Control methodologies for robust operation of a nucleator + growth cascade crystallizer: model based steady state and start-up optimization

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The development of optimal and robust operating and control strategies for continuous crystallisation process is paramount to ensure consistent and high quality pharmaceuticals and meet more effectively the regulatory requirements. A model-based approach for optimal steady state and start-up operation was developed for a two-stage cascade mixed-suspension, mixed-product removal (MSMPR) unseeded cooling crystallizers. The main idea was to develop optimal strategies for operating the first tank as a nucleator and the second as pure growth stage.

The dynamic mathematical model of the system was developed by combining of population balance, mass balances and heat transfer models. The objectives were (i) to optimize the first (nucleation) tank volume and two-stage temperatures, to achieve the largest number based mean size and (ii) to shorten the start-up time by optimizing the initial cooling rates of the two tanks. To simplify the physics, breakage and agglomeration of crystals were not considered, and the standard moments method was applied to solve the population balance. The case system studied was paracetamol (PCM) dissolved in a mixed water-propanol (IPA) solution. The mass ratio of water to IPA was 4:1.

The kinetic parameters for power-law nucleation and growth were estimated by the maximum likelihood method to minimize the differences between measured experimental data (solute concentration and particle size from batch experimental runs) and simulated results. Solute concentration was measured by UV/vis and off-line particle size measurements were obtained by MasterSzier.

A steady state optimization was conducted using sequential quadratic programming (SQP) method (MATLAB function ‘fmincon’). The feed flowrate and total volume of the two stages were fixed as 20 ml/min and 1000 ml, respectively, to maintain a fixed total mean residence time. Six constraints were applied: 1) the operating temperature range for both tanks was 10°C- 40°C;2) the second tank temperature should be lower than the temperature used for first tank (no dissolution); 3) the volume range of first tank was from 50 ml to 1000 ml; 4) the overall yield should be higher than 80% (to determine the second tank temperature); 5) the zeroth moment in the first tank should be higher or equal to the zeroth moment in the second tank to guarantee that the first tank operates as a nucleator; 6) the zeroth moment in the first tank ranges from 2000 #/g solvent to 5000 #/g solvent to limit the nucleation in favour of growing bigger crystals. The model-based optimization approach for steady state operation showed that a larger crystal mean size and yield can be achieved. Furthermore, a dynamic model-based optimization problem, based on the minimisation of start-up time, was developed using the initial cooling rates as the decision variables. A stochastic method based on a genetic algorithm was used to obtain the global solution of the optimization problem.