Optimization of two-stage cooling profile in unseeded batch crystallization *

Jared C. King^{*} Huayu Li^{*} Martha A. Grover^{*} Yoshiaki Kawajiri^{*} Ronald W. Rousseau^{*}

* School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, GA 30332-0100 USA (Tel: 404-894-2878; e-mail: martha.grover@chbe.gatech.edu).

Abstract: A two-stage cooling protocol for batch cooling crystallization was optimized to maximize mean crystal size while minimizing the variance in size. A population balance model represents the crystallization process, incorporating crystal growth and nucleation, for use in a multi-objective optimization. At all points along the Pareto front, the optimal strategy has the nucleation event occurring on the temperature plateau between the two cooling stages. This shortens the nucleation period—supersaturation is rapidly depleted, ultimately generating fewer crystals of larger size. In comparison to a simple linear cooling profile, the two-step strategy produces crystals of larger size with smaller variance.

Keywords: batch crystallization, crystal size distribution, optimization, crystallization kinetics

1. INTRODUCTION

Batch crystallization is a technique widely used in industry for the purpose of producing crystalline solids, which are a major final product in the fine chemical and pharmaceutical industries. The purity, morphology, and crystal size distribution (CSD) are three critical aims for the final products (Tung (2012)), which are controlled by both thermodynamics and kinetics. The monitoring and control of these crystal properties have been greatly aided by advances in the field of process analytical technologies (Simon et al. (2015)). One challenge in batch crystallization is controlling the initial nucleation of crystals. This event happens suddenly, often creating a large number of crystals that ultimately limits the maximum crystal size that can be achieved Mullin (2001). Seeding the batch with preformed crystals is one solution, which achieves large crystals of uniform size. Seeding has been studied extensively, by simulation and experiments, including studies on the CSD and loading of seeds (Chung et al. (1999); Kubota et al. (2001)), the preparation methods (Aamir et al. (2010)), and the cooling rate (Widenski et al. (2011)). All of these aspects strongly impact the final CSD.

A potentially simpler approach is to avoid material additions and use an unseeded process. However, with a linear cooling strategy, the temperature at the onset of nucleation may vary from batch-to-batch (Nývlt et al. (1970)), leading to unreproducible CSD. Furthermore, the driving force for nucleation increases as temperature decreases, so a nucleation event that occurs during cooling may rapidly produce an excessive number of crystals. Since the solute mass is fixed during batch crystallization, having a large number of crystals implies that the mean crystal size will

be small.

A wide range of strategies for optimization and feedback control have been proposed to control the crystal size distribution, as described in several reviews (Rawlings et al. (1993); Nagy and Braatz (2012); Nagy et al. (2013)). Here a simple, two-stage cooling profile is proposed, which requires only feedback control of the temperature and thus can be implemented without sophisticated control systems. The parameters defining this temperature trajectory can be optimized to achieve larger and uniformly sized crystals. The first cooling stage reduces the solution temperature to a predetermined value at which nucleation is expected. The temperature is then held constant for a period of time, during which the onset of nucleation is expected. Growth of nucleated crystals depletes the supersaturation and limits further nucleation or growth. The second cooling stage is then initiated, driving further crystal growth. Some nucleation of additional crystals is also possible during this stage, although it is not desired.

The rationale for this two-stage strategy is to limit the number of crystals that are generated during the initial nucleation event. By holding the temperature constant throughout the primary nucleation event, the driving force for nucleation is rapidly depleted. An additional advantage of the proposed strategy is to minimize variations from batch to batch. By controlling the temperature at which the initial nucleation event occurs, the process is made robust to variations in the time of nucleation. However, this additional advantageous feature is not explicitly investigated in this study. A similar strategy was computed in Nagy (2008), employing a temperature plateau between two cooling periods. However, in that study the strategy was qualitatively different, since the primary nucleation event occurred on the initial ramp, not on the temperature plateau.

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In this work, the two-stage cooling process is optimized using a population balance model. The parameters for nucleation and growth were obtained from our previous work, using *in situ* measurements (infrared and FBRM) and sieve analysis of the final crystals (Li et al. (2014)). The driving force for both nucleation and growth is the supersaturation of the solution, which is related to the difference between the actual concentration and the maximum concentration that is soluble in the solvent at equilibrium. Primary nucleation is defined as the birth of new crystals from a clear solution, not relying on pre-existing crystals. Primary nucleation usually requires a high supersaturation. Secondary nucleation, which is less sensitive to supersaturation, is defined as the birth of new crystals via the participation of existing crystals. The mechanisms for secondary nucleation remain poorly understood, but empirical models have been able to correlate secondary nucleation rate to mass of crystals, supersaturation, and temperature (Randolph & Larson, 1988). Growth is defined as the increase of the size of crystals, being a function of supersaturation and temperature (Mullin, 2001). One critical assumption of this work is that the growth rate for a given concentration and temperature is independent of crystal size or other factors.

The population balance model was approximated using the method of moments, and a multi-objective optimization was formulated in order to maximize the mean crystal size and minimize the variance in crystal size. The results show that the mean size can be tuned via the plateau temperature. It is also found that the optimal two-stage strategy is superior to a linear cooling strategy.

2. METHODS

The population balance equation (PBE) for the nucleation and growth of crystals in solution is (Randolph and Larson (1988))

$$\frac{\partial n}{\partial t} + G \frac{\partial n}{\partial L} = 0. \tag{1}$$

Here *n* is the number density of crystals $[\#/\mu m/kg \text{ solvent}]$, *t* is the time [min], *L* is the crystal size $[\mu m]$, and *G* is the size-independent crystal growth rate $[\mu m/min]$. In addition, B_1 is the primary nucleation rate [#/min/kg solvent], B_2 is the secondary nucleation rate [#/min/kg solvent], and $B = B_1 + B_2$ is the total nucleation rate. The nucleation rate does not appear in the population balance equation, but rather enters through the boundary condition

$$n(L=0,t) = \frac{B}{G} \tag{2}$$

as new crystals of approximately zero size are generated.

The mathematical forms for primary nucleation and secondary nucleation suggested by Randolph and Larson (1988) were used here. A form for growth rate which included temperature effects was suggested by Mullin (2001).

$$B_1 = k_{b1} \exp\left(\frac{-16\pi\gamma^3 v^2}{3k^3 T^3 ln^2(S)}\right)$$
(3)

$$B_2 = k_{b2}(S-1)^{\alpha} M_S^{\beta} \tag{4}$$

$$G = k_g \exp\left(\frac{E_a}{RT}\right) (C - C_s)^{\eta} \tag{5}$$

Here C is the concentration of solute [kg/kg solvent], C_S is the solubility [kg/kg solvent] at a given temperature, S is the supersaturation defined as C/C_S , M_S is the total mass of crystals [g/kg solvent], T is the temperature [K], v is the molecular volume of solute [m³], and k is the Boltzmann constant [J/K]. The parameters γ , k_{b1} , k_{b2} , k_g , E_a , α , β , and η are fitting constants, where γ represents the interfacial tension [J/m²].

Because growth is nonlinearly dependent on temperature and concentration, the PBE is difficult to solve analytically, and is generally solved numerically. A number of approximation methods are available for this class of system. In particular, the method of moments (Randolph and Larson (1988)) offers an approximation which is not time-intensive to solve. (Here MATLAB's ode45 function is used.) First the original PBE in (1) is multiplied by L^j and integrated over all sizes L:

$$\int_{0}^{\infty} \frac{\partial n}{\partial t} L^{j} dL = \int_{0}^{\infty} -G \frac{\partial n}{\partial L} L^{j} dL$$
(6)

The mathematical moments of the crystal number density are defined as

$$\mu_j = \int_0^\infty n L^j dL \tag{7}$$

and the boundary condition for μ_0 is

$$\frac{d\mu_0}{dt} = B \tag{8}$$

Subsequently, integration by parts can be used on (6) to obtain an arbitrary number of moments:

$$\frac{d\mu_j}{dt} = jG\mu_{j-1}, \qquad j = 1, 2, \dots$$
(9)

where the initial size of the crystals is assumed to be zero. The moments can be correlated with physical characteristics of the number density. For instance, the zeroth moment has a linear correlation with the number of crystals per kg solvent, while the first moment divided by the zeroth is equal to the average crystal size.

The number-weighted crystal size is heavily affected by small nuclei, so in some circumstances it makes more sense to optimize

$$\overline{L}_v = \frac{\mu_4}{\mu_3} \tag{10}$$

where \overline{L}_v is the volume-weighted mean size $[\mu m]$. It has previously been argued that number-weighted crystal size is preferable to \overline{L}_v , as large amounts of small crystals are difficult to process downstream (Nagy et al. (2008)). In this paper, \overline{L}_v is considered alongside the variance in a multiobjective optimization, providing a more explicit and transparent tradeoff between crystal size and variance. The volume-weighted standard deviation, σ_v [μm], is defined as

$$\sigma_v = \frac{1}{\mu_3} \sqrt{\mu_3 \mu_5 - \mu_4^2}.$$
 (11)

The parameters γ^3 , k_{b1} , k_{b2} , k_g , E_a , α , β , and η were fit to experimental data of paracetamol crystallization in ethanol, as given in Table 1. The CSD was characterized during crystallization using a focused beam reflectance measurement (FBRM), and the final product was characterized in a sieve analysis. The solute concentration during the process was also measured using total attenuated reflectance infrared absorption, with a ReactIR probe.

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Table 1.

Parameter Value for the Population Balance Model Variable Value



(b)

Fig. 1. A comparison of experimental data to the model used. (a) An example run with final CSD compared between experiment and fitted model. (b) An example run comparing experimental supersaturation, S, to that predicted from the model.

Data from a typical experiment are shown in Fig. 1(a), including a comparison to the model prediction using the population balance equation. Fig. 1(b) shows comparisons of measured and predicted supersaturations for a typical experiment.

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Fig. 2. A comparison of linear cooling with an optimized two-step cooling strategy. Note the indistinguishability of the temperatures after 170 minutes.

When a linear cooling rate is applied to the model, results such as those shown in Fig. 4 can be obtained. Once the temperature-dependent solubility drops below the solute concentration, there is a driving force for primary nucleation in the clear solution. Once crystals have been nucleated, then secondary nucleation and growth may also proceed.

For the purpose of optimization, a multi-step cooling strategy was used, in which two different periods of linear cooling are separated by a temperature plateau. This is illustrated in Fig. 2, and compared to a linear profile over the same time period. The total run time was fixed at $t_f = 500$ minutes, the inital temperature is 70°C, and the final temperature was 0°C. Using the method of moments, each cooling trajectory was simulated using (8) and (9). Each run can then be evaluated on the basis of its final mean size \overline{L}_v and standard deviation σ_v as defined in (10) and (11).

If the initial final temperatures are set, four degrees of freedom remain: the first cooling rate r_1 , the second cooling rate r_2 , the length of the plateau t_{plat} , and the temperature of the plateau T_{plat} . In this multi-objective formulation, the goal is to maximize the volume-weighted crystal size, while holding the variance in crystal size below a prespecified value. The problem then becomes a four-variable optimization problem outlined as follows:

$$\min_{\mathbf{x}} -\overline{L}_v(t_f) \tag{12a}$$

s.t.
$$r_1, r_2 \le 0.5^{\circ} \text{C/min},$$
 (12b)

$$t_1 + t_{plat} + t_2 \le t_f \tag{12c}$$

$$\sigma_v(t_f) \le \epsilon \tag{12d}$$

$$\mathbf{x} = [r_1, t_{plat}, r_2, T_{plat}]^T \tag{12e}$$

$$t_1 = (I_0 - I_{plat})/r_1 \tag{121}$$

$$\iota_2 = (I_{plat} - I_f)/T_2 \tag{12g}$$

Due to the presence of high nonlinearity in the model, MATLAB's genetic algorithm was selected for a global optimization. As shown in (12), practical constraints were



Fig. 3. A Pareto optimal front for the dual objectives of mean size and standard deviation.

added—the process was constrained to take no more than 500 minutes and to cool no faster than 0.5°C/min . In order to find the best possible mean size for a given standard deviation and vice versa, the epsilon constraint method for multi-objective optimization was used (Haimes et al. (1971)). In this method, one objective is constrained to be bounded by a given value, and the other objective is optimized given this constraint. In this work, standard deviation was constrained at regular intervals and the optimal mean size was found for each constraint.

3. RESULTS

The tradeoff between mean crystal size and standard deviation is shown by the Pareto optimal front (blue curve) in Fig. 3. Each point is representative of the best obtainable mean size, for a fixed standard deviation. For the system studied, the Pareto front contains a curved region at either end which represents a region where relatively little improvement in one objective corresponds to a relatively large loss in the other objective. Thus, the linear region of the Pareto front is the recommended operating region.

The blue curve in Fig. 3 can be compared to the red curve, which is associated with a simple linear cooling profile over the same period of time (500 minutes). In particular, the point marked " 0.14° C/min" is associated with a linear cooling from 70°C to 0°C over 500 minutes. The other points along the red curve are associated with a faster cooling rate. Once 0°C has been achieved, the temperature is then held constant for the remaining time. By comparing these curves, it can be seen that the multistep profile enables better overall performance, in terms of simultaneously maximizing size and minimizing standard deviation. Moreover, with a multi-step process it is possible to achieve much larger mean size, relative to the linear cooling process. Of course, this also comes along with a larger standard deviation.

In Fig. 4, the linear cooling rate from Fig. 2 is compared to an optimized cooling profile from the Pareto front that



Fig. 4. A comparison of the relative growth and nucleation rates for two different cooling trajectories. (a) A simple linear profile, identical to that shown in Fig. 2. (b) An optimized strategy from the Pareto front simultaneously optimizing the mean size and standard deviation of the CSD.

favored mean size. The growth rate G that is plotted in Fig. 4 is only a function of the supersaturation S, not the population of crystals. This is also true for primary nucleation B_1 , while secondary nucleation B_2 does depend on the total mass of crystals present. Thus, the growth rate curve depends only on the difference between the concentration and solubility curves, while the nucleation rate ($B = B_1 + B_2$) has a more complicated relationship, also depending of the crystal size distribution.

Some differences between the two scenarios are immediately apparent. In linear cooling, nucleation occurs at a lower temperature, compared to the optimized strategy. The overall integrated nucleation rate is thus higher, creating more crystals. Due to the fixed solute mass in the system, these crystals will therefore be smaller. However, the period of nucleation appears to be slightly longer in the



Fig. 5. A comparison of the mean size and standard deviation evolution over time for the two cooling profiles compared in Fig. 4



Fig. 6. A comparison of various final CSDs along the Pareto front, along with the final CSD from linear cooling.

optimized profile, resulting in crystals with a somewhat higher spread in sizes. In addition, a larger secondary nucleation event occurs at late times during the optimized profile, compared to the linear profile, as shown in Fig. 5. These late-appearing crystals will also cause an increase in the standard deviation in size, as they will not grow large by the end of the process.

Fig. 6 illustrates the differences in the final CSDs, comparing the linear profile with several optimal profiles along the Pareto front—one with the same standard deviation as the linear profile (black), one maximizing crystal mean size (green), and one minimizing standard deviation (red). The CSDs in Fig. 6 were generated by assuming a log-normal distribution and finding the mean and standard deviation from the moments. It can be seen that linear cooling does represent a good tradeoff between mean size and standard



Fig. 7. A comparison of various temperature trajectories along the Pareto front, corresponding to the CSDs shown in Fig. 6.

deviation. However, the linear cooling profiles limited to 500 minutes cannot compete with a multi-step profile in attaining a large mean size. In order to achieve even better performance, it might be possible to add a third cooling step, having a lower ramp rate in order to minimize the secondary nucleation that is observed during late times in Fig. 4(b). As a final note, the temperature plateau may have the additional advantage of making the process more robust to stochastic variations in nucleation time, although that stochastic feature was not included in this deterministic model.

The temperature trajectories corresponding to Fig. 6 are shown in Fig. 7. The black curve associated with intermediate crystal size is the most similar to the linear temperature profile, consistent with the similarity between the two CSD's in Fig. 6. To achieve larger crystals, the plateau temperature should be high. In this case the supersaturation will be lower during nucleation, ultimately generating fewer crystals that grow to larger sizes. However, these crystals also have a wider size distribution (shown in Fig. 6) because they are generated over a longer period of time. Conversely, with a low temperature on the plateau, the driving force for nucleation is higher, rapidly generating a large number of crystals that deplete the supersaturation quickly.

4. CONCLUSIONS

It has been shown that a two-step cooling strategy offers significant advantages over simple linear cooling, including a higher attainable mean size due to better growth and nucleation profiles, and a predictable outcome due to a known plateau temperature. Using a model obtained by fitting to FBRM, infrared, and sieve data, it was found that a temperature plateau allowed primary nucleation and initial growth to occur at a temperature more conducive to higher crystal growth relative to nucleation.

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