Development of Simultaneous Control Method of Quality and Crystallization Operability for Crystalline Particles

(結晶粒子群の品質と晶析操作性の同時制御法の開発)

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Contents

Chapter 1

Introduction

1-1. Background

Crystalline particles have been produced as products in the various fields such as pharmaceutical, food and fine chemicals. The crystallization method is the main method to obtain the crystalline particles. By using this method, the target component can be separated from the mixture and the crystalline particles are produced. When the crystallization method is used, it is typically important to control the degree of supersaturation which is the driving force of crystallization phenomena. This is because the all crystal qualities are strongly dependent on the crystallization phenomena. The specification of crystalline particles is determined by the crystal quality. Therefore, the controlling for degree of supersaturation has been attempted to obtain the crystalline particles with the desired specification.

There are the various crystal qualities such as polymorph, purity, crystal morphology and particle size. And, the desired specification is different in the various fields and products. For example, in food industry, it is necessary to focus the purity form the viewpoint of safety. In addition, in pharmaceutical industry, it is important to consider the polymorph from the viewpoint of solubility or stability. As described above, there is the crystal quality which should be focused in terms of the product quality in each fields and products. On the other hand, the operability is required from the viewpoint of production process when the crystalline particles are produced. The crystal quality affects not only the product quality but also the operability of production process. This is because the time and the energy in the production process are varied by the difference of operability of crystalline particles. For example, when the crystal morphology with large aspect ratio (such as Needle-like, Fiber-like and so on) is formed, it is possibility that the all processes stop by causing the problem in the crystallization or the downstream process. In addition, when the crystalline particles with small particle size are obtained, the long filtration time and the large filtration energy are needed in filtration process. As mentioned above, there is also the crystal quality which should be focused in terms of the operability in each fields and products.

Fig. 1-1 shows the relationship between the degree of supersaturation and the specification of crystalline product. As shown in **Fig. 1-1**, the degree of supersaturation separately affects the each crystal qualities. Generally, when the crystalline particles were produced as product, it is important to take into account the product quality and the operability of production process in various fields and products. Therefore, two crystal qualities (related to product quality and operability) should be particularly focused.

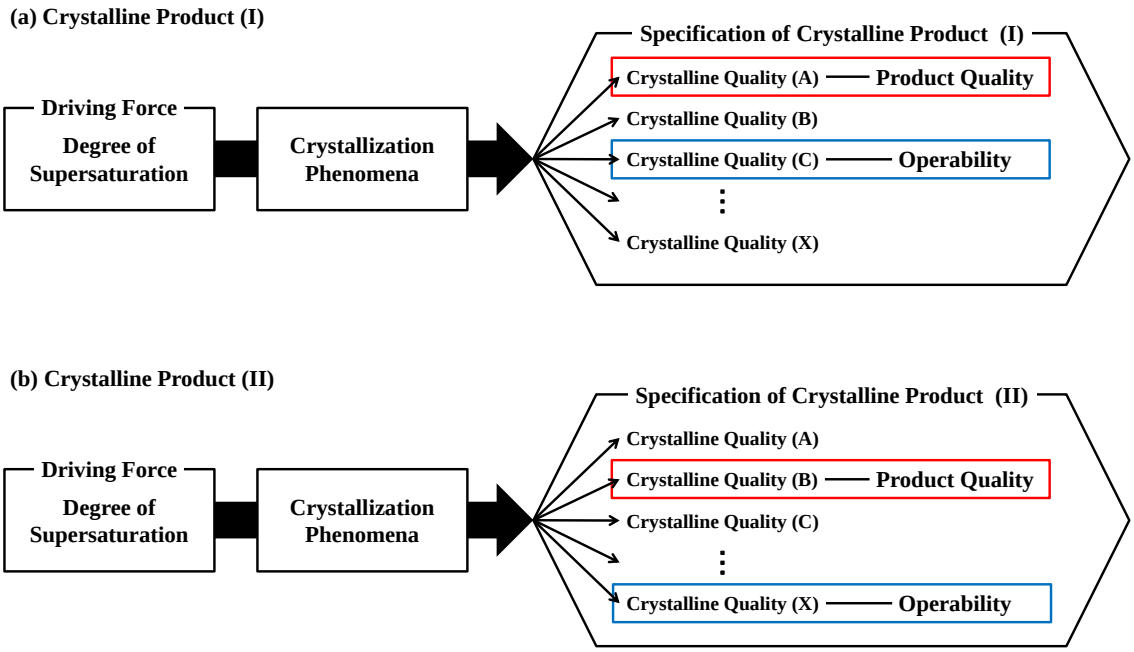

Fig. 1-1 Relationship between the degree of supersaturation and the specification of crystalline product

Then, there is possibility that the product quality and the operability cannot be satisfied simultaneously because it is not always possible to satisfy the operability by using the degree of supersaturation which is set to satisfy the product quality. At this time, there is trade-off relationship between the product quality and the operability. The cause of this problem is the trade-off relationship between two crystal qualities. In this present study, the crystal quality (related to the product quality) was defined as the product crystal quality (*PC*) and the crystal quality (related to the operability and having the trade-off relationship with *PC*) was defined as the operability crystal quality (*OC*), respectively. **Fig. 1-2(A)** is the conceptual diagram which shows the relationship between the *PC* and the degree of supersaturation (*PC*-*S*) and the relationship between the *OC* and the degree of supersaturation (*OC*-*S*). As shown in **Fig. 1-2(A)**, it is considered that these profiles have the trade-off relationship because there is trade-off relationship between the *PC* and the *OC*. When the low degree of supersaturation is selected, the high *PC* and the low *OC* are obtained as shown in **Fig. 1-2(B)**. Also, the low *PC* and the high *OC* are obtained as shown in **Fig. 1-2(D)** when the high degree of supersaturation is selected. So, the *PC* and the *OC* cannot be

satisfied simultaneously by only setting the degree of supersaturation. Therefore, as shown in **Fig. 1-2(C)**, the middle degree of supersaturation was selected in order to obtain the middle *PC* and the middle *OC* in many cases.

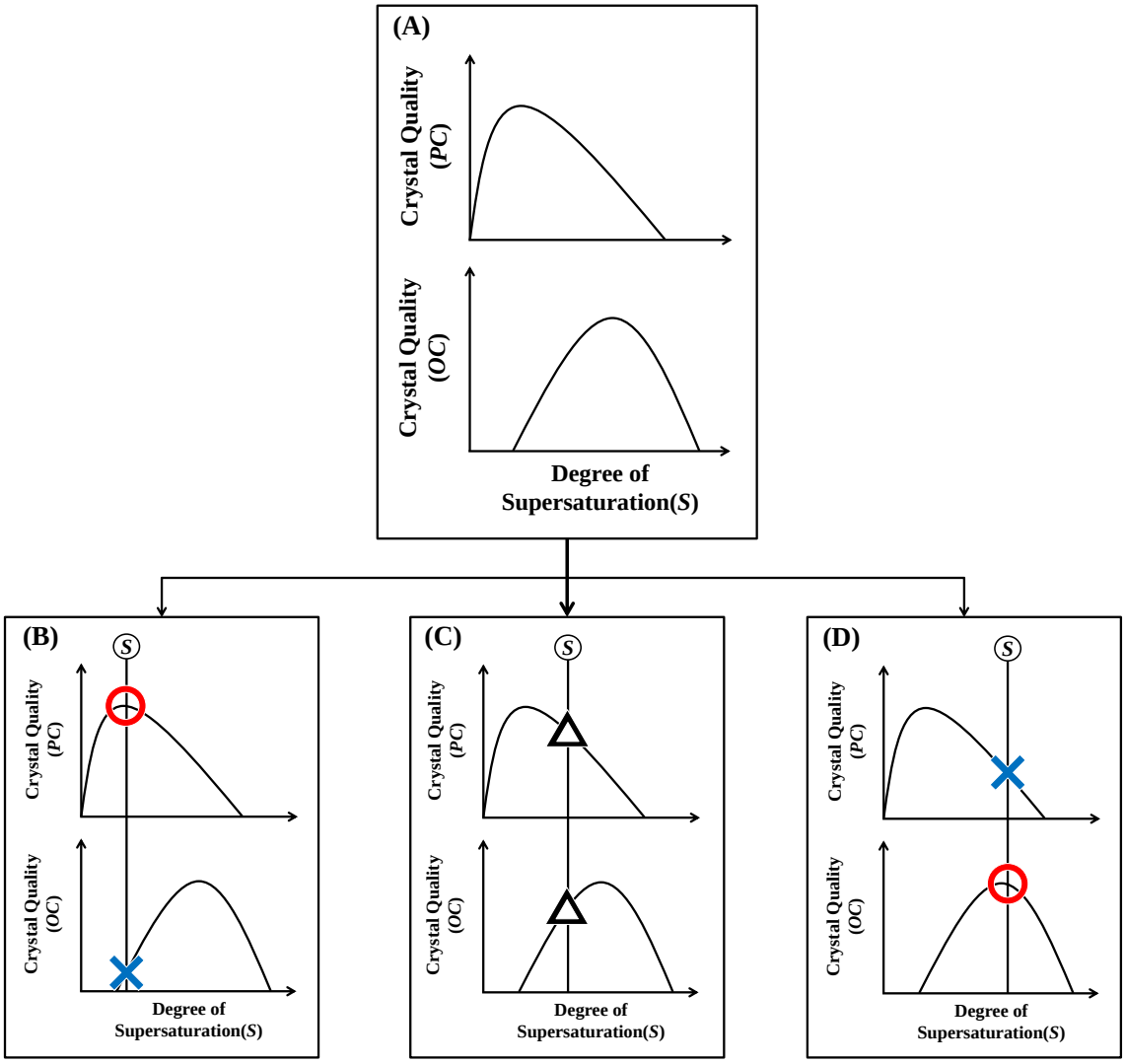

Fig. 1-2 Conceptual diagram of the relationship *PC*-*S* and *OC*-*S* (A); Low degree of supersaturation (B); Middle degree of supersaturation (C); High degree of supersaturation (D)

1-2. Control of crystal quality

In this section, some previous studies are introduced. In these previous studies, in order to control the crystal qualities, the degree of supersaturation was changed by using various methods. Polymorph and Purity were selected as *PC* and Crystal Morphology and Particle size were selected as *OC*, respectively. In addition, apart from them, it is also important to make the crystal quality uniform and many researchers have examined the new method in order to obtain the uniform quality. So, some previous studies which is focused on the uniform quality are introduced.

1-2-1. Polymorph and Purity (*PC*)

When the different polymorph is compared, the physical property of crystal is different. So, the polymorph strongly affected the physical property of crystal such as melting point, solubility, stability and so on. From the viewpoint of solubility and stability, polymorph is particularly important in the field of pharmaceutical and food (Martínez *et al.*, 2011). Therefore, in order to select the polymorph with higher solubility or higher stability, evaluation method of physical property has been investigated.

Karabas *et al.* examined the polymorph screening of Risperidone. It was important that identification of the polymorph of active pharmaceutical ingredient (API) in a pharmaceutical tablet because different polymorphs exhibit different physicochemical properties. The polymorph A of risperidone in film coated commercial tablets was identified by utilizing the IR spectroscopy, Raman spectroscopy and X-ray powder (XRPD). Furthermore, the stability of polymorph A was also examined during the manufacturing process. From the experimental results, the XRPD was only technique that could be used for identifying the presence of risperidone A in film coated commercial tablets. In addition, it was proved that the polymorph A of risperidone was stable during the manufacturing process and after a storage period of 2 years.

Hamdi *et al.* examined the polymorph screening of Indomethacin. It was well known that Indomethacin has polymorph and solvate. It was important to characterize the various polymorphs and solvates because the solubility and bioavailability were changed in the case of different polymorph or different solvate. In this previous study, seven kinds of solvate (Acetone, benzene, dichloromethane, tetrahydrofuran, propanol, chloroform and diethyl ether) were obtained and investigated. These chemical formulas were presented by using the thermogravimetric analysis and the X-ray patterns

in powder, and the behavior of desolvation was recorded and determined by DSC. In addition, the temperature and the melting enthalpy were measured, and the polymorph which was obtained by this method was estimated.

Li *et al*. examined the polymorph screening of investigational drug. As these screening results, two anhydrous polymorphs (Forms I and II) and two monohydrates (Forms III and IV) were found. Furthermore, as shown in **Figure 1-2-1**, the stability relationship between the four polymorphs was found by using thermal analysis, dissolution rate measurements and X-ray powder diffraction. The relationship of thermodynamic stability was estimated by using the melting data for Form I and Form II, and van't Hoff plot for Form III and Form IV. As a result, Form I was the more stable anhydrous form and Form III was the more hydrate form, respectively. Therefore, in this previous study, it was reported that anhydrous Form I should be selected in order to achieve the development of the investigational drug. In order to decide the desired polymorph, physical property of polymorph has been evaluated by using the various analysis methods.

When the desired polymorph was determined by using the physical property evaluation, as a next step, the control method was necessary to obtain the desired polymorph. So, the various control factors were investigated in order to develop the control method of polymorph. Also, it was important that the desired polymorph was obtained with high purity.

Kitamura *et al.* examined the control method of polymorph for 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid (BPT). BPT has three polymorphs (Forms A, B and C) and two solvated crystals (BH (water) and D (methanol)). The anti-solvent crystallization of BPT was carried out by addition of water to BPT-methanol solution. As the result, under the condition of 323 K, polymorph of BPT was strongly dependent on the water addition rate and the initial concentration of the BPT solution. In addition, the precipitation of BH was independent on the water addition rate. Under the condition of lower water addition rate and higher initial concentration of the BPT solution, BH-form and D-form were obtained. Furthermore, under the condition of low initial concentration of the BPT solution, the transformation from the BH-form to the A-form was observed and, under the condition of high initial concentration of the BPT solution, the transformation from the BH-form and D-form to the A-form was observed. And, under the condition of much higher initial concentration of the BPT solution, the D-form transformed to the BH-form and this transformation rate decreased with the addition rate. Therefore, it was reported that the polymorph of BPT was influenced by the water addition rate and the initial concentration of the BPT solution. As described above, the anti-solvent addition rate and the initial concentration of drug-good solution were focused as the control factor.

Crisp *et al.* examined the polymorph of lactose. When the water was used as good solvent, alpha lactose monohydrate ($L\alpha \cdot H_2O$) was usually obtained. In addition, it was reported that the transformation from $L\alpha \cdot H_2O$ to $L\beta$ was observed. In this previous study, the crystallization of lactose was carried out by using the mixture of water and polar solvent as anti-solvent. Then, the five kinds of polar solvents were used. As the experimental results, it was found that the large $L\alpha \cdot H_2O$ crystals formed under the condition of low anti-solvent content. And, when the anti-solvent content increased, the small needle-like crystal became more dominant. This result was valid because the transformation from $L\alpha \cdot H_2O$ to $L\beta$ was confirmed by using the XRD analysis. Therefore, in the case of lactose crystal, it was considered that the polymorph of lactose was dependent on the anti-solvent content. In this previous study,

the anti-solvent content was focused as the control factor of polymorph.

Cashell *et al.* examined the polymorph of L-glutamic acid. The crystal of L-glutamic acid was crystallized by cooling from 80 ℃ to 45 ℃. As the experimental results, it was found that the α-form of L-glutamic acid was stably obtained under the condition of rapid agitation speed and slow cooling speed. In addition, β-form of L-glutamic acid was stably obtained under the condition of rapid cooling speed with agitation and under the condition of slow cooling speed without agitation. From these results, two hypotheses were presented. It was difficult to transfer from α-form to β-form because the agitation inhibited the nucleation of β-form on the surface of α-form crystal. Furthermore, since α-form crystal which was obtained under the condition of slow cooling speed with agitation was small and poorly formed, the nucleation of β-form was difficult on the surface of α-form crystal. From these considerations, it was suggested that β-form crystal was stably obtained under the condition of rapid cooling speed with agitation. In this previous study, the cooling speed and agitation speed were focused as the control factor of polymorph.

Chen *et al.* examined the effect of surfactant on the polymorph of calcium carbonate ($CaCO_3$). In this previous study, sodium dodecyl sulfate (SDS) and hexadecyl (trimethyl) azanium bromide (CTAB) were used as the surfactant. These surfactants were used to mediate the nucleation and growth of calcium carbonate crystals. Furthermore, the mixture of these surfactants was investigated. Under the condition of the concentration of SDS (0.1 mM), the polymorph of calcium carbonate changed from pure vaterite to pure aragonite with increase of the ratio of CTAB to SDS. The various morphologies of vaterite and aragonite were obtained. This is the reason why the surface energy of the sample was changed by different adsorption of these surfactants. In this previous study, the kind of surfactant was focused as the control factor of polymorph.

Beckmann examined the effect of different solvent on the polymorph of Abecarnil. In this previous study, the isopropyl acetate and the methanol were selected as solvent. During the crystallization of abecarnil, induction times, crystal size distribution and polymorphism were observed. As the observation result, it was found that the abecarnil has different three polymorphs (A, B, and C). In addition, the dominant polymorph was dependent on the primary solvent used. However, when the degree of supersaturation increased, the polymorph was independent on the solvent and the method. In this way, the primary solvent used was focused as the control factor of polymorph.

Takiyama *et al.* examined the polymorph of Indomethacin in anti-solvent crystallization. In this previous study, anti-solvent crystallization was carried out in ternary system (Indomethacin – Acetone - Heptane). Then, anti-solvent feed rate was focused in ternary phase diagram. From experimental results, it was reported that the stability of polymorph in the solution was changed not only with temperature but also with composition of the mixed solvent in the case of Indomethacin. In this previous study, the composition of the mixed solvent was focused as the control factor of polymorph.

Qian *et al.* examined the relationship between the polymorph and purity of L-glutamic acid. In this previous study, L-aspartic acid was used as impurity. From the experimental results, it was found that the content of L-aspartic acid in β-form crystal was higher than that in α form. Furthermore, the purity of L-glutamic acid crystal decreased with the increase of the content of β-form in the final product. In this way, in order to decide the desired polymorph, the purity of L-glutamic acid crystal was evaluated.

Miki *et al.* examined the effect of crystal size on the inclusion of mother liquor about potassium chloride (KCl). In this previous study, the sodium chloride (NaCl) was used as impurity tracer. So, the purity was evaluated by using the content of NaCl in KCl crystal. In addition, the two different impellers (Rushton and Maxblend) were used for this crystallization. From the experimental results, it was found that the inclusion ratio in KCl crystals was dependent on the type of impeller and the residence time. In this previous study, the type of impeller and the residence time was focused as the control factor of purity.

Saito *et al.* examined the total volume of liquid inclusions per crystal for sodium chloride (NaCl). In this previous study, the crystal size of NaCl and the type of operation method (the batch crystallization and the continuous crystallization) were selected as operation conditions. And, the purity was evaluated by using the total volume of liquid inclusions per crystal. As the experimental results, it was found that the total volume of liquid inclusions per crystal increased with the crystal size. Furthermore, the purity of NaCl crystal was changed by the difference of the type of operation method. In this previous study, the crystal size and the type of operation method were focused as the control factor of purity.

Promraksa *et al.* examined the effect of crystallization conditions on the dextran partition coefficient. In this previous study, the purity of sugar crystal was evaluated by using dextran partition coefficient. Also, the concentration of impurity and temperature were selected as the operation conditions. The obtained experimental

results were organized by using the relative supersaturation and the mean growth rate, respectively. From these experimental results, it was found that the dextran partition coefficient increased with the relative supersaturation and the mean growth rate. Furthermore, the value of dextran partition coefficient became high under the condition of high temperature and low concentration of impurity.

Miki *et al.* (potassium dihydrogen phosphate) and McLachlan *et al.* (Urea) examined the effect of the agglomeration on the purity, respectively. In the case of the potassium dihydrogen phosphate (KDP), the purity of KDP crystal was evaluated by using the inclusion ratio of mother liquor. In this previous study, in order to measure the inclusion ratio of mother liquor sodium dihydrogen phosphate (SDP) was added as the impurity tracer. Also, the residence time was selected as the operating conditions. As the experimental results, the inclusion ratio increased with the crystal size which increased with the residence time. Furthermore, from the observation results, it was reported that the inclusion ratio was strongly dependent on the agglomeration ratio.

As described above, the various control factors were focused in order to control the polymorph and purity which was one of the crystal qualities. **Table 1-1** shows the summary of these previous studies. As shown in **Table 1-1**, from the viewpoint of driving force, it could be considered that the degree of supersaturation was controlled by changing the control factor in these previous studies.

Table 1-1 Previous studies for the crystal quality related the product quality (*PC*) such as polymorph and purity

Previous Study (*PC*)	Crystallization Method	Control Factor	Crystal Quality
Kitamura *et al.*	Anti-solvent crystallization	Anti-solvent addition rate Initial concentration of drug-good solution	Polymorph
Crisp *et al.*	Anti-solvent crystallization	Anti-solvent content	Polymorph
Cashell *et al.*	Cooling crystallization	Cooling speed Agitation speed	Polymorph
Chen *et al.*	Reaction crystallization	Kind of surfactant	Polymorph
Beckmann	Anti-solvent crystallization	Kind of primary solvent	Polymorph
Takiyama *et al.*	Anti-solvent crystallization	Composition of the mixed solvent	Polymorph
Qian *et al.*	Cooling crystallization	Kind of polymorph	Purity
Miki *et al.*	Cooling crystallization	Type of impeller Residence time	Purity
Saito *et al.*	Cooling crystallization	Crystal size Type of operation method	Purity
Promraksa *et al.*	Cooling crystallization	Temperature Concentration of impurity	Purity
Miki *et al.*	Cooling crystallization	Agglomeration ratio	Purity
McLachlan *et al.*	Cooling crystallization	Cooling speed Concentration of impurity	Purity

1-2-2. Crystal morphology and Particle size (*OC*)

Since the micromeritic properties of crystalline particles was strongly dependent on the crystal morphology or the particle size, it was important to control these crystal qualities. Therefore, in many previous studies, the various control factors were reported.

Takiyama *et al.* examined the effect of the degree of supersaturation and the initial supersaturation ratio on the crystal morphology. In ternary system (NaCl – Water – Ethanol), anti-solvent crystallization was carried out. The degree of supersaturation and the initial supersaturation ratio were set by using the ternary phase diagram. As the experimental results, the different crystal morphology was formed. In addition, it was found that rod-like crystal and plate-like crystal were mainly formed under the condition of low initial supersaturation ratio. On the other hand, cube-like crystal was mainly formed under the condition of high initial supersaturation ratio. In this previous study, the degree of supersaturation and the initial supersaturation ratio were focused as the control factor of crystal morphology.

Veesler *et al.* examined the effect of additive on the crystal morphology of gibbsite ($Al(OH)_3$). When the gibbsite crystal was obtained from the pure solution, crystal morphology of gibbsite was plate-like. Then, crystalline particles were obtained as agglomerates. In this previous study, four kinds of polycarboxylic acid were selected as additive. When the oxalic acid was selected, the morphology of gibbsite crystal was plate-like although the growth of (1 0 1) face and (1 1 2) face were promoted. On the other hand, when the DL-malic acid, tartaric acid or tartronic acid was selected as additive, the crystal morphology of gibbsite was needle-like since the growth of (1 0 1) face and (1 1 2) face were promoted. From these results, it was found that the crystal morphology of gibbsite crystal was changed by the difference of polycarboxylic acid. It was reported that the crystal morphology was changed because the growth of crystal face was inhibited by the additive. In this way, the kind of additive was focused as the control factor of crystal morphology.

Puel *et al.* examined the crystallization mechanism of acicular or needle-like crystals. The four kinds of organic molecules (Irbesartan, Product 2, Hydroquinone and Product 4) were investigated. From the observation results, the various mechanisms of nucleation and growth were found by the increase of supersaturation. In the case of Irbesartan, the top faces do not grow under the condition of lower supersaturation. On the other hand, in the case of Hydroquinone, the surface appearance was changed with the increase of supersaturations. In this previous study,

the effect of supersaturation on the crystal morphology was focused in order to prevent the formation of acicular or needle-like crystals.

Davey *et al.* examined the habit of succinic acid grown from different solvents. Succinic acid crystals were found to be plate-like when grown from aqueous solution. However, needle-like crystals were found from isopropanol solution. Morphological changes due to solvent effects were reported. {020} plane is dominant when crystals were grown from vapor phase and on the other hand, {100} plane with slower growth rate becomes important when crystals were grown from solution. This was the result of strong interaction of carboxylic acid group on {100} plane with the polar solvent. Also, at the same supersaturation ratio, crystal growth was slower in isopropanol compared to the crystal growth in water. It was considered that larger isopropanol molecule was more effective in inhibition of crystal growth. In this way, in this previous study, the kind of solvate was focused as the control factor of crystal morphology.

Gu *et al.* examined the crystal growth morphology of ginsenoside compound K solvates. In this previous study, the solvent effect on the crystal habits was investigated. Firstly, the single crystal structures of two solvates (acetone–water solvate, monohydrate) were obtained by using the single crystal X-ray diffraction. Secondly, crystal habits of ginsenoside compound K were predicted by using BFDH and AE models. Finally, it was reported that the obtained crystal habits were in good agreement with experimental results. In this way, in order to reveal the crystal growth morphology, the various methods were used. In other words, the control factor of crystal morphology was investigated by using the modeling.

Kim *et al.* examined the aggregation mechanism of cerium carbonate. In this previous study, the crystal of cerium carbonate was obtained by using reaction crystallization. Then, the sonication and turbulent agitation were used. From experimental results, it was found that the aggregation and agglomeration occurred simultaneously during the crystallization. Furthermore, crystal aggregation was involved with the physical adhesion of crystals. Finally, it was reported that the aggregation or the agglomeration during the crystallization could be prevented by using the sonication.

Ouyang *et al.* examined the effect of chondroitin sulfate A (C_4S) on the growth and aggregation of calcium oxalate monohydrate (COM) crystals. From the experimental results, it was found that the crystal growth was inhibited by the addition of C_4S. Furthermore, the aggregation of COM crystals was prevented. As the results, the COM crystal was obtained as the hexagonal prisms and three dimensional rhombus prisms. Therefore, the crystal morphology of COM was changed by preventing the

aggregation. In this previous study, the presence of additive was focused as the control factor of crystal morphology.

Tang *et al.* examined the effect of gallic acid on the morphology and growth of hydroxyapatite crystals. In this previous study, the hydroxyapatite crystal was obtained by mixing $CaCl_2$ and KH_2PO_4. Then, the crystallization time and the presence of gallic acid were selected as operating factor. After 14 days, since the polymorph was independent on the presence of gallic acid, the hydroxyapatite was obtained in both groups. However, it was reported that their morphologies were completely different. From these experimental results, the presence of gallic acid was strongly dependent on the crystal morphology of hydroxyapatite. In this previous study, the presence of additive was focused as the control factor of crystal morphology.

Slavin *et al.* examined the effect of the composition of the mixed solvent on the morphology of γ-form. In this previous study, the various solvents were used for the anti-solvent crystallization. As the experimental results, it was found that the morphology of the γ-form was not changed by the difference of solvent type. However, it was reported that the growth rates of the faces were changed with supersaturation. In this previous study, the solvent type was focused as the control factor of crystal morphology.

Martino *et al.* attempted to produce the spherical propyphenazone crystals by an agglomeration technique using a three solvents system. In this previous study, the best propyphenazone solvent (ethyl alcohol), non-solvent (demineralized water) and bridging liquid (isopropyl acetate) were selected after the various solvents were tested. As the experimental results, the spherical propyphenazone crystals were obtained. In this previous study, the agglomeration method was focused in order to change the crystal morphology.

Kecka *et al.* attempted to produce the drug nanocrystals in order to present the universal formulation approach for poorly soluble drugs. In this previous study, the drug nanocrystals were produced by using the bottom up techniques (precipitation). Then, the effect of homogenization on the the mean diameter was observed. From the experimental results, it was found that the mean diameter of the drug nanocrystals decreased with the increase of the homogenisation cycle. In this previous study, the homogenisation cycle was focused as the control factor of particle size.

Varughese *et al.* attempted to prepare the γ-Indomethacin (IMC) by using the supercritical anti-solvent (SAS) technique. In this previous study, the concentration, the pressure and the temperature were selected as the operating conditions in order to change the particle size. From the experimental results, the significant change in

particle size was dependent on these operating conditions. In this previous study, the concentration, the pressure and the temperature were focused as the control factor of particle size.

Ikegami *et al.* examined the spherical agglomerates of steroid KSR-592. In this previous study, these spherical agglomerates were prepared in liquid with a bridging liquid. From the experimental results, it was revealed that the growth rates of primary crystals and agglomerates increased with the temperature and/or the reduction of the agitation speed. It was reported that the growth of primary crystals in the spherical agglomerates could be explained by the mechanism of crystallization and fusion. In this way, the temperature and the reduction of the agitation speed were focused as the control factor of particle size.

Tanaka *et al.* attempted to control the crystal shape and particle size of glycine by using the Liquid–liquid interfacial crystallization. In this previous study, the crystallization was carried out on the interface forming two separate phases of aqueous solution and organic solvent. From the experimental results, it was found that the particle size of glycine was strongly dependent on the droplets conditions and the concentration of glycine solution. In this previous study, the droplets conditions and the concentration of glycine solution were focused as the control factor of particle size.

Yue *et al.* attempted to synthesize the spherical $Ni_{1/3}Co_{1/3}Mn_{1/3}(OH)_2$ agglomerates by using the co-precipitation method in the presence of ammonia. In this previous study, the spherical $Ni_{1/3}Co_{1/3}Mn_{1/3}(OH)_2$ agglomerates was prepared by using reaction crystallization. As the experimental results, it was found that the size of spherical agglomerates increased with the reaction time. Furthermore, the mean single crystal grain size was also dependent on the reaction time. In this previous study, the reaction time was focused as the control factor of particle size.

Yadav *et al.* examined the effect of different polymers on the spherical agglomerates of cefuroxime axetil (CFU). In this previous study, emulsion solvent diffusion (ESD) method was used. From the experimental results, it was found that the surface morphology of the spherical agglomerates was changed and that of micronization was achieved by using the polymer. In this way, the additive was focused as the control factor of particle size.

Kluge *et al.* examined the emulsion crystallization of phenanthrene through super critical fluid extraction of emulsions (SFEE). In this previous study, the crystallization of phenanthrene occurred by the solvent extraction from oil in water emulsions through dilution. Then, the temperature was particularly focused as the operating conditions. As the experimental results, it was found that the average

median x50 of the particle size distribution increased with the temperature. In this previous study, the temperature was focused as the control factor of particle size.

As described above, the various control factors were focused in order to control the crystal morphology and particle size which were one of the crystal qualities. **Table 1-2** shows the summary of these previous studies. As shown in **Table 1-2**, from the viewpoint of driving force, it could be considered that the degree of supersaturation was controlled by changing the control factor in these previous studies.

Table 1-2 Previous studies for the crystal quality related the operability (*OC*) such as morphology and particle size

Previous Study (*OC*)	Crystallization Method	Control Factor	Crystal Quality
Takiyama *et al.*	Anti-solvent crystallization	Degree of supersaturation Initial supersaturation ratio	Morphology
Veesler *et al.*	Reaction crystallization	Kind of additive	Morphology
Puel *et al.*	Cooling crystallization	Supersaturation	Morphology
Davey *et al.*	Cooling crystallization	Kind of solvate	Morphology
Gu *et al.*	Modelling	Supersaturation	Morphology
Kim *et al.*	Reaction crystallization	Agglomeration	Morphology
Ouyang *et al.*	Cooling crystallization	Presence of additive	Morphology
Tang *et al.*	Reaction crystallization	Presence of additive	Morphology
Slavin *et al.*	Anti-solvent crystallization	Solvent type	Morphology
Martino *et al.*	Anti-solvent crystallization	Agglomeration method	Morphology
Kecka *et al.*	Precipitation	Homogenisation cycle	Particle size
Varughese *et al.*	Supercritical anti-solvent technique	Pressure Temperature	Particle size
Ikegami *et al.*	Spherical agglomeration method	Reduction of the agitation speed Temperature	Particle size
Tanaka *et al.*	Liquid–liquid interfacial crystallization	Droplets conditions Concentration of glycine solution	Particle size
Yue *et al.*	Co-precipitation method	Reaction time	Particle size
Yadav *et al.*	Emulsion solvent diffusion method	Additive	Particle size
Kluge *et al.*	Supercritical fluid extraction of emulsions	Temperature	Particle size

1-2-3. Uniform quality

As described above, in order to control the various crystal qualities which were involved with the product quality (*PC*) or the operability (*OC*), the various control factors were focused. On the other hand, it was important to make these crystal qualities uniform. For example, the solubility and the dissolution rate of crystal were changed when the polymorph or the particle size was not uniform. So, it could be considered that the uniform quality is one of the crystal qualities.

Dombrowski *et al.* attempted to present the microfluidic process in order to produce the crystals of controlled size. In this previous study, the crystallization of lactose monohydrate was carried out in the monodisperse drops which were segmented by the mother liquor. Furthermore, the drop size and the initial supersaturation were selected as the operation conditions in order to control the mean crystal size. As the experimental results, it was found that the very narrow CSD of lactose monohydrate crystal under the condition of the high initial supersaturation when the single crystal exists in drop. In this previous study, the initial supersaturation was focused in order to make the particle size uniform.

Qiu *et al.* examined the method of spray drying in order to prepare the nano energetic materials with novel properties. In this previous study, cyclo trimethyl enetrinitramine (RDX) crystal was targeted. From the experimental results, it was reported that the size distribution of RDX crystals was strongly dependent on the droplet size. In this previous study, the droplet size was focused in order to make the particle size uniform.

Igarashi *et al.* examined the development of the mL-scale continuous crystallizer in order to produce small crystals with the narrow size distribution. In this previous study, anti-solvent crystallization was carried out for the glycine and the L-alanine. Then, the average residence time was selected as the operating conditions. From the experimental results, it was found that the particle size of the obtained crystal was smaller and more uniform than that of the crystal obtained by the conventional crystallizer because the short residence time is achieved by using the mL-scale continuous crystallizer. In addition, the size distribution was changed by the difference of the mixing ratio of anti-solvent. In this previous study, the residence time and the mixing ratio of anti-solvent were focused in order to make the particle size uniform.

Kucher *et al.* examined the precipitation of barium sulfate from aqueous solutions of barium chloride and sodium sulfate in a continuous Y-Mixer in order to avoid the mixing effect. In this previous study, the initial supersaturation and the

initial ratio R = C_{Ba}^{2+}/C_{SO4}^{2-} were selected as the operating conditions. From the experimental results, it was found that the obtained particle size distribution was dependent on the variation of the free lattice ions. Furthermore, it was reported that the smaller mean particle diameter was obtained under the condition of low supersaturation. In this way, the initial supersaturation and the variation of the free lattice ions were focused in order to make the particle size uniform.

Jongen *et al.* attempted to develop the continuous segmented flow tubular reactor (SFTR) in order to overcome the homogeneity and scale-up problem. In this previous study, the suspension was segmented by using the non-miscible fluid. From the experimental results, it was found that the narrower size distributions, the better particle morphology and the polymorph selectivity could be achieved by using the SFTR. In this previous study, the development of the new crystallizer is attempted to achieve the homogeneity of crystal quality.

Gonda *et al.* examined the effect of the solution concentration on the particle size distribution in the case of the anti-solvent crystallization with the ultrasonic spray nozzle. In this previous study, this anti-solvent crystallization was carried out at the liquid–liquid interface. From the experimental results, it was found that the particle size distribution of composite particles was strongly dependent on the solution concentration. The narrow size distribution was obtained under the condition of low solution concentration.

Chew *et al.* examined the anti-solvent vapour precipitation method in order to uniformly sized lactose microspheres. In this previous study, the ethanol vapour exposure and the convective drying technique were developed. It was found that the microspheres in the sub-micron scale could be obtained by using these devices. In addition, it was reported that these particles were independent on the ethanol exposure time and the drying temperature. In this previous study, the residence time and the mixing ratio of anti-solvent were focused in order to make the particle size uniform.

Yamamoto *et al.* examined the effect of template at the air/solution interface on the nucleation phenomenon in order to obtain the fine monomodal crystalline particles. In this previous study, the ternary system (glycine, water and L-leucine) was used. In addition, the formation of template interface was selected as the nucleation trigger. From the experimental results, it was reported that the monomodal crystalline particles of glycine crystal could be obtained by using the nucleation trigger. In this previous study, the new crystallization method is investigated in order to make the particle size uniform.

Yua *et al.* examined the effect of agitation speed and feeding rate on the agglomeration and crystal habit. In this previous study, the anti-solvent crystallization of paracetamol crystals was carried out in ternary system (paracetamol, water and acetone). In addition, the feeding rate was selected as the operating conditions. As the experimental results, the size distribution of crystalline particles was influenced by the difference of the feeding rate because the agglomeration degree of products increased with the feeding rate. Furthermore, it was reported that the agglomeration degree of crystals decreased with the increase of agitation speed. So, the particle size could be controlled by changing the agitation speed and feeding rate.

As described above, the various control factors were focused in order to make the crystal qualities uniform. **Table 1-3** shows the summary of these previous studies. As shown in **Table 1-3**, from the viewpoint of driving force, it could be considered that the degree of supersaturation was made uniform by using the various crystallization methods or the various devices in these previous studies.

Table 1-3 Previous studies related to make the crystal quality uniform

Previous Study	Crystallization Method	Control Factor	Crystal Quality
Dombrowski *et al.*	Microfluidic process	Initial supersaturation	Uniform quality
Qiu *et al.*	Spray drying	Droplet size	Uniform quality
Igarashi *et al.*	mL-scale continuous crystallizer	Residence time Mixing ratio of anti-solvent	Uniform quality
Kucher *et al.*	Continuous Y-Mixer	Variation of the free lattice ions	Uniform quality
Jongen *et al.*	Continuous segmented flow tubular reactor	Type of crystallizer	Uniform quality
Gonda *et al.*	Anti-solvent crystallization	Solution concentration	Uniform quality
Chew *et al.*	Anti-solvent vapour precipitation method	Residence time Mixing ratio of anti-solvent	Uniform quality
Yamamoto *et al.*	Templated crystallization	Formation of template interface	Uniform quality
Yua *et al.*	Anti-solvent crystallization	Agitation speed Feeding rate	Uniform quality

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1-3. Purpose of this thesis

As shown in **Table 1-1** or **Table 1-2**, it was found that the control method was investigated by controlling the degree of supersaturation from the viewpoint of one crystal quality. However, two crystal qualities are not satisfied simultaneously by using these control methods. So, it is considered that to propose the simultaneous control method of two crystal qualities is necessary.

Also, as shown in **Table 1-3**, the various crystallization methods and devices were investigated in order to make the crystal quality uniform. In these previous studies, it was particularly focused on the place where the degree of supersaturation was generated. In this present study, this place was termed as the crystallization field. In these previous studies, it could be seen that the technique which was made the crystallization field uniform was investigated. So, it is considered that the crystalline particles with the uniform crystal quality were obtained by utilizing the uniform crystallization field. In other words, it could be expected that the crystal quality might be changed by making the crystallization field non-uniform. Therefore, as shown in **Fig. 1-3(A")**, it was expected to change the profile of the *PC-S* or the *OC-S* by using the non-uniform crystallization field.

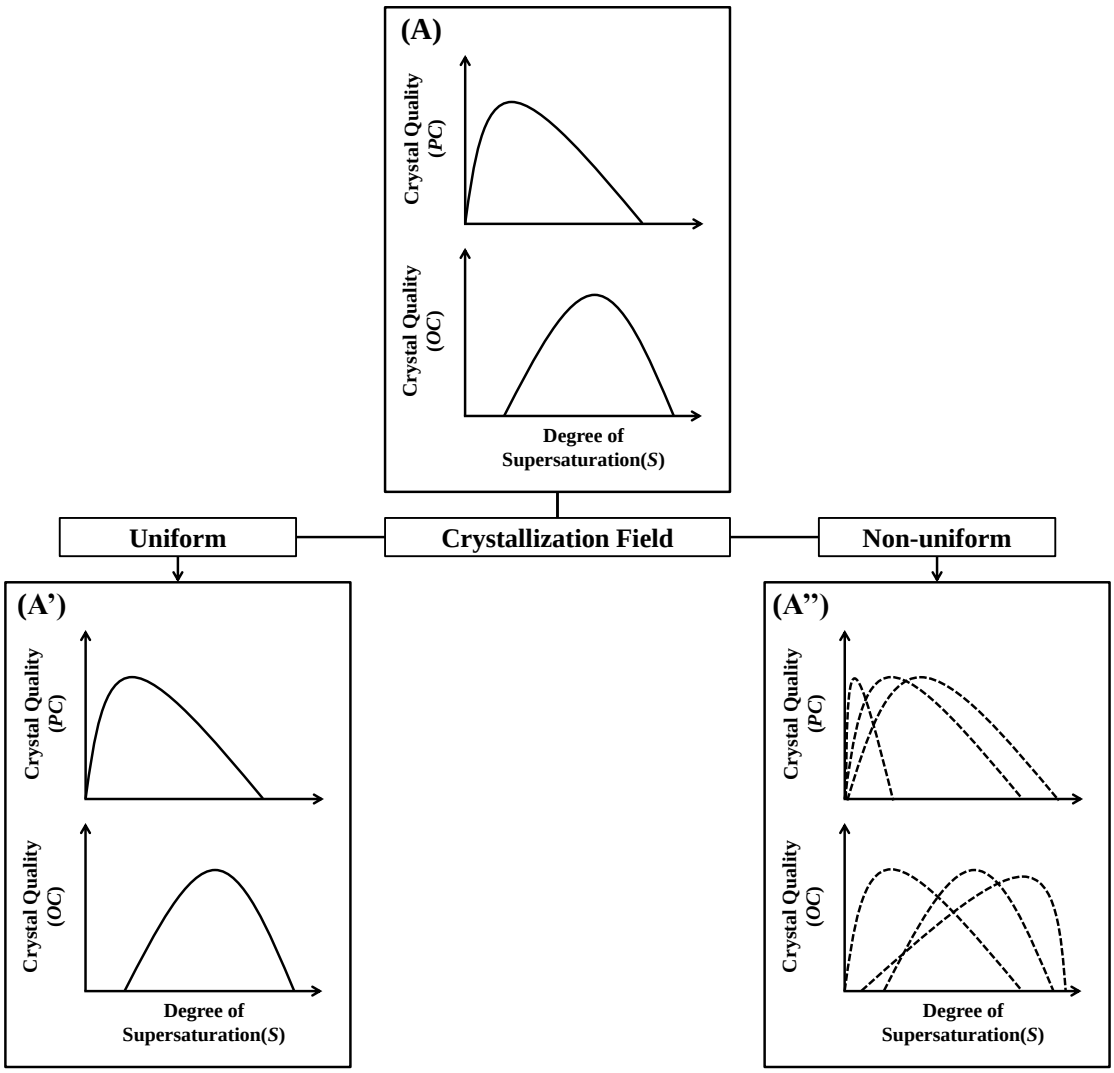


Fig. 1-3 Conceptual diagram of the relationship *PC*-*S* and *OC*-*S*; (A') Uniform crystallization field; (A'') Non-uniform crystallization field

When the profile of the *PC*-*S* or the *OC*-*S* could be changed, the trade-off relationship between the *PC*-*S* and the *OC*-*S* might be eliminated as shown in **Fig. 1-4(A*)**. Then, as shown in **Fig. 1-4(B*)**, there was possibility that the *PC* and the *OC* are satisfied simultaneously.

Therefore, in order to develop the crystallization method which can satisfy the product quality and the operability simultaneously, the purpose of this thesis is to propose the simultaneous control method of two crystal qualities from the viewpoint of the crystallization field. **Fig. 1-5** shows the conceptual diagram of the simultaneous control of *PC* and *OC* of this present study.

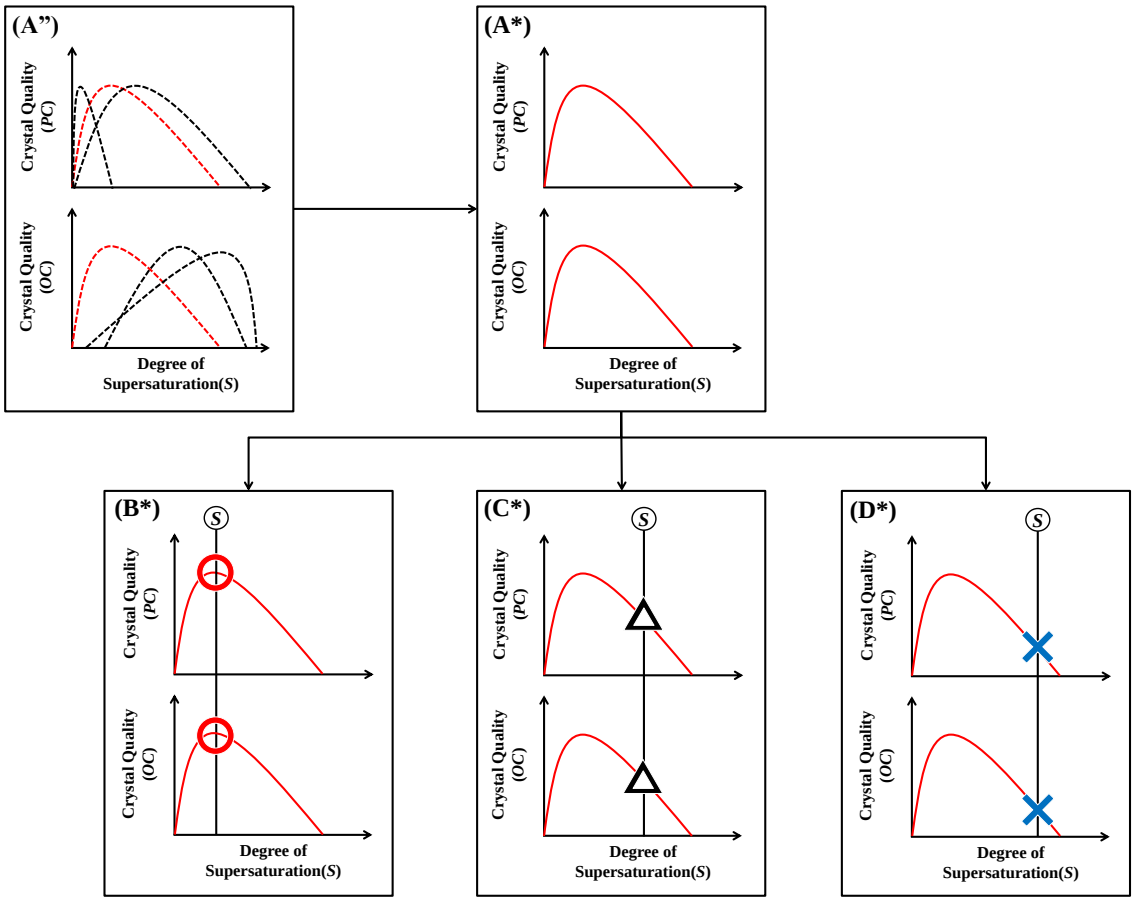


Fig. 1-4 Conceptual diagram of the desired relationship between *PC*-*S* and *OC*-*S* (A*); Low degree of supersaturation (B*); Middle degree of supersaturation (C*); High degree of supersaturation (D*)

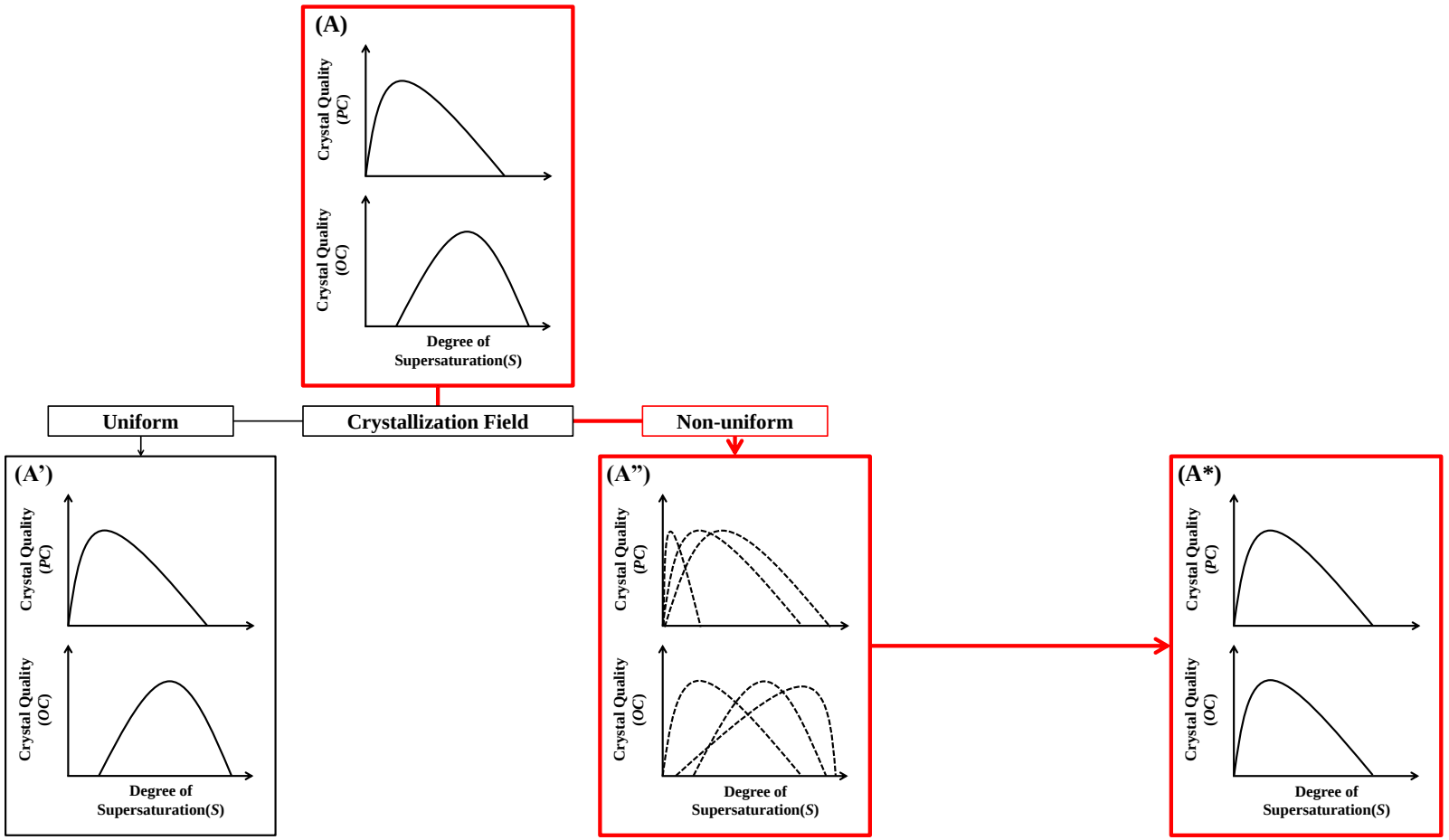


Fig. 1-5 Conceptual diagram of the simultaneous control of *PC* and *OC*

1-4. Scope

This thesis consists of five chapters:

Chapter 1 firstly introduced the background on the necessity to develop the simultaneous control method of two crystal qualities in order to satisfy the product quality and the operability simultaneously. Secondly, the previous studies related to the control method of various crystal qualities were reviewed. Finally, the purpose and the conceptual diagram of this thesis were mentioned.

Chapter 2 examines the prevention method of ultra-fine Magnesium Hydroxide (MH) crystal deposition when MH crystals are recovered from the sea water desalination process as valuable resource by using the reactive crystallization. It is because this deposition phenomenon of ultra-fine crystals results in the reduction of production efficiency. Therefore, it is desired to obtain the MH crystals with large particle size while maintaining the purity of MH crystals.

Chapter 3 examines the modification of the morphology (external shape) of α-form agglomerates in Indomethacin (IMC) crystallization. When the α-form (higher solubility of IMC for water) is obtained by using the conventional anti-solvent crystallization, the cotton agglomerates are generally formed in the solution. Then, stirring operation cannot be continued. So, it is desired to prevent the formation of cotton agglomerates while maintaining the polymorph in IMC crystallization.

Chapter 4 examines the effect of simultaneous control method of polymorph and morphology on the purity of IMC. The α-form spherical agglomerates are obtained by the addition of third component. Therefore, it is expected that the purity of the α-form spherical agglomerates is influenced by the amount of mother liquor which includes the third component. Therefore, it is attempted to evaluate the purity of α-form spherical agglomerates by using the newly defined evaluation index of the amount of mother liquor.

Chapter 5 organizes previous chapters, and then makes a general conclusion.

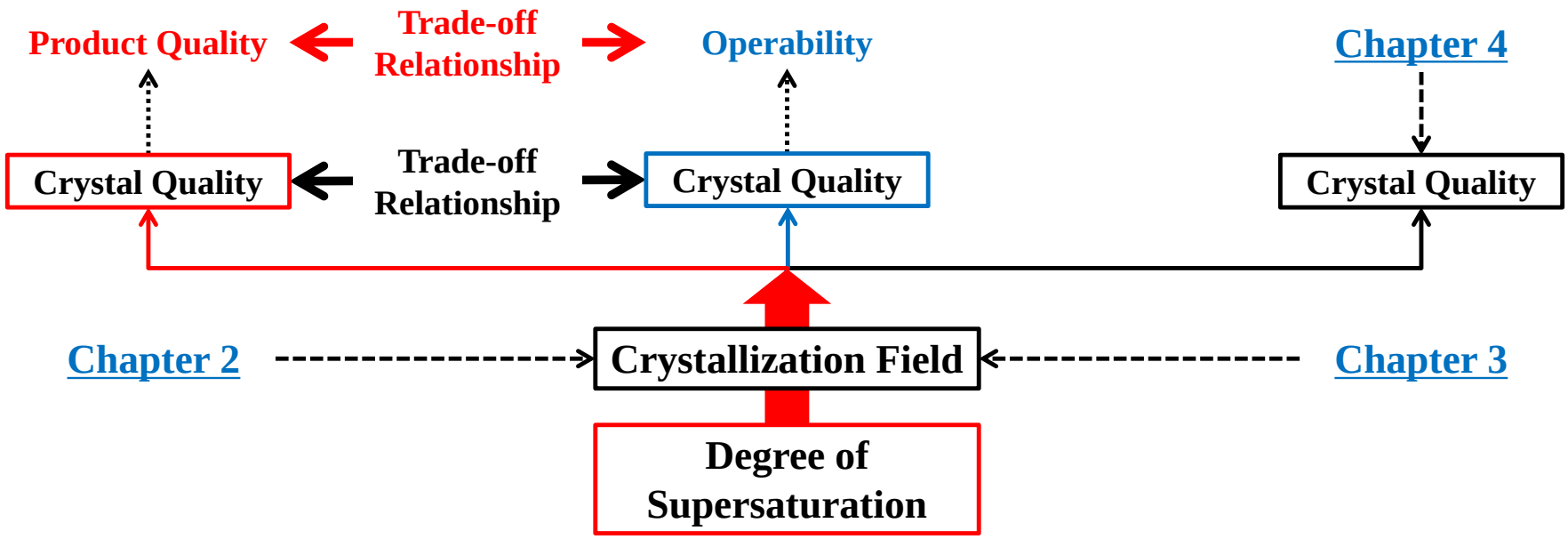


Fig. 1-6 Structure of this thesis

Chapter 2

Crystallization Operation Method for Recovering Mg Resources from the Sea Water Desalination Process

2.1 Introduction

In recent years, an integrated process combining sea water desalination and resources recovery (Morillo *et al*., 2014) has been of focus. When the process is achieved, environmental load can be reduced and valuable resources can be produced. Na^+ ion is the most abundant ion in sea water. The Na^+ ion recovery has been well established as a salt production process (Turek, 2003). Mg^{2+} ion is the second most abundant ion; however, the Mg^{2+} ion recovery is not sufficiently developed. In magnesium compounds, magnesium hydroxide (MH) has been of focus as a flame retardant material. Therefore, development of the Mg^{2+} ion recovery producing MH crystalline precipitates is desired. The crystallization method is one of the resource recovery technologies. MH has extremely low solubility in water ((Stephen and Stephen, 1963). Therefore, reactive crystallization is often used in order to separate MH crystalline precipitates from concentrated sea water containing admixture ions (Japan Monopoly Corporation, Kikaku Kaihatsu Honbu, 1971). However, a previous report (Tsuge and Matsuo, 1990) demonstrated that MH crystals precipitated as ultra-fine particles by using reactive crystallization. This deposition phenomenon of ultra-fine crystals results in the reduction of production efficiency. Therefore, the prevention of ultra-fine MH crystal deposition is necessary. Another previous study (Xue *et al*., 2009) showed that the filtration efficiency is improved by changing the crystal morphology of MH ultra-fine particles. However, MH crystal morphology with the highest filtration efficiency is prepared by hydrothermal reaction. In the sea water process with resource recovery, low operation cost is also required. In yet another previous study (Alamdari *et al*., 2008), the kinetic information of MH particle formation was investigated in order to improve the size distribution of product particles. The influence of admixture ions on agglomeration phenomena of MH ultra-fine particles is discussed. However, the discussion of MH crystal quality and the effects of raw resource material composition are also essential for improvements in the integrated resource recovery process.

When sea water desalination is integrated with the resource recovery process, brine and bittern are produced as byproducts. The brine and bittern are raw resource materials for MH crystal production. Therefore, it is necessary to consider where the

reactive crystallization is located in the integrated process. Typical integrated processes which combine the sea water desalination and the resources recovery are shown in **Figure 2-1**.

In the case of integrated process A in **Figure 2-1**, the raw resource material is brine for the reactive crystallization in order to recover MH. On the other hand, in the integrated process B, the raw resource material is bittern. However, there is little fundamental data of recovered MH crystal for comparison of the two integrated processes.

For the above reasons, the purpose of this present study is to develop a new prevention method of ultra-fine MH crystal deposition from concentrated sea water in the presence of admixture ions and to obtain the fundamental data for comparison of the integrated processes which are combined with the sea water desalination and MH recovery.

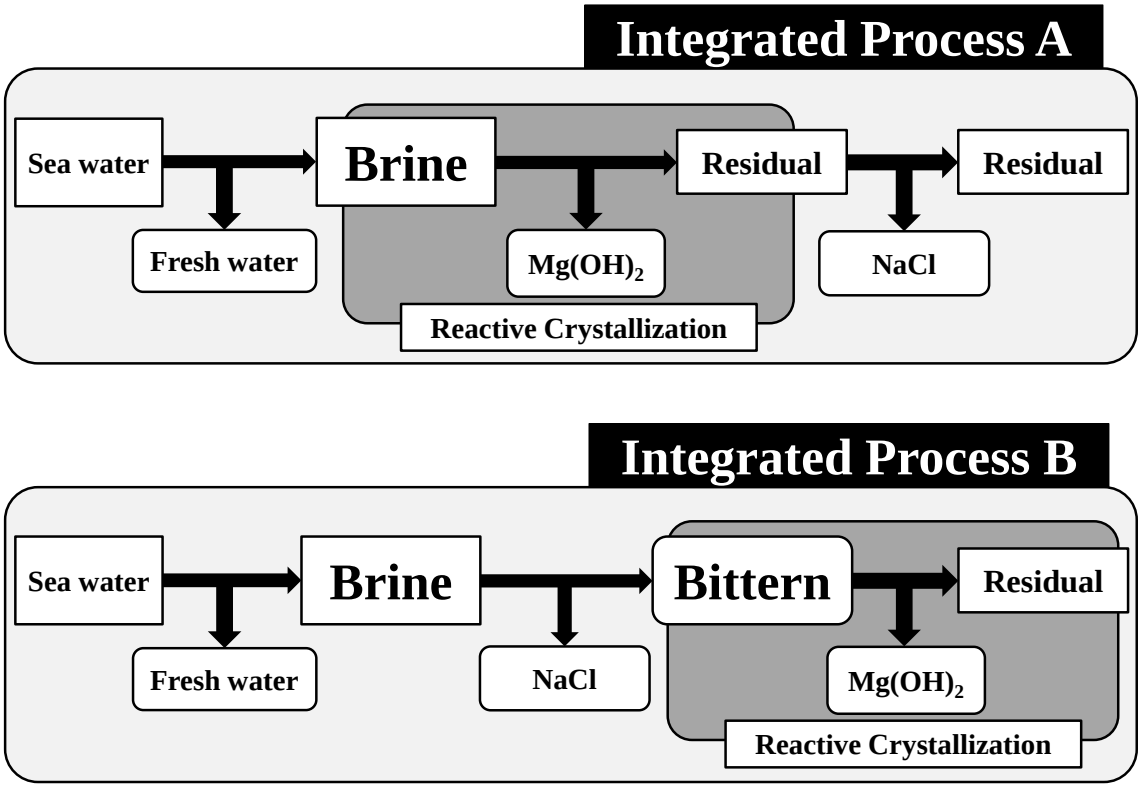


Fig. 2-1 Integrated process for obtaining MH from brine (Integrated Process A) and bittern (Integrated Process B)

2.2 Materials

Table 2-1 shows the composition of brine and bittern, respectively. Brine is the prepared solution, and bittern is an actual solution provided by DIASALT Co., Ltd.

In this present study, MH crystals were precipitated using calcium hydroxide (CH). CH was fed in solid form. The reactive crystallization was carried out by the following reactions.

$$Ca(OH)_2 \rightarrow Ca^{2+} + 2OH^- \quad (2\text{-}1)$$

$$Mg^{2+} + 2OH^- \rightarrow Mg(OH)_2 \quad (2\text{-}2)$$

The difference of MH reaction rate or MH supersaturation has the potential to change the MH crystal quality and MH crystal size. The MH precipitation begins from the dissolution of CH. In order to change the CH dissolution rate, modification of the CH addition method is proposed in this study. Therefore, it is strongly expected that the MH quality and MH crystal size were improved by modification of the CH addition method. Two types of CH addition methods were performed. One is the CH powder addition method, and the other is the CH tablet addition method. CH tablets were prepared by a micro tablet forming machine. The product model of the tablet forming machine is MP-1 mini press (JASCO CORPORATION).

Figure 2-2 shows a photomicrograph of the prepared CH tablet.

Table 2-1 Contents of Brine and Bittern of 500 g

Material		NaCl	$MgCl_2$	KCl	$CaCl_2$	$CaSO_4$
Brine	Mass[g]	86.1	2.8	1.5	1.2	0.23
	Composition [%]	17.2	0.56	0.3	0.24	0.05
Bittern	Mass[g]	16.3	84.5	24.3	28.9	1.12
	Composition [%]	3.3	16.9	4.9	5.8	0.22

2.3 Experimental

2.3.1 Effects of CH addition method

A 200 mL crystallizer was used in MH reactive crystallization. Two sets of brine solutions were prepared under three different temperature conditions, i.e. 303 K, 323 K and 343 K for powder and tablet additions, respectively. The amount of CH was 0.08 g at all experimental conditions.

In experiment (A) (Ex. (A)), the CH powder addition method was used. The reactive crystallization was carried out under stirring conditions over 3 days. In experiment (B) (Ex. (B)), the CH tablet addition method was used. In order to prevent CH tablets from disintegrated, the reactive crystallization with static condition was conducted for 3 days. The product MH crystals were filtered and dried after 3 days. The morphology of the product MH crystals was observed by a scanning electron microscope (SEM). The precipitates were identified by X-ray diffraction (XRD). MH crystallite size was calculated using Scherrer's Equation (Eq. (2-3)) from X-ray diffraction results.

$$\text{Crystallite size [nm]} = \frac{K\lambda}{b\cos\theta} \tag{2-3}$$

The θ value is the diffraction angle (θ = 37.98°). Scherrer constant K is a general value 0.9. The value of λ is the X-ray wavelength (λ = 1.54 Å). The b value is the half width of a specific peak at θ = 37.98°.

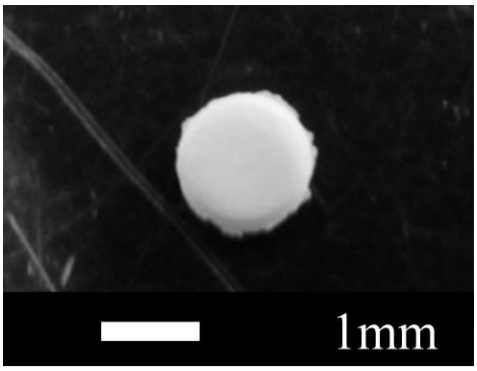


Fig. 2-2 Photomicrograph of the prepared CH tablet

2.3.2 Comparison between brine and bittern

The experiments were carried out under the same temperature conditions described in 2.1 by using brine and bittern, respectively. Reactive crystallization was carried out under the same conditions as Ex. (B), i.e. static conditions. The product MH crystals were filtered and dried after 3 days. The amount of MH was measured in order to calculate MH yield. MH yield was defined by Eq. (2-4).

$$\text{Yield}\ [-] = \frac{\text{Actual MH [mol]}}{\text{Theoretical MH [mol]}} \tag{2-4}$$

The morphology of product MH crystal was observed by SEM. The precipitates were identified by XRD. Moreover, the internal reference method is used in order to calculate the MH crystallinity. NaCl is used as the internal standard substance. The product precipitates were mixed with the standard substance in the same amount. The intensity ratio ($\boldsymbol{I}_{\mathrm{R}}$) was obtained from the X-ray diffraction peak. MH crystallinity was calculated by using Eq. (2-5).

$$\text{Crystallinity}\ [-] = \frac{\text{MH peak}\ \boldsymbol{I}_{\mathrm{R}}\ [-]}{\text{MH standard peak}\ \boldsymbol{I}_{\mathrm{R}}\ [-]} \tag{2-5}$$

MH yield and MH crystallinity are the fundamental data for development of the MH recovery process in an integrated process.

2.4 Results and Discussion

2.4.1 Effects of CH addition method

The influence of the CH addition method on MH crystal quality was investigated. **Figures 2-3(a) and (b)** show SEM photomicrographs of precipitates obtained from the CH tablet and CH powder addition methods, respectively. **Fig. 2-3(b)** shows a cross-section of the MH powder cake which consists of ultra-fine MH crystals. **Figure 2-4** shows an XRD powder pattern.

According to **Fig. 2-3(a)**, in the case of the CH tablet addition method, the MH crystal size is about 8 μm. On the other hand, in the case of the CH powder addition method, the MH crystal size is too small to observe using SEM. Therefore, it is suggested that the difference in addition method affected the particle size of MH crystals. The particle size of MH crystals was increased by the CH tablet addition method.

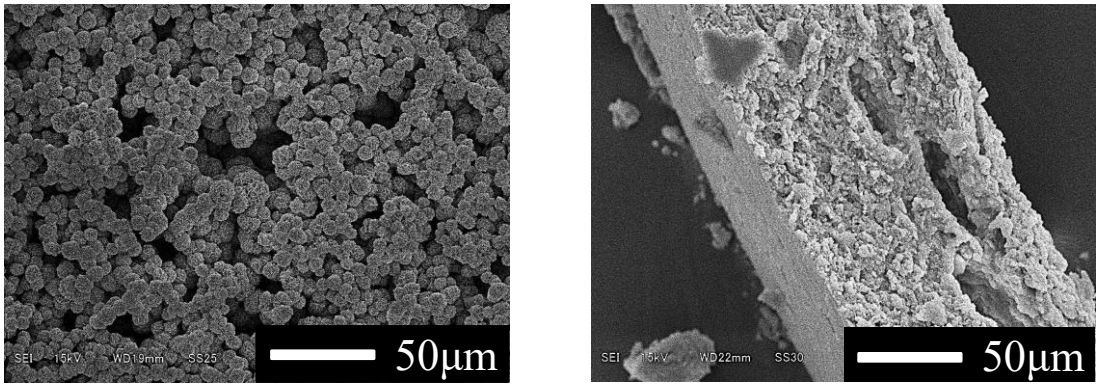


Fig. 2-3 SEM photomicrographs of precipitates obtained by using CH tablet (a) and powder (b)

In **Fig. 2-4**, (A), (B) and (C) show the XRD results from CH tablet addition, and (a), (b) and (c) show the results from CH powder addition under different temperatures (303 K, 323 K, 343 K) conditions, respectively. MH crystals were precipitated at all temperature conditions and addition methods. Crystallite size was calculated using each XRD peak in **Fig. 2-4**. **Figure 2-5** shows the temperature dependence of crystallite size under different CH addition methods.

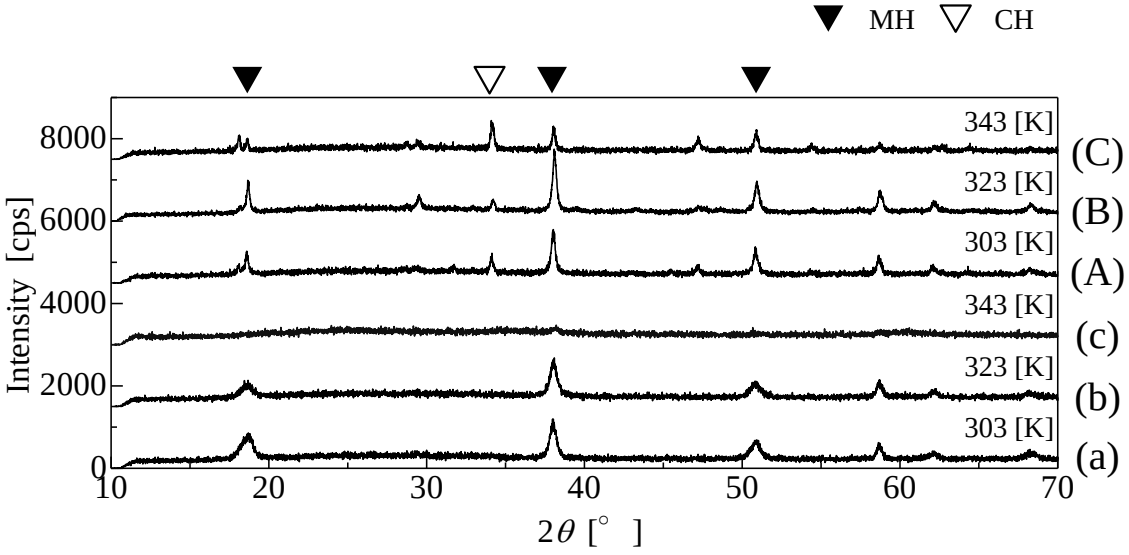


Fig. 2-4 XRD powder pattern of precipitates obtained using CH tablet (A, B and C) and powder (a, b and c) under different temperature conditions

It is clear that the crystallite size of MH precipitates obtained from CH tablet addition is larger than that from CH powder addition. In the case of CH tablet addition, the crystals were supposed to grow sufficiently. From the above results, the CH tablet addition method prevents precipitation of ultra-fine MH crystals. Therefore, the CH tablet addition method should be selected when MH crystals are produced from concentrated sea water.

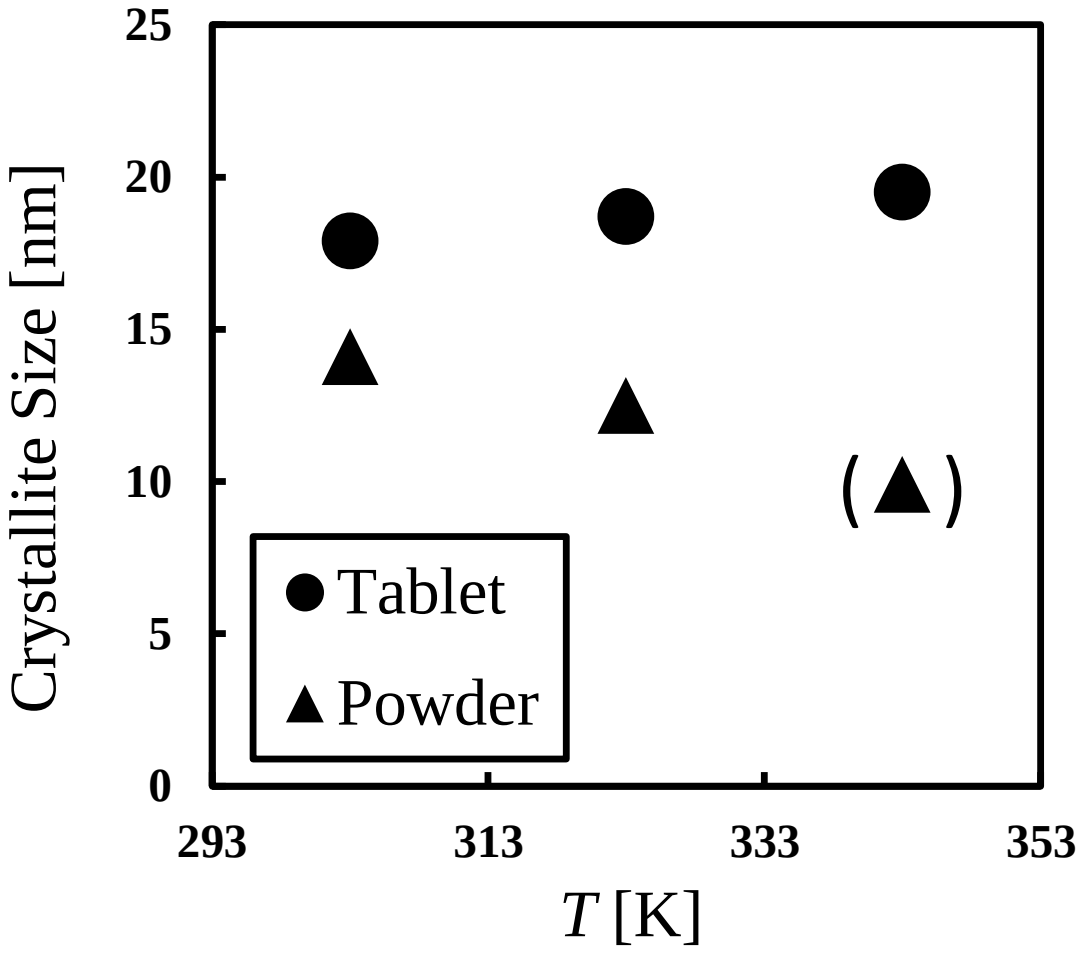
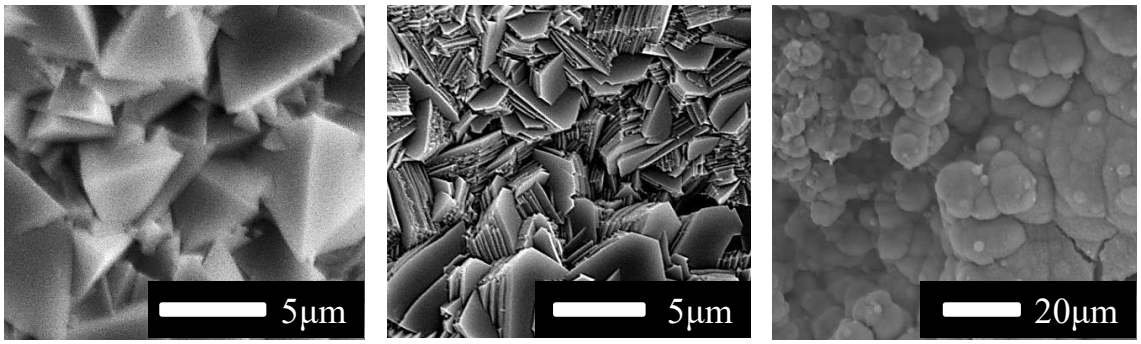


Fig. 2-5 Temperature dependence of crystallite size under different CH addition method

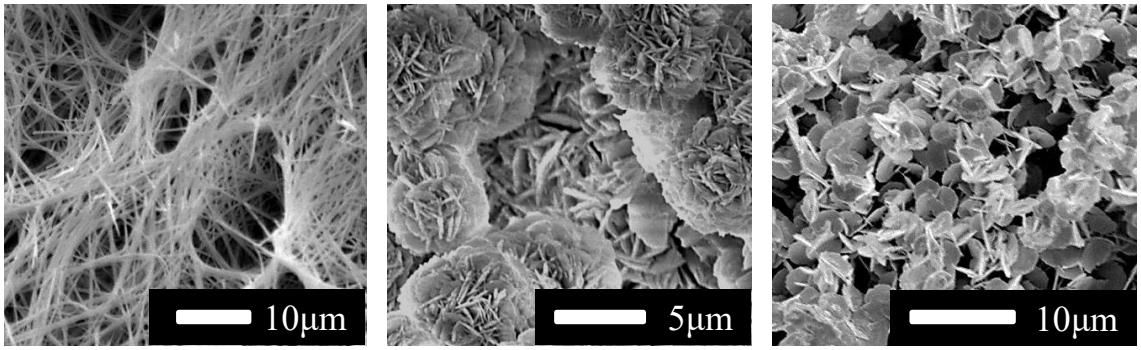
2.4.2 Comparison between brine and bittern

The influence of the kind of raw resource material on MH crystal quality was investigated. **Figures 2-6** and **2-7** show SEM photomicrographs of precipitates obtained from brine (X, Y and Z) and bittern (x, y and z), respectively.



(X) 303[K] (Y) 323[K] (Z) 343[K]

Fig. 2-6 SEM photomicrographs of precipitates obtained from brine



(x) 303[K] (y) 323[K] (z) 343[K]

Fig. 2-7 SEM photomicrographs of precipitates obtained from bittern

XRD results obtained from brine and bittern are shown in **Figure 2-8**.

According to **Fig. 2-6 and 2-7**, MH crystals have various morphologies while changing reaction temperature and raw resource material. From **Fig. 2-8**, MH crystals were obtained except for the low temperature (x) condition. Crystals obtained under (x) condition were a different Mg salt ($Mg_2(OH)_3Cl{\cdot}4H_2O$ (Altmaier *et al*., 2003)). Therefore, MH crystals cannot be obtained from bittern under the condition of low temperature. Crystallinity was calculated using each XRD peak in **Fig. 2-8**.

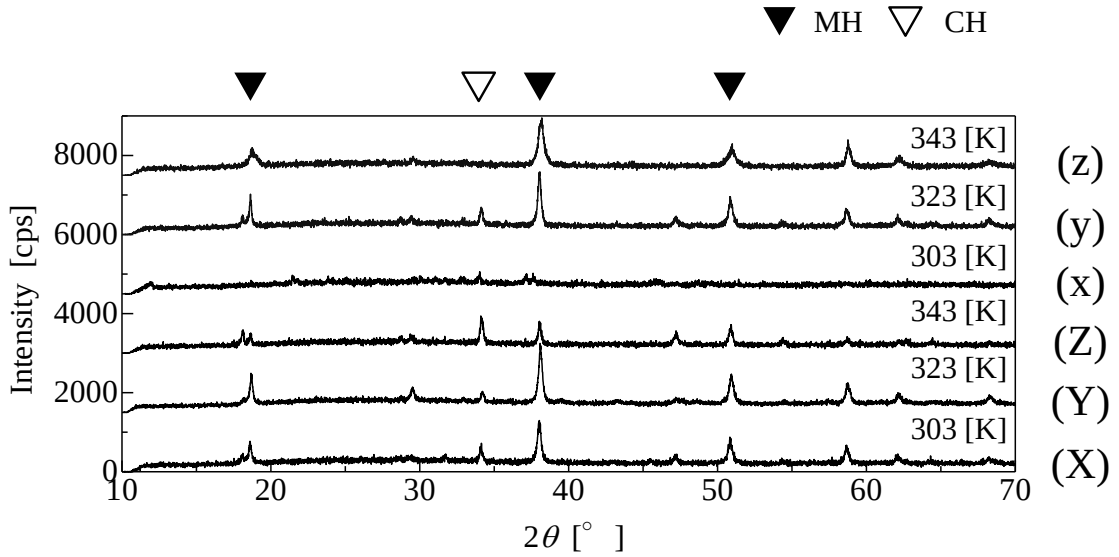


Fig. 2-8 XRD results obtained from brine and bittern

The relationship between MH yield and operation temperature is shown in **Figure 2-9**.

MH yield decreases with an increase in operation temperature for brine and bittern. The temperature dependency of MH solubility is positive. Therefore, the MH yield under high temperature conditions is smaller than that under low temperature conditions.

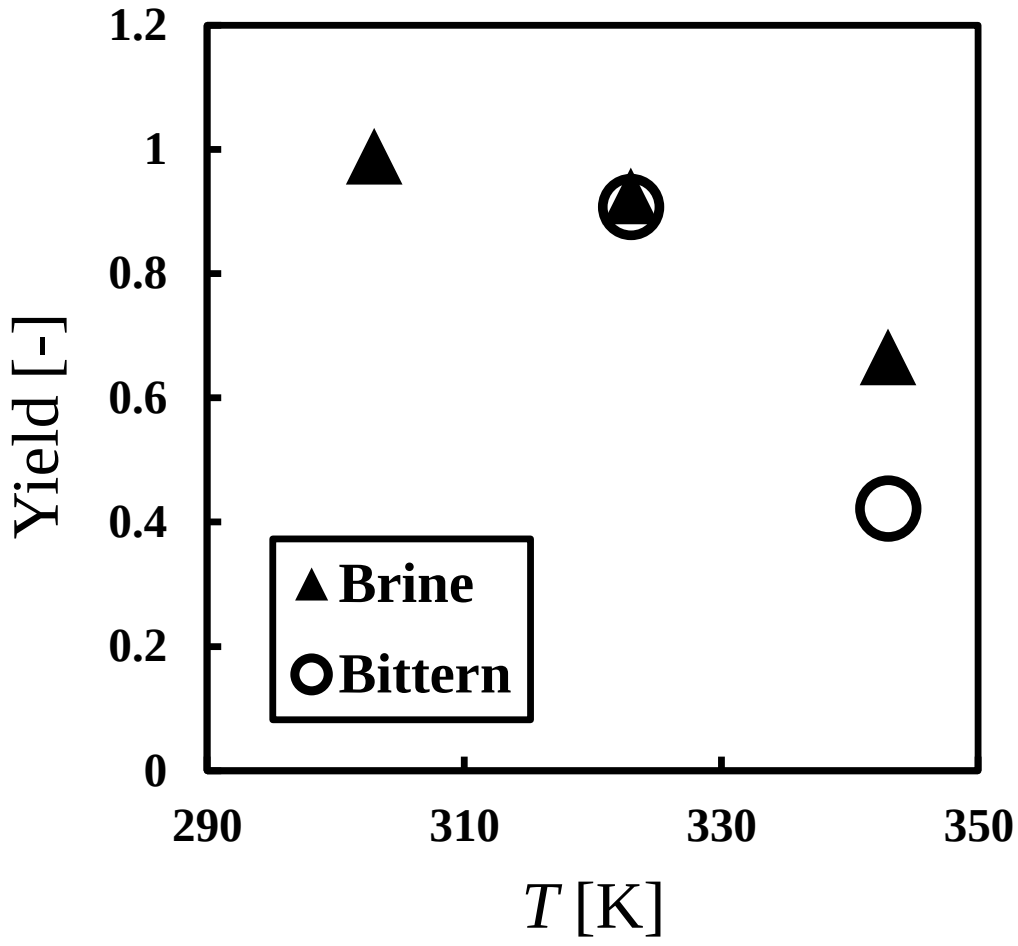


Fig. 2-9 Relationship between MH yield and operation temperature under the different raw resource material

The relationship between MH crystallinity and operation temperature is shown in **Figure 2-10**.

MH crystallinity increases with an increase in operation temperature in both raw resource materials, i.e. brine and bittern.

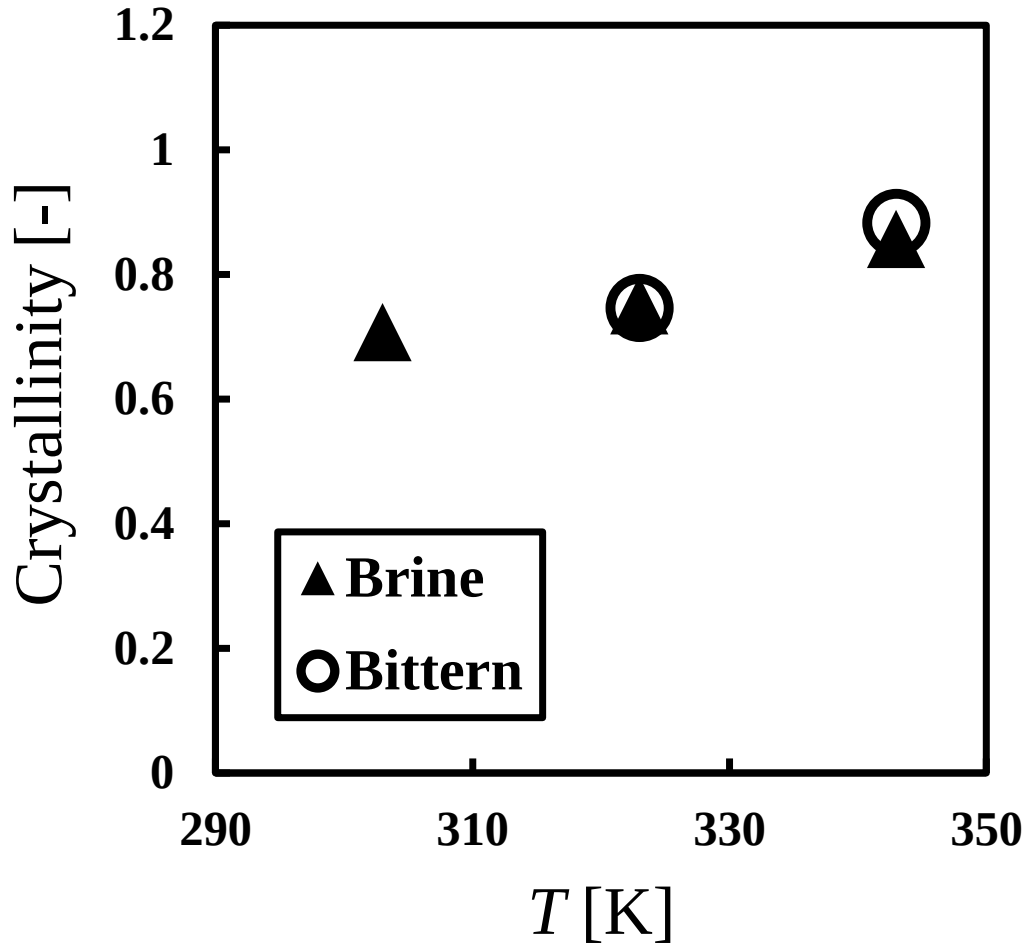


Fig. 2-10 Relationship between MH crystallinity and operation temperature under the different resources

There are two reasons for this result. The first reason is the temperature dependency of CH dissolution rate. The reaction rate of MH production is fast under high temperature conditions. The CH dissolution rate decreases with temperature increase ((Stephen and Stephen, 1963). The MH crystal has low growth rate when the dissolution rate of CH crystal becomes slow. Therefore, MH crystallinity becomes large.

The second reason is the temperature dependency of MH solubility. The MH solubility increases with temperature increase. Therefore, since supersaturation of MH in solution is small, MH crystallinity becomes large. From these two reasons, the crystallinity under high temperature conditions is improved rather than that under low temperature conditions.

From these results, a strategy for obtaining MH crystals can be proposed. Under the low temperature condition, brine should be used as a raw resource material in order to obtain MH crystals. Under the high temperature condition, there are two candidates in priority order. When MH yield has high priority, brine should be used as the raw resource material. On the other hand, bittern should be used when priority is given to MH crystallinity.

2.5 Conclusion

In this present study, the fundamental data for development of the MH recovery process has been investigated, and the following conclusions were obtained. First, from the result of comparison of the two kinds of CH addition methods into concentrated sea water, the CH tablet addition method prevents precipitation of ultra-fine MH crystals. These MH crystals had large crystallite size. Next, from the results of comparison between brine and bittern as the raw resource material, it was clear that the yield and crystallinity of MH crystals were strongly dependent on temperature and the raw resource material. The producing method of MH crystals with high yield and crystallinity has been proposed. These fundamental data can be expected to be useful in investigating the reaction dynamics required for elucidation of the mechanism for recovering the valuable resource from the sea water desalination process. In the future, these fundamental results will lead to the suggestion of a strategy for improvements in process efficiency when MH crystals are recovered from the sea water desalination process.

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Chapter 3

Development of Simultaneous Control of Polymorphism and Morphology in Indomethacin Crystallization

3.1 Introduction

Crystallization is widely used in pharmaceutical industry. There are many cases that pharmaceutical crystals are produced by using crystallization technology (Crisp *et al.*, 2011). Polymorphism is very common among pharmaceutical compounds (Li *et al.*, 2009) and is frequently defined as the ability of a substance to exist as two or more crystalline phases (Karabas *et al.*, 2007). Different polymorphs of a pharmaceutical compound may differ in their physical properties such as crystal morphology, solubility and stability (McGregor and Bines, 2008; Lee, 2014). The solubility is particularly important in pharmaceutical field, because the solubility affects the bioavailability. Moreover, poorly soluble pharmaceutical compounds have been increased with adding functionality and increasing molecular weight (Lipinski, 2000; Keck and Muller, 2006). Therefore, in order to improve the bioavailability, polymorph selection is important in pharmaceutical industry. There are many reports about the effects of additives and solvent composition on polymorph selection (Kitamura and Sugimoto, 2003; Okamoto *et al.*, 2004).

Indomethacin (IMC) is the poorly soluble pharmaceutical compounds. Many drug efficacy of IMC has been reported (Jain, 2007). Generally, IMC is a non-steroidal anti-inflammatory drug. Two common polymorphs have been reported for IMC (α-form and γ-form) (Hamdi *et al.*, 2003). From the viewpoint of bioavailability, α-form is advantageous (Yokoyama *et al.*, 1979; Varughese *et al.*, 2010). The individual crystal morphology of α-form is fiber-like, while γ-form is plate-like (Slavin *et al.*, 2002). As to be observed in IMC, many organic molecules exhibit anisotropic structural properties in individual crystal morphology (Puel *et al.*, 2008). The anisotropic morphology is usually not desirable because it will lead to problems in the operability of crystallization and downstream processes such as filtration. The effects of additives and stirring method on crystal morphology have been studied in many papers (Seyssiecq *et al.*, 1999; Hyung *et al.*, 2008). In order to simultaneously consider the bioavailability and operability, it is important to notice that the individual crystal morphology strongly depends on the polymorphism. Therefore, the simultaneous control of the polymorphism and the individual crystal morphology is not easy.

Furthermore, in the case of IMC, α-form crystals are usually formed as agglomerates in the crystallizer. When the morphology (external shape) of α-form crystals becomes cotton agglomerates in the slurry, stirring operation cannot be continued. Then, cotton agglomerates becomes the compressible cake as final crystalline product after filtration and drying (**Figure 3-1**). Thus, from the viewpoint of operability, α-form crystal is disadvantageous. In order to simultaneously satisfy the bioavailability and the operability of IMC production, the modification of the morphology of α-form agglomerates is important. Therefore, the purpose of this present study is the development of the crystallization method which is able to simultaneously control the polymorphism and the morphology (external shape).

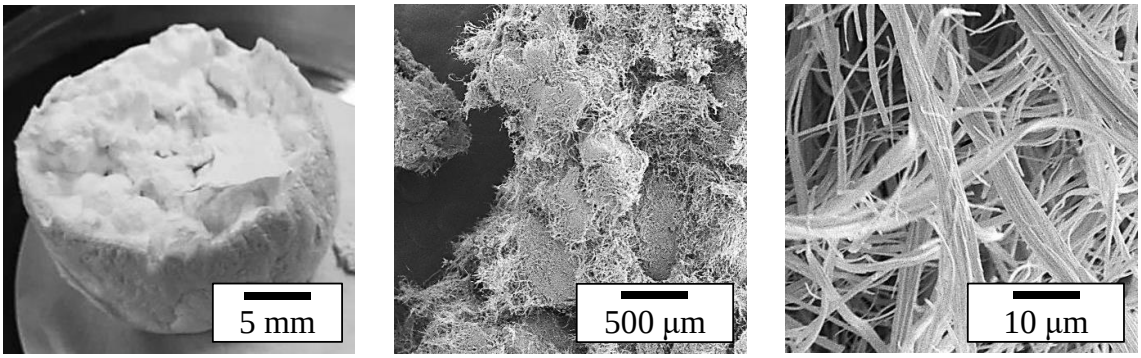

Fig. 3-1 Photomicrographs of the compressible cake with different magnification

3.2 Materials

Indomethacin (IMC) crystals were produced by anti-solvent crystallization. From the viewpoint of bioavailability, the target polymorph is α-form. The growth rate in the major axis direction of α-form crystal is very fast. Hence, the individual crystal morphology of α-form becomes fiber-like, and α-form crystals are usually agglomerated. Acetone was selected as a good-solvent (Martinez *et al.*, 2011) and aqueous solution was selected as an anti-solvent (Takiyama *et al.*, 2010).

In order to modify the morphology of α-form agglomerates, the addition of the third component was considered. An electrolyte was selected as the third component. Sodium chloride (NaCl) was selected as the electrolyte in this present study.

3.3 Experimental Method

3.3.1 The effect of NaCl concentration on the quality of IMC crystalline product

A 100 mL crystallizer was used in anti-solvent crystallization of IMC. By adding IMC into acetone under the temperature condition of 303K, the saturated solution was prepared. Approximately 15 g of acetone-IMC saturated solution was fed into the crystallizer. Then, by using a magnetic stirrer, stirring operation was carried out at 835 rpm. NaCl aqueous (NaCl aq.) solutions with six kinds of concentrations were prepared as the anti-solvent. NaCl aq. solution was added into the crystallizer. The concentrations of examined NaCl aq. solutions were 0 (pure water), 5, 10, 15, 20 and 25 mass%. The amounts of the NaCl aq. solutions were 13.8 (pure water), 14.3, 26.4, 30.8, 47.3 and 57.1 g, respectively. Under these conditions, IMC crystals can be obtained with the yield of over 80 mass%. The deposited crystals were filtered and washed by using the pure water, and then these crystals were dried for 24 hours. So, the final crystalline product was observed by optical microscope, and was identified by X-ray diffraction (XRD) analysis. The mean particle size (L_N) of final crystalline product was measured and the coefficient of variation of size distribution (CV) was calculated. The individual crystal morphology, of which final crystalline product consisted, was observed by using scanning electron microscope (SEM). The mixing state of acetone-IMC solution and NaCl aq. solution was observed by optical

microscope.

3.3.2 The effect of the stirring speed on the quality of IMC crystalline product

In order to investigate the effect of the stirring speed under the presence of the third component, the experiments were carried out under the condition of four kinds of stirring speed. Under these experimental conditions, anti-solvent crystallization was carried out by using the 20 mass% NaCl aq. solution as anti-solvent. Agitation was performed in the stirring speed of 0, 635, 835 and 1125 rpm. The deposited crystals were filtered and washed, and then dried for 24 hours. The final crystalline product was observed by optical microscope and, L_N and CV were measured.

3.4 Results and Discussion

3.4.1 The effect of NaCl concentration on the quality of IMC crystalline product

The effect of the electrolyte (NaCl) on the quality of IMC crystalline product was investigated. The experiments were carried out under the six kinds of conditions of the NaCl concentrations, respectively. First, the appearance of the final crystalline product was focused. **Figure 3-2** shows the photomicrographs of the appearance of product which was observed under the condition of different NaCl concentrations. As shown in **Fig. 3-2**, the appearance was changed with electrolyte concentration. Under the condition of 0 (pure water) and 5 mass% NaCl concentration, final crystalline product was obtained as the compressible cake (**Figs. 3-2(a), (b)**). The stirring operation could not be continued in the slurry under the conditions of these NaCl concentrations. On the other hand, under the condition of 10 (**Fig. 3-2(c)**), 15, 20 (**Fig. 3-2(d)**) and 25 mass% NaCl concentrations, the final crystalline products were obtained as spherical particles. In these conditions, the stirring operation could be continued in the slurry. Therefore, the operability of IMC production was satisfied. When the spherical particles were obtained, the mean particle L_N and CV were able to be measured. L_N and CV are also shown in **Fig. 3-2**.

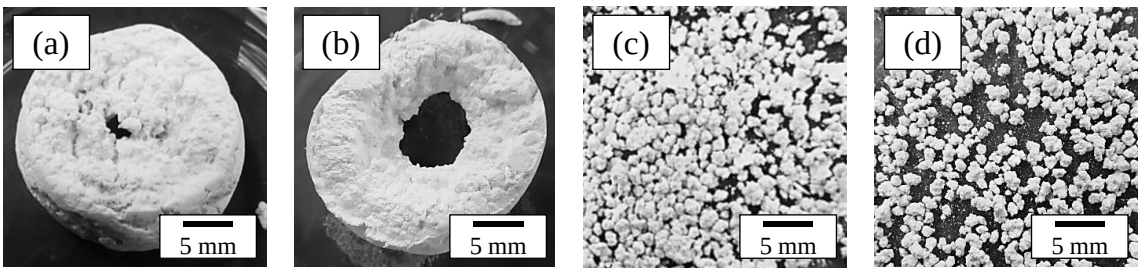

Fig. 3-2 Photomicrographs of the final crystalline product obtained from each anti-solvent: (a) 0 mass% NaCl aq. solution (Pure water); (b) 5 mass% NaCl aq. solution; (c) 10 mass% NaCl aq. solution (LN: 1280 μm, CV: 31%); (d) 20 mass% NaCl aq. solution (LN: 1530 μm, CV: 31%)

Figure 3-3 shows SEM photomicrographs of the final crystalline product under these conditions ((a) 0, (b) 5, (c) 10 and (d) 20 mass%). The individual crystal morphology was fiber-like in all of the experimental conditions. According to the individual crystal morphology, the polymorph could be decided as α-form which is the target polymorph. So, XRD analysis was carried out. **Figure 3-4** shows the XRD powder patterns. As show in XRD results, deposited crystals were identified as α-form. So, the target polymorph was obtained although the final crystalline product was obtained as spherical particles. From these results, it was found that the electrolyte affects the appearance, and on the other hand, does not affect the polymorph in this present study.

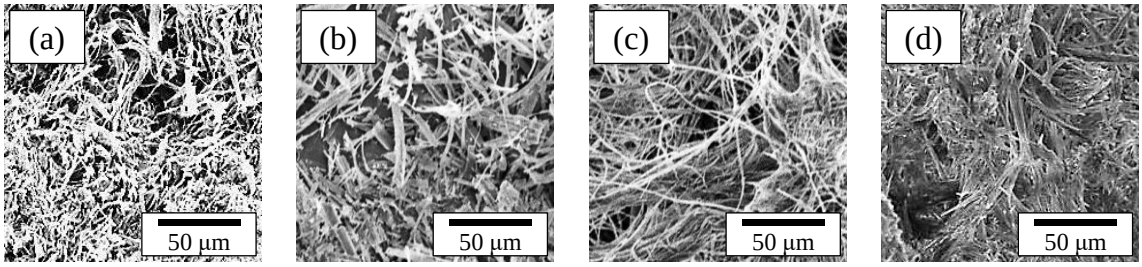

Fig. 3-3 SEM photomicrographs of individual crystal morphology, of which final crystalline product consisted, obtained from each anti-solvent: (a) 0 mass% NaCl aq. (Pure water); (b) 5 mass% NaCl aq. solution; (c) 10 mass% NaCl aq. solution; (d) 20 mass% NaCl aq. solution

The result of XRD analysis also shows that NaCl crystals were contaminated in the final product when NaCl aq. solution was used. The detail of the residual NaCl is discussed in **section 4.4**.

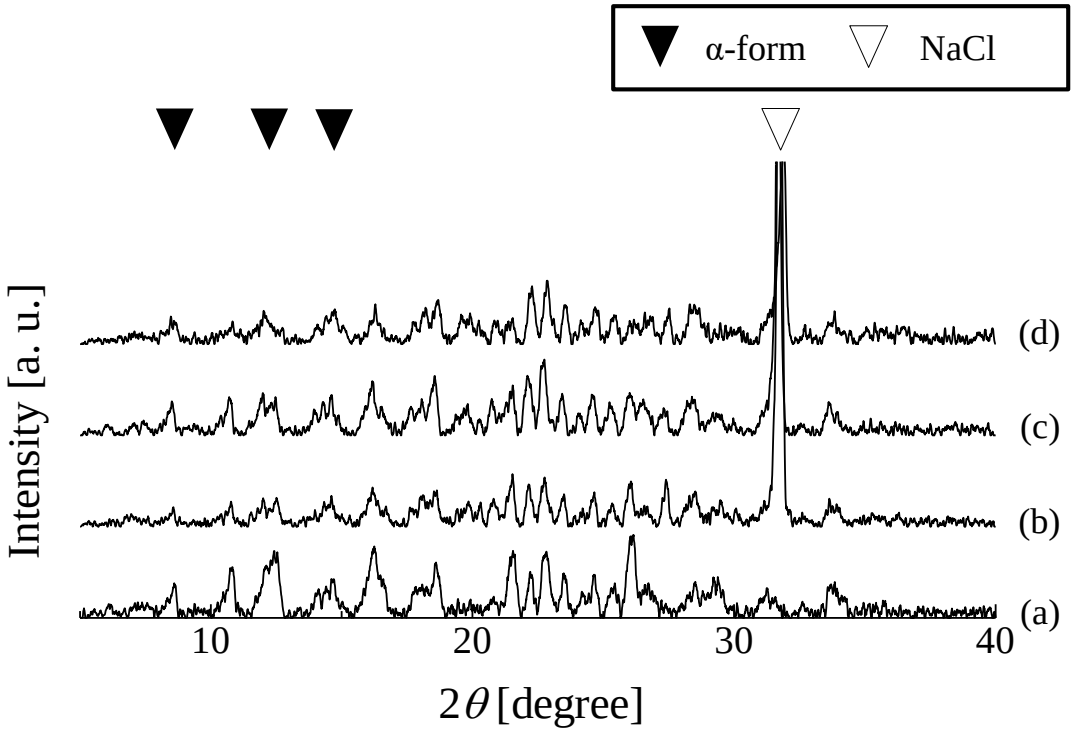

Fig. 3-4 XRD powder patterns of the final crystalline product obtained by using anti-solvent: (a) 0 mass% NaCl aq. solution (Pure water); (b) 5 mass% NaCl aq. solution; (c) 10 mass% NaCl aq. solution; (d) 20 mass% NaCl aq. solution patterns of precipitates obtained by using anti-solvent:

From the experimental results, it was possible to simultaneously satisfy the bioavailability of IMC and operability of the production when the final crystalline product is able to be obtained as spherical particles by changing the electrolyte concentration. So, in order to investigate the reason why the appearance changed depending on the electrolyte concentration, the mixing state of acetone-IMC solution and NaCl aq. solution was observed. In order to observe the mixing state, the stirring operation was stopped temporarily. As the results, there were two kinds of state of mixture as shown in **Figure 3-5**. **Fig. 3-5(i)** shows the homogeneous mixture which was observed under the condition of the 0 mass% of NaCl concentration. On the other hand, under the condition of the 20 mass% of NaCl concentration, the liquid-liquid phase separation (LLPS) occurred as shown in **Fig. 3-5(ii)**. It was considered that phase separation in the ternary system of acetone-water-sodium chloride is one of the reasons for the above mentioned LLPS (Marcilla *et al*., 1995). The LLPS occurred when 10, 15, 20 or 25 mass% NaCl aq. solution was used as the anti-solvent. Furthermore, the final crystalline product was obtained as spherical particles under LLPS conditions. Therefore, the appearance was dependent on whether LLPS occurs, and the state of mixture was influenced by the electrolyte concentration.

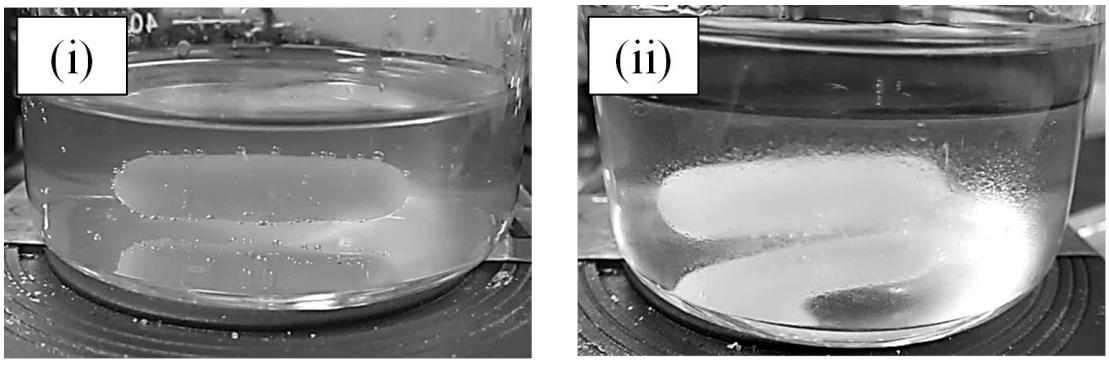

Fig. 3-5 Photomicrographs of the mixing state of acetone-IMC and electrolyte aqueous solutions: (i) the homogeneous mixture; (ii) the Liquid-liquid phase separation (LLPS)

3.4.2 The effect of the stirring speed on the quality of IMC crystalline product

It was considered that the appearance of the final product was changed by stirring after LLPS if the stirring (e.g. stirring speed) affects the state of the LLPS. In order to investigate the effect of the stirring speed on the quality of IMC crystalline product, four kinds of stirring speed were examined by using the 20 mass% NaCl aq. solution. It was confirmed that the LLPS occurs under this condition. The appearance of the final product was also changed with stirring speed as shown in **Figure 3-6**. The final crystalline product was obtained as the compressible cake under the condition of stirring speed at 0 rpm. On the other hand, under the condition of stirring speed at 635, 835 and 1125 rpm, the dispersion of droplets was observed in the solution and the spherical particles were obtained.

In addition, L_N and CV are also shown in **Fig. 3-6**. L_N decreased with increasing the stirring speed. According to these results, it is necessary to take into account not only the electrolyte concentration but also the stirring speed in order to change the appearance of the final crystalline product.

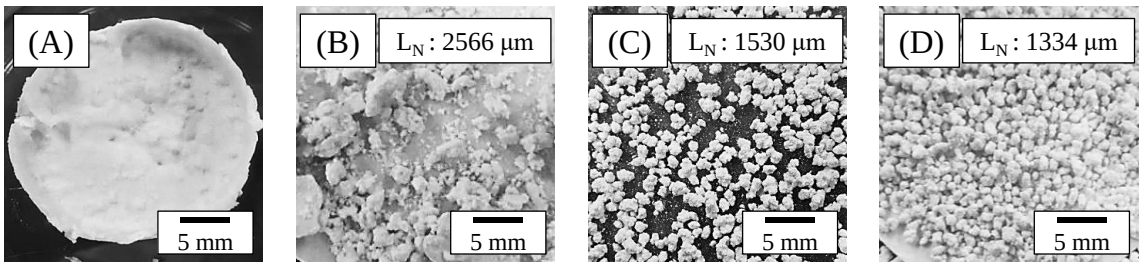

Fig. 3-6. Photomicrographs of the final crystalline product obtained by using 20 mass% NaCl aq. solution under the conditions of different stirring speed: (A) 0 rpm; (B) 635 rpm (LN: 2566 μm, CV: 92 %); (C) 835 rpm (LN: 1530 μm, CV: 31 %); (D) 1125 rpm (LN: 1334 μm, CV: 22 %)

3.4.3 The mechanism of production for IMC spherical particles

In order to investigate the mechanism of spherical particles production, the production paths were compared from the viewpoint of experimental conditions. **Figure 3-7** shows the production path (X) and (Y) in the case of the condition (a) and (d), respectively.

In production path (X), the electrolyte concentration was low, and hence the LLPS did not occur. Then, stirring could not be continued in the slurry because the cotton agglomerates were formed. As the result, the compressible cake was obtained after filtration and drying.

On the other hand, in production path (Y), the LLPS occurred because of the high electrolyte concentration. Moreover, the dispersion of droplets occurred because the stirring speed was high. Under this condition, spherical agglomerates of α-form were formed in the slurry and the stirring operation could be continued. Finally, the spherical particles were obtained.

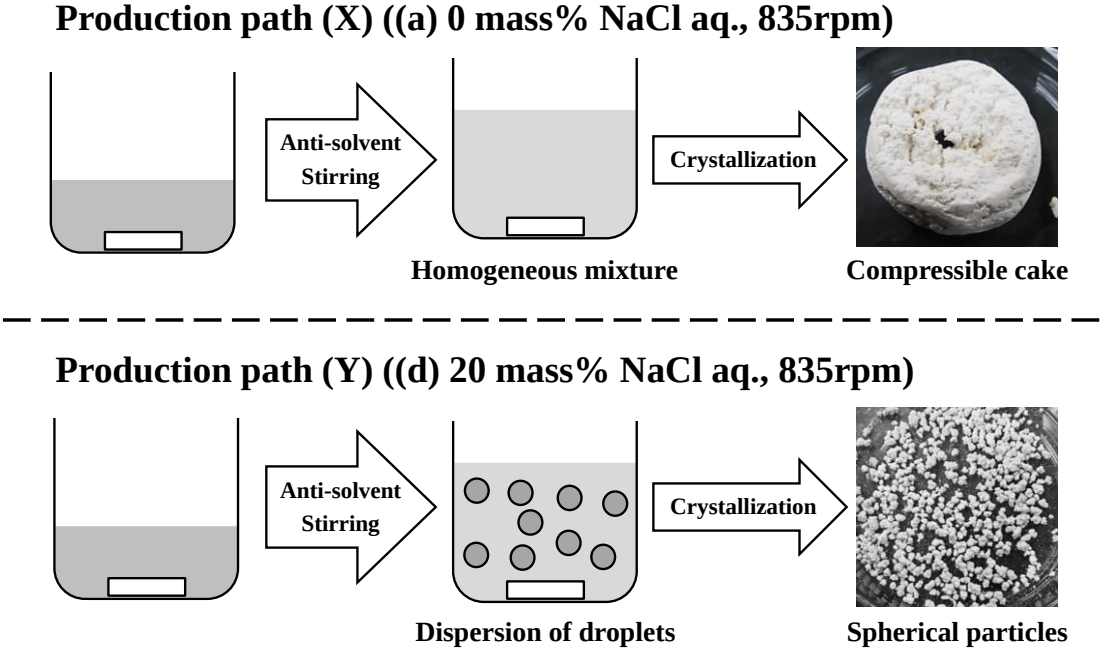

Fig. 3-7 Production paths of IMC: Production path (X) (under the condition of (a) 0 mass% NaCl aq. solution (Pure water), 835 rpm); Production path (Y) (under the condition of (d) 20 mass% NaCl aq. solution, 835 rpm)

3.4.4 The effect of the appearance of the final crystalline product on the quantity of the residual impurities

From the XRD powder pattern of **Fig. 3-4**, α-form and NaCl were deposited, simultaneously. So, the quantity of residual impurity resulting from the difference of the appearance was investigated by regarding NaCl as an impurity. **Figure 3-8** shows the result of XRD analysis under the conditions of different NaCl concentrations. **Figure 3-8(a)** was agreement with the XRD powder pattern of α-form. **Figure 3-8(b)** shows the XRD powder pattern of the compressible cake (5 mass% NaCl aq. solution) and was agreement with the pattern of α-form and NaCl mixture. **Figure 3-8(d)** shows powder pattern of the spherical particles (20 mass% NaCl aq. solution). From the comparison of **Fig. 3-8(b)** and **3-8(d)**, the peak intensity of NaCl in the vicinity of 32 degree (2θ) changed. The peak intensity is dependent on the quantity of the residual impurities. The relationship between the appearance and the quantity of the residual impurities was confirmed.

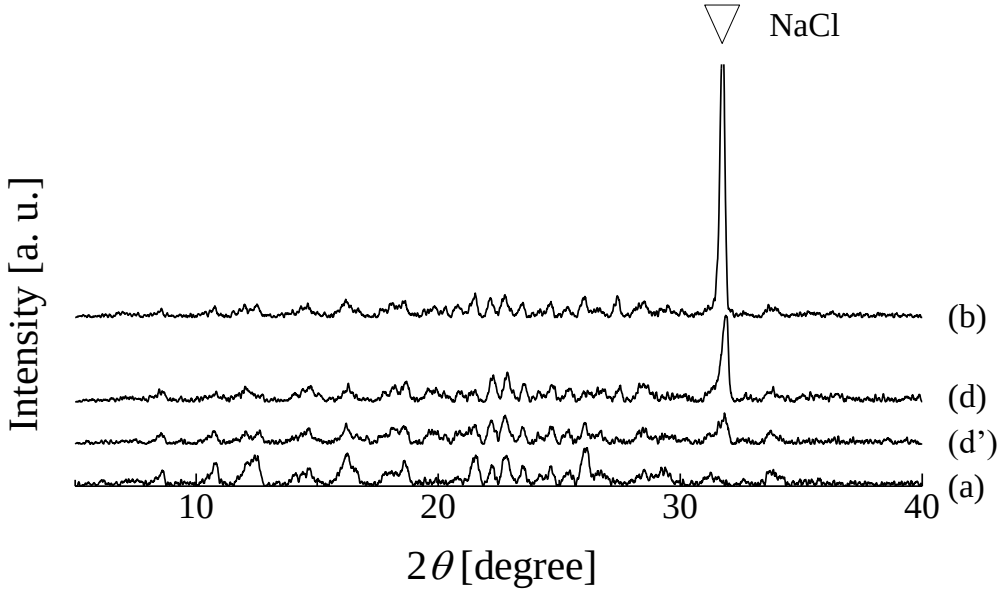

Fig. 3-8 XRD powder patterns of the final crystalline product obtained under the each experimental condition: (a) 0 mass% NaCl aq. solution (Pure water), 835 rpm; (b) 5 mass% NaCl aq. solution, 835 rpm; (d) 20 mass% NaCl aq. solution, 835 rpm, before the re-slurry washing; (d') 20 mass% NaCl aq. solution, 835 rpm, after the re-slurry washing

Furthermore, when the spherical particles were obtained, it was possible to carry out the re-slurry washing with the stirring operation in the pure water. The re-slurry washing operation was carried out under the experimental condition (d). The result of XRD powder pattern was shown in **Fig. 3-8(d')**. From the comparison of **Fig. 3-8(d)** and **3-8(d')**, the peak intensity of NaCl in the vicinity of 32 degree (2θ) more decreases by the re-slurry washing. As the results, the modification from α-form cotton agglomerates to α-form spherical agglomerates results in the reduction of the quantity of residual impurity.

3.5 Conclusion

In order to simultaneously satisfy the polymorphism and the morphology of IMC, anti-solvent crystallization was carried out by using the electrolyte aqueous solution (NaCl aq. solution) as the anti-solvent. As the results, the appearance of the final crystalline product was influenced by the electrolyte concentration and the stirring speed. Under the condition both of high electrolyte concentration and of high stirring speed, the dispersion of droplets was obtained in the solution, and the spherical agglomerates of α-form were formed in the slurry. The stirring operation could be continued in the slurry because the modification of α-form cotton agglomerates was achieved. So, the simultaneous control method of the polymorphism and the morphology in IMC crystallization was realized. In conclusion, it was able to propose the new crystallization method in order to simultaneously satisfy the bioavailability and the operability.

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Chapter 4

Proposal of Evaluation Method for Amount of Mother Liquor in Spherical Agglomerates

4.1 Introduction

Crystallization from solution is widely used as the separation technique in pharmaceutical industry (Beckmann, 1999; Crisp *et al.*, 2011). Many organic molecules exhibit anisotropic structural properties in their crystal morphology such as fiber-like or needle-like crystals (Puel *et al.*, 2008). In pharmaceutical industry, these crystals are usually not desirable because it will lead to problems in crystallization process and downstream process (filtration, drying, handling, etc.). Spherical crystallization technique is the method which can improve the micromeritic properties of drug crystal (Kawashima *et al.*, 1982). The spherical crystallization technique is the agglomeration technique that transforms crystals directly into a spherical form during the crystallization process. For example, this agglomeration technique was applied to Ibuprofen crystal (Teychene *et al.*, 2010), Naproxan crystal (Kulkami *et al.*, 2011) and so on.

Emulsion solvent diffusion (ESD) method is one of the spherical crystallization techniques (Patil Pradnya *et al.*, 2011). When the oil droplets are produced by the dispersion of the drug-good solvent solution in the anti-solvent, the ESD method is able to be realized (Martino *et al.*, 2000). In the case of the ESD method, the crystallization of the drug occurs within the droplet because the good solvent diffuses gradually out of the emulsion droplet into the outer anti-solvent phase. The quality of spherical particle is influenced by the operating conditions related to the formation of oil droplets (type or concentration of anti-solvent, stirring speed, etc.) since the spherical particle was obtained by the formation of oil droplets. From this reason, the relationship between the quality of spherical particle and the operating conditions is investigated in ESD method (Yadav and Yadav, 2009). In many researches of ESD method, the mean particle size or the particle shape is investigated from the viewpoint of the solubility (Sano et al., 1992; Hyung *et al.*, 2008). Also, from the viewpoint of toxicity, it has been confirmed whether additive (bridging liquid, polymer, stabilizer, etc.) has remained in spherical particle (Yadav and Yadav, 2009; Martino *et al.*, 2000; Kulkami *et al.*, 2011). Most of these additives exist in mother liquor during the crystallization process. From several reports on purity (Funakoshi et al., 2000; Miki *et al.*, 2005), it is considered that the agglomerates are easier to include the mother liquor than single

crystals. So, the purity of spherical agglomerates strongly depends on the amount of mother liquor in spherical agglomerates. From the above reasons, the evaluation method of the amount of mother liquor should be suggested, and then the purity of spherical agglomerates should be investigated.

Indomethacin (IMC) is one of the organic compounds of which it is desired to improve the micromeritic properties. IMC is a non-steroidal anti-inflammatory drug and is a poorly soluble compound (Yazdanian *et al.*, 2004). In the case of IMC, two common polymorphs have been reported (α-form and γ-form) (Hamdi *et al.*, 2003). From the viewpoint of bioavailability, α-form crystal has advantage. The crystal morphology of IMC (α-form) is fiber-like (Slavin *et al.*, 2002). These fiber-like crystals are easy to be agglomerated in the slurry and the cotton agglomerates are formed. When the cotton agglomerates are formed, the stirring operation cannot be continued. Therefore, from the viewpoint of operability, α-form crystal has disadvantage. By using the third component (NaCl), the modification of α-form agglomerates from cotton agglomerates to spherical agglomerates could be achieved (Wada *et al.*, 2016). As this result, the stirring operation could be continued and the operability of IMC production was able to be satisfied. Since the spherical agglomerates were formed in this modification method, the purity of spherical agglomerates should be also investigated. It is necessary to evaluate the amount of mother liquor. So, the purpose of this present study is to propose the method which can evaluates the amount of mother liquor in the spherical agglomerates.

4.2 Experimental

4.2.1 Chemicals

In this present study, Indomethacin (IMC) was selected as the target material. The sample of IMC was obtained from Sumitomo Chemical Co., Ltd., acetone was purchased from Wako Pure Chemical Industries, Ltd. IMC-acetone solution (IMC concentration 0.13 [-]) was prepared by adding IMC into acetone under the temperature condition of 303 K. Sodium chloride (NaCl) was purchased from Wako Pure Chemical Industries, Ltd. NaCl aqueous (NaCl aq.) solution was also prepared under the temperature condition of 303 K. In this present study, IMC-acetone solution was used as drug-good solvent solution and NaCl aq. solution was used as anti-solvent.

4.2.2 Anti-solvent crystallization for IMC under the various operating conditions

A 100 mL crystallizer was used in anti-solvent crystallization of IMC. Approximately 15 g of IMC-acetone solution was fed into the crystallizer under the temperature condition of 303 K. In previous study, the formation of oil droplets was observed when IMC-acetone solution and NaCl aq. solution were mixed under the condition of high NaCl concentration in anti-solvent and high stirring speed (Wada *et al.*, 2016). Therefore, in order to produce the oil droplets in anti-solvent crystallization of IMC, the addition of NaCl aq. solution is necessary. The prepared NaCl aq. solution was added into the crystallizer as anti-solvent under the stirring condition. The NaCl concentration and the stirring speed were selected as the operating conditions in this present study. Nine kinds of operation conditions were examined as follows: (A) (10 mass%, 835 rpm), (B) (15 mass%, 835 rpm), (C) (20 mass%, 835 rpm), (D) (10 mass%, 1125 rpm), (E) (15 mass%, 1125 rpm), (F) (20 mass%, 1125 rpm), (G) (10 mass%, 1660 rpm), (H) (15 mass%, 1660 rpm) and (I) (20 mass%, 1660 rpm), respectively. **Table 4-1** shows mass of the IMC-acetone solution and NaCl aq. solution which were used in the anti-solvent crystallization and, yield of IMC crystals which were obtained in each experimental condition. In this present study, the yield of IMC crystals was calculated by using the mass of IMC crystals which were actually obtained and the mass of IMC

crystals which were used in anti-solvent crystallization. Under these operation conditions, IMC crystals can be obtained with the yield over 80 mass% (approximately 85%). In order to distinguish the spherical material, the IMC crystals before drying was named as the spherical agglomerates and the IMC crystals after drying was named as the spherical particles, respectively. After the addition of anti-solvent, formation of the spherical agglomerates was observed. Then, the stirring operation was continued for 1 min. Since the spherical agglomerates were formed in this manner, washing operation was necessary. The spherical agglomerates were filtered, and then washed by using approximately 30 mL distilled water (anti-solvent for IMC and good solvent for NaCl). After the washing, these spherical agglomerates were dried for 24 h. The obtained spherical particles were observed by optical microscope. And, the XRD analysis was carried out.

Table 4-1 Operating conditions of anti-solvent crystallization in IMC-Acetone-NaCl aq. solution system

Run No.	NaCl concentration	Stirring speed	Mass of IMC-Acetone solution	Mass of NaCl aq. solution	Yield of IMC crystal
	[mass%]	[rpm]	[g]	[g]	[mass%]
(A)	10	835	15.1	26.4	87.4
(B)	15	835	15.1	39.5	82.2
(C)	20	835	15.1	46.3	84.0
(D)	10	1125	15.3	25.4	86.1
(E)	15	1125	15.2	34.2	86.7
(F)	20	1125	15.1	44.0	88.1
(G)	10	1660	15.1	22.6	86.7
(H)	15	1660	15.2	31.6	86.5
(I)	20	1660	15.1	37.9	83.9

4.2.3 Removable factor ω in the spherical agglomerates

In order to investigate the evaluation method about the amount of mother liquor, relationship between mother liquor and crystalline product was focused. **Figure 4-1** is conceptual diagram of the relationship between mother liquor and crystalline product until ideal washing. **Fig. 4-1(I)** shows relationship between mother liquor and single crystal which is not agglomerated. As shown in **Fig. 4-1(I)**, it is considered that there are liquid inclusion and adhering mother liquor in the case of single crystal after filtration. The adhering mother liquor is able to be removed by washing. However, liquid inclusion remained after ideal washing. In many researches, the liquid inclusion is focused in order to investigate purity of crystalline product which is not agglomerated (Saito *et al.*, 2000; Miki *et al.*, 2002). On the other hand, **Fig. 4-1(II)** shows the relationship between mother liquor and spherical agglomerates. As shown in **Fig. 4-1(II)**, it is considered that there are entrapped mother liquor, adhering mother liquor, liquid inclusion and liquid occlusion after filtration. Then, the entrapped mother liquor exists in empty space which is not completely enclosed and the liquid occlusion exists in sealed space. Therefore, the entrapped mother liquor and the adhering mother liquor are able to be removed by washing. However, the liquid inclusion and the liquid occlusion remained after ideal washing. From this consideration, in this present study, two kinds of mother liquor were defined as follows: (i) Removable mother liquor (the entrapped mother liquor and the adhering mother liquor) and (ii) Non-removable mother liquor (the liquid inclusion and the liquid occlusion). As in this present study, the attempt to segment the impurities into different parts has been also reported in the field of melt crystallization (Konig and Schreiner, 2001). The removable mother liquor is able to be removed by washing and the non-removable mother liquor remained after ideal washing. As shown in **Fig. 4-1(II)**, in the case of spherical agglomerates, the amount of removable mother liquor changes dynamically by washing operation (the washing method, the amount of washing solution and so on). This is because the washing effect on spherical agglomerates is depended on the aggregate structure (the bulk density, the porosity, and so on) of spherical agglomerates. Also, it is difficult to achieve the ideal washing for the spherical agglomerates in the actual washing process. Therefore, it was considered that the removable mother liquor remained after washing.

From these reasons, it is considered that the purity of spherical agglomerates is strongly influenced by the amount of removable mother liquor which is changed dynamically by aggregate structure. Therefore, the amount of removable mother liquor was focused in this present study.

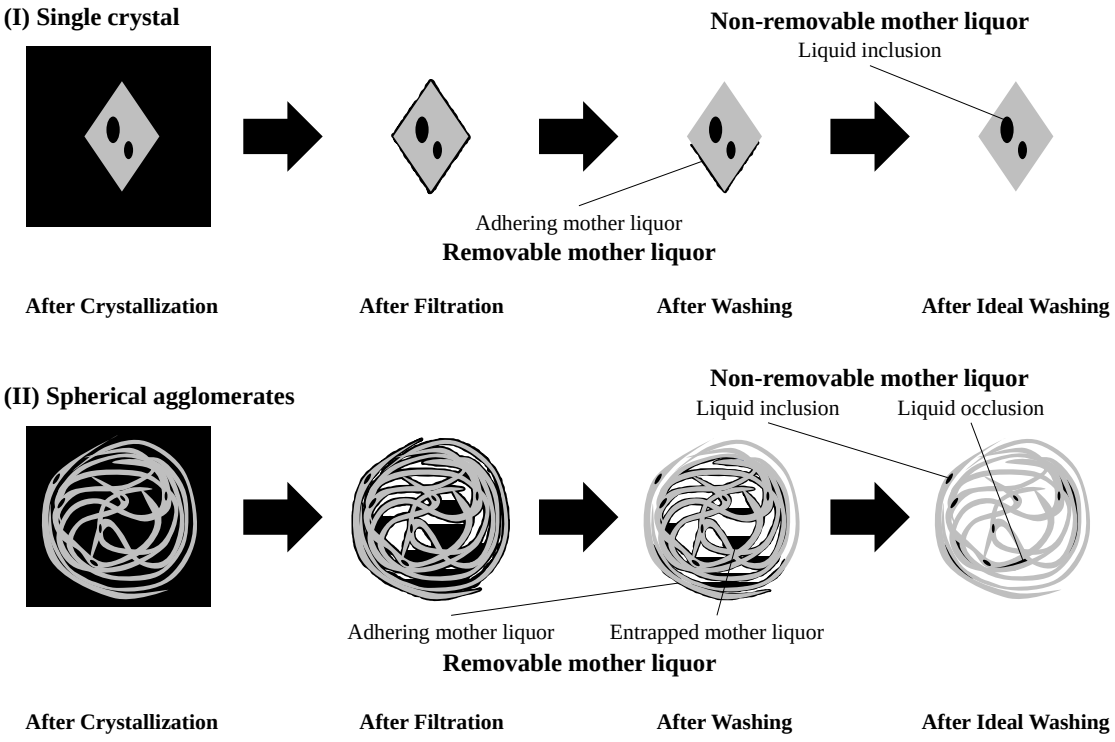

Fig. 4-1 Conceptual diagram of relationship between mother liquor and crystalline product until ideal washing: (I) Single crystal; (II) Spherical agglomerates

With regard to evaluation index for the purity of the crystalline product, inclusion factor α has been suggested (Hayakawa *et al.*, 1973). This inclusion factor α is fraction of the entrapped, adhered or included mother liquor (Matsuoka *et al.*, 1995). In this present study, in order to focus only the removable mother liquor, fraction of the removable mother liquor is defined as the removable factor ω and fraction of the non-removable mother liquor is defined as the non-removable factor δ, respectively. **Figure 4-2** is conceptual diagram of relationship among the inclusion factor α, the removable factor ω and the non-removable factor δ. This relationship could be expressed by the following equation:

$$\alpha = \omega + \delta \tag{4-1}$$

Fig. 4-2 shows relationship between the purity of crystalline product and the removable mother liquor. And, this relationship is expressed as Eq. (4-2):

$$M_S = (1 - \omega)M_S^* + \omega M_L \tag{4-2}$$

where M_S is apparent composition of crude crystal phase, M_S^* is composition of crystal including the non-removable mother liquor and M_L is composition of the mother liquor.

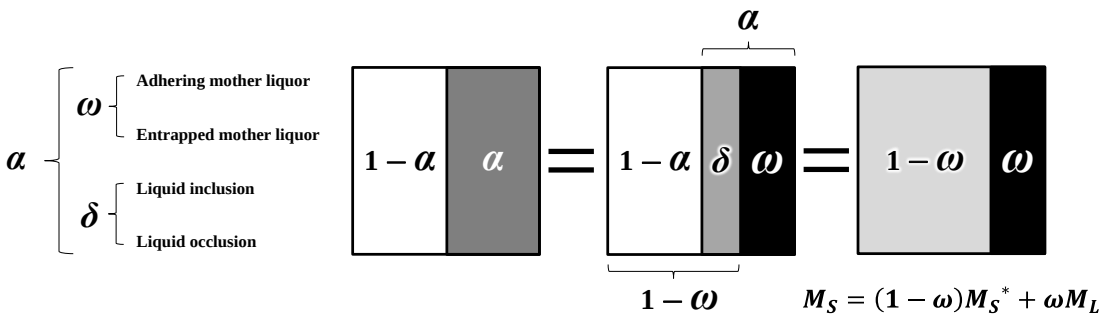

Fig. 4-2 Conceptual diagram of relationship among inclusion factor α, removable factor ω and non-removable factor δ

Figure 4-3 shows the drying process of spherical agglomerates. $M_{\text{IMC-I}}$ is mass of IMC crystal which was crystallized by anti-solvent crystallization, M_{REM} is mass of the removable mother liquor in spherical agglomerates, M_{NON} is mass of the non-removable mother liquor, $M_{\text{IMC-II}}$ is mass of the IMC crystal which was crystallized in the drying process and M_{NaCl} is mass of deposited NaCl in the spherical particle. As shown in **Fig. 4-3**, it was expected that the IMC crystals are crystallized and NaCl was deposited from the removable mother liquor in the drying process. When the spherical agglomerates after washing is completely dried and NaCl is not deposited in the non-removable mother liquor, M_{REM} is able to be calculated by using the following equation:

$$M_{\text{REM}} = \frac{R_{\text{NaCl}}}{C_{\text{NaCl}} - R_{\text{NaCl}} C_{\text{IMC}}} M_{\text{IMC-I}} \tag{4-3}$$

where R_{NaCl} is mass ratio of the deposited NaCl to IMC crystal, C_{NaCl} is NaCl concentration and C_{IMC} is IMC concentration in the mother liquor. R_{NaCl} was calculated from the XRD powder pattern by using the calibration curve of XRD peak intensity ratio and mass ratio. In this present study, ω is expressed as mass fraction of the removable mother liquor in spherical agglomerates after washing (Eq. (4-4)).

$$\omega = \frac{M_{\text{REM}}}{M_{\text{REM}} + M_{\text{IMC-I}} + M_{\text{NON}}} \tag{4-4}$$

By using ω, the amount of removable mother liquor in spherical agglomerates was evaluated.

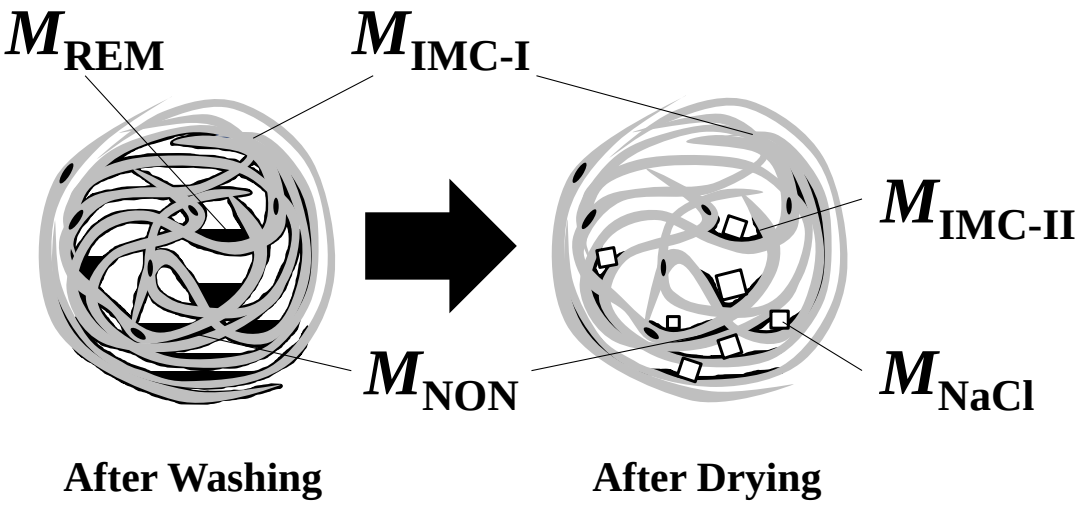

Fig. 4-3 Conceptual diagram of drying process about spherical agglomerates

4.3 Results and Discussion

4.3.1 Anti-solvent crystallization for IMC under the various operating conditions

The appearance of spherical particles was observed by using the optical microscope. **Figure 4-4** shows the typical photomicrographs for the appearance of spherical particles, the mean spherical particle size (L_M) and spherical particle size distribution under the different operating conditions ((A), (B), (C), (F) and (I)). The L_M and the spherical particle size distribution were obtained from each observation result. The L_M of 500 spherical particles was measured by using image analysis for each operating condition. As shown in **Fig. 4-4**, the spherical particles were obtained under all operating conditions. L_M tended to decrease with the increase of NaCl concentration ((A), (B) and (C)). In addition, L_M decreased with the increase of stirring speed ((C), (F) and (I)).

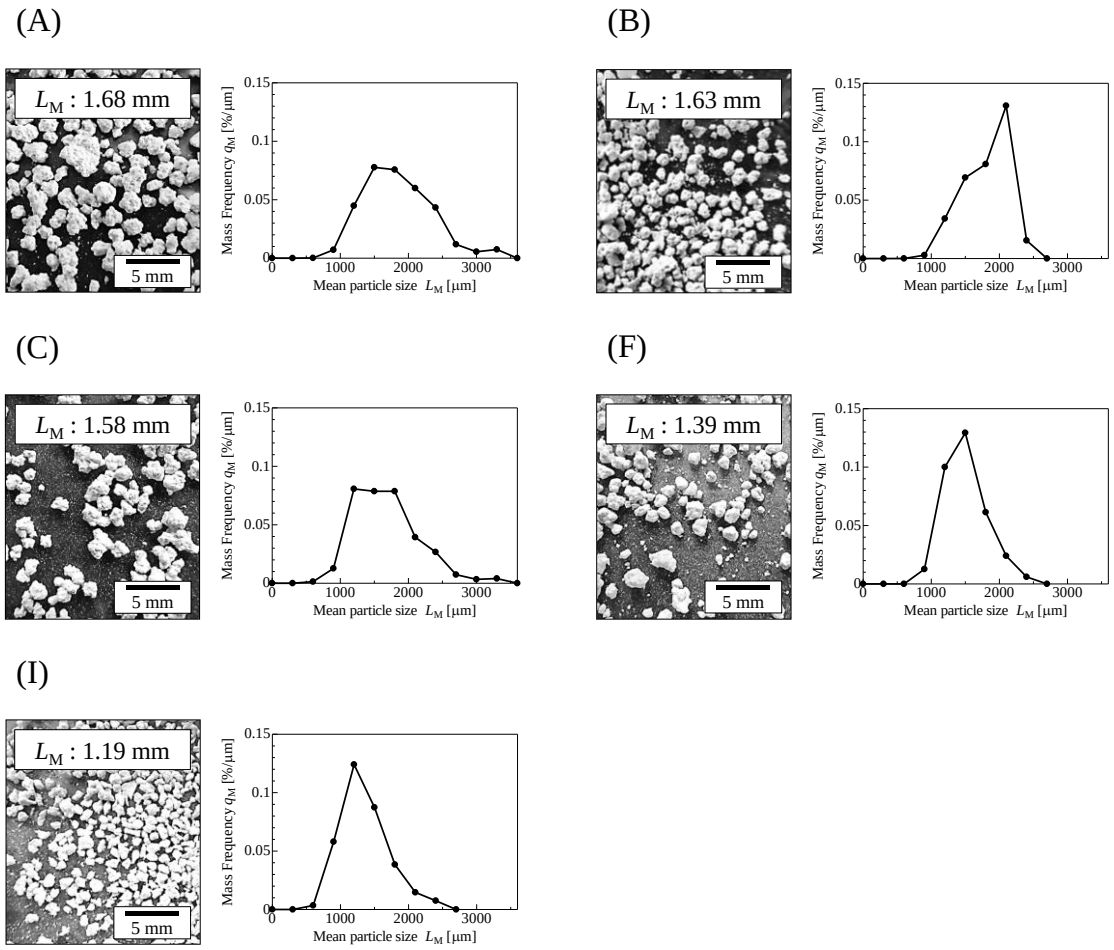

Fig. 4-4 Photomicrographs of the spherical particles which were obtained under different operating conditions (NaCl concentration, stirring speed): (A) 10 mass%, 835 rpm; (B) 15 mass%, 835 rpm; (C) 20 mass%, 835 rpm; (F) 20 mass%, 1125 rpm; (I) 20 mass%, 1660 rpm

XRD analysis was carried out for the spherical particles. **Figure 4-5** shows the typical X-ray diffraction patterns ((A), (B), (C), (F) and (I)). As shown in **Fig. 4-5**, IMC crystals (α-form) were crystallized and NaCl were deposited under the all operating conditions. Since the XRD peak intensity of NaCl was different, it was considered that the amount of deposited NaCl was changed depending on the operating conditions.

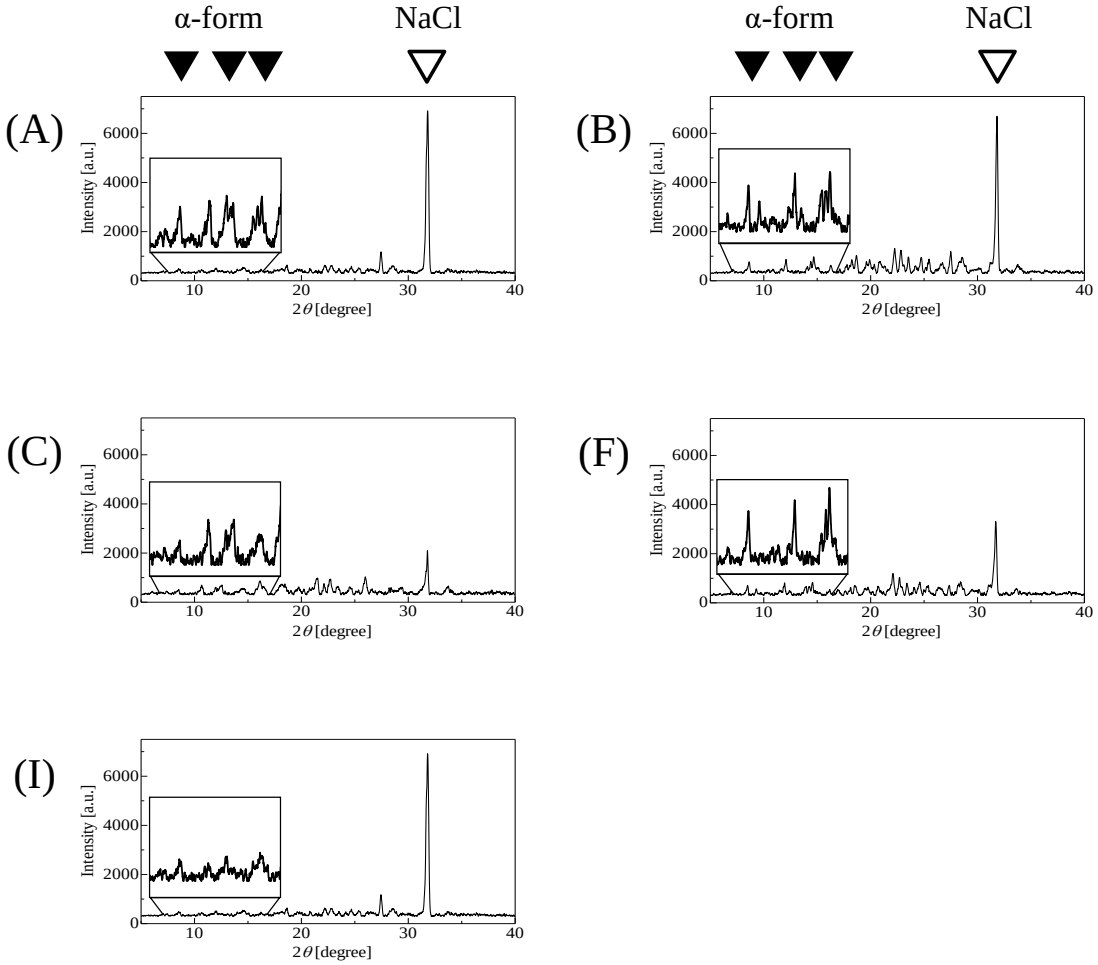

Fig. 4-5 X-ray diffraction patterns of the spherical particles which were obtained under different operating conditions

Figure 4-6 shows relationship between ω and operating conditions. As shown in **Fig. 4-6**, the value of ω was different when the spherical agglomerates were formed under the different operating conditions. So, it was found that ω was depended on the operating conditions. From the viewpoint of the relationship between ω and stirring speed at constant NaCl concentration, under the condition of low NaCl concentration, ω was almost not changed by the stirring speed. On the other hand, under the condition of high NaCl concentration, ω was significantly depended on the stirring speed and the value of ω decreased with the stirring speed. From the viewpoint of the relationship between ω and NaCl concentration at constant stirring speed under the condition of low stirring speed, ω was strongly influenced by the NaCl concentration. The value of ω decreased with the increase of NaCl concentration. On the other hand, under the condition of high stirring speed, ω was almost not changed by the NaCl concentration. From these results, it can be seen that ω decreased with the increase of NaCl concentration and the decrease of stirring speed. In this way, by using the removable factor ω, the amount of removable mother liquor in spherical agglomerates which were formed under the different operating conditions could be evaluated. Furthermore, in the case of this system, it was found that the value of ω was small under the condition of high NaCl concentration and low stirring speed.

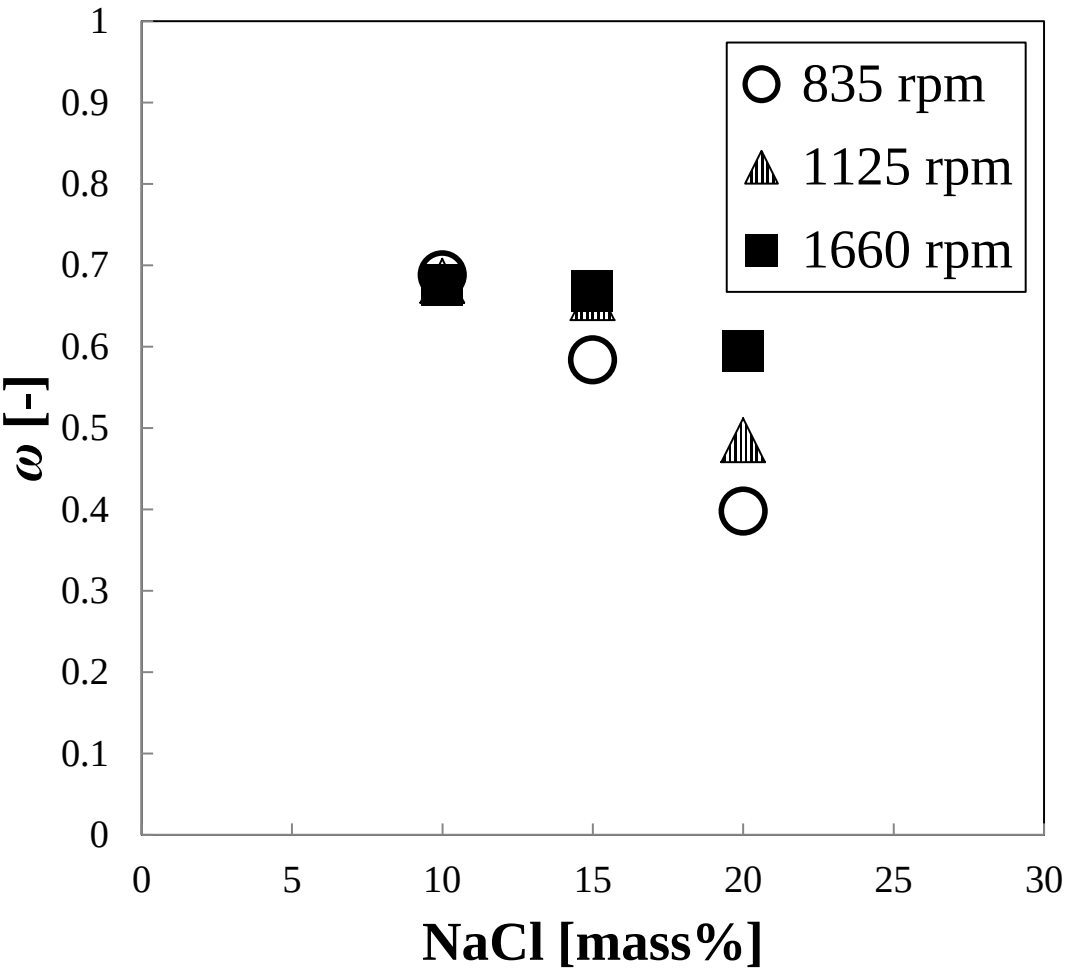

Fig. 4-6 Relationship between ω and operating conditions (NaCl concentration, stirring speed)

4.3.2 Relationship between the aggregate structure and the removable mother liquor

From the result of ω, it was considered that the aggregate structure of the spherical agglomerates was modified by the operating conditions. In many researches of spherical particle, it has been reported that density of the spherical particle is changed under the difference of operating conditions (Sano *et al.*, 1992; Martino *et al.*, 2000; Yadav and Yadav, 2009; Parida, 2010; Patil Pradnya *et al.*, 2011). So, in the case of IMC, the bulk density of the spherical agglomerates was also changed. However, since the removable mother liquor remained in empty space of the spherical agglomerates, it was considered that it was difficult to evaluate the amount of removable mother liquor. Therefore, in this present study, the porosity of spherical agglomerates φ was focused in order to evaluate the aggregate structure of spherical agglomerates. The value of φ was calculated by using the following equation (Parida, 2010):

$$\varphi = 1 - \frac{\rho}{\rho^*} \tag{4-5}$$

where ρ is the bulk density of spherical agglomerates and ρ^* is true density of the α-form crystal (1.40 [g/cm^3]) (Yoshioka *et al.*, 1994). When there is almost no difference between the mean spherical agglomerates size and the mean spherical particle size (L_M), the bulk density of spherical agglomerates ρ is able to be calculated by using the following equation:

$$\rho = \frac{M_P - M_{NaCl} - M_{IMC-II}}{V_P} \tag{4-6}$$

where M_P is mass of a spherical particle, M_{NaCl} is mass of deposited NaCl in a spherical particle and V_P is spherical particle volume which was calculated by using L_M. The relationship between aggregate structure of spherical agglomerates and removable mother liquor was investigated by using φ and ω.

Figure 4-7 shows results of φ and ω at each operating conditions. As shown in **Fig. 4-7**, value of φ decreased with the increase of NaCl concentration under the condition of all stirring speeds. However, the decrement of φ was depended on the stirring speed. Under the condition of low stirring speed, the value of φ significantly decreased with the increase of NaCl concentration. On the other hand, under the condition of high stirring speed, φ was almost constant. From these results, it was considered that the aggregate structure of spherical agglomerates was different at each stirring speed. It is whether or not the formed aggregate structure has the dependency of NaCl concentration on φ. From the viewpoint of ω, the formed spherical agglomerates under the condition of low stirring speed have advantage because the value of ω significantly decreased. So, it was concluded that the removable mother liquor was easy to be removed by washing from the spherical agglomerates obtained under the condition of the low stirring speed. Also, as shown in **Fig. 4-1(II)**, it was considered that the amount of removable mother liquor decreased with the value of φ. The value of φ was the lowest under the condition of high NaCl concentration. Therefore, from the viewpoint of φ, the value of ω was small under the condition of high NaCl concentration and low stirring speed. So, the validity of evaluation method by using ω was confirmed based on the consideration of aggregate structure.

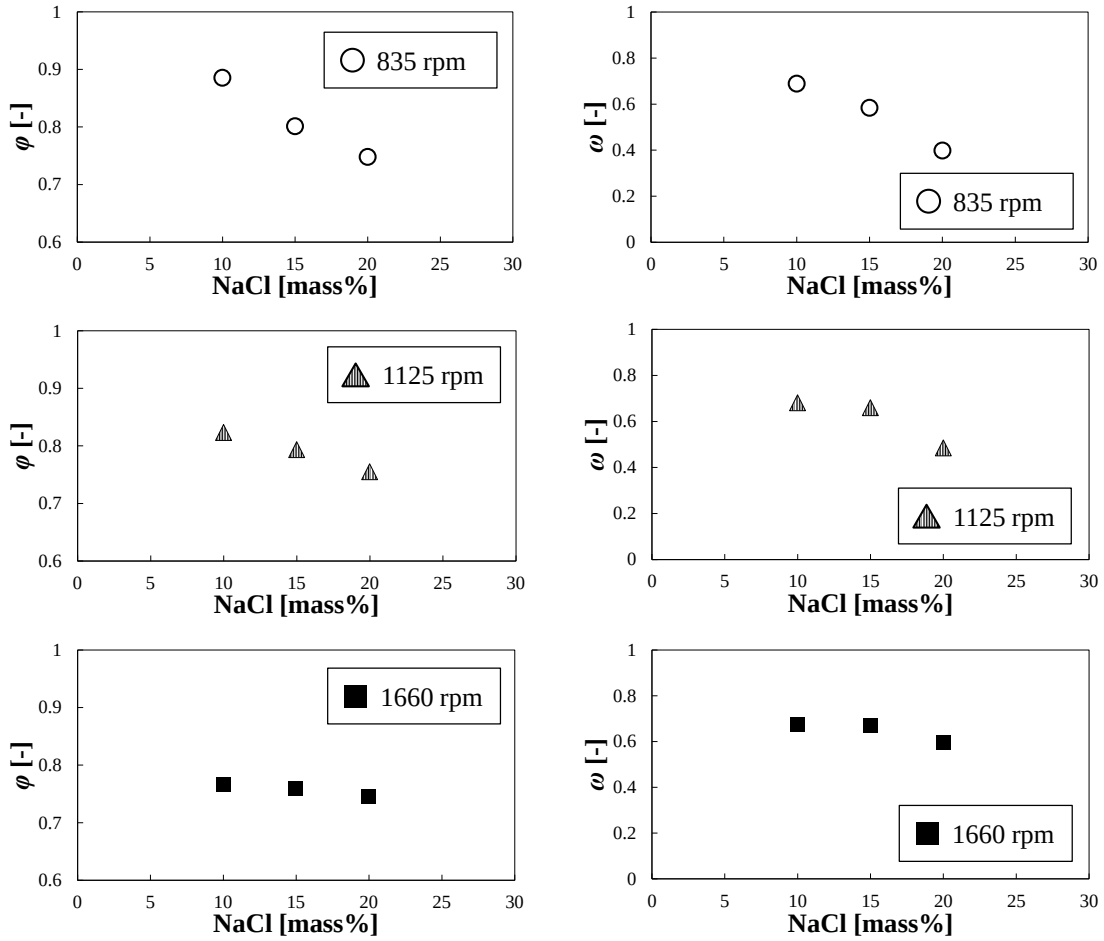

Fig. 4-7 Effect of NaCl concentration on φ (left side) and ω (right side) for each stirring speed

4.4 Conclusion

In order to investigate the amount of mother liquor in the spherical agglomerates, the removable mother liquor was focused and the removable factor ω (defined by the mass fraction of removable mother liquor) was newly proposed. In the case of IMC-Acetone-NaCl aq. solution system, the quality of spherical agglomerates depended on the NaCl concentration and stirring speed. The amount of removable mother liquor in spherical agglomerates which was obtained under these conditions was evaluated by using ω. From the experimental results, the removable factor ω depended on these operating conditions. Also, these experimental results were valid from the viewpoint of φ (porosity of spherical agglomerates) which was related to the aggregate structure. So, it was found that the removable factor ω evaluated the amount of removable mother liquor in spherical agglomerates. Under the condition of high NaCl concentration and low stirring speed, the value of ω was small. It was considered that the aggregate structure which was easy to remove the removable mother liquor by washing could be formed under these conditions.

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Chapter 5

Summary and Conclusions

In order to satisfy the product quality and the operability simultaneously, the simultaneous control method of two crystal qualities was examined. The main conclusions of the respective chapters are as follows:

In Chapter 1, “Introduction”, the background, the previous studies and the objective of this thesis was shown. Since it was important to consider the product quality and the operability of production process in various fields and products, it was required to develop the simultaneous control method of two crystal qualities. From the result of reviewing the previous studies, it was expected to change the relationship between the crystal quality and the degree of supersaturation when the crystallization field was non-uniform. Therefore, it was concluded that the objective of this thesis is to examine the development of the simultaneous control method of two crystal qualities from the viewpoint of the crystallization field.

In Chapter 2, “Crystallization operation method for recovering Mg resources from the sea water desalination process”, the prevention method of ultra-fine Magnesium Hydroxide (MH) crystal deposition was examined. In this present study, the powder addition method (Conventional) and the tablet addition method (New) were compared about the addition method of Calcium Hydroxide (CH) which is the raw material. As experimental results, it was found that the particle size of MH crystals increased in the case of the CH tablet addition method. So, it was considered that the purity and the particle size of MH crystal were satisfied simultaneously by using the CH tablet addition method. Then, in the case of CH tablet, it was expected that the dissolution rate was slow. So, the degree of supersaturation could be generated only around the CH tablet. It could be seen that the crystallization field was non-uniform by using the CH tablet addition method. So, it was considered that the simultaneous control method of two crystal qualities was achieved by using the non-uniform crystallization field in the case of MH crystallization.

In Chapter 3, “Development of simultaneous control of polymorphism and morphology in Indomethacin crystallization”, the modification of the morphology (external shape) of α-form agglomerates was examined in Indomethacin (IMC) crystallization. In this present study, the addition of third component was carried out for the anti-solvent crystallization (IMC-Acetone (good solvent)-Water (anti-solvent)) (Conventional). As the result of the addition of third component, the liquid-liquid phase separation (LLPS) occurred and then, the dispersion of oil droplets was produced

by stirring operation. After the filtration and the drying process, the α-form spherical particles were obtained as the final crystalline product. So, the polymorphism and the morphology could be simultaneously satisfied. Then, the degree of supersaturation was generated inside the each oil droplets because the oil droplets include the many IMC components. It could be seen that the crystallization field was non-uniform by the dispersion of oil droplets. So, it was considered that the simultaneous control method of two crystal qualities was achieved by using the non-uniform crystallization field in the case of IMC crystallization.

In Chapter 4, "Proposal of evaluation method for amount of mother liquor in spherical agglomerates", it was attempted to evaluate the purity of the α-form spherical agglomerates by using the evaluation index of the amount of mother liquor. In this present study, the removable factor ω (the mass fraction of removable mother liquor) was newly defined. By using this ω, the evaluation of purity was carried out for the spherical particles which were obtained under the various operation conditions. Then, the concentration of third component and the stirring speed were selected as the operation conditions because the dispersion of oil droplets was strongly dependent on these conditions. As the evaluation result, it was found that the value of ω decreased with the increase of the concentration of third component and the decrease of the stirring speed. So, the effect of the simultaneous control method (polymorph and crystal morphology) on other crystal quality (purity) could be investigated. In addition, from these results, it could be considered that the purity of α-form spherical agglomerates was changed by the difference of dispersion behavior of oil droplets.

In general conclusion, the simultaneous control method of two crystal qualities could be suggested from the viewpoint of crystallization field (**Fig. 5-1**). In the case of Magnesium hydroxide and Indomethacin, two crystal qualities could be satisfied simultaneously by utilizing the non-uniform crystallization field. Therefore, it was expected to change the relationship between the crystal quality and the degree of supersaturation by the difference of crystallization field. In addition, the effect of simultaneous control method of polymorph and morphology on the purity was investigated. As the evaluation result, it was expected to also change the relationship between the crystal quality and the degree of supersaturation by the difference of dispersion behavior of crystallization field. So, when the dispersion behavior of crystallization field was controlled, it was considered that the desired relationship between the crystal quality and the degree of supersaturation was selected.

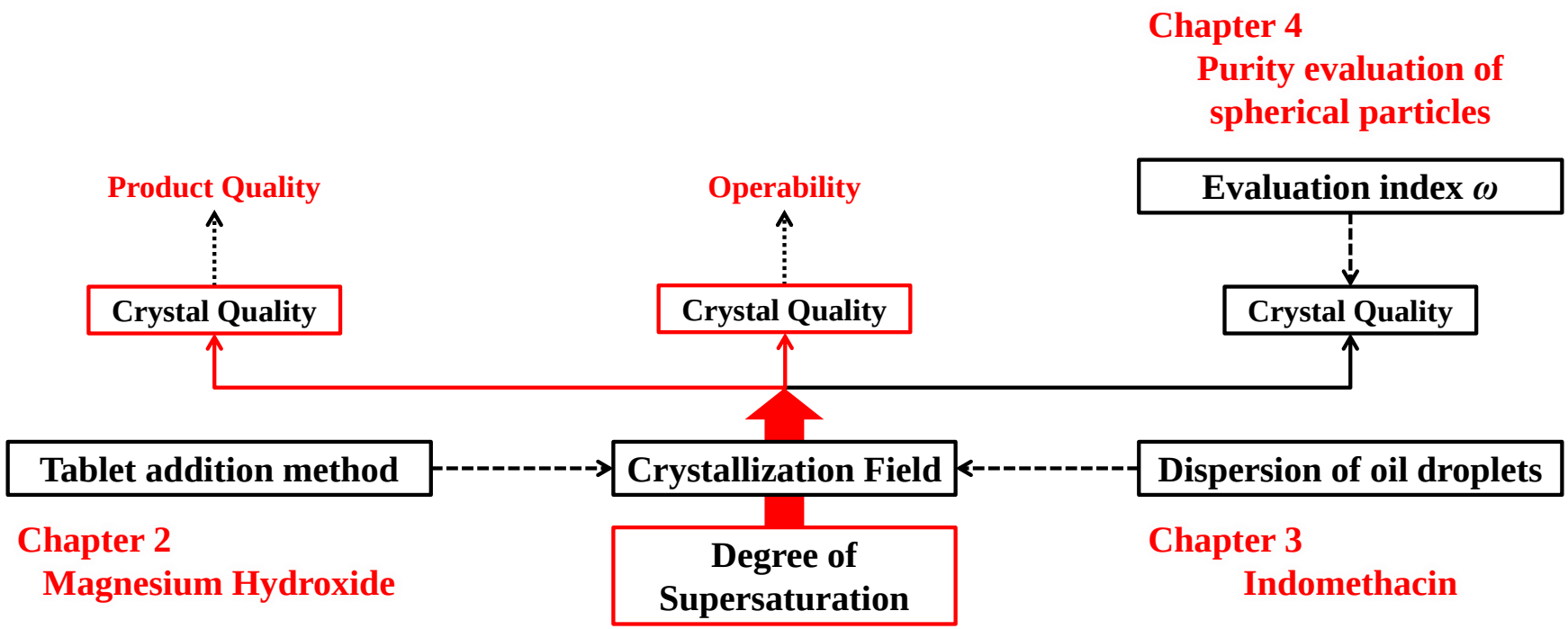

Fig. 5-1 Summary of this thesis

From the viewpoint of profile of *PC-S* or *OC-S*, the simultaneous control method of two crystal qualities could be considered. **Fig. 5-2** is the conceptual diagram of method to change the profile of *PC-S* or *OC-S*. By utilizing the non-uniform crystallization field, the profile of *PC-S* or *OC-S* is variously changed. Then, the desired profile might be selected by controlling the dispersion behavior of non-uniform crystallization field. As the result, two crystal qualities could be satisfied simultaneously. In the future, there is possibility that all crystal qualities are satisfied simultaneously by using this method.

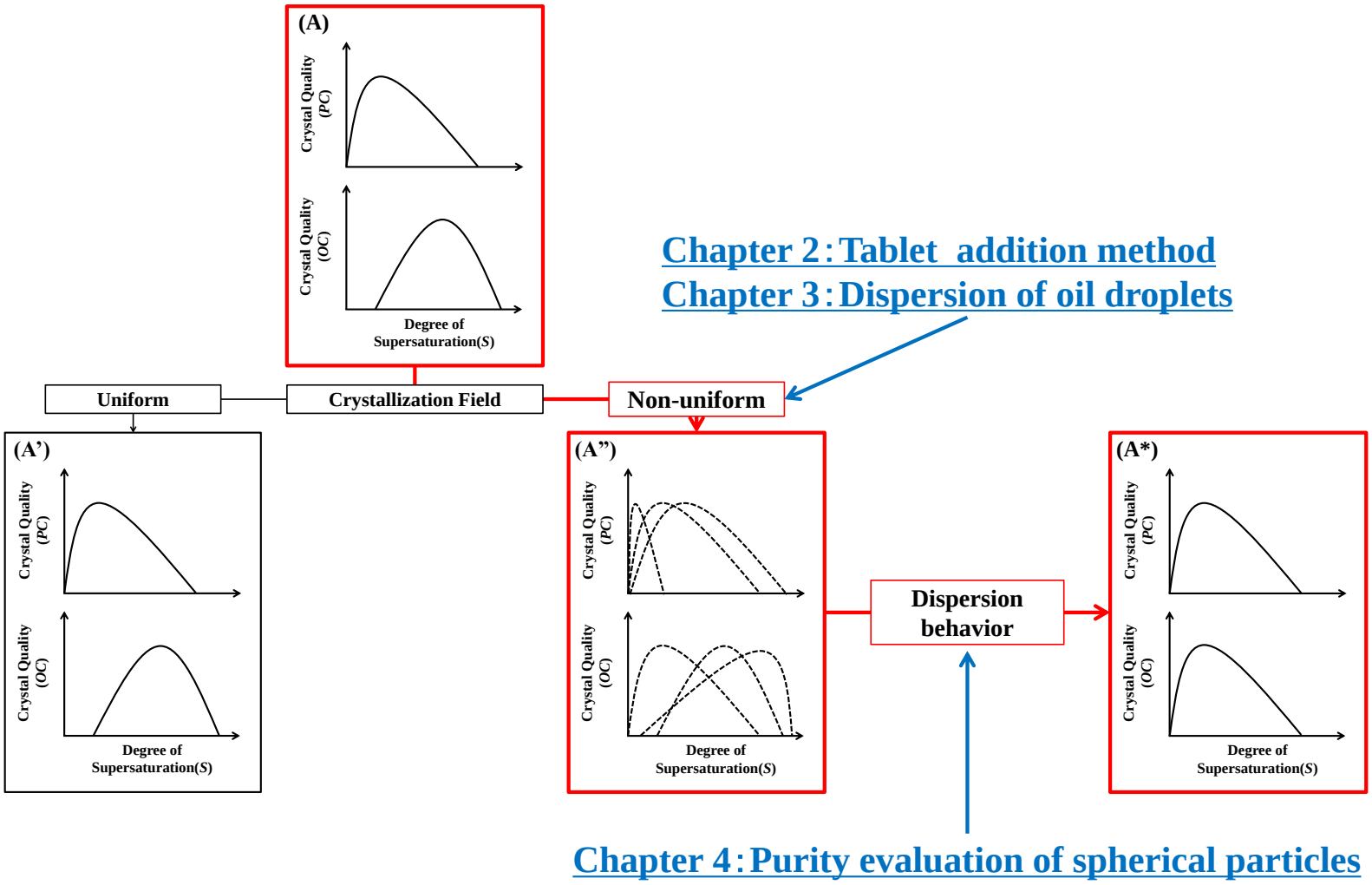

Fig. 5-2 Conceptual diagram of method to change the profile of *PC-S* or *OC-S*

List of publication

(1) Wada, S., J. Iijima, H. Takiyama, “Crystallization operation method for recovering Mg resources from the sea water desalination process”, *J. Chem. Eng. Jpn.*, **48**, 94-98 (2015.01.20) (Related to chapter 2)

(2) Wada, S., S. Kudo, H. Takiyama, “Development of simultaneous control of polymorphism and morphology in indomethacin crystallization”, *J. Cryst. Growth*, **435**, 37-41 (2016.02.01) (Related to chapter 3)

Submitted article

(1) Wada, S., H. Takiyama, “Proposal of evaluation method for amount of mother liquor in spherical agglomerates”, *J. Chem. Eng. Jpn.*, Accepted (2017.04.20) (Related to chapter 4)

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