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Solubility of Salicylic Acid in Some (Ethanol + Water) Mixtures at Different Temperatures: Determination, Correlation, Thermodynamics and Preferential Solvation

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Abstract
Equilibrium mole fraction solubility of salicylic acid in nine aqueous-ethanolic mixtures, as well as in neat water and neat ethanol, was determined at seven temperatures from $T = (293.15$ to $323.15)$ K. Salicylic acid solubility in these mixtures was adequately correlated with well-known correlation/prediction methods based on Jouyban-Acree model. Apparent thermodynamic quantities, *i.e.* Gibbs energy, enthalpy, and entropy, for the dissolution and mixing processes, were computed by means of the van't Hoff and Gibbs equations. The enthalpy–entropy compensation plot of enthalpy *vs.* Gibbs energy of dissolution was not linear exhibiting positive slopes from neat water to the mixture of $w_1 = 0.30$ and from the mixture of $w_1 = 0.50$ to neat ethanol indicating enthalpy-driven drug transfer processes but negative in the interval of $0.30 < w_1 < 0.50$ indicating entropy-driven drug transfer processes from more polar to less polar solvent systems. Moreover, by using the inverse Kirkwood–Buff integrals it is observed that salicylic acid is preferentially solvated by water molecules in water-rich mixtures but preferentially solvated by ethanol molecules in those mixtures of $0.24 < x_1 < 1.00$.

Keywords (Ethanol + water) mixtures · Jouyban–Acree model · Preferential solvation · Salicylic acid · Solubility · Solution thermodynamics

1 Introduction

Solubility is one of the most critical parameters in reaching the desired drug concentration to achieve the required pharmacological response [1, 2]. In this regard, because solubility is very important in pharmaceutical product design, formulation studies and its future developments, it must be addressed from the early phases of product discovery to avoid the production of candidates with insufficient solubility [3, 4]. In addition, the solubility information also plays a crucial role in the design

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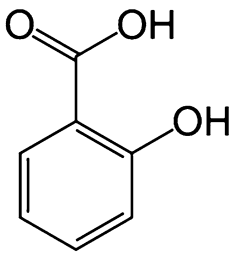

Fig. 1 Molecular structure of salicylic acid

of separation and purification processes such as crystallization, precipitation, and supercritical fluid extraction in the pharmaceutical industries [1, 2, 5]. Moreover, the dependence of solubility on temperature allows to carry out the relevant thermodynamic analysis to deeply insight into the molecular mechanisms involved in the dissolution process [6, 7].

Salicylic acid (IUPAC name: 2-Hydroxybenzoic acid, molecular structure shown in Fig. 1), a phenolic acid compound, is a metabolite of salicin, one of the oldest pain relievers derived from willow bark [8, 9]. At the same time, it is a precursor of a well-known drug, aspirin, and is widely used as an intermediate for production of many industrial compounds [8, 10–14]. In this sense, salicylic acid is one of the active ingredients of cosmetic products. In addition to being used as an antipyretic, antiinflammatory and analgesic, it is an antiseptic and food preservative in toothpaste [8–11, 15]. Salicylic acid is also known as a potent plant hormone as it affects the growth and development of plants by generating a wide range of metabolic and physiological responses [5, 10, 11, 16].

Salicylic acid is a poorly water-soluble compound according to the United States Pharmacopeia [17] and its solubility in various solvent mixtures (binary and ternary mixtures) is crucial as these mixtures are often used in purification processes [10]. In the literature, there are some studies on the solubility of salicylic acid in monosolvents or binary solvent mixtures at different temperatures [5, 8, 10, 12, 13, 15, 18–27]. Paruta *et al.* [18] measured the solubility of salicylic acid in various pure solvents and binary solvent mixtures at $T = 303.75$ K. Gurdial and Foster [19] determined the experimental equilibrium solubilities of salicylic acid in supercritical carbon dioxide at temperatures between $T =$ (308.15 and 328.15) K and for pressures from $p =$ (8 to 20.5) MPa. Ke *et al.* [20] evaluated the solubility of salicylic acid in supercritical carbon dioxide with cosolvent concentrations containing 0.0 mol % to 7.0 mol % ethanol at two temperatures, T=(308.15 K and 318.15 K) and at pressures up to $p = 16$ MPa. De Fina *et al.* [21] reported experimental solubilities of salicylic acid in 1-propanol, 2-propanol, 1-butanol, 2-butanol, 2-methyl-1-propanol, 2-methyl-2-propanol, 1-pentanol, 1-octanol, dibutyl ether, 1,4-dioxane, tetrahydrofuran, ethyl acetate, butyl acetate, 2-propanone, 2-butanone, and cyclohexanone at T=298.15 K. Peña *et al.* [22] studied the solubility of salicylic acid in water–dioxane mixtures at several temperatures, T=(283.15 to 313.15) K. Nordstrom and Rasmuson [12] investigated the solubility of salicylic acid in methanol, acetonitrile, acetic acid, acetone, water, and ethyl acetate at five temperatures from T=(283.15 to 323.15) K. Jouyban *et al.* [23] determined the solubility of salicylic acid in water–ethanol, water-propylene glycol, ethanol-propylene glycol mixtures for predicting the solubility of

a solute in ternary solvent systems based on model constants computed using solubility data of the solute in binary solvent systems. Shalmashi and Eliassi [13] examined the solubility of salicylic acid in water, ethanol, carbon tetrachloride, ethyl acetate and xylene between T=(298 and 348) K using a gravimetric method and correlated the solubility data against temperature. Mota *et al.* [15] measured the aqueous solubility of salicylic acid as a function of temperature, between T=(288.15 and 323.15) K, using the shake-flask method. Matsuda *et al.* [24] carried out the solubility of salicylic acid in monosolvents (water, methanol, ethanol, ethyl acetate, polyethylene glycol (PEG) 300, and 1,4-dioxane) and in various binary solvent mixtures (methanol + water, ethanol + water, ethanol + ethyl acetate, PEG 300 + water, and 1,4-dioxane + water) using high-performance liquid chromatography (HPLC). Peña *et al.* [25] performed the solubility of salicylic acid in ethanol–water and ethanol–ethyl acetate mixtures at different temperatures from T=(288.15 to 313.15) K. Jouyban *et al.* [10] reported solubility of salicylic acid in ethanol (EtOH), propylene glycol (PG), and *N*-methyl-2-pyrrolidone (NMP) at four temperatures, namely T=(298.2, 308.2, 318.2, and 328.2) K and also in the binary mixtures of EtOH + PG, NMP + EtOH, and NMP + PG at T = 298.2 K. Fakhree *et al.* [8] studied the solubility of salicylic acid in 1-propanol, 2-propanol, 2-propanone, and water at different temperatures, namely T=(298.2, 308.2, 318.2, 328.2, and 338.2) K and atmospheric pressure, as well as in binary solvent mixtures of 1-propanol (1) + water (2), 2-propanol (1) + water (2), and 2-propanone (1) + water (2) at T=298.2 K and atmospheric pressure. Pires and Franco [26] measured solubility of salicylic acid in aqueous solutions of five systems containing salicylic acid + water + salt (NaCl, KCl, NaBr, Na_2SO_4 and K_2SO_4) between T=(293.5 and 313.3) K at p=92.50 kPa by using an equilibrium still. Lim *et al.* [5] determined the solubility of salicylic acid in pure alcohols (ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol, 1-heptanol) at several temperatures, from T=(278.15 to 318.15) K, using a (solid + liquid) equilibrium measurement apparatus. More recently, Sadeghi and Rasmuson [27] evaluated the solubility of salicylic acid, in acetone, acetonitrile, ethyl acetate, and methanol in the range of T=(243.15 to 283.15) K using the gravimetric method. However, there is still a significant lack of solubility data for solubility prediction of salicylic acid in binary solvent mixtures with respect to temperature.

Based on the above reasons, the main purposes of this study are to, (1) determine the effect of the mixtures composition and temperature on the equilibrium solubility of salicylic acid in binary solvent mixtures of {ethanol (1) + water (2)} within the temperature range T=(293.15 to 323.15) K, (2) correlation the experimental solubility data using the selected mathematical models, (3) calculation of the apparent thermodynamic properties of salicylic acid dissolution in the binary solvent systems and (4) evaluate the preferential solvation parameters of salicylic acid by ethanol in solvent mixtures by means of the inverse Kirkwood-Buff integrals.

2 Experimental

2.1 Materials

Raw salicylic acid was of analytical reagent grade and provided by Sigma-Aldrich Chemical (Steinheim, Germany). Acetonitrile, ethanol and formic acid (more than

99.5 % pure) were bought at Merck Chemical (Istanbul, Turkey). Ultra-pure water (18.2 MΩ·cm) was obtained from the MilliPore Milli − Q − Gradient water purification system (Billerica, MA, USA). Detailed descriptions of all the chemicals are given in Table 1.

2.2 Solubility Determinations

All {ethanol (1) + water (2)} solvent mixtures were prepared by mass using a Kern ABJ 220-4NM analytical balance (Germany) with sensitivity ± 0.1 mg, in quantities of 50.00 g. The mass fractions of ethanol of the nine mixtures prepared, varied by 0.10 from $w_1 = 0.10$ to $w_1 = 0.90$.

Equilibrium solubility of salicylic acid against mass fraction of ethanol in {ethanol (1) + water (2)} binary mixtures in the temperature range of $T = (293.15$ to $323.15)$ K as a function of temperature at atmospheric pressure was measured by the analytical shake-flask method [28] and defined as follows. In this method, excess salicylic acid was placed in the sealed flask containing known mass ratios of pure solvents and binary solvent mixtures. Then, the suspensions were allowed to equilibrate in a constant-temperature bath (± 0.1 K) with shaking for 18 h. When the equilibrium was reached, all the saturated mixtures were centrifuged and an aliquot of the supernatant solution rapidly was diluted with the water − acetonitrile mixture (50:50 % v/v) for quantitative determination by chromatographic analysis. The solubility samples were then analyzed by HPLC and described following.

All HPLC analyses were performed in triplicate using an Agilent 1200 HPLC system (Santa Clara, CA, USA) coupled with a reversed-phase column Zorbax SB C18 (4.6 × 150 mm, 5 µm, Santa Clara, CA, USA). The salicylic acid samples were eluted using the mixture of acetonitrile:water:formic acid (20:79:1 % v/v/v) as mobile phase at the flow rate of 0.7 mL·min^{-1}. The volume of the injected sample was 10 µL and it was detected at 240 nm with a diode array detector. Salicylic acid determination was performed at ambient temperature.

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]
Salicylic acid	69-72-7	$C_7H_6O_3$	138.12	Sigma-Aldrich	≥ 0.995[b]	HPLC
Ethanol	64-17-5	C_2H_6O	46.07	Merck	> 0.995[b]	GC
Acetonitrile	75-05-8	C_2H_3N	41.05	Merck	≥ 0.999[b]	GC
Formic acid	64-18-6	CH_2O_2	46.03	Merck	≥ 0.999[b]	GC
Water	7732-18-5	H_2O	18.02	Obtained by Millipore Milli-Q-Gradient water purification system	> 0.999	–

[a]HPLC is high performance liquid chromatography, GC is gas chromatography

[b]As indicated by the suppliers

Apart from solubility measurement, thermal and spectroscopic analyzes such as differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD) were used to investigate the nature and crystal structure of raw and equilibrated salicylic acid samples before and after solubility determination.

2.3 Solid Phase Characterization

2.3.1 Differential Scanning Calorimetry Analysis

Solid samples of salicylic acid obtained after solubility determination were analyzed by means of a differential scanning calorimetric analyzer to identify the nature of the raw and equilibrated forms. DSC thermograms of samples was obtained using a Mettler Toledo STARe System DSC 3 series (Ohio, ABD). The device was calibrated by Indium standard to determine the accuracy of obtaining melting temperatures and heats of fusion. Solid samples of 4.0 − 6.0 mg were placed in a crimped sealed aluminum crucible. Then, the samples were heated under a dynamic nitrogen atmosphere (40 mL·min^{-1}) over the temperature range of t = (25 to 440) °C at a heating rate of 10 °C·min^{-1}.

2.3.2 X-Ray Diffraction Analysis

To determine the crystal form of salicylic acid, both raw and after equilibration in neat water, the mixture $w_1 = 0.50$, and neat ethanol, the X-ray powder diffraction analyses were conducted. The powder XRD patterns of the salicylic acid were recorded on Rigaku Smart Lab system (Tokyo, Japan) using CuKα radiation (1.5418 Å). The samples were scanned at 2θ° from ~ 10° to 90°.

3 Results and Discussion

3.1 Mole Fraction Solubility of Salicylic Acid

Mole fraction equilibrium solubility values of salicylic acid in neat solvents and nine {ethanol (1) + water (2)} mixtures at seven temperatures from T = (293.15 to 323.15) K and atmospheric pressure of 90 kPa are shown in Table 2 and depicted in Fig. 2. Minimum and maximum salicylic acid solubilities are, respectively, observed, in neat water and neat ethanol, at all temperatures studied. Salicylic acid solubility increases with temperature-arising, which imply endothermic dissolution processes. As indicated above, the solubility of this drug has been earlier reported in the literature and Fig. 3 allows the comparison at T = 298.15 K. It is noteworthy that our solubility values are in very good agreement with those reported by Jouyban *et al.* [23], although some differences are observed regarding those reported by Matsuda *et al.* [24], Peña *et al.* [25], Seidell [29] and Halford [30], in particular in mixtures of intermediate composition, however, these differences are lower than 3.0 % in almost all cases.

Table 2 Experimental and ideal mole fraction solubility of salicylic acid (x_3) in {ethanol (1) + water (2)} mixtures at several temperatures and $p = 90$ kPa[a,b]

w_1[a,b]	x_1[a,b]	T (K)[b]						
		293.15	298.15	303.15	308.15	313.15	318.15	323.15
0.000	0.0000	$2.33 \cdot 10^{-4}$	$2.84 \cdot 10^{-4}$	$3.47 \cdot 10^{-4}$	$4.22 \cdot 10^{-4}$	$5.14 \cdot 10^{-4}$	$6.29 \cdot 10^{-4}$	$7.55 \cdot 10^{-4}$
0.100	0.0417	$4.19 \cdot 10^{-4}$	$5.13 \cdot 10^{-4}$	$6.42 \cdot 10^{-4}$	$7.66 \cdot 10^{-4}$	$9.23 \cdot 10^{-4}$	$1.10 \cdot 10^{-3}$	$1.31 \cdot 10^{-3}$
0.200	0.0891	$8.05 \cdot 10^{-4}$	$9.74 \cdot 10^{-4}$	$1.16 \cdot 10^{-3}$	$1.40 \cdot 10^{-3}$	$1.67 \cdot 10^{-3}$	$2.01 \cdot 10^{-3}$	$2.44 \cdot 10^{-3}$
0.300	0.1436	$1.65 \cdot 10^{-3}$	$1.96 \cdot 10^{-3}$	$2.33 \cdot 10^{-3}$	$2.81 \cdot 10^{-3}$	$3.33 \cdot 10^{-3}$	$4.01 \cdot 10^{-3}$	$4.89 \cdot 10^{-3}$
0.400	0.2068	$4.46 \cdot 10^{-3}$	$5.26 \cdot 10^{-3}$	$6.61 \cdot 10^{-3}$	$7.95 \cdot 10^{-3}$	$9.40 \cdot 10^{-3}$	$1.10 \cdot 10^{-2}$	$1.34 \cdot 10^{-2}$
0.500	0.2812	$1.21 \cdot 10^{-2}$	$1.45 \cdot 10^{-2}$	$1.71 \cdot 10^{-2}$	$2.04 \cdot 10^{-2}$	$2.40 \cdot 10^{-2}$	$3.06 \cdot 10^{-2}$	$3.70 \cdot 10^{-2}$
0.600	0.3698	$2.77 \cdot 10^{-2}$	$3.33 \cdot 10^{-2}$	$3.90 \cdot 10^{-2}$	$4.63 \cdot 10^{-2}$	$5.43 \cdot 10^{-2}$	$6.90 \cdot 10^{-2}$	$8.33 \cdot 10^{-2}$
0.700	0.4772	$4.64 \cdot 10^{-2}$	$5.59 \cdot 10^{-2}$	$6.53 \cdot 10^{-2}$	$7.72 \cdot 10^{-2}$	$9.03 \cdot 10^{-2}$	0.112	0.131
0.800	0.6101	$7.42 \cdot 10^{-2}$	$8.95 \cdot 10^{-2}$	0.104	0.122	0.141	0.161	0.186
0.900	0.7788	0.109	0.122	0.139	0.157	0.172	0.189	0.211
1.000	1.0000	0.131	0.143	0.155	0.168	0.184	0.199	0.220
	Ideal	$8.27 \cdot 10^{-2}$	$9.21 \cdot 10^{-2}$	0.103	0.114	0.126	0.140	0.154

[a]p is the atmospheric pressure in Aksaray, Turkey. w_1 and x_1 are the mass and mole fractions of ethanol (1) in the {ethanol (1) + water (2)} mixtures free of salicylic acid (3), respectively

[b]Standard uncertainty in T is $u(T) = 0.10$ K. Relative uncertainty in p is $u_r(p) = 0.03$. Average relative uncertainties in w_1 and x_1 were $u_r(w_1) = 0.0018$ and $u_r(x_1) = 0.0018$. Average relative uncertainty in x_3, $u_r(x_3) = 0.03$

Moreover, Fig. 4 depicts the salicylic acid solubility as function of the Hildebrand solubility parameters of the {ethanol (1) + water (2)} mixtures (δ_{1+2}). Hildebrand solubility parameter of solvent mixtures is a polarity index widely used in pharmaceutical sciences. δ_{1+2} values were calculated from the corresponding δ values of the pure solvents, *i.e.* $\delta_1 = 26.5$ MPa$^{1/2}$ for ethanol and $\delta_2 = 47.8$ MPa$^{1/2}$ for water [31, 32] and mixtures compositions. Volume fractions (f_i) were considered by assuming additive behavior as described in Eq. 1 [33, 34]:

$$\delta_{1+2} = \sum_{i=1}^{2} f_i \delta_i \tag{1}$$

Accordingly, organic compounds reach maximum solubilities in solvent systems exhibiting the same or similar Hildebrand solubility parameters [35, 36]. Thus, the δ_3 value of salicylic acid would be lower than δ_1 (neat ethanol δ value, 26.5 MPa$^{1/2}$) at $T = 298.15$ K, where maximum solubilities are observed at all temperatures. Nevertheless, the calculated Fedors δ_3 value of salicylic acid is 31.3 MPa$^{1/2}$ as shown in Table 3 [37], which is higher than the ethanol δ value. This result demonstrates that some other solvent and solutes properties apart of polarity must be involved in drug solubility and dissolution processes.

Otherwise, Fig. 5 allows the comparison of equilibrium solubilities of salicylic acid (2-hydroxybenzoic acid) regarding benzoic acid at $T = 298.15$ K [38]. As

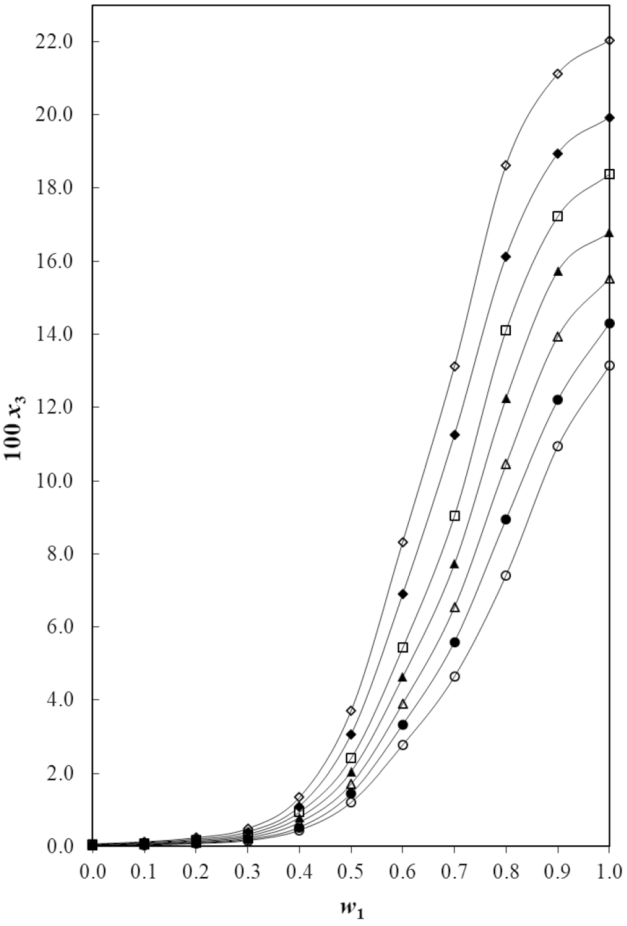

Fig. 2 Mole fraction solubility of salicylic acid (x_3) as function of the mass fraction of ethanol in {ethanol (1) + water (2)} mixtures at different temperatures. ○: $T = 293.15$ K; ●: $T = 298.15$ K, Δ: $T = 303.15$ K, ▲: $T = 308.15$ K, □: $T = 313.15$ K, ■: $T = 318.15$ K, ◇: $T = 323.15$ K. Lines are just a visual guide

observed, benzoic acid is more soluble than salicylic acid in the majority of the cases.

3.2 The Cosolvency Models Applied to Salicylic Acid Solubility

Among various cosolvency models used to calculate drug solubility in mixed solvents at an ambient and/or various temperatures [39, 40], the log-linear model of Yalkowsky is the simplest model [41], which requires only two experimental determinations to predict the solubility at other solvent compositions. The model calculates the solubility at isothermal condition and is:

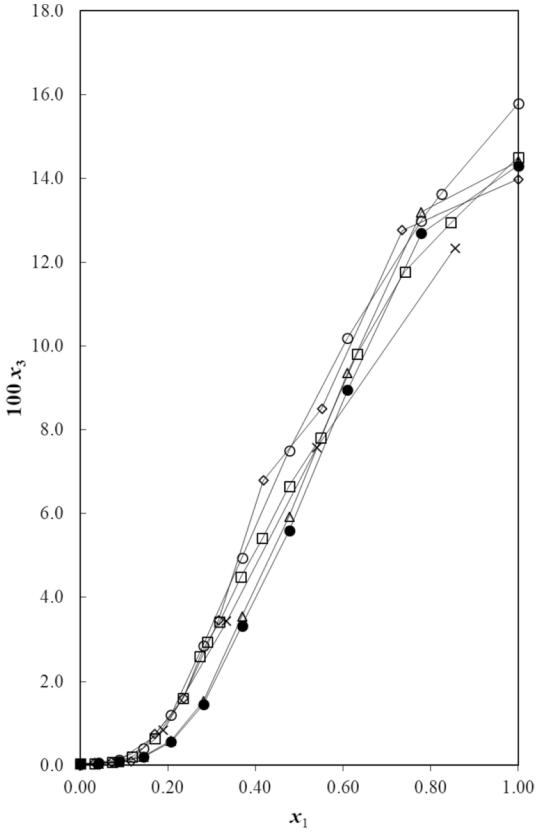

Fig. 3 Comparison of the mole fraction solubility of salicylic acid as function of the mole fraction of ethanol in {ethanol (1) + water (2)} mixtures at $T = 298.15$ K. x_1 is the mole fraction of ethanol in the aqueous cosolvent mixtures free of salicylic acid. ●: This work; ○: Seidell [29]; Δ: Jouyban *et al.* [23]; □: Matsuda *et al.* [24]; ◇: Peña *et al.* [25]; ×: Halford [30]. Lines are just a visual guide

$$\ln x_{3(1+2)} = w_1 \ln x_{3(1)} + w_2 \ln x_{3(2)} \tag{2}$$

where $x_{3\,(1+2)}$ is the mole fraction solubility of salicylic acid in the solvent mixtures, $x_{3(1)}$ is the mole fraction solubility in neat ethanol (component 1), $x_{3(2)}$ is the mole fraction solubility in neat water (component 2), and w_1 and w_2 are the mass fractions of ethanol (1) and water (2) in the solvent mixtures in the absence of salicylic acid (3). The obtained mean percentage deviation (MPD) values for calculating the solubility of salicylic acid in (ethanol + water) mixtures at $T = (293.15, 298.15, 303.15, 308.15, 313.15, 318.15$ and $323.15)$ K are (27.8, 28.9, 29.9, 31.0, 31.4, 32.9 and 34.2) %, respectively, with the overall MPD of 30.9 %. The MPD is computed using:

$$\mathrm{MPD} = \frac{100}{N} \sum \frac{\left| x_3^{cal} - x_3 \right|}{x_3} \tag{3}$$

where N is the number of experimental data points.

As mentioned above, Eq. 2 is capable of estimating drug solubility using solubility data in the mono-solvents. It could be combined with the van't Hoff equation as:

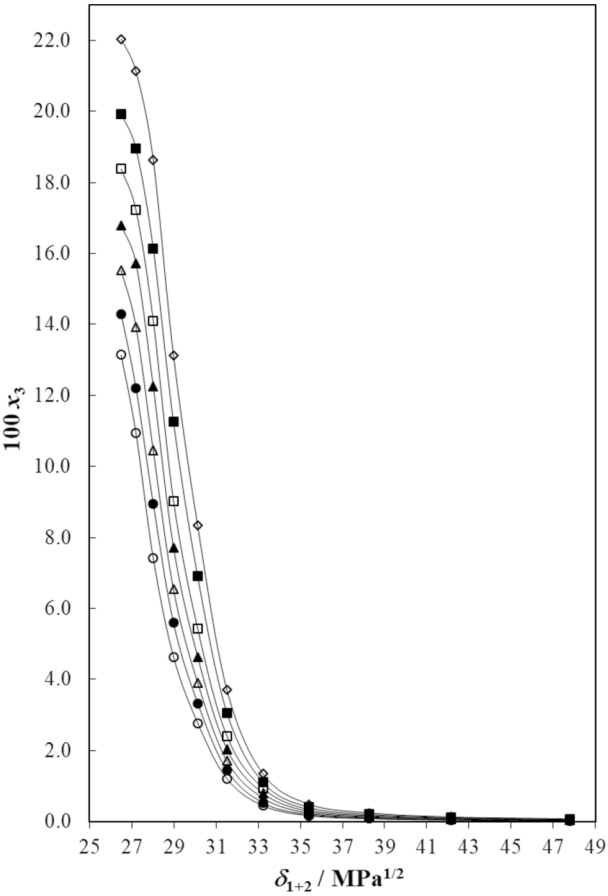

Fig. 4 Mole fraction solubility of salicylic acid (x_3) as function of the Hildebrand solubility parameter in {ethanol (1) + water (2)} mixtures at different temperatures. ○: $T = 293.15$ K; ●: $T = 298.15$ K, Δ: $T = 303.15$ K, ▲: $T = 308.15$ K, □: $T = 313.15$ K, ■: $T = 318.15$ K, ◇: $T = 323.15$ K. Lines are just a visual guide

Table 3 Internal energy, molar volume, and Hildebrand solubility parameter of salicylic acid according to the Fedors method

Group	Number	$\Delta U°$ (kJ·mol^{-1})	$V°$ (cm^3·mol^{-1})
Phenylene ring	1	31.9	52.4
–OH	1	29.8	10.0
–CO_2H	1	27.6	28.5
	Σ	89.3	90.9
	$\delta_3 = (89{,}300/90.9)^{1/2} = 31.3$ MPa$^{1/2}$		

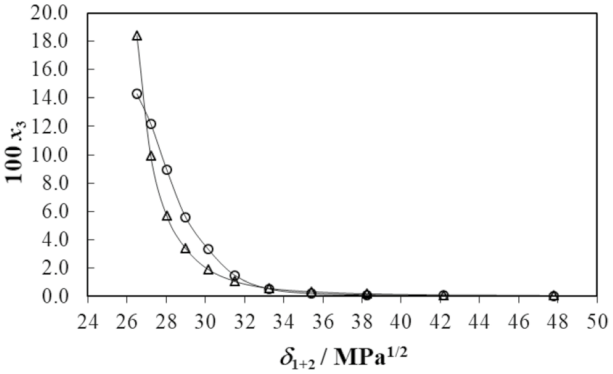

Fig. 5 Mole fraction solubility of salicylic acid (○) and benzoic acid (Δ) as function of the Hildebrand solubility parameter in {ethanol (1) + water (2)} mixtures at $T = 298.15$ K. Lines are just a visual guide

$$\ln x_{3(1+2),T} = w_1\left(A_1 + \frac{B_1}{T}\right) + w_2\left(A_2 + \frac{B_2}{T}\right) \tag{4}$$

to be applied for various temperatures ($x_{3(1+2),T}$) using a single equation. In Eq. 4, A and B terms are the model constants [42]. The obtained constants for solubility of salicylic acid in {ethanol (1) + water (2)} mixtures are $A_1 = 3.467$, $B_1 = -1614.446$, $A_2 = 4.340$ and $B_2 = -3728.254$ which resulted in the MPD of 31.0 %.

As an extension to the above mentioned models, the Jouyban-Acree model is presented by adding the two-body and three-body interaction terms and is the most accurate model to describe a drug solubility in mixed solvents at various temperatures and expressed as [23]:

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

where J_i terms are the model constants computed using a no intercept least square analysis [40]. The generated solubility of salicylic acid in {ethanol (1) + water (2)} was fitted to Eq. 5 and the trained model is:

$$\begin{aligned} \ln x_{3(1+2),T} = {} & w_1 \ln x_{3(1),T} + w_2 \ln x_{3(2),T} + \left(\frac{w_1 w_2}{T}\right) \\ & \left[1033.320 + 1454.727\left(w_1 - w_2\right) - 584.754\left(w_1 - w_2\right)^2\right] \end{aligned} \tag{6}$$

The F value of Eq. 6 was 751, the correlation and the model constants were significant with $p < 0.0005$. Equation 6 is valid for calculating the solubility of salicylic acid in {ethanol (1) + water (2)} mixtures at various temperatures by employing the solubility data of salicylic acid in ethanol and water at each T of interest. The obtained MPD for the back-calculated solubility data of salicylic acid using Eq. 6 was 8.0 %.

Although Eq. 6 provided accurate correlation for solubility of salicylic acid in {ethanol (1) + water (2)} mixtures, it requires the experimental solubility data in the neat ethanol and water at any temperature of interest (*i.e.* $x_{3(1),T}$ and $x_{3(2),T}$) to calculate the solubility of salicylic acid in binary mixtures. One may combine the trained version of Eq. 4 with Eq. 6 to provide a full predictive model as:

$$\begin{aligned}\ln x_{3(1+2),T} =& w_1\left(3.467 - \frac{1614.446}{T}\right) + w_2\left(4.340 - \frac{3728.254}{T}\right) \\ &+ \left(\frac{w_1 w_2}{T}\right)\left[1033.063 + 1454.259\left(w_1 - w_2\right) - 585.396\left(w_1 - w_2\right)^2\right]\end{aligned} \tag{7}$$

Equation 7 calculates the solubility data of salicylic acid in binary mixtures at various temperatures with the MPD of 8.1 % and does not require any experimental

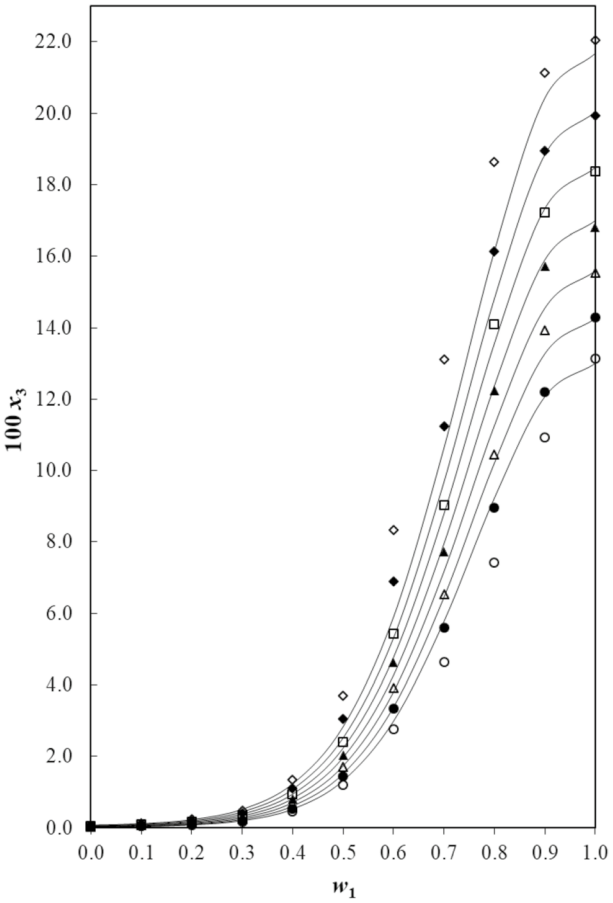

Fig. 6 Mole fraction solubility of salicylic acid (x_3) calculated by using Eq. 7 as function of the mass fraction of ethanol in {ethanol (1) + water (2)} mixtures at different temperatures. Trends are calculated values for highest temperature at top to lowest temperature at bottom. Symbols are experimental values as follows: ○: T = 293.15 K; ●: T = 298.15 K, Δ: T = 303.15 K, ▲: T = 308.15 K, □: T = 313.15 K, ■: T = 318.15 K, ◇: T = 323.15 K

input data. Moreover, Fig. 6 depicts the simulated values obtained by using Eq. 7 at all temperatures studied. As observed, deviations between experimental and calculated solubility values are not distributed regularly, being the higher deviations observed at highest and lowest temperatures.

In practical applications of Eq. 7, one may train the model using a minimum number of seven experimental data points and then predict the rest of required data in any solvent composition and temperature of interest as has been shown in an earlier work [43]. When the model trained with the solubility data in ethanol and water at $T = (293.15$ and $323.15)$ K (the lowest and highest temperature) and in $w_1 = 0.30$, 0.50 and 0.70 at $T = 298.15$ K (totally 7 data points):

$$\ln x_{3(1+2),T} = w_1\left(3.578 - \frac{1645.887}{T}\right) + w_2\left(4.363 - \frac{3733.709}{T}\right) + \left(\frac{w_1 w_2}{T}\right)\left[974.974 + 1532.605\left(w_1 - w_2\right) - 1731.142\left(w_1 - w_2\right)^2\right] \tag{8}$$

and the rest of data points were predicted with the MPD of 14.0 % ($N = 70$).

3.3 Solid Phases' Analyses

DSC thermograms of salicylic acid as original sample and after dissolving it in neat water, in the aqueous mixture of $w_1 = 0.50$, and in neat ethanol (Figs. S1 to S4 shown as supplementary material), exhibit two endothermic peaks corresponding to the melting and thermal degradation of salicylic acid, respectively. The X-ray diffraction spectra for salicylic acid without any treatment and after dissolving it in neat water, in the aqueous mixture of $w_1 = 0.50$, and in neat ethanol, are shown in Figs. S5-S8 (as supplementary material). As observed the positions of characteristic peaks are comparable in all samples. Thus, salicylic acid did not suffer crystal polymorphic transitions or solvates formation in these experiments.

3.4 Ideal Solubility and Activity Coefficients of Salicylic Acid in Mixed Solvents

Ideal solubility of salicylic acid (x_3^{id}) as a function of temperature was calculated by means of Eq. 9:

$$\ln x_3^{\mathrm{id}} = -\frac{\Delta_{\mathrm{fus}}H(T_{\mathrm{fus}} - T)}{RT_{\mathrm{fus}}T} + \left(\frac{\Delta C_p}{R}\right)\left[\frac{(T_{\mathrm{fus}} - T)}{T} + \ln\left(\frac{T}{T_{\mathrm{fus}}}\right)\right] \tag{9}$$

Here, $\Delta_{\mathrm{fus}}H$ is the molar enthalpy of fusion of the pure salicylic acid (at the melting point: 23.05 kJ·mol^{-1} [25]), T_{fus} is the absolute melting point (432.5 K), T is the absolute solution temperature, R is the gas constant (8.3145 J·mol^{-1}·K^{-1}), and ΔC_p is the difference between the molar heat capacity of the salicylic acid crystalline form and the molar heat capacity of the hypothetical super-cooled salicylic acid liquid form at the respective dissolution temperature [44]. Owing the difficulty in ΔC_p determination, it was considered as the same as the entropy of fusion ($\Delta_{\mathrm{fus}}S = \Delta_{\mathrm{fus}}H/T_{\mathrm{fus}}$, *i.e.* 53.29 J·mol^{-1}·K^{-1}). It is important to keep in mind that ideal

solubility involves the tendency of solute molecules in its solid state to separate into the hypothetical liquid state without considering the solvent nature and thus, it depends only on the melting properties of solute. Table 2 shows that the ideal solubilities of salicylic acid are higher than the experimental solubilities at all the temperatures studied in solvent systems of $0.0 \leq w_1 \leq 0.70$ but they are lower in ethanol-rich mixtures and neat ethanol.

Table 4 summarizes the salicylic acid activity coefficients (γ_3) in {ethanol (1) + water (2)} mixtures, which were calculated as the quotient: x_3^{id}/x_3 from the experimental and ideal solubilities summarized in Table 2. As observed, at $T = 298.15$ K γ_3 values vary from 324.5 in neat water (where the lower salicylic acid solubility is observed) to 0.644 in neat ethanol (where the higher salicylic acid solubility is observed). From neat water to the mixture of $w_1 = 0.80$ the γ_3 values decrease with the temperature-arising, whereas in the mixture of $w_1 = 0.90$ the γ_3 values are almost invariant with temperature, but in neat ethanol the γ_3 values increase with the temperature-arising. From neat water to the mixture of $w_1 = 0.70$ all γ_3 values are higher than the unit because the experimental solubilities are lower than x_3^{id} at all temperatures. Nevertheless, in solvent systems of $0.80 \leq w_1 \leq 1.00$ γ_3 values are lower than 1.00 in almost cases because the experimental solubilities are higher than x_3^{id} at all temperatures. On the other hand, a rough estimate of the respective solute–solvent intermolecular interactions can be made from γ_3 values based on the following expression [45]:

Table 4 Activity coefficients of salicylic acid (γ_3) in {ethanol (1) + water (2)} mixtures at several temperatures and $p = 90$ kPa[a,b]

w_1[a,b]	x_1[a,b]	T (K)[b]						
		293.15	298.15	303.15	308.15	313.15	318.15	323.15
0.000	0.0000	354.8	324.5	295.1	269.5	245.5	222.2	204.4
0.100	0.0417	197.5	179.8	159.7	148.6	136.7	127.0	118.0
0.200	0.0891	102.7	94.6	88.3	81.4	75.6	69.4	63.4
0.300	0.1436	50.2	47.0	44.1	40.5	37.9	34.9	31.5
0.400	0.2068	18.5	17.5	15.5	14.3	13.4	12.7	11.5
0.500	0.2812	6.85	6.35	6.00	5.58	5.25	4.56	4.17
0.600	0.3698	2.98	2.77	2.63	2.46	2.33	2.02	1.85
0.700	0.4772	1.78	1.65	1.57	1.47	1.40	1.24	1.18
0.800	0.6101	1.11	1.03	0.981	0.930	0.895	0.866	0.829
0.900	0.7788	0.756	0.755	0.736	0.724	0.733	0.737	0.731
1.000	1.0000	0.629	0.644	0.660	0.678	0.687	0.701	0.701

[a]p is the atmospheric pressure in Aksaray, Turkey. [a]w_1 and x_1 are the mass and mole fractions of ethanol (1) in the {ethanol (1) + water (2)} mixtures free of salicylic acid (3), respectively

[b]Standard uncertainty in T is $u(T) = 0.10$ K. Relative uncertainty in p is $u_r(p) = 0.03$. Average relative uncertainties in w_1 and x_1 were $u_r(w_1) = 0.0018$ and $u_r(x_1) = 0.0018$. Average relative uncertainty in γ_3 is $u_r(\gamma_3) = 0.038$

$$\ln \gamma_3 = (e_{ss} + e_{33} - 2e_{s3})\frac{V_3\varphi_s^2}{RT} \tag{10}$$

Here subscript s stands for the solvent system (which corresponds to the neat solvents or aqueous-ethanol binary mixtures), $e_{ss,}$ e_{33} and e_{s3} denote the solvent–solvent, solute–solute and solvent–solute interaction energies, respectively. However, it is necessary to keep in mind that in multicomponent systems like ethanol–water-salicylic acid, some water-cosolvent interactions are also present. These additional interactions could play a significant role in the magnitudes of dissolution and equilibrium solubility of drugs. V_3 is the molar volume of the super-cooled liquid salicylic acid and φ_s is the volume fraction of the solvent system in the saturated solutions. In the case of low x_3 values, the term ($V_3\varphi_s^2/RT$) may be considered almost constant regardless the composition of the solvent system. Thus, the γ_3 values would depend mainly on e_{ss}, e_{33} and e_{s3} [45]. Here, e_{ss} and e_{33} are unfavorable for salicylic acid dissolution and equilibrium solubility but e_{s3} favors the respective drug dissolution processes. The contribution of e_{33} towards the equilibrium solubility of salicylic acid could be considered as almost constant in all the solvent systems studied.

Thus, a qualitative analysis could be made based on the $e_{ss,}$ e_{33} and e_{s3} energetic terms described in Eq. 10. Thus, e_{ss} is highest in neat water ($\delta = 47.8$ MPa$^{1/2}$) and lowest in neat ethanol ($\delta = 26.5$ MPa$^{1/2}$) [31, 32]. Neat water and water-rich mixtures, exhibiting γ_3 values higher than 300, would imply high e_{ss} and low e_{s3} values. Otherwise, in ethanol-rich mixtures, exhibiting γ_3 values lower than 1.00, the e_{ss} values are relatively low and the e_{s3} values would be comparatively high.

3.5 Apparent Thermodynamic Functions of Dissolution

All apparent thermodynamic quantities of dissolution of salicylic acid in {ethanol (1) + water (2)} mixtures were estimated at $T = 298.15$ K. Thus, the apparent standard enthalpy changes of dissolution ($\Delta_{soln}H^\circ$) were obtained by means of the modified van't Hoff equation, as [46]:

$$\left(\frac{\partial \ln x_3}{\partial(1/T - 1/298.15)}\right)_P = -\frac{\Delta_{soln}H^\circ}{R} \tag{11}$$

The apparent standard Gibbs energy changes for the dissolution processes ($\Delta_{soln}G^\circ$) were calculated by means of Eq. 12:

$$\Delta_{soln}G^\circ = -R \cdot 298.15 \cdot \text{intercept} \tag{12}$$

Here, the intercepts used are those obtained in the regressions of ln x_3 *vs.* (1/T – 1/298.15). Figure 7 depicts the solubility van't Hoff plots for the neat solvents water and ethanol and nine {ethanol (1) + water (2)} mixtures. Linear regressions with determination coefficients higher than 0.993 were obtained in all cases [47–49]. Standard apparent entropic changes for dissolution process ($\Delta_{soln}S^\circ$) were obtained from the respective $\Delta_{soln}H^\circ$ and $\Delta_{soln}G^\circ$ values using Eq. 13 [46]:

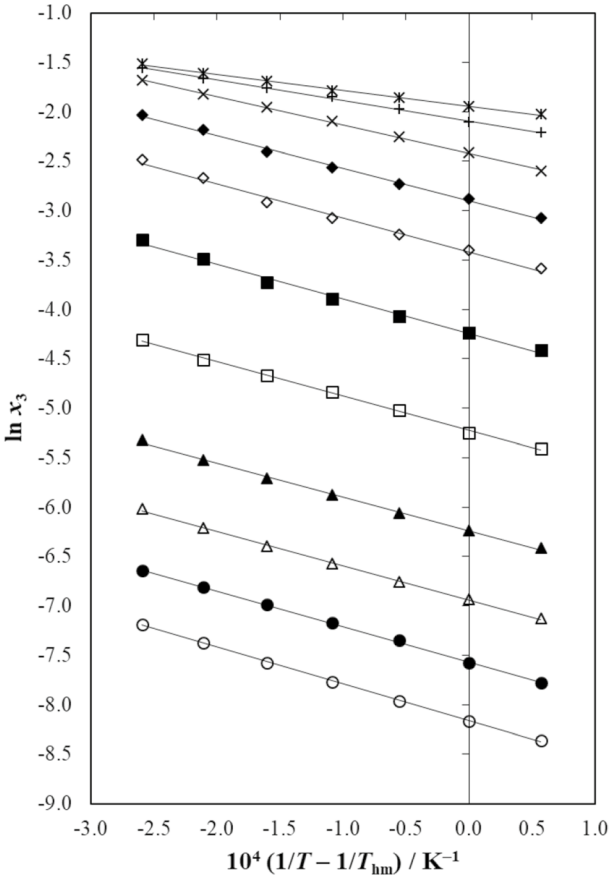

Fig. 7 van't Hoff plot of the solubility of salicylic acid (3) in some {ethanol (1) + water (2)} solvent systems. ○: $w_1 = 0.00$ (neat water), ●: $w_1 = 0.10$, Δ: $w_1 = 0.20$, ▲: $w_1 = 0.30$, □: $w_1 = 0.40$, ■: $w_1 = 0.50$, ◇: $w_1 = 0.60$, ◆: $w_1 = 0.70$, ×: $w_1 = 0.80$, +: $w_1 = 0.90$, ✳: $w_1 = 1.00$ (neat ethanol)

$$\Delta_{soln}S^{o} = \frac{\left(\Delta_{soln}H^{\circ} - \Delta_{soln}G^{\circ}\right)}{298.15} \tag{13}$$

Table 5 summarizes the standard apparent molar thermodynamic functions for dissolution of salicylic acid (3) in all the {ethanol (1) + water (2)} solvent systems at $T = 298.15$ K.

Apparent standard Gibbs energies, enthalpies and entropies of salicylic acid dissolution are positive in all cases, which implies endothermic and entropy-driven dissolution processes. Moreover, $\Delta_{soln}G^{\circ}$ values decrease continuously from neat water to neat ethanol indicating more affinity of salicylic acid by semipolar solvent media. As observed, initially the $\Delta_{soln}H^{\circ}$ values decrease from neat water to the mixture of $w_1 = 0.30$ and later they increase with the ethanol proportion to reach a new

Table 5 Apparent thermodynamic functions relative to dissolution processes of salicylic acid (3) in {ethanol (1) + water (2)} mixtures at $T = 298.15$ K and $p = 90$ kPa[a,b]

w_1[a,b]	x_1[a,b]	$\Delta_{soln}G^\circ$ (kJ·mol^{-1})[b]	$\Delta_{soln}H^\circ$ (kJ·mol^{-1})[b]	$\Delta_{soln}S^\circ$ (J·mol^{-1}·K^{-1})[b]	$T\Delta_{soln}S^\circ$ (kJ·mol^{-1})[b]	ζ_H[c]	ζ_{TS}[c]
0.000	0.0000	20.24	31.0	36.1	10.8	0.742	0.258
0.100	0.0417	18.76	29.9	37.4	11.1	0.729	0.271
0.200	0.0891	17.20	28.9	39.2	11.7	0.712	0.288
0.300	0.1436	15.46	28.4	43.5	13.0	0.687	0.313
0.400	0.2068	12.95	28.9	53.6	16.0	0.644	0.356
0.500	0.2812	10.52	29.2	62.6	18.7	0.610	0.390
0.600	0.3698	8.47	28.6	67.5	20.1	0.587	0.413
0.700	0.4772	7.18	27.2	67.2	20.0	0.576	0.424
0.800	0.6101	6.01	23.9	60.0	17.9	0.572	0.428
0.900	0.7788	5.19	17.3	40.6	12.1	0.588	0.412
1.000	1.0000	4.83	13.4	28.8	8.6	0.610	0.390
	Ideal	5.91	16.40	35.17	10.49	0.610	0.390

[a]p is the atmospheric pressure in Aksaray, Turkey. [a]w_1 and x_1 are the mass and mole fractions of ethanol (1) in the {ethanol (1) + water (2)} mixtures free of salicylic acid (3), respectively

[b]Standard uncertainty in T is $u(T) = 0.10$ K. Relative uncertainty in p is $u_r(p) = 0.03$. Average relative uncertainties in w_1 and x_1 were $u_r(w_1) = 0.0018$ and $u_r(x_1) = 0.0018$. Average standard uncertainty in Gibbs energy of dissolution is $u(\Delta_{soln}G^\circ) = 0.074$ kJ·mol^{-1}. Average relative standard uncertainty in enthalpies and entropies of real dissolution processes are $u_r(\Delta_{soln}H^\circ) = 0.045$, $u_r(\Delta_{soln}S^\circ) = 0.055$, $u_r(T\Delta_{soln}S^\circ) = 0.055$

[c]ζ_H and ζ_{TS} are the relative contributions by enthalpy and entropy toward apparent Gibbs energy of dissolution

maximum value in the mixture of $w_1 = 0.50$. After, they decrease continuously to reach the minimum value in neat ethanol. On the other hand, $\Delta_{soln}S^\circ$ values increase from neat water to the mixture of $w_1 = 0.60$ and later they decrease continuously with the ethanol proportion to reach the minimum value in neat ethanol. Otherwise, the relative contributions by enthalpy (ζ_H) and entropy (ζ_{TS}) toward the salicylic acid dissolution processes were calculated by means of the following equations [50]:

$$\zeta_H = \frac{\left|\Delta_{soln}H^\circ\right|}{\left|\Delta_{soln}H^\circ\right| + \left|T\Delta_{soln}S^\circ\right|} \tag{14}$$

$$\zeta_{TS} = \frac{\left|T\Delta_{soln}S^\circ\right|}{\left|\Delta_{soln}H^\circ\right| + \left|T\Delta_{soln}S^\circ\right|} \tag{15}$$

As shown in Table 5 the main contributor to the positive standard molar Gibbs energies of dissolution of salicylic acid in these solvent systems was the positive enthalpy, with values higher than 0.572, which demonstrates the energetic predominance toward all these dissolution processes. It is noteworthy that enthalpy and entropy contributions in the mixture of $w_1 = 0.50$ and neat ethanol are the same as those observed for ideal dissolution process.

3.6 Apparent Thermodynamic Quantities of Mixing

Global dissolution processes of salicylic acid in {ethanol (1) + water (2)} mixtures may be represented by means of the following hypothetical process:

$$\begin{aligned}\text{Solute}_{(\text{Solid})}\text{ at }T \rightarrow \text{Solute}_{(\text{Solid})}\text{ at }T_{\text{fus}} \rightarrow \text{Solute}_{(\text{Liquid})}\text{ at }T_{\text{fus}}\\ \rightarrow \text{Solute}_{(\text{Liquid})}\text{ at }T \rightarrow \text{Solute}_{(\text{Solution})}\text{ at }T.\end{aligned}$$

Here, the hypothetical stages are as follows: *i*) the heating and fusion of salicylic acid at $T_{\text{fus}} = 432.5$ K, *ii*) the cooling of the liquid salicylic acid to the considered temperature ($T = 298.15$ K), and *iii*) the subsequent mixing of both the hypothetical super-cooled liquid salicylic acid and the respective solvent system at this temperature [51]. This allowed the calculation of the individual thermodynamic contributions by fusion and mixing toward the overall dissolution process by means of the following equations:

$$\Delta_{\text{soln}}H^{\circ} = \Delta_{\text{fus}}H^{T_{298}} + \Delta_{\text{mix}}H^{\circ} \tag{16}$$

$$\Delta_{\text{soln}}S^{\circ} = \Delta_{\text{fus}}S^{T_{298}} + \Delta_{\text{mix}}S^{\circ} \tag{17}$$

where $\Delta_{\text{fus}}H^{T_{298}}$ and $\Delta_{\text{fus}}S^{T_{298}}$ represent the thermodynamic quantities of salicylic acid fusion and its cooling at $T = 298.15$ K, which in turn, are calculated by means of the following equations [52]:

$$\Delta_{\text{fus}}H^{T_{298}} = \Delta_{\text{fus}}H^{T_{\text{fus}}} - \Delta C_p\left(T_{\text{fus}} - 298.15\right) \tag{18}$$

$$\Delta_{\text{fus}}S^{T_{298\text{m}}} = \Delta_{\text{fus}}S^{T_{\text{fus}}} - \Delta C_p \ln\left(\frac{T_{\text{fus}}}{298.15}\right) \tag{19}$$

Table 6 summarizes the apparent thermodynamic quantities of mixing of hypothetical super-cooled liquid salicylic acid with all the aqueous-ethanol mixtures and the neat solvents at $T = 298.15$ K. Gibbs energies of mixing are positive from neat water to the mixture of $w_1 = 0.80$ because the experimental solubilities of salicylic acid are lower than the ideal solubilities, as indicated above. As observed, the contributions by the mixing thermodynamic quantities, $\Delta_{\text{mix}}H^{\circ}$ and $\Delta_{\text{mix}}S^{\circ}$ values are positive in neat water and in all the {ethanol (1) + water (2)} mixtures but negative in neat ethanol. In this way, entropy-driving is observed for salicylic acid mixing processes from neat water to the mixture of $w_1 = 0.90$ ($\Delta_{\text{mix}}H^{\circ} > 0$, $\Delta_{\text{mix}}S^{\circ} > 0$) but enthalpy-driving is observed for mixing in neat ethanol ($\Delta_{\text{mix}}H^{\circ} < 0$, $\Delta_{\text{mix}}S^{\circ} < 0$). Moreover, to compare the relative contributions by enthalpy (ζ_H) and entropy (ζ_{TS}) to the mixing processes, two equations analogous to Eqs. 14 and 15, were employed. Thus, in almost all cases the main contributor to Gibbs energy of mixing is the enthalpy, whereas, in the mixture of $w_1 = 0.90$ the mixing entropy is the dominant thermodynamic function.

Table 6 Apparent thermodynamic functions relative to mixing processes of salicylic acid (3) in {ethanol (1) + water (2)} mixtures at $T = 298.15$ K and $p = 90$ kPa[a,b]

w_1[a,b]	x_1[a,b]	$\Delta_{mix}G^\circ$ (kJ·mol^{-1})[b]	$\Delta_{mix}H^\circ$ (kJ·mol^{-1})[b]	$\Delta_{mix}S^\circ$ (J·mol^{-1}·K^{-1})[b]	$T\Delta_{mix}S^\circ$ (kJ·mol^{-1})[b]	ζ_H[c]	ζ_{TS}[c]
0.000	0.0000	14.33	14.6	0.9	0.3	0.982	0.018
0.100	0.0417	12.85	13.5	2.2	0.7	0.954	0.046
0.200	0.0891	11.29	12.5	4.0	1.2	0.912	0.088
0.300	0.1436	9.55	12.0	8.4	2.5	0.828	0.172
0.400	0.2068	7.04	12.5	18.5	5.5	0.695	0.305
0.500	0.2812	4.61	12.8	27.5	8.2	0.610	0.390
0.600	0.3698	2.56	12.2	32.3	9.6	0.559	0.441
0.700	0.4772	1.27	10.8	32.0	9.6	0.531	0.469
0.800	0.6101	0.10	7.5	24.8	7.4	0.503	0.497
0.900	0.7788	− 0.72	0.9	5.4	1.6	0.355	0.645
1.000	1.0000	− 1.08	− 3.0	− 6.4	− 1.9	0.610	0.390

[a] p is the atmospheric pressure in Aksaray, Turkey. [a] w_1 and x_1 are the mass and mole fraction of ethanol (1) in the {ethanol (1) + water (2)} mixtures free of salicylic acid (3)

[b] Standard uncertainty in T is $u(T) = 0.10$ K. Relative uncertainty in p is $u_r(p) = 0.03$. Average relative uncertainties in w_1 and x_1 were $u_r(w_1) = 0.0008$ and $u_r(x_1) = 0.0008$. Average standard uncertainty in Gibbs energy of mixing is $u(\Delta_{soln}G^\circ) = 0.10$ kJ·mol^{-1}. Average relative standard uncertainty in enthalpies and entropies of mixing processes are $u_r(\Delta_{mix}G^\circ) = 0.067$, $u_r(\Delta_{mix}H^\circ) = 0.083$, $u_r(\Delta_{mix}S^\circ) = 0.083$, $u_r(T\Delta_{mix}S^\circ) = 0.083$

[c] ζ_H and ζ_{TS} are the relative contributions by enthalpy and entropy toward apparent Gibbs energy of mixing

3.7 Enthalpy–Entropy Compensation Analysis

Extra-thermodynamic studies including enthalpy–entropy compensation analysis provide a powerful tool to inquiry the main molecular mechanisms involved in different chemical processes involving organic compounds [53, 54]. Non-enthalpy-entropy compensation effects have been reported in the dissolution processes of several drugs in {ethanol (1) + water (2)} mixtures as summarized in the literature [55]. Reported studies were performed to identify the main mechanisms involved in the dissolving cosolvent action of ethanol. Normally, weighted plots of $\Delta_{soln}H^\circ$ *vs.* $\Delta_{soln}G^\circ$ have been used for performing such an analysis [56–58]. Figure 8 shows that salicylic acid exhibits a non-linear $\Delta_{soln}H^\circ$ *vs.* $\Delta_{soln}G^\circ$ trend in {ethanol (1) + water (2)} mixtures with variable positive slopes from neat water to the mixture of $w_1 = 0.30$ and from the mixture of $w_1 = 0.50$ to neat ethanol but negative slopes in the interval of $0.30 \leq w_1 \leq 0.50$. Accordingly, in the first cases the transfer of salicylic from more polar to less polar solvent systems is enthalpy-driven, whereas, in the mixtures of $0.30 \leq w_1 \leq 0.50$ it is entropy-driven.

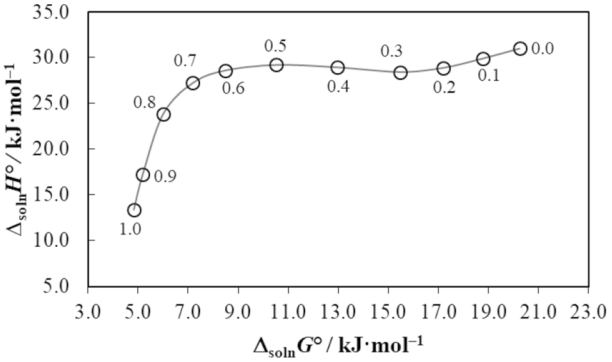

Fig. 8 $\Delta_{soln}H°$ *vs.* $\Delta_{soln}G°$ enthalpy–entropy compensation plot for dissolution process of salicylic acid (3) in {ethanol (1) + water (2)} mixtures at $T = 298.15$ K. Line is just a visual guide

3.8 Preferential Solvation of Salicylic Acid

The preferential solvation parameters of salicylic acid (compound 3) by ethanol (compound 1) in the {ethanol (1) + water (2)} mixtures ($\delta x_{1,3}$) are defined as Eq. 20:

$$\delta x_{1,3} = x_{1,3}^{L} - x_1 = -\delta x_{2,3} \tag{20}$$

where $x_{1,3}^{L}$ is the local mole fraction of ethanol in the molecular environment of salicylic acid and x_1 is the bulk mole fraction of ethanol in the initial binary solvent mixture free of salicylic acid. If $\delta x_{1,3}$ is positive salicylic acid is preferentially solvated by ethanol. On the contrary, salicylic acid is preferentially solvated by water if this parameter is negative. The values of $\delta x_{1,3}$ were obtained from the inverse Kirkwood–Buff integrals (IKBI) as described earlier [59–61], based on the following expressions:

$$\delta x_{1,3} = \frac{x_1 x_2 \left(G_{1,3} - G_{2,3}\right)}{x_1 G_{1,3} + x_2 G_{2,3} + V_{cor}} \tag{21}$$

with,

$$G_{1,3} = RT\kappa_T - \overline{V}_3 + x_2 \overline{V}_2 D/Q \tag{22}$$

$$G_{2,3} = RT\kappa_T - \overline{V}_3 + x_1 \overline{V}_1 D/Q \tag{23}$$

$$V_{cor} = 2522.5\left(r_3 + 0.1363\left(x_{1,3}^{L}\overline{V}_1 + x_{2,3}^{L}\overline{V}_2\right)^{1/3} - 0.085\right)^3 \tag{24}$$

Here, κ_T is the isothermal compressibility of the {ethanol (1) + water (2)} mixtures. $\overline{V}_1$ and $\overline{V}_2$ are the partial molar volumes of ethanol and water in the mixtures, and $\overline{V}_3$ is the partial molar volume of salicylic acid in the solvent mixtures.

The function D, described by Eq. 25, corresponds to the first derivative of the standard molar Gibbs energies of transfer of salicylic acid from neat water to {ethanol (1) + water (2)} mixtures regarding the mole fraction of ethanol in the solvent mixtures free of drug. The function Q, described by Eq. 26, involves the second derivative of the excess molar Gibbs energy of mixing of both solvents (G^{Exc}_{1+2}) regarding the mole fraction of water in the mixtures [59–61]. V_{cor} is the correlation volume and r_3 is the molecular radius of salicylic acid, which in turn is approximately calculated by means of Eq. 27, where N_{Av} is the Avogadro's number.

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

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

$$r_3 = \left(\frac{3 \cdot 10^{21} V_3}{4\pi N_{Av}} \right)^{1/3} \tag{27}$$

Definitive V_{cor} values require iteration because they depend closely on the local mole fractions of ethanol and water around the salicylic acid molecules. This iteration process was performed by replacing $\delta x_{1,3}$ and V_{cor} in the Eqs. 20, 21 and 24 to recalculate $x^L_{1,3}$ until obtaining a non-variant value of V_{cor}.

Figure 9 shows the Gibbs energies of transfer of salicylic acid from neat water to {ethanol (1) + water (2)} mixtures at $T = 298.15$ K. These values were calculated from the mole fraction solubility values reported in Table 2 using Eq. 28:

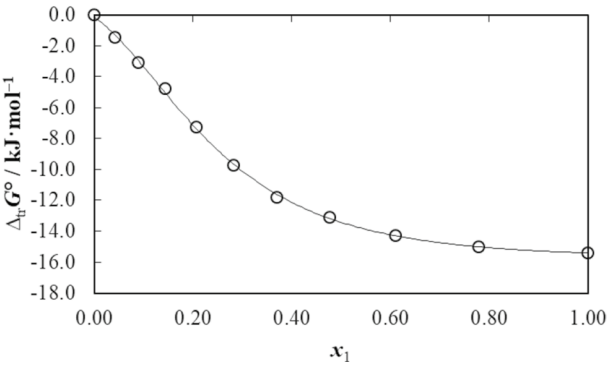

Fig. 9 Gibbs energy of transfer of salicylic acid (3) from neat water (2) to {ethanol (1) + water (2)} mixtures at $T = 298.15$ K. Line is just a visual guide

$$\Delta_{tr}G^{o}_{3,2\rightarrow 1+2} = RT \ln\left(\frac{x_{3,2}}{x_{3,1+2}}\right) \tag{28}$$

$\Delta_{tr}G^{o}_{3,2\rightarrow 1+2}$ values were correlated by the quotient polynomial shown as Eq. 29, obtaining adjusted $r^2 = 0.999$, typical error = 0.181, and $F = 2456$.

$$\Delta_{tr}G^{o}_{3,2\rightarrow 1+2} = \frac{-0.12 - 23.47x_1 - 125.00x_1^2}{1 + 0.206x_1 + 8.43x_1^2} \tag{29}$$

D values reported in Table 7 were calculated from the first derivative of Eq. 29 solved in successive steps of $x_1 = 0.05$. For {ethanol (1) + water (2)} mixtures the $\underline{Q}$, $RT\kappa_T$, $\overline{V}_1$ and $\overline{V}_2$ values at $T = 298.15$ K were taken from the literature [62, 63]. $\overline{V}_3$ was considered as the one calculated by the Fedors method, *i.e.* 90.9 $cm^3 \cdot mol^{-1}$ (Table 3). Table 7 shows that $G_{1,3}$ and $G_{2,3}$ values are negative in all the solvent systems. Salicylic acid r_3 value was calculated as 0.330 nm. As indicated above,

Table 7 Some properties associated to preferential solvation of salicylic acid (3) in {ethanol (1) + water (2)} mixtures at $T = 298.15$ K

x_1[a]	D (kJ·mol^{-1})	$G_{1,3}$ (cm^3·mol^{-1})	$G_{2,3}$ (cm^3·mol^{-1})	V_{cor} (cm^3·mol^{-1})	100 $\delta x_{1,3}$
0.00	− 23.45	− 260.7	− 89.8	553	0.00
0.05	− 33.30	− 346.8	− 129.9	569	− 2.40
0.10	− 38.11	− 392.3	− 191.2	585	− 4.84
0.15	− 38.11	− 393.1	− 254.3	615	− 5.21
0.20	− 34.82	− 362.5	− 303.3	662	− 2.73
0.25	− 29.98	− 317.8	− 332.3	715	0.70
0.30	− 24.85	− 272.2	− 344.0	763	3.42
0.35	− 20.13	− 232.1	− 343.9	805	5.08
0.40	− 16.09	− 199.7	− 337.4	841	5.92
0.45	− 12.78	− 174.4	− 328.5	874	6.20
0.50	− 10.13	− 155.0	− 319.5	905	6.16
0.55	− 8.03	− 140.1	− 311.2	935	5.90
0.60	− 6.38	− 128.4	− 303.2	963	5.48
0.65	− 5.08	− 118.8	− 293.4	991	4.90
0.70	− 4.05	− 110.5	− 278.2	1017	4.11
0.75	− 3.24	− 103.2	− 254.1	1042	3.14
0.80	− 2.60	− 97.1	− 221.0	1066	2.10
0.85	− 2.08	− 92.7	− 184.6	1091	1.19
0.90	− 1.67	− 90.1	− 152.7	1117	0.55
0.95	− 1.34	− 88.7	− 129.0	1145	0.18
1.00	− 1.07	− 88.0	− 113.3	1174	0.00

[a] x_1 is the mole fraction of ethanol (1) in the {ethanol (1) + water (2)} mixtures free of salicylic acid (3)

V_{cor} values reported in Table 7 were obtained after three iterations. Moreover, Table 7 also summarizes the preferential solvation parameters of salicylic acid by ethanol molecules ($\delta x_{1,3}$) at $T = 298.15$ K.

Figure 10 shows non-linear variation of salicylic acid $\delta x_{1,3}$ values regarding the ethanol mole fraction in the mixtures free of drug. Initially, the addition of ethanol to water makes negative the $\delta x_{1,3}$ values of salicylic acid in the composition interval $0.00 < x_1 < 0.24$. Maximum negative $\delta x_{1,3}$ value is obtained in the mixture $x_1 = 0.15$ ($\delta x_{1,3} = -5.21 \times 10^{-2}$), which is higher than $|1.0 \times 10^{-2}|$. Hence, these results could be considered as a consequence of real preferential solvation effects of this drug by water molecules, rather than a consequence of uncertainties propagation in performed IKBI calculations [64, 65].

In the mixtures composition interval of $0.24 < x_1 < 1.00$ the local mole fractions of ethanol around salicylic acid molecules are higher than those in the bulk mixtures free of drug. Maximum positive $\delta x_{1,3}$ value is obtained in the mixture $x_1 = 0.45$ ($\delta x_{1,3} = 6.20 \times 10^{-2}$), which is also higher than $|1.0 \times 10^{-2}|$. Thus, these results could be considered as a consequence of preferential solvation effects of this drug by ethanol molecules [64, 65]. In solution salicylic acid mainly acts as a Lewis acid due to the hydrogen atoms in its –COOH and –OH groups (Fig. 1) in order to establish hydrogen bonds with proton-acceptor functional groups in the solvents (free electron pairs in the oxygen atoms of the –OH groups). In addition, this drug could act as a Lewis base due to free electron pairs in oxygen atoms of carboxyl and hydroxyl and groups to interact with acidic hydrogen atoms in both solvents. Thus, it is conjecturable that in mixtures of $0.24 < x_1 < 1.00$ salicylic acid is acting as a Lewis acid with ethanol molecules because this cosolvent is more basic than water, as described by the Kamlet–Taft hydrogen bond acceptor parameters, namely $\beta = 0.75$ for ethanol and 0.47 for water [66].

Ultimately, Fig. 10 allows the comparison of preferential solvation results of salicylic acid regarding those of structurally related benzoic acid [38]. As observed, maximum negative $\delta x_{1,3}$ value is higher for salicylic acid, which could

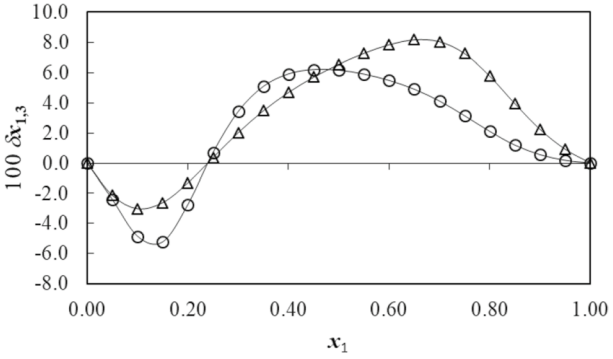

Fig. 10 Preferential solvation parameters ($\delta x_{1,3}$) of salicylic acid (○) and benzoic acid (Δ) by ethanol in {ethanol (1) + water (2)} mixtures at $T = 298.15$ K

be a consequence of the intramolecular hydrogen bonding between carboxyl and hydroxyl groups, although it is observed in different mixture compositions. However, maximum positive $\delta x_{1,3}$ value is higher for benzoic acid although it is also observed in different mixture composition.

4 Conclusions

Solubility and dissolution physicochemical properties of salicylic acid in {ethanol (1) + water (2)} mixtures depend strongly on the cosolvent mixtures composition. Experimental solubility values of salicylic acid were adequately correlated with the classical Jouyban–Acree model and other well-known correlation models. Apparent thermodynamic quantities of dissolution and mixing were calculated based on van't Hoff and Gibbs equations. Non-linear enthalpy-entropy compensation was found for salicylic acid in these mixtures indicating different transfer mechanisms regarding the solvent mixtures composition. Moreover, salicylic acid is preferentially solvated by water in water-rich mixtures but preferentially solvated by ethanol in mixtures of $0.24 < x_1 < 1.00$ at $T = 298.15$ K. Finally, the thermodynamic results presented in this communication could be useful in optimizing different physical and chemical processes involving salicylic acid.

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Author Contributions SA and BK performed solubility experiments and prepared first draft, MÁP and AJ performed correlation calculations, and FM performed thermodynamic and preferential solvation calculations and prepared final draft. All the authors checked and approved the complete manuscript.

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Data Availability Not applicable.

Declarations

Competing Interests The authors report no conflict of interest related with this manuscript.

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