Process intensification through control, optimization, and digitalization of crystallization systems

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Crystallization is a purity and particle control unit operation commonly used in industries such as pharmaceuticals, agrochemicals, and energetics. Often, the active ingredient's crystal mean size, polymorphic form, morphology, and distribution can impact the critical quality attributes of the final product. The active ingredient typically goes through a series of process development to optimize and scale-up to reach production scale. Guided by the FDA, the paradigm shift towards continuous processing and crystallization has shown benefits in introducing cheaper and greener technologies and relieving drawbacks of batch processing. To achieve successful batch scale-up or robust continuous crystallization design, process intensification of unit operations, crystallization techniques, and utilizing data driven approaches are effective in designing optimal process parameters and achieve target quality attributes.

In this thesis, a collection or toolbox of various process intensification techniques was developed to aid in control, optimization, and digitalization of crystallization processes. The first technique involved in developing a novel feedback control algorithm to control agrochemical crystals of high aspect ratio to improve the efficiency of downstream processes (filtration, washing, and drying). The second technique involves the further improvement of the first technique through digitalization of the crystallization process to perform model-based optimization and obtain a more optimal operating profile while reducing material consumption and experimentation time. The third method involves developing a calibration procedure and framework for in-line video microscopy. After a quick calibration, the in-line video microscopy can provide accurate real-time measurements to allow for future control capabilities and improve data scarcity in crystallization processes. The last technique addresses the need for polymorphic control and process longevity for continuous tubular crystallizers. Through a sequential stirred tank and tubular crystallizer experimental setup, the control of polymorphism, particle mean size, and size distribution were characterized. Each part of this thesis highlights the importance and benefits of process intensification by creating a wholistic process intensification framework coupled with novel equipment, array of PAT tools, feedback control, and model-based digital design.