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Mathematical modeling and optimal design of multi-stage slug-flow crystallization

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ABSTRACT

Inspired from experimental progress in continuous crystallizer designs based on air/liquid slug flow that generate crystals of target sizes at high production rates and low capital costs (e.g., Eder et al., 2010; 2011; Jiang et al., 2014; 2015; and citations therein), a mathematical model and procedure are derived for the design of slug-flow crystallizers with spatially varying temperature profiles. The method of moments is applied to a population balance model for the crystals, to track the spatial variation of characteristics of the crystal size distribution along the crystallizer length. Design variables for the cooling slug-flow crystallizer such as tubing lengths and types and numbers of heat exchangers are analyzed and optimized for product crystal quality (e.g., minimized secondary nucleation and impurity incorporation) and experimental equipment costs, while ensuring high yield. This study provides guidance to engineers in the design of slug-flow crystallizers including their associated heat exchanger systems.

1. Introduction

In the pharmaceutical industry, consistent in-spec products from a well-defined robust crystallization process design are crucial for both FDA regulation and operational practice (Yu et al., 2004; Nagy et al., 2008). Continuous-flow tubular crystallizers have shown potential for high reproducibility and process efficiency at low capital and production cost (Alvarez and Myerson, 2010; Lawton et al., 2009; Fergusen et al., 2012; Vacassy et al., 2000; Jiang et al., 2014; Eder et al., 2010, 2011). A technology that combines the advantages of continuous and batch crystallizers is the air/liquid slug-flow crystallizer (Jiang et al., 2014; Eder et al., 2010, 2011, 2012; and citations therein), which has advantages that include narrow residence time distribution, no stirrer for inducing particle attrition/breakage, and easy post-crystallization separation. The potential application of slug-flow crystallization in the final stage of pharmaceutical manufacturing motivates this design study.

As in batch crystallizers (e.g., Nagy and Braatz, 2012; Simon et al., 2015; and citations therein), the robustness of slug-flow crystallization process operation requires an understanding of how the supersaturation profile is affected by design variables (e.g., method and speed of supersaturation generation) and corresponding implementation. For example, supersaturation should be minimized so as to avoid impurity incorporation and secondary nucleation, which is important for slug-flow crystallization due to its typically short residence time (on the order of minutes, Eder et al., 2012; Jiang et al., 2014, 2015) and with fast heat transfer (from the large surface area to volume ratio of tubular crystallizers).

This article presents a design procedure for slug-flow continuous cooling crystallization with the objective of minimizing the maximum supersaturation. Two common methods of cooling are compared: heat baths and double-pipe heat exchangers (Levenspiel, 1962). The effect of design variables on the supersaturation profile is analyzed (e.g., temperatures and locations of heat baths/exchangers, length of tubing). A population balance model for batch crystallization (e.g., Hulburt and Katz, 1964; Randolph and Larson, 1974) is applied to individual slugs, with the batch residence time replaced by continuous residence time (running time). Unlike a past study that mathematical modeled a slug-flow crystallizer (Kubo et al., 1998), this article considers a different crystallization mechanism (cooling crystallization instead of reactive precipitation), different crystallization phenomena (growth of individual crystals instead of aggregation), and not only analyzes our experimental proof-of-concept demonstration (Jiang et al., 2014) but also analyzes the effect of the design variables and applies optimization (e.g., of the number of heat exchangers and the length of tubing in each heat bath/exchanger) while minimizing the total equipment cost.

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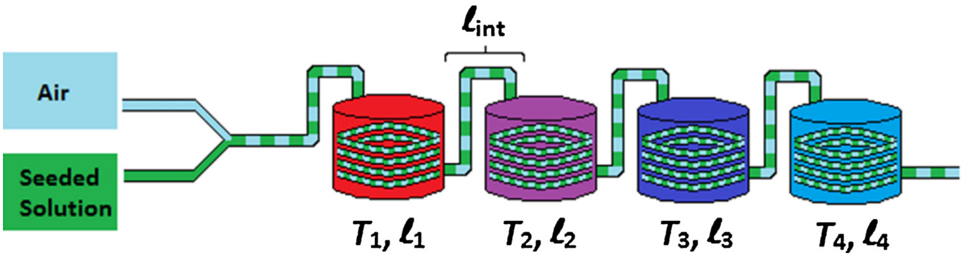

Fig. 1. Schematic for a multiple bath SFC fed with liquid solution with seed crystals, which can be continuously generated by micromixers or an ultrasonic probe (Jiang et al., 2014, 2015). A typical tube is made of silicone of Teflon with an inner diameter of 3.1 mm. During cooling, a typical tank temperature ranges from 60 to 20 ° Celsius.

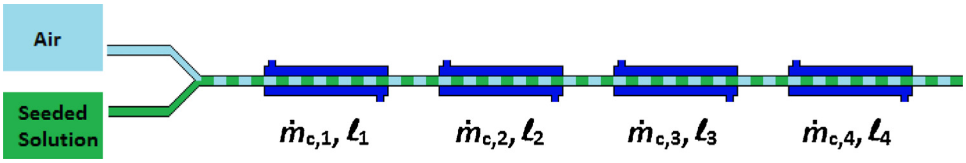

Fig. 2. Schematic for a multiple double-pipe heat exchanger SFC. The temperature of the inlet cooling water in the shell is constant, typically 25 °C or lower.

2. Methodology

A well-mixed batch crystallizer can be modeled using the population balance equation (Hulbert and Katz, 1964; Randolph and Larson, 1974)

$$\frac{\partial f}{\partial \tau} + \frac{\partial (Gf)}{\partial L} = B\delta(L - L_0), \tag{1}$$

$$f(\tau = 0, L) = f_0(L), \tag{2}$$

where G and B are growth and nucleation rates, respectively, f is the distribution of particle sizes at residence time τ, L is the particle size, L_0 is the size of nuclei, and δ is the Dirac delta function.

Fig. 1 is a schematic for one of the slug-flow crystallizers investigated in this. For the first system, a liquid solution containing solute and solvent(s) enters a tube and then undergoes ultrasonication under supersaturated conditions to generate seed crystals. The slurry containing seed crystals is then combined with a stream of air under flow conditions in which slugs spontaneously form. The inlet concentration in the slugs is denoted by C_0, and the inlet temperature by T_0. The tube passes first into a bath of temperature T_1. The bath is agitated to provide spatially uniform temperature and to promote heat transfer between the liquid in the bath and outer surface of the tube. The length of tubing inside the first bath is denoted by ℓ_1. The tube then passes into a second bath at a different temperature, T_2. The length of tubing in the second bath is denoted by ℓ_2, and the length of tubing in the interval between (and outside of) adjacent baths in denoted by ℓ_{int}. A total of four temperature baths are included in the experimental configuration.

An alternative system investigated here replaces the constant-temperature baths with counterflow single-pass double-pipe heat exchangers (Fig. 2). While the inlet shell-side temperature is equal for each heat exchanger i, the length ℓ_i and cooling water flowrate $\dot{m}_{c,i}$ can differ (Fig. 3).

3. Mathematical modeling of slugs as batch crystallizers

Experimental evidence indicates that each slug is well-mixed (Kashid et al., 2005; Jiang et al., 2014), so each slug operates as an individual batch crystallizer that is physically transported down the tube. For batch systems under low supersaturation, where nucleation can be considered negligible, the term on the right-hand side of Eq. (1) can be neglected. With the common assumptions of size-independent growth and no growth rate dispersion, the population balance model describing the evolution of the crystal size distribution in each slug is reduced to

$$\frac{\partial f}{\partial \tau} + G\frac{\partial f}{\partial L} = 0 \tag{3}$$

where τ is the time from when a slug enters the first bath. The growth rate can be defined for this system as (Randolph and Larson, 1974)

$$G = k_g[C - C_{sat}(T)]^g \tag{4}$$

where k_g and g are fit to data, C_{sat} is the solubility (aka saturation concentration) as a function of temperature, and C and T are the bulk concentration and temperature, respectively. A typical slug in the first bath starts at the concentration C_0 and temperature T_0 at supersaturated or saturated conditions ($C_0 \geq C_{sat}(T_0)$), inlet seed mass m_{seed}, and inlet crystal size distribution (CSD) f_0.

Attrition, aggregation, agglomeration, breakage, and nucleation within each slug are considered to be negligible, as has been observed in experiments (Jiang et al., 2015). The low levels of these phenomena are associated with the lack of any mixing blade, static mixers, or other internals to induce such phenomena for the

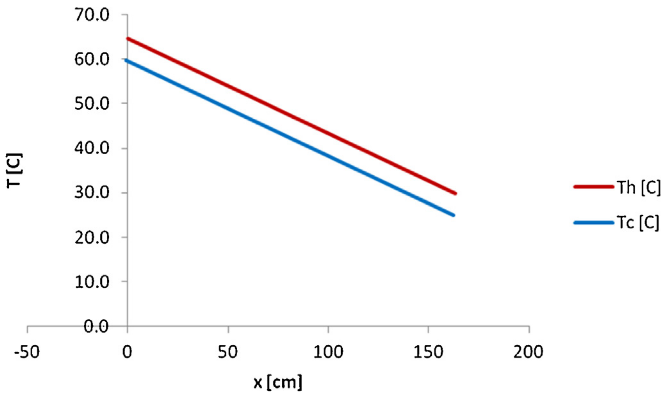

Fig. 3. Estimated temperature profile of a double-pipe heat exchanger designed with constant log mean temperature difference. The red line (upper line) marks the temperature of slugs in the tube and the blue line (lower line) marks the temperature of cooling water in the shell (for interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).