Solution thermodynamics and preferential solvation of sulfamethazine in (methanol + water) mixtures

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Abstract

The solubility of sulfamethazine (SMT) in {methanol (1) + water (2)} co-solvent mixtures was determined at five different temperatures from 293.15 K to 313.15 K. The sulfonamide exhibited its highest mole fraction solubility in pure methanol (δ_1 = 29.6 MPa$^{1/2}$) and its lowest mole fraction solubility in water (δ_2 = 47.8 MPa$^{1/2}$) at each of the five temperatures studied. The Jouyban-Acree model was used to correlate/predict the solubility values. The respective apparent thermodynamic functions Gibbs energy, enthalpy, and entropy of solution were obtained from the solubility data through the van't Hoff and Gibbs equations. Apparent thermodynamic quantities of mixing were also calculated for this drug using values of the ideal solubility reported in the literature. A non-linear enthalpy–entropy relationship was noted for SMT in plots of both the enthalpy vs. Gibbs energy of

mixing and the enthalpy vs. entropy of mixing. These plots suggest two different trends according to the slopes obtained when the composition of the mixtures changes. Accordingly, the mechanism for SMT transfer processes in water-rich mixtures from water to the mixture with 0.70 in mass fraction of methanol is entropy driven. Conversely, the mechanism is enthalpy driven in mixtures whenever the methanol composition exceeds 0.70 mole fraction. An inverse Kirkwood-Buff integral analysis of the preferential solvation of SMT indicated that the drug is preferentially solvated by water in water-rich mixtures but is preferentially solvated by methanol in methanol-rich mixtures.

Key words: Sulfamethazine, methanol, solubility, Jouyban-Acree model, activity coefficient, solution thermodynamic quantities, preferential solvation.

1. Introduction

Experimental determination of the solubility of drug molecules in aqueous-organic co-solvent systems is needed in order to design effective purification processes and to formulate suitable pharmaceutical drug delivery systems [1, 2]. For this, it is very important to determine systematically the solubility of pharmaceutical ingredients in mixtures containing different types of organic co-solvents in order to obtain complete physicochemical data about liquid pharmaceutical systems [3]. Sulfamethazine (SMT, also known as sulfadimidine, figure 1, molar mass 278.33 g·mol^{-1}, IUPAC name: 4-amino-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, CAS number: 57-68-1) is a commonly employed sulfonamide drug for the prevention and cure of various types of bacterial infections [4, 5]. SMT equilibrium solubility in water at room temperature is low and SMT is thus classified as a very slightly soluble drug [6, 7]. Added co-solvents often provide a convenient means to increase the solubility of slightly soluble drug molecule. Researchers have measured the solubility of SMT in several {hydroxyl-co-solvent (1) + water (2)} mixtures in order to provide useful information that is needed to develop some pharmaceutical dosage forms and/or to understand the main mechanisms involved in the drug solubilisation [8-10]. For example, the solubility and solution thermodynamics of SMT has been studied in {ethanol (1) + water (2)} [8] and {1-propanol (1) + water (2)} [9] binary mixtures; whereas, the preferential solvation of the drug by the solvent components has been studied in {ethanol (1) + water (2)} [11], {1-propanol (1) + water (2)} [12], and {propylene glycol (1) + water (2)} [10] binary mixtures.

Figure 1

The main goals of this research study are the following: i) to determine the equilibrium solubility of SMT in several {methanol (1) + water (2)} mixtures at five temperatures from 298.15 K to 318.15 K, ii) to calculate the respective thermodynamic quantities of solution and mixing of this drug in this binary aqueous-organic co-solvent system, and iii) to estimate the respective preferential solvation parameters of SMT as a function of binary solvent composition. Thus, this research would be a continuation of earlier studies published in the chemical and pharmaceutical literature for SMT dissolved in other aqueous-organic co-solvent mixtures [8-10]. We note that methanol is a semi-polar co-solvent completely miscible with water which is widely used as mobile phase in HLPC analytical techniques [13]. Methanol is sometimes utilized in microencapsulation procedures due to it has high solubilizing power [14]. Thermodynamic studies regarding the solubility of two other structurally related sulfonamides (sulfadiazine and sulfamerazine; see figure 1 for the molecular structures of both compounds) in aqueous-methanolic mixtures have been recently reported in the literature [15, 16]. Published solubility studies for both sulfadiazine and sulfamerazine further suggest the practical usefulness of aqueous-methanolic mixtures in the pharmaceutical field.

2. Experimental

2.1. Reagents

In this study, SMT (Sigma Chemical Co., USA, compound 3, with purity at least 0.990 in mass fraction), methanol A. R. (Merck, Germany, solvent component 1, purity at least 0.998 in mass fraction), and distilled water with conductivity < 2 $\mu S \cdot cm^{-1}$ (the solvent component 2), were used. Chemical suppliers, purities and other select properties of the reagents are summarized in table 1. The sample of SMT met the United States Pharmacopeia requirements [17].

Table 1

2.2. Preparation of solvent mixtures

All {methanol (1) + water (2)} solvent mixtures were prepared by mass, using an Ohaus Pioneer TM PA214 analytical balance with sensitivity ± 0.1 mg, in quantities of 50.00 g. The mass fractions of methanol, w_1, of the nine mixtures prepared varied by 0.10 from 0.10 to 0.90.

2.3. Solubility determinations

Solubilities were determined by a static spectrophotometric method. The experimental methodology was nearly identical to that reported previously for SMT dissolved in binary aqueous-alcoholic mixtures containing ethanol [8] and 1-propanol [9]. Briefly, an excess amount of SMT was added to approximately 10.0 g of each binary solvent mixture or pure solvent, in stoppered dark glass flasks. The flasks were then placed in an ultrasonic bath (Elma® E6011 Elmasonic, USA) for approximately 15 min and then transferred to thermostatted mechanical shakers (Julabo SW23, Germany) maintained at 303.15, 308.15, or 313.15 (± 0.05) K and to re-circulating thermostatted baths (Neslab RTE 10 Digital One Thermo Electron Company, USA) maintained at 293.15 K or 298.15 (± 0.05) K. The samples were allowed to equilibrate for at least four days to insure that saturation had been achieved. A four-day equilibrium time was previously established by measuring the drug concentrations in pure water until a constant solubility was obtained. After four days the supernatant solutions were filtered at isothermal conditions (Millipore Corp. Swinnex®-13, USA) to ensure that they were free of particulate matter before sampling. Drug concentrations were determined after appropriate gravimetric dilution with dehydrated ethanol by measuring the UV light absorbance at the wavelength of maximum absorbance, 268 nm (UV/VIS BioMate 3 Thermo Electron Company spectrophotometer, USA), and interpolation from a previously constructed UV spectrophotometric gravimetric calibration curve following a validated method [18]. Basically, the parameters evaluated during the validation were specificity, linearity, precision, and detection and quantification limits, as well as the drug stability under the solubility analysis conditions. The obtained calibration curve was $y = 1.2 \times 10^{-3} + 6.21 \times 10^{-2} x$, where y is the absorbance and x is the SMT concentration expressed in $\mu g \cdot g^{-1}$. This curve was constructed for drug concentrations from (2.0 to 15.0) $\mu g \cdot g^{-1}$ with absorbance lower than 1.00 [18]. It is important to note that the gravimetric dilution factors varied from almost 100 for pure water solutions to almost 2000 for pure methanol solutions. All the solubility experiments were performed at least three times. The density of the saturated solutions was measured using a digital density meter (DMA 45 Anton Paar, Austria) connected to re-circulating thermostatic baths (Neslab RTE 10 Digital One Thermo Electron Company, USA) in order to transform solubility values into different concentration scales [19]. The density meter was calibrated by using air and water as standards.

2.4. Calorimetric study

Melting point and enthalpy of fusion of SMT as original sample and bottom phases of saturated solutions in pure water, pure methanol and the mixtures with $w_1 = 0.50$ were determined by DSC studies (TA Instruments DSC 2920, USA). Thermal analyses were performed at a heating rate of 10

$K \cdot min^{-1}$ in a dynamic nitrogen atmosphere (10 $cm^3 \cdot min^{-1}$). Nearly 7.0 mg of SMT was used in each case. The equipment was calibrated using indium as standard.

2.5. X-ray diffraction analysis

In order to identify the SMT polymorph employed here as original sample and also in bottom phases of saturated solutions in pure water, pure methanol and the mixtures with $w_1 = 0.50$ the respective X-ray diffraction spectrum was carried out on the original of the sample was measured. The spectrum was obtained by using a PANalytical X'Pert PRO diffractometer with Cu Kα1 radiation line ($\lambda = 0.1540598$ nm) and Bragg-Brentano geometry. It was operated in continuous mode between $2\theta = 5°$ and $2\theta = 90°$ and angle variation of 0.02° with detector data acquisition time of 60 s.

3. Results and discussion

3.1. Equilibrium solubility of SMT

Table 2 reports the experimental solubility of SMT expressed both in mole fraction and molarity ($mol \cdot dm^{-3}$) at each of the five temperatures studied. Table 3 reports the density of the saturated solutions. These density values were used to convert the solubility values expressed in mole fraction into molarity ($mol \cdot dm^{-3}$). The equilibrium mole fraction solubility of SMT increased with increasing methanol concentration, from $x_3 = 2.81 \times 10^{-5}$ in pure water to $x_3 = 2.01 \times 10^{-3}$ in pure methanol at 298.15 K. On a mole fraction basis, SMT is approximately 72 times more soluble in methanol than in water at 298.15 K. Regarding the mole fraction solubility of SMT (3) in pure water (2) at temperatures from 298.15 K to 313.15 K our values are almost similar compared with those reported by Martínez and Gómez [20] and by Zhang *et al.* [21], except at 313.15 K (*i.e.* $x_3 = 2.896 \times 10^{-5}$ [20] and $x_3 = 2.919 \times 10^{-5}$ [21] at 298.15 K; $x_3 = 3.613 \times 10^{-5}$ [20] and $x_3 = 3.565 \times 10^{-5}$ [21] at 303.15 K; $x_3 = 4.244 \times 10^{-5}$ [20] and $x_3 = 4.188 \times 10^{-5}$ [21] at 308.15 K; and $x_3 = 5.175 \times 10^{-5}$ [20] and $x_3 = 4.903 \times 10^{-5}$ [21] at 313.15 K, respectively). Moreover, it is noteworthy that the values reported by Martínez and Gómez were determined in a buffer with ionic strength adjusted with potassium chloride to 0.15 $mol \cdot dm^{-3}$ instead of pure water (1) [20]. In the case of pure methanol, our solubility values are almost one-hundred times higher than those reported by Zhang *et al.* [22], *i.e.* at 298.15 K: $x_3 = 1.30 \times 10^{-5}$ compared with $x_3 = 2.01 \times 10^{-3}$ (table 2). A graphical comparison of SMT (3) solubility values in pure methanol (1) between our data and those reported by Zhang *et al.* [22] is depicted in figure 2. The solubility value reported by Zhang *et al.* seems abnormally low, and would mean that SMT is more soluble in water

than in pure methanol on both a mole fraction and molarity basis. The reasons for this high disagreement between experimental values are not clear because discrepancies between values measured by independent research groups are normally only a few relative per cent, and in the worst case differ by much as a factor of two or three [3]. X-ray diffraction and DSC analyses shown in figures 2 and 3 would demonstrate that no polymorphic or solvatomorphic transitions are observed after the SMT saturation in pure water, pure methanol and the mixture with w_1 = 0.50. Although, some polymorphic transitions and/or solvate formations have been reported in the literature [23, 24], apparently, this is not the case in our experiments because all the diffractograms are very similar (figures 3A, 3B, 3C, and 3D) and only one endothermic peak is observed in all the DSC analyses (figure 4). In this way, the onset fusion temperatures are almost the same as indicated as follows: 469.2 K for the original sample, 469.9 K for solid from pure water-saturation, 470.1 K for solid from pure methanol-saturation, and 469.7 K for solid from the methanol-water mixture-saturation. Mean standard uncertainty in SMT fusion temperature was ±0.4 K. These temperature values are similar to those reported in the literature for this drug, *i.e.* 469.0 K [20], 471.6 K [25], and 468.6 K [26]. Furthermore, the respective specific enthalpies of fusion are also very similar just as follows: 135.5 $J \cdot g^{-1}$ for the original sample, 135.5 $J \cdot g^{-1}$ for solid from pure water-saturation, 124.9 $J \cdot g^{-1}$ for solid from pure methanol-saturation, and 137.0 $J \cdot g^{-1}$ for solid from the methanol-water mixture-saturation. The mean standard uncertainty in SMT specific enthalpy of fusion was ±2.6 $J \cdot g^{-1}$. Nevertheless, these enthalpy values show some significant differences in comparison with those of the literature, *i.e.* 140.9 $J \cdot g^{-1}$ [20], 111.8 $J \cdot g^{-1}$ [25], and 161.0 $J \cdot g^{-1}$ [26]. These differences could be due to the thermal method employed, *i.e.* differential scanning calorimetry or differential thermal analysis, or even to the heating rate. On the other hand, to the best of our knowledge no solubility values for this drug in {methanol (1) + water (2)} mixtures have been reported and comparisons are not possible. It is interesting to note that SMT solubility in terms of both mole fraction and molar increases constantly from pure water (2) to pure methanol (1) reaching the solubility maximum in pure methanol (1) (table 1). Table 2 also reports the ideal solubility of SMT taken from the literature [8, 9]. To evaluate the effect of methyl groups substitution on solubility figure 5 compares the logarithmic mole fraction solubility of SMT, sulfadiazine [15] and sulfamerazine [16] in binary {methanol (1) + water} mixtures. It is clear that in all the solvent mixtures and in both pure solvents the solubility decreases in the following manner: SMT > sulfamerazine > sulfadiazine.

Tables 2 and 3, Figs. 2 to 5

As noted above, there is published literature data for the solubility of SMT dissolved in aqueous-ethanol and aqueous-propanol mixtures that can be used to study the effect that alkyl chain length has on the solubility of SMT. Methanol, ethanol and 1-propanol are all primary alcohols, and their molecular structures differ by a single CH_2 group. The mole fraction solubility of SMT in the fore-mentioned alcohols decreases with increasing alkyl chain length, *i.e.*, SMT solubility is largest in methanol (x_3 = 2.01 x 10^{-3}), slightly smaller in ethanol (x_3 = 9.18 x 10^{-4}; [8]), and smallest in 1-propanol (x_3 = 5.41 x 10^{-4}; [9]). The mole fraction solubility reported by Zhang *et al.* (x_3 = 1.30 x 10^{-5}; [22]) falls way out of line with this trend. Figure 6 shows the logarithmic mole fraction solubility profiles of SMT in {methanol (1) + water (2)}, {ethanol (1) + water (2)} [8], and {1-propanol (1) + water (2)} [9] mixtures, as a function of the Hildebrand solubility parameter of the mixtures free of drug (δ_{1+2}) at T = 298.15 K. For binary mixtures δ_{1+2} is calculated as [19, 27]:

$$\delta_{1+2} = f_1\delta_1 + (1 - f_1)\delta_2 \qquad (1)$$

A solute-free ideal volume fraction, f_1, average of the solubility parameter of the pure solvents (δ_1 = 29.6 $MPa^{1/2}$ for methanol, 26.5 $MPa^{1/2}$ for ethanol, 24.5 $MPa^{1/2}$ for 1-propanol, and finally, δ_2 = 47.8 $MPa^{1/2}$ for water; [28]). It is interesting to note that in this case the SMT solubility in {methanol (1) + water (2)} mixtures is higher in comparison with the other two {n-alcohol (1) + water (2)} mixtures in alcohol-rich mixtures but in water-rich mixtures it is similar to that exhibited in {ethanol (1) + water (2)} mixtures [8] and lower than reported in {1-propanol (1) + water (2)} [9] mixtures.

Figure 6

3.2. Log-linear model of Yalkowsky

Predictive methods to estimate the physicochemical properties of drug molecules dissolved in solvent mixtures are highly valued in practical pharmaceutical applications. Several methods have been proposed in the pharmaceutical and chemical literature over the years to estimate the solubility in aqueous-organic co-solvent mixtures. No one single model has been found to describe the variation of drug solubility with binary solvent composition. In fact several of the suggested methods have been challenged in the correlation of the equilibrium solubility of several drugs [3, 29, 30]. The simplest model to predict drug solubility in co-solvent mixtures is the one based on the algebraic rule of mixing [31] which is presented as:

$$\ln C'_{3-(1+2)} = f_1 \ln C'_{3-1} + f_2 \ln C'_{3-2} \quad (2)$$

where $C'_{3-(1+2)}$ is the molar drug solubility calculated in the respective co-solvent mixture, C'_{3-1} is the molar drug solubility in pure methanol (component 1), C'_{3-2} is the molar drug solubility in pure water (component 2), and f_1 and f_2 are the volume fractions of methanol and water in the mixtures free of drug. Although the original model was presented based on volume fractions of the solvent mixtures, it is possible to employ the model concerning the mass fractions or other composition expressions. Equation (2) is very useful from a practical point of view owing to its simplicity because it requires only the drug solubility in the pure solvents, *i.e.* water and the co-solvent under consideration. Nevertheless, some significant deviations to this simple model have been reported in the literature for several drugs [32-34]. In this way, figure 7 shows that negative and positive deviations are observed for SMT and sulfamerazine in {methanol (1) + water (2)} mixtures when the differences between experimental and ideal-additive solubility are plotted as a function of the volume fraction of methanol (1) in the mixtures free of drug. This behaviour is similar to those exhibited by sulfamethizole [32], sulfapyridine [33], and some alkyl p-hydroxybenzoates and alkyl p-aminobenzoates [34], in propylene {glycol (1) + water (2)} mixtures. It is relevant to consider that propylene glycol has a similar polarity compared with methanol [19, 28]. It is noteworthy that negative deviations in water-rich mixtures have been interpreted as a consequence of the possible auto-association of water molecules around the non-polar moieties of the drugs (*i.e.* hydrophobic hydration); whereas, positive deviations in co-solvent-rich mixtures have been discussed mainly in terms of a possible specific solvation of the drug by co-solvent molecules, which could be apparently modifying the polarity of the solute if this is considered in its solvated form [34].

Figure 7

A predictive version of the model was reported to predict the solubility of solutes in (methanol + water) mixtures as [35]:

$$\ln C'_{3-(1+2)} = \ln C'_{3-2} + f_1(0.89 \log K_{ow} + 0.36) \quad (3)$$

in which $\log K_{ow}$ is the logarithm of drug's partition coefficient (equal to 0.89 for SMT taken from the published literature [36]). It is important to keep in mind that Eqn. (3) was proposed to overcome the requirement of the drug solubility value in pure methanol as it is necessary in Eqn. (2) [35]. The mean

percentage deviation (MPD) for predicted solubility data of SMT using Eqn. (3) was 59.0 %. The MPD is computed using:

$$MPD = \frac{100}{N}\sum \frac{\left|C^{cal} - C\right|}{C} \tag{4}$$

where N is the number of experimental data points. It should be noted that Eqn. (3) requires only one datum, *i.e.* aqueous solubility of SMT for prediction of the values in (methanol + water) mixtures at each temperature.

3.3. Jouyban-Acree model

The solubility of solutes in mixed solvents could be computed using a number of co-solvency models reported in the literature [29]. The Jouyban-Acree model is perhaps one of the more accurate and versatile of the suggested models for mathematically representing the solubility of drugs in mixed solvents at various temperatures [37]. The general form of the model is presented as:

$$\ln C_{3-(1+2)} = w_1 \ln C_{3-1} + w_2 \ln C_{3-2} + \left(\frac{w_1 w_2}{T}\right)\sum_{i=0}^{2} J_i (w_1 - w_2)^i \tag{5}$$

where w_1 and w_2 are the mass fractions of solvents 1 (methanol in this work) and 2 (water in this work) and J_i terms are the model constants computed using a no intercept least square analysis [38]. The generated solubility of SMT in (methanol + water) was fitted to Eqn. (5) and the obtained model is:

$$\ln C_{3-(1+2)} = w_1 \ln C_{3-1} + w_2 \ln C_{3-2} + \left(\frac{w_1 w_2}{T}\right)\left[710.470 + 578.399(w_1 - w_2) - 193.549(w_1 - w_2)^2\right] \tag{6}$$

The correlation coefficient of Eqn. (6) was 0.991, F value was 937, the correlation and the model constants were significant with $p < 0.0005$. Equation (6) is valid for calculating the solubility of SMT in (methanol + water) mixtures at various temperatures by employing the solubility data of SMT in methanol and water at T. The obtained MPD for back-calculated solubility data of SMT using Eqn. (6)

was 4.1 %. The Jouyban-Acree model was combined with the van't Hoff equation to provide a more predictive model [39, 40] as:

$$\ln C_{3-(1+2)} = w_1\left(\alpha_1 + \frac{\beta_1}{T}\right) + w_2\left(\alpha_2 + \frac{\beta_2}{T}\right) + \left(\frac{w_1 w_2}{T}\right)\sum_{i=0}^{2} J_i (w_1 - w_2)^i \tag{7}$$

where α_i and β_i terms represent the intercept and slope of van't Hoff equation for pure solvent component i. The trained model for the solubility of SMT in (methanol + water) at various temperatures is:

$$\begin{aligned}\ln C_{3-(1+2)} = {} & w_1\left(9.631 - \frac{4724.452}{T}\right) + w_2\left(4.836 - \frac{4572.766}{T}\right) \\ & + \left(\frac{w_1 w_2}{T}\right)\left[618.007 + 543.944(w_1 - w_2) - 175.183(w_1 - w_2)^2\right]\end{aligned} \tag{8}$$

which correlates the measured solubility to within a MPD of 3.0%.

The Jouyban-Acree model could be trained for representing the mole fraction solubility of SMT as:

$$\ln x_{3-(1+2)} = w_1 \ln x_{3,1} + w_2 \ln x_{3,2} + \left(\frac{w_1 w_2}{T}\right)\left[620.144 + 560.791(w_1 - w_2) - 169.842(w_1 - w_2)^2\right] \tag{9}$$

where x is the mole fraction solubility of the solute and the subscripts are defined the same as Eqn. (6). Equation (9) back-calculates the solubility of SMT with the MPD of 4.0%.

A generally trained version of the Jouyban-Acree model employing Abraham parameters was developed to predict the solubility of drugs in binary solvent mixtures [41] as:

$$\ln C_{3-(1+2)} = w_1 \ln C_{3-1} + w_2 \ln C_{3-2}$$
$$+ 2.303\left(\frac{w_1 w_2}{T}\right)\begin{Bmatrix}1843.99 - 730.65\left[(c_1 - c_2)^2\right] - 1585.60\left[E(e_1 - e_2)^2\right] - 16.31\left[S(s_1 - s_2)^2\right] \\ + 0.89\left[A(a_1 - a_2)^2\right] + 1.40\left[B(b_1 - b_2)^2\right] + 1.98\left[V(v_1 - v_2)^2\right]\end{Bmatrix}$$
$$+ 2.303\left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right)\begin{Bmatrix}-833.40 + 860.17\left[(c_1 - c_2)^2\right] + 135.24\left[E(e_1 - e_2)^2\right] + 0.92\left[S(s_1 - s_2)^2\right] \\ + 34.99\left[A(a_1 - a_2)^2\right] - 2.03\left[B(b_1 - b_2)^2\right] - 2.94\left[V(v_1 - v_2)^2\right]\end{Bmatrix}$$
$$+ 2.303\left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right)\begin{Bmatrix}2281.87 - 1386.20\left[(c_1 - c_2)^2\right] - 166.92\left[E(e_1 - e_2)^2\right] - 16.60\left[S(s_1 - s_2)^2\right] \\ + 7.98\left[A(a_1 - a_2)^2\right] + 7.72\left[B(b_1 - b_2)^2\right] - 16.07\left[V(v_1 - v_2)^2\right]\end{Bmatrix} \quad (10)$$

where E is the 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 calculated from atomic group sizes and the number of chemical bonds in the solute molecule. The constant (c) and equation coefficients (*e, s, a, b* and *v)* that follow the solute descriptors in Eqn. (10) provide the complimentary properties of the respective solvent components. For example, the a_1 provides information pertaining to the hydrogen-bond basicity of solvent component 1, which when multiplied by solute descriptor A describes a hydrogen-bonding interaction where the solute functions as the H-bond donor and the solvent is the H-bond acceptor. The Abraham solvent coefficients (*c, e, s, a, b* and *v*) for methanol are 0.329, 0.299, –0.671, 0.080, –3.389 and 3.512, respectively. The corresponding values for water are –0.994, 0.577, 2.549, 3.813, 4.841 and –0.869. The numerical values of the Abraham solute parameters (*E, S, A, B* and *V*) for SMT were 2.13, 2.46, 0.59, 1.41 and 2.08, respectively [42]. The subscripts 1 and 2 denote methanol and water, respectively. The molar solubility of SMT was predicted using Eqn. (10) and the MPD value for the predicted data points was calculated as 21.5 % which is significantly less than 42.4 % of the original report [41] obtained for prediction of 47 drugs in aqueous mixtures of eight co-solvents at several temperatures. Eqn. (10) is very simple model that permits a straightforward computation of the solute's solubility in mixed solvents as described in XLS file of the supplementary information of a previous paper [41]. To use the XLS file one simply inserts the numerical values of Abraham solvent parameters for methanol, the Abraham solute parameters for SMT and the fractions of methanol. The solubility of STM will be computed automatically. It is noteworthy that MS Excel® and TableCurve 2D computer programs were used to perform the mathematical analysis along this research.

3.4. Activity coefficients of SMT

Table 4 gives the activity coefficients of SMT (3) γ_3, which were calculated as x_3^{id}/x_3 from the respective mole fraction solubility values presented in table 2. In almost all of the methanol-rich mixtures the calculated activity coefficients are smaller than those reported for this drug in other aqueous-ethanol and aqueous-propanol mixtures [8, 9] because the experimental solubility of SMT in {methanol (1) + water (2)} are larger. The calculated activity coefficients allow one to obtain a rough estimate of solute-solvent intermolecular interactions through Eqn. (11) [43]:

$$\ln \gamma_3 = (e_{11} + e_{33} - 2e_{13}) \frac{V_3 \varphi_1^2}{RT} \qquad (11)$$

Here subscript 1 stands for the solvent (which in the present case is the {methanol (1) + water (2)} solvent mixture), e_{11}, e_{33} and e_{13} represent the solvent-solvent, solute-solute and solvent-solute interaction energies, respectively, V_3 is the molar volume of the super-cooled liquid drug solute, and φ_1 is the volume fraction of the solvent mixture. For drugs with low mole fraction solubility (such as SMT) the volume fraction of the solvent is nearly unity and the $V_3\varphi_1^2/RT$ term can be considered a constant at the given temperature. Thus, γ_3 depends mainly on e_{11}, e_{33} and e_{13} [43]. The e_{11} and e_{33} terms are unfavourable for the dissolution processes, whereas the e_{13} term favours these processes. Generally, the contribution from the e_{33} term is considered as constant in all mixtures containing the dissolved solute. The term e_{33} represents solute-solute interactions, which to a first approximation would be the same irrespective of the properties of the dissolving solvent media.

Table 4

As was already described for SMT dissolved in other aqueous-organic co-solvent mixtures [8, 9], a qualitative analysis based on the magnitudes of the energetic quantities in the Eqn. (11) yielded the following observations: The e_{11} term is highest in pure water (2) (Hildebrand solubility parameter δ = 47.8 $MPa^{1/2}$) and is smallest in methanol (1) (δ = 29.6 $MPa^{1/2}$) [28]. Pure water (2) and water-rich mixtures exhibiting larger γ_3 values (even higher than 370 at 298.15 K) would imply high e_{11} and low e_{13} values. Otherwise, in methanol-rich mixtures (with w_1 higher than 0.80 and exhibiting γ_3 values lower than 8.0), the e_{11} values are relatively low and the e_{13} values would be relatively high. Accordingly, the solvation of SMT (3) would be higher in methanol-rich mixtures. In all cases, the γ_3 values are temperature dependent and diminish with increasing temperatures.

3.5. Apparent thermodynamic quantities of SMT dissolution

The apparent standard enthalpy change for the dissolution of SMT in aqueous-methanolic solvent mixtures was obtained from the Eqn. (12). The calculated mean harmonic temperature was T_{hm} = 303.0 K [44]. In all the mixtures and pure solvents, weighted linear regressions were used, obtaining determination coefficients (r^2) greater than 0.990.

$$\left(\frac{\partial \ln x_3}{\partial\left(1/T - 1/T_{hm}\right)}\right)_P = -\frac{\Delta_{soln}H^\circ}{R} \tag{12}$$

The apparent standard Gibbs energy change for the solution process ($\Delta_{soln}G^\circ$) at the mean harmonic temperature (303.0 K) is calculated by means of the following expression:

$$\Delta_{soln}G^\circ = -RT_{hm} \cdot \text{intercept} \tag{13}$$

using the approach proposed by Krug *et al.* [44] The numerical value of the intercept comes from the analysis of ln x_3 vs. $1/T - 1/T_{hm}$. Finally, the standard apparent entropic change for solution process ($\Delta_{soln}S^\circ$) is obtained by subtracting the respective $\Delta_{soln}H^\circ$ and $\Delta_{soln}G^\circ$ values at 303.0 K and then dividing the resulting value by the harmonic mean temperature [45]:

$$\Delta_{soln}S^\circ = \frac{\left(\Delta_{soln}H^\circ - \Delta_{soln}G^\circ\right)}{T_{hm}} \tag{14}$$

The standard apparent molar thermodynamic functions for dissolution of SMT (3) in all the {methanol (1) + water (2)} co-solvent mixtures, including those for the pure solvents and the ideal solution processes [8, 9], are presented in table 5.

Table 5

Examination of the numerical values in the second, third and fourth columns of Table 4 reveals that the $\Delta_{soln}G^\circ$, $\Delta_{soln}H^\circ$ and $\Delta_{soln}S^\circ$ values associated with dissolution of SMT (3) in all aqueous-methanolic solvent mixtures and in both pure solvents are all positive. Therefore, the global dissolution processes

are always endothermic and entropy-driven, which would be expected for the dissolving of a crystalline drug molecule in a liquid solvent. In general way, the $\Delta_{soln}G°$ values decrease from pure water (2) to pure methanol (1). Otherwise, the $\Delta_{soln}H°$ and $\Delta_{soln}S°$ values increase from pure water (2) to the mixture w_1 = 0.70 and then decrease from here to the pure methanol (1). It is noteworthy that the dissolution enthalpies are very similar in pure water and pure methanol. The relative enthalpic (ζ_H) and entropy (ζ_{TS}) contributions to the solution process are given by the Eqns. (15) and (16) [46]:

$$\zeta_H = \frac{|\Delta_{soln}H°|}{|\Delta_{soln}H°| + |T_{hm}\Delta_{soln}S°|} \tag{15}$$

$$\zeta_{TS} = \frac{|T\Delta_{soln}S°|}{|\Delta_{soln}H°| + |T_{hm}\Delta_{soln}S°|} \tag{16}$$

In all the cases studied, the main contributor to the positive standard molar Gibbs energy of dissolution of this drug is the positive enthalpy, indicating the energetic predominance on the dissolution processes. The contributions in pure methanol are nearly the same as in the dissolution ideal process.

3.6. Apparent thermodynamic quantities of SMT mixing

The dissolution process of this drug in these co-solvent mixtures may be represented by the following three hypothetic stages:

$$Solute_{(Solid)} \text{ at } T_{hm} \rightarrow Solute_{(Solid)} \text{ at } T_{fus} \rightarrow Solute_{(Liquid)} \text{ at } T_{fus} \rightarrow Solute_{(Liquid)} \text{ at } T_{hm} \rightarrow Solute_{(Solution)} \text{ at } T_{hm}$$

where the hypothetical dissolution stages are the heating and fusion of the solid drug, the cooling of the liquid drug to the harmonic mean temperature (T_{hm} = 303.0 K), and then the subsequent mixing of the hypothetical super-cooled liquid drug with the solvent mixture at this temperature [47]. As has been already described, this treatment also allows the calculation of the apparent partial thermodynamic contributions to the overall dissolution process by means of the following equations:

$$\Delta_{sol}H° = \Delta_{fus}H^{303} + \Delta_{mix}H° \tag{17}$$

$$\Delta_{soln}S^{\circ} = \Delta_{fus}S^{303} + \Delta_{mix}S^{\circ} \quad (18)$$

where $\Delta_{fus}H^{303}$ and $\Delta_{fus}S^{303}$ represent the thermodynamic functions of fusion of SMT and its cooling to the harmonic mean temperature. However, in this research the $\Delta_{soln}H^{\circ id}$ and $\Delta_{soln}S^{\circ id}$ values for the ideal solution processes were used instead of $\Delta_{fus}H^{308}$ and $\Delta_{fus}S^{308}$ for the reasons already described previously in the literature [48]. The same procedure was followed with this drug in other n-alcohol (1) + water (2) mixtures at T_{hm} = 303.0 K [8, 9]. Figure 8 depicts the apparent thermodynamic quantities of mixing of the super-cooled liquid SMT (3) with all the {methanol (1) + water (2)} co-solvent mixtures.

Figure 8

Gibbs energy of mixing is positive in all cases, which is similar to that observed for SMT in two other {alcohol (1) + water (2)} mixtures [8, 9]. As observed in table 5, the ideal dissolution contributions to the apparent enthalpy and entropy of overall dissolution of SMT ($\Delta_{soln}H^{\circ id}$ and $\Delta_{soln}S^{\circ id}$) are positive as they always are. Nevertheless, according to figure 7, the contribution of the thermodynamic quantities of mixing toward the overall dissolution processes is clearly dependent on the mixtures composition. $\Delta_{mix}H^{\circ}$ and $\Delta_{mix}S^{\circ}$ are positive in almost all systems with the exception of mixing–entropy in compositions $0.00 < x_1 \leq 0.20$. In this way, the molar $\Delta_{mix}G^{\circ}$ values diminish as the methanol (1) proportion increases in the mixtures; whereas, both $\Delta_{mix}H^{\circ}$ and $\Delta_{mix}S^{\circ}$ values increase nonlinearly from pure water (2) to the mixture with x_1 = 0.70 and then gradually decrease until the pure methanol (1).

The net variation in $\Delta_{mix}H^{\circ}$ values with the mixtures composition depends on the relative contribution of several types of molecular interactions. The enthalpy of cavity formation is endothermic because energy must be supplied in order to break the cohesive forces between neighboring solvent molecules. Solvent-solute interactions, on the other hand, are exothermic in nature and result mainly from van der Waals and Lewis acid-base interactions. On the other hand, the hydrophobic hydration around the non-polar groups of SMT would lead to decrease the net $\Delta_{mix}H^{\circ}$ to small or even negative values in water-rich mixtures [49]. This is not observed in figure 8 but the mixing-entropy is negative in water-rich mixtures as was already indicated.

3.7. Enthalpy-entropy compensation analysis of SMT

Instances of non-enthalpy-entropy compensation have been observed during the solubility analysis of drugs dissolved in different aqueous-organic co-solvent mixtures [50, 51]. These analyses were performed in order to identify the main mechanisms involved in the co-solvent action on solubility increasing. Graphs of $\Delta_{soln}H°$ as a function of $\Delta_{soln}G°$ or of $\Delta_{soln}H°$ as a function of $T\Delta_{soln}S°$ at the harmonic mean temperature proved useful in such analyses. Figure 9 shows that SMT (3) gives a non-linear $\Delta_{soln}H°$ vs. $\Delta_{soln}G°$ curve in the {methanol (1) + water (2)} co-solvent system with positive but variable slope over the entire binary solvent composition range. The $\Delta_{soln}H°$ / (kJ·mol^{-1}) values could be satisfactorily approximated by a regular fourth-degree polynomial in $\Delta_{mix}G°$ / (kJ·mol^{-1}) as:

$$\Delta_{soln}H°(\text{kJ·mol}^{-1}) = -58.0 + 31.9(\Delta_{mix}G°/(\text{kJ·mol}^{-1})) - 4.96(\Delta_{mix}G°/(\text{kJ·mol}^{-1}))^2 + 0.329(\Delta_{mix}G°/(\text{kJ·mol}^{-1}))^3 - 8.00\times10^{-3}(\Delta_{mix}G°(\text{kJ·mol}^{-1}))^4 \quad (19)$$

with $r^2 = 0.9913$, $N = 11$, typical error = 0.2830, and $F = 170.0$. In the composition interval $0.00 < x_1 \leq 0.70$ one notes a continuous but variable negative slope, suggesting that the driving mechanism of transfer of SMT from more polar to less polar media is entropic in nature. This is likely due to the loosening of the water structure around the non-polar moieties of the drug. In the remainder of the composition interval ($0.70 < x_1 \leq 1.00$) the positive slope is positive, and suggests that the transfer mechanism is enthalpic in nature. This would be consistent with better solvation of methanol molecules around SMT, as already discussed.

Figure 9

A second relevant kind of compensation plot is that one obtained by plotting $\Delta_{mix}H°$ as a function of $T\Delta_{mix}S°$, like that shown in figure 10. Thus, two different trends are observed according to the co-solvent mixtures composition. The first trend corresponds to methanol proportions varying from pure water to the mixture with $w_1 = 0.70$, which can be mathematically described the parabolic equation:

$$\Delta_{mix}H°(\text{kJ·mol}^{-1}) \quad 12.3 + 0.466\,(T\Delta_{mix}S°/(\text{kJ·mol}^{-1})) - 1.29\times10^{-2}(T\Delta_{mix}S°/(\text{kJ·mol}^{-1}))^2 \quad (20)$$

with $r^2 = 0.9978$, $N = 8$, typical error = 0.1245, and $F = 1124$. The second trend corresponds to methanol proportions from $w_1 = 0.70$ to pure methanol, which can be represented by the following linear equation:

$$\Delta_{mix}H°/(\text{kJ·mol}^{-1}) = 1.948 + 1.380\,(T\Delta_{mix}S°/(\text{kJ·mol}^{-1})) \quad (21)$$

with r^2 = 0.992, N = 4, typical error = 0.3045, and F = 262.2. Thus, as already described in the literature, the equations with slope values smaller than 1.0 correspond to entropy-driven dissolution processes; whereas, those with slope values higher than 1.0 represent enthalpy-driven processes [52, 53]. It is important to indicate that the variable slope of Eqn. (20) assumes mean values from 0.466 in pure water to 0.448 in the mixture with w_1 = 0.70, being them lower than 1.0 in all cases. In this way, Eqns. (20) and (21) are also finding that the drug transfer from pure water to the mixture with w_1 = 0.70 is driven by mixing-entropy and from w_1 = 0.70 to pure methanol the transfer process is driven by mixing-enthalpy. This second kind of compensation plots was used successfully for the solubility analysis of sulfanilamide and ketoprofen in {propylene glycol (1) + water (2)} mixtures [52, 53].

Figure 10

3.8. Preferential solvation of SMT

Experimental solubility data in binary solvent mixtures can be used to examine the preferential solvation of a solvent component around a dissolved solute molecule. In binary aqueous-methanol solvent mixtures the preferential solvation parameter of SMT (3) by methanol molecules ($\delta x_{1,3}$) is defined as:

$$\delta x_{1,3} = x_{1,3}^{L} - x_1 = -\delta x_{2,3} \tag{22}$$

Here, $x_{1,3}^{L}$ is the local mole fraction of methanol (component 1) in the environment near to SMT. If $\delta x_{1,3}$ > 0 the drug is preferentially solvated by methanol. Conversely if this parameter is < 0 the drug is preferentially solvated by water. Numerical values of $\delta x_{1,3}$ can be conveniently calculated from the inverse Kirkwood-Buff integrals for the individual solvent components based on select thermodynamic quantities as shown in Eqns. (23) and (24) [54-56]:

$$G_{1,3} = RT\kappa_T - V_3 + x_2 V_2 D/Q \tag{23}$$

$$G_{2,3} = RT\kappa_T - V_3 + x_1 V_1 D/Q \tag{24}$$

In these expressions, κ_T is the isothermal compressibility of the binary aqueous-methanol mixtures (expressed in GPa $^{-1}$), V_1 and V_2 are the partial molar volumes of the solvents in the mixtures (expressed in cm^3·mol^{-1}). Similarly V_3 is the partial molar volume of SMT in the mixed solvent (also expressed in cm^3·mol^{-1}). The function D is the first-derivative of the standard molar Gibbs energies of transfer of the drug from water to the aqueous-methanol mixture with respect to the co-solvent mole fraction (expressed in kJ·mol^{-1}, as also is RT). The function Q involves the second-derivative of the excess molar Gibbs energy of mixing of the two solvents (G_{1+2}^{Exc}) with respect to the mole fraction of water (2) in the mixtures (also expressed in kJ·mol^{-1}) [54-56]:

$$D = \left(\frac{\partial \Delta_{tr} G^{o}_{3,2\,\rightarrow 1+2}}{\partial x_1} \right)_{T,p} \tag{25}$$

$$Q = RT + x_1 x_2 \left(\frac{\partial^2 G^{Exc}_{1,2}}{\partial x_2^2} \right)_{T,p} \tag{26}$$

The preferential solvation parameter by methanol (1) is determined from the Kirkwood-Buff integrals as follows:

$$\delta x_{1,3} = \frac{x_1 x_2 \left(G_{1,3} - G_{2,3} \right)}{x_1 G_{1,3} + x_2 G_{2,3} + V_{cor}} \tag{27}$$

The correlation volume (V_{cor}) needed in Eqn. (27) is obtained by means of the following empirical expression [55, 56]:

$$V_{cor} = 2522.5\left(r_3 + 0.1363\left(x^{I}_{1,3} V_1 + x^{I}_{2,3} V_2 \right)^{1/3} - 0.085 \right)^3 \tag{28}$$

where r_3 is the molecular radius of the solute (expressed in nm). The definitive correlation volume of the drug requires iteration because it depends on the local mole fraction compositions of the solvent molecules around the dissolved drug molecule.

Table 6 and figure 11 show the Gibbs energy of transfer behaviour of SMT (3) from pure water to {methanol (1) + water (2)} mixtures at (293.15, 303.15 and 313.15) K. The numerical values were calculated according to Eqn. (29):

$$\Delta_{tr}G^{o}_{3,2\ \to 1+2} = RT \ln\left(\frac{x_{3,2}}{x_{3,1+2}}\right) \tag{29}$$

using the drug mole fraction solubility from table 2.

The $\Delta_{tr}G^{o}_{3,2\ \to 1+2}$ values were mathematically represented using the regular fourth-degree polynomials given by Eqn. (30). Numerical values of respective equation coefficients of Eqn. (30) at (293.15, 303.15 and 313.15) K are listed in table 7.

$$\Delta_{tr}G^{o}_{3,2\ \to 1+2} = a + bx_1 + cx_1^2 + dx_1^3 + ex_1^4 \tag{30}$$

Tables 6 and 7, Figure 11

The D values reported in table 8 were calculated from the first derivative of the polynomial models solved according to the mixtures composition varying by 0.05 in mole fraction of methanol (1).

Table 8

Q and $RT\kappa_T$ values of the binary aqueous-methanol mixtures at these temperatures, as well as the partial molar volumes of methanol and water were taken from the literature [15]. Otherwise, in a first approach the molar volume of SMT was considered in this research as independent of the mixtures composition, as it was calculated as V_3 = 179.0 $cm^3 \cdot mol^{-1}$ [11, 12], according to the groups contribution method proposed by Fedors [57]. Table 9 shows that the $G_{1,3}$ and $G_{2,3}$ values of SMT (3) are negative at each of the mixtures compositions, indicating that the drug exhibits an affinity for both solvent components.

Table 9

Solute radius value of r_3 = 0.391 nm, required to calculate the correlation volume, was also taken from the literature [11, 12]. We performed three iterations using Eqns. (22), (27) and (28) in order to obtain the values reported in table 10 for this research study.

Table 10

The calculated values of the preferential solvation parameter by methanol, $\delta x_{1,3}$, were found to vary non-linearly with the methanol composition. See last three columns in table 10 and the three curves depicted graphically in figure 12. Addition of methanol leads to negative $\delta x_{1,3}$ values for this drug at methanol compositions from $0.00 < x_1 < 0.31$. At all temperatures, $\delta x_{1,3}$ reaches a minimum value of about -1.7×10^{-2} in the binary mixture having a methanol mole fraction of $x_1 = 0.15$. Similar preferential solvation behaviour was exhibited by sulfadiazine and sulfamerazine in the same co-solvent mixtures [15, 16]. We believe that the $\delta x_{1,3}$ values in these water-rich regions is possibly due to the hydrophobic hydration around the non-polar groups of SMT (aromatic rings and methyl groups, Figure 1).

Figure 12

In the mixtures with methanol mole fraction compositions in the range of $0.31 < x_1 < 1.00$, the local mole fractions of methanol (1) are greater than the mole fractions in the bulk mixtures. Here, the co-solvent action may be related to the breaking of the ordered structure of voluminous water around the non-polar moieties of the drug, as was postulated previously. Preferential solvation by methanol solvent molecules reach a maximum value near $x_1 = 0.55$, with $\delta x_{1,3}$ near to 2.5×10^{-2} at 303.15 K. This behaviour is also similar to what was observed previously for both sulfadiazine and sulfamerazine [15, 16]. Based on the results of our preferential solvation compositions, it is reasonable to postulate that in intermediate compositions and in methanol-rich mixtures, SMT (3) is also acting as a Lewis acid in its molecular interactions with methanol molecules. As an informational note methanol is more basic than water according to the respective Kamlet-Taft hydrogen bond acceptor parameters, *i.e.* $\beta = 0.66$ for methanol and 0.47 for water [58, 59]. Despite our preferential solvation computations and analysis the specific solute-solvent interactions in this solvent system remain unclear because of the molecular complexity of this drug.

Figure 13 graphically compares the preferential solvation behaviour of SMT to that of both sulfadiazine [15] and sulfamerazine [16] at 303.15 K in binary aqueous-methanol solvent mixtures [15, 16]. The three drug molecules differ from one another by the number of methyl groups present in the diazine-moiety. Interestingly the composition intervals of preferential solvation by water (2) and by methanol (1) are the same for these three drugs. Maximum preferential solvation by methanol is observed for sulfadiazine and sulfamerazine in the binary mixture having $x_1 = 0.50$, with sulfamerazine having the larger value of $\delta x_{1,3}$. For SMT the maximum $\delta x_{1,3}$ is obtained at a slightly larger methanol mole fraction composition of $x_1 = 0.55$, and the maximum $\delta x_{1,3}$ value is similar in magnitude to that

exhibited by sulfamerazine. The maximum preferential solvation by water is obtained for these three sulfonamides in the mixture with $x_1 = 0.15$.

Figure 13

Finally, Figure 14 compares the preferential solvation of SMT (3) in {methanol (1) + water (2)}, {ethanol (1) + water (2)}, and {1-propanol (1) + water (2)} mixtures at 303.15 K [11, 12]. Noticeably large differences can be observed in the SMT behaviour depending on the n-alcohol under consideration. In particular, and unlike methanol + water mixtures, SMT is found to be preferentially solvated by water in the ethanol-rich and 1-propanol-rich mixtures as well. In the latter two solvent systems the maximum SMT solubility occurs in the binary mixture instead of in the pure n-alcohol [8, 9]. The composition intervals where the drug is preferentially solvated by water, *i.e.* the water-rich mixtures, diminish in the order: methanol + water > ethanol + water > 1-propanol + water mixtures, which are in the same order as diminishing n-alcohol polarity. Methanol is more polar than ethanol, which in turn is more polar than 1-propanol [28]. In the water-region composition regions the maximum preferential solvation values by water occur at methanol compositions of $x_1 = 0.15$, $x_1 = 0.10$, and $x_1 = 0.05$, for methanol-, ethanol- and 1-propanol-aqueous mixtures, respectively. The maximum preferential solvation by the alcohol occurs at alcohol composition of $x_1 = 0.55$ for methanol (1) + water (2) mixtures, and at $x_1 = 0.40$ for {ethanol (1) + water (2)} and {1-propanol (1) + water (2)}. Preferential solvation of SMT by water in water-rich mixtures in {methanol (1) + water (2)} mixtures is lower in comparison to preferential solvation in {ethanol (1) + water (2)} and {1-propanol (1) + water (2)} mixtures. It is noteworthy that observed preferential solvation by water in n-alcohol-rich mixtures is higher with 1-propanol-mixtures compared to ethanol-mixtures; nevertheless, the high negative magnitude of $\delta x_{1,3}$ in the former case could be a consequence of the high positive excess Gibbs energy of mixing between 1-propanol and water, which is affecting the term Q {Eq. (26)} as it was described previously [12]. Conversely, the preferential solvation by the alcohol co-solvent is greatest in the aqueous-methanol mixtures compared alcohol preferential solvation in either the aqueous-ethanol or aqueous-propanol systems [11, 12].

Figure 14

4. Conclusions

Based on the above discussion, we concluded that the dissolution process of {SMT (3) in methanol (1) + water (2)} mixtures is highly dependent on both temperature and mixture composition. This behaviour is similar to that reported for SMT dissolved in other {n-alcohol (1) + water (2)} mixtures [15, 16]. Jouyban-Acree model calculates adequately the solubility of SMT with respect to the mixture composition and temperature. Non-linear enthalpy-entropy compensation was found for this drug in these aqueous mixtures with variant positive slope in the plot of $\Delta_{soln}H°$ vs. $\Delta_{soln}G°$. Thus, entropy-driving or enthalpy-driving were observed for the transfer processes of this drug in water-rich and methanol-rich mixtures, respectively. Finally, the measured solubility as part of this study will expand the database regarding sulfonamide drugs dissolved in aqueous-organic co-solvent mixtures.

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Table 1. Source and purities of the compounds used in this research.

Compound	CAS	Formula	Molar mass / g mol^{-1}	Source	Purity in mass fraction	Analytic technique[a]
Sulfamethazine	57-68-1	$C_{12}H_{14}N_4O_2S$	278.33	Sigma Chemical Co., USA	0.990	HPLC
Methanol	67-56-1	CH_4O	32.04	Merck, Germany	0.998	GC
Water	7732-18-5	H_2O	18.02	Obtained by distillation	>0.999	-

[a] HPLC is high liquid performance chromatography; GC is gas chromatography.

Table 2. Experimental solubility of sulfamethazine (3) in {methanol (1) + water (2)} mixtures at several temperatures and local atmospheric pressure p = 73.9 kPa.

w_1[a,b]	x_3[b]				
	T = 293.15 K	T = 298.15 K	T = 303.15 K	T = 308.15 K	T = 313.15 K
0.000[c]	2.22×10^{-5}	2.81×10^{-5}	3.67×10^{-5}	4.33×10^{-5}	5.55×10^{-5}
0.100	3.36×10^{-5}	4.31×10^{-5}	5.63×10^{-5}	6.94×10^{-5}	8.73×10^{-5}
0.200	5.65×10^{-5}	7.27×10^{-5}	9.05×10^{-5}	1.19×10^{-4}	1.51×10^{-4}
0.300	1.01×10^{-4}	1.22×10^{-4}	1.62×10^{-4}	2.17×10^{-4}	2.68×10^{-4}
0.400	1.85×10^{-4}	2.30×10^{-4}	3.05×10^{-4}	4.00×10^{-4}	5.08×10^{-4}
0.500	2.93×10^{-4}	3.96×10^{-4}	5.14×10^{-4}	6.58×10^{-4}	8.51×10^{-4}
0.600	4.59×10^{-4}	6.18×10^{-4}	7.76×10^{-4}	1.05×10^{-3}	1.33×10^{-3}
0.700	7.02×10^{-4}	9.30×10^{-4}	1.24×10^{-3}	1.57×10^{-3}	2.05×10^{-3}
0.800	1.09×10^{-3}	1.34×10^{-3}	1.84×10^{-3}	2.24×10^{-3}	3.00×10^{-3}
0.900	1.39×10^{-3}	1.78×10^{-3}	2.31×10^{-3}	2.77×10^{-3}	3.61×10^{-3}
1.000	1.61×10^{-3}	2.01×10^{-3}	2.62×10^{-3}	3.20×10^{-3}	3.95×10^{-3}
Ideal[c]	8.88×10^{-3}	1.05×10^{-2}	1.24×10^{-2}	1.47×10^{-2}	1.72×10^{-2}
w_1[a]	mol·dm^{-3}[b]				
	T = 293.15 K	T = 298.15 K	T = 303.15 K	T = 308.15 K	T = 313.15 K
0.000[c]	1.23×10^{-3}	1.56×10^{-3}	2.03×10^{-3}	2.39×10^{-3}	3.06×10^{-3}
0.100	1.75×10^{-3}	2.24×10^{-3}	2.92×10^{-3}	3.59×10^{-3}	4.51×10^{-3}
0.200	2.76×10^{-3}	3.55×10^{-3}	4.41×10^{-3}	5.79×10^{-3}	7.30×10^{-3}
0.300	4.62×10^{-3}	5.60×10^{-3}	7.39×10^{-3}	9.86×10^{-3}	1.21×10^{-2}
0.400	7.90×10^{-3}	9.79×10^{-3}	1.30×10^{-2}	1.69×10^{-2}	2.14×10^{-2}
0.500	1.16×10^{-2}	1.57×10^{-2}	2.03×10^{-2}	2.58×10^{-2}	3.33×10^{-2}
0.600	1.68×10^{-2}	2.25×10^{-2}	2.81×10^{-2}	3.79×10^{-2}	4.77×10^{-2}
0.750	2.35×10^{-2}	3.09×10^{-2}	4.10×10^{-2}	5.16×10^{-2}	6.68×10^{-2}
0.800	3.30×10^{-2}	4.04×10^{-2}	5.52×10^{-2}	6.65×10^{-2}	8.82×10^{-2}
0.900	3.82×10^{-2}	4.83×10^{-2}	6.24×10^{-2}	7.41×10^{-2}	9.53×10^{-2}
1.000[c]	3.96×10^{-2}	4.90×10^{-2}	6.32×10^{-2}	7.66×10^{-2}	9.37×10^{-2}

[a] w_1 is the mass fraction of methanol (1) in the {methanol (1) + water (2)} mixtures free of sulfamethazine (3).

[b] Standard uncertainties are $u(T)$ = 0.05 K, $u(p)$ = 2.2 kPa, $u(w_1)$ = 0.0003. Average relative standard uncertainty in solubility, $u_r(x_3)$ and u_r(mol·dm^{-3}), are 0.025 (or 2.5%).

[c] Values from Ref. [8].

Table 3. Density of the saturated solutions of sulfamethazine (3) in {methanol (1) + water (2)} mixtures at several temperatures and local pressure p = 73.9 kPa.

w_1 [a,b]	ρ / g·cm^{-3} [b]				
	T = 293.15 K	T = 298.15 K	T = 303.15 K	T = 308.15 K	T = 313.15 K
0.000	0.9983	0.9972	0.9959	0.9943	0.9925
0.100	0.9816	0.9802	0.9788	0.9767	0.9750
0.200	0.9670	0.9654	0.9634	0.9610	0.9590
0.300	0.9522	0.9498	0.9471	0.9446	0.9424
0.400	0.9356	0.9329	0.9296	0.9271	0.9235
0.500	0.9197	0.9171	0.9152	0.9125	0.9099
0.600	0.9005	0.8967	0.8932	0.8900	0.8873
0.700	0.8755	0.8722	0.8689	0.8655	0.8627
0.800	0.8511	0.8472	0.8456	0.8404	0.8381
0.900	0.8255	0.8213	0.8177	0.8130	0.8089
1.000	0.7956	0.7920	0.7896	0.7861	0.7827

[a] w_1 is the mass fraction of methanol (1) in the {methanol (1) + water (2)} mixtures free of sulfamethazine (3).

[b] Standard uncertainties are $u(T)$ = 0.05 K, $u(p)$ = 2.2 kPa, $u(w_1)$ = 0.0003, $u(\rho)$ = 0.0007 g·cm^{-3}.

Table 4. Activity coefficients of sulfamethazine (3) in {methanol (1) + water (2)} mixtures at several temperatures and local pressure p = 73.9 kPa.

w_1 [a,b]	γ_3 [b]				
	T = 293.15 K	T = 298.15 K	T = 303.15 K	T = 308.15 K	T = 313.15 K
0.000 [c]	400	374	339	338	311
0.100	264	244	221	211	198
0.200	157	145	137	123	115
0.300	88.1	86.0	76.7	67.6	64.4
0.400	48.1	45.8	40.7	36.6	33.9
0.500	30.3	26.6	24.2	22.3	20.2
0.600	19.3	17.0	16.0	13.9	12.9
0.700	12.7	11.3	10.0	9.3	8.4
0.800	8.17	7.87	6.76	6.56	5.75
0.900	6.38	5.93	5.38	5.29	4.78
1.000	5.50	5.22	4.75	4.58	4.36

[a] w_1 is the mass fraction of methanol (1) in the {methanol (1) + water (2)} mixtures free of sulfamethazine (3).

[b] Standard uncertainties are $u(T)$ = 0.05 K, $u(p)$ = 2.2 kPa, $u(w_1)$ = 0.0003. Average relative standard uncertainty in activity coefficients are $u_r(\gamma_3)$ = 0.038 (or 3.8%)

[c] Values from Ref. [8].

Table 5. Apparent thermodynamic quantities relative to solution processes of sulfamethazine (3) in methanol (1) + water (2) mixtures, including ideal process, at T_{lm} = 303.0 K and local pressure p = 73.9 kPa.

w_1 [a,b]	$\Delta_{soln}G°$ / kJ·mol^{-1} [b]	$\Delta_{soln}H°$ / J· mol^{-1} [b]	$\Delta_{soln}S°$ / J· K^{-1}·mol^{-1} [b]	$T\Delta_{soln}S°$ / kJ·mol^{-1} [b]	ζ_H	ζ_{TS}
0.000 [c]	25.82	34.6	28.9	8.75	0.798	0.202
0.100	24.72	36.4	38.6	11.69	0.757	0.243
0.200	23.41	37.5	46.4	14.05	0.727	0.273
0.300	21.97	38.5	54.7	16.58	0.699	0.301
0.400	20.39	39.3	62.6	18.95	0.675	0.325
0.500	19.11	40.4	70.2	21.27	0.655	0.345
0.600	17.99	40.6	74.7	22.64	0.642	0.358
0.700	16.92	40.8	78.7	23.86	0.631	0.369
0.800	15.95	38.8	75.4	22.85	0.629	0.371
0.900	15.36	35.9	67.7	20.51	0.636	0.364
1.000	15.04	34.4	64.0	19.38	0.640	0.360
Ideal [c]	11.06	25.3	47.1	14.26	0.640	0.360

[a] w_1 is the mass fraction of methanol (1) in the {methanol (1) + water (2)} mixtures free of sulfamethazine (3).

[b] Standard uncertainties are $u(T_{lm})$ = 0.07 K, $u(p)$ = 2.2 kPa, $u(w_1)$ = 0.0003. Average relative standard uncertainty in the apparent thermodynamic quantities of real solution processes are $u_r(\Delta_{soln}G°)$ = 0.027 (or 2.7%), $u_r(\Delta_{soln}H°)$ = 0.032 (or 3.2%), $u_r(\Delta_{soln}S°)$ = 0.047 (or 4.7%), $u_r(T\Delta_{soln}S°)$ = 0.047 (or 4.7%). Standard relative uncertainty in thermodynamic quantities of ideal solution process are $u_r(\Delta_{soln}G°)$ = 0.020 or (2.0%), $u_r(\Delta_{soln}H°)$ = 0.025 or (2.5%), $u_r(\Delta_{soln}S°)$ = 0.038 (or 3.8%), $u_r(T\Delta_{soln}S°)$ = 0.038 (or 3.8%).

[c] Values from Ref. [8].

Table 6. Gibbs energy of transfer (kJ·mol^{-1}) of sulfamethazine (3) from pure water (2) to {methanol (1) + water (2)} mixtures at several temperatures.

x_1 [a]	T = 293.15 K	T = 303.15 K	T = 313.15 K
0.0000	0.00	0.00	0.00
0.0588	−1.01	−1.08	−1.18
0.1233	−2.27	−2.28	−2.60
0.1942	−3.69	−3.75	−4.10
0.2727	−5.16	−5.34	−5.76
0.3600	−6.28	−6.66	−7.11
0.4576	−7.38	−7.69	−8.27
0.5675	−8.42	−8.87	−9.40
0.6923	−9.48	−9.87	−10.39
0.8350	−10.09	−10.44	−10.87
1.0000	−10.44	−10.75	−11.11

[a] x_1 is the mole fraction of methanol (1) in the {methanol (1) + water (2)} mixtures free of sulfamethazine (3).

Table 7. Coefficients and some statistical parameters of the Equation (30) (kJ·mol^{-1}) applied to Gibbs energy of transfer of sulfamethazine (3) from pure water (2) to {methanol (1) + water (2)} mixtures at several temperatures.

Coefficient or parameter	T = 293.15 K	T = 303.15 K	T = 313.15 K
a	0.10	0.08	0.08
b	−21.27	−20.56	−23.07
c	8.13	0.25	4.05
d	7.02	19.91	17.82
e	−4.44	−10.45	−10.00
r^2	0.9993	0.9993	0.9996
N	11	11	11
Typical error	0.1245	0.1315	0.1080
F	2208	2144	3415

Table 8. D values (kJ·mol^{-1}) of sulfamethazine (3) in {methanol (1) + water (2)} mixtures at several temperatures.

x_1 [a]	T = 293.15 K	T = 303.15 K	T = 313.15 K
0.00	−21.27	−20.56	−23.07
0.05	−20.40	−20.39	−22.54
0.10	−19.45	−19.95	−21.76
0.15	−18.42	−19.28	−20.79
0.20	−17.32	−18.41	−19.63
0.25	−16.17	−17.35	−18.33
0.30	−14.98	−16.16	−16.91
0.35	−13.76	−14.86	−15.40
0.40	−12.53	−13.48	−13.83
0.45	−11.31	−12.05	−12.24
0.50	−10.09	−10.60	−10.65
0.55	−8.91	−9.17	−9.09
0.60	−7.77	−7.78	−7.60
0.65	−6.68	−6.48	−6.20
0.70	−5.66	−5.28	−4.92
0.75	−4.72	−4.22	−3.80
0.80	−3.88	−3.33	−2.85
0.85	−3.14	−2.65	−2.12
0.90	−2.52	−2.20	−1.64
0.95	−2.04	−2.02	−1.42
1.00	−1.71	−2.13	−1.51

[a] x_1 is the mole fraction of methanol (1) in the {methanol (1) + water (2)} mixtures free of sulfamethazine (3).

Table 9. $G_{1,3}$ and $G_{2,3}$ values ($cm^3 \cdot mol^{-1}$) of sulfamethazine (3) in {methanol (1) + water (2)} mixtures at several temperatures.

x_1 [a]	$G_{1,3}$			$G_{2,3}$		
	T = 293.15 K	T = 303.15 K	T = 313.15 K	T = 293.15 K	T = 303.15 K	T = 313.15 K
0.00	−335.7	−325.7	−338.9	−177.9	−177.8	−177.8
0.05	−320.8	−315.8	−327.0	−193.1	−192.7	−194.0
0.10	−309.7	−307.7	−316.8	−207.6	−207.7	−210.1
0.15	−300.6	−300.2	−307.2	−222.2	−223.1	−226.2
0.20	−292.3	−292.6	−297.8	−237.1	−238.9	−242.2
0.25	−284.2	−284.6	−287.9	−252.0	−254.7	−257.8
0.30	−275.5	−275.5	−277.3	−266.4	−269.7	−272.3
0.35	−265.8	−265.3	−265.9	−279.5	−282.9	−284.7
0.40	−254.9	−253.9	−253.7	−289.8	−293.0	−293.8
0.45	−243.1	−241.6	−240.9	−296.2	−298.7	−298.5
0.50	−230.9	−229.0	−228.0	−297.6	−298.9	−298.0
0.55	−218.9	−216.9	−215.8	−293.8	−293.6	−292.0
0.60	−208.0	−206.0	−205.0	−285.4	−283.4	−281.1
0.65	−198.8	−196.8	−195.9	−273.8	−269.8	−266.7
0.70	−191.4	−189.7	−188.8	−260.6	−254.7	−250.7
0.75	−186.0	−184.5	−183.7	−247.1	−239.9	−234.8
0.80	−182.1	−181.0	−180.3	−234.6	−226.8	−220.6
0.85	−179.5	−178.8	−178.2	−223.7	−216.6	−209.2
0.90	−177.7	−177.4	−177.0	−214.8	−210.0	−201.6
0.95	−176.7	−176.5	−176.3	−208.2	−207.7	−198.2
1.00	−176.0	−175.9	−175.8	−204.3	−210.5	−199.9

[a] x_1 is the mole fraction of methanol (1) in the {methanol (1) + water (2)} mixtures free of sulfamethazine (3).

Table 10. Correlation volume and $\delta x_{1,3}$ values of sulfamethazine (3) in {methanol (1) + water (2)} mixtures at several temperatures.

x_1 [a]	V_{cor} / cm^3·mol^{-1}			100 $\delta x_{1,3}$		
	T = 293.15 K	T = 303.15 K	T = 313.15 K	T = 293.15 K	T = 303.15 K	T = 313.15 K
0.00	768	769	770	0.000	0.000	0.000
0.05	789	786	787	−1.030	−0.997	−1.077
0.10	811	805	806	−1.548	−1.533	−1.640
0.15	835	826	828	−1.662	−1.662	−1.754
0.20	860	848	851	−1.445	−1.436	−1.488
0.25	885	872	875	−0.965	−0.918	−0.925
0.30	911	897	901	−0.295	−0.195	−0.169
0.35	937	923	927	0.471	0.620	0.658
0.40	963	948	953	1.219	1.399	1.427
0.45	988	974	979	1.836	2.015	2.022
0.50	1012	998	1003	2.233	2.382	2.363
0.55	1034	1021	1026	2.373	2.467	2.427
0.60	1055	1043	1049	2.277	2.305	2.246
0.65	1076	1064	1071	2.007	1.971	1.897
0.70	1095	1086	1092	1.643	1.556	1.469
0.75	1115	1107	1114	1.255	1.142	1.044
0.80	1134	1129	1136	0.892	0.781	0.680
0.85	1153	1151	1159	0.583	0.499	0.405
0.90	1172	1174	1182	0.337	0.295	0.221
0.95	1191	1197	1206	0.148	0.145	0.102
1.00	1211	1220	1230	0.000	0.000	0.000

[a] x_1 is the mole fraction of methanol (1) in the {methanol (1) + water (2)} mixtures free of sulfamethazine (3).

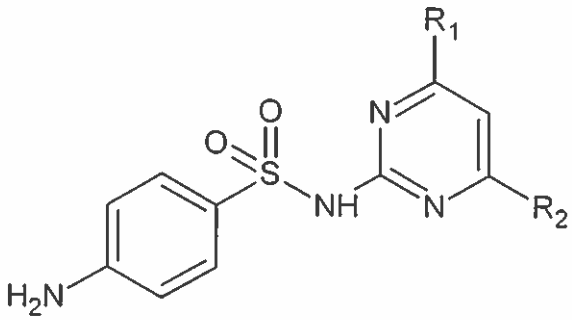


Figure 1. Molecular structure of the sulfonamides considered. Sulfadiazine: R_1 and R_2 = H. Sulfamerazine: R_1 = H, R_2 = CH_3. Sulfamethazine: R_1 and R_2 = CH_3.

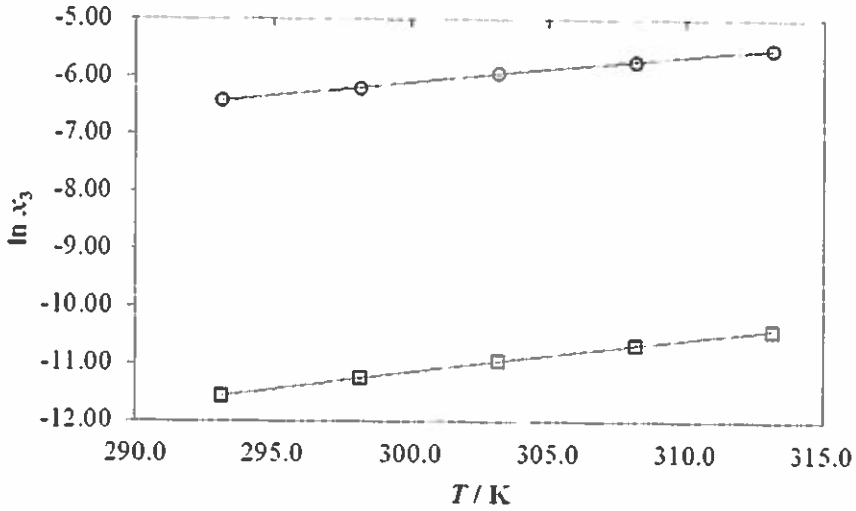
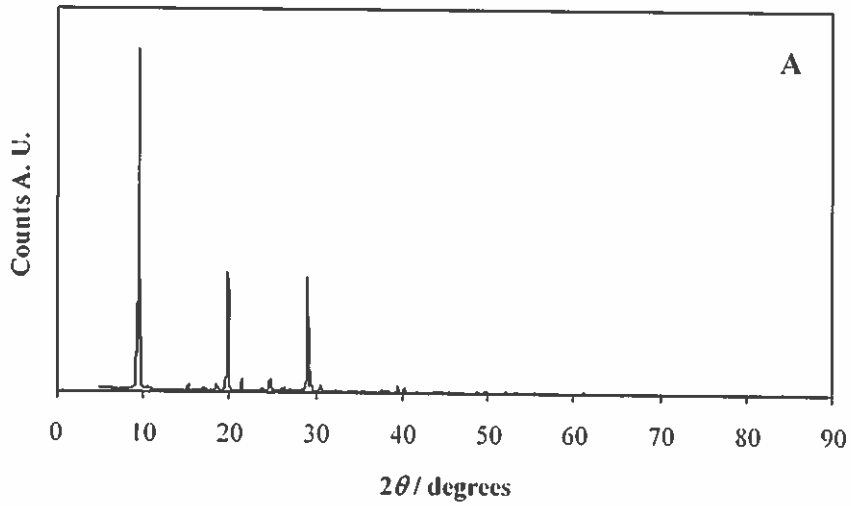


Figure 2. Logarithmic mole fraction solubility of sulfamethazine (3) in pure methanol (1) at several temperatures. (○): Our data (table 2); (□): Values reported by Zhang *et al.* [22]. Lines correspond to the best regular polynomials correlating the values.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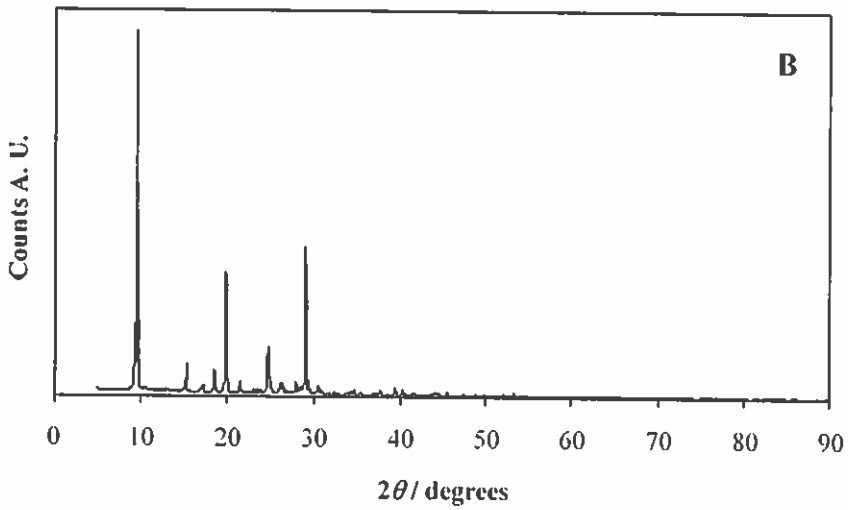
B
Counts A. U.
0
10
20
30
40
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80
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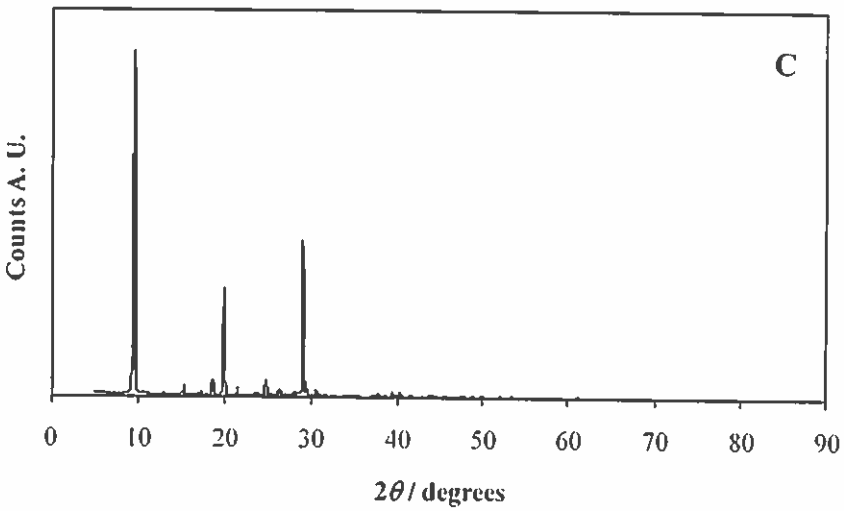
2θ / degrees


C
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50
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70
80
90
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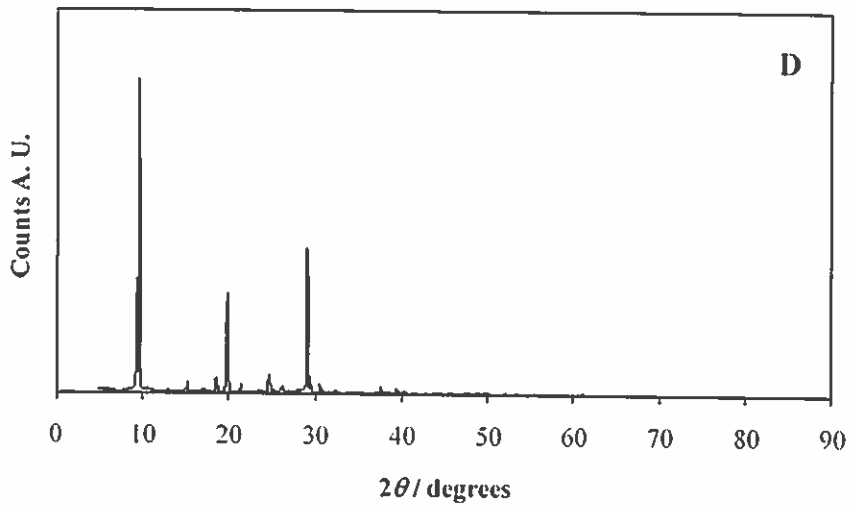

Figure 3. X-ray diffraction spectra of sulfamethazine as original sample (A) and bottom phases of saturated solutions in pure water (B), pure methanol (C) and the mixture with $w_1 = 0.50$ (D).

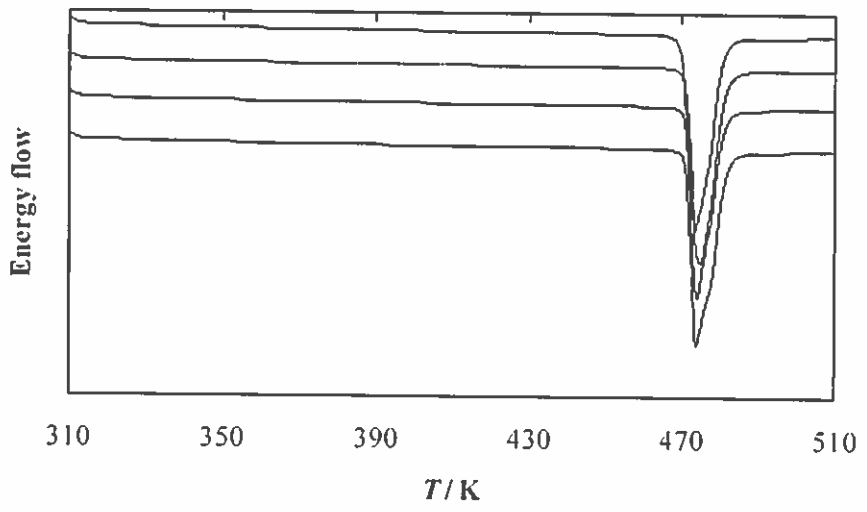

Figure 4. DSC analyses of sulfamethazine from the top to the bottom: original sample, solid phases of saturated solutions in pure water, pure methanol, and the mixture with $w_1 = 0.50$.

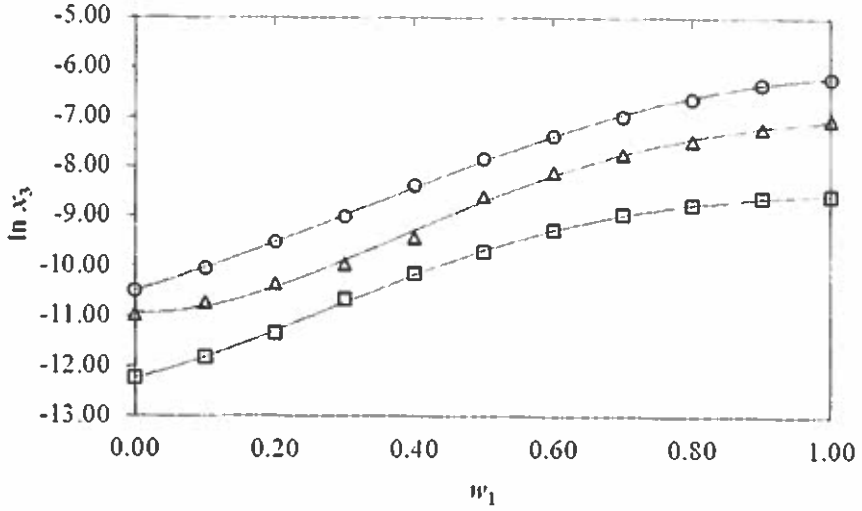

Figure 5. Logarithmic mole fraction solubility of some sulfonamides (3) in {methanol (1) + water (2)} mixtures at 298.15 K. (○): Sulfamethazine; (□): sulfadiazine [15]; (Δ): sulfamerazine [16]. Lines correspond to the best regular polynomials correlating the values.

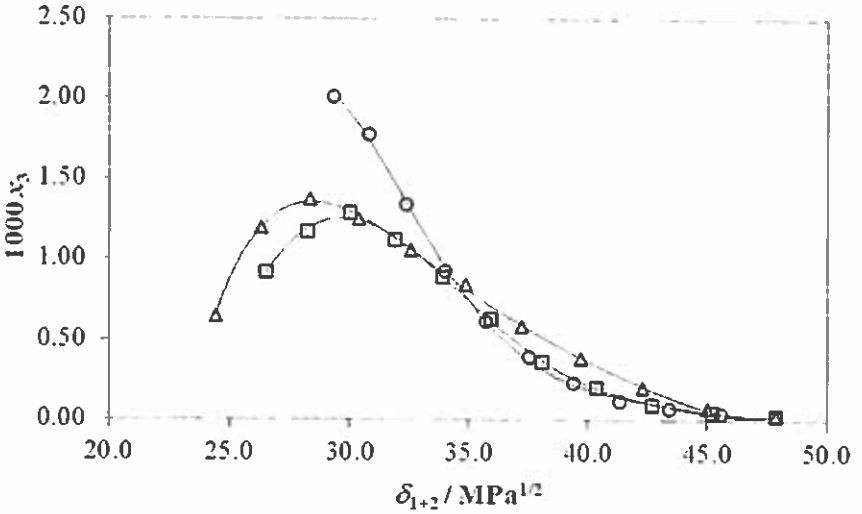

Figure 6. Mole fraction solubility of sulfamethazine (3) in some co-solvent mixtures as a function of the Hildebrand solubility parameter of the mixtures at 298.15 K. (○): methanol (1) + water (2); (□): ethanol + water (2) [8]; (Δ): 1-propanol (1) + water (2) [9]. Lines correspond to the best regular polynomials correlating the values.

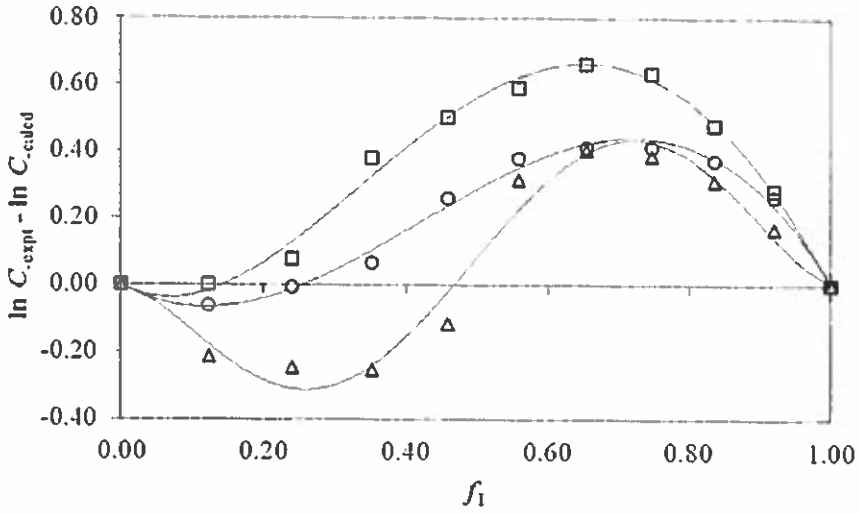

Figure 7. Excess logarithmic molar solubility of some sulfonamides (3) in methanol (1) + water (2) mixtures at 298.15 K. (○): Sulfamethazine; (□): sulfadiazine [15]; (Δ): sulfamerazine [16]. Lines correspond to the best regular polynomials correlating the values.

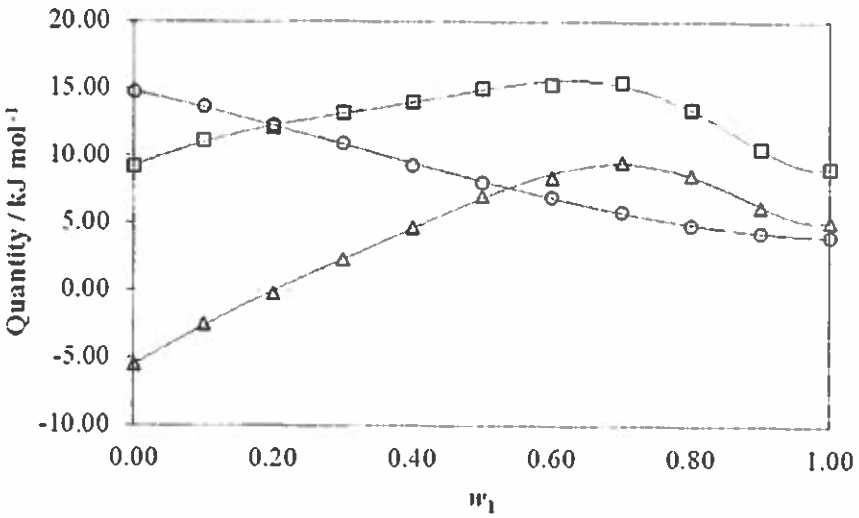

Figure 8. Apparent thermodynamic quantities of mixing of sulfamethazine (3) in methanol (1) + water (2) mixtures at 303.0 K as function of co-solvent mixtures composition. (○): $\Delta_{mix}G°$; (□): $\Delta_{mix}H°$; (Δ): $T\Delta_{mix}S°$. Lines correspond to the best regular polynomials correlating the values.

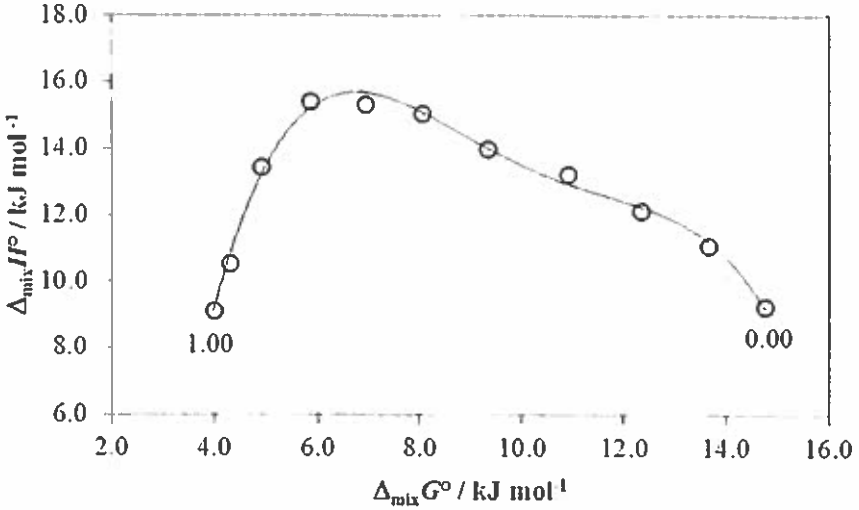

Figure 9. $\Delta_{mix}H°$ vs. $\Delta_{mix}G°$ enthalpy-entropy compensation plot for dissolution process of sulfamethazine (3) in {methanol (1) + water (2)} mixtures at 303.0 K. Line corresponds to the best regular polynomial correlating the values.

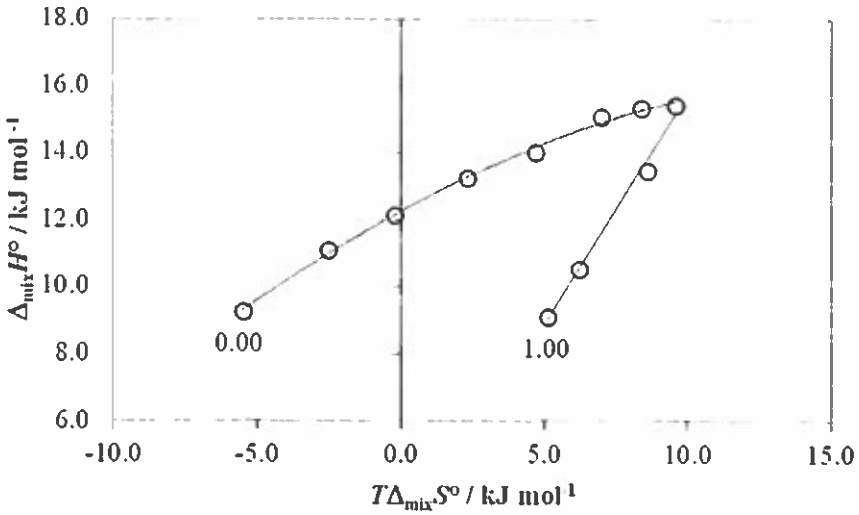

Figure 10. $\Delta_{mix}H°$ vs. $T\Delta_{mix}S°$ enthalpy-entropy compensation plot for dissolution process of sulfamethazine (3) in {methanol (1) + water (2)} mixtures at 303.0 K. Lines correspond to the best regular polynomials correlating the values.

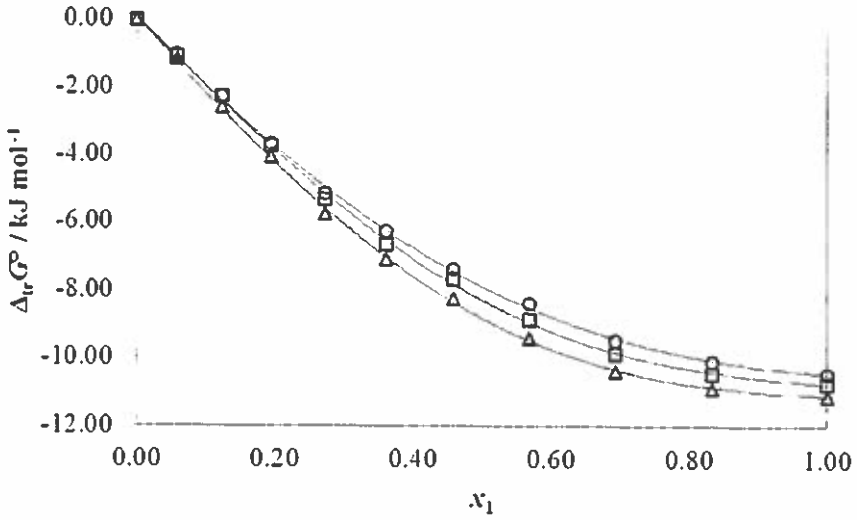

Figure 11. Gibbs energy of transfer of sulfamethazine (3) from pure water (2) to {methanol (1) + water (2)} mixtures at several temperatures. (○): 293.15 K; (□): 303.15 K; (Δ): 313.15 K. Lines correspond to the best regular polynomials correlating the values.

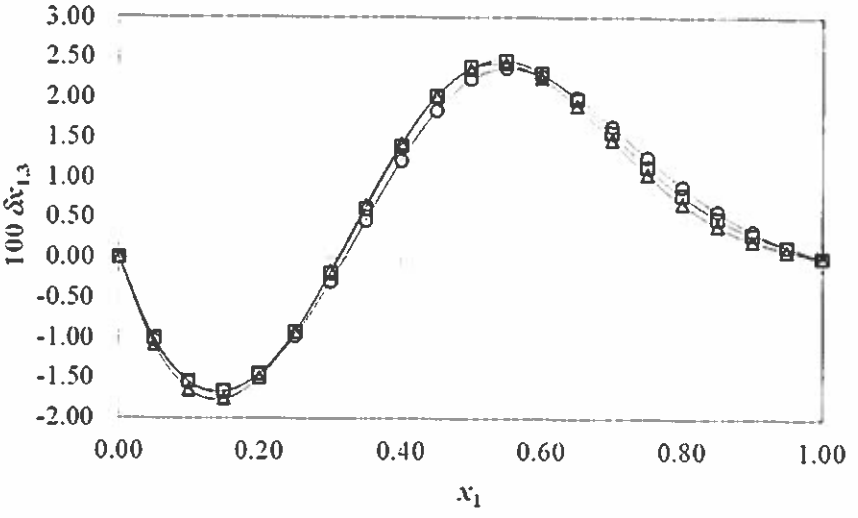

Figure 12. $\delta x_{1,3}$ values of sulfamethazine (3) in {methanol (1) + water (2)} mixtures at several temperatures. (○): 293.15 K; (□): 303.15 K; (Δ): 313.15 K. Lines correspond to the $\delta x_{1,3}$ values calculated with Eqn. (27) according to the solvent mixtures composition.

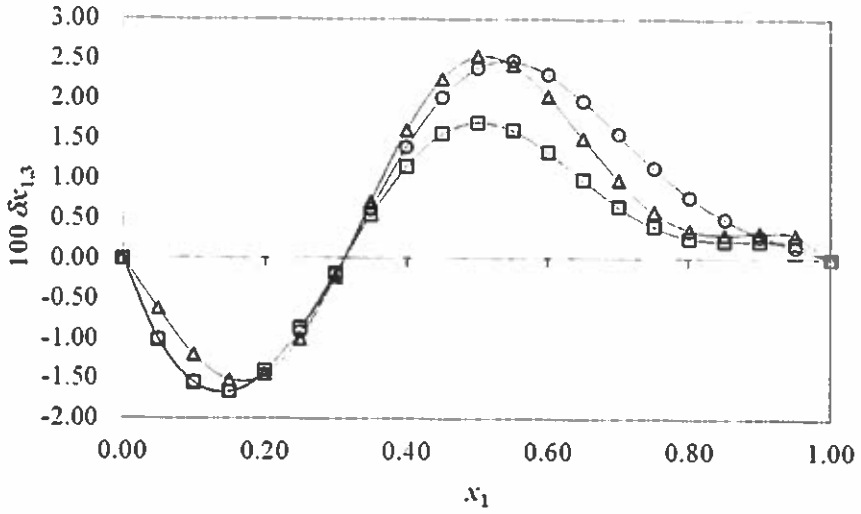

Figure 13. $\delta x_{1,3}$ values of some sulfonamides (3) in {methanol (1) + water (2)} mixtures at 303.15 K. (○): Sulfamethazine; (□): sulfadiazine [15]; (Δ): sulfamerazine [16]. Lines correspond to the $\delta x_{1,3}$ values calculated with Eqn. (27) according to the solvent mixtures composition.

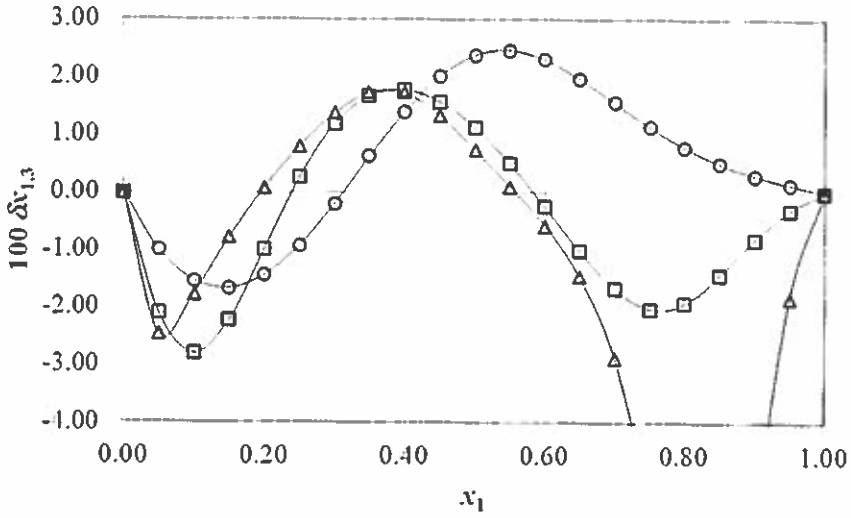

Figure 14. $\delta x_{1,3}$ values of sulfamethazine (3) in some co-solvent mixtures at 303.15 K. (○): methanol (1) + water (2); (□): ethanol (1) + water (2) [11]; (Δ): 1-propanol (1) + water (2) [12]. Lines correspond to the $\delta x_{1,3}$ values calculated with Eqn. (27) according to the solvent mixtures composition.