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Preparation of 2:1 urea-succinic acid cocrystals by sublimation

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ABSTRACT

The aim of this study is to introduce a sublimation method for preparing cocrystals. The 2:1 urea-succinic acid cocrystals were generated by a simple sublimation apparatus, analyzed by Powder X-ray Diffraction (PXRD), Transmission Fourier Transform Infrared (FTIR) and Differential Scanning Calorimetry (DCS). The role of supersaturations in vapor crystallization was also discussed in detail. This work showed sublimation was a promising method for cocrystallization.

1. Introduction

Cocrystal is a compound that contains two or more different components bound via intermolecular force: hydrogen bonding, π-stacking, van der Waals forces, etc. [1,2]. Cocrystals, as functional materials, have been widely applied in several fields, particularly synthetic organic chemistry, energetic materials and pharmaceutical [3,4].

The research of cocrystals has several decades' history up to now and many methods have been used to prepare cocrystals as well. The most prevailing method is grinding like neat grinding and liquid assisted grinding [5] which is a process of solvent free and avoid some problems caused by poor solubility of materials. Another method widely used by most researchers is solution crystallization which is preferred to generate single crystals [6] and contains solvent evaporation, solution crystallization by cooling and slurrying [7–10]. But it could be limited by the solubility of materials. Broadly speaking, if cocrystals could be obtained by solution crystallization successfully, the materials should be soluble in appropriate solvent and the purity of cocrystals is higher than other methods. In addition, some novel methods have also been applied in recent years, the 1:1 and 2:1 urea-succinic acid cocrystals were generated by spray drying successfully. The spray drying could offer a path for amorphous or metastable product which is propitious for transformation to cocrystals when the solvent evaporate instantaneously under the hot air [7,11]. However, amorphous or metastable product is thermodynamically unstable that could affect the yield and purity of cocrystals [12]. Isaac et al. prepared a 2:1 cocrystal involving diflunisal and nicotinamide by supercritical antisolvent (SAS) technique [13].

The potential preparing methods for cocrystals are equally as varied, and each has its advantages and disadvantages. For components with good solubility, solution crystallization is superior to other methods while grinding is good for insoluble components. It is reported that sublimation has been used in crystal engineering and more than half of organic compounds are able to sublimate directly to vapor on heating [14]. Compared with solution crystallization, sublimation is a solvent free process in which molecules interact with each other directly avoiding some problems caused by solubility of materials [15].

There have been few researches on preparation of cocrystals by sublimation technique [16,17]. This study contributes to prepare urea- succinic acid cocrystals by sublimation. Urea and succinic acid have been widely applied in crystal engineering and chemical synthesis as materials because of their specificity of the structure in the design and synthesis of the crystals [18]. The molecular structure of urea contains one carbonyl group (C═O) and two amino groups (N–H). In the meanwhile, succinic acid is a dicarboxylic acid including two carboxyl groups (C═O) which is beneficial to form hydrogen bonds with urea. Therefore, our group chosed urea and succinic acid as materials to prepare 2:1 urea-succinic acid (U-SA) cocrystals by sublimation as mentioned above.

2. Experimental section

2.1. Materials

Urea (mass purity $>99\%$) and Succinic acid (mass purity $>99\%$) were purchased from Alfa Aesar and were used as received without further purification.

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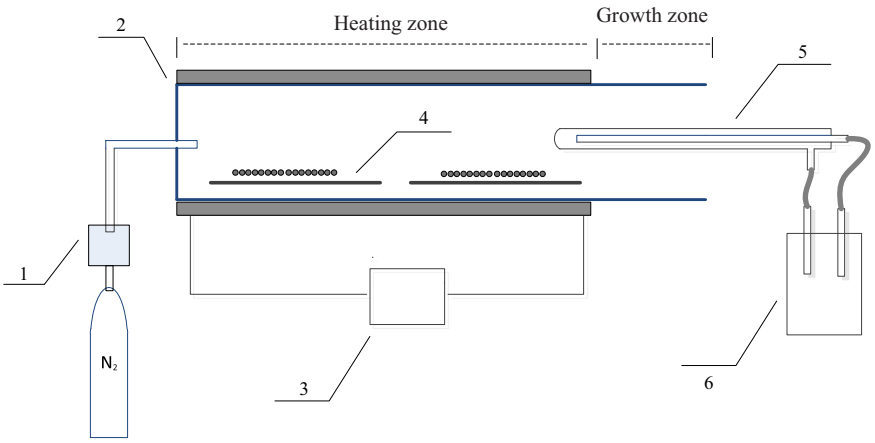

Fig. 1. Sublimation apparatus: 1. Gas flow meter; 2. Heating layer; 3. Temperature controller; 4. Loading plate; 5. Crystal growth tube; 6. Thermostatic waterbath.

2.2. Apparatus and methods

The cocrystals preparation from the gas phase was studied using the apparatus shown schematically in Fig. 1. A horizontal glass tube, as shown in Fig. 1, was used for the transport of the starting materials and the growth of cocrystals. The length of the tube is 300 mm in the heating zone and 100 mm in the crystal growth zone, with a constant inner diameter of 32 ± 0.2 mm. Heating was applied by a resistance furnace with an accuracy ± 1 °C. Two thin material loading plates with 100 mm in length and 24 mm in width were placed in the heating zone. In the crystal growth zone the temperature of crystallization tube (T_{CT}) was under the control of thermostatic waterbath.

Sublimation experiments were carried out by the transpiration method [19]. The carrier gas (N_2) passes above the sample on the loading plates and carries the sublimation gas phase from the heating zone to the crystal growth zone, simultaneously allowing filling and purging the reactor tube prior to heating. A too high flow rate of carrier gas may lead to the low gas concentration and consequent low supersaturation in growth zone. The optimal flow rate (50 mL/min) of carrier gas ensures the vapor sublimated carried away in time from the heating zone and provides enough residence time to crystallize in the crystal growth zone.

3. Analytical methods

3.1. Powder X-ray Diffraction (PXRD)

PXRD is usually used to identify and analyze the degree of crystallization of starting materials and cocrystals. The solid powder of samples was characterized by the Rigaku smaterlab X-ray diffractometer with Cu-Kα radiation (1.54 A°) and the diffractometer was operated at 40 kV and 150 mA. The sample was scanned from 5° to 60° (2θ) with a step of 0.01°. The instrument was precalibrated using a silicon standard.

3.2. Transmission Fourier Transform Infrared (FTIR) Spectroscopy

Infrared spectral is able to provide a bit of information which includes detecting functional groups formation, studying cocrystal interactions and distinguishing cocrystals from salts. FTIR spectra were collected by a BRUKER VERTEX70 FT-IR Spectrometer in a range of 4000–400 cm^{-1} using KBr pellets.

3.3. Differential Scanning Calorimetry (DSC)

Thermal analysis is utilized to determine the purity of cocrystals, to confirm phase transition temperature and to identify the enthalpy of fusion. DSC analytical data of samples placed in crucible was obtained by using a STA449F3Jupiter calorimeter with a heating rate of 10 K/min from 30 to 200 °C under a constant dry nitrogen atmosphere at a flow rate of 50 mL/min. The instrument was equipped with a refrigerated cooling system.

3.4. Scanning Electron Microscopy (SEM)

Scanning electron microscopy is mainly used to analyze the structure and components of crystals from microscopic by amplifying the material to the nanometer level. The SEM was performed on a TM3000 (Hitachi High-Technologies, Japan).

4. Results

4.1. The sublimation temperature

It is necessary to notice that the sublimation temperature should be controlled within a suitable range to avoid materials decomposing. According to our previous work [15] the sublimation temperature of succinic acid below 195 °C can eliminate the risk of dehydration reaction. The melting point of urea is about 130 °C, but two molecules of urea will lose an ammonia molecule into biuret at 115 °C [20].

Due to the inhomogeneity of temperature available in horizontal direction of heating zone, the temperatures of three positions (Left middle and right of heating zone) have been measured by an additional thermocouple (Table 1) and results showed some difference between set value and actual temperature. Fortunately, FTIR-spectra analysis was proven to be effective to differentiate the biuret from the urea (Fig. 2). By this apparatus a series of further sublimation experiments of urea showed 108 °C, the set value of temperature, is the upper limit to sublimate without decomposition. Here 105 °C was as the set temperature for final experiment. However, a lower temperature is unwise due to that succinic acid sublimes too slowly to form any sizeable crystals within a reasonable time frame. Considering the sublimation rate of material being proportional to the area of exposure, a suitable area ratio of

Table 1
The temperatures (°C) at different positions of heating zone.

$T_{set\ value}$	T_{left}	T_{middle}	T_{right}
110	109.4	111.7	110.8
105	104.0	106.9	104.6