

ABSTRACT

Crystallization is often the final stage in active ingredient production, where separation and purification are performed, and the resulting crystal size, shape, and polymorphic form, directly determine product purity, process yield, and downstream processability. Achieving precise control over these attributes is essential for producing high-quality solid products efficiently and safely; however, challenges in scale, variability, and experimental intensity limit process optimization efforts. While continuous crystallization offers advantages such as streamlined operations, reduced supply chain vulnerabilities, and lower costs, its complexity makes process development both experimentally both time-consuming and material intensive. Modeling approaches can help in predicting process behavior, yet these methods often require significant computational resources. To address these limitations, automation of the crystallization experiments can minimize human error, accelerate systematic exploration of operating conditions, and support automated model building to streamline the entire process development.

This thesis advances process intensification of crystallization through the development of continuous process platforms, modularization, model-based digital design, and automation. Continuous crystallization was investigated using three platforms, including a mixed-suspension, mixed-product removal (MSMPR) cascade system, an oscillatory MSMPR (MSMPRo), and a continuous oscillatory baffled crystallizer (DN15). Their performance was compared against batch crystallization in terms of size distribution, crystal quality, and production rate. A Kinetically Informed Thermodynamic (KIT) design framework was developed for solvent screening, enabling early prediction of solvent influence on crystallization behavior to guide process design. Population balance modeling was then applied to construct a digital twin of the process, allowing for multiobjective optimization. Finally, an automated experimental interface, Omnibus, was developed to control crystallization equipment, detect steady-state, and execute automated design of experiments in both batch and continuous operation with integration of modeling techniques for automated model building. Overall, these contributions demonstrate how process intensification strategies can improve control, safety, and efficiency in crystallization, enabling more systematic and efficient process development.