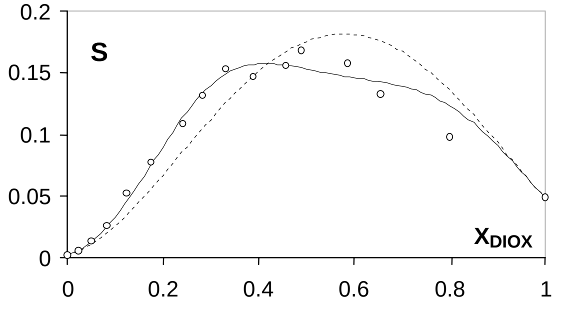

Fig. 2. Comparison between experimental (○) (Romero et al., 1996) and predicted (the solid line is based on Eq. (34), while the dashed line is based on the infinite dilution approximation (Ruckenstein and Shulgin, 2003a)) solubilities of the paracetomol (S is the mole fraction of paracetomol) in the binary solvent water/1,4-dioxane (x_{DIOX} is the mole fraction of dioxane) at room temperature.

Eq. (34) allows one to correct the solubility of a solute under the infinite dilution approximation if the properties of the binary solvent and the nonideality parameters Δ_{12} and Δ_{23} are known. Any of the methods available can be used to calculate the solubility of a solute under the infinite dilution approximation. For illustration purposes we selected a method suggested by us previously, and use Eq. (34) for the same 32 experimental sets, which were utilized there (Ruckenstein and Shulgin, 2003a). The results of the calculations are given in Table 2. Fig. 2 provides details for a particular case.

4. Discussion and conclusion

In contrast to previous papers (Ruckenstein and Shulgin, 2003a–d), the solubility of the drug in a binary solvent is considered to be finite, and the infinite dilution approximation is replaced by a more realistic one, the dilute solution approximation. An expression for the activity coefficient of a solute at low concentrations in a binary solvent was derived by combining the fluctuation theory of solutions (Kirkwood and Buff, 1951) with the dilute approximation. This procedure allowed one to relate the activity coefficient of a solute forming a dilute solution in a binary solvent to the solvent properties and some parameters characterizing the nonidealities of the various pairs of the ternary mixture.

Eq. (28) thus obtained can be used to represent the solubility of poorly soluble drugs in aqueous mixed solvents if information about the properties of the binary solvent (composition, phase equilibria and molar volume), the nonideality parameters and the constant $\bar{A}$ is available. These parameters can be considered as adjustable, and determined by fitting the experimental solubilities in the binary solvent. We applied such a procedure to the solubilities of caffeine in water/*N*,*N*-dimethylformamide (Herrador and Gonzalez, 1997) and water/1,4-dioxane (Adjei et al., 1980), of sulfamethizole in water/1,4-dioxane (Reillo et al., 1995) as well as of five solutes in water/propylene glycol (Rubino and Obeng, 1991). It was shown that Eq. (28) provides accurate correlations of the experimental data.

In essence, the developed computational scheme is a first order perturbation to the infinite dilution approximation. Therefore, the results regarding the solubility of poorly soluble drugs in aqueous mixed solvents obtained from the equations based on the infinite dilution approximation, can be slightly improved by the suggested method. The procedure was applied to 32 experimental data sets to show that the infinite dilution approximation is improved by the dilute solution approximation.

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