ELSEVIER

International Journal of Pharmaceutics 241 (2002) 263–278

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

New perspectives for the on-line monitoring of pharmaceutical crystallization processes using in situ infrared spectroscopy

Gilles Févotte *

LAGEP (Laboratoire d'Automatique et de Génie des Procédés) UMR CNRS 5007, Université Lyon 1, ESCPE-Lyon, Bât. 308G, 43 bld. du 11 novembre 1918, 69622 Villeurbanne Cedex, France

Received 30 January 2002; received in revised form 22 April 2002; accepted 25 April 2002

Abstract

Chemists and engineers involved in the industrial production of solid drugs have to deal with difficult new challenges, including the on-line mastery of the crystal habits and size distribution, the control of polymorphic transitions or the improvement of the chemical purity. A major limitation to improving the control of industrial crystallizers lies in the lack of versatile, accurate and reliable on-line sensors. It is shown that supersaturation measurements can be performed using in situ ATR mid-infrared spectroscopy thus providing valuable real-time information about the crystallization process. Several case studies are presented to illustrate new potential applications of the technique. The reported experimental results outline recent advances in the acquisition of key data characterizing the solute/solvent system in question (i.e. solubility, metastability, phase transformations…), the design of on-line control strategies capable of improving both the crystal size distribution (CSD) and the reproducibility of the quality of the final product, the assessment of improved operating strategies (e.g. seeding batch crystallizers), and the monitoring of polymorphic transitions during cooling crystallization operations. The possibility of evaluating on-line the process impurities, which could allow the reduction of batch-to-batch variations of the quality of the solid product, is also briefly envisaged.

Keywords: Spectroscopy; Industrial crystallization; Infrared sensor; Process control; Solubility; Polymorphism

1. Introduction

The manufacturing of high value-added pharmaceutical active ingredients often involves final or intermediate products in the solid form, where crystallization plays a key role as a separation and purification unit operation. The quality and end-use properties of the obtained particles are essentially determined by the crystals shape and the crystal size distribution (CSD) and, notably, by the amount of fines and/or large particles, the average size and the width of the size distribution.

It is clear that the pharmaceutical industry is confronted with increasing pressure to maximize production efficiency, whilst maintaining consis-

* Tel.: + 33-472-43-1885

E-mail address: fevotte@lagep.cpe.fr (G. Févotte).

0378-5173/02/$ - see front matter
PII: S0378-5173(02)00237-5

tency of final products. Such a statement is obviously true if one considers the manufacture of solid dosage forms which comprises multistage operation, requiring product quality appraisal on completion of each stage. For the sake of stability and ease of handling, many drugs are marketed in the crystalline solid state. The crystalline form of the drug (i.e. polymorphs, solvates, hydrates…) as well as the characteristics of the particles (i.e. the crystal habit, the CSD) determine the end-use properties of the pharmaceutical product such as the in vivo dissolution rate, and the various transport properties involved in the delivery of the active ingredient. It is therefore a major issue to select the most suitable form of the drug product in the initial stages of its development, and to design the manufacturing process so as to guarantee the reproducibility of the quality of product and the timelessness of its bioavailability.

In the early stages of drug development many analytical techniques are being currently used to characterize the crystalline form (e.g. Giron, 1995; Brittain, 1999a; Yu et al., 1998). With future advances in molecular simulation, the development of sophisticated computational tools is also expected to allow the prediction of crystalline structures and potential phase transition phenomena. However, many of the problems which are commonly encountered during drug development can only be solved through case by case studies. No general methodology appears to be sufficiently efficient, robust and versatile to allow systematic and safe characterization and prediction of the solid forms which can appear during the industrial production and the marketing of a given drug (Vippagunta et al., 2001).

After a drug has been selected and tested in a solid form, produced in small quantities at the lab-scale or even at the pilot-scale, and approved by the US Food and Drug Administration (FDA), many problems can still be encountered during the implementation of the industrial crystallization process. Roughly speaking, the following types of problems can arise:

- Even if cautious studies of the phase equilibria governing the crystallization system were performed, the unexpected appearance or disappearance of a crystalline form can jeopardize the production, and lead to serious pharmaceutical consequences if the transition takes place in the final dosage product.
- Moreover, scaling up the whole chemical process—and notably the crystallization process—from the lab-scale to the industrial-scale is not an easy task and requires specific expertise in process engineering sciences. In practice, little time is generally devoted to studies focused on industrial crystallization, process modelling, reactor design or advanced process control: this can lead to real losses of productivity and to a lack of mastery over the quality of the final particles. It is a common experience that underestimating the problems related to industrial operation (e.g. unsuitable stirring/mixing equipment, wrong choices concerning the way of ensuring supersaturation during the crystallization process, etc.) results in serious concerns with respect to the safety and the timelessness of the process, and in significant wastes of time and money during the industrial production.
- The need to control the morphology and the size distribution of crystals is often underestimated at the lab-scale while these parameters are of tremendous importance to determine the quality of the product. The mastery of the CSD, and notably the improvement of its reproducibility, is a key-issue since most quality requirements and end-use properties of the crystals are strongly dependent on the CSD. In particular, the ease of downstream processing of the solid is strongly related to the crystal habit and to the CSD (e.g. Nyvlt et al., 1985; Mullin, 1993; Lee and Monnier, 1999; Braatz and Hasebe, 2001). For example, the ease of filtration, the flowability, or the chemical purity of the particles may be severely impaired if excessive amounts of fines have been generated during the batch operation.
- The course of supersaturation is known to have a considerable effect on the final CSD (see e.g. Mersmann, 1995; Braatz and Hasebe, 2001; Eaton and Rawlings, 1990), and in the case of batch processes, it is worth noting that the width of the CSD generally tends to increase in an undesirable fashion as a function of time.

This is the reason why the development of in situ, on-line supersaturation and CSD sensors still remains a major concern.

Decisions concerning the satisfactory completion of each unit operation are usually made on the basis of in-process measurements, often a mechanical or physical measurement, or external reference chemical analysis. Unfortunately, usual available information is not always a relevant indicator of the performances of the process, and does not necessarily allow forecast of the appraisal of the quality of the final product. Moreover, reference laboratory analysis generally leads to sampling difficulties and significant time delays which can really reduce the efficiency of the production process, and are unable to allow appropriate measures to be taken when corrections of the actual product are required.

In such a context it has been recognized by the industry, and accepted in principle by regulators, that "usual" approaches are not necessarily the best way to guarantee consistent quality in the final product. Therefore, interest in the concept of "quality by design"—by which final product consistency is ensured through controlling the performances of known critical steps in the manufacturing process—has developed in recent years (Day, 2001). Again, it is clear that the development of new on-line and non-destructive sensors is a key issue; and among the rising technologies, near and mid infrared spectroscopic techniques (i.e. NIR or MIR) are really promising. This explains why significant efforts are now devoted to the use of spectroscopic techniques where the spectrophotometers traditionally used in the laboratory may be displaced to the industrial environment in a remote manner through the use of fiber-optic waveguides; in-situ measurements can thus be ensured for a number of applications.

Infrared spectroscopy is well suited to provide real-time structural and kinetic data about dissolved organic molecules, particles in suspension during solid/liquid operations (e.g. crystallization or precipitation processes) or drugs in the solid form without complicated hardware developments. The processing of NIR (Aldridge et al., 1996; Lane and Buckton, 2000; Vippagunta et al., 2001) or MIR (for recent papers see e.g. Brittain, 1999a; Rustichelli et al., 2000; Lewiner et al., 2001a; Vippagunta et al., 2001) spectral data was shown to allow the evaluation of key parameters such as solute concentration(s) and supersaturation during crystallization processes (Lewiner et al., 2001a) or potential fluctuations in the quality of raw materials (e.g. Day, 2001; Kamat et al., 1998). The evaluation of more specific variables such as amorphous to crystalline ratio (Markovich et al., 1997; Buckton et al., 1998), or polymorphic transformations (Salari and Young, 1998; Skrdla et al., 2001; Lewiner et al., 2001a) was also shown to be possible.

The MIR region expresses much of the same chemical and structural information as the near-infrared, but the information tends to be more selective so that the calibration procedures allowing the quantitative measurement of chemical species from the recorded spectra require less tedious and less time-consuming work than using NIR data. Recently, several groups (Dunuwila et al., 1994; Dunuwila, 1996; Dunuwila and Berglund, 1997; Groen and Roberts, 1999; Togkalidou et al., 2000; Braatz and Hasebe, 2001; Lewiner et al., 2001a) have shown that the in situ ATR FTIR technique can be successfully applied to the on-line measurement of supersaturation during the solution crystallization of organic products and, consequently, of drugs. However, very few applications of the sensor to the monitoring and control of organic crystallization operations were published. Actually, most pharmaceutical applications of IR spectroscopy have so far been focused on the off-line characterization of raw materials and manufactured products, and in particular to the detection of "off-specification" products.

This paper is devoted to the presentation of some perspectives opened up by the on-line use of ATR probes in the MIR. In order to illustrate the presentation, experimental results are reported and discussed. After a brief presentation of the ATR FTIR technique and of a "standard" bench-scale experimental set-up, several topics, which all have significant implications in the industrial production of active principles, are envisaged.

2. An experimental setup for the real time monitoring of industrial batch crystallizers

Fig. 1 shows a schematic representation of the bench-scale evaporative crystallizer used for the different studies mentioned in the present paper. The 5-l glass vessel is equipped with a jacket and a condenser. The jacket is baffled with a helicoïdal ribbon and a centrifugal pump forces the circulation. The stainless steel vessel lid is jacketed to limit heat losses. Stainless-steel baffles are used in conjunction with a speed-controlled stirrer. A high efficiency propeller (Mixel TT™) is used to maintain a good homogeneity of particles in the slurry. The geometry of the plant (i.e. the dimensions of the crystallizer, baffles, propeller…) as well as the main operating variables (stirring rate, heating and cooling rates…) are designed to obtain similarity to industrial equipment. The whole operating device is instrumented and microcomputer-controlled in order to allow the tracking of temperature trajectories. Cooling can be ensured by means of controlled evaporation and/or of heat transfer through the jacket wall. More details on the reactor configuration and automation are given elsewhere (Févotte and Klein, 1994).

In situ measurements were performed using the infrared spectrometer Protégé 460™ manufactured by Nicolet, equipped with an ATR immersion probes manufactured by Axiom Analytical corporation: DPR®-207 with ZnS conical internal reflection element. As shown in Fig. 1, the ATR probe is linked to the spectrometer through an Axiot optical conduit. The measurement cell, the optical conduit and the probe were purged using nitrogen in order to avoid difficulties related to the sensitivity of the measurements to the time variations of the concentration of water and carbon dioxide in the ambient air. Details about the advantages offered by the use of ATR probes for the on-line monitoring of supersaturation were presented by Lewiner et al. (2001a).

Calibration models relating both the temperature of the slurry and the solute concentration to the MIR spectra can be obtained using "standard" or advanced chemometrics softwares (Togkalidou et al., 2000). Simplified approaches based on the measurement of absorbencies at well chosen wavelengths were also reported

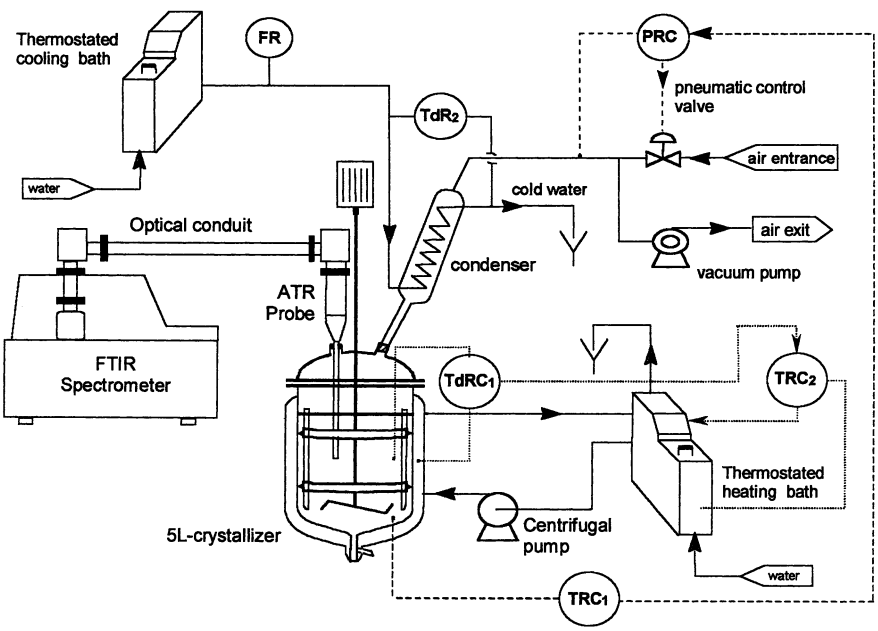

Fig. 1. Experimental set-up: bench-scale multipurpose batch crystallizer equipped with an in situ ATR FTIR probe.

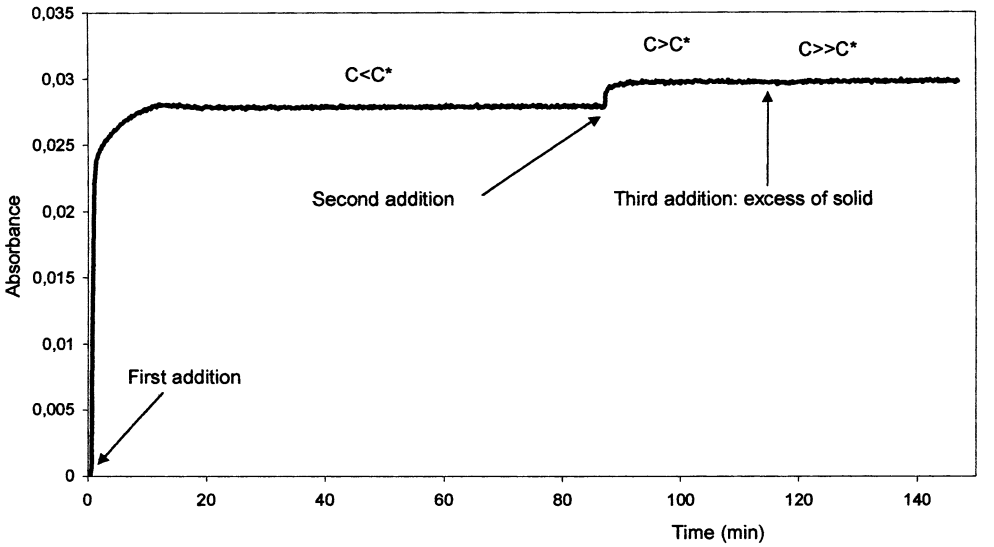

Fig. 2. Isothermal determination of the solubility equilibrium. Time variations of absorbance during successive additions of B in Methanol until an excess of solid has been reached (Wavenumber = 1292 cm^{-1}).

(Dunuwila, 1996; Groen and Roberts, 1999; Lewiner et al., 2001a). The "inversion" of such models provides on-line estimates of the dissolved solid concentration and, consequently, of the supersaturation.

3. Determination of the solubility curve of drugs, and of the limits of metastable zones

Since these parameters determinate the main operating conditions of the process, the evaluation of solubility and metastability curves is required to design any solution crystallization operation. In usual industrial practice, little time may be devoted to such an evaluation, and only few data points of the curves in question are generally known. In order to shorten and to refine the determination of the solubility curve, two procedures were developed. As an example, the cooling crystallization in methanol of an organic product B is presented:

- The solvent is thermostated at a chosen set-point temperature T^* and an excess of solid is introduced in the crystallizer (around 10% above the solubility). As displayed in Fig. 2, the solubility equilibrium is reached when a steady-state absorbance is observed after transient variations of the FTIR measurements. Such on-line monitoring allows the user to optimize the time spent before the equilibrium is reached, and can easily be adapted to other systems. Once the plateau is reached, the concentration is recorded.
- To check the solubility, an additional known amount of solute is introduced in the crystallizer. The new steady state concentration is then compared to the previous one.
- If the two values can be considered equal, the solubility is recorded and the solution is heated up to the next chosen temperature. If the two concentrations are not close enough, a third addition of solid is performed.

With the system under consideration, Fig. 2 clearly demonstrates that 20–30 min may be enough to determine whether the solubility at a given temperature has been reached, or not. The duration of the procedure obviously depends on the dissolution rate. In the present case, the solubility results were satisfactorily compared with off-line HPLC measurements of B concentration.

The previous method provides a measurement of the solubility curve which can be referred to as an "undersatured approach". Moreover, under

supersaturated conditions, if the cooling rate remains moderate and/or if the growth rate is high, the concentration profile reaches quickly the solubility curve, and therefore provides a way to measure it. Such an experimental determination of the solubility can be referred to as a "supersaturated approach". As demonstrated in Figs. 3 and 4, such a situation occurs after the primary nucleation of B and I, respectively. Fig. 3 also demonstrates that the solute concentration does not converge on the solubility when seeding is performed. In opposition to usual solubility determinations, this second method provides a continuous solubility curve which offers attractive potential advantages:

- Continuous data have a richer information content than usual discrete data obtained from samples, and might therefore be used to improve the knowledge of the crystallization system. For example, the evaluation of crystallization enthalpies from van't Hoff plots and the detection of transition points (Brittain and Grant, 1999) could obviously be more accurate and reliable using continuous curves.
- The solute concentration profiles allow the user to know with assurance when the equilibrium has been reached. Such information represents significant saving of time during the determination of the solubility curve.
- The measured solute concentration profiles can provide valuable information about the dissolution mechanisms and kinetics.

The evaluation of the limits of the metastable zone is also an important issue of crystallization processes. It is well known that many practical and fundamental aspects of nucleation phenomena arise from the variability of the limit of metastability curves (Mersmann, 1996) which have to be investigated in relationship with operating conditions such as the way of cooling (evaporation and/or use of a jacket…), the rate of temperature decrease, the effect of the hydrodynamic conditions in the crystallizer or of potential impurities, etc.

To assess the limits of the metastable zone, a solution of known concentration is maintained under undersatured conditions at a given temperature. Then the temperature is decreased according to a pre-set cooling rate while the FTIR spectrometer monitors on-line the evolution of concentration. When nucleation occurs, the con-

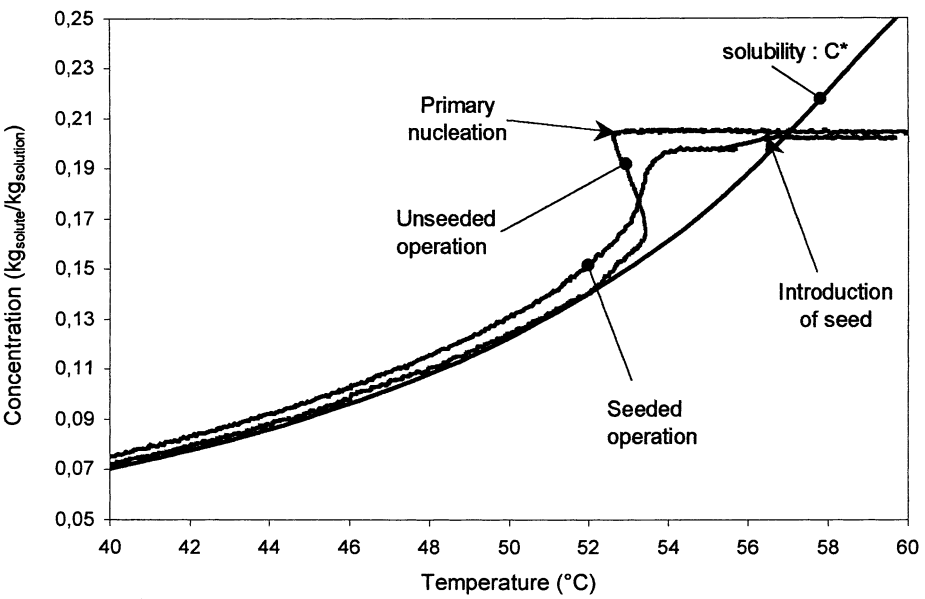

Fig. 3. ATR FTIR on-line measurement of dissolved solid concentration. Typical concentration profiles for batch seeded and unseeded cooling crystallizations of B in Methanol.

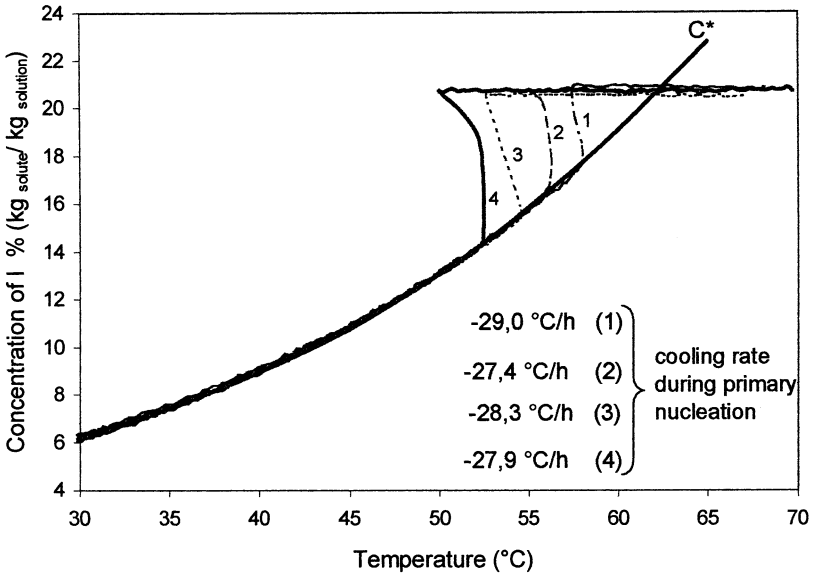

Fig. 4. Concentration profiles of dissolved I during unseeded batch crystallizations in Ethanol. C^* is the solubility concentration.

centration decreases strongly and the corresponding temperature is recorded. In addition to the solubility curve, Fig. 3 shows two limits of the metastable zone for unseeded and seeded operation (i.e. for primary and secondary heterogeneous nucleation of B, respectively), when the initial solute concentration is 20%. For unseeded crystallizations, the effect of the cooling slope was also investigated; as expected the width of the metastable zone was found to increase with the cooling rate.

By using both the calibration procedure and the solubility curve of the system under consideration it is finally a straightforward exercise to compute on-line the time variations of supersaturation (see e.g. Lewiner et al., 2001a). Several definitions of supersaturation can be used; we refer below to the following relative expression, where $C^*(T)$ is the solubility concentration at temperature T:

$$\sigma = \frac{C(t) - C^*(T(t))}{C^*(T(t))} \quad (1)$$

Examples of supersaturation profiles obtained during typical cooling crystallization operations are given in Figs. 5 and 8 below.

The experimental results briefly presented in this section show that ATR FTIR allows significant savings of time in the determination of both solubility and metastability data, while the accuracy and the relevancy of the same data are significantly improved with respect to data obtained through usual experimental approaches.

4. Perspectives in process control

It was shown earlier that the principal consequences of a bad control of crystallizers are the non-reproducibility and the low quality of the

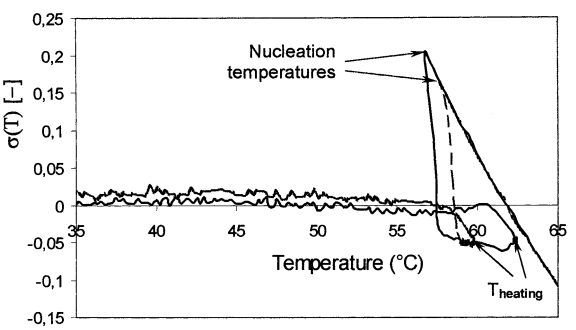

Fig. 5. Typical supersaturation profiles measured during two batch unseeded crystallizations of I, with application of the fines dissolution procedure monitored using ATR FTIR.

solid produced (Nyvlt et al., 1985; Mullin, 1993). Consequently, the feedback control of industrial crystallizers or at least the optimization of operating conditions is of potentially great importance. Since the generation of supersaturation conditions in solution crystallization mainly depends on the cooling rate, substantial research activity has been devoted to the computation of optimal temperature trajectories (Mullin and Nyvlt, 1971; Jones, 1974; Jones and Mullin, 1974), or optimal operating policies (Chianese et al., 1984). Several review papers were focused on that topic (Eaton and Rawlings, 1990; Rawlings et al., 1992; Braatz and Hasebe, 2001). However, at least two questions arise from the reported theoretical and experimental results:

1. The efficiency of such control policies strongly depends upon the accuracy of the nucleation and growth kinetic parameters which are required to calculate optimal temperature profile (Bohlin and Rasmuson, 1992; Chung et al., 1999; Ma et al., 1999; Braatz and Hasebe, 2001). Moreover, the assessment of these parameters requires cautious and complex experimental work, which is almost inconceivable in the context of industrial development.
2. The optimal strategies in question are basically "open-loop" and as such (i.e. they do not require any on-line measurement of the crystallization advancement) many possible drifts of the quality, productivity and reproducibility are likely to happen due to usual unavoidable industrial disturbances (i.e. batch-to-batch variations of impurities or of solid contents, drifts of the operating parameters, unexpected fouling of the crystallizer…). An obvious solution to this problem lies in the closed-loop control of crystallizers, which remains a very active and opened field of research. Review papers were also published on this subject (Miller and Rawlings, 1984; Eaton and Rawlings, 1990; Braatz and Hasebe, 2001).

Although improvements in product CSD can be made by controlled operation or seeding (Chung et al., 1999), some fines can still be formed by secondary nucleation. Fines dissolution policies should also be considered as an efficient way of correcting the damage caused by excessive primary and/or secondary nucleation mechanisms. Fines dissolution can occur either just after nucleation or at any time during the crystallization operation (Rawlings et al., 1992), and can be implemented through different methodologies (Rohani and Bourne, 1990; Rohani et al., 1990; Heffels and de Jong, 1991; Sotowa et al., 1999). Anyway, it is obvious that time-variations of relevant output variables such as CSD or supersaturation must be available through on-line measurements in order to allow any kind of feedback control strategy to be implemented.

Our group has published recent results relating the design and application of a fines dissolution procedure monitored by using ATR FTIR measurements of the dissolved solid concentration of an organic product which will be referred to as I below (Lewiner et al., 2002). Several batch runs were performed to estimate the final quality of I crystals obtained after primary nucleation and "usual" cooling procedures. For other runs, the suspension was deliberately heated up after nucleation—between 2 and 3.4 °C—in order to study the effect of a possible fines dissolution on the final CSD. In addition to the on-line FTIR measurement of supersaturation, the CSD of the final product was measured through image analysis. The results allowed the computation of both the number average length and width of the sample ($\bar{L}$ and $\bar{l}$, respectively). A mass balance based on the values of the initial and final solute concentrations was then applied to compute the final particle number, N_T, and the weight mean sizes. More details are given by Lewiner et al. (2001b)

The solubility curve and the limit of metastable zone were determined as described above. Typical concentration profiles reconstructed from the FTIR ATR measurement during batch unseeded cooling crystallizations of I in ethanol are displayed in Fig. 4. After crossing the solubility curve, primary nucleation is detected: the sharp decrease in concentration is associated to the growth of nucleï generated at the nucleation point. Two series of ten identical crystallization experiments were performed to confirm the variability of the onset of primary nucleation. The results displayed in Fig. 4 correspond to the crystallization of I, with initial concentration of 20%

and average cooling rate of about −28 °C/h: the phenomenon of primary nucleation takes place with large and random variations. With a cooling rate of about −20 °C/h the nucleation point was found to occur in the range of temperature [48.4–55.1 °C]. Consequently, according to the level of supersaturation at which nucleation occurs, the variability of the nucleation rate impairs the final size distribution. As expected, significant reductions in the particle sizes were observed and related to late nucleation temperature. Consequently, for such a system the quality of the particles is subject to large batch-to-batch variations.

An in situ fines dissolution technique was designed as a possible means of improving the quality and the reproducibility of the final CSD, and several experiments were carried out to assess its efficiency. The following procedure was applied: the solution was cooled until nucleation, then the temperature was maintained constant until the concentration equilibrium was reached (detected using the FTIR measurements). The slurry was then heated until a setpoint temperature, T_{heating}, and cooling was then carried out. Two typical supersaturation trajectories measured during crystallization operations performed with the dissolution procedure are displayed in Fig. 5. One can observe the unusual loop inside the undersaturated region which can be monitored through the FTIR measurement. Such procedure was expected to dissolve a possible excess of fine particles, and therefore reduce the batch-to-batch variations in the final particle number, N_{T}, and average sizes. In order to optimize the heating of the suspension, the on-line measurements of supersaturation were used to decide when to start and stop the heating process. It turned out that, depending on the heating up temperature, the average size can be increased by 90%: after setting appropriate final heating-up temperature, particles with final average length of about 1200 μm were obtained while the average length without heating procedure was of the order of 620 μm.

To optimize the quality of the product, the influence of the final heating up temperature was investigated for runs where nucleation took place around the same temperature (57–57.5 °C). The experimental results show that the final average size depends on the setpoint value of T_{heating}. Heating up the slurry therefore appears to be a good means of mastering the product quality. It is however necessary to find a good compromise between a high average size—which is accompanied by a significant population of fine particles—and a narrow distribution, through the optimization of the fines dissolution procedure.

After the determination of the appropriate heating up temperature it was also an important issue to study the efficiency of the dissolution procedure in improving the reproducibility of the final CSD during operations exhibiting various nucleation temperatures. With this aim in view, slurries obtained with different nucleation temperatures were heated up until the same final dissolution temperature (around 59.7 °C). Fig. 6 shows the final length distributions measured through image analysis for dissolution-controlled experiments performed with random nucleation temperatures. It clearly appears that the control procedure increases the reproducibility of the average crystal length; the same was observed for the distribution of the final crystal width as the batch-to-batch variations of the length/width ratio remained moderate.

As advanced model-based control schemes require kinetic models and parameters which are almost impossible to estimate in industry, it still remains extremely difficult to design efficient control schemes improving the CSD of particles generated during industrial crystallization. A possible solution to this problem lies in the use of on-line particle size analyzers for feedback control purposes, however it is well known that the analyzers available on the market do not provide "real" measurements of the CSD, especially when the particles are far from being spherical. Even though they only allow supersaturation measurements, it was shown in the present section that ATR probes can be used to develop simple yet efficient monitoring strategies. In the present case, the measured supersaturation was used to apply a fines dissolution procedure which resulted in significant improvements of the final CSD.

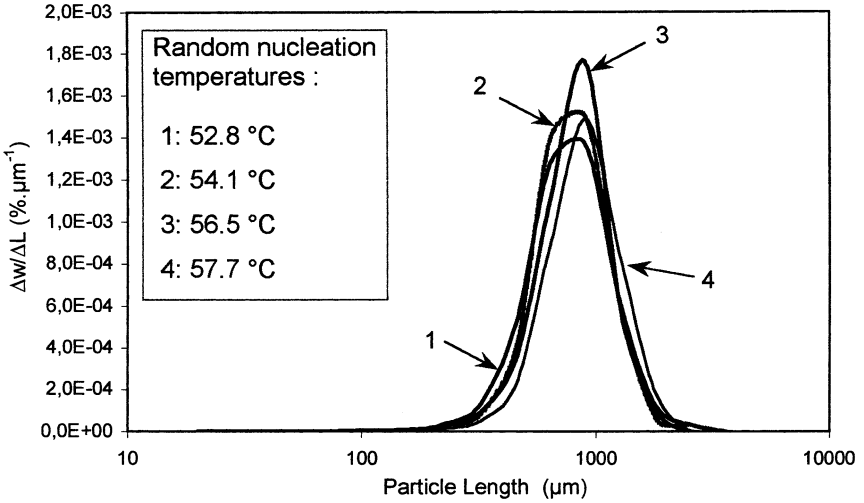

Fig. 6. Final discrete-sized distribution of I crystals after applying the fines dissolution procedure with different nucleation temperatures: improvement of the reproducibility of the product for four batch crystallization operations.

5. Assessment of improved operating strategies such as seeding for batch crystallizers

The assessment of improved operating parameters for seeded batch crystallizations is also a major issue in the field of the industrial crystallization of active principles. In the case of the cooling crystallization of the organic compound I, encouraging results were obtained through the use of on-line ATR FTIR spectroscopy (Lewiner et al., 2001b). Particular attention was focused on the determination of appropriate seeding parameters such as the cooling rate of seeded slurries, the temperature of introduction, T_s, and the amount of seed crystals.

The ATR FTIR measurements of supersaturation showed that early seeding does not keep supersaturation from increasing, until the occurrence of a burst of secondary nucleation. On the other hand, late seeding is followed by a very sudden decrease of the solute concentration, and here again the final CSD measurements clearly show that the introduction of seed is accompanied by a significant burst of nucleation. Finally, it turns out that intermediate values of T_s lead to improved final average particle sizes and CV. From these preliminary experiments, the seeding temperature, $T_s = 33.7$ °C, was selected as a relevant operating condition. The seed crystals were sieved between 63 and 80 μm. Further experiments were performed to investigate the effects of the cooling rate and of the mass of seed on the final CSD.

As generally expected, the final crystal number was found to increase with the cooling rate, which means that secondary nucleation is enhanced by increasing supersaturation after seeding. In comparison with unseeded crystallizations, the experimental results show that the number average size of the plate-like final particles can significantly be increased if the cooling rate does not exceed − 20 °C/h. At higher cooling rates, the average final small size reaches a constant value $\overline{l}$, of about 100 μm. One can therefore reasonably assume that the selected seeding temperature lies below the limit of metastable zone of activated surface nucleation of I in ethanol (see e.g. Mersmann, 1996 for a detailed description and modelling of nucleation phenomena). Increasing excessively the cooling rate probably allows the supersaturation to reach the metastable zone for secondary 'true' nucleation, and therefore reduces the final average size. Fig. 7, which displays the measured ATR FTIR concentration profiles for four typical seeded batch experiments, provides additional information to interpret the effect of the cooling rate on

the final product: increasing values of supersaturation are obtained during the growth period following seeding when increasing cooling rates are applied. Higher levels of supersaturation induce higher nucleation rates and, consequently, lead to a decrease of the final weight mean size.

In order to investigate the effect of the mass of seed on the final CSD and on the supersaturation profiles, both the seeding temperature and the cooling rate were then kept constant (33.7 °C and − 12 °C/h, respectively). The mass of seed was set between few crystals and 2% of the final mass of particles. As one can see in Fig. 8, except with 2% in weight, seeding allows a further increase in supersaturation, until a maximum level is reached. As expected, the maximum is reduced by increasing the mass of seed: the surface of seed crystals promotes the consumption of supersaturation due to the growth of particles; and therefore reduces potential activated secondary nucleation mechanisms. The introduction of high amount of seed (i.e. supersaturation profile obtained with 2% seed, displayed in Fig. 8) is immediately followed by a reduction in the level of supersaturation, which confirms the hypothesis concerning the reduction of activated secondary nucleation rates with increasing surfaces of seed.

It was shown that industrialists can obviously make use of ATR FTIR measurements to optimize, or at least improve, the operating conditions of batch seeded crystallizations. Experimental results were briefly presented in this section to demonstrate that the analysis of the supersaturation profiles measured using ATR FTIR allows some interpretation of mechanisms governing the final CSD, and consequently, the proposal of improved operating parameters.

6. Monitoring of polymorphic transformations during crystallization processes

The pharmaceutical product under investigation, F, exhibits four known polymorphs, denoted F-I to F-IV in the sequel. The concentration will be expressed in Standard Unit (SU). The FTIR measurements were performed with the ReactIRTM 1000 equipped with a diamond probe (DiComp™). The experimental set-up is similar to the one described previously except the size of the vessel is a 1-l crystallizer in this case. Several seeded and unseeded cooling operations were carried out. Seeded operations were performed with dry unsieved seed crystals using 1% of the weight

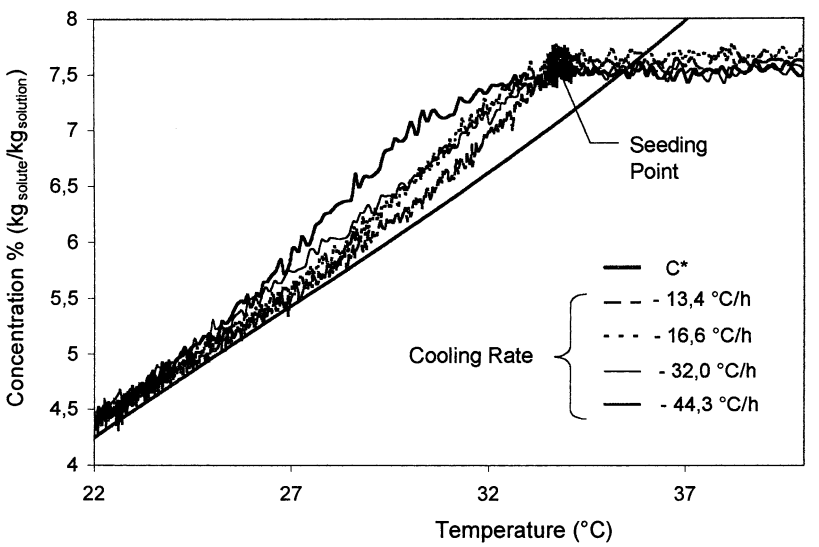

Fig. 7. Concentration profiles measured during batch seeded crystallizations of I. For constant seeding temperature (33.7 °C) and seed concentration (0.5%) various cooling rates were applied after seeding.

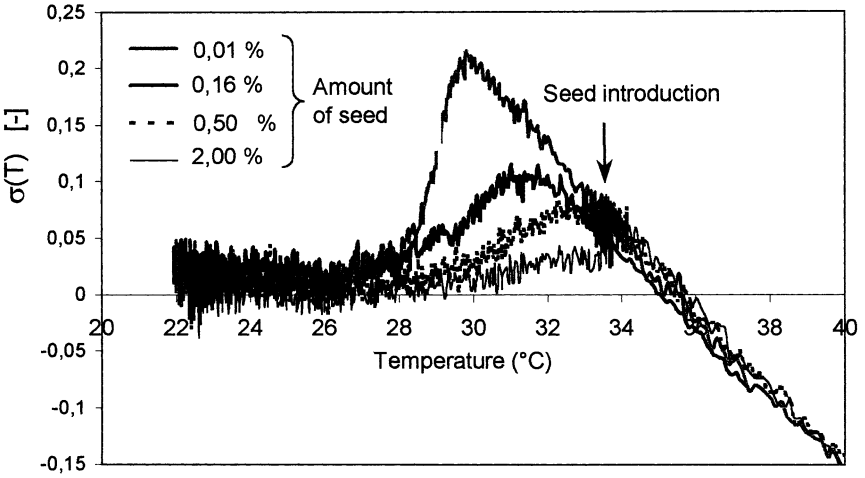

Fig. 8. Supersaturation profiles measured during seeded crystallization of I performed with various amounts of seed.

of final solid. The seeding temperature was set between 55 and 60 °C, according to the polymorph under consideration. Final samples were withdrawn from the reactor, and X-ray diffraction was used to characterize the obtained polymorphic form.

The solubility curve and the limit of metastable zone of F-IV were determined according to the method described previously. As F-IV is the most stable polymorph, such an experimental determination did not require any specific precaution. The solubility of F-III was then determined as follows. A slightly undersaturated solution of F-IV was prepared at a given controlled temperature, and F-III crystals were then added in the crystallizer until no significant variation in the measured absorbance was observed. The equilibrium concentration was finally computed and registered. This procedure which was repeated at different temperatures led to satisfactory results as polymorph IV did not nucleate before the solubility of F-III. The solubility curves for F-III and F-IV are represented in Fig. 9.

Batch cooling crystallizations were monitored before and after F-IV crystal seeds were introduced in the metastable zone. An example is represented in Fig. 9, curve 2. As F-IV is the most stable form, the concentration trajectory quickly converges on the solubility curve. The concentration profile appears to be more complex, yet consistent with Ostwald's step rule (Brittain, 1999b), when primary nucleation occurs at a concentration higher than the solubility of the unstable polymorph F-III. Fig. 9 (curve 1) shows that the concentration profile presents two distinct periods as cooling is carried on. After primary nucleation, the fast growth of F-III nuclei makes the concentration quickly get near the F-III solubility curve; then, below 49 °C, a phase transition takes places so that the mass flow to the crystal significantly increases. During this last period, the concentration progressively meets the F-IV solubility curve. Several crystallizations were also seeded with F-II and F-III crystals. In both cases, the measured concentration profiles were similar to curve 2 in Fig. 9. X-ray diffraction spectra of sample crystals withdrawn from the reactor showed that F-IV appears very quickly after seeding.

Even though, for complex polymorphic systems, the calibration of the ATR FTIR measurement of concentration was found to be rather tricky, the technique is certainly very promising for the monitoring of phase transitions during the crystallization of complex organic molecules. The technique also allowed determination in real-time of the concentration profiles of two distinct polymorphs, which is usually considered as a difficult and uncertain task.

7. Assessment of the concentration of impurities during crystallization operations

Batch-to-batch variations of the concentration of impurities during the crystallization of organic products are known to allow significant changes in the quality of the final crystals. It is well established that changes in crystal habits, in the CSD and in chemical purity of the products can be observed with increase in process impurity concentrations (see e.g. Prasad et al., 2001). As outlined in Section 1, the control of these latter properties represents a real challenge and has a tremendous impact on the ease of downstream processing of the crystallized solid. This is the reason why the availability of information on the impurity content of a solution at the early stages of the crystallization process could certainly be valuable to better operate industrial crystallizers. In particular, early measurements of the concentration of impurities in the mother liquors could allow the design of new feedback control policies aiming at reducing fluctuations in the final solid quality. For example, adaptive model-based control strategies could be developed to anticipate and to reduce the detrimental effects of the concentration of dissolved impurities on the nucleation and growth kinetics and, consequently, on the final CSD.

The on-line measurement of impurities was investigated for the crystallization of an organic molecule—which will be referred below to as the main product MP—in the presence of varying concentrations of undesired amounts of residual reactants which have a significant effect on the pH of the initial solution. A chemical homologue of the main product is the principal impurity HP. The concentration of HP, C_{HP}, usually varies between 100 and 500 ppm.

The calibration of the MIR measurements represents here a rather tedious work as one has to get enough reference spectral data in the field of variation of the four variables involved during the time and batch-to-batch variations of the recorded spectra (i.e. C_{MP}, C_{HP}, T and pH). The tools provided by the Thermo Nicolet's Omnic Spectroscopy Software allowed the computation of such a calibration model using Partial Least Squares (PLS) techniques. The model was then validated through its on-line use during batch cooling crystallization operations of pure MP with known amounts of impurity HP. The average error of calibration was found to

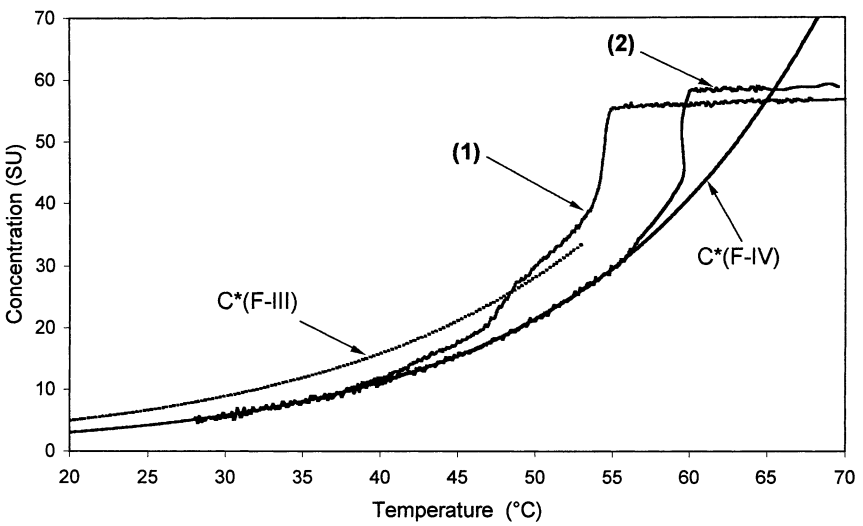

Fig. 9. Solubility curves and concentration profiles of the F-III and F-IV polymorphs. (1) Concentration profile measured during the unseeded crystallization of F-IV and (2) concentration profile obtained during the crystallization of F after seeding with F-IV crystals.

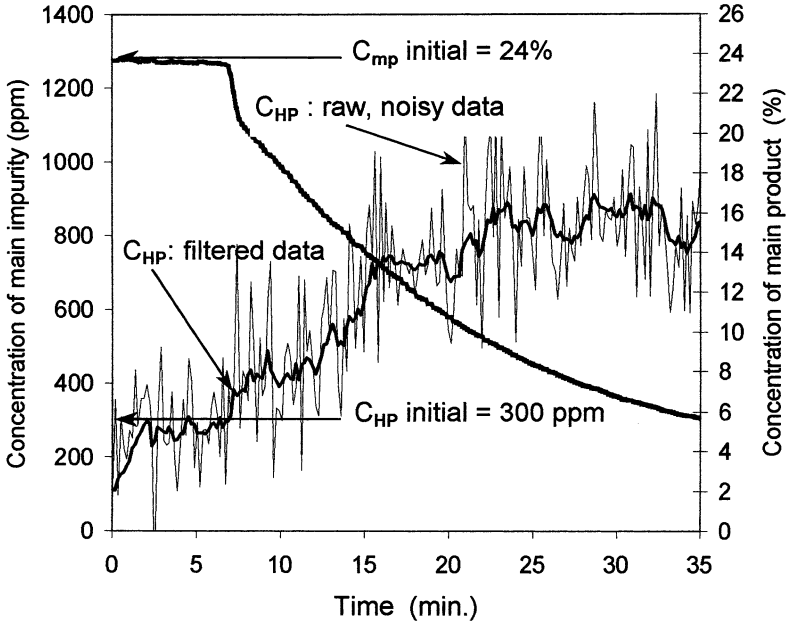

Fig. 10. On-line measurement of the concentrations of the main product, MP, and of the main impurity (homologue product HP) during the batch cooling crystallization of MP.

be 52 ppm, for measurements of C_{HP} between 0 and 1000 ppm and C_{MP} between 2 and 20 wt-%.

As an example, Fig. 10 presents experimental results showing on-line monitoring of the dissolved impurities during batch organic crystallization performed using in situ ATR FTIR. It clearly appears that the initial concentration of the main impurity is satisfactorily estimated by the MIR sensor. However, it should be noticed that after primary nucleation (i.e. in the presence of the solid phase), the measured concentration of impurity does not match the real one. Actually, the calibration data set was mainly obtained from solutions, which probably explains the lack of accuracy of the FTIR measurements in the supersaturated region. The addition of calibration data recorded from slurries could probably improve this point. Moreover, even though the on-line estimates of C_{HP} are characterized by a poor signal/noise ratio, future works of our group will aim at showing that the obtained information is very useful to relate the final quality to the initial concentration of impurities. Such a kind of application opens up promising control perspectives since one could now design control schemes taking into account the initial impurities content, and therefore reduce a major cause of batch-to-batch variations of the quality of the final solid product.

Through partial and preliminary experimental results it was shown that, in addition to supersaturation, the concentration of impurities in industrial mother liquors can be performed using on-line ATR FTIR spectroscopy, which makes the technique really powerful and flexible. Such results clearly show that infrared sensors open up promising perspectives for new monitoring and control approaches in the field of industrial crystallization. For example, even though such real-time applications were never published before, one can now envisage the control on-line of any chemical specie having a real impact on the quality and reproducibility of the solid product, such as solvent, additives or any mixture of secondary products.

8. Conclusion

By using cautious and rigorous calibration procedures accounting for the temperature depen-

dency of MIR spectra, the in situ ATR FTIR technique can be successfully applied to the investigation and the monitoring of crystallization processes. The experimental results reported in the present paper demonstrate the relevance as well as the accuracy of such measurements.

The design of automatic procedures for the acquisition of fundamental data such as solubility or limit of metastability is shown to be rather easy and time saving for process development purposes. The on-line ATR FTIR sensor also offers a unique means of monitoring polymorphism, and therefore provides a new tool to better investigate phase transition phenomena.

Through both measurements of supersaturation using ATR FTIR, and of final CSD through image analysis, one can investigate and improve the industrial crystallization of organic solute/solvent systems. In particular, the possibility of increasing the final mean size by means of appropriate seeding policies was underlined, provided that appropriate seeding parameters are selected. In the reported example, the on-line measurements of supersaturation allowed the assessment of satisfactory seeding policies, which lead to a real increase in the quality of the final particles.

The ATR FTIR sensing technique was also shown to be valuable for process control purposes. An in situ dissolution procedure was designed and applied using the on-line measurements of solute concentration. The efficiency of such monitoring policy in reducing the batch-to-batch variability of the quality of the crystals (i.e. the final CSD) was found to be quite promising. Finally, new monitoring and control perspectives were also outlined thanks to the measurement of the concentration of impurities in the initial load of the crystallizer.

References

Aldridge, P.K., Evans, C.L., Ward, H.W. II, Colgan, S.T., Boyer, N., Gemperline, P.J., 1996. Near-IR detection of polymorphism and process-related substances. Anal. Chem. 68, 997–1002.

Bohlin, M., Rasmuson, A.C., 1992. Application of controlled cooling and seeding in batch crystallization. Can. J. Chem. Eng. 70, 120–126.

Braatz, R.D., Hasebe, S., 2001. Particle size and shape control in crystallization process. Preprints for International Conference on Chemical Process Control (CPC VI), Tucson, AZ, January, 2001.

Brittain, H.G., 1999a. Methods for the characterization of polymorphs and solvates. In: Brittain, H.G. (Ed.), Polymorphism in Pharmaceutical Solids, vol. 95. Marcel Dekker, New York, pp. 227–278.

Brittain, H.G., 1999b. Theory and origin of polymorphism. In: Brittain, H.G. (Ed.), Polymorphism in Pharmaceutical Solids, vol. 95. Marcel Dekker, New York, pp. 1–33.

Brittain, H.G., Grant, D.J.W., 1999. Effects of polymorphism and solid-state solvation on solubility and dissolution rate. In: Brittain, H.G. (Ed.), Polymorphism in Pharmaceutical Solids, vol. 95. Marcel Dekker, New York, pp. 279–330.

Buckton, G., Yonemochi, J., Hammond, A., Moffat, A., 1998. The use of near infra-red spectroscopy to detect changes in the form of amorphous and crystalline lactose. Int. J. Pharm. 168, 291–296.

Chianese, A., di Cave, S., Mazzarotta, B., 1984. Investigation of some operating factors influencing batch cooling crystallization. In: Jancic and de Jong (Eds.), Proceedings of the 9th Symposium on Industrial Crystallization, Amsterdam, The Netherlands.

Chung, S.H., Ma, D.L., Braatz, R.D., 1999. Optimal seeding in batch crystallization. Can. J. Chem. Eng. 77, 590–596.

Day, M., 2001. Optimizing the manufacture of solid dosage forms with NIR spectroscopy. Pharm. Technol. Eur. 13, 22–27.

Dunuwila, D., Caroll, L.B., 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. J. Crystal Growth 137, 561–568.

Dunuwila D., 1996. An investigation of the feasibility of using in situ ATR FTIR spectroscopy in the measurement of crystallization phenomena for research and development of batch crystallization processes. Ph.D. Thesis Dissertation, Michigan State University, Dept. of Chem. Eng., USA.

Dunuwila, D., Berglund, K.A., 1997. ATR FTIR spectroscopy for in situ measurement of supersaturation. J. Crystal Growth 179, 185–193.

Eaton, J.W., Rawlings, J.B., 1990. Feedback control of chemical processes using on-line optimization techniques. Computers Chem. Eng. 14, 469–479.

Févotte, G., Klein, J.P., 1994. Application of on-line calorimetry to the advanced control of batch evaporative crystallizers. Chem. Eng. Sci. 49, 1323–1336.

Giron, D., 1995. Thermal analysis and calorimetric methods in the characterization of polymorphs and solvates. Thermochim. Acta 248, 1–59.

Groen, H., Roberts, K.J., 1999. Application of ATR FTIR spectroscopy for on-line determination of solute concentration and solution supersaturation. In: Proceedings of the 14th International Symposium on Industrial Crystallization, Cambridge, UK.

Heffels, S.K., de Jong, E.J., 1991. Improved Operation and Control of Batch Crystallisers, AIChE Symp. Series, 87 (284, Part Des. Cryst.), 170–181.

Jones, A.G., 1974. Optimal operation of a batch cooling crystallizer. Chem. Eng. Sci. 29, 1075–1087.

Jones, A.G., Mullin, J.W., 1974. Programmed cooling crystallization of potassium sulphate solutions. Chem. Eng. Sci. 26, 369–377.

Kamat, M.S., Lodder, R.A., DeLuca, P., 1998. Near-infrared spectroscopic determination of residual moisture in lyophilised sucrose through intact glass vials. Pharm. Res. 6, 961–965.

Lane, R.A., Buckton, G., 2000. The novel combination of dynamic vapour sorption gravimetric analysis and near infra-red spectroscopy as a hyphenated technique. Int. J. Pharm. 207, 49–56.

Lee, M.Y., Monnier, O., 1999. The control of crystal morphology of pharmaceutical products. In: Proceedings of the 14th International Symposium on Industrial Crystallization, Cambridge, UK.

Lewiner, F., Klein, J.P., Puel, F., Févotte, G., 2001a. On line ATR FTIR measurement of supersaturation during solution crystallization processes: calibration and applications on three solute/solvant systems. Chem. Eng. Sci. 56, 2059–2084.

Lewiner, F., Févotte, G., Klein, J.P., Puel, F., 2001b. Improving batch cooling seeded crystallization of an organic weed-killer using on-line ATR FTIR measurement of supersaturation. J. Crystal Growth 226, 348–362.

Lewiner, F., Févotte, G., Klein, J.P., Puel, F., 2002. An on-line strategy to increase the average crystal size during organic batch cooling crystallization, Ind. Eng. Chem. Res. 41, 1321–1328.

Ma, D., Chung, S.H., Braatz, R.D., 1999. Worst-case performance analysis of optimal batch control trajectories. AIChE J. 45, 1469–1476.

Markovich, R.J., Anderson Evans, C., Coscolluela, C.B., Zibas, S.A., Rosen, J., 1997. Spectroscopic identification of an amorphous-to-crystalline drug transition in a solid dispersion SCH 48461 capsule formulation. J. Pharm. Biomed. Anal. 16, 661–673.

Mersmann, A., 1995. Fundamentals of crystallization. In: Mersmann, A. (Ed.), Crystallization Technology Handbook. Marcel Dekker, New York.

Mersmann, A., 1996. Supersaturation and nucleation. Trans. I Chem. E. 74 (part A), 812–820.

Miller, S.M., Rawlings, J.B., 1984. Model identification and control strategies for batch cooling crystallizers. AIChE J. 40, 1312–1327.

Mullin, J.W., Nyvlt, J., 1971. Programmed cooling of batch crystallizers. Chem. Eng. Sci. 26, 369–377.

Mullin, J.W., 1993. Crystallization, 3rd ed. Butterworth-Heinemann, London.

Nyvlt, J., Sohnel, O., Matuchova, M., Broul, M., 1985. The Kinetics of Industrial Crystallization. Elsevier, New York.

Prasad, K.V.R., Ristic, R.I., Sheen, D.B., Sherwood, J.N., 2001. Crystallization of paracetamol from solution in the presence and absence of impurity. Int. J. Pharm. 215, 29–44.

Rawlings, J.B., Sink, C.W., Miller, S.M., 1992. Control of crystallization processes. In: Myerson (Ed.), Handbook of Industrial Crystallization, pp. 179–207.

Rohani, S., Bourne, J.R., 1990. Self-tuning control of crystal size distribution in a cooling crystallizer. Chem. Eng. Sci. 45, 3457–3466.

Rohani, S., Tavare, N.S., Garside, J., 1990. Control of crystal size distribution in a batch cooling crystallizer. Can. J. Chem. Eng. 68, 260–267.

Rustichelli, C., Gamberini, G., Ferioli, V., Gamberini, M.C., Ficarra, R., Tommasini, S., 2000. Solid-state study of polymorphic drugs: carbamazepine. J. Pharm. Biomed. Anal. 23, 41–45.

Salari, A., Young, R.E., 1998. Application of attenuated total reflectance FTIR spectroscopy to the analysis of mixtures of pharmaceutical polymorphs. Int. J. Pharm. 163, 156–157.

Sotowa, K.I., Naito, K., Kano, M., Hasebe, S., Hashimoto, I., 1999. A Study on the effects of fines dissolution on the stabilizing control of continuous DTB crystallizers. In: Proceedings of the 14th International Symposium on Industrial Crystallization, Cambridge, UK.

Skrdla, P.J., Antonucci, V., Crocker, L.S., Wenslow, R.M., Wright, L., Zhou, G., 2001. A simple quantitative FT-IR approach for the study of a polymorphic transformation under crystallization slurry conditions. J. Pharm. Biomed. Anal. 25, 731–739.

Togkalidou, T., Fujiwara, M., Patel, S., Braatz, R.D., A robust chemometrics approach to inferential estimation of supersaturation. In: Proceedings of the American Control Conference, Chicago, June, 2000, pp. 1732–1736.

Vippagunta, S.R, Brittain, H.G., Grant, D.J.W., 2001. Crystalline solids. Adv. Drug Deliv. Rev. 48, 3–26.

Yu, L., Reutzel, S.M., Stephenson, G.A., 1998. Physical characterization of polymorphic drugs: an integrated characterization strategy. Sci. Pharm. 1, 118–127.