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MORPHOLOGY CHANGE IN CRYSTALLIZATION OF α L-GLUTAMIC ACID IN THE PRESENCE OF L-PHENYLALANINE

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Abstract Effect of L-phenylalanine(L-Phen) on the precipitation behavior and morphology of α L-glutamic acid (L-Glu) crystals, and inclusion of L-Phen in L-Glu crystals were investigated. L-Phen suppresses both nucleation rate and growth rate of L-Glu. The morphology of L-Glu was observed to change depending on L-Phen concentration. Two predominant morphologies were obtained, which have the large (111) face and the new face of (110), respectively. Irregular increase of the molar ratio of L-Phen to L-Glu in nucleated crystals was detected and it was attributed to the morphology change of L-Glu crystals. Dependence of R on L-Phen concentration appeared to be different between the nucleated crystals and seed crystals.

INTRODUCTION

Physical properties and various functionality of crystals(e.g. bioavailability[1], optical non linearity[2]) are different between polymorphs due to the difference of structures. These problems require the accurate control of the polymorphism in industrial crystallization to obtain the suitable polymorphous crystals[3]. However, there are many obscure points in the precipitation mechanism of the polymorphs and the work with quantitative treatment of the polymorphism is scarcely found. The precipitation process of the polymorphs is considered to comprise of (1)competitive nucleation, (2) competitive growth and (3)transformation from metastable form to stable form[3,4]. It was shown previously[5] that the precipitation behavior of the polymorphs of L-glutamic acid(L-Glu), which are α and β (both are orthorhombic), is influenced with temperature, stirring and supersaturation degree. Furthermore, the precipitation and transformation of

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L-Glu polymorphs are effected by the additive of L-phenylalanine (L-Phen). At 45°C, the nucleation and growth rates of β L-Glu are suppressed selectively by L-Phen, and transformation(α→β) of l-glutamic acid crystals is retarded remarkably[6]. On the other hand, at 25°C only α tends to precipitate and transformation does not occur. However, the precipitation rate and the morphology of α were influenced. In this paper, effect of L-Phen on the precipitation behavior and morphology of α crystals, and inclusion of L-Phen in L-Glu crystals are investigated.

EXPERIMENTAL

Solubilities of α and β are shown in Figure 1, indicating that α is metastable and β is stable form. Crystallization was carried out by cooling rapidly the under saturated solutions at points, s in Figure 1 to the set temperature (25°C)[5,6]. Solutions containing various concentrations of L-Glu and L-Phen were used for the crystallization. Induction time for the nucleation was measured and the crystals precipitated were sampled and L-Phen in crystals was analyzed by a liquid chromatography. Concentrations of L-Glu and L-Phen in solutions were determined with the same method. Seed crystals of L-Glu were used for the measurement to compare with the nucleated crystals.

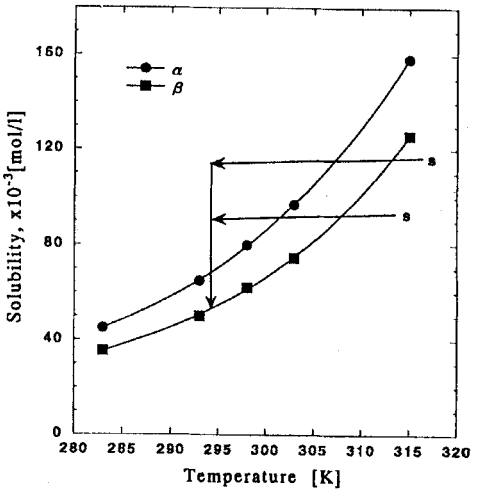

Figure 1. Solubilities of L-glutamic acid polymorphs

RESULTS AND DISCUSSION

Effect of L-Phen on nucleation

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When L-Phen is added in the solution containing a constant concentration of L-Glu(c=0.204 mol/l), the induction period for the nucleation (τ) was elongated as shown in Figure 2. It takes more than 5 hours for the nucleation at L-Phen concentration(Cp) of 50×10^{-3} mol/l. The precipitated species were confirmed only α type. It is expected that L-Phen disturbs the formation of the cluster of α type, which is the precursor of the nucleation.

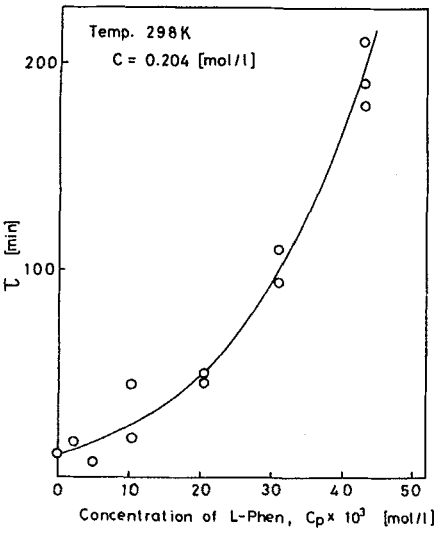

Figure 2. Induction period (τ) of nucleation

In Figure 3 decrease of the solution concentration in a progress of the precipitation is shown. A dotted line indicates the solubility of α L-Glu. It can be seen that the

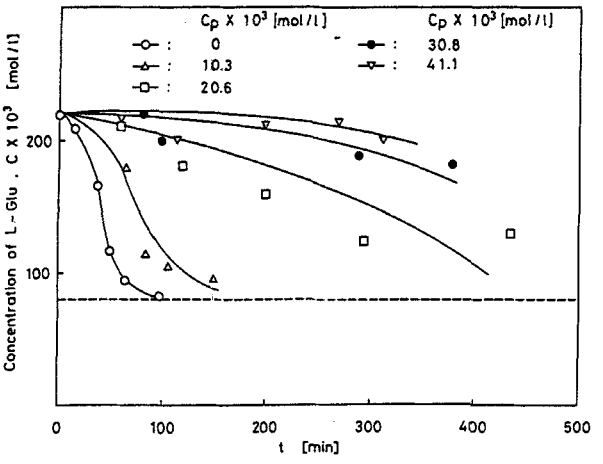

Figure 3. Precipitation rates of α L-glutamic acid crystals

precipitation rates are intensively lowered with L-Phen concentration and at L-Phen concentrations higher than $30x10^{-3}$mol/l, more than 200 minutes is necessary to attain the solubility. These results mean that the growth rate of α crystals is suppressed as well as β crystals.

Inclusion of L-Phen in L-Glu crystals

It is interesting problem that whether L-Phen is included in L-Glu crystals in the growth process. Crystals obtained from solutions containing various amounts of L-Phen were analyzed. The results are shown by a dotted line in Figure 4. R in the Figure 4 means the molar ratio of L-Phen over L-Glu. It can be seen that R value increases with L-Phen concentration(C_p) in solutions, and at higher concentration of L-Phen R value abnormally increases.

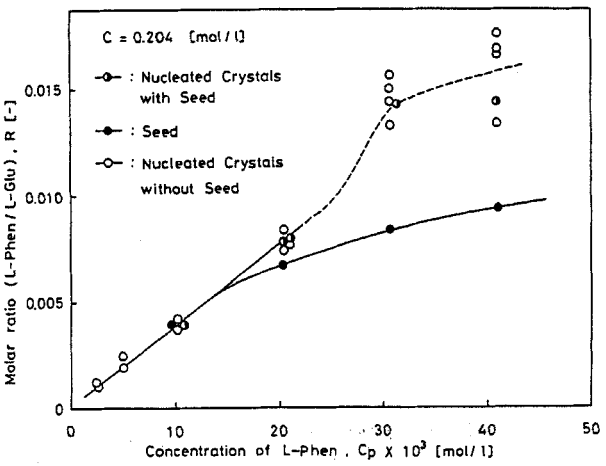

Figure 4. Inclusion of L-Phen in L-Glu crystals

As the cause of inclusion of L-Phen in crystals, mainly two cases can be considered, i.e. (1) inclusion in crystal structure by adsorption and (2) inclusion with mother liquor as adhesive on crystal surface or liquid droplet included in the irregular growth process(e.g. step bunching). To discriminate these cases crystals were

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washed with pure water several times and L-Phen in crystals was analyzed. the washing test was examined. In Figure 5 dependence of R and weight of crystals(weight % to the initial quantity) on the wash number is shown. For both of the L-Phen concentration ocases f 30.80x 10-3 and reproducibility of this tendency was observed in crystals obtaine41.07x10-3mol/l, although weight % of crystals decreased with wash number, R kept to be almost constant. Good d in the different batch operation. These results may suggest that L-Phen is included in the crystal structure by adsorption.

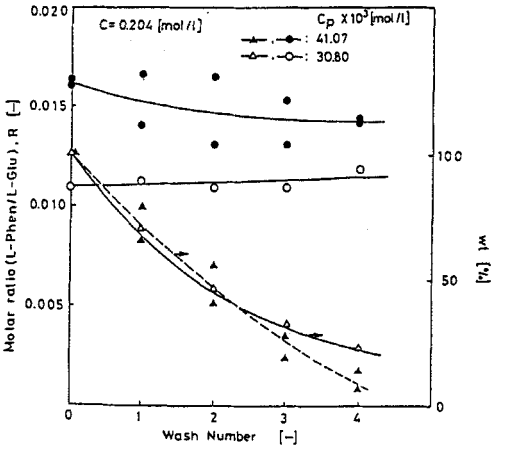

Figure 5. dependence of R and wt% on wash number

Morphological change

Morphological change of L-Glu crystals was detected with microscopic observation.From pure solutions the same crystals with that we have reported previously (Figure 6(a)) were obtained. However, in solutions at low concentrations of L-Phen a small change in the morphology was observed as shown in Figure 6(b), i.e. (111) face seems to get larger. When the concentration of L-Phen was higher than $30x10^{-3}$mol/l, further change in the morphology occurred and new face appeared (Figure 6(c)). With analysis of X-ray diffraction the face index of the new face was determined as (110). These results indicate that the morphological change is not simple and it dynamically changes depending on the crystallization conditions. This fact suggests that the morphology obtained is not determined only by the molecular structure of additive and the structure of crystals. These

process of morphological change is to be investigated in detail using a single crystal in a flow system in connection with the structure of the crystal surface[7].

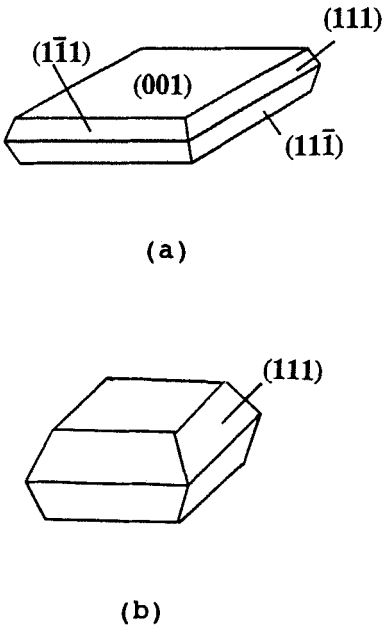

Figure 6. Change in the morphology of L-Glu crystals

Inclusion mechanism of L-Phen and comparison between the nucleated crystals and seed crystals

The inclusion behavior of L-Phen in Figure 4 may be related to the morphology change mentioned above. It cleared that when crystals with the morphology of (c) in Figure 6 appeared, the value of R increased largely. This means that L-Phen is included more advantageously in new face of the crystals. Accordingly, it is expected that if seed crystal is used at the L-Phen concentration more than 30×10^{-3} mol/l, the amount of inclusion of L-Phen may be different from that in Figure 4. On this account, the seed with the morphology of Figure 6(a) was added in the solution and when the seed grew up to several times of initial size the seed crystals were analyzed. The results shown by the solid line in Figure 4 was obtained. The value of R in solid line smoothly increases even at higher concentrations of L-Phen

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and the tendency is different from the dotted line. With microscopic observation only the small change in the morphology (Figure 6(b)) was detected at the higher concentrations of L-Phen. These result supports the presumption described previously and indicates that the inclusion of addititive is closely related to the morphology change. When the seed crystals were added in solutions the nucleation was accelerated clearly and the "secondary nucleation" occurred. These fine crystals were sampled and analyzed. However, the results of R completely coincided with those for crystals produced by "primary nucleation"(dotted line in Figure 4).

In the growth process of L-Glu, the surface of crystals should be continuously refreshed and on the new surface the adsorption of L-Phen may occur continuously. On this respect the value of R may be determined by the ratio of growth rate of L-Glu and adsorption rate of L-Phen. However, at this stage, assuming that adsorption equilibrium is established instantly , Langmuir isotherm equation (1) was applied to solid-liquid distribution of L-Phe.

$$\theta = \frac{R}{R_0} = \frac{KCp}{1 + KCp} \qquad (1)$$

where θ is coverage, R_0 is the value of R at saturated state, K is equilibrium constant.

Equation (1) can be transformed to Equation (2).

$$\frac{Cp}{R} = \frac{1}{KR0} + \frac{Cp}{R0} \qquad (2)$$

Relationships between Cp/R and Cp is shown in Figure 7. Although for the nucleated crystals a straight line could not be obtained , however, for the seed crystals Langmuir isotherm seems to be established for the distribution of L-Phen between solid and solution.

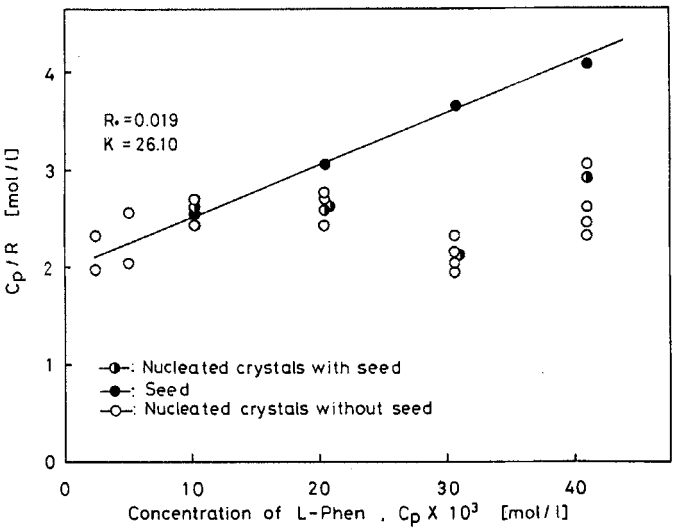

Figure 7. Relationship between Cp/R and Cp in Langmuir plots

CONCLUSION

It was confirmed that L-Phen retards both nucleation rate and growth rate of L-Glu. Depending on L-Phen concentration, the morphology changes were observed. The behavior of it was complicated and two typical morphologies were obtained. One of them has the large (111) face and the other has the new face of (110). Irregular increase of R for the nucleated crystals was observed and the increase was attributed to the morphology change of L-Glu crystals. Dependence of R on L-Phen concentration appeared to be different between the nucleated crystals and seed crystals.

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