

# Multiple Feeding Strategy for Phase Transformation of GMP in Continuous Couette–Taylor Crystallizer

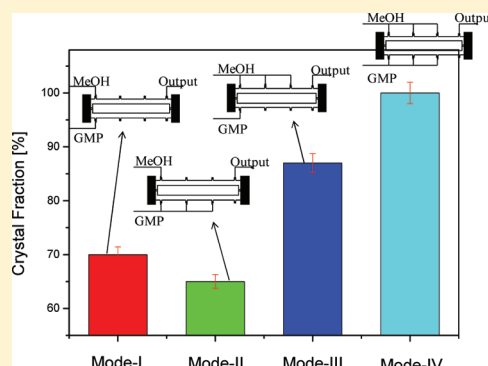
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## S Supporting Information

**ABSTRACT:** A continuous Couette–Taylor (CT) crystallizer with a multiple feed mode was developed to promote the phase transformation of guanosine 5-monophosphate (GMP). In drowning-out crystallization, amorphous GMP is initially precipitated and then transformed into hydrate GMP crystals via the spontaneous nucleation of hydrate crystals and consecutive dissolution of the amorphous GMP and growth of hydrate GMP crystals. Importantly, the multiple feeding strategy had a significant accelerating effect on the phase transformation process, resulting in the complete conversion of the amorphous GMP into hydrate crystals within an overall mean residence time of 2.5 min, even with a high GMP feed concentration of 152.8 g/L and low rotation speed of 300 rpm. Thus, the phase transformation in the continuous CT crystallizer with the multiple feed mode (feeding mode IV) was at least 2 times faster than the phase transformation with the conventional feeding mode (feeding mode I), and 10 times faster when compared to the phase transformation in a continuous MSMPR crystallizer. The effectiveness of the multiple feeding mode for the phase transformation can be explained in terms of independently controlling the supersaturation, mean residence time, seeding effect, and mass transfer rates in each region of CT crystallizer depending on the multiple feeding strategy and feeding distribution ratio.



## 1. INTRODUCTION

Phase transformation, meaning the change of one solid state form to another during crystallization, is important as regards the production of functional solid materials, such as food additives, pharmaceuticals, and fine chemicals, as the different solid state forms have different physical-chemical properties of solubility, hardness, stability, and bioavailability.<sup>1–4</sup> Thus, many studies have attempted to control the process of phase transformation to enable accurate and effective production of the desired solid state form during crystallization. Many crystallization operating factors have already been identified as critical to phase transformation, including the seeding, agitation speed, solvent, temperature, additive, initial solute concentration.<sup>5–19</sup> For example, phase transformation is significantly facilitated when using seed crystals of the stable form of carbamazepine (CBZ) and caffeine (CAF), as these seed crystals easily initiate secondary nucleation of the stable form.<sup>12</sup> Meanwhile, the effect of the initial solute concentration has been demonstrated in the phase transformation of 2,6-dihydroxybenzoic acid (DHB),<sup>13</sup> where increasing the initial feed concentration increases the nucleation rate of the stable form, thereby promoting the phase transformation. In the case of Taltireline, agitation has been found to promote the nucleation of the stable form and mass transfers for the reconstruction of metastable form crystals into stable form crystals.<sup>14</sup> Thus, the phase transformation time is reduced when increasing the agitation speed.

The influence of the unique vortex flow in a Couette–Taylor crystallizer on phase transformation has also been demonstrated in previous studies by the current authors,<sup>20–22</sup> where the periodic flow pattern of a turbulent Taylor vortex was found to be highly effective for the phase transformation of guanosine 5-monophosphate (GMP)<sup>20,21</sup> and sulfamerazine (SMZ).<sup>22</sup> Because of the strong and periodic toroidal vortex flow caused by the centrifugal force of the azimuthal fluid motion resulting from the rotation of the inner cylinder, the induction of stable form crystals of SMZ was significantly promoted in a Couette–Taylor (CT) crystallizer when compared with that in a turbulent mixing crystallizer,<sup>22</sup> and the phase transformation of GMP in a continuous CT crystallizer was 5 times faster than that in a continuous MSMPR crystallizer.<sup>20,21</sup> It was also reported that the reconstruction of metastable crystals into stable ones was markedly accelerated, as the mass transfers for the dissolution of the metastable crystals and growth of stable ones in the turbulent Taylor vortex were 4–8 times faster than those in a random turbulent eddy at the same turbulent intensity (viscous energy dissipation).<sup>23,24</sup>

Varying the feeding mode has also been explored as an important operating strategy, especially in the case of reaction crystallization in order to control the mean crystal size and

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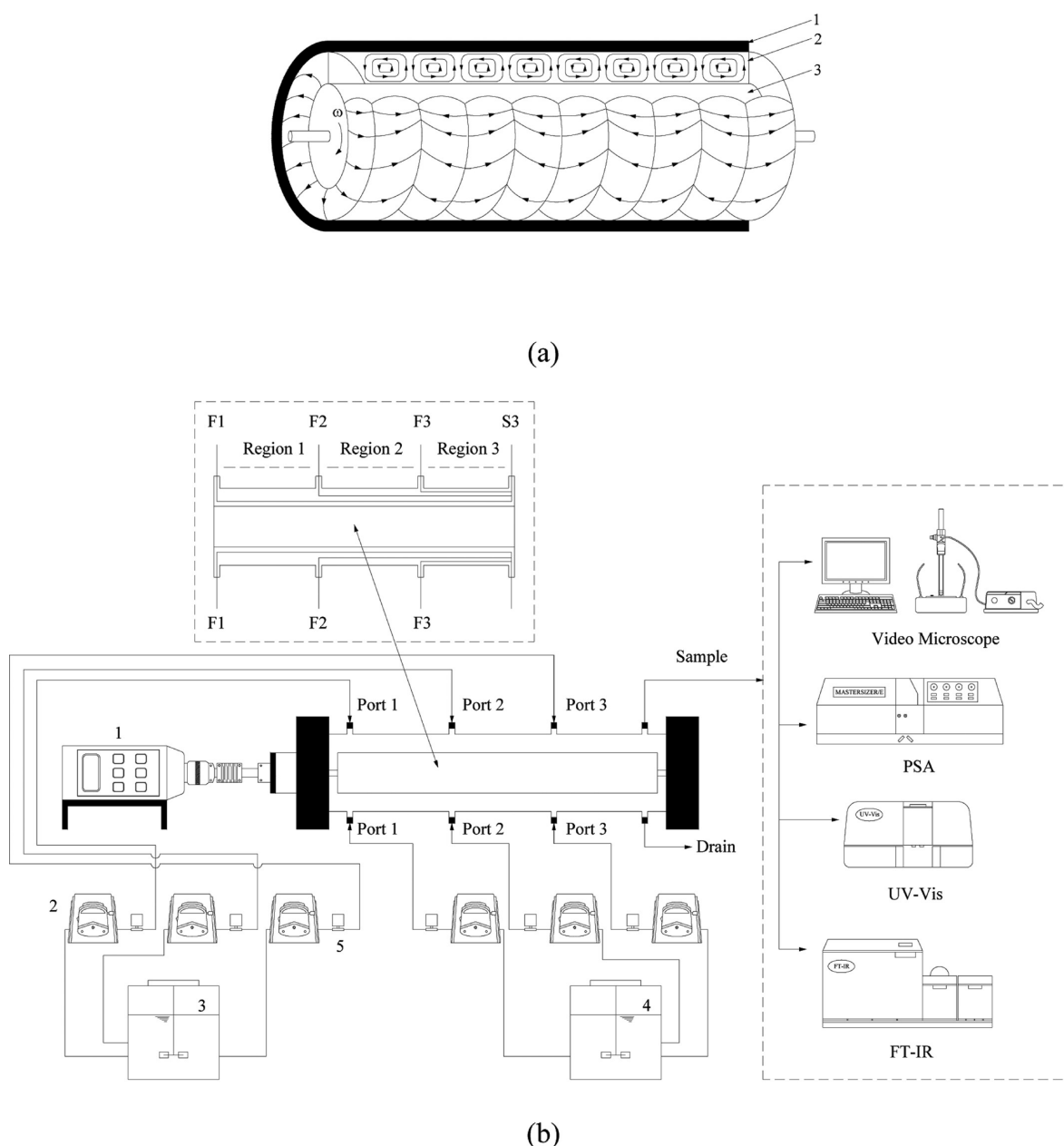


**Figure 1.** Schematic diagram of continuous drowning-out crystallization of GMP using Couette–Taylor Crystallizer. (a) Taylor vortices in Couette–Taylor crystallizer (1, stationary outer cylinder; 2, Taylor vortices; 3, rotating inner cylinder) and (b) experimental apparatus of multiple feeding mode system for drowning-out crystallization (1, motor; 2, pump; 3, methanol; 4, feed GMP solution; 5, damper).

crystal size distribution of the product crystals.<sup>25–30</sup> For example, Wong et al and Baldyga et al<sup>25,26</sup> found that the mean crystal size of barium sulfate in reaction crystallization was significantly reduced when two reactant feed streams were located near the impeller of the crystallizer. When using this feeding mode, the direct mixing of the two reactants near the impeller provided a high local supersaturation, which resulted in the nucleation of huge numbers of crystals and a product of small-sized barium sulfate crystals. Conversely, the crystal size of the barium sulfate was enlarged due to a low local supersaturation when positioning two reactant feed streams far away from the impeller. A similar influence from the feeding mode strategy on the barium sulfate crystallization was also observed in continuous MSMRP and semibatch crystallizers.<sup>27,28</sup> In addition, Alvarez and Myerson<sup>29</sup> demonstrated that a feeding mode strategy in a continuous plug flow

crystallizer was effective in controlling the crystal size and distribution of pharmaceutical compounds of ketoconazole, flufenamic acid, and L-glutamic acid in the case of drowning-out crystallization. As such, the mean crystal size of flufenamic acid was larger when distributively injecting the antisolvent along the axial position of the plug flow crystallizer than when injecting all the antisolvent through the same inlets at the front end of the crystallizer with the solute solution, as the distributive injection mode controlled the supersaturation at a low level along the crystallizer, thereby suppressing crystal nucleation and supporting crystal growth. Therefore, when increasing the number of distributive injection points for the antisolvent, the crystal size increased. However, in the case of L-glutamic acid, the crystal size was minimized when using a two-point distributive injection of the antisolvent, and then enlarged when further increasing the number of distributive injection

points. Also, the crystal size distribution varied significantly according to the distributive injection strategy.

While the above-mentioned studies have demonstrated the use of feeding mode strategies for controlling crystal size and distribution, however, few studies have yet investigated the influence of the feeding mode on phase transformation during crystallization. In the present study, we investigated the effect of multiple feeding modes in a continuous CT crystallizer on the phase transformation of GMP in drowning-out crystallization. To vary the feeding mode, the GMP solution and antisolvent feed streams were distributively injected along the axial position of the CT crystallizer, where the number of distributive injection points was varied from one to three and each feed stream was alternatively distributively injected. Thus, when the GMP solution feed stream was distributively injected, the antisolvent feed stream was input through only one inlet, and vice versa. The distribution ratio and flow rate of the feed streams were varied to optimize the effectiveness of the feeding mode strategy for the phase transformation of GMP in the continuous CT crystallizer. Plus, the rotation speed of the inner cylinder in the CT crystallizer and GMP feed concentration were also considered as operating factors influencing the phase transformation.

## 2. EXPERIMENTAL SECTION

The Couette–Taylor (CT) crystallizer consisted of an inner cylinder made of stainless steel and outer cylinder made of transparent acrylic plastic, allowing visual observation of the Taylor vortex flow in the gap between the two cylinders. As described in our previous study,<sup>20</sup> the dimensions of the CT crystallizer were 5 cm for the outer cylinder radius, 4 cm for the inner cylinder radius, and 40 cm for the cylinder length, making a working volume (gap volume) of 1.13 L. Shown in Figure 1b, the crystallizer was placed horizontally to eliminate any hydrostatic pressure. Several pairs of ports were installed in the outer cylinder along the axial direction of the crystallizer to facilitate distributive injection of the feed streams (called “multiple feeding”) and also sampling of the product suspensions. To induce a Taylor vortex flow, the inner cylinder was rotated using a DC motor, where the rotation speed was controlled from 300 to 700 rpm.

The raw GMP material (99.9% purity) supplied by CJ Co. (Korea) was used without any further purification. The GMP feed solution was prepared by dissolving the raw GMP material in distilled water at a concentration varying from 61 to 153 g/L. Methanol (ACS grade) purchased from Duksan Pure Chemical Co., LTD, (Korea) was used as the antisolvent for the drowning-out crystallization.

The CT crystallizer was initially filled with distilled water. The GMP feed solution and methanol were then distributively injected into the crystallizer through the pairs of input ports, where the ports in each pair were located on adjacent sides of the same axial position. Plus, each distributive injection was individually fed by a pump (StepDos 08, KNF, Germany) (Figure 1b). Using these pairs of input ports, the multiple-injection feeding mode was operated for drowning-out crystallization. While keeping a fixed total flow rate for the feed streams, the flow rates at each port were distributed to create a variety of multiple feeding modes. The details of the multiple feeding modes will be discussed in a later section.

The port used to take the product samples was always positioned at back end of the CT crystallizer. At a steady state, the product samples were quickly filtered using a vacuum, then dried in a dry desiccator for one day and analyzed as regards the polymorphic fraction and crystal size using FT-IR (Perkin, System 2000, U.S.A.) and a video microscope (IT System, Somatech, USA), respectively, as described in our previous studies.<sup>20,31</sup> Meanwhile, the filtered solution was analyzed for the GMP concentration, which was monitored using a UV–vis (JASCO, V-570, USA). In addition, an XRD (X-ray diffractometer, MAC Science, M18XHF-SRA, CuK $\alpha$  line, Japan) was

used to confirm the solid structures of the amorphous GMP and hydrate GMP crystals.

## 3. RESULTS AND DISCUSSION

**3.1. Feeding Mode Strategy for Phase Transformation.** The various multiple feeding modes used for the continuous drowning-out crystallization of GMP in a Couette–Taylor crystallizer are shown in Figure 2. The

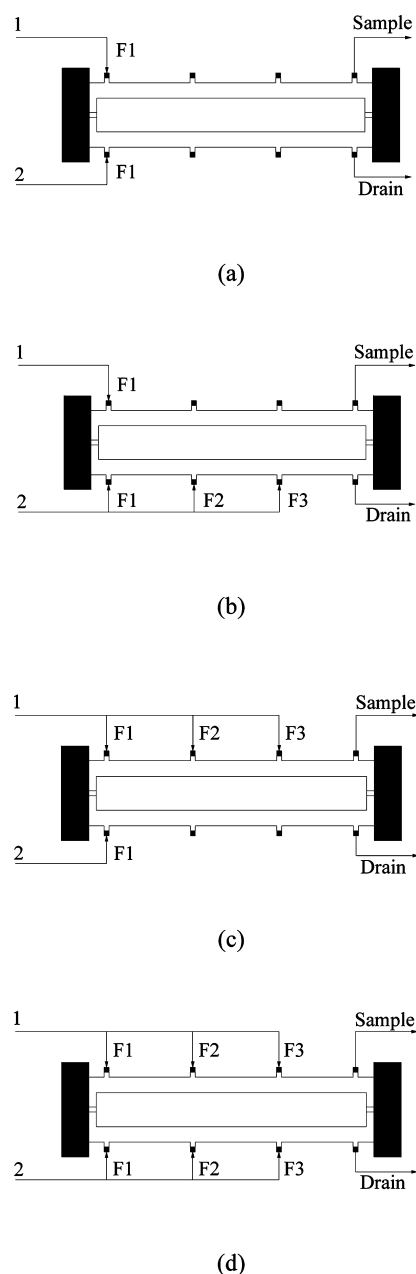


**Figure 2.** Multiple feeding modes of Couette–Taylor crystallizer (1: methanol antisolvent solution; 2: GMP feed solution). (a) Feeding mode I, (b) feeding mode II, (c) feeding mode III, and (d) feeding mode IV.

simplest feeding mode (feeding mode I) involved injecting the GMP feed solution and methanol antisolvent through inlet ports positioned axially at the front end of the crystallizer, and draining the product suspension through outlet ports positioned axially at the back end of the crystallizer (Figure

2a). In fact, this is the typical feeding mode invariably applied to continuous CT crystallizers in previous studies.<sup>20</sup> In the case of feeding modes II and III (Figure 2b and c), only one feed stream of the GMP feed solution or methanol antisolvent was distributively fed into the crystallizer along the axial position, while the other feed stream was injected through one inlet port at the front end of the crystallizer. Finally, for feeding mode IV, both feed streams were distributively fed into the crystallizer. For all feeding modes, the total flow rate of the GMP feed solution and methanol antisolvent was always fixed at a drowning-out ratio of 1.

The typical influence of the multiple feed modes on the GMP drowning-out crystallization is presented in Figure 3. In general, the phase transformation of amorphous GMP to the hydrate crystals is a time-consuming process. Thus, according to previous studies of GMP crystallization in a continuous CT crystallizer using the simplest feeding mode (feeding mode I), a short mean residence time was not enough to completely convert the initially precipitated amorphous GMP to the hydrate crystals, resulting in the solid mixture of the amorphous and hydrate crystalline GMP in the product suspension. Also, the higher GMP feed concentration had required the longer mean residence time for the complete phase transformation. So, the mean residence time longer than 5 min was necessary to obtain the product suspension of the purely hydrate crystal GMP at a GMP feed concentration of 152.8 g/L. Thereby, the 2.5 min mean residence time in the present study was clearly too short for the complete phase transformation of the GMP with the same feeding mode I and same feed concentration of 152.8 g/L, resulting in a 70% phase conversion to hydrate crystals in the product suspension. However, the GMP crystallization including the phase transformation in the crystallizer was significantly changed with the multiple feeding modes. When using distributive feeding for the antisolvent (feeding mode III), the hydrate crystal fraction in the product suspension, defined as weight percent of hydrate GMP crystals in the solid product, was enhanced to almost 90%, while complete conversion was achieved when using distributive feeding for both the GMP solution and the antisolvent (feeding mode IV) even at the mean residence time of 2.5 min.

These results can be explained in terms of the supersaturation level and mean residence time in each region of the crystallizer, called as regional mean residence time (shown in Figure 1b) when varying the feeding modes. In the present study, even though the mean residence time of the crystallizer ( $\tau = V/F_T$ ), defined as ratio of total volume of crystallizer ( $V$ ) to total input flow rate to the crystallizer ( $F_T$ ), was same, the regional mean residence time ( $\tau_i = V_i/F_i$ ) in the crystallizer, defined as ratio of regional volume of crystallizer ( $V_i$ ) to input flow rate to the region ( $F_i$ ), was significantly changed with the feeding mode (see the Supporting Information S1). As such, when using the simplest feeding mode (feeding mode I), the regional mean residence time at each region would equally be  $\tau/3$ . However, when using the distributive feeding modes, the regional mean residence times in the crystallizer were varied as  $\tau_1 = (V/3)/(F_1)$  in the region 1,  $\tau_2 = (V/3)/(F_1 + F_2)$  in the region 2 and  $\tau_3 = (V/3)/(F_1 + F_2 + F_3)$  in the region 3, respectively. For example, in case of the equally distributed multiple feeding mode ( $F_1 = F_2 = F_3 = F_T/3$ ), the regional mean residence time were calculated as  $\tau$  in the region 1,  $\tau/2$  in the region 2 and  $\tau/3$  in the region 3. It indicated that the distributive feeding mode would provide much longer regional mean residence time in the crystallizer than the simple feeding

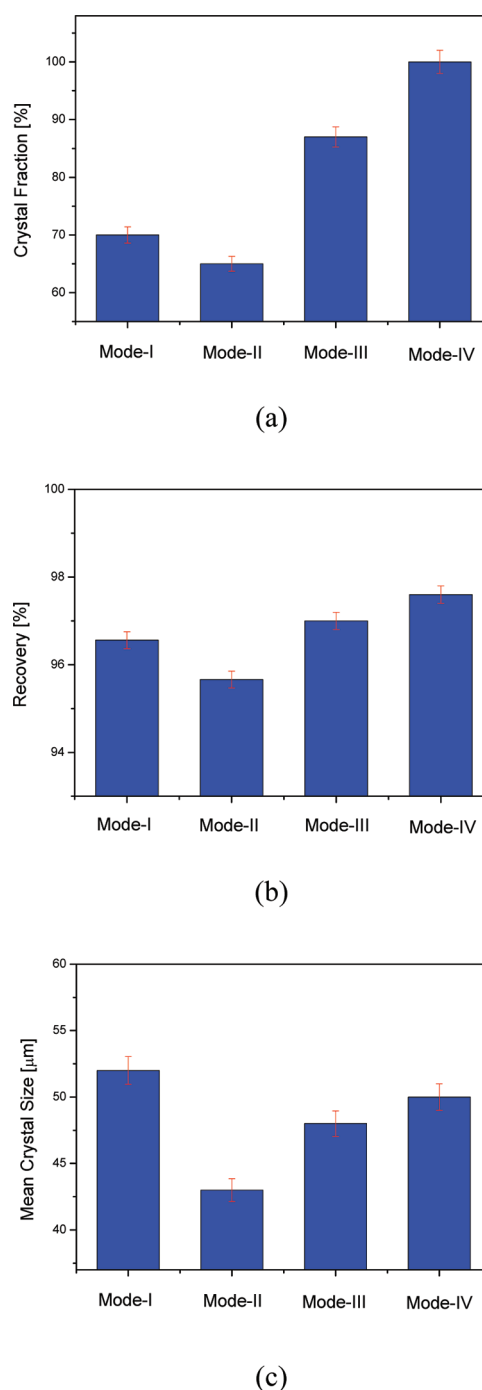


**Figure 3.** Influence of multiple feeding modes on phase transformation in steady state. The crystallization conditions were fixed at 25 °C temperature, 2.5-min mean residence time, 300 rpm rotation speed for inner cylinder, 152.8 g/L GMP feed concentration, 1:1 drowning-out ratio (GMP solution: methanol), and 0.5:0.44:0.06 distribution ratio ( $F_1:F_2:F_3$ ). (a) Crystal fraction, (b) recovery ratio of solid GMP and (c) mean crystal size.

mode (feeding mode I). Consequently, the higher phase transformation (higher crystal fraction) in region 1 could be achieved with the multiple feeding mode IV produced than the feeding mode I. The hydrate crystals transformed in region 1 then became seeds of the stable hydrate form for the phase transformation in the next regions, where the amorphous GMP was being consecutively precipitated by the distributively injected feed streams. Plus, the distributive injections induced

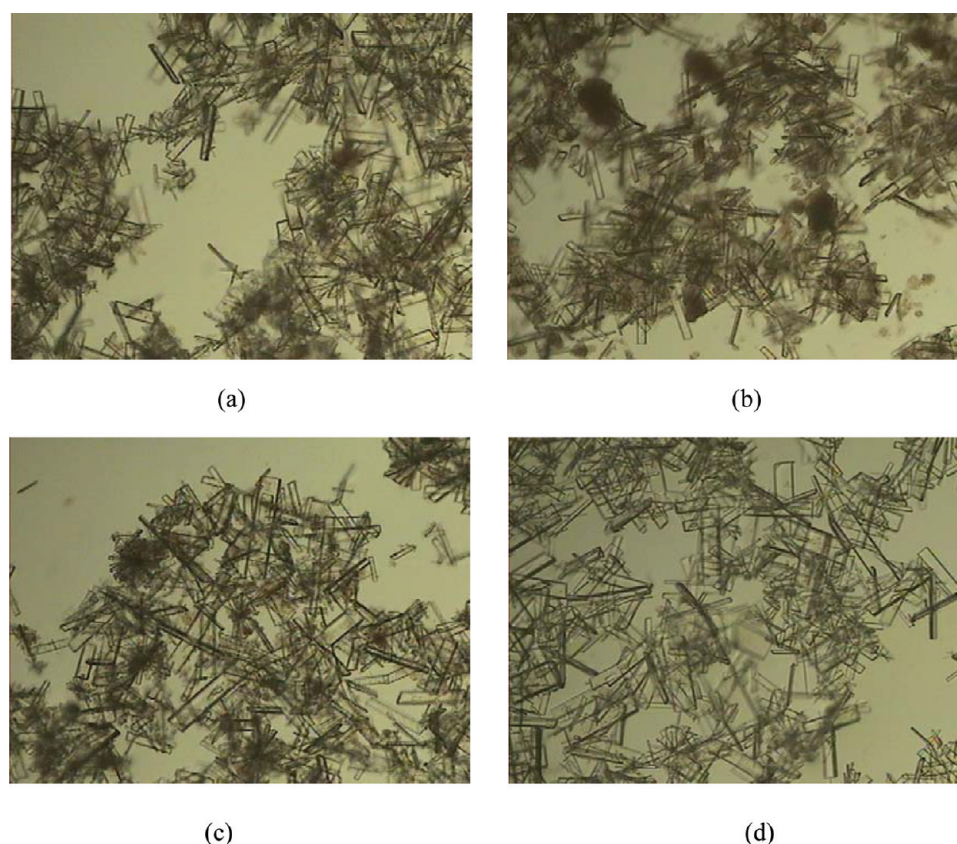


**Figure 4.** Influence of multiple feeding modes on morphology of GMP solids at steady state. The crystallization conditions were fixed at 25 °C temperature, 2.5-min mean residence time, 300 rpm rotation speed for inner cylinder, 152.8 g/L GMP feed concentration, 1:1 drowning-out ratio (GMP solution: methanol), and 0.5:0.44:0.06 distribution ratio ( $F_1/F_2/F_3$ ). (a) Feeding mode I, (b) feeding mode II, (c) feeding mode III, and (d) feeding mode IV.

a lower supersaturation in each region than that induced with the total feeding mode (feeding mode I), resulting in a facile phase transformation. Furthermore, the flow regime of the Taylor vortex was more destabilized by the distributive feeding modes than by the total feeding mode (feeding mode I), promoting the mass transfer rates of the phase transformation. The mass transfer depending on the Taylor vortex regime combined with the axial flow rate will be discussed later in more detail using experimental data (Figures 7 and 8).

Similarly, in the case of feeding mode III when only the methanol antisolvent was distributively injected, a higher crystal fraction in the product suspension was obtained, comparing with the case of the simple feeding mode, due to a longer regional mean residence time in the crystallizer. In addition, a lower regional drowning-out ratio (a ratio of the antisolvent flow rate to the GMP feed flow rate in the region) with the distributive feed mode III inducing a lower regional supersaturation level contributed to a facile phase transformation. However, in the case of feeding mode II, the distributive injections of the GMP feed solution caused a high regional drowning-out ratio, inducing a high regional supersaturation level and resulted in a low crystal fraction in the product suspension.

A similar influence of the feeding mode on the recovery of solid GMP from the product was observed. As such, the highest recovery was achieved with feeding mode IV and the lowest with feeding mode II. It should be noted, however, that the recovery of solid GMP was always over 95%, even with feeding mode II. Notwithstanding, due to the consecutive nucleation of

hydrate crystals in the crystallizer with the distributive feeding, the mean crystal sizes produced were smaller than those with feeding mode I. In particular, because of the regional high supersaturation level induced with feeding mode II, this mode produced the smallest crystal size among all the feeding modes.

The influence of the multiple feeding modes on the GMP phase transformation in the CT crystallizer was visually confirmed by microscopic images, as shown in Figure 4. Under the same crystallization conditions for the CT crystallizer as those in Figure 3, while a certain amount of amorphous GMP was obvious in the product solids with feeding mode I and feeding mode II (Figure 4a and b, respectively), no amorphous GMP was found in the product with feeding mode IV, indicating the complete conversion to hydrate crystals, as expected from Figure 3a. Consequently, the microscopic observations were consistent with the crystal fractions measured for the various feeding modes and supported the effectiveness of the multiple feeding modes as regards the phase transformation of GMP in a CT crystallizer. It should also be mentioned that the distribution ratio of the feed streams for the above experiments (Figures 3 and 4) was optimized at  $F_1/F_2/F_3 = 0.5:0.44:0.06$ . The influence of the distribution ratio of the feed stream on the phase transformation of GMP in the CT crystallizer is summarized in the Supporting Information (Figure S2).

**3.2. Influence of Crystallization Conditions on Phase Transformation.** When using feeding mode IV, the crystallization conditions, including the rotation speed of the inner cylinder, GMP feed concentration, and mean residence

time, were all modified to investigate their impact on the phase transformation in the CT crystallizer via monitoring the crystal fraction, recovery ratio, and mean crystal size of GMP in the product suspensions at a steady state. Here, the total drowning-out ratio of the two feed streams for the crystallization was always unity, and their distribution ratio was also fixed at the optimized values of  $F_1/F_2/F_3 = 0.5: 0.44: 0.06$ .

Figure 5 shows the influence of the mean residence time on the GMP phase transformation, where even with the optimized

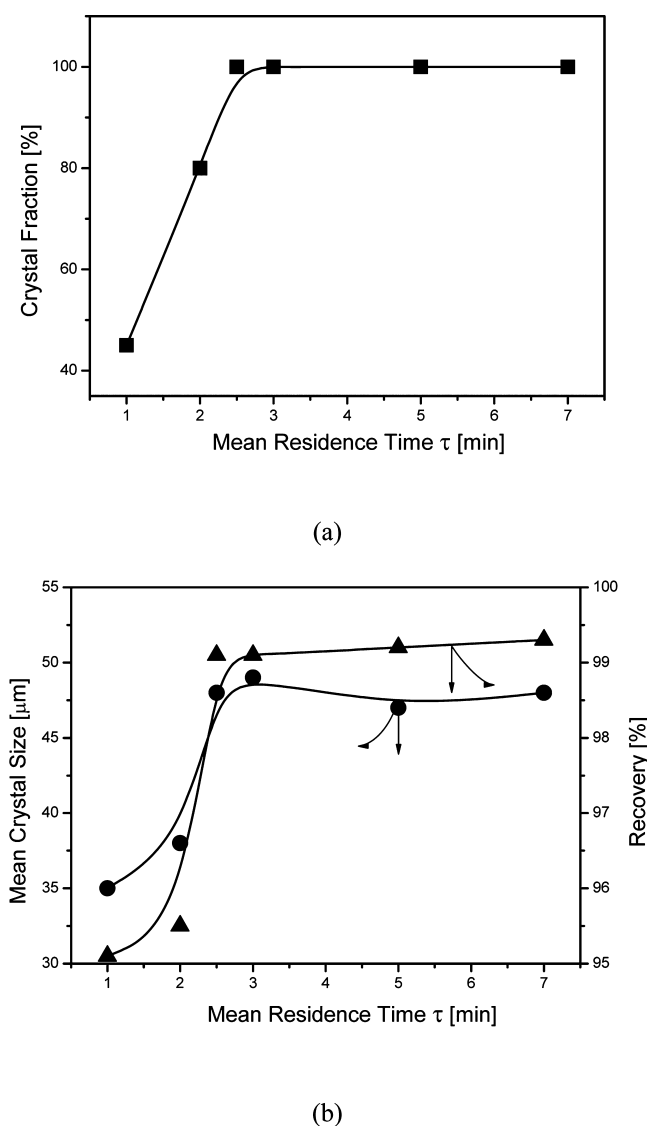


**Figure 5.** Influence of mean residence time on phase transformation with feeding mode IV at steady state. The crystallization conditions were fixed at 25 °C temperature, 2.5-min mean residence time, 300 rpm rotation speed for inner cylinder, 152.8 g/L GMP feed concentration, 1:1 drowning-out ratio (GMP solution = methanol), and 0.5:0.44:0.06 distribution ratio ( $F_1/F_2/F_3$ ). (a) Crystal fraction and (b) mean crystal size and recovery ratio of solid GMP.

distributive feeding strategy (feeding mode IV), a mean residence time below 1 min was too short for complete conversion of the amorphous GMP into hydrate crystals, resulting in a crystal fraction below 45% in the product solids. However, when increasing the mean residence time in the crystallizer, the conversion was enhanced, reaching a crystal fraction of 100% with a mean residence time above 2.5 min

(Figure 5a). The dependency of the crystal size and recovery ratio of GMP on the mean residence time was also similar to that of the above-mentioned crystal fraction (Figure 5b), improving when increasing the mean residence time to 2.5 min, and then leveling off. In particular, the recovery ratio almost reached 100% with a mean residence time above 2.5 min. Thus, when compared with the GMP phase transformation in a continuous MSMPR crystallizer that requires a mean residence time above 25 min,<sup>20</sup> the multiple feeding strategy in the continuous CT crystallizer was 10 times more productive for the crystallization of GMP. Plus, it was two times more effective for crystallizing out the pure GMP hydrate crystals without a significant trade-off as regards the crystal size when compared with the crystallization in a continuous CT crystallizer with the conventional feeding mode (feeding mode I).<sup>20,21</sup>

In Figure 6, the influence of the rotation speed of the inner cylinder and GMP feed concentration on the phase transformation is examined with a mean residence time of 2 min. The Taylor vortex flow, dictating the mass transfer rates for the dissolution and growth processes, was critical in determining the phase transformation rate. Due to the strong and periodical radial motion of a Taylor vortex, the phase transformation was promoted when increasing the rotation speed of the inner cylinder, resulting in a higher crystal fraction in the product solids (Figure 6a). This dependency of the crystal fraction on the rotation speed of the inner cylinder also became evident when increasing the GMP feed concentration. It is interesting to note that the interfacial mass transfer coefficient between solid and solution in the Taylor vortex is 4–8 times higher than that in the random turbulent eddy induced by the impeller agitation, even at the same turbulent mixing intensity (energy dissipation).<sup>20,23,24</sup> In addition, the enhanced mass transfer rate from the Taylor vortex motion resulted in an increased recovery ratio when increasing the rotation speed (Figure 6b). It should be mentioned that the crystal fractions with a low GMP feed concentration of 61 g/L were always 100% across the whole range of rotation speeds tested because of the simultaneous nucleation of amorphous solids and hydrate crystals with the low supersaturation.<sup>31</sup>

As a result of the effective mixing of the feed streams by the Taylor vortex motion, a high supersaturation was induced in the inlet areas of the injection ports, resulting in a high nucleation of hydrate crystals.<sup>21</sup> Thus, the mean crystal size in the product suspension was reduced with increasing the rotation speed and GMP feed concentration (Figure 6c). In addition, crystal breakage by crystal collision and the turbulent shear in the Taylor vortex flow may also have contributed to the reduction of the mean crystal size when increasing the vortex intensity.

**3.3. Phase Transformation Profile in Crystallizer.** To understand the influence of the distributive feeding on the phase transformation, the crystallization profiles along the axial position of the CT crystallizer were investigated in the steady state, as shown in Figure 7. Here, the GMP feed concentration and rotation speed were kept at 152.8 g/L and 300 rpm, respectively. The distribution ratio of the feed streams with feeding mode IV was fixed at 0.5: 0.44: 0.06. When using a mean residence time of 2.5 min, the crystal fraction profile revealed that feeding mode IV achieved complete phase transformation in all regions of the crystallizer. Because of the long regional mean residence time in the early region (region 1) of the crystallizer, the amorphous GMP precipitated in this region was completely converted to hydrate crystals,

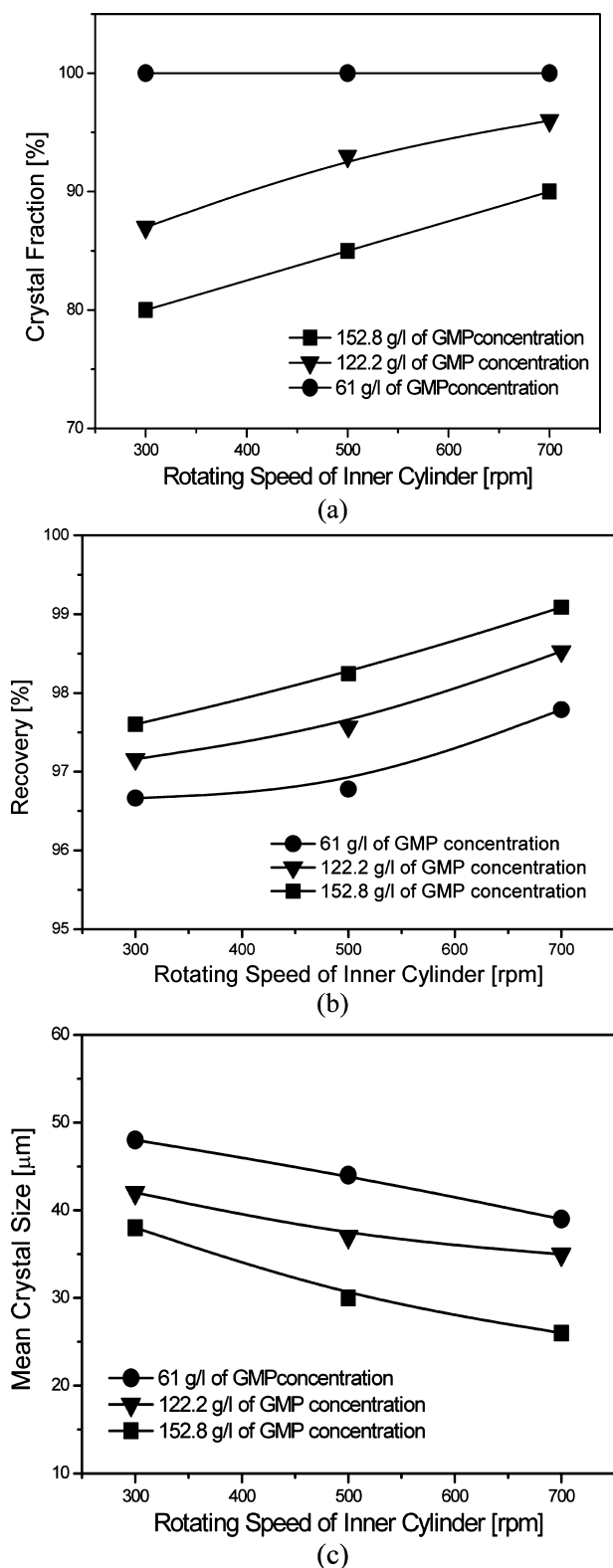


**Figure 6.** Influence of rotation speed of inner cylinder and GMP feed concentration on GMP phase transformation with feeding mode IV in steady state. The crystallization conditions were fixed at 25 °C temperature, 2-min mean residence time, 300 rpm rotation speed for inner cylinder, 152.8 g/L GMP feed concentration, 1:1 drowning-out ratio (GMP solution = methanol), and 0.5:0.44:0.06 distribution ratio ( $F_1/F_2/F_3$ ). (a) Crystal fraction, (b) recovery ratio of solid GMP, and (c) mean crystal size.

which in turn became seed crystals to accelerate the phase transformation of amorphous GMP in the next region. In the case of feeding mode I, however, due to the large amount of amorphous GMP and relatively short regional mean residence time in the early region (region 1) of the crystallizer, only about 50% of the amorphous GMP was converted to hydrate crystals. Even in the following regions in the crystallizer, not much more was transformed, so that the final crystal fraction in the product was only 70%. In contrast, the crystal fraction profile for feeding mode IV with a mean residence time of 1.6 min differed from the above-mentioned results. Because of the reduced regional mean residence time in the early region (region 1), not enough amorphous GMP was converted to hydrate crystals to accelerate the phase transformation of the amorphous GMP consecutively precipitated in the following regions, resulting in a decrease in the crystal fractions along the axial position of the crystallizer.

This influence of the multiple feeding mode on the phase transformation was also consistently reflected in the solute concentration profiles for the crystallizer (Figure 7b). With a mean residence time of 2.5 min with feeding mode IV, the solute concentration level in region 1 was as low as the solubility of the hydrate crystals (9.5 g/L), indicating a sufficient regional mean residence time for complete phase transformation in this region. However, the solute concentration level then increased along the axial position of the crystallizer, due to the consecutive GMP precipitation and reduced regional mean residence time in the consecutive regions. With the mean residence time of 1.6 min, the solute concentration profile was similar, yet the level was much higher than with a mean residence time of 2.5 min because of the incomplete phase transformation. However, with feeding mode I, the solute concentration level monotonically dropped along the axial position of the crystallizer. Because of the huge precipitation of amorphous GMP in region 1, the solute concentration level almost reached the solubility of the amorphous GMP (13.0 g/L), and then gradually reduced according to the phase transformation to hydrate crystals along the axial flow. Meanwhile, for all the feeding modes, the crystal size became larger along the axial position of the crystallizer, due to continuous growth via the phase transformation (Figure 7c). Therefore, the above profiles for the crystal fraction, solute concentration, and crystal size all clearly support the explanation provided in section 3.1 for the complete phase transformation in the CT crystallizer with feeding mode IV.

It is already well-known that Taylor vortex regimes, such as a laminar Taylor vortex, wavy vortex, quasi-periodic wavy vortex, weakly turbulent vortex, turbulent Taylor vortex, and turbulent flow, are determined based on the Taylor number relatively to the critical Taylor number that depends on the axial flow (axial Reynolds number).<sup>32–34</sup> That is, when increasing the axial Reynolds number, the critical Taylor number tends to increase. Thus, the Taylor vortex regime is stabilized at a fixed rotation speed of the cylinder, reducing the hydrodynamic effect of the Taylor vortex on the mass transfer and mixing. Therefore, using the Sherwood number (Sh) correlation in the Taylor vortex flow suggested by Strong and Carlucci,<sup>34</sup> the influence of the mean residence time and distributive feeding on the mass transfer rate in the present CT crystallizer was estimated, as shown in Figure 8. The mass transfer rate (Sh) was significantly diminished when decreasing the mean residence time (equivalent to increasing the axial Reynolds number). Interestingly, a short mean residence time of 1 min reduced

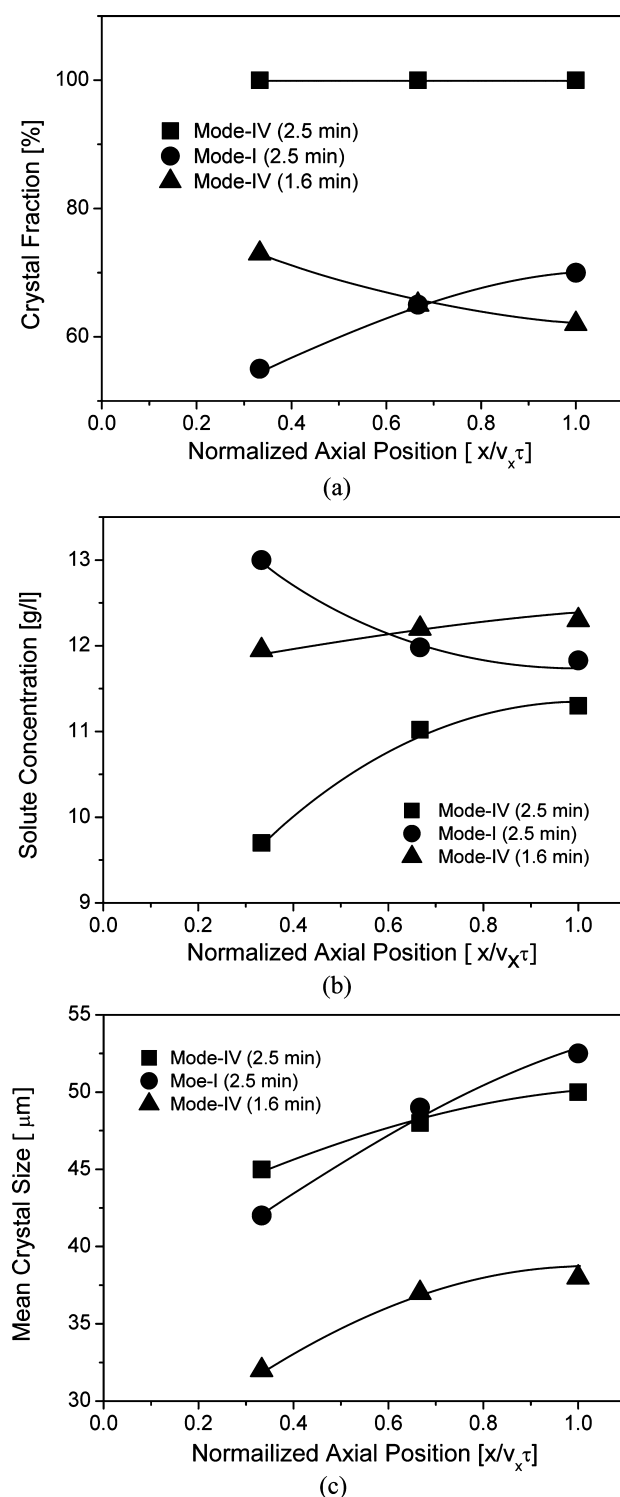


**Figure 7.** Typical axial profiles of phase transformation in steady state Couette–Taylor crystallizer. The crystallization conditions were fixed at 25 °C temperature, 300 rpm rotation speed for inner cylinder, 152.8 g/L GMP feed concentration, 1:1 drowning-out ratio (GMP solution: methanol), and 0.5:0.44:0.06 distribution ratio ( $F_1/F_2/F_3$ ). (a) Crystal fraction, (b) solute concentration, and (c) mean crystal size.

the mass transfer rate to about one-seventh of that with a long mean residence time of 60 min (Figure 8a), implying that the mean residence time of the CT crystallizer was not only an issue of the time period required for the phase transformation, but also an issue of the required mass transfer rate.

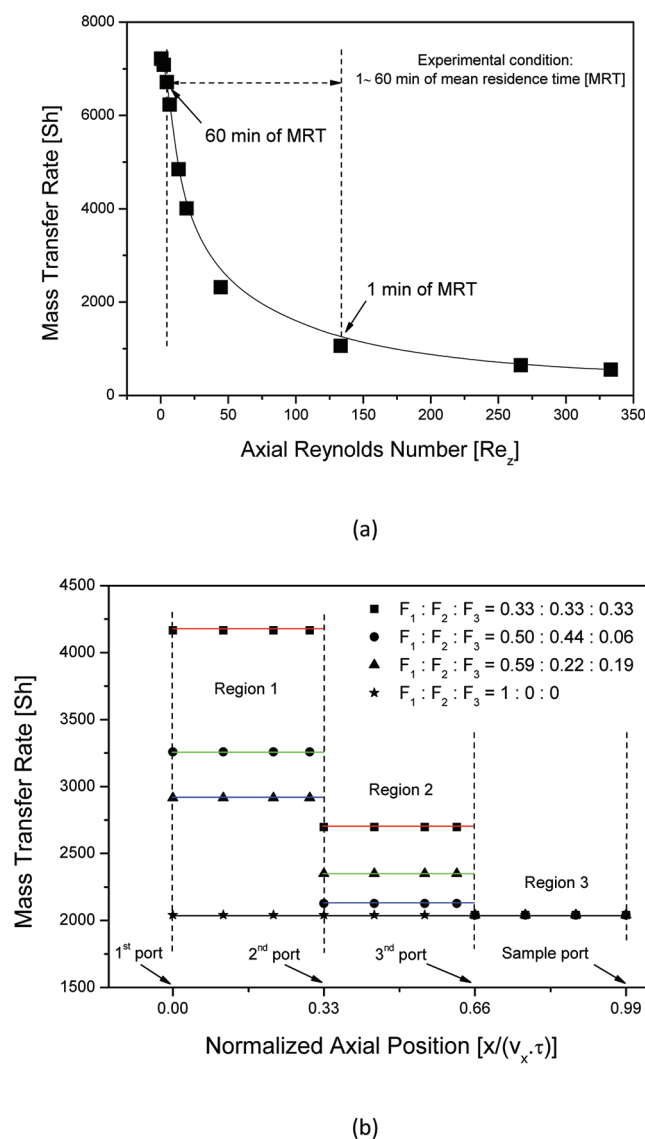


**Figure 8.** Influence of axial flow rate on mass transfer coefficient in Couette–Taylor crystallizer. (a) Estimation of mass transfer rate in Couette–Taylor crystallizer when varying axial Reynolds number and (b) profiles of regional mass transfer rates in Couette–Taylor crystallizer when varying distribution ratio of multiple feeding mode.

When using the distributive feeding modes, the regional mass transfer rate in the CT crystallizer was also predicted with the above Sherwood number correlation, as shown in Figure 8b. When compared with the simple feeding mode (feeding mode I), the regional mass transfer rate with feeding mode IV was much higher in the early region of the crystallizer, reflected by the lower axial Reynolds number, indicating that the distributive feeding was more effective for the phase transformation. It is interesting to note that an even distribution ratio of  $F_1:F_2:F_3 = 0.33:0.33:0.33$  appeared the most effective for the regional mass transfer. However, this was not exactly reflected to the actual experimental results of the phase transformation, due to a large amount of amorphous GMP precipitation in a later region (region 3), which meant the crystal fraction in the product was only 70% (Supporting Information-S2). Therefore, when designing an optimal feeding mode for phase transformation, the amount of amorphous GMP precipitated in the various regions in the CT crystallizer

should also be considered when determining the distribution ratio of the feed streams. In the present study, the optimal feeding strategy was established as a distribution ratio of  $F_1/F_2/F_3 = 0.5: 0.44: 0.06$  with feeding mode IV.

#### 4. CONCLUSION

The effects of multiple feeding modes in a continuous CT crystallizer were demonstrated via the phase transformation of GPM in drowning-out crystallization. When compared with the conventional simple feeding mode (feeding mode I), distributive feeding of the GMP solution and methanol antisolvent added some unique advantages to the phase transformation, including adjustment of the regional supersaturation level, regional residence time, and regional mass transfer rates in each segment of the crystallizer. For example, the distributive feeding provided a longer regional mean residence time in the early region (region 1) and a lower supersaturation level in the early region than those with the simple feeding mode. It also allowed less precipitation and more conversion of the amorphous GMP into hydrate crystals in the early region, and these crystals then became seeds for the phase transformation in the following regions in the crystallizer. However, the distributive feeding also created some disadvantageous conditions for the phase transformation, including the consecutive generation of amorphous GMP and a reduction of the regional mean residence time in the following regions in the crystallizer. Therefore, an optimized distribution ratio was required for the feeding in the different regions of the crystallizer, which was determined as  $F_1/F_2/F_3 = 0.5: 0.44: 0.06$  for feeding mode IV to achieve complete phase transformation with a 2.5 min of the mean residence time. Consequently, a multiple feeding strategy was found to be quite effective for producing hydrate GMP crystals in a continuous CT crystallizer without any serious trade-off as regards the crystal size and recovery. The multiple feeding strategy also provided a highly productive crystallization process for GMP, which was at least 2 times more effective than a CT crystallizer with simple feeding and 10 times more effective than a MSMR crystallizer.

#### ■ ASSOCIATED CONTENT

##### Supporting Information

The influence of multiple feeding on GMP phase transformation at various distribution ratios, and the definition of mean residence time of Couette–Taylor crystallizer with multiple feeding. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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##### Notes

The authors declare no competing financial interest.

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