

## Effect of temperature and composition on solubility and thermodynamics of salicylic acid in aqueous mixtures of betaine-based deep eutectic solvents

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**Abstract**—Solubility of salicylic acid in binary mixtures of water and betaine/propylene glycol (Bet/PG, molar ratio of 1 : 5), betaine/ethylene glycol (Bet/EG, molar ratio of 1 : 3) or betaine/glycerol (Bet/Gly, molar ratio of 1 : 3) deep eutectic solvents (DESs) was investigated via the shake flask method at 293.15–313.15 K under atmospheric pressure ( $\approx 85$  kPa). The results indicate that the solubility values are enhanced with mass fraction of each DES and temperature and DES containing PG is the best cosolvent. The Hansen solubility parameter (HSP) of salicylic acid, neat solvents of each DES and water was calculated and used to predict the solubility of drug in each neat solvent. The experimental solubility values were in good agreement with the ones predicted from HSPs. Three cosolvency models (Jouyban-Acree, Jouyban-Acree-van't Hoff and the modified version of Jouyban-Acree-van't Hoff) and two activity coefficient models (NRTL and UNIQUAC) were selected to correlate the solubility data. Based on the obtained percentage mean relative deviations (MRD%) for back-calculated data, all the investigated models show good correlation and validation. Additionally, investigation of the apparent thermodynamic analysis presented an endothermic and entropy-driven dissolution of salicylic acid in all cosolvent compositions including neat DESs and water.

Keywords: Salicylic Acid, Betaine-based Deep Eutectic Solvents, Hansen Solubility Parameters, Apparent Thermodynamic Analysis, Cosolvency Models, Activity Coefficient Models

### INTRODUCTION

Salicylic acid (ortho-hydroxybenzoic acid or 2-hydroxybenzoic acid,  $C_7H_6O_3$ , with molecular structure given in Table 1) is considered as an inhibitor of cyclo-oxygenases 1 and 2 and it is able to decrease the formation of prostaglandins and thromboxanes from arachidonic acid. This alteration in the production of prostaglandins and thromboxanes is utilized to manage the majority of disorders which result from inflammation [1]. Salicylic acid is currently used in the manufacture of a well-known drug, *i.e.* aspirin [2], and many other medicinal compounds involving salicylates (its ester and salt derivatives). It also an active metabolite of acetylsalicylic acid, represents anti-inflammatory effects and is applied in topical formulations as a chemical exfoliating agent [1]. According to the United States Pharmacopeia, salicylic acid is a chemical slightly soluble in water [3] and improvement in its solubility in water is necessary. Drug solubility in water is an essential process for investigation of biological activity and preparation of many liquid dosage forms as well as the formulation of soft gelatin capsules [4–7]. On the other hand, the biopharmaceutical and pharmacokinetic properties of drugs can be affected by their low aqueous solubilities [8]. Several

methods have been developed to increase the solubility of drugs, including the use of soluble cyclodextrin complexes, self-emulsifying drug delivery systems, solid dispersions, nanonization, ordered mesoporous silica, nanocrystals, cosolvency, and so on [9,10]. Considering the importance of cosolvent+water mixtures in chemical and pharmaceutical industries as a recrystallization solvent or reaction medium [7,11], cosolvency is introduced as an effective and optional solubilization method. Thereby, it is essential to systematically determine the solubility of poorly soluble drugs such as salicylic acid in variety aqueous and nonaqueous solvent mixtures [12].

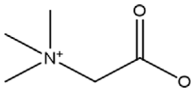
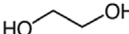
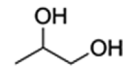
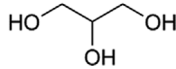
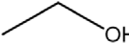
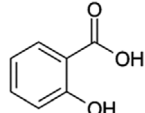
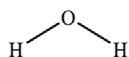
Up to now, the solubility of salicylic acid has been investigated in mono-solvents of sodium dodecyl sulfate and polyvinyl pyrrolidone with different molar masses, Solutol Hs 15, polidocanol and Lutrol F-68 [13], water [14–16], alcohols from methanol to heptanol [13,14,16], ethyl acetate, acetone and acetonitrile [15–17], xylene and chloroform ( $CCl_4$ ) [15], polyethylene glycol 300 (PEG 300) and 1, 4-dioxane [16], propylene glycol (PG) and N-methyl-2-pyrrolidone (NMP) [1]. Besides, the binary solvent mixtures of methanol, ethanol, 1-propanol or 2-propanol+water [14,16], PEG 300 or 1, 4-dioxane+water [16], PG, NMP or ethyl acetate+ethanol [1,16] and NMP+PG [1] have been reported for investigation of salicylic acid solubility. However, some of these investigated solvent mixtures include the low-vapor pressure highly-toxic and costly solvents. This issue could be solved by using low-toxic and biodegradable solvents such as ionic liquids (ILs) and deep eutectic solvents [18].

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**Table 1. Some details of the purity and chemical structure of the employed materials<sup>a</sup>**

Material	Molecular formula	Molar mass (g mol <sup>-1</sup> )	Molecular structure	Mass fraction purity	Source
Betaine (Bet)	C <sub>5</sub> H <sub>11</sub> NO <sub>2</sub>	117.15		>0.990	Dae-Jung of Korea
Ethylene glycol (EG)	C <sub>2</sub> H <sub>6</sub> O <sub>2</sub>	62.07		>0.995	Merck, German
Propylene glycol (PG)	C <sub>3</sub> H <sub>8</sub> O <sub>2</sub>	76.09		>0.990	Merck, German
Glycerol (Gly)	C <sub>3</sub> H <sub>8</sub> O <sub>3</sub>	92.09		>0.990	Merck, German
Ethanol	C <sub>2</sub> H <sub>5</sub> OH	46.07		>0.935	Jahan Alcohol Teb, Iran
Salicylic acid	C <sub>7</sub> H <sub>6</sub> O <sub>3</sub>	138.121		>0.980	Julian Kimia Sanat, Tabriz, Iran
Water	H <sub>2</sub> O	18.02		Distilled deionized water with conductivity<0.1 μS cm <sup>-1</sup>	-

<sup>a</sup>The purity of the employed chemicals was provided by the suppliers.

DESs are a new category of green solvents which are formed by mixing at least two organic chemicals, *i.e.*, a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA) with forming hydrogen bond ability [19]. DESs are non-flammable, thermally stable, less toxic than organic solvents and ILs, economical to prepare and most of them are colorless, liquid at room temperature and usually biodegradable [20,21]. Also, DESs have a high solubilization power especially for some of the poorly water-soluble compounds [22]. In this respect, our research group used successfully used the low-toxic biodegradable betaine or choline chloride-based DESs for acetaminophen and naproxen solubilization and reported a high power solubilization of these DESs [18,23,24]. Betaine (Bet) is a methyl group donor utilized for the treatment of homocystinuria to reduce elevated homocysteine blood levels. It has gained more attention from the scientific community due to its plant nature and lower toxicity as well as its lower cost in comparison to ChCl which is used commonly as an HBA in preparation of DESs [25,26]. The asymmetric structure of Bet and its polar functional groups allow to easily form a eutectic bond with diversity of HBDs [25-29]. There are some reports in the literature about utilizing of aqueous solutions of Bet-based DESs as a solubilizer and stabilizer agent for drugs and enzymes in the pharmaceutical industrial [29-33].

Based on the literature review, there is no report about the solubility profile of salicylic acid in mono-solvents of Bet-based DESs and their binary aqueous mixtures. Hence, the main goal of this work is studying the equilibrium solubility of salicylic acid in the mono-solvents of Bet/PG and Bet/EG DESs along with the binary (Bet/PG, Bet/EG or Bet/Gly DESs+water) mixtures in DES mass fractions from 0.1 to 0.9 using a shake flask technique [34] at 293.15-313.15 K and ambient pressure ( $\approx 85$  kPa). Hansen solubility parameters (HSPs) were also computed for salicylic acid, neat solvents of each DES and water to predict the solubilization power

of each neat solvent for salicylic acid. The solubility values determined for salicylic acid in the aforementioned systems were then correlated by three cosolvency models of Jouyban-Acree [35], Jouyban-Acree-van't Hoff [36] and the modified version of Jouyban-Acree-van't Hoff [37,38] along with the activity coefficient models of nonrandom two-liquid (NRTL) [39] and universal quasi chemical (UNIQUAC) [40,41]. Finally, the apparent thermodynamic parameters for salicylic acid dissolution and mixing processes in Bet/PG, Bet/EG or Bet/Gly DESs+water were determined to report its main driving force.

## CHEMICALS AND METHODS

### 1. Chemicals

A brief summary of the purity and chemical structure of the utilized materials is provided in Table 1. Betaine-based DESs were synthesized according to the described method in a reference [42]. In brief, a certain amount of Bet as a HBA and PG, EG or Gly as HBDs was put in a 50-mL round-bottom flask with molar ratios of 1 : 5, 1 : 3 and 1 : 3, respectively, followed by placing the flask in an oil bath under 80 °C using a hot plate stirrer (with an accuracy of  $\pm 0.01$  °C). Then, the as-prepared mixtures were stirred until forming a homogeneous and clear self-made liquid solvent without any precipitation.

### 2. Solubility Determination of Salicylic Acid in Aqueous Mixtures of Bet-based DESs

The shake flask method [43] has been employed for determination the solubility of salicylic acid in each mono-solvent and the binary (Bet/EG, Bet/PG or Bet/Gly+water) mixtures. First, certain amounts (in grams) of each solvent (Bet/EG, Bet/PG or Bet/Gly DESs and water) were weighted with an analytical balance (Shimadzu, 321-34553, Shimadzu Co., Japan) with a precision  $\pm 0.1$  mg

to prepare different mixtures in mass fractions of DESs ( $w_2$ ) from 0.0 to 1.0. In the case of Bet/Gly DES, the solubility values of salicylic acid in Bet/Gly DES+water mixtures were measured in  $w_2 < 0.9$  due to a high viscosity of DES which did not allow drug homogenization and further analysis in its neat state (*i.e.*,  $w_2=1.0$ ). Next, excess amounts of salicylic acid were added to sealed vials containing the as-prepared neat solvents or binary solvent mixtures. The vials were placed in an incubator (Nabziran Industrial Group, Tabriz, Iran) on a shaker (Behdad, Tehran, Iran) for shaking at a defined temperature with the uncertainty of 0.1 K for 2 days. After equilibration, the solid phase was removed by centrifugation at 1,000 rpm for 30 min and the obtained each clear solution was diluted by ethanol:water mixture (70:30 v/v%) followed then by recording the absorbance of these solutions at 236 nm with a UV-Vis spectrophotometer (Shimadzu UV-1800, Kyoto, Japan). The dilution order of each saturated solution was approximately between 150 to 28140, 150 to 42084, 150 to 4854 for Bet/PG, Bet/EG and Bet/Gly DESs, respectively, depending on the DES mass fractions in the studied mixtures and temperatures; so that, the saturated solutions were more diluted by increasing DES mass fractions as well as enhancing temperature due to more solubilization of salicylic acid. In the maximum wavelength of salicylic acid, the absorbance of aqueous solutions of three DESs in the absence of salicylic acid and the same conditions was recorded and they were  $\leq 0.006$ , which shows there is no interference between salicylic acid and the investigated DESs absorbance in water medium. Thereby, the salicylic acid concentrations for the diluted solutions in mass fraction unit ( $w_1$ ) were determined from the calibration curve plotted for salicylic acid in ethanol:water mixtures (in volume percent of 70:30) at the same wavelength (as seen in Fig. 1). Each experimental data point was the mean of at least three experimental measurements. Finally, the values of  $w_1$  in pseudo-ternary systems of (salicylic acid (1)+Bet/EG, Bet/PG or Bet/Gly DESs (2)+water (3)) were converted to the mole fraction values ( $x_{1,T}$ ) by the help of Eq. (1). This equation has been recently utilized in pseudo-ternary systems containing drug, ChCl-based DESs and water [44,45].

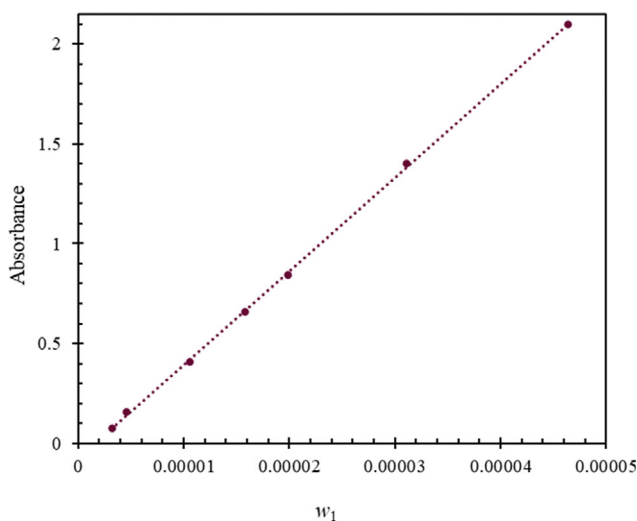


Fig. 1. The calibration curve for salicylic acid (absorbance against mass fraction of salicylic acid ( $w_1$ )).

$$x_{1,T} = \frac{\frac{w_1}{M_1}}{\frac{w_1}{M_1} + \frac{w_2}{M_2} + \frac{w_3}{M_3}} \quad (1)$$

where,  $M_i$  and  $w_i$  correspond to the molar masses and mass fractions of component  $i$  in the studied mixtures. The molar masses of DESs were calculated by Eq. (2) which was reported recently in Ref. [46].

$$M_2 = \frac{x_{HBA} M_{HBA} + x_{HBD} M_{HBD}}{x_{HBA} + x_{HBD}} \quad (2)$$

where,  $x_{HBA}$ ,  $x_{HBD}$ ,  $M_{HBA}$  and  $M_{HBD}$  are the molar ratios and molar masses of Bet as an HBA and EG, PG or Gly as HBDs, respectively.

### 3. Correlation Section

Three cosolvency models including Jouyban-Acree [35], Jouyban-Acree-van't Hoff [36] and the modified version of Jouyban-Acree-van't Hoff [37,38] along with two activity coefficient models of NRTL [39] and UNIQUAC [41] were used for modelling the values of  $x_{1,T}$  measured for salicylic acid in (salicylic acid (1)+Bet/PG, Bet/EG or Bet/Gly DESs (2)+water (3)) systems. More details of each model are provided in the next subsections.

#### 3-1. Cosolvency Model

The models of Jouyban-Acree [35], Jouyban-Acree-van't Hoff [36] and the modified version of Jouyban-Acree-van't Hoff [37,38] as precise descriptions of temperature and compositions dependency of solubility data were employed to correlate the experimental values of  $x_{1,T}$  for salicylic acid in Bet-based DESs+water mixtures. The general form of these models respectively is:

$$\ln x_{1,T} = w_2 \ln x_{2,T} + w_3 \ln x_{3,T} + \frac{w_2 w_3}{T} \sum_{i=0}^2 J_i \cdot (w_2 - w_3)^i \quad (3)$$

$$\ln x_{1,T} = w_2 \left( A_2 + \frac{B_2}{T} \right) + w_3 \left( A_3 + \frac{B_3}{T} \right) + \frac{w_2 w_3}{T} \sum_{i=0}^2 J_i \cdot (w_2 - w_3)^i \quad (4)$$

$$\ln x_{1,T} = D_1 + \frac{D_2}{T} + D_3 w_2 + D_4 \frac{w_2}{T} + D_5 \frac{w_2^2}{T} + D_6 \frac{w_2^3}{T} + D_7 \frac{w_2^4}{T} \quad (5)$$

in Eqs. (3)-(5),  $x_{1,T}$ ,  $x_{2,T}$  and  $x_{3,T}$  are the solubility of salicylic acid in terms of mole fraction in the investigated mixtures, neat Bet/PG, Bet/EG or Bet/Gly DESs and water, respectively, at temperature  $T$ /K. The model constants, *i.e.*,  $J_i$  terms, were determined by a linear regression of  $\ln x_{1,T} - w_2 \ln x_{2,T} - w_3 \ln x_{3,T}$  or  $\ln x_{1,T} - \left( w_2 \left( A_2 + \frac{B_2}{T} \right) + w_3 \left( A_3 + \frac{B_3}{T} \right) \right)$  against  $\frac{w_2 w_3}{T}$ ,  $\frac{w_2 w_3}{T} (w_2 - w_3)$  and  $\frac{w_2 w_3}{T} (w_2 - w_3)^2$ , respectively, as reported previously in a reference [47].  $w_2$  and  $w_3$  are the mass fractions of Bet/PG, Bet/EG or Bet/Gly DESs and water in the absence of salicylic acid.  $A_1$ ,  $B_1$ ,  $A_2$ ,  $B_2$  are the model constants of the van't Hoff equation. Besides,  $D_1$  to  $D_7$  are related to the model constants of Eq. (5).

#### 3-2. Activity Coefficient Models

The activity coefficient models of NRTL [39] and UNIQUAC [40,41] are semi-empirical models with adjustable parameters. These two semi-empirical models work for a wide range of ideal and non-ideal solvents, including alcohols, ketones, amines, ionic liquids, deep eutectic solvents and water. For a solution with  $m$  components,

the UNIQUAC model is described as:

$$\ln \gamma_i = \ln \frac{\Phi_i}{X_i} + \frac{z}{2} q_i \ln \frac{\theta_i}{\Phi_i} + l_i - \frac{\Phi_i}{X_i} \sum_{j=1}^m X_j l_j - q_i' \ln \left( \sum_{j=1}^m \theta_j' \tau_{ji} \right) + q_i' - q_i' \sum_{j=1}^m \frac{\theta_j' \tau_{ji}}{\sum_{k=1}^m \theta_k' \tau_{ki}} \quad (6)$$

where,

$$\Phi_i = \frac{r_i X_i}{\sum_{j=1}^m r_j X_j}; \theta_i = \frac{q_i X_i}{\sum_{j=1}^m q_j X_j}; \theta_i' = \frac{q_i' X_i}{\sum_{j=1}^m q_j' X_j} \quad (7)$$

$$\tau_{ij} = \exp \left( - \left( a_{ij}' + \frac{b_{ij}'}{T} \right) \right); \tau_{ji} = \exp \left( - \left( a_{ji}' + \frac{b_{ji}'}{T} \right) \right); l_j = \frac{z}{2} (r_j - q_j) - (r_j - 1) \quad (8)$$

in Eq. (8),  $a_{ij}'$  and  $b_{ij}'$  correspond to the adjustable parameters of the UNIQUAC equation and  $z$  is assumed to be equal to 10. The dimensionless parameters  $r$ ,  $q$  and  $q'$  are pure component constants which depend on the van der Waals area and volume as follows [48]:

$$r_i = \frac{Q_i}{15.17}; q_i = \frac{R_i}{2.5 \times 10^9} \quad (9)$$

where,  $Q_i$  and  $R_i$  denote the van der Waals molar volume and area of the molecules. Basically,  $q'$  is equal to  $q$  except for alcohols [49]. The van der Waals area and volume of many compounds have been reported by Yaws and coworkers [50] and they can be calculated for cases that are not available in the literature using the functional group approach suggested by Fredenslund and coworkers [51].

The NRTL model for a solution with  $m$  components is:

$$\ln \gamma_i = \frac{\sum_{j=1}^m \tau_{ij} G_{ij} X_j}{\sum_{l=1}^m \tau_{il} X_l} + \sum_{j=1}^m \frac{X_j G_{ij}}{\sum_{l=1}^m G_{lj} X_l} \left( \tau_{ij} - \frac{\sum_{r=1}^m \tau_{rj} G_{rj} X_r}{\sum_{l=1}^m G_{lj} X_l} \right) \quad (10)$$

$$\tau_{ji} = \frac{g_{ji} - g_{ii}}{RT} = a_{ij} + \frac{b_{ij}}{T}; g_{ji} = \exp(-\alpha_{ji} \tau_{ji}); \alpha_{ij} = \alpha_{ji} \quad (11)$$

where,  $\tau_{ij}$ ,  $\tau_{ji}$  and  $\alpha_{ij}$  are the adjustable parameters, and  $g_{ij}$  is an energy parameter characteristic of the  $i$ - $j$  interaction. To use these models, the melting temperature ( $T_m$ ) and fusion enthalpy ( $\Delta_{fus}H$ ) of salicylic acid are needed and they were obtained from Ref. [52] as 431.8 K and 24.6 kJ mol<sup>-1</sup>, respectively. In the NRTL model, the non-randomness factors  $\alpha_{12}$ ,  $\alpha_{13}$  and  $\alpha_{23}$  are set to 0.4, 0.4 and 0.04, respectively. In the case of UNIQUAC model, the values of  $r$  and  $q$  for salicylic acid, water and Bet/PG, Bet/EG and Bet/Gly DESs are reported in Table S1.

The percentage mean relative deviation (MRD%) (Eq. (12)) is calculated to report the capability of each model in representation of experimental solubility data.

$$\text{MRD}\% = \frac{100}{N} \sum \left( \frac{x_{1,T}^{\text{exp}} - x_{1,T}^{\text{cal}}}{x_{1,T}^{\text{exp}}} \right) \quad (12)$$

where,  $N$ ,  $x_{1,T}^{\text{exp}}$  and  $x_{1,T}^{\text{cal}}$  are the number of data points, the experimental and calculated solubility of salicylic acid in term of mole fraction, respectively.

#### 4. Hansen Solubility Parameters (HSPs) of Salicylic Acid and Each Neat Solvent

For investigation of the solubilization power of the selected DESs for salicylic acid, Hansen solubility parameters (HSPs) were used as a proper method to predict and choose a suitable solvent. The concept of a solubility parameter ( $\delta$ ) was first introduced by Hildebrand and Scott, who proposed that components with similar values of  $\delta$  would be miscible [53]. As illustrated in the following equation, it can be seen that the second root of the solubility parameter ( $\delta^2$ ) is a result of dividing the vaporization energy ( $\Delta E$ ) by the molar volume ( $V_m$ ):

$$\delta^2 = \frac{E_{\text{coh}}}{V_m} \quad (13)$$

Depending on the solubility parameters, the tendency of a solvent for solubilization of a solute can be determined. It was found that the solubility of two compounds will be increased when their solubility parameters are more similar. Based on the Charles Hansen concept, the solubility parameter of one material contains three factors: dispersion forces ( $\delta_d^2$ ), polar interactions ( $\delta_p^2$ ) and hydrogen bonds ( $\delta_h^2$ ) [54,55].

$$\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (14)$$

The HSP difference between a cosolvent and a pure chemical substance can be calculated using the following equation:

$$\Delta \delta_{i,j} = \sqrt{4(\delta_d^i - \delta_d^j)^2 + (\delta_p^i - \delta_p^j)^2 + (\delta_h^i - \delta_h^j)^2} \quad (15)$$

$\Delta \delta_{i,j}$  presents the level of difference; and the symptoms  $i$  and  $j$  denote the solvent (we considered the influences of PG, EG and Gly alone, since water and Bet exist in three systems) and salicylic acid as a solute, respectively. For estimation of the partial solubility parameters of pure organic compounds, Hoftyzer and van Krevelen [56] proposed a method according to group contributions method using Eqs. (16) to (18).

$$\delta_d = \frac{\sum F_d}{V_m} \quad (16)$$

$$\delta_p = \frac{\sqrt{\sum F_p^2}}{V_m} \quad (17)$$

$$\delta_h = \frac{\sqrt{\sum E_h}}{V_m} \quad (18)$$

where,  $F_d$  and  $F_p$  are the group contributions of the dispersion and polar component, respectively, and  $E_h$  is hydrogen-bonding energy per structural group. This method has been recently utilized for determination of HSPs for several chemicals involving drugs, traditional organic solvents, polymers and DESs in the literature [57-59]. The numerical values of  $F_d$ ,  $F_p$ ,  $E_h$  and  $V$  of common structural groups are in Table S2.

#### 5. Dissolution and Mixing Properties

During the dissolution process of a solute, its thermodynamic properties in solvent mixtures can provide useful information. The apparent standard dissolution enthalpy ( $\Delta_{\text{sol}}H^\circ$ ) for dissolution process of salicylic acid in (Bet/EG, Bet/PG and Bet/Gly DESs+water) mixtures can be obtained from the van't Hoff analysis [60,61].

$$\Delta_{sol}H^o = -R \left( \frac{\partial \ln x_{1,T}}{\partial (1/T)} \right)_p = -R \left( \frac{\partial \ln x_{1,T}}{\partial [(1/T) - (1/T_{hm})]} \right)_p \quad (19)$$

where,  $R$  is the universal gas constant and it has a value of  $8.314 \text{ J K}^{-1} \text{ mol}^{-1}$ .  $T_{hm}$  is harmonic temperature and it is achieved from Eq. (20).

$$T_{hm} = \frac{N}{\sum_{i=1}^N \frac{1}{T_i}} \quad (20)$$

The standard Gibbs free energy of dissolution ( $\Delta_{sol}G^o$ ) and the values of  $\Delta_{sol}H^o$  for the saturated mixed solutions were calculated from the intercept and the slope of the plot of  $\ln x_{1,T}$  against  $1/T - 1/T_{hm}$ , respectively. Also, Gibbs equation was used for calculation the values of standard entropy of dissolution ( $\Delta_{sol}S^o$ ) [62]. The relative contributions of enthalpy ( $\zeta_H^{sol}$ ) and entropy ( $\zeta_{TS}^{sol}$ ) to  $\Delta_{sol}G^o$  for dissolution of salicylic acid in the studied mixtures were determined with the following equations [63]:

$$\zeta_H^{sol} = \frac{|\Delta_{sol}H^o|}{|\Delta_{sol}H^o| + |T_{hm}\Delta_{sol}S^o|} \quad (21)$$

$$\zeta_{TS}^{sol} = \frac{|T_{hm}\Delta_{sol}S^o|}{|\Delta_{sol}H^o| + |T_{hm}\Delta_{sol}S^o|} \quad (22)$$

The obtained values for thermodynamic parameters of salicylic acid dissolution were then used to calculate the mixing thermodynamic functions (*i.e.*  $\Delta_{mix}H^o$  and  $\Delta_{mix}S^o$ ) using Eqs. (23) and (24) [62,64]:

$$\Delta_{sol}H^o = \Delta_{fus}H^{303} + \Delta_{mix}H^o \quad (23)$$

$$\Delta_{sol}S^o = \Delta_{fus}S^{303} + \Delta_{mix}S^o \quad (24)$$

where,  $\Delta_{fus}H^{303}$  and  $\Delta_{fus}S^{303}$  correspond to thermodynamic functions of fusion process at  $T_{hm}$  and they achieved from Eqs. (25)-(27).

$$\Delta_{fus}H^{303} = \Delta_{fus}H^{T_{fus}} - \Delta C_p(T_{fus} - T_{hm}) \quad (25)$$

$$\Delta_{fus}S^{303} = \Delta_{fus}S^{T_{fus}} - \Delta C_p \ln \left( \frac{T_{fus}}{T_{hm}} \right) \quad (26)$$

$$\Delta C_p \approx \frac{\Delta_{fus}H^{T_{fus}}}{T_{fus}} \quad (27)$$

Using the values of  $\Delta_{fus}H^{T_{fus}}$  ( $24.6 \text{ kJ mol}^{-1}$ ) and  $T_{fus}$  ( $431.8 \text{ K}$ ) for salicylic acid from Ref. [52], the changes of enthalpy ( $\Delta_{fus}H^{303}$ ) and entropy of fusion ( $\Delta_{fus}S^{303}$ ) at  $T_{hm}$  were calculated as  $17.26 \text{ kJ mol}^{-1}$  and  $36.79 \text{ J mol}^{-1} \text{ K}^{-1}$ , respectively. The enthalpic ( $\zeta_H^{mix}$ ) and entropic ( $\zeta_{TS}^{mix}$ ) contributions to  $\Delta_{mix}G^o$  could be determined as:

**Table 2. Experimental mole fraction solubilities ( $10^3 \cdot x_{m,T}$ ) as the average of three measured for salicylic acid in the binary (Bet/PG, Bet/EG or Bet/Gly DESs+water) at  $T=293.15$  to  $313.15 \text{ K}$  and atmospheric pressure ( $\approx 85 \text{ kPa}$ )<sup>a</sup>**

Bet/PG DES (molar ratio of 1 : 5)+water		Bet/EG DES (molar ratio of 1 : 3)+water		Bet/Gly DES (molar ratio of 1 : 3)+water	
T/K	$10^3 \cdot x_{1,T}$	T/K	$10^3 \cdot x_{1,T}$	T/K	$10^3 \cdot x_{1,T}$
$w_2^b=0.00$					
293.15	$0.205 \times 10^{-3}$	293.15	$0.205 \times 10^{-3}$	293.15	$0.205 \times 10^{-3}$
298.15	$0.251 \times 10^{-3}$	298.15	$0.251 \times 10^{-3}$	298.15	$0.251 \times 10^{-3}$
303.15	$0.306 \times 10^{-3}$	303.15	$0.306 \times 10^{-3}$	303.15	$0.306 \times 10^{-3}$
308.15	$0.372 \times 10^{-3}$	308.15	$0.372 \times 10^{-3}$	308.15	$0.372 \times 10^{-3}$
313.15	$0.460 \times 10^{-3}$	313.15	$0.460 \times 10^{-3}$	313.15	$0.460 \times 10^{-3}$
$w_2=0.10$					
293.15	0.710	293.15	0.903	293.15	0.814
298.15	0.928	298.15	1.153	298.15	0.928
303.15	1.128	303.15	1.350	303.15	1.093
308.15	1.371	308.15	1.495	308.15	1.256
313.15	1.644	313.15	1.673	313.15	1.425
$w_2=0.20$					
293.15	1.241	293.15	1.534	293.15	1.286
298.15	1.553	298.15	1.872	298.15	1.381
303.15	1.863	303.15	2.189	303.15	1.552
308.15	2.234	308.15	2.428	308.15	1.743
313.15	2.509	313.15	2.729	313.15	1.990
$w_2=0.30$					
293.15	1.971	293.15	2.428	293.15	1.891
298.15	2.507	298.15	2.908	298.15	2.051
303.15	2.861	303.15	3.333	303.15	2.299
308.15	3.215	308.15	3.702	308.15	2.493
313.15	3.690	313.15	4.084	313.15	2.870

Table 2. Continued

Bet/PG DES (molar ratio of 1 : 5 )+water		Bet/EG DES (molar ratio of 1 : 3)+water		Bet/Gly DES (molar ratio of 1 : 3)+water	
T/K	$10^3 \cdot x_{1,T}$	T/K	$10^3 \cdot x_{1,T}$	T/K	$10^3 \cdot x_{1,T}$
$w_2=0.40$					
293.15	3.303	293.15	3.890	293.15	2.599
298.15	4.105	298.15	4.691	298.15	2.815
303.15	4.659	303.15	5.208	303.15	3.244
308.15	5.242	308.15	5.820	308.15	3.589
313.15	6.194	313.15	6.394	313.15	4.144
$w_2=0.50$					
293.15	6.573	293.15	6.522	293.15	3.971
298.15	7.944	298.15	8.125	298.15	4.264
303.15	8.911	303.15	9.473	303.15	4.744
308.15	10.027	308.15	10.913	308.15	5.480
313.15	11.539	313.15	12.065	313.15	6.489
$w_2=0.60$					
293.15	13.756	293.15	12.555	293.15	6.361
298.15	15.891	298.15	15.836	298.15	7.096
303.15	17.918	303.15	19.355	303.15	8.288
308.15	19.960	308.15	22.116	308.15	9.418
313.15	22.445	313.15	24.231	313.15	11.030
$w_2=0.70$					
293.15	29.816	293.15	26.302	293.15	11.701
298.15	34.288	298.15	31.556	298.15	13.588
303.15	39.849	303.15	37.218	303.15	16.244
308.15	44.225	308.15	41.437	308.15	18.179
313.15	48.997	313.15	45.624	313.15	21.566
$w_2=0.80$					
293.15	65.710	293.15	57.823	293.15	30.290
298.15	72.078	298.15	66.867	298.15	36.306
303.15	78.950	303.15	76.154	303.15	41.734
308.15	84.927	308.15	85.301	308.15	47.102
313.15	92.770	313.15	90.177	313.15	52.411
$w_2=0.90$					
293.15	118.635	293.15	84.023	293.15	37.231
298.15	138.385	298.15	92.643	298.15	43.917
303.15	151.665	303.15	99.647	303.15	49.764
308.15	166.935	308.15	107.176	308.15	55.051
313.15	181.775	313.15	114.779	313.15	61.140
$w_2=1.0$					
293.15	128.858	293.15	90.177	293.15	- <sup>c</sup>
298.15	153.030	298.15	100.444	298.15	- <sup>c</sup>
303.15	166.384	303.15	109.318	303.15	- <sup>c</sup>
308.15	180.024	308.15	116.212	308.15	- <sup>c</sup>
313.15	193.938	313.15	125.898	313.15	- <sup>c</sup>

<sup>a</sup>Standard uncertainty (u) for pressure and temperature are u (P)=0.5 kPa, u (T)=0.1 K; the relative standard deviation for the mole fraction of salicylic acid and mass fraction of betaine-based DESs are  $u_r(x_{1,T})=4.8\%$  and  $u_r(w_2)=0.1\%$ , respectively.

<sup>b</sup> $w_2$  is mass fraction of Bet/PG, Bet/EG or Bet/Gly DESs with molar ratios of 1 : 5, 1 : 3 and 1 : 3, respectively, in the binary mixtures of betaine-based DESs and water in the absence of salicylic acid along with the standard uncertainty (u) of DES molar ratio equal with u (molar ratio)=0.1.

<sup>c</sup>These values could not be experimentally measured due to the high viscosity value of neat Bet/Gly DES.

$$\zeta_H^{mix} = \frac{|\Delta_{mix} H^0|}{|\Delta_{mix} H^0| + |T_{hm} \Delta_{mix} S^0|} \quad (28)$$

$$\zeta_{TS}^{mix} = \frac{|T_{hm} \Delta_{mix} S^0|}{|\Delta_{mix} H^0| + |T_{hm} \Delta_{mix} S^0|} \quad (29)$$

## RESULTS AND DISCUSSION

### 1. Experimental Solubility

The measured values of  $x_{1,T}$  for salicylic acid in cosolvent mixtures of (Bet/PG DES (molar ratio of 1:5)+water), (Bet/EG DES (molar ratio of 1:3)+water) and (Bet/Gly DES (molar ratio of 1:3)+water) are listed in Table 2. To check the accuracy and reliability of the experimental method employed in present work, we compared our measured solubility  $x_{1,T}=0.205 \times 10^{-3}$ ,  $0.251 \times 10^{-3}$ ,  $0.306 \times 10^{-3}$ ,  $0.372 \times 10^{-3}$  and  $0.460 \times 10^{-3}$  in water at 293.15, 298.15, 303.15, 308.15 and 313.15 K, respectively, with those reported in the literature [65], i.e.,  $x_{1,T}=0.208 \times 10^{-3}$ ,  $0.247 \times 10^{-3}$ ,  $0.304 \times 10^{-3}$ ,  $0.368 \times 10^{-3}$  and  $0.452 \times 10^{-3}$  at 293.15, 298.15, 303.15, 308.15 and 313.15 K, respectively. The individual percentage deviations (IPDs%) calculated by Eq. (30) between our determined solubility data and the literature values [65] are 1.4%, 1.6%, 0.7%, 1.1% and 1.8% at 293.15, 298.15, 303.15, 308.15 and 313.15 K, respectively, which may be related to the distinction of impurities in the salicylic acid, experimental error, and/or analysis method.

$$IPD\% = \frac{x_{1,T}^{exp} - x_{1,T}^{rep}}{x_{1,T}^{rep}} \times 100 \quad (30)$$

where,  $x_{1,T}^{exp}$  and  $x_{1,T}^{rep}$  are the experimental and reported in the literature mole fractions of salicylic acid in water. The relationship between the values of  $x_{1,T}$ , temperature and cosolvent composition are plotted graphically in Fig. 2. It can be observed from Table 2 and also Fig. 2 that the solubility data of salicylic acid is a function of temperature and cosolvent composition for the all (cosolvent+solvent) mixtures, so that they are increased with increasing temperature and mass fraction of Bet/PG, Bet/EG or Bet/Gly DESs. Apparently, the maximum solubility of salicylic acid is observed in neat Bet/PG or Bet/EG DESs and 0.9 mass fractions of Bet/Gly DES. Table 2 also demonstrates that the solubility of salicylic acid in (Bet/PG DES+water) is greater than those in (Bet/EG DES+water) or (Bet/Gly+water) systems at the same temperature and cosolvent composition.

### 2. HSP Results

The HSPs for salicylic acid, neat solvents of Bet/PG, Bet/EG and Bet/Gly DESs were computed using the suggested method by Hoftyzer and van Krevelen [56] and the results are listed in Table 3 along with the values of  $\Delta\delta$  (MPa<sup>1/2</sup>) determined for the (salicylic acid+water or Bet-based DES) systems. The HSP for water ( $\delta_s$ ) was gathered from Ref. [55] and it was 47.8 MPa<sup>1/2</sup>. The values of  $\Delta\delta$  reported in Table 3 follow the order: Bet/PG DES (15.8 MPa<sup>1/2</sup>) < Bet/EG DES (17.7 MPa<sup>1/2</sup>) < Bet/PG DES (19.5 MPa<sup>1/2</sup>) < water (32.5 MPa<sup>1/2</sup>), indicating the high miscibility of salicylic acid occurs by Bet/PG DES. This result is in good agreement with our solubility measurements.

The solubilization power of Bet/PG, Bet/EG and Bet/Gly DESs

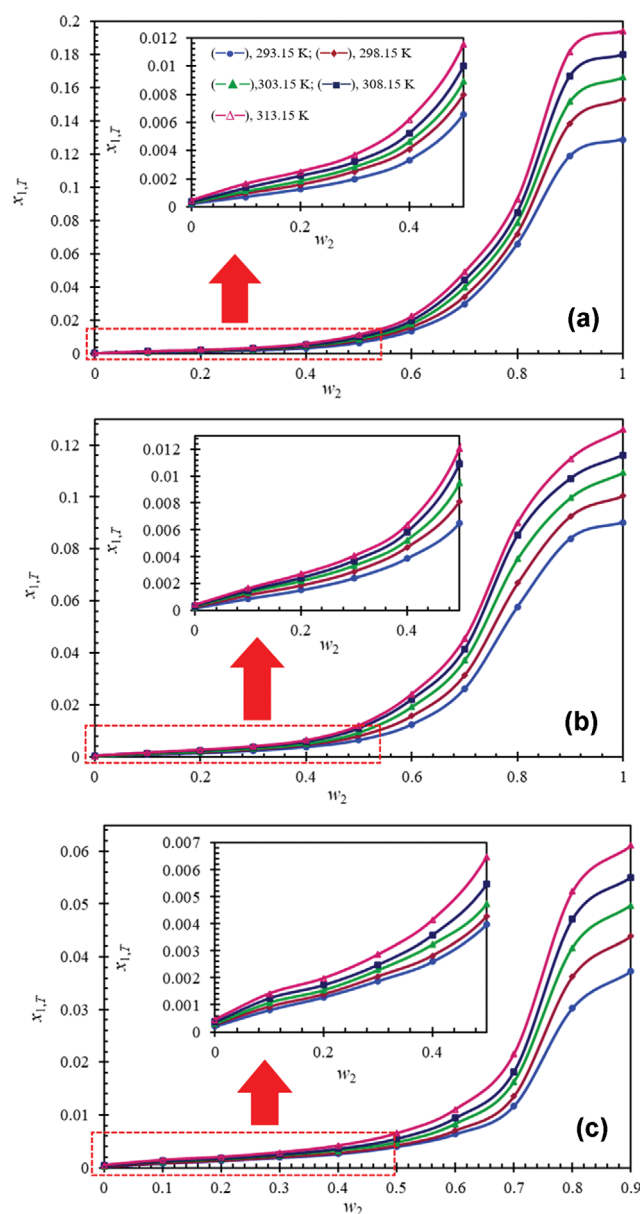


Fig. 2. Experimental solubility of salicylic acid expressed in mole fraction ( $x_{m,T}$ ) in (a) Bet/PG DES (molar ratio of 1:5)+water, (b) Bet/EG DES (molar ratio of 1:3)+water mixtures and (c) Bet/Gly DES (molar ratio of 1:3)+water mixtures at different mass fractions of DESs and  $T=293.15$  K to 313.15 K.

for salicylic acid was compared with another binary solvent mixture reported in the literature by calculation two parameters: one useful parameter defined by Yalkowsky ( $\sigma$ ) [66] (Eq. (31)) and another definition derived from Jouyban-Acree model ( $\omega$ ) [4] (Eq. (32)). The results are listed in Table 4.

$$\sigma = \log \left( \frac{\text{Solubility of salicylic acid in binary solvent}}{\text{Solubility of salicylic acid in water}} \right) \quad (31)$$

$$\omega = \frac{\log \left( \frac{\text{Maximum solubility of salicylic acid in cosolvent}}{\text{Solubility of salicylic acid in water}} \right)}{w_{\text{cosolvent, max}}} \quad (32)$$

**Table 3. Solubility parameter for the used materials along with the values of  $\Delta\delta$  for salicylic acid as a solute and each DES used as a cosolvent**

Materials	$\delta_d$ (MPa <sup>1/2</sup> )	$\delta_p$ (MPa <sup>1/2</sup> )	$\delta_h$ (MPa <sup>1/2</sup> )	$\delta_t$ (MPa <sup>1/2</sup> )
Water [55]	15.5	16.0	42.3	47.8
Propylene glycol [55]	16.8	9.4	23.3	30.2
Ethylene glycol [55]	17.0	11.0	26.2	33.1
Glycerol [55]	17.4	12.1	29.3	36.1
Salicylic acid	22.6	0.3	17.7	28.7
$\Delta\delta$ values				
Bet/PG DES	Bet/EG DES		Bet/Gly DES	
15.8	17.7		19.5	
			32.5	

**Table 4. Comparison of the solubilization powers of different cosolvents utilized for salicylic acid**

Solvent mixtures	$\sigma$	$\omega$	Ref.
Bet/PG DES (molar ratio of 1 : 5)+water	5.60	5.63	This work
Bet/EG DES (molar ratio of 1 : 3)+water	5.40	5.44	This work
Bet/Gly DES (molar ratio of 1 : 3)+water	5.12	5.69	This work
Methanol+water	2.34	2.61	[16]
Ethanol+water	2.64	2.68	[16]
PEG 300+water	2.95	3.22	[16]
1,4-Dioxane+water	2.86	2.94	[16]
1-Propanol+water	2.67	2.97	[14]
2-Propanol+water	2.68	2.69	[14]
2-Propanone+water	2.76	3.45	[14]
Ethanol	-	1.86	[15]
Carbon tetrachloride	-	0.22	[15]
Ethyl acetate	-	1.66	[15]
Xylene	-	0.55	[15]
Ethanol	-	2.56 <sup>a</sup>	[13]
1-Propanol	-	2.59 <sup>a</sup>	[13]
1-Butanol	-	2.60 <sup>a</sup>	[13]
1-Pentanol	-	2.61 <sup>a</sup>	[13]
1-Hexanol	-	2.62 <sup>a</sup>	[13]
1-Octanol	-	2.62 <sup>a</sup>	[13]

<sup>a</sup>For calculation of these values the mole fraction of salicylic acid in water at 318.15 K ( $0.507 \times 10^{-3}$ ) reported in Ref. [14] was used.

where,  $w_{\text{cosolvent}, \text{max}}$  is the cosolvent mass fraction which provides the highest solubility of salicylic acid. From Table 4, it is clearly obvious that the DES-based systems present a high ability to solubilize salicylic acid in an aqueous medium than that of the traditional organic cosolvent, and they can be considered as a proper cosolvent for solubilization of salicylic acid.

### 3. Thermodynamic Modeling

For description of the equilibrium solubility in the mixed solvents, thermodynamic correlation models have been used and reviewed systematically in a reference [5]. In the present work, five thermodynamic models were utilized to fit the solubility of salicylic acid in cosolvent mixtures of (Bet/PG DES+water) and (Bet/EG DES+water), which correspond to Jouyban-Acree [35], a combination of the Jouyban-Acree model with van't Hoff [36], a modified version of Jouyban-Acree-van't Hoff [37,38], NRTL [39] and UNIQUAC [40,41]. Note that the Jouyban-Acree and Jouyban-Acree-van't Hoff models were not used for correlation of the experimental solubility data of salicylic acid in Bet/Gly DES+water mixtures, since we did not measure the drug solubility in neat Bet/Gly DES due to its high viscosity. So, these data were fitted with the modified version of Jouyban-Acree-van't Hoff and two activity coefficient models of NRTL and UNIQUAC. Based on the measured solubility data, the parameters of Eqs. (3) to (6) and (10) can be calculated by the software of SPSS and Mathcad. The attained values of each model parameters together with the MRDs% $\pm$ (SDs) are listed in Tables 5 and 6. It can be observed from Tables 5 and 6 that for the studied pseudo-binary solvent mixtures, the minimum values of MRD% $\pm$ SD be-

**Table 5. The parameters of Jouyban-Acree, Jouyban-Acree-van't Hoff and the modified version of Jouyban-Acree-van't Hoff and the corresponding MRDs% for salicylic acid in Bet/PG (1 : 5 molar ratio) or Bet/EG (1 : 3 molar ratio) DESs+water mixtures**

Jouyban-Acree		Jouyban-Acree-van't Hoff		Modified version of Jouyban-Acree-van't Hoff	
Bet/PG DES+water mixtures					
J <sub>0</sub>	204.242	A <sub>2</sub>	4.143	D <sub>1</sub>	4.369
J <sub>1</sub>	40.207	B <sub>2</sub>	−1,805.192	D <sub>2</sub>	−3,690.607
J <sub>2</sub>	2,480.182	A <sub>3</sub>	4.103	D <sub>3</sub>	−0.810
		B <sub>3</sub>	−3,694.827	D <sub>4</sub>	2,211.740
		J <sub>0</sub>	204.449	D <sub>5</sub>	117.041
		J <sub>1</sub>	40.076	D <sub>6</sub>	−199.576
		J <sub>2</sub>	2,480.700	D <sub>7</sub>	NS <sup>a</sup>
MRD%±SD	4.5±4.4		4.8±4.2		18.4±8.9



Table 5. Continued.

Jouyban-Acree		Jouyban-Acree-van't Hoff		Modified version of Jouyban-Acree-van't Hoff	
Bet/EG DES+water mixtures					
J <sub>0</sub>	541.036	A <sub>2</sub>	2.706	D <sub>1</sub>	3.085
J <sub>1</sub>	−73.436	B <sub>2</sub>	−1,495.166	D <sub>2</sub>	−3,292.255
J <sub>2</sub>	2,604.473	A <sub>3</sub>	4.103	D <sub>3</sub>	0.745
		B <sub>3</sub>	−3,694.827	D <sub>4</sub>	2,004.763
		J <sub>0</sub>	541.362	D <sub>5</sub>	−400.750
		J <sub>1</sub>	−73.351	D <sub>6</sub>	−88.358
		J <sub>2</sub>	2,605.286	D <sub>7</sub>	NS <sup>a</sup>
MRD%±SD	6.6±5.9		6.8±5.7		19.4±11.1
Bet/Gly DES+water mixtures					
J <sub>0</sub>	<sup>-b</sup>	A <sub>2</sub>	<sup>-b</sup>	D <sub>1</sub>	1.142
J <sub>1</sub>	<sup>-b</sup>	B <sub>2</sub>	<sup>-b</sup>	D <sub>2</sub>	−2,734.869
J <sub>2</sub>	<sup>-b</sup>	A <sub>3</sub>	<sup>-b</sup>	D <sub>3</sub>	3.645
		B <sub>3</sub>	<sup>-b</sup>	D <sub>4</sub>	1,412.784
		J <sub>0</sub>	<sup>-b</sup>	D <sub>5</sub>	−2,823.139
		J <sub>1</sub>	<sup>-b</sup>	D <sub>6</sub>	2,147.106
		J <sub>2</sub>	<sup>-b</sup>	D <sub>7</sub>	NS <sup>a</sup>
MRD%±SD					16.5±10.1

<sup>a</sup>NS denotes to not statistically significant (p-value>0.05).

<sup>b</sup>Since we did not measure the drug solubility in neat Bet/Gly DES due to its high viscosity, these data were not fitted with these models.

Table 6. Values of parameters of NRTL and UNIQUAC models, as a function of temperature, for the (salicylic acid (1)+Bet/PG, Bet/EG or Bet/Gly DESs (2)+water (3)) system at T=(293.15 to 313.15) K

NRTL model					
Bet/PG DES+water mixtures		Bet/EG DES+water mixtures		Bet/Gly DES+water mixtures	
A <sub>12</sub>	3.7315	A <sub>12</sub>	2.6302	A <sub>12</sub>	−0.4986
B <sub>12</sub>	1.0057	B <sub>12</sub>	0.5000	B <sub>12</sub>	0.5351
A <sub>21</sub>	−1.0422	A <sub>21</sub>	−0.5501	A <sub>21</sub>	−0.1185
B <sub>21</sub>	0.9561	B <sub>21</sub>	0.4454	B <sub>21</sub>	0.0992
A <sub>13</sub>	2.2965	A <sub>13</sub>	4.4083	A <sub>13</sub>	4.6649
B <sub>13</sub>	0.9931	B <sub>13</sub>	0.5057	B <sub>13</sub>	0.5432
A <sub>31</sub>	3.5328	A <sub>31</sub>	4.1981	A <sub>31</sub>	4.2338
B <sub>31</sub>	1.0076	B <sub>31</sub>	0.5042	B <sub>31</sub>	0.4396
A <sub>23</sub>	51.2487	A <sub>23</sub>	19.5852	A <sub>23</sub>	21.2539
B <sub>23</sub>	1.0024	B <sub>23</sub>	0.5047	B <sub>23</sub>	0.5053
A <sub>32</sub>	−80.8816	A <sub>32</sub>	−1.2799	A <sub>32</sub>	−1.3777
B <sub>32</sub>	1.0017	B <sub>32</sub>	0.5071	B <sub>32</sub>	0.5684
MRD%±10 <sup>2</sup> .SD	1.2±0.5	MRD%±10 <sup>2</sup> .SD	1.8±0.8	MRD%±10 <sup>2</sup> .SD	2.2±0.5
UNIQUAC model					
Bet/PG DES+water mixtures		Bet/EG DES+water mixtures		Bet/Gly DES+water mixtures	
a' <sub>12</sub>	−0.7846	a' <sub>12</sub>	−0.3318	a' <sub>12</sub>	−0.7824
b' <sub>12</sub>	0.4975	b' <sub>12</sub>	0.6093	b' <sub>12</sub>	0.5025
a' <sub>21</sub>	1.6199	a' <sub>21</sub>	0.7982	a' <sub>21</sub>	1.7686
b' <sub>21</sub>	0.7394	b' <sub>21</sub>	0.5966	b' <sub>21</sub>	0.5043
a' <sub>13</sub>	−1.1248	a' <sub>13</sub>	−0.7364	a' <sub>13</sub>	−1.0519
b' <sub>13</sub>	0.5140	b' <sub>13</sub>	0.5504	b' <sub>13</sub>	0.5028
a' <sub>31</sub>	2.2262	a' <sub>31</sub>	1.2746	a' <sub>31</sub>	2.0199
b' <sub>31</sub>	0.4905	b' <sub>31</sub>	0.5086	b' <sub>31</sub>	0.5015
a' <sub>23</sub>	1.5652	a' <sub>23</sub>	1.0237	a' <sub>23</sub>	1.7219
b' <sub>23</sub>	0.4780	b' <sub>23</sub>	0.4761	b' <sub>23</sub>	0.5022
a' <sub>32</sub>	−0.4032	a' <sub>32</sub>	−0.3692	a' <sub>32</sub>	−0.5501
b' <sub>32</sub>	0.4929	b' <sub>32</sub>	0.4416	b' <sub>32</sub>	0.4974
MRD%±10 <sup>2</sup> .SD	1.2±1.9	MRD%±10 <sup>2</sup> .SD	2.2±1.3	MRD%±10 <sup>2</sup> .SD	1.4±0.5

**Table 7.** The parameters of Jouyban-Acree, Jouyban-Acree-van't Hoff and modified version of Jouyban-Acree-van't Hoff models along with the corresponding MRDs%±SDs for salicylic acid in the aqueous mixtures of Bet/PG or Bet/EG DESs with selection of minimum solubility data, *i.e.*, the values of  $x_{1,T}$  in neat Bet/PG or Bet/EG DESs and water at 293.15 K and 313.15 K and DESs+water mixtures with  $w_2=0.3, 0.5$  and  $0.7$  at 298.15 K

Jouyban-Acree		Jouyban-Acree-van't Hoff		the modified version of Jouyban-Acree-van't Hoff	
Bet/PG DES+water mixtures					
J <sub>0</sub>	296.955	A <sub>2</sub>	4.143	D <sub>1</sub>	4.090
J <sub>1</sub>	88.436	B <sub>2</sub>	−1,805.192	D <sub>2</sub>	−3,686.031
J <sub>2</sub>	1,725.357	A <sub>3</sub>	4.103	D <sub>3</sub>	0.174
		B <sub>3</sub>	−3,694.827	D <sub>4</sub>	2,180.027
		J <sub>0</sub>	316.288	D <sub>5</sub>	−58.454
		J <sub>1</sub>	114.431	D <sub>6</sub>	−283.495
		J <sub>2</sub>	1,748.372	D <sub>7</sub>	NS <sup>a</sup>
MRD%±SD	6.6±6.8		6.8±6.5		18.5±12.5
Bet/PG DES+water mixtures					
J <sub>0</sub>	574.895	A <sub>2</sub>	2.706	D <sub>1</sub>	2.243
J <sub>1</sub>	−23.067	B <sub>2</sub>	−1,495.166	D <sub>2</sub>	−3,000.393
J <sub>2</sub>	2,145.279	A <sub>3</sub>	4.103	D <sub>3</sub>	2.082
		B <sub>3</sub>	−3,694.827	D <sub>4</sub>	1,397.879
		J <sub>0</sub>	580.001	D <sub>5</sub>	−111.993
		J <sub>1</sub>	−14.009	D <sub>6</sub>	−191.539
		J <sub>2</sub>	2,151.357	D <sub>7</sub>	NS <sup>a</sup>
MRD%±SD	7.4±6.8		7.4±6.6		19.1±13.4

<sup>a</sup>NS denotes to not statistically significant (p-value>0.05).

**Table 8.** Apparent thermodynamic parameters for salicylic acid dissolution behavior in the binary (Bet/PG, Bet/EG or Bet/Gly DESs+water) mixtures at  $T_{hm}=303.0$  K

$w_2^a$	$\Delta_{sol}G^o$ (kJ mol <sup>-1</sup> )	$\Delta_{sol}H^o$ (kJ mol <sup>-1</sup> )	$\Delta_{sol}S^o$ (J mol <sup>-1</sup> K <sup>-1</sup> )	$T\Delta_{sol}S^o$ (kJ mol <sup>-1</sup> )	$\zeta_H^{sol}$	$\zeta_{TS}^{sol}$
Bet/PG DES+water						
0.00	20.38	30.74	34.18	10.36	0.748	0.252
0.10	17.14	31.67	47.96	14.53	0.685	0.315
0.20	15.89	27.09	36.97	11.20	0.707	0.293
0.30	14.82	22.99	26.96	8.17	0.738	0.262
0.40	13.56	22.96	31.03	9.40	0.710	0.290
0.50	11.91	20.74	29.15	8.83	0.701	0.299
0.60	10.16	18.42	27.26	8.26	0.690	0.310
0.70	8.18	19.09	35.99	10.90	0.637	0.363
0.80	6.42	13.04	21.85	6.62	0.663	0.337
0.90	4.78	15.93	36.80	11.15	0.588	0.412
1.00	4.57	15.00	34.43	10.43	0.590	0.410
Bet/EG DES+water						
0.00	20.38	30.74	34.18	10.36	0.748	0.252
0.10	16.77	22.88	20.16	6.11	0.789	0.211
0.20	15.52	21.60	20.05	6.08	0.780	0.220
0.30	14.44	19.59	17.01	5.15	0.792	0.208
0.40	13.28	18.51	17.24	5.22	0.780	0.220
0.50	11.81	23.36	38.13	11.55	0.669	0.331
0.60	10.07	25.26	50.13	15.19	0.624	0.376
0.70	8.39	21.02	41.68	12.63	0.625	0.375
0.80	6.55	17.30	35.50	10.76	0.617	0.383
0.90	5.82	11.76	19.60	5.94	0.664	0.336
1.00	5.61	12.44	22.53	6.83	0.646	0.354

Table 8. Continued

$w_2^a$	$\Delta_{\text{sol}}G^\circ$ (kJ mol <sup>-1</sup> )	$\Delta_{\text{sol}}H^\circ$ (kJ mol <sup>-1</sup> )	$\Delta_{\text{sol}}S^\circ$ (J mol <sup>-1</sup> K <sup>-1</sup> )	$T\Delta_{\text{sol}}S^\circ$ (kJ mol <sup>-1</sup> )	$\zeta_H^{\text{sol}}$	$\zeta_{TS}^{\text{sol}}$
Bet/Gly DES+water						
0.00	20.38	30.74	34.18	10.36	0.748	0.252
0.10	17.20	21.71	14.86	4.50	0.828	0.172
0.20	16.26	16.86	1.97	0.60	0.966	0.034
0.30	15.31	15.72	1.38	0.42	0.974	0.026
0.40	14.45	17.94	11.52	3.49	0.837	0.163
0.50	13.39	18.75	17.70	5.36	0.778	0.222
0.60	12.08	21.11	29.83	9.04	0.700	0.300
0.70	10.43	23.11	41.82	12.67	0.646	0.354
0.80	8.06	20.75	41.88	12.69	0.621	0.379
0.90	7.61	18.61	36.28	10.99	0.629	0.371

<sup>a</sup> $w_2$  is mass fraction of Bet/PG, Bet/EG or Bet/Gly DESs in the binary (Bet/PG, Bet/EG or Bet/Gly DESs+water) in the absence of salicylic acid.

tween the computed and experimental values were  $4.5\% \pm 4.4$  and  $1.2\% \pm 0.5$  which obtained with Jouyban-Acree-van't Hoff and NRTL models for the system of (Bet/PG DES+water).

In high throughput crystallization methods, time is a vital factor and solubility is the most basic information in this process. It is well-known that solubility measurements are commonly a time-

consuming process because of the requirement to reach thermodynamic equilibrium. On the other hand, in many cases, there are only a few grams of an expensive pharmaceutical or fine chemical to make a large number of crystallization experiments. So, it is important to predict the solubility of a compound over a wide range of temperatures, by measuring a minimum data point. For achieving

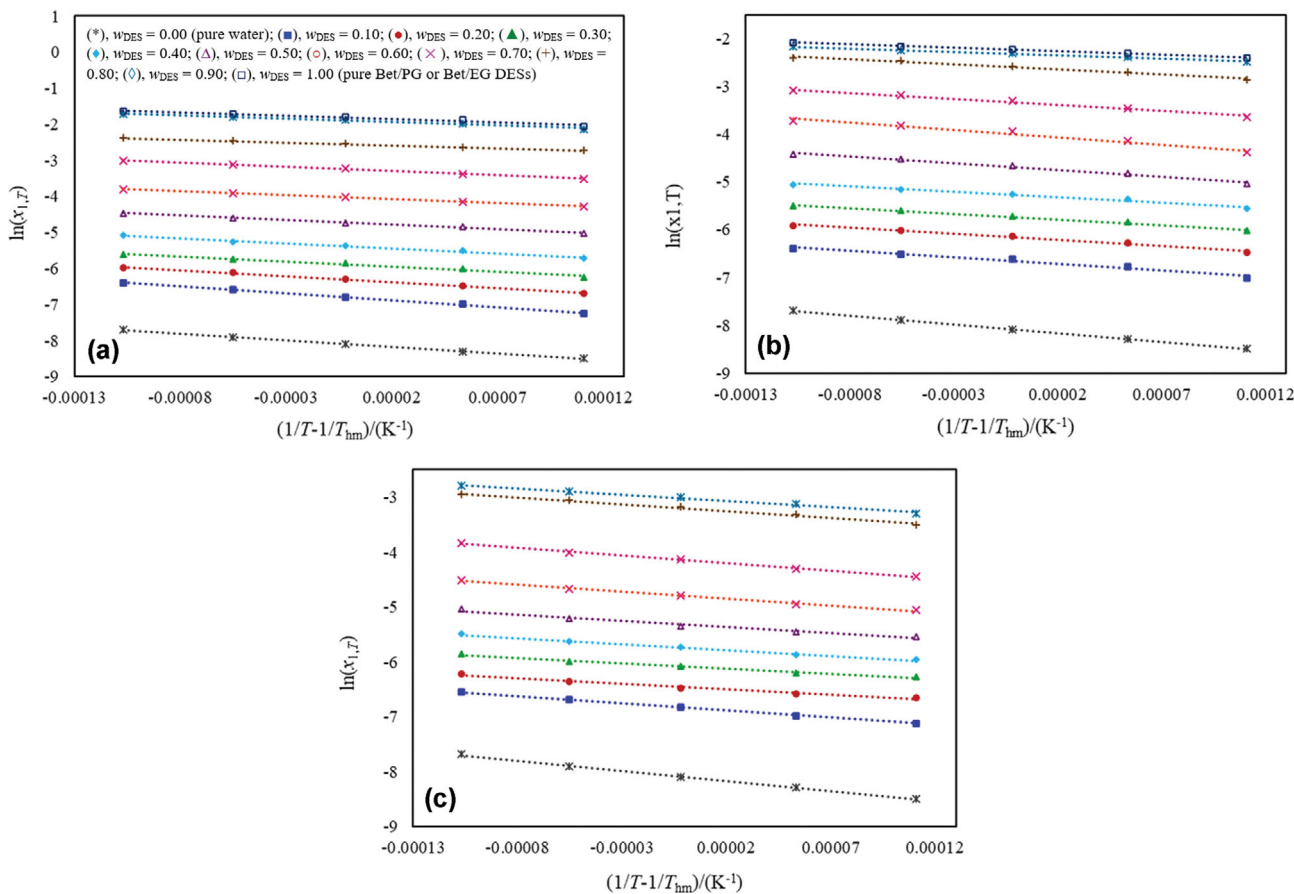


Fig. 3. The van't Hoff plots of salicylic acid solubility in (a) Bet/PG DES+water, (b) Bet/EG DES+water and (c) Bet/Gly DES+water.

this purpose, it is necessary to use thermodynamic models to predict the compound solubility data. In this work, we checked the prediction capability of simple cosolvency models by using the minimum number of experimental data points, *i.e.*, solubility data in water, neat Bet/PG or Bet/EG DESs at 293.15 and 313.15 K and also in mixed solvents with Bet/PG or Bet/EG DESs mass frac-

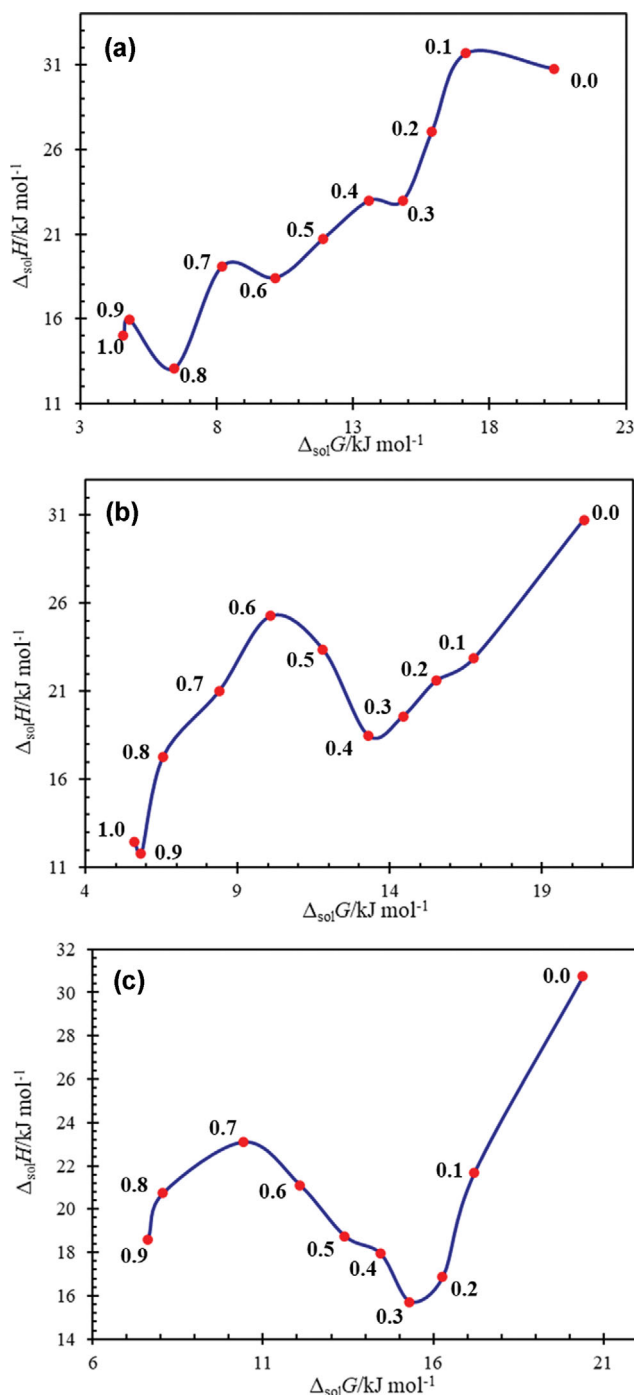


Fig. 4. Enthalpy-entropy compensation plots for salicylic acid in (a) Bet/PG DES+water, (b) Bet/EG DES+water and (c) Bet/Gly DES+water mixtures at  $T_m=303.0$  K. The points present the mass fractions of Bet/PG, Bet/EG or Bet/Gly DESs in the investigated mixtures in the absence of salicylic acid.

tions of 0.3, 0.5 and 0.7 at 298.15 K. The adjustable parameters of each model are estimated using these minimum data points followed then by extrapolation of their predictive capability over a wide range of operating conditions. The parameters of each trained models are given in Table 7. Based on the MRDs%±SDs in this Table, it is found that the prediction ability of the three modes is acceptable and the overall MRDs%±SDs follow the order: Jouyban-Acree model (7.0%±6.8)≤Jouyban-Acree-van't Hoff model (7.1%±6.6)≤the modified version of Jouyban-Acree-van't Hoff model (18.8%±13.0); however, the prediction ability of Jouyban-Acree and Jouyban-Acree-van't Hoff models is higher than that of a modified version of Jouyban-Acree-van't Hoff.

#### 4. Calculation of Thermodynamic Parameters for Salicylic Acid Dissolution and Mixing Processes

The values of  $\Delta_{sol}H^\circ$  and  $\Delta_{sol}G^\circ$  for salicylic acid dissolution in (Bet/PG, Bet/EG or Bet/Gly DESs+water) mixtures were estimated by plotting van't Hoff curves (Fig. 3), and the values of  $\Delta_{sol}S^\circ$  were also calculated by Gibbs equation. The results are summarized in Table 8. The  $\Delta_{sol}H^\circ$  values are found to be positive with a maximum value (30.74 kJ mol<sup>-1</sup>) at  $w_2=0.0$  and minimum values of 13.04 kJ mol<sup>-1</sup>, 11.76 kJ mol<sup>-1</sup> and 15.72 kJ mol<sup>-1</sup> for 0.8 mass fraction of Bet/PG, 0.9 mass fraction of Bet/EG and 0.3 mass fraction of Bet/Gly DESs, respectively. The  $\Delta_{sol}G^\circ$  values are also positive and in the range of 4.57 to 20.38 kJ mol<sup>-1</sup>, 5.61 to 20.38 kJ mol<sup>-1</sup> and 7.61 to 20.38 kJ mol<sup>-1</sup> for Bet/PG, Bet/EG and Bet/Gly DESs, respectively, with the minimum values in neat Bet/PG DES, Bet/EG DES and 0.9 mass fraction of Bet/Gly DES where salicylic acid presents the maximum solubility. The positive values of  $\Delta_{sol}H^\circ$  and  $\Delta_{sol}G^\circ$  show an endothermic and more favorable dissolution process for salicylic acid in neat Bet/PG DES, Bet/EG DES and 0.9 mass fraction of Bet/Gly DES. The  $\Delta_{sol}S^\circ$  values for salicylic acid dissolution in each solvent mixtures and also in all compositions are positive, illustrating that salicylic acid dissolution process has an entropy driven mechanism in aqueous Bet-based DESs mixtures.  $\zeta_H^{sol}$  and  $\zeta_{TS}^{sol}$  values are also reported in Table 8. For all mixtures, the values of  $\zeta_H^{sol}$  are higher than that of  $\zeta_{TS}^{sol}$  values which shows that the enthalpy is the main

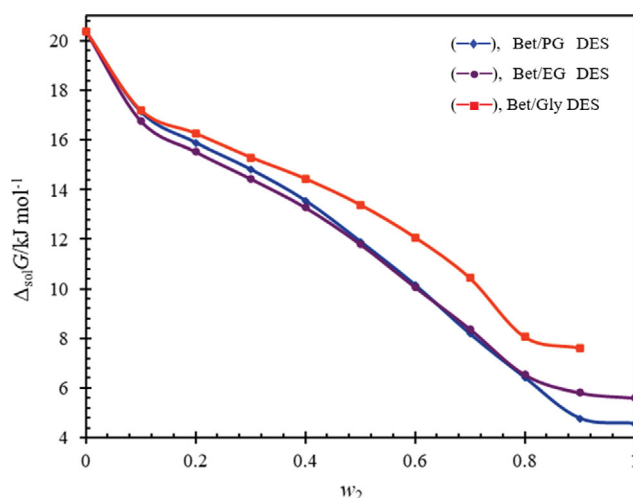


Fig. 5. The  $\Delta_{sol}G^\circ$  values for dissolution processes of salicylic acid in the binary mixtures of Bet-based DESs and water vs. mass fraction of DES ( $w_2$ ) at harmonic temperature.

contributor of  $\Delta_{\text{sol}}G^\circ$  in the dissolution processes of salicylic acid.

The enthalpy-entropy compensation plots for salicylic acid dissolution processes in (Bet/PG, Bet/EG or Bet/Gly DESs+water) mixtures are displayed in Fig. 4. It can be observed that salicylic acid in the mixtures of  $0.0 \leq w_2 \leq 0.1$ ,  $0.3 \leq w_2 \leq 0.4$  and  $0.8 \leq w_2 \leq 0.9$  for (Bet/PG DES+water) system,  $0.4 \leq w_2 \leq 0.6$  and  $0.9 \leq w_2 \leq 1.0$  for (Bet/EG DES+water) system and  $0.3 \leq w_2 \leq 0.7$  for (Bet/Gly DES + water) system presents an almost-linear curve of  $\Delta_{\text{sol}}H^\circ$  vs.  $\Delta_{\text{sol}}G^\circ$  with the positive slope values. On the other hand, in the regions of  $0.1 \leq w_2 \leq 0.3$ ,  $0.4 \leq w_2 \leq 0.6$ ,  $0.7 \leq w_2 \leq 0.8$  and  $0.9 \leq w_2 \leq 1.0$  for (Bet/PG

DES+water) system,  $0.0 \leq w_2 \leq 0.4$  and  $0.6 \leq w_2 \leq 0.9$  for (Bet/EG DES+water) system and also  $0.0 \leq w_2 \leq 0.3$  and  $0.7 \leq w_2 \leq 0.9$  for (Bet/Gly DES+water) system salicylic acid dissolution demonstrates a negative slope. Regions with positive and negative slopes represent an enthalpy- and entropy-driving mechanism for salicylic acid transfer from more polar to less polar systems in the mixtures of Bet-PG, Bet/EG or Bet/Gly DESs and water. Moreover, a plot of  $\Delta_{\text{sol}}G^\circ$  values against mass fraction of each DES presented that by enhancing drug solubility, these values decrease and become lowest at neat solvents of Bet/PG or Bet/EG DESs and also 0.9 mass fractions of

**Table 9. Thermodynamic functions relative to mixing process of salicylic acid in the binary mixtures of Bet/PG, Bet/EG or Bet/Gly DESs and water at 303 K**

$w_{\text{DES}}^a$	$\Delta_{\text{mix}}G^\circ$ (kJ mol <sup>-1</sup> )	$\Delta_{\text{mix}}H^\circ$ (kJ mol <sup>-1</sup> )	$\Delta_{\text{mix}}S^\circ$ (J mol <sup>-1</sup> K <sup>-1</sup> )	$T\Delta_{\text{mix}}S^\circ$ (kJ mol <sup>-1</sup> )	$\zeta_H^{\text{mix}}$	$\zeta_{TS}^{\text{mix}}$
Bet/PG DES+water						
0.00	14.27	13.48	-2.61	-0.79	0.945	0.055
0.10	11.02	14.41	11.17	3.38	0.810	0.190
0.20	9.77	9.83	0.18	0.05	0.995	0.005
0.30	8.71	5.73	-9.83	-2.98	0.658	0.342
0.40	7.44	5.70	-5.76	-1.75	0.765	0.235
0.50	5.79	3.48	-7.64	-2.31	0.601	0.399
0.60	4.05	1.16	-9.53	-2.89	0.286	0.714
0.70	2.07	1.83	-0.80	-0.24	0.884	0.116
0.80	0.30	-4.22	-14.94	-4.53	0.482	0.518
0.90	-1.34	-1.33	0.01	0.00	1.000	0.000
1.00	-1.55	-2.26	-2.36	-0.72	0.758	0.242
Bet/EG DES+water						
0.00	14.27	13.48	-2.61	-0.79	0.945	0.055
0.10	10.66	5.62	-16.63	-5.04	0.527	0.473
0.20	9.41	4.34	-16.74	-5.07	0.461	0.539
0.30	8.32	2.33	-19.78	-5.99	0.280	0.720
0.40	7.17	1.25	-19.55	-5.92	0.174	0.826
0.50	5.69	6.10	1.34	0.41	0.937	0.063
0.60	3.96	8.00	13.34	4.04	0.664	0.336
0.70	2.28	3.76	4.89	1.48	0.718	0.282
0.80	0.43	0.04	-1.29	-0.39	0.093	0.907
0.90	-0.29	-5.50	-17.19	-5.21	0.514	0.486
1.00	-0.50	-4.82	-14.26	-4.32	0.527	0.473
Bet/Gly DES+water						
0.00	14.27	13.48	-2.61	-0.79	0.945	0.055
0.10	11.09	4.45	-21.93	-6.64	0.401	0.599
0.20	10.15	-0.40	-34.82	-10.55	0.037	0.963
0.30	9.19	-1.54	-35.41	-10.73	0.126	0.874
0.40	8.33	0.68	-25.27	-7.66	0.082	0.918
0.50	7.27	1.49	-19.09	-5.78	0.205	0.795
0.60	5.96	3.85	-6.96	-2.11	0.646	0.354
0.70	4.32	5.85	5.03	1.52	0.794	0.206
0.80	1.95	3.49	5.09	1.54	0.694	0.306
0.90	1.50	1.35	-0.51	-0.15	0.900	0.100

<sup>a</sup> $w_2$  is mass fraction of Bet/PG, Bet/EG or Bet/Gly DESs in the binary (Bet/PG, Bet/EG or Bet/Gly DESs+water) in the absence of salicylic acid.

Bet/Gly DES (as seen in Fig. 5).

Table 9 summarizes the thermodynamic functions of mixing for solubility of salicylic acid in (Bet/PG, Bet/EG and Bet/Gly DESs+water) mixtures. As listed in this table, the  $\Delta_{mix}H^\circ$  is positive in water and in the most of mixtures containing DES, and becomes negative in the aqueous mixtures containing Bet/PG, Bet/EG and Bet/Gly DESs with  $w_2 \geq 0.8$ ,  $w_2 \geq 0.9$  and  $0.2 \leq w_2 \leq 0.3$ , respectively. The neat values of  $\Delta_{mix}H^\circ$  can originate from the contribution of various kinds of interactions: (i) the enthalpy of cavity formation is endothermic because of the needed energy to overcome the cohesive forces of the solvent, which decreases solubility of drug [4]. On the other hand, the enthalpy of solute-solvent interaction is exothermic and results mainly from the van der Waals and Lewis acid-base interaction [4]. The structuring of water molecules around the nonpolar groups of solutes (hydrophobic hydration) contributes to decrease the neat heat of mixing to small or even negative values in aqueous solutions. Besides, the  $\Delta_{mix}S^\circ$  values in water have a negative value and they become less negative at high mass fraction of each DES. According to Table 9, the  $\Delta_{mix}G^\circ$  values are decreased by increasing mass fraction of three DESs reaching the lowest values at high mass fractions of DESs, i.e.,  $w_2=1.0$  for Bet/PG ( $-1.55 \text{ kJ mol}^{-1}$ ) or Bet/EG DESs ( $-0.50 \text{ kJ mol}^{-1}$ ) and  $w_2=0.9$  for Bet/Gly ( $1.50 \text{ kJ mol}^{-1}$ ), which show the highest values of salicylic acid solubility.

## CONCLUSION

The equilibrium solubility values of salicylic acid (1) were experimentally determined in three neat solvents of water, Bet/PG DES (molar ratio of 1 : 5) and Bet/EG DES (molar ratio of 1 : 3) along with the three aqueous solutions containing Bet/PG, Bet/EG or Bet/Gly DESs at temperatures ranging from 293.15 to 313.15 K. At the same mass fractions of Bet/PG, Bet/EG or Bet/Gly DESs and temperature, the mole fraction solubility of salicylic acid was maximum in the Bet/PG DES (molar ratio of 1 : 5) (2)+water (3) mixtures. The salicylic acid solubility was mathematically correlated by the models of Jouyban-Acree, Jouyban-Acree-van't Hoff, the modified version of Jouyban-Acree-van't Hoff, NRTL and UNIQUAC and the obtained percentage mean relative deviations (MRDs%) no higher than 6.8%, except for the modified version of Jouyban-Acree-van't Hoff model which its MRDs% was  $\leq 19.1$ . Prediction of solvent influence in solubilization of salicylic acid by Hansen solubility parameters revealed that the solubility of the goal drug was maximum in the Bet/PG DES+water mixtures in good accordance with the experimental results. From investigation of the thermodynamic parameters of dissolution and mixing processes of salicylic acid, an entropy-driven and endothermic dissolution process was concluded with the lower Gibbs free energy values for salicylic acid in Bet/PG DES+water mixtures compared with the others. Therefore, preliminary results demonstrate that the Bet/PG DES is a more proper solvent for improvement of salicylic acid solubility in aqueous medium than the others.

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## CRediT AUTHORSHIP CONTRIBUTION STATEMENT

**Parisa Jafari:** Formal analysis, Investigation, Writing original draft.

**Mohammad Barzegar-Jalali:** Writing - review & editing, Formal analysis, Funding acquisition.

**Abolghasem Jouyban:** Conceptualization, Writing - review & editing, Supervision.

## DECLARATION OF COMPETING INTEREST

The authors declare no conflict of interest.

## SUPPORTING INFORMATION

Additional information as noted in the text. This information is available via the Internet at <http://www.springer.com/chemistry/journal/11814>.

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## Supporting Information

### Effect of temperature and composition on solubility and thermodynamics of salicylic acid in aqueous mixtures of betaine-based deep eutectic solvents

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**Table S1. UNIQUAC r and q parameters for the used materials in pseudo-ternary systems composed betaine-based DESs, water and salicylic acid**

Component	r	q
Salicylic acid	2.8326	2.8240
Water [1]	0.9200	1.4000
Betaine	4.6650	4.0560
Propylene glycol [2]	3.0824	2.7840
Ethylene glycol [1]	2.4088	2.2480
Glycerol [1]	3.8399	3.6800
Betaine/propylene glycol DES with a molar ratio of 1 : 5	20.0770	17.9760
Betaine/ethylene glycol DES with a molar ratio of 1 : 3	11.2824	10.8000
Betaine/glycerol DES with a molar ratio of 1 : 3	15.5757	15.096

**Table S2. The numerical values of solubility parameter component group contributions utilized in Hoftyzer and Van Krevelen's method [3]**

Structural group	$F_d/((\text{MJ m}^{-3})^{1/2} \text{mol}^{-1})$	$F_p/((\text{MJ m}^{-3})^{1/2} \text{mol}^{-1})$	$E_t/(\text{J mol}^{-1})$
Benzen	1,430	110	0
-COOH	530	420	10,000
-COO-	390	490	7,000
-OH	210	500	20,000
-NH <sub>2</sub>	280	-	8,400
>N-	20	800	5,000
-CH <sub>2</sub> -	270	0	0
-CH <sub>3</sub>	420	0	0
>CH-	80	0	0

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