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Simulation of antisolvent crystallization in impinging jets with coupled multiphase flow-micromixing-PBE

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HIGHLIGHTS

- High-resolution central schemes by Kurganov & Tadmor is extended to general form.
- The coupled multiphase flow-micromixing-PBE model is developed.
- The model is validated in OpenFOAM for antisolvent crystallization of lovastatin.
- The effect of the existence of crystal phase on flow field and CSD is studied.
- Geometric size partition considerably improves predicted CSDs in some cases.

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ABSTRACT

The KT (Kurganov and Tadmor, 2000) finite-volume central scheme is one of the most promising high-resolution numerical methods to solve the widely-used population balance equation (PBE) in crystallization and other areas. To meet the practical purpose of geometric-type particle size grid, the primary KT scheme was extended to a general form and validated for pure growth in homogeneous systems. Based on the extended KT scheme, a solver was developed that couples the general discretized PBE and micromixing and a CFD mixture model in OpenFOAM (open-source field operation and manipulation). The simulation uses published parameters from and is compared to experimental antisolvent crystallization of lovastatin from a methanol-water mixture in an impinging jet. The effect of the existing solid crystals on some crystal properties is investigated in this work for the first time. The shapes of crystal size distribution (CSD) at various jet velocities are consistent with experimental observations. The geometric particle size partition is shown to be capable of improving the accuracy of simulation in divisions of the highest particle number densities or steep gradients in the number density. The existing solid crystals are also shown to have a non-negligible effect on the slurry flow crystallization systems once the mean crystal size reaches 20 μm.

1. Introduction

Antisolvent crystallization, in which a supersaturated solution of a desired solute is created by addition of antisolvent, is widely used in the pharmaceutical industry. This technique is advantageous for crystallizing heat-sensitive organic pharmaceuticals without introducing large temperature changes (Mullin, 2001). Most antisolvent crystallizations have very fast spatially localized dynamics where the two liquid streams become in contact. Mixing of the antisolvent with the solution, which affects the localized supersaturation and then the crystallization process, can drastically affect the properties of the final product including crystal size distribution (CSD), morphology, and purity (Mahajan and Kirwan, 1996).

The operating conditions influence directly on the mixing conditions and the properties of crystal products. As summarized by Woo et al. (2006) and Pirkle et al. (2015), the operating conditions in antisolvent crystallization such as agitation rate, solvent composition, mode of addition, addition rate, and crystallizer configuration strongly affect the CSD and can also affect the polymorphic or pseudo-polymorphic form. Investigating the combinations of

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operating conditions to obtain the desired product by bench-scale experiments is time consuming and costly, and the recipe for producing the desirable product might not be optimal after scale-up, as the mixing effects and the spatial distribution of supersaturation can be vastly different (Green, 2002; Paul et al., 2004). For gaining insight into these processes and reducing development period and cost, computational fluid dynamics (CFD) coupled with population balance equation (PBE) (and suitable micromixing models) has been employed in recent years to aid the experimental investigation and design of the these mixing-sensitive crystallization processes.

Using moment closure methods for the PBE, many simulation studies on mixing-sensitive crystallization have been performed. Several geometric configurations including impinging jet mixers have been used as the model apparatuses (Marchisio et al., 2002; Choi et al., 2005; Bałdyga et al., 2007; Gavi et al., 2007a,b; Metzger and Kind, 2017). Most were focused on precipitation while a few on antisolvent crystallization. Micromixing was generally modelled by a presumed probability density function (PDF) approach (Fox, 2003). Moment closure methods track the integral properties of CSD instead of CSD itself directly. Often low-order moments of CSD are sufficient to characterize crystal quality. However, in some processes, for example in pharmaceutical crystallization, precise control of the full CSD can be required such as in inhaler and direct tablet compression applications. The CSD could be reconstructed from two or three low-order moments by using relevant numerical techniques or by assuming a simple *a priori* shape for the CSD(Gaussian, log-normal, etc.), but these numerical techniques are numerically unstable and are not universally applicable (John et al., 2007).

To be applicable to any CSD, a CFD-discretized PBE coupled model has been employed to simulate crystallization processes, for example, precipitation of inorganic salts (such as $BaSO_4$) in a 3D stirred tank (Cheng et al., 2012) and cooling crystallization of fine organic chemicals (such as amlodipine maleate) (Kougoulos et al., 2006; Pohar and Likozar, 2014). A micromixing model was incorporated by Veroli and Rigopoulos (2010) to simulate the precipitation of $BaSO_4$ in a 2D pipe. The CFD-micromixing-discretized PBE coupled model has been applied to antisolvent crystallization processes. Woo et al. (2006) simulated the antisolvent crystallization of paracetamol from an acetone-water mixture in a 2D stirred tank. The PBE was solved using the high-resolution, finite-volume semidiscrete central scheme of Kurganov and Tadmor (2000). The effects of operating conditions and scale-up rules on the full CSD were well analyzed. Woo (2007) and Woo et al. (2009) then employed this approach to model the antisolvent crystallization of lovastatin from an methanol-water mixture. Recently, Pirkle et al. (2015) extended the work by Woo et al. (2009) to model the same crystallization system in a coaxial jet mixer, where the effect of heat of crystallization and mixing was accounted for.

The interactions between the solid crystal phase and the solution have not been addressed in the reported simulation studies on mixing-sensitive crystallization processes. In particular, the solid crystals have been assumed to follow streamlines of the continuous solution phase. Most studies employed the single-phase model, while some treated the slurry as a pseudo-homogeneous fluid with the local effective viscosity and/or the mixture density dependent on the local solid holdup (Woo et al., 2006; Woo, 2007; Metzger and Kind, 2017). The single-phase or pseudo-homogeneous assumption is a reasonable approximation for the precipitation of $BaSO_4$ as the crystal sizes are generally several micrometers or smaller, and the solid fraction is often very low. In contrast, the crystal sizes obtained in the antisolvent crystallization of pharmaceuticals can be as large as a few hundred micrometers, depending on the operating conditions. An aim of this work is to investigate the effect of the existence of solid crystals on the crystal properties like CSD, by a coupled multiphase CFD, PBE, and micromixing model. Some guidance on the suitability of the single-phase or pseudo-homogeneous assumption is also given.

Regarding the advective growth term in the discretized PBE, the presence of moving sharp fronts or discontinuities is unavoidable due to the hyperbolic nature of the PBE (Kumar and Ramkrishna, 1997). Careful treatment for this term is required, otherwise an artificial viscosity would be introduced, leading to the smearing of the solution around discontinuities or steep fronts (Kumar and Ramkrishna, 1997; Qamar and Warnecke, 2007). Several finite-difference-type schemes such as upwind, central and the weighted essentially non-oscillatory (WENO) ones have been employed (Braatz, 2002). These schemes showed more or less inevitable loss of accuracy near steep fronts or discontinuities, and/or nonphysical oscillations. Combining one of these discretization schemes with the method of characteristics (MOC) is a good way to solve these problems (Braatz, 2002; Qamar and Warnecke, 2007). However, the stiff nucleation term and the use of moving bins need to introduce new bins and/or the adaptive mesh method (Lee et al., 2001), which greatly increases the complexity and computational burden even in homogeneous systems. Moreover, when coupling with CFD, the combination with MOC is intractable since every physical grid cell has its own growth rate (Cheng et al., 2012).

High-resolution finite-volume methods have been used primarily in the applied mathematics and computational physics literature, mainly for the numerical solution of hyperbolic systems such as astrophysical flows and aerodynamics (Ma et al., 2002a, b). Great attention has been paid to employing these methods for solving the growth term in recent years, see Ma et al. (2002a,b), Woo et al. (2006), Gunawan et al. (2008), Qamar et al. (2009) and Pirkle et al. (2015). Kurganov and Tadmor (2000) introduced a new family of high-resolution finite-volume central schemes (abbreviated for the primary KT scheme). This primary KT scheme enjoys a much smaller numerical viscosity and can be used very efficiently with small time steps, since the numerical viscosity is there independent of $1/\Delta t$. Moreover, nonphysical oscillations, which are common for many second-order accurate numerical methods, cannot occur with this scheme due to its satisfaction in the scalar total-variation-diminishing property with the minmod reconstruction. The semi-discrete version of this primary KT scheme has been adopted successfully to solve the PBE in the CFD-PBE coupled modeling of antisolvent crystallization processes (Woo et al., 2006, 2009; Pirkle et al., 2015).

The primary KT scheme can be applied only to a uniform particle size grid. In crystallization a particle size grid of geometric type sometimes is desirable, as the size range generally spans over several orders of magnitude and we want the size grid to be fine somewhere (in the range of small size or with high number density) and coarse elsewhere. In this work, we will extend the primary KT scheme to a general form, which can be applied to a particle size grid of either geometric or uniform type. The general KT scheme is then validated in homogeneous systems for pure constant and linear growth processes before coupling with CFD.

OpenFOAM (open-source field operation and manipulation) is a free source CFD package written in C++ which uses classes and templates to manipulate and operate scalar, vectorial and tensorial fields (Jasak et al., 1999). Combined with implementations of adequate numerical methods to the discretization of partial differential equations and to the solution of the resulting linear systems, OpenFOAM is a good choice to handle CFD problems (Silva and Lage, 2011). Its open-source characteristics facilitate the implementation of any addition or modification in the source code. As regarding the CFD packages for simulating the mixing-sensitive crystallization processes, most are multi-purpose commercial packages, with a few in-house codes for authors-specific features (Cheng et al., 2009; Veroli and Rigopoulos, 2010). However, the