Solid-liquid equilibrium of erythromycin thiocyanate dihydrate in four mono-solvents and three binary solvent mixtures

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ABSTRACT: Solid-liquid equilibrium data of erythromycin thiocyanate dihydrate in four mono-solvents (methanol, ethanol, n-propanol and isopropanol) and three organic + water solvent mixtures (acetonitrile + water, acetone + water and ethanol + water) were determined by a gravimetric method under atmospheric pressure. The effects of content of organic solvents and temperature on the solubility were investigated and discussed. It was found that the content of organic solvents can significantly affect the solubility of erythromycin thiocyanate dihydrate. The modified Apelblat equation and NRTL model were applied to correlate the solubility data in mono-solvents. The (CNIBS)/R-K

1 equation, two modified Jouyban-Acree models (the Van't-JA equation and the Apel-JA
2 equation) and NRTL model were used to correlate the experimental data in three binary
3 solvents systems. Computational results indicated that the two Jouyban-Acree models and
4 NRTL model have lower *AIC* (Akaike's Information Criterion) value than (CNIBS)/R-K
5 model in binary solvents mixtures, which means that these three models are better for
6 correlating the experimental solubility data. In addition, the mixing thermodynamic
7 properties of erythromycin thiocyanate dihydrate in different solvents were also
8 calculated based on the experimental solubility data and the NRTL model.

9 **Keywords:** Solubility; Erythromycin thiocyanate dihydrate; *AIC*; Mixing thermodynamic
10 properties

11

12

1. Introduction

Solid-liquid equilibrium data is one of the important thermodynamic properties since it can provide essential information for the design, analysis and optimization of the separation and purification processes in various fields e.g. pharmaceutical, chemical, food, petrochemical and material [1-3]. The model compound, erythromycin thiocyanate ($C_{38}H_{68}N_2SO_{13}$, CAS Registry NO: 7704-67-8), is an antibiotic drug which is highly effective against gram-positive bacteria and mycoplasma infection. As shown in Fig. 1, it possesses a 14-membered lactone ring, a cladinose moiety and a desosamine moiety which is widely used as veterinary medicine or important intermediate for the preparation of other macrolide antibiotics [4]. Erythromycin thiocyanate is reported to have three hydrate forms, and dihydrate form is the most widely used form in industry [5-6]. During the manufacturing of erythromycin thiocyanate dihydrate (abbreviated as ETD hereafter in this work), the crystallization process directly affects the final quality of the ETD product [7]. Although it has been a long time since the launch of ETD, no experimental or theoretical study about the thermodynamics of ETD has been found from bibliographic retrieval.

In this work, the solubility data of ETD in four alcohol organic solvents (methanol, ethanol, n-propanol and isopropanol) and three different kinds of solvent mixtures (acetonitrile + water, acetone + water, ethanol + water) were experimentally measured under atmospheric pressure for the first time. The modified Apelblat equation and NRTL

1 model were applied to correlate the solubility data in mono-solvents. The effects of
2 cosolvent (organic solvents) and temperature on the solubility of ETD in binary solvent
3 mixtures were also investigated and discussed. To extend the applicability of the
4 solubility data, the (CNIBS)/R-K, two modified Jouyban-Acree models and NRTL model
5 were used to correlate the experimental solubility data in three binary solvent mixtures.
6 The mixing thermodynamic properties were also determined by the NRTL model and
7 experimentally measured solubility data.

8
9 **Fig. 1.** Molecular structure of erythromycin thiocyanate.

10 **2. Experimental section**

11 **2.1. Materials**

12 Erythromycin thiocyanate dihydrate was supplied by Shanghai Tonglian Pharm. Co.
13 Ltd. (China). The water content of the provided ETD was determined to be 4.51 ± 0.2
14 mass% with a V20 Volumetric Karl Fischer Titrator (Mettler Toledo, Switzerland), which
15 is close to the theoretical value 4.35%. The distilled deionized water was used
16 throughout. Detailed information about methanol, ethanol, n-propanol, isopropanol,

1 acetonitrile and acetone is given in Table 1.

2 **Table 1. Sources and mass fraction purity of chemicals.**

Chemicals	Mass purity	Molar mass	Source
ETD	≥ 0.984 (HPLC ^a)	829.05	Shanghai Tonglian Pharm. Co., Ltd
Methanol	≥ 0.995 (GC ^b)	32.04	Tianjin Jiangtian Chemical Co., Ltd.
Ethanol	≥ 0.997 (GC ^b)	46.07	Tianjin Jiangtian Chemical Co., Ltd.
n-propanol	≥ 0.995 (GC ^b)	60.10	Tianjin Jiangtian Chemical Co., Ltd.
Isopropanol	≥ 0.995 (GC ^b)	60.10	Tianjin Jiangtian Chemical Co., Ltd.
Acetonitrile	≥ 0.9999 (GC ^b)	41.05	Tianjin Jiangtian Chemical Co., Ltd.
Acetone	≥ 0.995 (GC ^b)	58.08	Tianjin Jiangtian Chemical Co., Ltd.

3 ^a High-performance liquid chromatography.

4 ^b Gas-liquid chromatography.

5 2.2 Characterization by X-ray diffraction and DSC/TG

6 The X-ray diffraction patterns of the samples were measured to identify the
7 crystallinity and identity of the experimental samples. Data collection was performed on
8 Rigaku D/max-2500 (Rigaku, Japan) by using Cu K α radiation (0.71073 Å). The data
9 was collected in 2θ range from 2° to 50° by using the scanning rate of 1 step·s⁻¹.

10 Differential scanning calorimetry (DSC 1/500, Mettler Toledo, Switzerland) was used
11 to obtain the melting properties of ETD under the protection of nitrogen (70 mL·min⁻¹).
12 The mass of samples was 5-10 mg. The heating rate of samples was set at 10 K·min⁻¹ and
13 the temperature range of the experiment was from 308.15 to 458.15 K.
14 Thermogravimetric was conducted on a Rigaku PTC-10A instrument. The sample (5-10
15 mg) was heated up at a rate of 10 K·min⁻¹ and the TG curve was recorded from 293.15 K
16 to 463.15 K under dry nitrogen protection (90 mL·min⁻¹).

17 2.3 Measurements of ETD solubility

The gravimetric method described in literature was applied to determine the solubility data of ETD [8]. For each measurement, mono-solvents or binary solvent mixtures with suitable content were prepared. The temperature was maintained at preset value by electrical heating. Excess amount of solute was added into small glass reactors (provided by EasyMaxTM, Mettler Toledo, Switzerland, $V = 20$ mL) with pre-weighted solvents. Equilibrium was achieved by continuous magnetic mixing (400 rpm) for 8 hours and the solution was kept static for another 2 hours before 5 mL upper solution was withdrawn and filtered by using a preheated syringe with a membrane (0.45 μ m) filter. The withdrawn clear solution was moved into another previously weighted petri dish (m_0). The petri dish was quickly and tightly closed and weighted (m_1') to determine the mass of the solution ($m_1' - m_0$). After the solvent was completely evaporated in an oven at 313.15 K, the petri dish was reweighed (m_1'') to determine the mass of the obtained solid ($m_1 = m_1'' - m_0$). All the samples were weighted using an analytical balance (Model AB204, Mettler-Toledo, Switzerland) with an accuracy of ± 0.0001 g. Each experimental data point was an average of at least three experimental measurements to ensure the reliability of the solubility data. After solubility experiments, the identity of the solid phase samples was confirmed by PXRD and DSC.

Based on experimental data, the mole fraction solubility (x_1) can be calculated according to Eq. (1):

$$x_1 = \frac{m_1 / M_1}{\sum_{i=1}^n m_i / M_i} \quad (1)$$

1 where m_i represents the mass of solute and solvents, and M_i stands for the molar mass
 2 ($\text{g}\cdot\text{mol}^{-1}$) of solute and solvents. In this work, $n = 2$ represents mono-solvent, while $n = 3$
 3 represents binary solvent mixtures. Among them, m_1 and M_1 represent the mass and molar
 4 mass of the solute, while m_2 and M_2 represent the mass and molar mass of the organic
 5 solvent (methanol, ethanol, n-propanol and isopropanol, acetonitrile and acetone),
 6 respectively. When the solvents were binary solvent mixtures (acetonitrile + water,
 7 acetone + water and ethanol + water), m_3 and M_3 represent the mass and molar mass of
 8 the water.

9 **3. Models for solid-liquid equilibrium data**

10 3.1. The modified Apelblat equation

11 Apelblat equation has been generally deemed that it could be well used in correlating
 12 the solubility in various solvents [9]. The equation is shown as Eq. (2)

$$\ln x_1 = A + B/T + C \ln T \quad (2)$$

13 where A, B and C were defined as parameters of the equation.

14 3.2. The (CNIBS)/R-K equation

15 The Combined Nearly Ideal Binary Solvent/Redlich-Kister (CNIBS)/R-K model was
 16 widely used to correlate the experimental solubility data of compounds in solvent
 17 mixtures [10-12]. The model proposed by Acree and his co-workers is shown as Eq. (3).

$$\ln x_1 = x_2^0 \ln(x_1)_2 + x_3^0 \ln(x_1)_3 + x_2^0 x_3^0 \sum_{i=0}^n s_i (x_2^0 - x_3^0)^i \quad (3)$$

where x_2^0 and x_3^0 refer to the initial mole fraction of the organic solvent and water under the assumption of solute is not present; $(x_1)_i$ represents the saturated mole fraction solubility of the solute in pure solvent i ; s_i is the model constant and n is the number of curve-fit parameters used, respectively. This model provides very precise mathematical descriptions of how the solute solubility varies with solvent composition at certain temperature. For binary solvents, when substituting $(1 - x_2^0)$ for x_3^0 together with $n = 2$, the rearrangement of Eq. (3) gives Eq. (4).

$$\ln x_1 = B_0 + B_1 x_2^0 + B_2 (x_2^0)^2 + B_3 (x_2^0)^3 + B_4 (x_2^0)^4 \quad (4)$$

where B_0, B_1, B_2, B_3, B_4 are the parameters of this model which can be obtained by least-square analyzing the experimental solubility data.

3.3. Two modified Jouyban-Acree equations

As the (CNIBS)/R-K model does not include the solution temperatures, Jouyban-Acree model was applied to describe the solubility of compounds in solvent mixtures at the whole range of experimental temperature as follows [13-14]:

$$\ln x_1 = x_2^0 \ln(x_1)_2 + x_3^0 \ln(x_1)_3 + x_2^0 x_3^0 \sum_{i=0}^n J_i (x_2^0 - x_3^0)^i / T \quad (5)$$

where J_i is the model constant.

As the solubility of solute in the pure solvent systems will also vary with temperature, the van't Hoff equation can combine with the Jouyban-Acree model [15].

1 $(x_1)_2$ and $(x_1)_3$, can be obtained from Eq. (6) and Eq. (7):

$$\ln(x_1)_2 = a_2 + b_2/T \quad (6)$$

$$\ln(x_1)_3 = a_3 + b_3/T \quad (7)$$

2 When $n = 2$, substituting them into Eq. (5), a new equation (called the Van't-JA
3 equation) can be obtained. Introducing constant terms to Eq. (5), it can be further
4 simplified as Eq. (8).

$$\ln x_1 = V_0 + V_1/T + V_2x_2^0 + \left[V_3x_2^0 + V_4(x_2^0)^2 + V_5(x_2^0)^3 + V_6(x_2^0)^4 \right]/T \quad (8)$$

5 where V_0 to V_6 are the model parameters.

6 $\ln(x_1)_2$ and $\ln(x_1)_3$ can also be taken place by the Apelblat model as Eq. (9) and Eq.
7 (10).

$$\ln(x_1)_2 = a_2 + b_2/T + c_2 \ln T \quad (9)$$

$$\ln(x_1)_3 = a_3 + b_3/T + c_3 \ln T \quad (10)$$

8 When $n = 2$, take the Eq. (9) and Eq. (10) into Eq. (5) to rearrange as

$$\ln x_1 = A_0 + A_1/T + A_2 \ln T + A_3x_2^0 + \left[A_4x_2^0 + A_5(x_2^0)^2 + A_6(x_2^0)^3 + A_7(x_2^0)^4 \right]/T + A_8x_2^0 \ln T \quad (11)$$

9 where A_0 to A_8 are the model parameters.

10 3.4. NRTL model

11 The local composition models are widely adopted in order to obtain the fugacity
12 coefficients of solute in the solid-liquid equilibrium. A general simplified equation
13 deduced from literature is shown in Eq. (12) [16].

$$\ln x_1 = \frac{\Delta H_m}{R} \left(\frac{1}{T_m} - \frac{1}{T} \right) - \ln \gamma_1 \quad (12)$$

1 where x_1 and T stand for the mole fraction of the solute and the temperature of the
2 solution, respectively; R is the gas constant; ΔH_m and T_m represent the melting enthalpy
3 and melting temperature, respectively; γ_1 represents the activity coefficient of solute in
4 the solvent. The activity coefficient of the solute calculated by NRTL model in the
5 solvents can be obtained from the following equation.

$$\begin{aligned} \ln \gamma_1 = & \frac{(G_{ji}x_j + G_{kj}x_k)(\tau_{ji}G_{ji} + \tau_{ki}G_{ki}x_k)}{(x_i + G_{ji}x_j + x_k G_{ki}x_k)^2} \\ & + \frac{\tau_{ij}G_{ij}x_j^2 + G_{ij}G_{kj}x_jx_k(\tau_{ij} - \tau_{kj})}{(x_j + G_{ij}x_i + x_k G_{kj})^2} \\ & + \frac{\tau_{ik}G_{ij}x_j^2 + G_{ij}G_{kj}x_jx_k(\tau_{ik} - \tau_{jk})}{(x_k + G_{ik}x_i + x_j G_{jk})^2} \end{aligned} \quad (13)$$

6 where x_i , x_j and x_k represent the mole fraction of the component i, j and k in the solution.

7 G_{ij} , G_{ik} , G_{ji} , G_{jk} , G_{ki} , G_{kj} , τ_{ij} , τ_{ik} , τ_{ji} , τ_{jk} , τ_{ki} , and τ_{kj} are parameters of this model.

$$\begin{aligned} G_{ij} &= \exp(-\alpha_{ij}\tau_{ij}) \quad \tau_{ij} = \frac{(g_{ij} - g_{jj})}{RT} = \frac{\Delta g_{ij}}{RT} \\ G_{ik} &= \exp(-\alpha_{ik}\tau_{ik}) \quad \tau_{ik} = \frac{(g_{ik} - g_{kk})}{RT} = \frac{\Delta g_{ik}}{RT} \\ G_{ji} &= \exp(-\alpha_{ji}\tau_{ji}) \quad \tau_{ji} = \frac{(g_{ji} - g_{ii})}{RT} = \frac{\Delta g_{ji}}{RT} \\ G_{jk} &= \exp(-\alpha_{jk}\tau_{jk}) \quad \tau_{jk} = \frac{(g_{jk} - g_{kk})}{RT} = \frac{\Delta g_{jk}}{RT} \\ G_{ki} &= \exp(-\alpha_{ki}\tau_{ki}) \quad \tau_{ki} = \frac{(g_{ki} - g_{ii})}{RT} = \frac{\Delta g_{ki}}{RT} \\ G_{kj} &= \exp(-\alpha_{kj}\tau_{kj}) \quad \tau_{kj} = \frac{(g_{kj} - g_{jj})}{RT} = \frac{\Delta g_{kj}}{RT} \end{aligned} \quad (14)$$

8

1 where Δg_{ij} , Δg_{ik} , Δg_{ji} , Δg_{jk} , Δg_{ki} , and Δg_{kj} are the cross interaction energy parameters
 2 which are independent of the composition and temperature. The non-random parameters
 3 α_{ij} , α_{ik} , α_{ji} , α_{jk} , α_{ki} and α_{kj} represent empirical constants ($\alpha_{ij} = \alpha_{ji}$, $\alpha_{ik} = \alpha_{ki}$, $\alpha_{jk} = \alpha_{kj}$), which
 4 generally range from 0 to 1.

5 3.5. Evaluation of thermodynamic models

6 These four models were adopted to correlate the experimental solubility data of ETD
 7 by matlab program. The average relative deviation (*ARD*) was used to evaluate the
 8 correlation accuracy of the models.

$$9 \quad ARD = \frac{1}{n} \sum_{i=1}^n \left| \frac{x_i^{cal} - x_i^{exp}}{x_i^{exp}} \right| \quad (15)$$

10 where n is the number of experimental points, x_i^{cal} and x_i^{exp} represent the calculated
 11 solubility data and experimental solubility data respectively.

12 However it is still not enough to tell which model is better only from *ARD* value. For
 13 this reason, the Akaike's Information Criterion (*AIC*) was adopted to evaluate the relative
 14 quality of these models [17]. Generally, the lower *AIC* value is, the better model will be.

15 The value of *AIC* is defined as [18]:

$$16 \quad AIC = -2\ln(L) + 2\kappa \quad (16)$$

17 where κ is the number of model parameters, L represents the maximized value of the
 18 likelihood function.

1 Supposed that the variance of model errors is unknown but equal for all models, Eq.
 2 (16) changes into:

$$3 \quad AIC = n \times [\ln(2\pi \times RSS / n) + 1] + 2\kappa \quad (17)$$

4 where n refers to the number of experimental points, RSS is the estimated residual of
 5 correlated models which is defined as follows:

$$6 \quad RSS = \sum_{i=1}^n (x_i^{\text{cal}} - x_i^{\text{exp}})^2 \quad (18)$$

7 In order to describe the results more intuitively, Akaike weight ω_i [19] was used to
 8 interpret the relative probability that the i th model minimizes the (estimated) solubility
 9 loss for each of the models. It is usually defined as:

$$10 \quad \omega_i = \frac{\exp((AIC_{\min} - AIC_i) / 2)}{\sum_{i=1}^S \exp((AIC_{\min} - AIC_i) / 2)} \quad (19)$$

11 where S is the number of models in the comparison. $AIC_{\min}$ is minimum AIC value while
 12 AIC_i is the i th model AIC value. Generally, the model with higher ω_i will give better
 13 correlation results.

14 **4. Results and discussion**

15 **4.1. Characterization of ETD**

16 The X-ray power diffraction (PXRD) pattern of ETD samples used in this study is
 17 shown in Fig. 2 which imply that the samples used in this study have high crystallinity
 18 and no phase transformation. As the basic thermodynamic properties, melting

1 temperature T_m and enthalpy of fusion $\Delta_{\text{fus}}H$ are quite necessary for building
2 thermodynamic models. By thermal analysis (TGA/DSC) of ETD which is shown in Fig.
3 3, it can be seen that the samples went through a dehydration process and then
4 decomposed at 440.15 K during the melting process. This phenomenon indicates that
5 ETD doesn't not have a real melting point and the melting temperature T_m could not be
6 obtained by this conventional calorimetric method. It has been known that the melting
7 point of compounds can be estimated through group contribution method according to the
8 literature. In this paper, the group contribution method [20-21] was used to predict the
9 melting temperature T_m and the enthalpy of fusion $\Delta_{\text{fus}}H$ of ETD.

10
11 **Fig. 2.** Powder X-ray diffraction pattern of ETD.

Fig. 3. Thermal analysis (TGA/DSC) data of ETD.

The estimation method was performed at three levels. The first level used contributions from basic groups that can be allowed describing a wide variety of organic compounds, while the higher levels involved polyfunctional and structural groups that provide more information about molecular fragments whose description through first-order groups was not possible. The estimated values of $\Delta_{\text{fus}}H$ and T_{m} for ETD are $102.57 \text{ kJ}\cdot\text{mol}^{-1}$ and 508.87 K , respectively. However, the estimated values here were only used for calculation and prediction, not as a result of the real physical properties of ETD. Therefore, different values could be found in other references through different methods.

4.2. Solubility of ETD in mono-solvents

The mole fraction solubility data of ETD at various temperatures (from 288.15 K to 318.15 K) in selected alcohol solvents (methanol, ethanol, n-propanol and isopropanol) are given in Table 2 and graphically shown in Fig. 4 respectively. The standard uncertainty $u(x)$ can be calculated by the Eq. (20):

$$u(x) = \left[\frac{\sum_{i=1}^n (x_i - \bar{x})^2}{(n-1)} \right]^{1/2} \quad (20)$$

Fig. 4. Experimental and correlated solubility of ETD at different temperatures in four mono-solvents : ★, methanol; ■, ethanol; ▲, n-propanol; ▼, isopropanol; -, calculated values based on modified Apelblat equation.

Table 2. The experimental ($x_{1,\text{exp}}$) and calculated ($x_{1,\text{cal}}$) mole fraction solubility of ETD in mono-solvents at various temperatures ($p/\text{MPa} = 0.1$).^{a,b,c,d}

T/K	$10^3 x_{1,\text{exp}}$	$10^3 x_{1,\text{cal}}$		T/K	$10^3 x_{1,\text{exp}}$	$10^3 x_{1,\text{cal}}$	
		Apelblat	NRTL			Apelblat	NRTL
methanol				ethanol			
288.15	12.2	12.1	12.6	288.15	4.30	4.30	4.37
293.15	13.1	13.4	13.5	293.15	4.80	4.78	4.79
298.15	14.8	14.8	14.4	298.15	5.31	5.35	5.32
303.15	16.3	16.2	15.8	303.15	5.93	6.01	5.97
308.15	17.9	17.8	17.4	308.15	6.88	6.79	6.73
313.15	19.6	19.5	19.4	313.15	7.79	7.71	7.68
318.15	21.2	21.3	21.9	318.15	8.71	8.78	8.85
n-propanol				isopropanol			
288.15	4.12	4.07	4.04	288.15	1.04	1.05	0.934

293.15	4.41	4.48	4.49	293.15	1.21	1.20	1.07
298.15	4.93	5.00	5.03	298.15	1.36	1.37	1.25
303.15	5.73	5.64	5.66	303.15	1.57	1.56	1.46
308.15	6.51	6.43	6.45	308.15	1.76	1.77	1.74
313.15	7.36	7.40	7.42	313.15	2.01	2.01	2.07
318.15	8.55	8.58	8.54	318.15	2.28	2.27	2.49

^a The relative standard uncertainty of the solubility measurement u is $u_r(x_1) = 0.05$.

^b The standard uncertainty of the pressure u is $u(p) = 6$ kPa.

^c The standard uncertainty of temperature u is $u(T) = 0.05$ K.

^d $x_{1,\text{exp}}$ is the experimental mole fraction solubility and $x_{1,\text{cal}}$ is the calculated values of the mole fraction solubility correlated by the modified Apelblat equation and the NRTL model.

The results indicate that, the solubility of ETD increases with the increasing of temperature in each solvent. Over the temperature range tested in this work, the solvency of ETD ranked as methanol > ethanol > n-propanol > isopropanol. Specifically, the compound was freely soluble in methanol (1.216×10^{-2} at 288.15 K). While in the isopropanol, the solubility values illustrated a slightly soluble behavior (only 1.042×10^{-3} at 288.15 K), and almost did not change with the temperature. It also should be noted that the solubility in ethanol and n-propanol solvents are quite close to each other. Therefore, methanol, ethanol and n-propanol could be used as good solvents while the isopropanol could be used as an antisolvent. The solubility diversity of ETD in different organic solvents are attributed to molecular structures of solvents, which could be explained by the interaction between solute and solvent molecules. Given that ETD contains 5 HBDs (hydrogen bond donate) and 16 HBAs (hydrogen bond accept) in its structure, hydrogen bond donating solvents were assumed to be easily coordinated in the vicinity of the

1 strong hydrogen bond accepting molecules. The order of HBD propensities of the alcohol
2 solvents rank as methanol (0.43) > ethanol (0.37) = n-propanol (0.37) > isopropanol
3 (0.33), and the order of HBA rank as methanol (0.47) < ethanol (0.48) = n-propanol
4 (0.48) < isopropanol (0.56). Thus, the HBD and HBA propensities of solvents can
5 partially explain the solubility order of ETD in these four alcohol organic solvents.

6 The model parameter values for ETD solubility correlation were regressed from the
7 experimental values and listed in Table S1 and Table S2. Using the parameters obtained,
8 the calculated solubilities of ETD were obtained according to Eq. (2) and Eq. (12). The
9 calculated solubility values and the relative deviations are listed in Table 2 and Table S1
10 and are compared with the experimental values. The slight 10^4 *RMSD*, which is lower
11 than 1.1 over the whole temperature scale, and 10^2 *ARD*, which is lower than 1.2, indicate
12 the modified Apelblat equation is more suitable for the solubility correlation of ETD in
13 mono-solvents than NRTL model. The interpolation of solubility with accurate precision
14 at any temperature from 288.15 K to 318.15 K can be calculated from Eq. (2) or Eq. (12).

15 4.3. Solubility of ETD in binary solvent mixtures

16 The mole fraction solubility data of ETD at various organic contents and temperatures
17 in acetonitrile + water, acetone + water and ethanol + water systems are given in Tables
18 3-5 respectively and graphically shown in Figs. 5-7. It can be seen from Figs. 5-7 that the
19 solubility data of ETD in these three systems are apparently affected by the contents of
20 organic solvents. The trends of solubility data in acetonitrile + water and acetone + water

1 systems are similar. The experimental solubility data firstly increase with the increasing
2 of acetonitrile or acetone content and reach maximum at around $x_2^0 \approx 0.50$ and then
3 slowly decrease. In ethanol + water system, the solubility profile of ETD is a little
4 different. It reaches maximum at $x_2^0 = 0.909$ and then decreases with the increasing of
5 ethanol content.

6
7 **Fig. 5.** Experimental and correlated solubility of ETD in acetonitrile + water solvent
8 mixtures at different temperatures: ★, 293.15 K; ◆, 298.15 K; ▼, 303.15 K; ▲,
9 308.15 K; ●, 313.15 K; ■, 318.15 K; -, calculated values based on
10 (CNIBS)/R-Kequation.
11

Fig. 6. Experimental and correlated solubility of ETD in acetone + water solvent mixtures at different temperatures: ▼, 293.15 K; ▲, 303.15 K; ●, 313.15 K; ■, 318.15 K; -, calculated values based on (CNIBS)/R-K equation.

Fig. 7. Experimental and correlated solubility of ETD in ethanol + water solvent mixtures at different temperatures: ▼, 293.15 K; ▲, 303.15 K; ●, 313.15 K; ■, 323.15 K; -, calculated values based on (CNIBS)/R-K equation.

1 **Table 3. The experimental ($x_{1,\text{exp}}$) and calculated ($x_{1,\text{cal}}$) mole fraction solubility of**
2 **ETD in acetonitrile + water solvent mixtures at various temperatures ($p/\text{MPa} = 0.1$).**
3 *a,b,c,d*

x_2^0	$10^3 x_{1,\text{exp}}$	$10^3 x_{1,\text{cal}}$			
		(CNIBS)/R-K	Van't-JA	Apel-JA	NRTL
$T/\text{K} = 293.15$					
0.870	0.953	0.946	0.954	0.968	0.892
0.749	1.42	1.46	1.46	1.48	1.50
0.682	1.79	1.78	1.78	1.81	1.87
0.581	2.28	2.24	2.23	2.26	2.38
0.504	2.59	2.52	2.50	2.52	2.62
0.442	2.50	2.60	2.57	2.59	2.68
0.341	2.29	2.30	2.25	2.27	2.32
0.256	1.61	1.63	1.61	1.62	1.62
0.188	0.973	0.943	0.938	0.943	0.939
0.105	0.288	0.291	0.301	0.302	0.298
$T/\text{K} = 298.15$					
0.870	1.19	1.18	1.16	1.16	1.07
0.749	1.75	1.80	1.75	1.74	1.73
0.682	2.17	2.16	2.10	2.10	2.12
0.581	2.70	2.63	2.60	2.59	2.64
0.504	2.97	2.89	2.88	2.87	2.88
0.442	2.86	2.93	2.93	2.92	2.92
0.341	2.46	2.56	2.55	2.54	2.52
0.256	1.83	1.83	1.81	1.81	1.75
0.188	1.12	1.07	1.06	1.06	1.03
0.105	0.34	0.342	0.343	0.342	0.334
$T/\text{K} = 303.15$					
0.870	1.42	1.41	1.40	1.39	1.30
0.749	1.99	2.06	2.07	2.05	2.04
0.682	2.47	2.45	2.47	2.45	2.46
0.581	3.06	2.97	3.00	2.98	3.00
0.504	3.30	3.25	3.29	3.27	3.23
0.442	3.19	3.29	3.33	3.31	3.25
0.341	2.78	2.83	2.87	2.85	2.78
0.256	2.00	2.01	2.04	2.02	1.94
0.188	1.23	1.19	1.19	1.19	1.15
0.105	0.391	0.396	0.389	0.388	0.383
$T/\text{K} = 308.15$					

0.870	1.66	1.64	1.69	1.67	1.60
0.749	2.29	2.35	2.44	2.42	2.44
0.682	2.74	2.79	2.88	2.86	2.90
0.581	3.55	3.38	3.46	3.43	3.43
0.504	3.84	3.71	3.75	3.72	3.64
0.442	3.62	3.74	3.77	3.75	3.66
0.341	3.07	3.20	3.22	3.21	3.12
0.256	2.20	2.25	2.28	2.27	2.18
0.188	1.42	1.32	1.34	1.33	1.30
0.105	0.426	0.437	0.439	0.438	0.444
<i>T</i> /K = 313.15					
0.870	2.05	2.03	2.02	2.02	1.97
0.749	2.77	2.85	2.87	2.86	2.90
0.682	3.36	3.34	3.35	3.34	3.39
0.581	4.06	3.98	3.96	3.95	3.97
0.504	4.38	4.28	4.26	4.25	4.17
0.442	4.19	4.27	4.25	4.25	4.16
0.341	3.47	3.58	3.61	3.60	3.55
0.256	2.50	2.51	2.54	2.54	2.50
0.188	1.53	1.47	1.49	1.49	1.50
0.105	0.493	0.500	0.495	0.494	0.525
<i>T</i> /K = 318.15					
0.870	2.44	2.43	2.40	2.44	2.44
0.749	3.44	3.44	3.35	3.39	3.47
0.682	3.90	3.97	3.87	3.92	4.03
0.581	4.66	4.58	4.52	4.57	4.64
0.504	4.96	4.84	4.81	4.86	4.84
0.442	4.68	4.79	4.78	4.82	4.81
0.341	3.98	4.03	4.02	4.05	4.08
0.256	2.83	2.84	2.82	2.84	2.89
0.188	1.72	1.68	1.66	1.67	1.75
0.105	0.557	0.561	0.555	0.557	0.626

- 1 ^a The relative standard uncertainty of the solubility measurement u is $u_r(x_1) = 0.05$.
- 2 ^b The standard uncertainty of the pressure u is $u(p) = 6$ kPa.
- 3 ^c The standard uncertainty of temperature u is $u(T) = 0.05$ K.
- 4 ^d $x_{1,\text{exp}}$ is the experimental mole fraction solubility and $x_{1,\text{cal}}$ is the calculated values of the
- 5 mole fraction solubility correlated by the (CNIBS)/R-K equation, Van't-JA equation,
- 6 Apel-JA equation and the NRTL model.
- 7

1 **Table 4. The experimental and calculated mole fraction solubility of ETD in acetone**
2 **+ water solvent mixtures at various temperatures ($p/\text{MPa} = 0.1$). ^{a,b,c,d}**

x_2^0	$10^3 x_{1,\text{exp}}$	$10^3 x_{1,\text{cal}}$			
		(CNIBS)/R-K	Van't-JA	Apel-JA	NRTL
$T/\text{K} = 293.15$					
0.899	0.683	0.678	0.710	0.719	0.713
0.798	1.31	1.34	1.30	1.32	1.31
0.697	2.07	2.06	1.96	1.98	2.06
0.597	2.76	2.69	2.58	2.62	2.73
0.597	3.03	3.07	3.00	3.05	3.11
0.358	2.70	2.71	2.74	2.78	2.66
0.269	1.79	1.84	1.87	1.90	1.79
0.199	1.10	1.06	1.06	1.08	0.965
0.099	0.274	0.277	0.263	0.268	0.184
$T/\text{K} = 303.15$					
0.899	0.998	0.989	0.949	0.933	0.953
0.798	1.61	1.66	1.70	1.66	1.62
0.697	2.50	2.43	2.50	2.45	2.48
0.597	3.22	3.19	3.26	3.18	3.26
0.597	3.64	3.70	3.76	3.67	3.67
0.358	3.25	3.31	3.42	3.32	3.21
0.269	2.34	2.25	2.35	2.29	2.23
0.199	1.27	1.30	1.35	1.31	1.30
0.099	0.352	0.352	0.350	0.339	0.290
$T/\text{K} = 313.15$					
0.899	1.25	1.23	1.24	1.24	1.21
0.798	2.01	2.10	2.18	2.16	2.11
0.697	3.10	3.04	3.16	3.14	3.16
0.597	4.11	3.94	4.06	4.02	4.07
0.597	4.49	4.54	4.64	4.60	4.58
0.358	3.92	4.13	4.21	4.16	4.10
0.269	2.91	2.88	2.92	2.89	2.94
0.199	1.75	1.69	1.71	1.69	1.80
0.099	0.454	0.461	0.459	0.453	0.470
$T/\text{K} = 318.15$					
0.899	1.48	1.45	1.42	1.44	1.43
0.798	2.39	2.52	2.45	2.48	2.45
0.697	3.60	3.57	3.53	3.58	3.62
0.597	4.78	4.52	4.50	4.59	4.60

0.597	5.26	5.22	5.13	5.23	5.12
0.358	4.57	4.94	4.64	4.74	4.64
0.269	3.45	3.50	3.24	3.30	3.39
0.199	2.19	2.02	1.90	1.95	2.14
0.099	0.474	0.488	0.522	0.534	0.605

^a The relative standard uncertainty of the solubility measurement u is $u_r(x_1) = 0.05$.

^b The standard uncertainty of the pressure u is $u(p) = 6$ kPa.

^c The standard uncertainty of temperature u is $u(T) = 0.05$ K.

^d $x_{1,\text{exp}}$ is the experimental mole fraction solubility and $x_{1,\text{cal}}$ is the calculated values of the mole fraction solubility correlated by the (CNIBS)/R-K equation, Van't-JA equation, Apel-JA equation and the NRTL model.

Table 5. The experimental and calculated mole fraction solubility of ETD in ethanol + water solvent mixtures at various temperatures ($p/\text{MPa} = 0.1$) .^{a,b,c,d}

x_2^0	$10^3\ x_{1,\text{exp}}$	$10^3\ x_{1,\text{cal}}$			
		(CNIBS)/R-K	Van't-JA	Apel-JA	NRTL
$T/\text{K} = 293.15$					
1.000	4.80	5.04	4.92	4.95	4.83
0.909	5.86	5.16	5.18	5.18	5.58
0.800	4.03	4.21	4.05	4.03	4.39
0.712	2.78	3.05	2.86	2.83	3.03
0.608	2.11	2.10	2.03	2.00	2.04
0.507	1.47	1.43	1.51	1.48	1.49
0.405	1.07	0.946	1.12	1.09	1.08
0.291	0.514	0.583	0.739	0.716	0.785
0.208	0.310	0.307	0.352	0.339	0.476
$T/\text{K} = 303.15$					
1.000	5.93	5.88	6.19	6.15	5.97
0.909	6.65	6.68	6.64	6.63	7.07
0.800	5.15	5.34	5.34	5.37	5.27
0.712	3.95	3.83	3.88	3.92	3.73
0.608	2.87	2.83	2.85	2.90	2.80
0.507	2.34	2.26	2.18	2.23	2.04
0.405	1.71	1.83	1.67	1.72	1.54
0.291	1.26	1.29	1.14	1.18	1.11
0.208	0.657	0.609	0.566	0.589	0.693
$T/\text{K} = 313.15$					

1.000	7.98	7.91	7.67	7.62	7.32
0.909	8.22	8.34	8.36	8.36	8.23
0.800	6.77	6.82	6.91	6.94	6.29
0.712	5.14	5.13	5.17	5.22	4.99
0.608	4.02	3.93	3.90	3.96	3.84
0.507	3.17	3.15	3.07	3.14	2.97
0.405	2.54	2.52	2.42	2.48	2.26
0.291	1.63	1.80	1.70	1.75	1.69
0.208	1.05	0.943	0.882	0.915	1.04
$T/K = 323.15$					
1.000	9.48	9.35	9.38	9.44	10.1
0.909	10.3	10.4	10.4	10.4	9.67
0.800	8.00	8.55	8.80	8.75	8.75
0.712	6.60	6.45	6.77	6.69	6.82
0.608	5.52	5.05	5.25	5.16	5.32
0.507	4.35	4.23	4.24	4.15	4.34
0.405	3.23	3.58	3.42	3.33	3.48
0.291	2.39	2.64	2.48	2.40	2.57
0.208	1.61	1.34	1.34	1.28	1.61

^a The relative standard uncertainty of the solubility measurement u is $u_r(x_1) = 0.05$.

^b The standard uncertainty of the pressure u is $u(p) = 6$ kPa.

^c The standard uncertainty of temperature u is $u(T) = 0.05$ K.

^d $x_{1,\text{exp}}$ is the experimental mole fraction solubility and $x_{1,\text{cal}}$ is the calculated values of the mole fraction solubility correlated by the (CNIBS)/R-K equation, Van't-JA equation, Apel-JA equation and the NRTL model.

From Figs. 5-7, it can also be seen that the solubility of ETD increases with the increasing of temperature in all tested solvents, indicating that the dissolution process is endothermic. Besides, the solubility curves show that the dissolving capacity of ETD in ethanol + water system is stronger than that in acetonitrile + water and acetone + water systems under the same conditions, which is in accordance with the empirical rule "like dissolves like" since five hydroxyl groups are contained in ETD molecule. The order of

1 solubility of ETD in the three systems at the same temperature is: acetonitrile < acetone <
2 ethanol.

3 The (CNIBS)/R-K model, two modified Jouyban-Acree equations and NRTL model
4 were used to correlate the experimental solubility data of ETD in three solvent mixtures
5 systems. The correlated solubility data of ETD in binary solvent mixtures are given in
6 Tables 3-5. Tables S3-S5 give the values of model parameters for (CNIBS)/R-K
7 equation, two modified Jouyban-Acree equations and NRTL model together with *ARD*. It
8 can be seen from the tables that these models exhibit satisfied applicability for correlating
9 the solubility data of ETD under various temperature ranges. Specifically, the 10^2 *ARD*
10 from Apel-JA equation in acetone + water and ethanol + water systems are smaller than
11 the other three models, which gives a better correlation.

12 The calculated results of *AIC* values for all four models are listed in Tables S6. As
13 shown in Tables S6, the values of *AIC* of (CNIBS)/R-K is much higher than the other
14 three models, which means that (CNIBS)/R-K would be not good for correlating the
15 experimental solubility data in the binary solvents mixtures compared with the other three
16 models. This is due to the fact that the (CNIBS)/R-K model correlates the solubility data
17 with the change of solvent composition and this model has 5 parameters when correlating
18 the solubility data with only 9 or 10 experimental points. As to van't-JA, Apel-JA and
19 NRTL models, it takes both the change of solution composition and the change of
20 temperature into consideration. Although this equation has 9 parameters (for van't-JA is 7

1 parameters), it correlates the solubility data with all the experimental points in the certain
2 binary solvent mixtures and gives better correlation results.

3 As can be seen from Table S6, ω_i values of the Jouyban-Acree models for correlating
4 the experimental solubility data in binary solvent systems of acetonitrile + water and
5 ethanol + water are much higher than that of the other two models. In the binary solvent
6 systems of acetone + water, ω_i value is higher than the other models. It means that these
7 three models have higher probability of giving better correlation results. These results are
8 consistent with the conclusions from *AIC* values.

9 4.5. Mixing thermodynamics properties

10 For a nonideal solution, it is necessary to calculate the mixing thermodynamic
11 properties of the solution in mono-solvents or different binary solvent mixtures, such as
12 the mixing enthalpy ($\Delta_{mix}H$), the mixing Gibbs energy ($\Delta_{mix}G$) and the mixing entropy
13 ($\Delta_{mix}S$). The mixing thermodynamic properties can be calculated by the following
14 equation [22]:

$$\Delta_{mix}M = \Delta_{mix}M^{id} + M^E \quad (21)$$

15 where M can be replaced by G , H and S . $\Delta_{mix}M^{id}$ refers to the mixing properties of the
16 ideal systems and M^E is the excess properties. For the ideal solution, $\Delta_{mix}H^{id}$ is zero.

17 The mixing thermodynamic properties of the nonideal solution can be calculated by
18 Eqs. (22)-(24) [23].

$$\Delta_{mix}G = RT \sum_n^i x_i \ln x_i + RT \sum_n^i x_i \ln \gamma_i \quad (22)$$

$$\Delta_{mix}H = -RT^2 \sum_n^i x_i \left(\frac{\partial \ln \gamma_i}{\partial T} \right)_{p,x} \quad (23)$$

$$\Delta_{mix}S = \frac{\Delta_{mix}H - \Delta_{mix}G}{T} \quad (24)$$

where x_i and γ_i represent the mole fraction and activity coefficient of component i in real solution, respectively. γ_i can be calculated by the NRTL model.

The calculated mixing Gibbs energy ($\Delta_{mix}G$) and the mixing entropy ($\Delta_{mix}S$) in mono-solvents and three binary solvent mixtures are listed in Tables 6-9. As shown in these Tables, it can be easily found that the values of $\Delta_{mix}G$ are all negative, which means the mixing of ETD in the investigated solvents is a spontaneous process. The values of $\Delta_{mix}S$ are positive, which proves that the mixing process in all solvents measured is entropy-driven. These results are useful for the optimization of the mixing and crystallization process of ETD.

Table 6. The mixing thermodynamic properties of ETD in four mono-solvents.^a

T/K	$\Delta_{mix}G/$ (J·mol ⁻¹) ^a	$\Delta_{mix}S/$ (J·K ⁻¹ ·mol ⁻¹) ^a	T/K	$\Delta_{mix}G/$ (J·mol ⁻¹) ^a	$\Delta_{mix}S/$ (J·K ⁻¹ ·mol ⁻¹) ^a
methanol					
288.15	-579	5.79	308.15	-782	7.16
293.15	-613	5.99	313.15	-838	7.52
298.15	-676	6.46	318.15	-890	7.82
303.15	-727	6.80			
ethnaol					
288.15	-203	2.04	308.15	-297	2.74

293.15	-221	2.18	313.15	-329	2.98
298.15	-240	2.31	318.15	-360	3.19
303.15	-262	2.47			

n-propanol

288.15	-194	1.94	308.15	-281	2.57
293.15	-203	1.98	313.15	-311	2.79
298.15	-223	2.12	318.15	-354	3.11
303.15	-253	2.36			

isopropanol

288.15	-48.6	0.472	308.15	-75.6	0.671
293.15	-55.3	0.525	313.15	-84.9	0.738
298.15	-60.7	0.563	318.15	-94.2	0.801
303.15	-69.0	0.626			

^a The combined expanded uncertainties U are $U_c(\Delta_{\text{mix}}G) = 0.050\Delta_{\text{mix}}G$, $U_c(\Delta_{\text{mix}}S) = 0.055\Delta_{\text{mix}}S$ (0.95 level of confidence).

3
4

Table 7. The mixing thermodynamic properties of ETD in acetonitrile + water binary solvent mixtures.^{a,b}

x_2^{0a}	$\Delta_{\text{sol}}G/$ (kJ·mol ⁻¹) ^b	$\Delta_{\text{sol}}S/$ (J·K ⁻¹ ·mol ⁻¹) ^b	x_2^{0a}	$\Delta_{\text{sol}}G/$ (kJ·mol ⁻¹) ^b	$\Delta_{\text{sol}}S/$ (J·K ⁻¹ ·mol ⁻¹) ^b
$T/K = 293.15$					
0.870	-0.843	3.18	0.442	-1.40	5.10
0.749	-1.19	4.49	0.341	-1.30	4.41
0.682	-1.31	4.98	0.256	-1.13	3.46
0.581	-1.41	5.35	0.188	-0.950	2.62
0.504	-1.43	5.38	0.105	-0.656	1.61
$T/K = 298.15$					
0.870	-0.867	3.27	0.442	-1.44	5.23
0.749	-1.22	4.62	0.341	-1.33	4.46
0.682	-1.34	5.13	0.256	-1.16	3.54
0.581	-1.45	5.52	0.188	-0.974	2.68
0.504	-1.47	5.52	0.105	-0.672	1.64
$T/K = 303.15$					
0.870	-0.891	3.35	0.442	-1.48	5.33
0.749	-1.25	4.70	0.341	-1.36	4.57
0.682	-1.38	5.22	0.256	-1.19	3.60
0.581	-1.49	5.63	0.188	-0.997	2.73
0.504	-1.51	5.62	0.105	-0.687	1.68

T/K = 308.15					
0.870	-0.914	3.43	0.442	-1.52	5.47
0.749	-1.28	4.79	0.341	-1.40	4.66
0.682	-1.41	5.30	0.256	-1.22	3.67
0.581	-1.53	5.80	0.188	-1.02	2.80
0.504	-1.55	5.80	0.105	-0.702	1.70
T/K = 313.15					
0.870	-0.943	3.56	0.442	-1.57	5.66
0.749	-1.32	4.96	0.341	-1.44	4.78
0.682	-1.46	5.52	0.256	-1.25	3.77
0.581	-1.58	5.96	0.188	-1.05	2.84
0.504	-1.60	5.97	0.105	-0.718	1.73
T/K = 318.15					
0.870	-0.972	3.69	0.442	-1.61	5.80
0.749	-1.37	5.18	0.341	-1.48	4.94
0.682	-1.50	5.68	0.256	-1.28	3.87
0.581	-1.62	6.14	0.188	-1.07	2.90
0.504	-1.64	6.14	0.105	-0.734	1.76

- 1 ^a x_2^0 is the initial mole fraction of acetonitrile in the binary solvent mixture.
- 2 ^b The combined expanded uncertainties U are $U_c(\Delta_{\text{mix}}G) = 0.050\Delta_{\text{mix}}G$, $U_c(\Delta_{\text{mix}}S) =$
- 3 $0.055\Delta_{\text{mix}}S$ (0.95 level of confidence).
- 4

5 **Table 8. The mixing thermodynamic properties of ETD in acetone + water binary**

6 **solvent mixtures.**^{a,b}

x_2^{0a}	$\Delta_{\text{sol}}G/$ (kJ·mol ⁻¹) ^b	$\Delta_{\text{sol}}S/$ (J·K ⁻¹ ·mol ⁻¹) ^b	x_2^{0a}	$\Delta_{\text{sol}}G/$ (kJ·mol ⁻¹) ^b	$\Delta_{\text{sol}}S/$ (J·K ⁻¹ ·mol ⁻¹) ^b
T/K = 293.15					
0.899	-1.24	9.16	0.358	-2.64	21.3
0.798	-2.03	16.2	0.269	-2.18	16.3
0.697	-2.57	21.3	0.199	-1.72	11.5
0.597	-2.87	24.4	0.099	-1.18	5.47
0.597	-2.94	24.9			
T/K = 303.15					
0.899	-1.56	12.4	0.358	-2.57	20.1
0.798	-2.02	15.5	0.269	-2.11	15.3
0.697	-2.55	20.4	0.199	-1.64	10.6

0.597	-2.83	23.2	0.099	-1.14	5.01
0.597	-2.89	23.7			
T/K = 313.15					
0.899	-1.26	8.57	0.358	-2.51	19.0
0.798	-2.02	14.9	0.269	-2.05	14.4
0.697	-2.54	19.6	0.199	-1.58	9.88
0.597	-2.81	22.3	0.099	-1.11	4.61
0.597	-2.85	22.7			
T/K = 318.15					
0.899	-1.27	8.47	0.358	-2.49	18.6
0.798	-2.03	14.7	0.269	-2.03	14.0
0.697	-2.54	19.3	0.199	-1.55	9.63
0.597	-2.82	22.0	0.099	-1.09	4.42
0.597	-2.85	22.3			

- 1 ^a x_2^0 is the initial mole fraction of acetone in the binary solvent mixture.
- 2 ^b The combined expanded uncertainties U are $U_c(\Delta_{\text{mix}}G) = 0.050\Delta_{\text{mix}}G$, $U_c(\Delta_{\text{mix}}S) =$
- 3 $0.055\Delta_{\text{mix}}S$ (0.95 level of confidence).
- 4

5 **Table 9. The mixing thermodynamic properties of ETD in ethanol + water binary**

6 **solvent mixtures.** ^{a,b}

x_2^{0a}	$\Delta_{\text{sol}}G/$ (kJ·mol ⁻¹) ^b	$\Delta_{\text{sol}}S/$ (J·K ⁻¹ ·mol ⁻¹) ^b	x_2^{0a}	$\Delta_{\text{sol}}G/$ (kJ·mol ⁻¹) ^b	$\Delta_{\text{sol}}S/$ (J·K ⁻¹ ·mol ⁻¹) ^b
T/K = 293.15					
1.00	-0.224	2.14	0.500	-4.32	27.0
0.900	-2.82	23.8	0.400	-3.89	23.5
0.800	-3.96	29.2	0.300	-3.25	19.0
0.700	-4.44	30.4	0.200	-2.44	13.8
0.600	-4.53	29.5			
T/K = 303.15					
1.00	-0.265	2.38	0.500	-4.34	26.3
0.900	-2.78	22.5	0.400	-3.92	22.9
0.800	-3.93	28.0	0.300	-3.30	18.6
0.700	-4.44	29.3	0.200	-2.48	13.5
0.600	-4.53	28.4			
T/K = 313.15					
1.00	-0.341	2.91	0.500	-4.37	25.5

0.900	-2.77	21.6	0.400	-3.95	22.4
0.800	-3.92	27.0	0.300	-3.32	18.2
0.700	-4.44	28.3	0.200	-2.51	13.2
0.600	-4.55	27.6			
T/K = 323.15					
1.00	-0.392	3.17	0.500	-4.40	24.9
0.900	-2.79	21.0	0.400	-3.98	21.8
0.800	-3.91	26.0	0.300	-3.37	17.8
0.700	-4.44	27.5	0.200	-2.55	13.0
0.600	-4.57	26.9			

- 1 ^a x_2^0 is the initial mole fraction of ethanol in the binary solvent mixture.
- 2 ^b The combined expanded uncertainties U are $U_c(\Delta_{\text{mix}}G) = 0.050\Delta_{\text{mix}}G$, $U_c(\Delta_{\text{mix}}S) =$
- 3 $0.055\Delta_{\text{mix}}S$ (0.95 level of confidence).

4

5 **5. Conclusions**

6 In this work, the solubility data of ETD in four alcohol organic solvents (methanol,

7 ethanol, n-propanol and isopropanol) and three kinds of organic + water solvents

8 mixtures (acetonitrile + water, acetone + water and ethanol + water) within the

9 temperature ranges from 288.15 K to 323.15 K were determined. The PXRD and Karl

10 Fischer method were applied to verify the crystal form of ETD during the solubility

11 measurement. By experimental measurement and theoretical correlation, it was found that

12 ETD possesses cosolvent ability in these three binary solvent mixtures. The solubility

13 order for ETD in alcohol solvents is: methanol > ethanol > n-propanol > isopropanol. The

14 modified Apelblat equation and NRTL model were applied to correlate the solubility data

15 in mono-solvents. The CNIBS/R-K empirical equation and two modified versions of

16 Jouyban-Acree equation (Van't-JA and Apel-JA equations), together with NRTL model

1 were utilized to correlate the experimental solubility data in binary solvent mixtures. All
2 the selected models gave satisfactory correlation results. Also, the thermodynamic
3 properties of the mixing process were obtained and discussed. According to the results,
4 the negative values of mixing Gibbs energy indicate the mixing process of ETD is
5 spontaneous. The positive values of mixing Entropy proves that the mixing process in all
6 tested solvents is entropy-driven.

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