ABSTRACT

The purification of most active pharmaceutical ingredients (APIs) is primarily achieved through crystallization, conducted in batch, semi-batch, or continuous modes. Recently, continuous crystallization has gained interest in the pharmaceutical industry for its potential to reduce manufacturing costs and maintenance. Crystal characteristics such as size, purity, and polymorphism significantly affect downstream processes like filtration and tableting, as well as physicochemical properties like bioavailability, flowability, and compressibility. Developing an optimal operation that meets the critical quality attributes (CQAs) of these crystal properties is essential.

This dissertation begins by focusing on designing an innovative integrated crystallization system to enhance control over crystalline material properties. The system expands the attainable region of crystal size distribution (CSD) by incorporating multiple Mixed-Suspension Mixed-Product Removal (MSMPR) units and integrating wet milling, classification, and a recycle loop, enhancing robustness and performance. Extensive simulations and experimental data validate the framework, demonstrating significant improvements in efficiency and quality. The framework is further generalized to optimize crystallizer networks for controlling critical quality attributes such as mean size, yield, and CSD by evaluating various network configurations to identify optimal operating parameters.

The final part of this work concentrates on using the framework to improve continuous production of a commercial API, Atorvastatin calcium (ASC), aiming for higher yield and lower costs. This approach establishes an attainable region to increase crystal sizes and productivity. Due to ASC's nucleation-dominated nature, the multi-stage system could not grow the crystals sufficiently to bypass granulation, the bottleneck process in ASC manufacturing. Therefore, spherical agglomeration was proposed as an intensification process within an integrated two-stage crystallization spherical agglomeration system to control the size and morphology of ASC crystals and improve downstream processing and tableting. This method proved highly successful, leading to the development of an end-to-end continuous manufacturing process integrating reaction, crystallization, spherical agglomeration, filtration, and drying. This modular system effectively addressed challenges in integrating various unit operations into a coherent continuous process with high production rates.