**Kinetic Assessment for Continuous Crystallization Process of Early Development Compound**

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**Highlights**

* Kinetic assessment for continuous crystallization developed
* Population balance kinetic model (PBM) built for two solvent systems to evaluate solvent dependency
* MSMPR process parameters optimized and validated through PBM

**1. Introduction**

In the pharmaceutical industry, crystallization is a key unit operation utilised to produce particles with desired properties, such as the particle size distribution, as this has an influence on downstream processes such as filtration and drying. The acquisition of reliable kinetic correlations that describe how rates of nucleation and growth vary over the crystallization design space is necessary for enabling robust prediction of crystallizer performance. The aim of this study was to generate a standardised workflow approach for the generation of crystallization kinetics data using population balance modelling (PBM), and to assess the batch crystallization process for feasibility of continuous processing for an early development compound.

**2. Methods**

Initially, the crystallization growth kinetics were estimated by means of seeded isothermal desupersaturation experiments in a batch reactor. PAT tools such as Attenuated Total Reflectance-Fourier Infrared (ATR-FTIR) spectroscopy and Focused Beam Reflectance Measurement (FBRM) were utilised for *in situ* to track the desupersaturation profile and the progression of the seed distribution, respectively. The initial crystal size distributions (CSDs) and desupersaturation profiles were used to estimate the growth kinetics as a function of temperature and supersaturation. Two solvent systems were tested to extract growth kinetics and were used for comparison. Furthermore, activity coefficients as a function of temperature and composition were considered in the kinetic model, which enabled to directly evaluate the solvent dependency effect. Following satisfactory validation of crystal growth kinetics, a continuously operated single-stage mixed suspension mixed product removal (MSMPR) crystallizer was used to extract the secondary nucleation kinetics.

**3. Results and discussion**

Three seeded isothermal desupersaturation experiments were performed to estimate the crystal growth kinetics, which are outlined in Table 1. A conservative approach of using a high seed loading of 50% allowed for the estimation of growth kinetics in the absence of nucleation. Furthermore, the temperature and initial relative supersaturation range covered in the parameter estimation was between 0 to 30°C and 0.226 to 0.670, which ensured that the entire phase diagram was covered and that the estimated parameters could describe the growth over a wide range of operating conditions. One experiment (exp 4) was performed to validate whether the growth is size dependent or independent by using a larger seed fraction.

Table 1. Experimental conditions for parameter estimation for solvent system 1

|  |  |  |  |
| --- | --- | --- | --- |
| **Experiment** | **Temperature (°C)** | **Relative S0 (-)** | **Seed Loading (%)** |
| 1 | 0 | 0.670 | 50 |
| 2 | 15 | 0.474 | 50 |
| 3 | 30 | 0.226 | 50 |
| 4 | 30 | 0.226 | 50 |

During the continuous crystallization study, a recycling system was employed to significantly reduce the waste of raw materials during the MSMPR study prior to the onset of steady state, which can be very useful during the early stages of process development where limited amount of product is available. Furthermore, problems such as blocking of transfer line and feed inlet were eliminated, by applying a rapid intermittent withdrawal of slurry via dipped pipe1, and by using a tube-in-tube configuration to insulate the feed inlet line. Finally, a novel 3D printed jacketed nozzle was attached at the end of the feed inlet line to avoid the saturated solution from crystallizing which can lead to blockage. Based on PBM and utilisation of the kinetic data2, CSD was simulated and residence time distribution, operating temperature and productivity of the MSMPR were optimised and finally experimentally verified. Overall, a standardised workflow was developed for the kinetic assessment of an early development compound for continuous crystallization.

**References**

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