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Research Article

Further Numerical Analyses on the Solubility of Sulfapyridine in Ethanol + Water Mixtures

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ABSTRACT

Background: Dissolution thermodynamic quantities of sulfapyridine (SP) have been reported in the literature for aqueous alcoholic mixtures. Nevertheless, no attempts to evaluate the preferential solvation of this drug in this binary system, have been reported. In this way, the inverse Kirkwood-Buff integrals (IKBI) were used to evaluate this behavior in solution.
Methods: Solubility data for SP dissolved in binary ethanol (EtOH) + water mixtures at various temperatures were mathematically represented using the Jouyban-Acree (J-A) model. The preferential solvation parameters of SP by EtOH ($\delta x_{1,3}$) in EtOH + water mixtures were obtained from some thermodynamic properties of the mixtures by means of the IKBI method.
Results: Solubility of SP in EtOH + water mixtures is adequately described by the J-A model in second order. Moreover, SP is sensitive to specific solvation effects, so the $\delta x_{1,3}$ values are negative in water-rich and EtOH-rich mixtures indicating preferential solvation by water in these mixtures. By contrary, $\delta x_{1,3}$ values are positive in the range $0.24 < x_1 < 0.53$ indicating preferential solvation by EtOH in these mixtures.
Conclusion: It can be assumed that in water-rich mixtures the hydrophobic hydration around the aromatic rings plays a relevant role in the solvation. The higher drug solvation by EtOH in mixtures of similar solvent proportions could be due to polarity effects. Moreover, in EtOH + water mixtures SP could be acting as a Lewis acid with the EtOH molecules and in EtOH-rich mixtures the drug could be acting as a Lewis base with water molecules.

Introduction

Sulfapyridine (SP, Figure 1A, $C_{11}H_{11}N_3O_2S$, molar mass of 249.29 g mol^{-1}, 4-amino-*N*-pyridin-2-yl-benzenesulfonamide, CAS number: 144-83-2) and sulfadiazine (SD, Figure 1B, $C_{10}H_{10}N_4O_2S$, 250.278 g mol^{-1}, 4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide, CAS number: 68-35-9) are sulfonamides that are sometimes used in treatment of some infections.[1,2] The aqueous solubilities of SP and SD are really low[3] and several non-toxic aqueous cosolvent mixtures have been evaluated to increase the solubilities.[4-8] Although some thermodynamic analyses were performed on sulfonamides in cosolvent + water mixtures, no attempt was made to correlate the equilibrium solubility with temperature and mixture's composition in the published papers.

The main goals of this work are to correlate the solubility of these drugs in ethanol (EtOH) + water mixtures by means of the Jouyban-Acree model, which is the most versatile and useful correlation-prediction model,[9] and also to evaluate the preferential solvation of SP in these mixtures by using the inverse Kirkwood-Buff integrals (IKBI),[10-12] as has been reported earlier for SD.[13] Thus, this work is similar to those reported previously in the literature with other pharmaceutical compounds.[14-16] As it is well known, the availability of this information is very important to understand the intermolecular interactions involved in the solubility

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of pharmaceutical compounds in cosolvent + water mixtures.[17] Moreover, EtOH and propylene glycol (PG) are the cosolvents more widely used in the development of homogeneous pharmaceutical dosage forms, due to their low toxicities, very good stabilities, and low costs.[18,19]

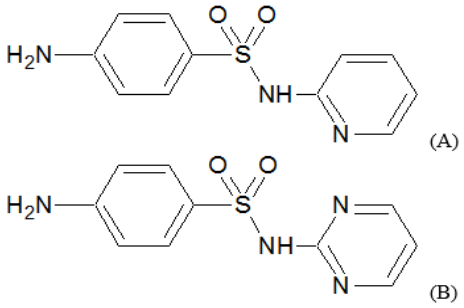

Figure 1. Molecular structure of sulfapyridine (A) and sulfadiazine (B).

In recent years there have been a growing number of experimental solubility studies for drugs dissolved in binary aqueous-organic solvent mixtures. Despite these experimental efforts, solubility measurements for all possible drug-solvent mixture combinations are not feasible. To address the needs of the pharmaceutical industry in predicting the solubility data in various solvent compositions and temperatures of interest, a number of mathematical models were presented to calculate the solubility of drugs in cosolvent + water mixtures.[20-21] The Jouyban-Acree model is one of the most versatile models that have been suggested thus far. The model is capable of predicting the solubility of drugs with an acceptable deviation from experimental data. The mathematical form of the model for representing solute solubility in a binary solvent mixture at various temperatures is:[21]

$$\ln x_{m,T}^{Sat} = m_1 \ln x_{1,T}^{Sat} + m_2 \ln x_{2,T}^{Sat} + \frac{m_1 m_2}{T} \sum_{i=0}^{2} J_i (m_1 - m_2)^i \quad \text{Eq.(1)}$$

where $x_{m,T}^{Sat}$ is the solute mole fraction solubility in the mixture at temperature T, m_1 and m_2 are the mass fractions of solvents 1 and 2 in the absence of the solute; $x_{1,T}^{Sat}$ and $x_{2,T}^{Sat}$ denote the mole fraction solubility of the solute in the mono-solvents 1 and 2 at the mixture temperature; and the J_i terms are the constants of the model computed by a regression analysis.[22] It should be noted that the solvent composition could be expressed as mole fraction, mass fraction or volume fraction. Slight variations in the numerical values of the J terms are expected for various units.

Solubility of a solute in a given solvent system at different temperatures (x_T^{Sat}) is calculated using the van't Hoff equation. The equation is:[23]

$$\ln x_T^{Sat} = A + \frac{B}{T} \quad \text{Eq.(2)}$$

where A and B are the model constants calculated using a least square method. Combination of the Jouyban-Acree and van't Hoff model provides a prediction tool for estimating the solubility of drugs in mixed solvents at various temperatures after one has determined the equation coefficients. The training process for calculating the equation coefficients employs two solubility data points; e.g. at the lowest and highest temperatures for each solvent.[24,25] The combined version could be represented be:

$$\ln x_{m,T}^{Sat} = m_1 \left(A_1 + \frac{B_1}{T} \right) + m_2 \left(A_2 + \frac{B_2}{T} \right) + \frac{m_1 m_2}{T} \sum_{i=0}^{2} J_i (m_1 - m_2)^i \quad \text{Eq.(3)}$$

where A_1, B_1, A_2, B_2 and J_i terms are the model constants. The mean relative deviation *(MRD)* was computed to evaluate prediction accuracy of different numerical methods using:

$$MRD = \frac{100}{N} \sum \left[\frac{\left| (x_{m,T}^{Sat})_{pred} - (x_{m,T}^{Sat})_{exp} \right|}{(x_{m,T}^{Sat})_{exp}} \right] \quad \text{Eq.(4)}$$

in which N is the number of data points in each set.

Results and Discussion

Jouyban-Acree model

The Jouyban-Acree model was trained using the solubility of SP in EtOH + water mixtures at different temperatures and the obtained model is:

$$\ln x_{m,T}^{Sat} = m_1 \ln x_{1,T}^{Sat} + m_2 \ln x_{2,T}^{Sat} + 1755.2 \left(\frac{m_1 m_2}{T} \right) + 852.0 \left(\frac{m_1 m_2 (m_1 - m_2)}{T} \right) - 758.2 \left(\frac{m_1 m_2 (m_1 - m_2)^2}{T} \right) \quad \text{Eq.(5)}$$

which correlates the solubility data with the correlation coefficient of 0.988, F value of 6829 and the MRD of 11.0 ± 11.1% (N=55).

The Jouyban-Acree model was globally trained using the solubilities of various drugs in EtOH + water mixtures at different temperatures and Abraham solute parameters. The obtained model is:[26]

$$\ln x_{m,T}^{Sat} = m_1 \ln x_{1,T}^{Sat} + m_2 \ln x_{2,T}^{Sat} + 2.303 \left(\frac{m_1 m_2}{T} \right) \{ 558.45 + 358.60E + 22.01S - 352.97A + 130.48B - 297.10V \} + 2.303 \left(\frac{m_1 m_2 (m_1 - m_2)}{T} \right) \{ 45.67 - 165.77E - 321.55S + 479.48A - 409.51B + 827.63V \} + 2.303 \left(\frac{m_1 m_2 (m_1 - m_2)^2}{T} \right) \{ -493.81 - 341.32E + 866.22S - 36.17A + 173.41B - 555.48V \} \quad \text{Eq.(6)}$$

where E is the solute's excess molar refraction, S is dipolarity/polarizability of solute, A denotes the solute's hydrogen-bond acidity, B stands for the solute's hydrogen-bond basicity and V is the McGowan volume of the solute. Equation 6 predicts the solubility of SP in EtOH + water mixtures at various temperatures with the MRD of 22.6 ± 31.3%. The computed numerical values of E, S, A, B and V for SP are 2.04, 2.58, 0.59, 1.40 and 1.7225, respectively.[27]

Equations (5) and (6) require experimental solubility data of the solute in both water and EtOH at each temperature of interest in the prediction process. As described above, Eq. (3) could be used to overcome this limitation. The trained version of Eq. (3) for solubility of SP in EtOH + water mixtures at various temperatures is:

$$\ln X_{m,T}^{Sat} = m_1\left(5.51-\frac{3970.5}{T}\right)+m_2\left(6.20-\frac{5034.9}{T}\right)+1761.7\left(\frac{m_1.m_2}{T}\right)+797.5\left(\frac{m_1.m_2(m_1-m_2)}{T}\right)-741.9\left(\frac{m_1.m_2(m_1-m_2)^2}{T}\right) \quad \text{Eq.(7)}$$

which correlates the solubility data with the correlation coefficient of 0.988, F value of 6829 and the MRD of 6.0 ± 5.7% (N=55).

Preferential solvation

Preferential solvation studies provide valuable information regarding molecular interactions and the solvent distribution surrounding a drug molecule dissolved in aqueous-organic cosolvent mixtures. Preferential solvation leads to a solvent distribution around that the dissolved solute that is different from the bulk solvent composition. The preferential solvation parameter of SP by EtOH in EtOH + water mixtures ($\delta x_{1,3}$) is defined as:[10-12]

$$\delta x_{1,3} = x_{1,3}^{L} - x_1 = -\delta x_{2,3} \quad \text{Eq.(8)}$$

the difference in the local mole fraction of EtOH in the environment near to SP, $x_{1,3}^{L}$, minus the bulk phase mole fraction composition of EtOH. SP is preferentially solvated by EtOH whenever $\delta x_{1,3} > 0$. Conversely, if $\delta x_{1,3}$ takes on a negative numerical value then SP is preferentially solvated by water. Numerical values of $\delta x_{1,3}$ are calculated from the inverse Kirkwood-Buff integrals for the individual solvent components as shown in the following equations:

$$G_{1,3} = RT\kappa_T - V_3 + x_2 V_2 D / Q \quad \text{Eq.(9)}$$

$$G_{2,3} = RT\kappa_T - V_3 + x_1 V_1 D / Q \quad \text{Eq.(10)}$$

Here κ_T is the isothermal compressibility of the solvent mixtures (given in units of GPa^{-1}), V_1 and V_2 are the respective partial molar volumes of the solvent components 1 and 2, and V_3 is the partial molar volume of SP. The functions D and Q are defined as follows:

$$D = \left(\frac{\partial \Delta_{tr} G^{o}_{3,2\rightarrow 1+2}}{\partial x_1}\right)_{T,p} \quad \text{Eq.(11)}$$

$$Q = RT + x_1 x_2 \left(\frac{\partial^2 G^{Exc}_{1+2}}{\partial x_2^2}\right)_{T,p} \quad \text{Eq.(12)}$$

In Eqs. (11) and (12) $\Delta_{tr}G^{o}_{3,2\rightarrow 1+2}$ is the standard molar Gibbs energy of transfer of SP from neat water to EtOH + water mixtures and G^{Exc}_{1+2} is the excess molar Gibbs energy of mixing of the binary aqueous-EtOH solvent mixture free of SP. The preferential solvation parameter, expressed in terms of the above quantities, can be calculated from the inverse Kirkwood-Buff integrals by means of Eq. (13):

$$\delta x_{1,3} = \frac{x_1 x_2 (G_{1,3} - G_{2,3})}{x_1 G_{1,3} + x_2 G_{2,3} + V_{cor}} \quad \text{Eq.(13)}$$

The correlation volume (V_{cor}) needed in the $\delta x_{1,3}$ computation is obtained by means of the following expression:

$$V_{cor} = 2522.5\left(r_3 + 0.1363\left(x_{1,3}^{L} V_1 + x_{2,3}^{L} V_2\right)^{1/3} - 0.085\right)^3 \quad \text{Eq.(14)}$$

where r_3 is the molecular radius of SP (expressed in nm). Calculation of correlation volume is achieved through an iterative process by replacing $\delta x_{1,3}$ in Eq. (8) to calculate $x_{1,3}^{L}$ until a non-variant value of V_{cor} is obtained.

Table 1 summarizes the Gibbs energy of transfer behavior for SP from neat water to binary EtOH + water mixtures at all five temperatures studied and Figure 2 depicts the behavior at the mean temperature, T_{mean} = 303.15 K. The tabulated numerical values were obtained from the mole fraction solubility of SP reported by Delgado *et al.*,[4] using the following equation:

$$\Delta_{tr}G^{o}_{3,2\rightarrow 1+2} = RT \ln\left(\frac{x_{3,2}}{x_{3,1+2}}\right) \quad \text{Eq.(15)}$$

The $\Delta_{tr}G^{o}_{3,2\rightarrow 1+2}$ values were correlated with the regular polynomial presented as Eq. (16). The curve-fit parameters are listed Table 2 for all five temperatures for which solubility were performed. The $\Delta_{tr}G^{o}_{3,2\rightarrow 1+2}$ values of SD were also shown in Figure 2 in the same mixtures at 303.15 K in which the trends exhibited by both drugs are very similar which is expectable from the Jouyban-Acree analysis.

$$\Delta_{tr}G^{o}_{3,2\rightarrow 1+2} = RT\ \ln\left(\frac{x_{3,2}}{x_{3,1+2}}\right) = a + bx_1 + cx_1^2 + dx_1^3 + ex_1^4 \quad \text{Eq.(16)}$$

The D values were calculated from the first derivative of the polynomial models solved according to the mixture's composition and listed in Table 3. The values of Q, $RT\kappa_T$ and partial molar volumes of the solvents in the mixtures were taken from the literature.[28] The molar volume of SP was also calculated by the Fedors' method (158.5 cm^3 mol^{-1}).[4,29]

$G_{1,3}$ and $G_{2,3}$ values (Tables 4 and 5) for most of the solvent compositions are negative indicating that SP exhibits affinity for both solvents in the mixtures, i.e. EtOH and water. Solute radius value (r_3) was also taken from the literature as 0.398 nm.[30] The correlation volume (V_{cor}) of SP was iterated three times by using Eqs. (8), (13) and (14) to obtain the numerical values reported in Table 6.

Table 1. Gibbs energy of transfer (kJ mol^{-1}) [a] of sulfapyridine in ethanol + water mixtures at several temperatures.

x_1 [b]	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.0000	0.00	0.00	0.00	0.00	0.00
0.0417	–0.20	–0.69	–0.88	–1.34	–1.77
0.0891	–1.64	–2.24	–2.61	–3.14	–3.63
0.1436	–3.73	–4.21	–4.40	–5.01	–5.63
0.2068	–5.22	–5.57	–5.94	–6.40	–6.84
0.2812	–6.37	–6.72	–7.00	–7.48	–7.86
0.3698	–7.24	–7.57	–7.82	–8.22	–8.59
0.4772	–7.61	–8.02	–8.16	–8.56	–8.92
0.6101	–7.72	–8.04	–8.25	–8.66	–8.94
0.7788	–7.31	–7.59	–7.82	–8.18	–8.31
1.0000	–6.53	–6.82	–6.93	–7.19	–7.42

[a] Calculated from sulfapyridine solubility values reported by Delgado *et al.*[4]
[b] x_1 is the mole fraction of ethanol in the ethanol + water mixtures free of sulfapyridine.

Table 2. Coefficients of the Eq. (16) (kJ mol^{-1}) applied to the Gibbs energy of transfer of sulfapyridine from neat water to ethanol + water mixtures at several temperatures.

Coefficient	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
a	0.68	0.41	0.33	0.20	0.07
b	–36.74	–38.28	–40.86	–46.47	–51.36
c	49.71	53.69	63.24	86.06	104.88
d	–20.17	–22.65	–35.32	–67.78	–92.06
e	–	–	5.66	20.79	31.06

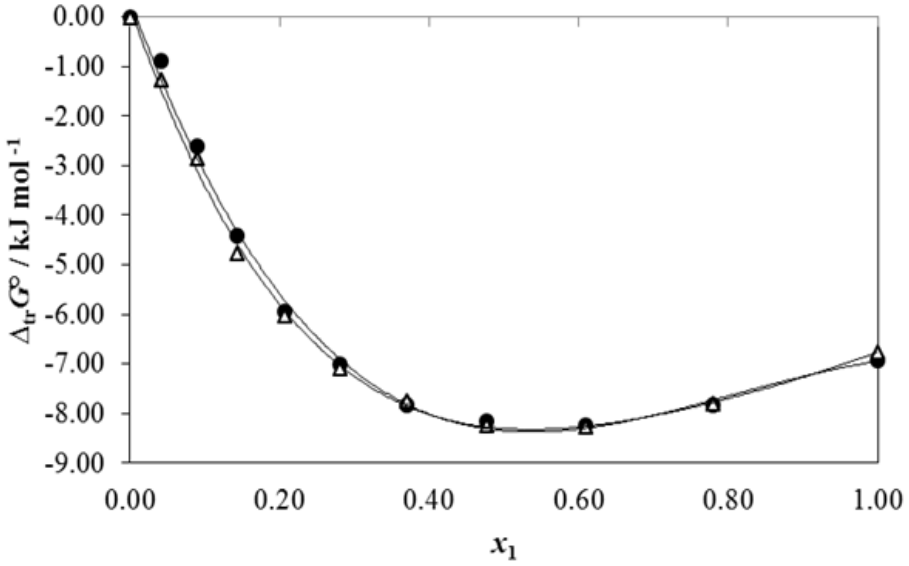

Figure 2. Gibbs energy of transfer of sulfapyridine (●) and sulfadiazine (Δ) from neat water to ethanol + water mixtures at 303.15 K.

Table 3. *D* values (kJ mol^{-1}) for sulfapyridine in ethanol + water mixtures at several temperatures.

x_1 [a]	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	–36.74	–38.28	–40.86	–46.47	–51.36
0.05	–31.92	–33.08	–34.80	–38.36	–41.54
0.10	–27.40	–28.22	–29.25	–31.21	–33.02
0.15	–23.18	–23.70	–24.20	–24.94	–25.69
0.20	–19.27	–19.52	–19.63	–19.51	–19.46
0.25	–15.66	–15.68	–15.51	–14.85	–14.24
0.30	–12.35	–12.18	–11.84	–10.89	–9.93
0.35	–9.35	–9.02	–8.60	–7.57	–6.44
0.40	–6.65	–6.20	–5.78	–4.84	–3.69
0.45	–4.25	–3.72	–3.34	–2.62	–1.57
0.50	–2.15	–1.57	–1.28	–0.85	0.01
0.55	–0.35	0.23	0.42	0.52	1.14
0.60	1.14	1.69	1.77	1.56	1.91
0.65	2.33	2.81	2.80	2.33	2.42
0.70	3.22	3.60	3.52	2.89	2.76
0.75	3.80	4.04	3.95	3.32	3.02
0.80	4.08	4.14	4.10	3.66	3.30
0.85	4.06	3.91	4.00	3.98	3.70
0.90	3.74	3.33	3.66	4.34	4.29
0.95	3.12	2.42	3.09	4.81	5.18
1.00	2.19	1.16	2.31	5.45	6.46

[a] x_1 is the mole fraction of ethanol in the ethanol + water mixtures free of sulfapyridine.

Table 4. $G_{1,3}$ values (cm^3 mol^{-1}) of sulfapyridine in ethanol + water mixtures at several temperatures.

x_1 [a]	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	–429.5	–436.5	–450.6	–485.8	–515.2
0.05	–402.3	–412.7	–427.6	–457.0	–484.0
0.10	–370.6	–381.3	–394.2	–415.3	–436.2
0.15	–337.2	–345.9	–355.0	–366.8	–379.1
0.20	–304.6	–310.1	–314.8	–318.1	–321.9
0.25	–274.3	–276.4	–277.4	–274.5	–271.8
0.30	–247.2	–246.5	–244.8	–238.5	–231.8
0.35	–223.6	–220.8	–217.7	–210.3	–202.1
0.40	–203.2	–199.3	–195.8	–188.9	–180.8
0.45	–185.9	–181.4	–178.3	–173.2	–166.2
0.50	–171.1	–166.8	–164.5	–161.6	–156.4
0.55	–158.8	–155.0	–153.8	–153.3	–149.9
0.60	–148.9	–145.8	–145.8	–147.4	–145.8
0.65	–141.7	–139.5	–140.3	–143.5	–143.5
0.70	–138.1	–136.7	–137.7	–141.5	–142.6
0.75	–138.4	–137.7	–138.5	–141.7	–143.2
0.80	–142.2	–142.0	–142.2	–143.9	–145.1
0.85	–147.3	–147.6	–147.3	–147.4	–147.9
0.90	–151.7	–152.1	–151.7	–150.9	–150.9
0.95	–154.5	–154.7	–154.4	–153.7	–153.5
1.00	–155.7	–155.6	–155.6	–155.5	–155.5

[a] x_1 is the mole fraction of ethanol in the ethanol + water mixtures free of sulfapyridine.

V_{cor} values increase slightly with temperature in EtOH-rich mixtures as expected from the respective molar expansibilities of the cosolvent mixtures in the absence of drug.[31]

Table 7 (at all temperatures) and Figure 3 (at 303.15 K) show that the $\delta x_{1,3}$ values vary non-linearly with the EtOH proportion in EtOH + water mixtures. Thus, the addition of EtOH to water leads to negative $\delta x_{1,3}$ values of SP from neat water to the mixture x_1 = 0.24, reaching a minimum value in the mixture x_1 = 0.10 with $\delta x_{1,3}$ = –2.494 x 10^{-2}. The negative values become more negative with increasing temperature. The hydrophobic hydration around the non-polar moieties of SP may possibly contribute to lower the net $\delta x_{1,3}$ to negative values in the water-rich mixtures, as was described earlier from classical thermodynamic analysis.[4]

Table 5. $G_{2,3}$ values ($cm^3\ mol^{-1}$) of sulfapyridine in ethanol + water mixtures at several temperatures.

x_1 [a]	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	–157.4	–157.4	–157.3	–157.3	–157.3
0.05	–195.4	–197.2	–199.9	–204.9	–209.4
0.10	–228.5	–232.5	–237.4	–245.1	–252.7
0.15	–254.4	–259.6	–265.2	–272.2	–279.6
0.20	–272.0	–276.9	–281.3	–284.3	–288.0
0.25	–281.1	–284.0	–285.6	–282.8	–280.5
0.30	–282.0	–281.7	–279.7	–271.1	–262.3
0.35	–275.1	–270.9	–265.6	–252.4	–238.2
0.40	–260.6	–252.3	–244.6	–229.3	–211.4
0.45	–238.2	–226.2	–217.6	–203.2	–183.9
0.50	–207.2	–192.3	–184.6	–174.6	–156.2
0.55	–166.7	–150.1	–145.3	–143.2	–128.4
0.60	–116.2	–99.4	–99.4	–108.4	–99.8
0.65	–57.9	–42.7	–48.1	–70.1	–70.1
0.70	0.2	12.3	2.9	–29.9	–39.5
0.75	42.8	50.6	41.4	6.1	–11.0
0.80	54.2	55.8	52.2	28.1	9.4
0.85	31.7	25.0	29.7	29.1	16.5
0.90	–12.0	–27.1	–14.2	13.2	11.9
0.95	–60.3	–81.8	–61.5	–9.0	2.0
1.00	–103.3	–128.1	–101.6	–29.3	–7.5

[a] x_1 is the mole fraction of ethanol in the ethanol + water mixtures free of sulfapyridine.

Table 6. Correlation volume of ($cm^3\ mol^{-1}$) of sulfapyridine in ethanol + water mixtures at several temperatures.

x_1 [a]	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	759	760	760	760	761
0.05	784	785	784	783	783
0.10	819	819	819	818	817
0.15	861	861	862	863	863
0.20	906	907	910	912	913
0.25	952	954	957	959	961
0.30	996	998	1001	1003	1005
0.35	1037	1040	1042	1043	1045
0.40	1076	1078	1080	1081	1082
0.45	1112	1113	1116	1117	1118
0.50	1146	1147	1149	1151	1152
0.55	1177	1178	1181	1184	1186
0.60	1207	1209	1213	1217	1220
0.65	1237	1239	1244	1250	1255
0.70	1268	1271	1276	1283	1289
0.75	1302	1306	1311	1318	1325
0.80	1341	1345	1350	1356	1362
0.85	1382	1387	1391	1395	1402
0.90	1424	1429	1433	1437	1442
0.95	1464	1469	1474	1477	1483
1.00	1501	1506	1512	1517	1523

[a] x_1 is the mole fraction of ethanol in the ethanol + water mixtures free of sulfapyridine.

In the range of $0.24 < x_1 < 0.53$, the local mole fractions of EtOH are higher than in the bulk mixtures as evidenced by the positive $\delta x_{1,3}$ values. Therefore, the cosolvent action of EtOH to increase the SP solubility could be related to the breaking of the ordered structure of water around the non-polar moieties of SP, *i.e.* the aromatic rings. This increases the solvation by EtOH exhibiting a maximum value in the mixture $x_1 = 0.35$ with $\delta x_{1,3} = 1.373 \times 10^{-2}$ at 303.15 K. The positive values diminish with the temperature arising. It is conjecturable that in this region SP is acting as a Lewis acid with EtOH molecules because EtOH is more basic than water. Accordingly, the Kamlet-Taft hydrogen bond acceptor parameters (β) are 0.75 for EtOH and 0.47 for water[32,33] and SP would prefer EtOH instead of water.

In EtOH-rich mixtures ($0.53 < x_1 < 1.00$), SP is

preferentially solvated by water again. Maxima negative values are obtained in x_1 = 0.75. Except at 293.15 K the negative values also diminish with the temperature arising. Here SP could be acting mainly as a Lewis base in favor of the water molecules because the Kamlet-Taft hydrogen bond donor parameters (α) are 1.17 for water and 0.86 for EtOH, respectively.[34,35] Thus, water is more acidic than EtOH. This behavior is similar to that exhibited by acetaminophen and some other sulfonamides in the same mixtures.[13,28] It is noteworthy that all these sulfonamides, SP, SD, sulfamerazine and sulfamethazine exhibit the maximum solubility in the mixture with mass fraction of 0.80 of EtOH (x_1 = 0.6101);[4,5,35] whereas, acetaminophen exhibits its maximum solubility in the mixtures with mass fraction of 0.90 of EtOH (x_1 = 0.7788).[36]

Table 7. IKBI $\delta x_{1,3}$ values (x 100) of sulfapyridine in ethanol + water mixtures at several temperatures.

x_1 [a]	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.00	0.000	0.000	0.000	0.000	0.000
0.05	–1.698	–1.776	–1.887	–2.116	–2.332
0.10	–2.219	–2.344	–2.494	–2.756	–3.025
0.15	–1.778	–1.870	–1.962	–2.091	–2.230
0.20	–0.832	–0.851	–0.865	–0.872	–0.877
0.25	0.188	0.211	0.227	0.229	0.240
0.30	1.007	1.016	1.001	0.922	0.852
0.35	1.502	1.449	1.373	1.189	1.003
0.40	1.642	1.504	1.371	1.116	0.831
0.45	1.444	1.222	1.062	0.802	0.464
0.50	0.943	0.660	0.516	0.329	–0.003
0.55	0.192	–0.118	–0.204	–0.242	–0.509
0.60	–0.733	–1.029	–1.025	–0.862	–1.010
0.65	–1.696	–1.943	–1.846	–1.475	–1.470
0.70	–2.478	–2.654	–2.502	–1.994	–1.839
0.75	–2.810	–2.905	–2.771	–2.283	–2.039
0.80	–2.539	–2.547	–2.496	–2.208	–1.979
0.85	–1.809	–1.738	–1.776	–1.765	–1.640
0.90	–0.978	–0.872	–0.956	–1.134	–1.121
0.95	–0.341	–0.263	–0.333	–0.517	–0.553
1.00	0.000	0.000	0.000	0.000	0.000

[a] x_1 is the mole fraction of ethanol in the ethanol + water mixtures free of sulfapyridine.

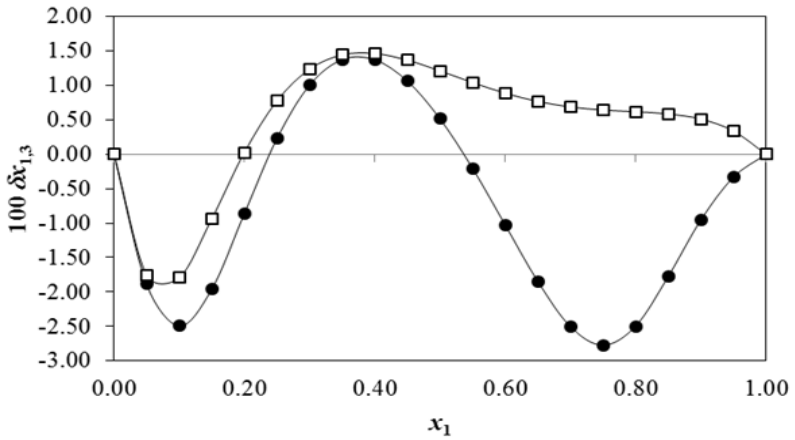

Figure 3. IKBI $\delta x_{1,3}$ values for sulfapyridine in ethanol + water (●) and propylene glycol + water (□) mixtures at 303.15 K.

Figure 3 also compares the preferential solvation of SP in EtOH + water mixtures with PG + water mixtures at 303.15 K.[30] The magnitude of preferential solvation of SP by water is higher in EtOH + water mixtures compared to PG + water mixtures. The maximum solvation magnitudes by the cosolvents are nearly the same and occur at approximately the same mixture compositions. It is important to note that EtOH is less polar than PG as described by their Hildebrand solubility parameters, *i.e.* δ = 26.5 MPa$^{1/2}$ for EtOH and 30.2 MPa$^{1/2}$ for PG.[37] Otherwise, a high difference in the solvation trends is that no preferential solvation by water is observed in PG-rich mixtures as it is in the case of the EtOH-rich mixtures. In this way, it is noteworthy that the maximum solubility of SP in PG + water

mixtures is obtained in the neat cosolvent.[6] This behavior is similar to that exhibited by acetaminophen,[38] but different compared with the behaviors exhibited by ketoprofen, indomethacin and daidzein. For the latter three solutes no preferential solvation by water was observed in EtOH-rich mixtures.[39-41]

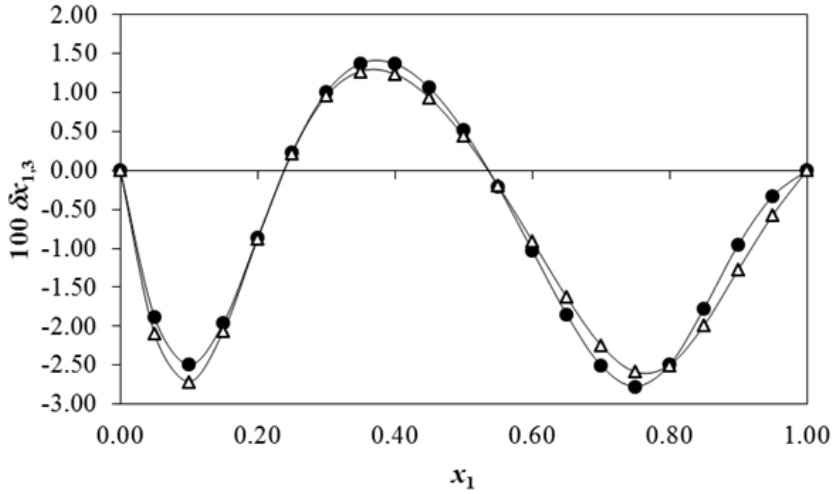

Figure 4. IKBI $\delta x_{1,3}$ values for sulfapyridine (●) and sulfadiazine (Δ) in ethanol + water mixtures at 303.15 K.

Finally, Figure 4 shows that no significant differences in preferential solvation of SP and SD by water and EtOH are observed at 303.15 K. This could be a consequence of the similar values of $\Delta_{tr}G^{o}_{3,2\rightarrow1+2}$ as depicted in Figure 2, although the Fedors' molar volumes are slightly different, *i.e.* 158.5 cm^3 mol^{-1} for SP and 150.0 cm^3 mol^{-1} for SD.[4,5]

Conclusions

The experimental mole fraction solubility data of SP in EtOH + water mixtures at various temperatures was mathematically represented using the Jouyban-Acree model with acceptable error levels. The reported work is a continuation of our earlier reports on generating experimental solubility data,[42-45] extending the available solubility data of pharmaceuticals[9] and also providing the derived thermodynamic parameters of the solutions composed of a drug and a binary solvent mixture.[46-48] Quantitative values relative to the local mole fraction of EtOH and water around SP were derived on the basis of the IKBI method applied to the equilibrium solubility of this drug in EtOH + water and at several temperatures. Thus, SP is preferentially solvated by water in water-rich mixtures and EtOH-rich but preferentially solvated by EtOH in those mixtures with similar proportion of solvents. In this way, some significant differences between the behaviors of SP in EtOH + water and PG + water mixtures were found. On the other hand, the preferential solvation trend of SP by water and EtOH in EtOH + water mixtures is almost the same as that exhibited by SD in the same mixtures.

Conflict of interests

The authors claim that there is no conflict of interest.

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