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Effect of polymorphism on thermodynamic properties of cefamandole nafate

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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 (278.15–308.15) 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.

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 Fig. 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

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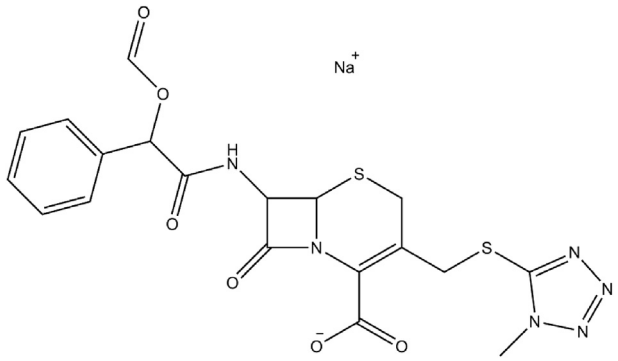

Fig. 1. Chemical structure of cefamandole nafate.

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 Ka radiation (0.1541845 nm). Samples were analyzed over a diffraction-angle (2θ) range of (2–50)°, at a step size of 0.02°, 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 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 5×10^{-6} kg sample was put into the crucible and heated from (298.15–453.15) K at a heating rate of 5 K 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, 429.8 K; $\Delta_{fus}H = 0.25$ J mol^{-1}) and n-dodecane (melting temperature, 263.5 K; $\Delta_{fus}H = 1.27$ J 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 298.15 K. In the polymorphic transformation experiment, about 30 mL of solvent and excess cefamandole nafate were put into a 50 mL conical flask with a glass stopper and then was maintained at 298.15 K inside an incubator shaker (HNY–211B, Tianjin Honor Instrument Co., Ltd. of China) with temperature uncertainty of ±0.01 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

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.