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Control of solvent-mediated transformation of crystal polymorphs using a newly developed batch crystallizer (WWDJ-crystallizer)

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Abstract

Using a newly developed batch crystallizer (WWDJ-crystallizer) equipped with a slurry sprinkler named Wall Wetter and a double-deck jacket, a suppression of the solvent-mediated transformation of the metastable polymorphic crystals was attempted. Crystallization of L-glutamic acid was carried out to show an example of the suppression. The target polymorphic crystals, namely the metastable α-form crystals were exclusively obtained from the aqueous solution without transformation to the stable β-form polymorph even at a temperature where the transformation could not be avoided if a conventional batch crystallizer was used. The characteristic size of crystals obtained by WWDJ-crystallizer was large and their size distribution was narrow, comparing with those obtained by a conventional crystallizer.

Keywords: Wall Wetter; Batch crystallizer; WWDJ-batch crystallizer; Control polymorphs; Transformation; L-glutamic acid; Crystal size distribution

1. Introduction

Many kinds of organic compounds have crystal polymorphs [1–4] which are different in the crystal characteristics in terms of solubility, dissolution rate, and crystal habit. A failure in selection of the most suitable polymorphs may result in serious trouble in industrial processes and in the end use of products. For example it may lead to difficulties of solid–liquid separation. With particular reference to pharmaceuticals, polymorphs must be strictly controlled as they may affect the characteristics of medicines such as stability and bioavailability [5]. Consequently, the control of polymorphs is an important problem in industrial crystallization.

Under appropriate solvent or mixed solvent conditions only one polymorph might precipitate, thus excluding other polymorphs. There is no cause for concern if the precipitate is a target polymorph. However, if several kinds of polymorph crystals precipitate and the target polymorph crystal is not stable but metastable, the solvent-mediated polymorph transformation must be completely suppressed in order to avoid contamination of the stable polymorph crystals.

Solvent-mediated transformation is affected by many factors such as initial supersaturation, agitation rate, kinds and components of solvent, impurities, etc. Temperature is also an important parameter to control polymorph formation. The polymorph transformation rate of taltirelin was increased with a decrease in temperature [6].

We have developed a novel batch crystallizer. The crystallizer, named as WWDJ-batch crystallizer, is equipped with a double-deck jacket and Wall Wetter that is a slurry sprinkler. The aim of the present study is to show an example that the crystal polymorph transformation is well suppressed by using the WWDJ-batch crystallizer and that exclusive production of metastable crystals can be achieved.

L-glutamic acid was used as a model compound. It is well known that the crystal of L-glutamic acid has two polymorphs, named α-form and β-form [7,8]. Both are orthorhombic with a space group of $P2_12_12_1$, but their crystal habits and lattice parameters, and thermodynamic stability are different [9–11]. Crystal habit of the α-form is preferable for solid–liquid separation, because the α-form crystals are prismatic, while the β-form crystals are needle-like. The α-form crystal is metastable while the β-form crystal is stable. The transformation from the α-form to the β-form proceeds spontaneously in aqueous solution and is sensitive to crystallization temperature [8]. In the present study, we attempted to produce exclusively the α-form crystals using the WWDJ-batch crystallizer.

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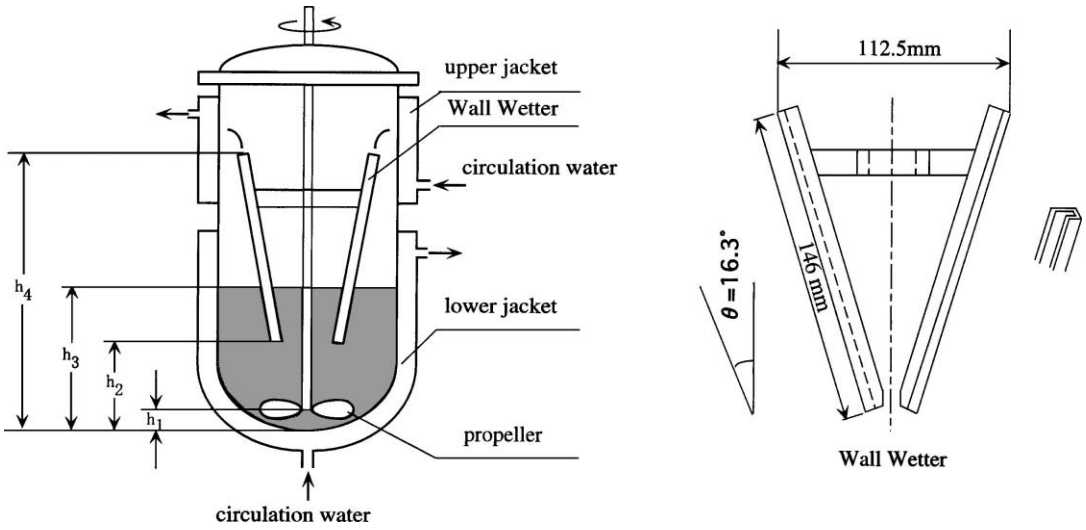

Fig. 1. Schematic diagram of WWDJ-batch crystallizer and Wall Wetter.

2. Experimental

2.1. Materials and crystallizer

The L-glutamic acid used in this experiment was of reagent grade and was purchased form Wako Pure Chemical Industries.

The WWDJ-batch crystallizer is shown in Fig. 1 [12], and its dimension is shown in Table 1. The crystallizer is a cylindrical glass vessel with a round bottom, which was covered with a double-deck jacket. The crystallizer was equipped with a Wall Wetter that is a slurry sprinkler, namely a device specially designed for agitating a slurry or a solution, and sprinkling it on the wall of the crystallizer headspace. The crystallizer was also equipped with a four-blade impeller on the same shaft of the Wall Wetter located in the center of the crystallizer. Agitation was provided by the impeller and also by the Wall Wetter. The Wall Wetter adopted in this study was composed of two channel bars with a J-shaped cross-section as also shown in Fig. 1. The slurry was raised along the channel by centrifugal force and sprinkled over the headspace, then fell down the wall. The working volume of the crystallizer, corresponding to the volume of the part covered by the lower jacket is 2.0 l. Crystallization temperature was controlled by circulating water through the double-deck jacket, where the temperature of the upper and lower jackets was separately controlled. The temperature in the crystallizer was measured with a sensor.

Table 1
Dimension of WWDJ-batch crystallizer

Parameter	Dimension
Inner diameter of crystallizer (cm)	14.0
Height of the upper jacket (cm)	10.0
Height of the lower jacket (cm)	17.0
Height of the space between the two jackets (cm)	2.0
h_1 (cm)	1.2
h_2 (cm)	9.4
h_3 (cm)	16.3
h_4 (cm)	23.5
Volume of solution (l)	2.0
Diameter of propeller (cm)	4.8
Wall Wetter (J-shaped cross-section)	See Fig. 1

2.2. Crystallization using WWDJ-crystallizer

Two modes of crystallization were carried out, namely PWW-mode crystallization and P-mode crystallization. PWW-mode crystallization was performed using the WWDJ-batch crystallizer equipped with the Wall Wetter and a propeller. P-mode crystallization was performed using a modified WWDJ-batch crystallizer from which the Wall Wetter was detached, i.e. in P-mode crystallization the crystallizer was used as a conventional batch crystallizer equipped with only a propeller.

PWW-mode crystallization was carried out as follows. A given amount of L-glutamic acid was added to 2.0 l of distilled water and heated to 85 °C until completely dissolved. The pH was 3.2. The solution was quickly introduced into the WWDJ-crystallizer while the Wall Wetter and the propeller were rotating at the same low speed. Agitation was then adjusted to 290 rpm. The recycling rate of the slurry at 290 rpm was 324 ml/min. Crystallization temperature was adjusted to a temperature with water circulating through the upper and lower jackets.

In all crystallization experiments carried out in the present study, the initial concentration of L-glutamic acid was 50 mg/ml.

2.3. Determination of ratio of the two polymorphs and concentration of L-glutamic acid

A sample (5 ml) of slurry was withdrawn at regular intervals during crystallization. The crystals were immediately separated by filtration and dried at room temperature in air and then used for the measurements of the ratio of the two polymorphs. The ratio of the two polymorphs was determined by powder X-ray diffraction analysis based on their characteristic peaks ($2\theta = 18.3^\circ$ for the α-form and $2\theta = 21.4^\circ$ for the β-form) [8]. Samples were prepared by crushing the crystals into a fine powder and dispersing them on a glass slide. Samples were measured with a scanning rate of 1 °C/min covering the range from 16° to 24 °C. The filtrate was used for the determination of L-glutamic acid concentration by UV spectroscopy at 210 nm.

2.4. Determination of crystal size distribution

After a certain crystallization time, the slurry was directed to a filter through the bottom exit. The crystals on the filter were then washed several times with methanol. This ensured that agglomeration of crystals did not occur. The washed crystals were carefully transferred to a watch glass and dried at room temperature for 12 h. The photographs of dry crystals thus obtained were taken under the microscope using a CCD camera and supplied to crystal size distribution (CSD) analysis by image processing.

The evaluation function of CSD used in this experiment is given by the Rosin Rammler Sperling Bennet (RRSB) distribution [13]

$$R(D_p) = 100 \times \exp\left[-\left(\frac{D_p}{D_e}\right)^n\right] \quad (1)$$

where $R(D_p)$ is the weight percentage for crystals retained on a sieve of aperture D_p, D_e the size of crystals corresponding to $R(D_p) = 36.8\%$ of the product oversize fraction and n the classification exponent. The larger the value of n is, the narrower the CSD. A graph of $\ln(\ln(R(D_p)))$ plotted against $\ln(D_p)$ gives a straight line using the equation as follows:

$$\ln\left[\ln\left[\frac{100}{R(D_p)}\right]\right] = n\ln(D_p) - n\ln(D_e) \quad (2)$$

Thus the D_e and n can be determined.

3. Results and discussion

3.1. Polymorph of the initial precipitates

In order to obtain the fundamental data to produce exclusively the metastable α-form crystals, polymorphs of the initial precipitates were investigated by preliminary experiments using a conventional 200 ml batch crystallizer with agitation at 100 rpm. The crystallization was carried out changing the crystallization temperature and the initial concentration of L-glutamic acid. To minimize the effect of polymorph transformation on the observation of polymorphs of initial precipitates, the initial precipitates, which appeared in trace amounts, were gathered by repeating the same experiment until a sufficient amount of crystals for X-ray analysis was obtained.

Table 2
Dependency of the α-form ratio in initial precipitates on initial concentration of L-glutamic acid and crystallization temperature[a]

Initial concentration of L-glutamic acid (mg/ml)	The α-form ratio in initial precipitates (%)				
	10 (°C)	20 (°C)	30 (°C)	40 (°C)	50 (°C)
10	53.9	–	–	–	–
20	71.1	53.1	52.1	–	–
30	86.4	62.1	61.4	51.9	–
40	94.8	78.4	64.5	54.7	50.1
50	100.0	100.0	81.6	70.1	57.7

[a] -:unsaturated condition.

In Table 2, the ratio of the α-form in the initial precipitates was presented in weight percent against the initial concentration of L-glutamic acid and the crystallization temperature. The covering range of the two parameters was 10–50 mg/ml and 10–50 °C, respectively. The ratio of the α-form crystals in the initial precipitates critically depends on the crystallization temperature. When the initial concentration of L-glutamic acid is 50 mg/ml, only the α-form crystals were precipitated at lower than 20 °C. Contrary to the result obtained by Kitamura [8] that only the α-form crystals precipitated at 25 °C regardless of the initial supersaturation ratio, in the present study the α-form ratio was significantly affected by the initial concentration of L-glutamic acid. Unfortunately, we cannot explain the difference between the present and previous results, but we know that the initial precipitates are not always metastable as reported for taltirelin [14] and cimetidine [15,16]. In the crystallization of taltirelin from the aqueous solution containing 30% methanol, the stable crystals precipitated despite the addition of the metastable crystals as seeds. In the crystallization of cimetidine at a low initial supersaturation ($S = 1.3$–2.2) [15], contrary to the result in an earlier paper [5] that only the metastable form is crystallized from IPA solution, not only the metastable form but also the stable form was crystallized, corresponding to the form of seed. Kitamura [8] also reported for the crystallization of L-glutamic acid at 25 °C that the crystal recovered from the stagnant solution was not the α-form, but a 50/50% mixture of the α-form and the β-form. Further investigations on the crystallization of polymorphs should be conducted.

In order to understand totally the effects of the temperature and initial supersaturation on the ratio of the α-form crystals shown in Table 2, a graph of the α-form ratio in precipitates against $\ln(C/C_{s,\alpha})$ was plotted and shown in Fig. 2. Here the $C_{s,\alpha}$ is the solubility of the α-form crystal that could be expressed by Eq. (3) as a function of the absolute

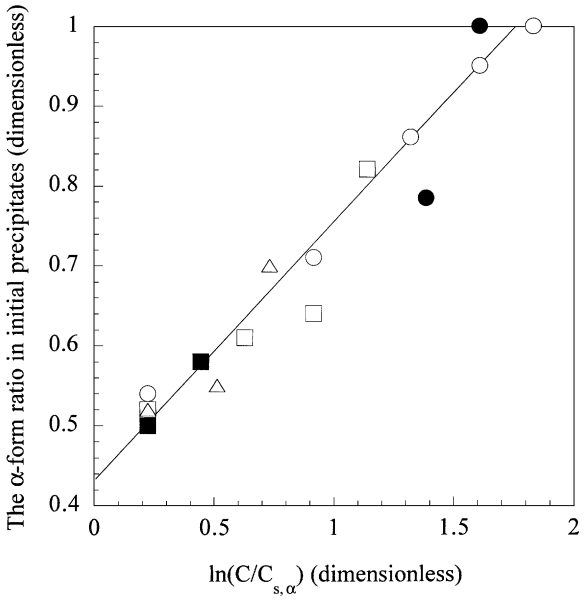

Fig. 2. The relationship between the α-from crystal ratio in the initial precipitates and supersaturation: (○) 10 °C, (●) 20 °C, (□) 30 °C, (△) 40 °C, (■) 50 °C.

temperature, T:

$$C_{s,\alpha}(\text{in mg/ml}) = 6.13 \times 10^{-5} \exp(4.11 \times 10^{-2} T) \quad (3)$$

The $C/C_{s,\alpha}$ is supersaturation ratio with respect to the α-form crystal. It is shown that their relationship gives a straight line covering the range of the two parameters described above. Based on the straight line, we obtain the α-form ratio in precipitates, F_α, as a function of supersaturation as follows:

$$F_\alpha = \begin{cases} 0.43 + 0.33 \ln\left(\dfrac{C}{C_{s,\alpha}}\right), & \left(\dfrac{C}{C_{s,\alpha}} < 5.7\right) \\ 1.0, & \left(\dfrac{C}{C_{s,\alpha}} \geq 5.7\right) \end{cases} \quad (4)$$

These data were used for finding an operational condition to produce exclusively the metastable α-form crystals.

3.2. Strategy for the exclusive production of metastable crystals

The strategy for the production of metastable polymorph crystals can be expressed as follows. First, nucleation of metastable polymorph crystals must be exclusively achieved, then those nuclei must be grown under a complete suppression of their transformation to the stable polymorph. We attempted to realize this strategy by controlling the temperature of the two jackets of the WWDJ-crystallizer.

Temperature setting was performed as follows: the nucleation must be performed at a low temperature so that the supersaturation larger than 5.7 can be attained (Eq. (4)). Since the crystallization is performed from 50 mg/ml L-aspartic acid solution, the supersaturation ratio of 5.7 corresponds to the crystallization temperature of 16 °C. However, the setting of the temperature of crystal growth is not so simple. The crystal growth may be done successfully at the same temperature as that of nucleation, or at a lower temperature, because at such the low temperature the transformation of the α-form to the β-form is difficult. However, in the present work we excluded such an operation. Our purpose in the present study was, as described above, to show that metastable crystals can be produced with no contamination of stable crystals even when the crystallization is carried out at a high temperature. From this viewpoint, we chose a high temperature, 30 °C, as an example. If the crystallization of 50 mg/ml L-glutamic

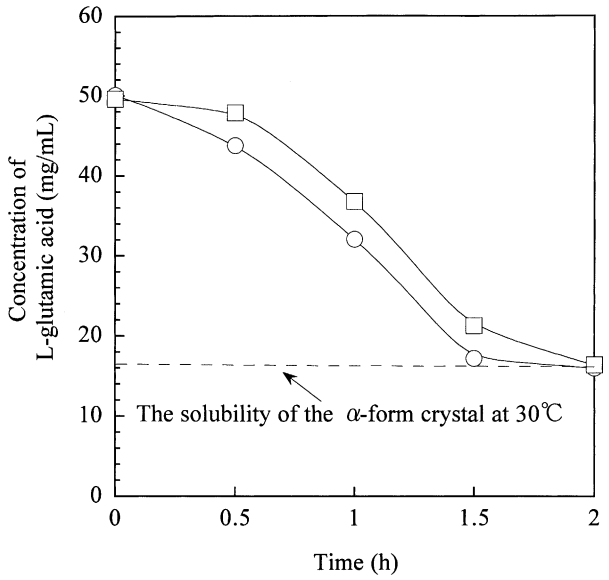

Fig. 3. The change of concentration during crystallization under Operation I: (○) PWW-mode crystallization, (□) P-mode crystallization.

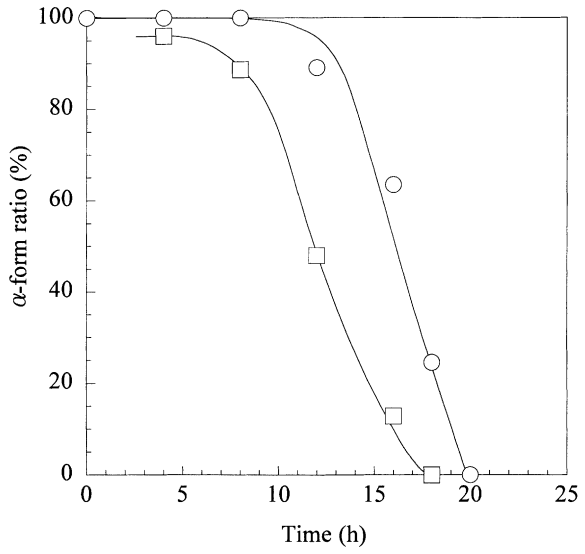

Fig. 4. The change of the α-from crystal ratio in precipitates during crystallization under Operation I: (○) PWW-mode crystallization, (□) P-mode crystallization.

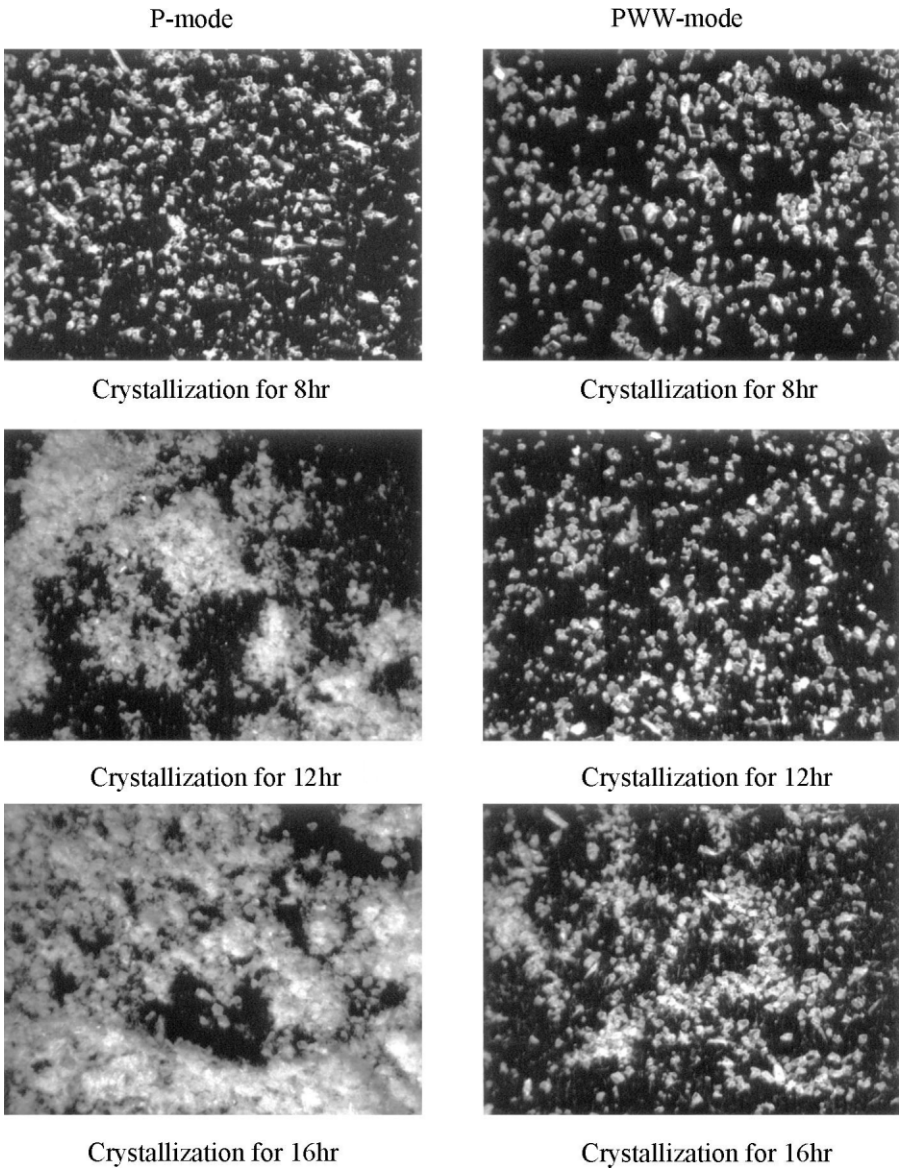

Fig. 5. Comparison of crystals between P-mode and PWW-mode crystallization under Operation I: prism crystals are the α-form and needle-like crystals are the β-form.

Table 3
Process condition of the experiment

Parameter	PWW-mode		P-mode
	Operation I	Operation II	
Wall Wetter	O[a]	O	X[b]
Propeller	O	O	O
Temperature of the lower jacket (°C)	36.5	23.3	30.0
Temperature of the upper jacket (°C)	16.0	40.0	30.0
Temperature of bulk slurry (i.e. crystallization temperature) (°C)	30.0	30.0	30.0
Agitation rate (rpm)	290	290	290

[a] O means that it was used.
[b] X means that it was not used.

acid is carried out at 30 °C using a conventional batch crystallizer, then the precipitation of the β-form crystals at initial and the transformation from the α-form to the β-form cannot be avoided.

3.3. Exclusive production of metastable polymorph crystals by using WWDJ-crystallizer

As the crystallization mainly proceeds in the lower part of vessel covered with the lower jacket of WWDJ-crystallizer, we call the temperature at that part the crystallization temperature. The crystallization temperature was adjusted to 30 °C. In PWW-mode crystallization, there are two ways to set the crystallization temperature. Namely, the crystallization temperature can be kept at 30 °C by setting the temperature of the upper jacket less than 30 °C and that of the lower jacket more than 30 °C, and vice versa. The former operation was performed as Operation I and the latter was performed as Operation II. The temperature adopted in the two operations and other conditions are listed in Table 3.

First, the crystallization in Operation I was carried out. Fig. 3 presents changes in L-glutamic acid concentration during PWW-mode crystallization carried out in Operation I. The result obtained in P-mode crystallization is also presented in Fig. 3. The period of induction was observed, which should be the time required for the formation of effective and/or sufficient nuclei. The period of induction in the PWW-mode crystallization was shorter than that in the P-mode crystallization, indicating that the nucleation was accelerated in the PWW-mode crystallization performed in Operation I. This acceleration of nucleation can be explained in terms of excess supersaturation at the cold surface (16.6 °C) of the upper wall. The initial supersaturation ratio at 16.6 °C is 1.76 times larger than that at 30.0 °C. Fig. 3 also shows that the precipitation of crystals was completed within 2 h in each crystallization.

Fig. 4 shows the changes in the α-form ratio of the precipitates during crystallization shown in Fig. 3. Fig. 4 shows that in PWW-mode crystallization carried out in Operation I, the α-form crystals were exclusively produced within 8 h. On the other hand, in the P-mode operation, the polymorph transformation occurred from the beginning. Under the microscope the changes of the α-form ratio during crystallization were discriminated as shown in Fig. 5 and it was found that the transformation was clearly suppressed in PWW-mode crystallization.

The temperature of heating surface covered with the lower jacket in Operation I was 33.1 °C, while the crystallization temperature was 30 °C, so there was a film between the slurry bulk and heating surface with temperature distribution. Although, it was expected that the nucleation of the β-form is possibly accelerated in this film due to high temperature, this effect was hardly noticeable. Perhaps the film was too thin to have such an effect.

Secondly, the PWW-mode crystallization in Operation II was attempted. The heating water of 40.0 °C was circulated through the upper jacket while cooling water of 23.3 °C was circulated through the lower jacket. The other conditions were the same as those in Operation I.

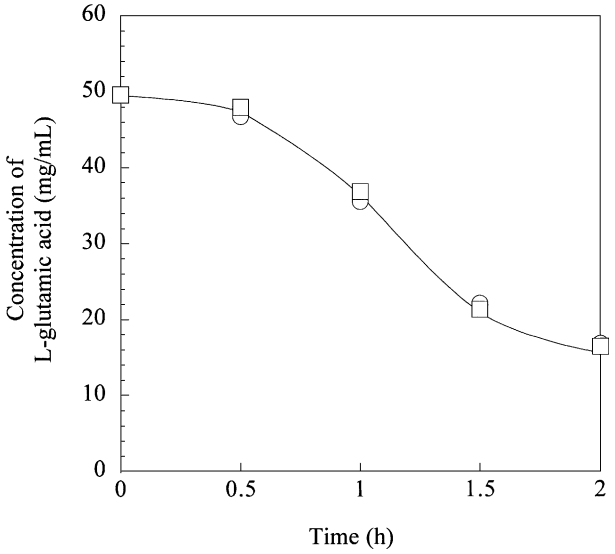

Fig. 6. The change of concentration during crystallization under Operation II: (○) PWW-mode crystallization, (□) P-mode crystallization.

Fig. 6 presents a change in L-glutamic acid concentration during PWW-mode crystallization carried out in Operation II. The result of P-mode crystallization is also represented in Fig. 6. The two changes were almost same. The change of the ratio of the α-form crystal in precipitates was also measured as shown in Fig. 7. The ratio of the α-form in the early stage of crystallization was not as small as expected from the temperature of the surface of the upper wall, namely about 70% at 40 °C ($C/C_s = 2.1$). Data from Figs. 6 and 7 suggest that the nucleation in PWW-mode crystallization

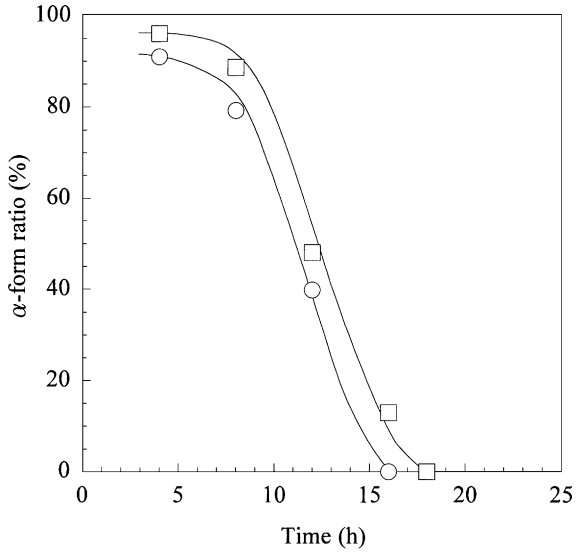

Fig. 7. The change of the α-form crystal ratio in precipitates during crystallization under Operation II: (○) PWW-mode crystallization, (□) P-mode crystallization.

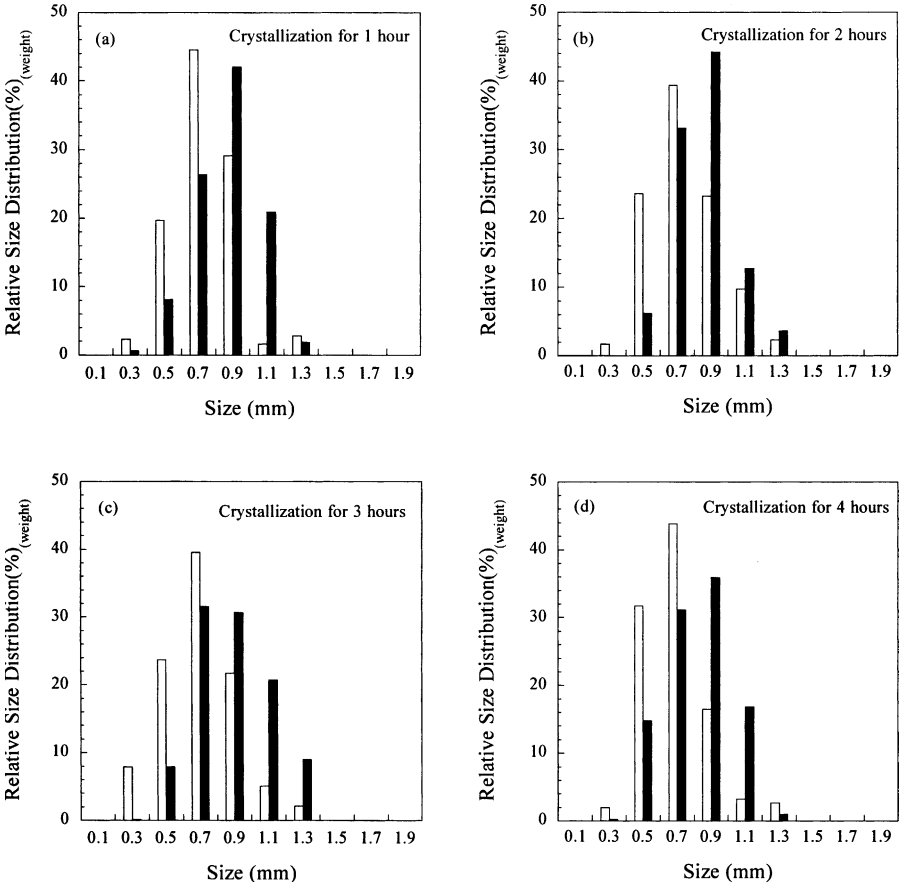

Fig. 8. The change of CSD of the α-form crystals during crystallization: (■) PWW-mode crystallization, (□) P-mode crystallization.

was mainly derived in the bulk solution at 30 °C and that the heating of the slurry at the surface of the upper wall promoted the transformation of the α-form crystals.

Figs. 4 and 7 indicate that the PWW-mode crystallization is useful for the exclusive production of metastable crystals even when the crystallization was carried out at a such a high temperature that the polymorph transformation could not be avoided in the conventional batch crystallizer. These figures also indicate that the crystallization temperature must be controlled as in Operation I.

3.4. Change of the α-form crystal size distribution during crystallization

The CSD was compared between the PWW-mode crystallization carried out in Operation I and P-mode crystallization. Under the microscope, it was difficult to discriminate the α-form crystals very clearly from the β-form crystals after the appearance of large quantities of the β-form crystals. The CSD was therefore measured for the crystals recovered within the initial 4 h in PWW-mode crystallization and P-mode crystallization, respectively. The results are illustrated in Figs. 8 and 9. The crystals obtained in PWW-mode crystallization were larger than those in P-mode operation and also showed a narrower CSD. These results are represented in RRSB distribution parameters shown in Fig. 9 as large D_e and also large n. These desirable characteristics of crystals were probably derived by a partial dissolution of fine crystals in the vicinity of the lower wall surface where

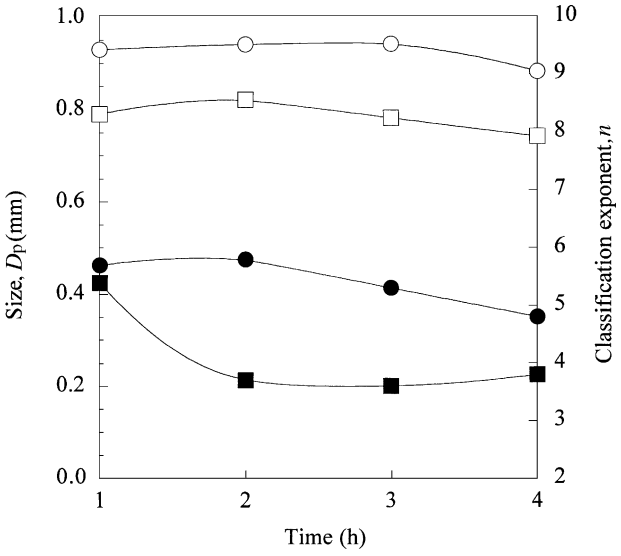

Fig. 9. The change of D_e and classification exponent n: (○) PWW-mode crystallization (D_e), (□) P-mode crystallization (D_e), (●) PWW crystallization (n), (■) P-mode crystallization (n).

the temperature should be close to the jacket temperature, i.e. 36.5 °C [13].

4. Conclusion

Using WWDJ-crystallizer and L-glutamic acid, we showed that metastable crystals can be obtained even when the crystallization is carried out at a high temperature such that the solvent-mediated transformation cannot be avoided in a conventional batch crystallizer. The exclusive production of the metastable crystals at such a high crystallization temperature is possible with the crystallizer where the crystallization temperature can be controlled separately from the nucleation temperature. In the present work, we showed that an exclusive production of a metastable polymorph through such temperature control can be performed successfully with a WWDJ-batch crystallizer.

The WWDJ-crystallizer was also useful for the production of large crystals with a narrow size distribution.

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