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Solubility of drugs in aqueous solutions Part 3: Multicomponent mixed solvent

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Abstract

The results obtained previously by Ruckenstein and Shulgin [Int. J. Pharm. 258 (2003a) 193; Int. J. Pharm. 260 (2003b) 283] via the fluctuation theory of solutions regarding the solubility of drugs in binary aqueous mixed solvents were extended in the present paper to multicomponent aqueous solvents. The multicomponent mixed solvent was considered to behave as an ideal solution and the solubility of the drug was assumed small enough to satisfy the infinite dilution approximation.

An expression derived for the activity coefficient of a solid solute in a multicomponent solvent was used to obtain an equation for the solubility of a drug in terms of its solubilities in two subsystems of the multicomponent solvent and their molar volumes. Ultimately the solubility can be expressed in terms of those in binary or even in individual solvents and their molar volumes.

The method was applied to the solubility of tioconazole and 19-Nor-1α,25-dihydrovitamin D_2 in several ternary and in a quaternary aqueous mixed solvents. The predicted solubilities were compared with experimental data and good agreement was found.

Keywords: Solubility of drugs; Multicomponent mixed solvent; Fluctuation theory

1. Introduction

The two previous papers (Ruckenstein and Shulgin, 2003a, b) of this series were focused on the solubility of a solid (particularly a drug) in binary mixed (mainly aqueous) solvents. The present paper extends the method suggested in the above publications to the solubility of drugs in ternary and multicomponent mixed solvents.

While the binary aqueous mixed solvents usually increase the solubility of a poorly soluble drug compared to that in pure water, they could also increase the risk of toxicity. The right selection of a ternary and multicomponent aqueous mixed solvent can, however, improve the solubility of the drug with minimal toxic effects (Lachman et al., 1976).

The pharmaceutical practice has shown that many marketed liquid formulations, which utilize cosolvents, involve multiple solvents (Yalkowsky and Roseman, 1981). However, the experimental determinations of the solubilities in multicomponent solutions are time-consuming because of the large number of compositions needed to cover the concentration ranges of interest and can be very expensive because of the high prices of some modern drugs. For this reason, it is important to provide a reliable method for predicting the solubility of drugs in multicomponent

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mixed solvents from available experimental solubilities in subsystems such as pure solvents, binary mixed solvents, etc.

For the solubility of a solid (solute, component 2) in a $(n-1)$ multicomponent mixed solvent one can write the following equation (Acree, 1984; Prausnitz et al., 1986):

$$\ln(x_2^n) = \ln\left(\frac{f_2^{\mathrm{S}}}{f_2^{\mathrm{L}}(T,P)}\right) - \ln(\gamma_2^n(T,P,\{x\})) \qquad (1)$$

where x_2^n is the solubility (mole fraction) of the solid component 2 in a $(n-1)$-component mixed solvent, γ_2^n is the activity coefficients of the solid in its saturated solutions (n-component mixture composed of solute + $(n-1)$-component mixed solvent), $f_2^{\mathrm{L}}(T,P)$ is the hypothetical fugacity of the solid as a (subcooled) liquid at a given pressure (P) and temperature (T), f_2^{S} is the fugacity of a pure solid component 2, and $\{x\}$ indicates that the activity coefficient of the solid solute depends on composition. If the solubility of a $(n-1)$-component mixed solvent in the solid phase is negligible, then the right hand side of Eq. (1) depends only on the properties of the solute and its activity coefficient in the saturated solution of the n-component mixture.

The calculation of the activity coefficient of a solid in a saturated solution of a n-component mixture constitutes the main difficulty in predicting the solid solubility. Generally speaking, the activity coefficient of a solid in a saturated solution of a n-component mixture can be predicted using either group-contribution methods, such as UNIFAC and ASOG, or the experimental solubilities of the solid in subsystems of the multicomponent mixed solvent combined with the Wilson, NRTL, etc. equation (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 UNIFAC was inaccurate in predicting the solubilities of solids in aqueous solutions (Fan and Jafvert, 1997). Furthermore, the application of the traditional UNIFAC to mixtures containing a polymer or another large molecule, such as a drug, and low molecular weight solvents is debatable (Fredenslund and Sørensen, 1994). The reason is that the UNIFAC parameters were determined mostly from equilibrium properties of mixtures formed of low molecular weight compounds.

The prediction of the activity coefficient of a solid in its saturated solution in a n-component mixture from the experimental solubilities of the solid in subsystems, such as binary mixed solvents or even individual solvents, is very attractive, because the solubilities in many of the binary mixed solvents and individual solvents are known or can be determined rapidly and their determinations are cheaper than for multicomponent mixed solvents. The method most often used for the solubility of a solid in ternary and multicomponent mixed solvents is the combined nearly ideal binary solvent/Redlich–Kister equation (Acree et al., 1991). This method was applied to the solubility of a solid in ternary nonaqueous mixed solvents and even to the solubility of a solid in a 7-component nonaqueous mixed solvent (Jouyban-Gharamaleki et al., 2000a; Deng et al., 1999). Jouyban-Gharamaleki et al. (2000b) suggested to apply this method also to the solubility of drugs in multicomponent aqueous mixed solvents.

Recently (Ruckenstein and Shulgin, 2003c), a method was suggested to calculate the activity coefficient of a poorly soluble solid in an ideal multicomponent solvent in terms of its activity coefficients at infinite dilution in some subsystems of the multicomponent solvent. The method, based on the fluctuation theory of solutions (Kirkwood and Buff, 1951), provided the following expression for the activity coefficient of a poorly soluble solid solute in an ideal multicomponent solvent:

$$(\ln\gamma_2^{n,\infty})_{x_{i\neq1,3}^n} = -\left(\frac{B\ln V}{(V_3^0 - V_1^0)}\right)_{x_{i\neq1,3}^n} + A \qquad (2)$$

where $\gamma_2^{n,\infty}$ is the activity coefficient of the solid solute (denoted 2) in a n-component mixture (solute + $(n-1)$-component solvent), V is the molar volume of an ideal $(n-1)$-component solvent, V_i^0 is the molar volume of the individual i-solvent, x_i^n is the mole fraction of component i in the n-component mixture, and A and B are composition independent constants. The constants A and B can be determined from the activity coefficients of the solid solute in two $(n-1)$-component mixtures with the mole fraction of component 1 zero in one of them and the mole fraction of component 3 zero in the other one. Expression

(2) was used to predict the gas solubilities and the solubilities of solid nonelectrolytes in multicomponent mixed solvents (Ruckenstein and Shulgin, 2003c).

Expression (2) implies that $V_1^0 \neq V_3^0$. When $V_1^0 = V_3^0$, another expression for the activity coefficient of a poorly soluble solid solute in an ideal multicomponent solvent was obtained (Ruckenstein and Shulgin, 2003a):

$$(\ln \gamma_2^{n,\infty})_{x_{i\neq 1,3}^n} = -\left(\frac{Bx_3^n}{V}\right)_{x_{i\neq 1,3}^n} + A \qquad (2A)$$

Details regarding such cases are provided in the above cited paper. In the present paper, only expression (2) will be employed to predict the solubility of drugs in ternary and quaternary aqueous mixed solvents. It should be emphasized that Eq. (2) remains valid even for small differences between V_1^0 and V_3^0; it is not valid only when V_1^0 is mathematically equal to V_3^0 (very rare case).

2. Solubility of drugs in a multicomponent mixed solvent

In order to apply Eq. (2) to the solubility of a solid solute in a $(n-1)$-component solvent, one must calculate the constants A and B. For this purpose, we consider a $(n-1)$-component solvent with mole fractions $x_1^n, x_3^n, \ldots, x_n^n$, among which, as required by Eq. (2), all mole fractions with the exception of x_1^n and x_3^n are constant. Because $x_1^n + \sum_{i=3}^n x_i^n = 1$, it is clear that the sum of the mole fractions of components 1 and 3 must be constant. Consequently, the composition of the $(n-1)$-component solvent can be changed along the line $x_1^n + x_3^n = \text{const}$. To determine the constants A and B one can use two limiting $(n-2)$-component solvents (along the line $x_1^n + x_3^n = \text{const}$); the mole fraction of component i in one of them will be denoted y_i^{n-1} and in the other z_i^{n-1}. In the first, the mole fraction of component 3, y_3^{n-1}, and in the other one the mole fraction of component 1, z_1^{n-1}, is taken zero. Because $y_1^{n-1} + y_3^{n-1} = z_1^{n-1} + z_3^{n-1} = x_1^n + x_3^n = \text{const}$, one obtains that $y_1^{n-1} = x_1^n + x_3^n$ and $z_3^{n-1} = x_1^n + x_3^n$.

Consequently,

- In the first limiting case, denoted I, the mole fractions are $y_1^{n-1} = x_1^n + x_3^n$, $y_3^{n-1} = 0$, $y_4^{n-1} = x_4^n, \ldots, y_n^{n-1} = x_n^n$ with $y_1^{n-1} + \sum_{i=3}^n y_i^{n-1} = 1$ and the mole fraction of the solute is y_2^{n-1}.
- In the second limiting case, denoted II, the mole fractions are $z_1^{n-1} = 0$, $z_3^{n-1} = x_1^n + x_3^n$, $z_4^{n-1} = x_4^n, \ldots, z_n^{n-1} = x_n^n$ with $\sum_{i=3}^n z_i^{n-1} = 1$ and the mole fraction of the solute is z_2^{n-1}.
- In the limiting cases I and II, Eq. (2) acquires the form:

$$\ln(\gamma_2^{n-1(\mathrm{I}),\infty}) = -\frac{B \ln V^{(\mathrm{I})}}{(V_3^0 - V_1^0)} + A \qquad (3)$$

$$\ln(\gamma_2^{n-1(\mathrm{II}),\infty}) = -\frac{B \ln V^{(\mathrm{II})}}{(V_3^0 - V_1^0)} + A \qquad (4)$$

where $V^{(\mathrm{I})}$ and $V^{(\mathrm{II})}$ are the molar volumes of the mixtures composed of $(n-2)$-component solvents I and II and the solid solute, respectively. Furthermore, for a poorly soluble solid, the molar volumes of the mixtures can be taken equal to the molar volumes of the solvents.

When the solubility of the solute is small (which is typical for drugs in aqueous mixed solvents), one can write the following expressions (see Eq. (1)) for the solubility of a solute in the above multicomponent mixed solvents:

$$\ln(x_2^n) = \ln\left(\frac{f_2^{\mathrm{S}}}{f_2^{\mathrm{L}}(T,P)}\right) - \ln(\gamma_2^{n,\infty}) \qquad (5)$$

$$\ln(y_2^{n-1}) = \ln\left(\frac{f_2^{\mathrm{S}}}{f_2^{\mathrm{L}}(T,P)}\right) - \ln(\gamma_2^{n-1(\mathrm{I}),\infty}) \qquad (6)$$

and

$$\ln(z_2^{n-1}) = \ln\left(\frac{f_2^{\mathrm{S}}}{f_2^{\mathrm{L}}(T,P)}\right) - \ln(\gamma_2^{n-1(\mathrm{II}),\infty}) \qquad (7)$$

where $\gamma_2^{n-1(\mathrm{I}),\infty}$ and $\gamma_2^{n-1(\mathrm{II}),\infty}$ are the activity coefficients of the solid solute at infinite dilution in the $(n-2)$-component solvents I and II, respectively.

Taking into account Eqs. (3) and (4), Eq. (2) can be recast as:

$$(\ln \gamma_2^{n,\infty})_{x_{i\neq 1,3}^n} = \frac{(\ln V - \ln V^{(\mathrm{II})})\ln(\gamma_2^{n-1(\mathrm{I}),\infty}) + (\ln V^{(\mathrm{I})} - \ln V)\ln(\gamma_2^{n-1(\mathrm{II}),\infty})}{\ln V^{(\mathrm{I})} - \ln V^{(\mathrm{II})}} \qquad (8)$$

Eq. (8) provides an expression for the activity coefficient of a poorly soluble solid at infinite dilution in an ideal $(n-1)$-component mixed solvent in terms of its molar volume and the activity coefficients at infinite dilution in the two limiting cases I and II and their molar volumes.

The combination of Eq. (8) with Eqs. (5)–(7) yields an expression for the solubility of a poorly soluble solid in an ideal $(n-1)$-component mixed solvent in terms of its solubilities in the ideal $(n-2)$-component mixed solvents I and II and their molar volumes.

$$\ln(x_2^n) = \frac{(\ln V - \ln V^{(\mathrm{II})})\ln(y_2^{n-1}) + (\ln V^{(\mathrm{I})} - \ln V)\ln(z_2^{n-1})}{\ln V^{(\mathrm{I})} - \ln V^{(\mathrm{II})}} \quad (9)$$

Furthermore, the solubilities of a poorly soluble solid in ideal $(n-2)$-component mixed solvents I and II can be expressed through those in the ideal $(n-3)$-component mixed solvents and so on. Therefore, the suggested procedure allows one to predict the solubility of a poorly soluble solid in an ideal $(n-1)$-component mixed solvent from the solubilities in binary mixed solvents or even from the solubilities in the individual solvents.

3. Comparison with experiment

3.1. Ternary mixed solvents

The experimental solubility of tioconazole (Gould et al., 1984) in the following mixed solvents:

(1) ethanol–propylene glycol–water,
(2) ethanol–polyethylene glycol 400 (PEG 400)–water,
(3) propylene glycol–PEG 400–water,
and the solubility of 19-Nor-1α,25-dihydrovitamin D_2 (an analog of vitamin D_2) (Stephens et al., 1999) in
(4) ethanol–propylene glycol–water

were selected for comparison of the developed method with experiment.

The above systems were selected because the experimental solubilities of tioconazole in the binary mixed solvents: ethanol–water, propylene glycol–water and PEG 400–water, and the solubilities of 19-Nor-1α,25-dihydrovitamin D_2 in the binary mixed solvents: ethanol–water and propylene glycol–water are available (Gould et al., 1984; Stephens et al., 1999).

The solubilities of the drugs in ternary aqueous mixed solvents were calculated from those in binary aqueous mixed solvents using Eq. (9). The solubilities in the limiting binary aqueous mixed solvents (y and z) were evaluated using two different procedures:

(1) The experimental solubility data were correlated using the following relation (Ruckenstein and Shulgin, 2003a):

$$\ln(x_2^{(\mathrm{b})}) = \frac{(\ln V^{(\mathrm{b})} - \ln V^{(\mathrm{H_2O})})\ln(x_2^{(\mathrm{co})}) + (\ln V^{(\mathrm{co})} - \ln V^{(\mathrm{b})})\ln(x_2^{(\mathrm{H_2O})})}{\ln V^{(\mathrm{co})} - \ln V^{(\mathrm{H_2O})}} \quad (10)$$

where $x_2^{(\mathrm{b})}$ is the drug solubility in the binary solvent: water + cosolvent (co), $x_2^{(\mathrm{H_2O})}$ and $x_2^{(\mathrm{co})}$ are the drug solubilities in water and cosolvent, respectively, $V^{(\mathrm{H_2O})}$ and $V^{(\mathrm{co})}$ are the molar volumes of water and cosolvent at 25 °C, respectively, and $V^{(\mathrm{b})} = x_{\mathrm{co}}^{\mathrm{b}} V^{(\mathrm{co})} + x_{\mathrm{H_2O}}^{\mathrm{b}} V^{(\mathrm{H_2O})} + e x_{\mathrm{co}}^{\mathrm{b}} x_{\mathrm{H_2O}}^{\mathrm{b}}$, where $x_{\mathrm{co}}^{\mathrm{b}}$ and $x_{\mathrm{H_2O}}^{\mathrm{b}}$ are the mole fractions of the cosolvent and water, respectively, in the mixed solvent: water + cosolvent and e is an adjustable parameter introduced in a previous paper (Ruckenstein and Shulgin, 2003a).

Finally, the solubility of the drug for the compositions of the mixed solvents corresponding to the limiting binary mixtures I and II were calculated using Eq. (10).

(2) The solubilities in binary aqueous mixed solvents (y and z) were evaluated graphically from experimental data.

A comparison between predicted and experimental drug solubilities in ternary aqueous mixed solvents is made in Table 1.

It is worth mentioning that all the predictions listed in Table 1 were obtained on the basis of experimental drug solubilities in binary aqueous mixed solvents, without using any experimental drug solubilities in ternary aqueous mixed solvents.

One can see from Table 1 that the drug solubilities in ternary aqueous mixed solvents could be accurately predicted using the experimental drug solubilities in binary aqueous mixed solvents.

Table 1
Comparison between predicted and experimental drug solubilities in ternary solvents

Solute	Mixed solvent	Reference	Deviation (%) between experimental and predicted (Eq. (9)) solubilities[a]	
			The solubilities in binary solvents calculated using Eq. (10)[b]	The solubilities in binary solvents evaluated graphically from experimental data
Tioconazole	Ethanol–propylene glycol–water	Gould et al. (1984)	10.4	6.8
	Ethanol–PEG 400–water		19.6	15.4
	Propylene glycol–PEG 400–water		39.1	15.2
19-Nor-1α,25-dihydrovitamin D_2	Ethanol–propylene glycol–water	Stephens et al. (1999)	55.4	15.0

[a] Deviation from experimental data calculated as MPD (%) (mean percentage deviation) defined as $[100\sum_{i=1}^{N}|(x_i^{exp} - x_i^{calc})/x_i^{exp}|]/N$, where x_i^{exp} and x_i^{calc} are experimental and calculated (using Eq. (9)) solubilities (mole fractions) and N is the number of experimental points.
[b] Because we could not find in literature the solubilities of 19-Nor-1α,25-dihydrovitamin D_2 in ethanol and propylene glycol, they were taken equal to the solubility of vitamin D_2 in ethanol (Penau and Hagemann, 1946).

The difference in predicted solubilities when the solubilities in binary aqueous mixed solvents (y and z) were evaluated using Eq. (10) or obtained graphically from experimental data is understandable. The accuracy of Eq. (10) for predicting the drug solubility in binary aqueous mixed solvents is about 14% (the mean percentage deviation) (Ruckenstein and Shulgin, 2003a) and this inaccuracy plays a role in the prediction of the drug solubilities in ternary aqueous mixed solvents (see Table 2 for details).

3.2. Quaternary mixed solvent

We found in literature only one example regarding the drug solubilities in quaternary aqueous mixed solvents: the solubility of tioconazole in ethanol–propylene glycol–PEG 400–water (Gould et al., 1984).

The prediction of the solubility of tioconazole in ethanol–propylene glycol–PEG 400–water was carried out using the following steps:

(1) Two ternary solvents: I (ethanol–propylene glycol–water) and II (ethanol–PEG 400–water) were selected,
(2) The solubilities of tioconazole in the above ternary solvents were calculated as described in the previous section (Eq. (10) was used to evaluate the solubility of tioconazole in binary aqueous mixed solvents, see Table 2 for details),
(3) The solubilities of tioconazole in ethanol–propylene glycol–PEG 400–water mixed solvent

Table 2
Comparison between calculated (using Eq. (10)) and experimental drug solubilities in aqueous binary solvents

Solute	Cosolvent	Deviation from experimental data[a]	Value of e (cm^3/mol)[b]
Tioconazole	Ethanol	4.12	40.87
Tioconazole	Propylene glycol	7.74	37.75
Tioconazole	PEG 400	18.60	507.09
19-Nor-1α,25-dihydrovitamin D_2[c]	Ethanol	27.56	−34.71
19-Nor-1α,25-dihydrovitamin D_2[c]	Propylene glycol	8.72	−78.63

[a] Deviation from experimental data calculated as MPD (%) (mean percentage deviation) defined as $[100\sum_{i=1}^{N}|(x_i^{exp} - x_i^{calc})/x_i^{exp}|]/N$, where x_i^{exp} and x_i^{calc} are experimental and calculated (using Eq. (10)) solubilities (mole fractions) and N is the number of experimental points.
[b] Parameter e was used in the following equation for molar volume of binary mixed solvent (see Ruckenstein and Shulgin, 2003a) $V^{(b)} = x_{co}^{b} V^{(co)} + x_{H_2O}^{b} V^{(H_2O)} + e x_{co}^{b} x_{H_2O}^{b}$.
[c] Because we could not find in literature the solubilities of 19-Nor-1α,25-dihydrovitamin D_2 in ethanol and propylene glycol, they were taken equal to the solubility of vitamin D_2 in ethanol (Penau and Hagemann, 1946).

Table 3
Comparison between predicted and experimental tioconazole solubilities in quaternary solvent

Solute	Mixed solvent	Reference	Deviation (%) between experimental and predicted (Eq. (9)) solubilities[a]
Tioconazole	Ethanol–propylene glycol–PEG 400–water	Gould et al. (1984)	10.6

[a] Deviation from experimental data calculated as MPD (%) (mean percentage deviation) defined as $[100\sum_{i=1}^{N}|(x_i^{\exp} - x_i^{\text{calc}})/x_i^{\exp}|]/N$, where $x_i^{\exp}$ and x_i^{calc} are experimental and calculated (using Eq. (9)) solubilities (mole fractions) and N is the number of experimental points.

were calculated with Eq. (9), using the solubilities of tioconazole in the ternary solvents obtained in the previous step.

The results of the predictions are listed in Table 3, which show that there is an excellent agreement between the experimental and predicted solubilities.

It is also noteworthy to emphasize that all the predictions listed in Table 3 were made on the basis of experimental drug solubilities in binary aqueous mixed solvents, without using any experimental drug solubilities in ternary and quaternary aqueous mixed solvents.

4. Discussion and conclusion

As in our previous publications regarding the solubility of drugs in aqueous mixed solvents (Ruckenstein and Shulgin, 2003a, b), the fluctuation theory of solutions was used as a theoretical tool. However, whereas the above publications were devoted to binary mixed solvents, the present one provides a predictive method for the solubility of drugs in multicomponent aqueous mixed solvents.

First, a rigorous expression for the activity coefficient of a solid solute at infinite dilution in an ideal multicomponent solvent was derived using the fluctuation theory of solution. Second, the obtained expression was used to express the solubility of a poorly soluble solid in an ideal multicomponent solvent in terms of the solubilities of this solid in two subsystems of the multicomponent solvent and their molar volumes. Finally, the developed procedure was used to predict the drug solubilities in ternary and quaternary aqueous mixed solvents using the drug solubilities in the constituent binary aqueous mixed solvents. The predicted solubilities were compared with the experimental ones and good agreement was found.

It is worth noting that good agreement was found despite two important limitations imposed on our method: (a) the multicomponent solvent was considered ideal, and (b) the drug solubility in a mixed solvent was supposed to be small enough to satisfy the infinite dilution approximation.

The developed predictive method can be applied not only to ternary and quaternary mixed solvents, but also to any multicomponent solvent.

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