Control of Batch Cooling Crystallization of Glycine

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Abstract

Traditionally, temperature control strategies are used for cooling crystallization, whereby the temperature of the solution is controlled to follow a pre-set cooling profile determined in the laboratory from small scale crystallization experiments. In recent years, with the advancement in in-line technologies for measuring particles and solution concentrations, more sophisticated control strategies have been proposed by various researchers. The benefits claimed for such new approaches are more consistent product and easier scale-up. Therefore, the main purpose of this paper is to evaluate the benefits, or lack thereof, of new methods for controlling crystallizations over conventional methods using temperature-control. The present work uses glycine-water as a model system to demonstrate the effects of the various modes of crystallization process control and of scale-up.

In-line sensors, including FTIR-ATR and Lasentec FBRM, have been used to monitor the cooling crystallization of glycine. Making use of information from the sensors, different control strategies have been implemented. Industrial applicability, especially with regards to practicality and robustness will be discussed.

Introduction

Crystallization is often the most important step for isolation and purification in the manufacture of pharmaceuticals and fine chemicals. Good control of the crystallization process is crucial to ensure the end product possesses the desired properties, such as downstream processability and bioavailability. Once a process has been developed and is in operation, batch-to-batch consistency is of paramount concern.

The control objectives for batch crystallization processes are defined in terms of product purity, crystal habit or morphology, average particle size, crystal size distribution, bulk density, product filterability, and dry solid flow properties. Crystallization from solution is an important unit operation in the industry due to its ability to provide high purity separations. For efficient downstream operations (such as filtration and drying) and product efficacies (such as

bioavailability and tablet stability), the control of crystal size distribution (CSD) and morphology can be critically important.

Although CSD is a function of the supersaturation in the solution, cooling crystallizations on scales larger than 5-litres are conventionally controlled by applying a pre-set cooling profile. This profile is determined by small scale experiments and often does not result in the same product quality in the production scale. The use of such pre-set cooling profile also suffers from the inability to respond dynamically to any changes in the crystallization system such as a change in impurities content. This has a serious impact on the batch-to-batch uniformity and consistency.

The reason for the prevalent use of the indirect approach is the lack of accurate on-line sensors for the measurement of particle size and solution concentrations. In recent years, accurate on-line sensors that are robust enough to be used in production environment have become available. This opens up the possibility of using such measurements to control crystallizations interactively. This is an area of active academic research. The claimed benefits for this new approach are more consistent product and easier scale-up.

However, proof of these claimed benefits is lacking. The authors are not aware of laboratory comparisons of controlled and uncontrolled crystallizations in the laboratory or at scale. The purpose of this paper was to test the hypothesis that in-line control makes a difference to the outcome of a cooling crystallisation.

Materials and Methods

Crystallization experiments were performed using glycine (≥99% purity, obtained from Sigma) in a 500 ml jacketed flat bottom flask with a Teflon stirrer agitating the system at 550 rpm. De-ionized water was used to prepare the solutions. During the experiments, chord length distributions (CLD) and mean size of glycine crystals in solution were obtained every 10 seconds using Lasentec FBRM D600 probe connected to a Pentium 4 computer installed with version 6.0b16 of the FBRM Control Interface Software. Solute concentration was measured every minute using a Nicolet Nexus 4700 FTIR equipped with an Axiom Analytical ATR probe. The system temperature was controlled by a Julabo HP50 circulator using deionised water pumped through the jacket of the crystallizer. The crystallizer temperature was measured every 2 seconds using a stainless steel Pt100 thermocouple. The same experimental set-up was used for all experiments.

An appropriate amount of glycine corresponding to a saturation temperature of 50 ^{o}C was dissolved in de-ionized water in the 500 ml crystallizer. The system was then heated to and maintained at 60 ^{o}C for at least 30 minutes to ensure complete dissolution of the raw solid glycine. The final temperatures for all experiments were 20 ^{o}C. Supersaturation-control is such that the concentration of the system is controlled in a region between the solubility curve and

the metastable limit through manipulation of the system temperature (Figure 1). Such a profile ensures that growth of crystals dominates while nucleation is suppressed, hence ensuring a narrower product CSD.

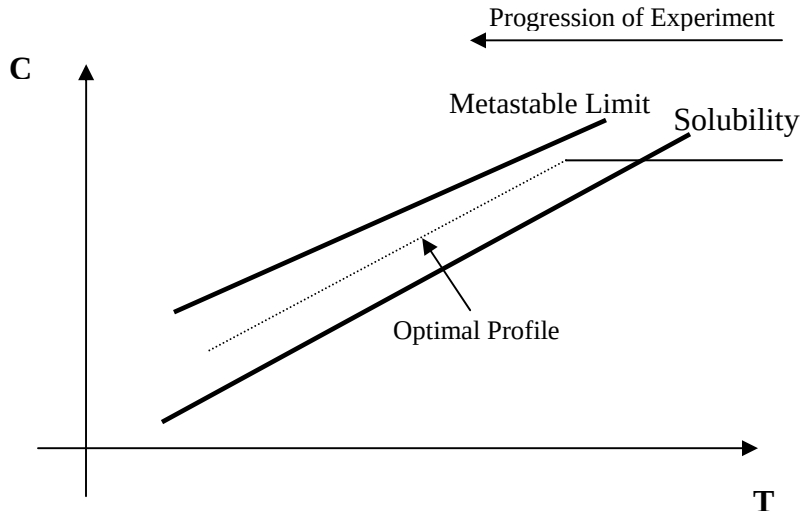


Figure 1: Concentration vs Temperature Profile for seeded systems: The optimal profile is one that is between the solubility curve and the metastable limit, such that growth dominates over nucleation.

For unseeded systems, the system was cooled until the metastable limit was exceeded to generate nuclei, then supersaturation-control or temperature-control was implemented only after the detection of nucleation. The cooling rate in approaching nucleation of 0.5 ^{o}C/min was chosen because this gave a rather reproducible nucleation temperature and sufficient nuclei for a smooth CLD. Higher rates gave less reproducible nucleation temperature, while lower rates gave insufficient nuclei and hence noisy CLDs.

For seeded systems, the system was cooled to a point midway between the solubility curve and the metastable limit before seeds were added. This was to ensure that the seeds did not dissolve and that primary nucleation was avoided. As in unseeded systems, the same cooling rate of 0.5 ^{o}C/min was used to approach nucleation. Seeds corresponding to 1% of the amount of total glycine added were used, since this amount corresponded to similar amount of nucleation generated in unseeded systems, as reflected by the counts detected by FBRM. Supersaturation-control or temperature-control was implemented after seeds were added.

In the temperature-control experiments, convex cubic and linear cooling profiles have been implemented in the preliminary study. In the supersaturation-control experiments, the supersaturation level was controlled to maintain at a constant value after the detection of nucleation (unseeded systems) or seeds addition (seeded systems). Natural cooling of the system was also implemented to verify if control is required at all.

Results and Discussions

Calibration of the ATR-FTIR using robust chemometrics (Togkalidou et al., 2001, 2002) gave a relative error of less than 1% with respect to our lowest concentration measurement. The absolute error values at different calibration temperatures and solute concentrations are shown in Figure 2.

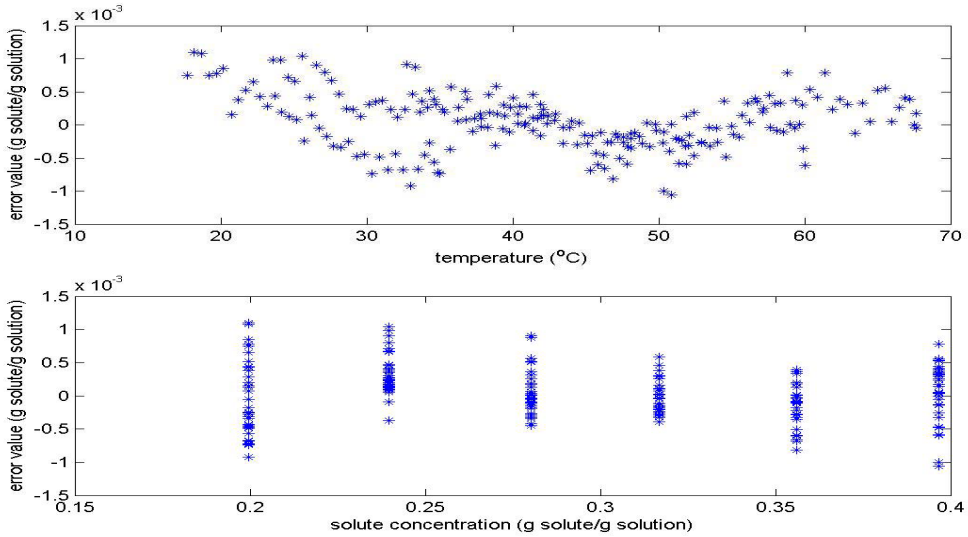
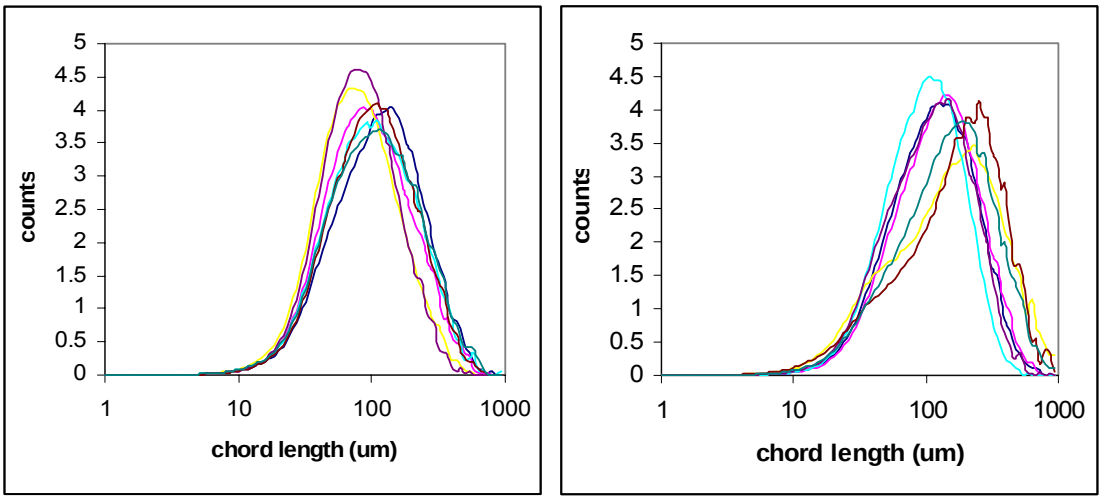


Figure 2: ATR-FTIR calibration error is less than 1% with respect to our lowest concentration measurement.

Fig. 3 shows the final square-weighted CLDs from all the supersaturation-control experiments of seeded and unseeded systems. The raw material, seed crystals and product crystals were confirmed to be α-form by powder X-ray diffraction. Square-weighted CLDs were used for comparison because they were found to be more similar to the CSD measured under the microscope. Unseeded experiments generated slightly wider CLDs than seeded experiments. This is mainly due to the lack of control of the size distribution of initial nuclei resulted from spontaneous nucleation. There are also clearly more variability between the CLDs of unseeded system than seeded system. This is confirmed by quantitative comparison of the CLDs. The statistics of the CLDs together with the corresponding average deviations are listed in Table 1. The statistics shown are average values of seven runs each for seeded and unseeded systems. In general, the average deviations (numbers after the ± signs) are significantly lower for unseeded systems, indicating that seeding improves the product consistency when supersaturation-control is employed. The lower reproducibility of unseeded systems is expected because nucleation is relatively unpredictable and there is no control over the size distribution of the initial nuclei.



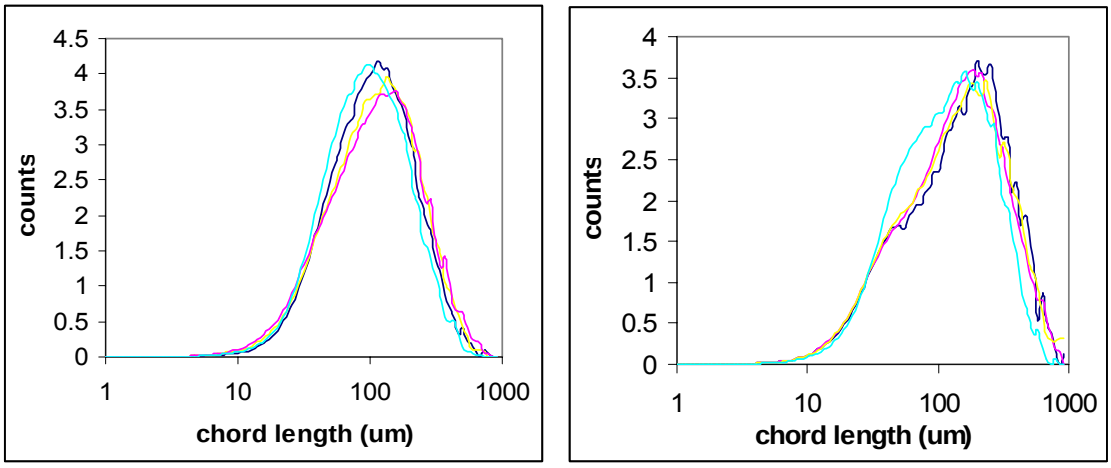
(a) (b)

Fig. 3 Final square-weighted chord length distributions for (a) seeded and (b) unseeded supersaturation-control experiments

Table 1 Comparison between seeded and unseeded supersaturation-control experiments (Data shown are the average values of seven runs)

	Seeded	Unseeded
Average mean, square-weighted (μm)	134.79 ± 17.60	168.51 ± 36.60
Average standard deviation, square-weighted	102.36 ± 13.28	124.75 ± 35.54
Average median, non-weighted (μm)	25.21 ± 1.69	23.77 ± 6.13
Average standard deviation, non-weighted	37.77 ± 3.64	42.25 ± 2.74

Fig. 4 shows the final CLDs of temperature-control experiments. In both the seeded and unseeded systems, there is hardly any discernable difference between the CLDs obtained when different cooling profiles were applied. This agrees with the statistics listed in Tables 2 and 3. The standard deviations of the CLD, which represent the widths of the CLDs, are similar for all cooling profiles in both seeded and unseeded systems. This suggests that the product CLD is not affected by different cooling profiles. Extremes of cooling rates may have more prominent effects on the CLDs but it is unlikely that such cooling rates will be used in industrial scale operation. Seeding did not show any advantage in the temperature-control experiments judging from the fact that the standard deviations do not differ significantly between seeded and unseeded system. This is rather unexpected and further investigation is required to confirm this observation.



(a) (b)

Fig. 4 Square-weighted chord length distributions of product crystals for (a) seeded and (b) unseeded temperature-control experiments (__ natural cooling, __ cubic profile run 1, __ cubic profile run 2, __ linear cooling). Linear cooling rates are 0.7 ^{o}C/min and 0.3 ^{o}C/min for seeded and unseeded systems respectively.

Table 2 Statistics of product crystals from seeded temperature-control experiments

Seeded	Mean, square-weighted	Standard deviation, square-weighted	Median, non-weighted	Standard deviation, non-weighted
Natural cooling	135.59	26.95	99.92	39.36
Cubic profile run 1	142.84	21.26	107.17	38.20
Cubic profile run 2	147.17	19.47	115.37	37.25
Linear cooling 0.7 ^{o}C/min	123.11	26.21	89.09	36.30

Table 3 Statistics of product crystals from unseeded temperature-control experiments

Unseeded	Mean, square-weighted	Standard deviation, square-weighted	Median, non-weighted	Standard deviation, non-weighted
Natural cooling	199.96	16.71	161.78	39.85
Cubic profile run 1	187.74	17.37	153.78	39.71
Cubic profile run 2	187.61	17.57	163.00	37.46
Linear cooling 0.3 ^{o}C/min	155.22	21.63	119.11	38.79

Comparing the results shown in Table 1 to Tables 2 and 3, supersaturation-control did not display any advantage over temperature-control since the standard deviations of the CLDs are similar. The insignificant difference between the effectiveness of supersaturation-control and temperature-control may be due to the fast growth rate of glycine. The average linear growth rate at cooling rate of 0.3 ^{o}C/min is estimated to be 62 nm/s by optical microscopy

(details of the measurement will be covered in a full paper), and that is equivalent to at least 124 molecules being incorporated onto the crystal per second. As a result, the controlling factor in glycine crystallization is the nucleation step. Once nuclei are formed (or seeds are introduced), the cooling rate will not make a significant difference because of the rapid growth rate. Therefore the only observable difference in this work is between the seeded and unseeded experiments under supersaturation-control.

Conclusion

Supersaturation-control and temperature-control have been tested on cooling crystallization of glycine from water. Results show that sophisticated control strategy was unnecessary for glycine. This may be because glycine grows rapidly at low supersaturation. In this case, this conclusion may be generally valid for all fast-growing systems.

Acknowledgement

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