

ABSTRACT

Yang, Yang. Ph.D., Purdue University, December 2016. Development of Novel Design and Control Approaches for Integrated Crystallization Operation and Systems. Major Professor: Zoltan K. Nagy.

Crystallization is an important separation and purification technique for a wide variety of solid products in pharmaceutical, food and fine chemical industries. The production of more than 90% of the active pharmaceutical ingredients (APIs) involves crystallization. Therefore, it is crucial to design and control pharmaceutical crystallization processes so that the desired process requirement and product critical quality attributes (CQAs), including process yield, crystal purity, crystal size distribution (CSD), crystal shape and polymorphic form can be obtained. Studies about cooling or antisolvent only batch crystallization of pure APIs have been extensively reported in the literature in the last century. But design and control of more complex and integrated crystallization operation and systems require further development to meet the needs of improved CQAs, simplified process design and automated process control in pharmaceutical manufacturing.

This dissertation focuses on the development of novel design and control approaches for three different types of integrated crystallization operation and systems: (1) combined cooling/antisolvent crystallization (CCAC) systems; (2) integrated crystallization and wet milling operation; (3) crystallization systems in the presence of impurities. The design and control of both batch and, more recently, continuous crystallization systems were studied using population balance model (PBM), process analytical technology (PAT) and feedback control strategies.

First, CCAC systems in both batch and continuous mixed suspension mixed product removal (MSMPR) cascade crystallizer configurations were designed and controlled via model-based approaches. PBM-based optimization techniques were used. A linear operating profile based fast

design strategy was developed to achieve desired crystal size and yield for batch CCAC systems, which was experimentally validated. The steady-state operation of continuous MSMPR cascade crystallizers was optimized and compared with batch operation. An efficient startup procedure was modeled and demonstrated able to provide large improvement on startup duration and waste minimization. In addition, two control frameworks, decentralized proportional-integral-derivative (PID) control and nonlinear model predictive control (NMPC), were investigated in two stage MSMPR cascade crystallizers, with both yield and crystal size targeted as controlled variables, providing a systematic strategy to compute attainable regions of particle size under different control configurations.

The second part of this dissertation is dedicated to design and control integrated crystallization and wet milling operation. A toothed rotor-stator lab scale wet mill unit was integrated with continuous mixed suspension mixed product removal crystallizer (MSMPRC). It was used upstream as a continuous nucleator for in situ seed generation, and used downstream as a continuous size reduction unit through recycling. The experimental results indicate that the integrated crystallization and wet milling operation can lead to improved yield, CSD and process startup compared to crystallization operation without wet milling. A PAT-based feedback control approach called automated direct nucleation control (ADNC), was developed to achieve consistent and automated closed-loop control on CSD in continuous MSMPR cascade crystallizers. This ADNC approach was also extended to integrated crystallization and wet milling operation, and a wet milling based automated direct nucleation control (WMADNC) approach was developed to achieve improved control of CSD.

In the last part of this dissertation, an ultra-performance liquid chromatography (UPLC) system with automated process sampling and dilution was developed as an online PAT tool for the first

time to monitor crystallization systems in the presence of impurities. Three online UPLC-based applications were proposed and implemented, including concentration monitoring in crystallization and degradation, quick calibration for UV/vis and Raman spectroscopy, and real-time crystallization product purity monitoring.

In this dissertation, a series of novel applications were proposed and validated via simulation and/or experimental studies that demonstrated the significance of quality-by-control (QbC) approaches for complex and integrated crystallization operation and systems.