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Crystal morphology optimization of thiamine hydrochloride in solvent system: Experimental and molecular dynamics simulation studies

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ABSTRACT

Thiamine hydrochloride (THCL) was produced in methanol accompanied with agglomeration in industry, the plate like morphology of THCL in methanol was not deserve to have a good quality. Selecting a suitable solvent should be considered because solvent could be one of the essential factors to impact morphology. Methanol and methanol/ethyl acetate solvent (0.2 vol fraction of methanol) was selected as the solvent system in reactive crystallization of THCL. The experiment results show the THCL crystal morphology in methanol/ethyl acetate solvent system was granular and more regular than that in methanol. In order to explicate the different crystal morphology in different solvents, molecular dynamics (MD) simulation was introduced to simulate crystal morphology in different solvents. The attachment energy (AE) model was employed to investigate the morphology of THCL under vacuum conditions, methanol and methanol/ethyl acetate solvent conditions, respectively. The simulation crystal morphology was in a good agreement with that of experimented. The particle of THCL in methanol/ethyl acetate solvent has less tendency to agglomeration, and then it is favorable to the downstream process, such as filtration, storage and transportation.

1. Introduction

Crystal morphology has a great impact on drug manufacture, moreover, it is the key factor to affect the industrial purity. According to Sun [1], physical, chemical and bioavailability properties of active pharmaceutical ingredient (API) are usually influenced by crystal morphology. In drug manufacture, spherical and granular crystal is usually desirable because of good mechanical properties, while need-like or plate like crystal exhibits poor mechanical strength during tableting. Besides, stability, which is essential to crystal during storage such as drug and explosive, is influenced by crystal morphology. For example, Duan et al. [2] and Liu et al. [3] found that the crystal morphology is an impact factor for controlling sensitivity of HMX and DNTF (explosive).

Crystal morphology usually governed by two factors [2], the internal structure and external parameters including solvents, supersaturation, temperature, stirring rate, additives and so on. Among them, the effect of solvents is especially important [4,5]. In Meir Lahav's [6] theory, solvents can absorb at specific faces, causing certain faces grow faster and finally disappear, some certain faces grow slowly to expand. It is determined by energy of absorption, which can be calculated by attachment energy (AE) model and Bravais-Friedel-Donnay-Harker (BFDH) model [7].

Thiamine hydrochloride ($C_{12}H_{18}Cl_2N_4OS{\cdot}HCl$, THCL), a kind of vitamin B_1, is an important drug or healthcare production. Thiamine hydrochloride can be used to treat inappetence and dermatophytosis. More importantly, it is contributed to metabolize in human body. Neurotransmission will be affected if a person lacks of thiamine hydrochloride [8]. Hence, thiamine hydrochloride is widely used in human's life, besides, it can be used as feed in agriculture and synthetic intermediates in industry.

Thiamine hydrochloride has four crystal forms, nonstoichiometric hydrate [9] ($C_{12}H_{18}Cl_2N_4OS{\cdot}nH_2O$, NSH), hemihydrate [9–11] ($C_{12}H_{18}Cl_2N_4OS{\cdot}0.5H_2O$, HH), anhydrous form [9,11,12] ($C_{12}H_{18}Cl_2N_4OS$, AH) and methanol solvate [13] ($C_{12}H_{18}Cl_2N_4OS{\cdot}CH_3OH$, MM). These solid-state forms could convert into each other in specific conditions [9,12–18]. The transformation can be shown in Table 1. It can be seen that hemihydrate (HH) is the most stable crystal form since anhydrous thiamine hydrochloride (AH) and nonstoichiometric hydrate (NSH) can convert to hemihydrate (HH) and irreversible. Actually, hemihydrate (HH) do not lose water even heated until 393 K because of strong hydrogen bonds between water and THCL [10], and it decomposes when continue heating.

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Table 1
Transformation conditions of THCL crystal forms.

Crystal form after transformation	Crystal form before transformation			
	HH	MM	AH	NSH
HH	Keep origin form under 105 °C [9]	Room temperature, humanity at 40–75% [13];	Room temperature, room humanity, enough time [12] Agglomeration[9]	Suspension in water <12 h, filter and dry on 40 °C [9,12];
MM	Expose to methanol vapor or methanol solvent [13];	Nonpolar solvents [12]	Expose to vapor or methanol solvent [13]	Expose to vapor or methanol solvent [13]
AH	Suspension in ethanol solvent [10]; dehydration and decomposition at 120 °C [9,10,19,20];	Heat more than 150 °C[13]; Expose to polar solvent, faster in stronger polar solvents [13];	–	Dehydration <40 °C [12],with no change of lattice structure [14–17];Mix with AH on 1:1 (mass ratio), humanity at 11% [18]
NSH	Partial dehydration at 60–90 °C, 20–760 mTorr [12]	Room temperature, humanity at 11–40% [13];	Room temperature, room humanity[12];Mix with NSH on 1:1 (mass ratio), humanity at 33–69% [18]	–

In industrial manufacturing, thiamine hydrochloride is produced by thiamine nitrate using reactive crystallization in methanol solvent. And the equation is shown as:

$$C_{12}H_{17}N_5O_4S + 2HCl \rightarrow C_{12}H_{17}ClN_4OS \cdot HCl + HNO_3 \quad (1)$$

An appropriate mass of thiamine nitrate and methanol were mixed in a reactor with stirring rake, after a period of time, hydrochloric acid (HCl) was added slowly into the suspension, the reactor was kept in a certain temperature. Cooling down the temperature when the reaction finished, and thiamine hydrochloride started to crystallize. Then methanol solvate was obtained. However, the particle produced by reactive crystallization in methanol is plate like habit and it agglomerates seriously.

In order to optimize the crystal morphology of THCL, methanol and methanol/ethyl acetate (0.2 vol fraction of methanol) mixed solvents were selected to investigate the crystal morphology of thiamine hydrochloride by reactive experiments. MD simulation was introduced to explicate the different crystal morphology caused by solvents. Moreover, particle size distribution (PSD) and bulk density analysis were measured to characterize crystal morphology of THCL.

2. Methods

2.1. Materials

Thiamine nitrate, with a mass purity of 98.0%, was supplied by Shanghai Molbase biochemical technology Co. Ltd., China. And pure solvents (AR, >99%) such as methanol, ethyl acetate, ethanol, acetone (dehydration by molecular sieve) were supplied by Tianjin Kewei Chemical Co. Ltd., China. Distilled-deionised water (conductivities <0.5 μs cm^{-1})

2.2. Reactive crystallization

In this experiment, pure methanol, binary mixed solvent ethyl acetate + methanol (0.2 vol fraction of methanol) were used as solvent to obtain the products.

The crystallization was conducted in a 250 mL crystallizer connected with a thermostat bath at 333.15 K. An agitator with a speed of 280 rpm was used to mix the solvent and the solute. For the experiment, 10 g thiamine nitrate was added into the crystallizer, then 100 ml methanol or methanol/ethyl acetate (volume fraction ratio: 20:80) were introduced to the crystallizer, these two experiments were named experiment A, B, respectively. 6.05 g hydrochloric acid (37.2% of mass ratio) was heated and HCl was created. Subsequently, HCl was introduced slowly to concentrated sulphuric acid (98% of mass ratio) to remove water vapor (hydrochloric acid was not introduced into crystallizer directly because of large solubility of THCL in water). When the reaction finished, the supersaturation was obtained by cooling down the solution to 283.15 K. It took about 5 h to reach the final temperature.

Furthermore, samples were observed and analyzed by scanning electron microscope (SEM).

2.3. Characterization analysis

X-ray power diffraction (XRPD) was used to characterize polymorphs of sample in experiment A, B. The analysis was carried out using the D/MAX-2500 (Rigaku, Japan) by Cu Kα radiation (λKα = 0.15406 nm) at 100 mA and 40 kV, over a diffraction angle (2θ) range of 2–50 degree with a scanning rate of 8 degree per minute.

Besides, the thermal analysis of products of experiments A and B were measured by DSC simultaneous thermal analyzer (TGA/DSC 1, Mettler-Toledo, Switzerland). About 5 mg of sample was used with a heating rate of 10 K min^{-1} under a dynamic nitrogen atmosphere and temperature was from 298.15 K to 573.15 K.

2.4. Particle size distribution (PSD) analysis

PSD analyzer (Malvern Instruments Mastersizer 3000 particle size analyzer) was used to measure the PSD of thiamine hydrochloride in methanol and mixed solvent. Mie-Scattering analysis model was used for diffraction pattern measurement. Thiamine hydrochloride suspension with acetone was introduced to a designated vessel. Each sample was measured five times, and the average value was taken as the final result.

2.5. Bulk density

The bulk density was calculated by the volume and weight of the powder. The powder tap density was measured by the powder comprehensive characteristic testing instrument [21] (BT-1000, Bettersize instruments Ltd., China).

2.6. Molecular dynamics simulation

In the work, MD simulation was used to simulate crystal morphology of THCL simply by software (Materials Studio 7.0, Accelrys Inc., USA).