Abstract

The most challenging task in any crystallization process is to produce crystals consistently with desired attributes such as size, purity, polymorphic form, etc. Controlling these attributes is of great importance for product effectiveness and efficient downstream processing. However, achieving desired attributes in crystallization processes are generally difficult due to the stochastic nature of the nucleation event and the limited number of manipulated variables. In this context ultrasound (US) can be used as an additional manipulated variable to control crystallization process.

In this PhD project, we investigated various aspects of sonocrystallization and sonofragmentation of organic or pharmaceutical crystals. Firstly, we developed a predictive dynamic model based on population balance framework for unseeded batch cooling sonocrystallization of L-asparagine monohydrate(LAM). The population balance model considered here includes the relevant fundamental events of the crystallization process, such as nucleation, growth, and breakage phenomena. An additional kinetic expression is introduced to account for induced nucleation due to US irradiation. The population balance model was thoroughly validated using independent experiments. Application of US induces energy into the system and this in turn leads to temperature rise of the crystallizer. We, therefore, included the energy balance equations and Generic Model Control algorithm into the population balance framework to perform closed-loop simulations in order to model this temperature rise. The improved model is then used to determine the region of attainable sizes for batch cooling sonocrystallization process by solving appropriate dynamic optimization problems. The model is also used to determine optimal operating conditions for achieving a target crystal size distribution (CSD). The experimental validation of the simulation results points to the effi-

ciency of the model based particle engineering for the crystallization process.

We also developed an event driven constant number Monte Carlo (MC) algorithm to simulate the sonofragmentation of two-dimensional plate-like pharmaceutical crystals. The MC simulations were performed by considering the breakage across the width of the particles and restricting the randomness of the break up point within a zone around the mid-plane spanning 20 % of the crystal length on each side of the mid-plane. The proposed MC approach has only one tuning parameter, total number of breakage events per unit time (f_{event}), depending on the ultrasonic amplitude. The estimated value of f_{event} ranges from 1.07×10^5 to 2.60×10^5 s^{-1} for a ultrasonic amplitude in the range of 10-50 %. The relative average deviation (RAD) of 5.48 and 3.76 % are obtained for predicting number average length and width of the crystals, respectively. Similarly, the RAD for predicting full width at half maximum (FWHM) along both length and width axis are obtained as 6.16 and 5.59 %, respectively. Finally, we presented a novel hybrid framework for solution of one and two-dimensional population balance equations by integrating finite volume and MC methods. The hybrid approach is first validated using the results of one-dimensional PBE developed for unseeded batch cooling sonocrystallization of LAM. The computation time for solving the PBE using hybrid approach and high resolution finite volume scheme is 25.8 and 26.9 s, respectively. An application of the proposed hybrid scheme is also presented for the solution of two-dimensional PBE involving growth and breakage of two-dimensional plate-like crystals.

Keywords: ***Crystal size distribution, Ultrasound, Population balance framework, Sonocrystallization, L-asparagine monohydrate, Generic Model Control, Sonofragmentation, Monte Carlo algorithm***