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Advanced control approaches for combined cooling/antisolvent crystallization in continuous mixed suspension mixed product removal cascade crystallizers

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HIGHLIGHTS

- Systematic analysis of a MIMO control system for continuous crystallization.
- Attainable regions defined for size and yield using different control approaches.
- Feasibility of decentralized PID control approach is analyzed.
- Different nonlinear model predictive control approaches are proposed and analyzed.

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ABSTRACT

The control approaches for a continuous two stage mixed suspension mixed product removal (MSMPR) cascade crystallizer are studied in this work. Both cooling and antisolvent addition are applied at both stages to manipulate the process. Considering both crystal size and yield as controlled variables, the attainable region of crystal size and yield is obtained. Two advanced control schemes are discussed: (1) decentralized proportional-integral-derivative (PID) control; and (2) nonlinear model predictive control (NMPC). While decentralized PID control framework is proved to require change of control structure when a relatively large operating region is essential, nonlinear model predictive control scheme shows superior performance for fast target product property change-over and disturbance rejection.

1. Introduction

Crystallization is an efficient and economical unit operation that is extensively used in pharmaceutical industry to purify active pharmaceutical ingredients (APIs) (Qamar et al., 2010). Typically a batch crystallizer is utilized, with either cooling, antisolvent addition or evaporation applied to generate supersaturation, which is the thermodynamic driving force for a crystallization process. In addition, for high yield purpose, combined cooling/antisolvent crystallization (CCAC) is also widely used (Sheikhzadeh et al., 2008). Additionally, CCAC has great advantages to achieve desired crystal size distribution (CSD) (Nagy et al., 2008; Yang and Nagy, 2014; Lindenberg et al., 2009), which not only determines the efficiency of downstream operations (e.g. filtration, washing and drying), but also influences bioavailability and dissolution behavior of an API (Nagy et al., 2011; Vetter et al., 2014). Thus it is essential to design suitable control strategies for crystallization processes.

In general, the crystallization process can be controlled via either model-free or model-based approaches. The applications of both approaches in batch crystallization have been studied in depth in literature. Model-free approaches, such as direct nucleation control (DNC) (Abu Bakar et al., 2009; Saleemi et al., 2012), or supersaturation control (SSC) (Gron et al., 2003; Nagy and Aamir, 2012) are methodologies that maintain the operating curve within the metastable zone to avoid or control nucleation or generate controlled dissolution. For model-based approaches, typically a population balance model (PBM) is used to describe the evolution of the CSD in the crystallization process and to obtain open-loop optimal temperature or/and antisolvent addition profiles that can produce desired CSD (Acevedo and Nagy, 2014; Rawlings et al., 1993; Xie et

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al., 2001; Zhang and Rohani, 2003). In addition, more advanced model-based approaches that solve the open loop optimization repeatedly, such as model predictive control (MPC) has been applied in batch crystallization process (Hermanto et al., 2009; Kalbasenka et al., 2007; Nagy and Braatz, 2003). MPC uses the mathematical model and real time measurements to optimize the current operating curve, based on the predicted future behavior of the system. For systems of high complexity and nonlinearity, nonlinear model predictive control (NMPC) is used instead of linear model predictive control (LMPC). Hermanto et al. (2009) utilized NMPC strategy to control the polymorphic transformation in a batch crystallization process. It was proved to be more robust than other existing control strategies like temperature control or concentration control. A robust extended Kalman filter-based NMPC framework was developed by Nagy and Braatz (2003) for batch crystallization processes. The proposed NMPC approach considerably enhanced robust performance as compared with open-loop optimal control. Although in general these model-based approaches are more complicated to design compared to model-free approaches, they can enhance process understanding, provide theoretically optimal recipe, and require much smaller number of experiments than statistical experimental design (Nagy et al., 2008; Nagy and Aamir, 2012).

Due to great operating flexibility and short development time required, the widespread industrial use of batch crystallizer is very common (Randolph and Larson, 1988). However, the intrinsic disadvantages of batch crystallization, such as low process and equipment efficiency and batch to batch inconsistency, have strongly motivated the development of continuous crystallization systems. Theoretically, continuous crystallization could have much better quality consistency, process and equipment efficiency, and productivity as compared with batch crystallization (Quon et al., 2012). Several types of continuous crystallizers have been developed, including mixed suspension mixed product removal (MSMPR) crystallizer (Alvarez et al., 2011; Quon et al., 2012; Wong et al., 2012; Zhang et al., 2012), plug flow crystallizer (PFC) (Alvarez and Myerson, 2010; Eder et al., 2010; Vetter et al., 2014) and oscillatory baffled crystallizer (OBC) (Lawton et al., 2009) to name only a few. Compared to the other two, MSMPR crystallization processes are more frequently applied in industrial crystallization since they provide a smaller technology change from batch and are simpler to operate (Vetter et al., 2014). MSMPR crystallizer is an ideally well-mixed vessel that has feed solution continuously entering and product slurry continuously withdrawn. It can be used in various configurations, including single stage, multistage, or with recycle loops (Alvarez et al., 2011; Quon et al., 2012; Su et al., 2015; Vetter et al., 2014; Wong et al., 2012; Zhang et al., 2012). Cooling, or antisolvent addition, or both could be applied to generate supersaturation at a certain MSMPR crystallization stage. It can be operated at steady-state to produce crystals of consistent purity, yield, CSD and polymorphic form. Vetter et al. (2014) modeled an MSMPR cascade crystallization process using PBM. CCAC of aspirin was used as a case study, in which the particle size attainable regions of MSMPR cascade crystallizer of different number of stages were obtained and compared with batch crystallizer and PFC. Quon et al. (2012) implemented and optimized a two stage MSMPR cascade crystallizer for continuous reactive cooling crystallization of aliskiren hemifumarate. Crystals of both high yield and purity were obtained. Alvarez et al. (2011) implemented a three stage continuous MSMPR cascade crystallizer to produce cyclosporine crystals using cooling to generate supersaturation. A PBM was developed in the same work, and used to optimize crystal size, yield and purity, as well as to obtain crystallization kinetic parameters. Wong et al. (2012) constructed two continuous single stage MSMPR crystallizers with recycling loop for cooling crystallization and CCAC. They experimentally demonstrated the feasibility and potential advantages (e.g. high yield) of having recycle loop in a single stage MSMPR crystallizer. A continuous CCAC process using two stage MSMPR cascade crystallizer was implemented by Zhang et al. (2012), and was experimentally proved to be able to well control CSD, yield and purity. In these continuous MSMPR crystallization systems, process analytical technology (PAT) tools like focused beam reflectance measurement (FBRM) and high performance liquid chromatography (HPLC) were successfully implemented. In addition, novel PAT implementations like video camera have also been applied in some other continuous processes (Simon and Myerson, 2011). The development of novel PAT tools has enabled the progress of both model-free and model-based control approaches (e.g. NMPC) (Nagy et al., 2013; Simone et al., 2014a, 2014b).

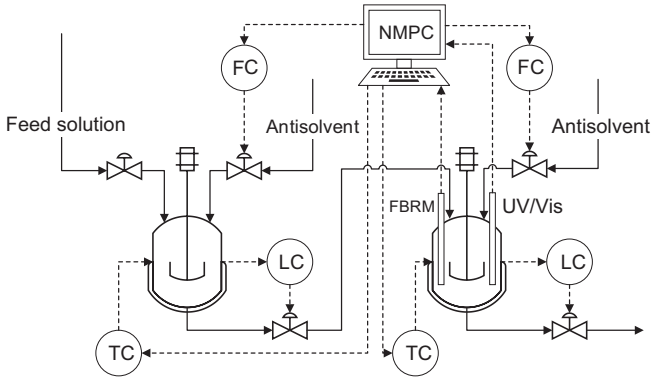

Fig. 1. Schematic representation of a hierarchical NMPC implementation structure. FC, TC, LC are flow rate controller, temperature controller and level controller, respectively.

While model-based optimization, design and experimental investigation of continuous single stage and multistage MSMPR systems is becoming more common in the literature, to the author's best knowledge, currently there are no published papers working on model-based advanced control approaches for CCAC in MSMPR cascade crystallizers, with both crystal size and yield controlled at the same time. To achieve this goal, this work systematically studied the feasibility of two different control schemes: decentralized PID control and nonlinear model predictive control (NMPC). For decentralized PID control approach, local linearization method and relative gain array (RGA) analysis were used to examine its feasibility. Whereas for NMPC approach, its performance was evaluated under both servo control and regulatory control scenarios. In this work, not only nucleation and growth kinetics, but also controlled dissolution kinetics were considered. In the case study, aspirin (acetylsalicylic acid), ethanol and water were used as model compound, solvent and antisolvent, respectively.

The schematic representation for a closed-loop hierarchical NMPC implementation structure in continuous two stage MSMPR cascade crystallizer is presented in Fig. 1. In principle, PAT tools like FBRM and UV/Vis spectroscopy can be used for online measurements of CSD and solute concentration, from which mean crystal size and yield can be inferred in real time. As a result, the process model can be updated during the process using those measurements via closed-loop optimal control. Sensor noise and error were not considered in this work. In addition, in practice typically low level flow rate and temperature controllers would be used in a hierarchical control structure with the NMPC, as shown in Fig. 1. In this work, in order to simplify the simulation study, antisolvent addition rates and temperatures were manipulated directly from NMPC scheme.

2. Population balance model of the continuous two-stage CCAC-MSMPR system

In this work, a continuous two stage MSMPR cascade crystallizer is modeled using PBM. Both the temperature and antisolvent