SONOCRYSTALLIZATION OF PYRAZINAMIDE: MULTI-DIMENSIONAL POPULATION BALANCE MODELLING AND MONTE-CARLO SIMULATION

Abstract

This work focuses on experiments, multidimensional population balance modelling, and Monte Carlo simulation of unseeded batch sonocrystalliztion of δ-polymorph of pyrazinamide. First, we identified a set of five solvents and anti-solvents (acetone-toluene, acetone-cyclohexane, 1,4-dioxane-toluene, 1,4-dioxane-cyclohexane, and methanol-toluene) pairs that produce δ-polymorph pyrazinamide using solution crystallization. The solubility of pyrazinamide in different solvent-antisolvent (0 to 70 wt% antisolvent) compositions at different temperatures (293.15 K to 333.15 K) are measured and three different thermodynamic models, namely, UNIQUAC, Wilson, and NRTL, are successfully used to correlate the experimental solubility data. According to Akaike Information Criterion (AIC), the UNIQUAC model best fits the experimental data for all the five systems studied. Next, we investigated in detail the effect of ultrasound amplitudes (10, 30 and 50%) on the metastable zone width (MSZW), induction time and nucleation kinetics of pyrazinamide. For a given cooling rate and saturation temperature, the MSZW decreases by almost 50% with increase in ultrasound amplitude from 0% to 50%. The application of ultrasound enhances the nucleation rate by five to eight times compared to silent case and significantly decreases the interfacial energy. Further, metastable zone width is also estimated from induction time data using the concept of nucleation potential. The accuracy in determining the MSZW using the above approach is 80 - 85% for lower saturation temperature and 66 - 72% for higher saturation temperature.

Mathematical models play very important role in crystallization process understanding, design and optimization. The population balance approach along with solute mass balance is a powerful tool for modelling crystallization systems. The crystal size distribution and concentration profiles are used to develop two-dimensional population balance models for crystallization of δ-pyrazinamide from 1,4-dioxane solution, and solved using high resolution finite volume discretization method. First, a set of experiments is conducted to study the effect of ultrasound and its amplitude (10 and 50%) on only nucleation and crystal growth. The various kinetic parameters are estimated based on uncertainty quantification and sensitivity analysis. The Polynomial Chaos Expansion (PCE) is used to quantify the uncertainties in model prediction and sensitivity analysis is performed to rank the parameters using total order Sobol sensitivity indices derived from PCE model. Based on estimated kinetic parameters, an event-driven constant volume Monte-Carlo scheme is developed which predicts the results of univariate and multivariate sonocrystallization with good accuracy. Next, another set of experiments is performed to study the effect of ultrasonic amplitude (10, 20, 30 and 50%) on nucleation, growth, and breakage phenomena. The two-dimensional population balance equation and event-driven Monte-Carlo algorithm are extended to include breakage of particles. All the models are validated with separate set of experiments. These models can be further used for optimization and control strategies for achieving particles

with desired attributes.

Keywords: ***Pyrazinamide*, *Polymorphism*, *Sonocrystallization*, *Solubility*, *Metastable zone width*, *Induction time*, *Multi-dimensional Population balance model*, *High resolution finite volume scheme*, *Monte Carlo algorithm***