Novel Continuous Crystallization Configurations for Improved Yield, Purity and Controlled Crystal Size Distribution

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Continuous crystallization process has potential advantages such as lower cost and improved flexibility in pharmaceutical production when compared to batch crystallization. A good continuous crystallization process should achieve a high product yield and purity comparable to current batch crystallization processes. The aim of this thesis is to develop novel continuous crystallization processes to enhance the final yield while control the quality of the crystal product. Three different approaches were studied: (1) the use of continuous solids recycle to enhance the yield by increasing the crystal surface area and total crystal mass deposition; (2) the optimization of multistage continuous mixed-suspension, mixed-product removal (MSMPR) crystallization cascade to minimize the number of stages and total residence time; (3) the combination of impurity complexation and nanofiltration to remove the impurity that has similar molecular weight and structure to the active pharmaceutical ingredient (API).

The first method, solids recycle, successfully increased the surface area of crystals in the crystallizer thus increasing the mass deposition rate. With solids recycle to the second stage and both stages, yield close to that of a batch at equilibrium was achieved. The product purity remained the same while the yield was enhanced. The second method proved that optimization of stage conditions could help obtain high yield and purity within short residence time. Different behaviors of the impurities were investigated and the impurity distribution model estimated the highest product purity achievable of the process. A population balance model combined with distribution coefficient of different impurities was developed to optimize the process. The third method took the advantages of the two established approaches: impurity complexation and nanofiltration. Complexing agent formed hydrogen bonds with the impurity specifically, thus reduced the structure similarity of the API and impurity. Nanofiltration membrane separated the API and complex in the mother liquor. By recycling the purified mother liquor back to the crystallizer, the process yield and product purity were improved at the same time.

This thesis demonstrates that process design and optimization based understanding of crystallization kinetics at different operation conditions can benefit the performance of continuous crystallization at steady state and thus help the pharmaceutical industry in moving from batch to continuous manufacturing.

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