Effect of polymorphism on thermodynamic properties of cefamandole nafate

Fang He ^a, Yongli Wang ^{a, b}, Qiuxiang Yin ^{a, b}, Linggang Tao ^c, Jun Lv ^c, Zhao Xu ^{a, b},
Jinxu Wang ^a, Hongxun Hao ^{a, b, *}

^a School of Chemical Engineering and Technology, Tianjin University, Tianjin
300072, China

^b The Co-Innovation Center of Chemistry and Chemical Engineering of Tianjin,
Tianjin 300072, China

^c Lionco Pharmaceutical Group, Haikou, Hainan 570100, China

Abstract:

For solid state active pharmaceutical ingredient (API), it might be able to exist in different crystal structures, which is well known as polymorphism. Different polymorphs of the same pharmaceutical might exhibit different physicochemical properties. In this work, the effect of polymorphism on thermodynamic properties of cefamandole nafate was investigated in detail. Two new polymorphic forms of cefamandole nafate were successfully prepared and characterized by powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC). It was found that form IV has higher melting temperature than form V. By using dynamic method, the solid-liquid equilibrium of cefamandole nafate form IV and form V were experimentally determined and compared in (ethanol + water) binary solvent mixtures over the temperature ranges of (278.15 to 308.15) K. The effects of solvent and temperature on the solubility of these two forms were discussed. It was found that the solubility data of cefamandole nafate form V are higher than those of form IV. The experimental solubility data were correlated by the modified Apelblat equation, the CNIBS/R-K equation and the Jouyban-Acree model, respectively. Furthermore, the dissolution thermodynamic properties, including the enthalpy, entropy and Gibbs free energy change, were also calculated. Combining the results of DSC analysis, the solubility and the thermodynamic properties, it can be concluded that the thermodynamic properties of the two forms are apparently different.

Keywords: polymorphism; thermodynamic properties; cefamandole nafate; stability

1. Introduction

Polymorphism, which refers to the ability of a substance to exist in two or more crystalline structures, is an important aspect of pharmaceutical products. The fact that chemical species can exist in different lattice structures often leads to significant variations in the physical properties of such crystals. The characteristics affected by the polymorphism include solubility, dissolution rate, density, stability, hygroscopicity and solid-state reactivity. In addition, different forms may have different pharmaceutical bioavailabilities if they are mediated via dissolution.[1] For pharmaceuticals which exhibit polymorphism, it is crucial to understand the effect of polymorphism on their thermodynamic properties.

The model pharmaceuticals, cefamandole nafate ($C_{19}H_{17}N_6NaO_6S_2$, CAS NO. 42540-40-9, as shown in Figure 1) is a broad-spectrum antibiotic and has been widely applied to the treatment of infections caused by sensitive bacteria. Compared with other antibacterial agents, cefamandole nafate has a strong effect on gram-negative bacteria and is to be most effective for haemophilus. In clinical practice, cefamandole nafate is a safe and effective antimicrobial agent due to its less side effect and drug tolerance.[2-4] Most researches about cefamandole nafate are mainly concentrated on its synthesis, characteristics and application.[5] The polymorphism of cefamandole nafate which is necessary for the safe application of cefamandole nafate is not well understood. From literature review,[6-8] three polymorphic forms of cefamandole nafate have been reported. Since these three forms were not named in the literature, they are named as form I, form II and form III in this work according the publishing

time of them. The PXRD and DSC data of the three forms are presented in Supporting Information Figure S1-S4 and Table S1. To ensure the safe usage of cefamandole nafate, it is necessary to investigate the polymorphisms of cefamandole nafate and to find new forms which have better properties. In this work, two new forms of cefamandole nafate was discovered and its effect on the thermodynamic properties was investigated. These new polymorphs of cefamandole nafate, named as form IV and form V, were isolated and characterized. The stability of the two forms were compared. The solubility data of cefamandole nafate form IV and form V in (ethanol + water) mixtures were determined by a dynamic method and compared with each other. The experimental solubility data of cefamandole nafate form IV and form V were correlated by using the modified Apelblat equation, the CNIBS/R-K equation and the Jouyban-Acree model. In addition, the molar enthalpy, entropy and Gibbs energy change during the dissolution of cefamandole nafate in binary mixtures of ethanol + water systems were also calculated and analyzed.

2. Experimental section

2.1. Materials.

Cefamandole nafate form III was supplied by Lionco Pharmaceutical Group of China. Distilled deionized water was prepared in our laboratory. All of the organic solvents used in this study, including ethanol, isopropyl alcohol and acetone, were purchased from Tianjin Kewei Chemical Co. of China with mass fraction purity

higher than 99.5%. The details of the chemicals used in this study are listed in Table 1.

2.2. Apparatus and procedure

2.2.1. Characterization by X-ray diffraction

The Powder X-ray Diffraction (PXRD) patterns of cefamandole nafate form IV and form V were used to identify and characterize their crystallinity forms. All samples' PXRD patterns were carried out on Rigaku D/max-2500 (Rigaku, Japan) by using Cu K α radiation (0.1541845 nm). Samples were analyzed over a diffraction-angle (2θ) range of (2 to 50) $^{\circ}$, at a step size of 0.02 $^{\circ}$, a dwell time of 1 s, a voltage of 40 kV, and an electric current of 100 mA.

2.2.2. Measurements of melting properties and thermal stability

DSC 1/500 (Mettler Toledo, Switzerland) was used to determine the melting property of cefamandole nafate form IV and form V with a heating rate of 1 K $\cdot$ min $^{-1}$ and under protection of nitrogen. The uncertainties of the measurements are 0.5 K for the melting temperature and around 3% for the enthalpy of fusion.

In order to further study thermal stability of the two forms of cefamandole nafate, thermogravimetric analyses (TGA) of both forms were also carried out. An approximately $5 \cdot 10^{-6}$ kg sample was put into the crucible and heated from (298.15 to 453.15) K at a heating rate of 5 K $\cdot$ min $^{-1}$. The results indicate that there is no mass loss in the experimental temperature range. The experimental data are presented in Supporting Information Figure S5. It can be proved that both cefamandole nafate forms are not solvated and hydrated forms. Indium (melting temperature, 429.8K;

$\Delta_{\text{fus}}H = 0.25 \text{ J}\cdot\text{mol}^{-1}$) and n-dodecane (melting temperature, 263.5 K; $\Delta_{\text{fus}}H = 1.27 \text{ J}\cdot\text{mol}^{-1}$) were used to calibrate the instrument and an empty pan was used as reference. The relative uncertainty of the measurement was estimated to 0.03.

2.2.3. Preparation of cefamandole nafate form IV and form V

Cefamandole nafate form IV was obtained by solution-mediated polymorphic transformation of commercial raw material in the solvent of acetone while form V were obtained by solution-mediated polymorphic transformation of commercial raw material in the solvent of dioxane at 298.15K. In the polymorphic transformation experiment, about 30mL of solvent and excess cefamandole nafate were put into a 50mL conical flask with a glass stopper and then was maintained at 298.15K inside an incubator shaker (HNY-211B, Tianjin Honor Instrument Co., Ltd. of China) with temperature uncertainty of $\pm 0.01 \text{ K}$. The suspensions were shaken in the incubator for about 24 h. After that, the shaking of the incubator shaker was stopped, and the residual bottom suspensions were filtered. The obtained solids were dried under vacuum and analyzed by XRD to confirm their crystal form. The mass fraction purities of both forms are above 99%, which were determined by High-performance liquid chromatography (HPLC).

2.2.4. Measurements of solubilities of cefamandole nafate form IV and form V

In industrial production, water is the most commonly used solvent while ethanol is the most commonly used anti-solvent in the crystallization processes of many compounds, including the model compound of this study. So we determine the solubility of cefamandole nafate in the binary system of water and ethanol. The

solubility data of cefamandole nafate form IV and form V in (ethanol + water) mixtures were measured by a dynamical method which is similar to the method described in literature.[9,10] All experiments were carried out in a jacked glass vessel (20 mL) with a magnetic stirrer. The temperature of the vessel was controlled by a thermostat (type 501A, Shanghai Laboratory Instrument Works Co., Ltd, China). The temperature of the solution in the vessel was measured by a mercury-in-glass thermometer (uncertainty of ± 0.05 K). The dissolution of the particles was monitored by the laser light passing through the reactors. At the beginning of all experiments, a small amount of cefamandole nafate with known mass was gradually added into certain amount of solvent at constant temperatures. The solute then began to dissolve under the continuous agitation. When the added solute dissolved completely, the intensity of laser beam which passes through the solution reached maximum. Then, more known amount of cefamandole nafate $((2 \text{ to } 5) \cdot 10^{-6} \text{ kg})$ was added into the vessel. This process was repeated until the penetrated laser intensity was just 90 percent of the maximum value and the system would be considered to have reached equilibrium. The same experiment was repeated at least 4 times to get an average value in order to minimize the experimental errors. The masses of the samples and solvents were weighed by using an analytical balance (Mettler Toledo AB204-N, Switzerland) with an uncertainty of ± 0.0001 g.

The mole fraction solubility of the solute (x) in solution was calculated as follows:

$$x = \frac{m / M}{m / M + m_E / M_E + m_W / M_W} \quad (1)$$

The mole fraction of water (x_w) in the solution was calculated as follows:

$$x_w = \frac{m_w / M_w}{m_E / M_E + m_w / M_w} \quad (2)$$

where m , m_E and m_w represent the mass of the solute, the mass of ethanol and the mass of water respectively; M , M_E and M_w represent the molecular weight of the solute, ethanol and water respectively.

3. Thermodynamic models

To expand the application scope of the solubility data measured in experiments, the experimental solubility data were correlated by the modified Apelblat equation, CNIBS/R-K model and Jouyban-Acree model

3.1. The modified Apelblat equation

The modified Apelblat equation is widely used to express the relationship between the solubility and the temperature. The equation is shown as following:[11]

$$\ln x = A + B/T + C \ln(T) \quad (3)$$

where x is the mole fraction solubility, T is the absolute temperature, and A , B and C are the empirical constants. The values of A and B refer to the variations in the solution activity coefficient, and the value of C reflects the effect of temperature on the fusion enthalpy.

3.2. The CNIBS/R-K model

The CNIBS/R-K model is used to describe the relationship between the solubility and the solvent composition. The model is presented as following:[12,13]

$$\ln x = x_{\text{W}}^0 \ln(x)_{\text{W}} + x_{\text{E}}^0 \ln(x)_{\text{E}} + x_{\text{W}}^0 x_{\text{E}}^0 \sum_{i=0}^N S_i (x_{\text{W}}^0 - x_{\text{E}}^0)^i \quad (4)$$

where x is the solubility of the solute, x_{E}^0 is the initial mole fraction composition of ethanol in the (ethanol + water) mixtures in the absence of solute and x_{W}^0 is the initial mole fraction composition of water in the (ethanol + water) mixtures in the absence of solute. $(x)_i$ denotes the saturated mole fraction solubility of the solute in pure solvent i . S_i is the model constant and N is the number of “curve-fit” parameters. For a binary solvent system, when substituting x_{E}^0 with $(1 - x_{\text{W}}^0)$ and $N = 2$, eq 4 can be transformed into eq 5:

$$\begin{aligned} \ln x = & (\ln(x)_{\text{W}} - \ln(x)_{\text{E}} + S_0 - S_1 + S_2)x_{\text{W}}^0 + (-S_0 + 3S_1 - 5S_2)(x_{\text{W}}^0)^2 \\ & + (-2S_1 + 8S_2)(x_{\text{W}}^0)^3 + (-4S_2)(x_{\text{W}}^0)^4 + \ln(x)_{\text{E}} \end{aligned} \quad (5)$$

A new equation can be obtained by introducing constant terms to eq 5:

$$\ln x = B_1 + B_2 x_{\text{W}}^0 + B_3 (x_{\text{W}}^0)^2 + B_4 (x_{\text{W}}^0)^3 + B_5 (x_{\text{W}}^0)^4 \quad (6)$$

where the right side is a four-order polynomial and B_i are model constants.

3.3. The Jouyban-Acree model

The Jouyban-Acree model is used to correlate the solubility data with both temperature and solvent composition. The model can be represented as following:[14]

$$\ln x = x_{\text{W}}^0 \ln(x)_{\text{W}} + x_{\text{E}}^0 \ln(x)_{\text{E}} + \frac{x_{\text{W}}^0 x_{\text{E}}^0}{T} \sum_{i=0}^2 J_i (x_{\text{W}}^0 - x_{\text{E}}^0)^i \quad (7)$$

where J_i terms are model constants, T is the absolute temperature, and the other symbols denote the same meanings as eq 4.

In this model the saturated mole fraction solubility of the solute in pure solvent i ($(x)_i$) are needed. According to the modified Apelblat equation, $(x)_{\text{W}}$ and $(x)_{\text{E}}$ can be expressed by:

$$\ln(x)_w = a_1 + b_1 / T + c_1 \ln T \quad (8)$$

$$\ln(x)_E = a_2 + b_2 / T + c_2 \ln T \quad (9)$$

When substituting eq 8 and eq 9 into eq 7 and x_E^0 is substituted with $(1 - x_w^0)$, a new equation can be obtained as following:

$$\begin{aligned} \ln x = & a_1 + \frac{b_1}{T} + c_1 \ln T + (a_1 - a_2)x_w^0 + (b_1 - b_2 + J_0 - J_1 + J_2) \frac{x_w^0}{T} \\ & + (3J_1 - J_0 - 5J_2) \frac{(x_w^0)^2}{T} + (8J_2 - 2J_1) \frac{(x_w^0)^3}{T} \\ & + (-4J_2) \frac{(x_w^0)^4}{T} + (c_1 - c_2)x_w^0 \ln T \end{aligned} \quad (10)$$

By introducing constant terms, the eq 10 can be further simplified as following:

$$\begin{aligned} \ln x = & A_1 + \frac{A_2}{T} + A_3 \ln T + A_4 x_w^0 + A_5 \frac{x_w^0}{T} + A_6 \frac{(x_w^0)^2}{T} \\ & + A_7 \frac{(x_w^0)^3}{T} + A_8 \frac{(x_w^0)^4}{T} + A_9 x_w^0 \ln T \end{aligned} \quad (11)$$

Where A_1 to A_9 are model constants and the other symbols denote the same meanings as in eq 4. The Jouyban-Acree model can correlate the experimentally solubility data with both temperature and initial mole fraction of binary solvent mixtures.

3.4. Calculating methods for dissolution thermodynamics

For a non-ideal solution, the dissolution phenomenon can be considered to be composed by four energetic steps from the kinetic perspective theoretically. Supposing that the dissolution process is comprised of heating, fusion, cooling and mixing processes, the thermodynamic parameters of dissolution should be judged by the overall dissolution process:

Where the solute is heated to T_m firstly, then melts at T_m , and cooled to T , finally mixed with the solvent at T . This hypothesis permits us to calculate the partial thermodynamic contributions to the overall dissolution process by means of following equations:

$$\Delta_{\text{dis}}M = x(\Delta_{\text{heat}}M + \Delta_{\text{fus}}M + \Delta_{\text{cool}}M) + \Delta_{\text{mix}}M \quad (12)$$

$$\Delta_{\text{mix}}M = \Delta_{\text{mix}}M^{\text{id}} + M^{\text{E}} \quad (13)$$

Where M can be replaced by H , S and G . x refers to the mole fraction solubility of the solute. $\Delta_{\text{fus}}M$ refers to the fusion thermodynamic properties. $\Delta_{\text{mix}}M^{\text{id}}$ and M^{E} represent the mixing properties of ideal solution and the excess properties, respectively. $\Delta_{\text{heat}}M$ and $\Delta_{\text{cool}}M$ represent the thermodynamic properties of heating and cooling process, respectively. They can be calculated as following equations:

$$\Delta_{\text{heat}}H = C_{\text{p(s)}}(T_m - T) \quad (14)$$

$$\Delta_{\text{heat}}S = C_{\text{p(s)}} \ln \frac{T_m}{T} \quad (15)$$

$$\Delta_{\text{cool}}H = C_{\text{p(l)}}(T - T_m) \quad (16)$$

$$\Delta_{\text{cool}}S = C_{\text{p(l)}} \ln \frac{T}{T_m} \quad (17)$$

It could be assumed that the heat capacity of the solid of cefamandole nafate and the supercooled liquid of cefamandole nafate are pretty close. In this situation, the item of $(\Delta_{\text{heat}}M + \Delta_{\text{cool}}M)$ will be approximately equal to zero and the sum of the two terms will be able to be ignored. During the phase transition of solute, the system is in equilibrium, so $\Delta_{\text{fus}}G = 0$.

To predict the mixing properties of the cefamandole nafate solution, the activity coefficient of solute in the liquid phase (γ_A) is needed. If the system is considered as a

binary system which includes solvent and solute, the Wilson model could be used to correlate the relationship between activity coefficient and mole fraction:[15]

$$\ln \gamma_A = -\ln(x_A + \Lambda_{AS}x_S) + x_S \left(\frac{\Lambda_{AS}}{x_A + \Lambda_{AS}x_S} - \frac{\Lambda_{SA}}{x_S + \Lambda_{SA}x_A} \right) \quad (18)$$

where Λ_{AS} and Λ_{SA} can be calculated as following.

$$\Lambda_{AS} = \frac{v_S}{v_A} \exp\left(-\frac{\lambda_{AS} - \lambda_{AA}}{RT}\right) = \frac{v_S}{v_A} \exp\left(-\frac{\Delta\lambda_{AS}}{RT}\right) \quad (19)$$

$$\Lambda_{SA} = \frac{v_A}{v_S} \exp\left(-\frac{\lambda_{AA} - \lambda_{AS}}{RT}\right) = \frac{v_A}{v_S} \exp\left(-\frac{\Delta\lambda_{SA}}{RT}\right) \quad (20)$$

where $\Delta\lambda_{AS}$ and $\Delta\lambda_{SA}$ represent the cross interaction energy parameters which are independent of the composition and temperature; v_A and v_S are the molar volumes of the solute and solvent; x_A and x_S are the mole fractions of solute and solvent, respectively.

For an ideal system, the mixing properties can be calculated by the following equation.[16]

$$\Delta_{\text{mix}} G^{\text{id}} = RT(x_A \ln x_A + x_S \ln x_S) \quad (21)$$

$$\Delta_{\text{mix}} S^{\text{id}} = -R(x_A \ln x_A + x_S \ln x_S) \quad (22)$$

$$\Delta_{\text{mix}} H^{\text{id}} = 0 \quad (23)$$

where x_A and x_S refer to the mole fraction of solute and the solvent, respectively. $\Delta_{\text{mix}} G^{\text{id}}$, $\Delta_{\text{mix}} S^{\text{id}}$ and $\Delta_{\text{mix}} H^{\text{id}}$ refer to mixing Gibbs energy, mixing entropy and mixing enthalpy of the ideal solution.

Based on the Wilson model, the excess mixing properties can be calculated by the following equation:[17]

$$G^E = RT(x_A \ln \gamma_A + x_S \ln \gamma_S) \quad (24)$$

$$H^E = -T^2 \left[\frac{\partial(G^E/T)}{\partial T} \right] \quad (25)$$

$$S^E = (H^E - G^E)/T \quad (26)$$

4. Results and discussion

4.1. Polymorph identification and characterization

The PXRD data of cefamandole nafate form IV and form V have not been published anywhere and are given in Figure 2. It can be seen from Figure 2 that there are many differences between the PXRD data of form IV and form V. The PXRD data of these two forms are apparently different from the PXRD data of the previously published form I, II and III which are given in supporting information. Compared with cefamandole nafate form IV, cefamandole nafate form V have characteristic peaks at 2θ of 4.12° , 6.30° , 7.54° , 16.68° and 19.56° .

In order to compare the stability of these two forms, the DSC data of the two forms are given and plotted in Figure 3. From Figure 3, it can be seen that the DSC curve of form IV shows a single endothermic peak with onset temperature of 442.5 K and enthalpy of fusion $18.88 \text{ kJ}\cdot\text{mol}^{-1}$ while the DSC curve of form V exhibits a single endothermic peak with onset temperature of 437.0 K and enthalpy of fusion $13.93 \text{ kJ}\cdot\text{mol}^{-1}$. It can be found that the melting point of form IV and form V are higher than that of form III, which indicates that form IV and form V are more stable than form III. Since form I and form II were not successfully obtained in our lab although we have tried many crystallization methods (including the method described

in the literature), the melting properties of form I and form II were not compared with form IV and form V. Compared with form V, form IV has higher melting temperature and higher enthalpy of fusion. In general, the polymorph with the higher fusion point should be the more stable one.[18] Thus form IV should be the more stable form compared with form V. It can be inferred that the relationship between cefamandole nafate form IV and form V is monotropic and form IV can be obtained by transformation from form V.

4.2. Solubility data

The solubility data of cefamandole nafate form IV and form V in (ethanol + water) mixtures in temperature ranges of (278.15 to 308.15) K were experimentally measured by a dynamics method. The results are plotted in Figure 4 and Figure 5 graphically and listed in Table 2 and Table 3. As shown in Figure 4 and Figure 5, the solubility data of both cefamandole nafate form IV and form V increase with the increasing of temperature in (ethanol + water) mixtures. In addition, the solubility data of both cefamandole nafate form IV and form V decrease with the increasing of the composition of ethanol in (ethanol + water) mixtures. Cefamandole nafate is an ionic and polar compound. According to the observation of “like dissolves like”, it should be more soluble in water than in ethanol. Cefamandole nafate contains -NH which is the hydrogen-bond donor and -COO- which is the hydrogen-bond acceptor. Because of the existence of hydrogen bond and electrostatic force, the intermolecular forces between cefamandole nafate and water should be more powerful than those of cefamandole nafate and ethanol. Therefore, it can be observed that the solubility data

of cefamandole nafate in water are higher than those in (ethanol + water) mixtures. With the increase of concentration of ethanol, the intermolecular forces between ethanol molecules are enhanced and the intermolecular forces between cefamandole nafate and water are weakened, which will result in the decrease of the solubility of cefamandole nafate.[19,20]

Furthermore, to compare the dissolving properties and the thermodynamic stability of these two forms, the solubilities of the two forms in the same (ethanol + water) mixtures are also graphically plotted in Figure 6. It can be seen that the solubility data of cefamandole nafate form V are higher than the solubility data of form IV in all (ethanol + water) mixtures. According to the method described by Haleblan and McCrone, the more stable polymorph should have lower solubility at a given temperature and pressure.[21] Therefore, cefamandole nafate form IV which has lower solubility data should be the more stable form at room temperature.

The calculated solubility data of the two forms of cefamandole nafate are also listed in Table 2 and Table 3. The calculated model parameters are listed in Supporting Information Tables S2-S4, respectively.

To evaluate the applicability of the tested models, the average relative deviation (*ARD*) was applied to evaluate the accuracy of the models. The *ARD* is defined as following.[22]

$$ARD\% = \frac{1}{N_p} \sum_{i=1}^{N_p} \left| \frac{x_i^{cal} - x_i^{exp}}{x_i^{exp}} \right| 100 \quad (27)$$

where N_p refers to the number of data points; the superscripts exp and cal denote the experimental and calculated solubility data respectively.

The *ARD%* of different correlation models are shown in Tables S2-S4 as well. As shown in Tables S2-S4, the *ARD%* values of all models for the two cefamandole nafate forms are less than 7.0%. It can also be seen from Table 2 and Table 3 that the calculated results of solubility of the two forms by the modified Apelblat equation, CNIBS/R-K model, and Jouyban-Acree model are consistent with the experimental results of solubility. This confirms that all tested models can be used to correlate the experimental solubility data.

4.3. Thermodynamic properties of the dissolution process

On the basis of the solubility data of cefamandole nafate in different binary (ethanol + water) solvent mixtures, the thermodynamic properties in the process of dissolution can be calculated.

The calculated results of $\Delta_{\text{dis}}H$, $\Delta_{\text{dis}}S$ and $\Delta_{\text{dis}}G$ are given in Table 4 and Table 5. From the data in Table 4 and Table 5, it can be found that the dissolution process of cefamandole nafate in ethanol aqueous solutions is endothermic and entropy-driven because $\Delta_{\text{dis}}H$ and $\Delta_{\text{dis}}S$ of dissolution are all positive in the studied (ethanol + water) mixtures. The negative values of $\Delta_{\text{dis}}G$ indicate that the dissolution process of cefamandole nafate form IV and form V is a spontaneous and favorable process. Furthermore, it can also be found that the values of $\Delta_{\text{dis}}G$ increases with the decrease of solubility data in the dissolution process, which is consistent with general thermodynamic principles. Additionally, the values of $\Delta_{\text{dis}}H$ and $\Delta_{\text{dis}}G$ of form IV are higher than those of form V, which is consistent with the solubility data and further confirms that cefamandole nafate form IV is more stable than form V. And the

differences in dissolution properties between these two forms might arise from the different molecular arrangements of cefamandole nafate molecules.

5. Conclusions

Two new polymorphs of cefamandole nafate, namely form IV and form V, were prepared and characterized. From the DSC data, it was found that form IV is the more stable form because it has higher melting point compared with form V. The experimental solubility data of cefamandole nafate form IV and form V in (ethanol + water) solvent mixtures were obtained in temperatures range from 278.15 K to 308.15 K by a dynamic method. Comparison of solubility of form IV and form V confirms that cefamandole nafate form IV is thermodynamically more stable at the given conditions. The solubility data of cefamandole nafate form IV and form V increase with the increasing of temperature in (ethanol + water) solvent mixtures while decrease with the increasing of the mole fraction of ethanol. The experimental solubility of cefamandole nafate form IV and form V were well correlated by using the modified Apelblat equation, the CNIBS/R-K model, and the Jouyban-Acree. The Gibbs energy change, the enthalpy and the entropy of dissolution processes of both forms in (ethanol + water) solvent mixtures were determined and compared. It was further confirmed that form IV is more stable than form V. The thermodynamic data also show that the dissolution processes of both forms are entropy-driven, endothermic and spontaneous.

Associated content

Corresponding Author

*Tel.: 86-22-27405754. Fax: +86-22-27374971. E-mail: hongxunhao@tju.edu.cn.

Supporting Information

The PXRD and DSC data of cefamandole nafate forms I, II and III. The experimental data of thermogravimetric analyses (TGA) and calculated parameters and *ARD*% for different models.

Acknowledgments

The authors are very thankful to the National Science Foundation of China (No. 21376165) and Program of International S&T Cooperation from China Ministry of Science and Technology (No. 2013DFE43150) for the financial support.

References:

- [1] J. Lu, S. Rohani, Curr. Med. Chem. 16 (2009) 884-905
- [2] D.L. Hemsell, F.G. Cunningham, B. Nobles, Obstet. Gynecol. 61 (1983) 635-640.
- [3] T.S. Foster, R.P. Shrewsbury, J.D. Coonrod, J. Clin. Pharmacol. 20 (1980) 526-533.
- [4] G. Donelli, I. Francolini, D. Romoli, E. Guaglianone, A. Piozzi, C. Ragunath, J.B. Kaplan, Antimicrob. Agents. Ch. 51 (2007) 2733-2740.
- [5] H.M. Moody, P.J.D Maas, T. Schmitges, WO Patent 2013057197-A1 (2013).
- [6] Z.-h. Xia, X.-d. Zhou, CN Patent 102766148-A (2012).
- [7] C.-z. Hu, M. -l. Li, CN Patent 103044453-A (2013).

- [8] X. -y. Yan, H. -p. Liang, CN Patent CN103145736-A (2013).
- [9] U. Domanska, M.K. Kozłowska, J. Chem. Eng. Data. 48 (2003) 557–563.
- [10] H.-x. Hao, J.-k. Wang, Y.-l. Wang, J. Chem. Eng. Data. 49 (2004) 1697–1698.
- [11] A. Apelblat, E. Manzurola, J. Chem. Thermodyn. 31 (1999) 85–91.
- [12] W.E. Acree, Thermochim. Acta. 198 (1992) 71–79.
- [13] R.R. Pawar, C.S. Aher, J.D. Pagar, S.L. Nikam, M. Hasan, J. Chem. Eng. Data. 57 (2012) 3563–3572.
- [14] H. Sun, M. Li, J. Jia, F. Tang, E. Duan, J. Chem. Eng. Data. 57 (2012) 1463–1467.
- [15] H. Yan, Z. Wang, J.-k. Wang, Ind. Eng. Chem. Res. 51 (2012) 2808–2813.
- [16] J.-m. Smith, H.-c.v. Ness, M.-m. Abbott, Introduction to Chemical Engineering Thermodynamics. 2001.
- [17] R.-v. Orye, J.-m. Prausnitz, Ind. Eng. Chem. 57 (1965) 18–26.
- [18] R. Barbas, F. Martí, R. Prohens, C. Puigjaner, Cryst. Growth Des. 6 (2006) 1463.
- [19] Y. Hu, Z. Cao, J. Li, W. Yang, Y. Kai, W. Zhi, J. Chem. Eng. Data. 58 (2013) 2913–2918.
- [20] Q.-l. Chen, J.-k. Wang, Y. Bao, Fluid Phase Equilibr. 313 (2012) 182–189.
- [21] J. Halebian, W. McCrone, J. Pharm. Sci. 58 (1969) 911.
- [22] L. Yang, Q.-x. Yin, B. Hou, Y.-l. Wang, Y. Bao, J.-k. Wang, H.-x. Hao, Ind. Eng. Chem. Res. 52 (2013) 2477.

Table 1. Details of the chemicals used in this study

Table 2. Mole fraction solubility (x) of cefamandole nafate form IV in the binary ethanol + water solvent mixtures (0.1MPa)

Table 3. Mole fraction solubility (x) of cefamandole nafate form V in the binary ethanol + water solvent mixtures (0.1MPa)

Table 4. Thermodynamic functions related to dissolution process of cefamandole nafate form IV in (ethanol + water) systems

Table 5. Thermodynamic functions related to dissolution process of cefamandole nafate form V in (ethanol + water) systems

Figure 1. Chemical structure of cefamandole nafate.

Figure 2. Powder X-ray diffraction patterns for form IV and form V of cefamandole nafate.

Figure 3. Thermal analysis data (DSC) for form IV and form V of cefamandole nafate.

Figure 4. Solubility of cefamandole nafate form IV in the ethanol + water mixtures.

Figure 5. Solubility of cefamandole nafate form V in the ethanol + water mixtures.

Figure 6. Mole fraction solubility of cefamandole nafate form IV and form V in different binary ethanol + water solvent mixtures: (a) $x_w=1.00$, (b) $x_w=0.80$, (c) $x_w=0.70$, (d) $x_w=0.60$, (e) $x_w=0.55$, (f) $x_w=0.50$, (g) $x_w=0.45$, (h) $x_w=0.40$, (i) $x_w=0.30$, (j) $x_w=0.15$, (k) $x_w=0$; solid lines, calculated data by the Modified Apelblat Model.

Table 1. Details of the chemicals used in this study

chemical name	source	mass fraction purity	analysis method
water	Lab made	> 0.990	none
ethanol	Tianjin Kewei Chemical Co, China	> 0.995	GC ^b
isopropyl alcohol	Tianjin Kewei Chemical Co, China	> 0.995	GC ^b
acetone	Tianjin Kewei Chemical Co, China	> 0.995	GC ^b
cefamandole nafate	Lionco Pharmaceutical Group of China	> 0.990	HPLC ^a

^a High performance liquid chromatography.

^b Gas liquid chromatography.

Table 2. Mole fraction solubility (x) of cefamandole nafate form IV in the binary ethanol + water solvent mixtures (0.1MPa) ^a

x_w	$10^3 x^{\text{exp}}$	$10^3 x^{\text{cal}}(\text{eq 3})$	$10^3 x^{\text{cal}}(\text{eq 6})$	$10^3 x^{\text{cal}}(\text{eq 11})$
$T=278.15\text{K}$				
1.000	5.845	5.645	5.866	6.046
0.7994	4.755	4.868	4.593	4.548
0.6986	3.595	3.471	3.719	3.676
0.5985	2.542	2.565	2.655	2.631
0.5498	2.081	2.170	2.147	2.131
0.4992	1.712	1.574	1.672	1.660
0.4496	1.437	1.552	1.275	1.267
0.3995	0.9834	1.112	0.9542	0.9469
0.2999	0.4578	0.3920	0.5314	0.5239
0.1498	0.2870	0.2833	0.2691	0.2594
0.0000	0.2779	0.3068	0.2811	0.2615
$T=283.15\text{K}$				
1.000	9.221	9.521	9.178	8.893
0.7994	5.800	5.460	5.980	6.268
0.6986	4.810	4.725	4.629	4.909
0.5985	3.227	3.061	3.287	3.413
0.5498	2.629	2.552	2.686	2.727
0.4992	2.231	2.198	2.129	2.097
0.4496	1.765	1.790	1.662	1.580
0.3995	1.169	1.141	1.276	1.167

0.2999	0.7357	0.8086	0.7451	0.6299
0.1498	0.3877	0.4094	0.3764	0.2996
0.0000	0.3142	0.2991	0.3168	0.2866

$T=288.15\text{K}$

1.000	14.00	14.20	13.94	13.61
0.7994	8.210	7.756	8.383	9.051
0.6986	6.551	6.298	6.473	6.893
0.5985	4.505	4.241	4.556	4.671
0.5498	3.764	3.729	3.684	3.690
0.4992	2.874	2.799	2.875	2.805
0.4496	2.315	2.282	2.199	2.091
0.3995	1.592	1.499	1.648	1.527
0.2999	0.8605	0.8428	0.9123	0.8073
0.1498	0.4585	0.4467	0.4369	0.3708
0.0000	0.3921	0.3662	0.3969	0.3384

$T=293.15\text{K}$

1.000	22.89	23.89	22.77	21.59
0.7994	13.98	14.98	14.43	13.65
0.6986	10.82	11.70	10.67	10.14
0.5985	7.560	8.145	7.096	6.721
0.5498	5.360	5.225	5.583	5.256
0.4992	4.425	4.782	4.242	3.956
0.4496	3.006	2.770	3.171	2.921
0.3995	2.252	2.101	2.330	2.114

0.2999	1.298	1.383	1.253	1.098
0.1498	0.587	0.5585	0.5862	0.4892
0.0000	0.512	0.4938	0.5139	0.4282

$T=298.15\text{K}$

1.000	32.99	30.19	32.88	35.45
0.7994	20.50	20.43	20.62	21.42
0.6986	15.00	14.75	15.43	15.58
0.5985	10.63	10.67	10.38	10.13
0.5498	8.472	8.770	8.201	7.852
0.4992	6.258	6.593	6.244	5.861
0.4496	4.544	4.512	4.665	4.293
0.3995	3.571	3.759	3.415	3.083
0.2999	1.648	1.552	1.806	1.577
0.1498	0.8484	0.8748	0.8002	0.6850
0.0000	0.6356	0.5966	0.6445	0.5779

$T=303.15\text{K}$

1.000	62.21	64.11	62.16	60.04
0.7994	33.94	33.56	34.14	34.90
0.6986	24.15	23.87	24.26	24.92
0.5985	16.29	15.95	15.64	15.94
0.5498	12.31	12.14	12.14	12.27
0.4992	8.455	7.848	9.102	9.090
0.4496	6.859	7.128	6.712	6.616
0.3995	4.804	4.791	4.862	4.721

0.2999	2.621	2.641	2.538	2.385
0.1498	1.114	1.113	1.130	1.014
0.0000	0.9524	1.047	0.9497	0.8282
$T=308.15\text{K}$				
1.000	103.9	103.5	103.5	104.7
0.7994	60.23	60.35	61.15	58.87
0.6986	40.85	40.96	41.63	41.38
0.5985	27.07	27.17	25.48	26.10
0.5498	19.54	19.57	19.32	19.97
0.4992	14.71	14.89	14.18	14.71
0.4496	9.569	9.468	10.28	10.65
0.3995	6.860	6.840	7.335	7.565
0.2999	4.011	4.014	3.731	3.785
0.1498	1.533	1.530	1.550	1.581
0.0000	1.056	1.024	1.057	1.255

^a x_w is the initial mole fraction of water in the binary solvent mixture; x^{cal} is the experimentally determined solubility; x^{cal} (eq 3), x^{cal} (eq 6) and x^{cal} (eq 11) are the calculated solubility according to eq 3, eq 6, eq 11, respectively. The standard uncertainty of T is $u(T) = 0.05\text{K}$. The relative standard uncertainty of the solvent composition is $u_r(x_w) = 0.05$. The relative standard uncertainty of solubility measurement is $u_r(x) = 0.1$. The relative uncertainty of pressure is $u_r(P) = 0.05$.

Table 3. Mole fraction solubility (x) of cefamandole nafate form V in the binary ethanol + water solvent mixtures (0.1MPa) ^a

x_w	$10^3 x^{\text{exp}}$	$10^3 x^{\text{cal}}$ (eq 3)	$10^3 x^{\text{cal}}$ (eq 6)	$10^3 x^{\text{cal}}$ (eq 11)
$T=278.15\text{K}$				
1.000	35.00	32.50	35.06	38.00
0.7967	21.01	19.21	20.84	22.32
0.6993	16.03	15.03	16.14	16.53
0.5999	11.35	10.25	11.25	10.99
0.5499	8.924	8.224	8.949	8.555
0.4998	6.892	6.692	6.877	6.464
0.4492	5.120	5.015	5.109	4.744
0.3997	3.514	3.493	3.719	3.432
0.2999	2.011	2.036	1.860	1.727
0.1498	0.6537	0.6249	0.6790	0.6660
0.0000	0.3826	0.3701	0.3796	0.4094
$T=283.15\text{K}$				
1.000	50.40	53.20	50.37	47.42
0.7967	28.03	28.83	28.16	26.97
0.6993	20.23	20.83	20.35	19.69
0.5999	13.84	14.24	13.37	12.91
0.5499	10.59	10.59	10.42	9.998
0.4998	7.609	7.109	7.911	7.514
0.4492	5.663	5.309	5.862	5.487
0.3997	4.320	4.479	4.297	3.953

0.2999	2.335	2.263	2.235	1.972
0.1498	0.8810	0.9511	0.9005	0.7503
0.0000	0.5456	0.5988	0.5433	0.4512

$T=288.15\text{K}$

1.000	62.41	63.31	62.52	60.62
0.7967	35.95	38.25	35.38	33.66
0.6993	25.10	26.50	25.79	24.30
0.5999	16.89	18.09	16.93	15.79
0.5499	13.39	14.39	13.12	12.18
0.4998	10.13	10.53	9.878	9.124
0.4492	7.479	7.764	7.226	6.644
0.3997	4.554	4.084	5.214	4.774
0.2999	2.881	2.793	2.607	2.371
0.1498	0.9533	0.9156	0.9871	0.8946
0.0000	0.5827	0.5495	0.5789	0.5293

$T=293.15\text{K}$

1.000	80.95	81.05	81.63	79.23
0.7967	43.61	44.11	41.59	43.28
0.6993	30.00	29.90	30.85	31.02
0.5999	20.26	21.06	21.01	20.05
0.5499	16.37	17.37	16.62	15.43
0.4998	13.25	14.45	12.77	11.54
0.4492	9.569	10.23	9.519	8.392
0.3997	6.605	7.007	6.975	6.025

0.2999	3.954	4.189	3.555	2.989
0.1498	1.243	1.242	1.334	1.124
0.0000	0.7565	0.7403	0.7433	0.6583

$T=298.15\text{K}$

1.000	105.6	103.4	106.2	105.7
0.7967	55.32	53.42	53.89	57.20
0.6993	38.46	37.06	38.95	40.85
0.5999	25.47	25.47	25.86	26.34
0.5499	19.92	19.82	20.26	20.26
0.4998	15.84	16.04	15.46	15.15
0.4492	11.49	11.57	11.47	11.03
0.3997	7.992	8.161	8.401	7.923
0.2999	4.720	4.715	4.312	3.939
0.1498	1.566	1.535	1.655	1.485
0.0000	0.9396	0.9068	0.9273	0.8645

$T=303.15\text{K}$

1.000	146.8	147.7	146.7	143.8
0.7967	77.89	77.69	78.87	77.58
0.6993	55.46	55.86	54.01	55.37
0.5999	33.58	31.68	33.75	35.73
0.5499	25.64	23.94	25.80	27.52
0.4998	19.54	17.94	19.33	20.61
0.4492	14.14	13.22	14.20	15.03
0.3997	9.711	9.360	10.38	10.82

0.2999	5.929	5.769	5.432	5.410
0.1498	2.140	2.180	2.223	2.052
0.0000	1.294	1.361	1.284	1.194
$T=308.15\text{K}$				
1.000	200.1	200.1	199.2	199.1
0.7967	110.2	110.6	112.6	107.8
0.6993	78.95	79.05	79.76	77.09
0.5999	52.69	53.49	50.79	49.94
0.5499	39.88	40.58	38.87	38.56
0.4998	30.02	30.62	28.95	28.97
0.4492	20.80	21.17	21.01	21.20
0.3997	13.29	13.40	15.08	15.32
0.2999	8.006	8.070	7.496	7.720
0.1498	2.806	2.794	2.797	2.961
0.0000	1.527	1.502	1.533	1.730

^a x_w is the initial mole fraction of water in the binary solvent mixture; x^{cal} is the experimentally determined solubility; x^{cal} (eq 3), x^{cal} (eq 6) and x^{cal} (eq 11) are the calculated solubility according to eq 3, eq 6, eq 11, respectively. The standard uncertainty of T is $u(T) = 0.05\text{K}$. The relative standard uncertainty of the solvent composition is $u_r(x_w) = 0.05$. The relative standard uncertainty of solubility measurement is $u_r(x) = 0.1$. The relative uncertainty of pressure is $u_r(P) = 0.05$.

Table 4. Thermodynamic functions related to dissolution process of cefamandole nafate form IV in (ethanol + water) systems ^a

x_w	$\Delta_{\text{dis}}H(\text{J}\cdot\text{mol}^{-1})$	$\Delta_{\text{dis}}G(\text{J}\cdot\text{mol}^{-1})$	$\Delta_{\text{dis}}S(\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1})$
T=278.15K			
1.0000	568.70	-41.312	2.8084
0.7994	340.04	-37.361	1.5826
0.6986	297.17	-29.924	1.2667
0.5985	189.44	-21.555	0.9633
0.5498	157.21	-17.753	0.7173
0.4992	127.61	-14.492	0.5803
0.4496	89.993	-12.256	0.4518
0.3995	68.633	-9.3413	0.3118
0.2999	44.441	-5.3155	0.2095
0.1498	11.502	-3.2927	0.0616
0.0000	7.4149	-2.8273	0.0391
T=283.15K			
1.0000	863.58	-58.873	3.9185
0.7994	458.20	-44.045	2.5757
0.6986	329.57	-37.803	1.4762
0.5985	227.89	-26.209	1.3258
0.5498	172.06	-21.506	0.8676
0.4992	131.81	-17.969	0.6284
0.4496	98.984	-14.524	0.4821
0.3995	72.893	-10.064	0.4238

0.2999	41.077	-6.4068	0.2795
0.1498	14.859	-3.9135	0.0894
0.0000	10.154	-3.1523	0.0524

T=288.15K

1.0000	1395.7	-81.606	5.3382
0.7994	622.67	-57.745	3.0865
0.6986	425.67	-48.192	1.9279
0.5985	322.07	-34.057	1.4394
0.5498	252.57	-28.469	1.2691
0.4992	179.26	-21.993	0.9860
0.4496	143.96	-18.026	0.6319
0.3995	84.589	-12.863	0.3632
0.2999	54.598	-7.3239	0.2912
0.1498	21.456	-4.3057	0.0843
0.0000	11.026	-3.6532	0.0586

T=293.15K

1.0000	1636.9	-120.13	6.0875
0.7994	874.78	-86.175	3.2701
0.6986	587.31	-70.286	2.9858
0.5985	402.59	-50.233	1.6989
0.5498	344.97	-37.322	1.5059
0.4992	300.84	-30.49	1.0205
0.4496	182.62	-22.145	0.7924
0.3995	140.78	-15.627	0.5119

0.2999	76.835	-10.048	0.3318
0.1498	24.710	-5.3432	0.1057
0.0000	15.120	-4.5979	0.0693

T=298.15K

1.0000	1905.8	-161.94	7.9034
0.7994	1043.708	-115.36	3.7892
0.6986	795.00	-90.108	3.3188
0.5985	582.15	-64.993	1.9459
0.5498	426.24	-52.445	1.7606
0.4992	369.14	-39.581	1.5714
0.4496	223.57	-30.149	1.2216
0.3995	198.11	-23.666	0.6350
0.2999	96.505	-12.102	0.3627
0.1498	31.489	-7.4253	0.1795
0.0000	18.432	-5.6475	0.0810

T=303.15K

1.0000	2663.2	-272.81	10.173
0.7994	1885.0	-169.15	5.8152
0.6986	1026.6	-128.36	4.0192
0.5985	626.11	-89.233	3.3821
0.5498	524.44	-69.227	2.5840
0.4992	426.07	-49.656	1.7445
0.4496	283.94	-40.772	1.0742
0.3995	230.64	-29.535	0.7346

0.2999	152.92	-16.987	0.4454
0.1498	38.151	-9.1721	0.2014
0.0000	25.533	-7.6667	0.1076
T=308.15K			
1.0000	3704.3	-420.96	13.220
0.7994	2534.8	-263.93	7.7227
0.6986	1539.4	-190.5	5.2352
0.5985	1093.7	-130.17	4.1728
0.5498	805.30	-97.375	3.0942
0.4992	583.99	-74.272	2.2149
0.4496	453.13	-52.106	1.8134
0.3995	283.82	-38.298	1.0938
0.2999	214.66	-25.646	0.5811
0.1498	54.105	-13.133	0.3153
0.0000	51.792	-9.9352	0.1246

^aThe combined expanded uncertainties U are $Uc(\Delta H_d) = 0.060\Delta H_d$, $Uc(\Delta S_d) = 0.065\Delta S_d$, $Uc(\Delta G_d) = 0.070\Delta G_d$ (0.95 level of confidence).

Table 5. Thermodynamic functions related to dissolution process of cefamandole

nafate form V in (ethanol + water) systems ^a

x_w	$\Delta_{\text{dis}}H(\text{J}\cdot\text{mol}^{-1})$	$\Delta_{\text{dis}}G(\text{J}\cdot\text{mol}^{-1})$	$\Delta_{\text{dis}}S(\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1})$
$T=278.15\text{K}$			
1.0000	545.32	-40.460	2.7934
0.7967	332.69	-36.470	1.5639
0.6993	252.40	-26.940	1.1936
0.5999	179.41	-20.065	0.8555
0.5499	142.13	-16.682	0.6806
0.4998	111.22	-13.248	0.5349
0.4492	84.146	-11.575	0.4034
0.3997	58.990	-8.9010	0.2824
0.2999	33.787	-4.5730	0.1691
0.1498	11.193	-2.9453	0.0605
0.0000	7.3085	-2.5512	0.0375
$T=283.15\text{K}$			
1.0000	790.78	-57.700	3.8715
0.7967	438.78	-43.210	2.0194
0.6993	320.34	-36.840	1.4649
0.5999	219.60	-25.807	1.0174
0.5499	169.84	-20.532	0.7896
0.4998	125.63	-17.525	0.5816
0.4492	94.518	-13.832	0.4392
0.3997	70.964	-9.2700	0.3378

0.2999	39.702	-5.4790	0.1922
0.1498	14.816	-3.7657	0.0728
0.0000	9.830562	-3.1346	0.0467

$T=288.15\text{K}$

1.0000	1000.0	-75.250	4.6731
0.7967	568.03	-68.550	2.5161
0.6993	401.40	-45.570	1.7703
0.5999	272.14	-33.420	1.2103
0.5499	217.93	-26.995	0.9692
0.4998	166.04	-20.768	0.7474
0.4492	124.40	-17.813	0.5601
0.3997	77.960	-10.885	0.3523
0.2999	48.467	-6.3620	0.2305
0.1498	16.087	-4.2742	0.0777
0.0000	10.754	-3.4033	0.0493

$T=293.15\text{K}$

1.0000	1331.8	-103.66	5.8764
0.7967	718.13	-81.260	2.9817
0.6993	500.89	-62.540	2.0687
0.5999	342.07	-48.820	1.4178
0.5499	271.74	-36.565	1.1543
0.4998	221.83	-27.607	0.9447
0.4492	159.12	-19.359	0.6939
0.3997	110.26	-13.353	0.4878

0.2999	67.393	-9.3740	0.3036
0.1498	20.952	-4.8864	0.0980
0.0000	14.010	-4.3634	0.0619

$T=298.15\text{K}$

1.0000	1753.5	-159.37	7.4139
0.7967	927.26	-106.82	3.6787
0.6993	647.60	-86.610	2.5747
0.5999	436.34	-60.490	1.7321
0.5499	343.85	-51.730	1.3689
0.4998	271.66	-38.705	1.1019
0.4492	197.85	-25.742	0.8122
0.3997	142.06	-20.499	0.5745
0.2999	81.130	-11.844	0.3531
0.1498	27.306	-6.5640	0.1196
0.0000	17.544	-5.3056	0.0746

$T=303.15\text{K}$

1.0000	2534.2	-259.59	9.8513
0.7967	1329.6	-153.79	4.9853
0.6993	943.48	-106.05	3.5619
0.5999	586.62	-80.830	2.2080
0.5499	449.41	-63.760	1.7067
0.4998	338.72	-43.310	1.3219
0.4492	251.53	-36.427	0.9714
0.3997	175.31	-23.583	0.6790

0.2999	106.05	-12.776	0.4291
0.1498	36.954	-8.1480	0.1567
0.0000	24.614	-6.8835	0.0983
<i>T</i> =308.15K			
1.0000	3532.4	-342.66	12.774
0.7967	1934.3	-201.32	6.7793
0.6993	1368.8	-158.59	4.8717
0.5999	917.19	-121.23	3.2895
0.5499	692.28	-89.890	2.5188
0.4998	524.72	-67.870	1.9264
0.4492	362.35	-49.147	1.3602
0.3997	239.58	-36.334	0.8907
0.2999	150.53	-20.207	0.5552
0.1498	50.599	-12.812	0.2062
0.0000	41.082	-9.8997	0.1027

^a The combined expanded uncertainties *U* are $Uc(\Delta H_d) = 0.060\Delta H_d$, $Uc(\Delta S_d) = 0.065\Delta S_d$, $Uc(\Delta G_d) = 0.070\Delta G_d$ (0.95 level of confidence).

Figure 1. Chemical structure of cefamandole nafate.

Figure 2. Powder X-ray diffraction patterns for form IV and form V of cefamandole nafate.

Figure 3. Thermal analysis data (DSC) for form IV and form V of cefamandole nafate.

Figure 4. Solubility of cefamandole nafate form IV in the ethanol + water mixtures.

Figure 5. Solubility of cefamandole nafate form V in the ethanol + water mixtures.

Figure 6. Mole fraction solubility of cefamandole nafate form IV and form V in different binary ethanol + water solvent mixtures: (a) $x_w=1.00$, (b) $x_w=0.80$, (c) $x_w=0.70$, (d) $x_w=0.60$, (e) $x_w=0.55$, (f) $x_w=0.50$, (g) $x_w=0.45$, (h) $x_w=0.40$, (i) $x_w=0.30$, (j) $x_w=0.15$, (k) $x_w=0$; solid lines, calculated data by the Modified Apelblat Model.