15th Triennial World Congress, Barcelona, Spain

ON LINE MONITORING OF BATCH PHARMACEUTICAL CRYSTALLIZATION USING ATR FTIR SPECTROSCOPY

G. Févotte

LAGEP UMR CNRS 5007, Université Lyon 1, ESCPE. Bât. 308G, 43 bld. du 11 novembre 1918. 69622 Villeurbanne Cedex. France (email fevotte@lagep.univ-lyon1.fr)

Abstract: Chemists and engineers involved in the production of solid drugs have to deal with difficult new challenges, including the on-line mastery of the crystal habits and size distribution or the control of polymorphic transitions. A major limitation to improving the control of industrial crystallizers lies in the lack of versatile and reliable on-line sensors. Supersaturation measurements can be performed using *in situ* Mid-Infrared spectroscopy. New potential applications of the technique are described : the acquisition of key data characterising the solute/solvent system in question, the design of improved monitoring and/or operating strategies, and the monitoring of polymorphic transitions during crystallization operations. *Copyright © 2002 IFAC*

Keywords: Chemical sensors, Batch control, Particulate processing, Process automation, Product quality, Spectroscopy, Pharmaceutical industry, Crystallization, Polymorphism.

1. INTRODUCTION

It is clear that the pharmaceutical industry is confronted with increasing pressure to maximise production efficiency, whilst maintaining consistency of final products. Such 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 Crystal Size Distribution, 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 the product and the timelessness of its bioavailability.

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 to forecast the appraisal of the quality of the final product. Moreover, reference laboratory analysis generally lead 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 recognised 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). In such a context it is clear that the development of new on-line and non destructive

sensors is a key issue; and among the raising technologies, Near and Mid InfraRed spectroscopic techniques (NIR or MIR) are really promising.
IR Spectroscopy is well suited to provide real-time structural and kinetic data about dissolved organic molecules or particles in suspension during solid/ liquid operations (e.g. crystallization processes) without complicated hardware developments.
The MIR region expresses much of the same chemical and structural information as the NIR, 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 tasks than using NIR data. Recently, several groups (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 (Attenuated Total Reflectance Fourier Transform IR) 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. Most pharmaceutical applications of IR spectroscopy have so far been focused on the off-line characterisation of raw materials and manufactured products, and in particular to the detection of "off-specification" products.
This paper presents some perspectives opened up by the on line use of ATR probes. Recent experimental results are reported and discussed.

2. TYPICAL APPLICATIONS OF ATR FTIR SPECTROSCOPY TO THE MONITORING AND CONTROL OF BATCH CRYSTALLIZATIONS

2.1 Determination of the main crystallization data.

The evaluation of solubility and metastability curves is required to design any industrial solution crystallization operation. In usual industrial practice, few time may be devoted to such an evaluation, and only few data points of the curves in question are generally available. In order to shorten and to refine the determination of the solubility curve a procedure using ATR FTIR was developed. As an example, the cooling crystallization in Methanol of an organic product B was presented (Lewiner, *et al.*, 2001a).
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 Fig. 1 this situation occurs after the primary nucleation of B. Figure 1 also demonstrates that the solute concentration does not converge on the solubility when seeding is performed. In opposition to usual solubility determinations, this new method provides continuous solubility curves which offer attractive potential advantages :

- Continuous data have a richer information content than usual discrete data obtained from samples, and might 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) will 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, especially in the field of pharmacy.

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.

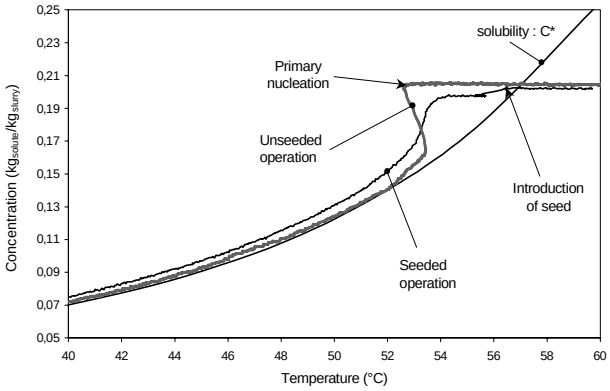

Fig. 1. FTIR measurement of solute concentration. Concentration profiles for batch seeded and unseeded cooling crystallizations of B in Methanol.

To assess the limits of metastable zone, a solution of known concentration is maintained under undersatured conditions at a given temperature. The temperature is then decreased according to a pre-set cooling rate while the FTIR spectrometer monitors on-line the evolution of solute concentration. When nucleation occurs the concentration decreases strongly and the corresponding temperature is recorded. Fig.1 shows two limits of 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%. See also Fig. 2 which displays random limits of metastable zone for another organic product.
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.*, 2000a). We refer below to the following relative expression, where *C*(T)* is the solubility concentration at temperature *T*:

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

Examples of supersaturation profiles obtained during typical cooling crystallization operations are given in Figs. 3 and 5 below.

2.2 Perspectives in process control.

It was early shown that the principal consequences of a bad control of crystallizers are the poor reproducibility and the low quality of the solid produced (Eaton and Rawlings,1990; Rawlings, *et al.*, 1992; Braatz and Hasebe, 2001). Consequently, the feedback control of industrial crystallizers or at least the optimisation of operating conditions is of potentially great importance.
Recent results relating the design and application of a fines dissolution procedure monitored using ATR FTIR measurements of the solute concentration were published, with an organic product which will be referred to as I (Lewiner, *et al.*, 2002). Several batch runs were performed to estimate the final quality of crystals obtained after primary nucleation and "usual" cooling procedures. For other runs, the suspension was deliberately heated up after nucleation, 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 samples ($\bar{L}$ and $\bar{l}$, respectively).

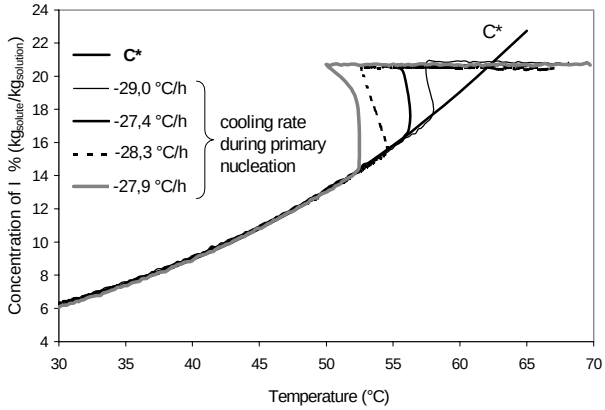

Fig. 2. Concentration of dissolved I during unseeded batch cooling crystallizations. C* is the solubility.

The results displayed in Fig. 2 correspond to the crystallization of I, with an initial concentration of 20% and cooling rate of about -28°C/h : the phenomenon of primary nucleation takes place with large and random variations. Consequently, according to the level of supersaturation at which nucleation occurs, the variability of the highly non linear nucleation rate impairs the final size distribution. As expected, significant reductions in the particle sizes were measured in relationship with late nucleation temperature. Consequently, for such a system, the quality of the particles was found to be subject to large batch-to-batch variations.
To improve the reproducibility of the product, the following procedure was applied : the solution was cooled until nucleation, and 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 carried on. Two typical supersaturation trajectories measured during crystallization operations performed with and without the dissolution procedure are displayed in Fig. 3. One can observe the unusual loop inside the undersaturated region which can be monitored through the FTIR measurements. Such monitoring was expected to dissolve a possible excess of fine particles, and therefore reduce the batch-to-batch variations in the final particle number and in the average sizes. In order to optimise the heating of the suspension, the on-line measurements of supersaturation were used to decide when to start and stop the heating process. It finally turned out that, depending on the heating up temperature, the average size can be increased by 90%.

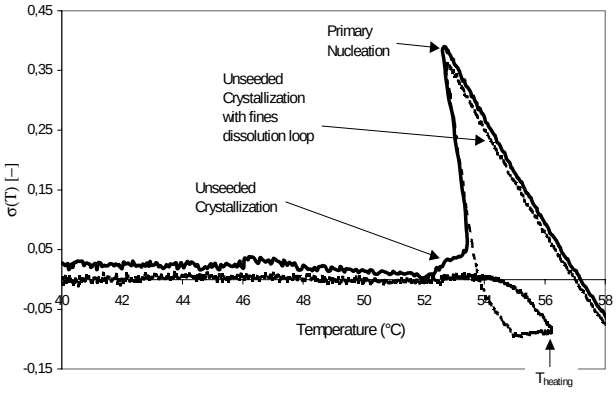

Fig. 3. Supersaturation profiles measured during the batch unseeded crystallization of I.

After the determination of the appropriate heating up temperature (Lewiner, *et al.*, 2002) it was also an important issue to study the efficiency of the controlled dissolution in improving the reproducibility of the final CSD during operations exhibiting various nucleation tempera-tures. 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. 4 shows the size distributions measured through image analysis for dissolution-controlled experiments performed with random nucleation temperatures. In comparison with the dispersed CSD's measured in the case of "usual" cooling operations, it clearly appears that the control procedure increases the reproducibility of both the average size and the width of the size distribution of the final product. One can

therefore say that the ATR FTIR monitoring strategy is advantageous to improve the final CSD.

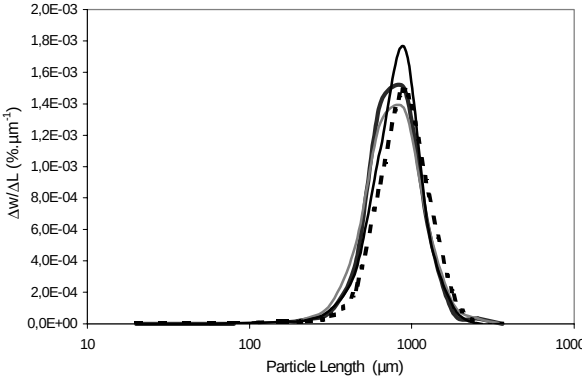

Fig. 4. CSD of crystals after applying the fines dissolution procedure with different nucleation temperatures. Reproducibility of the product I.

2.3 Assessment of improved operating strategies for the crystallization of drugs.

The assessment of improved operating parameters for seeded batch crystallizations is also an important issue in the field of the industrial crystallization of drugs. In the case of the cooling crystallization of the organic compound I, encouraging results were obtained through the on-line use of the ATR probe (Lewiner, *et al*., 2001b). A particular attention was focused on the determination of seeding parameters such as the cooling rate of seeded slurries, the temperature of introduction, T_s , and the amount of seed crystals. The results demonstrate that the analysis of the measured supersaturation profiles allows some interpretation of mechanisms governing the final CSD, and consequently, the proposal of improved operating parameters.

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 clearly shows 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. 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 be significantly increased if the cooling rate does not exceed -20°C/h. 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). Increasing excessively the cooling rate probably allows the supersaturation to reach the metastable zone for secondary 'true' nucleation, which results in the reduction of the final average size.

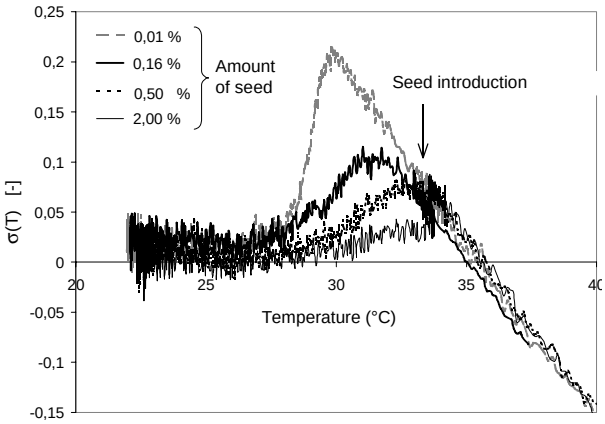

Fig. 5. Supersaturation profiles measured during seeded crystallization of I performed with various amounts of seed.

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 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. 5, 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. 5) is immediately followed by a reduction in the level of supersaturation, which confirms the previous hypothesis.

Actually, it turns out that introducing very small amounts of seed results in decreasing the final particle number and increasing the final average sizes while the initial supersaturation, as Fig. 5 shows, goes on increasing after seeding. Such observation is surprising since one could expect an optimal amount of seed to result in a maximal final mean size : an excessive number of seed crystal should lead to a large final number of particles, especially if "raw" seed crystals are used (i.e. raw seed particles induce "false nucleation"); while insufficient seeding is generally assumed to be unsuitable as it allows further enhanced secondary nucleation. With the system under consideration the average sizes were found to increase with the reduction of the amount of seed, even with very low amounts of seed. Such results may therefore appear as contradictory. It was finally suggested (Lewiner, *et al.*, 2001b) that the effect of the mass of seed could be explained if one assumes

that seeding, even with low seed quantities, leads to secondary nucleation phenomena which differ in the mechanisms involved after primary nucleation during unseeded operations (Mersmann, 1996). A detailed kinetic study of the various possible nucleation mechanisms involved after seeding could probably explain the experimental results. Anyway, industrialists can obviously make use of such results to optimise, or at least improve, the operating conditions of batch seeded crystallizations of pharmaceutical ingredients.

2.4 Monitoring polymorphic transformations during the crystallization of drugs.

The crystalline form of a drug (i.e. polymorphs, solvates, hydrates) as well as 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 essential to select the most suitable form of the drug in the initial stages of its development, and to design the manufacturing process so as to obtain the desired phase of the product.

The drug 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 ReactIR^{TM} 1000 equipped with a diamond probe (DiComp^{TM}).

Several seeded and unseeded cooling operations were carried out. Seeded operations were performed using 1% in weight of dry seed crystals. Final samples were withdrawn from the reactor, and X-ray diffraction was used to characterise the obtained polymorph.

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 polymorphic form, 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, 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 lead 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 displayed in Fig. 6.

As far as polymorphic transformations are concerned, the monitoring of the crystallization of F in Ethanol presents a particular interest. From this point of view, two different series of experiments were performed: phase transitions between polymorphs F-III and F-IV were observed during both isothermal seeded operations and unseeded cooling crystallizations. Slightly undersaturated solutions of F-IV were prepared and the temperature was controlled to remain constant. Crystals of the form F-III were added until the solubility equilibrium was reached. Seed F-IV crystals were then introduced in the crystallizer. From the FTIR measurements of concentration, it clearly appeared that the solution quickly returns to the solubility of F-IV. X-ray diffraction spectra of sample crystals withdrawn from the reactor showed that F-IV appears very quickly after seeding.

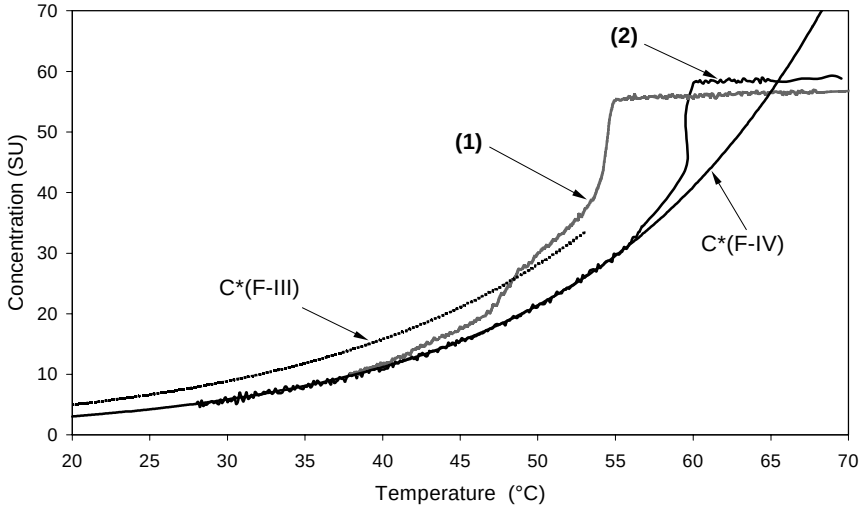

Fig. 6. Solubility curves and Concentration profiles of the F-III and F-IV polymorphs. (1) Concentration profile measured during the unseeded crystallization of F-IV and (2) Concentration profile obtained during the crystallization of F after seeding with F-IV crystals.

In the case of primary nucleation, the fast growth of F-III nuclei makes the concentration quickly get near the F-III solubility curve, which is consistent with Ostwald's rule. Then, below 49°C, a phase transition takes places so that the mass flow to the crystal significantly increases. As one can see in Fig. 6, during this last period the concentration progressively meets the F-IV solubility curve.

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 us to determine in real-time the concentration profiles of two distinct polymorphs, which is usually considered as a difficult and uncertain task.

2.5 On-line monitoring of process impurities.

Batch-to-batch variations of the concentration of impurities during the crystallization of drugs are known to allow significant changes in the quality of the products. It is therefore obvious that the evaluation of the impurity content of the initial content of the crystallizer could allow real improvements in the industrial practice of the crystallization of drugs.

Figure 7 presents experimental results showing on-line monitoring of dissolved impurities during batch organic crystallization performed using in situ ATR FTIR. In the present case, the concentration of a main product in water, C_{MP}, was measured together with the concentration of an homologue product, C_{HP}, which is a well-known impurity of the process. The initial concentration C_{HP} involved here is 300 ppm. As the two molecules are very similar, the calibration of the measurements was difficult and required significant experimental work. The main difficulty arose from the fact that the calibration should be performed with various initial concentrations of nitric acid, which is also a well-known impurity of the process.

Even though the on-line estimates of C_{HP} are characterised by a poor signal/noise ratio, the obtained information turned out to be very useful to relate the final quality to the initial concentration of impurities. Such kind of application opens up promising control perspectives since one could now design feedback control schemes which will account for the impurities content, and therefore reduce a major cause of batch-to-batch variations of the quality (CSD, chemical purity and crystal habit) of the final solid product.

3. CONCLUSION

Full mastery of the crystal morphology, as well as polymorphic content and chemical purity of solid drugs has become increasingly important in the pharmaceutical industry; and requires new powerful analytical tools. In such a context the availability of *in situ* ATR FTIR measurements of supersaturation opens up new perspectives. Some of these perspectives are presented in the present paper through experimental results obtained during the crystallization of organic molecules. Among these applications, the real-time monitoring of polymorphic transformations is certainly a major issue.

While NIR spectroscopy is now significantly used for the monitoring of pharmaceutical manufacturing processes (Day, 2001), almost no industrial applications of ATR FTIR are reported in the literature. However, it is very likely that the potential benefits of the technique will appear more and more clearly in the next few years.

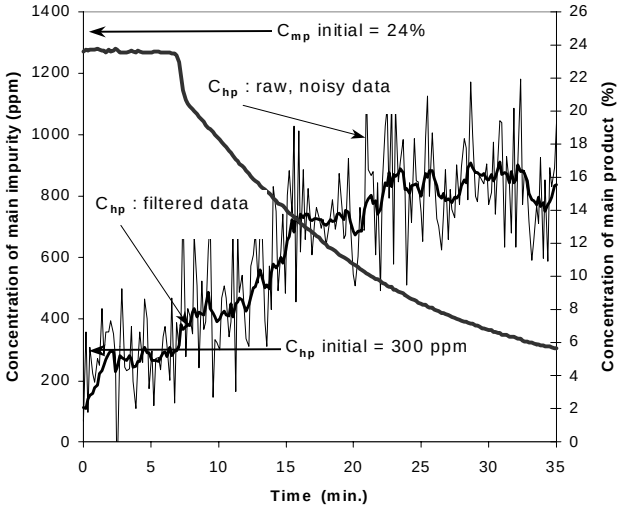

Fig. 7. Simultaneous on-line ATR FTIR monitoring of the concentration of a crystallizing organic product and of its main impurity.

REFERENCES

Braatz, R.D., Hasebe, S. (2001). *Preprints for International Conference on Chemical Process Control* (CPC VI), Tucson, AZ, January 2001.

Brittain, H.G., Grant, D.J.W., 1999. Effects of polymorphism and solid-state solvation on solubility and dissolution rate, in:, *Polymorphism in pharmaceutical solids*, H.G. Brittain (Ed.), **95**, 279-330, Marcel Dekker, New York.

Day, M. (2001). *Pharmaceutical Technology Europe*, **13**, 4, 22-27.

Dunuwila, D., Berglund, K.A. (1997). *J. Crystal Growth*, **179**, 185-193.

Groen, H., Roberts, K.J. (1999). *Proceedings of the 14th Internat. Symposium on Industrial Crystallization*. Cambridge, UK.

Lewiner, F., Klein, J.P., Puel, F. Févotte, G. (2001a). *Chem. Eng. Sci.* **56**, 6, 2059-2084.

Lewiner, F., Févotte, G., Klein, J.P., Puel, F. (2001b). *J. Crystal Growth*, **226**, 2-3, 348-362.

Lewiner, F., Klein, J.P., Puel, F. Févotte, G. (2002). *Ind. & Engng. Chemistry Research* (in Press)

Mersmann, A., 1996. Supersaturation and nucleation. *Trans.IChem E.*, **74**, Part A, 812-820.

Togkalidou, T., Fujiwara, M., Patel, S., Braatz, R.D. (2000). *Proceedings of the American Control Conference*, Chicago, June 2000, 1732-1736.