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Development of Continuous Crystallization to Control the Properties of NaCl Crystals －Spherical Crystallization Using MSMPR Crystallizer－

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Summary

Inorganic salts such as NaCl are generally industrially produced by evaporative crystallization, but there are also many reports on poor solvent addition crystallization (antisolvent method) without evaporation operation. The antisolvent method can generally be operated at room temperature, and it is advantageous in view of energy without heating or cooling operation during crystallization. In addition, there is an advantage that high-purity crystals can be obtained in a relatively high yield in a relatively instant. However, the obtaining crystals have various shapes, resulting in low crystal quality. It is difficult to control the crystal quality required for production, particularly control of particle size and particle size distribution.

We have developed integration and serialization of pharmaceutical manufacturing processes so far. Further, our group are focusing on the spherical crystallization method which can also control the particle agglomerates during the crystallization process based on antisolvent method. In conventional antisolvent method, two kinds of solvents, a good solvent and a poor solvent, are used, but in the spherical crystallization particle method, by adding a small amount of a third solvent which lead to phase separation in mother liquor. The third solvent works as a binder between crystalized fine particles, and then granulation proceeds during crystallization. Furthermore, in this method, the particle diameter can be controlled by the amount of bound solvent.

Therefore, in this research, the spherical crystallization established in the pharmaceutical field was applied to the salt production process, and the crystal quality which is a disadvantage of the antisolvent salt have possible to improve to a practically usable level. Meanwhile, batch preparation requires scale-up study for commercial production. Therefore, a continuous process of spherical crystallization was performed using a mixed-suspension, mixed-product-removal (MSMPR) crystallizer.

First, the experimental conditions of NaCl spherical crystallization in batch process was optimized. In this study, water was used as a good solvent for NaCl, ethanol was used as a poor solvent, and dichloromethane was used as a binding solvent. Continuous spherical crystallization was performed with an MSMPR crystallizer using the conditions that enabled spherical crystallization in a batch process.

In the spherical crystallization of NaCl crystal, it was possible to prepare a granulated product in which primary fine particles were agglomerated. In addition, the NaCl spherical crystallization was able to apply a continuous process by MSMPR. In this study, dichloromethane was used as a bonding solvent, but it is necessary to examine other excipients for granulation for practical use in the future.