



Chemical Engineering Thermodynamics

Thermodynamic properties of metamizol monohydrate in pure and binary solvents at temperatures from (283.15 to 313.15) K☆



Mingxia Guo¹, Qiuxiang Yin^{1,2}, Chang Wang¹, Yaohui Huang¹, Yang Li¹, Zaixiang Zhang¹, Xia Zhang¹, Zhao Wang^{1,2}, Meijing Zhang^{1,2}, Ling Zhou^{1,*}

¹ School of Chemical Engineering and Technology, State Key Laboratory of Chemical Engineering, Tianjin University, Tianjin 300072, China

² The Co-Innovation Center of Chemistry and Chemical Engineering of Tianjin, Tianjin University, Tianjin 300072, China

ARTICLE INFO

Article history:

Received 19 November 2016

Received in revised form 25 January 2017

Accepted 17 March 2017

Available online 25 March 2017

Keywords:

Metamizol monohydrate

Solubility

Thermodynamic properties

Correlation

ABSTRACT

The thermodynamic properties of metamizol monohydrate in pure solvents (methanol, ethanol, *n*-propanol and isopropanol) and two binary mixed solvent systems including (methanol + ethanol) and (methanol + isopropanol) were measured from 283.15 K to 313.15 K by gravimetric method under atmospheric pressure thought as 0.1 MPa. The modified Apelblat equation, the CNIBS/R-K equation, the Hybrid model and the NRTL model were used to correlate the solubility of metamizol monohydrate, respectively. The results show that the solubility of metamizol monohydrate in all the tested solvents increases with the rising temperature which means that it has temperature dependence. What's more, the effects of solvent components of the binary solvent mixtures on solubility were discussed, it illustrates that the increasing of the molar fraction of methanol gives the system a greater dissolving power. Furthermore, according to the NRTL model, the enthalpy, the Gibbs energy and the entropy of the mixing process were also obtained and discussed.

© 2017 The Chemical Industry and Engineering Society of China, and Chemical Industry Press. All rights reserved.

1. Introduction

Metamizol monohydrate ($C_{13}H_{18}N_3NaO_5S$, CAS Registration No. 5907-38-0, Fig. 1) is a well-known and widely used analgetic and antipyretic drug employed for multicomponent preparations. It is also one of the five active ingredients of Pentalgin-FS tablets produced by Farmstandart-Leksredstva [1]. However, some problems are still urgent in the industrial producing process of metamizol monohydrate, such as the long production period, small particle size, maldistribution and long drying and filtration time. Optimizing the cooling crystallization process and determining the optimum operating curve of the high-quality products are supposed to be the best way to solve these problems [2].

In the pharmaceutical manufacturing industry, the unit operation of crystallization plays a major role which can determine the final product qualities like crystal size distribution, crystal form, product purity and so on. Moreover, the design of this significant crystallization process partly relies on the solid–liquid equilibrium solubility of the product, which is deeply influenced by the temperature and the solvent components [3]. Therefore, solubility, a basic data of crystallization, is very important when it comes to the control and optimization of the drug producing process. However, poor data about the thermodynamic properties of

metamizol monohydrate in the pure and binary mixed solvent systems at different temperatures is available in the existing literature.

In this work, the solubility data of metamizol monohydrate in four pure solvents (methanol, ethanol, *n*-propanol and isopropanol) and two binary mixed solvent systems (methanol + ethanol) and (methanol + isopropanol) was measured from 283.15 K to 313.15 K at 0.1 MPa by gravimetric method [4–9]. The samples were characterized by PXRD which can help to guarantee the same crystal form during the dissolving process. The DSC analysis was also used to determine the melting point and the enthalpy fusion of metamizol monohydrate. Several classical equations were applied to correlate the solubility of metamizol monohydrate in the investigated solvent systems. Among them, the modified Apelblat equation, the CNIBS/R-K equation, the Hybrid equation and the NRTL model were applied to investigate the impact of the temperature and the influence of the solvent components on the solubility, respectively. In addition, the mixing thermodynamic properties of metamizol monohydrate solution were discussed by the NRTL model, like the enthalpy, the Gibbs energy and the entropy during the mixing process in all the discussed solvent systems.

2. Experiment Section

2.1. Materials

Metamizol monohydrate was supplied by the Shandong Xinhua Pharmaceutical Co., Ltd., China. Anhydrous methanol, anhydrous

☆ Supported by National Natural Science Foundation of China (21206109) and China Ministry of Science and Major National Scientific Instrument Development Project (21527812).

* Corresponding author.

E-mail address: zhouling@tju.edu.cn (L. Zhou).

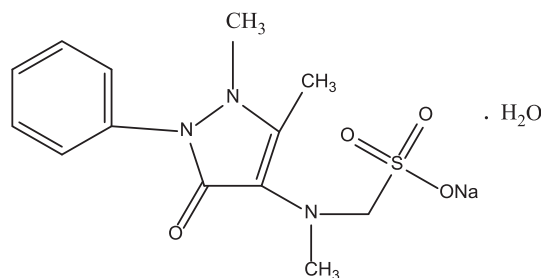


Fig. 1. Chemical structure of metamizol monohydrate.

ethanol, isopropanol and *n*-propanol were purchased from Jiangtian Chemical Technique Co., Ltd. (Tianjin, China). The purity analysis had been done by the suppliers and all chemicals were used without further purification. More detailed information about the materials used in this work has been listed in Table 1.

2.2. Characterization of metamizol monohydrate

To ensure that the crystal form of metamizol monohydrate remains same during the experiments, Powder X-ray Diffraction (PXRD) patterns of excess solid and dried samples of metamizol monohydrate were all measured in the tested solvents at different temperature ($T = 283.15\text{ K} - 313.15\text{ K}$) after stirring 24 h. The PXRD patterns were obtained using Cu K_{α} radiation (0.154 nm) on Rigaku D/max-2500 (Rigaku, Japan). The samples were conducted over a 2-theta range from 2° to 50° at a scanning rate of 1 step per second.

To determine the melting temperature and enthalpy fusion of metamizol monohydrate, a thermogravimetric/differential scanning calorimetry (Mettler-Toledo, Switzerland) was used for thermal analysis experiment under a nitrogen atmosphere.

2.3. Determination of solubility

The solubility of metamizol monohydrate was measured by the gravimetric method which was widely described in literature [10–12]. A 50 ml cylindrical double-jacketed crystallizer was used to contain solvents, into which the excess amount of metamizol monohydrate was added. The jacketed temperature was controlled within $\pm 0.1\text{ K}$ by a thermostat (XOYS-2006, Nanjing Xianou Instrument Manufacturing Co., Ltd., China). The solid–liquid mixtures should be under stirring for 10 h, which was experimentally proved to be long enough to reach equilibrium. Then the agitation was stopped and the solution was kept still for about 4 h to make sure that the undissolved particles settled down. The upper clear saturated solution was filtered with a filter membrane ($0.22\text{ }\mu\text{m}$) and moved into a glass dish. Subsequently, the filtrate was weighed as quickly as possible and dried at 50°C until no mass change was observed. An analytical balance (type AL 204, Mettler Toledo, Switzerland) with uncertainty of $\pm 0.0001\text{ g}$ was used to measure all the masses including the solutions and the glass dishes in this work. Each experiment was repeated three times and the average value was used to calculate the mole fraction solubility.

The mole fraction solubility (x_1) of metamizol monohydrate in pure solvents was calculated by the following Eq. (1):

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

where m_1 is the mass of the solute, m_2 is the mass of the solvent; M_1 and M_2 are the molecular masses of solute and solvent, respectively.

The molar fraction solubility (x_1) of metamizol monohydrate in binary mixed solvent systems and the initial mole fraction (x_2^0) of methanol in the solvent mixtures can be obtained by the following Eqs. ((2)–(3)):

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (2)$$

$$x_2^0 = \frac{m_2/M_2}{m_2/M_2 + m_3/M_3} \quad (3)$$

where m_1 , m_2 are the mass of metamizol monohydrate and methanol, respectively. m_3 represents the mass of ethanol or isopropanol which based on the choice of the solvents in the experiments. M_1 , M_2 and M_3 are the corresponding molecular mass of them.

3. Results and Discussion

3.1. Material characterization

In this work, the PXRD pattern of purchased material as well as the sediments and dried sediments were all tested and the results turned out to be as same as the counterpart of metamizol monohydrate. As shown in Fig. 2, we take the PXRD patterns of the metamizol

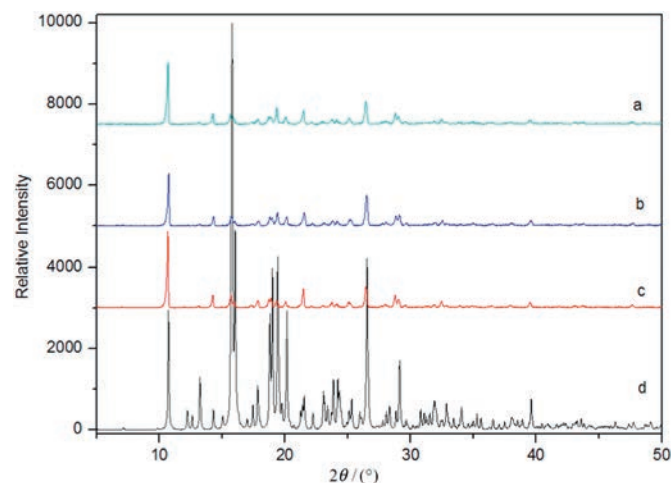


Fig. 2. Power X-ray diffraction pattern of metamizol monohydrate ($T = 303.15\text{ K}$, methanol + ethanol, ($x_2^0 = 0.5$)): a, raw material; b, solid filtered after stirring; c, dried product; d, anhydrous analgin.

Table 1

Properties of materials used in this work

Material	Molar mass /g·mol ^{−1}	Mass fraction purity	Source	Purification method	Analysis method
Metamizol monohydrate	351.34	≥0.995	Shandong Xinhua Pharmaceutical Co., Ltd., China	None	HPLC ^①
Methanol	32.04	≥0.995	Jiangtian Chemical Technology Co., Ltd., China	None	GC ^②
Ethanol	46.07	≥0.995	Jiangtian Chemical Technology Co., Ltd., China	None	GC ^②
Isopropanol	60.10	≥0.995	Jiangtian Chemical Technology Co., Ltd., China	None	GC ^②
<i>N</i> -propanol	60.10	≥0.995	Jiangtian Chemical Technology Co., Ltd., China	None	GC ^②

^① High-performance liquid chromatography.

^② Gas chromatography.

monohydrate, solid filtered in solution after stirring 24 h, dried product in the binary solvents (methanol + ethanol, $x_2^0 = 0.5$) at temperature $T = 303.15$ K as an example. All the PXRD patterns of the tested materials have the same characteristic peaks of metamizol monohydrate. The PXRD pattern of anhydrous analgin which is the dehydrated product of metamizol monohydrate, obtained from the single crystal structure of anhydrous analgin with Mercury 3.3 [13], is also showed in Fig. 2. It confirms that the solute used in this study is metamizol monohydrate and there is no polymorphism, amorphous or dehydration during the process.

As can be seen from the TGA analysis (Fig. 3), there are two stages in the thermal decomposition process. The first one corresponds to crystal water loss which is about 4.8% and the second step from 510.15 K with a weight loss because of the decomposition. The DSC analysis indicates that the exothermic and endothermic peaks both appear from 505 K to 525 K which suggests that metamizol monohydrate melt with decomposition. Therefore, the thermal analysis experiment cannot provide the melting temperature, neither nor the enthalpy of fusion of metamizol monohydrate.

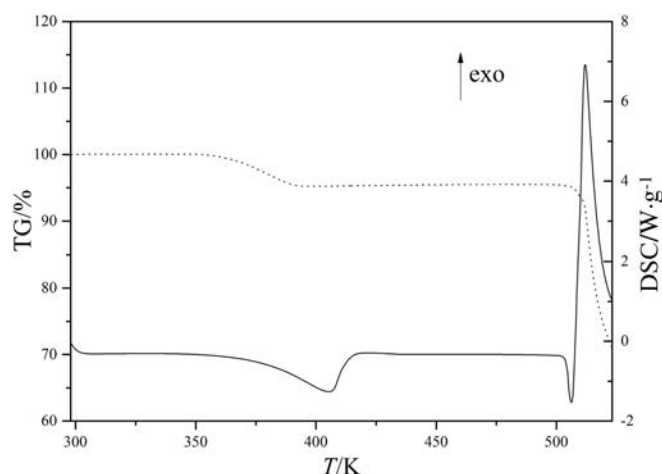


Fig. 3. Thermal analysis (TGA/DSC) of metamizol monohydrate. The solid and dashed lines are the DSC and TGA curves, respectively.

In this study, the melting temperature and the enthalpy of fusion of metamizol monohydrate have been estimated by a method called group-contribution which has been proved to be accurate enough to determine these properties [14]. In the determination of melting properties for more than 2000 materials reported in papers using this method, the absolute errors of melting temperature and fusion enthalpy are less than 33.87 K and $4.160 \text{ kJ} \cdot \text{mol}^{-1}$, respectively [14]. The melting properties of metamizol monohydrate can be estimated by Eqs. (4) and (5).

$$T_m = T_{m0} \ln \left(\sum_i n_i T_{m1i} + \sum_j m_j T_{m2j} + \sum_k o_k T_{m3k} \right) \quad (4)$$

$$\Delta_{\text{fus}} H = H_{\text{fus}0} + \left(\sum_i n_i H_{\text{fus}1i} + \sum_j m_j H_{\text{fus}2j} + \sum_k o_k H_{\text{fus}3k} \right) \quad (5)$$

where T_{m0} and $H_{\text{fus}0}$ are the parameters, the values of which are 147.45 K and $-2.806 \text{ kJ} \cdot \text{mol}^{-1}$, respectively. The contribution of the first-order group, second-order group and third-order group for the melting temperature is expressed by T_{m1i} , T_{m2j} and T_{m3k} , respectively. With respect to the enthalpy of fusion, the contribution of these groups is represented by $H_{\text{fus}1i}$, $H_{\text{fus}2j}$ and $H_{\text{fus}3k}$, respectively. In these equations, the values of T_{m1i} , T_{m2j} , T_{m3k} , $H_{\text{fus}1i}$, $H_{\text{fus}2j}$ and $H_{\text{fus}3k}$ of all the investigated groups can be got through literature [14]. With this

group-contribution method, the estimated melting point of metamizol monohydrate is 507.30 K and the predicted fusion enthalpy is $17.56 \text{ kJ} \cdot \text{mol}^{-1}$.

3.2. Solubility of metamizol monohydrate in four pure solvents

The experimental solubility of metamizol monohydrate in the pure solvents from 283.15 K to 313.15 K is shown in Table 2 and plotted against temperature in Fig. 4. It can be seen clearly from the results that the solubility of metamizol monohydrate in methanol, ethanol, n-propanol and isopropanol all increase slowly with the rise of the temperature. The interesting thing is that the dissolving capacity order of the solvents for metamizol monohydrate is as same as the polarity order of these solvents, which can be arranged as methanol > ethanol > n-propanol > isopropanol in literature [15,16]. This coincidence means that the polarity of solvents must play a major role in affecting the solubility of metamizol monohydrate.

In order to research the influence factors of solubility deeply, different models has been introduced to correlate the solubility data. The average relative deviation percentage (ARD) is a useful index which can not only calculate the differences between the experimental and calculated data but can also help us to choose the best model. The ARD is defined as:

$$ARD = \frac{100\%}{N} \sum_{i=1}^N \left| \frac{x_{1,i} - x_{1,i}^{\text{cal}}}{x_{1,i}} \right| \quad (6)$$

Table 2

Experimental solubility of metamizol monohydrate in four pure solvents at different temperatures (0.1 MPa)

T/K	$x_1 \times 10^2$
<i>Methanol</i>	
283.15	4.32
288.15	4.696
293.15	5.031
298.15	5.439
303.15	5.979
308.15	6.706
313.15	7.302
<i>Ethanol</i>	
283.15	0.733
288.15	0.855
293.15	0.919
298.15	1.01
303.15	1.134
308.15	1.284
313.15	1.469
<i>N-propanol</i>	
283.15	0.1566
288.15	0.1973
293.15	0.2446
298.15	0.2815
303.15	0.3749
308.15	0.4496
313.15	0.5551
<i>Isopropanol</i>	
283.15	0.047
288.15	0.0582
293.15	0.0692
298.15	0.0814
303.15	0.097
308.15	0.1184
313.15	0.1432

x_1 represents the experimental solubility. The standard uncertainty of temperature is $u_c(T) = 0.06$ K. The relative standard uncertainty of the solubility measurement is $u_r(x_1) = 0.03$. The standard uncertainty of pressure is $u_c(P) = 6$ kPa.

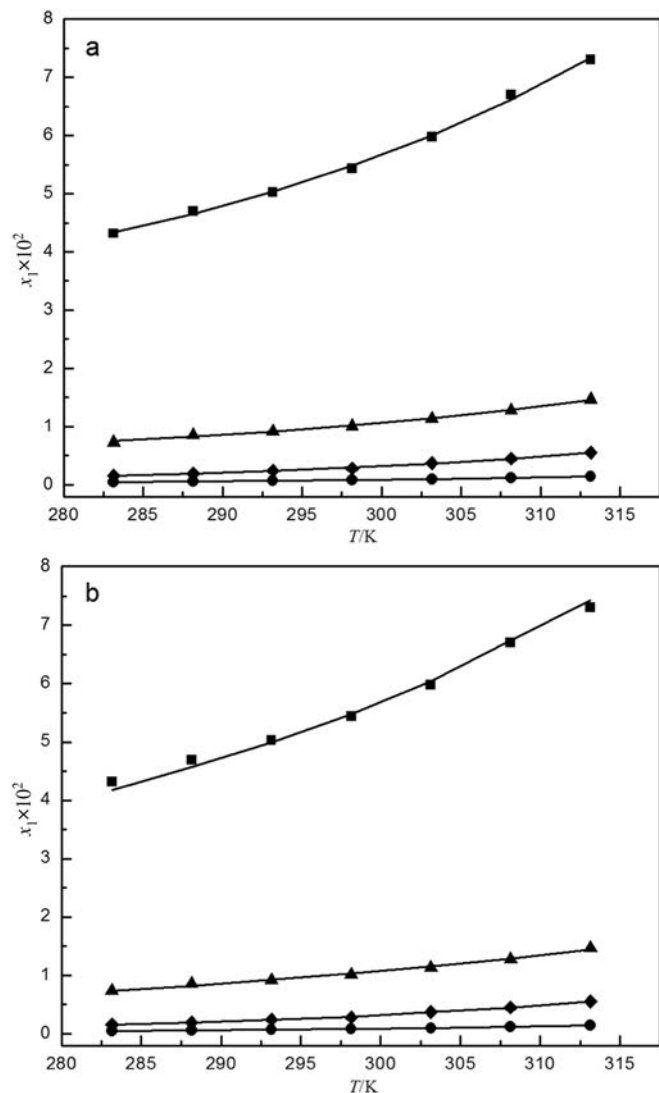


Fig. 4. Experimental solubility data of metamizol monohydrate in four pure solvents: ■, methanol; ▲, ethanol; ◆, *n*-propanol; ●, isopropanol. The solid lines represent the correlated solubility by a) the modified Apelblat model and b) the NRTL model.

where N is the number of the experimental points. $x_{1,i}$ and $x_{1,i}^{\text{cal}}$ are the experimental and the calculated solubility value, respectively.

MATLAB software, including many correlated equations, was used to correlate the solubility of metamizol monohydrate. Among them, the modified Apelblat equation, a semi-empirical model, has three parameters which is widely used in correlating solubility data [17–20]:

$$\ln x_1 = A + \frac{B}{T} + C \ln T \quad (7)$$

where x_1 represents the mole fraction solubility of solute. T is the absolute experimental temperature. A and B reflect the non-ideality of the real solution because of the variation of activity coefficient in the solution, while C means the effect of temperature on the fusion enthalpy. A , B , and C are all empirical constants.

The correlated solubility data of analgin by modified Apelblat equation is represented in Fig. 4a). The values of correlated model parameters and average relative deviation (ARD) are given in Table 3.

Table 3

Parameters and ARDs of the modified Apelblat equation about the solubility of metamizol monohydrate in four pure solvents ($P = 0.1$ MPa)

Parameters	Methanol	Ethanol	<i>N</i> -propanol	Isopropanol
A	−216.44	−250.86	−166.95	−229.25
B	8168.21	9278.03	3996.44	7137.41
C	32.67	37.76	25.93	34.79
$ARD \times 10^2$	0.62	1.27	1.74	1.05

These results show that the correlation equation in this work can give good correlation results, which means that the solubility has temperature dependence in these dissolving processes.

The activity coefficient (γ) was introduced to estimate the thermodynamic properties in real solutions, which can be calculated through the local composition model-NRTL model. The correlated solubility data, the enthalpy, the Gibbs energy and the entropy of the mixing process can be also obtained from this model [21]. At phase equilibrium including solid and liquid, the fugacity of the solute in the solid phase and that in the liquid phase must be the same one, which can be interpreted as the following Eq. (8):

$$f_i^1(T, p, x_i) = f_i^s(T, p) \quad (8)$$

Adopting some assumptions, the equation can be expressed as follows:

$$\ln x_i = \frac{\Delta_{\text{fus}} H}{R} \left(\frac{1}{T_m} - \frac{1}{T} \right) - \ln \gamma_i \quad (9)$$

where $\Delta_{\text{fus}} H$ (enthalpy of fusion) and T_m (melting point) were obtained using the group-contribution method mentioned in Section 3.1.

The values of activity coefficient γ_i can be calculated from the following equation in NRTL model:

$$\ln \gamma_i = x_j^2 \left[\frac{\tau_{ji} G_{ji}^2}{(x_i + G_{ji} x_j)^2} + \frac{\tau_{ij} G_{ij}}{(x_j + G_{ij} x_i)^2} \right] \quad (10)$$

where G_{ij} , G_{ji} , τ_{ij} and τ_{ji} are the parameters of this model. Their values can be calculated as:

$$G_{ij} = \exp(-\alpha_{ij} \tau_{ij}) \quad (11)$$

$$\tau_{ij} = (g_{ij} - g_{jj}) / RT = \Delta g_{ij} / RT \quad (12)$$

where a is an adjustable empirical constant. τ is a constant used to express the nonrandomness of the mixture. g means the Gibbs energy of intermolecular interaction. The calculated solubility values of metamizol monohydrate by NRTL model are plotted in Fig. 4b), and the model parameters are listed in Table 4. These results indicate that the good correlation results can be obtained from NRTL model, which means that it can be used in the analysis of the thermodynamic properties during the mixing process in the next section.

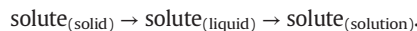
Table 4

Parameters for the NRTL model in four pure solvents ($P = 0.1$ MPa)

Parameters	Methanol	Ethanol	<i>N</i> -propanol	Isopropanol
$\Delta g_{12} \times 10^{-4}$	−1.01	3.96	0.10	0.44
$\Delta g_{21} \times 10^{-4}$	1.77	−2.96	0.73	0.90
a	0.12	0.01	0.99	0.60
$ARD \times 10^2$	1.53	1.71	1.23	1.51

3.3. The thermodynamic properties of mixing in pure solvents

The dissolving process can be divided into three hypothetical steps [22]:



The fusion of the solute, the cooling of the liquid solute and the mixing of the liquid solute constitute this dissolving process. As for the crystal structure of metamizol monohydrate are supposed to determine the fusion properties, the major determined factor to explore this whole dissolving process must be the mixing properties of the solution.

The following equations explain how to calculate the thermodynamic properties of mixing process in four pure solvents. The mixing Gibbs free energy (ΔG_m), the mixing enthalpy (ΔH_m) and the mixing entropy (ΔS_m) can be obtained by:

$$\Delta M_m = \Delta M^{\text{id}} + M^{\text{E}} \quad (13)$$

where M can be substituted by G , H , and S . ΔM^{id} is the mixing property of the ideal solution, while M^{E} is the excess property.

The ΔG_m , ΔH_m and ΔS_m of the ideal solution are calculated by [23]:

$$\Delta G_m^{\text{id}} = RT \sum_{i=1}^n x_i \ln x_i \quad (14)$$

$$\Delta S_m^{\text{id}} = -R \sum_{i=1}^n x_i \ln x_i \quad (15)$$

$$\Delta H_m^{\text{id}} = 0 \quad (16)$$

where x_i is the mole fraction of every component in the solution. n is the total components of the solution. $n = 2$ or 3 means the dissolving process happened in pure solvents or in the binary mixed solvent systems respectively.

The excess mixing Gibbs energy (ΔG^{E}), mixing entropy (ΔS^{E}) and mixing enthalpy (ΔH^{E}) are calculated as [24]:

$$\Delta G^{\text{E}} = RT \sum_{i=1}^n x_i \ln \gamma_i \quad (17)$$

$$\Delta S^{\text{E}} = -\frac{\partial \Delta G^{\text{E}}}{\partial T} = -R \sum_{i=1}^n x_i \ln \gamma_i - R \sum_{i=1}^n x_i \left(\frac{\partial \ln \gamma_i}{\partial T} \right)_{p,x} \quad (18)$$

$$\Delta H^{\text{E}} = -T^2 \frac{\partial \left(\frac{\Delta G^{\text{E}}}{T} \right)}{\partial T} = -RT^2 \sum_{i=1}^n x_i \left(\frac{\partial \ln \gamma_i}{\partial T} \right)_{p,x} \quad (19)$$

where γ_i is the activity coefficient of every component in the solution. $n = 2$ or 3 means the dissolving process happened in pure solvents or in the binary mixed solvent systems respectively.

The calculated thermodynamic properties of mixing of metamizol monohydrate are shown in Table 5. The negative values of every ΔG_m mean that the mixing process is all spontaneous in the pure solvents used in this work. However, the values of ΔS_m are all positive, which illustrates that this process is entropically favorable. Furthermore, the mixing process in *n*-propanol and isopropanol is endothermic according to the positive values of ΔH_m while the counterpart in methanol and ethanol is exothermic based on the negative values of ΔH_m .

3.4. Solubility of metamizol monohydrate in binary mixed solvent systems

The solubility of metamizol monohydrate in two binary mixed solvent systems containing good solvent and poor solvent was measured to meet the demand of controlling and optimizing the drug producing

Table 5

The thermodynamic properties of mixing for solution with four pure solvents from 283.15 K to 313.15 K ($P = 0.1$ MPa)

T/K	$\Delta G_m/J \cdot \text{mol}^{-1}$	$\Delta S_m/J \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$	$\Delta H_m/J \cdot \text{mol}^{-1}$
<i>Methanol</i>			
283.15	−409.4398	0.1083	−378.7980
288.15	−438.4302	0.1473	−396.0131
293.15	−463.9596	0.1910	−407.9943
298.15	−494.3281	0.2332	−424.8331
303.15	−533.7672	0.2739	−450.7709
308.15	−585.2028	0.3106	−489.5278
313.15	−626.7717	0.3573	−514.9262
<i>Ethanol</i>			
283.15	−73.8239	0.2160	−12.6905
288.15	−84.2434	0.2465	−13.2441
293.15	−90.2796	0.2650	−12.6319
298.15	−98.3395	0.2892	−12.1637
303.15	−108.7621	0.3201	−11.7735
308.15	−120.9197	0.3561	−11.2519
313.15	−135.2950	0.3986	−10.5468
<i>N-propanol</i>			
283.15	−15.3544	0.0916	10.5595
288.15	−19.1372	0.1112	12.8846
293.15	−23.2558	0.1333	15.8078
298.15	−26.6018	0.1491	17.8426
303.15	−34.2250	0.1877	22.6595
308.15	−40.4364	0.2165	26.2322
313.15	−48.6130	0.2542	30.9455
<i>Isopropanol</i>			
283.15	−4.7147	0.0310	4.0655
288.15	−5.7380	0.0374	5.0352
293.15	−6.7592	0.0435	5.9902
298.15	−7.8872	0.0501	7.0497
303.15	−9.2802	0.0583	8.3992
308.15	−11.0976	0.0693	10.2387
313.15	−13.1572	0.0815	12.3615

ΔG_m , ΔS_m and ΔH_m are calculated by Eq. (13). The mixing parameters reported in the table are per mole of total mixture. The expanded uncertainties are $U(\Delta G_m) = 0.06\Delta G_m$, $U(\Delta S_m) = 0.07\Delta S_m$ (0.95 level of confidence).

process. As a result, the experimental solubility data of metamizol monohydrate in the binary mixed solvent systems including (methanol + ethanol) and (methanol + isopropanol) from 283.15 K to 313.15 K under atmospheric pressure (0.1 MPa) are shown in Tables 6 and 7 and plotted in Figs. 5–8 respectively. From the solubility data, we can easily find that the solubility trends conform to the famous rule “dissolve like dissolve” [25]. What's more, the solubility of metamizol monohydrate increases with the rise of the methanol composition in binary mixed solvent systems at a constant temperature. Additionally, although the solvent composition kept unchanged, the solubility of metamizol monohydrate increases with the rise of the temperature.

The modified Apelblat equation, the CNIBS/R–K model, the Hybrid model and the NRTL model were all applied to correlate the solubility of metamizol monohydrate in the binary mixed solvent systems including (methanol + ethanol) and (methanol + isopropanol). And the calculated solubilities are all plotted in Figs. 5–8, respectively. The modified Apelblat equation was applied to explain the relationship between temperature and solubility; the CNIBS/R–K model was used to explain the relationship between the solvent component and the isothermal solubility; the Hybrid model was supposed to illustrate the relationship among solubility, temperature and solvent component; the NRTL model was applied to correlate the solubility and the thermodynamic properties.

The values of correlated model parameters and average relative deviation (ARD) of modified Apelblat equation mentioned about the solubility of metamizol monohydrate in the component solvent are given in Table 8. The data shows that this modified equation in binary

Table 6

Mole fraction solubility (x_1) of metamizol monohydrate in the binary (methanol (2) + ethanol (3)) solvent mixtures at different temperatures from 283.15 K to 313.15 K ($P = 0.1$ MPa).

x_2^0	$x_1 \times 10^2$	x_2^0	$x_1 \times 10^2$
$T = 283.15$ K			
0.0	0.7330	0.6	2.9910
0.1	0.7962	0.7	3.5490
0.2	0.9744	0.8	4.2090
0.3	1.2350	0.9	4.7800
0.4	1.5330	1.0	5.4390
0.5	1.8680	$T = 303.15$ K	
0.6	2.2750	0.0	1.1340
0.7	2.6850	0.1	1.3640
0.8	3.0540	0.2	1.6000
0.9	3.7250	0.3	2.0350
1.0	4.3200	0.4	2.3990
$T = 288.15$ K			
0.0	0.8550	0.5	2.9060
0.1	0.9514	0.6	3.3840
0.2	1.0740	0.7	3.9620
0.3	1.3920	0.8	4.6100
0.4	1.6790	0.9	5.2520
0.5	2.0890	1.0	5.9790
0.6	2.4370	$T = 308.15$ K	
0.7	2.9270	0.0	1.2840
0.8	3.4660	0.1	1.5920
0.9	4.0340	0.2	1.8480
1.0	4.6960	0.3	2.3010
$T = 293.15$ K			
0.0	0.9190	0.4	2.7440
0.1	1.0520	0.5	3.2560
0.2	1.2200	0.6	3.8360
0.3	1.5760	0.7	4.4820
0.4	1.8640	0.8	5.1000
0.5	2.2700	0.9	5.8380
0.6	2.6940	1.0	6.7060
0.7	3.2150	$T = 313.15$ K	
0.8	3.8740	0.0	1.4690
0.9	4.3810	0.1	1.8200
1.0	5.0310	0.2	2.1380
$T = 298.15$ K			
0.0	1.0100	0.3	2.5800
0.1	1.2060	0.4	3.1570
0.2	1.3890	0.5	3.7170
0.3	1.7710	0.6	4.3170
0.4	2.0960	0.7	5.0490
0.5	2.5390	0.8	5.6380
		0.9	6.5880
		1.0	7.3020

x_2^0 is the initial mole fraction of methanol in the binary mixed solvent system; x_1 is the experimentally determined solubility. The standard uncertainty of temperature is $u_c(T) = 0.06$ K. The relative standard uncertainty of the solubility measurement is $u_r(x_1) = 0.02$. The standard uncertainty of pressure is $u_c(P) = 6$ kPa. The relative standard uncertainty in mole fraction of methanol (2) in the binary mixed solvent systems is $u_r(x_2^0) = 0.0001$.

mixed solvent systems gives good correlation results just like that in the pure solvents, indicating that the solubility has temperature dependence, either.

The CNIBS/R-K model was introduced to correlate the solubility of metamizol monohydrate in the two binary mixed solvent systems [26,27], which can give us a clearly explain about the effect of solvent component on the solubility ability. The equation can be expressed as:

$$\ln x_1 = x_2^0 \ln(x_1)_2 + x_3^0 \ln(x_1)_3 + x_2^0 x_3^0 \sum_{i=0}^n s_i (x_2^0 - x_3^0)^i \quad (20)$$

where x_2^0 and x_3^0 express the initial mole fraction of methanol and the initial mole fraction of ethanol (isopropanol) in the binary mixed solvent system methanol + ethanol (methanol + isopropanol) without solute metamizol monohydrate. And x_1 denotes the mole fraction solubility of the metamizol monohydrate, while $(x_1)_i$ is the mole fraction solubility of the metamizol monohydrate in

Table 7

Mole fraction solubility (x_1) of metamizol monohydrate in the binary (methanol (2) + isopropanol (3)) solvent mixtures at different temperatures from 283.15 K to 313.15 K ($P = 0.1$ MPa).

x_2^0	$x_1 \times 10^2$	x_2^0	$x_1 \times 10^2$
$T = 283.15$ K			
0.00	0.0470	0.60	1.3650
0.10	0.0781	0.70	2.0650
0.20	0.1411	0.80	2.8320
0.30	0.2375	0.90	4.0630
0.40	0.3723	1.00	5.4390
0.50	0.5821	$T = 303.15$ K	
0.60	0.9802	0.00	0.0970
0.70	1.5330	0.10	0.1406
0.80	2.1540	0.20	0.2247
0.90	3.1830	0.30	0.3769
1.00	4.3200	0.40	0.5738
$T = 288.15$ K			
0.00	0.0582	0.50	0.9328
0.10	0.0871	0.60	1.5640
0.20	0.1495	0.70	2.3390
0.30	0.2588	0.80	3.2350
0.40	0.3945	0.90	4.4970
0.50	0.6384	1.00	5.9790
0.60	1.0656	$T = 308.15$ K	
0.70	1.6480	0.00	0.1184
0.80	2.3650	0.10	0.1706
0.90	3.3850	0.20	0.2625
1.00	4.6960	0.30	0.4436
$T = 293.15$ K			
0.00	0.0692	0.40	0.6795
0.10	0.1001	0.50	1.1100
0.20	0.1663	0.60	1.8350
0.30	0.2872	0.70	2.6510
0.40	0.4302	0.80	3.6540
0.50	0.7145	0.90	5.0030
0.60	1.2062	1.00	6.7060
0.70	1.8390	$T = 313.15$ K	
0.80	2.5480	0.00	0.1432
0.90	3.7440	0.10	0.2191
1.00	5.0310	0.20	0.3183
$T = 298.15$ K			
0.00	0.0814	0.30	0.5276
0.10	0.1181	0.40	0.8256
0.20	0.1898	0.50	1.3020
0.30	0.3269	0.60	2.1450
0.40	0.4946	0.70	3.0510
0.50	0.8124	0.80	4.2140
		0.90	5.6570
		1.00	7.3020

x_2^0 is the initial mole fraction of methanol in the binary mixed solvent system; x_1 is the experimentally determined solubility. The standard uncertainty of temperature is $u_c(T) = 0.06$ K. The relative standard uncertainty of the solubility measurement is $u_r(x_1) = 0.05$, except at $T = 283.15$ K, $x_2^0 = 0.1$: $u_r(x_1) = 0.18$; $x_2^0 = 0.2$: $u_r(x_1) = 0.09$. The standard uncertainty of pressure is $u_c(P) = 6$ kPa. The relative standard uncertainty in mole fraction of methanol (2) in the binary mixed solvent systems is $u_r(x_2^0) = 0.0001$.

pure solvent I; s_i represents the model parameter; n represents the number of “curve-fit” parameters. In the two binary mixed solvent systems, n should be assigned a value as two, then the equation can be simplified to the following equation when x_3^0 replaced with $(1 - x_2^0)$ in Eq. (20):

$$\ln x_1 = B_0 + B_1 x_2^0 + B_2 (x_2^0)^2 + B_3 (x_2^0)^3 + B_4 (x_2^0)^4 \quad (21)$$

The model parameters of the (NIBS)/Redlich–Kister model and the calculated ARDs in this correlation are listed in Table 9. The result illustrates that this model is very suitable to correlate the experimental solubility, showing that the solubility data has a great dependence on the solvent component.

Taking the influence of temperature and solvent component on the solubility of metamizol monohydrate into consideration, the Hybrid

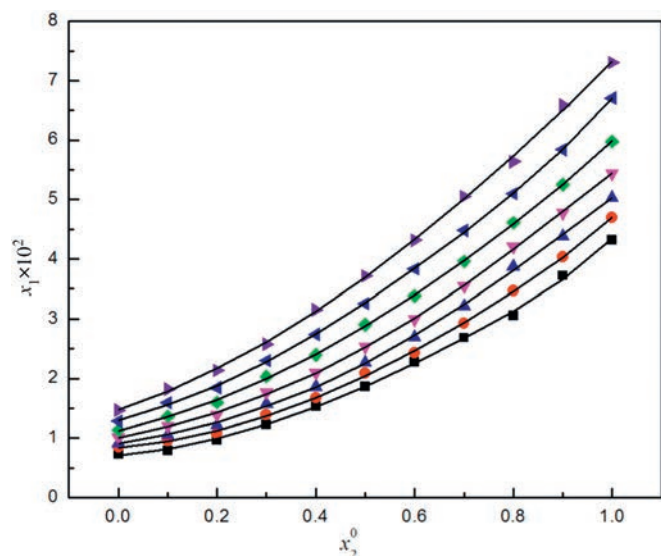


Fig. 5. Mole fraction solubility (x_1) of metamizol monohydrate versus mole fraction of methanol (x_2^0) in methanol (2) + ethanol (3) binary mixed solvent systems from 283.15 K to 313.15 K ($P = 0.1$ MPa): ■, $T = 283.15$ K; ●, $T = 288.15$ K; ▲, $T = 293.15$ K; ▼, $T = 298.15$ K; ◆, $T = 303.15$ K; ◀, $T = 308.15$ K; ▶, $T = 313.15$ K. The solid lines represent the correlated solubility by the CNIBS/R-K model.

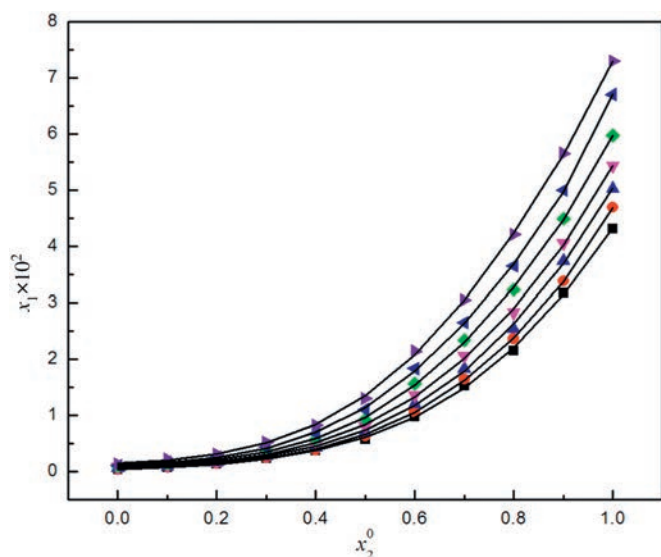


Fig. 6. Mole fraction solubility (x_1) of metamizol monohydrate versus mole fraction of methanol (x_2^0) in methanol (2) + isopropanol (3) binary mixed solvent systems from 283.15 K to 313.15 K ($P = 0.1$ MPa): ■, $T = 283.15$ K; ●, $T = 288.15$ K; ▲, $T = 293.15$ K; ▼, $T = 298.15$ K; ◆, $T = 303.15$ K; ◀, $T = 308.15$ K; ▶, $T = 313.15$ K. The solid lines represent the correlated solubility by the CNIBS/R-K model.

model, a combination of the modified Apelblat equation and Jouyban–Acree model, was used to correlate the solubility in two binary mixed solvent systems from 283.15 K to 313.15 at 0.1 MPa [28]. The hybrid model can be expressed as:

$$\ln x_1 = x_2^0 \ln(x_1)_2 + x_3^0 \ln(x_1)_3 + x_2^0 x_3^0 \sum_{i=0}^2 \frac{J_i (x_2^0 - x_3^0)^i}{T} \quad (22)$$

where x_1 , x_2^0 and x_3^0 express the mole fraction of metamizol monohydrate, the initial mole fraction of methanol and the initial mole

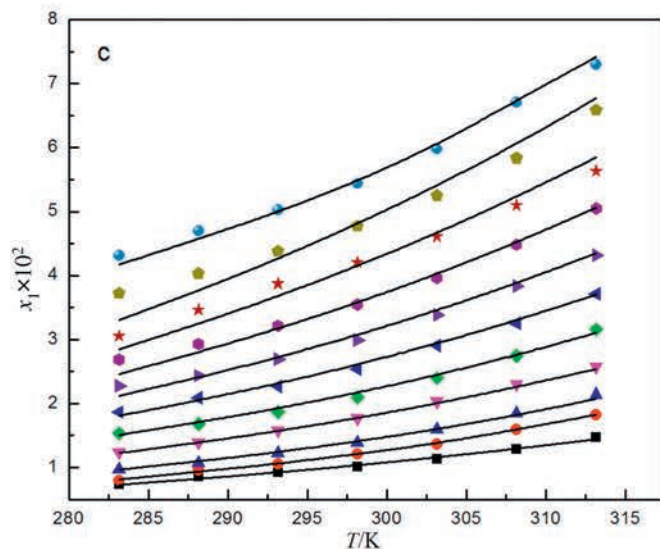
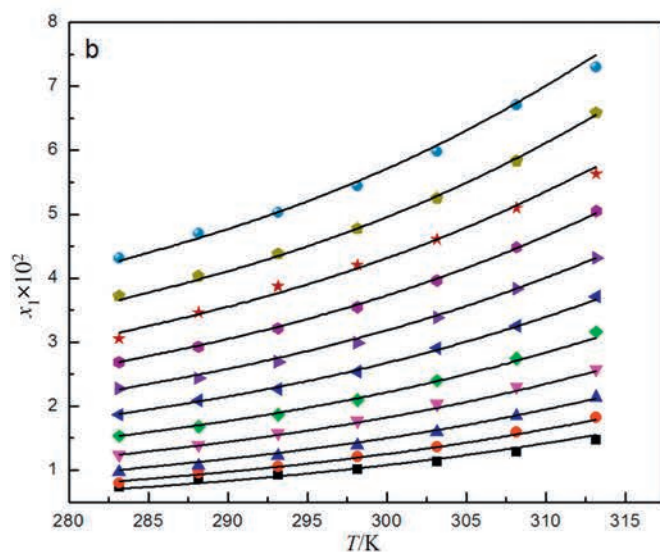
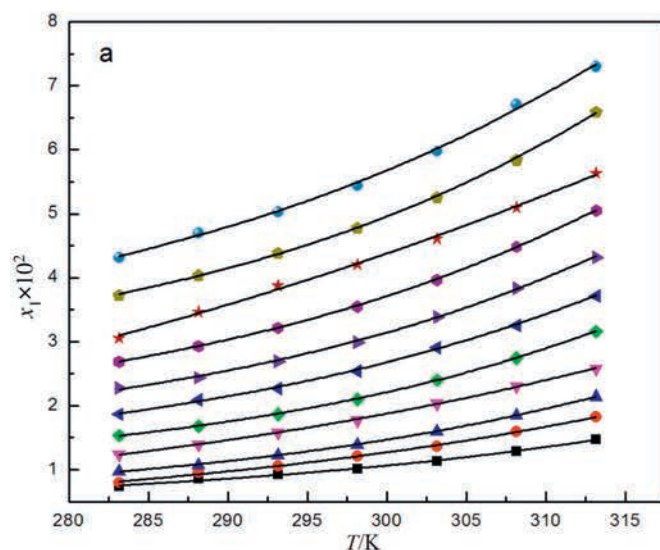


Fig. 7. Mole fraction solubility (x_1) of metamizol monohydrate versus temperature T in methanol (2) + ethanol (3) binary mixed solvent systems from 283.15 K to 313.15 K ($P = 0.1$ MPa): ■, $x_2^0 = 0$; ●, $x_2^0 = 0.1$; ▲, $x_2^0 = 0.2$; ▼, $x_2^0 = 0.3$; ◆, $x_2^0 = 0.4$; ◀, $x_2^0 = 0.5$; ▶, $x_2^0 = 0.6$; ●, $x_2^0 = 0.7$; ★, $x_2^0 = 0.8$; ●, $x_2^0 = 0.9$; ●, $x_2^0 = 1$. The solid lines represent the correlated solubility by a) the modified Apelblat model, b) the Hybrid model and c) the NRTL model.

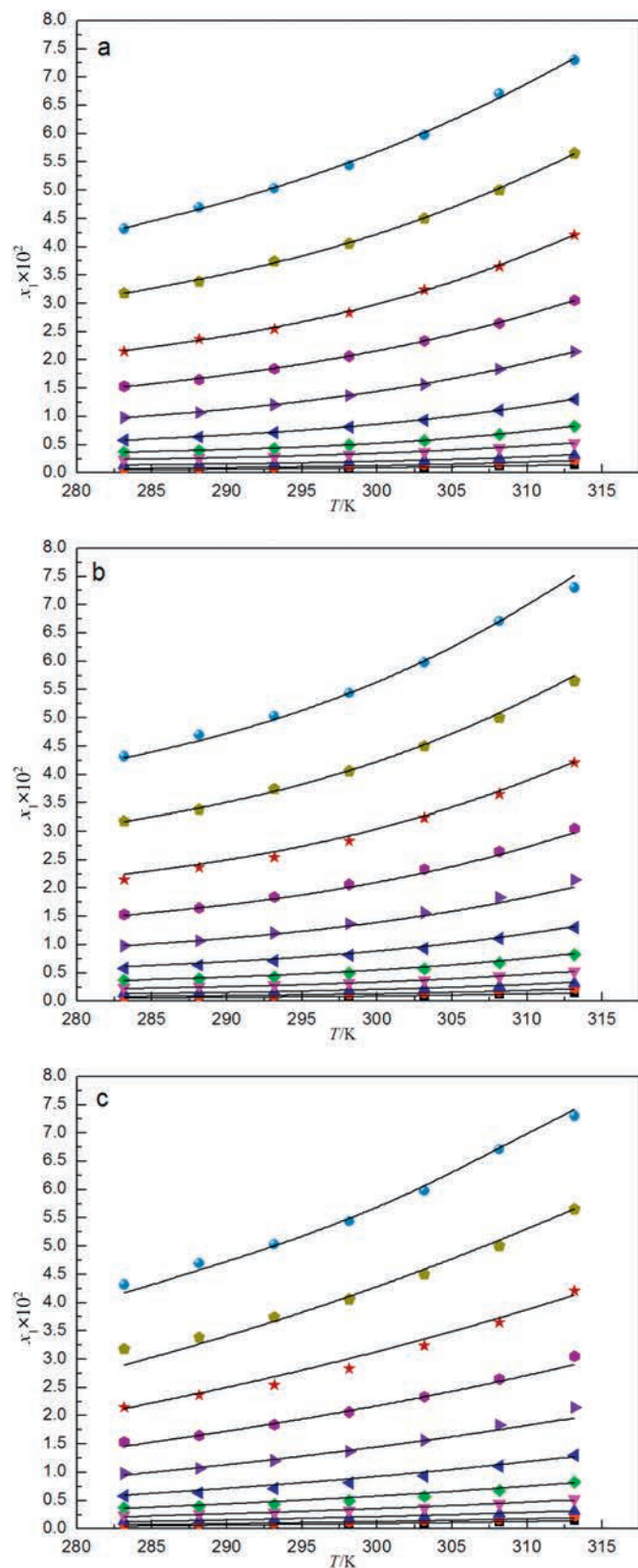


Fig. 8. Mole fraction solubility (x_1) of metamizol monohydrate versus temperature T in methanol (2) + isopropanol (3) binary mixed solvent systems from 283.15 K to 313.15 K ($P = 0.1$ MPa): ■, $x_2^0 = 0$; ●, $x_2^0 = 0.1$; ▲, $x_2^0 = 0.2$; ▼, $x_2^0 = 0.3$; ◆, $x_2^0 = 0.4$; ◆, $x_2^0 = 0.5$; ◆, $x_2^0 = 0.6$; ◆, $x_2^0 = 0.7$; ◆, $x_2^0 = 0.8$; ◆, $x_2^0 = 0.9$; ◆, $x_2^0 = 1.0$. The solid lines represent the correlated solubility by a) the modified Apelblat model, b) the Hybrid model and c) the NRTL model.

Table 8

Parameters of the modified Apelblat equation for metamizol monohydrate in different binary mixed solvent systems ($P = 0.1$ MPa)

x_2^0	A	B	C	ARD $\times 10^2$
(Methanol + ethanol)				
0.00	-250.8578	9278.0347	37.7618	1.27
0.10	-151.8520	4527.4840	23.2112	0.99
0.20	-281.0511	10,303.1770	42.5125	0.38
0.30	-84.1676	1690.0850	13.0713	0.44
0.40	-324.2827	12,412.7963	48.9309	0.29
0.50	-256.4053	9513.4352	38.7586	0.62
0.60	-291.4005	11,152.1010	43.9644	0.60
0.70	-268.9271	10,216.0018	40.6006	0.18
0.80	-12.7000	-1076.8077	2.2998	0.78
0.90	-275.7336	10,707.2423	41.5577	0.35
1.00	-216.4351	8168.2149	32.6691	0.62
Overall				ARD $\times 10^2 = 0.59$
(Methanol + isopropanol)				
0.00	-229.2495	7137.4076	34.7865	1.05
0.10	-741.3135	30,090.3329	111.2113	0.67
0.20	-641.6194	26,166.2335	96.1098	0.72
0.30	-528.7347	21,237.3139	79.2931	0.11
0.40	-718.8887	29,700.2007	107.7577	0.42
0.50	-468.8402	18,590.2469	70.4992	0.32
0.60	-411.7878	16,126.1445	62.0273	0.39
0.70	-323.7871	12,468.9466	48.8073	0.40
0.80	-388.3935	15,428.6979	58.4612	0.54
0.90	-291.5063	11,369.7270	43.9079	0.38
1.00	-216.4351	8168.2149	32.6691	0.62
Overall				ARD $\times 10^2 = 0.51$

fraction of ethanol or isopropanol, respectively. J_i is supposed to be a constant. According to the modified Apelblat equation, $(x_1)_2$ and $(x_1)_3$ can be replaced by the following Eqs. ((22)–(23)):

$$\ln(x_1)_2 = a_1 + b_1/T + c_1 \ln T \quad (23)$$

$$\ln(x_1)_3 = a_2 + b_2/T + c_2 \ln T \quad (24)$$

Table 9

Parameters of the CNIBS/R-K equation for metamizol monohydrate in different binary mixed solvent systems at the temperature from 283.15 K to 313.15 K ($P = 0.1$ MPa)

T/K	B_1	B_2	B_3	B_4	B_5	ARD $\times 10^2$
(Methanol + ethanol)						
283.15	-4.9438	1.0640	3.9969	-5.8194	2.5644	1.36
288.15	-4.7756	0.8626	3.7605	-4.8502	1.9453	1.18
293.15	-4.7026	1.4034	1.6372	-1.8585	0.5298	1.24
298.15	-4.5993	1.6597	0.7943	-0.9784	0.2114	0.93
303.15	-4.4851	1.7913	0.7843	-1.5546	0.6474	0.78
308.15	-4.3436	1.7007	1.1937	-2.3540	1.1006	0.72
313.15	-4.2180	1.9451	0.0782	-0.7245	0.3051	0.96
Overall						ARD $\times 10^2 = 1.02$
(Methanol + isopropanol)						
283.15	-7.6574	5.2767	0.2022	-1.0888	0.1263	2.28
288.15	-7.3576	2.9251	7.5322	-9.9277	3.7696	3.11
293.15	-7.3646	4.2939	3.2437	-4.7940	1.6329	3.05
298.15	-7.1214	3.1423	6.9279	-9.4201	3.5610	2.28
303.15	-6.8656	2.1044	9.9534	-12.9346	4.9261	2.77
308.15	-6.6829	1.8875	11.0903	-15.0301	6.0336	2.42
313.15	-6.4884	2.3566	8.7036	-11.5484	4.3601	2.24
Overall						ARD $\times 10^2 = 2.59$

Table 10Parameters of the Hybrid model for metamizol monohydrate in different binary solvent systems at the temperature from 283.15 K to 313.15 K ($P = 0.1$ MPa)

Parameters	(Methanol + ethanol)	(Methanol + isopropanol)
A_1	−212.0541	−579.4180
A_2	7235.5384	22846.2301
A_3	32.1546	86.9920
A_4	−5.4317	261.2933
A_5	771.6544	−10352.2784
A_6	785.5401	1162.2558
A_7	−1155.4664	−1556.9648
A_8	490.1057	499.8094
A_9	0.72360	−39.0854
$ARD \times 10^2$	2.22	3.93

Table 11Parameters of the NRTL model for metamizol monohydrate in different binary solvent systems at the temperature from 283.15 K to 313.15 K ($P = 0.1$ MPa)

Parameters	(Methanol + ethanol)	(Methanol + isopropanol)
$\Delta g_{12} \times 10^{-3}$	0.4615	−1.3612
$\Delta g_{13} \times 10^{-3}$	−12.8613	23.0803
$\Delta g_{21} \times 10^{-3}$	−0.5507	1.5743
$\Delta g_{23} \times 10^{-3}$	−4.5792	−0.3222
$\Delta g_{31} \times 10^{-3}$	25.8497	−8.3904
$\Delta g_{32} \times 10^{-3}$	−2.2696	−6.9880
α_1	0.1	0.05
α_2	0.9	0.9
α_3	0.14	0.05
$ARD \times 10^2$	2.22	3.93

Replacing x_3^0 with $(1 - x_2^0)$, a new equation can be obtained:

$$\ln x_1 = a_1 + \frac{b_1}{T} + c_2 \ln T + (a_1 - a_2)x_2^0 + (b_1 - b_2 + J_0 - J_1 + J_2) \frac{x_2^0}{T} \\ + (3J_1 - J_0 - 5J_2) \frac{(x_2^0)^2}{T} + (8J_2 - 2J_1) \frac{(x_2^0)^3}{T} + (-4J_2) \frac{(x_2^0)^4}{T} \quad (25) \\ + (c_1 - c_2)x_2^0 \ln T$$

it can be simplified by adding several constant terms to the Eq. (26):

$$\ln x_1 = A_1 + \frac{A_2}{T} + A_3 \ln T + A_4 x_2^0 + A_5 \frac{x_2^0}{T} + A_6 \frac{(x_2^0)^2}{T} + A_7 \frac{(x_2^0)^3}{T} \\ + A_8 \frac{(x_2^0)^4}{T} + A_9 x_2^0 \ln T \quad (26)$$

where A_1 to A_9 are the model parameters.

The model parameters and the calculated ARDs of this model are listed in Table 10. The results illustrate that this mixed model is good to correlates the solubility of metamizol monohydrate in the measured binary mixed solvent systems at different solvent component and temperatures, the range of which is confined from 283.15 K to 313.15 K.

The activity coefficients of metamizol monohydrate (γ_i) in the binary mixed solvent systems including (methanol + ethanol) and (methanol + isopropanol) were also obtained by the NRTL model

Table 12The mixing thermodynamic properties of metamizol monohydrate in binary solvent mixtures (methanol + ethanol) from 283.15 K to 313.15 K ($P = 0.1$ MPa)

x_2^0	$\Delta G_m/\text{KJ} \cdot \text{mol}^{-1}$	$\Delta S_m/\text{J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$	$\Delta H_m/\text{KJ} \cdot \text{mol}^{-1}$
$T = 283.15$ K			
0.10	−2.6382	1.9250	−2.0931
0.20	−3.7727	2.6575	−3.0203
0.30	−4.2854	3.6152	−3.2617
0.40	−4.4239	4.5022	−3.1491
0.50	−4.2955	5.1145	−2.8473
0.60	−3.9529	5.3392	−2.4411
0.70	−3.4166	5.1022	−1.9719
0.80	−2.6865	4.3555	−1.4532
0.90	−1.7552	3.0480	−0.8922
$T = 288.15$ K			
0.10	−2.6309	1.9623	−2.0655
0.20	−3.7716	2.6427	−3.0101
0.30	−4.2973	3.6283	−3.2518
0.40	−4.4444	4.5279	−3.1397
0.50	−4.3248	5.1527	−2.8400
0.60	−3.9839	5.3706	−2.4364
0.70	−3.4524	5.1350	−1.9728
0.80	−2.7305	4.3911	−1.4652
0.90	−1.7920	3.0808	−0.9043
$T = 293.15$ K			
0.10	−2.6221	2.1797	−1.9831
0.20	−3.7731	2.9006	−2.9228
0.30	−4.3106	3.8177	−3.1915
0.40	−4.4663	4.6388	−3.1065
0.50	−4.3528	5.2099	−2.8255
0.60	−4.0185	5.4026	−2.4347
0.70	−3.4902	5.1532	−1.9795
0.80	−2.7741	4.4113	−1.4809
0.90	−1.8315	3.1115	−0.9193
$T = 298.15$ K			
0.10	−2.6170	2.3057	−1.9296
0.20	−3.7760	3.0248	−2.8741
0.30	−4.3243	3.9163	−3.1567
0.40	−4.4898	4.7131	−3.0846
0.50	−4.3835	5.2621	−2.8146
0.60	−4.0543	5.4389	−2.4327
0.70	−3.5297	5.1807	−1.9851
0.80	−2.8141	4.4365	−1.4914
0.90	−1.8737	3.1482	−0.9351
$T = 303.15$ K			
0.10	−2.6130	2.4263	−1.8775
0.20	−3.7810	3.1525	−2.8254
0.30	−4.3403	4.0228	−3.1208
0.40	−4.5152	4.7926	−3.0623
0.50	−4.4169	5.3208	−2.8039
0.60	−4.0932	5.4797	−2.4320
0.70	−3.5718	5.2105	−1.9923
0.80	−2.8571	4.4640	−1.5038
0.90	−1.9200	3.1901	−0.9529
$T = 308.15$ K			
0.10	−2.6129	2.5611	−1.8236
0.20	−3.7876	3.2810	−2.7766
0.30	−4.3564	4.1243	−3.0855
0.40	−4.5414	4.8735	−3.0396
0.50	−4.4494	5.3752	−2.7931
0.60	−4.1331	5.5209	−2.4318
0.70	−3.6177	5.2434	−2.0019
0.80	−2.9038	4.4940	−1.5190
0.90	−1.9723	3.2383	−0.9744
$T = 313.15$ K			
0.10	−2.6138	2.6902	−1.7713
0.20	−3.7960	3.4116	−2.7277
0.30	−4.3730	4.2241	−3.0503
0.40	−4.5690	4.9574	−3.0166
0.50	−4.4844	5.4357	−2.7822
0.60	−4.1735	5.5629	−2.4315
0.70	−3.6642	5.2761	−2.0120
0.80	−2.9520	4.5257	−1.5348
0.90	−2.0327	3.2981	−0.9999

Notes to Table 12

ΔG_m , ΔS_m and ΔH_m are calculated by Eq. (13). The mixing parameters reported in the table are per mole of total mixture. The relative standard uncertainty in mole fraction of methanol (2) in the binary mixed solvent systems is $u_r(x_2^0) = 0.0001$. The expanded uncertainties are $U(\Delta G_m) = 0.07\Delta G_m$, $U(\Delta S_m) = 0.07\Delta S_m$ (0.95 level of confidence).

mentioned in Section 3.2. The γ_i in the binary mixed solvent systems can be expressed as:

$$\ln \gamma_i = (G_{ji}x_j + G_{kj}x_k)(\tau_{ji}G_{ji}x_j + \tau_{ki}G_{ki}x_k) / (x_i + x_jG_{ji} + x_kG_{ki})^2 \\ + [\tau_{ij}G_{ij}x_j^2 + G_{ij}G_{kj}x_jx_k(\tau_{ij} - \tau_{kj})] / (x_j + x_iG_{ij} + x_kG_{kj})^2 \quad (27) \\ + [\tau_{ik}G_{ik}x_k^2 + G_{ik}G_{jk}x_jx_k(\tau_{ik} - \tau_{jk})] / (x_k + x_iG_{ik} + x_jG_{jk})^2$$

where 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 the model parameters. Their definition is as same as the counterparts in Section 3.2. The binary NRTL parameters can be used for the ternary system prediction, especially in the vapor–liquid equilibria systems [29–31]. However, a considerable deviation often exists in solid–liquid equilibrium when using this way to predict the solubility for the ternary system's complexity [32–35]. In order to avoid that deviation, people even developed some revised NRTL equation like NRTL-SAC model to predict ternary solubility depending on the binary parameters to eliminate error as far as possible [34,35]. Here, we tried to predict the solubility for the ternary systems using the binary NRTL parameters. However, the ARDs were both higher than 20%, which revealed that it was not suitable here to predict the ternary solubility by the binary system parameters in these systems. So, we correlated the solubility data using parameters came from ternary systems for their good correlated results. The optimized fitting model parameters were listed in Table 11.

3.5. The thermodynamic properties of mixing in binary mixed solvent systems

The thermodynamic properties of the mixing process in the two binary mixed solvent systems were calculated by Eq. (13) and represented in Tables 12 and 13 respectively. It can be seen that $\Delta G_m < 0$ and $\Delta S_m > 0$ in both solution systems with binary solvents, indicating that the mixing process in the two binary mixed solvent systems (methanol + ethanol) and (methanol + isopropanol) is spontaneous and entropically favorable. What's more, the mixing processes are both exothermic because of the negative values of the ΔH_m .

4. Conclusions

In this work, under the atmospheric pressure (0.1 MPa), the solubility of metamizol monohydrate in four pure solvents (methanol, ethanol, *n*-propanol and isopropanol) and two binary mixed solvent systems (methanol + ethanol) and (methanol + isopropanol) were measured by gravimetric method from 283.15 K to 313.15 K.

In four pure solvents, the solubility increases with the increasing of the temperature. What's more, under a constant temperature, the dissolving capacity of these solvents corresponded with the polarity order which is methanol > ethanol > *n*-propanol > isopropanol. The modified Apelblat equation and the NRTL model are verified that both have the ability to correlate the experimental solubility of metamizol monohydrate with the low ARD values. The second model also can be used to predict the thermodynamic properties in the four pure solvents.

In the binary mixed solvent systems, the solubility of metamizol monohydrate also shows temperature dependence just like that in the pure solvents. In addition, at a given temperature, the solubility of the metamizol monohydrate is mainly influenced by the different solvent components of the binary solvents. What's more, the results show that the experimental data can be well correlated by several classical models,

Table 13

The mixing thermodynamic properties of metamizol monohydrate in binary solvent mixtures (methanol + isopropanol) from 283.15 K to 313.15 K ($P = 0.1$ MPa)

x_2^0	$\Delta G_m/\text{kJ} \cdot \text{mol}^{-1}$	$\Delta S_m/\text{J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$	$\Delta H_m/\text{kJ} \cdot \text{mol}^{-1}$
<i>T</i> = 283.15 K			
0.10	−2.6399	1.9214	−2.0958
0.20	−3.7741	2.6560	−3.0221
0.30	−4.2863	3.6121	−3.2636
0.40	−4.4244	4.5010	−3.1499
0.50	−4.2956	5.1134	−2.8478
0.60	−3.9527	5.3378	−2.4413
0.70	−3.4161	5.1009	−1.9718
0.80	−2.6859	4.3540	−1.4531
0.90	−1.7548	3.0464	−0.8923
<i>T</i> = 288.15 K			
0.10	−2.6324	2.0667	−2.0369
0.20	−3.7730	2.7736	−2.9738
0.30	−4.2982	3.7146	−3.2279
0.40	−4.4448	4.5667	−3.1289
0.50	−4.3249	5.1633	−2.8371
0.60	−3.9837	5.3665	−2.4374
0.70	−3.4520	5.1254	−1.9751
0.80	−2.7301	4.3822	−1.4674
0.90	−1.7919	3.0769	−0.9052
<i>T</i> = 293.15 K			
0.10	−2.6236	2.1811	−1.9842
0.20	−3.7745	2.8973	−2.9252
0.30	−4.3114	3.8137	−3.1935
0.40	−4.4668	4.6378	−3.1073
0.50	−4.3528	5.2083	−2.8260
0.60	−4.0182	5.4009	−2.4349
0.70	−3.4899	5.1517	−1.9796
0.80	−2.7737	4.4100	−1.4809
0.90	−1.8311	3.1097	−0.9195
<i>T</i> = 298.15 K			
0.10	−2.6182	2.3016	−1.9320
0.20	−3.7772	3.0226	−2.8760
0.30	−4.3251	3.9139	−3.1582
0.40	−4.4902	4.7107	−3.0857
0.50	−4.3836	5.2608	−2.8151
0.60	−4.0541	5.4373	−2.4330
0.70	−3.5293	5.1794	−1.9851
0.80	−2.8138	4.4352	−1.4915
0.90	−1.8736	3.1469	−0.9353
<i>T</i> = 303.15 K			
0.10	−2.6142	2.4271	−1.8784
0.20	−3.7822	3.1498	−2.8273
0.30	−4.3412	4.0192	−3.1228
0.40	−4.5156	4.7905	−3.0633
0.50	−4.4169	5.3187	−2.8046
0.60	−4.0928	5.4781	−2.4321
0.70	−3.5716	5.2093	−1.9924
0.80	−2.8568	4.4624	−1.5040
0.90	−1.9198	3.1879	−0.9534
<i>T</i> = 308.15 K			
0.10	−2.6142	2.5609	−1.8251
0.20	−3.7888	3.2776	−2.7788
0.30	−4.3573	4.1225	−3.0869
0.40	−4.5419	4.8720	−3.0406
0.50	−4.4496	5.3734	−2.7938
0.60	−4.1329	5.5196	−2.4321
0.70	−3.6172	5.2415	−2.0021
0.80	−2.9035	4.4924	−1.5191
0.90	−1.9721	3.2368	−0.9747
<i>T</i> = 313.15 K			
0.10	−2.6149	2.6876	−1.7733
0.20	−3.7972	3.4091	−2.7296
0.30	−4.3738	4.2209	−3.0520
0.40	−4.5693	4.9542	−3.0179
0.50	−4.4845	5.4330	−2.7831
0.60	−4.1732	5.5604	−2.4319
0.70	−3.6638	5.2741	−2.0122
0.80	−2.9518	4.5238	−1.5352
0.90	−2.0323	3.2957	−1.0003

Notes to Table 13

ΔG_m , ΔS_m and ΔH_m are calculated by Eq. (13). The mixing parameters reported in the table are per mole of total mixture. The relative standard uncertainty in mole fraction of methanol (2) in the binary mixed solvent systems is $u_r(x_2^0) = 0.0001$. The expanded uncertainties are $U(\Delta G_m) = 0.07\Delta G_m$, $U(\Delta S_m) = 0.07\Delta S_m$ (0.95 level of confidence).

like the modified Apelblat equation, the CNIBS/R-K equation, the Hybrid model and the NRTL model.

Furthermore, the thermodynamic properties of the mixing process in four pure solvents and two binary mixed solvent systems were all obtained by NRTL model in order to get a deep understanding about the solubility. It turns out that the mixing process of metamizol monohydrate in all tested solvent systems is always spontaneous and entropically favorable, which has instructional function to the further study about the crystallization of metamizol monohydrate.

Nomenclature

A, B, C	empirical parameter for the modified Apelblat equation
A_i ($i = 1-9$)	empirical parameters for Jouyban-Acree equation
ARD	average absolute deviation between experimental and calculated solubility
a_{ij}	the adjustable empirical constant for the NRTL model
B_i ($i = 1-5$)	empirical parameters for CNIBS/R-K equation
G^E	excess Gibbs energy of solution, $J \cdot mol^{-1}$
ΔG_m	the mixing Gibbs energy of solution, $J \cdot mol^{-1}$
ΔG_m^{id}	the mixing Gibbs energy of ideal solution, $J \cdot mol^{-1}$
ΔG_{ij}	parameters for the NRTL model, $J \cdot mol^{-1}$
H^E	excess enthalpy of solution, $J \cdot mol^{-1}$
ΔH_m	the mixing enthalpy of solution, $J \cdot mol^{-1}$
ΔH_m^{id}	the mixing enthalpy of ideal solution, $J \cdot mol^{-1}$
M_1	the molecular mass of metamizol monohydrate, $g \cdot mol^{-1}$
M_2	the respective molecular mass of pure solvents (methanol, ethanol, <i>n</i> -propanol and isopropanol), $g \cdot mol^{-1}$
M_3	the respective molecular mass of the second solvent in binary mixed solvent systems (ethanol or isopropanol), $g \cdot mol^{-1}$
m_1	the mass of metamizol monohydrate, g
m_2	the mass of pure solvents (methanol, ethanol, <i>n</i> -propanol and isopropanol), g
m_3	the mass of the second solvent in binary mixed solvent systems (ethanol or isopropanol), g
N	number of experimental points in each system
p	pressure, MPa
R	gas constant, $J \cdot mol^{-1} \cdot K^{-1}$
S^E	excess entropy of solution, $J \cdot mol^{-1} \cdot K^{-1}$
ΔS_m	the mixing entropy of solution, $J \cdot mol^{-1} \cdot K^{-1}$
ΔS_m^{id}	the mixing entropy of ideal solution, $J \cdot mol^{-1} \cdot K^{-1}$
T	absolute temperature, K
x_1	experimental solubility of the solute, $mol \cdot mol^{-1}$
x_2^0	the initial mole fraction of methanol in the binary mixed solvent systems, $mol \cdot mol^{-1}$
γ_i	the activity coefficient at equilibrium

References

- G.B. Golubitskii, A.V. Kostarnoi, E.V. Budko, V.M. Ivanov, E.M. Basova, Decomposition of Analgin in aqueous acetonitrile solutions, *J. Anal. Chem.* 61 (10) (2006) 997–1001.
- W.O. Mar, J.U. Irich, Solid liquid equilibrium, metastable zone, and nucleation parameters of the oxalic acid–water system, *Cryst. Growth Des.* 6 (8) (2006) 1927–1930.
- H. Wu, L. Dang, H. Wei, Solid–liquid phase equilibrium of nicotinamide in different pure solvents: measurements and thermodynamic modeling, *Ind. Eng. Chem. Res.* 53 (2014) 1707–1711.
- D. Jia, X. Zhang, J. Li, C. Li, Measurement and correlation of the solubility of N-(phosphonomethyl)iminodiacetic acid in different organic solvents, *Fluid Phase Equilib.* 382 (2014) 54–58.
- G. Wang, Y. Wang, X. Hu, Y. Ma, H. Hao, Determination and correlation of cefoperazone solubility in different pure solvents and binary mixture, *Fluid Phase Equilib.* 361 (2014) 223–228.
- Z. Chen, J. Z. X. L. S. M, Solubility measurement and correlation of the form A of ibuprofen in organic solvents from 278.15 to 323.15 K, *J. Chem. Thermodyn.* 103 (2016) 342–348.
- H. Wang, Y. Wang, G. Wang, J. Zhang, H. Hao, Q. Yin, Solid–liquid equilibrium of sulbactam in pure solvents and binary solvent mixtures, *Fluid Phase Equilib.* 382 (2014) 197–204.
- Y. Wang, Q. Yin, X. Sun, Y. Bao, J. Gong, B. Hou, Y. Wang, M. Zhang, C. Xie, H. Hao, Measurement and correlation of solubility of thiourea in two solvent mixtures from $T = (283.15 \text{ to } 313.15) \text{ K}$, *J. Chem. Thermodyn.* 94 (2016) 110–118.
- D. Han, X. Li, H. Wang, Determination and correlation of pyridoxine hydrochloride solubility in different binary mixtures at temperatures from (278.15 to 313.15) K, *J. Chem. Thermodyn.* 94 (2016) 138–151.
- P. Cui, Q. Yin, J. Gong, Solubility of candesartan cilexetil in different solvents at various temperatures, *J. Chem. Eng. Data* 56 (3) (2011) 658–660.
- X. Yang, X. Wang, C. Ching, Solubility of form α and form γ of glycine in aqueous solutions, *J. Chem. Eng. Data* 53 (5) (2008) 1133–1137.
- Y. Yin, Y. Bao, Z. Gao, Solubility of cefotaxime sodium in ethanol + water mixtures under acetic acid conditions, *Chem. Eng. Data* 59 (6) (2014) 1865–1871.
- T.P. Singh, T.N. Bhat, M. Vijayan, Crystallization and crystal data of acetaminophen and metamizol, *Curr. Sci. India* 42 (11) (1973) 384.
- J. Marrero, R. Gani, Group-contribution based estimation of pure component properties, *Fluid Phase Equilib.* 183 (2001) 183–208.
- I.M. Smallwood, Handbook of Organic Solvent Properties, Halsted Press, London, 1996.
- C. Reichardt, T. Welton, Solvents and Solvent Effects in Organic Chemistry, John Wiley & Sons, New York, 2011.
- A. Apelblat, E. Manzurola, Solubilities of o-acetylsalicylic, 4-aminosalicylic, 3,5-dinitrosalicylic, and p-toluic acid, and magnesium-DL-aspartate in water from $T = (278 \text{ to } 348) \text{ K}$, *J. Chem. Thermodyn.* 31 (1999) 85–91.
- A. Apelblat, E. Manzurola, Solubilities of L-glutamic acid, 3-nitrobenzoic acid, p-toluic acid, calcium-L-lactate, calcium gluconate, magnesium-DL-aspartate, and magnesium-L-lactate in water, *J. Chem. Thermodyn.* 34 (2002) 1127–1136.
- A. Xu, R. Xu, J. Wang, Solubility determination and thermodynamic modelling of terephthalaldehyde in ten organic solvents from $T = (273.15 \text{ to } 318.15) \text{ K}$ and mixing properties of solutions, *J. Chem. Thermodyn.* 102 (2016) 188–198.
- J. Xu, S. Han, Y. Cong, Thermodynamic functions of 1-methyl-4-(methylsulfonyl)benzene solubility in nine organic solvents from $T = (278.15 \text{ to } 318.15) \text{ K}$, *J. Chem. Thermodyn.* 103 (2016) 234–243.
- H. Renon, J. Prausnitz, Local compositions in thermodynamic excess functions for liquid mixtures, *AIChE* 14 (1968) 135–144.
- M.A. Ruidiaz, D.R. Delgado, F. Martínez, Y. Marcus, Solubility and preferential solvation of indomethacin in 1,4-dioxane + water solvent mixtures, *Fluid Phase Equilib.* 299 (2010) 259–265.
- J.M. Smith, H.C.V. Ness, M.M. Abbott, Introduction to Chemical Engineering Thermodynamics, McGraw-Hill, New York, 2001.
- S.M. Walas, Phase Equilibria in Chemical Engineering, Butterworth–Heinemann, New York, 1985.
- A.J.Q. Parker, The effects of solvation on the properties of anions in dipolar aprotic solvents, *Rev. Chem. Soc.* 16 (2) (1962) 163–187.
- W.E. Acree Jr, Mathematical representation of thermodynamic properties: Part 2. Derivation of the combined nearly ideal binary solvent (NIBS)/Redlich-Kister mathematical representation from a two-body and three-body interactional mixing model, *Thermochim. Acta* 198 (1992) 71–79.
- Y. Hu, Y. Kai, Z. Cao, J. Li, W. Yang, Measurement and correlation solubility and mixing properties of dimethyl succinylsuccinate in pure and mixture organic solvents from (278.15 to 333.15) K, *Fluid Phase Equilib.* 354 (2013) 259–264.
- D.R. Delgado, G.A. Rodríguez, A.R. Holguín, F. Martínez, A. Jouyban, Solubility of sulfapyridine in propylene glycol + water mixtures and correlation with the Jouyban–Acree model, *Fluid Phase Equilib.* 341 (2013) 86–95.
- K. Kurihara, M. Nakamichi, K. Kojima, Isobaric vapor–liquid equilibria for methanol + ethanol + water and the three constituent binary systems, *J. Chem. Eng. Data* 38 (1993) 446–449.
- K. Bitchikh, A.H. Meniai, W. Louaer, Measurement and prediction of binary and ternary liquid–solid equilibria of pharmaceutical and food systems, *Energy Procedia* 18 (2) (2012) 1152–1164.
- J. Wang, Z. Bao, Investigation on vapor–liquid equilibrium for 2-propanol + 1-butanol + 1-pentanol at 101.3 kPa, *Fluid Phase Equilib.* 341 (2013) 30–34.
- H. Lin, Y. Chou, F. Wu, M. Lee, Solid–liquid equilibria of closely boiling compounds of 4-methoxyphenol and catechol with p-cresol, *Fluid Phase Equilib.* 220 (2004) 71–76.
- A. Arce, M. Blanco, J.M. Ageitos, I. Vidal, Analysis of the relationship between ternary mixtures and their binary sub-systems as represented by the UNIQUAC and NRTL models, *Thermochim. Acta* 261 (1995) 59–68.
- C. Chen, Y. Song, Solubility modeling with a nonrandom two-liquid segment activity coefficient model, *Ind. Eng. Chem. Res.* 43 (26) (2004) 8354–8362.
- P.B. Kokitkar, E.C. Plocharczyk, C. Chen, Modeling drug molecule solubility to identify optimal solvent systems for crystallization, *Org. Process Res. Dev.* 12 (2) (2008) 249–256.