Abstract

Crystallization of active pharmaceutical ingredients (API) is one of the most important separation and purification operations in pharmaceutical industry. However, it is also one of the most complex ones. Desired physicochemical properties of solid crystalline product, such as particle size distribution, can be achieved by choosing appropriate operating conditions. This requires a detailed understanding of the process. Mathematical modelling is a useful tool for design, optimization and control of crystallization processes. However, due to the complexity of the process, it has not yet been generalized to a similar extent as modelling of other unit operations. Its potential is thus much greater than its current contribution.

In this doctoral research work, we developed a mathematical model for batch crystallization of fesoterodine fumarate ingredient. The model is based on population, mass and energy balance equations, thermodynamic equilibrium between solid ingredient and its solution and kinetic equations of nucleation, crystal growth, agglomeration, and dissolution. In the first part of the work, crystallization of fesoterodin fumarate from 2-butanone was studied. Based on thermodynamic equilibrium, a specified number of crystallization and dissolution experiments under various operating conditions was performed. Both processes were monitored by different in-line analytical techniques, while initial and final crystal populations were characterized by microscopic techniques. Kinetic parameters were determined by regression analysis of simulated and experimental results. High secondary nucleation rate and slow crystal growth rate are characteristic for fesoterodine fumarate crystallization in 2-butanone. Cooling rate was found to be the most important operating condition for crystallization progress. The usefulness of the model was validated by temperature cycling crystallization experiments, where we showed good final particle size distribution prediction.

In the second part of the work, we used a similar approach to study fesoterodin fumarate crystallization from 2-butanone and cyclohexane as antisolvent. The presence of cyclohexane was found to decrease solubility and increase kinetic rates of all studied mechanisms. The extended model was validated by comparison with temperature cycling and antisolvent addition experiments, as well as smaller and larger scale experiments. In all cases, good agreement between model and experimental results was observed. Finally, we showed that the model may be used for prediction of optimal cooling rate, stirring rate, and amount of seed to crystallize products with desired crystal size distribution.