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Crystal shape and size control using a plug flow crystallization configuration

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HIGHLIGHTS

- Dynamic modeling of the evolution of crystal shape and size in continuous plug flow crystallization.
- Simulation and optimization of operating conditions.
- Feed disturbance handling with feed-forward control in plug flow crystallization.
- Simulation results exemplify shape control of lysozyme protein crystals of different feed seed distributions.

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ABSTRACT

This work focuses on modeling and control of a continuous plug flow crystallizer (PFC) used to produce tetragonal hen-egg-white (HEW) lysozyme crystals and proposes an optimization-based control scheme to produce crystals with desired size and shape distributions in the presence of disturbances. Initially, a kinetic Monte Carlo (kMC) model is developed to simulate the crystal growth in a seeded PFC, which consists of five distinct segments. The crystal growth rate equations taken from (Durbin and Feher, 1986) are used in the kMC simulations for the modeling of the crystal growth in the direction of (110) and (101) faces. Then, a population balance equation (PBE) is presented to describe the spatio-temporal evolution of the crystal volume distribution of the entire crystal population, and the method of moments is applied to derive a reduced-order moment model. Along with the mass and energy balance equations, the leading moments that describe the dominant dynamic behavior of the crystal volume distribution are used in the optimization-based controller to compute optimal jacket temperatures for each segment of the PFC and the optimal superficial velocity, in order to minimize the squared deviation of the average crystal size and shape from the set-points throughout the PFC. Furthermore, a feed-forward control (FFC) strategy is proposed to deal with feed flow disturbances that occur during the operation of the PFC. Using the proposed optimization and control schemes, crystals with desired size and shape distributions are produced in the presence of significant disturbances in the inflow solute concentration and size distribution of seed crystals.

1. Introduction

Crystallization plays an essential role in the context of separation and purification methods for the production of therapeutic drugs. Considering the fact that crystal size and shape distributions have significant influence on the bioavailability of drugs such as the dissolution rate, filterability, and stability as a carrier to the target site, it becomes of particular interest to the pharmaceutical industry to produce crystals with desired size and shape distributions (Patience and Rawlings, 2001; Yang et al., 2006; Wang et al., 2008).

Traditionally, batch crystallization processes have been widely used in the pharmaceutical industry. However, the batch process has a few well-known potential drawbacks such as the batch-to-batch variability, and the difficulty in the scale-up and the consistent production of crystals with desired crystal size and/or shape distributions. Motivated by this, a mixed suspension mixed product removal (MSMPR) crystallization process, which is analogous to the conventional continuously stirred tank crystallizer

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(CSTC), has received a growing attention, and many efforts have been made in order to produce crystals from the MSMPR process with a higher production rate and desired product quality (Griffin et al., 2010; Alvarez et al., 2011; Hou et al., 2014; Ferguson et al., 2014). However, due to the presence of back-mixing, which is commonly modeled by employing the residence time mixing model, those crystals nucleated at a later stage during the crystallization process will reside a relatively short amount of time in the crystallizer and thus they will end up leaving the crystallizer with undesired size and shape distributions (Kwon et al., 2014). To this end, plug flow crystallizer (PFC) has been proposed to produce crystals with narrow size and shape distributions (Eder et al., 2011; Vetter et al., 2014).

More specifically, a strategy for the fines removal in the PFC was proposed through the manipulation of the growth and dissolution rates (Majumder and Nagy, 2013). Furthermore, the effect of the antisolvent injections along the axial direction of the PFC on the crystal volume distribution has been investigated (Alvarez and Myerson, 2010; Ferguson et al., 2013; Ridder et al., 2014).

Model-free control schemes such as a proportional-integral-derivative (PID) control scheme and a direct nucleation control approach are not able to handle alone constraints on the inputs, the outputs, and the rate of change of inputs while computing optimal jacket temperature values. Therefore, the necessity of incorporating the constraints to account for the physical limitations on the manipulated inputs and operating conditions makes the model-based control strategy (Miller and Rawlings, 1994; Worlitschek and Mazzotti, 2004; Shi et al., 2005; Mesbah et al., 2010) the method of choice for crystal size distribution control. Specifically, the model predictive control (MPC) scheme was employed by Kalbasenka et al. (2007) and Kwon et al. (2013, 2014, in press) in order to control the crystal size and shape distributions along with the consideration of the crystal growth and nucleation processes in both batch and MSMPR processes based on a reduced-order model. Furthermore, in addition to model-based optimization to compute optimal jacket temperature values, a feed-forward control (FFC) is proposed in the present work for the production of crystals with desired size and shape distributions owing to its unique ability to deal with feed flow disturbances that occur during the operation of the PFC though the use of the online measurements of the inflow solute concentration, PFC temperature, and crystal seed size.

In the pharmaceutical industry, disturbances (e.g., changes in the inflow solute concentration) influence the size and shape distributions of the crystal products during the steady-state operation of the PFC process (Sen et al., 2014). However, the conventional operating strategy such as the constant supersaturation control (CSC) scheme is not able to deal with the disturbances because it is not able to predict the spatio-temporal transient behavior of the system in response to disturbances in the inflow solute concentration and the seed size distribution.

Motivated by the above considerations, this work focuses on modeling and control of a continuous PFC used to produce tetragonal HEW lysozyme crystals and proposes an optimization-based control scheme to produce crystals with desired size and shape distributions in the presence of feed disturbances. Initially, we model a continuous plug flow crystallizer with 5 segments for the production of lysozyme crystals through kinetic Monte Carlo (kMC) simulation methods in the way described in Kwon et al. (2013) using the rate equations originally developed by Durbin and Feher (1991). A seeding strategy is used to decouple the nucleation from the crystal growth processes (Liu et al., 2010; Eder et al., 2011; Besenhard et al., 2014; Ferguson et al., in press). Furthermore, an upper bound of the supersaturation level is imposed as a constraint so that the system is enforced to stay in the metastable regime where the degree of primary nucleation is negligible (Shi et al., 2005). Then, a population balance equation (PBE) is presented to describe the spatio-temporal evolution of the crystal volume distribution, and by applying the method of moments to the PBE, a reduced-order moments model is derived because kMC models are not available in a closed form (Kalani and Christofides, 2002; Cogoni et al., 2014). Together with the mass and energy balance equations, the leading moments are used for the estimation of the spatio-temporal evolution of the crystal size and shape distributions in an optimization problem. Specifically, the crystallizer jacket temperatures at each segment and the superficial flow velocity are chosen as the decision variables in the optimization problem and the objective function is defined by the sum of the squared deviation of the average crystal size and shape from desired set-points throughout the PFC. Subsequently, the dynamic model developed in Section 2 is used for the design of an FFC strategy for the production of crystals with desired size and shape distributions properly suppressing the undesired effect caused by disturbances (Gnoth et al., 2007). Lastly, the simulation results are presented followed by discussion and conclusions.

2. Modeling of plug flow crystallizer

2.1. Process configuration

We consider a continuous plug flow crystallizer used to produce crystals with desired size and shape distributions through the manipulation of a set of jacket temperatures and of the superficial flow velocity which are computed by solving a multivariable optimization problem. The system parameters for the crystallizer considered in this work are taken from Alvarez and Myerson (2010) and Majumder and Nagy (2013), and are presented as follows: each segment of the PFC is 400 cm in length and 1.27 cm in inner diameter, and the PFC consists of 5 segments where the configuration of the PFC is presented in Fig. 1. It is assumed that the segments are connected without any gap. Additionally, we assume that the PFC is perfectly mixed in the radial direction and there is no back-mixing in the axial direction.

In order to study the effect of a set of jacket temperatures on the shape and size distributions of crystals produced by the plug flow crystallizer, it is operated in the regime where the primary nucleation is negligible. Therefore, a number of seed crystals with

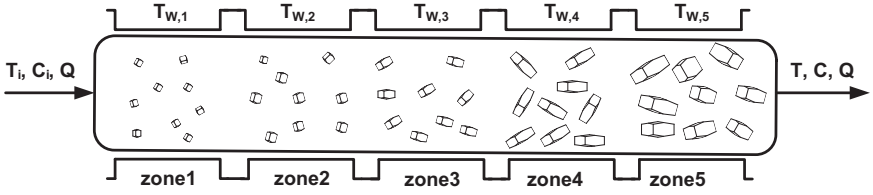

Fig. 1. Plug flow crystallizer configuration. T is the crystallizer temperature, T_i is the inflow temperature, $T_{w,k}$ is the crystallizer jacket temperature at segment k, C_i is the inflow solute concentration, C is the solute concentration, and Q is the flow rate of the inflow stream.