POLYMORPHISM IN THE CRYSTALLIZATION OF GLYCINE

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Abstract

Glycine crystallizes in more than three different polymorphic forms, α, β and γ. The form α and form γ have been prepared by recrystallization and quench-cooling method, respectively. The physicochemical properties of α- and γ-forms of glycine were investigated. Techniques used to study the polymorphs include X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), solubility determination at 10–70°C and inverse gas chromatography (IGC). Based on the surface free energy analysis and solubility measurement, the γ-form is more stable than the α-form at ambient temperature. The influence of additive, sodium chloride, in the determination of the polymorphs was studied. The conformational change of the α-form to γ-form is enhanced by sodium chloride through glycine–NaCl interaction. In the NaCl solution, the nucleation and crystal growth of the γ-form crystals are promoted while the crystallization of α-form is prevented.

Key words: Polymorph, Additive, Glycine, Nucleation, Crystal growth

1. Introduction

The phenomenon of polymorphism is well-known as the property of a solid with different arrangements of molecules or conformations in the crystal lattice [1]. The possibility of polymorphism may exist for any particular compounds, but the conditions and systematic methods required to prepare certain polymorphs are still challenges for many years [2]. The control and optimization of the polymorphic form play key roles in the crystallization process, especial in the pharmaceutical industry. Polymorphic crystallization is affected by various factors, such as cooling rate [3], supersaturation [4], agitation [5], solvent [6], pH values [7], additives [8], solution concentration [9], impurity [10], seeding [11].

Glycine (NH_2CH_2COOH) was chose as the model compound in this study. In the gaseous phase, glycine can exist as a nonionic form, while exist as a zwitterion in solution and solid form [12]. Under different conditions, glycine crystallites exist in at least three kinds of polymorphs, α, β and γ, which have different relative stabilities [13], crystal shape [14], thermal, and physical properties [15]. The α- and γ-forms have quite different conformations [16]. The two polymorphs differ in the different hydrogen bond networks, which are formed between NH_3^+ groups and COO^- groups [17]. Accordingly, the α-form appears in centrosymmetric space group $P2_1/n$ [18], while the γ-form crystallizes in noncentrosymmetric space group $P3_1$ [19]. Crystallization of glycine solutions in the water at isoelectric point always produced the α form [20] while the γ-form apparently appears when crystallization takes place from solution is acidified, made alkaline [21] or by the addition of compounds that inhibit the growth of α-form [22].

This study is to determine how additive affects the polymorphic forms of glycine. The relationship between the solubility of the two polymorphs in different solutions is discussed.

2. Experiment

Glycine (99%) and sodium chloride (99.5%) employed for the present study was obtained from Sigma Aldrich. All experiments used double-ionized water.

The α-form was prepared by recrystallization from aqueous solution. The γ-form was obtained by quench cooling process. In this process, purchased glycine was dissolved in water and mixed with a saturated solution of NaCl in different ratios. The resulting solution was filtered and then quench-cooled in refrigerator at -18°C. The solid samples were dried in a vacuum oven at 60–65°C and the polymorphic types were checked by the FTIR or XRD.

DSC thermogram was recorded using a Mettler Toledo STAR^e system equipped with a DSC-822^e calorimetric cell and Mettler TA-STAR^e software. Samples (5–7 mg) were weighed using a Mettler MT 5 microbalance, placed in a 40 μL crimped aluminum pan (closed lid without pinhole) and placed in the DSC module, using an empty aluminum crimped pan as the reference. The sample was heated at a rate of 10°C/min from 30°C to 200°C. Nitrogen flow was maintained at 40 mL/min and

Liquid nitrogen was used as the coolant. The DSC was calibrated by using extrapolated onset temperatures of the fusion endotherms of indium and zinc pure standards.

The powder X-ray diffraction pattern of the product crystals was recorded on a BRUKER-axs-D8 X-ray diffractometer using Cu K_α radiation (λ= 1.54 Å), with a scan rate of 2^o/min, step size of 0.02, and a 2θ range of 10–40^o. The sample was powdered finely and placed in a plastic sample holder.

The FTIR spectrum for the samples was recorded in the range 400–4000 cm-1 using the Digilab FTS-3000. The samples used were in pellet form in KBr phase. The structure of each crystal was found to be neither altered nor destroyed by pelletting.

Surface thermodynamic parameters of adsorption for each sample were determined by inverse gas chromatography (Surface Measurement Systems Ltd.) at infinite dilution using a Gas Chromatograph (6890N) equipped with a thermal conductivity detector (TCD) and a flame ionization detector (FID).

A 250mL jacketed crystallizer with an electromagnetically driven stirrer was employed for solubility experiment. The temperature was controlled by a Julabo programmable circulator FP50-ME. Saturated solutions were prepared by introducing excess amounts of form α and form γ. After 48 h when the sample had reached the equilibrium and then the stirring was stopped. The solution was allowed to settle at least for 6h and the remaining solid was allowed to precipitate. A sample of approximately 10 mL was withdrawn by using a syringe and filtered through filter paper (Whatman, PTFE, 0.45 μm). The clear liquid was inserted into a glass vessels (previously weighted) and weighted. Then the saturated solution was completely dried in the drying stove at 60^oC. Considering the transformation between the two forms, the excess solid of each measurement was analyzed by FTIR or XRD. The mass of sodium chloride in these solutions was taken into account in calculating the solubility of the glycine.

3. Results and Discussion

3. 1 Characterization of the products

Fig. 1 illustrates PXRD pattern of the α-form and γ-form of glycine crystals. It can be seen that there are some clearly distinct features between their profiles and the positions of the peaks are found to be in good agreement with the data in JCPDS files. Hence the pure γ-polymorph can be prepared by quench-cooled glycine solution with NaCl before melting.

DSC result for form γ is shown in Fig. 2. The peak observed at 168^oC is due to the phase transition from γ-form to α-form, which is in agreement with the reported work [23, 24]. Based on this result, γ-form is more thermodynamically stable than α-form at ambient conditions.

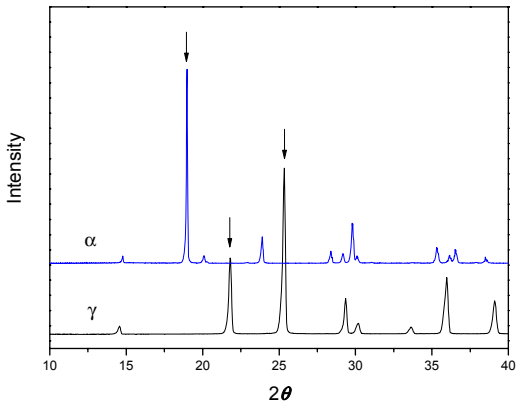

Figure 1. PXRD patterns of glycine solids.

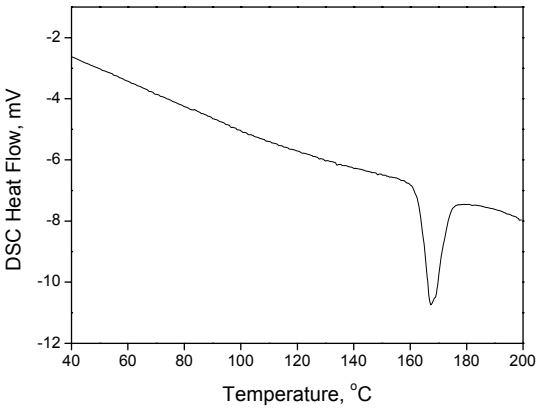

Figure 2. DSC thermograms of the γ-form.

The FTIR spectra of the two forms are observed in the range from 500 to 4000cm^{-1} and is shown in Fig. 3. It can be seen that glycine crystal possesses a characteristic peak at 910 cm^{-1} for α-form and 930 cm^{-1} for γ-form and a common peak at 890 cm^{-1}. Therefore, FTIR is one of the useful tools to identify the two forms.

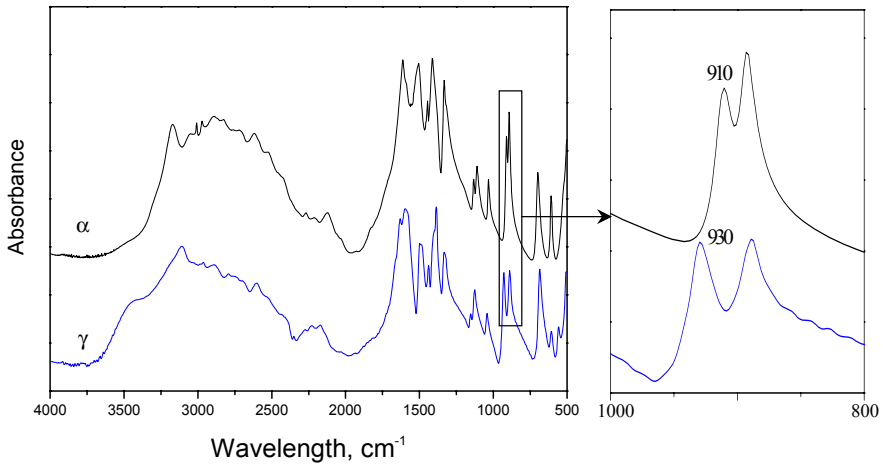

Figure 3. FTIR spectra of glycine solids.

3.2 Relative physical stability and solubility of glycine polymorphs

Thermodynamic stability can be characterized by a thermodynamic parameter – Gibbs energy. Smaller the free energy, more stable the polymorph [25]. From the results of IGC, the dispersive components of surface free energy, γ_s^D, of the α- and γ-form are 46.07 and 43.12 mJm^{-2}, respectively. Thus, the order of the stability of the glycine polymorphs at ambient temperature was shown to be $\gamma > \alpha$.

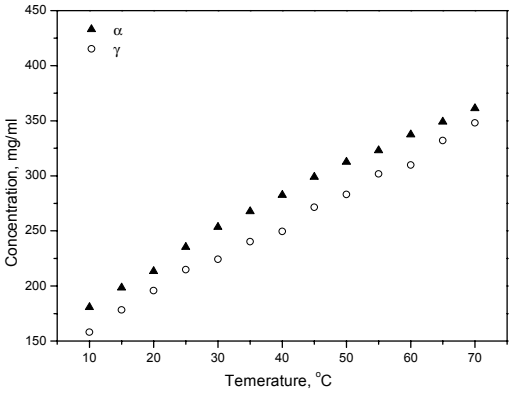

Figure 4. Solubility of α and γ glycine in water.

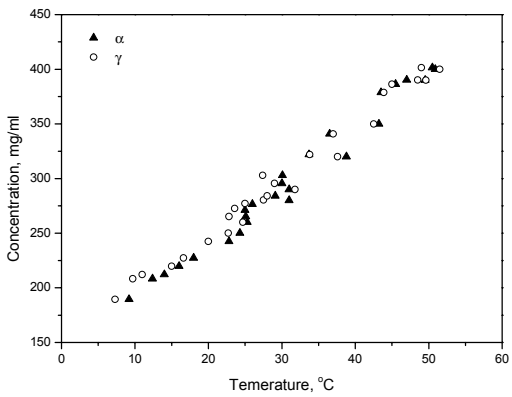

Figure 5. Solubility of α and γ glycine in NaCl solution

Polymorphs of a substance can have different solubility, and the solubility of most stable form is always less comparing to that of metastable form. The results of solubility measurement of the two forms in water are given in Fig. 4. It can be seen that the solubility of α-form is higher than that of γ-form. This result confirms that γ-form of glycine is the stable and less water soluble form at room temperature.

Fig. 5 shows the solubility of the two polymorphs of glycine in sodium chloride solution with NaCl concentration of 12 wt.%. The solubility of each polymorph is increased with addition of NaCl in solution. Obviously, the solubility of the γ-form is increased more than that of the α-form by introducing NaCl.

It was found that only the pure γ-form crystallized from the solution with 12 wt.% NaCl no matter what initial concentration of glycine or cooling rate. Based on the solubility results, it is proposed that the interaction between sodium ions and glycine molecules plays an important role in the nucleation of each polymorph. This interaction may include electrostatic interaction and van der Waals attraction. To confirm the effect of NaCl on the conformation of the products, the nature of the polymorph that crystallized from solutions with different NaCl concentrations was analyzed. At low concentrations of NaCl (0-4 wt.%), the α-form always appears, while at higher concentrations of NaCl, the γ-form may be preferable. Thus, a possible explanation for the change in the relative stability of the two forms in the NaCl solution is that the addition of Na^+ ions is in favor of the nucleation and growth of the γ-polymorph, which is due to the interaction between the Na^+ ions and conformer of the γ-form. Higher Na^+ ions concentration, stronger the interaction.

4. Conclusions

The two forms of glycine (form α and γ) produced by recrystallization and quench-cooling method, respectively, exhibit high polymorphic purity, which were confirmed by XRD, FTIR and DSC. Based on the IGC analysis and the solubility data, it is clear that the γ-form is basically the stable form and the α-form is the metastable form at ambient temperature. The effect of sodium chloride on the polymorphism of glycine crystallization was studied. It is proposed that the solute–solvent interaction

plays an important role in the nucleation of each polymorph. In water, the nucleation and growth rate of the α-form crystal may be preferable, while the appearance of γ-form crystal can be promoted in the NaCl solution.

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