

Polymorphic Crystallization of Sulfamerazine in Taylor Vortex Flow: Polymorphic Nucleation and Phase Transformation

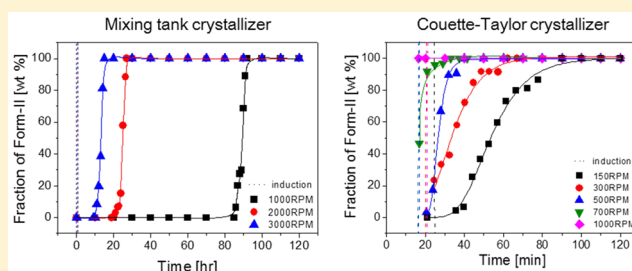
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S Supporting Information

ABSTRACT: The influence of a periodic Taylor vortex flow on the polymorphic crystallization of sulfamerazine (SMZ), including polymorphic nucleation and phase transformation, was investigated using a Couette–Taylor (CT) crystallizer, and also compared with the influence of a random turbulent flow in a mixing tank (MT) crystallizer. In the MT crystallizer, the induction of the metastable phase (form-I) occurred first, which was then followed by the induction of the stable phase (form-II) 10–85 h later. However, this whole process was significantly reduced to a half hour in the CT crystallizer, demonstrating the high efficiency of a Taylor vortex flow for the induction of polymorphic nucleation. The efficiency of the Taylor vortex flow was also enhanced when increasing the rotation speed. As a result, the stable and metastable phases were simultaneously nucleated at the first induction with a rotation speed above 300 rpm; plus the stable-phase fraction nucleated at the first induction increased when increasing the rotation speed. In addition, the polymorphic nucleation was facilitated when decreasing the dimension of the Taylor vortex flow, which was proportional to the gap size between the inner and outer cylinders. The periodic Taylor vortex flow was also more effective than the random turbulent flow for the phase transformation from the metastable phase to the stable phase. Thus, the time period for the complete phase transformation (called the reconstruction time) in the CT crystallizer was 5–10 times shorter than that in the MT crystallizer. Furthermore, the phase transformation was enhanced when decreasing the dimension of the Taylor vortex due to the promotion of the mass transfer. Finally, the polymorphic nucleation and phase transformation that varied with the rotation speed and gap size of the CT crystallizer were linearly correlated with one parameter: the viscous energy dissipation, representing the hydrodynamic intensity of the Taylor vortex flow.



INTRODUCTION

Polymorphism is defined as the ability of a substance to exist in more than one crystalline form, each of which has a chemically identical structure, yet different arrangements and/or conformations of the molecules in the crystal lattice.¹ Different polymorphs exhibit different mechanical, thermal, and physicochemical properties, including the melting point, solubility, crystal habits, and density, thereby affecting the stability, structural energy, morphology, dissolution rate, and bioavailability.² Thus, polymorphic crystallization, including polymorphic nucleation and phase transformation, has been attracting significant attention for the production of desired polymorphs.

In many previous investigations, the cooling/evaporation rate,^{3–5} supersaturation,⁴ solvent,^{4,6} agitation,^{7–9} and seeding¹⁰ have all been considered as critical operating variables to control the polymorphic nucleation. In the cooling crystallization of piracetam, a low cooling rate was found to favor stable-phase nucleation, as a low supersaturation was induced for a slow nucleation process, allowing the rearrangement of the

solute molecules into a thermodynamically stable state in molecular clusters.³ Conversely, a high cooling rate provided a high supersaturation, resulting in metastable-phase nucleation. Similarly, in the evaporation crystallization of glycine, the metastable zone width was reduced when decreasing the evaporation rate, resulting in stable-phase nucleation.⁵ Lu et al. also demonstrated the influence of the supersaturation and solvent on the polymorphic nucleation of famotidine.⁴ In this case, when providing different initial supersaturations using various solvents of water, methanol, and acetonitrile with different saturated concentrations, the polymorphic nucleation was found to be based on the conformational polymorphism. That is, a stable conformer with an unfolded configuration of the solute molecules was formed by the weak interaction between the solute molecules in the low initial supersaturation,

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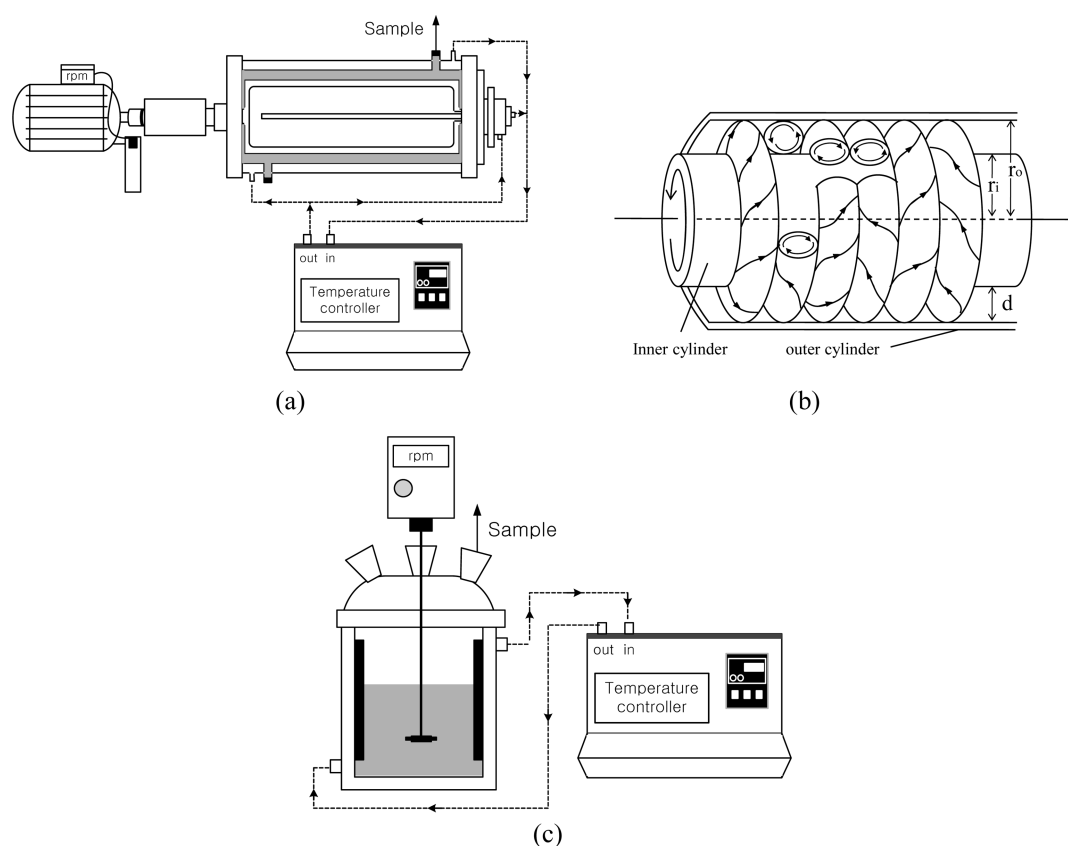


Figure 1. Experimental system for polymorphic crystallization of sulfamerazine: (a) Couette–Taylor (CT) crystallizer, (b) schematic drawing of Taylor vortex flow, and (c) mixing tank (MT) crystallizer.

resulting in stable-phase nucleation, whereas a metastable conformer with a folded configuration of the solute molecules was formed in the high initial supersaturation, resulting in metastable crystals. The effect of the solvent composition on polymorphic nucleation was also studied by Kitamura et al.⁶

When investigating the effect of hydrodynamic fluid motion on polymorphic nucleation in the case of the cooling crystallization of *L*-glutamic acid, the metastable phase was nucleated when the solution was agitated, whereas a polymorphic mixture of the stable and metastable phase was nucleated without any agitation.⁷ This was attributed to the uniformity of the supersaturation in the crystallizer resulting from the agitation. That is, a uniform supersaturation was generated in the crystallizer when agitating the solution, inducing metastable-phase nucleation, whereas a nonuniform supersaturation was created with no agitation, resulting in both stable and metastable-phase nucleation. The influence of hydrodynamic fluid motion on polymorphic nucleation was also reported by Sypek et al.⁹ In the cooling crystallization of carbamazepine, stable-phase crystals were obtained in a turbulently agitated solution, whereas metastable-phase nucleation occurred in a stationary solution. Similarly, Lee et al. found that stable phase nucleation in a metastable equilibrium suspension of metastable crystals was promoted by a turbulent fluid motion and Taylor vortex fluid motion.¹¹ Plus, Liu et al. demonstrated the effect of fluid shear on the polymorphic nucleation of *m*-hydroxybenzoic acid, where the polymorphic fractions of stable and metastable-phase nucleation varied significantly according to the agitation speed and agitation pattern.⁸

The phase transformation is also strongly affected by hydrodynamic fluid motion. For example, while the complete transformation of metastable crystals of 2,6-dihydroxybenzoic acid into stable crystals in a stationary suspension takes over 20 days, this was significantly reduced to 2–3 days in an agitated suspension and even further reduced when increasing the agitation speed.¹² A similar effect of agitation was also observed in the phase transformation of taltireline, where agitation was attributed with promoting stable-phase nucleation.¹³ Plus, Lee et al. showed the effect of a Taylor vortex flow, a unique periodic fluid motion, on the phase transformation.¹¹ In their study, the phase transformation from metastable seed crystals of sulfamerazine to stable crystals was promoted over 10-fold by the oriented fluid shear/elongation of the Taylor vortex when compared with the use of a random turbulent eddy.

Accordingly, the present study further investigated the influence of a Taylor vortex flow on polymorphic crystallization to determine whether the periodic fluid motion of a Taylor vortex could directly induce the nucleation of stable crystals of sulfamerazine. A Taylor vortex flow was induced in the gap between coaxially aligned inner and outer cylinders, where the inner cylinder was rotating and the outer one remained stationary. The Taylor vortex fluid motion was modified by varying the rotation speed of the inner cylinder and gap-size between the two cylinders. The influence of the Taylor vortex flow on the polymorphic crystallization was compared with that of random turbulent agitation in the mixing tank.

■ EXPERIMENTAL SECTION

SMZ and acetonitrile (ACN) used as the solute and solvent for the crystallization, respectively, were purchased from Sigma-Aldrich (ACS

grade) and Daejung Co (purity over 99.5%), respectively, and used without further purification. The SMZ feed solution was prepared by dissolving the SMZ in ACN at 48 °C. The SMZ feed solution was filtered using a microfilter to eliminate any solid impurities and then heated to 55 °C for complete dissolution.

The CT crystallizer was composed of two annular cylinders, where the inner cylinder was rotated to induce a Taylor vortex fluid motion in the gap between the two annular cylinders, while the outer cylinder remained stationary, as shown in Figure 1a,b. The flow regime of the Taylor vortex was varied using the rotation speed of the inner cylinder, ranging from 300 to 1000 rpm. Plus, the dimension of the Taylor vortex was modified by varying the gap-size between the inner and outer cylinders. In the present experiment, the radius of the inner cylinder (r_i) was varied from 3.6 to 4.0 cm, while the radius of the outer cylinder (r_o) was always fixed at 4.2 cm. As such, the radius ratio ($\eta = r_i/r_o$) between the two cylinders ranged from 0.86 to 0.95. The CT crystallizer was preheated to match the temperature (55 °C) of the SMZ feed solution and then filled with the SMZ feed solution. After waiting 1 h to eliminate any uncertain crystallization during the solution feeding process, the SMZ solution was cooled to 10 °C at a constant cooling rate for the polymorphic crystallization. Cooling jackets were installed on both cylinders for uniform cooling of the CT crystallizer. The cooling rate was varied from 10 to 360 °C/h. For comparison, a similar polymorphic crystallization of SMZ was also carried out using a standard Rushton mixing tank (MT) crystallizer equipped with a cooling jacket round the outer wall (Figure 1c). In the MT crystallizer, a random turbulent fluid motion was generated using a six-paddle impeller, where the agitation speed was varied from 1000 to 3000 rpm.

During the cooling crystallization, suspension samples were taken intermittently from the crystallizers to analyze the polymorphic crystallization of SMZ. The suspension samples were quickly filtered using a vacuum pump and then completely dried in a convection oven. The polymorphism and phase transformation of SMZ were analyzed using an FT-Raman spectrometer (Renishaw, RENISHAW pic, UK) and FE-SEM (LEO SUPRA 55, Carl Zeiss, Germany), as described in our previous study.¹¹ The above cooling crystallization was repeated at least three times to confirm the reproducibility of the polymorphic crystallization, including the polymorphic nucleation and phase transformation. The solubilities of the stable and metastable crystals were measured using a thermogravimetry method, as shown in the Supporting Information (Figure S1).

RESULTS AND DISCUSSION

The polymorphic crystallization of SMZ was conducted in two different crystallizers, a CT crystallizer and mixing tank (MT) crystallizer with distinct hydrodynamic fluid motions, as shown in Figure 2. The rotation of the inner cylinder in the CT crystallizer generated a periodic fluid motion of axisymmetric toroidal vortices, while the agitation of the impeller in the MT crystallizer created a random fluid motion of turbulent eddies. When the cooling crystallization of SMZ was carried out in the MT crystallizer at a constant cooling rate of 30 °C/h and 1000 rpm agitation speed, the initial nucleation of metastable form-I phase crystals occurred after about 1 h (first induction of nucleation), while the first stable form-II phase crystals appeared 85 h later (second induction of nucleation) (Figure 2a), which is typical for polymorphic crystallization.¹⁴ The metastable crystals then transformed into stable crystals via a reconstruction process in the solution. This long time-gap between the induction of the metastable crystals and the induction of the stable crystals was due to a high activation energy barrier for polymorphic nucleation of the stable phase.^{15,16} Thus, polymorphic nucleation of the stable phase was facilitated when increasing the agitation speed of the MT crystallizer, where the second induction was achieved within 10 h when using an agitation speed of 3000 rpm. Notwithstanding,

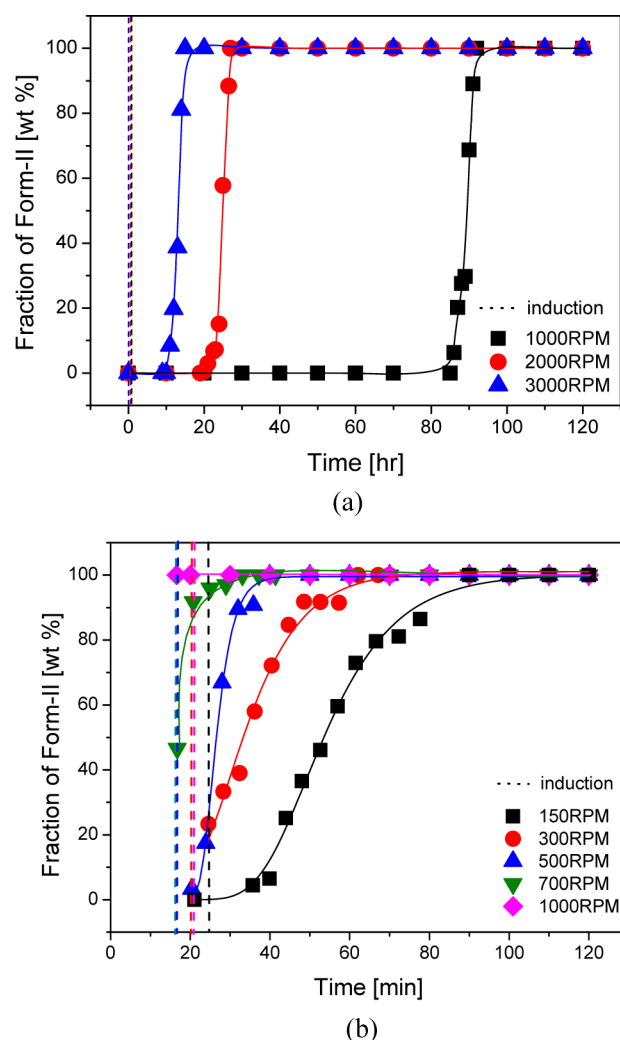


Figure 2. Effect of hydrodynamic fluid motions on polymorphic crystallization of sulfamerazine in (a) mixing tank (MT) crystallizer and (b) Couette–Taylor (CT) crystallizer. Cooling rate was fixed at 30 °C/h in both CT and MT crystallizers.

across the whole range of agitation speeds, the polymorphic crystallization in the MT crystallizer consistently exhibited the same phase transformation behavior: nucleation of the metastable phase first, followed by nucleation of the stable phase.

Meanwhile, in the CT crystallizer, the polymorphic crystallization of SMZ, including polymorphic nucleation and phase transformation, was more dramatic according to the rotation speed of the inner cylinder. At a low rotation speed of 150 rpm, nucleation of the metastable phase was induced first, followed by nucleation of the stable phase (Figure 2b), similar to the polymorphic nucleation behavior in the MT crystallizer. However, the time scale of the polymorphic nucleation in the CT crystallizer was much shorter than that in the MT crystallizer, showing that the periodic toroidal Taylor vortex flow was much more effective for polymorphic nucleation than the random turbulent flow.¹¹ Indeed, the metastable-phase nucleation (first induction point) occurred within 20 min, while the stable-phase nucleation (second induction point) occurred 15 min later. This time interval between the first and second induction points was also shortened when increasing the rotation speed of the inner cylinder. Eventually, the metastable

and stable phases were simultaneously nucleated at the first induction point with a rotation speed above 300 rpm. These polymorphic nucleation behavior differences between the CT and MT crystallizers originated from the different hydrodynamic fluid motions, which will be further discussed later.

The stable-phase fraction (mass fraction of stable phase in product crystals) at the first induction point varied according to the intensity of the fluid motion, as shown in Figure 3. This

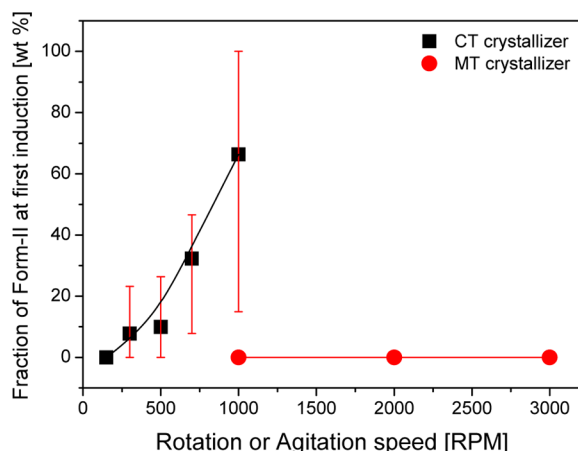


Figure 3. Variation of polymorphic fraction of stable form (form-II) at the first induction point of nucleation with hydrodynamic conditions in Couette–Taylor (CT) crystallizer and mixing tank (MT) crystallizer. Cooling rate was fixed at 30 °C/h in both CT and MT crystallizers.

fraction in the CT crystallizer increased significantly when increasing the rotation speed, and reached over 60% at a rotation speed of 1000 rpm. In contrast, the MT crystallizer only nucleated the metastable phase at the first induction point across the whole range of agitation speeds up to 3000 rpm. It should be noted that the polymorphic crystallization of SMZ was repeated at least three times under each crystallization condition, and the average values of these three runs are presented as the experimental results. On the basis of the multiple runs, the stable-phase fraction at the first induction point in the CT crystallizer was found to fluctuate. Below a rotation speed of 300 rpm, the stable-phase fraction at the first induction point only fluctuated within the error range. However, this fluctuation was amplified when increasing the rotation speed over 500 rpm, eventually resulting in a stable-phase fraction of 100% at the first induction point in one run when using a rotation speed of 1000 rpm. Therefore, the multirun experimental results clearly showed that the periodic toroidal fluid motion of the Taylor vortex flow in the CT crystallizer was highly effective for polymorphic nucleation when compared with the random turbulent flow in the MT crystallizer.

The polymorphic nucleation in the CT and MT crystallizers was confirmed by microscopic images, as shown in Figures 4 and 5, respectively. In the CT crystallizer at a rotation speed of 150 rpm, only metastable crystals (form-I) shaped like flat plates were observed at the first induction point (Figure 4a). At a higher rotation speed above 300 rpm, a polymorphic mixture of metastable (form-I) and stable (form-II) crystals (Figure 4c,d) was simultaneously nucleated at the first induction point. Plus, at a rotation speed of 1000 rpm, only stable crystals shaped like bulky polyhedrons were nucleated at the first

induction point, as observed in Figure 4e. In contrast, all the crystals nucleated in the MT crystallizer at the first induction point were metastable crystals shaped like flat plates, regardless of the different agitation speeds (Figure 5). Stable phase bulky-shaped crystals were newly formed at the second induction point 85 h later (Figure 5b), and the plate-shaped crystals were then completely transformed to bulky-shaped crystals several hours later, as shown in Figure 5c.

Figures 6 and 7 present quantitative information on the polymorphic nucleation and phase transformation extracted from the above polymorphic crystallization profiles (Figure 2). With regard to the polymorphic nucleation, the metastable induction time (t_m) and stable induction time (t_s) were defined as the time period until the first nucleation of the metastable phase (form-I) and stable phase (form-II), respectively. Plus, the reconstruction time (t_R) was defined as the time period until the complete phase transformation of the metastable crystals into stable crystals after the induction of the stable phase. On the basis of these definitions, the polymorphic induction times according to the agitation speed of the MT crystallizer are displayed in Figure 6a. At an agitation speed of 1000 rpm, the metastable induction time was about 24 min, and the stable induction occurred 85 h later. These times were significantly reduced to 16 min and 10 h, respectively, when increasing the agitation speed up to 3000 rpm. Therefore, this result suggests that the polymorphic nucleation depended on the hydrodynamic fluid motion.

The polymorphic induction times in the CT crystallizer differed significantly from those in the MT crystallizer, as shown in Figure 6b. At a low rotation speed below 500 rpm, the metastable induction in the CT crystallizer occurred at around 20 min and was then quickly followed by the stable induction 5–8 min later. The first induction time (metastable induction time) in the CT crystallizer was also found to be very close to that in the MT crystallizer. However, a significant reduction in the second induction time (stable induction time) was found in the CT crystallizer when compared to that in the MT crystallizer. Thus, the experimental results indicated that the periodic Taylor vortex flow in the CT crystallizer was more effective than the random turbulent eddy flow in the MT crystallizer for the induction of stable phase nucleation.¹¹ However, at a rotation speed above 700 rpm, both inductions (metastable and stable phases) occurred simultaneously at the first induction point after about 16 min.

In this study, the promoted stable phase induction of SMZ can be explained in terms of the viscous energy dissipation and molecular alignment effect of the hydrodynamic fluid motion on the polymorphic nucleation.^{11,17} The velocity gradient in the flow field created viscous frictional energy dissipation, thereby overcoming the energy barrier related to polymorphic nucleation. Since the amount of energy dissipated by the viscous friction increased when increasing the velocity gradient in the flow field, this further promoted the polymorphic nucleation. As a result, the polymorphic induction time was significantly reduced when increasing the rotation/agitation speed in both the CT and MT crystallizers. However, it is also interesting to note that the polymorphic inductions, especially the stable induction, in the CT crystallizer were always much faster than those in the MT crystallizer, even though the viscous energy dissipation in the CT crystallizer was much smaller than that in the MT crystallizer. This may have been due to the efficiency of the fluid motions for nucleation induction, referred to as the molecular alignment effect of the fluid motion. That is,

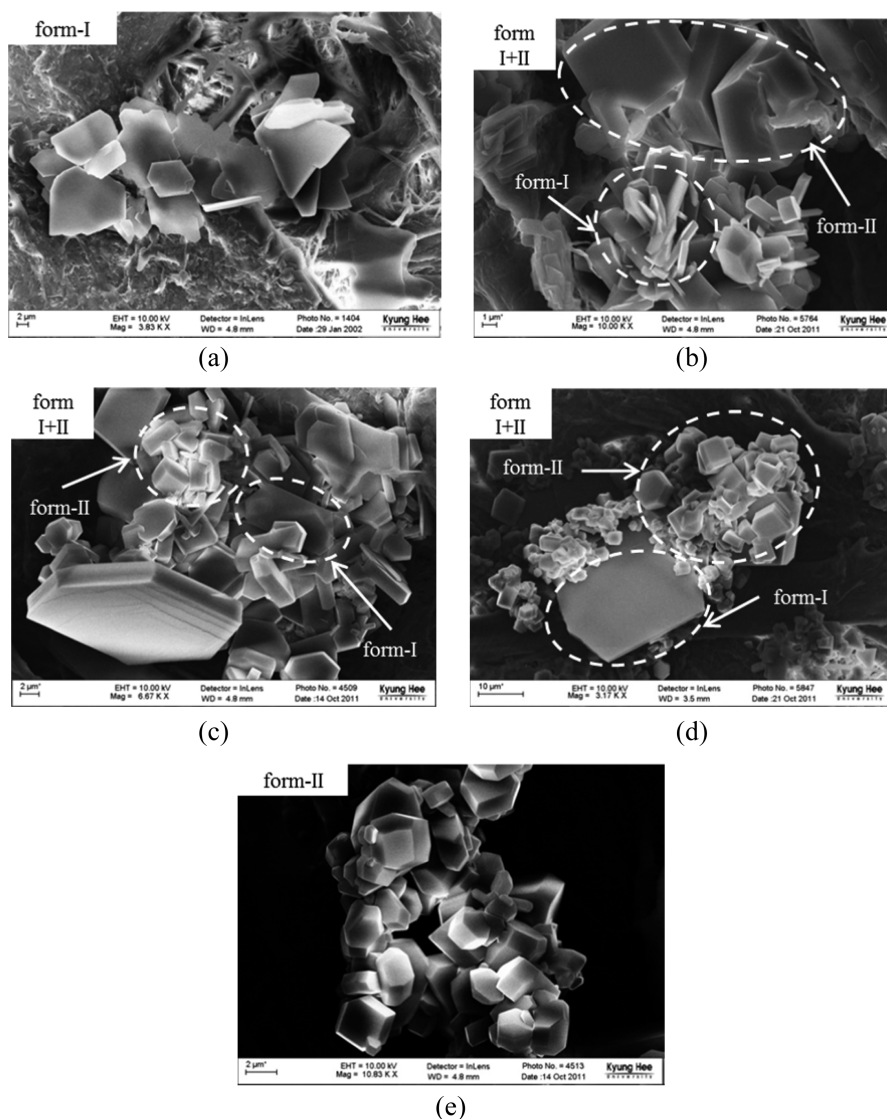


Figure 4. Morphology of crystals at first induction point of nucleation in the Couette–Taylor (CT) crystallizer at rotation speeds of (a) 150 rpm, (b) 300 rpm, (c) 500 rpm, (d) 700 rpm, and (e) 1000 rpm.

the velocity gradient induced a fluid shear/elongation stress in the flow field that aligned the molecules in the direction of the fluid stress, as demonstrated in previous studies.^{18–21} For example, the random-coil configurations of diblock copolymer (polystyrene and poly(ethylene propylene)) chains at equilibrium are aligned with the direction of the stress in shear and elongation flows. Two-dimensional SAX has also been used to show the reorientation of a polymer structure in the direction of the elongation stress in an elongation flow.²⁰ Plus, sudden contraction geometry has shown randomly oriented fibers in a fluid to be well aligned with the flow direction inducing a strong elongation stress.²¹ Thus, based on the above studies, it can be inferred that the periodic fluid motion of the Taylor vortex was much more efficient for molecular alignment and thus advantageous for the induction of nucleation than the random fluid motion of the turbulent eddy, even though the periodic Taylor vortex dissipated less viscous frictional energy than the random turbulent eddy. Therefore, polymorphic induction, especially stable-phase induction, was more significantly promoted in the CT crystallizer than in the MT crystallizer.

The effect of the hydrodynamic fluid motion on the polymorphic nucleation was also reflected in the induction temperature, as shown in Figure 7. In both crystallizers, the metastable induction temperatures varied in a range from 36 to 40 °C according to the rotation/agitation speed. However, the two crystallizers showed significantly different stable induction temperatures. In the MT crystallizer, the stable induction temperature was always 10 °C, which was then programmed as the final setting temperature for the cooling crystallization, regardless of the agitation speed. However, in the CT crystallizer, the stable induction temperature varied from 34 to 40 °C according to the rotation speed. Therefore, these results suggest that the stable induction in the CT crystallizer occurred at a lower supersaturation than that in the MT crystallizer. According to Davey and Garside,²² supersaturation is one of the critical factors determining polymorphic nucleation. While a high supersaturation is favorable for inducing the metastable phase, a low supersaturation is preferable for inducing the stable phase.^{1,23,24} Thus, the supersaturation at a high induction temperature of around 40 °C in the CT crystallizer (with a rotation speed of 700 and

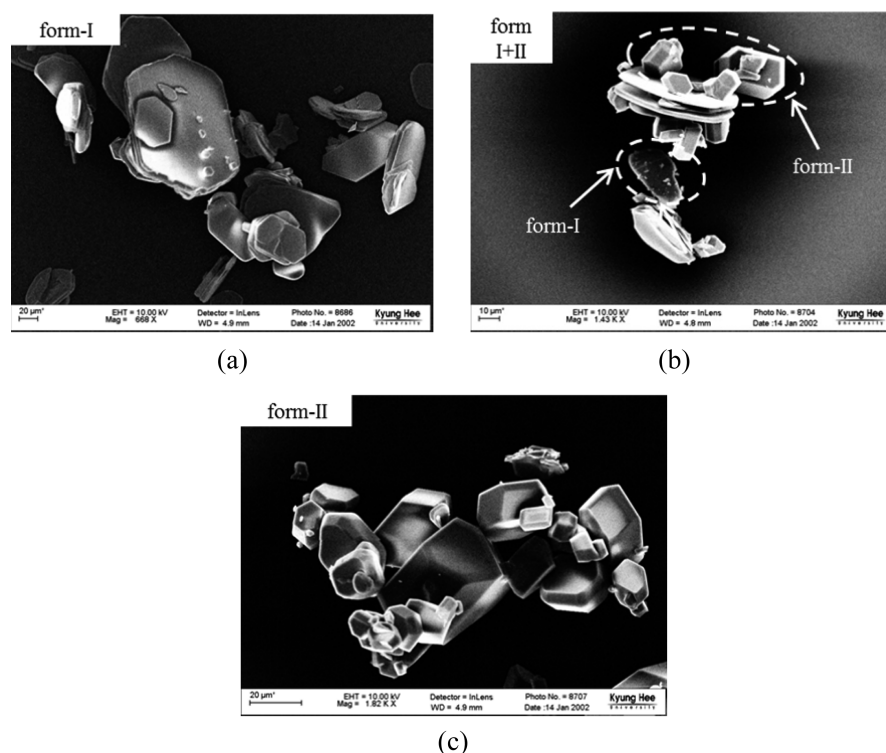


Figure 5. Morphological changes of crystals during polymorphic crystallization in mixing tank (MT) crystallizer at (a) 85 h, (b) 90 h, and (c) 93 h. Agitation speed was 1000 rpm.

1000 rpm) was likely low enough to favor the nucleation of the stable phase of SMZ (form-II). It should be noted that induction also occurred in the MT crystallizer at 40 °C (agitation speed of 3000 rpm), yet only the metastable phase. Therefore, these results strongly indicate that the periodic Taylor vortex flow was more efficient than the random turbulent eddy flow for the induction of the stable phase.

The reconstruction time for the complete phase transformation also depended on the type of fluid motion and its intensity, as shown in Figure 8. Since the reconstruction process is predominantly determined by a mass transfer for the dissolution of the metastable crystals and the growth of the stable crystals, the reconstruction times in both crystallizers were reduced when increasing the rotation/agitation speed. However, the reconstruction time in the CT crystallizer was 5–10 times shorter than that in the MT crystallizer, implying that the mass transfer in the Taylor vortex flow was much more effective than that in the random turbulent eddy flow.

The influence of the cooling rate on the polymorphic crystallization was also investigated, as shown in Figures 9–11. In the CT crystallizer, the metastable and stable induction times were monotonically reduced when increasing the cooling rate. While the metastable and stable inductions both occurred at the same time at a low cooling rate below 30 °C/h, they became separated when increasing the cooling rate above 150 °C/h, as shown in Figure 9a, where the time gap between the metastable and stable inductions was as short as 10 min. In the MT crystallizer, the induction times for the two phases always appeared separately across the whole range of cooling rates. That is, the metastable induction came first, followed by the stable induction 65–85 h later. Both induction times monotonically decreased, and the time gap between the two inductions was also reduced when increasing the cooling rate (Figure 9b).

When the polymorphic nucleation in each crystallizer was expressed in terms of the induction temperature, the polymorphic induction in the CT crystallizer was split into metastable (form-I) and stable (form-II) above a cooling rate of 150 °C/h, whereas they occurred at the same temperature below a cooling rate of 30 °C/h. The metastable (form-I) induction temperature increased up to 46 °C when increasing the cooling rate, whereas the stable (form-II) induction temperature was reduced to 25 °C (Figure 10a). This result reveals that although the first nucleation was induced at a high temperature of 46 °C (low supersaturation), it only produced metastable (form-I) crystals. While this would seem to contradict the above-mentioned hypothesis that stable induction is favored at a low superaturation^{1,23,24} and the above-mentioned result that the first induction of nucleation at 40 °C produced stable (form-II) crystals (shown in Figure 7b), this result may originate from the enantiotropic polymorphism of SMZ. According to Zhang et al.²⁵ and Figure S1 (Supporting Information), the transient temperature of SMZ in an ACN solution is about 51–54 or 48 °C. Thus, since form-I crystals become stable phase above the transient temperature, the nucleation of form-I crystals may have been favored as they were induced at a temperature close to the transient temperature. A similar induction temperature when changing the cooling rate was also observed in the MT crystallizer. Metastable induction always occurred first, and its temperature increased up to 46 °C with a cooling rate above 150 °C/h, whereas the following stable induction always occurred at 10 °C, which was programmed as the final setting temperature for the cooling crystallization (Figure 10b).

The polymorphic fractions of the stable phase generated at the first induction of nucleation in the crystallizers are summarized in the Supporting Information (Figure S2). In the CT crystallizer, the stable phase fraction of as much as 60%

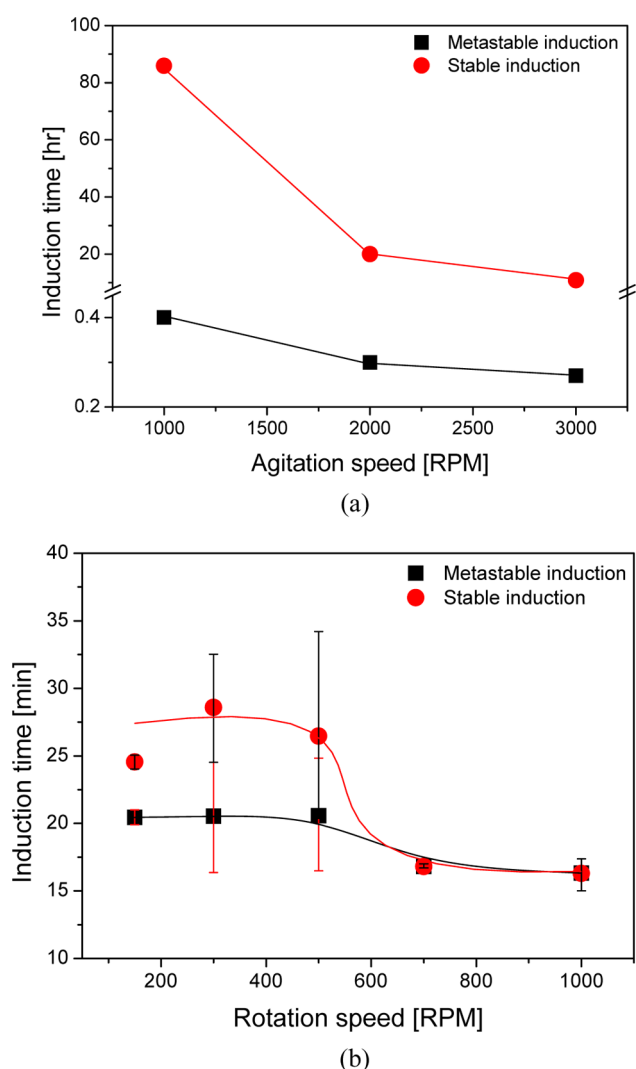


Figure 6. Influence of hydrodynamic intensity on metastable and stable induction times in (a) mixing tank (MT) crystallizer and (b) Couette–Taylor (CT) crystallizer. Cooling rate was fixed at 30 °C/h in both CT and MT crystallizers.

at a cooling rate of 10 °C/h was reduced 0% when increasing the cooling rate above 150 °C/h. Meanwhile, the MT crystallizer only produced the metastable phase at the first induction of nucleation at all the cooling rates.

Since the reconstruction process of polymorphs is predominantly dictated by mass transfer, the reconstruction times in both crystallizers were minimally influenced by the cooling rate, as shown in Figure 11. Notwithstanding, the reconstruction time in the CT crystallizer was only about one-eighth of that in the MT crystallizer. This result also suggests that the Taylor vortex flow was highly efficient for promoting the mass transfer when compared with the turbulent eddy flow in the MT crystallizer.

The influence of the dimension of the Taylor vortex on the polymorphic crystallization was investigated, as shown in Figure 12. The toroidal dimension of a Taylor vortex is proportional to the gap size between the inner and outer cylinders.^{26,27} In the present CT crystallizer, this gap was modified by varying the inner cylinder radius, and described as the ratio of the inner cylinder radius (r_i) to the outer cylinder radius (r_o): $\eta = r_i/r_o$. Thus, a high η meant a narrow gap size, implying the formation

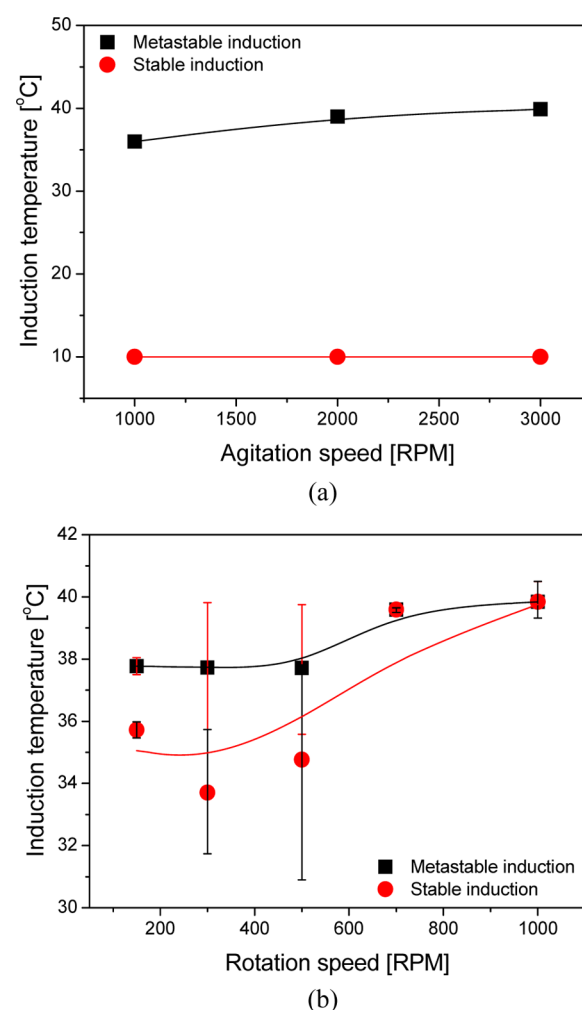


Figure 7. Influence of hydrodynamic intensity on metastable and stable induction temperatures in (a) mixing tank (MT) crystallizer and (b) Couette–Taylor (CT) crystallizer. Cooling rate was fixed at 30 °C/h in both CT and MT crystallizers.

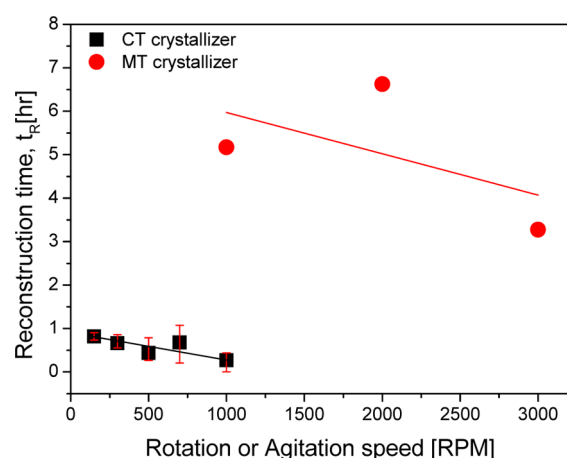
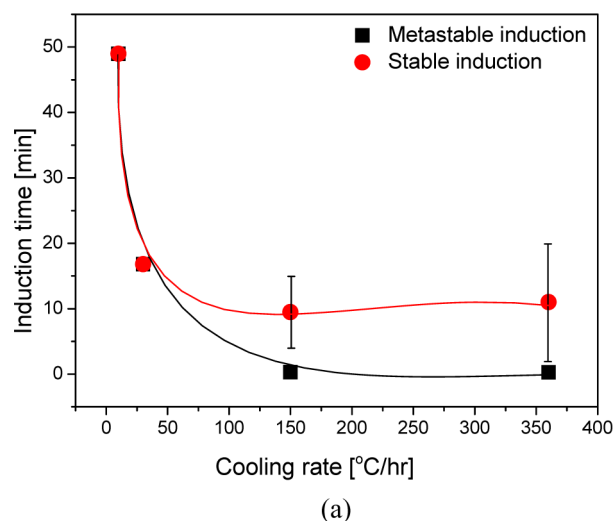
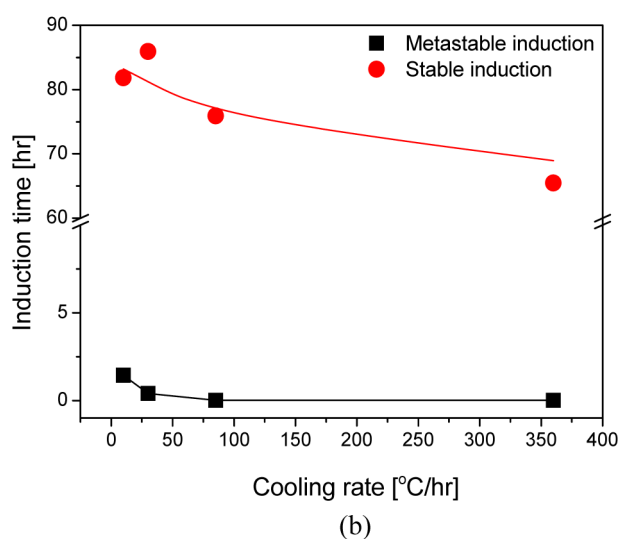


Figure 8. Influence of hydrodynamic intensity on reconstruction time in Couette–Taylor (CT) crystallizer and mixing tank (MT) crystallizer. Cooling rate was fixed at 30 °C/h in both CT and MT crystallizers.

of a smaller dimensional Taylor vortex in the CT crystallizer. Both phases were simultaneously generated at the first induction of nucleation with all the gap sizes (Supporting



(a)

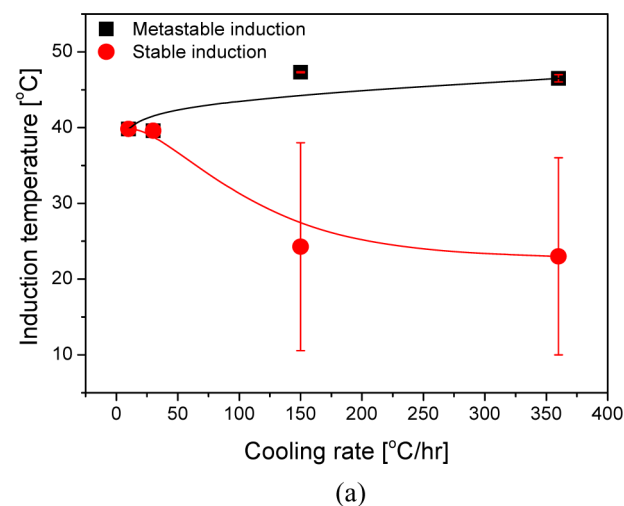


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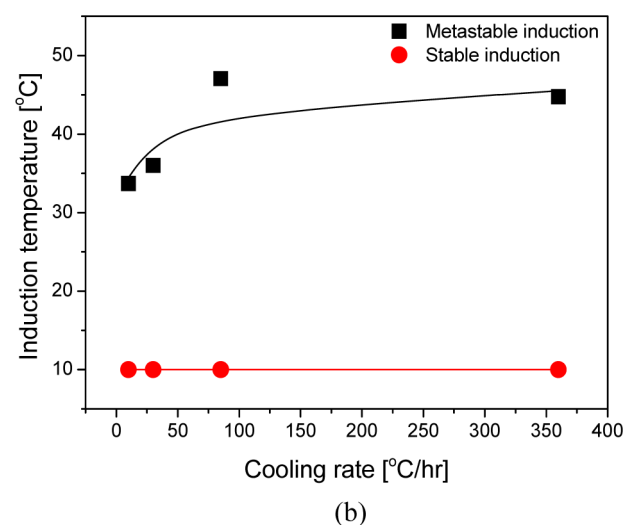
Figure 9. Influence of cooling rate on metastable and stable induction times in (a) Couette–Taylor (CT) crystallizer and (b) mixing tank (MT) crystallizer. Rotation speed of CT crystallizer and agitation speed of MT crystallizer were fixed at 700 and 1000 rpm, respectively.

Information, Figure S3), and the stable-phase fraction at the first induction was enhanced about 25–40% when increasing η from 0.86 to 0.95 (Figure 12a). However, the reconstruction time decreased from about 40 to 30 min when increasing η , implying promotion of the mass transfer, as shown in Figure 12b.

These results can be explained in terms of the hydrodynamic intensity of the Taylor vortex influencing the polymorphic nucleation and reconstruction. The viscous energy dissipation (ϵ) is generally used as a quantitative scale for the intensity of a hydrodynamic fluid motion. For a Taylor vortex, the viscous energy dissipation has been suggested as $\epsilon = ((\pi L_C r_i^4 \omega_i^3) / (V_C)) 0.8 (d/r_i)^{0.35} ((\omega_i r_i d) / \nu)^{-0.53}$.^{28,29} Here, L_C and V_C are the length and volume of the CT crystallizer, respectively; r_i is the radius of the inner cylinder; d is the gap size between the two cylinders; ν is the kinematic viscosity of the solution; and ω_i is angular velocity of the inner cylinder. As such, this equation indicates that the viscous energy dissipation depends on the rotation speed (angular velocity) of the inner cylinder and gap size (d). Therefore, the viscous energy dissipation in the present CT crystallizer increased when increasing the rotation



(a)



(b)

Figure 10. Influence of cooling rate on metastable and stable induction temperatures in (a) Couette–Taylor (CT) crystallizer and (b) mixing tank (MT) crystallizer. Rotation speed of CT crystallizer and agitation speed of MT crystallizer were fixed at 700 and 1000 rpm, respectively.

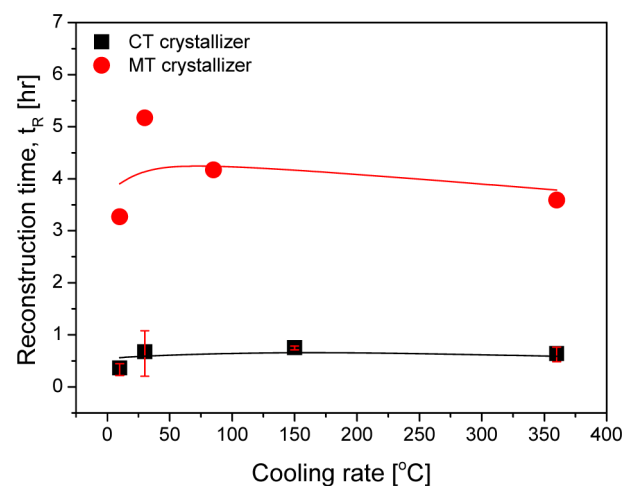


Figure 11. Influence of cooling rate on reconstruction time in Couette–Taylor (CT) and mixing tank (MT) crystallizers. Rotation speed of CT crystallizer and agitation speed of MT crystallizer were fixed at 700 and 1000 rpm, respectively.

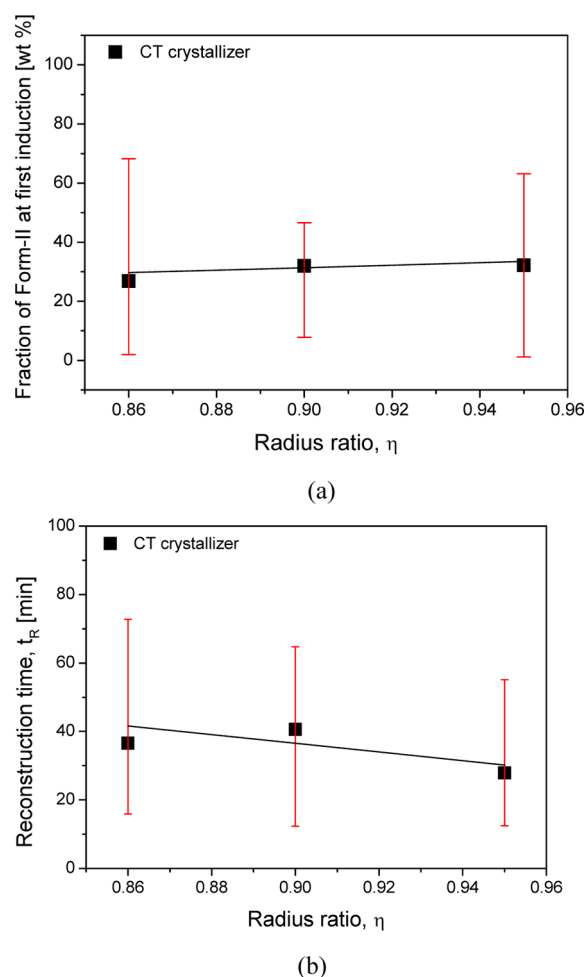


Figure 12. Influence of gap size between inner and outer cylinders of Couette–Taylor crystallizer on (a) polymorphic fraction of stable form (form-II) at first induction point of nucleation and (b) reconstruction time. Radius ratio means ratio of inner cylinder radius to outer cylinder radius. Rotation speed and cooling rate were fixed at 700 rpm and 30 °C/h, respectively.

speed and decreasing the gap size (increase of η), as shown in Figure S4 (Supporting Information). Thus, supposing that the stable-phase fraction at the first induction is proportional to the nucleation rate, which varies according to two operating variables: the rotation speed and gap size (Figures 3 and 12a), this can be linearly plotted in terms of a single variable: the viscous energy dissipation (ϵ), as shown in Figure 13a. In this figure, it was found that the stable polymorphic nucleation at the first induction was exponentially enhanced when increasing the viscous energy dissipation.

Furthermore, the reconstruction process can be described using the mass transfer rate, as suggested by Lee et al.¹¹ That is, the reconstruction time (t_R) is inversely proportional to the mass transfer rate, which is expressed as a function of the Taylor number as $Sh = 2.0 + 0.4Ta_p^{0.53}Sc^{1/3}$, where the Taylor number is defined as $Ta_p \equiv ((\omega r_i d_p)/\nu)(d/r_i)^{1/2}$.³⁰ Thus, when combining this mass transfer correlation with the above equation for the viscous energy dissipation, the reconstruction time can be expressed as a function of the viscous energy dissipation as $t_R^{-1} \approx k_m \approx \epsilon^{0.21}$.¹¹ According to this expression, since the mass transfer coefficient also varies with the rotation speed (angular velocity) of the inner cylinder and gap size, it can be correlated with one variable: the viscous energy

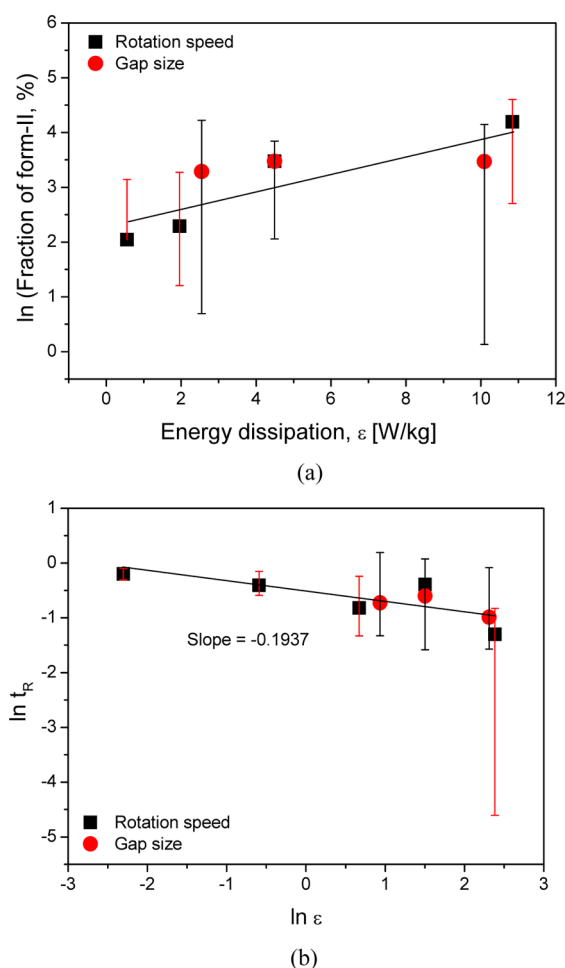


Figure 13. Correlations of polymorphic crystallization depending on rotation speed and gap size with viscous energy dissipation (ϵ) when changing rotation speed and gap size: (a) polymorphic fraction of stable form (form-II) at first induction point of nucleation and (b) reconstruction time (t_R).

dissipation. Therefore, in the present study, the reconstruction times depending on the rotation speed (Figure 8) and gap size (Figure 12b) fitted well with the viscous energy dissipation, as shown in Figure 13b, indicating that the mass transfer was promoted when increasing the hydrodynamic intensity of the Taylor vortex flow. It should also be mentioned that the slope of 0.194 in this linear fit of the reconstruction time was highly consistent with the slope of 0.21 in our previous study.¹¹ In addition, the induction temperature and time were almost independent of the gap size (d), as shown in the Supporting Information (Figure S3).

CONCLUSION

A Taylor vortex flow, a unique periodical toroidal fluid motion, was demonstrated to be highly effective for the polymorphic crystallization of SMZ. The polymorphic nucleation of SMZ was induced much faster in the periodic Taylor vortex flow than in the random turbulent eddy flow, due to the more efficient molecular alignment of the periodic fluid motion on the induction of nucleation. When increasing the rotation speed of the CT crystallizer, the molecular alignment effect of the periodic Taylor vortex flow was further reinforced. Thus, the stable phase (form-II) was simultaneously nucleated at the first induction in the CT crystallizer at a rotation speed above 500

rpm. This result was significantly different from the polymorphic nucleation in the MT crystallizer, in which the metastable phase induction always occurred first and was then followed by the stable phase induction 10–85 h later. The molecular alignment effect of the periodic Taylor vortex flow was also modified by the dimension of the Taylor vortex, varying with the gap size between the inner and outer cylinders. Reducing the gap size intensified the molecular alignment effect of the Taylor vortex flow, promoting fast induction of the polymorphic nucleation. Since the polymorphic nucleation varied according to both the rotation speed and the gap size of the CT crystallizer, it was linearly expressed using a single parameter: the viscous energy dissipation, representing the hydrodynamic intensity of the Taylor vortex flow. This correlation supports the notion that fluid motion is involved in the nucleation process, and the periodic motion of the Taylor vortex flow is very effective for promoting nucleation.

The periodic Taylor vortex flow was also more efficient than the random turbulent flow for promoting mass transfer. As a result, the reconstruction of the metastable phase into the stable phase was 5–10 times faster in the CT crystallizer than in the MT crystallizer. The Taylor vortex flow was intensified when increasing the rotation speed and reducing the gap size between the two cylinders of the CT crystallizer. This promoted the mass transfer rate for the phase transformation, thereby reducing the reconstruction time. The reconstruction time was thus linearly correlated with the mass transfer coefficient expressed in terms of the viscous energy dissipation, indicating that the reconstruction process in the solution was dominantly controlled by the mass transfer process.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.5b00002.

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Notes

The authors declare no competing financial interest.

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