

Influence of salt additives on phase transformation of guanosine 5-monophosphate disodium in anti-solvent crystallization

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ABSTRACT

The influence of sodium chloride (NaCl) as an additive on the anti-solvent crystallization of guanosine 5-monophosphate disodium (GMP-2Na) was investigated in continuous Couette–Taylor (CT) and batch mixing tank (MT) crystallizers. The anti-solvent crystallization initially precipitated amorphous solids of GMP-2Na, which then slowly transformed into hydrate crystals in the solution. However, the phase transformation of GMP-2Na was markedly promoted by the sodium chloride additive due to the common ion effect. While the normal phase transformation in the batch MT crystallizer required over 120 min of crystallization time without using the sodium chloride additive, the process was completed within 60 min when a small amount of the salt additive was added. The phase transformation was also significantly accelerated in the continuous CT crystallizer. Without using the sodium chloride additive, 7 min of the mean residence time was required for the production of 100% hydrate GMP crystals. However, when using the sodium chloride additive, a mean residence time of only 2 min was sufficient to completely transform the amorphous solids of GMP-2Na into hydrate crystals due to the common ion effect combined with the effective fluid motion of the Taylor vortex for the mass transfer.

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1. Introduction

The phase transformation during crystallization is an important process for producing polymorphic crystals used by the food additive, pharmaceutical, chemical, and biochemical industries. The crystallization of organic materials in a solution frequently exhibits polymorphic nucleation, where metastable crystals are first crystallized out and then transformed to stable crystals via re-crystallization. However, this phase transformation proceeds slowly, making it the most time-consuming process of crystallization. Therefore, to design an efficient crystallization process, many studies have already attempted to promote the phase transformation. [1–4]

The phase transformation in a solution is implemented via the simultaneous dissolution of metastable crystals and growth of stable crystals [5]. Thus, the hydrodynamic conditions of the suspension are considered an important influential operating factor for the phase transformation, as they dictate the mass transfer for the dissolution of metastable crystals and growth of stable crystals. Accordingly, a Taylor vortex was previously applied by the present authors to promote the phase transformation [5–7], where a periodic Taylor vortex was found to be highly effective for the phase transformation of guanosine 5-monophosphate

disodium (GMP-2Na) [5,6] and sulfamerazine (SMZ) [7]. Due to the strong and periodic toroidal flow of the Taylor vortex, the phase transformation of GMP-2Na was 5 times faster than that with a random turbulent eddy generated by impeller agitation [5,6]. The induction of stable crystals of SMZ was also significantly promoted by a Taylor vortex when compared with turbulent agitation [7]. Plus, the phase transformation of taltireline has been shown to improve when increasing the agitation speed [8].

Other crystallization operating conditions, such as the temperature, initial concentration, pH, seeding, and additives, have also been considered as influencing factors on phase transformation, where additives have attracted particular attention. According to Wang et al. [9], the phase transformation of α -glycine to γ -glycine was significantly accelerated when using sodium chloride as a salt additive. In this case, the phase transformation was completed within 3 h when adding 120 mg/ml of the salt additive, whereas it took more than 34 h without the salt additive. This experimental result originated from selective nucleation of γ -glycine, where the alignment of glycine molecules for γ -form nuclei was markedly promoted by the addition of the salt additive, thereby accelerating the nucleation of γ -glycine and enhancing the phase transformation. Meanwhile, Myerson et al. [10] demonstrated that the phase transformation of L-phenylalanine was markedly retarded when ammonium sulfate was used as a salt additive. Due to the high water affinity of the salt additive, the water solubility of the L-phenylalanine

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was reduced, resulting in a slow phase transformation. Thus, the total time for the complete phase transformation of the anhydrate form to the monohydrate form was extended to 19 h on adding the salt additive, whereas it was normally achieved within 9 h without the salt additive.

In the anti-solvent crystallization of GMP-2Na, amorphous solids are precipitated and then slowly transformed to the crystalline hydrate, which requires a long crystallization time for the complete phase transformation (about 9 h in the industrial crystallization process). Accordingly, the present study uses a salt additive to promote the phase transformation of GMP-2Na in anti-solvent crystallization. Using continuous and batch crystallization in a Couette–Taylor (CT) and mixing tank (MT) crystallizer, respectively, the influence of the salt additive on the phase transformation is also mechanistically investigated.

2. Theoretical background

For the Taylor vortex in the CT crystallizer, the mass transfer coefficient at the solid–liquid interface was estimated using the Sherwood (Sh) correlation as follows [11]:

$$Sh = 2 + 0.4Ta_p^{0.53}Sc^{1/3} \quad (1)$$

where the Sherwood number is defined as $Sh = kd_p/D_f$. Here, k is the mass transfer coefficient, d_p is the particle diameter and D_f is the diffusion coefficient of the solute. In addition, Ta_p and Sc are the particle Taylor number and Schmidt number, respectively, which are defined as $Ta_p = (\omega r_i d_p / \nu)(d/r_i)^{1/2}$ and $Sc = \nu/D_f$, respectively. Here, ω is the angular velocity of the inner cylinder of the CT crystallizer, r_i is the radius of the inner cylinder, ν is the kinematic viscosity of the solution, and d is the gap between the inner and outer cylinders.

Meanwhile, for the random turbulent fluid motion in the MT crystallizer, the mass transfer coefficient was estimated using the Sherwood number correlation as follows [12]:

$$Sh = 2 + 0.47 \left(\frac{\varepsilon^{1/3} d_p^{4/3}}{\nu} \right)^{0.63} Sc^{1/3} \quad (2)$$

where ε is the viscous energy dissipation of the turbulent fluid motion, as defined in Ref. [13].

The influence of the sodium chloride additive on the mass transfer was counted in terms of the dynamic viscosity (μ) and diffusion coefficient (D_f) of the solute, as defined below [13–15]

$$\mu = \mu_0 \left(1 + 0.0067 \times \sqrt{[NaCl]} + 0.0244 \times [NaCl] \right) \quad (3)$$

$$D_f = 7.4 \times 10^{-8} \frac{(\phi_s M_s)^{1/2}}{V^{0.6}} \left(\frac{T}{\mu} \right) \quad (4)$$

where μ_0 is the dynamic viscosity of the solution in the absence of sodium chloride (NaCl), ϕ_s is the association parameter and M_s is the molecular weight of the solution. In addition, V and T are the molar volume of the solute and absolute temperature, respectively. Combining Eqs. (3) and (4) with the Sherwood numbers (Eqs. (1) and (2)) then allowed the variation of the mass transfer coefficient according to the salt additive concentration to be estimated in both the CT and MT crystallizers.

3. Experiments

The raw guanosine 5-monophosphate disodium (GMP-2Na) hydrate (99.9% purity) was supplied by the CJ Company (Korea). The anti-solvent methanol (99.8% purity) and sodium chloride additive (NaCl, 99.5% purity) were purchased from the Duksan Company and Sigma-Aldrich Company, respectively. The GMP feed solution was prepared by dissolving the raw GMP-2Na in distilled water. A certain amount of the sodium chloride additive was then added to the GMP feed solution.

The Couette–Taylor (CT) crystallizer was composed of two co-axial cylinders: the inner cylinder was made of stainless steel and the outer one made of lucite acrylic plastic to allow observation of the Taylor vortex flow. The diameters of the inner and outer cylinders were 4.0 and 5.0 cm, respectively, and the length of the cylinder was 40 cm. Thus, the working volume of the crystallizer was 1.13 l. As shown in Fig. 1, the crystallizer was placed horizontally to eliminate any hydrostatic pressure. The injection ports for the GMP feed solution and methanol (anti-solvent) were located separately at the beginning of the outer

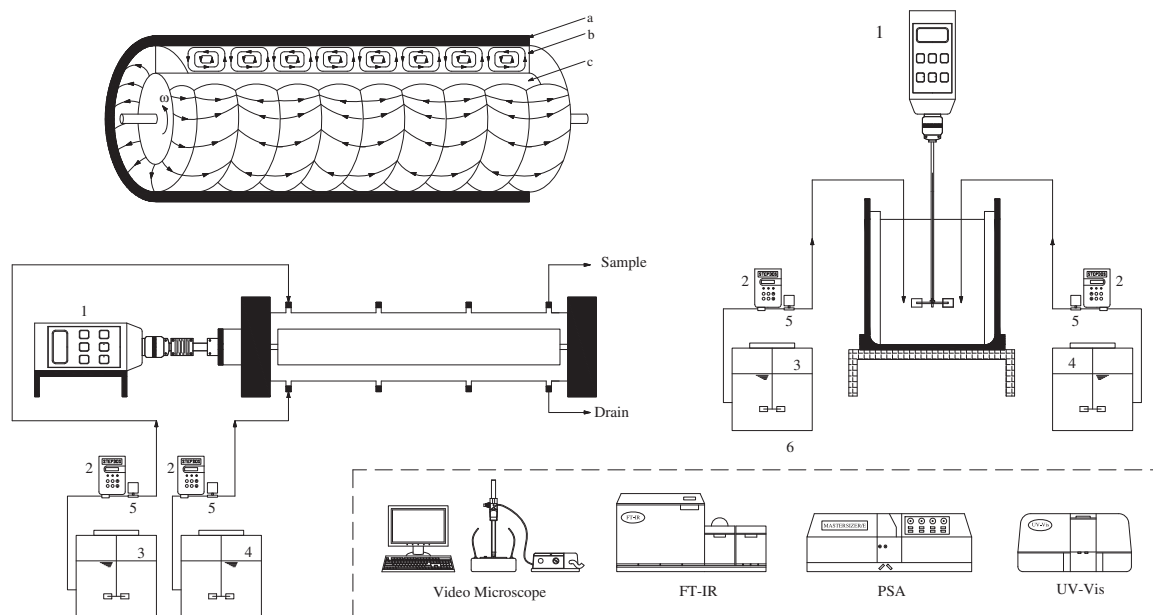


Fig. 1. Experimental setup for CT and MT crystallizers: (a) stationary outer cylinder, (b) rotating inner cylinder, and (c) Taylor vortex. 1. DC motor, 2. pumps, 3. GMP feed solution, 4. methanol solution, 5. damper, and 6. analytical instruments.

cylinder. The feed concentration and rotation speed of the inner cylinder were fixed at 150 g/l and 300 rpm, respectively. Meanwhile, the mixing tank (MT) crystallizer with a working volume of 500 ml was designed based on a standard Rushton tank [16], and was made of pyrex glass with a propeller-type impeller and baffles for effective mixing. Here, the feed concentration and agitation speed were fixed at 60 g/l and 600 rpm, respectively.

The CT crystallizer was used for the continuous crystallization of GMP-2Na, where the GMP feed solution and methanol (anti-solvent) were simultaneously and continuously injected at equal flow rates into the crystallizer that had been initially filled with distilled water. The MT crystallizer was used for the batch crystallization of GMP-2Na, where the GMP and methanol feed solutions were quickly mixed in the crystallizer. The crystallizations in the CT and MT crystallizers were run at room temperature (25 °C).

Samples of the product suspension were taken intermittently from both crystallizers and quickly filtered through 0.45 µm pore-size filter paper using a vacuum. The filtered GMP-2Na solids were then dried in a desiccator for one day to analyze the crystal fraction, shape, and size. Here, the crystal fraction of the GMP solid products was analyzed using FTIR (Perkin, System 2000, U.S.A.), as described in our previous study [5], the crystal shape and size were monitored using an optical microscope (IT System, Somatech, USA), the solid structures of the amorphous and hydrate GMP-2Na crystals were confirmed using XRD (MAC Science, M18XHF-SRA, CuK_α line, Japan) and a thermogravimetric analyzer (TGA), and the solute concentration was monitored using UV–vis spectroscopy (Jasco, V-570, USA).

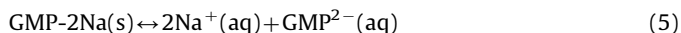
4. Results and discussion

4.1. Solubility of GMP

To understand the influence of the sodium chloride additive on the phase transformation of guanosine mono-phosphate di-sodium (GMP-2Na), the solubility of the GMP-2Na solids (amorphous solids of GMP-2Na and hydrate crystals) in the water–methanol mixture was measured according to the sodium chloride concentration. As shown in Fig. 2, the solubility of the

amorphous solids and hydrate crystals was monotonically reduced on increasing the sodium chloride concentration in the mixture. Due to the unstable structure of the amorphous solids, their solubility was always higher than that of the hydrate crystals across the whole range of sodium chloride concentrations, indicating a monotropic relationship between the two phases of GMP.

The reduction of the solubility when increasing the sodium chloride additive concentration was due to the common ion effect. That is, the GMP-2Na was equilibrated in the solution as described as below,



The solubility product of GMP-2Na can then be expressed as,

$$K_{SP} = a_{\text{Na}}^2 a_{\text{GMP}} = \text{constant} \quad (6)$$

The activity of the solution can be defined in terms of the ionic activity coefficient ($\gamma_{\pm}$) as $a_{\pm} = \gamma_{\pm} C_{\pm}$. Thus, the equilibrium concentration of GMP can be expressed as,

$$[\text{Na}^+]_{\text{eq}}^2 [\text{GMP}^{2-}]_{\text{eq}} = K_{SP} / \gamma_{\pm}^3 \quad (7)$$

Meanwhile, from the Debye–Hückel theory, the ionic activity coefficient is expressed as [1],

$$\log \gamma_{\pm} = -A |z_+ z_-| I^{1/2} \quad (8)$$

where A is a constant of 0.509 at 25 °C. Plus, z_+ and z_- are the valence of the cation and anion, respectively. Also, the ionic strength (I) is expressed as

$$I = \frac{1}{2} \sum C_i z_i^2 \quad (9)$$

Using Eqs. (7)–(9), the equilibrium concentration of GMP in the solution was estimated, as shown in Table 1. When increasing the sodium chloride additive concentration, the activity coefficient increased, resulting in a decreased solubility. Also, the initial supersaturation increased with the sodium chloride additive concentration. This prediction of the common ion effect on the solubility matched well with the experimental measurements (Fig. 2).

4.2. Phase transformation of GMP

The typical profiles for the phase transformation of GMP in the continuous CT and batch MT crystallizers are presented in Fig. 3. In the case of the CT crystallizer, the crystallization always reached a steady state after 5 times the mean residence time, regardless of the sodium chloride additive. (Fig. 3(a)) However, there was a marked difference in the crystal fraction and GMP concentration in the product stream when using the sodium chloride additive and not using it. Without the sodium chloride additive, the mean residence time of 2 min was not enough for the complete conversion of the amorphous solids of GMP-2Na into hydrate crystals in the crystallizer. Thus, the crystal fraction in the product suspension was only about 40%, indicating that 60% of the total solids of GMP-2Na in the product stream remained unconverted. According to our previous study, a mean residence time of at least 7 min is required for complete transformation in a CT crystallizer [5,6]. The GMP concentration in the product stream was measured as 11.3 g/l, which was even higher than the metastable solubility (10.2 g/l, solubility of the amorphous solid of GMP-2Na).

However, when using a small amount of the sodium chloride additive (0.47 g/l), the crystal fraction in the product suspension was 100%, even with a 2 min of the mean residence time, indicating that the phase transformation of the GMP-2Na was significantly promoted by the sodium chloride. As predicted in

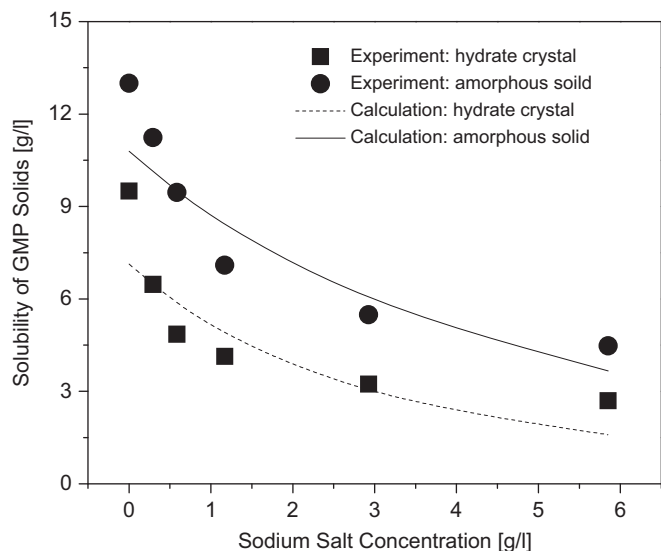


Fig. 2. Solubility of amorphous GMP solid and hydrate crystals according to sodium chloride additive concentration. The solubility prediction was based on the common ion effect. The composition of the water–methanol mixture was 50:50%.

Table 1Influence of sodium chloride additive on solubility C_{eq} [g/l], ionic activity coefficient ($\gamma_{\pm}$), initial supersaturation ($\sigma = C_{initial}/C_{eq}$), and mass transfer coefficient (k).

Operation conditions		Solubility C_{eq} [g/l]		Ionic activity coefficient ($\gamma_{\pm}$)	Initial supersaturation (CT) (σ)	Mass transfer coefficient k (10^5 m/s) in crystallizers	
NaCl [g/l]	$C_{initial}$ [g/l]	Experiment	Calculation			CT	MT
0	75	9.5	7.13	0.93	7.9	26.11	5.46
0.29	75	6.47	6.47	1.02	11.6	26.77	5.49
0.59	75	4.85	5.86	1.13	15.5	27.75	5.53
1.17	75	4.13	4.8	1.37	18.2	28.85	5.56
2.93	75	3.23	2.77	2.38	23.2	36.9	5.63
5.85	75	2.69	1.59	4.15	27.9	41.28	6.07

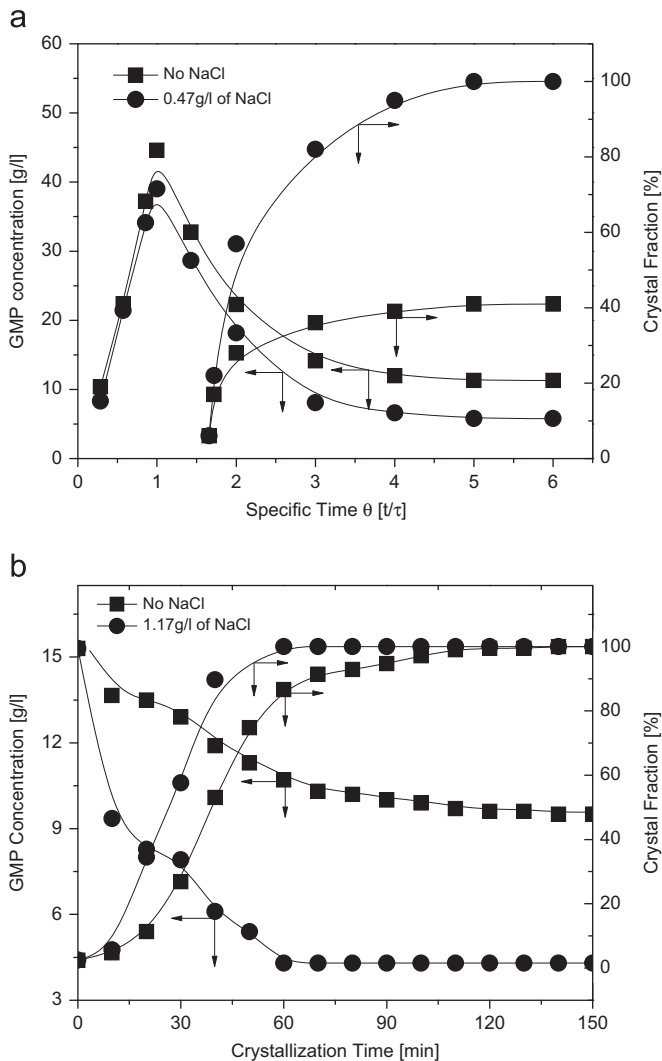
**Fig. 3.** Typical dynamic profiles of crystal fraction and solute concentration: (a) in CT crystallizer and (b) in MT crystallizer.

Table 1, the sodium chloride additive enhanced the mass transfer coefficient at the solid–liquid interface, contributing to the complete phase transformation with a short mean residence time (2 min) in the continuous CT crystallizer. Also, the GMP concentration in the product stream was low at 5.8 g/l, which was close to the stable solubility (5.7 g/l, solubility of the hydrate crystals), indicating the high efficiency of the CT crystallizer in recovering GMP-2Na crystals during the crystallization. This result was due to the promotion of the mass transfer and reduction of the stable solubility by the sodium chloride additive. A more detailed discussion will be included later in this section.

A similar effect of the sodium chloride additive on the GMP crystallization was observed in the batch MT crystallizer, as shown in Fig. 3(b). Without the salt additive, it took almost 120 min of crystallization time for the complete conversion of the amorphous solid into hydrate crystals. However, this crystallization time was reduced to 60 min when using the sodium chloride additive. It should be noted that the MT crystallizer had to be operated at a GMP feed concentration below 60 g/l, otherwise the amorphous solid suspension initially precipitated during the crystallization was too thick for the impeller to agitate the suspension.

The phase transformation of GMP solids during the crystallization was visually confirmed, as shown in Fig. 4. When using no salt additive, the product solid at the steady state in the CT crystallizer was a mixture of the amorphous solid and hydrate crystals (Fig. 4(a)). However, when using 0.47 g/l of the sodium chloride additive, the product solids at the steady state contained only hydrate crystals (Fig. 4(b)). In the MT crystallizer, when using no salt additive, a mixture of the amorphous solid and hydrate crystals was observed after 60 min of crystallization time and then complete conversion after 120 min (Fig. 4(c) and (d)). Yet, on using 1.17 g/l of the sodium chloride additive, pure hydrate crystals were observed even after 60 min of crystallization time (Fig. 4(e) and (f)). This observation was consistent with the abovementioned crystal fraction profile during the crystallization in the CT and MT crystallizers.

It should be mentioned that a comparable promotion of the phase transformation of GMP-2Na was achieved when using a sodium sulfate additive due to the same common ion effect. However, when using non-common ion additives, such as potassium chloride or calcium chloride, the phase transformation was extremely inhibited as the potassium and calcium ions replaced the sodium ions in the GMP-2Na to form an insoluble GMP-salt.

The influence of the sodium chloride additive on the crystallization of GMP is summarized in Fig. 5. In the CT crystallizer, the crystal fraction rapidly increased on increasing the sodium chloride concentration, and reached 100% with only a small concentration (0.47 g/l) of sodium chloride. Also, the GMP-2Na recovery was enhanced when the sodium chloride concentration was increased (Fig. 5(a)). In the MT crystallizer, the crystallization time for complete conversion also followed a similar behavior, as presented in Fig. 5(b). Table 1 shows the mass transfer coefficient was significantly enhanced on increasing the sodium chloride concentration, thereby promoting the phase transformation. Thus, the complete conversion of the amorphous solids into hydrate crystals was achieved within a short mean residence time (2 min) in the CT crystallizer and short crystallization time in the MT crystallizer (40 min). Furthermore, the influence of the sodium chloride additive on the mass transfer was higher in the CT crystallizer than in the MT crystallizer due to the effective fluid motion of the Taylor vortex in the CT crystallizer compared to the random turbulent eddy in the MT crystallizer. Thus, the mass transfer coefficient in the CT crystallizer was always 5 to 7-fold

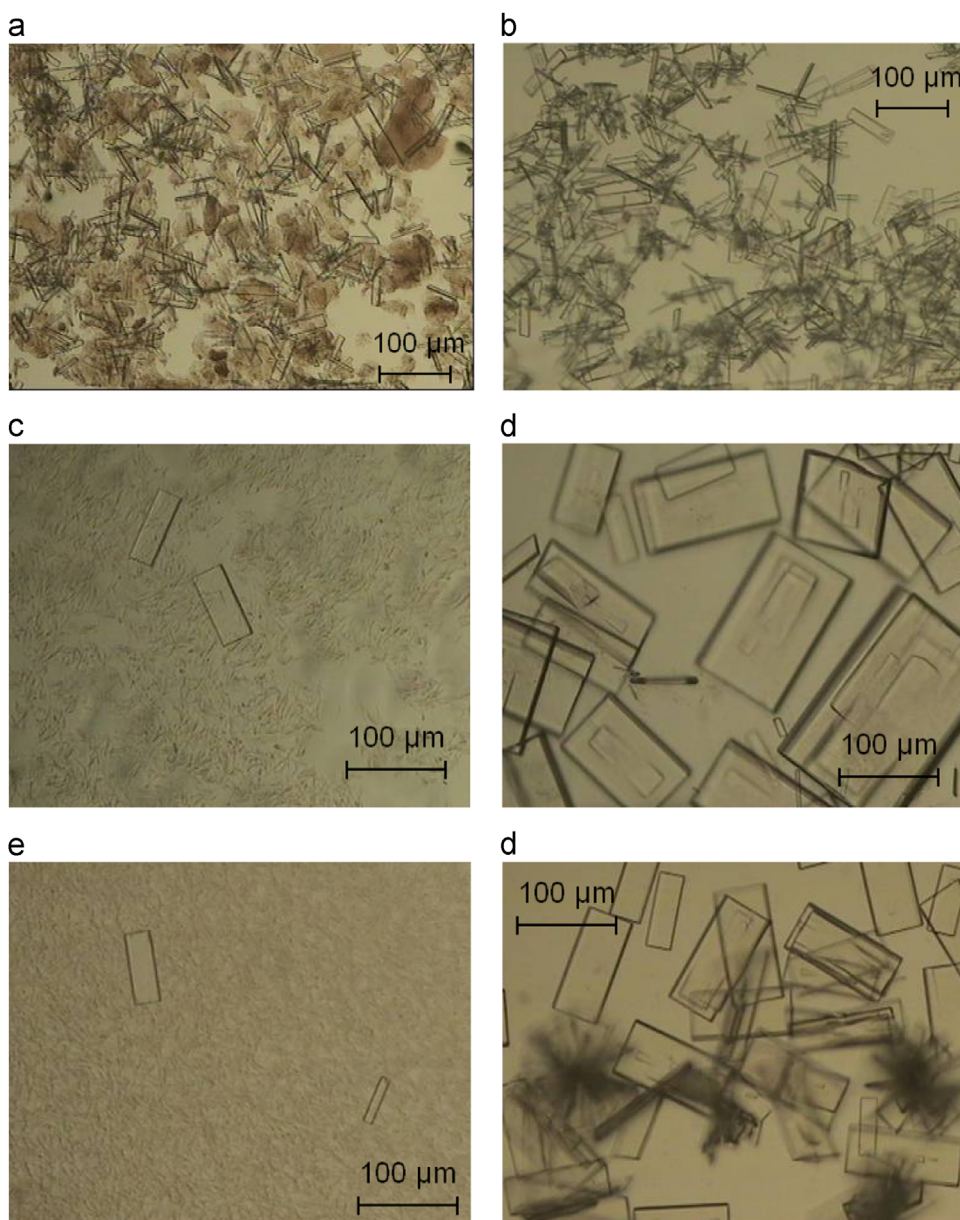


Fig. 4. Visual confirmation of sodium salt effect on phase transformation: (a) crystal habit of GMP solid products without sodium chloride additive in CT crystallizer at steady state, (b) crystal habit of GMP solid products with sodium chloride additive (0.47 g/l) in CT crystallizer at steady state, (c) crystal habit of GMP solid products without sodium chloride additive in MT crystallizer after 30 min, (d) crystal habit of GMP solid products without sodium chloride additive in MT crystallizer after 120 min, (e) crystal habit of GMP solid products with sodium chloride additive (1.17 g/l) in MT crystallizer after 20 min, and (f) crystal habit of GMP solid products with sodium chloride additive (1.17 g/l) in MT crystallizer after 60 min.

greater than that in the MT crystallizer, which is the main reason why the 2 min of mean residence time in the CT crystallizer was enough for the complete phase transformation in contrast to the over 40-min crystallization time in the MT crystallizer.

Fig. 5(c) shows the influence of the sodium chloride additive on the mean crystal size and shape of the hydrate crystals. When increasing the sodium chloride concentration, the mean crystal size was reduced due to the decreased solubility. Essentially, the lower solubility induced a higher supersaturation, as shown in Table 1, resulting in a higher nucleation of hydrate crystals. Thus, smaller sized crystals were obtained on increasing the sodium chloride concentration. Meanwhile, the shape factor of the crystals, defined as the length ratio between the long and short axis, remained invariant for the whole range of sodium chloride concentrations, implying a negligible influence of the sodium chloride additive on the crystal habit. Consequently, it can

be inferred that the effectiveness of the Taylor vortex combined with the common ion effect of the sodium chloride additive greatly accelerated the phase transformation of GMP-2Na, resulting in the surprisingly high crystallization productivity in the CT crystallizer.

5. Conclusions

Sodium chloride as an additive was found to have a significant influence on the phase transformation of GMP-2Na in anti-solvent crystallization. During crystallization, amorphous solids of GMP-2Na were initially precipitated and then slowly transformed into hydrate crystals via re-crystallization in the solution. Due to the common ion effect of the sodium chloride additive, the phase transformation was significantly enhanced. That is, the addition of the sodium common ions in the salt additive increased the

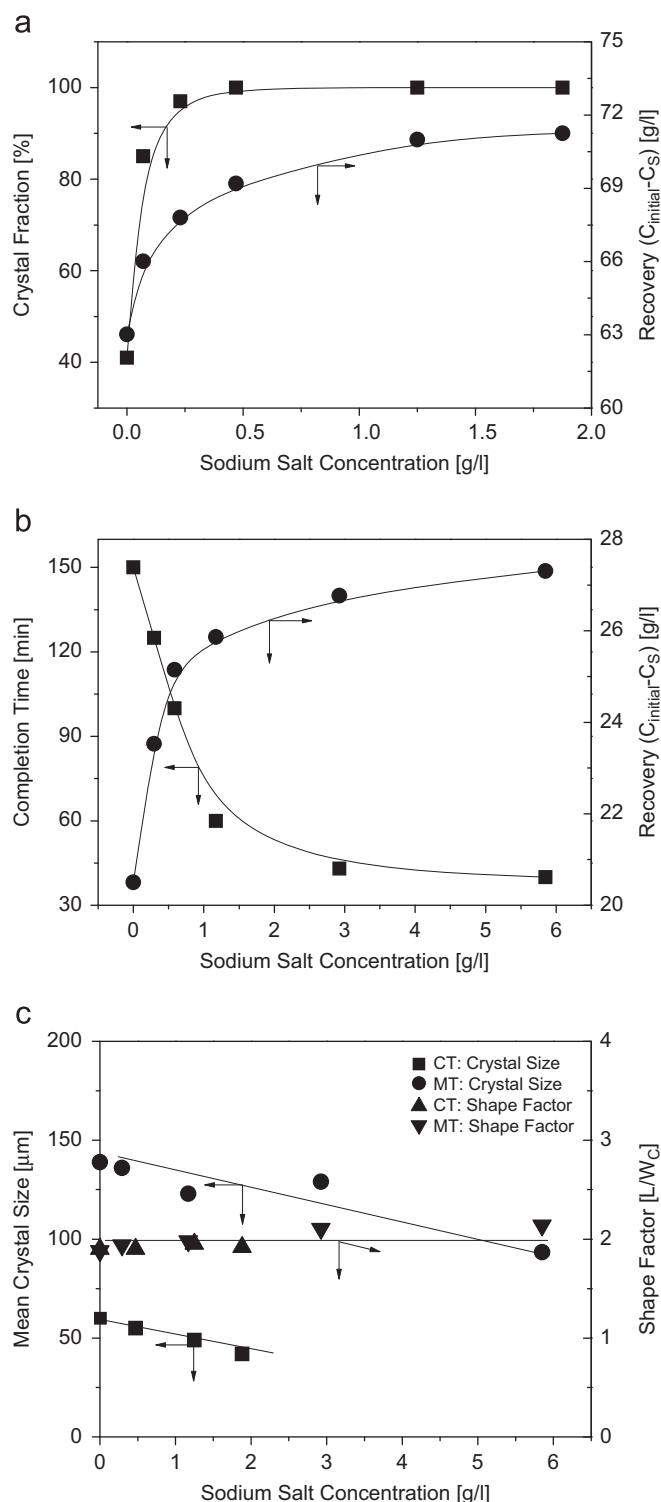


Fig. 5. Influence of sodium chloride additive on crystallization: (a) crystal fraction and recovery in CT crystallizer at steady state, (b) completion time and recovery in MT crystallizer, and (c) crystal size and shape factor in CT and MT crystallizers. Here, the crystal size and shape were measured at the steady state in case of the continuous CT crystallizer and at the completion time in case of the batch MT crystallizer.

activity of the solution, thereby reducing the solubility of the GMP. As a result, a relatively higher supersaturation was induced by the addition of the sodium common ions, resulting in a higher

nucleation of hydrate crystals. This provided large crystal interfacial areas for the phase transformation. In addition, the mass transfer rate for the phase transformation was also promoted by the sodium chloride additive. Consequently, the addition of sodium chloride accelerated the phase transformation at least 2.5 times in the CT crystallizer and 2.0 times in the MT crystallizer when compared to the phase transformation without using the salt additive. Finally, due to the highly effective fluid motion of the Taylor vortex for the mass transfer, the phase transformation in the CT crystallizer was much faster than that in the MT crystallizer where the random turbulent fluid motion was generated by impeller agitation. Thus, the beneficial combination of the Taylor vortex effect and common ion effect in the CT crystallizer meant that only a 2 min of mean residence time was enough for the complete phase transformation of the GMP.

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