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Computational fluid dynamics modeling of mixing effects for crystallization in coaxial nozzles

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ABSTRACT

A leading method for the crystallization of pharmaceutical compounds is to rapidly mix an antisolvent with a solvent saturated with the desired drug. Compared to cross-flow mixers, coaxial nozzles have negligible buildup of crystalline material on their surfaces and are less likely to plug. Rather than requiring moving parts, the inlet velocities of the input solvent and antisolvent streams provide the necessary mechanical energy for turbulent mixing. Computational fluid dynamics (CFD), micromixing modeling, and the population balance equation (PBE) are coupled in the simulation of coaxial nozzle crystallization of lovastatin-saturated methanol by intense mixing with the antisolvent water. The simulations show that flow rates of inlet streams have a profound effect on crystal size distribution (CSD), which is caused by different degrees of inhomogeneity in the supersaturation and nucleation and growth rates. Other important process parameters are pipe length of pipe downstream of the injection point and the inner and outer pipe diameters. To the authors' knowledge, this is the most detailed simulation study on coaxial crystallizers reported to date. The simulation results show the feasibility of tailoring a specific crystal size distribution by adjusting the operating conditions (such as inlet stream velocities) of the coaxial crystallizer.

1. Introduction

Pharmaceutical crystals should be optimally sized to dissolve at the proper therapeutic rate. More specifically, controlling the crystal size distribution (CSD) is necessary to meet product specifications, such as bioavailability, and to ensure the efficiency of downstream processes (e.g., filtration and drying) [1–3]. Otherwise, additional processes such as milling and granulation are required [4–5].

Antisolvent crystallization refers to addition of a miscible "antisolvent" to the solvent saturated with the desired solute. Since the solubility of the solute in the antisolvent is very low, supersaturation is quickly induced, creating a driving force for crystallization. An advantage of using antisolvent crystallization is its ability to induce the crystallization of thermally sensitive pharmaceuticals without large temperature variations [6–7]. However, this method requires rapid and sufficient mixing of the antisolvent with the solute dissolved in solvent, which, in turn, necessitates the design of an appropriate mixer/crystallizer to accomplish intense mixing and crystallization on a fine scale.

Several different types of antisolvent mixers have been used for crystallization. State-of-the-art crystallization units, such as coaxial mixer/crystallizers (Fig. 1), utilize high intensity mixing of the antisolvent and the solution to produce crystals smaller than 25 μm, which improves the bioavailability and increases the dissolution rate of the final drug product [1–3]. The ability to obtain such small crystals can also allow the elimination of undesirable unit operations such as milling [4–5]. Agitated semibatch mixers/crystallizers [38] and impinging jet mixers/crystallizers [9] are two additional types of crystallizers commonly used in industry.

Many crystallizer designs have been explored to generate high supersaturation in such mixtures as an approach for generating consistent crystal nuclei that are subsequently grown to a desired size [3,10–14]. Compared to cross-flow mixers, coaxial jet mixers have negligible buildup of crystalline material on their surfaces and are less likely to plug. Coaxial mixers can be designed to deliver rapid turbulent mixing using short sections of pipe. As the energy required for mixing is provided by the inlet streams, with no moving metal parts and no bearings, these devices have simple maintenance and operation. Some experimental and modeling

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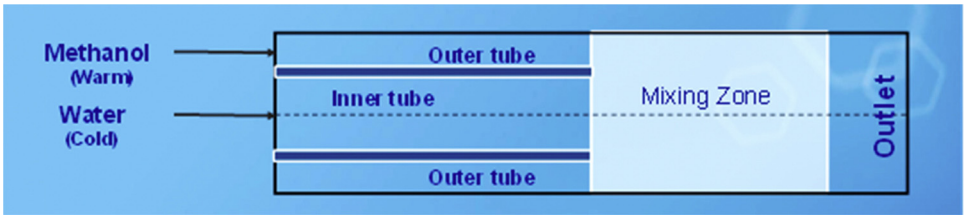

Fig. 1. Diagram of coaxial nozzle used as a mixer/crystallizer (courtesy of Parkaj Doshi).

studies of coaxial crystallizers have been published to gain deeper understanding and to facilitate more efficient development and optimization of the coaxial mixer crystallization process [15–18].

Various experimental studies of antisolvent crystallization in an agitated semibatch vessel indicate that the crystal size distribution (CSD) depends strongly on operating conditions such as agitation rate, mode of addition (direct or reverse), addition rate, solvent composition, and size of the crystallizer [3,19–25,26–31]. The polymorphic or pseudopolymorphic form can also depend on the operating conditions [32–37].

The number of operating conditions that can be investigated is large, so that investigating these combinations by bench-scale experiments can be time consuming and costly. This development time and cost can be reduced by using computer simulation to augment the experimental approach to mixer/crystallizer investigation and design. This article considers important design parameters for crystallization in coaxial mixers: the length of pipe downstream of the injection point, the velocity and temperature of the inlet streams, and the inner and outer pipe diameters.

Computer simulation is used throughout industry to gain understanding and guidance in development of manufacturing processes. These simulation problems usually involve large systems of algebraic equations (AEs) and ordinary and partial differential equations (ODEs, PDEs). In the case of pharmaceutical crystallization, a meaningful description of the process requires PDE/AEs over a multiscale spatial domain. For a dynamic model, the independent variables consist of time (t), spatial location (X–Y–Z) within the crystallizer, and geometric variables for the crystal, such as a characteristic size r. In addition, some critical transport processes occur at a subgrid, or sub-cellular level, which can be handled without increasing the number of independent variables through use of probability density functions.

This article describes an effort whose goal is to speed up the design of the coaxial crystallizers to tailor the crystal size distribution according to the bioavailability and drug administration requirements. Dynamic simulations of a confirmed coaxial crystallizer were carried out that simultaneously solve partial differential equations for macromixing, micromixing, and a population balance for the crystals. The computational model [38–40] was used, which replaces a quadrature-method-of-moments model used to simulate the time evolution of the particle size distribution by Rodney Fox [41] with a full spatially varying population balance model implemented using a high resolution finite-volume method. This article employs an extension of the model [38–40] to include temperature effects on the crystallization. Our simulations were used to perform a parameter sensitivity analysis (see Varma et al. [42] for background on such analyses) to identify the key model parameters and to simulate variations in their values on the full crystal size distribution (CSD) in the antisolvent crystallization of lovastatin, using kinetics reported in the literature [43]. The effects of inlet concentrations and stream flow rates on CSD were numerically investigated and compared with CSDs obtained in a dual-impinging jet crystallizer [40]. As observed in simulations of dual impinging jets, the mean crystal size and the width of the distribution are found to decrease with an increase in inlet stream velocity. The simulation results show different degrees of inhomogeneity in the supersaturation and the nucleation and growth rates for different inlet stream flow rates.

2. Model equations

2.1. Multi-scale modeling

A multi-scale system of algebraic and partial differential equations is solved in order to simulate a pharmaceutical crystallizer. For a dynamic system, time (t) is one of the independent variables, which will range from 0 to a value sufficiently large to approximate steady state. The axial and transverse coordinates X–Y–Z represent the location in the mixer/crystallizer. For an axisymmetric mixer such as the coaxial mixer, a two-dimensional X–Y grid can be used to lower computational cost. Although modeling the turbulent macromixing processes requires the use of only these spatial coordinates and time as independent variables, a higher resolution of the flow field is required to model the interactions between hydrodynamics, nucleation, and growth. An additional geometric independent variable is also introduced, which is associated with the crystal size represented by a single characteristic dimension r.

The approach used here couples a turbulent computational fluid dynamic (CFD) code with a multienvironment probability density (PDF) model, which captures the micromixing in the subgrid scale, and the population balance equation (PBE), which models the evolution of the crystal size distribution.

2.2. Macro-mixing equations (CFD code)

Turbulent transport of mass, momentum, and energy is discussed thoroughly in Pope's definitive textbook [44]. The Fluent User's Manual summarizes the relevant equations, and Fluent 13 was used to obtain solutions to these equations [45]. The version of Fluent used for the calculations presented in this paper is included in Ansys 14.5 [46]. In general form, the equations are:

$$\text{Continuity equation}: \frac{\partial \rho}{\partial t} + \nabla\cdot(\rho v) = 0 \tag{1}$$

Momentum conservation equation :

$$\frac{\partial}{\partial t}(\rho \boldsymbol{v}) + \nabla\cdot(\rho \boldsymbol{v}\boldsymbol{v}) = -\nabla p + \nabla\cdot(\bar{\bar{\tau}}) + \rho\vec{g}$$

Standard $k-\varepsilon$ equations :

$$\frac{\partial}{\partial t}(\rho k) + \nabla\cdot(\rho k \boldsymbol{v}) = \nabla\cdot\left[\left(\mu + \frac{\mu_t}{\sigma_k}\right)\nabla\cdot k\right] + G_k - \rho\varepsilon + S_k$$

$$\frac{\partial}{\partial t}(\rho \varepsilon) + \nabla\cdot(\rho \varepsilon \boldsymbol{v}) = \nabla\cdot\left[\left(\mu + \frac{\mu_t}{\sigma_\varepsilon}\right)\nabla\times\varepsilon\right] + C_{1\varepsilon}\frac{\varepsilon}{k}G_k - C_{2\varepsilon}\rho\frac{\varepsilon^2}{k} + S_\varepsilon$$

$$\text{where} \mu_t = \rho C_\mu \frac{k^2}{\varepsilon}. \tag{3}$$

Scalar transport equation :