Abstract

Crystallization is a commonly used operation in pharmaceuticals, fine chemicals, and agrochemicals industries for the production, separation and purification of solid crystals. Controlling the crystal size distribution (CSD) is often the primary goal of a crystallization operation because of the close relation of the CSD to the characteristics and efficiency of the crystalline product. As the CSD of the product crystals strongly depend on the supersaturation profile, controlling the supersaturation profile during the crystallization process is considered as key to the successful control of the process. A considerable effort has been put into developing crystallization processes that would allow effective control of crystal size. To this end, combining cooling and antisolvent modes of crystallization is advantageous as it enhances yield and also offers two manipulative variables to influence the supersaturation profile and thus the outcome of the crystallization process. The work in this thesis investigates various aspects of combined cooling and antisolvent crystallization of L- asparagine monohydrate (LAM) from it's aqueous solution using isopropanol as antisolvent.

This thesis first describes the experimental determination of solubility and metastable zone width (MSZW) that defines the operating region for the system. The experimental solubility data are correlated with thermodynamic models such as Universal quasi chemical (UNIQUAC) and Non random two liquid (NRTL). In order to calculate various nucleation parameters, the obtained MSZW data are analysed using classical Nyvlt theory and Kubota method. Based on the solubility information, a set of cooling-only and antisolvent-only crystallization is first conducted using three different control profiles for each and then combined cooling and antisolvent crystallization experiments are conducted using all possible nine combinations of these control profiles. These various combinations of cooling and antisolvent addition profiles generate diverse supersaturation profiles leading to various crystal sizes or crystal size distributions. A significant enhancement in the yield has been observed in all combined modes compared to individual modes of crystallization. The yield obtained for combined cooling and antisolvent crystallization is 42.45% higher than cooling-only crystallization and 30.65% higher than antisolvent-only crystallization. The experiments conducted produced enough data for developing a predictive model for the system. Both one-dimensional and two-dimensional population balance models are developed for the system and solved using high resolution finite volume discretization with a flux limiter. Finally, a model-free approach is developed for effective control of CSD using internal seeding with a cooling/heating cycle for the combined cooling and antisolvent crystallization process. this strategy increases the mean crystal size

by 45% as compared to conventional cooling/anti-solvent crystallization experiments.
Keywords: ***Combined cooling and antisolvent crystallization, L-asparagine monohydrate, Solubility, Metastable zone width, Crystal size distribution, Population balance modelling, Internal seeding***