529f Concentration-Control of Anti-Solvent Crystallization Using Atr-Ftir

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Tightening regulations and intensifying competition in the markets for pharmaceuticals, agrochemicals and fine chemicals have confronted industries with increasing pressure to optimize their production processes. Since many of these products appear in crystalline solid form, robust control of crystallization stands out as an essential step in achieving the optimization goals. Solute concentration measured by ATR FTIR has been successfully employed as feedback signals in cooling crystallization [1-4] (termed as concentration-control) and the particle size distribution (PSD) of crystal products thus yielded has exhibited significant improvement. As far as anti-solvent crystallization is concerned, studies on the use of ATR-FTIR have been limited to the measurement of supersaturation degree [5] and its use for closed-loop control of crystallizers has not been reported.

In this study, calibration of ATR FTIR using chemometric methods [5] was carried out for the ternary system consisting of paracetamol (solute), acetone and water (anti-solvent). Calibration results showed that solute concentration and solvent composition can be measured simultaneously with high accuracy. Using the measurements of ATR FTIR as feedback signals, a closed control loop for the addition rate of anti-solvent was then constructed to maintain the relative supersaturation constant during crystal growth. Process dynamics in anti-solvent crystallization was analyzed and incorporated into the control logic. The concentration-control strategy was implemented in a 1-liter flat-bottomed crystallizer equipped with a marine-type impeller. Both unseeded and seeded crystallization experiments were carried to assess the performance of the concentration-control strategy.

Results showed that the coefficient of variation of PSD, mean size of crystals and batch time were significantly improved compared to those obtained at constant addition rate of anti-solvent. For unseeded crystallization, the efficacy of concentration-control may be compromised if too many nuclei are created, which means anti-solvent must be added at a relatively slow rate during nucleation stage. For seeded crystallization, the trajectory of accumulated mass of anti-solvent and batch time depends on seed loadings. It was also found that the profiles of accumulated mass of anti-solvent are cubic with time when relative supersaturation was kept constant, analogous to the temperature profile in cooling crystallization.

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