Operation Design of Reactive Crystallization for the Quality Improvement of Crystalline Particles

H. Takiyama
Department of Chemical Engineering, Tokyo University of Agriculture and Technology (TUAT)
E-mail: htakiyam@cc.tuat.ac.jp

Abstract: Some organic crystals used in pharmaceuticals have complex external shapes, such as sea urchin-like. However, such crystals are avoided due to concerns about crystal quality, such as morphology, particle size distribution and purity. To improve the quality of crystalline particles, establishment of built-in quality method is needed. Seeding method is used as one of method to built-in quality for size distribution. The inner seeding method has an advantage because generates seed crystals without contamination within the crystallizer. One method of producing inner seed is to use modulation operation in the initial stage of crystallization operation [1,2]. Particularly the modulation operation with undersaturation may have the effect of disintegrating agglomeration by dissolving the sea urchin-like crystals. Furthermore, it has been reported that modulation operation with undersaturation is also effective in improving the external shape [1]. Therefore, the goal of this study is to investigate modulation operation with undersaturation and the use of inner seed to build-in quality. The conceptual diagram is shown in **Fig. 1**.

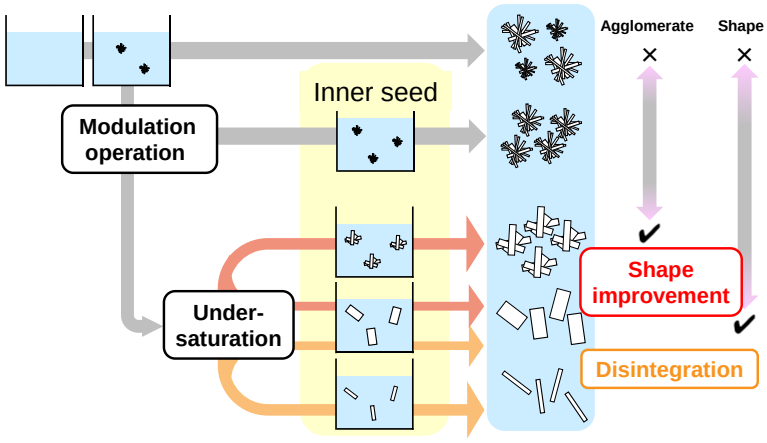

Fig. 1 Conceptual diagram of strategy for quality improvement.

The effect of modulation operation with undersaturation on the external shape was investigated. The reaction system was L-Aspartate sodium (L-AspNa) - HCl, the target was L-Aspartic acid (L-Asp). The modulation operation with undersaturation was performed by alternately adding L-AspNa solution or HCl solution at pump. The total amount of L-AspNa and HCl substance in all experiments was remained constant. First, modulation operation was performed to produce inner seed, but the degree of agglomeration was worse than that of control experiment without producing inner seed. The dissolution of sea urchin-like crystals was observed using a growth cell [3] to investigate why disintegration did not occur.

The modulation operation was changed to increase the amount of inner seed, the percentage of product crystalline particles classified as high agglomeration was improved. When modulation operation by intermittent solution addition was also introduced to grow the inner seed, the generation of sea urchin-like crystals was suppressed.

It was found that the external shape of crystalline particles can be improved by modulation operation of producing inner seed, and the particle size distribution can be improved by devising a method of producing seed crystals.

Reference:

1) Sato, E., Y. Seki and H. Takiyama, Control of reaction crystallization of organic compounds using the supersaturation profile, *Journal of Chemical Engineering of Japan*, 2019, **52**, 7, 599-604
2) Ohyama, M., S. Amari and H. Takiyama, Operation design of reactive crystallization using homogeneity evaluation for the quality improvement of agglomerated crystalline particles, *Crystals*, 2021, **11**, 844
3) Abe, S., S. Amari and H. Takiyama, Crystal size distribution and morphology control of sea urchin-like crystal by using irreversibility of external shape change, *Journal of Crystal Growth*, 2023, **614**, 127216

Keywords: Reactive crystallization; Modulation operation; Agglemeration