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# Solubility of drugs in aqueous solutions Part 1. Ideal mixed solvent approximation

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**Abstract**

The present paper deals with the application of the fluctuation theory of solutions to the solubility of poorly soluble drugs in aqueous mixed solvents. The fluctuation theory of ternary solutions is first used to derive an expression for the activity coefficient of a solute at infinite dilution in an ideal mixed solvent and, further, to obtain an equation for the solubility of a poorly soluble solid in an ideal mixed solvent. Finally, this equation is adapted to the solubility of poorly soluble drugs in aqueous mixed solvents by treating the molar volume of the mixed solvent as nonideal and including one adjustable parameter in its expression. The obtained expression was applied to 32 experimental data sets and the results were compared with the three parameter equations available in the literature.


*Keywords:* Drug solubility; Fluctuation theory; Aqueous mixed solvents

## 1. Introduction

It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs (Yalkowsky and Roseman, 1981). This fact is important for pharmaceutics because a poor aqueous solubility can often affect the drug efficiency. For this reason, the prediction of the solubility of drugs in aqueous mixed solvents or even a reliable correlation of the available experimental data is of interest to the pharmaceutical science and industry.

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

$$\frac{f_2^{\mathrm{S}}}{f_2^{\mathrm{L}}(T,P)} = x_2^{\mathrm{b}_1}\gamma_2^{\mathrm{b}_1}(T,P,\{x\}) \tag{1}$$

$$\frac{f_2^{\mathrm{S}}}{f_2^{\mathrm{L}}(T,P)} = x_2^{\mathrm{b}_3}\gamma_2^{\mathrm{b}_3}(T,P,\{x\}) \tag{2}$$

$$\frac{f_2^{\mathrm{S}}}{f_2^{\mathrm{L}}(T,P)} = x_2^{\mathrm{t}}\gamma_2^{\mathrm{t}}(T,P,\{x\}) \tag{3}$$

In Eqs. (1)–(3), $x_2^{\mathrm{b}_1}$, $x_2^{\mathrm{b}_3}$ and $x_2^{\mathrm{t}}$ are the solubilities (mole fractions) of the solid component 2 in the cosolvent, water, and their mixture, respectively, $\gamma_2^{\mathrm{b}_1}$, $\gamma_2^{\mathrm{b}_3}$ and $\gamma_2^{\mathrm{t}}$ are the activity coefficients of the solid in its saturated solutions in the cosolvent, water, and

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mixed solvent, $f_2^{\mathrm{L}}(T, P)$ is the hypothetical fugacity of a solid as a (subcooled) liquid at a given pressure ($P$) and temperature ($T$), $f_2^{\mathrm{S}}$ is the fugacity of a pure solid component 2, and $\{x\}$ designates that the activity coefficients of the solid 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. Eqs. (1)–(3) show that the solubilities of solid substances in pure and mixed solvents can be calculated if its activity coefficients in the binary and ternary saturated solutions (1–2, 2–3, and 1–2–3) are known. The activity coefficients of a solute in a pure and mixed solvent can be calculated by group-contribution methods, such as UNIFAC or ASOG (Acree, 1984; Prausnitz et al., 1986). The application of UNIFAC to the solubility of naphthalene in nonaqueous mixed solvents provided satisfactory results when compared to experimental data (Acree, 1984). However, the accuracy of the UNIFAC was poor for the solubility of solids in aqueous solutions (Fan and Jafvert, 1997).

The activity coefficients of a solute in a mixed solvent could be also calculated by employing various well-known phase equilibria models, such as the Wilson, NRTL, Margules, etc., which using information for binary subsystems could predict the activity coefficients in ternary mixtures (Fan and Jafvert, 1997; Domanska, 1990).

Many other methods, mainly empirical and semiempirical, were suggested for the correlation and prediction of the solubility of solids in a mixed solvent. Details regarding these methods and their comparison with experiment were summarized in books and recent publications (Acree, 1984; Prausnitz et al., 1986; Barzegar-Jalali and Jouyban-Gharamaleki, 1996; Jouyban-Gharamaleki et al., 1999).

The solubility of drugs in aqueous mixed solvents often exhibits a maximum in the curve solubility versus mixed solvent composition. This "enhancement" in solubility often greatly exceeds the solubilities not only in water, which is quite natural, but also in nonaqueous cosolvents. Such a dependence could not be explained by simple equations like the log-linear model for the solubility in a mixed solvent (Yalkowsky and Roseman, 1981)

$$\ln x_2^{\mathrm{t}} = \varphi_1 \ln x_2^{\mathrm{b}_1} + \varphi_3 \ln x_2^{\mathrm{b}_3} \tag{4}$$

where $\phi_i$ ($i = 1, 3$) is the volume fraction of component $i$ in the mixed solvent 1–3. One should mention that such simple equations provided satisfactory results for systems which did not exhibit maxima.

Various other models for drug solubility in aqueous mixed solvents have been proposed and the results were compared (Barzegar-Jalali and Jouyban-Gharamaleki, 1996; Jouyban-Gharamaleki et al., 1999).

The main difficulty in predicting the solid solubility in a mixed solvent consists in calculating the activity coefficient of a solute in a ternary mixture ($\gamma_2^{\mathrm{t}}$). In this paper, the Kirkwood–Buff (KB) theory of solutions (or fluctuation theory) (Kirkwood and Buff, 1951) is employed to analyze the solid (particularly drug) solubility in mixed (mainly aqueous) solvents. The analysis is based on results obtained previously regarding the composition derivatives of the activity coefficients in ternary solutions (Ruckenstein and Shulgin, 2001). These equations were successfully applied to gas solubilities in mixed solvents (Ruckenstein and Shulgin, 2002; Shulgin and Ruckenstein, 2002).

Thus, the aim of the present paper is to apply the fluctuation theory for ternary mixtures to the solubility of drugs in aqueous mixed solvents and to suggest on this basis a simple and accurate method for its correlation.

## 2. Theory

### 2.1. The Kirkwood–Buff theory of solution

The KB theory of solution (Kirkwood and Buff, 1951) connects the macroscopic properties of solutions, such as the isothermal compressibility, the concentration derivatives of the chemical potentials, and the partial molar volumes to their microscopic characteristics in the form of spatial integrals involving the radial distribution function.

The key quantities in the KB theory of solution are the so-called Kirkwood–Buff integrals (KBIs), defined as

$$G_{\alpha\beta} = \int_0^\infty (g_{\alpha\beta} - 1) 4\pi r^2 \, \mathrm{d}r \tag{5}$$

where $g_{\alpha\beta}$ is the radial distribution function between species $\alpha$ and $\beta$, and $r$ is the distance between the

centers of molecules $\alpha$ and $\beta$. The isothermal compressibility, the concentration derivatives of the chemical potentials, and the partial molar volumes in any multicomponent mixture can be expressed in terms of the KBIs. In this paper, the attention is focused on the concentration derivatives of the chemical potentials, because they can provide useful information regarding the activity coefficient of a solute in a ternary mixture ($\gamma_2^t$).

Kirkwood and Buff (Kirkwood and Buff, 1951) obtained the following expression for the concentration derivative of the activity coefficient of component $\alpha$ in a binary mixture $\alpha$–$\beta$:

$$\left(\frac{\partial \ln \gamma_\alpha}{\partial x_\alpha}\right)_{P,T} = \frac{c_\beta^0(G_{\alpha\alpha} + G_{\beta\beta} - 2G_{\alpha\beta})}{1 + c_\alpha^0 x_\beta(G_{\alpha\alpha} + G_{\beta\beta} - 2G_{\alpha\beta})} \quad (6)$$

where $x_i$ and $\gamma_i$ are the mole fraction and the activity coefficient of component i in the binary mixture $\alpha$–$\beta$ and $c_i^0$ is the bulk molecular concentrations of component $i$. The present authors (Ruckenstein and Shulgin, 2001) established explicit expressions for the concentration derivatives of the activity coefficients in a ternary mixture. These expressions are more complicated than Eq. (6), and the only derivative which is of interest in the present paper has the form

$$\left(\frac{\partial \ln \gamma_{2,t}}{\partial x_3^t}\right)_{T,P,x_2^t} = -\frac{(c_1 + c_2 + c_3)(c_1[G_{11} + G_{23} - G_{12} - G_{13}] + c_3[-G_{12} - G_{33} + G_{13} + G_{23}])}{c_1 + c_2 + c_3 + c_1c_2\Delta_{12} + c_1c_3\Delta_{13} + c_2c_3\Delta_{23} + c_1c_2c_3\Delta_{123}} \quad (7)$$

where $\Delta_{\alpha\beta}$ and $\Delta_{123}$ are defined as follows:

$$\Delta_{\alpha\beta} = G_{\alpha\alpha} + G_{\beta\beta} - 2G_{\alpha\beta}, \quad \alpha \neq \beta \quad (8)$$

and

$$\Delta_{123} = G_{11}G_{22} + G_{11}G_{33} + G_{22}G_{33} + 2G_{12}G_{13} + 2G_{12}G_{23} + 2G_{13}G_{23} - G_{12}^2 - G_{13}^2 - G_{23}^2 - 2G_{11}G_{23} - 2G_{22}G_{13} - 2G_{33}G_{12} \quad (9)$$

The factors in the square brackets in the numerator of Eq. (7) and $\Delta_{123}$ can be expressed in terms of $\Delta_{\alpha\beta}$ as follows

$$G_{12} + G_{33} - G_{13} - G_{23} = \frac{\Delta_{13} + \Delta_{23} - \Delta_{12}}{2} \quad (10)$$

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

and

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

The insertion of Eqs. (10)–(12) into Eq. (7) provides a rigorous expression for the derivative $(\partial \ln \gamma_{2,t}/\partial x_3^t)_{T,P,x_2^t}$ in terms of $\Delta_{\alpha\beta}$ and concentrations.

It should be noted that $\Delta_{\alpha\beta}$ is a measure of the nonideality (Ben-Naim, 1977) of the binary mixture $\alpha$ and $\beta$, because for an ideal mixture $\Delta_{\alpha\beta} = 0$. For a ternary mixture 1–2–3, $\Delta_{123}$ also constitutes a measure of nonideality. Indeed, inserting $G_{\alpha\beta}^{id}$ for an ideal mixture (Ruckenstein and Shulgin, 2001) into the expression of $\Delta_{123}$ one obtains that for an ideal ternary mixture $\Delta_{123} = 0$.

### 2.2. The activity coefficient of a solute in a mixed solvent at infinite dilution

At infinite dilution of a solute, Eq. (7) can be recast as follows:

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

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

For a binary 1–3 solvent, Eq. (6) can be rewritten as follows:

$$\left(\frac{\partial \ln \gamma_3}{\partial x_3}\right)_{P,T} = \frac{c_3^0\Delta_{13}}{1 + c_3^0x_1\Delta_{13}} \quad (6a)$$

Eq. (6a) allows one to obtain for $\Delta_{13}$ the following expression:

$$\Delta_{13} = \frac{(\partial \ln \gamma_3/\partial x_3)_{P,T}}{c_3^0 - c_3^0x_1(\partial \ln \gamma_3/\partial x_3)_{P,T}} \quad (6b)$$

Introducing $\Delta_{13}$ from Eq. (6b) in Eq. (13) and integrating yields

$$\ln\gamma_2^{t,\infty} = -\int (c_1^0 + c_3^0)\frac{(\Delta_{12} - \Delta_{23})_{x_2^t=0}}{2}\left[1 + x_3^{b,1-3}\left(\frac{\partial \ln \gamma_3^{b,1-3}}{\partial x_3^{b,1-3}}\right)_{P,T}\right] dx_3^{b,1-3} + \frac{1}{2}\int \frac{(x_1^{b,1-3} - x_3^{b,1-3})}{x_1^{b,1-3}}\left(\frac{\partial \ln \gamma_3^{b,1-3}}{\partial x_3^{b,1-3}}\right)_{P,T} dx_3^{b,1-3} + A \quad (14)$$

where $x_i^{b,1-3}$ ($i = 1, 3$) is the mole fraction of component $i$ in the mixed solvent, $\gamma_2^{t,\infty}$ is the activity coefficient of a solute in a mixed solvent at infinite dilution and $A$ is a constant of integration.

Eq. (14) will be used in the next section to derive an expression for the solubility of a solid in a mixed solvent.

### 2.3. Solubility of poorly soluble solids in an ideal mixed solvent

For poorly soluble solids one can use the infinite dilution approximation and consider that the activity coefficient of a solute in a mixed solvent is equal to the activity coefficient at infinite dilution. Thus, Eqs. (1)–(3) can be rewritten as follows:

$$\frac{f_2^S}{f_2^L(T, P)} = x_2^t \gamma_2^{t,\infty} \quad (15)$$

$$\frac{f_2^S}{f_2^L(T, P)} = x_2^{b_1} \gamma_2^{b_1,\infty} \quad (16)$$

and

$$\frac{f_2^S}{f_2^L(T, P)} = x_2^{b_3} \gamma_2^{b_3,\infty} \quad (17)$$

where $\gamma_2^{b_1,\infty}$ and $\gamma_2^{b_3,\infty}$ are the activity coefficients at infinite dilution of the solute in the pure solvents 1 and 3.

Eq. (14) is a rigorous equation applicable to any ternary mixture.

At this point, two simplifications are introduced which allow one to obtain working expressions for the solubility of poorly soluble solids in an ideal mixed solvent:

(a) $(\Delta_{12})_{x_2^t=0} = (G_{11} + G_{22} - 2G_{12})_{x_2^t=0}$ and $(\Delta_{23})_{x_2^t=0} = (G_{22} + G_{33} - 2G_{23})_{x_2^t=0}$ are independent of the composition of the solvent mixture, and

(b) the binary solvent 1–3 is ideal and therefore $\gamma_3^{b,1-3} = 1$ and

$$V = x_1^{b,1-3} V_1^0 + x_3^{b,1-3} V_3^0 \quad (18)$$

where $V$ is the molar volume of the binary mixture 1–3, and $V_1^0$ and $V_3^0$ are the molar volumes of the individual solvents 1 and 3.

With these two simplifications, Eq. (14) can be rewritten, when $V_1^0 \neq V_3^0$, in the form

$$\ln \gamma_2^{t,\infty} = A(P, T) - \frac{B(P, T)\ln(x_1^{b,1-3} V_1^0 + x_3^{b,1-3} V_3^0)}{V_3^0 - V_1^0} \quad (19)$$

where $B(P, T) = (\Delta_{12} - \Delta_{23})_{x_2^t=0}/2$.

The constants $A(P, T)$ and $B(P, T)$ can be obtained using the following limiting expressions:

$$(\ln \gamma_2^{t,\infty})_{x_1^{b,1-3}=0} = \ln \gamma_2^{b,2-3,\infty} \quad (20)$$

and

$$(\ln \gamma_2^{t,\infty})_{x_3^{b,1-3}=0} = \ln \gamma_2^{b,1-2,\infty} \quad (21)$$

Combining Eqs. (19)–(21) yields the following expression for the activity coefficient of a solute in an ideal mixed solvent at infinite dilution when $V_1^0 \neq V_3^0$

$$\ln \gamma_2^{t,\infty} = \frac{(\ln V - \ln V_3^0)\ln \gamma_2^{b,1-2,\infty} + (\ln V_1^0 - \ln V)\ln \gamma_2^{b,2-3,\infty}}{\ln V_1^0 - \ln V_3^0} \quad (22)$$

Inserting expressions (15–17) into Eq. (22) yields the following equation for the solubility of a poorly soluble solid in an ideal mixed solvent:

$$\ln x_2^t = \frac{(\ln V - \ln V_3^0)\ln x_2^{b_1} + (\ln V_1^0 - \ln V)\ln x_2^{b_3}}{\ln V_1^0 - \ln V_3^0}, \quad V_1^0 \neq V_3^0 \quad (23)$$

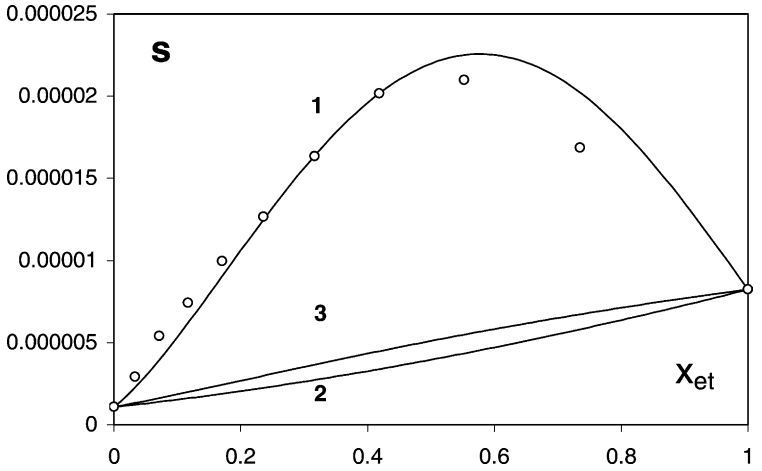


Fig. 1. Comparison between experimental (○) (Jouyban et al., 2002) and predicted (solid lines) solubilities of oxolinic acid ($S$ is the mole fraction of oxolinic acid) in the mixed solvent water/ethanol ($x_{et}$ is the mole fraction of ethanol) at room temperature. 1—solubility calculated using Eqs. (23) and (25), 2—solubility calculated using Eqs. (23) and (18), and 3—the solubility calculated using Eq. (4).

However, when $V_1^0 = V_3^0$, Eq. (23) leads to a nondetermination 0/0. In this case, using the same approximations as in the previous case and taking into account that $V = V_1^0 = V_3^0$, Eq. (14) leads to

$$\ln x_2^{t} = x_1^{b,1-3} \ln x_2^{b_1} + x_3^{b,1-3} \ln x_2^{b_3} \tag{24}$$

Eq. (24) is similar to Eq. (4) with the difference that the volume fractions for the mixed solvent are replaced by mole fractions.

Eq. (23), which was derived using the KB theory of solutions for a ternary mixture, can predict the solubility of a poorly soluble solid in an ideal mixed solvent in terms of the solubilities of the solid in the individual constituents of the mixed solvent and their molar volumes.

However, Eq. (23) cannot describe the maximum in the curve of solubility versus mixed solvent composition which was frequently observed experimentally for the solubilities of drugs in aqueous mixed

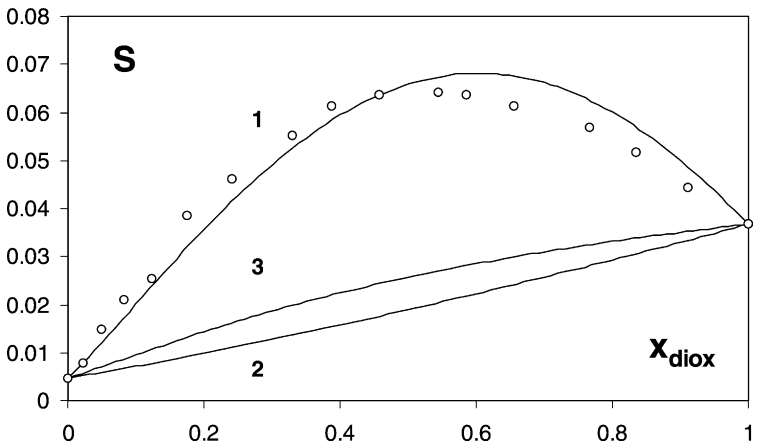


Fig. 2. Comparison between experimental (○) (Bustamante et al., 1993) and predicted (solid lines) solubilities of sulfadiazine ($S$ is the mole fraction of sulfadiazine) in the mixed solvent water/dioxane ($x_{diox}$ is the mole fraction of dioxane) at room temperature. 1—solubility calculated using Eqs. (23) and (25), 2—solubility calculated using Eqs. (23) and (18), and 3—the solubility calculated using Eq. (4).

solvents (Jouyban-Gharamaleki et al., 1999 and references therein). To accommodate this feature of the solubility curve, the molar volume of the mixed solvent will be replaced in Eq. (23) by

$$v = x_1^{b,1-3} V_1^0 + x_3^{b,1-3} V_3^0 + e x_1^{b,1-3} x_3^{b,1-3} \quad (25)$$

where $e$ is an empirical parameter which is evaluated from the solubility data in a mixed solvent. One should not expect for Eq. (25) to satisfactorily represent the molar volume of the mixed solvent. The insertion of Eq. (25) into Eq. (23) leads to a one-parameter semiempirical equation for the solubility of a solid in a mixed solvent. This equation exhibits a maximum in the curve of solubility versus mixed solvent composition (Figs. 1 and 2).

## 3. Results and discussion

In order to verify the applicability of Eq. (23) combined with the nonideal molar volume of a mixed solvent to the solubility of a drug in an aqueous mixed solvents, 32 experimental sets were selected. Most of them were taken from the paper of

Table 1
The experimental data[a] regarding the solubilities (at room temperature) of drugs in aqueous mixed solvents used in calculations

| Systems no. | Cosolvent | Solute | $n$[b] | Reference | Value of e ($cm^3$/mol) in Eq. (25) |
|---|---|---|---|---|---|
| 1 | *N*,*N*-Dimethylformamide | Sulfadiazine | 14 | Martin et al. (1982) | 49.3 |
| 2* | *N*,*N*-Dimethylformamide | Theophyllene | 11 | Gonzalez et al. (1994) | 45.2 |
| 3* | *N*,*N*-Dimethylformamide | Caffeine | 11 | Herrador and Gonzalez (1997) | 42.8 |
| 4 | Dioxane | Caffeine | 16 | Adjei et al. (1980) | 1433.9 |
| 5 | Dioxane | *p*-Hydroxybenzoic acid | 13 | Wu and Martin (1983) | 183.2 |
| 6 | Dioxane | Paracetamol | 17 | Romero et al. (1996) | 365.4 |
| 7 | Dioxane | Phenacetin | 13 | Bustamante and Bustamante (1996) | 249.8 |
| 8 | Dioxane | Sulfadiazine | 17 | Bustamante et al. (1993) | 325.9 |
| 9 | Dioxane | Sulfadimidine | 19 | Bustamante et al. (1993) | 220.5 |
| 10 | Dioxane | Sulfamethizole | 19 | Reillo et al. (1995a) | 678.6 |
| 11 | Dioxane | Sulfamethoxazole | 15 | Bustamante et al. (1993) | 199.0 |
| 12 | Dioxane | Sulfapyridine | 17 | Reillo et al. (1995b) | 390.5 |
| 13 | Dioxane | Sulfamethoxypyridazine | 19 | Bustamante et al. (1993) | 252.9 |
| 14 | Dioxane | Sulfanilamide | 16 | Reillo et al. (1993) | 256.3 |
| 15 | Dioxane | Sulfisomidine | 21 | Martin et al. (1985) | 536.0 |
| 16 | Dioxane | Theobromine | 11 | Martin et al. (1981) | 348.8 |
| 17 | Dioxane | Theophyllene | 21 | Martin et al. (1980) | 2317.7 |
| 18 | Ethanol | Paracetamol | 13 | Romero et al. (1996) | 108.3 |
| 19 | Ethanol | Sulfamethazine | 11 | Bustamante et al. (1994) | 152.0 |
| 20 | Ethanol | Sulfanilamide | 12 | Bustamante et al. (1994) | 113.0 |
| 21* | Ethanol | Oxolinic acid | 11 | Jouyban et al. (2002) | 261.3 |
| 22 | Ethylene glycol | Naphthalene | 18 | Khossravi and Connors (1992) | 2.2 |
| 23 | Ethylene glycol | Theophyllene | 17 | Khossravi and Connors (1992) | 24.7 |
| 24 | Methanol | Theophyllene | 13 | Khossravi and Connors (1992) | 151.2 |
| 25 | Propylene glycol | Butyl *p*-aminobenzoate | 11 | Rubino and Obeng (1991) | 32.5 |
| 26 | Propylene glycol | Butyl *p*-hydroxybenzoate | 11 | Rubino and Obeng (1991) | 19.6 |
| 27 | Propylene glycol | Ethyl *p*-aminobenzoate | 11 | Rubino and Obeng (1991) | 44.5 |
| 28 | Propylene glycol | Ethyl *p*-hydroxybenzoate | 11 | Rubino and Obeng (1991) | 40.5 |
| 29 | Propylene glycol | Methyl *p*-aminobenzoate | 11 | Rubino and Obeng (1991). | 43.1 |
| 30 | Propylene glycol | Methyl *p*-hydroxybenzoate | 11 | Rubino and Obeng (1991). | 46.8 |
| 31 | Propylene glycol | Propyl *p*-aminobenzoate | 11 | Rubino and Obeng (1991). | 34.2 |
| 32 | Propylene glycol | Propyl *p*-hydroxybenzoate | 11 | Rubino and Obeng (1991). | 21.8 |

[a] Most of the references were taken from the paper of Jouyban-Gharamaleki et al. (Jouyban-Gharamaleki et al., 1999), but some additional data (*) were also included.
[b] $n$ is the number of experimental points in each data set.

Table 2
Comparison between the drug solubilities calculated using Eqs. (23) and (25) and literature models

| Number of constants | MPD (%)[a] | | |
|---|---|---|---|
| | Using Eqs. (23) and (25) | MRS[b] | GSM[c] |
| 3 | 14.1 | 15.9 | 15.9 |

[a] MPD (%) is the mean percentage deviation defined as $\frac{100\sum_{j=1}^{M}\sum_{i=1}^{N_j}|(x_i^{\exp}-x_i^{\text{calc}})/x_i^{\exp}|}{\sum_{j=1}^{M}N_j}$ where $x_i^{\exp}$ and $x_i^{\text{calc}}$ are experimental and calculated solubilities (mole fractions), $N_j$ is the number of experimental points in the data set $j$ (Table 1), $M$ 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. (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. (Jouyban-Gharamaleki et al., 1999) paper.

Jouyban-Gharamaleki et al. (Jouyban-Gharamaleki et al., 1999), but some additional data were also included. All selected mixtures and the results of calculations are listed in Tables 1 and 2.

There is only one adjustable parameter ($e$) in our equation. However, the solubilities of the solute in the individual constituents of the mixed solvent are also needed. Therefore, one can consider our equation as a three-parameter one. For this reason, our results in Table 2 are compared to the best three-parameter equations. One can see from Table 2 that Eq. (23) with the molar volume given by Eq. (25) provides slightly better results than the three-parameter equations available in literature.

Generally speaking, the correlating equations should meet the following criteria:

(a) provide an accurate enough representation of the experimental data,
(b) use a minimum number of adjustable constants,
(c) have some theoretical justification, and
(d) have predictable power.

Regarding criterion (a), 30% for the mean percentage deviation is considered an acceptable error range (Reillo et al., 1995b). Therefore, all equations listed in Table 2 satisfy criterion (a). Of course, one can achieve a much better mathematical representation of the data by using a larger number of adjustable parameters. In the paper by Jouyban-Gharamaleki et al. (Jouyban-Gharamaleki et al., 1999), equations with 4, 5, and 6 adjustable parameters were listed. However, they are devoid of any physical meaning and require numerous experimental points for the parameter estimation. The adjustable parameter ($e$) in our equation can be found from a single solubility measurement. Furthermore, our Eq. (23) was derived using the fluctuation theory for ternary mixtures and is rigorously valid. It is clear that the idealized model employed cannot predict some peculiar features of real systems, such as the maximum in the curve of solubility versus mixed solvent composition. However, a simple modification (Eq. (25)) enabled Eq. (23) to represent this maximum.

An inspection of the values of the parameter ($e$) (Table 1) shows that this parameter has always positive values for the systems investigated and depends on the natures of both the drug and cosolvent. For the solubilities of structurally related caffeine and theophyllene in aqueous *N*,*N*-dimethylformamide, the values of ($e$) are close to each other (45.2 and 42.8). However, the values of ($e$) for the structurally more different sulfonamides (sulfadiazine, sulfadimidine, sulfamethizole, sulfamethoxazole, sulfapyridine, sulfamethoxypyridazine, sulfanilamide, and sulfisomidine) in water/dioxane mixtures differ by a factor of two and even three for sulfamethizole.

The limitations of the proposed method are directly related to the simplifications made. The two most important ones are: (1) the ideality of the mixed solvents and (2) the infinite dilution approximation. Our next papers will be focused on nonideal mixed solvents and on the effect of the finite concentration of a solute.

## 4. 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 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 a solute at infinite dilution in an ideal mixed solvent and an expression for the solubility of a poorly soluble solid in an ideal mixed solvent (Eq. (23)). This simple equation can predict the solubility in terms of those in the individual constituents of the mixed solvent and

their molar volumes. However, this simple equation cannot explain the maximum observed experimentally in the curve of solubility versus mixed solvent composition. By considering that the molar volume of the mixed solvent is nonideal and that the excess volume depends on its composition, the above equation was modified by including one adjustable parameter. This modified equation can be considered a three parameter equation (parameter ($e$) in Eq. (25) and the two solubilities of the solid in the individual constituents). The semiempirical equation proposed was compared with other three parameter equations for the solubility of drugs in an aqueous mixed solvent.

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