REVIEW PAPER

RECENT ADVANCES IN CRYSTALLIZATION CONTROL
An Industrial Perspective

Z. Q. Yu[1], J. W. Chew[1], P. S. Chow[1] and R. B. H. Tan[1,2,*]

[1]Institute of Chemical and Engineering Sciences Ltd, Singapore.
[2]Department of Chemical & Biomolecular Engineering, National University of Singapore, Singapore.

Abstract: Crystallization is the most important unit operation for the separation and purification of chemicals in the pharmaceutical and fine chemical industries. Crystallization processes in pharmaceutical active ingredient manufacturing have been traditionally a recipe-based operations, offering little scope for dynamic process control and improvement. With the change in regulatory climate from quality-by-testing (QbT) to quality-by-design (QbD) and with the advent of the process analytical technology (PAT) initiative, it is timely to examine the impact of such quality-based emphasis on crystallization control. In this paper, we review the important recent developments in the control of crystallization process, and discuss their feasibility and scope for implementation in industrial processes. The control methods to achieve different aspects of crystal product quality, including particle size distribution (PSD), crystal habit and polymorphic form, are discussed separately.

Keywords: crystallizaton; PAT; quality by design; PSD; crystal habit; polymorph control.

*Corresponding to:
Associate Professor
R.B.H. Tan, Institute of Chemical and Engineering Sciences Ltd, 1 Pesek Road, Jurong Island,
Singapore 627833.
E-mail: reginald_tan@ices.a-star.edu.sg

DOI: 10.1205/cherd06234

0263–8762/07/
$30.00 + 0.00

Chemical Engineering Research and Design

Trans IChemE,
Part A, July 2007

INTRODUCTION

Crystallization of the solid phase from solution remains the predominant process for separation and purification of pharmaceuticals and fine chemicals. The operating conditions of a crystallization process determine the properties of the crystal product such as purity, size and shape distributions and polymorphic form. These properties in turn affect the downstream processing and handling, e.g., filtration and drying, and eventually the therapeutic properties and shelf-life of the final formulated product. As such, the control and consistency of solid phase properties through crystallization has been the focus of considerable industrial and academic research.

Crystallization control is essentially product quality control, i.e, how to operate the process to obtain the desired product quality in terms of crystal solid attributes such as particle size and shape, particle size distribution (PSD) and polymorphic form. Pharmaceutical manufacture has traditionally been a recipe-based operation, in which the processes are controlled such that the trajectories follow the specifications submitted for regulatory filings. There is also little scope for crystallization process control apart from low-level control such as temperature control to ensure the specified temperature profile is followed throughout the process. The quality of the product is only determined by testing at the end. Such a quality-by-testing (QbT) approach often leads to failed batches and loss of profit to the company. In view of these shortcomings, the regulatory environment has been changed recently to shift from regulating of the process to regulating of the product, i.e., from a QbT to QbD (quality-by-design) approach.

The FDA (Food and Drug Administration) now advocates the adoption of the QbD approach with the aim that product quality and performance are achieved and assured by design of effective and efficient manufacturing processes based on the mechanistic understanding of the underlying science (Hussain, 2006; McKenzie *et al.*, 2006). Manufacturers would be given certain degree of flexibility to make changes to process as long as they can show that the changes made are within the design space and that the quality of the product is maintained. Therefore, there is more scope for optimal and adaptive processes as long as quality can be assured.

Under QbD, real-time optimisation would be possible, with real economic benefits, e.g., maximizing yield or productivity, and reducing wastage due to failed batches compared with previous recipe-based operation.

Crystal quality is a result of the interplay among state variables in the course of crystallization as illustrated schematically in Figure 1. The interaction network is represented by notched arrows. Various control strategies of crystallizers differ in the use of open loop or closed loop, or which state variables are used as feedback signal in closed loop, or which state variable is treated as the controlled variable (solid-state attributes or supersaturation).

Solid-state attributes under frequent study include particle size distribution (PSD), polymorphic specificity and crystal habit. Most previous studies have been targeted at optimising PSD (especially in cooling crystallization), probably because the formation mechanism and manipulation approach of PSD are better established than those of other solid-state attributes. It has been reported that desirable PSDs are sometimes a compromise between conflicting requirements of downstream processing (Kim *et al.*, 2003; Liotta and Sabesan, 2004). Methods and algorithms developed for PSD control can be adopted for the control of other solid-state attributes, and tightening of crystallization control is an essential part of the initiative to improve the performance of pharmaceutical processes from two Sigma (4.6% defectives) to six Sigma (2 ppb defectives) (Leuenberger and Lanz, 2005).

The emergence and development of the latest generation of state-of-the-art PAT (process analytical technology) tools and techniques have been very much in step with the emphasis on process understanding of QbD and open up tremendous new opportunities for effecting process control. Yu *et al.* (2004) provided a review of the applications of PAT to crystallization processes.

In this paper, we review the important recent developments in crystallisation control, and discuss their feasibility and scope for implementation in industrial processes. Control of PSD, polymorph and crystal habit will be dealt with in the next three sections respectively. Challenges and future developments will be considered at the end of this review.

CONTROL OF CRYSTALLIZATION TO OBTAIN DESIRED PSD

A Historical Viewpoint of PSD Engineering: From Meta-Stable Zone to Optimal Control

The metastable zone, the region bound by the solubility curve and the metastable limit in which spontaneous primary nucleation does not occur, is a fundamental concept in crystallisation control. It is considered the ideal region for crystal growth once the nuclei have formed. Therefore the temperature profiles used during cooling crystallization are usually designed to progress within the meta-stable zone. Different temperature profiles have been derived either empirically or mathematically. In the pioneering work by Mullin and Nyvlt (1971), they derived 'programming cooling' profiles by establishing mathematical models for cooling crystallization of potassium sulphate and ammonium sulphate. The temperature profiles were derived such that the supersaturation was kept constant throughout the crystallization. It has been reasoned that the supersaturation does not necessarily have to be constant, and it can be allowed to fluctuate within the meta-stable zone as long as secondary nucleation is suppressed (Jones and Mullin, 1974). On the other hand, keeping it constant simplifies the deduction of operating profile to some degree. For instance, Wey and Karpinski (2002) deduced the following temperature profile for seeded crystallization under the assumptions of no spontaneous nucleation, constant growth rate G and a linear solubility-temperature relation:

$$T = T_{\mathrm{I}} - \frac{3M_{\mathrm{S}}}{aM_{\mathrm{sol}}}\left(\frac{G^3t^3}{3L_{\mathrm{S}}^3} + \frac{G^2t^2}{L_{\mathrm{S}}^2} + \frac{Gt}{L_{\mathrm{S}}}\right) \tag{1}$$

where T stands for temperature, M for mass, t for time, L_{S} for seed size, and T_{I} for initial slurry temperature. Subscripts S and sol represent seed and solvent and a is the slope in a linearised solubility-temperature relation:

$$c^* = aT + b \tag{2}$$

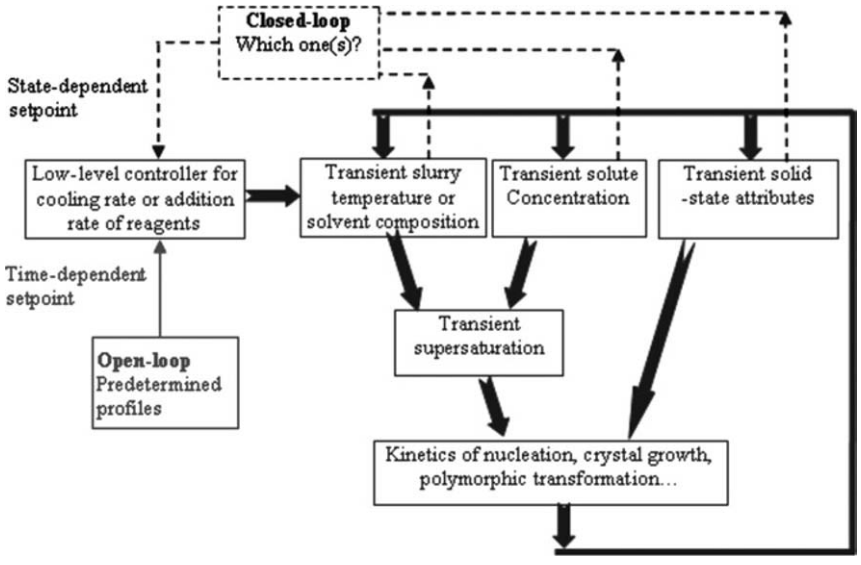

Figure 1. Interplay among state variables of the crystallizer.

Assuming further that the initial seed size is virtually zero compared with their subsequent size, Mullin pointed out that the temperature profile to maintain a constant supersaturation should be cubic in time in seeded crystallisation (Jones and Mullin, 1974; Mullin, 2001):

$$T = T_{\mathrm{I}} - (T_{\mathrm{I}} - T_{\mathrm{F}})\left(\frac{t}{\tau}\right)^3, \tag{3}$$

where τ is the overall batch time. T_{F} denotes the final slurry temperature.

For the case of semi-batch crystallizations, several studies have shown that more uniform and larger crystals can be produced in reactive crystallizations when reagents are added according to curved profiles rather than at constant rates. Karpinski and Wey (2002) proposed a growth ramp equation similar to equation (1) for the precipitation of silver bromide and found very good agreement between measured and calculated final size of crystals. Kim *et al.* (2005) adopted a simple growth ramp analogical to equation (3) for agent addition in reactive crystallization of an active pharmaceutical ingredient (API) in Bristol-Myers Squibb. Results showed that a cubic addition profile yielded larger and more well-defined crystals than constant addition rate. The same principle also applies to the addition rate of anti-solvent in anti-solvent crystallization as described by Tavare (1995).

The concept of 'optimal operation' of crystallizers (Jones, 1974) takes a step further from the abovementioned 'programmed cooling' in that a specific control objective is defined in terms of desired properties of final crystal products, such as maximum average size, a narrow crystal size distribution, minimum mass ratio of newly-formed crystals to grown seeds, shortest batch time or combination of these. The objective is targeted by manipulation of temperature trajectory based on *a priori* knowledge of nucleation and growth kinetics as a function of supersaturation. This is often referred to as the first-principles approach (Rawlings *et al.*, 1993; Braatz, 2002), where optimisation procedures and process modelling are needed to generate the optimal temperature profiles. For a detailed overview of model development for solution crystallization, the readers are referred to the review article by Rawlings *et al.* (1993).

Renewed interest in optimal design of crystallizers has been partly fuelled by a fundamental shift in the regulatory climate of API manufacturing towards a QbD approach (Ma *et al.*, 2002; Zhang and Rohani, 2003; Choong and Smith, 2004; Patience *et al.*, 2004; Togkalidou *et al.*, 2004; Worlitschek and Mazzotti, 2004; Costa *et al.*, 2005; Hu *et al.*, 2005). Advances in computer hardware and software allow more factors to be accounted for in crystallization models than possible previously. Hu *et al.* (2005) included growth rate dispersion in their model for ammonium sulphate–water system and Costa *et al.* (2005) included agglomeration in their model for adipic acid–water system. Ma *et al.* (2002) generated optimal temperature profiles for potassium dihydrogen phosphate–water system where two-dimensional growth was considered in crystallization modelling. The optimal temperature profiles (and thus supersaturation profiles) depend heavily on the expression of the objective function (Chung *et al.*, 1999; Ward *et al.*, 2006). For example, minimization of coefficient of variation of PSD in unseeded crystallization leads to fast cooling at the beginning of operation with the aim to generate nuclei in a short time interval, while maximization of mass-based average crystal size necessitates convex temperature profiles. Most of these optimization studies consider a single objective even though crystallization typically has multiple performance objectives, e.g., achieving CSD with narrow size distribution and specified end size in a minimum time of operation. The recent work by Sarkar *et al.* (2006) demonstrated the potential for multi-objective optimization approach for a batch cooling crystallization process.

The model-based optimization studies mentioned so far only concentrate on batch cooling crystallization. There are few reports on the modelling of anti-solvent or drowning out crystallization processes because of the additional complexity associated with mixing. The assumption of perfect mixing used in most studies may not be applicable for practical anti-solvent systems because supersaturation level—and therefore nucleation and crystallization kinetics—is heavily dependent on how the different components are mixed. A recent paper by Woo *et al.* (2006) has addressed this issue by incorporating a turbulent computational fluid dynamics (CFD) code with a multi-environment probability density function (PDF) model, and the population balance equation (PBE). This coupled CFD-PDF-PBE algorithm was able to simulate the evolution of the crystal size distribution of a semi-batch anti-solvent crystallization process taking into account micromixing between the different components. This modelling effort provides valuable understanding of the effects of mixing on crystallization and would offer a more scientific basis for the design and scale-up of crystallizers. It can be used to test the robustness of the optimal control profile to the 'mixing perturbations' for a given crystallizer configuration and scale as illustrated in Figure 2. If the simulation results show that the optimal profile does not produce the desired crystal product quality when imperfect mixing is considered, simulating the process using the CFD-PDF-PBE model for a range of profiles can guide the process

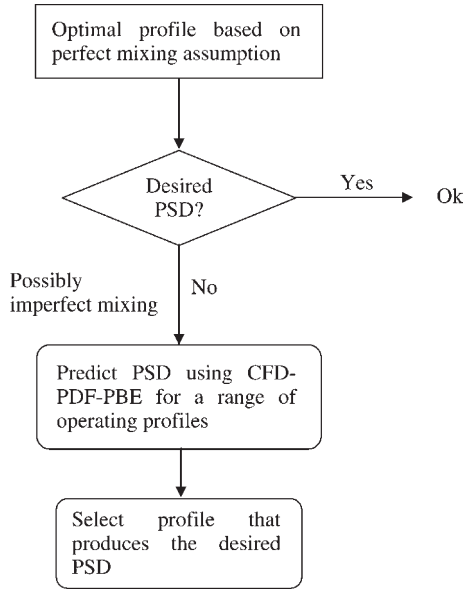

Figure 2. Procedure for testing the robustness of the optimal control profile to the 'mixing perturbations' for a given crystallizer configuration and scale.

designer to systematically select the control profile that gives the desired product quality. This can reduce the number of experiments required to arrive at a robust design.

After a temperature or anti-solvent/reactant addition profile as a function of time corresponding to constant supersaturation or optimal operation has been generated, it is traditionally tracked by a low-level temperature controller of PID type. Crystallizers are largely operated in 'open-loop' mode, in which solid-state attributes and supersaturation are not used as feedback signals. Performance is subject to model imprecision, uncertainties in parameter estimation and operating disturbances. Simplified models may fail to capture the process dynamics satisfactorily, causing the computed trajectory deduced from modelling to result in sub-optimal operation. In addition, uncertainties in parameter estimation are inherent and related to the random errors in real data. Operating disturbances are inevitable since crystallizers are located downstream to various synthesis trains. The actual supersaturation therefore may be far from its theoretical values in open-loop control strategies. Efforts have been made to handle these issues via model improvement and robust control theory (Ma *et al.*, 1999; Matthews *et al.*, 1996; Nagy and Braatz, 2004).

Although the first-principles approach has the advantages of enhancing process understanding and potential use in process scale-up, the considerable expertise and time required in process modelling and optimization has limited its research and application mainly to small scale laboratory studies. The application of first-principles approach to industrial scale has been rarely reported. A simpler approach, termed the direct design approach, is more amenable for large-scale implementation in industry. In this approach, feedback control is used to follow a setpoint based on a state measurement which may include temperature, solution concentration, or crystal size and shape distribution. Direct design approaches based on measurements of solution concentration, crystal size and shape distribution and polymorphic form will be discussed in the following sections.

Control Strategy for PSD Based on Concentration Measurement

The predominant role of supersaturation in particle formation as illustrated in Figure 1 has prompted its use as the controlled variable in the feedback control of crystallization. The direct design approach had been attempted based on concentration measurement from online techniques such as densitometry, conductivity and refractometry as early as the 1980s and 1990s (Bordui *et al.*, 1985; Gabas and Laguerie, 1992; Gutwald and Mersmann, 1990), but the implementation of this approach has not been widespread because of the limitations associated with the online sensors at that time. As attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) and other *in situ* techniques such as ATR-UV and Raman for concentration measurement became available, interest in the direct design approach has been renewed. Since ATR-FTIR is the most widely-used technique for concentration measurement during crystallization, the following discussion will focus only on this technique. The advantages of ATR-FTIR include accurate liquid phase concentration measurement even in the presence of solids, the capability to measure multiple components simultaneously, and eliminating the need for an external sampling stream. The measurement principles of ATR-FTIR and its first use for in situ measurement of supersaturation are described in Dunuwila *et al.* (1994).

The feasibility and usefulness of ATR-FTIR have been demonstrated by several research groups for feedback control of cooling crystallisation (Feng and Berglund, 2002; Grön *et al.*, 2003; Jones and Teodossiev, 1988; Lewiner *et al.*, 2001; Liotta and Sabesan, 2004) and anti-solvent crystallization (Yu *et al.*, 2006a; Zhou *et al.*, 2006). This strategy has a two-level structure (Liotta and Sabesan, 2004) and is often termed as 'supersaturation control' or 'concentration control'. The transient value of supersaturation measured by ATR-FTIR is compared with its setpoint and the difference is translated to an updated cooling or anti-solvent addition rate for a low-level controller. In other words, the setpoints for lower level controllers are not time-dependent as in open-loop control but state-dependent (Fujiwara *et al.*, 2005). Obviously supersaturation control possesses the capability to absorb some disturbances in operating conditions, such as changes in initial solute concentration, seed loading and crystal growth rate, and so on. For example, the anti-solvent crystallization of paracetamol remained at the supersaturation setpoint of 0.05 even when the seed loading was doubled (Figure 3) (Yu *et al.*, 2006a). As was obvious in this example, batch time is allowed to vary in order to accommodate the operating disturbances or changes.

With supersaturation control in place, the determination of a setpoint supersaturation becomes the key consideration. Choosing a constant supersaturation level within the metastable zone would be the simplest option compared to any supersaturation profile that varies with time. The study by Worlitschek and Mazzotti (2004) showed that optimized cooling did not produce crystals with CSD any more superior to a simple constant supersaturation operation. Moreover, constant supersaturation is claimed to be beneficial in developing a well-defined crystal morphology (Karpinski and Wey, 2002). The proper set point value of supersaturation and corresponding batch time can be determined readily from a small number of batches along with other operating parameters aided by design of experiment (DOE).

Supersaturation control has been proven to be a beneficial technique for obtaining product crystals of better quality, yet it is not always necessary. Chew *et al.* (2007) have reported that for a fast growth system, sophisticated methods of

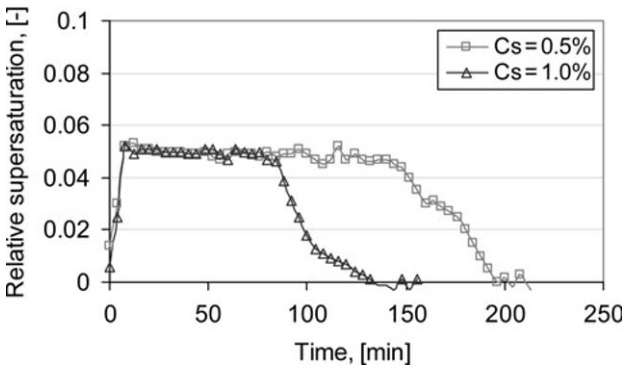

Figure 3. Relative supersaturation was maintained at a constant level by feedback control although seed loading (C_s) was doubled (Yu *et al.*, 2006a).

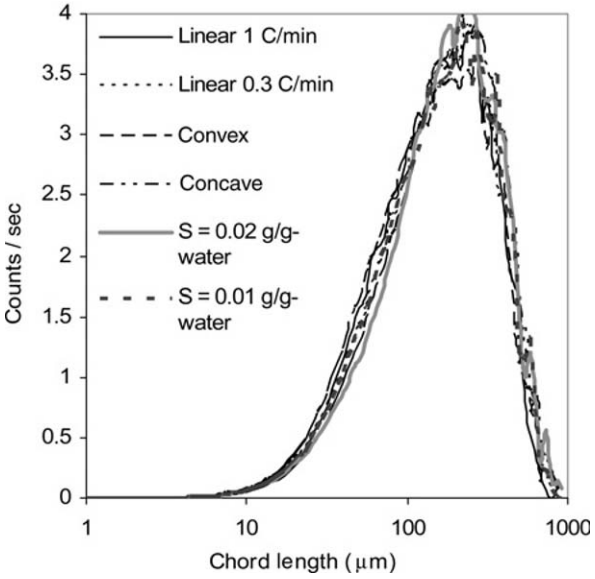

Figure 4. Normalized square-weighted chord length distributions (CLD) obtained from cooling crystallization of glycine using open-loop temperature control following four different temperature profiles and feedback concentration control at two different supersaturation levels (Chew *et al.*, 2007).

control did not prove advantageous. Figure 4 shows that open-loop temperature control following different temperature trajectories and feedback concentration control did not differ much in terms of chord length distribution (CLD), which is related to PSD.

One of the advantages of the ATR-FTIR technique is its ability to measure concentrations of multiple components simultaneously after careful calibration (Togkalidou *et al.*, 2002), which is highly desirable for monitoring of industrial processes wherein changes in concentrations of impurities may pose problem to crystal quality. However, its calibration in industrial context may be difficult because of the difficulty in manipulating the concentration of impurities in calibration solutions. The concentration range of both impurities and desired solute in calibration solutions must cover the possible fluctuations in commercial crystallizers to achieve a satisfactory measurement precision. Additionally, from an industrial standpoint, the vulnerability of the ATR element poses several setbacks (Lewiner *et al.*, 2001). Mechanical damage or chemical deterioration of the ATR element immediately affects the accuracy of the calibration; and encrustation of the probe can easily occur. These concerns pose difficulties in implementing ATR-FTIR in industrial crystallizers. Supersaturation measurement is often seen as too troublesome or complex for routine industrial crystallizations, but may become a critical factor in the control of specific polymorphs (Kee *et al.*, 2006) as discussed later.

Feedback Control Based on PSD Measurements

If the ultimate control target is PSD, one may think that using PSD measurements directly as feedback signal is the most sensible way forward instead of using supersaturation. This approach has, however, been hampered by the lack of reliable *in-situ* sizing devices. Off-line sensors for the measurement of PSD typically rely on good sampling which is difficult to achieve. Changes to the crystals may occur during the transfer of samples to the offline devices and therefore dynamic changes of the process cannot be tracked accurately. In recent years, probe-based Lasentec focused beam reflectance measurement (FBRM) has gained popularity for *in situ* characterization of high-concentration particulate slurries. The FBRM probe utilizes laser light backscattering technology to supply, in real time, a chord length distribution (CLD) that is a function of the number, size, and shape of particles under investigation (Barrett and Glennon, 1999).

FBRM measures the backscattering properties of suspensions, and FBRM data are related not only to PSD but also to refractive index of solvents and particles, as well as particle morphology. Research work has been reported to restore PSD from FBRM data based on first principles (Barthe and Rousseau, 2006; Bloemen and De Kroon, 2005; Hukkanen and Braatz, 2003; Li and Wilkinson, 2005; Togkalidou *et al.*, 2004; Worlitschek and Mazzotti, 2002; Wynn, 2003). However this is an extremely difficult job and many assumptions have to be made to accomplish the restoration. Although these authors were able to verify their models with experimental data, their algorithms are only applicable to well defined systems with known shape and optical properties and may not be extendable to systems in general. Much work needs to be done in understanding the optics and physics of backscattering before PSD data can be restored reliably from FBRM data. Another way to use FBRM data is to empirically correlate the statistics of CLD with the results of traditional sizing techniques. Heath *et al.* (2002) presented a comprehensive review on correlation studies of FBRM data where the similarity between PSD and square-weighted CLD was confirmed experimentally in some particulate systems. De Clercq *et al.* (2004) performed a comparative study of FBRM data with results obtained via laser diffraction and image analysis, and concluded that although the measurement principles are completely different, PSDs with number-weighted mean diameters above 150 μm were similar for all measurement techniques. Nevertheless, most of these correlations are system-specific and are difficult to generalize.

More often, FBRM data are used qualitatively for monitoring the process evolution with time, e.g., to identify the onset of primary nucleation, detect attrition and agglomeration. A widely used statistic of CLD is the counts of chord lengths in the whole range or certain channels of chord length. A jump in the total counts in the whole range can be used to indicate the onset of nucleation, so it can be used in measuring meta-stable limit (Barrett and Glennon, 2002; Fujiwara *et al.*, 2002; Kline *et al.*, 2006; Liotta and Sabesan, 2004). A continuous increase in total counts during crystallization was sometimes interpreted as the result of secondary nucleation (Doki *et al.*, 2004). The counts in different channels have been frequently used to isolate nucleation events and crystal growth. The counts in channels of short chord length are related with fines and thus with nucleation, while those in channels of long chord length are associated with big crystals and thus with crystal growth. The dividing line between 'short' and 'long' chord length is not universally agreed upon, and is somewhat arbitrary depending on the specifics of particulate systems and individual judgement. For example, in the study by Lafferrère *et al.* (2004), the change in counts from 1 to 50 μm were used to interpret nucleation and those from 50 to 160 μm

were used for indicating crystal growth. Barrett and Glennon (2002) adopted a different dividing line: 0–20 μm and20–250 μm. Similarly, counts of chord lengths were also used to explain the changes in PSD due to agglomeration and breakage (Richmond *et al.*, 1998). Moreover, FBRM has also been used to monitor polymorphic forms (O'Sullivan *et al.*, 2003; Schöll *et al.*, 2006).

Due to the complicated relationship between CLD and PSD, there have been few reports on the use of FBRM signal for feedback control despite the widespread use of FBRM in process monitoring. Tadayyon and Rohani (2000) constructed a feedback control system for a continuous cooling crystallizer using FBRM signals (counts of chord lengths smaller than 125 μm) in which the flow rate of fines dissolution stream was adjusted in a real-time manner to increase average crystal size.

Most recently, Chew (2006) demonstrated that a fully-automated technique using FBRM measurements and feedback control of temperature was successful in achieving consistent PSD in repeated batch crystallizations of glycine and paracetamol. Figure 5(a) shows the temperature–time profile for a typical run. The saturated solution (Point A) is cooled at a pre-set rate until nucleation is detected by the FBRM (Point B). The system is allowed to stabilize at the temperature of Point B until primary nucleation is completed. Then, a heating ramp is implemented while using the FBRM to monitor the PSD of the 'seed' crystals. The heating gradually redissolves the fines, thereby narrowing the PSD towards the setpoint of coefficient of variation of CLD which is used as the controlled variable. When the desired quality of these internally generated 'seeds' is achieved (Point D), the system is cooled at a constant rate to allow the crystals to grow until the final yield is attained (Point E). Figure 5(b) reveals that a desirable CLD (and, by inference, PSD) could be consistently achieved using this technique. This new development appears to be very promising for implementation at industrial scale owing to its simplicity and robustness.

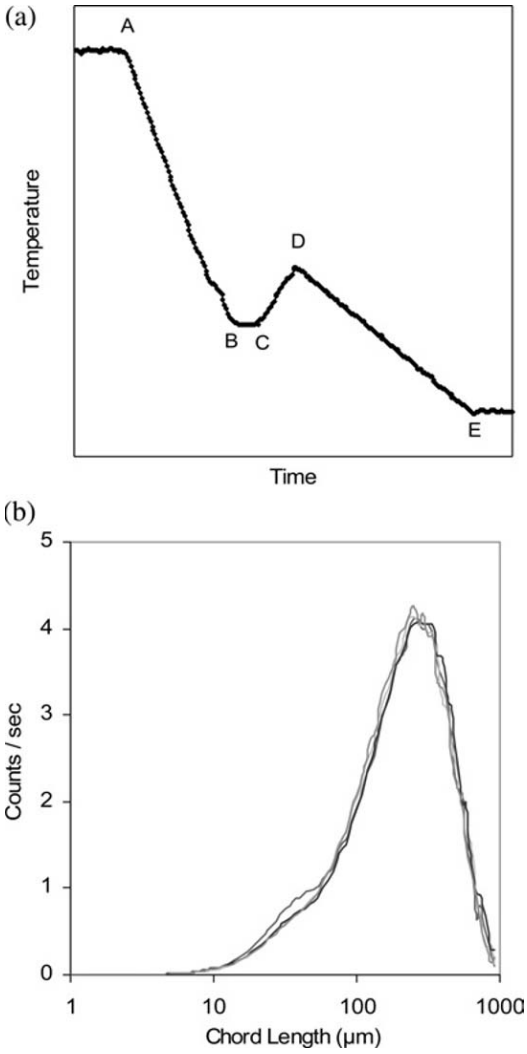

Figure 5. Temperature–time profile for a typical run, (b) CLDs recorded at the end of eight different batches of cooling crystallization runs of glycine using the FBRM control technique by Chew (2006).

Effectiveness of Seeding in PSD Engineering

Seeding is often employed to obviate the adverse impacts of uncontrolled unseeded crystallizations, namely encrustation on internal fittings of crystallizers, and random variations in the number of nuclei leading to inconsistent product and possibly unfavourable PSD with a large amount of fines. It is estimated that up to 30–50% of solutes crash out of solution rapidly through spontaneous nucleation for organic systems (Beckmann, 2000), leaving little that can be done about PSD engineering through supersaturation control (Chew *et al.*, 2007). Seeding is also especially important for systems which are difficult to nucleate or tend to induce liquid-phase separation, because in this case, it reduces nucleation time that may be otherwise too long from an economic perspective. Seeding is also known to be advantageous in ensuring product consistency because the size range of the seeds, whether the seeds are added dry or wet, the temperature at which the seeds are added, and the amount of seeds are all pre-determined.

In PSD engineering, the purpose of seeding a supersaturated solution is to provide starting surface area for crystal growth and avoid nucleation as much as possible. Seed loading, seed size and timing of seeding are three critical quantitative parameters in a seeding policy towards such a goal.

Seed loading and size

Research on seeding techniques has been mainly targeted towards how to determine seed size and seed loading. Kubota *et al.* (2001) emphasized the importance of seed loading to guarantee the unimodal distribution of final products. Their work showed that unimodal distribution of final products could be achieved over a wide range of generation rates of supersaturation when seed loading exceeded a critical value which was determined empirically. One consequence of accommodating high generation rates of supersaturation is the high seed loading which inevitably compromises productivity. Lung-Somarriba *et al.* (2004) put forward a procedure to determine seed size and seed loading which took into consideration the attrition of large crystals. They proposed that the seed size should be smaller than one quarter of the maximal product size over which attrition will hinder crystal growth. Similar to the critical seed loading

proposed by Kubota *et al.* (2001), they used critical surface area obtained empirically to determine the size-mass couple of seeds.

Gutwald and Mersmann (1994) incorporated generation rate of supersaturation in the calculation of seed loading. For a given cooling crystallization system with a cooling rate of $\dot{T}$, the necessary seed mass M_S was:

$$M_S = -\frac{\varphi_v}{\varphi_a}\left(\frac{dc^*}{dT}\right)M_{sol}\frac{\dot{T}\,\overline{L}_S}{G_{met}}\left(1+\frac{1}{2}\frac{G_{met}\Delta T_{met}}{\dot{T}\,L_S}\right)^2 \quad (4)$$

where ϕ_v and ϕ_a are the volume and surface shape factors of crystals respectively, $\overline{L}_S$ the average seed size, dc^*/dT the slope of the solubility curve, M_{sol} the mass of solvent, G_{met} the maximum allowable growth rate within metastable zone, ΔT_{met} the maximum allowable undercooling. It can be seen that this seeding policy integrates important operating parameters, two of which need to be measured separately, namely G_{met} and ΔT_{met}.

Combination of seeding technique and manipulating the profile of supersaturation-generating variables increases the likelihood of removing inconsistency from final PSD. Mullin (2001) proposed an expression to determine the seed mass-size couple which has the following equivalent form:

$$\left(\frac{\overline{L}_S}{\overline{L}_P}\right)^3 = \frac{M_S}{M_P} \quad (5)$$

where $\overline{L}_P$ and M_P stand for the final average product size and mass (the product mass consists of two parts: seed mass and the mass of solute that has deposited on seed surfaces) respectively. This expression is derived from a mass balance of the crystallization batch by assuming the number of product crystals to be equal to that of seeds and that secondary nucleation, agglomeration and attrition are negligible. It should be noted that $\overline{L}_S$ and $\overline{L}_P$ are number-mean size, defined as the first moment of population density function. In conjunction with programmed cooling, it is assumed that nucleation is subdued to such a degree that almost all solute molecules deposit on the seed surfaces, and the product size is then related to seed mass-size couple by equation (5). Genck (2000) gave two examples of the application of this methodology to cooling and evaporative crystallizations. Yu *et al.* (2006b) examined the applicability of equation (5) to the anti-solvent crystallization of paracetamol–acetone–water system. Despite the tendency of agglomeration (Yu *et al.*, 2005), when coupled with supersaturation control, equation (5) was found to be a good starting point for the refinement of particle size distribution and adjustment of batch time in different circumstances to obtain a target average crystal size with narrow size distribution. Figure 6 shows the PSDs of products using equation 5 as first estimate for seed mass-size couple and when the seed loading was doubled. By simply doubling the seed loading, the fines fraction has significantly reduced to a narrower and unimodal distribution.

Seed loading and size was also studied through crystallization modelling and optimisation. Chung *et al.* (1999) and Choong and Smith (2004) included seed properties as the optimised variables along with temperature profile in the formulation of optimization problems. The relationship between the properties of seeds and products is complicated by secondary nucleation whose rate is usually a function of the third moment and/or average size of the particles in the slurry.

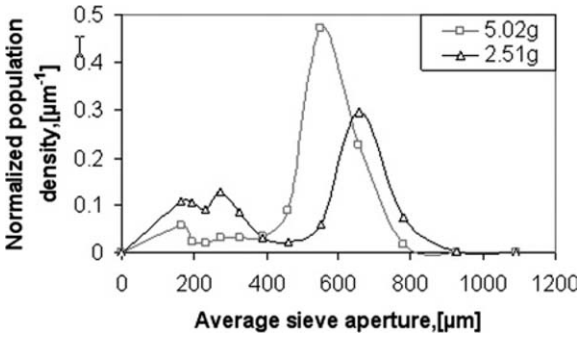

Figure 6. PSD of product crystals obtained from anti-solvent crystallization seeded with seeds of size fraction 212–250 μm (Yu *et al.*, 2006b).

'Internal seeding'

Despite the apparent advantages of using seeds, seeding may not be feasible all the time due to operational or safety concerns, e.g., unavailability of ports for addition of seeds, potential additional hazards associated with operator's exposure to API and solvent, dust explosion and so on.

In contrast to seeded systems in which the amount of seeds added is specific, the initial nuclei formed by primary nucleation in unseeded systems are random and irreproducible for different runs. Even with exactly the same initial conditions and cooling rate in approaching nucleation, primary nucleation gives different number of nuclei; hence product consistency cannot be guaranteed for every run (Chew *et al.*, 2007). This therefore motivates a means to manipulate the nuclei generated by primary nucleation in unseeded systems to achieve consistent nuclei from primary nucleation in different runs, which thereby provides a viable alternative to external seeding. The FBRM-based technique developed by Chew (2006) can be viewed as a reliable means of 'internal seeding', as it involves the automatic detection of nucleation followed by feedback monitoring and tuning of the primary nuclei formed to achieve a desired distribution of seed sizes. Results show that the batch-to-batch consistency achieved using this new technique was comparable to or even surpassed that with traditional external seeding. Hence, 'internal seeding' with the aid of PAT may be a viable industrial alternative in view of the added complexities and uncertainties of external seeding.

POLYMORPH MONITORING AND CONTROL

Crystallization of a desired solid form from a solute-solvent system exhibiting polymorphism is one of the most important considerations in crystallization process design and control. Polymorphism has profound influences on the properties of the API and dosage form such as bioavailability and stability. Recent high profile cases involving pharmaceutical products in which the unexpected appearance of a second polymorphic form resulted in withdrawal of the products, have highlighted the importance of better understanding of the whole area of polymorph formation, prediction, transformation and stability. Here we adopt a broad definition of

polymorph to include hydrate and solvates (also known as pseudo-polymorphs) because their impacts on crystallization design and control are the same.

Thermodynamic stability alone is not sufficient to ensure that the stable polymorph will always be produced (Saranteas *et al.*, 2005). The unstable polymorph or psuedopolymorph may crystallize out first during primary nucleation in an unseeded system in accordance with the Oswald's rule of stages (Threlfall, 2003). Often it is the transformation kinetics between the metastable and stable forms that govern the final isolatable form. Solvent-mediated transformation has been considered the main mechanism by which polymorph transformation takes place during crystallization (Beckmann, 2000). Cardew and Davey (1985) and Davey *et al.* (1986) expressed solvent-mediated transformation as a two-step process in which the metastable form is first dissolved, followed by the crystallization of the stable form. An understanding of the controlling step in such polymorphic transformations is crucial for the design of the crystallization process to obtain a single desired polymorph. This has motivated several recent studies on polymorphic transformation (Brittain, 2004; Dharmayat *et al.*, 2006; Gu *et al.*, 2001; Hu *et al.*, 2005; Kitamura and Sugimoto, 2003; Mukuta *et al.*, 2005; Murphy *et al.*, 2002; O'Brien *et al.*, 2004; O'Sullivan *et al.*, 2003; O'Sullivan and Glennon, 2005; Ono *et al.*, 2004a, b; Qu *et al.*, 2006; Roelands *et al.*, 2006; Saranteas *et al.*, 2005; Schöll *et al.*, 2006; Skrdla *et al.*, 2001; Starbuck *et al.*, 2002; Tian *et al.*, 2006; Wang *et al.*, 2000).

In-Situ Monitoring of Polymorphs

Traditionally, offline analytical techniques such as powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), solid state NMR and infrared spectroscopy (IR) have been used to characterize polymorphs. However, due to the dynamic nature of polymorphic transformation and the instability of certain polymorphs, real time monitoring of polymorphs would be advantageous. During process development, in-situ monitoring provides kinetic data of the process that would enable a robust process to be designed to produce consistently the right crystal form. During production, the ability to identify and quantify undesirable polymorphs in real time would enable the appropriate remedial action to be taken, e.g., by increasing batch time to allow complete conversion of metastable form to the stable form. Recently Raman spectroscopy has been successfully applied to monitor the polymorphic transformation in situ (Agarwal and Berglund, 2003; Falcon and Berglund, 2003; Hu *et al.*, 2005; O'Brien *et al.*, 2004; O'Sullivan *et al.*, 2003; Ono *et al.*, 2004b; Qu *et al.*, 2006; Schöll *et al.*, 2006; Starbuck *et al.*, 2002; Wang *et al.*, 2000). Falcon and Berglund (2003) demonstrated the versatility of Raman spectroscopy in simultaneous monitoring of solute concentration as well as polymorphic form during the anti-solvent crystallization of cortisone acetate. In this case, the on-line Raman measurements were used quantitatively for solute concentration measurement but only qualitatively for polymorph monitoring. Despite the success of a few research papers in using Raman spectroscopy for quantitative analysis of polymorphic content, calibration of Raman signals for analysis of solid form in a slurry is still a challenging task because the variation in spectra depends not only on the amount of polymorphic form present but also on the particle size. As particle size distribution is constantly evolving during crystallization, accurate calibration of Raman spectra with respect to the relative polymorphic content is difficult to achieve. Therefore, O'Sullivan *et al.* (2003) cautioned that the technique may only be useful in a qualitative sense, for example to detect the existence of different polymorphs in the crystallizer, unless corrections for particle size effects were considered.

As polymorphic changes are often accompanied by a change in morphology, alternative techniques such as FBRM and online video microscopy have been used to monitor polymorphic transformations. Relying on the distinct morphological difference between the δ and ß polymorphs, O'Sullivan and Glennon (2005) successfully monitored the polymorphic transformation of D-mannitol in aqueous solution using FBRM and *in situ* ATR-FTIR. Their results identified the transformation mechanism to be solvent-mediated transformation instead of solid-state transition. Dharmayat *et al.* (2006) and De Anda *et al.* (2005a, c) studied polymorphic transformation of L-glutamic acid using in-process image analysis. The volume fraction of each polymorph was derived from the real time images and the crystal growth dynamics and related polymorphic phase transitions in the batch cooling crystallization process could be obtained.

Control of Process to Consistently Produce the Desired Polymorph

Unlike the control of PSD described earlier where PSD information acquired by FBRM can be used as input signal for feedback control, direct real time feedback of polymorphic information measured by the various inline techniques to crystallization control has proved difficult to implement. Instead, the general approach is to design the process based on information on thermodynamics and transformation kinetics (i.e., the first-principle method of control), usually combined with seeding to ensure that the desired polymorphic form is obtained as the final product. There are several reported studies on the determination of operating conditions (solvent type, temperature range, cooling rate, seeding strategy, additives) for the selective crystallization of the desired polymorph. Beckmann (2000) has provided a comprehensive guide into how polymorphism can be controlled via seeding. Muller *et al.* (2006) and Saranteas *et al.* (2005) presented examples of process design and scale-up methodology to ensure the manufacture of the desired polymorph. Once the operating conditions or constraints (solubility and metastable limit of each polymorph) are established, control method can be implemented to guide the temperature or anti-solvent addition trajectory. A recent paper by Kee *et al.* (2006) described the application of feedback concentration control using ATR-FTIR to selectively crystallize the metastable α-form of L-glutamic acid. A temperature range for seeding was carefully chosen to avoid the nucleation and growth of β crystals and a suitable supersaturation value was selected as the control setpoint to ensure that the solution concentration stayed within the metastable limit and minimize secondary nucleation. Figure 7 shows that α-crystals of fairly uniform size were obtained with minimal secondary nucleation or agglomeration.

A few attempts have been made recently to develop population balance based process models that take into account solvent-mediated transformation kinetics of polymorphs (Ma *et al.*, 2006; Ono *et al.*, 2004a; Roelands *et al.*, 2006;

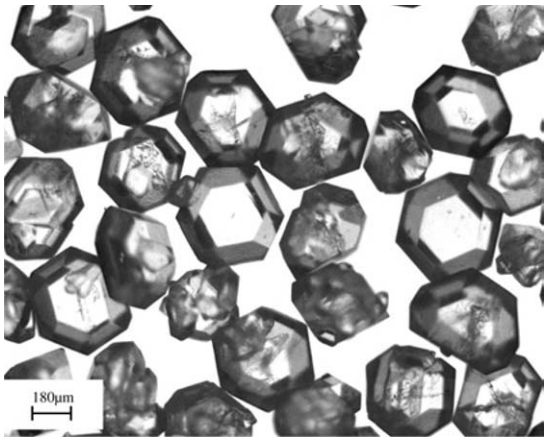

Figure 7. Microscopy image of α-form of L-glutamic acid crystals obtained using feedback concentration control (Kee *et al.*, 2006).

Schöll *et al.*, 2006). Ono *et al.* (2004a) combined PBE with kinetic expressions for the polymorphic transformation that include growth and secondary nucleation rates of β-form, and dissolution rate of α-form of L-glutamic acid. Using the process model developed, process simulation data (e.g., separate CSD information of the different polymorphs) which is otherwise difficult or impossible to measure can be obtained. Schöll *et al.* (2006) incorporated more complex kinetic expressions into their process model of crystallization of L-glutamic acid, e.g., heterogeneous and surface nucleation rates. Their simulation results showed that the overall transformation rate depends mainly on the available surface of α crystals. Roelands *et al.* (2006) simulated the overall effect of competitive nucleation and growth rates of polymorphs during a batch anti-solvent crystallization of L-histidine. Ma *et al.* (2006) developed a multi-dimensional population balance model for the crystallization of β-form of L-glutamic acid that incorporates real-time crystal shape measurement via an in-process imaging technique. Mazzotti *et al.* (2006) presented a population balance model that accounts for the nucleation, growth and agglomeration for a pH shift precipitation of L-glutamic acid. Despite the computational complexity and the difficulties in estimating rate parameters accurately, such modelling efforts are still valuable as they provide a deeper understanding of the transformation process and the influences of different operating parameters, and thereby could facilitate more robust control of the process.

PARTICLE MORPHOLOGY MONITORING AND CONTROL

Particle morphology or habit is an important property that affects not only the downstream processing and handling but also the end-use functional properties. Crystal habit is closely associated with filterability, flowability and compaction behaviour amongst other properties. A sudden change in crystal habit may suggest the appearance of a new polymorph or the presence of trace impurities. Agglomeration may lead to profound changes in final product quality, as well as entrapment of unacceptable levels of occluded solvent, causing difficulties in washing and drying.

Particle morphology has been traditionally analysed by means of off-line microscopy. The availability of in-situ video camera systems such as the Particle Vision and Measurement system (PVM) developed by Lasentec and the online high-speed imaging system developed by GlaxoSmithKline (de Anda *et al.*, 2005–c; Dharmayat *et al.*, 2006) offer the opportunity for real-time monitoring as well as control of shapes and sizes of crystals during crystallization process. Until recently, information from in-line and on-line imaging systems has only been used in a qualitative manner to complement data from other sensors such as FBRM and Raman spectroscopy. Quantitative analysis of images acquired online from crystalliser has not been successful using commercial image analysis software mainly due to the inherent poor quality of the images, which often are out-of-focus, poorly lit and contain overlapping particles.

Image Segmentation and Morphological Quantification

The first step towards quantitative analysis of images is image segmentation in which the particles are identified and extracted from the image background. Various image segmentation techniques have been reported recently, as reviewed by De Anda *et al.* (2005b). As mentioned before, online images taken in crystallizer containing slurries with particles suspended in a solution are particularly challenging to analyse because of out-of-focus and overlapping particles and uneven background intensity. De Anda *et al.* (2005b) presented a multi-scale Canny method to segment in situ images of varied background pixel intensity resulting from the light effect and temporal changes of hydrodynamics within the crystallizer. Larsen *et al.* (2006) developed an algorithm to deal with images of high-aspect-ratio particles captured in moderately dense suspensions.

After segmentation, one straightforward way to quantify particle morphology is to use simple descriptors such as aspect ratio, parameter ratio, robustness, concavity index, heterogeneity, fractal dimension, and so on (Belaroui *et al.*, 2002; BernardMichel *et al.*, 1997; Hentschel and Page, 2003). However, any single simple descriptor describes only one global feature of particle morphology and similar values may be obtained for particles of visually quite different shapes. The lack of mapping uniqueness has prompted the simultaneous use of multiple simple descriptors to achieve a more comprehensive and discriminating description of particle morphology. BernardMichel *et al.* (1997) used a set of seven simple descriptors to classify general particle shape. Ålander *et al.* (2004); Faria *et al.* (2003) quantified agglomeration degree of crystals on the basis of seven and six simple descriptors respectively.

A more structured method for shape representation is to use boundary Fourier descriptors which are a series of coefficients obtained by applying one-dimensional Fourier transform on the shape signature function of particle images. Resolution of description can be adjusted according to requirements: coarse shape features can be captured by lower order coefficients and finer features by higher order coefficients. Such a structure affords robustness, compactness and computational efficiency. Its application in classification of particle shape has been demonstrated in several recent studies (BernardMichel *et al.*, 1997; De Anda *et al.*, 2005b; Raj and Cannon, 1999). Yu *et al.* (2006c) derived

another series of coefficients by applying two-dimensional Fourier transform to particle images, which was proved to be complementary to the boundary Fourier descriptors in morphological representation.

Use of *in Situ* Images in Feedback Control and Process Monitoring

Patience and Rawlings (2001) developed a feedback control scheme for cooling crystallization wherein quantitative information of crystal habit was extracted from *in situ* particle images. The concentration of an additive used to modify crystal habit was adjusted in response to changes in crystal habit. As knowledge of interactions between crystal faces and additive molecules is improved (Davey *et al.*, 2002; Poornachary *et al.*, 2007; Scott and Black, 2005; Weissbuch *et al.*, 2003), 'spiking' the crystallization medium with trace amounts of approved impurities to engineer crystal habit may become a common manipulated variable in industrial control systems. De Anda *et al.* (2005a) employed a multi-scale Canny method to segment *in situ* crystal images and boundary Fourier transform to characterize crystal habit. Their monitoring system successfully followed the polymorphic transformation process of L-glutamic acid where the polymorphs concerned exhibit distinctive characteristic habits. The monitoring system can also be used to extract two-dimensional crystal growth kinetic parameters (Ma *et al.*, 2006; Wang, 2006).

CHALLENGES AND FUTURE DEVELOPMENTS

The FDA's PAT initiative and QbD approach have motivated the use of the latest generation of PAT to improve and ensure quality and consistency of crystallization products. Recent research has shown that several techniques are very promising for the monitoring and control of crystallization processes. These include Lasentec FBRM and PVM, ATR-FTIR and Raman spectroscopy. In laboratory studies, feedback control strategies based on these sensors exhibit more robustness than traditional open-loop strategies. The challenge remains to implement these methods successfully and ubiquitously in pharmaceutical and fine chemicals industries. Some of the hurdles to be overcome include calibration of ATR-FTIR in the presence of multiple impurities, decoupling PSD effect from polymorphic content for quantitative use of Raman spectra, correlation of FBRM data with process performance of crystals and segmentation of low-quality on-line images of particle. Resolution of these issues will expedite the transfer of advanced control strategies from academia to industry, advancing quality control towards six-Sigma in pharmaceutical and fine chemical production.

Advanced on-line sensors help to improve the understanding of crystallization process, thereby enabling more efficient and cost-effective process design and control. More work remains to be done to improve the understanding of the working principles of each PAT system in order to exploit the full potential of each tool. If the relationship between CLD and PSD can be better established, it may be possible to use FBRM data more precisely for feedback control. If the particle size effect on Raman signals can be decoupled from polymorphic purity, one can envision the use of Raman signals quantitatively for optimal process design and eventually real-time feedback control instead of simply using the technique to identify the end-point of crystallization processes. The vast amount of data collected by PAT systems implemented online has posed a practical data management problem. Efficient data analysis and mining methods, such as chemometrics, are required to identify the crucial information from the data acquired.

Operation protocols developed in laboratory scale crystallizers during process development are expected to reproduce crystal quality (at least in a number of key solid-state attributes) on production scale. However, crystal quality often suffers in larger scales due to great inhomogeneities in space and time. A new trend in the scale-up study relies on process modelling which integrates computational fluid dynamics (CFD) and crystallization simulation (Woo *et al.*, 2006; Zauner and Jones, 2000). Some of the parameters in the crystallization model need to be calculated from detailed information of flow field and turbulent energy dissipation rate which can be provided by CFD. Crystallization kinetics are then derived from smaller scale experimental data and transferred directly to larger scale. Changes in mixing processes and thus the scale-up effects on crystallization are accounted for by the model parameters determined using CFD. Simulation results offer valuable insights for determining optimal operating conditions and equipment parameters on scale. Meanwhile, improvement in crystallization modelling will enhance the validity of these model-based approaches. For example, crystal breakage resulting from crystal–crystal, wall–crystal and crystal–impeller collisions may be a serious concern in industrial-scale crystallizers. Since the relative collision area of crystallizer wall and impeller changes with scale, breakage due to crystal–wall and crystal impeller will change along with breakage due to crystal–crystal collisions. New and more complex modelling will be required to address these factors at multiple size-scales.

NOMENCLATURE

a, b	coefficients in equation (2)
c^*	saturation concentration of solute, g/g solvent
t	any time during the process, min
G_{met}	maximum allowable growth rate within metastable zone, m s^{-1}
L	crystal size, μm
$\bar{L}$	number-average size, μm
M	mass, g
T	temperature, °C
$\dot{T}$	cooling rate, °C s^{-1}
ΔT_{met}	the maximum allowable undercooling, °C
φ_v, φ_s	volume and surface shape factors of crystals
τ	the overall batch time, [s]

Subscripts

sol	solvent
S, P	seed and product respectively
I, F	initial and final condition respectively

REFERENCES

Agarwal, P. and Berglund, K.A., 2003, In situ monitoring of calcium carbonate polymorphs during batch crystallization in the presence of polymeric additives using Raman spectroscopy, *Crystal Growth & Design*, 3(6): 941–946.

Ålander, E.M., Uusi-Penttila, M.S. and Rasmuson, A.C., 2004, Agglomeration of paracetamol during crystallization in pure and mixed solvents, *Ind Eng Chem Res*, 43(2): 629–637.

Barrett, P. and Glennon, B., 1999, In-line FBRM monitoring of particle size in dilute agitated suspensions, *Particle & Particle Systems Characterization*, 16(5): 207–211.

Barrett, P. and Glennon, B., 2002, Characterizing the metastable zone width and solubility curve using Lasentec FBRM and PVM, *Chem Eng Res Des*, 80(A7): 799–805.

Barthe, S. and Rousseau, R.W., 2006, Utilization of focused beam reflectance measurement in the control of crystal size distribution in a batch cooled crystallizer, *Chem Eng Technol*, 29(2): 206–211.

Beckmann, W., 2000, Seeding the desired polymorph: background, possibilities, limitations, and case studies, *Organic Process Research & Development*, 4(5): 372–383.

BernardMichel, B., Rohani, S., Pons, M.N., Vivier, H. and Hundal, H.S., 1997, Classification of crystal shape using Fourier descriptors and mathematical morphology, *Particle & Particle Systems Characterization*, 14(4): 193–200.

Belaroui, K., Pons, M.N. and Vivier, H., 2002, Morphological characterisation of gibbsite and alumina, *Powder Technol*, 127(3): 246–256.

Bloemen, H.H.J. and De Kroon, M.G.M., 2005, Transformation of chord length distributions into particle size distributions using least squares techniques, *Particulate Science and Technology*, 23(4): 377–386.

Bordui, P.F., Herko, S.P. and Kostecky, G., 1985, Computer-controlled crystal growth of KDP from aqueous solution, *Journal of Crystal Growth*, 72(3): 756.

Braatz, R.D., 2002, Advanced control of crystallization processes, *Annual Reviews in Control*, 26(1): 87–99.

Brittain, H.G., 2004, Fluorescence studies of the transformation of carbamazepine anhydrate form III to its dihydrate phase, *Journal of Pharmaceutical Sciences*, 93(2): 375–383.

Cardew, P.T. and Davey, R., 1985, The kinetics of solvent-mediated phase-transformations, *Proceedings of the Royal Society of London, Series A*, 398, 415–428.

Chew, J.W., 2006, Experimental investigation of the applicability of FBRM in the control of batch cooling crystallization, MEng thesis, Department of Chemical and Biomolecular Engineering, National University of Singapore, Singapore.

Chew, J.W., Black, S.N., Chow, P.S. and Tan, R.B.H., 2007, A comparison between open-loop temperature-control and closed-loop supersaturation-control for cooling crystallization of glycine, *Ind Eng Chem Res*, 46(3): 830–838.

Choong, K.L. and Smith, R., 2004, Novel strategies for optimisation of batch, semi-batch and heating/cooling evaporative crystallization, *Chem Eng Sci*, 59(2): 329–343.

Chung, S.H., Ma, D.L. and Braatz, R.D., 1999, Optimal seeding in batch crystallization, *Canadian Journal of Chemical Engineering*, 77(3): 590–596.

Costa, C.B.B., da Costa, A.C. and Maciel, R., 2005, Mathematical modelling and optimal control strategy development for an adipic acid crystallization process, *Chemical Engineering and Processing*, 44(7): 737–753.

Davey, R.J., Cardew, P.T., Mcewan, D. and Sadler, D.E., 1986, Rate controlling processes in solvent-mediated phase-transformations, *Journal of Crystal Growth*, 79(1–3): 648–653.

Davey, R.J., Allen, K., Blagden, N., Cross, W.I., Lieberman, H.F., Quayle, M.J., Righini, S., Seton, L. and Tiddy, G.J.T., 2002, Crystal engineering-nucleation, the key step, *CrystEngComm*, 257–264.

De Anda, J.C., Wang, X.Z., Lai, X. and Roberts, K.J., 2005a, Classifying organic crystals via in-process image analysis and the use of monitoring charts to follow polymorphic and morphological changes, *Journal of Process Control*, 15(7): 785–797.

De Anda, J.C., Wang, X.Z. and Roberts, K.J., 2005b, Multi-scale segmentation image analysis for the in-process monitoring of particle shape with batch crystallisers, *Chem Eng Sci*, 60(4): 1053–1065.

De Anda, J.C., Wang, X.Z., Lai, X., Roberts, K.J., Jennings, K.H., Wilkinson, M.J., Watson, D. and Roberts, D., 2005c, Real-time product morphology monitoring in crystallization using imaging technique, *AIChE J*, 51(5): 1406–1414.

De Clercq, B., Lant, P.A. and Vanrolleghem, P.A., 2004, Focused beam reflectance technique for in situ particle sizing in wastewater treatment settling tanks, *Journal of Chemical Technology and Biotechnology*, 79(6): 610–618.

Dharmayat, S., De Anda, J.C., Hammond, R.B., Lai, X.J., Roberts, K.J. and Wang, X.Z., 2006, Polymorphic transformation of L-glutamic acid monitored using combined on-line video microscopy and x-ray diffraction, *Journal of Crystal Growth*, 294(1): 35–40.

Doki, N., Seki, H., Takano, K., Asatani, H., Yokota, M. and Kubota, N., 2004, Process control of seeded batch cooling crystallization of the metastable alpha-form glycine using an in-situ ATR-FTIR spectrometer and an in-situ FBRM particle counter, *Crystal Growth & Design*, 4(5): 949–953.

Dunuwila, D.D., Carroll, L.B. and Berglund, K.A., 1994, An investigation of the applicability of attenuated total-reflection infrared-spectroscopy for measurement of solubility and supersaturation of aqueous citric-acid solutions, *Journal of Crystal Growth*, 137(3–4): 561–568.

Falcon, J.A. and Berglund, K.A., 2003, Monitoring of antisolvent addition crystallization with Raman spectroscopy, *Crystal Growth & Design*, 3(6): 947–952.

Faria, N., Pons, M.N., de Azevedo, S.F., Rocha, F.A. and Vivier, H., 2003, Quantification of the morphology of sucrose crystals by image analysis, *Powder Technol*, 133(1–3): 54–67.

Feng, L.L. and Berglund, K.A., 2002, ATR-FTIR for determining optimal cooling curves for batch crystallization of succinic acid, *Crystal Growth & Design*, 2(5): 449–452.

Fujiwara, M., Chow, P.S., Ma, D.L. and Braatz, R.D., 2002, Paracetamol crystallization using laser backscattering and ATR-FTIR spectroscopy: Metastability, agglomeration, and control, *Crystal Growth & Design*, 2(5): 363–370.

Fujiwara, M., Nagy, Z.K., Chew, J.W. and Braatz, R.D., 2005, First-principles and direct design approaches for the control of pharmaceutical crystallization, *Journal of Process Control*, 15(5): 493–504.

Gabas, N. and Laguerie, C., 1992, Batch crystallization of D-xylose by programmed cooling or by programmed adding of ethanol, *Chem Eng Sci*, 47(12): 3148–3151.

Genck, W.J., 2000, Better growth in batch crystallisers, *Chemical Engineering*, 107(8): 90–95.

Grön, H., Borissova, A. and Roberts, K.J., 2003, In-process ATR-FTIR spectroscopy for closed-loop supersaturation control of a batch crystalliser producing monosodium glutamate crystals of defined size, *Ind & Engi Chem Res*, 42(1): 198–206.

Gu, C.H., Young, V. and Grant, D.J.W., 2001, Polymorph screening: Influence of solvents on the rate of solvent-mediated polymorphic transformation, *Journal of Pharmaceutical Sciences*, 90(11): 1878–1890.

Gutwald, T. and Mersmann, A., 1990, Batch cooling crystallization at constant supersaturation: Technique and experimental results, *Chemical Engineering & Technology-CET*, 13(1): 229–237.

Gutwald, T. and Mersmann, A., 1994, Evaluation of kinetic-parameters of crystallization from batch and continuous experiments, *Separations Technology*, 4(1): 2–14.

Heath, A.R., Fawell, P.D., Bahri, P.A. and Swift, J.D., 2002, Estimating average particle size by focused beam reflectance measurement (FBRM), *Particle & Particle Systems Characterization*, 19(2): 84–95.

Hentschel, M.L. and Page, N.W., 2003, Selection of descriptors for particle shape characterization, *Particle & Particle Systems Characterization*, 20(1): 25–38.

Hu, Q., Rohani, S., Wang, D.X. and Jutan, A., 2005, Optimal control of a batch cooling seeded crystalliser, *Powder Technol*, 156(2–3): 170–176.

Hukkanen, E.J. and Braatz, R.D., 2003, Measurement of particle size distribution in suspension polymerization using in situ laser backscattering, *Sensors and Actuators B-Chemical*, 96(1–2): 451–459.

Hussain, A.S., 2006, Quality by Design (QbD) – integration of prior knowledge and pharmaceutical development into CMC submission and review, *AAPS workshop on Pharmaceutical Quality Assessment – A Science and Risk-based CMC Approach in the 21st Century*, North Bethesda, Maryland, USA.

Jones, A.G., 1974, Optimal operation of a batch cooling crystalliser, *Chem Eng Sci*, 29(5): 1075–1087.

Jones, A.G. and Mullin, J.W., 1974, Programmed cooling crystallization of potassium sulphate solutions, *Chem Eng Sci*, 29(1): 105.

Jones, A.G. and Teodossiev, N.M., 1988, Microcomputer programming of dosage rate during batch precipitation, *Crystal Research and Technology*, 23(8): 957–966.

Karpinski, P.H. and Wey, J.S., 2002, Precipitation processes, in Myerson, A.S. (ed.). *Handbook of Industrial Crystallization*, 151 (Butterworth Heinemann, Boston, USA).

Kee, N.C.S., Tan, R.B.H. and Braatz, R.D., 2006, Selective crystallization of metastable α-form of L-glutamic acid through feedback concentration control, *AIChE Annual Meeting*, San Francisco, USA.

Kim, S.J., Wei, C.K. and Kiang, S., 2003, Crystallisation process development of an active pharmaceutical ingredient and particle engineering via the use of ultrasonics and temperature cycling, *Organic Process Research & Development*, 7(6): 997–1001.

Kim, S., Lotz, B., Lindrud, M., Girard, K., Moore, T., Nagarajan, K., Alvarez, M., Lee, T., Nikfar, F., Davidovich, M., Srivastava, S. and Kiang, S., 2005, Control of the particle properties of a drug substance by crystallization engineering and the effect on drug product formulation, *Organic Process Research & Development*, 9(6): 894–901.

Kitamura, M. and Sugimoto, M., 2003, Anti-solvent crystallization and transformation of thiazole-derivative polymorphs—I: Effect of addition rate and initial concentrations, *Journal of Crystal Growth*, 257(1–2): 177–184.

Kline, B.J., Saenz, J., Stankovic, N. and Mitchell, M.B., 2006, Polymorph and particle size control of ppar compounds pf00287586 and ag035029, *Organic Process Research & Development*, 10(2): 203–211.

Kubota, N., Doki, N., Yokota, M. and Sato, A., 2001, Seeding policy in batch cooling crystallization, *Powder Technol*, 121(1): 31–38.

Lafferrère, L., Hoff, C. and Veesler, S., 2004, In situ monitoring of the impact of liquid-liquid phase separation on drug crystallization by seeding, *Crystal Growth & Design*, 4(6): 1175–1180.

Larsen, P.A., Rawlings, J.B. and Ferrier, N.J., 2006, An algorithm for analyzing noisy, in situ images of high-aspect-ratio crystals to monitor particle size distribution, *Chem Eng Sci*, 61(16): 5236–5248.

Leuenberger, H. and Lanz, M., 2005, Pharmaceutical powder technology—from art to science: The challenge of the FDA's process analytical technology initiative, *Advanced Powder Technology*, 16(1): 3–25.

Lewiner, F., Fevotte, G., Klein, J.P. and Puel, F., 2001, Improving batch cooling seeded crystallization of an organic weed-killer using on-line ATR FTIR measurement of supersaturation, *Journal of Crystal Growth*, 226(2–3): 348–362.

Li, M.Z. and Wilkinson, D., 2005, Determination of non-spherical particle size distribution from chord length measurements. Part 1: Theoretical analysis, *Chem Eng Sci*, 60(12): 3251–3265.

Liotta, V. and Sabesan, V., 2004, Monitoring and feedback control of supersaturation using ATR-FTIR to produce an active pharmaceutical ingredient of a desired crystal size, *Organic Process Research & Development*, 8(3): 488–494.

Lung-Somarriba, B.L.M., Moscosa-Santillan, M., Porte, C. and Delacroix, A., 2004, Effect of seeded surface area on crystal size distribution in glycine batch cooling crystallization: A seeding methodology, *Journal of Crystal Growth*, 270(3–4): 624–632.

Ma, D.L., Chung, S.H. and Braatz, R.D., 1999, Worst-case performance analysis of optimal batch control trajectories, *AIChE J*, 45(7): 1469–1476.

Ma, D.L., Tafti, D.K. and Braatz, R.D., 2002, Optimal control and simulation of multidimensional crystallization processes, *Computers & Chemical Engineering*, 26(7–8): 1103–1116.

Ma, C.Y., Wang, X.Z., de Anda, J.C. and Roberts, K.J., 2006, Multi-dimensional population balance modelling incorporated with real-time crystal shape measurement via in-process imaging, *Control of Particulate Processes VII*, Harrison Hot Springs, BC, Canada.

Matthews, H.B., Miller, S.M. and Rawlings, J.B., 1996, Model identification for crystallization: Theory and experimental verification, *Powder Technol*, 88(3): 227–235.

Mazzotti, M., Vicum, L., Lindenberg, C., Schöll, J. and Brozio, J., 2006, The kinetics of L-glutamic acid precipitation: Characterisation and modelling, *AIChE Annual Meeting*, San Francisco, USA.

McKenzie, P., Kiang, S., Tom, J., Rubin, A.E. and Futran, M., 2006, Can pharmaceutical process development become high tech? *AIChE J*, 52(12): 3990–3994.

Mukuta, T., Lee, A.Y., Kawakami, T. and Myerson, A.S., 2005, Influence of impurities on the solution-mediated phase transformation of an active pharmaceutical ingredient, *Crystal Growth & Design*, 5(4): 1429–1436.

Muller, M., Meier, U., Wieckhusen, D., Beck, R., Pfeffer-Hennig, S. and Schneeberger, R., 2006, Process development strategy to ascertain reproducible API polymorph manufacture, *Crystal Growth & Design*, 6(4): 946–954.

Mullin, J.W., 2001, *Crystallisation* (Butterworth-Heinemann, Oxford, UK).

Mullin, J.W. and Nÿvlt, J., 1971, Programmed cooling of batch crystallisers, *Chem Eng Sci*, 26(3): 369–377.

Murphy, D., Rodriguez-Cintron, F., Langevin, B., Kelly, R.C. and Rodriguez-Hornedo, N., 2002, Solution-mediated phase transformation of anhydrous to dihydrate carbamazepine and the effect of lattice disorder, *International Journal of Pharmaceutics*, 246 (1–2): 121–134.

Nagy, Z.K. and Braatz, R.D., 2004, Open-loop and closed-loop robust optimal control of batch processes using distributional and worst-case analysis, *Journal of Process Control*, 14(4): 411–422.

O'Brien, L.E., Timmins, P., Williams, A.C. and York, P., 2004, Use of in situ FT-Raman spectroscopy to study the kinetics of the transformation of carbamazepine polymorphs, *Journal of Pharmaceutical and Biomedical Analysis*, 36(2): 335–340.

O'Sullivan, B., Barrett, P., Hsiao, G., Carr, A. and Glennon, B., 2003, In situ monitoring of polymorphic transitions, *Organic Process Research & Development*, 7(6): 977–982.

O'Sullivan, B. and Glennon, B., 2005, Application of in situ FBRM and ATR-FTIR to the monitoring of the polymorphic transformation of D-mannitol, *Organic Process Research & Development*, 9(6): 884–889.

Ono, T., Kramer, H.J.M., ter Horst, J.H. and Jansens, P.J., 2004a, Process modelling of the polymorphic transformation of L-glutamic acid, *Crystal Growth & Design*, 4(6): 1161–1167.

Ono, T., ter Horst, J.H. and Jansens, P.J., 2004b, Quantitative measurement of the polymorphic transformation of L-glutamic acid using in-situ Raman spectroscopy, *Crystal Growth & Design*, 4(3): 465–469.

Patience, D.B. and Rawlings, J.B., 2001, Particle-shape monitoring and control in crystallization processes, *AIChE J*, 47(9): 2125–2130.

Patience, D.B., Dell'Orco, P.C. and Rawlings, J.B., 2004, Optimal operation of a seeded pharmaceutical crystallization with growth-dependent dispersion, *Organic Process Research & Development*, 8(4): 609–615.

Poornachary, S.K., Chow, P.S., Tan, R.B.H. and Davey, R., 2007, Molecular speciation controlling stereoselectivity of additives: Impact on the habit modification in alpha-glycine crystals, *Crystal Growth & Design*, 7(2): 254–261.

Qu, H.Y., Louhi-Kultanen, M., Rantanen, J. and Kallas, J., 2006, Solvent-mediated phase transformation kinetics of an anhydrate/hydrate system, *Crystal Growth & Design*, 6(9): 2053–2060.

Raj, P.M. and Cannon, W.R., 1999, 2-D particle shape averaging and comparison using Fourier descriptors, *Powder Technol*, 104(2): 180–189.

Rawlings, J.B., Miller, S.M. and Witkowski, W.R., 1993, Model identification and control of solution crystallization processes—a review, *Ind Eng Chem Res*, 32(7): 1275–1296.

Richmond, W.R., Jones, R.L. and Fawell, P.D., 1998, The relationship between particle aggregation and rheology in mixed silica-titania suspensions, *Chemical Engineering Journal*, 71(1): 67–75.

Roelands, C.P.M., Jiang, S.F., Kitamura, M., ter Horst, J.H., Kramer, H.J.M. and Jansens, P.J., 2006, Antisolvent crystallization of the polymorphs of L-histidine as a function of supersaturation ratio and of solvent composition, *Crystal Growth & Design*, 6(4): 955–963.

Saranteas, K., Bakale, R., Hong, Y.P., Luong, H., Foroughi, R. and Wald, S., 2005, Process design and scale-up elements for solvent mediated polymorphic controlled tecastemizole crystallization, *Organic Process Research & Development*, 9(6): 911–922.

Sarkar, D., Rohani, S. and Jutan, A., 2006, Multi-objective optimisation of seeded batch crystallization processes, *Chem Eng Sci*, 61(16): 5282–5295.

Schöll, J., Bonalumi, D., Vicum, L., Mazzotti, M. and Muller, M., 2006, In situ monitoring and modelling of the solvent-mediated polymorphic transformation of L-glutamic acid, *Crystal Growth & Design*, 6(4): 881–891.

Scott, C. and Black, S., 2005, In-line analysis of impurity effects on crystallization, *Organic Process Research & Development*, 9(6): 890–893.

Skrdla, P.J., Antonucci, V., Crocker, L.S., Wenslow, R.M., Wright, L. and Zhou, G., 2001, A simple quantitative FT-IR approach for the study of a polymorphic transformation under crystallization slurry conditions, *Journal of Pharmaceutical and Biomedical Analysis*, 25(5–6): 731–739.

Starbuck, C., Spartalis, A., Wai, L., Wang, J., Fernandez, P., Lindemann, C.M., Zhou, G.X. and Ge, Z.H., 2002, Process optimisation of a complex pharmaceutical polymorphic system via in situ Raman spectroscopy, *Crystal Growth & Design*, 2(6): 515–522.

Tadayyon, A. and Rohani, S., 2000, Control of fines suspension density in the fines loop of a continuous KCl crystalliser using transmittance measurement and an FBRM (R) probe, *Canadian Journal of Chemical Engineering*, 78(4): 663–673.

Tavare, N.S., 1995, *Industrial Crystallization*, 112–118 (Plenum Press, New York, USA).

Threlfall, T., 2003, Structural and thermodynamic explanations of Ostwald's rule, *Organic Process Research & Development*, 7(6): 1017–1027.

Tian, F., Zeitler, J.A., Strachan, C.J., Saville, D.J., Gordon, K.C. and Rades, T., 2006, Characterizing the conversion kinetics of carbamazepine polymorphs to the dihydrate in aqueous suspension using Raman spectroscopy, *Journal of Pharmaceutical and Biomedical Analysis*, 40(2): 271–280.

Togkalidou, T., Tung, H.H., Sun, Y.K., Andrews, A. and Braatz, R.D., 2002, Solution concentration prediction for pharmaceutical crystallization processes using robust chemometrics and ATR FTIR spectroscopy, *Organic Process Research & Development*, 6(3): 317–322.

Togkalidou, T., Tung, H.H., Sun, Y., Andrews, A.T. and Braatz, R.D., 2004, Parameter estimation and optimisation of a loosely bound aggregating pharmaceutical crystallization using in situ infrared and laser backscattering measurements, *Ind Eng Chem Res*, 43(19): 6168–6181.

Wang, X.Z., 2006, Shape—the final frontier, *Control of Particulate Processes VII*, Harrison Hot Springs, BC, Canada.

Wang, F., Wachter, J.A., Antosz, F.J. and Berglund, K.A., 2000, An investigation of solvent mediated polymorphic transformation of progesterone using in situ Raman spectroscopy, *Organic Process Research & Development*, 4(5): 391–395.

Ward, J.D., Mellichamp, D.A. and Doherty, M.F., 2006, Choosing an operating policy for seeded batch crystallization, *AIChE J*, 52(6): 2046–2054.

Weissbuch, I., Lahav, M. and Leiserowitz, L., 2003, Toward stereochemical control, monitoring, and understanding of crystal nucleation, *Crystal Growth & Design*, 3(2): 125–150.

Wey, J.S. and Karpinski, P.H., 2002, Batch crystallization, in Myerson, A.S. (ed.). *Handbook of Industrial Crystallization*, 245 (Butterworth Heinemann, Boston, USA).

Woo, X.Y., Tan, R.B.H., Chow, P.S. and Braatz, R.D., 2006, Simulation of mixing effects in antisolvent crystallization using a coupled CFD-PDF-PBE approach, *Crystal Growth & Design*, 6(6): 1291–1303.

Worlitschek, J. and Mazzotti, M., 2002, On-line monitoring of batch cooling crystallization, *Chem Eng Trans*, 1, 1317–1322.

Worlitschek, J. and Mazzotti, M., 2004, Model-based optimisation of particle size distribution in batch-cooling crystallization of paracetamol, *Crystal Growth & Design*, 4(5): 891–903.

Wynn, E.J.W., 2003, Relationship between particle-size and chord-length distributions in focused beam reflectance measurement: Stability of direct inversion and weighting, *Powder Technology*, 133(1–3): 125–133.

Yu, L.X., Lionberger, R.A., Raw, A.S., D'Costa, R., Wu, H.Q. and Hussain, A.S., 2004, Applications of process analytical technology to crystallization processes, *Advanced Drug Delivery Reviews*, 56(3): 349–369.

Yu, Z.Q., Tan, R.B.H. and Chow, P.S., 2005, Effects of operating conditions on agglomeration and habit of paracetamol crystals in anti-solvent crystallization, *Journal of Crystal Growth*, 279(3–4): 477–488.

Yu, Z.Q., Chow, P.S. and Tan, R.B.H., 2006a, Application of attenuated total reflectance-Fourier transform infrared (ATR-FTIR) technique in the monitoring and control of anti-solvent crystallization, *Ind Eng Chem Res*, 45(1): 438–444.

Yu, Z.Q., Chow, P.S. and Tan, R.B.H., 2006b, Seeding and constant-supersaturation control by ATR-FTIR in anti-solvent crystallization, *Organic Process Research & Development*, 10(4): 717–722.

Yu, Z.Q., Chow, P.S. and Tan, R.B.H., 2006c, Quantification of particle morphology by boundary Fourier transform and generic Fourier transform, *Chem Eng Sci*, submitted.

Zauner, R. and Jones, A.G., 2000, Mixing effects on product particle characteristics from semi-batch crystal precipitation, *Chem Eng Res Des*, 78(A6): 894–902.

Zhang, G.P. and Rohani, S., 2003, On-line optimal control of a seeded batch cooling crystallizer, *Chem Eng Sci*, 58(9): 1887–1896.

Zhou, G.X., Fujiwara, M., Woo, X.Y., Rusli, E., Tung, H.H., Starbuck, C., Davidson, O., Ge, Z.H. and Braatz, R.D., 2006, Direct design of pharmaceutical antisolvent crystallization through concentration control, *Crystal Growth & Design*, 6(4): 892–898.

The manuscript was received 30 November 2007 and accepted for publication after revision 9 February 2007.