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Solubility of drugs in aqueous solutions
Part 5. Thermodynamic consistency test for the solubility data

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Abstract

This paper is devoted to the verification of the quality of experimental data regarding the solubility of sparingly soluble solids, such as drugs, environmentally important substances, etc. in mixed solvents. A thermodynamic consistency test based on the Gibbs–Duhem equation for ternary mixtures is suggested. This test has the form of an equation, which connects the solubilities of the solid, and the activity coefficients of the constituents of the solute-free mixed solvent in two mixed solvents of close compositions.

The experimental data regarding the solubility of sparingly soluble substances can be verified with the suggested test if accurate data for the activity coefficients of the constituents of the solute-free mixed solvent are available.

The test was applied to a number of systems representing the solubilities of sparingly soluble substances in mixed solvents. First, the test was scrutinized for four nonaqueous systems for which accurate solubility data were available. Second, the suggested test was applied to a number of systems representing experimental data regarding the solubility of sparingly soluble substances in aqueous mixed solvents.

Keywords: Drug solubility; Mixed solvent; Thermodynamic consistency test

1. Introduction

The solubility of drugs in water and aqueous mixed solvents is one of the important topics in pharmaceutical science and industry. However, the literature data regarding the aqueous solubility are not always reliable and large discrepancies between the data from different authors are typical. Indeed, according to a recently published compilation of aqueous solubilities (Yalkowsky and He, 2003), the aqueous solubility of naphthalene at room temperature measured by different authors varies from 0.0125 to 0.04 g/L, for anthracene from 3×10^{-4} to 7.3×10^{-4} g/L, and so on. The same or even worse situation could be observed for the solubilities of drugs in aqueous mixed solvents. Consequently, it is difficult

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to judge whether the solubility data are accurate or not, and it is important to have a rigorous test for checking the experimental solubility data and selecting the correct ones. Because we could not find such a method in the literature, the purpose of the present paper is to suggest a thermodynamic method for testing the accuracy of the experimental data regarding the solubility of drugs in aqueous mixed solvents.

Thermodynamic consistency tests are well known, and have been frequently used for vapour–liquid equilibrium data in binary mixtures (for reviews one can see Gmehling and Onken, 1977; Acree, 1984; Prausnitz et al., 1986). These tests are based on the Gibbs–Duhem equation and allow one to grade the experimental data for vapor–liquid equilibrium in binary mixtures. A more difficult problem is the consistency of data regarding vapor–liquid equilibrium in ternary or multicomponent mixtures. However, several thermodynamic consistency tests, also based on the Gibbs–Duhem equation, were suggested for vapor–liquid equilibrium in ternary or multicomponent mixtures (Li and Lu, 1959; McDermott and Ellis, 1965).

2. General relations for multicomponent mixtures

The isothermal–isobaric Gibbs–Duhem equation for an N-component mixture ($N \geq 2$) can be written as follows

$$\sum_{i=1}^{N} x_i \mathrm{d}(\ln \gamma_i) = 0 \tag{1}$$

where x_i and γ_i are the mole fraction and the activity coefficient of component i in the N-component mixture. Integrating Eq. (1) directly along a loop of points a, b, c, ..., y, z, ... by using the trapezoidal rule, one can obtain the following equation (Li and Lu, 1959)

$$\sum_{i=1}^{N} \left\{ \frac{x_i^{(a)} + x_i^{(b)}}{2} [\ln \gamma_i^{(b)} - \ln \gamma_i^{(a)}] + \frac{x_i^{(b)} + x_i^{(c)}}{2} [\ln \gamma_i^{(c)} - \ln \gamma_i^{(b)}] + \cdots + \frac{x_i^{(y)} + x_i^{(z)}}{2} [\ln \gamma_i^{(z)} - \ln \gamma_i^{(y)}] + \cdots \right\} = 0 \tag{2}$$

McDermott and Ellis (1965) applied Eq. (2) to a pair of points c and d. In this case, Eq. (2) reduces to

$$\sum_{i=1}^{N} (x_i^{(c)} + x_i^{(d)})[\ln \gamma_i^{(d)} - \ln \gamma_i^{(c)}] = 0 \tag{3}$$

The McDermott and Ellis consistency test means that if the vapor–liquid equilibrium data for points c and d are correct, then Eq. (3) should be satisfied. Eq. (3) will be used to derive a thermodynamic consistency test for verifying the experimental data regarding the solubility of drugs in aqueous mixed solvents.

3. Thermodynamic consistency test regarding the solubility of drugs in binary aqueous mixed solvents

For the solubility of a solid substance (solute, component 2) in a mixed solvent 1–3, one can write the following equation (Prausnitz et al., 1986):

$$\frac{f_2^{\mathrm{S}}}{f_2^{\mathrm{L}}(T, P)} = x_{2,t} \gamma_{2,t}(T, P, \{x\}) \tag{4}$$

where $x_{2,t}$ and $\gamma_{2,t}$ are the solubility (mole fraction) and the activity coefficient of the solid in its saturated solution in a mixed solvent, $f_2^{\mathrm{L}}(T, P)$ is the hypothetical fugacity of a solid as a (sub-cooled) 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 depends on composition. If the solubility of the mixed solvent in the solid phase is negligible, then the left hand side of Eq. (4) depends only on the properties of the solute.

Rewriting of Eq. (3) for a ternary mixture yields the expression

$$(x_1^{(c)} + x_1^{(d)})[\ln \gamma_1^{(d)} - \ln \gamma_1^{(c)}] + (x_2^{(c)} + x_2^{(d)}) \times [\ln \gamma_2^{(d)} - \ln \gamma_2^{(c)}] + (x_3^{(c)} + x_3^{(d)}) \times [\ln \gamma_3^{(d)} - \ln \gamma_3^{(c)}] = 0 \tag{5}$$

Let us consider the solubilities of a poorly soluble solid in two mixed solvents of close compositions (points c and d). Because these solubilities satisfy Eq. (4), one can express the activity coefficients of the solid via Eq. (4), and Eq. (5) acquires the form

$$\begin{aligned}&(x_1^{(c)}+x_1^{(d)})[\ln\gamma_1^{(d)}-\ln\gamma_1^{(c)}]+(x_2^{(c)}+x_2^{(d)})\\&\quad\times[\ln x_2^{(c)}-\ln x_2^{(d)}]+(x_3^{(c)}+x_3^{(d)})\\&\quad\times[\ln\gamma_3^{(d)}-\ln\gamma_3^{(c)}]=0\end{aligned}\qquad(6)$$

Let us suppose that the solubility of the solid in the mixed solvent is so low, that one can consider the activity coefficients of the solvent and cosolvent equal to those in the solute-free binary solvent mixture ($\gamma_{1,0}$ and $\gamma_{3,0}$). In addition, the following relations for the mole fractions of the constituents of the solvent can be used

$$x_{1,t}=x_{1,0}-x_{1,0}x_{2,t}\qquad(7)$$

and

$$x_{3,t}=x_{3,0}-x_{3,0}x_{2,t}\qquad(8)$$

where $x_{1,0}$ and $x_{3,0}$ are the mole fractions of constituents 1 and 3 in a solute-free mixed solvent.

Consequently, Eq. (6) becomes

$$\begin{aligned}&(x_{1,0}^{(c)}+x_{1,0}^{(d)}-x_{1,0}^{(c)}x_2^{(c)}-x_{1,0}^{(d)}x_2^{(d)})[\ln\gamma_{1,0}^{(d)}-\ln\gamma_{1,0}^{(c)}]\\&\quad+(x_2^{(c)}+x_2^{(d)})[\ln x_2^{(c)}-\ln x_2^{(d)}]+(x_{3,0}^{(c)}+x_{3,0}^{(d)}\\&\quad-x_{3,0}^{(c)}x_2^{(c)}-x_{3,0}^{(d)}x_2^{(d)})[\ln\gamma_{3,0}^{(d)}-\ln\gamma_{3,0}^{(c)}]=0\end{aligned}\qquad(9)$$

The last equation can be simplified by applying Eq. (5) to the pair of binary mixed solvent mixtures of compositions ($x_{1,0}^{(c)}$, $x_{3,0}^{(c)}$) and ($x_{1,0}^{(d)}$, $x_{3,0}^{(d)}$). For this pair, Eq. (5) becomes

$$\begin{aligned}&(x_{1,0}^{(c)}+x_{1,0}^{(d)})[\ln\gamma_{1,0}^{(d)}-\ln\gamma_{1,0}^{(c)}]\\&\quad+(x_{3,0}^{(c)}+x_{3,0}^{(d)})[\ln\gamma_{3,0}^{(d)}-\ln\gamma_{3,0}^{(c)}]=0\end{aligned}\qquad(10)$$

Subtracting Eq. (10) from Eq. (9) yields

$$\begin{aligned}&(x_{1,0}^{(c)}x_2^{(c)}+x_{1,0}^{(d)}x_2^{(d)})[\ln\gamma_{1,0}^{(d)}-\ln\gamma_{1,0}^{(c)}]+(x_2^{(c)}+x_2^{(d)})\\&\quad\times[\ln x_2^{(d)}-\ln x_2^{(c)}]+(x_{3,0}^{(c)}x_2^{(c)}+x_{3,0}^{(d)}x_2^{(d)})\\&\quad\times[\ln\gamma_{3,0}^{(d)}-\ln\gamma_{3,0}^{(c)}]=0\end{aligned}\qquad(11)$$

Eq. (11) provides a thermodynamic consistency test for the solubility of poorly soluble substances, such as drugs, environmentally important substances, etc. in mixed solvents in terms of the activity coefficients of the constituents of the binary solute-free mixed solvent and mixed solvent composition.

Two limitations are involved in the derivation of the above equation: (1) the compositions of mixed solvents (points c and d) should be close enough to each other for the trapezoidal rule used to integrate the Gibbs–Duhem equation to be valid, (2) the solubility of the solid should be low enough for the activity coefficients of the solvent and cosolvent to be taken equal to those in a solute-free binary solvent mixture. In addition, the fugacity of the solid phase in Eq. (4) should remain the same for all mixed solvent compositions considered.

4. Numerical estimations

Of course, for real mixtures the left hand side of Eq. (11) is not exactly equal to zero; it has certain finite values even for very accurate data. Let us denote that value with D. McDermott and Ellis (McDermott and Ellis, 1965) suggested that the vapor–liquid equilibrium data in a ternary mixture are thermodynamically consistent if $|D|$ for Eq. (6) is smaller than $D_{\max}=0.01$. Now we should find the value of $D_{\max}$ for the solubility of poorly soluble substances in mixed solvents for Eq. (11). Of course, this value should differ from that for the vapor–liquid equilibrium.

In order to find $D_{\max}$ the following procedure was employed:

1. Several data sets for the solubilities of poorly soluble substances in mixed solvents were selected from Solubility Data Series (Acree, 1995);
2. The selected data were correlated with reliable equations (Ruckenstein and Shulgin, 2003a,b);
3. Using the above equations, the solubility of the solute was calculated for small changes in the mixed solvent composition (2.5 mol%);
4. The value of D was calculated for each of the two neighboring points;
5. Artificial deviations (“errors”) were added to selected points and a criterium for thermodynamic consistency was identified.

Table 1
Correlation of the experimental data regarding the solubility (at room temperature) of anthracene in mixed solvents

Solvent + cosolvent	Solute	Reference	Deviation from experimental data[a]	
			3-Parameter equation (Ruckenstein and Shulgin, 2003a)	4-Parameter equation (Ruckenstein and Shulgin, 2003b)
1-Propanol-2-propanol	Anthracene	Acree, 1995	0.41	0.39
n-Hexane-cyclohexane	Anthracene	Acree, 1995	0.48	0.29

[a] Deviation from experimental data calculated as the mean percentage deviation (MPD) (%) defined as $\left(100\sum_{i=1}^{N_j}|(x_i^{\mathrm{exp}}-x_i^{\mathrm{calc}})/(x_i^{\mathrm{exp}})|\right)/N_j$, 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.

5. The use of the solubilities of anthracene in 1-propanol-2-propanol and anthracene in *n*-hexane–cyclohexane mixtures for the determination of the $D_{\max}$ value

The experimental data regarding the solubility of anthracene in 1-propanol-2-propanol and anthracene in *n*-hexane–cyclohexane mixtures were taken from the Solubility Data Series (Acree, 1995) and correlated with equations based on the fluctuation theory of solutions (Ruckenstein and Shulgin, 2003a,b). The results of these correlations are presented in Table 1. The values of D, calculated using Eq. (11), are plotted in Fig. 1a and b (Throughout this paper, the activity coefficients of the constituents of a solute-free mixed solvent were calculated with the Wilson equation (Wilson, 1964), using the Wilson parameters the values listed in Gmehling's vapor–liquid compilation (Gmehling and Onken, 1977)). In order to understand how the errors affected the values of D, 20% "error" was added to every second point and the D values were again calculated via Eq. (11). The results of these calculations are presented in Fig. 2. Figs. 1 and 2 show that for thermodynamically consistent data $|D| < D_{\max} = 10^{-4}$. One should note that the solubility of anthracene in 1-propanol-2-propanol varies in the range 4.1×10^{-4} to 5.9×10^{-4} mole fraction and the solubility of anthracene in *n*-hexane-cyclohexane varies in the range 1.3×10^{-3} to 1.6×10^{-3} mole fraction. It is of interest to calculate the D values for more soluble substances. We carried out such calculations (Fig. 3) for the solubility of pyrene in 1-propanol-2-propanol (for which the solubility varies in the range 3.9×10^{-3} to 4.3×10^{-3} mole fraction) and pyrene in *n*-hexane–cyclohexane mixtures (for which the solubility varies in the range 8.5×10^{-3} to 10.9×10^{-3} mole fraction) (Acree, 1995; Zvaigzne et al., 1995). Fig. 3 shows that the established limit ($|D| < D_{\max} = 10^{-4}$) is valid when the mole fraction solubility is smaller than 1 mol%.

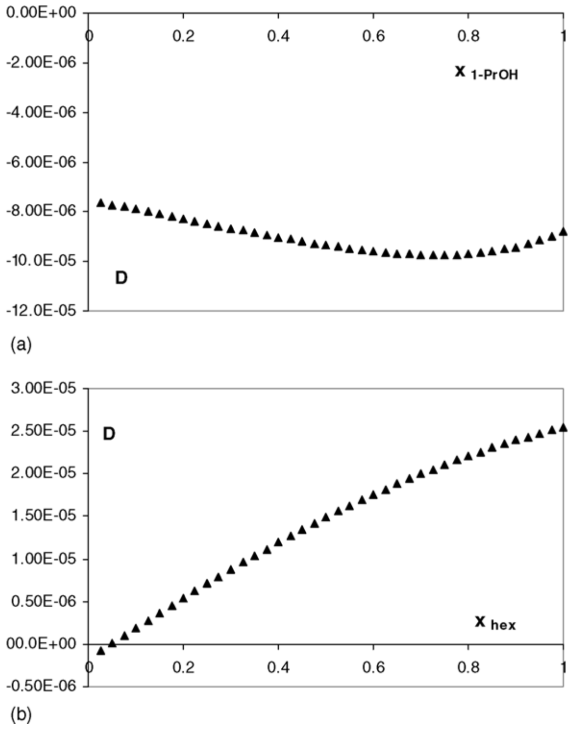

Fig. 1. D values obtained via Eq. (11) for the solubilities of anthracene in 1-propanol-2-propanol (a) and anthracene in *n*-hexane-cyclohexane (b).

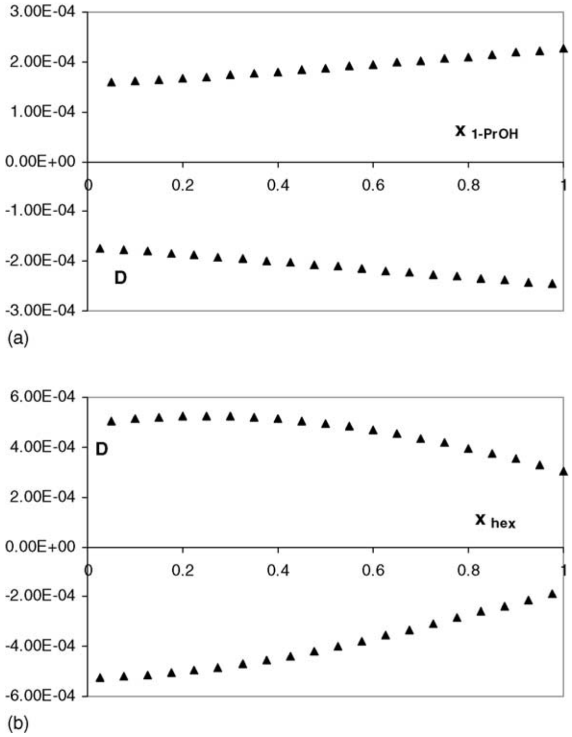

Fig. 2. *D* values obtained via Eq. (11) for the solubilities of anthracene in 1-propanol-2-propanol (a) and anthracene in *n*-hexane-cyclohexane (b) when 20% "errors" were added to every second point.

6. Application of Eq. (11) to the solubility of poorly soluble solids in aqueous mixed solvents

6.1. *Solubility of naphthalene in ethanol–water mixtures*

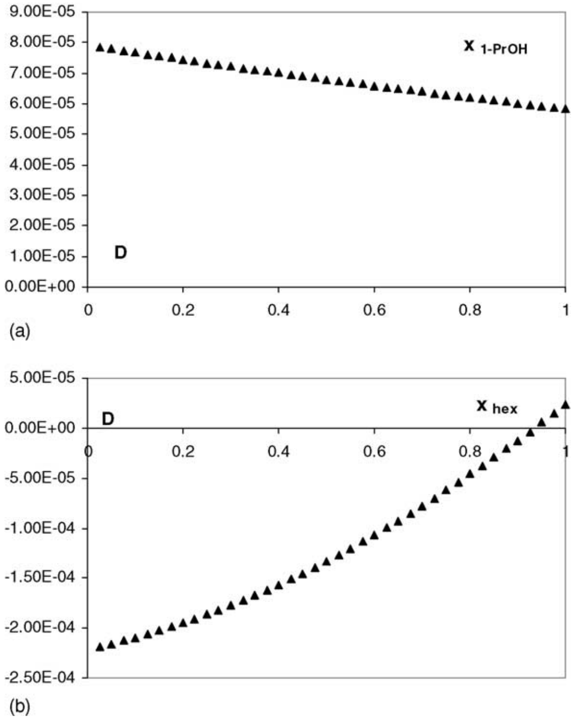

Fig. 3. *D* values obtained via Eq. (11) for the solubilities of pyrene in 1-propanol-2-propanol (a) and pyrene in *n*-hexane-cyclohexane (b).

There are several experimental determinations of the solubility of naphthalene in ethanol–water mixtures at room temperature (Bennett and Canady, 1984; Morris, 1988; Dickhut et al., 1989; LePree et al., 1994). These data deviate appreciably from each other (Fig. 4). The analysis of the above data with Eq. (11) (Table 2) indicated that those regarding the solubility of naphthalene in ethanol–water mixtures at room temperature, obtained by various authors, were thermodynamically consistent in the dilute region; however, the data of LePree et al. (1994), and Morris (1988) are thermodynamically inconsistent at high mole fractions of ethanol. Only the data for ethanol mole fractions less than 0.3 were analyzed by us, because the experimental determinations in the above publications were made with small changes in composition in that range only, and with large changes outside that range. For the latter cases, the trapezoidal rule for the integration of the Gibbs–Duhem equation might no longer be valid.

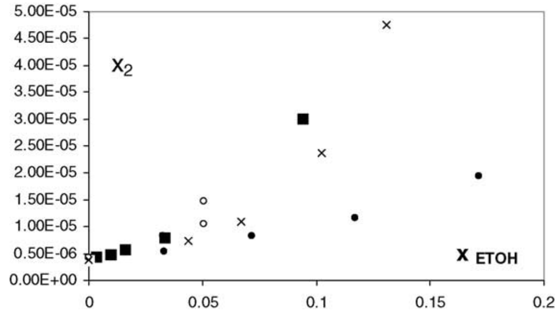

Fig. 4. The solubility of naphthalene (x_2) in ethanol–water mixtures at room temperature: (○) Bennett and Canady, 1984; (●) Morris, 1988; (■) Dickhut et al., 1989; (×) LePree et al., 1994). x_{ETOH} is the mole fraction of ethanol in the solute-free mixed solvent.

Table 2
D values obtained via Eq. (11) for data regarding the solubility of naphthalene in ethanol–water mixtures

Mole fraction of ethanol in the solute-free mixed solvent	Mole fraction of naphthalene solubility	Reference	*D*
0.0333	5.3E−06	A	
0.0720	8.2E−06	A	−5.9E−06
0.1173	1.2E−05	A	−6.6E−06
0.1713	1.9E−05	A	−1.6E−05
0.2367	2.3E−04	A	−6.2E−04
0.0159	5.9E−06	B	
0.0329	8.3E−06	B	−3.1E−06
0.0508	1.1E−05	B	−4.9E−06
0.0508	1.5E−05	B	−4.5E−06
0.0031	4.5E−06	C	
0.0095	4.8E−06	C	−5.5E−07
0.0161	5.8E−06	C	−2.0E−06
0.0333	8.0E−06	C	−4.4E−06
0.0937	3.0E−05	C	−5.1E−05
0.0438	7.3E−06	E	
0.0672	1.1E−05	E	−7.0E−06
0.1024	2.4E−05	E	−7.5E−06
0.1308	4.8E−05	E	−2.7E−05
0.1826	1.6E−04	E	−5.0E−05
0.2101	2.7E−04	E	−2.5E−04

A (Morris, 1988); B (Bennett and Canady, 1984); C (Dickhut et al., 1989); E (LePree et al., 1994).

In the present paper, Eq. (11) was used to analyze separately each of the sets of experimental data listed above. Therefore, each of the examinations was concerned with the internal consistency of a selected set.

6.2. *Solubility of naphthalene in acetone–water mixtures*

The analysis of the experimental solubilities of naphthalene in acetone–water mixtures at room

Table 3
D values obtained via Eq. (11) for data regarding the solubility of naphthalene in acetone–water mixtures

Mole fraction of ethanol in the solute-free mixed solvent	Mole fraction of naphthalene solubility	Reference	*D*
0.0176	7.4E−06	A	
0.0557	2.9E−05	A	−5.0E−05
0.0907	7.3E−05	A	−1.3E−04
0.1339	2.9E−04	A	−4.6E−04
0.1816	4.2E−04	A	−2.6E−04
0.2261	1.9E−03	A	−3.5E−03
0.0128	1.0E−05	B	
0.0266	1.7E−05	B	−1.3E−05
0.0580	6.9E−05	B	−1.2E−04
0.0954	2.0E−04	B	−2.8E−04
0.1410	7.2E−04	B	−1.2E−03
0.1975	2.3E−03	B	−3.5E−03
0.0266	9.3E−06	C	
0.0580	3.0E−05	C	−4.6E−05
0.0954	7.9E−05	C	−1.1E−04
0.1410	3.1E−04	C	−5.2E−04
0.1975	1.2E−03	C	−2.1E−03

A (LePree et al., 1994); B (Fu and Luthy, 1985); C (Morris, 1988).

temperature (LePree et al., 1994; Fu and Luthy, 1985; Morris, 1988), summarized in Table 3, shows that, as in the previous case, there is thermodynamic consistency in the diluted region. However, the data become increasingly inaccurate in more concentrated mixed solvents. Again, only the data for mole fractions of acetone less than 0.3 were considered.

6.3. *Solubility of naphthalene in ethylene glycol–water mixtures*

The analysis of the experimental solubilities of naphthalene in ethylene glycol–water mixtures at room temperature (Khossravi and Connors, 1992; Huot et al., 1991) showed that both experimental sets were accurate in a wide composition range with the exception of the points between $X_{\mathrm{ETD}} \approx 0.5$ and 0.6 (Fig. 5).

6.4. *Solubility of sulphamethoxypyridazine in ethanol–water mixtures*

The solubility of sulphamethoxypyridazine in ethanol–water mixtures represents a rare kind of drug solubility in an aqueous mixed solvent, because it exhibits two solubility maxima on the curve solubility versus mixed solvent composition (Escalera et al., 1994). It is of interest to verify if such behavior satisfies the thermodynamic consistency criterion. The values of D were calculated using Eq. (11), and the results are presented in Fig. 6. The latter figure shows that the second maximum (mole fraction of ethanol approximately 0.75) is thermodynamically less consistent than the first maximum (mole fraction of ethanol approximately 0.5).

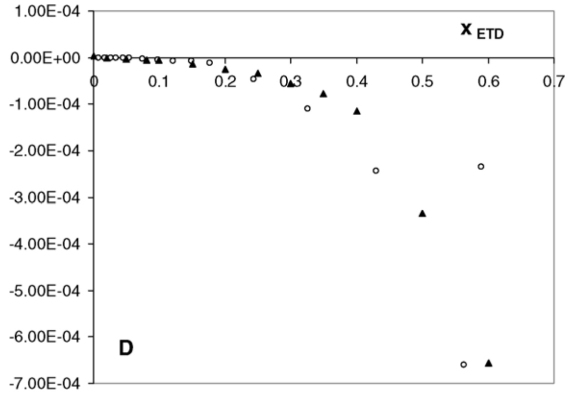

Fig. 5. D values calculated with Eq. (11) for the solubility of naphthalene in ethylene glycol–water mixtures at room temperature; (○) (Khossravi and Connors, 1992); (▲) (Huot et al., 1991). x_{ETD} is the mole fraction of ethylene glycol in a solute-free ethylene glycol–water mixture.

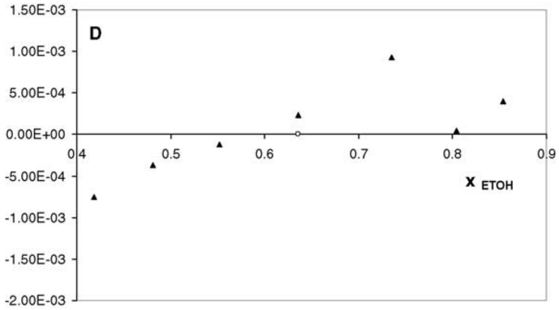

Fig. 6. D values (▲) calculated with Eq. (11) for the solubility of sulphamethoxypyridazine in ethanol–water mixture at room temperature. x_{EtOH} is the mole fraction of ethanol in a solute-free ethanol–water mixture.

7. Discussion and conclusion

The Gibbs–Duhem equation for ternary mixtures is used to analyze the quality of experimental data pertaining to the solubility of drugs and other poorly soluble solids in a binary mixed solvent. In order to test the quality of the data, a thermodynamic consistency test is suggested. This test is based on the thermodynamic relation between the solubilities of a solid in a binary mixed solvent at two different compositions and the activity coefficients of the constituents of the solute-free mixed solvent. The suggested test is applicable to all kinds of systems with the following limitations: (1) the solubility of the solid should be low, (2) the above two compositions of the mixed solvent should be close enough to each other.

The test was applied to a number of systems representing different types of solubilities of drugs and other poorly soluble substances in binary mixed solvents. It was shown that the suggested test could be helpful in the analysis of such experimental data.

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