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Polymorphism of L-glutamic Acid: Influence of the Additive Ammonium Sulphate upon the Phase Change between α- and β-polymorphs

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The effect of salt additive $(NH_4)_2SO_4$ on the phase transformation of L-glutamic acid was investigated in cooling crystallization. L-glutamic acid has two kinds of polymorph including α-form and β-form that are known as the metastable and stable form, respectively. In cooling crystallization, the α-form was initially generated, after that it slowly transformed into the β-form in the solution, where the phase transformation required at least 25 h for completion. However, the present study indicated that the phase transformation of L-glutamic acid was significantly promoted as using the salt additive $(NH_4)_2SO_4$, where it completely transformed within 12 h as using salt additive of 4 g/l. That means the phase transformation was markedly accelerated more than 2.0 times as using the salt additive. Here, the solute concentration during the phase transformation was monitored by the UV/Vis spectroscopy, while the shape and crystal fraction of α- and β-form were confirmed by the optical microscope and FT-IR spectroscopy, respectively.

Key words: Crystallization, polymorphism, phase transformation, additive effect

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Polymorphism is an important phenomenon of materials that is able to adopt more than one crystal structure, where each polymorphic crystal has its own unique combination of mechanical, thermal, physical and chemical properties such as solubility, hardness, stability, and bioavailability, etc. [1–8, 10–15]. Therefore, the production of specific and well-defined polymorphs of material is crucial in chemical manufacture.

In order to achieve the desired polymorphic crystal, the phase transformation of unstable phase to stable phase in crystallization should be controlled. The phase transformation of polymorphic crystal depends on many operating conditions such as the additive, fluid hydrodynamic, seed, etc. [1–8, 10–15]. For example, Wang *et al*. [2] indicate that the phase transformation of glycine from unstable phase to stable phase is significantly enhanced as using the salt additive (NaCl). Here, the salt additive effect is considered a key factor to determine molecular arrangement in the solution of the stable phase nuclei, so the nucleation rate of stable phase is certainly promoted as using the salt additive (NaCl), which result in acceleration of phase transformation rate. In case of GMP phase transformation, Tuan *et al*. [3–7] also reported that the dissolution of amorphous and the growth rate of hydrate crystal during the phase transformation are simultaneously promoted as using the periodical Taylor vortices flow in Couette-Taylor crystallizer, in which the phase transformation rate is significantly facilitated at least 5.0 times compared to that in the conventional mixing tank crystallizer. Mazzotti *et al*. [8] also reveal that the phase transformation of α-form to β-form L-glutamic acid is markedly accelerated as using the β-form seed crystals, where the β-form seed crystals neglect the period of β-form nucleation, so the phase transformation rate is certainly promoted.

In the present study, the effect of salt additive $(NH_4)_2SO_4$ on the phase transformation of

L-glutamic acid was firstly investigated in cooling crystallization. Here, the solute concentration and crystal fraction of β-form were detected by the UV/Vis and FTIR spectroscopy, while the shape and crystal structure were monitored and defined by the optical microscope and X-ray patterns, respectively.

EXPERIMENTAL

The L-glutamic acid material (99% purity) and salt additive ammonium sulphate ($(NH_4)_2SO_4$, 99% purity) were purchased from the Sigma Aldrich Company. The feed solution was prepared by dissolving the material in distilled water and the concentration was varied from 30 g/l to 45 g/l. After that, a certain amount of salt additive ammonium sulphate was added to the L-glutamic acid feed solution. The temperature of feed solution was always fixed at 70 °C. During cooling crystallization, the temperature of crystallizer gradually decreased from 70 °C to 30 °C at 4 °C/min cooling rate as using the circulating coolant from the chiller. Here, the crystallizer was designed following the standard Rushton mixing tank [9], where it was made of pyrex glass with the outer cooling jacket, four baffles and six-blade turbine impeller for effective mixing. The agitation speed of impeller in crystallizer was changed from 360 rpm to 600 rpm.

The samples of the product were periodically taken from the crystallizers and quickly filtered by using a vacuum pump. The solid samples were then dried in a desiccator and analyzed to define the shape, crystal structure and crystal fraction of β-form. The shape of crystal product was monitored by the optical microscope (IT System, Sometech, USA), while the crystal structure and crystal fraction were confirmed and estimated by the XRD patterns (X-ray diffractometer, MAC Science, M18XHF-SRA, CuK_α line, Japan) and FT-IR spectroscopy (Tensor 27 Bruker, Germany), respectively. The solute concentration was analyzed by using the absorbance at 193 nm of the UV/Vis spectroscopy (UV-1800, Shimadzu, Japan). Meanwhile, the temperature of suspension was continuously monitored by the temperature controller (National Instruments, Korea), respectively.

RESULTS AND DISCUSION

Characterization of α-form and β-form

The typical shape of α-form was prism, and it was clearly distinguished with the needle shape of β-form, as shown in Figure 1(a). Furthermore, the crystal structure of two polymorphs was obviously different as using the X-ray patterns, as shown in Figure 1(b). Here, the different characteristic peaks of two polymorphs were clearly visible at 10°, 15°, 16°, 18°, 21°, 23°, 26.5°, 27.5° degrees.

The solubility of α-form and β-form was investigated under various concentration of salt additive $(NH_4)_2SO_4$. Here, the solubility of each crystal form at a certain amount of salt additive was measured via the following method. That is

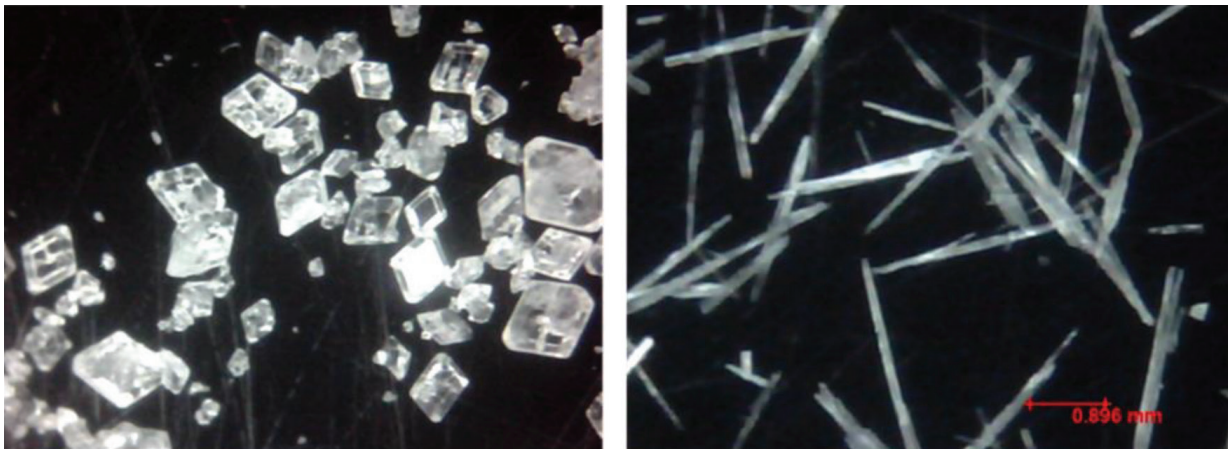

Figure 1(a). Typical shape of α-form and β-form.

the saturated solution with each crystal form was quickly filtered and the solute concentration was analyzed by the UV/Vis spectroscopy. As shown in Figure 2, the solubility of the α-form and β-form monotonically increased when increasing the salt concentration. Due to the unstable structure of the α-form, the solubility of α-form was always higher than that of the β-form across the whole range of salt concentrations, indicating the monotropic system between the two polymorphs of L-glutamic acid. Moreover, the solubility difference between two polymorphs is known as the driving force of the phase transformation in the solution [10].

Due to the distinct molecular arrangement in crystal structures of L-glutamic polymorphs, the IR spectroscopy with the characteristic bonding peaks of each form was detected [1]. As shown in Figure 3(a), the characteristic peak of the α-form occurred at 2129 cm^{-1}, corresponding to the N-H stretching vibration of the amine group, shifted to 2080 cm^{-1} in the β-form due to the different intermolecular hydrogen bonding strength of the amine groups in the two different solid structures. It revealed that the peak intensity ratio $I_\alpha/(I_\alpha+I_\beta)$ of α-form and β-form directly depended on the fraction of β-form in the solid mixture. Thus, the peak ratio could be used to calibrate the crystal fraction between the α-form and β-form in the mixture solid [Figure 3(b)]. According to the calibration curve, the mass fraction of β-form in the solid mixture was estimated.

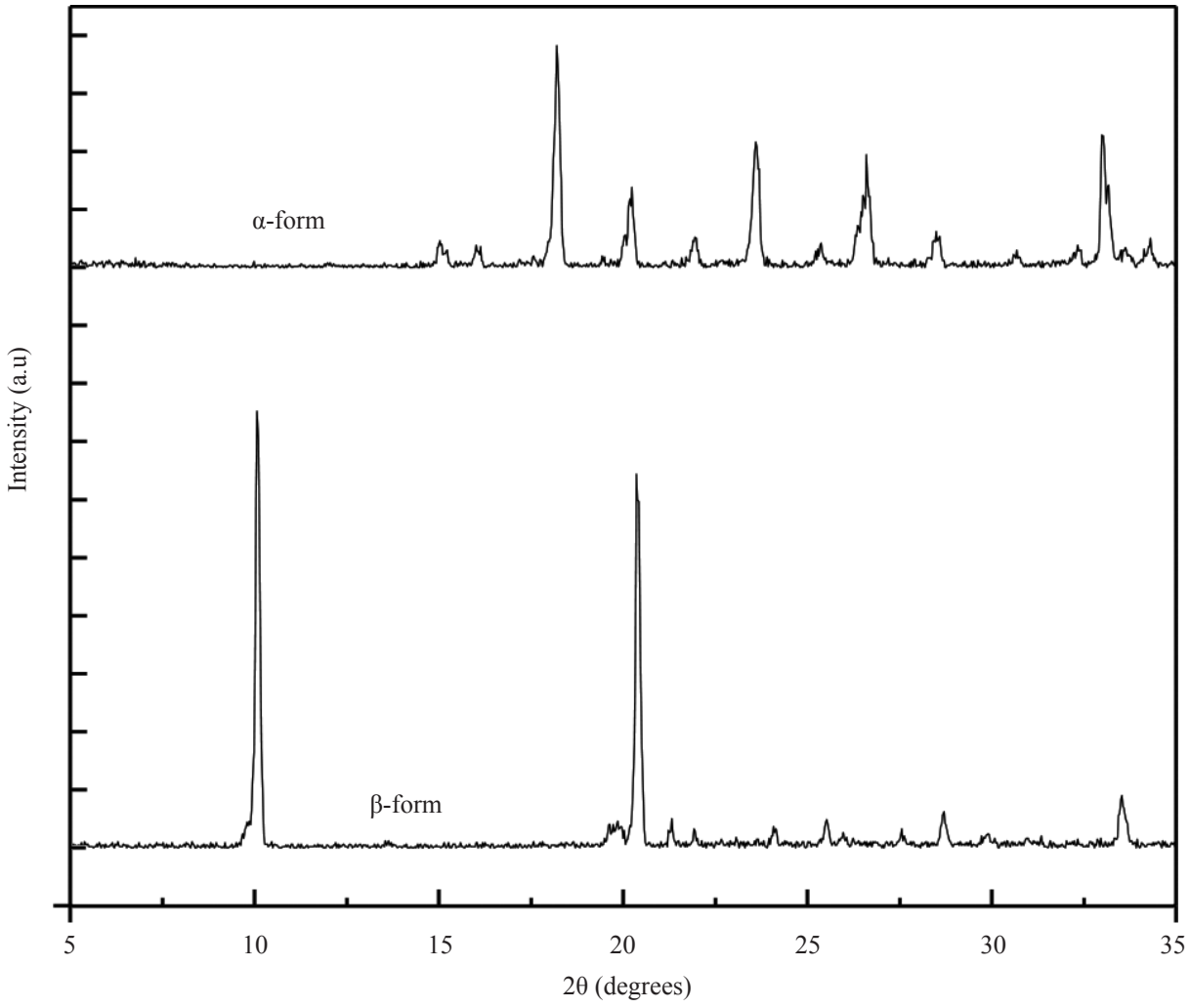

Figure 1(b). X-ray patterns of α-form and β-form crystal structure.

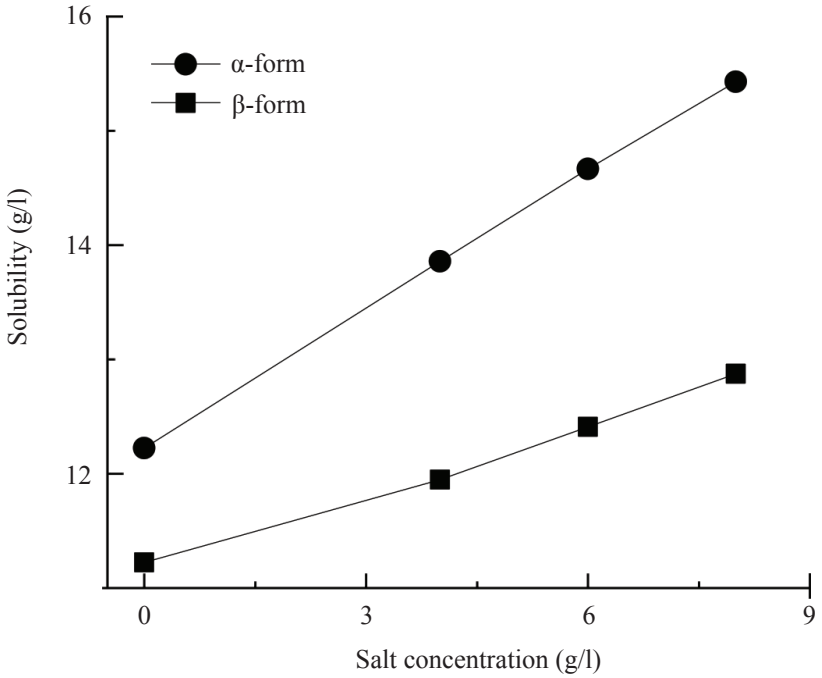

Figure 2. Solubility of α-form and β-form with varied salt concentrations.

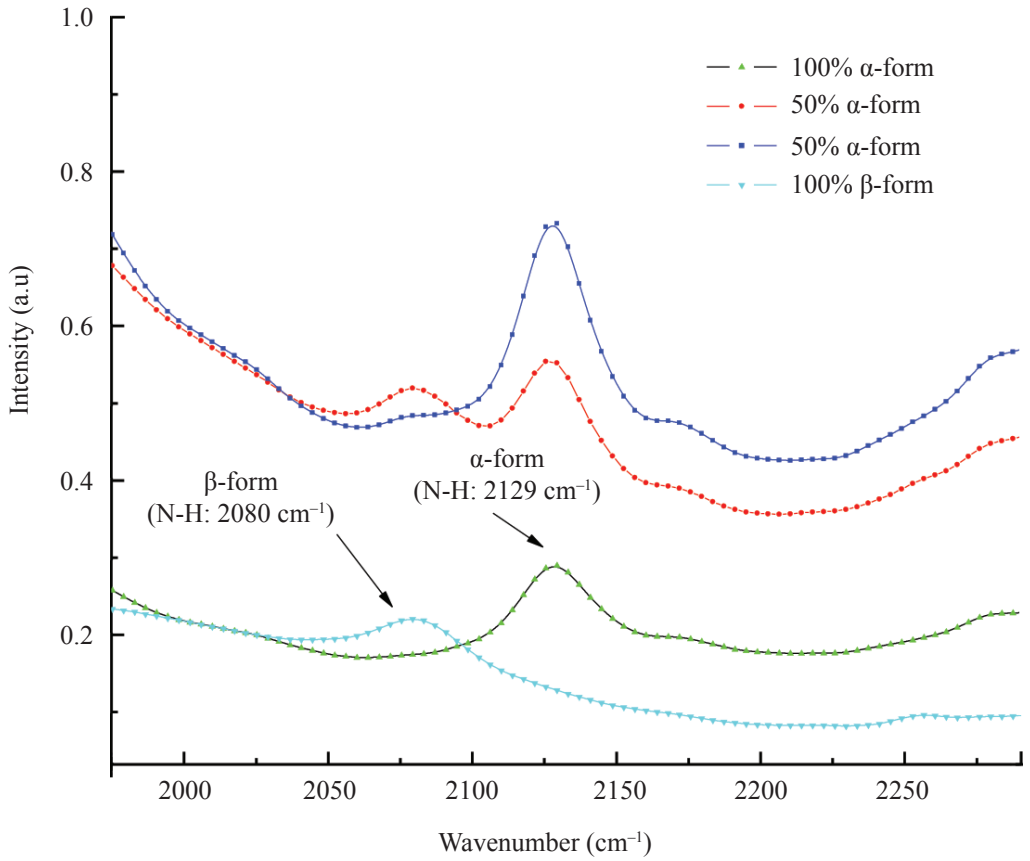

Figure 3(a). FT-IR spectroscopy of α-form, β-form and mixture of solid product (α- and β-form).

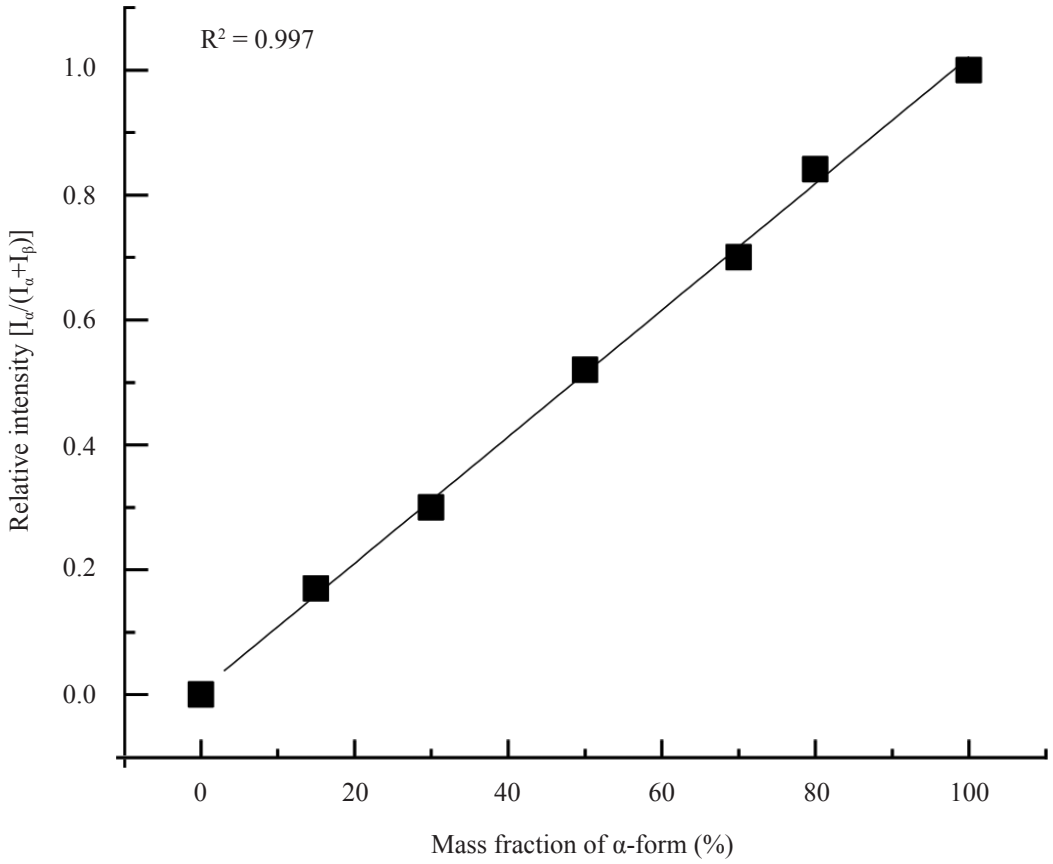

Figure 3(b). Calibration curve of α-form and β-form in solid mixture.

Phase Transformation of α-form to β-form

The phase transformation of α-form to β-form was investigated in cooling crystallization, as shown in Figures 4–5. The shape of the α-form and β-form were optically observed, as shown in Figure 4. The prism shape of α-form crystals was initially generated in the early stage of crystallization [Figure 4(a)], after that it partially disappeared, while the needle shape of β-form crystals appeared at 1 h of crystallization time [Figure 4(b)]. At 25 h of crystallization time, only the needle-shaped b-form crystals appeared without any prism shape of α-form crystals, as shown in [Figure 4(d)]. These microscopic observations were consistent with the IR spectroscopy of the solid product, as shown in Figure 5, where the crystal fraction of β-form gradually increased with the crystallization time and achieved 100%wt after 25 h. It was well known that the secondary nuclei of β-form crystals appeared and grew on the surface of the α-form crystals [Figure 4(b)], which was reported by Davey *et al*. [11]. As such, the phase transformation of α-form to β-form crystal was interpreted that the α-form crystal was initially generated in the early stage of crystallization, after that it slowly dissolved to the solution and created the supersaturation for the formation of β-form nuclei happening on the surface of α-form crystal. During the phase transformation, the α-form and β-form crystals were simultaneously dissolved and grown in the solution. The phase transformation of α-form to β-form crystals was completed after the last α-form crystal had dissolved and the remaining β-form crystal had grown at the stable solubility. The crystallization time required for the completed phase transformation was called the completion time. As shown in Figure 5, the 100%wt crystal fraction of β-form in the solid mixture corresponding to the pure β-form was achieved after 25 h of crystallization time at 30 g/l feed concentration and 360 rpm agitation speed.

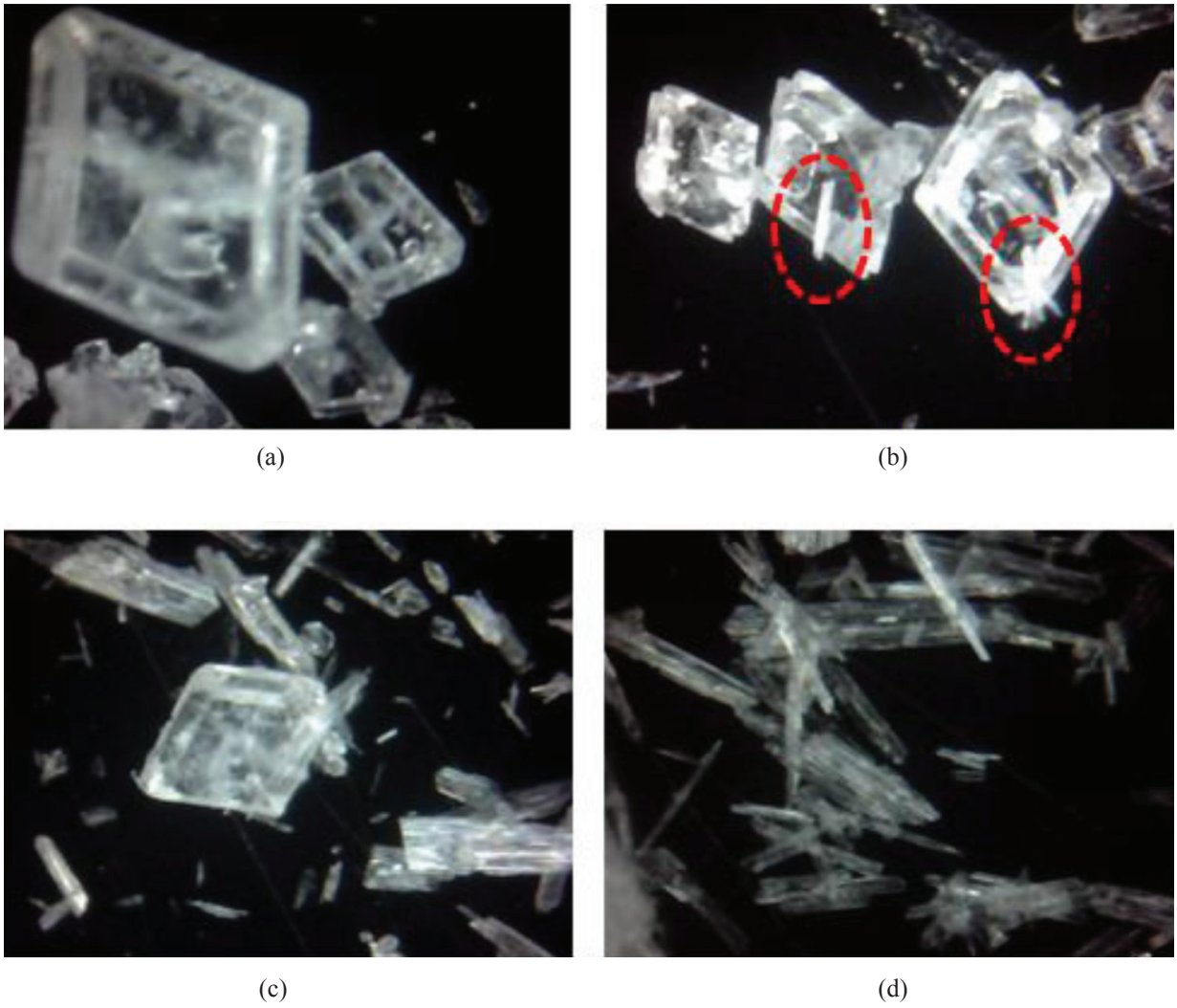

Figure 4. Typical shape of polymorphic crystals during the phase transformation with 30 g/l feed concentration and 360 rpm agitation speed: (a) at τ = 30 min, (b) τ = 1 h, (c) τ = 12 h and (d) τ = 25 h.

The influence of the crystallization conditions including feed concentration and agitation speed on the phase transformation was also investigated. As shown in Figure 5, the completion time significantly reduced from 25 h – 15 h when increa-sing the feed concentration from 30 g/l – 45 g/l. Further, by increasing the agitation speed from 360 rpm – 600 rpm, the completion time also decreased from 25 h – 20 h. This result indicated that the higher feed concentration generated a larger amount of α-form crystals, so the epitaxial sites for the formation of secondary β-form nuclei on the surface of α-form crystals increased. This resulted in acceleration of the phase transformation rate. Moreover, when increasing the agitation speed, both the dissolution rate of α-form and the growth of β-form were definitely accelerated. Thus, the phase transformation rate was certainly promoted.

As shown in Figure 5, without the salt additive effect, the phase transformation was completed after 25 h at feed concentration of 30 g/l and agitation speed of 360 rpm. However, as using the salt additive $(NH_4)_2SO_4$, the phase transformation was significantly accelerated. Here, the completion time dramatically decreased from 25 h to only 12 h at 4 g/l salt additive, as shown in Figure 6(a). Further increasing the salt additive concentration up to 8 g/l, the completion time continuously de-creased and approached to only 10 h, as shown

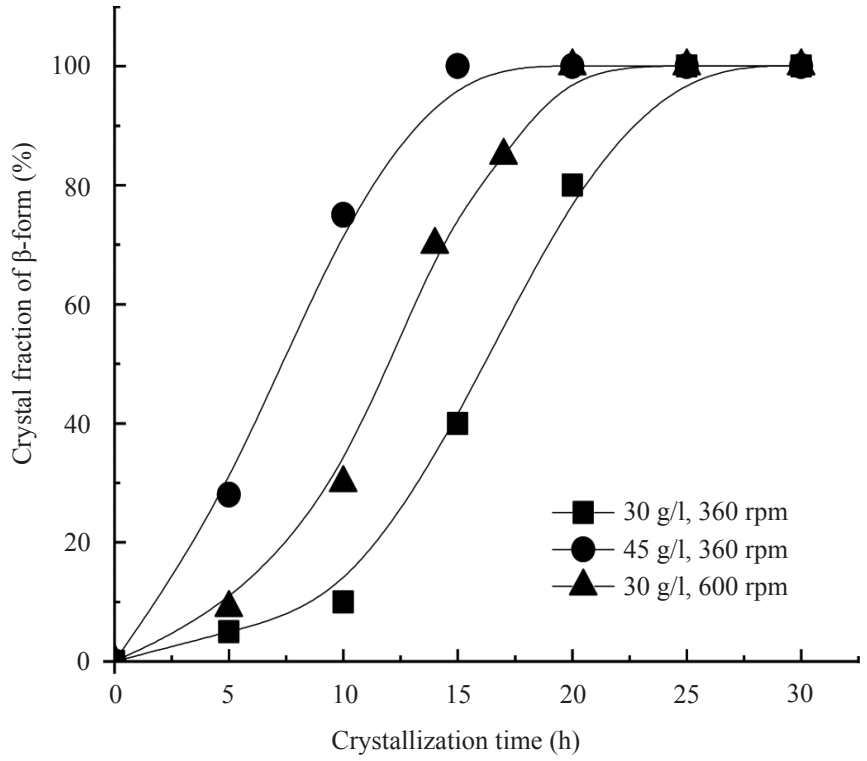

Figure 5. Typical profile of crystal fraction of β-form during the crystallization with varied feed concentrations and agitation speeds without salt additive effect.

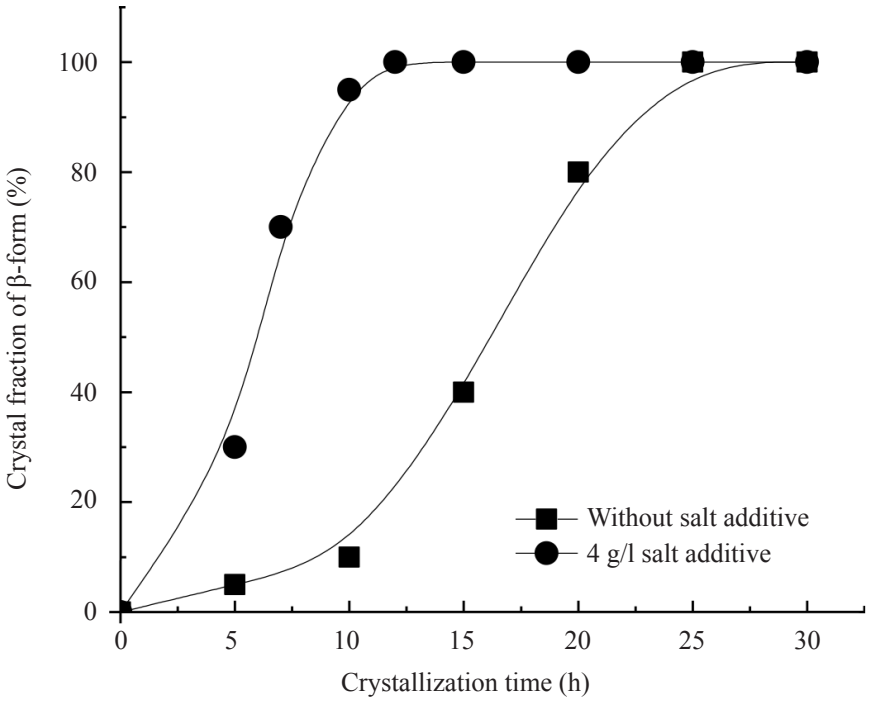

Figure 6(a). Typical profile of crystal fraction of β-form during the crystallization with 30 g/l feed concentration and 360 rpm agitation speed.

in Figure 6(b). As such, the phase transformation of α-form to β-form crystal was significantly promoted more than 2.0 times as using the salt additive $(NH_4)_2SO_4$.

In order to understand the effect of salt additive on the phase transformation, the dependency of driving force of phase transformation on the salt additive concentration was estimated, as shown in Table 1. Here, when increasing the salt additive concentration from 0 to 8 (g/l), the driving force of phase transformation (Δσ) remarkably increased from 0.09 to 0.20. As such, the driving force of phase transformation (Δσ) was enhanced at least 2.0 times as using the salt additives. That means both the dissolution rate of α-form crystal and the growth rate of β-form crystal were accelerated more than 2.0 times as using the salt additive, which resulted in promotion of phase transformation rate.

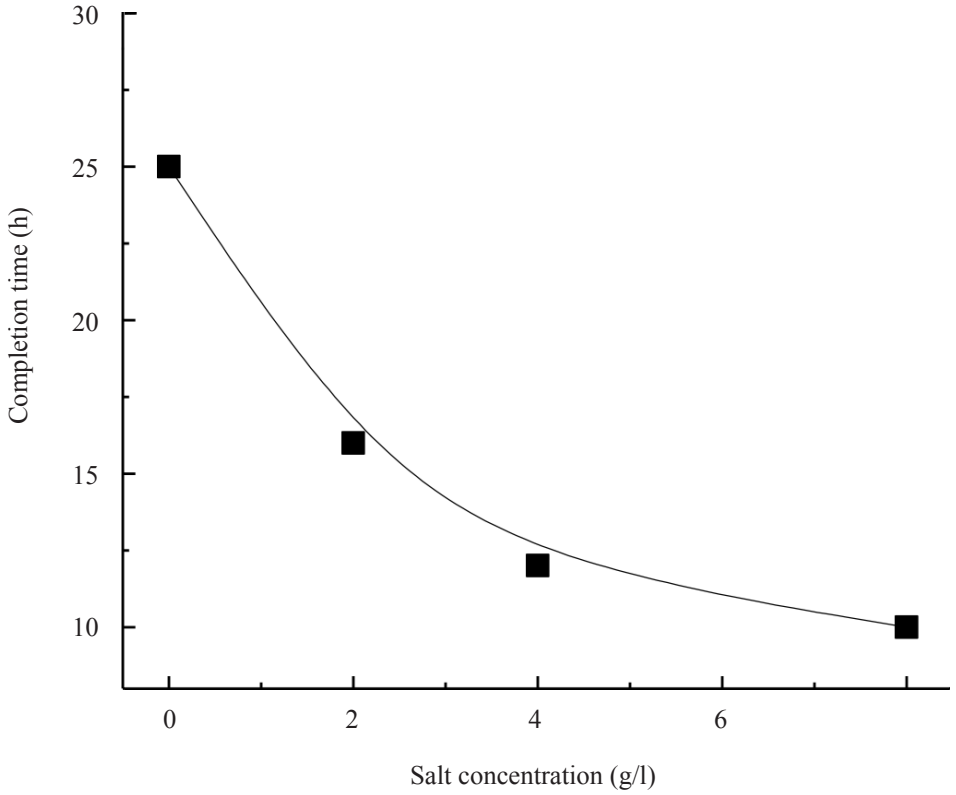

Figure 6(b). Effect of salt additive concentration on the completion time of phase transformation with 30 g/l feed concentration, 360 rpm agitation speed.

Table 1. Influence of salt additive on the driving force of phase transformation $\Delta\sigma = (C_\alpha - C_\beta)/C_\beta$

Salt concentration (g/l)	Solubility C_{eq} (g/l)		Driving force of phase transformation (Δσ)
	α-form	β-form	
0	12.23	11.23	0.09
2	13.86	11.95	0.16
4	14.67	12.41	0.18
8	15.43	12.87	0.20

CONCLUSIONS

The present study found that phase transformation of L-glutamic acid in cooling crystallization was significantly promoted by using the salt additive $(NH_4)_2SO_4$. The salt additive effect was considered a key factor to enhance the driving force of phase transformation, where it was remarkably facilitated at least 2.0 times by using the salt additive $(NH_4)_2SO_4$. That means both the dissolution rate of α-form crystal and growth rate of β-form crystal were accelerated over 2.0 times by using the salt additive $(NH_4)_2SO_4$. As a result, the period of phase transformation markedly reduced from 25 h to only 12 h at a certain amount of salt additive effect.

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