Chapter 3
Anti-solvent Crystallization Method for Production of Desired Crystalline Particles

Hiroshi Takiyama

Abstract Anti-solvent crystallization is widely used in the pharmaceutical industry from the viewpoint of the ambient temperature operating condition and high yield production. In the anti-solvent crystallization, the quality control of crystalline particles is necessary. Since polymorphism phenomena affect dissolution property, productivity, and bioavailability, it is important to control polymorph formation. The consideration of the solution addition methods to control polymorph in anti-solvent crystallization is engineering challenge. In this chapter, the operation design and/or operating strategies to obtain crystalline particles with the desired polymorph are described. The ternary phase diagram is proposed to control polymorphs. In order to determine both the anti-solvent addition rate and a temperature profile, the temperature-dependent solid–liquid equilibrium (ternary phase diagram) is necessary. By using this operation design and the simulation, the required polymorph is successfully obtained in the anti-solvent crystallization. The proposed operation design method by using the operation point trajectory is effective for controlling crystal quality in the anti-solvent crystallization.

Keywords Anti-solvent crystallization · Ternary phase diagram · Polymorphism · Pharmaceuticals

3.1 Introduction

Crystal products are widely found in pharmaceutical, food, fine chemicals, agrichemicals, cosmetic, and many other industries. Crystallization is the process of formation of ordered three-dimensional molecular array (crystal) from solution, melt, or gas. This process has been used as a method to produce crystalline particles and as a way to separate and purify the desired component. There are many types of crystallization. In each type, the solubility of solute is reduced by lowering the temperature

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(cooling crystallization), removing the solvent (evaporative crystallization), the addition of anti-solvent (anti-solvent/drowning-out crystallization), activating a reaction (reaction crystallization), and sublimation of solute (vapor crystallization). As in most industrial crystallization processes, polymorph, crystal morphology, and size are important qualities of crystal products. These qualities can have a huge impact on downstream processes. Fluidity, granularity, and compressibility of crystals may differ due to the polymorph, morphology, and size. Hence, solid–liquid separation characteristics, washing and drying process, tableting operation will be affected. Eventually, the time of process, purity, and cost of the products will also be affected. In addition, solubility of crystals also varies with crystal polymorph, morphology, and size. This causes significant effects on the bioavailability and safety of medicine in pharmaceutical field. Therefore, it is crucial to control the crystal polymorph, morphology and size. In anti-solvent crystallization, when anti-solvent or solvent mixture is added into the crystallizer, the solubility of the solute will be reduced, and supersaturation which acts as the driving force of crystallization is generated. Since this method can be carried out in ambient temperature, it is suitable for the production or separation of heat-sensitive materials.

Polymorphism means that a compound has two or more crystal structures. Differences in crystal structures cause changes in physicochemical properties. In the pharmaceutical industry, it is necessary to control polymorphs because of their differences in bioavailability. There are many papers on the effects of operation factors such as solvent and solution concentration. In particular, polymorphic crystallization is affected by solvents, different polymorphs can be obtained from solutions with different solvents. In the manufacture of pharmaceuticals, anti-solvent crystallization is widely used from the viewpoint of high yield production. However, it is difficult to select the suitable operating conditions for controlling polymorph formation in anti-solvent crystallization because a particular polymorph may precipitate at limited temperatures and in limited solvent compositions.

Much effort has been devoted to determine the influence of operating conditions on crystal polymorph in anti-solvent crystallization, such as feeding rate, feed and bulk concentration, agitation rate, and so on. It was found out that the operating conditions have strong effects on the qualities of crystalline particles. Therefore, if the relationship between crystal polymorph and operating conditions can be clarified, we can easily determine the operating conditions and design the optimum method to obtain desired crystal polymorph.

3.2 Anti-solvent Crystallization

3.2.1 Theory and Characteristics

In anti-solvent crystallization, supersaturation (driving force) is produced by adding anti-solvent or solvent mixture into a solution. This will reduce the solubility of the

solute in the solution and crystal will be produced. This crystallization process is often used especially in pharmaceutical industry.

The characteristics of anti-solvent crystallization are described as follows [1]:

(a) Operation at ambient temperature
This crystallization method is operated at ambient temperature and it is not necessary to heat up or cool down the crystallizer in order for crystallization. This will have huge benefits in terms of cost and expenditure. Additionally, it is suitable for crystallization of heat-sensitive materials such as biomaterial and pharmaceutical products. Moreover, crystallization of soluble materials whose solubility is weak in temperature dependency can be carried out too.

(b) High yield in productivity
Just by adding the solution, supersaturation will be generated and crystal will be produced within a shorter period of time. Besides that, in the case where there is still solute dissolved in solution, adding more anti-solvent will help in the solute recovery process.

(c) Unique product quality
Compared to cooling crystallization, wide attainability of supersaturation can be achieved. With higher supersaturation, nucleation rate will increase and fine crystals can be easily produced. However, with the generation of more fine crystals, crystals will agglomerate and there will be difficulty in solid–liquid separation process.

3.2.2 Ternary Phase Diagram

In order to further understand the anti-solvent crystallization process, it is easier to use a ternary phase diagram. Considering a solute dissolved at an arbitrary temperature. The solubility curve is shown in a ternary phase diagram as in Fig. 3.1. E (solute)–B (original solvent)–A (anti-solvent) system is considered. Solution A is the anti-solvent-rich solution and solution B is the original solvent-rich saturated solution. When solution A and B with mass m_A and m_B are mix together the mass ratio will become $m_A : m_B = \alpha:\beta$ from the principle of lever rule, and the apparent mix solution will be at point M. Since solution M is supersaturated, crystals will be generated and the composition of the solution will move to point S which is the equilibrium point.

Concentration difference, ΔC can be express as

$$\Delta C = C_0 - C^* \tag{3.1}$$

C^* represents the equilibrium concentration. Saturation ratio, S and Supersaturation ratio, σ can be written as

$$\ln\frac{C_0}{C^*} = \ln S = \ln\left(1 + \frac{(C_0 - C^*)}{C^*}\right) = \ln\left(1 + \frac{\Delta C}{C^*}\right) = \ln(1+\sigma) \cong \sigma \tag{3.2}$$

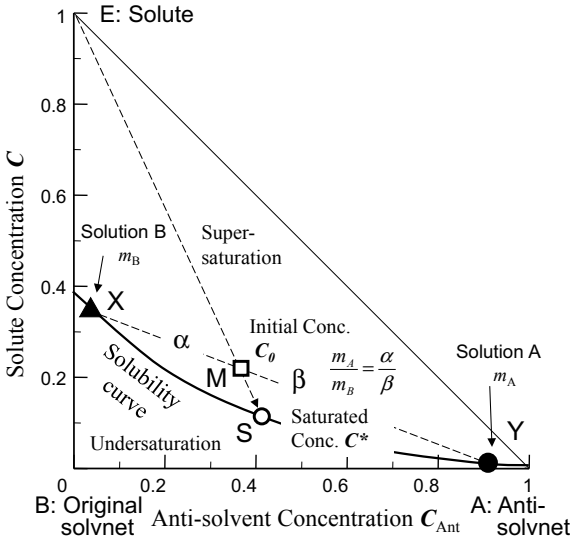

Fig. 3.1 Definition of anti-solvent crystallization using ternary phase diagram

3.3 Crystal Polymorph

Polymorphism means the phenomenon in which the same compound shows two or more crystal structures. In the case of the organic substances, the network structure of the hydrogen bond is different in every polymorph [2]. The characterization of polymorph is possible by X-ray powder diffraction (XRD) and thermal analysis. If the crystallization of each polymorph is not controlled, various problems of production or quality occur.

(1) Stability [3]:
Transformation from a metastable polymorph to a stable polymorph occurs, and crystalline qualities are not guaranteed.
(2) Industrial characteristics:
Solid–liquid separation performance changes because crystal morphology also changes.
(3) Bioavailability [4]:
Since the solubility, shape, density, etc. change bioavailability change as the result.

When crystal polymorph is produced selectively, it is very important to consider supersaturation change. For example, when crystallization material has two polymorphs, the precipitation behavior of the polymorph in a solution can be explained as Fig. 3.2 (monotropic system in which solubility does not cross). Metastable Form I deposits and solution concentration becomes the point Q with the growth of Form I. The solution state of the point Q is saturation for Form I, however, the solution state

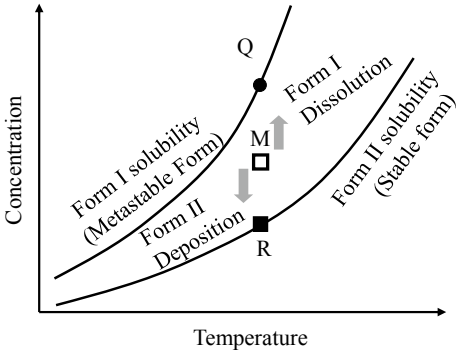

Fig. 3.2 Solution-mediated polymorph transformation

is supersaturation condition for Form II. If the nucleation of Form II occurs here, crystallization of Form II starts and solution concentration decreases. Since, the solution becomes undersaturated for Form I, Form I which already deposited dissolves. Therefore, in the region between solubility curves, solution-mediated transformation occurs as shown in Fig. 3.3.

Anti-solvent crystallization method is also important for the control of crystal polymorph [5] and morphology [6, 7]. Then, let's consider the operation of anti-solvent crystallization in which an operation point (solution concentration in ternary phase diagram) does not exceed the solubility of metastable form in ternary phase diagram. The example is explained in Fig. 3.4. If a pure anti-solvent is added in the solution (point *S*), the solution composition moves to the right along the straight line

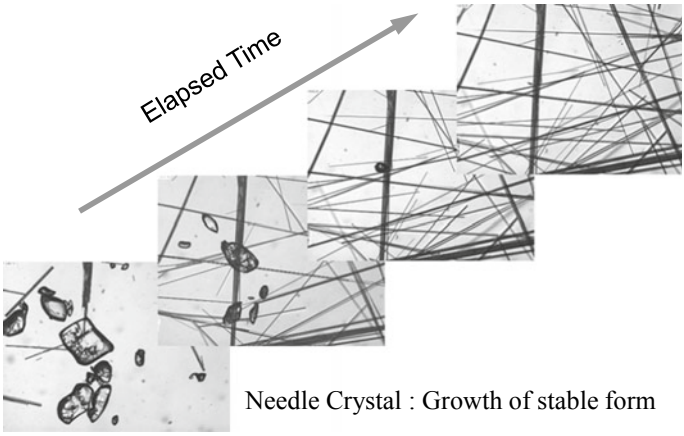

Fig. 3.3 Changes in polymorph crystals during solution-mediated polymorph transformation

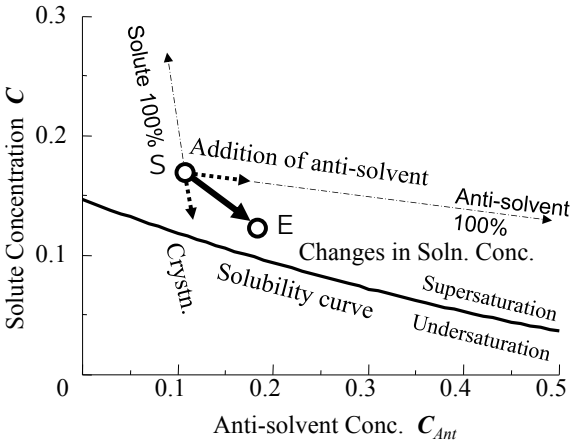

Fig. 3.4 Operation point for controlling polymorphism in anti-solvent crystallization

passing through the anti-solvent apex. Then, crystals deposit and solution composition move downward along the straight line which connects the apex of solute. Finally, solution composition moves in the direction of the lower right (point *E*). In this way, the traveling rate of operation point (solution composition) is decided by the addition rate of an anti-solvent, and the deposition rate of crystals [8, 9]. That is, the trajectory of operation point on a phase diagram is decided by the addition rate of an anti-solvent, and the deposition rate of crystals. Therefore, an operation design can be achieved if the solubility of the three-component system [10] is known in polymorph control of anti-solvent crystallization [5].

3.4 Controlling Polymorphism in Anti-solvent Crystallization

In order to select the suitable operating conditions for controlling polymorph formation in anti-solvent crystallization is difficult because a particular polymorph may precipitate at limited temperature and solvent composition [11, 12]. The crystallization behavior of polymorphous crystals depends on the anti-solvent addition rate and the initial concentration of the solution in the anti-solvent crystallization [7]. These phenomena were explained with operation point trajectory in phase diagram in which the stability regions of each polymorph were described. So it is necessary to determine the operating conditions such as anti-solvent feed rate for controlling polymorph formation. If several kinds of polymorph crystals precipitate and the target polymorph crystal is the stable form, the solvent-mediated transformation of metastable polymorph crystals must be completely suppressed in order to avoid contamination. To obtain only desired stable polymorph, it is required not to be precipitated metastable polymorph crystals. In the anti-solvent crystallization,

solubility profiles are essential data for crystallization operation design to selectively isolate the target polymorph. By using solubility data, operation strategies were designed [13], and the anti-solvent was added at controlled rates as reflected by the changes in the solubility curves. In such a way the operating conditions should be designed to obtain the target polymorph with consideration of solubility.

3.4.1 Operation Design of Anti-solvent Crystallization

Indomethacin (IMC)–Acetone (original solvent)–Heptane (anti-solvent) is a target system in this chapter. There are several polymorphs and solvates in IMC [14, 15]. Two polymorphs (α-form and γ-form) were mainly handled this study chapter. The solubility of each polymorph was measured in detail by using pure α-form and γ-form crystals. Temperature and composition of mixed solvent (acetone and heptane) were changed as the experimental conditions. The stable and metastable polymorph solubilities were determined by measuring solution concentration during solution-mediated transformation. From the experimental results, the ternary phase diagram of IMC–acetone–heptane system was prepared based on the mass fraction.

In the anti-solvent crystallization for IMC, supersaturation was generated by adding heptane (anti-solvent) and the crystals were precipitated. Operation strategy for controlling polymorph formation based on ternary phase diagram is shown in Fig. 3.5 as a rectangular triangle diagram. Figure 3.5 is the part of ternary phase diagram. In order to perform anti-solvent crystallization in the operation area where only a certain polymorphism (γ-form was a target polymorph in this study) deposits, it is necessary to control the feed rate of heptane according to the deposition rate of γ-form. If α-form crystals deposit in the solution, it is difficult to agitate the slurry because agglomerated α-form crystals have cotton-like shape. By the consideration of a ternary phase diagram [16], an operation point leaves from a solubility curve by addition of heptane. According to ternary phase diagram, when the anti-solvent is fed to the solution, an operation point moves to $w_{\mathrm{H}} = 1.0$ by using lever rule along with the line *A*. When the crystals are deposited, an operation point closes to solubility curve along the line *B* by using lever rule. Finally, an operation point moves toward resultant vector of anti-solvent addition rate and crystal deposition rate. An operation point becomes higher supersaturation by anti-solvent addition and then an operation point approaches a solubility curve by precipitation of IMC. Hence, the operation point can pass through a specific solution concentration range which does not exceed the solubility of α-form (undesired polymorph) by choosing the optimal anti-solvent feed rate suitably.

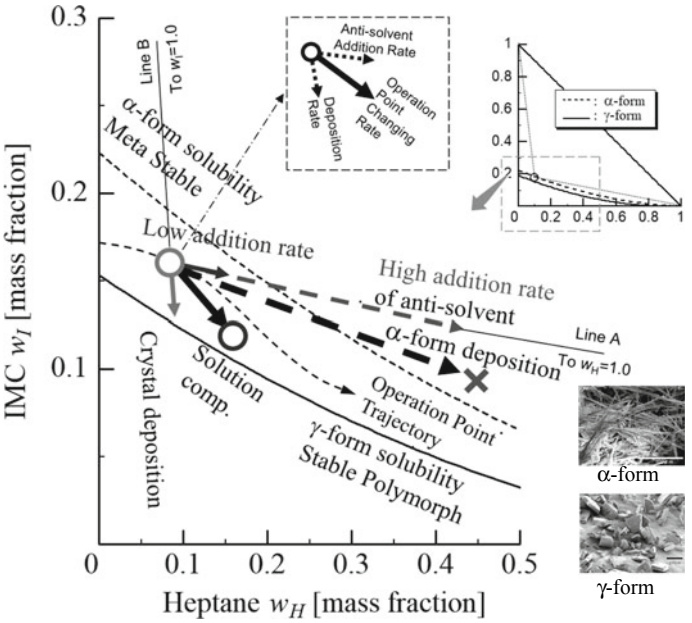

Fig. 3.5 Operation strategy for controlling polymorphism in IMC anti-solvent crystallization

3.4.2 Simulation Model for Operation Point Trajectory

In order to determine suitable anti-solvent feed rate, the anti-solvent crystallization model for calculating the operation point during crystallization was proposed. The assumptions of this operation model for seeding type anti-solvent crystallization are as follows.

(1) The shape of crystal (γ-form) does not change.
(2) The supersaturation of a solution is consumed with growth of γ-form seed crystals.

The growth rate expressed the difference of solution concentration as a driving force (Eqs. 3.3 and 3.4).

$$\frac{\mathrm{d}W}{\mathrm{d}t} = K\Phi_{\mathrm{s}}\left(\frac{W}{\Phi_s \rho_{\mathrm{c}}}\right)^{2/3} \rho_{\mathrm{L}}\left(w - w^*\right)^m \tag{3.3}$$

$$\frac{\mathrm{d}W}{\mathrm{d}t} = K_{\mathrm{g}}^{'}(W)^{2/3}\left(w - w^*\right)^m \tag{3.4}$$

Growth rate constant K'_{g} and the growth order m were computed by optimization calculation from the solution concentration change of preliminary γ-form crystal precipitation experiments.

The IMC concentration change of the solution was predicted from the simulation result. The operation model is as follows.

$$\frac{\mathrm{d}W}{\mathrm{d}t} + \frac{\mathrm{d}M}{\mathrm{d}t} = P_{\mathrm{H}} \tag{3.5}$$

$$\frac{\mathrm{d}W}{\mathrm{d}t} + M\frac{\mathrm{d}w}{\mathrm{d}t} + w\frac{\mathrm{d}M}{\mathrm{d}t} = 0 \tag{3.6}$$

$$w_{\mathrm{H}}(t) = \frac{\int_0^t P_{\mathrm{H}}\mathrm{d}t}{Mw + M_0 - M_0 w_0 + \int_0^t P_{\mathrm{H}}\mathrm{d}t} \tag{3.7}$$

Equation (3.5) is total mass balance of semi-batch operation for anti-solvent crystallization. Equation (3.6) is IMC component mass balance and Eq. (3.7) is heptane composition in the solution at time t.

3.4.3 *Simulation Results Under the Condition of Isothermal*

The solution concentration (operation point) simulation which changed the feed rate of anti-solvent during crystallization was carried out, and the results of solution concentration change are shown in Fig. 3.6. The results obtained under the condition of three different feed rates are compared. Operating period until the solution composition w_H reaches 0.4 is shown in Table 3.1.

Under the conditions of feed rate $P_{\mathrm{H}} = 0.01$, an operation point does not exceed the solubility of α-form (undesired polymorph). However, operating period became long. On the other hand, when the feed rate is fast (for example, $P_{\mathrm{H}} = 0.1$), the

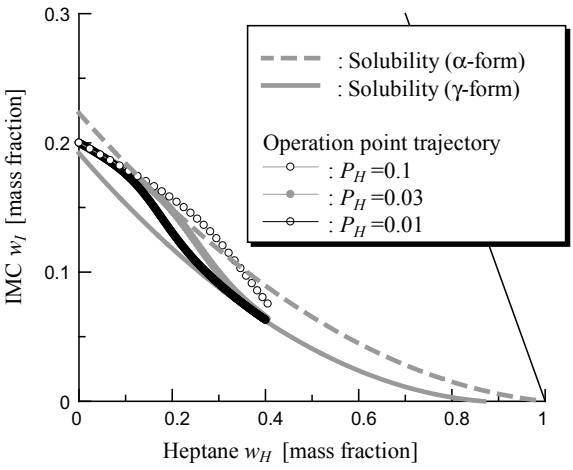

Fig. 3.6 Changes in solution concentration and operation point depending on anti-solvent feed rate ($\boldsymbol{w_{\mathrm{H}}} <$ 0.4)

Table 3.1 Comparison of operating period (crystallizer volume = 1000 mL, w_H = 0.4)

P_H (g/s)	Operating period (h)
0.01	4.2
0.03	1.4
0.1	0.4

operation point exceeds the solubility of α-form. From the simulation using the proposed model, the anti-solvent feed rate conditions that an operation point does not exceed the solubility of α-form can be decided.

3.4.4 Operation Strategies of Anti-solvent Addition Rate

From the simulation results, when anti-solvent composition of mixed solution increased, it was clear that the driving force generated by addition of anti-solvent was consumed immediately. From these results, it is possible to increase the feed rate of anti-solvent in the latter half of anti-solvent crystallization operation, and it is expected that operating period can be shortened. Based on the result of $P_H = 0.03$, the simulation result under the conditions in which the feed rate of the anti-solvent is made to increase gradually according to solvent composition is shown in Fig. 3.7. The feed rate was changed from 0.02 g/s to 1.0 g/s (Profile-A: $P_H = 0.02$; $0 < t <$ 4200 s, $P_H = 0.06$; $4200 < t < 5100$ s, $P_H = 1.0$; $5100 < t < 5400$ s). According to the simulation result, an operation point does not exceed the solubility of α-form.

Under Profile-A condition, the anti-solvent crystallization was carried out by using 1000 mL crystallizer. From the comparison between simulation and experimental results, the simulation results for solution concentration were good agreement with

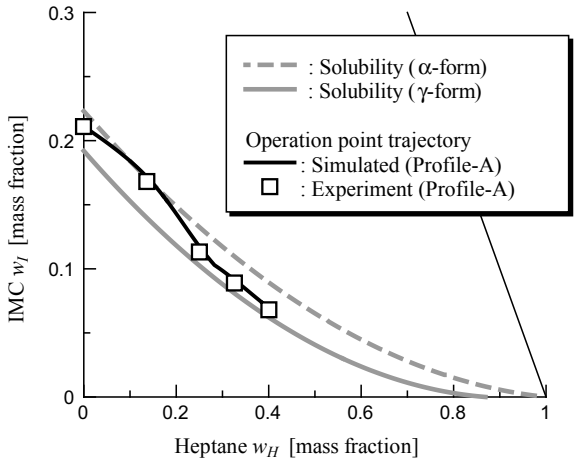

Fig. 3.7 Comparison between simulation and experimental results (Profile-A)

experimental results (Fig. 3.7). As the experimental result under Profile-A condition, the product crystal identified to be γ-form.

3.4.5 *Operation Strategies of Solution Addition Method*

In order to establish a production method of the target polymorph in the anti-solvent crystallization, the simulation model was proposed [5] to determine anti-solvent feed rate based on the ternary phase diagram. The stability of the polymorph of indomethacin (IMC) crystal in the solution changed not only with temperature but with the composition of the mixed solvent. And the design strategy of anti-solvent crystallization was proposed. It was reported that the modulation operation is effective for the improvement of crystal quality. The temperature modulated operation [17] was effective for improvement of crystal size distributions. So, the crystal quality may be further improved by integrating some crystallization operations. In the case of anti-solvent crystallization, desired crystal polymorphism may be achieved by integrating with solution addition method and temperature change operation.

Three kinds of anti-solvent addition methods were carried out. The anti-solvent addition rates in each experiment were determined by the simulation. Method A is the method that an anti-solvent is added at the constant flow rate. Method B is the method that the addition rate of anti-solvent increases in three stages. Method C is the method that an anti-solvent is added intermittently at the constant rate. The experimental conditions are summarized in Table 3.2.

Table 3.2 Experimental conditions and results in isothermal anti-solvent crystallization

Run	Method	Anti-solvent		Batch time (h)	Yield (%)	Polymorph
		Addition rate (g/min)	Addition period (min)			
1	A	0.726	120	2	29	γ-form
2	A	2.46	120	2	63	α- and γ-form
3	A	3.68	120	2	77	α- and γ-form
4	B	0.726 2.40 4.90	70 (0 $-$ 70) 30 (70 $-$ 100) 20 (100 $-$ 120)	2	58	γ-form
5	C	3.60	100 (20 min intermission)	2	59	α- and γ-form
6	C	2.46	110 (10 min intermission)	2	63	γ-form

3.4.5.1 Method A (Constant Addition Rate)

In Run 1, precipitation of α-form was not observed during the experiment. It became clear that γ-form can be selectively obtained from this result by using an anti-solvent addition rate with which solution composition does not approach the solubility of α-form.

In Run 2 and Run 3, α-form deposited during the experiment (Table 3.2). In order to obtain γ-form in stability, there is an anti-solvent addition rate that does not exceed the solubility curve of α-form. It is confirmed that it is important to control the solution composition in the operation area where only γ-form deposits using the ternary phase diagram and the simulation. However, under the conditions of a constant addition rate, the batch operation time becomes long.

3.4.5.2 Method B (Gradual Change of Addition Rate)

It was understood that a crystal growth rate constant K'_g becomes large with anti-solvent (heptane) composition (Fig. 3.8). Using the nature of this crystallization phenomenon, if an anti-solvent addition rate increases gradually, the batch operation time will be shortened. Then, the endpoint of Method A and Method B (Run 4) were compared by the simulation. The results of the solution composition trajectory are shown in Fig. 3.9.

Under the same batch time condition, the endpoint of Method A (Run 1) is $w_H = 0.29$ (yield 29%) and Method B (Run 4) is $w_H = 0.52$ (yield 58%), respectively. In this way, when Method B is used, it is expected that the yield can increase even in the same batch operation time. From the experimental result of Run 4, γ-form was selectively obtained in 2 h after the experiment start-up (Table 3.2).

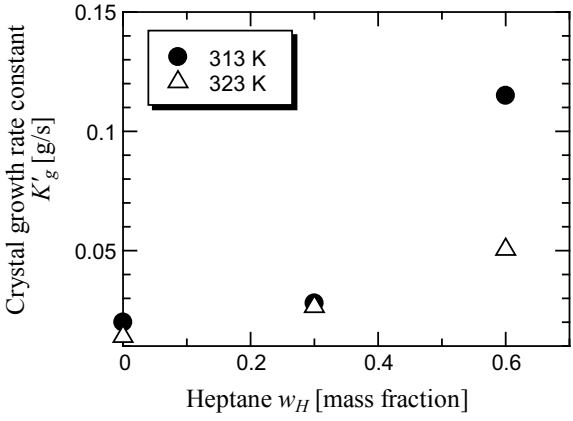

Fig. 3.8 Anti-solvent composition dependence crystal growth rate constant K'_g at 313 and 323 K

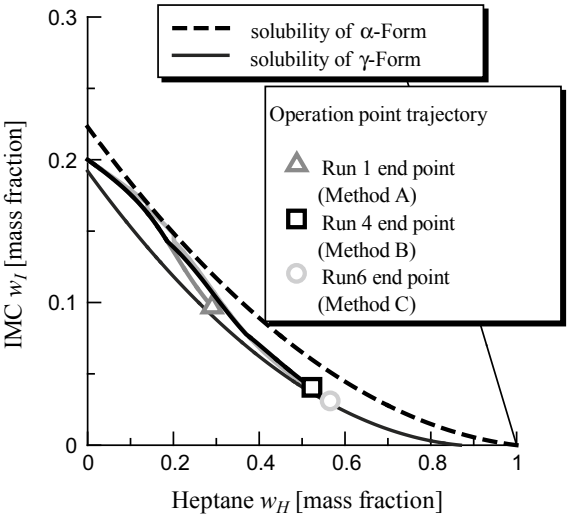

Fig. 3.9 Solubility curves for α-form and γ-form, and solution composition trajectories of Method A (Run 1), Method B (Run 4) and Method C (Run 6)

3.4.5.3 Method C (Intermittent Anti-solvent Addition)

In order to shorten batch operation time, it is necessary to supply an anti-solvent at a high addition rate. However, the existence of local supersaturation near the anti-solvent addition position is a problem under this operating condition. If the crystallization is carried out by using the lower addition rate than the critical rate at which the accumulation of α-form occurs by local supersaturation, and in the operation region in which solution composition does not exceed the solubility of α-form, it is considered that γ-form can be obtained selectively. In the early stage of Run 5, the plate-like crystal (γ-form) deposited. However, in the middle stage of Run 5, the cotton-like crystal deposited in large quantities. In Run 6, although the cotton-like crystal deposited in the middle of the experiment, the crystals which suspended at the end of batch operation time became only γ-form (Fig. 3.9).

3.4.5.4 Analysis of Precipitated Crystal and Existence of A′-Form

The cotton-like crystal deposited in the middle stage of the experiment not only under the condition of Method C but also under the condition with which does not exceed the solubility of α-form. There is a report that solvate deposits in crystallization of IMC from an acetone solution. When the precipitated crystal was analyzed in detail, the cotton-like crystal was the solvate of acetone. Therefore, if the solubility of solvate (α'-form) is not taken into consideration, γ-form cannot be obtained selectively. The solubilities of each polymorph are shown in Fig. 3.10.

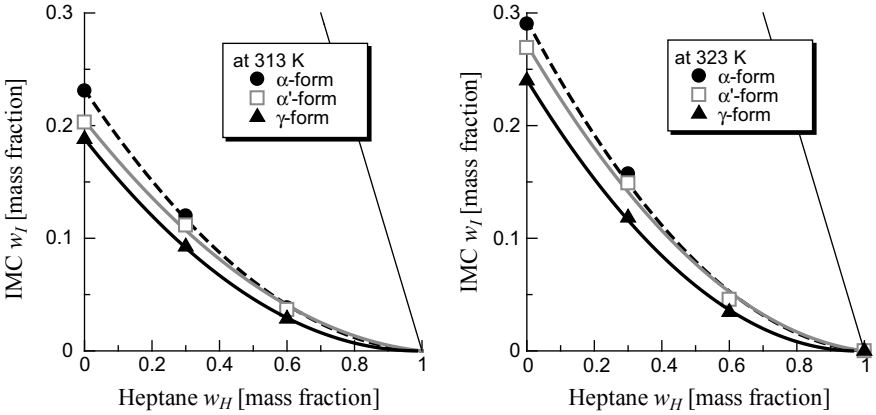

Fig. 3.10 Solubility curves of three kinds of IMC polymorph (α-form, α'-form and γ-form) at 313 and 323 K

3.4.5.5 Proposed Method D (Anti-solvent Crystallization with a Particular Temperature Profile)

If the operation point trajectory is maintained in the range between γ-form and α'-form solubility, a batch operation time becomes long under isothermal conditions. From the results of operation point trajectories, if the solution is heated when operation point approaches close to the solubility of α- or α'-form, it is possible to eliminate the limitation of the anti-solvent addition rate. In order to realize the anti-solvent crystallization incorporating heating operation, the temperature-dependent ternary phase diagram (Fig. 3.10) is necessary.

It is necessary to accelerate the anti-solvent addition rate in the early stages of an experiment for batch operation time shortening. Then, if the temperature-dependent solubility is applied, the increase in an addition rate is possible. As for the solubility of IMC in this system, temperature dependency becomes small in the region where heptane composition is high (Fig. 3.10). So, the increase in the addition rate in early stages of a batch operation time is the efficient crystallization method. Furthermore, since the deposition rate became accelerating in the high heptane composition region, it was considered that crystallization could be carried out without exceeding the solubility of α'-form. The experimental conditions are shown in Table 3.3.

In Run 7, linear heating was carried out from 313 to 333 K. The experimental result is shown in Fig. 3.11. Only γ-form was obtained without solution composition which exceeds the solubility of α'-form. However, the crystallization yield decreases, since the temperature of the end of operation becomes high when heating operation is incorporated. In this ternary system, a deposition rate increases with heptane concentration. If this crystallization phenomenon is used, recovery of yield is possible by incorporating cooling operation in the latter half of a batch operation time.

Table 3.3 Experimental conditions and results of Method D

Run	Method	Anti-solvent addition rate (g/min)	Batch time (h)	Temperature profile (K)	Final poly	Yield (%)
7	D	2.70	2	From 313 to 333	γ-form	27
8	D	2.70	2	From 313 to 323 and from 323 to 313	γ-form	65

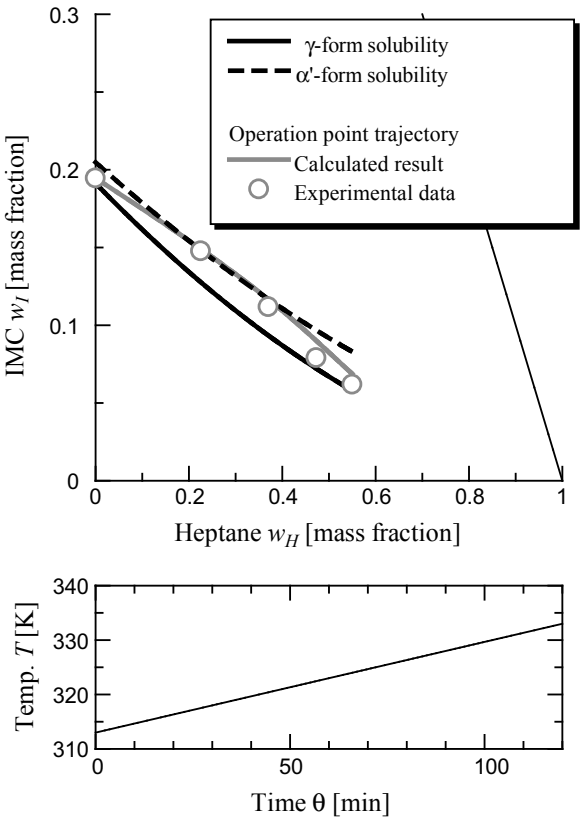

Fig. 3.11 Solubility curves for α'-form and γ-form in the ternary phase diagram and operation point trajectories of Method D (Run 7), and temperature profile of Run 7

In Run 8, the solution was heated by 10 K/h, and solution temperature was kept at 323 K for 30 min, and then it was cooled by 20 K/h for the last 30 min of a batch operation time (Fig. 3.12). Actual solution composition could be maintained in the region between α'-form and γ-form, and γ-form was obtained selectively. Thus, the particular temperature operation integrating the suitable temperature change was

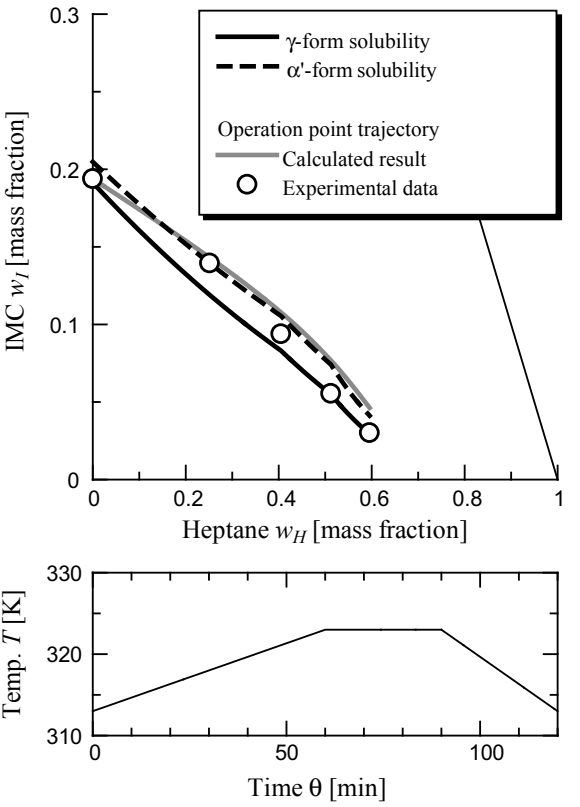

Fig. 3.12 Solubility curves for α'-form and γ-form in the ternary phase diagram and operation point trajectories of Method D (Run 8), and the particular temperature profile of Run 8

carried out for anti-solvent addition crystallization, and desired γ-form was able to be obtained in a short time with a certain level of yield.

3.5 Summary

The operation design of anti-solvent crystallization based on ternary phase diagram is proposed and the polymorphism precipitation phenomenon is discussed. The stability of the polymorph crystal in the solution changes not only with temperature but with the composition of the mixed solvent. The modeling of the crystallization operation for determining the optimal anti-solvent feed rate was carried out by using the ternary phase diagram, and the operation strategy for considering control of polymorph formation was proposed.

In the isothermal anti-solvent crystallization experiment, stable form is able to be selectively obtained by using the anti-solvent addition rate determined with the phase diagram. However, the solubility difference between metastable and stable

form is narrow. Therefore, if the operation point trajectory should not exceed the solubility of metastable form, the batch operation time becomes long by the limitation of anti-solvent addition rate. Then, by incorporating heating operation in anti-solvent crystallization, it becomes possible to increase an anti-solvent addition rate. Moreover, when the particular temperature operation is integrated into anti-solvent crystallization, target polymorph is successfully obtained with high yield compared with isothermal conditions.

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