Growth and Nucleation Kinetics in Continuous Antisolvent Crystallization Systems

by

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Technical Summary

Continuous manufacturing is increasingly viewed as a viable means of producing pharmaceuticals. Multiple drugs have been commercialized employing continuous processes due to the advantages continuous processing can provide over batch processing: enhanced process control, more consistent final product quality, the potential for increased productivity using smaller equipment, and the ability to maintain smaller chemical inventories. Within continuous manufacturing, small-scale continuous crystallization is an area of special importance, as crystallization represents the unit operation where the product transitions from a liquid solution to an ordered, purified, solid phase. The products of crystallization determine the downstream processing scheme, yield, purity, and – ultimately – the dissolution and bioavailability of the active pharmaceutical ingredient (API) being manufactured. Crystallization process design entails selecting process conditions to achieve key final product quality attributes by generating supersaturation for nucleating and growing crystals at advantageous rates. Though there are many methods for generating supersaturation and affecting crystallization kinetics, antisolvent addition is of particular interest because it enables the crystallization of many heat-sensitive compounds and materials that have a weak solubility dependence on temperature.

In this thesis, we evaluated the impact of solvent composition on antisolvent crystallization kinetics in continuous crystallizers. Specifically, we applied our study of solvent composition to mixed-segment, mixed-product removal (MSMPR) combined cooling and antisolvent crystallization (CCAC) cascades.

To put this thesis into practice, a commercially-produced, confidential API-solvent-antisolvent system was studied to determine API solubility throughout the specified temperature and solvent composition space. Then, solvent-dependent growth and nucleation kinetic parameters were regressed from single-stage, steady-state MSMPR experiments to develop empirical formulas for lumped nucleation and growth kinetic parameters as functions of solvent composition and temperature. These models were validated using additional steady-state, single-stage MSMPR data. The regressed kinetic parameters quantify for the first time that both nucleation and growth kinetics are functions of solvent composition beyond supersaturation effects.

Using solvent-dependent kinetics, we simulated and optimized a multi-stage MSMPR crystallization cascade to maximize yield, given constraints on operating conditions and the crystal size distribution (CSD). Our work demonstrates that solvent effects must be incorporated in kinetic expressions for proper antisolvent MSMPR crystallization cascade design, as solvent composition effects may dominate temperature and residence time effects. From a

thermodynamic perspective, an increase in antisolvent fraction minimizes solubility at low solvent fractions, increasing supersaturation. From a kinetic perspective, nucleation and growth kinetic prefactors increase exponentially at low solvent fractions. Both phenomena result in increased nucleation and growth rates at low solvent fractions. Attainable regions for yield and mean crystal size were also simulated, demonstrating that the set of optimal process operating conditions in the antisolvent MSMPR cascade is not intuitive.

Beyond demonstrating the need to include solvent-dependent kinetics in antisolvent crystallizer design, we also demonstrated that many of the commonly-employed crystallization process design heuristics should not be used for processes that have strongly solvent-dependent kinetics. For example, we demonstrated that it may be beneficial to reduce and then increase the temperature in successive MSMPR crystallizers to maximize API production rates.

To continue improving the MSMPR cascade models, additional assumptions were explored regarding solvent effects. Many of the traditional assumptions regarding supersaturation calculations, such as having a low supersaturation or having an activity coefficient ratio of one at supersaturated conditions, do not apply to antisolvent or mixed-solvent systems. Traditional, simplified supersaturation assumptions were evaluated against the expression for mole fraction and activity-dependent (MFAD) supersaturation in antisolvent crystallization systems. Our work demonstrates that failing to incorporate activity coefficient-dependent supersaturation estimates leads to not only substantial errors in supersaturation calculations, but also large errors in predicting growth and nucleation kinetics, crystallization yields, and crystal size distributions. To develop a viable crystallization cascade model, one should carefully incorporate activity-, temperature- and solvent-dependent supersaturation expressions with solvent- and temperature-dependent kinetics models, combining these expressions with the proper population balance and material balance equations.

The multi-stage MSMPR cascade represents a robust, continuous process that will enable us to manufacture products with acceptable yield while meeting constraints on crystal size distribution, polymorphism, and purity. However, when solvent-dependent kinetics are incorporated in antisolvent crystallization cascade design, the optimal MSMPR cascade may not be intuitive. This thesis considers both the thermodynamic and kinetic effects of solvent composition on continuous MSMPR antisolvent crystallization processes, detailing where common crystallization assumptions fail and suggesting methods for improved continuous antisolvent crystallization process design in the future. In this thesis, we have successfully implemented solvent-dependent growth and nucleation kinetic models to rationally design a multi-stage, continuous, combined cooling/antisolvent crystallization process for an industrially-relevant drug. Our findings provide a framework for future continuous antisolvent crystallization process design.

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