

Taylor Vortex Effect on Phase Transformation of Guanosine 5-Monophosphate in Drowning-Out Crystallization

Anh-Tuan Nguyen,[†] Jong-Min Kim,[‡] Sang-Mok Chang,[‡] and Woo-Sik Kim^{*,†}

Department of Chemical Engineering, ILRI, Kyung Hee University, Seocheon-Dong, Giheung-Gu, 446-701 Yongin-Si, Korea, and Department of Chemical Engineering, Dong-A University, 840 Hadan2-Dong, Saha-Gu, 604-714 Busan, Korea

A continuous Couette–Taylor (CT) crystallizer exploiting a Taylor vortex was developed to promote the phase transformation of guanosine 5-monophosphate (GMP). In drowning-out crystallization, amorphous GMP is initially generated and then transformed into hydrate GMP crystals via the consecutive dissolution of the amorphous GMP and nucleation and growth of hydrate GMP crystals. Because of the intensive mixing of the Taylor vortex, the dissolution of the amorphous GMP and growth of the hydrate GMP crystals were both markedly promoted, allowing the phase transformation to be completed within a mean residence time of 5 min, even with a high GMP feed concentration of 150 g/L and moderate rotation speed of 300 rpm. This result was at least 5 times faster than the phase transformation in a mixed suspension, mixed product removal (MSMPR) crystallizer under the same crystallization conditions. The phase transformation efficiency of the Taylor vortex over the turbulent eddy in the MSMPR crystallizer was explained in terms of the effectiveness of the turbulence for the mass transfer at the solid–liquid interface.

1. Introduction

The hydrodynamic conditions play an important role in crystallization, as they influence the generation of supersaturation, crystal nucleation, crystal growth, phase transformation, polymorphs, and agglomeration/breakage of crystals. Thus, the hydrodynamic conditions are often a key design factor when developing a crystallization process to achieve crystals with certain properties, covering the size distribution, shape, structure, and purity.^{1,2}

A Couette–Taylor fluid motion is one of the most interesting and well-defined flow regimes, due to its unique flow behavior and features. First, a lamina Couette fluid motion is induced in coaxial cylinders when rotating the inner cylinder; however, this motion changes to a unique turbulent motion, called a Couette–Taylor vortex, beyond a certain rotation speed of the inner cylinder, called the critical Taylor number, due to hydrodynamic instability. As a result, this radial vortex combined with a small axial dispersion, as shown in Figure 1a, provides a homogeneous intensity of turbulent mixing, allowing many beneficial applications, including polymerization,³ ceramic membranes,⁴ photocatalytic,⁵ filtration,⁶ and biological systems.⁷ For example, a continuous Couette–Taylor reactor can achieve the complete polymerization of polystyrene within a short mean residence time.³ An intensive Taylor vortex is also effective in the production of a narrow distribution of small-sized polystyrene particles without agglomeration. Furthermore, the use of a Couette–Taylor reactor in ceramic processes allows a high mass transfer coefficient and large specific interface area to be achieved between the gas–liquid phases.⁴

In the area of crystallization, a Taylor vortex has already been applied to the gas (CO₂)–liquid (Ca(OH)₂) reaction crystallization of calcium carbonate to promote gas (CO₂) absorption.^{8,9} Here, because of the strong and homogeneous mixing of the vortex in this continuous crystallizer (called a continuous

Couette–Taylor (CT) crystallizer), the gaseous reactant is quickly absorbed to induce a high and uniform supersaturation around the inlet region of the crystallizer, resulting in a narrow size-distribution and uniform-shaped crystals in the product suspension of the outlet stream. In addition, the promotion of CO₂ absorption by the vortex changes the calcite morphology when increasing the rotation speed. Thus, since the CO₂ absorption at a low rotation speed falls short of a stoichiometric reaction with Ca(OH)₂, the excess Ca²⁺ ions remain as an ionic additive during the crystal growth, resulting in spindle calcite. Meanwhile, the crystal shape shifts to a rhombohedron when increasing the rotating speed, as the reaction conditions approach stoichiometry.^{10,11}

Crystals frequently undergo a phase transformation during crystallization, especially in the case of organic material crystallization, for example, pharmaceuticals and food additives. Plus, since the physical–chemical properties of crystals, including their solubility, hardness, stability, and bioavailability, depend directly on their crystal structure, phase transformation is an essential crystallization process to achieve certain crystal structures among various polymorphs.^{12–14} Thus, the accurate control of phase transformation is highly desirable to produce the desired polymorphic crystals in crystallization, and many studies of phase transformation have already been carried out based on varying the crystallization parameters, such as the seeding, solvent/antisolvent, temperature, additive/impurity, humidity, concentration, and agitation.^{15–22}

However, in most cases of crystallization, the phase transformation is a time-consuming process, due to the intrinsic mass transfer property of the materials. For example, in the drowning-out crystallization of guanosine 5-monophosphate (GMP) in a stirred batch crystallizer (working volume of 23 m³), the phase transformation of amorphous GMP solids into a crystalline GMP hydrate requires more than 6 h (technical report of CJ Co., Korea). Also, the transformation of sulfamerazine crystals from form-I (metastable phase) to form-II (stable phase) in an acetonitrile solution takes more than 14 days in an agitated crystallizer, due to a slow mass transfer for the dissolution of the metastable crystals and growth of the stable crystals.^{23,24}

* To whom correspondence should be addressed. Tel.: +82-31-201-2970. Fax: +82-31-273-2971. E-mail: wskim@khu.ac.kr.

[†] Kyung Hee University.

[‡] Dong-A University.

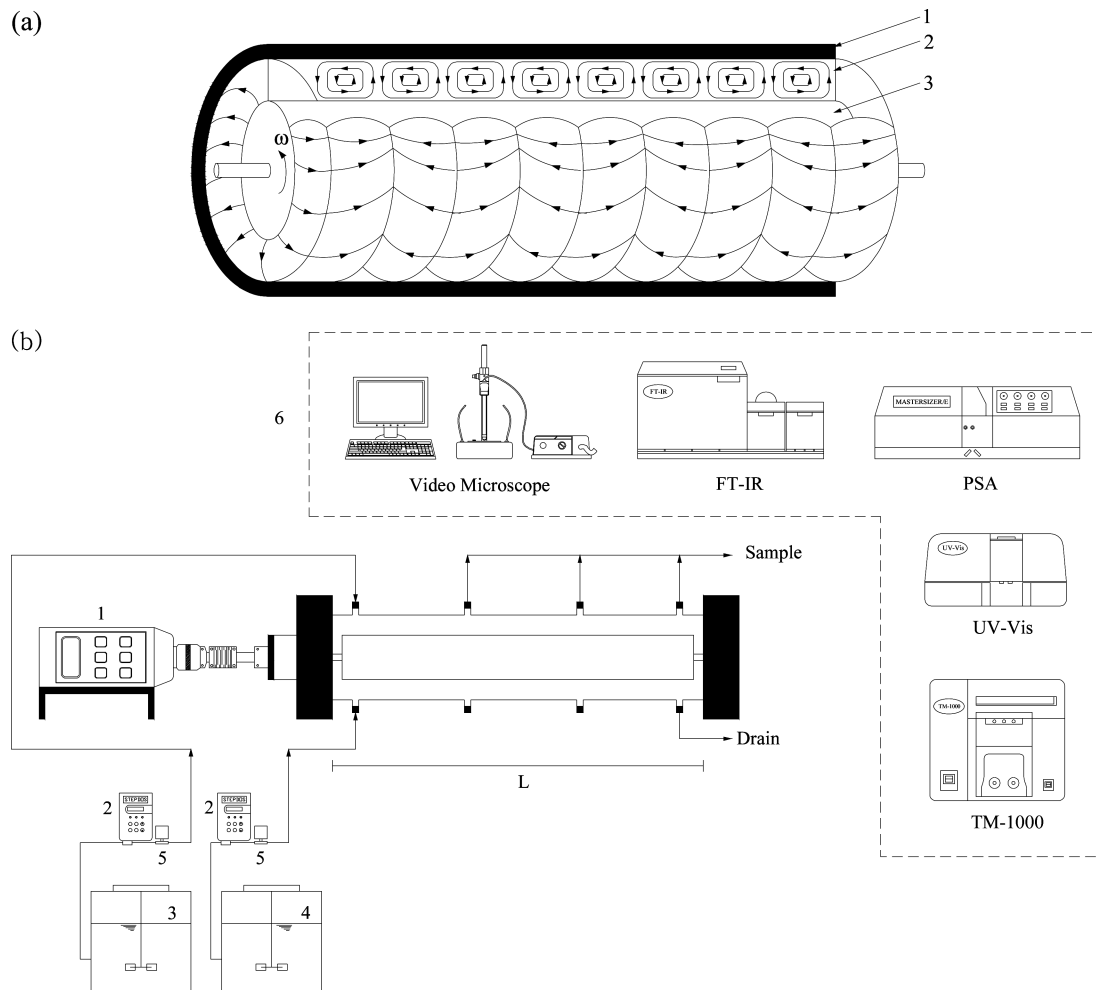


Figure 1. (a) Schematic drawings of Taylor vortices (1, stationary outer cylinder; 2, Taylor vortices; 3, rotating inner cylinder) and (b) experimental system for CT crystallizer (1, dc motor; 2, pump StepDos; 3, GMP feed solution; 4, methanol solution; 5, damper; 6, analysis).

Accordingly, the present study applies a Taylor vortex to the continuous drowning-out crystallization of guanosine 5-mono-phosphate (GMP) to facilitate the phase transformation. The drowning-out crystallization of GMP is involved in the initial precipitation of amorphous GMP solids and their subsequent transformation into hydrate GMP crystals via recrystallization. During the investigation of the Taylor vortex effect on the phase transformation and crystallization, the rotation speed of the inner cylinder, mean residence time of the crystallizer, and GMP feed concentration are all varied. In addition, the contribution of the Taylor vortex to the phase transformation in the crystallization is evaluated in terms of the mass transfer of the dissolution of the amorphous GMP and growth of the hydrate GMP crystals and then compared with that of a turbulent eddy in a mixed suspension, mixed product removal (MSMPR) crystallizer.

2. Experimental Section

The Couette–Taylor (CT) crystallizer was composed of two annular cylinders, where the inner cylinder was made of stainless steel and the outer made of Lucite acrylic plastic to allow visual observation of the Taylor vortices. As summarized in Table 1, the crystallizer geometry (d/r_i) was fixed at 0.25, where d was the annular gap between the inner and outer cylinders and r_i was the radius of the inner cylinder. The working volume of the CT crystallizer was 1.1 L. As shown in Figure 1b, the crystallizer was placed horizontally to eliminate any effects of hydrostatic pressure, and three sample ports for taking suspen-

Table 1. Dimensions of Couette–Taylor Crystallizer

radius of outer cylinder, r_o	5×10^{-2} m
radius of inner cylinder, r_i	4×10^{-2} m
gap between two cylinders, d	1×10^{-2} m
length of cylinder, L_c	40×10^{-2} m

sion samples were installed in the outer cylinder along the axial direction of the crystallizer. To induce a Taylor vortex, the inner cylinder of the crystallizer was rotated using a dc motor, where the rotation speed was controlled from 300 to 700 rpm

The raw GMP solid (99.9% purity) supplied by CJ Co. (Korea) was used without any further purification. The GMP feed solution was prepared by dissolving the raw material in distilled water at 60–150 g/L. Also, methanol (ACS grade, Duksan Pure Chemical Co., Korea) was used as the antisolvent. The CT crystallizer was initially filled with distilled water, and the GMP solution and methanol were then simultaneously injected into the crystallizer through two opposite inlet ports using pumps (StepDos 08, KNF, Germany) with an equal flow rate. The flow rate of the feeds was varied from 18.8 to 1130 mL/min to change the mean residence time of the CT crystallizer from 1 to 60 min.

For the comparison, a conventional MSMPR crystallizer was also designed using a standard Rushton tank.²⁵ The MSMPR crystallizer (working volume of 0.8 L) was made of Lucite acrylic plastic and equipped with four baffles and a six-blade turbine impeller for effective mixing. The MSMPR crystallizer

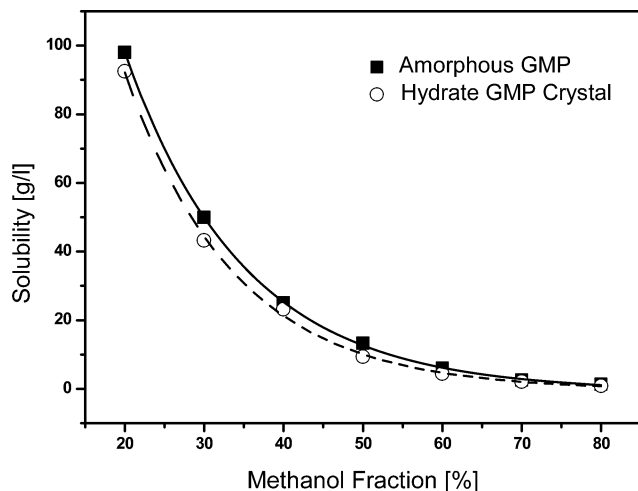


Figure 2. Solubility of GMP polymorphs in methanol–water solvent.

was run at the same agitation speed, GMP feed concentration, and mean residence time as the CT crystallizer.

Samples of the product suspension were taken from the crystallizer in a steady state and quickly filtered using a vacuum. The sample solids were then dried in a dry desiccator for 1 day and analyzed with regards to the crystal fraction of the solid and mean crystal size. Meanwhile, the GMP concentration in the solutions was analyzed to estimate the GMP solid recovery. Here, the crystal fraction and mean crystal size of the sample solid were measured using a Fourier transform-infrared (FT-IR) (Perkin, System 2000) and optical microscope⁹ (IT System, Sometch), respectively, while the GMP concentration in the sample solution was monitored using a UV–vis (JASCO, V-570). In addition, an X-ray diffractometer (XRD, MAC Science, M18XHF-SRA, CuK α line, Japan) was used to confirm the solid structures of the amorphous GMP and hydrate GMP crystals.

3. Results and Discussion

3.1. Characterization of GMP Pseudopolymorphs. The solubility of the GMP pseudopolymorphs was measured in a water–methanol mixture, as shown in Figure 2. Because of its structural stability, the amorphous GMP was always more soluble than the hydrate GMP crystals in all the mixture compositions, indicating a monotropic behavior between the two forms of GMP solid. As such, this solubility difference was a driving force of the phase transformation of the amorphous GMP into hydrate GMP crystals in the solution.

Since the GMP pseudopolymorphs were primarily the result of the different intermolecular interactions in the molecular arrangement of the solute and different lattice incorporation of the solvent, distinct IR characteristic bonding peaks were produced for each form. Thus, as shown by the FT-IR spectra in Figure 3a, the characteristic peak in the amorphous GMP occurring at 1694 cm⁻¹, corresponding to the C=O stretching vibration of the amide group, shifted to 1677 cm⁻¹ in the crystal GMP hydrate due to the different intermolecular hydrogen bonding strengths of the carbonyl groups in the two different solid structures. That is, in the case of the hydrate GMP crystals, the water molecules incorporated into the crystal lattice induced a strong hydrogen bonding of the carbonyl groups between the molecules, resulting in a position shift of the characteristic peak for the C=O bonds to a lower frequency.²⁶ Here, it was interesting to note that the peak intensity of the C=O bonds was directly dependent on the fraction of hydrate crystals in

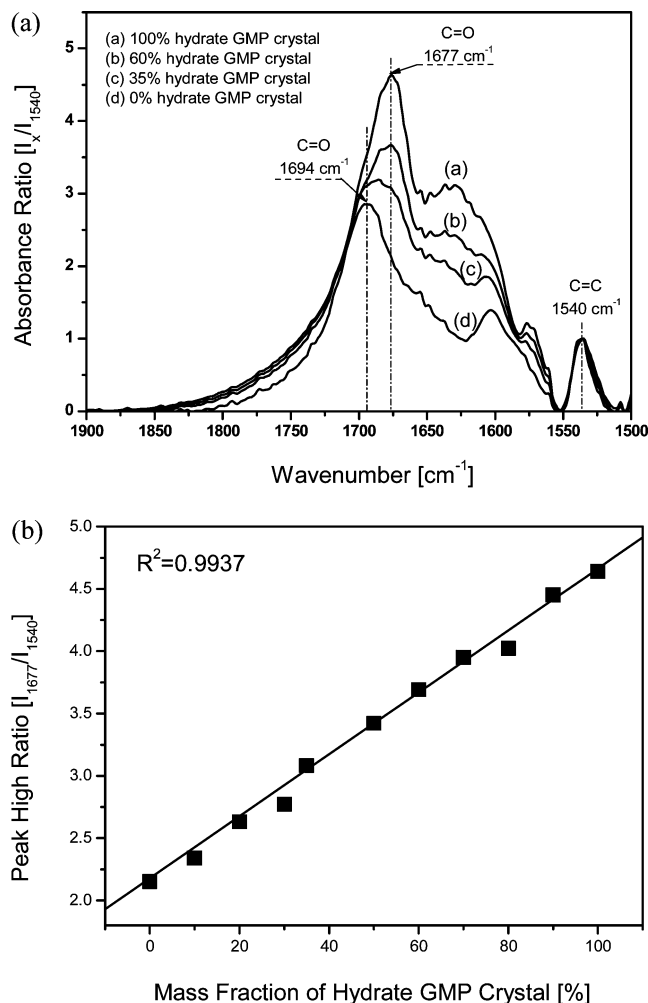


Figure 3. FT-IR spectra for various solid mixtures of amorphous GMP and hydrate GMP crystals: (a) characteristic peaks of GMP solid mixtures and (b) calibration curve of GMP solid composition.

the solid mixture. Meanwhile, the reference absorption bond at 1540 cm⁻¹, corresponding to the C=C stretching vibration, was linearly proportional to the quantity of GMP molecules, regardless of the GMP solid structure. Therefore, based on Beer's Law,²⁷ the peak ratio (I_{1677}/I_{1540}) between the C=O and C=C bonds was used to calibrate the structural fraction between the amorphous GMP and the hydrate GMP crystals in the mixture solid, as shown in Figure 3b. This calibration was then used to estimate the mass fraction of hydrate GMP crystals, hereafter referred to as the crystal fraction, in the product suspension.

3.2. Crystallization in Couette–Taylor Crystallizer. The drowning-out crystallization occurred spontaneously when injecting the GMP feed solution and methanol antisolvent into the CT crystallizer. The typical transient behavior of the crystallization in the crystallizer was then monitored in terms of the GMP concentration in the solution, crystal fraction, and mean crystal size of the GMP solids in the product stream, as shown in Figure 4a. During the initial stage, the GMP concentration in the solution increased rapidly above the solubility of the amorphous GMP (called the metastable solubility) and then quickly decreased to the solubility of the hydrate GMP crystals (called the stable solubility) due to the extensive crystallization of GMP solids. After 5 times the mean residence time (7 min), the GMP concentration remained almost invariant, implying a steady state of crystallization in the CT crystallizer. This steady state of crystallization in the CT crystallizer was also confirmed by the invariant dynamic profile

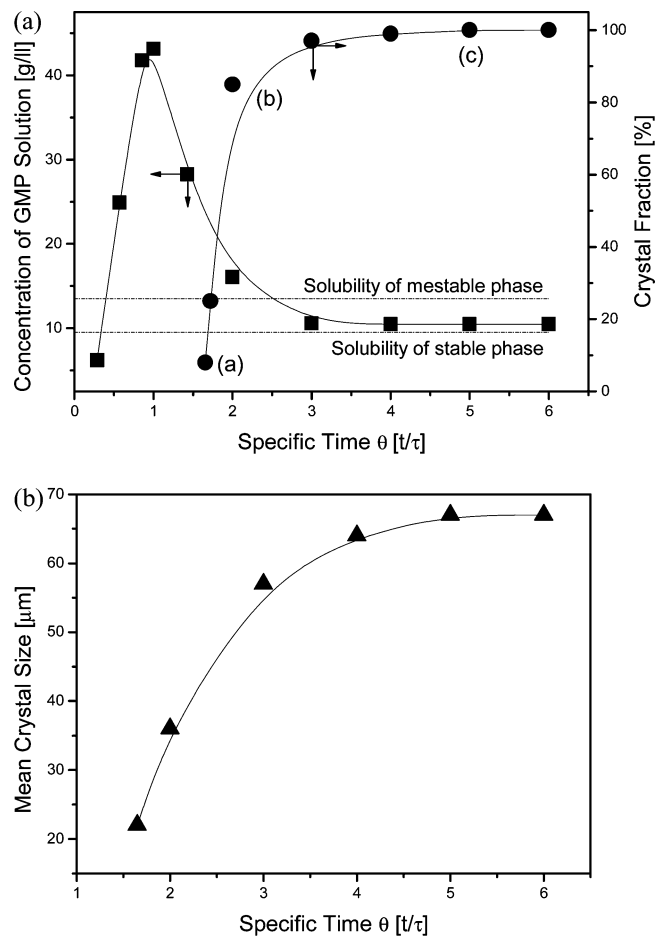


Figure 4. Typical dynamic profiles of GMP crystallization during drowning-out crystallization at 25 °C with 300 rpm rotation speed for the inner cylinder, 150 g/L GMP feed concentration, 7 min mean residence time, and 5:5 feed ratio (GMP solution–methanol): (a) dynamic profiles of GMP concentration in the product solution and crystal fraction of GMP in the product solid and (b) dynamic profile of mean crystal size of product solid.

of the crystal fraction after 5 times the mean residence time. Here, it was interesting to note that, during the early stages, the GMP solid product was mostly amorphous and then quickly became completely crystals when reaching the steady state, indicating that the 7 min mean residence time was sufficient for the complete transformation of the amorphous GMP into hydrate crystals in the CT crystallizer.

When the crystal size is measured during the transient period (Figure 4b), the mean crystal size increased monotonically, eventually reaching about 70 μ m in the final steady state. It should be noted that only the hydrate GMP crystals were counted for the mean value, as it was not technically possible to define the characteristic dimensions of the amorphous GMP.

The morphological behavior of the GMP solids in the CT crystallizer was optically observed using a video microscope, as shown in Figure 5. While a significant amount of amorphous GMP solids was generated during the early stage of crystallization (Figure 5a), the amorphous GMP then partially disappeared and small rod-shaped GMP crystals appeared (Figure 5b). Thereafter, in the steady state, the GMP crystals appeared without any amorphous solids (Figure 5c). These microscopic observations were consistent with the above transient profiles of the GMP concentration, crystal fraction, and mean crystal size. Here, it should also be mentioned that the amorphous and crystal forms of GMP in the product suspension were both

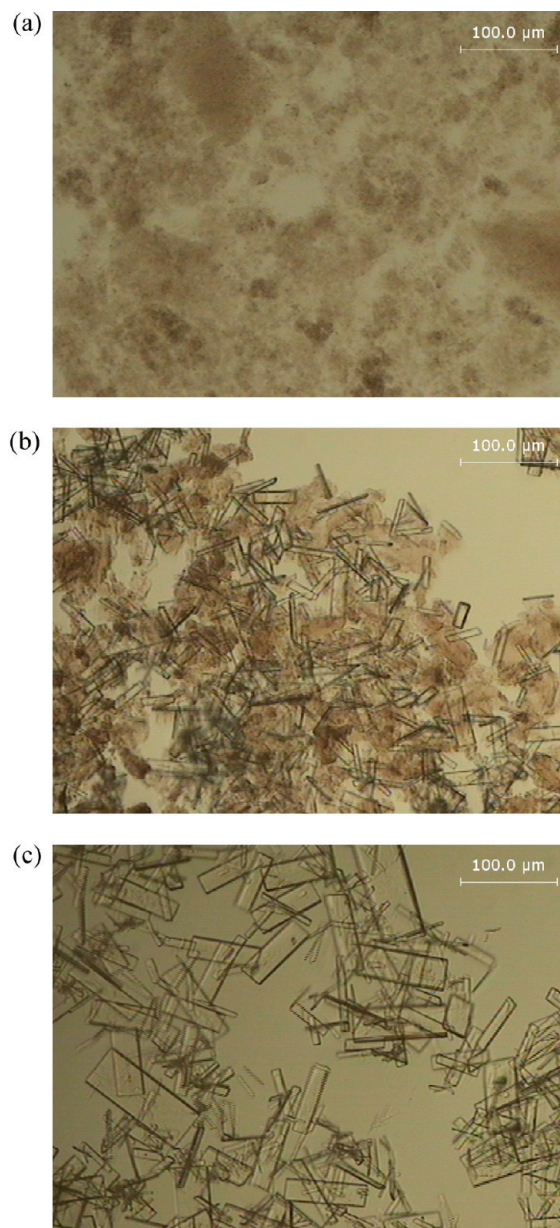


Figure 5. Typical morphology of GMP solid in product during crystallization at 25 °C with 300 rpm rotation speed for inner cylinder, 150 g/L GMP feed concentration, 7 min mean residence time, and 5:5 feed ratio (GMP solution–methanol): (a) at 1.6 times the mean residence time, (b) 2 times the mean residence time, and (c) 5 times the mean residence time.

confirmed using power pattern XRD. Meanwhile, on the basis of a thermogravimetric analysis (TGA), the GMP crystals were found to lose 23% of their weight within a temperature range of 30–150 °C, indicating 7-hydrate crystals (Figure S1 in Supporting Information). In addition, the residence time distributions of liquid and GMP crystals in the Couette–Taylor crystallizer were the same (Figure S2 in Supporting Information).

The influence of the crystallization conditions on the crystal fraction, mean crystal size, and GMP recovery at the steady state of the CT crystallizer were investigated by varying the rotation speed of the inner cylinder, GMP feed concentration, and mean residence time. As shown in Figure 6, the GMP crystallization varied significantly according to the mean residence time of the CT crystallizer. With a short mean residence time of 1 min, only a small amount of amorphous GMP was converted to hydrate GMP crystals, resulting in a

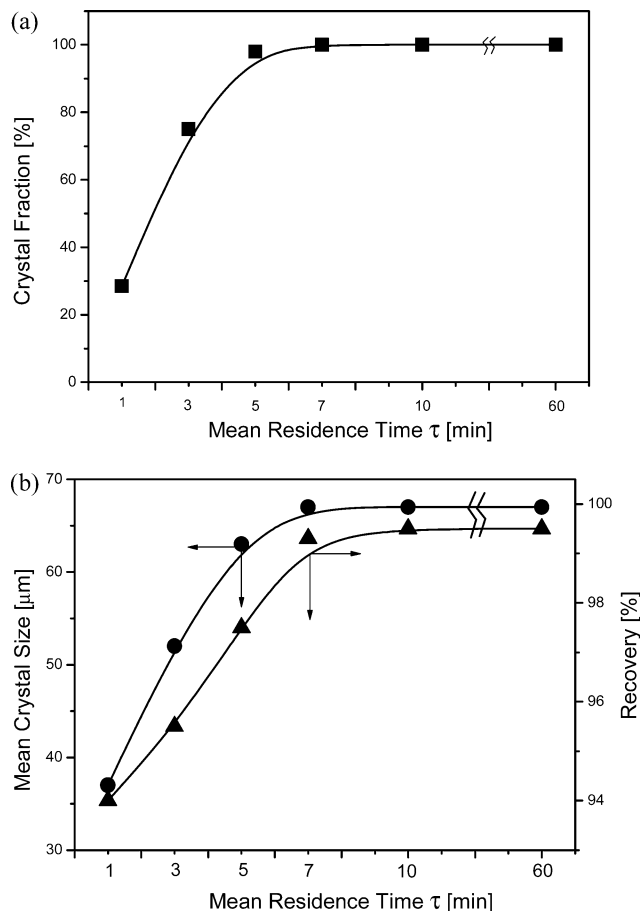


Figure 6. Influence of mean residence time on GMP crystallization at 25 °C with 300 rpm rotation speed for the inner cylinder, 150 g/L GMP feed concentration, and 5:5 feed ratio (GMP solution–methanol): (a) crystal fraction of GMP in product solid and (b) mean crystal size and recovery in product solid.

low crystal fraction (30%) in the product solids, although the GMP recovery reached 94%. Here, the GMP recovery was defined as the mass ratio of GMP solids actually obtained to the ideal amount corresponding to the concentration difference between the GMP feed solution and the stable solubility. Thus, the recovery would be 100% when the solid GMP is equilibrated with a stable solubility.

When the mean residence time is increased, the crystal fraction and recovery of solid GMP were rapidly enhanced and reached 100% after only a 5 min mean residence time. Thus, when considering that the practical drowning-out crystallization of GMP in a batch crystallizer has a holding time of 6 h (CJ Co. in Korea), completing the phase transformation within a 5 min mean residence time in a continuous mode in the CT crystallizer was certainly effective.

The phase transformation of GMP in drowning-out crystallization is practically based on the principle of recrystallization in a solution.^{28,29} That is, since hydrate GMP crystals grow under metastable supersaturation conditions, representing the range between the metastable and stable solubilities, the amorphous GMP is simultaneously dissolved to balance the metastable supersaturation consumed by the growth of the hydrate crystals. Thus, in the present study, the direct dependence of the phase transformation of the GMP solids on the mass transfer processes was clearly strongly influenced by the fluid motion of the Taylor vortex. As shown in Figure 7, the dependency of the phase transformation of the crystal fraction on the fluid motion (Taylor vortex) in the CT crystallizer was

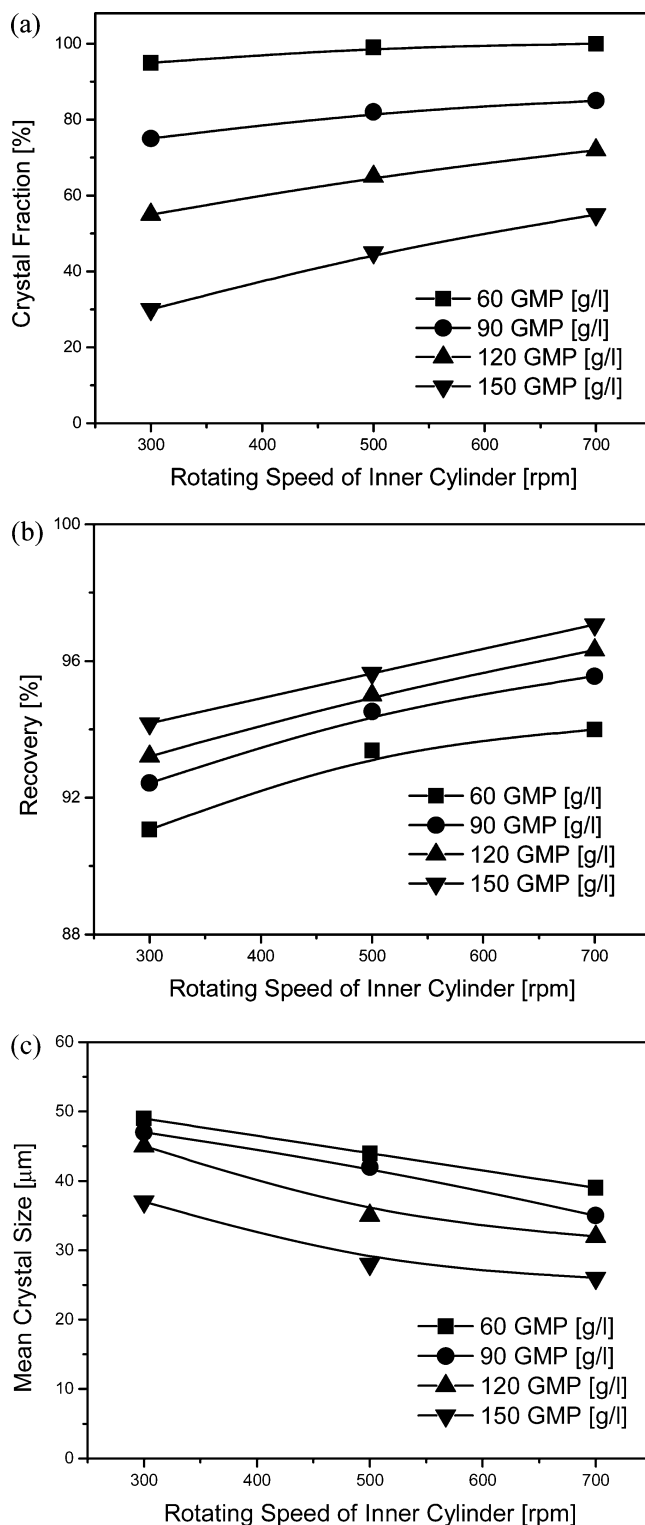


Figure 7. Influence of rotation speed and feed concentration on GMP crystallization at 25 °C with 1 min mean residence time and 5:5 feed ratio (GMP solution–methanol): (a) crystal fraction of GMP in product solid, (b) GMP recovery in product solid, and (c) mean crystal size in product solid.

most clearly demonstrated with a short mean residence time of 1 min. The crystal fraction of the product solid with a high feed concentration of 150 g/L improved from 30% to 53% (75% enhancement of crystal fraction) when increasing the rotation speed of the inner cylinder from 300 to 700 rpm (Figure 7a). However, the influence of the vortex on the crystal fraction of the product solid was attenuated when decreasing the feed

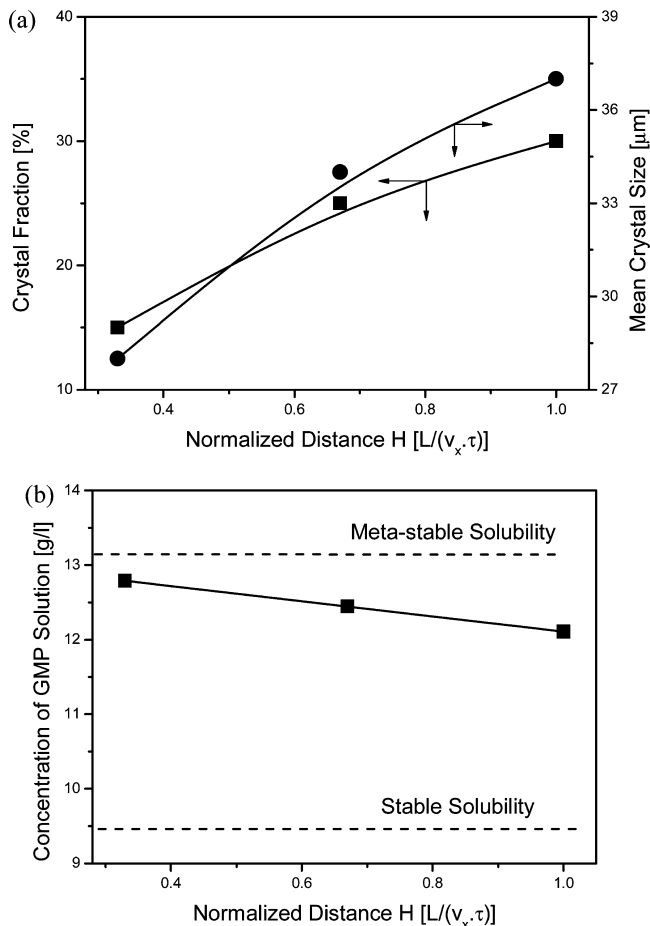


Figure 8. Axial profiles of GMP crystallization in Couette-Taylor crystallizer at 25 °C with 300 rpm rotation speed for the inner cylinder, 150 g/L GMP feed concentration, 1 min mean residence time, and 5:5 feed ratio (GMP solution-methanol): (a) crystal fraction and mean crystal size and (b) GMP concentration in solution.

concentration, although the crystal fraction consistently remained at almost 100% with a feed concentration of 60 g/L. Also, increasing the rotation speed slightly promoted the recovery of the GMP solids (Figure 7b).

The influence of the Taylor vortex on the crystal size of the GMP hydrate is shown in Figure 7c), where the vortex in the crystallizer promoted the dissolution of the amorphous GMP, providing a rather high supersaturation level during the phase transformation and resulting in a high nucleation of hydrate crystals. Also, since crystal breakage can be caused by crystal collisions and the turbulent shear in the vortex, the mean crystal size was reduced when increasing the rotation speed and feed concentration. Nonetheless, it should be mentioned that with a mean residence time of 7 min, the phase transformation of the amorphous GMP was always completed in the crystallizer, even at the lowest rotation speed of 300 rpm and highest feed concentration of 150 g/L. However, the dependency of the GMP recovery and mean crystal size on the vortex was quite similar to that with a mean residence time of 1 min, although the recovery was always higher than 95% and the mean crystal size reached 70 μm .

The crystallization profiles in the axial direction of the CT crystallizer were also examined in the steady state, as shown in Figure 8. With a feed concentration of 150 g/L, rotation speed of 300 rpm, and mean residence time of 1 min, the phase transformation proceeded continuously in the crystallizer, resulting in a monotonous increase in the crystal fraction and mean

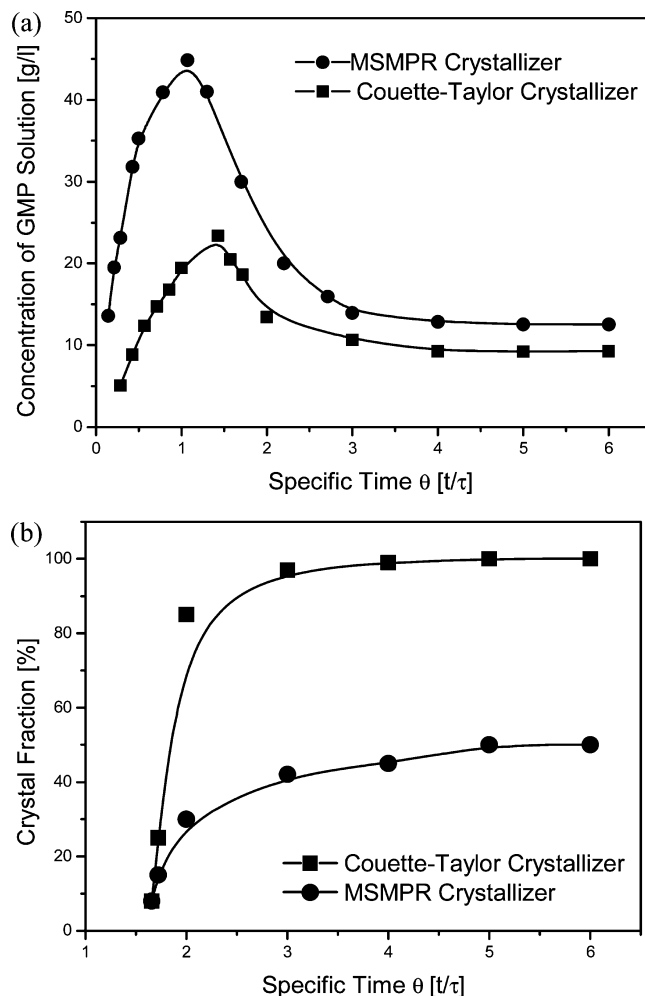


Figure 9. Comparison of GMP crystallization dynamics in a continuous Couette-Taylor crystallizer and continuous MSMPR crystallizer at 25 °C when using 300 rpm rotation speed for the inner cylinder, 150 g/L GMP feed concentration, 7 min mean residence time, and 5:5 feed ratio (GMP solution-methanol): (a) dynamic profiles of GMP concentration in product solution and (b) crystal fraction of GMP in product solid.

crystal size along the axial direction of the crystallizer. However, the GMP concentration along the axial direction was reduced based on consumption by the growth of the hydrate GMP crystals. It was interesting to note that the GMP concentration in the crystallizer always remained slightly below the metastable solubility. Thus, the present results revealed a few interesting facts, for example, the amorphous GMP was completely drowned out around the inlet region of the CT crystallizer and the phase transformation occurred along the axial flow. Furthermore, the phase transformation was mostly rate-determined by the growth step of the hydrate GMP crystals, as the concentration difference for dissolution was smaller than that for growth.

3.3. Comparison of Couette-Taylor and MSMPR Crystallizers. The crystallization performance of the CT crystallizer was compared with that of a typical MSMPR crystallizer designed based on a standard Rushton tank with a working volume of 0.8 L. As shown in Figure 9, when the crystallization conditions were fixed at a mean residence time of 7 min, feed concentration of 150 g/L, and rotation speed of 300 rpm, the CT and MSMPR crystallizers both reached a steady state after 5 times the mean residence time. However, the product suspensions from each crystallizer in a steady state were quite different. For example, the GMP concentration in the

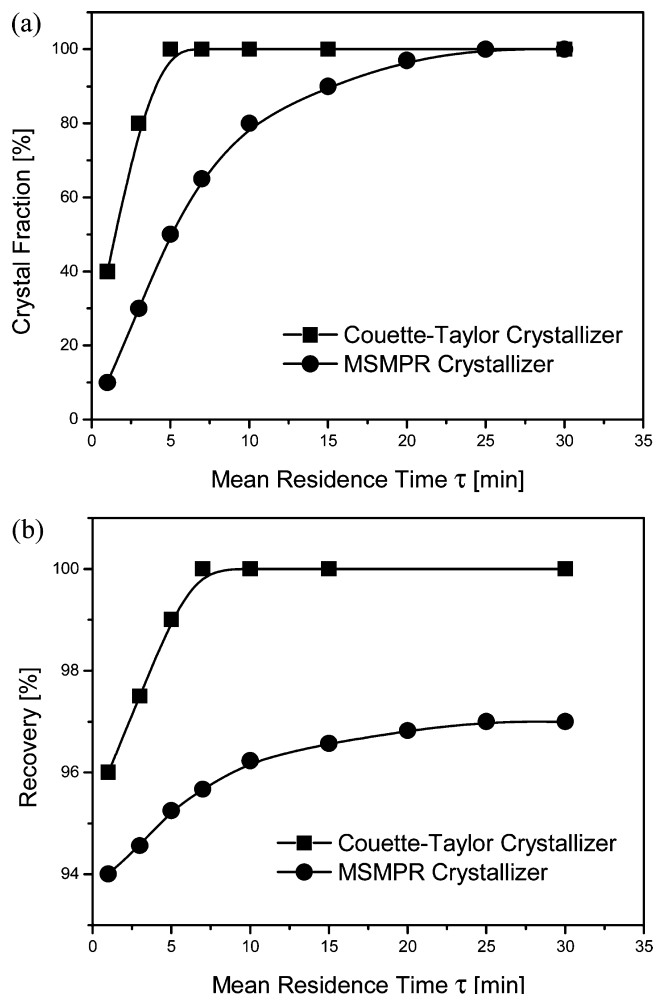


Figure 10. Comparison of GMP crystallization in a continuous Couette-Taylor crystallizer and continuous MSMPR at steady state and 25 °C when varying mean residence time with 700 rpm rotation speed for the inner cylinder, 150 g/L GMP feed concentration, and 5:5 feed ratio (GMP solution-methanol): (a) crystal fraction of GMP in product solid and (b) GMP recovery in product solid

MSMPR crystallizer was about 25% higher than that in the CT crystallizer, implying a lower recovery of GMP solids from the product suspension (Figure 9a). Furthermore, the crystal fraction in the MSMPR crystallizer was only 50% compared to 100% in the CT crystallizer (Figure 9b).

Figure 10 shows a comparison of the steady-state crystallization in the CT and MSMPR crystallizers when varying the mean residence time with a fixed rotation speed of 700 rpm and GMP feed concentration of 150 g/L. The GMP crystal fraction in the product solid from the MSMPR crystallizer was always lower than that from the CT crystallizer and only reached 100% with a mean residence time above 25 min, which was 5 times longer than that required for the CT crystallizer (Figure 10a). Furthermore, the recovery of GMP solids from the MSMPR crystallizer was always lower than that from the CT crystallizer (Figure 10b). Therefore, the experimental results highlighted the outstanding performance of the CT crystallizer over the MSMPR crystallizer for the drowning-out crystallization of GMP, due to the effective turbulent motion of the Taylor vortex for the drowning-out and phase transformation.

The effectiveness of the Couette-Taylor vortex for the phase transformation can be explained in terms of the mass transfer involved in the dissolution of the amorphous GMP and growth of the hydrate crystals. In general, the intensity of a turbulent

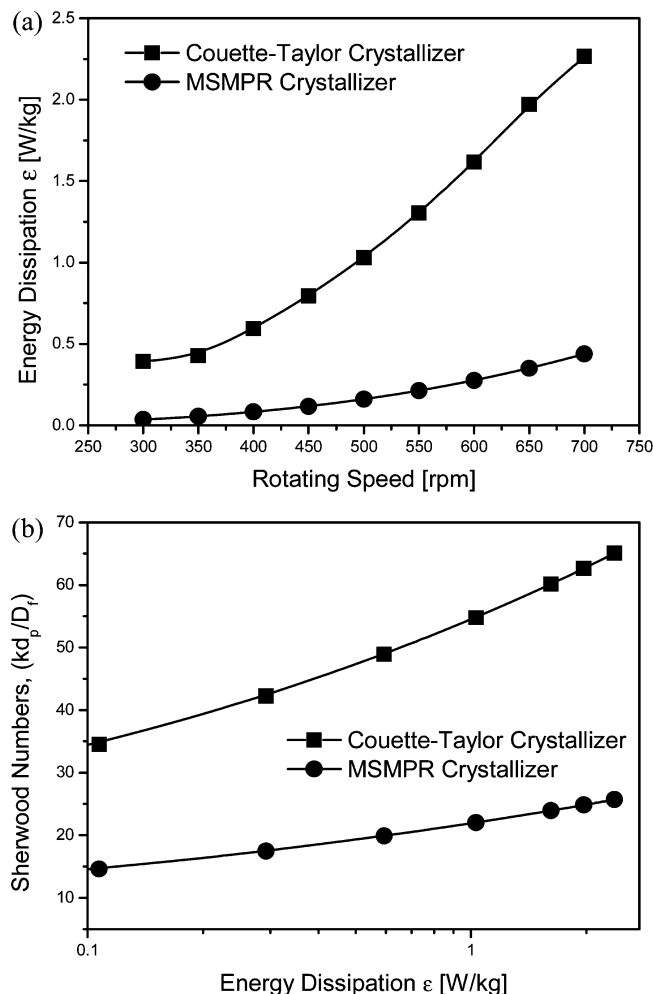


Figure 11. Estimation of turbulent effectiveness in a Couette-Taylor crystallizer and MSMPR crystallizer: (a) energy dissipation for turbulent motion and (b) Sherwood numbers for turbulent motion.

motion can be quantitatively indicated by the energy dissipation (power input per unit mass of the solution). Accordingly, the energy dissipation^{25,30,31} in the CT and MSMPR crystallizers was estimated in terms of the rotation speed (agitation speed) and crystallizer geometry (inner cylinder radius, annulus gap, and impeller diameter). On the basis of these correlations, as shown in Figure 11, the energy dissipation in each crystallizer was compared. With a fixed rotation speed (agitation speed), the CT crystallizer was always 8–10 times more effective in terms of dissipating the turbulent motion than the MSMPR crystallizer (Figure 11a), as the large contact surface of the inner cylinder in the CT crystallizer was more efficient for viscous dissipation than the inertia-driven turbulence from the impeller in the MSMPR crystallizer. Furthermore, when correlating the mass transfers in the turbulent flows,^{32,33} it was found that, even with the same energy dissipation, the mass transfer coefficient in the CT crystallizer was always 4–8 times higher than that in the MSMPR crystallizer (Figure 11b), representing the primary reason why the phase transformation of GMP in the CT crystallizer was so effective when compared with that in the MSMPR crystallizer.

4. Conclusions

This study demonstrated that a turbulent Taylor vortex in a CT crystallizer was highly effective for promoting the phase transformation of GMP solids in drowning-out crystallization.

Since both mass transfer steps in the phase transformation, including the dissolution of the amorphous GMP and growth of hydrate GMP crystals, were highly facilitated by the intensive turbulent vortex, a purely crystalline GMP product was obtained in the continuous mode CT crystallizer with a mean residence time of 5 min. This result was quite surprising when compared with the phase transformation in a continuous MSMPR crystallizer, which required a mean residence time of at least 25 min.

The viscous shear of the rotating cylinder in the CT crystallizer was more effective for the viscous energy dissipation than the turbulent eddy in the MSMPR crystallizer. In addition, when correlating the mass transfer at the solid–liquid interface in the turbulent fluid motions, the Taylor vortex flow in the CT crystallizer was shown to be more effective for promoting the interfacial mass transfer than the turbulent eddy in the MSMPR crystallizer, thereby representing the apparent primary reason for the effective phase transformation in the CT crystallizer.

Acknowledgment

This work was financially supported by NRF.

Supporting Information Available: Thermogravimetric analysis (TGA) of hydrate GMP crystals confirming weight loss of 23%, indicating 7-hydrate crystal form at heating rate of 10 °C/min, and residence time distribution of liquid and GMP crystal (53–100 μm) at 25 °C with 7 min mean residence, 300 rpm rotation speed for the inner cylinder, and 150 g/L GMP feed concentration. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Literature Cited

- (1) Davey, R.; Garside, J. *From Molecules to Crystallizers*; Oxford University Press: Oxford, U.K., 2000; Chapter 7, p 53.
- (2) Kulikov, V.; Briesen, H.; Marquardt, W. A Framework for the Simulation of Mass Crystallization Considering the Effect of Fluid Dynamics. *Chem. Eng. Process.* **2006**, *45*, 886–899.
- (3) Kataoka, K.; Ohmura, N.; Kouzu, M.; Simamura, Y.; Okubo, M. Emulsion Polymerization of Styrene in a Continuous Taylor Vortex Flow Reactor. *Chem. Eng. Sci.* **1995**, *50*, 1409–1416.
- (4) Dluska, E.; Wolinski, J.; Wronski, S. Toward Understanding of Two-Phase Eccentric Helical Reactor Performance. *Chem. Eng. Technol.* **2005**, *28*, 1016–1021.
- (5) Sczechowski, J. G.; Koval, C. A.; Noble, R. D. A Taylor Vortex Reactor for Heterogeneous Photocatalysis. *Chem. Eng. Sci.* **1995**, *50*, 3136–3173.
- (6) Holeschovsky, U. B.; Cooney, C. L. Quantitative Description of Ultrafiltration in a Rotating Filtration Device. *AIChE J.* **1991**, *37*, 1219–1226.
- (7) Giordano, R. L. C.; Giordano, R. C.; Cooney, C. L. Performance of a Continuous Taylor-Couette-Poiseuille Vortex Flow Enzymatic Reactor with Suspended Particles. *Process Biochem. (Amsterdam, Neth.)* **2000**, *35*, 1093–1101.
- (8) Kang, S. H.; Lee, S. G.; Jung, W. M.; Kim, M. C.; Kim, W. S.; Choi, C. K.; Feigelson, R. S. Effect of Taylor Vortices on Calcium Carbonate Crystallization by Gas-Liquid Reaction. *J. Cryst. Growth* **2003**, *254*, 196–205.
- (9) Jung, W. M.; Kang, S. H.; Kim, W. S.; Choi, C. K. Particle Morphology of Calcium Carbonate Precipitated by Gas-Liquid Reaction in a Couette-Taylor. *Chem. Eng. Sci.* **2000**, *55*, 733–747.
- (10) Chakraborty, D.; Agarwal, V. K.; Bhatia, S. K.; Bellare, J. Steady-State Transitions and Polymorph Transformations in Continuous Precipitation of Calcium Carbonate. *Ind. Eng. Chem. Res.* **1994**, *33*, 2187–2197.
- (11) Jung, T.; Kim, W. S.; Choi, C. K. Effect of Nonstoichiometry on Reaction Crystallization of Calcium Carbonate in a Couette-Taylor Reactor. *Cryst. Growth Des.* **2004**, *4*, 491–495.
- (12) Bernstein, J. *Polymorphism in Molecular Crystals*; Oxford University Press: Oxford, U.K., 2002.
- (13) Hilfiker, R. *Polymorphism in the Pharmaceutical Industry*; Wiley-VCH: Weinheim, Germany, 2006.
- (14) Brittain, H. G. *Polymorphism in Pharmaceutical Solids*; Marcel Dekker, Inc.: New York, 1999.
- (15) Mukuta, T.; Lee, A. Y.; Kawakami, T.; Myerson, A. S. Influence of Impurities on the Solution-Mediated Phase Transformation of an Active Pharmaceutical Ingredient. *Cryst. Growth Des.* **2005**, *5*, 1429–1436.
- (16) Cornel, J.; Lindenberg, C.; Mazzotti, M. Experimental Characterization and Population Balance Modeling of the Polymorph Transformation of L-Glutamic Acid. *Cryst. Growth Des.* **2009**, *9*, 243–252.
- (17) Scholl, J.; Bonalumi, D.; Vicum, L.; Mazzotti, M. In Situ Monitoring and Modeling of the Solvent-Mediated Polymorphic Transformation of L-Glutamic Acid. *Cryst. Growth Des.* **2006**, *6*, 881–891.
- (18) Wikstrom, H.; Rantanen, J.; Gift, A. D.; Taylor, L. S. Toward an Understanding of the Factors Influencing Anhydrate-to-Hydrate Transformation Kinetics in Aqueous Environments. *Cryst. Growth Des.* **2008**, *8*, 2684–2693.
- (19) Qu, H.; Kultanen, M. L.; Rantanen, J.; Kallas, J. Solvent-Mediated Phase Transformation Kinetics of an Anhydrate/Hydrate System. *Cryst. Growth Des.* **2006**, *6*, 2053–2060.
- (20) Maruyama, S.; Ooshima, H.; Kato, J. Crystal Structures and Solvent-Mediated Transformation of Taltireline Polymorphs. *J. Chem. Eng.* **1999**, *75*, 193–200.
- (21) Cheng, W. T.; Lin, S. Y. Famotidine Polymorphic Transformation in the Grinding Process Significantly Depends on Environmental Humidity or Water Content. *Int. J. Pharm.* **2008**, *357*, 164–168.
- (22) Yang, X.; Lu, J.; Wang, X. J.; Ching, C. B. Effect of Sodium Chloride on the Nucleation and Polymorphic Transformation of Glycine. *J. Cryst. Growth* **2008**, *310*, 604–611.
- (23) Kurotani, M.; Hirasawa, I. Polymorph Control of Sulfamerazine by Ultrasonic Irradiation. *J. Cryst. Growth* **2008**, *310*, 4576–4580.
- (24) Gong, Y.; Collman, B. M.; Mehrens, S. M.; Lu, E.; Miller, J. M.; Blackburn, A.; Grant, D. J. W. Stable-Form Screening: Overcoming Trace Impurities That Inhibit Solution-Mediated Phase Transformation to the Stable Polymorph of Sulfamerazine. *J. Pharm. Sci.* **2008**, *97*, 2130–2144.
- (25) McCabe, W. L.; Smith, J. C.; Harriott, P. *Unit Operations of Chemical Engineering*, 6th ed.; McGraw Hill: Boston, MA, 2001; Chapter 9, p 238.
- (26) Skrovanek, D. J.; Painter, P. C.; Coleman, M. M. Hydrogen Bonding in Polymers. 2. Infrared Temperature Studies of Nylon 11. *Macromolecules* **1986**, *19*, 699–705.
- (27) Griffiths, P. R.; de Haseth, J. A. *Fourier Transform Infrared Spectrometry*; Wiley: New York, 1986.
- (28) Davey, R. J.; Cardew, P. T. The Kinetics of Solvent-Mediated Phase Transformations. *Proc. R. Soc. London* **1985**, *A398*, 415–428.
- (29) Davey, R. J.; Cardew, P. T. Rate Controlling Processes in Solvent-Mediated Phase Transformations. *J. Cryst. Growth* **1986**, *79*, 648–653.
- (30) Sinevic, V.; Kuboi, R.; Nienow, A. W. Power Numbers, Taylor Numbers and Taylor Vortices in Viscous Newtonian and Non-Newtonian Fluids. *Chem. Eng. Sci.* **1986**, *41*, 2915–2923.
- (31) Atsumi, K.; Makino, T.; Kato, K. Frictional Resistance of Grooved Rotor in Cylindrical Dynamic Filter Chamber without Permeation or Throughflow. *Kagaku Kogaku Ronbunshu* **1988**, *14*, 16–19.
- (32) Nakahara, S. Mass Transfer from Single Sphere in Taylor Vortex. *Kagaku Kogaku Ronbunshu* **1977**, *3*, 435–439.
- (33) Kikuchi, K.; Tadakuma, Y.; Sugawara, T.; Ohashi, H. Effect of Inert Particle Concentration on Mass Transfer Between Particles and Liquid in Solid-Liquid Two-Phase Upflow Through Vertical Tubes and in Stirred Tanks. *J. Chem. Eng. Jpn.* **1987**, *20*, 134–140.

Received for review December 7, 2009

Revised manuscript received March 29, 2010

Accepted April 7, 2010

IE901932T