Investigation of Operation Strategy Based on Solution pH for Improving the Crystal Quality Formed during Reactive Crystallization of L-Aspartic Acid

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ABSTRACT: The production of crystalline particles with a thick and low degree of agglomeration is required because the agglomerated crystals with thin primary particles, which are frequently formed during reactive crystallization, deteriorate the crystal size distribution (CSD) of the final product due to their fragile morphology. This study aimed to develop an operation strategy for improving the degree of agglomeration and thickness of crystalline particles in the reactive crystallization considering the effect of the solution pH using L-aspartic acid as an experimental system. The scanning electron microscopy observations showed that the thickness of primary particles which form agglomerated crystals could be increased by operating the crystallization under low solution pH conditions. In contrast, it was found that operating the crystallization under high solution pH led to a decrease in the nucleation rate of crystalline particles, which resulted in a decrease in the degree of agglomeration. Then, an operation method, that is, changing the addition method of feed solutions to overcome the trade-off between the thickness and degree of agglomeration, was proposed by considering the effect of solution pH. Consequently, crystalline particles with a narrow CSD could be successfully obtained using the proposed method due to the suppression of the agglomeration and increase of the thickness. Therefore, the development of the operation strategy based on the effect of the solution pH on the degree of agglomeration and thickness is important to produce crystalline particles with improved CSD in reactive crystallization.

1. INTRODUCTION

Crystallization is a key process in the production of crystalline particles. It enables the separation or purification of crystalline particles from different mixtures in the pharmaceutical industry.1–3 Recently, reactive crystallization has attracted considerable attention due to its many advantages.4–6 Notably, reactive crystallization is more energy-efficient than processes such as cooling7–9 or evaporative crystallization10–12 because the reactive crystallization provides crystalline particles by mixing the feed solutions without temperature change such as cooling or heating operation. Furthermore, reactive crystallization can play roles of the synthesis and purification processes, which allow a reduction of energy consumption, capital cost, and waste emission due to the simplified manufacturing process.13,14

Normally, the operation method during crystallization directly influences the quality of crystalline particles. Additionally, the quality of crystalline particles significantly affects the ease and efficiency of downstream processes such as solid–liquid separation and caking.15 In the case of reactive crystallization, previous studies reported that agglomerated crystals composed of thin primary particles are frequently formed due to random nucleation upon mixing of the feed solutions.16–18 It is known that thin primary particles are fragile, which deteriorates the crystal size distribution (CSD).19 In addition, the agglomerated crystals deteriorate CSD as a result of secondary particle enlargement.20 Thus, the development of an operation strategy for improving the quality of crystalline particles is important for the improvement of productivity and economic efficiency of the manufacturing process.

The crystal quality is influenced by supersaturation, which is the driving force for crystallization phenomena.21 Generally, supersaturation is defined as the difference between the apparent solute concentration, which means the operation
point on the phase diagram, and its equilibrium concentration during the crystallization. Additionally, the crystal quality is also influenced by the solution conditions. For instance, in the case of the cooling crystallization, crystal quality depends on the solution temperature, even if supersaturation remains the same because the temperature affects mass transfer or viscosity, which are key factors of the nucleation and crystal growth. On the other hand, in the case of reactive crystallization, the property of a crystallized substance such as solubility frequently depends on the solution pH. Thus, we expected that the solution pH will affect the crystal quality in reactive crystallization. Therefore, the effects of not only supersaturation but also solution pH should be considered for improving the crystal quality in reactive crystallization. Some previous reports focused on the effect of solution pH on the crystal quality of the organic compound having functionality for which solubility varies with pH such as amino acids in terms of crystallography. However, there are few reports that focus on proposing an operation strategy for the production of crystalline particles with a favorable crystal quality considering the effect of solution pH. The purpose of this present study is the development of an operation strategy based on the effect of the solution pH for improving the crystal quality in reactive crystallization. In this article, the release reaction of L-aspartic acid \[\text{HOOCCH}_2\text{CH(NH}_2\text{)COOH, L-AspH}\], which is reported as a chemical substance of reactive crystallization, was employed as an experimental system. Furthermore, an operation strategy considering the relationship between solution pH and crystal quality was proposed for improving the crystal quality in terms of the CSD.

2. EXPERIMENTAL SECTION

2.1. Materials and Methods. The L-aspartic acid sodium salt monohydrate \[\text{[NaOOCCH}_2\text{CH(NH}_2\text{)COOH-H}_2\text{O, L-AspNa, 97.0%, Wako Pure Chemical Industries, Ltd., Osaka, Japan]}\] and 0.5 M hydrochloric acid (HCl, Wako Pure Chemical Industries, Ltd., Osaka, Japan) for volumetric analysis were used as received without further purification. Distilled water, which was purified by a deionizer (RT-S23JO and RG-12, ORGANO Corporation, Tokyo, Japan), was used for the experiments.

Based on previous studies, which demonstrated that crystalline particles frequently agglomerated under these reactive crystallization conditions, the reaction between L-AspNa and HCl to produce L-AspH \((\text{eq 1})\) was used as the experimental system in this work. In this reaction, L-aspartic acid is the crystallized substance.

\[
\text{L-AspNa + HCl → L-AspH + NaCl} \tag{1}
\]

To investigate the effect of solution pH on crystal quality, the operation point which was determined by the theoretical concentration of L-AspH and initial solution pH was set under various solution pH values with same supersaturation.

The feed solutions were L-AspNa and HCl aqueous solutions. 30 mL of the L-AspNa aqueous solution was prepared by completely dissolving L-AspNa-H_2O, the amount of which was measured using an electronic balance (AUW220D Shimadzu Corporation, Kyoto, Japan), in water. 30 mL of the solution of HCl was prepared by mixing 15 mL of 0.5 M HCl with 15 mL of water.

Experiments were carried out in a double-jacketed glass crystallizer (407 mm inner diameter, 818 mm height), as shown in Figure 1.

The L-AspNa aqueous solution was poured into the crystallizer and stirred with a mechanical stirrer (FBL3000 DC, Shinto Scientific Co., Ltd., Tokyo, Japan) at 200 rpm using flat six-bladed steel disc turbine impellers. 30 mL of the prepared HCl aqueous solution was added into the crystallizer with stirring. The temperature of the solution in the crystallizer was kept at 303 K by circulating water through the jacket using a constant temperature water bath (NTT-1200, Tokyo Rikakakai Co., Ltd., Tokyo, Japan). The solution pH in the crystallizer was monitored using the pH meter (HM-30R and ELP-037, TOA DKK Co., Tokyo, Japan) and measured immediately after the addition of the HCl aqueous solution and then monitored at 5 min intervals. The employed experimental conditions are summarized in Table 1 and Figure 2. The total volume of the HCl aqueous solution added into the crystallizer was the same for each experimental condition. At the end of the crystallization process, a 1 mL suspension was collected from the crystallizer using a syringe. The crystalline particles in the suspension were collected using 0.45 μm membrane (Omnipore, Merck, Darmstadt, Germany) and dried in a vacuum oven (AVO-250, AS ONE, Osaka, Japan) for a half day.

2.2. Calculation of the Supersaturation. The supersaturation \(\Delta C\) of L-AspH, which is the driving force for crystallization phenomena, was determined using the following equation

\[
\Delta C = C_{\text{theoretical}} - C_S \tag{2}
\]

where \(C_{\text{theoretical}}\) is the theoretical concentration, while \(C_S\) refers to the saturated concentration at the solution pH immediately after the HCl aqueous solution was added and mixed with L-Asp aq. solution into the crystallizer (pH\(_{\text{initial}}\)). \(C_{\text{theoretical}}\) was calculated based on the concentration and mixing volume ratio of each feed solution. In this experimental system, L-AspNa and HCl react in a 1:1 molar ratio. In addition, the amount (moles) of HCl which was mixed was the same and less than that of L-AspNa under each experimental condition. Therefore, \(C_{\text{theoretical}}\) was the same for each experimental condition. \(C_S\) was calculated using the same method which is shown in the reference.

2.3. Definition of the Induction Time. In this experimental system, the solution pH changes due to the consumption of HCl as the reaction progresses. Thus, the induction time was evaluated as the time from the mixing of
the feed solution until the change in pH occurred. The time in which pH change occurred was determined by the intersection of the tangent line of the slope and the horizontal line extending pH$_{\text{initial}}$.

2.4. Definition of the Solution pH through the Time.
In this experiment, the solution pH changes over time during the crystallization due to the batch process. Thus, the amount of variation of the solution pH at time $t$ ($\Delta$ pH) was determined to investigate the effect of solution pH based on the initial solution pH in the mixture using the following equation

$$\Delta \text{pH} = \left( \text{pH}_t - \text{pH}_{\text{initial}} \right) / \text{pH}_{\text{initial}}$$ (3)

where pH$_t$ refers to the pH values of the mixture at time $t$ after the addition of the HCl aqueous solutions into the crystallizer.

2.5. Characterization of the Crystalline Particles.
The crystalline particles which were obtained at each experiment were observed by scanning electron microscopy (SEM) using the JEOL JSM model 6510 (JEOL Ltd., Tokyo, Japan).

Previous study$^{18}$ reported that L-Asp usually precipitates as the plate-like crystal. Thus, the thickness of the primary particles was evaluated as the length of the thinnest face, as shown in Figure 3a. The thickness was measured manually using 50 primary particles which are randomly selected from the SEM images to minimize the measurement error.

Additionally, the size of agglomerated crystals was measured as a Feret diameter (Figure 3b). The CSD was estimated from the Feret diameter of agglomerated crystals using the 50 agglomerated crystals from the SEM images.

The agglomeration behavior of crystalline particles for each experiment was estimated as a degree of agglomeration ($A_{\text{agg}}$). $A_{\text{agg}}$ was calculated using eq 4, which was reported in previous studies.$^{29,30}$

$$A_{\text{agg}} = 100\left( P_b^S + 4/3P_b^{LA} + 5/3P_b^{MA} + 2P_b^{HA} - 1 \right)$$ (4)

3. RESULTS AND DISCUSSION
3.1. Effect of the Solution pH on the Crystal Quality.
The SEM images of the crystalline particles obtained from each experiment are shown in Figure 5. It was found that agglomerated crystals were formed under all pH conditions. Thus, we confirmed that agglomeration occurred under each experimental condition in this reactive

Table 1. Experimental Conditions Based on Theoretical Concentrations Obtained by Mixing Feed Solutions$^{a}$

| run | $\text{L-AspNa aqueous solution}$ | $\text{HCl aqueous solution}$ | $\supersaturation \Delta C^b$ [mol/L] | pH$_{\text{initial}}^c$ [-] |
|-----|-------------------------------|-------------------------------|--------------------------------------|-----------------------------|
| 1   | 0.25                          | 30                            | 0.086                                | 2.9                         |
| 2   | 0.50                          | 30                            | 0.089                                | 3.8                         |
| 3   | 1.0                           | 30                            | 0.089                                | 4.2                         |

$^a$It was assumed that no crystalline particles precipitated. $^b$The theoretical value calculated from the concentration and the mixing ratio of feed solutions. $^c$The measured value immediately (within 10 s) after HCl aqueous solution was added to the crystallizer.

**Figure 2.** Solubility plot for L-AspH and operation point for the experimental conditions used in runs 1–3.

**Figure 3.** SEM images and measurement of the (a) thickness of the primary particles and (b) Feret diameter of agglomerated crystals.

In the above equation, $P_b^S$ is the probability of the agglomerated crystals; S, single crystal; LA, low agglomeration; MA, medium agglomeration; and HA, high agglomeration. Previous studies have shown that the $A_{\text{agg}}$ should be equal to zero when none of the crystals are agglomerated. To calculate each probability according to the method proposed by Ohyama et al.$^{18}$ in this work, the formed crystalline particles were classified into four different categories on the basis of the number of primary particles ($N$) in the agglomerated crystal (Figure 4).

**Figure 4.** Classification of the $A_{\text{agg}}$ for L-AspH on the basis of the number of primary particles ($N$) in the agglomerated crystals.

The $A_{\text{agg}}$ was also measured manually using more than 50 agglomerated crystals which are randomly selected from the SEM images for each experiment.
crystallization. The $A_{gg}$ was quantitatively estimated for each experiment condition (Figure 6).

It was determined that the thickness of primary particles for the agglomerated crystals decreased with an increase in the solution pH. Additionally, the size of the agglomerated crystals formed in each experiment was several-hundred micrometers. Thus, we revealed that the solution pH affected the thickness of primary particles for the agglomerated crystals, such as $A_{gg}$.

Notably, operating the reactive crystallization under low pH conditions resulted in the formation of thick particles. From these results, we found a certain correlation between solution pH and crystal quality such as $A_{gg}$ and thickness. According to the previous study, the production of nonagglomerated crystals with prism-like shapes is desired to improve CSD.31 Therefore, operating the reactive crystallization of L-AspH under high pH condition positively affected the $A_{gg}$ of the obtained crystalline particles (Figure 6). On the other hand, operating the reactive crystallization under low pH conditions is desired in terms of improving the thickness (Figure 7). Hence, these results indicated that the $A_{gg}$ and thickness of the crystalline particles in the reactive crystallization exhibit a trade-off relation with the solution pH from a viewpoint of improving CSD.

### 3.2. Effect of the Solution pH on Induction Time

The effect of the solution pH on induction time for the precipitation of crystalline particles was investigated to elucidate the relationship between the solution pH and $A_{gg}$ in the reactive crystallization. Figure 8 shows the change in the induction time as a function of solution pH.

![Figure 5. SEM images of the crystalline particles obtained under different pH values (a−c) 2.9, (d−f) 3.8, and (g−i) 4.2.](image1)

![Figure 6. Effect of the solution pH on $A_{gg}$ of the obtained crystalline particles.](image2)

![Figure 7. Relationship between the solution pH and thickness of primary particles for the agglomerated crystals.](image3)

![Figure 8. Dependence of the induction time on the solution pH for L-AspH crystalline particles.](image4)
It was found that the induction time decreased with a decrease in the solution pH. It is known that the induction time is related to the nucleation rate of crystalline particles in the solution.\textsuperscript{32} Specifically, when the induction time is short, the nucleation rate is high. Additionally, the nucleation rate increases with an increase of the density of nuclei during the nucleation process in solution. Typically, agglomeration easily occurs when the number of nuclei during the nucleation process increases. Therefore, this result suggests that the improvement of the $A_{gg}$ under high pH conditions was due to a decrease of the number of nuclei during the nucleation process. Accordingly, it was suggested that controlling the solution pH during the nucleation process is important to improve the $A_{gg}$ of the crystalline particles in the reactive crystallization.

### 3.3. Operation Strategy for the Improvement of CSD.

As discussed in Section 3.2, the $A_{gg}$ is influenced by the solution pH during the nucleation process. This means that to reduce the $A_{gg}$, the solution pH immediately after mixing the feed solutions should be high. Moreover, the thickness of primary particles for the agglomerated crystals could be improved by operating the reactive crystallization under low pH conditions. This means that conventional methods that do not consider the solution pH (runs 1–3) are not suitable for overcoming the revealed relationship and obtaining crystalline particles with favorable properties from the viewpoint of CSD. Accordingly, it was suggested that controlling the solution pH after mixing the feed solutions would induce nucleation and crystal growth under favorable pH conditions. Thus, we proposed an operation strategy which modifies the addition method of the HCl aqueous solution to induce nucleation and crystal growth processes under different solution pH values. Specifically, half of the total volume of the HCl aqueous solution was added to the mixture in the crystallizer at once. Then, the remaining HCl aqueous solution is added gradually to enhance the crystal growth under low pH conditions. Additionally, the proposed method was performed using 30 ml of 1.0 M HCl aqueous solution and 30 mL of 0.25 M l-AspNa aqueous solution, which is the same experiment condition of run 3.

As the result, the pH value after the complete addition of HCl aqueous solution of the proposed method was 4.5, which corresponded to that of run 3. Figure 9 shows the SEM images of the crystalline particles obtained using the proposed method.

The thickness of the primary crystal for the agglomerated crystals obtained using the proposed method was approximately 10 μm, which was 2 times higher than the thickness of primary particles for the agglomerated crystals formed under high pH conditions (run 3). Furthermore, it was clearly shown that the developed approach yielded crystalline particles exhibiting lower $A_{gg}$ (run 1) compared to the low pH condition. Additionally, the crystalline particles obtained by the proposed method had a lower $A_{gg}$ (49%) than those formed under low pH conditions (run 1, $A_{gg}$ = 100%). This suggested that operating the reactive crystallization under high pH conditions in the initial term led to the suppression of the number of nuclei during the nucleation process, which caused a decrease in the $A_{gg}$. Figure 10 shows the variation of the solution pH ($\Delta$P) of the mixture that is calculated by eq 3 as a function of normalized time $\tau$ which is a ratio of the elapsed time to the total time of crystallization during the reactive crystallization using each method.

**Figure 10.** $\Delta$P of the solution in the crystallizer as a function of normalized time for each method.
other methods. Moreover, number-based coefficient variation (CV) of the CSD (22%) for the crystalline particles obtained by the proposed method was lower than that obtained by conventional methods (approx. 35%). These results indicated that controlling the solution pH during reactive crystallization effectively overcame the trade-off between the thickness and \( A_{gg} \) to solution pH. Therefore, it was suggested that the development of an operation strategy considering the influence of the solution pH on the crystal quality during nucleation and growth processes is significantly important to obtain crystalline particles with improved properties.

4. CONCLUSIONS

In conclusion, in the present study, an effective strategy to improve the crystal quality obtained by reactive crystallization of L-AspH was investigated by considering the effect of the solution pH. The SEM observation showed that the crystal quality was strongly influenced by the solution pH during reactive crystallization. Specifically, we found that there is a trade-off between the \( A_{gg} \) and thickness in the solution pH. Furthermore, evaluation of the induction time for the precipitation of the crystalline particles from solution demonstrated that the \( A_{gg} \) depended on the solution pH during the nucleation process. From these results, we proposed an operation strategy, in which the nucleation and growth were induced under different pH conditions to overcome the trade-off between the \( A_{gg} \) and thickness of the crystalline particles. Consequently, we successfully improved the \( A_{gg} \) and thickness of the crystalline particles and refined their CSD. Thus, we expect that the investigation of an operation strategy considering the effect of solution pH during the crystallization is an effective approach to produce crystalline particles with favorable properties in reactive crystallization.

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Notes
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■ NOMENCLATURE

L-AspH, L-aspartic acid; L-AspNa, L-aspartate sodium; HCl, hydrochloric acid; \( A_{gg} \), degree of agglomeration; SEM, scanning electron microscopy; CSD, crystal size distribution; CV, coefficient of variation; \( \Delta \text{pH} \), amount of variation for solution pH based on initial solution pH in a mixture; \( \tau \), normalized time

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