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Development of Crystallization Operation for Obtaining Desired Crystalline Particles Based on Salting-out Phenomena

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Summary

Spherical crystallization produces agglomerated crystalline particles, which has been attracting attention improve particle handling. The previous study reported that indomethacin (IMC) α-form crystals, which is usually cotton-like crystal, were formed spherical crystalline agglomerates through the liquid-liquid phase separation (LLPS) by using NaCl as an entrainer. However, the NaCl and the mother liquor in which the crystallized substance was dissolved are usually trapped inside the agglomerated particle as an occlusion, resulting in a significant decrease in purity. Therefore, removing the mother liquor including the NaCl from crystalline agglomerated particles is important to improve crystal quality.

Conventionally, reslurry that is diffusive washing operation is empirically used to remove the mother liquor trapped in the particles. Since particles determine the removal rate of the mother liquor during the reslurry operation, investigation of the influence of the particle properties on removal of the mother liquor from the particles is required to recover the purity.

The purpose of this study is investigation of the particle design for the effective removal of mother liquor based on the quantitative evaluation of mother liquor discharge during reslurry operation. In this study, an anti-solvent crystallization system that involved an IMC–acetone–NaCl aqueous solution was used. The reslurry was performed using particles of various sizes prepared by controlling the agitation speed during crystallization.

It was found that the removal ratio of the mother liquor from the crystalline agglomerates was affected by the particle size. The relationship between the particle size and the reslurry rate was determined by evaluating the reslurry rate coefficient using kinetic analysis. The results showed that the reslurry rate was strongly dependent on the particle size. Consequently, we revealed a design strategy of crystalline agglomerated particles obtained by crystallization for improving the reslurry rate.