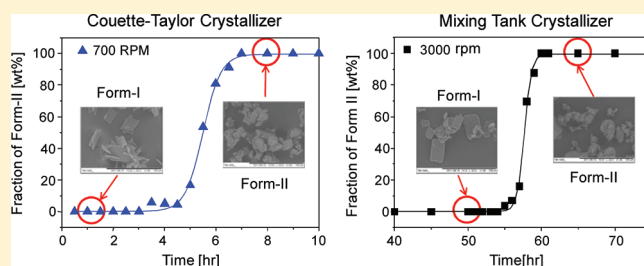


Phase Transformation of Sulfamerazine Using a Taylor Vortex

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ABSTRACT: A Couette–Taylor (CT) crystallizer was used to demonstrate the unique fluid dynamic properties of a Taylor vortex for the phase transformation of sulfamerazine (SMZ). With a conventional Rushton mixing tank (MT) crystallizer, the phase transformation from a metastable crystalline phase to the stable crystalline phase took more than 60 h with acetonitrile (ACN) as the solvent and an agitation rate of 3000 rpm. Using a CT crystallizer, this phase transformation occurred within 3–7 h with rotation speeds in the CT crystallizer of 300–1000 rpm. Increasing the rotation speed of the CT crystallizer also significantly enhanced the phase transformation, whereas adding water to the solvent increased the solubility difference between the two polymorphs and accelerated the phase transformation in both crystallizers. The phase transformation in the CT crystallizer was always many times faster than that in the MT crystallizer. Nucleation and mass-transfer models were used to describe the nucleation induction time of the stable crystal form and the transformation of metastable crystals into stable crystals. The influence of the fluid motions of the periodic Taylor vortex and random eddy in the CT and MT crystallizer, respectively, on the induction time was correlated by the nucleation enhancement factor, which was expressed as function of energy dissipation. The resulting induction and transformation times correlated well with the experimental data in terms of the energy dissipation and solubility difference across the whole range of phase transformation conditions, including rotation speeds, water fractions, and temperatures.



■ INTRODUCTION

Polymorphs of active pharmaceutical ingredients (APIs) are of great importance to the pharmaceutical industry, as they determine the solubility and dissolution rate of APIs, thereby affecting their bioavailability. In most cases, pharmaceutical companies choose the most stable polymorph at the isolation temperature as the API. In cases where a metastable kinetic polymorph is formed, solution-mediated phase transformation is often used to obtain the desired form.

Solution-mediated phase transformation is generally considered as a consecutive process of two major steps: the nucleation of stable crystals and the recrystallization of metastable crystals into stable ones in a solution.¹ The driving force for this process is the solubility difference between the stable and metastable crystal forms. Many primary factors have already been identified as influencing phase transformation, such as temperature,^{2,3} solvent,^{2,3} additives,^{4,5} agitation,^{6–8} viscosity,² external surface area,⁷ suspension density,⁵ seed crystals,⁵ crystal size,⁶ and magnetic field.^{9,10} For example, the phase transformation of α -form stearic acid into β -form stearic acid is much faster in the protic solvent methanol than in the aprotic solvent hexane, because of the formation of dimeric stearic acid in aprotic solvents.² Similarly, the transformation of anhydrous crystals of carbamazepine into hydrate crystals is facilitated by increasing the water fraction in a mixed solvent because of the increased water activity in the solvent.³ In

enantiotropic polymorphic systems, the temperature has a significant influence on the phase transformation. Thus, in the case of stearic acid and carbamazepine, the solubility declines at lower temperatures (below the transition temperature), and the nucleation and growth of the stable polymorph are slow, thus reducing the rate of the phase transformation. Qu et al.⁴ demonstrated that the rate of phase transformation can be controlled by modifying the solubility difference using an additive. For example, addition of hydroxyl propylmethyl cellulose increases the solubility of the stable polymorph and thus decreases the solubility difference between the forms, resulting in a reduction of the phase transformation rate. In contrast, the addition of sodium lauryl sulfate increases the solubility of the metastable polymorph and increases the solubility difference, thereby promoting the phase transformation rate. In the case of sulfamerazine,¹¹ additives of N4-sulfamerazine, sulfadiazine, and sulfamethazine are adsorbed on the crystal surface of the polymorphs, which retards the phase transformation by inhibiting the dissolution of the metastable polymorph and inhibiting the growth of the stable polymorph.

Agitation of the suspension has frequently been identified as an important factor for phase transformation, as it can influence

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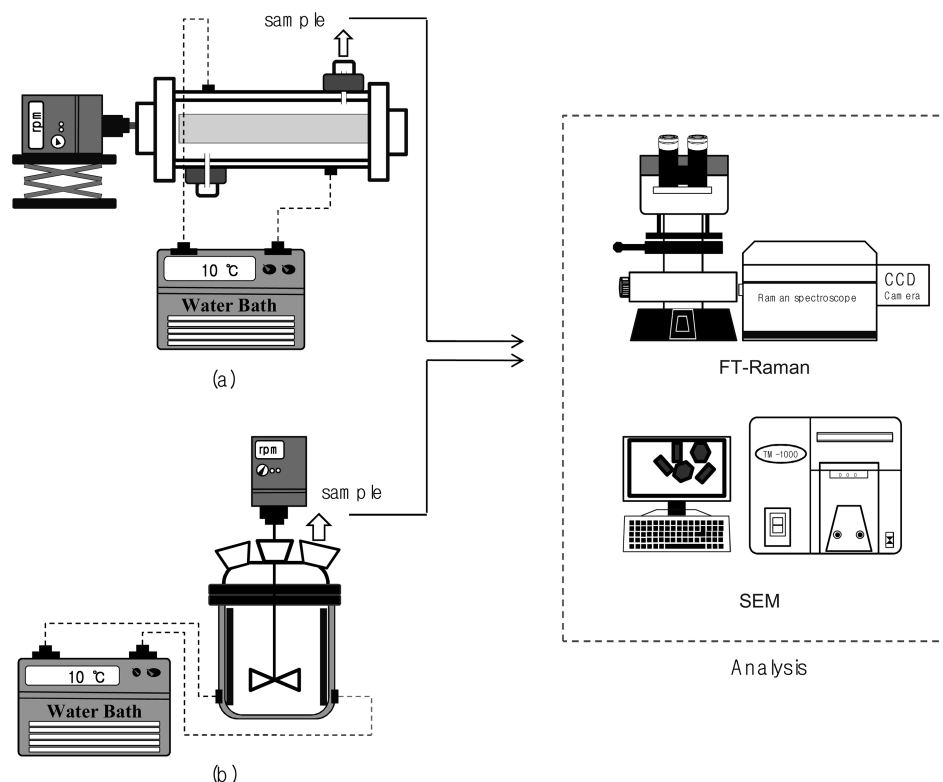


Figure 1. Schematic diagram of the experimental apparatus used for the phase transformation of sulfamerazine: (a) Couette–Taylor crystallizer, (b) Rushton mixing tank crystallizer.

the nucleation and growth of the stable polymorph, as found for the phase transformation of L-glutamic acid.^{6,7} In these studies, the formation and growth of the stable polymorph was enhanced with the agitation speed, resulting in a fast phase transformation. In addition, as the formation of the stable polymorph is based on heterogeneous nucleation, this formation is significantly promoted by the heterogeneous interface of the crystallizer wall and impeller with a low interfacial tension that lowers the energy barrier for nucleation. However, the best interface to induce nucleation is actual crystals of the stable polymorph. Thus, seed crystals of the stable polymorph are frequently used to control the phase transformation.⁵ In the case of caffeine, the nucleation of the stable polymorph is the most time-consuming step in the phase transformation, because of the high energy barrier for primary nucleation. Thus, seed crystals of the stable polymorph help to induce secondary nucleation of the stable polymorph, thereby reducing the time period of the phase transformation.

For certain APIs of sulfamerazine, aripirazol, and famotidine, the transformation of metastable polymorphs into stable forms takes an extraordinarily long time, because of their small solubility differences and high energy barriers.^{12–14} For example, aripirazol requires over 48 h for a complete phase conversion from form-3 to form-H₁,¹² whereas only 10% of metastable β -form famotidine is transformed into stable α -form famotidine after 96 h.¹³ In addition, in the case of sulfamerazine, the phase transformation from the metastable polymorph (form I) to the stable polymorph (form II) in pure ACN solvent does not occur even after 14 days.¹⁴ However, when Kurotani and Hirasawa¹⁵ applied ultrasonication as an external energy source to initiate the nucleation of the stable-form crystals, the transformation was completed within about 20 h. Similarly, for the crystallization

of dextrose monohydrate, Devarakonda et al.^{16,17} demonstrated that ultrasonic energy significantly promoted nucleation through the cavitation effect and creation of heterogeneous nucleation sites.

This study attempts to promote the phase transformation of sulfamerazine using a Taylor vortex, which is a unique periodic turbulent flow motion with an effective dissipation of viscous friction energy. Sulfamerazine [4-amino-*N*-(4-methylpyrimidin-2-yl)benzene-1-sulfonamide, C₁₁H₁₂N₄O₂S], an antibacterial agent, has enantiotropic polymorphs denoted form I and form II. Below the transition temperature of 54 °C, form II is stable, and form I is metastable. Therefore, the stable form of sulfamerazine is preferred in the production because of its superior characteristics from the tablet over the metastable form.¹⁸

A Taylor vortex has already been used in the crystallization reaction of calcium carbonate,^{19–21} producing excellent micro-mixing effects and resulting in crystals with a uniform size and shape in a continuous crystallizer. Also, it has been confirmed that the Taylor vortex is quite effective in facilitating interfacial mass transfer between solid and liquid. The phase transformation of guanosine monophosphate from the amorphous phase to the hydrate crystalline phase was significantly accelerated in a Taylor vortex flow.^{22,23} The present study systematically investigated the influence of a Taylor vortex on the phase transformation, considering both nucleation and mass transfer. The experimental results are explained using model equations based on nucleation and mass-transfer theories. The impact of the Taylor vortex on phase transformation is also compared with that of a turbulent eddy in a Ruston mixing tank.

EXPERIMENTS

The phase transformation of sulfamerazine (SMZ) was conducted in a Couette–Taylor (CT) crystallizer composed of two annular cylinders

made of stainless steel, as shown in Figure 1. The inner cylinder of the crystallizer was rotated to induce a Taylor vortex in the gap between the two annular cylinders, whereas the outer cylinder remained stationary. The intensity of the Taylor vortex was controlled by the rotation speed of the inner cylinder, which ranged from 300 to 1000 rpm. To control the temperature of the crystallizer, the surfaces of both cylinders (i.e., the inner surface of the outer cylinder and outer surface of the inner cylinder) were cooled with a coolant. Thus, an outer jacket was used to allow cooling of the outer cylinder, and the coolant was circulated inside the inner cylinder. The same temperature was maintained for both cylinder surfaces, and it was varied from 10 to 30 °C to adjust the phase transformation of the sulfamerazine (SMZ).

Sulfamerazine (SMZ) was purchased from Sigma-Aldrich (ACS grade) and used without further purification. The acetonitrile (ACN) used as the solvent for the phase transformation was supplied from Daejung Co. (purity 99.5%). For the phase transformation experiments, form-I crystals of SMZ were prepared by cooling crystallization, where 50 g/L of SMZ was dissolved in pure ACN at 50 °C and the solution was cooled to 5 °C for the crystallization of form-I crystals. The structure of the form-I crystals was confirmed using XRD and FT-Raman spectroscopy. After being separated from the solution and completely dried in a convection oven, the crystals were sieved to classify size (mesh size 100–210 μm). The crystals were then stored in a desiccator until use in experiments.

A solvent mixture of ACN and water was saturated with the form-I crystals of SMZ at a set temperature. Using this saturated solvent, a suspension of the form-I crystals (33.3 g/L) was then prepared at the same set temperature and fed into the CT crystallizer, which had already been cooled to the same set temperature. After the CT crystallizer had been completely filled, the CT vortex was induced by rotating the inner cylinder for the phase transformation of SMZ. In this experiment, the phase transformation in the crystallizer was run in batch mode, and the ACN content in the solvent mixture was varied from 60% to 100%.

To compare the phase transformation rate, a similar batch run for the phase transformation of the form-I crystals was carried out in a standard Rushton tank crystallizer equipped with a cooling jacket around the outer wall. Here, a six-paddle impeller was used for turbulent agitation, which was varied from 2000 to 3000 rpm.

During the phase transformation, samples were taken intermittently from the crystallizer and quickly filtered using a vacuum. Simultaneously, the CT crystallizer was refilled with a fresh suspension of the form-I crystals to maintain a consistent fluid motion from the Taylor vortex. The filtered sample crystals were completely dried in a convection oven and then analyzed using an FT-Raman spectrometer (Renishaw, RE-NISHAW pic) for the crystal phase and an electron microscope (Hitachi, TM-1000) for the crystal shape.

RESULTS AND DISCUSSION

Solubility of SMZ. The solubility difference between the two polymorphs of SMZ (forms I and II) was found to be an important driving force for the phase transformation. As shown in Figure 2, the solubilities of the SMZ polymorphs were measured using UV–vis spectroscopy. When increasing the temperature of the ACN–water mixed solvent (80% ACN + 20% water), the solubilities of both polymorphs (form I and form II) increased. In addition, because of the lower stability of the metastable structure of the form-I crystals, their solubility was higher than that of the stable form-II crystals up to a temperature of 30 °C. However, the solubility difference between the two polymorphs was reduced when the temperature was further increased because of their enantiotropic relationship.

The solubility of the SMZ crystals also changed markedly according to the composition of the ACN–water mixed solvent

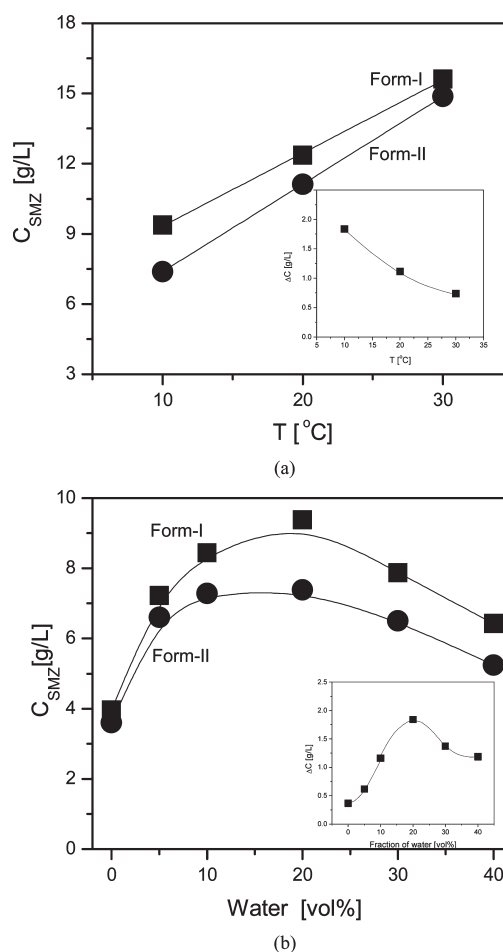


Figure 2. Dependencies of the solubility of polymorphic crystals of sulfamerazine on (a) temperature at a water fraction of 20% in mixed solvent and (b) water fraction of mixed solvent at a temperature of 10 °C.

(Figure 2b). When water was added to the mixture, the solubility of the SMZ polymorphs was enhanced up to a 20% water fraction and then reduced with the further addition of water above 20%. Similarly, the solubility difference was maximized when the water fraction in the mixture was around 20%.

Phase Transformation of SMZ. To quantitatively monitor the phase transformation, standard structural fractions were calibrated for the two polymorphs using FT-Raman spectroscopy. Because of the different packing arrangements of SMZ molecules in the solid forms, each polymorph has unique peak shifts in the Raman spectrum. As shown in Figure 3, the stretching vibration peak of SO_2 , occurring at 1145–1150 cm^{-1} in the case of free interaction, shifted to 1106 and 1116 cm^{-1} for the form-I and -II crystals, respectively, because of the different intermolecular interactions. As these peak intensities were clearly proportional to the mass fractions of the two polymorphs ($R^2 = 0.990$), they were then used to estimate the polymorphic fractions of SMZ crystals during the phase transformation.

The phase transformation of the SMZ crystals was carried out in the CT crystallizer at varying rotation speeds, as shown in Figure 4. When pure ACN solvent was used, the phase transformation of the form-I crystals to the form-II crystals at the rotation speed of 300 rpm was completed within 11 h, and this time period was greatly reduced as the rotation speed was increased.

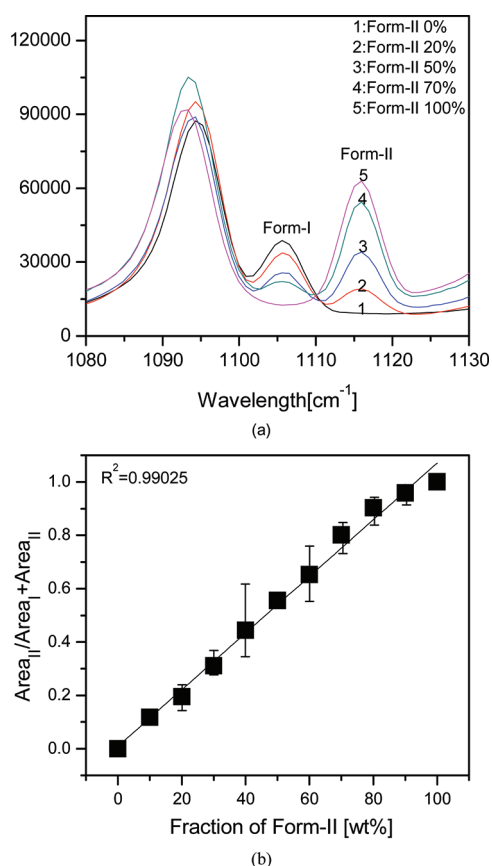


Figure 3. Analysis of the polymorphic fraction of sulfamerazine using FT-Raman spectroscopy: (a) variation of characteristic peak intensities of polymorphs with weight fraction of polymorphs, (b) standard calibration of characteristic peaks by weight fraction of polymorphs.

For example, the form-I crystals were completely converted into form-II crystals within about 6 h at a rotation speed of 1000 rpm (Figure 4). These CT crystallizer results were quite interesting when compared with the SMZ crystal phase transformation in the Rushton mixing tank (MT) crystallizer, where it took more than 50 h for the phase transformation even at a high agitation speed of 3000 rpm. For an agitation speed of 2000 rpm, the phase transformation required more than 100 h. Similar experimental results were also observed by Gu et al.¹⁴ and Kurotani and Hirasawa.¹⁵ According to their studies, no nucleation of form-II SMZ crystals occurred in pure ACN solvent in a gently agitated crystallizer, meaning that the form-I SMZ crystals remained untransformed for more than several weeks.

When considering the small solubility difference between the form-I and form-II SMZ crystals in pure ACN solvent as the driving force for phase transformation, as shown in Figure 2b, minimal nucleation of form-II SMZ crystals is a reasonable expectation. Therefore, the successful phase transformation into form-II crystals by the CT crystallizer would seem to be attributable to the highly effective fluid motion of the Taylor vortex in the nucleation of the form-II crystals in the CT crystallizer. That is, the uniquely periodic turbulent motion of Taylor vortices would seem to provide a strong alignment of the molecules, thereby promoting the nucleation of form-II crystals, whereas the random turbulent eddy in the MT crystallizer is inadequate. In particular, the elongation fluid motion was highly effective in aligning the molecules in the fluid, thereby promoting nucleation,

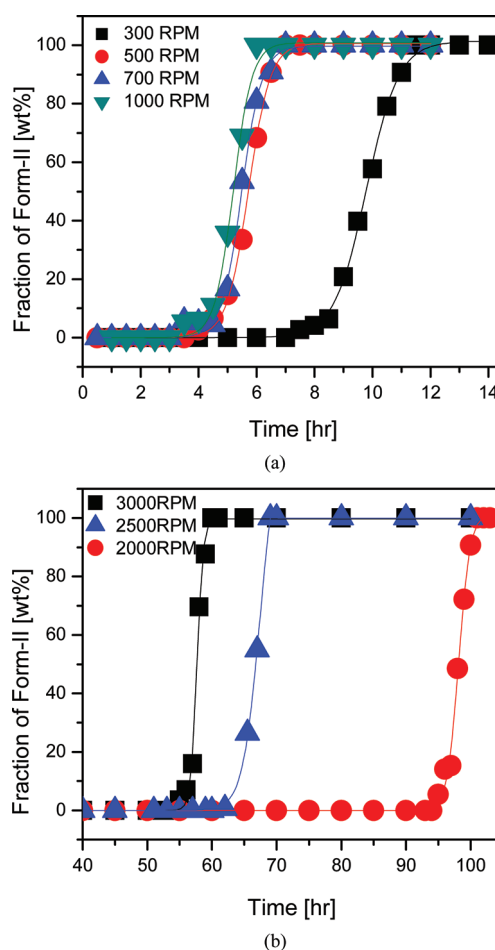


Figure 4. Polymorphic fraction change of sulfamerazine during phase transformation in a Couette–Taylor crystallizer. The solvent for phase transformation was pure acetonitrile, and the temperature was 10 °C.

as has already been demonstrated in the flow-induced crystallization of polymers.²⁴ In addition, a Taylor vortex would be a high source of external energy that allows the molecules to overcome the energy barrier for the nucleation of form-II crystals. Sinevic et al.²⁵ and Atsumi et al.²⁶ previously demonstrated that a Taylor vortex is always 8–10 times more effective in terms of dissipating viscous energy than a random turbulent eddy, as the large contact surface of the inner cylinder in a CT crystallizer is more efficient for viscous dissipation than the inertia-driven turbulence from the impeller in a MT crystallizer. Similarly, the contribution of external energy to the induction of form-II SMZ crystals was also demonstrated by Kurotani and Hirasawa¹⁵ using ultrasonication. According to their study, external energy from ultrasonication above a certain level was required to overcome the energy barrier for the nucleation of form-II SMZ crystals, and the induction of nucleation was further facilitated by increasing the ultrasonic power input. A similar effect of ultrasonication on nucleation was reported by Devarakonda et al.,^{16,17} as the cavitation generated by the ultrasound provided localized energy to induce the nucleation. As a result, the nucleation rate of dextrose monohydrate was markedly enhanced by ultrasonication.

The influence of the Taylor vortex on the phase transformation was examined using seed crystals of form II (Supporting Information, Figure S1). Here, a certain amount of seed crystals

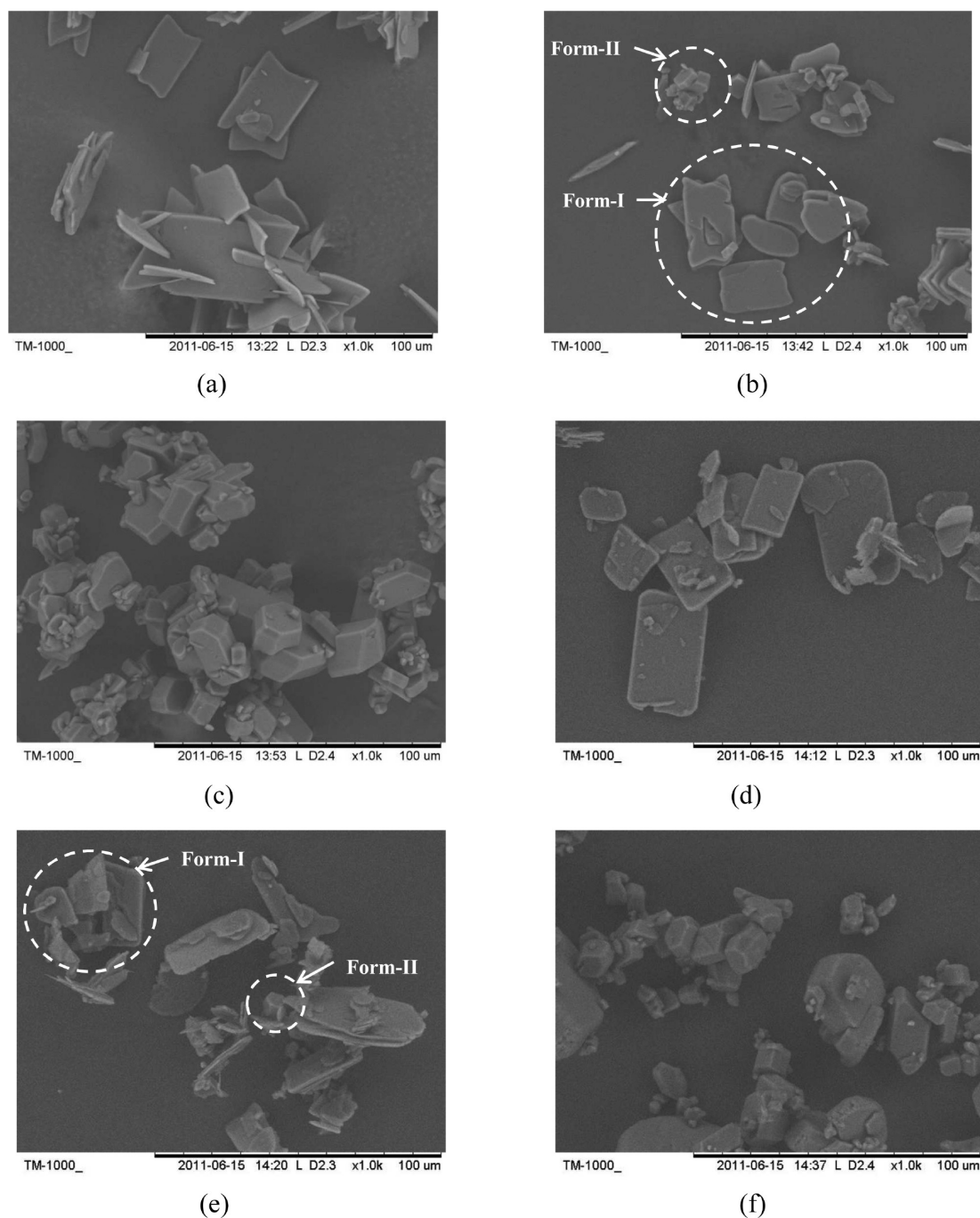


Figure 5. Morphological changes of crystals during phase transformation in (a–c) a Couette–Taylor crystallizer at a rotation speed of 700 rpm and (d–f) a Rushton mixing tank crystallizer at an agitation speed of 3000 rpm. Pure acetonitrile was used as the solvent for phase transformation. Shape of crystals at (a) 1, (b) 5.5, and (c) 7 h of phase transformation in the Couette–Taylor crystallizer and at (d) 50, (e) 57, and (f) 64 h of phase transformation in the Rushton mixing tank crystallizer.

was mixed with the form-I crystals to promote the phase transformation. The time period for the phase transformation in the CT crystallizer was reduced from 7 to 3.5 h, as the weight fraction of seed crystals in the crystal mixture was increased (Supporting Information, Figure S2). A significant promotion of the phase transformation was observed in the MT crystallizer. With 0.1 wt % seed crystals, the phase transformation was accomplished in 60 h at 1000 rpm. The promotion of the phase transformation was accelerated as the weight fraction of seed crystals was increased,

and the time period was reduced to 25 h with 1 wt % seed crystals (Supporting Information, Figure S2). From the Supporting Information, it can be concluded that the CT crystallizer was much more effective in promoting the phase transformation than the MT crystallizer even when seed crystals were used. The secondary nucleation occurred through the dissociation of embryos created on the mother crystal surface by the fluid shear.²⁷ Thereby, it was clearly deduced from the dynamic profiles of the phase transformation that the Taylor vortex was even more effective for

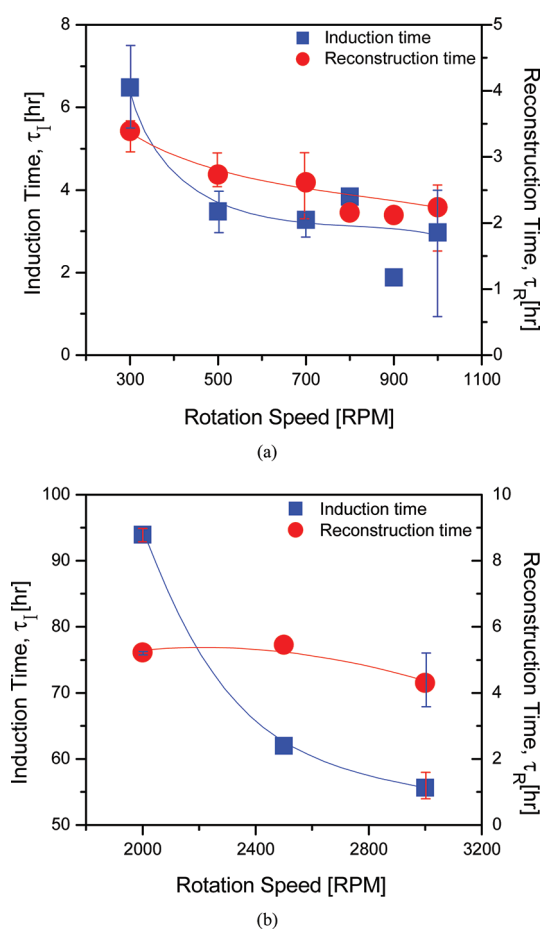


Figure 6. Changes of induction and reconstruction times with rotation speed in (a) Couette–Taylor and (b) Rushton mixing tank crystallizers. Pure acetonitrile was used as the solvent for phase transformation.

the secondary nucleation of the form-II crystals than the random turbulent eddy.

A more dramatic promotion of the phase transformation was achieved by using pretreated seed crystals of form II. Here, three kinds of pretreatment were applied to the crystals. Specifically, one pretreatment was the grinding of the form-I crystals, the second was the grinding of the form-II seed crystals, and the third was the washing of the ground form-II seed crystals. Typical morphologies of the pretreated crystals are displayed in Figure S3 (Supporting Information). When ground seed crystals were used, the time required for the phase transformation in both the CT and MT crystallizers was dramatically reduced because of the increased specific surface area of the seed crystals promoting the secondary nucleation of the form-II crystals and mass transfer for crystal growth (Supporting Information, Figure S4). The experimental conditions of phase transformation using pretreated crystals are summarized in Table S1 (Supporting Information).

The phase transformation in pure ACN solvent was visually confirmed by SEM images of the SMZ crystals, as shown in Figure 5. In the CT crystallizer at 700 rpm, all of the crystals in the initial suspension were form I with a rectangular shape (Figure 5a). After 5 h, some form-II crystals with a bulky shape were observed (Figure 5b), and after 7 h, all of the crystals were completely converted to the form-II phase (Figure 5c).

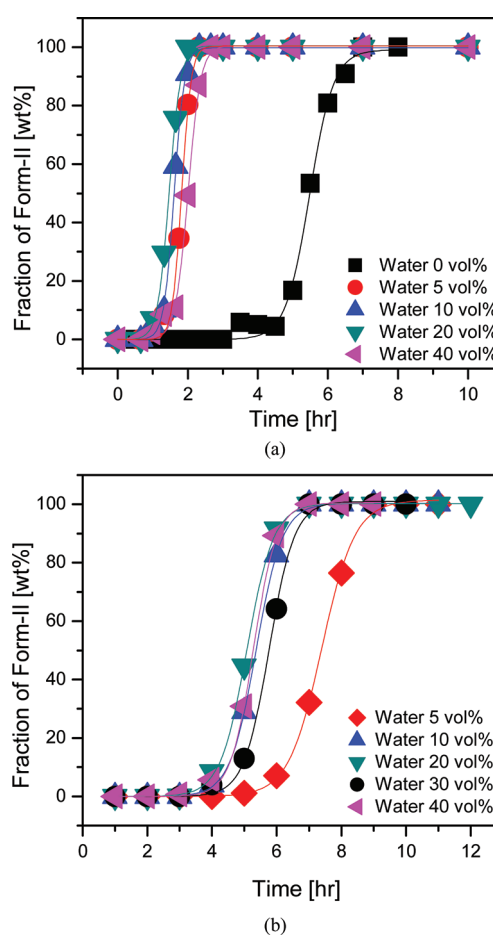


Figure 7. Effects of water fraction in the mixed solvent on the phase transformation in (a) Couette–Taylor and (b) Rushton mixing tank crystallizers. The temperature of the phase transformation was fixed at 10 °C, and the rotation and agitation speeds of the Couette–Taylor and Rushton mixing tank crystallizers, respectively, were fixed at 700 rpm.

Meanwhile, in the MT crystallizer at 3000 rpm, no phase transformation was observed until 50 h. Thus, all of the crystals remained in the form-I phase, and their shape became round because of attrition resulting from the high agitation (Figure 5d). The phase transformation appeared to begin after 57 h (Figure 5e) and then to be completed at 64 h (Figure 5f).

The phase transformation of the SMZ crystals included two typical crystallization phenomena: the nucleation of stable crystals (form II) and the reconstruction of the crystal phase by the dissolution of metastable crystals (form I) and growth of stable crystals. Thus, based on the dynamic profile of the phase transformation (Figure 4), estimates were made for the induction time of form-II crystals (τ_i), defined as the time period until the first nucleation of form-II crystals, and the reconstruction time (τ_R), defined as the time required for the depletion of the form-I crystals after the induction point. As shown in Figure 6, both the induction and reconstruction times were significantly reduced when the rotation speed of the CT crystallizer was increased, which implies that the Taylor vortex influenced both the nucleation process and the mass-transfer process of reconstruction.

To modify the phase transformation of the SMZ crystals, water was added to the ACN solvent. As shown in Figure 7a, the inclusion of water in the mixed solvent had a significant influence on the phase transformation of the SMZ crystals. In contrast to

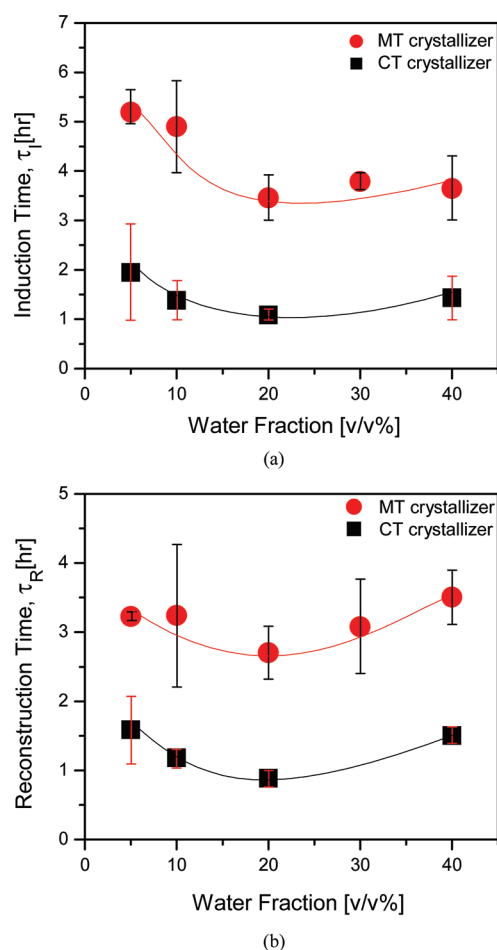


Figure 8. Influence of water fraction on the phase transformation in Couette–Taylor and Rushton mixing tank crystallizers: (a) induction time and (b) reconstruction time as functions of the water fraction of the mixed solvent. The temperature of the phase transformation was fixed at 10 °C, and the rotation and agitation speeds of the Couette–Taylor and Rushton mixing tank crystallizers, respectively, were fixed at 700 rpm.

the situation in pure ACN, form-II crystals were rapidly induced in the ACN–water mixed solvent, resulting in complete phase transformation in the CT crystallizer within couple of hours. This phase transformation was further facilitated when the water fraction was increased to 20% but hindered slightly with higher water fractions. Similar phase transformation phenomena occurred with the MT crystallizer using ACN–water mixed solvent, as shown in Figure 7b. The addition of even a small amount of water to the solvent quickly initiated the nucleation of form-II crystals and completed the reconstruction of the crystal phases.

The influence of the water fraction in the mixed solvent on the induction and transformation of the SMZ crystals can be assessed from Figure 8. When the rotation speed of the CT crystallizer was fixed at 700 rpm, it took about 2 h for the induction of form-II crystals with a 5% water fraction and about 1.5 h for the transformation. The induction and transformation times were both minimized with a water fraction of 20%. The phase transformation of SMZ was also achieved in the MT crystallizer by adding water to the solvent, where form-II crystals were induced even at an impeller speed of 700 rpm, resulting in complete transformation of the crystals, although the time scale was 2–3 times higher than that in the CT crystallizer. In addition,

the dependency of the phase transformation on the water fraction in the MT crystallizer was similar to that in the CT crystallizer.

The effect of water on the phase transformation was probably related to a solubility change according to the water fraction in the mixed solvent. That is, the solubility difference between the two polymorphs in the mixed solvent was maximized at a water fraction of 20% (Figure 2b), representing the maximum driving force for nucleation. In addition, the solubility difference also had an influence on the mass transfer for reconstruction: a larger solubility difference induced a higher mass-transfer rate for the dissolution and crystal growth in reconstruction. As a result, the dependency of the induction and reconstruction on the water fraction was well matched with the change in the solubility difference according to the water fraction.

Because the solubilities of the polymorphs also varied with the temperature, as mentioned above (Figure 2a), the temperature was included as an influencing factor for the phase transformation, as shown in Figure 9. In both crystallizers, the induction and reconstruction times for the SMZ crystals increased when the solubility difference between the two polymorphs was reduced by increasing the temperature. Nonetheless, the CT crystallizer still produced a much faster phase transformation than the MT crystallizer, as the turbulent Taylor vortex was more effective for nucleation and mass transfer than the random turbulent eddy. Thus, the induction and reconstruction times with the CT crystallizer were many times shorter than those with the MT crystallizer. Similar experimental results have also been previously observed in the phase transformation of guanosin monophosphate (GMP), where the phase transformation of GMP solids in a continuous CT crystallizer was 4–5 times faster than that in a continuous mixed-suspension, mixed-product-removal (MSMPR) crystallizer, which was attributed to more effective energy dissipation in the CT crystallizer, resulting in faster mass transfer.^{22,23}

DESCRIPTION OF PHASE TRANSFORMATION

The induction time (τ_i) depends on the supersaturation (S) and temperature (T) and is inversely proportional to the nucleation rate (J) as follows²⁸

$$J \sim 1/\tau_i \quad (1)$$

In general, the nucleation of stable crystals for phase transformation is considered to be heterogeneous in nature.^{5,8} As such, the heterogeneous nucleation rate can be expressed using the classical model as^{28,29}

$$J = A \exp\left(\frac{-\phi\Delta G^*}{kT}\right) \quad (2)$$

where ΔG^* is the energy barrier for homogeneous nucleation, defined as $16\pi\sigma^3/[3(kT \ln S)^2]$, with σ being the surface energy of the nuclei; A is the pre-exponential constant, including kinetic factors for molecular diffusion and so on, and ϕ is a factor to account for heterogeneous nucleation. From eqs 1 and 2, the induction time can be expressed as

$$\tau_i \sim \exp\left(\frac{\Delta G^*}{kT}\right) \quad (3)$$

Based on the assumption that the reconstruction of the SMZ crystals depends directly on the mass transfer for the dissolution

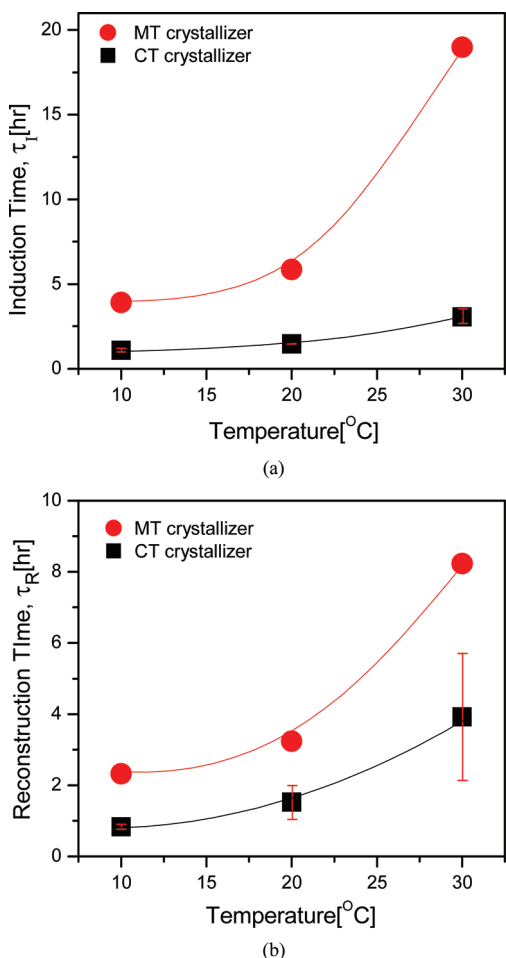


Figure 9. Influence of temperature on the phase transformation in Couette–Taylor and Rushton mixing tank crystallizers: (a) induction time and (b) reconstruction time as functions of temperature. The water fraction of the mixed solvent was fixed at 20%, and the rotation and agitation speeds of the Couette–Taylor and Rushton mixing tank crystallizers, respectively, were fixed at 700 rpm.

of the form-I crystals and the growth of the form-II crystals, the reconstruction time (τ_R) can be expressed as

$$\frac{dm_i}{dt} = S_{Ai} k_i \Delta C_i \quad (4)$$

where m_i is the polymorph mass; S_{Ai} is the surface area related to the polymorph mass as $\sim m_i^{2/3}$; and k_i and ΔC_i are the mass-transfer coefficient and concentration difference, respectively, for the dissolution and growth. Under the assumption of a constant concentration difference, eq 4 can be integrated for the form-II crystals to give

$$m_{II}^{1/3} \sim k_{II} \Delta C_{II} \tau_R \quad (5)$$

With a fixed mass of form-II crystals, the reconstruction time is related to the mass-transfer coefficient and concentration difference as

$$\tau_R \sim \frac{1}{k_{II} \Delta C_{II}} \quad (6)$$

Using eqs 3 and 6, the induction and reconstruction times for the phase transformation can be correlated in terms of experimental

parameters such as temperature, supersaturation, mass-transfer coefficient, and concentration difference.

COMPARISON

From the above experimental results obtained in CT and MT crystallizers, it is obvious that the nucleation and reconstruction of the phase transformation was influenced directly by the fluid motion in the crystallizers. In the polymer spinning process, flow-induced crystallization is commonly observed, in which the nucleation and growth of the polymer is promoted by the elongation fluid motion. In addition, a nucleation enhancement factor (f) was suggested in terms of the internal tensor stress of the fluid motion to analytically predict the flow-induced crystallization of Nylon-6,6 by melt spinning.²⁴ Thus, in the present study, a nucleation enhancement factor was similarly introduced to the classical nucleation model in order to describe its influence on the nucleation, as $J \sim \exp\{-[\phi \Delta G^* f / (kT)]\}$. Instead, it was simply assumed to be a function of the turbulent energy dissipation, as $f(\varepsilon) = 1 - \xi \varepsilon$, where ξ represents a molecular alignment factor depending on the fluid motion. That is, a high alignment factor indicates a highly aligned fluid motion promoting a nucleation. Considering previous studies in which external energy such as ultrasonication was used to initiate nucleation, the term for turbulent energy dissipation in the simple description of the nucleation enhancement factor seems reasonable.

Combining the nucleation enhancement factor with eq 2, the induction time (τ_I) can be simply correlated as a function of the energy dissipation of the turbulent flow as

$$\ln \tau_I \sim C_1 - C_2 \varepsilon \quad (7)$$

The energy dissipation by the turbulent Taylor vortex can be defined as²⁵

$$\varepsilon = \frac{\pi L_C r_i^4 \omega_i^3 f_C}{V_R} \quad (8)$$

where L_C and V_C are the length and volume, respectively, of the CT crystallizer; r_i is the radius of the inner cylinder; and ω_i is the angular velocity of the inner cylinder. In addition, f_C is the friction factor defined above the critical Reynolds number ($Re_C = 112$) as²⁶

$$f_C = 0.8 \left(\frac{d}{r_i} \right)^{0.35} Re^{-0.53} \quad \text{for } Re \geq Re_C \quad (9)$$

where the Reynolds number (Re) is defined as $Re = n D_i^2 \rho / \eta = \omega_i r_i d / \nu$. In the present study, the Reynolds number was greater than 2300. Meanwhile, the energy dissipation of the turbulent flow in the MT crystallizer can be estimated as³⁰

$$\varepsilon = \frac{5.6 n^3 D_i^5}{V_R} \quad (10)$$

where D_i is the impeller diameter and n is the impeller speed (rps). Thus, the energy dissipation in the CT and MT crystallizers can be estimated using eqs 8 and 10, respectively.

Furthermore, the influence of the turbulent flow on the mass transfer for the reconstruction of the SMZ crystals can be estimated based on an empirical equation using the Sherwood number (Sh). In the turbulent Taylor vortex, the Sherwood number is suggested to be a function of the particle Taylor

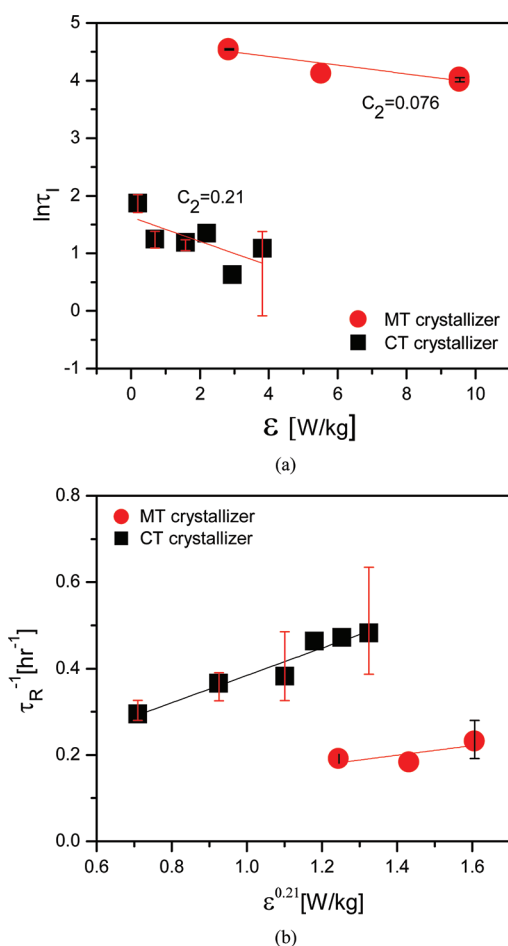


Figure 10. Correlation of the phase transformation in terms of energy dissipation when the rotation and agitation speeds of crystallizers were changed: correlations of (a) induction time and (b) reconstruction time with energy dissipation. CT and MT indicate Couette–Taylor and Rushton mixing tank crystallizers, respectively.

number (Ta_p) and the Schmidt number (Sc) as³¹

$$Sh = 2.0 + 0.4Ta_p^{0.53}Sc^{1/3} \quad (11)$$

$$Ta_p = \left(\frac{\omega_i r_i d_p}{\nu} \right) \left(\frac{d}{r_i} \right)^{1/2} \quad (12)$$

where ν is the kinematic viscosity of the solution and d_p is the particle diameter.

At the same time, the energy dissipation of the Taylor vortex is also related to the angular velocity from eqs 8 and 9 as^{25,26}

$$\epsilon = \frac{\pi L C r_i^4 \omega_i^3}{V_R} 0.8 \left(\frac{d}{r_i} \right)^{0.35} \left(\frac{\omega_i r_i d}{\nu} \right)^{-0.53} \sim \omega_i^{2.47} \quad (13)$$

Therefore, if the second term on the right-hand side of eq 11 ($0.4Ta_p^{0.53}Sc^{1/3}$) is much greater than 2.0, the Sherwood number can be simply correlated with the energy dissipation as

$$Sh \sim k_C \sim \epsilon^{0.21} \quad (14)$$

By combining eq 14 with eq 6, one can describe the reconstruction time (τ_R) using a function of the energy dissipation as

$$\tau_R^{-1} \sim \epsilon^{0.21} \quad (15)$$

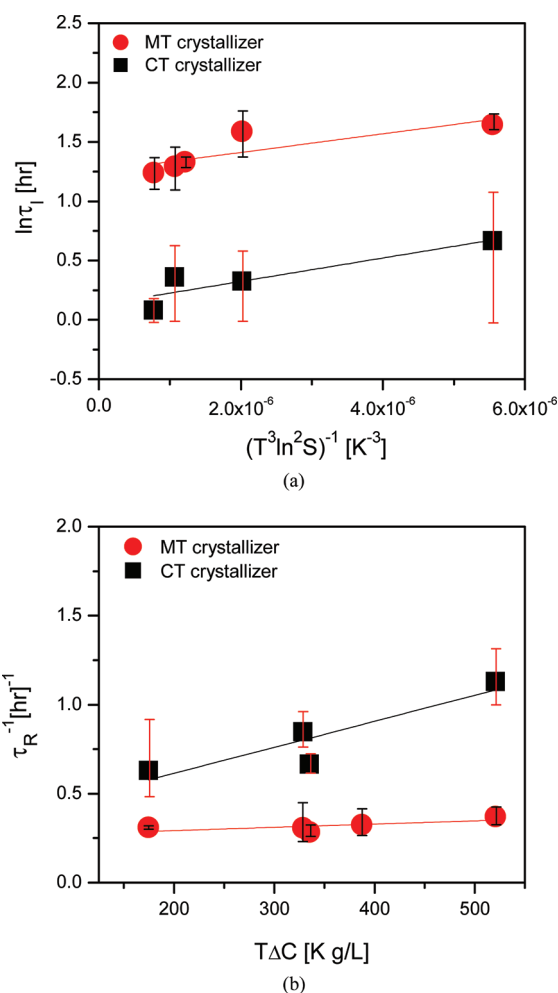


Figure 11. Correlation of phase transformation in terms of solubility differences between the two polymorphs when the water fraction of the mixed solvent was changed: correlations of (a) induction time with supersaturation and (b) reconstruction time with solubility difference between the two polymorphs. CT and MT indicate Couette–Taylor and Rushton mixing tank crystallizers, respectively.

In the case of the turbulent flow in the MT crystallizer, the Sherwood number is suggested to be³²

$$Sh = 2 + 0.47Re_p^{0.63}Sc^{1/3} \quad (16)$$

where Re_p is defined as $[1/(33d_p^{4/3})]/\nu$. Therefore, if the second term on the right-hand side of eq 16 ($0.47Re_p^{0.63}Sc^{1/3}$) is much greater than 2.0, the reconstruction time in the MT crystallizer can be correlated with the energy dissipation as

$$\tau_R^{-1} \sim \epsilon^{0.21} \quad (17)$$

Coincidentally, the reconstruction times in the CT and MT crystallizers were almost identically related with the energy dissipation, as shown in eqs 15 and 17. Thus, based on the above relationship of the energy dissipation with the phase transformation, the experimental measurements of the induction and reconstruction times in the CT and MT crystallizers were linearly correlated, as shown in Figure 10. In both crystallizers, induction and reconstruction were promoted by increasing the energy dissipation. Interestingly, the induction and reconstruction times in the CT crystallizer were much shorter than those in the MT

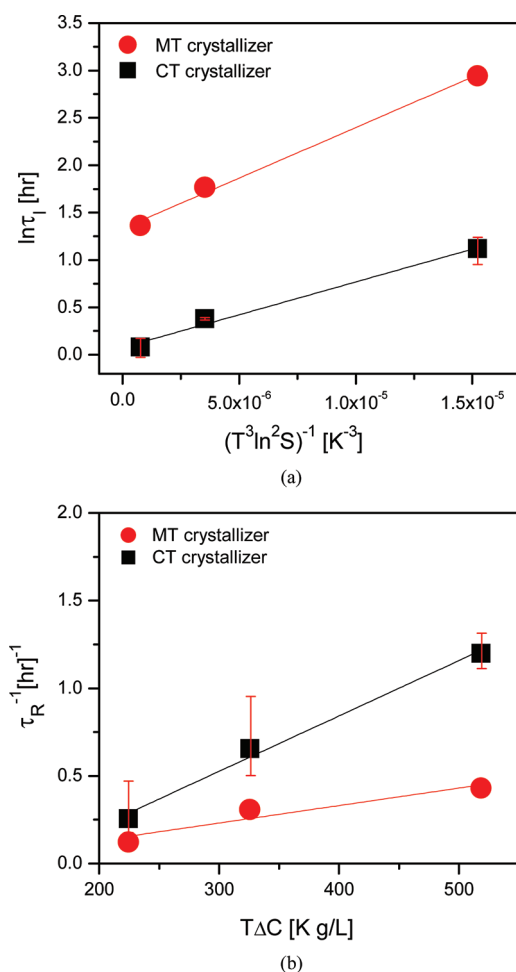


Figure 12. Correlation of phase transformation in terms of the solubility difference between two polymorphs when the temperature of the phase transformation was changed: correlations of (a) induction time with supersaturation and (b) reconstruction time with the solubility difference between the two polymorphs. CT and MT indicate Couette–Taylor and Rushton mixing tank crystallizers, respectively.

crystallizer even though the energy dissipation in the CT crystallizer was much lower than that in the MT crystallizer, because of the higher molecular alignment effect of the Taylor vortex compared to the random turbulent eddy. This molecular alignment effect of the fluid motion was clearly reflected in the higher slope (C_2) of the induction time in CT crystallizer than in the MT crystallizer.

When the water fraction in the mixed solvent was changed, the phase transformation of the SMZ crystals (from form I to form II) was also seemingly correlated in terms of the solubility difference between the two forms. Thus, the induction and reconstruction times for the form-II crystals were correlated with the supersaturation using eqs 2 and 6, respectively, as

$$\ln \tau_I \sim \frac{1}{T^3 (\ln S)^2} \quad (18)$$

$$\tau_R^{-1} \sim \Delta C \quad (19)$$

where S is the supersaturation, defined as the solubility ratio of form-I crystals to form-II crystals, and ΔC is the solubility gap between the two polymorphs. As shown in Figure 11, the

experimental induction and reconstruction times correlated well with eqs 18 and 19. Owing to the more effective turbulent motion of the Taylor vortex, the induction and reconstruction times in the CT crystallizer were much shorter than those in the MT crystallizer. Therefore, it is reasonable to suppose that the effect of water on the phase transformation of the SMZ crystals in terms of modifying the solubility difference between the two forms had a direct influence on the nucleation and mass transfer.

Similarly, because the solubility of the two polymorphs varied with the temperature, the phase transformation was also seemingly correlated in terms of the supersaturation and solubility gap, as shown in Figure 12. The variations of the induction and reconstruction times with the temperature were consistently described using eqs 18 and 19, indicating that the promotion of the phase transformation by decreasing the temperature resulted primarily from an increase in the supersaturation for nucleation and an increase in the solubility gap for mass transfer. This also confirmed that the Taylor vortex in the CT crystallizer was more effective for nucleation and reconstruction than the random eddy in the MT crystallizer.

CONCLUSIONS

The significant influence of the unique turbulent flow motion of a Taylor vortex on phase transformation was demonstrated using SMZ, which has pharmaceutical polymorphs that require a long phase transformation period. The present study found a long time period of over 60 h for the phase transformation when an MT crystallizer was used with pure ACN solvent and rigorous agitation at 3000 rpm. However, when a CT crystallizer was used with pure ACN solvent, phase transformation was achieved within several hours even at a low rotation speed of 300 rpm.

Because of the molecular alignment effect of the periodic flow pattern, the Taylor vortex was much more promotive for nucleation of the stable form-II crystals than the random eddy. Also, the effective viscous energy dissipation of the Taylor vortex contributed to overcome the energy barrier for the nucleation of the stable crystals and promote the reconstruction of the metastable crystals into stable crystals through dissolution and growth processes.

Certain crystallization conditions, including the addition of water to the solvent and lowering of the temperature, also had a significant influence on the phase transformation of the SMZ crystals by varying the solubility difference between the two polymorphs. For example, the solubility difference increased when the water fraction in the solvent was increased to 20%, thereby promoting the phase transformation. However, a further increase of the water fraction hindered the phase transformation, because of a resulting decrease in the solubility difference. Similarly, increasing the temperature reduced the phase transformation rate by decreasing the solubility difference. Nevertheless, when one compares the two crystallizers, the phase transformation of induction and reconstruction in the CT crystallizer was always many times faster than that in the MT crystallizer because of the more effective turbulent fluid motion of the Taylor vortex.

Considering the phase transformation as consisting of two consecutive steps, the nucleation of stable crystals and the reconstruction of metastable crystals into stable crystals by dissolution and growth, one can quantitatively measure the two steps in terms of an induction time and a reconstruction time, respectively. These times were also analytically estimated using nucleation and mass-transfer models, respectively, where the fluid

motion in induction and reconstruction was described in terms of the energy dissipation. The induction time was then correlated as $\ln \tau_1 \sim C_1 - C_2 \varepsilon$, and the reconstruction time was correlated as $\tau_R^{-1} \sim \varepsilon^{0.21}$. In addition, the variation of the solubility difference between the two polymorphs according to the water fraction in the solvent and temperature was described as $\ln \tau_1 \sim 1/[T^3(\ln S)^2]$ for the induction time and $\tau_R^{-1} \sim \Delta C$ for the reconstruction time. The model correlations for the induction and reconstruction times matched the experimental data well across the whole range of crystallization conditions, including rotation speeds, water fractions, and temperatures. Thus, according to the correlations, it was found that the unique periodic Taylor vortex in the CT crystallizer is much more efficient for phase transformation than the random turbulent eddy in the MT crystallizer.

■ ASSOCIATED CONTENT

S Supporting Information. Summary of experimental conditions for phase transformation using pretreatment of form-I and from-II seed crystals in Couette–Taylor (CT) and Rushton mixing tank (MT) crystallizers, effects of form-II seed crystals on phase transformation and phase transformation time in CT and MT crystallizers, morphologies of SMZ crystals, and typical dynamic profiles of phase transformations of SMZ crystals using pretreated form-II seed crystals in CT and MT crystallizers. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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