

## **529b Simulation of Mixing Effects in Antisolvent Crystallization Using a Coupled CFD-Micromixing-Pbe Approach**

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A pressing issue for the pharmaceutical industry is the regulatory requirement of consistency in the various chemical and physical properties of the crystals, including the crystal size distribution (CSD), during scale-up (Paul et al., 2005). This has been one of the key motivations behind numerous research efforts geared towards the understanding of the effects of mixing on crystallization. The sensitivity of the crystal quality to mixing can be greater for reactive and antisolvent crystallization due to the dispersion of a reactant or solvent, which results in concentration gradients. Based on experimental studies alone (e.g. Budz et al., 1986; Kaneko et al., 2002; Kitamura and Sugimoto, 2003; Plasari et al., 1997; Torbacke and Rasmuson, 2004), it is difficult to draw general conclusions on the effects of mixing on the crystal product because the dependence of nucleation and growth rates on supersaturation is specific to the crystal-solvent system and particulars of the crystallizer. A more in-depth understanding of the hydrodynamic effects can be obtained through first-principles modeling, which requires the coupling of the population balance equation (PBE) with the transport equations of species, momentum, and energy (Hulburt and Katz, 1964). In addition, micromixing models have to be included to capture the mixing on a molecular scale (Baldyga and Orciuch, 1997; Kresta et al., 2005; Marchisio et al., 2001, Zauner and Jones, 2000).

An algorithm has been developed that integrates (1) the computational fluid dynamics, which models the turbulent flow field at a high resolution, (2) the probability density function model, which gives the statistical description of the species concentration at the subgrid scale (i.e., micromixing) (Fox, 2003), and (3) the solution of the population balance equation, which predicts the entire crystal size distribution. The growth rate incorporates both surface integration and mass transfer steps, where the latter has a nonlinear dependence on particle size. To the authors' knowledge, this is the first time the spatially-varying population balance equation, along with nucleation and size-dependent growth and dissolution kinetics, is coupled with a CFD-Micromixing model that simulates the hydrodynamic effects.

The coupled algorithm is applied to model an antisolvent crystallization process in a semibatch stirred vessel and in an impinging jet. For the semibatch vessel, which is the typical operating mode for antisolvent crystallization, the effects of agitation speed, addition mode (i.e. direct or reverse), and scale-up on the final crystal size distribution were numerically investigated. Furthermore, the spatial distributions of nucleation and growth rates obtained from the simulations provided insights into the effects of hydrodynamics on the crystal quality. For the case of impinging jets, which is the current-state-of-the-art technology for producing small and uniform-sized crystals (Midler et al., 1994), the effects of jet velocity and inlet compositions were studied. The development of this integrated model provides a better understanding of the effects of hydrodynamics on crystallization, thus offering a more scientific basis for the design and scale-up of crystallizers, which can reduce the number of trial-and-error experiments required.

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