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Control of Crystallization Processes in the Pharmaceutical Industry

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An overview of the control of crystal properties in the crystallization of pharmaceutical solids will be presented. Two case studies will be considered: first, crystallization of stavudine with emphasis on the effect of process variables is investigated. Next, crystallization of paracetamol from water-isopropanol using a real-time optimal control will be discussed. The concentration and chord length counts were measured using an in-situ ATR-FTIR and an in-situ FBRM® probe, respectively. A two-input two-output control strategy (cooling rate and flow-rate of anti-solvent as inputs and the mean size and the total chord length counts, as outputs) was used for the optimal control. The nucleation and growth kinetic parameters of paracetamol in an isopropanol-water cooling, anti-solvent batch crystallizer were estimated by non-linear regression in terms of the moments of the crystal population density. Moments of crystal population were estimated using the measured chord length distribution (CLD), generated by the FBRM, and the supersaturation was measured by ATR-FTIR spectroscopy. The real-time optimal control resulted in an increase in the volume-weighted mean size by approximately 100 μm and 15% of theoretical yield compared to the best result obtained in an offline optimal control strategy.

Introduction

Efforts to implement 'process control' strategies on batch cooling crystallizers go back to early 1970s where it was shown that a narrower size distribution and a larger mean particle size can be ensured by using an off-line or open-loop optimal control policy. The major limitation of the open-loop optimal control policy is its insensitivity to batch-to-batch variations and process disturbances. In addition, in order to determine the optimal cooling policy, a reliable model of the crystallizer with the nucleation and growth kinetics is needed. The crystallizer model used in the above-mentioned work was either based on the population balance equation (involving an integro-partial differential equation) or the moments equations (a set of ordinary differential equations). The latter, however, does not produce an explicit representation of the crystal size distribution. Real-time optimal control can address the limitations of the off-line optimal control policies. In this approach the optimal policy (e.g. the optimal

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temperature profile in a cooling crystallizer) is updated as soon as new information becomes available from the process.

The objective of this communication is to review different approaches for the control of batch crystallization processes. It is shown that proper manipulation of process variables can guarantee the desirable polymorphic outcome and a larger mean product size and a shorter crystallization time may be achieved by real time optimal control of supersaturation and chord length counts.

Materials and Experimental Methods

The experiments were performed in a 1-L glass jacketed vessel (Simular, Automated Chemical Reactors and Calorimeters; HEL Ltd., Vinelean, NJ). An electronic balance (Oxford, B41002) was used for recording the amount of the anti-solvent added to the solution. Moving average chord length distribution measurements were collected every 1 min using the *in-situ* FBRM® probe (Mettler Toledo, Redmond, WA). An in-situ ATR-FTIR (Hamilton Sundstrand, CA and DMD-270 diamond ATR immersion probe) was used for in-line collecting of infrared spectra. The FTIR spectra were related to the solute concentration in the solution using the calibration curve developed. Particle size distribution of the final product was measured by Malvern 2000 SCIRRCCO (Malvern Instruments Ltd., UK).

Crystallization of Stavudine, preparation of Form 1, Form 2 and Hydrate

Stavudine, (Zerit®) is an anti-viral drug that is used for the treatment of HIV/AIDS. The chemical formula of stavudine, 2',3'-Didehydro-3'-deoxythymidine, is $C_{10}H_{12}N_2O_4$. Stavudine has two polymorphs (Form 1 is the stable form), one hydrate and several solvates. The two polymorphs are monotropically related. The provided stavudine contained observable amounts of fibres that may have been introduced during the filtration process. Initially, Form 1 was dissolved in isopropanol (IPA) solvent at 50 °C and filtered to remove the insoluble suspended particles. The clean filtrate was cooled down to 25 °C with a linear cooling profile at a rate of 0.1 °C/min while agitating the solution to recrystallize the stavudine. The DSC and FTIR analyses confirmed that pure Form 1 of stavudine was produced. To produce Form 2, the purified stavudine Form 1 was dissolved in isopropanol at 48 °C and cooled down to 25 °C in 10 minutes (approximately linearly) without mixing. The final product was identified as pure Form 2 with DSC and FTIR. The hydrate form was obtained with the same procedure as Form 1, with the exception that the solvent was deionised water instead of isopropanol. DSC, TGA and FTIR confirmed the identity of the hydrate form. To study the effect of solvent on polymorphism and crystal habit, water, methanol, isopropanol, acetonitrile and MEK were used at a moderate degree of supersaturation (Mirmehrabi et al., 2006).

Effect of Impurity on Polymorphism and Crystal habit

Thymine and thymidine were used as two impurities in the crystallization media. The experiments were performed using just one impurity and also their mixture. The amounts of impurities were considered as 0.25-wt%, 0.5-wt% and 1-wt% of the total consumed stavudine in crystallization. For each impurity concentration, the experiments

were replicated three times. The supersaturation and crystallization conditions were similar to those in the solvent effects experiments. All the experiments were performed in isopropanol.

Effect of Supersaturation and Mixing on Polymorphism

Supersaturation (S) was defined as $S = a/a^*$, where a and a^* are the activity of the solution with supersaturated and saturated concentrations. The activity ($a = \gamma \cdot x$) was calculated from the semi-empirical activity coefficient (γ) models and the experimental solubility data (x). Isopropanol and acetonitrile were used for studying the effect of supersaturation on the polymorphism of stavudine. Supersaturations in the range of S = 1.7 to 2.5 were employed with the cooling rate of 1 °C/min and nucleation temperature of 25 °C. Two sets of experiments were performed for studying the effect of mixing. In the first set, a stirring rate of 100 rpm was used during the whole process. In the second set, mixing was stopped before cooling the clear solution. Once the temperature reached 25 °C, mixing was resumed at 100 rpm. Among the solvents used, water offers the strongest hydrogen bonding donor capability and dipole-dipole interaction expressed in terms of the polarity index (PI). However, its hydrogen bonding ability is not as strong as between the stavudine molecules (which is larger than 1.64). The major difference of water molecule over stavudine molecule is its higher mobility due to its smaller molecular size. Water may establish a type of hydrogen bonding with stavudine, which may lead toward hydrate formation. A hydrate with 3:1 stoichiometric ratio of stavudine/water was observed in this study. However, if the crystallization process were very slow, then the stavudine molecules would have enough time to form inter-molecular hydrogen bonding and not let the water molecules attach to the stavudine molecules to form a hydrate. This phenomenon was observed in the production of single crystals. All of the single crystals that were grown in water turned out to be Form 1 and not the hydrate.

Thymine as an impurity improved the crystal habit and filtration time. The interaction between the thymine ring and the stavudine molecule inhibited the growth of the fastest growing face resulting in a rod-like habit with small aspect ratio. Neither of impurities studied resulted in a change in polymorphic outcome and in all cases just Form 1 precipitated.

Almost the same range of supersaturation (S = 1.8 to 2.45) was employed for the experiments with and without initial mixing. In all cases, the spontaneous nucleation initiated a few minutes after mixing was started. The induction time was inversely related to the supersaturation. Depending on the degree of supersaturation at T = 25 °C, a specific polymorph or a mixture of Forms 1 and 2 was obtained. In isopropanol, below $S \cong 2.05$, only pure Form 1 was obtained and above $S \cong 2.12$, pure Form 2 was the product. Between $S \cong 2.05$ and $S \cong 2.12$, a mixture of the two polymorphs was produced concomitantly (See Figure 1).

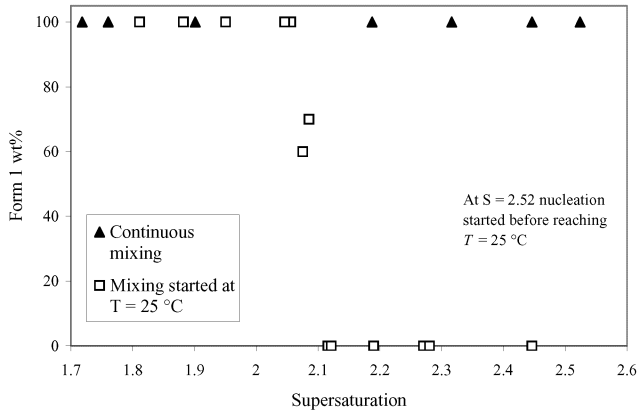

Figure 1. The effect of initial mixing and supersaturation on polymorphic outcome of stavudine.

Crystallization of Paracetamol and Real-Time Optimal Control

The chord length distributions measured by FBRM® were used to compute the moments of the particle population density. The growth and nucleation rates were calculated from the moments directly, without converting the CLD measurements to the PSD. The CLD information from 1 to 1000 μm was collected in 90 channels. The moments of the CLD were calculated as

$$\mu_j(t) \equiv \int_0^{\infty} r^j n(r,t)dr \equiv \sum_{i=1}^{FBRM_{final\ channel}} r_{ave,i}^j . N_i(r_{ave,i},k) \qquad 1$$

where r_i and N_i are the chord length and number of particles in channel i, respectively, and k is the discrete time counter. r_{ave}^j is expressed as:

$$r_{ave,i} = \frac{r_i + r_{i-1}}{2} \qquad 2$$

The objective function of the nonlinear parameter estimation algorithm at the end of the batch, $F(t_{final})$, was to minimize the difference of sum-of-squares in growth and nucleation rates calculated ($B_{exp,k}$ and $G_{exp,k}$) and those predicted by the model ($B_{pred,k}$ and $G_{pred,k}$) at each sampling interval k (Hojjati and Rohani, 2006; Mersmann, 2002; Hu et al., 2005).

To evaluate the accuracy of the model, simulation and experimental results of the final particle size distribution and supersaturation corresponding to three different open-loop anti-solvent feeding policies, were compared. The validated model was used to compute the optimal anti-solvent feeding profile for single-objective (S/O) and multi-objective (M/O) optimizations.

Result and Discussion

The objective function of the crystallization process was expressed in terms of the properties associated with the product quality such as, large crystal size, narrow PSD,

and high yield. The solutions of the optimal anti-solvent profiles were obtained by applying constrained nonlinear single-objective and multi-objective optimization algorithms to crystallization model. The MATLAB optimization function *fmincon* was used for solving the single-objective optimization problem and *fminimax* optimization function was used for the multi-objective optimization problem. Both functions are based on a sequential quadratic programming (SQP) and require the initial guess for the anti-solvent flow-rate feeding policy.

Case I – Single-objective 1 (S/O-1)

The first objective function was defined in terms of the nucleation and growth rates. The minimization of this objective results in suppressing nucleation and enhancing the growth of the existing seeds. The control variable was the anti-solvent flow-rate profile (*FR*).

$$\begin{cases} \underset{FR(t)}{Minimize}\ J_1 = \dfrac{B}{G} \\ subject\ to \\ \quad c_1 : \dfrac{dFR}{dt} \le 0.5\, g/\min.\min \\ \quad c_2 : C > C^* \\ \quad c_3 : t_{final} = t_{\max} \\ \quad c_4 : FR_{\min} < FR < FR_{\max} \end{cases} \qquad 3$$

The equality and non-equality constraints were chosen based on the knowledge gained from the open-loop experiments. The final-time constraint, c_3, was specified so that there is enough time allowed for the growth of particles.

Case II – Single Objective 2 (S/O-2)

In this case, minimization of the ratio of the third moments of the newly nucleated and the seed crystals in each optimization segment was attempted.

$$\begin{cases} \underset{FR(t)}{Minimize}\ J_2 = \dfrac{\mu_3^n}{\mu_3^s} \\ subject\ to\ c_1,\ c_2,\ c_3,\ c_4 \end{cases} \qquad 4$$

where μ_3^n and μ_3^s are the third moments of the PSD of the newly nucleated and the seed crystals, respectively.

Case III – Multi-objective (M/O)

The objective for the third case, J_3, was a vector consisting of three single objective functions. The first two were already presented in the single-objective study cases, while the third one deals with mimization of the coefficent of variation of the PSD. The worst case scenario of these three objective functions was chosen in each optimization segment. The best PSD result was obtained from the M/O optimal profile, which was expected considering that the objective function dealt with minimization of the coefficient of variation and suppressing the nucleation simultaneously. The shape of the PSD corresponding to the multi-objective optimization

case showed a complete shift of the seed PSD to larger sizes, which indicated good growth of particles with minimal breakage and agglomeration. The comparison between the yield, surface-weighted mean, and the volume-weighted mean between the above mentioned profiles is given in Table 2. These results show the superiority of the M/O profile with respect to the all tested criteria.

$$\begin{cases} \underset{FR(t)}{Minimize}\ J_{31} = \dfrac{\mu_3^n}{\mu_3^s} \\ \underset{FR(t)}{Minimize}\ J_{32} = \dfrac{B}{G} \\ \underset{FR(t)}{Minimize}\ J_{33} = \sqrt{\dfrac{\mu_3^s \mu_5^s}{(\mu_4^s)^2} - 1} \\ subject\ to\ c_1,\ c_2,\ c_3,\ c_4 \end{cases} \qquad 5$$

Table 2. Comparison between end of batch properties for different experiments

	Seed	Policy 3	S/O-1	S/O-2	M/O
yield (%)	-	48.5	48.7	49.5	50.1
Surface weighted mean (μm)	75.8	74.2	83.2	74.2	87.1
Volume weighted mean (μm)	290.5	342.1	362.4	343.0	369.6

Conclusions

The kinetic parameters of paracetamol in IPA and water were estimated from the CLD data measured by the FBRM probe. The single and multi-objective non-linear constrained optimization was performed on the validated model in order to obtain the optimal profiles that applied to the system. The multi-objective optimization function resulted in the best product properties in terms of the final PSD and product yield.

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