Solubility of cefoxitin acid in different solvent systems

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ABSTRACT: Cefoxitin acid is one kind of important pharmaceutical intermediate. Its solubility is crucial for designing and optimizing the crystallization processes. In this work, the solubility of cefoxitin acid in organic solvents (methanol, acetonitrile, ethanol, isopropanol, n-propanol and ethyl acetate), water and water-methanol mixtures was measured spectrophotometrically using a shake-flask method within the temperature range 278.15 K to 303.15 K. PXRD data and the Karl Fischer method were used to verify the crystal form stability of cefoxitin acid in the solubility measuring process. The melting points, the enthalpy and entropy of fusion were estimated. Results showed that the solubility of cefoxitin acid increases with the increasing temperature in all tested solvents in this work, and the solubility of

cefoxitin acid increases with the increasing methanol concentration in water-methanol mixtures. The experimental solubility values were well correlated using the modified Apelblat equation, NRTL model and CNIBS/R-K model. An equation proposed by Williamson was adopted to calculate the molar enthalpy during the dissolution process.

Keywords: cefoxitin acid; anhydrate; hydrate; solubility; dissolution enthalpy

1. Introduction

Cefoxitin acid ((6R)-3-carbamoyloxymethyl-7c-methoxy-8-oxo-7t-(2-thiophen-2-yl-acetylamino)-(6rH-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid, CAS No. 35607-66-0) (figure1) is a semi-synthetic cephamycin and possesses important biochemical characteristics that are not found in other β -lactam antibiotics due to its 7c-methoxyl group [1,2]. It is also an important intermediate for the production of cefoxitin sodium in the pharmaceutical industry. Since the quality of cefoxitin acid is largely affected by the purification and crystallization process, it is crucial to develop and design an optimized crystallization process for cefoxitin. Therefore, a knowledge of the solubility which is essential for crystallization process design needs to be determined [3,4]. However, solubility of cefoxitin acid in various solvents at different temperatures has not been reported until now.

In this work, the solubility of cefoxitin acid in methanol, acetonitrile, ethanol,

isopropanol, n-propanol, ethyl acetate, water and water-methanol mixtures was determined from 278.15 K to 308.15 K by ultraviolet spectrophotometry (UV) under atmospheric pressure.

2. Experimental

2.1. Materials

Cefoxitin acid monohydrate (0.995 mass fraction purity) was supplied by Hebei Huamin Pharmaceutical Co., Ltd. of China. The water content of the purchased cefoxitin acid monohydrate was determined to be (4.12 ± 0.2) mass % with a V20 Volumetric Karl Fischer Titrator from Mettler Toledo. Cefoxitin acid anhydrate was prepared by anti-solvent crystallization in water-methanol mixtures, using the aforementioned cefoxitin acid hydrate as raw material. Cefoxitin acid hydrate (2.4 g) was completely dissolved with 50 mL methanol in a glass jacketed crystallizer with agitation at 300 rpm and temperature of 283.15 K. Water (60 mL) was added to the solution with dosing rate of $1 \text{ mL} \cdot \text{min}^{-1}$. The product was filtered and washed with water for several times, and finally dried at 303.15 K for 24 h in a vacuum oven. The identification of the product obtained was confirmed to be anhydrous cefoxitin acid by PXRD analysis. The mass fraction purity of cefoxitin acid anhydrate is above 0.998 which was determined by high performance liquid chromatography (HPLC) (Agilent 1200 Series system, U.S.A.). The water content of cefoxitin acid anhydrate was determined to be (0.20 ± 0.2) mass %. The organic solvents (methanol, acetonitrile, ethanol, isopropanol, 1-propanol and ethyl acetate) used in this study are

analytical reagent. Water for all experiments was purchased from Nankai University, China. The conductivity of the used water was $0.055\ \mu\text{S}\cdot\text{cm}^{-1}$. All the solvents were used without further purification or prior treatment. More details of the materials are listed in table 1.

2.2. Characterization of cefoxitin acid anhydrate and its hydrate

Cefoxitin acid anhydrate and its hydrate were characterized by the powder X-ray diffraction (PXRD), Tabletop microscopy, Thermo Gravimetric Analyzer and Differential Scanning Calorimetry Synchronous Analyzer (TGA/DSC), and Raman spectroscopy. The PXRD was obtained by using Cu K α radiation ($1.54\times 10^{-8}\ \text{cm}$) on a Rigaku D/max-2500 (Rigaku, Japan). The analyses were carried out over a 2-theta range of (2–40) ° at a step size of 0.02 °, a voltage of 40 kV, and an electric current of 100 mA. The crystal habits were observed using a Tabletop Microscope (TM3000, HITACHI, Japan). The thermal analysis experiment was carried out by using a TGA/DSC simultaneous thermal analyser (Model TGA/DSC 1, Mettler-Toledo, Switzerland), which was carried out with a heating rate of $10\ \text{K}\cdot\text{min}^{-1}$ under the protection of nitrogen. The Raman spectra were collected with a Kaiser RamanRXN2 Hybrid System from Kaiser Optical System, Inc. The P^hAT probe was used to *ex situ* collect the Raman spectra of cefoxitin acid anhydrate and its hydrate.

2.3. Solubility measurements

The solubility of cefoxitin acid was measured by a shake-flask method. The measurements were carried out in a METTLER TOLEDO EasyMaxTM 102

Workstation (hereinafter referred to as EasyMaxTM). The EasyMaxTM can be used to perform multiple solubility experiments since it has 6 heavy walled borosilicate glass tubes (volume of 25 mL). A magnetic stir bar was used to mix the solution. A type *T* thermocouple was used for monitoring the temperature inside the glass tubes with a resolution of 0.05 K. For the methanol-water mixtures (0.1013, 0.2011, 0.2933, 0.4020, 0.5003, 0.5993 mole fraction of methanol, $x_0 \geq 2$), prior to the solubility experiments, the solvent mixtures were prepared using an analytical balance with a resolution of 0.0001 g. During the solubility experiments, 10 mL of the solvents (pure solvents or any of the aqueous mixtures) and excess solute (1 g, cefoxitin acid anhydrate or its hydrate) were poured into the corresponding glass tube of the EasyMaxTM. Once the tube was carefully capped to avoid evaporation, the solute-solvent mixture was continuously agitated at 300 rpm at constant temperature. Time of agitation was preliminarily determined by measuring the concentration of the solute at different time intervals (from 4h to 8h). Eight hours were proven to be enough to reach the solid-liquid equilibrium. After 8 h agitation, the saturated solution was kept static for 1h at the same temperature, allowing suspended solids to settle down. Then, about 1 mL sample was taken from the supernatant solution to a volumetric flask with a preheated micropipette and quickly weighted using the analytical balance. The withdrawn cefoxitin acid organic saturated solutions were diluted with corresponding organic solvent while the cefoxitin acid methanol aqueous saturated solutions were diluted with phosphate buffer to an appropriate concentration for UV analysis. Absorbance of standard solutions and samples were determined at

262 nm by an U-3010 UV–VIS Spectrophotometer (Hitachi High-technologies Co., Tokyo, Japan). The true absorbance at 262 nm was obtained by applying a suitable baseline correction and solvent deduction [5,6].

The mole fraction solubility of cefoxitin acid in organic solvent was obtained from Eq.(1).

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

where x_1 is the mole fraction solubility of cefoxitin acid, m_1 and M_1 are the mass and molar mass of cefoxitin acid, respectively; m_2 and M_2 are the mass and molar mass of the solvent, respectively.

The mole fraction solubility of cefoxitin acid in water and methanol-water mixtures was obtained from Eq.(2).

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

where x_1 is the mole fraction solubility of cefoxitin acid, m_1 , m_2 , and m_3 are the mass of cefoxitin acid, methanol and water, respectively. M_1 , M_2 and M_3 are the molar mass of cefoxitin acid, methanol and water, respectively. The value of m_3 includes the initial water mass and additional water mass from the dissolved hydrate.

Each experiment was performed three times and the average value was used to calculate the solubility. The residual powder of solute were filtered, dried and then analysed by PXRD and Karl Fischer titration.

3. Models for solubility of cefoxitin acid

3.1. The modified Apelblat equation

The experimental solubility values can be correlated as a function of temperature by the modified Apelblat equation, an extensively used semi-empirical model as following [7].

$$\ln x_1 = A + \frac{B}{T / K} + C \ln(T / K) \quad (3)$$

where x_1 and T represent the mole fraction of the solute and the temperature of the solution, respectively. A , B , C are the parameters of the modified Apelblat equation, which can be obtained by using a non-linear regression method.

3.2. NRTL model

The local composition models are widely applied to calculate the fugacity coefficients of solute in the solid-liquid equilibrium. A general simplified equation, which can be deduced from literature, is described in Eq.(4) [8].

$$\ln x_1 = \frac{\Delta H_m}{R} \left(\frac{1}{T_m} - \frac{1}{T} \right) - \ln \gamma_1 \quad (4)$$

where x_1 and T represent the mole fraction of the solute and the temperature of the solution, respectively; R is the gas constant; ΔH_m and T_m stand for the melting enthalpy and melting temperature, respectively; γ_1 represents the activity coefficient of cefoxitin acid in the solvent. The activity coefficient of the solute calculated by NRTL

model in the pure solvents or methanol-water mixtures can be obtained from the following equation.

$$\ln \gamma_i = \frac{(G_{ji}x_j + G_{kj}x_k)(\tau_{ji}G_{ji}x_j + \tau_{ki}G_{ki}x_k)}{(x_i + G_{ji}x_j + x_k G_{ki}x_k)^2} \quad (5)$$

$$+ \frac{\tau_{ij}G_{ij}x_j^2 + G_{ij}G_{kj}x_jx_k(\tau_{ij} - \tau_{kj})}{(x_j + x_iG_{ij} + x_kG_{kj})^2}$$

$$+ \frac{\tau_{ik}G_{ij}x_j^2 + G_{ij}G_{kj}x_jx_k(\tau_{ik} - \tau_{jk})}{(x_k + x_iG_{ik} + x_jG_{jk})^2}$$

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

$$G_{ij} = \exp(-\alpha_{ij}\tau_{ij}) \quad \tau_{ij} = \frac{(g_{ij} - g_{jj})}{RT} = \frac{\Delta g_{ij}}{RT}$$

$$G_{ik} = \exp(-\alpha_{ik}\tau_{ik}) \quad \tau_{ik} = \frac{(g_{ik} - g_{kk})}{RT} = \frac{\Delta g_{ik}}{RT}$$

$$G_{ji} = \exp(-\alpha_{ji}\tau_{ji}) \quad \tau_{ji} = \frac{(g_{ji} - g_{ii})}{RT} = \frac{\Delta g_{ji}}{RT}$$

$$G_{jk} = \exp(-\alpha_{jk}\tau_{jk}) \quad \tau_{jk} = \frac{(g_{jk} - g_{kk})}{RT} = \frac{\Delta g_{jk}}{RT}$$

$$G_{ki} = \exp(-\alpha_{ki}\tau_{ki}) \quad \tau_{ki} = \frac{(g_{ki} - g_{ii})}{RT} = \frac{\Delta g_{ki}}{RT}$$

$$G_{kj} = \exp(-\alpha_{kj}\tau_{kj}) \quad \tau_{kj} = \frac{(g_{kj} - g_{jj})}{RT} = \frac{\Delta g_{kj}}{RT} \quad (6)$$

where Δg_{ij} , Δg_{ik} , Δg_{ji} , Δg_{jk} , Δg_{ki} , and Δg_{kj} represent the cross interaction energy parameters which are independent of the composition and temperature. The

non-random parameters α_{ij} , α_{ik} , α_{ji} , α_{jk} , α_{ki} and α_{kj} are empirical constants ($\alpha_{ij} = \alpha_{ji}$, $\alpha_{ik} = \alpha_{ki}$, $\alpha_{jk} = \alpha_{kj}$), which generally varies between 0 and 1.

3.3. The CNIBS/R-K model

The CNIBS/R-K model, expressed by Eq. (7), is suggested to be one of the best models to correlate the solubility in binary solvent systems [9].

$$\ln x_1 = x_2^0 \ln(x_1)_2 + x_3^0 \ln(x_1)_3 + x_2^0 x_3^0 \sum_{i=1}^N S_i (x_2^0 - x_3^0)^i \quad (7)$$

where x_1 is the mole fraction solubility of solute, while x_2^0 and x_3^0 represent the initial mole fraction composition of methanol and water in methanol-water mixtures, respectively; $(x_1)_2$ and $(x_1)_3$ are the mole fraction solubility of cefoxitin acid in pure methanol and water respectively; S_i is the model constant.

For binary solvent system, when x_3^0 is replaced by $(1 - x_2^0)$ and $N = 2$ is used, a general single model can be obtained as Eq. (8).

$$\ln x_1 = B_0 + B_1 x_2^0 + B_2 (x_2^0)^2 + B_3 (x_2^0)^3 + B_4 (x_2^0)^4 \quad (8)$$

where B_0 , B_1 , B_2 , B_3 and B_4 are empirical parameters of the CNIBS/R-K model, which can be calculated by correlating the values of the experimental solubility.

4. Results and discussion

4.1. Identification and characterization of materials.

The PXRD patterns of cefoxitin acid anhydrate and its hydrate are shown in figure 2. It can be seen that cefoxitin acid anhydrate exhibit the characteristic peaks of 6.76°,

11.86°, 12.32°, 13.64°, 14.73°, 15.60°, 17.98°, 18.18°, 18.66°, 19.08°, 19.86°, 20.28°, 20.68°, 21.26°, 21.62°, 22.46° while the characteristic peaks of cefoxitin acid hydrate are at 12.42°, 13.32°, 16.27°, 17.04°, 18.86°, 19.64°, 20.00°, 22.76°, 24.54°, 25.00°, 25.92°, 26.20°, 26.96°, 27.86°, 29.72°. In addition, the morphology of these two forms of cefoxitin acid (figure 3) shows that the crystal habit of cefoxitin acid anhydrate is rod-like while the crystal habit of cefoxitin acid hydrate is prism-like.

The TG/DSC data of the two forms were determined and plotted in figure 4. From the TG/DSC curves, it can be seen that cefoxitin acid anhydrate shows an exothermic peak and quick mass decreasing at 447.93K (onset point 437.45 K), which should represent its decomposition since the melting process should be endothermic. For cefoxitin acid hydrate, an endothermic peak at 374.38 K (onset point 355.43 K) and an exothermic peak at 442.46 K (onset point 432.23 K) were observed, respectively. It can also be seen that the sample weight of cefoxitin acid hydrate declines continuously from 355.43 K until it reaches a constant. Then at about 432.23 K, the TG curve of cefoxitin acid hydrate declines sharply. The endothermic peak could be explained by the de-solvation of the solvent molecules in the crystal lattice and the exothermic peak should result from the decomposition of the dehydrated cefoxitin acid.

Furthermore, the *ex situ* Raman spectroscopy was also used to distinguish the differences between cefoxitin acid anhydrate and its hydrate. The characteristic peaks for these two forms are shown in figure 5. As shown in figure 5, there are some distinct differences between cefoxitin acid anhydrate and its hydrate. The peaks at

1716 cm⁻¹ and 1792 cm⁻¹ can be assigned as the characteristic peaks of cefoxitin acid anhydrate, while the peak at 1730 cm⁻¹ and 1754 cm⁻¹ can be assigned as the characteristic peaks of its hydrate. These differences can be used to distinguish them easily.

4.2. Melting properties

According to the study of Yalkowsky and Akash Jain [10-12], the enthalpy of melting ($\Delta_{\text{fus}}H$) can be estimated by additive group contributions.

$$\Delta_{\text{fus}}H = \sum n_i m_i + \sum n_j m_j \quad (9)$$

where n_i and n_j respectively represent the number of times that group i and proximity factor j appears in a compound, m_i and m_j are the contribution of group i and proximity factor j to the enthalpy of melting, respectively.

The melting entropy ($\Delta_{\text{fus}}S$) can be estimated by a semi-empirical equation with two non-additive molecular properties, rotational symmetry and flexibility. Bondi [13] has found that the melting entropy of a compound is the sum of its positional, rotational, and conformational components. On account of the very small volume change associated with melting process, the melting entropy of an organic molecule is primarily the contribution of its rotational and conformational entropies. Eq.(10) provides a method to estimate the entropy of melting.

$$\Delta_{\text{fus}}S / (\text{J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}) = 50 - 8.3124 \ln \sigma + 7.382\tau \quad (10)$$

where σ = rotational symmetry number, τ = flexibility number. They account for the changes in geometrical restriction that accompany the process of melting. Since the molecular structure of cefoxitin acid has no symmetry, the σ value of cefoxitin acid is 1. Dannenfelser [11] put forward that the flexibility number τ of a compound can be calculated using the following semi-empirical equation.

$$\tau = SP3 + 0.5SP2 + 0.5RING - 1 \quad (11)$$

where $SP3 = \Sigma \text{ Nonring (CH}_2, \text{CH, C, NH, N, O, S)}$, $SP2 = \Sigma \text{ Nonring (=CH, =C, =N, C=O)}$, $RING = \Sigma \text{ Independent single, fused, or conjugated aromatic ring systems}$. According to the structure of cefoxitin acid, the value of $SP3$, $SP2$ and $RING$ are 12, 10, 3, respectively.

By using the aforementioned method, the enthalpy and entropy of melting were estimated to be $71.58 \text{ kJ} \cdot \text{mol}^{-1}$ and $179.185 \text{ J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$, respectively. At the melting point, the Gibbs energy of transition is equal to zero and the melting temperature is estimated to be 399.475 K by the following Eq.(12).

$$T_{\text{fus}} = \Delta_{\text{fus}}H / \Delta_{\text{fus}}S \quad (12)$$

4.3 Solubility values

The UV calibration curves were obtained from the relationship between standard solution concentration and absorbance. For the standard solution, cefoxitin acid anhydrate was dissolved and diluted with the phosphate buffer (prepared by dissolving 1.0 g monobasic potassium phosphate and 1.8 g of anhydrous dibasic

sodium phosphate in water to make 1000 mL) or the organic solvents [5]. The function that relates the concentration of each solute with its absorbance was determined by fitting the absorbance data of standard solutions to a straight line. The calibration curves were shown in figure S1 of SUPPORTING INFORMATION. The values of the slope and intercept ([slope, intercept]) of calibration curves in methanol, ethanol, acetonitrile, ethyl acetate, isopropanol, n-propanol and phosphate buffer are determined to be [0.01676, 0.02354], [0.01579, 0.01432], [0.01559, -0.00964], [0.01535, 0.0069], [0.01475, 0.09179], [0.01449, 0.03107] and [0.02167, 0.00126] with $R^2=0.99909$, 0.99945, 0.99986, 0.99904, 0.99981, 0.99936 and 0.99925, respectively.

The PXRD patterns of the residual powder of cefoxitin acid in different solvents from $T=278.15$ K to $T=308.15$ K are given in figure S2 of SUPPORTING INFORMATION. As shown in figure 2 and figure S2, cefoxitin acid anhydrate was stable in pure organic solvent within the experimental temperature range. Cefoxitin acid hydrate was stable in pure water and water-methanol solvent mixtures when methanol mole fraction was less than 0.6. The water content of the residual cefoxitin acid crystal was determined via Karl Fischer titration, which was in accordance with the water content of the cefoxitin acid monohydrate.

The experimental solubility of cefoxitin acid in methanol, acetonitrile, ethanol, isopropanol, n-propanol, ethyl acetate are shown in figure 6 and table 2. It can be seen that the solubility of cefoxitin acid increases with rising temperature in all solvents investigated. At a given temperature, the order of cefoxitin acid anhydrate solubility is

methanol > ethanol $\approx$ acetonitrile > n-propanol $\approx$ isopropanol $\approx$ ethyl acetate. This phenomenon can be interpreted by hydrogen-bonding interaction and “like dissolves like” principle. According to the dielectric constant theory, the dielectric constant of solvent plays a very important role in solution, and the polarity of the material increases with the increasing of dielectric constant [14]. The order of the polarity of pure solvents used in this study is acetonitrile > methanol > ethanol > n-propanol > isopropanol > ethyl acetate. Three amides groups and one carboxyl group exist in the molecular structure of cefoxitin acid, which can act as H-bond donor and acceptor. Compared with methanol, acetonitrile has lower ability to form H-bond with cefoxitin acid and therefore has lower ability to dissolve cefoxitin acid. The solubility values of cefoxitin acid in water and water-methanol mixtures are shown in figure 7 and table 3. It is found that the solubility of cefoxitin acid increases as the mole fraction of methanol in the solvent mixture increases. This phenomenon can be explained by the fact that molecular interaction between cefoxitin acid and methanol molecules is stronger than the interaction between cefoxitin acid and water molecule. At the same composition of the binary solvent mixtures, the solubility of cefoxitin acid increases with increasing temperature. The solubility results can be used for designing and optimizing the process of crystallization of cefoxitin acid.

In this work, three thermodynamic models, including the modified Apelblat model, NRTL model and CNIBS/R-K model, were used to correlate the solubility of cefoxitin acid. The applicability of these models was evaluated by using the relative deviations (RD) and relative average deviations (ARD). The RD and ARD are defined as Eqs.

(13) and (14) [15].

$$RD = \frac{x_{1,i}^{\text{exp}} - x_{1,i}^{\text{cal}}}{x_{1,i}^{\text{exp}}} \quad (13)$$

$$ARD = \frac{1}{n} \sum_{i=1}^n \left| \frac{x_{1,i}^{\text{exp}} - x_{1,i}^{\text{cal}}}{x_{1,i}^{\text{exp}}} \right| \quad (14)$$

Here $x_{1,i}^{\text{exp}}$ and $x_{1,i}^{\text{cal}}$ are experimental solubility and calculated solubility, respectively; n is the number of experimental points. The calculated results of RD and ARD are shown in tables 2 to 8. The model parameters obtained for cefoxitin acid in the organic solvents are shown in tables 4 and 5 while the model parameters obtained for cefoxitin acid in water and water-methanol mixtures are shown in tables 6 to 8. From tables 2 to 8, it is found that the correlated results by the modified Apelblat equation, NRTL model and CNIBS/R-K model show good consistency with the experimental solubility with ARD values less than 8% and these models are all suitable for correlating the solubility of cefoxitin acid in the selected solvents. Obviously, the modified Apelblat equation can give better correlation results with ARD values less than 5%.

4.4. The calculation of dissolution enthalpy

Following the rigorous thermodynamic treatment of the solubility of solutes (electrolytes and nonelectrolytes) in solvents given by Williamson [16,17,18], the molar enthalpy of solution $\Delta_{\text{sol}}H$ can be determined by,

$$\Delta H_{\text{sol}} = \nu \left(1 - \frac{hm_1M_2}{1000}\right) RT^2 \left(\frac{dm_1}{dT}\right)_{\text{sat}} \left[\left(\frac{\partial \ln a_2}{\partial m_1} \right)_{T, \text{sat}} \right] \quad (15)$$

In this precise equation, $\Delta_{\text{sol}}H$ is the enthalpy absorbed per mole of solute dissolved in the nearly saturated solution, or the enthalpy evolved per mole on crystallisation. The ν denotes the total number of ions formed by one molecule of solute, and $\nu = 1$ is introduced for nonelectrolytes, h is the hydration number, m_1 is the molality of the solute, R is the gas constant and M_2 and a_2 are the molecular mass and activity of the solvent, respectively. In terms of experimentally available mean activity coefficients $\gamma_{\pm}$, Eq.(15) becomes,

$$\Delta H_{\text{sol}} = \nu \left(1 - \frac{hm_1M_2}{1000}\right) RT^2 \left(\frac{dm_1}{dT}\right)_{\text{sat}, T} \left[\left(\frac{\partial \ln \gamma_{\pm}}{\partial m_1} \right)_{\text{sat}, T} + \left(\frac{1}{m_1} \right)_{\text{sat}} \right] \quad (16)$$

In the case of nonelectrolytes, the mean activity coefficient is replaced by the activity coefficient of the solute (γ_1). Beside, $m_1 = \frac{1000x_1}{(1-x_1)M_2}$ (M_2 and x_1 are the molecular mass of the solvent and mole fraction of the solute, respectively) and, in the case of this work, $x_1 < 1$. Therefore, ΔH_{sol} can be calculated by

$$\Delta H_{\text{sol}} = \nu \left(1 - \frac{hx_1}{1-x_1}\right) RT^2 \left[\left(\frac{d \ln x_1}{dT} \right)_{\text{sat}} + \left(\frac{dx_1}{dT} \right)_{\text{sat}} \left(\frac{\partial \ln \gamma_1}{\partial x_1} \right)_{\text{sat}, T} \right] \quad (17)$$

For cefoxitin acid, $\nu = 1$. $h=0$ and 1 represents anhydrate and hydrate of cefoxitin acid, respectively. The terms $\left(\frac{d \ln x_1}{dT} \right)_{\text{sat}}$ and $\left(\frac{dx_1}{dT} \right)_{\text{sat}}$ can be calculated from Eq. (3) and $\left(\frac{\partial \ln \gamma_1}{\partial x_1} \right)_{\text{sat}, T}$ can be calculated by Eq. (5). The calculated results of $\Delta_{\text{sol}}H$ of the

dissolution process are listed in table 9 and table 10. It is found that the values of $\Delta_{\text{sol}}H$ are all positive in the solvents investigated, indicating that the dissolution process is endothermic.

5. Conclusions

The solubility of cefoxitin acid in six pure organic solvents (methanol, acetonitrile, ethanol, isopropanol, n-propanol and ethyl acetate), pure water and water-methanol mixtures was measured using a UV method within the temperature range 278.15 K to 303.15 K. The PXRD data and Karl Fischer method were used to verify the crystal form stability of cefoxitin acid in the solubility measuring process. The melting enthalpy was estimated from group contributions as $71.58 \text{ kJ}\cdot\text{mol}^{-1}$, whereas the melting entropy was estimated using a semi-empirical equation as $179.185 \text{ J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$. The melting temperature was calculated from the ratio of the enthalpy and entropy of melting as 399.475 K. Results shows that the solubility of cefoxitin acid increases with rising temperature in all solvents used in this work. The order of solubility of cefoxitin acid anhydrate is methanol > ethanol $\approx$ acetonitrile > n-propanol $\approx$ isopropanol $\approx$ ethyl acetate. This phenomenon can be interpreted by hydrogen-bonding interaction and “like dissolves like” principle. The solubility of cefoxitin acid in water and water-methanol mixtures increases with increasing methanol concentration. The modified Apelblat equation and NRTL model were used to correlate the experimental solubility values of cefoxitin acid in pure organic solvents while the CNIBS/R-K model was also utilized to correlate the solubility of cefoxitin acid in water and methanol-water solvents. All the selected thermodynamic models gave satisfactory correlation results. The dissolution enthalpy was precisely calculated by the equation put forward by Williamson.

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Figure captions:

Figure 1. Chemical structure of cefoxitin acid.

Figure 2. X-ray power diffraction pattern of cefoxitin acid anhydrate (a) and hydrate (b).

Figure 3. Microscope pictures of cefoxitin acid anhydrate (a) and its hydrate (b).

Figure 4. Thermal analysis (TGA/DSC) of cefoxitin acid. The TGA curves of cefoxitin acid anhydrate (a) and hydrate (b), and the DSC curves of cefoxitin acid anhydrate (c) and hydrate (d).

Figure 5 Raman spectra of cefoxitin acid anhydrate (red) and its hydrate (blue).

Figure 6. Experimental solubility values of cefoxitin acid in methanol (■), n-propanol (▼), isopropanol(◄), ethanol (►), acetonitrile(▲), ethyl acetate (●), Calculated solubilities with Eq.(3) for cefoxitin acid (solid line) are also included.

Figure 7. Experimental solubility values of cefoxitin acid in water (■) and water-methanol mixtures ($x_0 = 0.1013$ (●), 0.2011 (▲), 0.2933 (▼), 0.4020 (◄), 0.5003 (►), 0.5993 (◆)). Calculated solubility with Eq.(3) for cefoxitin acid in water and methanol-water mixtures (solid line) are also included.

Table headings:

Table 1 Provenance and mass fraction purity of cefoxitin acid and solvents.

Table 2 Experimental and correlated mole fraction solubility of cefoxitin acid (x_1^{exp} and x_1^{cal}) in methanol, acetonitrile, ethanol, isopropanol, n-propanol and ethyl acetate ($p = 0.1$ MPa).

Table 3 Experimental and correlated mole fraction solubility of cefoxitin acid (x_1^{exp} and x_1^{cal}) in water and (methanol + water) mixtures at different initial mole fractions of methanol (x_0) and different temperatures ($p = 0.1$ MPa).

Table 4 Parameters of the modified Apelblat equation for the solubility of cefoxitin

acid in methanol, acetonitrile, ethanol, isopropanol, n-propanol and ethyl acetate.

Table 5 Parameters of the NRTL model for the solubility of cefoxitin acid in methanol, acetonitrile, ethanol, isopropanol, n-propanol and ethyl acetate.

Table 6 Parameters of the modified Apelblat equation for the solubility of cefoxitin acid in water and (methanol + water) mixtures at different initial mole fractions of methanol (x_0 2).

Table 7 Parameters of the NRTL model for the solubility of cefoxitin acid in water and (methanol + water) mixtures.

Table 8 Parameters of the CNIBS/R-K model for the solubility of cefoxitin acid in water and (methanol + water) mixtures.

Table 9 Molar enthalpy ($\Delta_{\text{sol}}H$) of the cefoxitin acid dissolution process in methanol, acetonitrile, ethanol, isopropanol, n-propanol and ethyl acetate.

Table 10 Molar enthalpy ($\Delta_{\text{sol}}H$) of the cefoxitin acid dissolution process in water and (methanol + water) mixtures at different initial mole fractions of methanol (x_0 2).

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Table 1

Provenance and mass fraction purity of cefoxitin acid and solvents.^{a,b}

Chemicals	Mass purity	Method of Purification	Analysis method	Source
Cefoxitin acid monohydrate	≥ 0.995	None	HPLC ^a	Hebei Huamin Pharmaceutical Co., Ltd.
Cefoxitin acid anhydrate	≥ 0.998	None	HPLC ^a	Lab-Synthesis
Methanol	≥ 0.995	None	GC ^b	Tianjin Jiangtian Chemical Co., Ltd.
Ethanol	≥ 0.995	none	GC ^b	Tianjin Jiangtian Chemical Co., Ltd.
n-propanol	≥ 0.995	none	GC ^b	Tianjin Jiangtian Chemical Co., Ltd.
Isopropanol	≥ 0.995	none	GC ^b	Tianjin Jiangtian Chemical Co., Ltd.
Ethyl acetate	≥ 0.995	none	GC ^b	Tianjin Jiangtian Chemical Co., Ltd.
Acetonitrile	≥ 0.995	none	GC ^b	Tianjin Jiangtian Chemical Co., Ltd.

^aHigh-performance liquid chromatography;

^bGas-liquid chromatography.

Table 2

Experimental and correlated mole fraction solubilities of cefoxitin acid (x_1^{exp} and x_1^{cal}) in methanol, acetonitrile, ethanol, isopropanol, n-propanol and ethyl acetate ($p = 0.1$ MPa).^{a,b,c,d,e}

Apelblat	NRTL
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T/K	$10^4 x_1^{\text{exp}}$	$10^4 x_1^{\text{cal}}$	10^2RD	$10^4 x_1^{\text{cal}}$	10^2RD
Methanol					
278.15	56.46	55.60	1.5	59.48	-5.3
283.15	65.75	66.05	-0.45	66.84	-1.7
288.15	77.17	78.24	-1.4	76.50	0.87
293.15	91.94	92.43	-0.53	89.31	2.9
298.15	109.7	108.9	0.71	106.0	3.4
303.15	128.9	128.0	0.67	127.1	1.4
308.15	149.5	150.1	-0.42	153.8	-2.9
Ethyl acetate					
278.15	2.289	2.3	-0.49	2.386	-4.2
283.15	2.412	2.4	-0.064	2.396	0.65
288.15	2.571	2.5	1.3	2.464	4.2
293.15	2.668	2.7	-0.29	2.584	3.2
298.15	2.825	2.8	-0.087	2.762	2.3
303.15	2.964	3.0	-1.0	2.998	-1.1
308.15	3.198	3.2	0.62	3.305	-3.3
Acetonitrile					
278.15	4.521	4.6	-0.78	4.708	-4.1
283.15	4.914	4.9	0.57	4.895	0.39
288.15	5.278	5.3	0.10	5.189	1.7
293.15	5.795	5.7	1.2	5.605	3.3
298.15	6.206	6.2	-0.66	6.142	1.0
303.15	6.773	6.9	-1.2	6.830	-0.84
308.15	7.602	7.6	0.68	7.700	-1.3
n-propanol					
278.15	2.092	2.1	-0.86	2.073	0.88
283.15	2.534	2.5	2.8	2.400	5.3
288.15	2.858	2.9	-1.1	2.810	1.7
293.15	3.375	3.4	-0.81	3.325	1.5
298.15	3.935	4.0	-2.2	3.970	-0.90
303.15	4.917	4.8	3.0	4.786	2.7
308.15	5.613	5.7	-1.0	5.795	-3.2
Isopropanol					
278.15	0.440	0.5	-13	0.530	-21
283.15	0.719	0.7	-1.8	0.719	0.0088
288.15	1.094	1.0	4.7	0.975	11
293.15	1.508	1.4	4.9	1.322	12
298.15	1.858	1.9	-2.9	1.790	3.7
303.15	2.428	2.5	-1.9	2.420	0.30
308.15	3.138	3.1	0.9	3.268	-4.1
Ethanol					
278.15	4.034	4.0	1.6	4.180	-3.6
283.15	4.838	4.9	-2.0	5.012	-3.6

288.15	6.029	6.0	-0.16	5.992	0.60
293.15	7.389	7.3	1.4	7.146	3.3
298.15	8.521	8.7	-1.6	8.505	0.19
303.15	10.28	10.2	1.1	10.09	1.8
308.15	11.76	11.8	-0.31	11.96	-1.8

^aThe reported results were the average values of three determinations;

^bThe standard uncertainty of temperature is $u(T) = 0.03$ K;

^cThe relative standard uncertainty of the solubility measurement is $u_r(x_1) = 0.05$; the standard uncertainty of the pressure is $u(p) = 10$ kPa;

^dRD is the relative deviation;

^eThe residual solid phase of cefoxitin acid in the solubility experiments was anhydrous cefoxitin acid.

Table 3

Experimental and correlated mole fraction solubilities of cefoxitin acid (x_1^{exp} and x_1^{cal}) in water and (methanol + water) mixtures at different initial mole fractions of methanol ($x_0 = 2$) and different temperatures ($p = 0.1$ MPa).^{a,b,c,d,e,f}

T/K	$10\ x_2$	$10^5x_1^{\text{exp}}$	Apelblat		NRTL		CNIBS/R-K	
			$10^5x_1^{\text{cal}}$	10^2RD	$10^5x_1^{\text{cal}}$	10^2RD	$10^5x_1^{\text{cal}}$	10^2RD
Water								
278.15	0.0000	2.460	2.453	0.30	2.883	-17	1.893	23
283.15	0.0000	3.028	3.120	-3.0	3.780	-25	2.356	22
288.15	0.0000	4.025	3.991	0.85	4.930	-22	3.399	16
293.15	0.0000	5.127	5.130	-0.05	6.399	-25	4.132	19
298.15	0.0000	6.918	6.623	4.3	8.268	-20	5.723	17
303.15	0.0000	8.227	8.586	-4.4	10.64	-29	6.740	18
308.15	0.0000	11.29	11.17	1.0	13.62	-21	9.753	14
$x_0\ 2=0.1013$								
278.15	1.0129	5.674	5.613	1.1	5.256	7.4	6.029	-6.3
283.15	1.0129	7.130	7.232	-1.4	6.791	4.7	7.537	-5.7
288.15	1.0128	9.227	9.251	-0.26	8.736	5.3	9.554	-3.5
293.15	1.0128	11.76	11.76	0.0002	11.19	4.8	12.43	-5.8
298.15	1.0127	15.09	14.84	1.7	14.27	5.4	16.07	-6.5
303.15	1.0126	18.36	18.62	-1.4	18.13	1.2	19.50	-6.3
308.15	1.0125	23.30	23.22	0.33	22.95	1.5	24.54	-5.3
$x_0\ 2=0.2011$								
278.15	2.0106	10.86	10.49	3.4	9.848	9.3	11.39	-4.9
283.15	2.0105	13.18	13.43	-1.9	12.54	4.9	13.86	-5.1
288.15	2.0103	16.48	17.05	-3.5	15.90	3.5	17.50	-6.2
293.15	2.0101	21.77	21.46	1.4	20.09	7.7	22.74	-4.4

298.15	2.0099	27.29	26.80	1.8	25.30	7.3	28.26	-3.5
303.15	2.0097	32.79	33.21	-1.3	31.75	3.2	34.09	-4.0
308.15	2.0094	40.94	40.86	0.19	39.71	3.0	42.85	-4.7
$x_0 = 0.2933$								
278.15	2.9319	19.49	19.39	0.52	17.75	8.9	18.35	5.8
283.15	2.9316	23.23	23.99	-3.3	22.29	4.1	21.78	6.2
288.15	2.9312	29.87	29.72	0.50	27.89	6.6	28.01	6.2
293.15	2.9308	37.87	36.83	2.7	34.80	8.1	35.69	5.8
298.15	2.9303	46.03	45.66	0.80	43.30	5.9	43.44	5.6
303.15	2.9298	55.08	56.62	-2.8	53.72	2.5	51.75	6.0
308.15	2.9288	70.85	70.23	0.88	66.43	6.2	66.56	6.1
$x_0 = 0.402$								
278.15	4.0173	33.30	33.05	0.76	34.62	-4.0	34.05	-2.3
283.15	4.0169	38.83	40.35	-3.9	42.76	-10	39.80	-2.5
288.15	4.0160	49.69	49.35	0.67	52.68	-6.0	50.88	-2.4
293.15	4.0150	62.43	60.45	3.2	64.77	-3.7	63.93	-2.4
298.15	4.0140	74.84	74.15	0.91	79.50	-6.2	76.71	-2.5
303.15	4.0129	88.11	91.06	-3.4	97.41	-11	90.51	-2.7
308.15	4.0109	113.1	111.9	1.1	118.9	-5.1	116.2	-2.7
$x_0 = 0.5003$								
278.15	4.9969	60.99	60.08	1.5	58.43	4.2	60.74	0.41
283.15	4.9959	70.70	72.92	-3.1	71.20	-0.71	70.37	0.46
288.15	4.9942	87.82	88.52	-0.79	86.60	1.4	87.42	0.46
293.15	4.9919	110.7	107.4	3.0	105.2	5.0	110.2	0.47
298.15	4.9898	131.4	130.4	0.80	127.7	2.8	130.8	0.50
303.15	4.9876	154.4	158.2	-2.5	154.9	-0.40	153.5	0.55
308.15	4.9837	193.3	191.8	0.77	187.3	3.1	192.2	0.56
$x_0 = 0.5993$								
278.15	5.9826	87.17	85.57	1.8	84.97	2.5	87.21	-0.043
283.15	5.9812	98.08	102.4	-4.4	102.6	-4.6	98.13	-0.051
288.15	5.9784	121.9	122.9	-0.87	123.8	-1.6	121.9	-0.051
293.15	5.9745	154.5	148.0	4.2	149.1	3.5	154.6	-0.052
298.15	5.9714	180.5	178.6	1.1	180.0	0.28	180.6	-0.058
303.15	5.9680	208.3	216.0	-3.7	217.3	-4.4	208.4	-0.065
308.15	5.9613	264.8	261.8	1.2	261.3	1.3	265.0	-0.064

^aThe reported results were the average values of three determinations;

^bThe standard uncertainty of temperature is $u(T) = 0.03$ K;

^cThe relative standard uncertainties are $u_r(x_1) = 0.05$, $u_r(x_2) = 0.05$, $u_r(x_0) = 0.02$; the standard uncertainty of the pressure is $u(p) = 10$ kPa;

^d x_2 is the mole fraction of methanol in the final saturated ternary mixture; x_0 is the initial mole fraction of methanol in methanol + water mixture;

^eRD is the relative deviation;

^fThe residual solid phase of cefoxitin acid in the solubility experiments was cefoxitin acid monohydrate.

Table 4

Parameters of the modified Apelblat equation for the solubility of cefoxitin acid in methanol, acetonitrile, ethanol, isopropanol, n-propanol and ethyl acetate.^{a,b,c}

Solvent	A^a	B^a	C^a	R^{2b}	10^2ARD^c
Methanol	-65.070	232.67	10.490	0.9983	0.81
Acetonitrile	-192.55	6881.8	28.449	0.9962	0.74
Ethanol	180.16	-10857	-26.467	0.9934	1.18
Isopropanol	506.80	-27056	-74.526	0.9885	4.26
n-propanol	-209.64	6433.7	31.635	0.9930	1.68
Ethyl acetate	-100.31	3249.9	14.259	0.9935	0.55

^a A, B, C are the parameters of the modified Apelblat equation;

^b R^2 is the coefficient of determination;

^cARD is the average relative deviation.

Table 5

Parameters of the NRTL model for the solubility of cefoxitin acid in methanol, acetonitrile, ethanol, isopropanol, n-propanol and ethyl acetate.^{a,b}

Solvent	Δg_{12}^a	Δg_{21}^a	α_{12}^a	10^2ARD^b
Methanol	-51993	81734	0.025	2.62
Acetonitrile	-56757	100905	0.025	1.81
Ethanol	126982	-35939	0.025	2.13
Isopropanol	-43934	71676	0.025	7.40
n-propanol	-52196	89674	0.025	2.30
Ethyl acetate	-58715	108382	0.025	2.70

^a $\Delta g_{12}, \Delta g_{21}$ and α_{12} are the parameters of the NRTL equation;

^bARD is the average relative deviation.

Table 6

Parameters of the modified Apelblat equation for the solubility of cefoxitin acid in water and methanol + water mixtures at different initial mole fractions of methanol (x_0).^{a,b}

x_0	A^a	B^a	C^a	10^2ARD^b
Water	-295.950	8849.94	45.0445	1.98

0.1013	-31.9812	-2445.94	5.50571	0.89
0.2011	10.6099	-4138.98	-0.86920	1.92
0.2933	-172.833	4098.29	26.5719	1.65
0.4020	-185.574	4842.02	28.4554	1.98
0.5003	-142.868	3139.01	22.0614	1.78
0.5993	-199.374	5732.69	30.5074	2.47

^aA, B, C are the parameters of the modified Apelblat equation;

^bARD is the average relative deviation.

Table 7

Parameters of the NRLT model for the solubility of cefoxitin acid in water and methanol + water mixtures.^{a,b}

Parameters	Values	Parameters	Values
Δg_{12}^a	-36744	α_{12}^a	0.025
Δg_{13}^a	106763	α_{13}^a	0.025
Δg_{23}^a	-25082	α_{23}^a	0.025
Δg_{21}^a	59153	$10^2 \text{ARD}^b = 7.18$	
Δg_{31}^a	-31229		
Δg_{32}^a	-24978		

^a Δg_{12} , Δg_{13} , Δg_{23} , Δg_{21} , Δg_{31} , Δg_{32} , α_{12} , α_{13} and α_{23} are the parameters of the NRTL equation;

^bARD is the average relative deviation.

Table 8

Parameters of the CNIBS/R-K model for the solubility of cefoxitin acid in water and (methanol + water) mixtures.^{a,b}

T/K	B_0^a	B_1^a	B_2^a	B_3^a	B_4^a	10^2ARD^b
278.15	-10.8749	15.8208	-54.1776	116.4181	-87.2201	6.11
283.15	-10.6559	16.1752	-58.1972	126.4758	-95.2406	6.04
288.15	-10.2895	13.8061	-44.6419	97.0002	-73.9492	4.92
293.15	-10.0941	15.0459	-51.5239	110.4736	-82.7065	5.47
298.15	-9.7684	14.1842	-49.5196	108.3484	-82.0530	5.14
303.15	-9.6049	14.7845	-53.3034	116.4815	-88.0379	5.38
308.15	-10.8749	15.8208	-54.1776	116.4181	-87.2201	6.11

^a B_0 , B_1 , B_2 , B_3 , B_4 are the parameters of the CNIBS/R-K equation;

^bARD is the average relative deviation.

Table 9

Molar enthalpy ($\Delta_{\text{sol}}H$) of the cefoxitin acid dissolution process in methanol, acetonitrile, ethanol, isopropanol, n-propanol and ethyl acetate.^a

T/K	$\Delta_{\text{sol}}H$ $/(\text{kJ}\cdot\text{mol}^{-1})$	T/K	$\Delta_{\text{sol}}H$ $/(\text{kJ}\cdot\text{mol}^{-1})$
Methanol		Acetonitrile	
278.15	18.81	278.15	8.70
283.15	18.72	283.15	9.70
288.15	18.50	288.15	10.71
293.15	18.07	293.15	11.70
298.15	17.48	298.15	12.70
303.15	16.83	303.15	13.67
308.15	16.13	308.15	14.61
Ethanol		Isopropanol	
278.15	24.28	278.15	21.60
283.15	24.64	283.15	22.22
288.15	25.02	288.15	22.83
293.15	25.40	293.15	23.43
298.15	25.76	298.15	24.04
303.15	26.15	303.15	24.63
308.15	26.52	308.15	25.21
n-propanol		Ethyl acetate	
278.15	19.56	278.15	23.48
283.15	20.16	283.15	23.80
288.15	20.77	288.15	24.11
293.15	21.35	293.15	24.44
298.15	21.93	298.15	24.75
303.15	22.45	303.15	25.07
308.15	23.01	308.15	25.36

^aCombined expanded uncertainties U are $U_{\text{c}}(\Delta_{\text{sol}}H)=0.040\Delta_{\text{sol}}H$ (0.95 level of confidence).

Table 10

Molar enthalpy ($\Delta_{\text{sol}}H$) of the cefoxitin acid dissolution process in water and methanol + water mixtures at different initial mole fractions of methanol (x_0 2).^a

T/K	$\Delta_{\text{sol}}H$ $/(\text{kJ}\cdot\text{mol}^{-1})$	T/K	$\Delta_{\text{sol}}H$ $/(\text{kJ}\cdot\text{mol}^{-1})$
Water		x_0 2=0.1013	
278.15	30.60	278.15	33.07
283.15	32.48	283.15	33.29
288.15	34.36	288.15	33.52

293.15	36.24	293.15	33.75
298.15	38.12	298.15	33.98
303.15	40.00	303.15	34.21
308.15	41.90	308.15	34.43
$\times 10^{-2}=0.2011$		$\times 10^{-2}=0.2933$	
278.15	32.40	278.15	27.37
283.15	32.36	283.15	28.47
288.15	32.32	288.15	29.58
293.15	32.29	293.15	30.68
298.15	32.25	298.15	31.78
303.15	32.21	303.15	32.88
308.15	32.17	308.15	33.98
$\times 10^{-2}=0.402$		$\times 10^{-2}=0.5003$	
278.15	25.54	278.15	24.90
283.15	26.72	283.15	25.82
288.15	27.90	288.15	26.73
293.15	29.08	293.15	27.64
298.15	30.26	298.15	28.55
303.15	31.43	303.15	29.46
308.15	32.61	308.15	30.36
$\times 10^{-2}=0.5993$			
278.15	22.87		
283.15	24.13		
288.15	25.39		
293.15	26.65		
298.15	27.91		
303.15	29.17		
308.15	30.41		

^aCombined expanded uncertainties U are $U_c(\Delta_{\text{sol}}H)=0.040\Delta_{\text{sol}}H$ (0.95 level of confidence).