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Applications of NIR spectroscopy to monitoring and analyzing the solid state during industrial crystallization processes

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Abstract

Fiber-optic near infrared (NIR) spectroscopy was used to investigate several key features of the polymorphic transitions observed during the crystallization and the filtration of SaC, an Active Pharmaceutical Ingredient (API) produced by Sanofi-Synthelabo. Using few samples, the spectroscopic data were calibrated to provide measurements of the polymorphic composition of the solid product which is likely to appear in two crystalline forms or in the amorphous state. Both qualitative and quantitative methods were successfully evaluated to characterize the API. The NIR spectroscopy measurement was then applied to investigate the kinetic behavior of the phase transition phenomena against various operating conditions. From the viewpoint of industrial process development several applications are presented. The effects of temperature and seed crystal habits on the rate of transition of filtration cakes are briefly investigated; and a study of the effect of residual water in the solvent on the transition occurring during filtration is more deeply analyzed. The experimental results demonstrate that highly valuable information can be provided by the NIR spectroscopy measurements, when one aims at understanding more deeply and optimizing the consequences of various and complex phenomena involved during the solid processing chain.

Keywords: Near infrared spectroscopy; Process Analytical Technologies (PAT); Crystal habits; Polymorphism; Crystallization; Filtration

1. Introduction

In order to improve the safety, the productivity and the reproducibility of the crystallization of Active Pharmaceutical Ingredients (APIs), the development of robust and accurate sensors still remains a key issue. Obviously, the availability of real-time information about a crystallization process allows monitoring more pertinently its progress, analyzing the effects and the causes of potential disturbances and consequently developing more advanced control policies. Due to the increasing demand for the production of API with well-defined and reproducible end-use properties at the solid state, great attention is now being paid to finding rapid, reliable and relevant methods by which the mastery over the industrial production can be improved. Actually, even though this remains difficult, it is clear that an "ideal" control situation is ensured when one is in a position to monitor both the production rate (i.e. supersaturation and/or solute consumption during crystallization) and any variable related to the quality of the particulate product (i.e. the Crystal Size Distribution or CSD, the crystal habits or the solid phase composition). From this latter point of view, the polymorphic composition of the solid is of capital importance during its production and when considering its further processing, as most

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properties which are specific to APIs depend on the polymorphic state (Brittain, 1999).

Among the sensing technologies, near infrared (NIR) spectroscopic techniques are really promising and significant efforts are now devoted to the development of on-line equipment where the spectrophotometers traditionally used in the laboratory may be moved to the industrial environment in a remote manner through the use of fiber-optic waveguides. In the past 10 years, NIR spectroscopy has mostly been used in the pharmaceutical industry for the characterization of raw materials and is now regarded as a standard method (Day, 2001). But as far as process optimization and control are concerned, the possibility of monitoring pharmaceutical plants through in-line in situ NIR measurements have obviously been held back by the lack of robust industrial probes.

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; Févotte, 2002) have shown that the in situ Attenuated Total Reflectance Fourier Transform Infrared (ATR FTIR) technique can be successfully applied to the in-line measurement of supersaturation during the solution crystallization of drugs. Mid-IR measurements were thus demonstrated to be useful for a number of applications.

NIR spectroscopy is well suited to provide real-time structural and kinetic data without complicated hardware developments (Aldridge et al., 1996). The NIR spectral region, which covers the range from 700 to 2500 nm, expresses much of the chemical and structural information on the reaction medium as the mid-IR region, but the information tends to be in broad and overlapped bands. The processing of NIR spectral data was shown to allow the real-time evaluation of many parameters, such as the moisture content of solids (Kamat et al., 1989, with sucrose); the amorphous content of drugs (Colombano et al., 2002, with salbutamol sulphate; Hogan and Buckton, 2001, with raffinose) or the crystallinity (Blanco et al., 2000, with amorphous miokamycin; Gombas et al., 2003 and Lane and Buckton, 2000, with alpha-lactose; Markovich et al., 1997). Due to the diversity of available probes (i.e. transmission, diffusive reflectance, transflectance) another advantage of the NIR technique is the possibility of analyzing almost any kind of sample: solutions, suspensions, emulsions or powders; and the analysis can be performed through various containers, such as glass vessels or polymeric bags, which makes many manipulations easier. Moreover, using fiber-optic connections allows one to obtain frequent, real-time data, without requiring any sampling, preparation or dilution procedure. Obviously, this latter advantage reduces significantly the loss of accuracy which is inherent to the manipulation of samples: imperfect dilution, poor representativeness of the sample, time variations of its actual state, etc. By reason of these many advantages, among raising Process Analytical Technologies (PAT), NIR spectroscopy is perhaps one of the most amenable to routine, on-line or in-line (Stephenson et al., 2001).

In order to use NIR spectroscopy as a “direct” sensor, reference NIR spectra are collected using samples that should be representative of the time variations of the dispersed medium during the solids elaboration process. The reference spectroscopic data are then related to the variables of interest through the design and computation of a calibration model usually solved using chemometrics. Actually, the calibration model establishes a “one-to-one” relationship between any collected reference spectrum and the value of the related variable of interest, which is measured using reference analytical techniques, such as Gas Chromatography (GC), Differential Scanning Calorimetry (DSC), Karl Fisher, High Pressure Liquid Chromatography (HPLC), etc. The predictive features of the model strongly depend on the calibration data set which should contain as many sources of sample variation as possible (Stephenson et al., 2001). The “parameters” of the calibration model should be validated using samples that were not used in the calibration data set. The success of further predictions depends on various criteria: the sampling technique, the off-line reference analytical method used and finally, the processing algorithm applied to the spectrum in order to draw the appropriate criterion.

In an industrial environment, the design and application of robust, accurate and reliable NIR procedures for the quantitative characterization of the solid state still requires further investigations, but one can reasonably consider that the great interest of the NIR spectroscopy techniques is already established. However, one of the most awkward drawbacks of NIR spectroscopy sensors arises from the requirement for cautious and time consuming calibration procedures. In order to put this problem into perspective, it is the aim of the present paper to describe some typical applications of NIR measurements presenting an obvious interest for process development and optimization purposes. The main issue here will not be to describe rigorous calibration and measurement procedures developed in the laboratory, but rather to show how coarse calibrations allow valuable information to be obtained and analyzed.

2. Experimental

SaC is an active ingredient which, during its industrial processing, is likely to appear in three possible solid phases: polymorphs I and II (SaC-I and SaC-II) and amorphous state (SaC-Am). SaC acts against hyper tension, it is crystallized through cooling of its solution in acetone. As displayed in Fig. 1, the habits of forms I and II significantly differ; SaC-I crystals present two different habits: compact parallelepipeds or thin needles while SaC-II present a needle-like shape. Moreover, form SaC-I which was initially produced at the industrial scale became difficult to obtain after the first appearance of form SaC-II, due to the stability of the latter. For monitoring and control, as well as for process optimization and development purposes, it turned out to be a major issue to characterize quantitatively the phase composition of the API.

In the following, form I samples were obtained from batch cooling operations performed before the onset of the more stable form II. Pure form II was obtained easily afterwards. Amorphous particles were produced through fast vaporization of acetone solutions. Before being used, every sample was checked through DSC analysis.

The spectral analysis in the NIR region was carried out using an industrial NIRVIS spectrophotometer marketed by Büchi, sweeping the spectral area extending from 1000 to 2500 nm. Both diffusive reflectance and transflectance probes were available which could be connected to the spectrophotometer using fiber-optics. The diffusive reflectance probe was used to characterize solid particles while the transflectance probe was used to analyze suspensions. The processing of the NIR data was carried out by using NIRCAL: spectral analysis software provided with the NIR instrument.

The transition of form I into the more stable form II was investigated in suspension using the NIR measurements obtained after applying the calibration procedure described in the following. In order to do so, phase transitions were monitored using the NIR spectroscopy diffusive reflectance probe placed above filtration cakes of SaC particles. The filtrations were carried out under vacuum, using a lab-scale glass drying filter. The volume of the filtration cell was 500 ml, with a diameter of 10 cm; it was equipped with a stainless steel stirrer. Additional experiments were performed in a pilot-scale 5 l drying filter.

The following operating conditions were applied:

- 150 g of dry SaC-I were introduced in the lab-scale filter with 500 ml solvent (acetone, or industrial mother liquors, or acetone + small amounts of water, as explained in the following).
- The suspension was kept under stirring for 10 min.
- 2% (in weight) of dry seed crystals (form II) were then introduced in the drying filter and stirring was carried on for 10 more minutes.
- The suspension was filtered under vacuum until a moist cake with desired solvent content was obtained.
- Cake samples were withdrawn from the filter and placed at 100 °C for 15 min in a moisture analyzer equipped with a weighting chamber, in order to measure the liquid content of the cake.

Preliminary experiments were carried out to check that the final drying of the cake samples did not significantly affect their polymorphic composition, before their characterization using NIR spectroscopy.

The goal of the NIR analysis was twofold: on the one hand, it was essential to monitor quantitatively the various forms of the API in question during its processing, on the other hand, after the appearance of a more stable form, it was necessary to understand the mechanisms involved during the phase transition process and the operating conditions which could allow improved mastery over the phase of the final product.

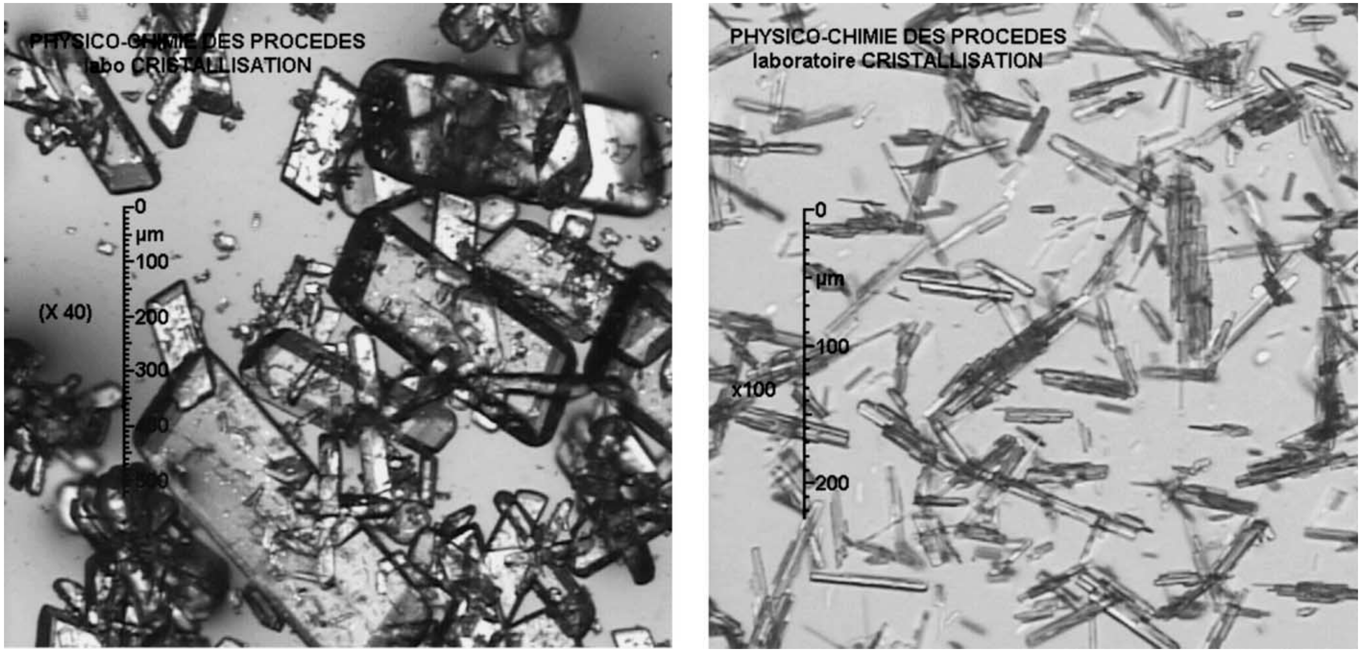

Fig. 1. Microscopic pictures of SaC crystals. Form I, compact parallelepipeds (left) and form II, needles (right).

3. Determination of the solid state of solid samples of SaC

3.1. Qualitative characterization of the solid state using NIR spectroscopy

In order to assess the possibility of detecting, using NIR spectroscopy, the crystal forms occurring during the crystallization and after further processing of the solid, 12 samples (about 6 g) of binary mixtures of SaC-I, SaC-II and SaC-Am were prepared as follows: A layer of amorphous product was placed between two layers of crystallized solid, and the whole sample was mixed manually during 3 min so as to avoid any variation of the initial solid composition. The samples were then placed under the diffusive reflectance probe and the corresponding spectra were recorded for further data processing. Several calibration procedures were then tested in order to select the more appropriate model relating the spectral data to the solid composition. The criteria of such a choice were the following: (1) Both Standard Error of Prediction (SEP) and Standard Error of Calibration (SEC) values should be as close to 1 as possible. (2) The ratio SEP/SEC should be as close to 1 as possible. (3) Both intercepts of the calibration and validation curves should be as close to 0 as possible. Finally, a two-factor Principal Component Regression (PCR) model was found to provide the best estimates, when used with the following pre-processing: First derivative BCAP (a cluster analysis application from Büchi), Multiplicative Scatter Correction (MSC) amplification and third derivative (Taylor, 5 points).

As far as qualitative determination of the solid form is concerned, a two-dimensional plot of the parameters computed after the PCR analysis allows one to visualize easily the ability of the method to separate the three crystal forms. Fig. 2 clearly demonstrates that the model allows separating satisfactorily the three solid states under investigation.

However, as outlined by Stephenson et al. (2001), it should be noted that, given the large number of data recorded in a given spectrum, one can easily correlate any property of the product to the spectral data. Therefore, one should carefully check that the calibration data are not indirectly correlated to unexpected parameters, such as the particle size or shape. This is particularly true in the present study since, as outlined above, the shape of the particles changes with the solid state. This is the reason why the PCR analysis was applied to SaC samples presenting batch-to-batch variations in their final CSD. The results displayed in Fig. 2, which correspond to different crystalline samples, show that the procedure remains efficient in identifying both the solid state and habit, despite variations of the granulometric quality of the final crystals.

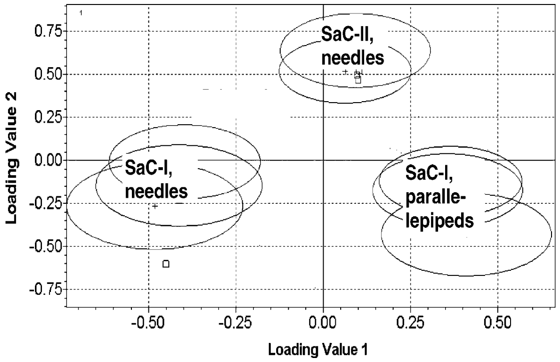

Fig. 2. Validation of the NIR identification of the solid state using various industrial solid samples.

As far as industrial applications of the technique are concerned, it should be noticed that this latter result appears as a necessary but insufficient condition for robust and flexible monitoring of crystallization processes. In order to assess the possibility of such in-line monitoring, NIR spectroscopy measurements were performed using a transflectance probe immersed in a pilot-scale batch cooling crystallizer. Actually, no specific calibration was performed in order to account for the temperature variations of the suspension, which of course affect the recorded spectra; this is why no quantitative estimation was expected from the measurements. Moreover, it is clear that the spectral data also depend on the CSD obtained during the cooling crystallization. Fig. 3 shows how the trajectories of the loading values behave when SaC-I and SaC-II crystals are growing in the suspension. Despite the inevitable enlargement of the confidence intervals with time, it is clear that the two polymorphs can be differentiated by the in-line PCR analysis.

3.2. Quantitative characterization of the solid state using NIR spectroscopy

For process monitoring purposes, the quantitative analysis of the solid state of the product is a major is-

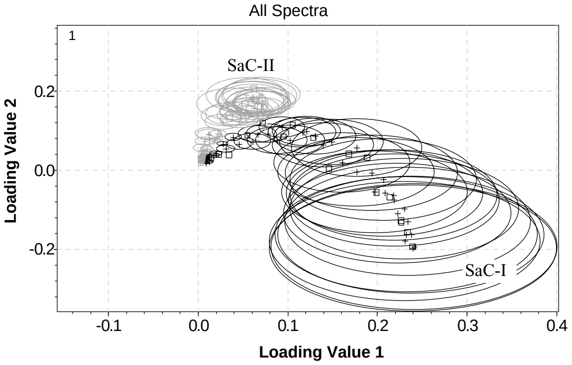

Fig. 3. Trajectories of the loading values during the crystallization of SaC-I and SaC-II crystals.

sue, especially when slow phase transition phenomena are involved or when undesirable disturbances (e.g. presence of impurities, input of water, etc.) are likely to happen during the industrial production. Actually, such kind of events should be carefully monitored in order to avoid detrimental effect on the final quality of the product. This is the reason why calibration procedures were developed to relate the concentration of binary mixtures (i.e. SaC-I/SaC-II, SaC-I/SaC-Am, SaC-II/SaC-Am) to the time variations of the recorded NIR spectral data.

To illustrate the obtained results, the PCR calibration curves of the NIR measurement of SaC-I/SaC-Am and SaC-II/SaC-Am mixtures are displayed in Fig. 4. Six samples were used for the calibrations in question (SaC-I/SaC-Am and SaC-II/SaC-Am, respectively).

It turns out that the maximal relative uncertainty of calibration was 4% with SaC-I/SaC-Am mixtures while it was reduced to less than 1% with SaC-II/SaC-Am mixtures. The slopes, regression intercept and regression coefficients were found to be 0.9987, 0.0003, 0.9994 and 0.9999, 0, 0.9999, respectively. Given the small number of samples which were used, such results can be regarded as really satisfactory. The measurement technique was then applied in order to investigate key features of the crystallization process, and notably the transition kinetics in suspension, as a function of the amount of seed SaC-II crystal, temperature, moisture contents and crystal habits.

3.3. *Quantitative characterization of the solid state: a comparative study*

As outlined in Section 1, NIR spectroscopy is now more and more widely used in the chemical industry to assess the quality and the end-use properties of many products. It is therefore of major interest to evaluate to which extent in-line NIR equipments could replace “usual analytical techniques” for quality control purposes. This is why the NIR characterization of the solid state was compared with usual X-Ray Diffraction (XRD) and DSC quantitative measurements.

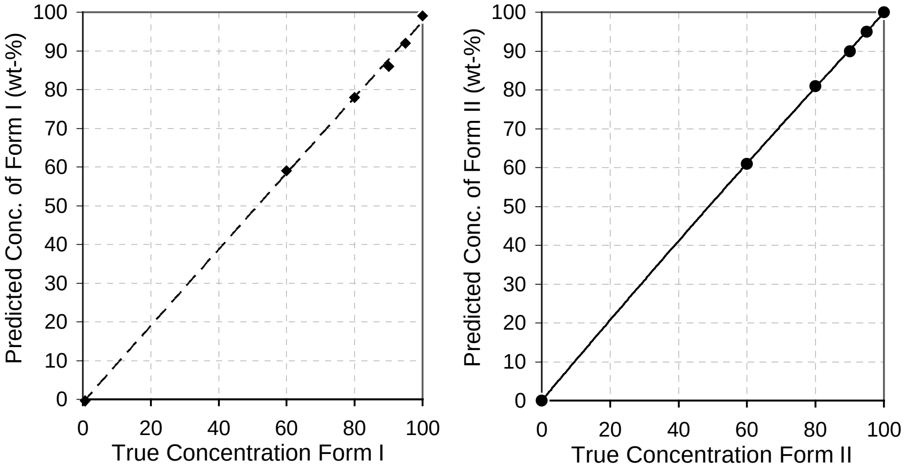

Fig. 4. NIR calibration curves for the measurement of the weight concentrations of forms I (left) and II (right) in binary mixtures with amorphous particles.

Table 1
Comparison between DSC, XRD and NIR spectroscopy for the measurement of the polymorphic composition of solid samples of SaC

Sample number	Lab. No. 1: NIR spectroscopy	Lab. No. 1: DSC	Lab. No. 2: DSC	Lab. No. 2: XRD	True value
1	92.4	90.7	91.3	92.3	90.0
2	50.1	53.4	50.0	56.2	50.0
3	97.8	94.8	94.6	96.5	95.0
4	8.3	4.9	5.3	5.3	5.0
5	22.5	21.6	22.2	23.4	20.0
6	81.0	80.7	80.3	85.2	80.0
7	13.4	10.4	9.5	11.6	10.0
Average absolute error	2.21	1.01	0.71	2.93	

Seven samples with various SaC-I/SaC-II contents were prepared “blindly” and sent for analysis to laboratories performing routine determinations of the polymorphic composition of SaC. The laboratories are referred to as Lab. No. 1 and Lab. No. 2 in Table 1. The measurements obtained using NIR by Lab. No. 1—where DSC measurements were also currently performed—were compared with those of Lab. No. 2 (XRD and DSC). Table 1 summarizes the results compared with the true values. Even though DSC measurements provide the more accurate results, it is clear that the quality of NIR spectroscopy measurements is satisfactory, with an average absolute uncertainty of the order of 2.2%, compared with XRD. If one considers the key advantages of NIR spectroscopy, which were outlined in introduction, it is clear that the technique is highly valuable as a Process Analytical Technique.

4. Quantitative monitoring of polymorphic transitions in suspension using NIR spectroscopy

During the crystallization process and the downstream filtration of the API particles, several problems were encountered which, at first glance, appeared to be rather contradictory. In particular, despite similar operating conditions notably in terms of temperature control, the transition rates of form I into form II were found to vary significantly from batch to batch. The effect of slight variations of the composition of the solvent was not clear and yet seemed to be essential. It was clearly established that the rate of transition was much higher in the industrial mother liquors than in pure acetone, which was not that obvious to explain. This is why a series of experiments was planned to assess the role played by several operating parameters: temperature, quality of seed crystals and composition of the solvent involved.

4.1. Temperature dependency of the transition kinetics

Four experiments were performed with increasing suspension temperatures. The suspensions were prepared in the drying filter, as described in the experimental part. The suspensions, which contained the same amount of solvent (about 16 wt.%) were seeded using 10% SaC-II crystals in order to initiate the phase transition process. Fig. 5 shows the experimental results obtained. Even though the final part of the transition would have deserved more data points, the time variations of the stable form usually present sigmoid patterns. As expected the observed transition kinetics show increasing rates with temperature increase. However, it should be noted that the initial SaC-II contents of the suspension is rather poorly estimated (i.e. between 16 and 20% instead of 10%). Even though such experimental drift was rather disappointing, it could be attributed to the large time interval between the calibration experiments and the use of the calibration model for kinetic measurements. Moreover, one can reasonably consider that, during its further use, the calibration model could be significantly improved through the introduction of new data.

As one can see, the insufficient number and accuracy of the data points—notably for both temperatures 30 and 40 °C—do not allow reliable estimation of the kinetic parameters of the turnover rate. Anyway, such estimation was not an objective of the present paper. Moreover, as demonstrated in the fol-

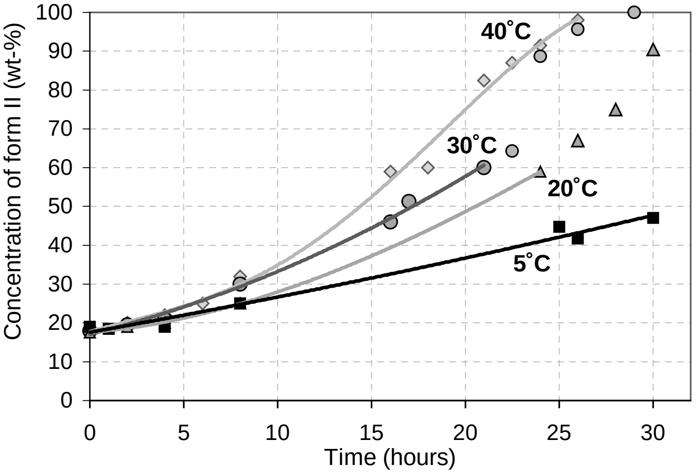

Fig. 5. NIR measurement of the time variations of the solid composition during the transition I → II, as a function of temperature.

lowing, any underestimation of the effect of the water contents of the solvent may lead to significant errors in the interpretation of the experimental results. Such effect was not clearly identified when the present experiments were carried out, which explains the poor quality of the transition curves displayed in Fig. 5.

Additional experiments were performed after the key role played by water in the filtration cake was identified. Improved results were then obtained with reproducible amount and composition of the solvent in the cake.

4.2. Effect of the habit and size of SaC-II seed crystals on the transition kinetics

Three isothermal phase transition experiments were performed after seeding with 2 wt.% form II suspensions of form I in the drying filter. All experiments were performed at 20 °C with 30% pure acetone in the filtration cake. For these experiments, the seed crystals were prepared in order to present different habits and specific areas. The specific areas of seeds were measured using the Brunauer–Emmett–Teller (BET) technique, and found to be 0.54, 0.47 and 0.14 m^2/g,

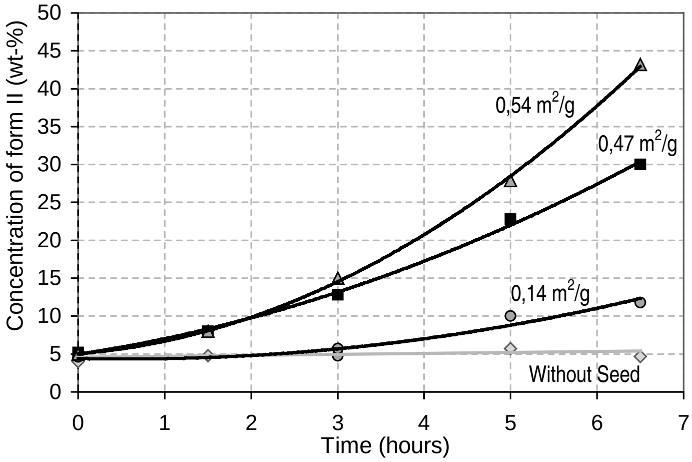

Fig. 6. Transition kinetics at 20 °C, with 2% seed, as a function of the specific area of the seed form II crystals.

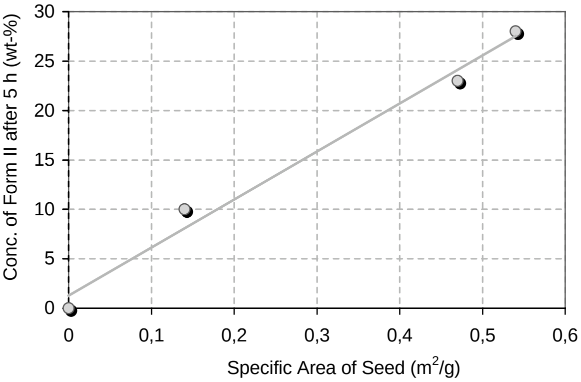

Fig. 7. Transition kinetics at 20 °C, measured concentration of form II after 5 h, as a function of the specific area of the seed form II crystal.

respectively. The phase transition was then monitored using the NIR spectroscopy equipment, as displayed in Fig. 6. Similar experiment performed without adding seed, but using the same operating conditions was considered as a reference experiment.

It turns out that the rate of the phase transition process increases with increasing specific area, which is not that surprising. The transition is promoted by the surface of stable form II crystals present in the suspension. Additional experiments should be performed to determine whether such promotion is due to secondary nucleation of new germs of stable SaC-II at the surface of seed crystals, or not. Anyway, for process development purposes, it is an interesting result to demonstrate the clear relationship between the rate of transition and the seed surface. From this point of view, Fig. 7 shows how a given percentage of stable form can be obtained after 5 h, as a function of the specific area of the seed.

4.3. Effect of the quality of the solvent on the transition kinetics

Significant effects of the quality of the solvent, the concentration of water in particular, were suspected to explain the batch-to-batch variability of the polymorphic composition of the API under investigation. Actually, even though this observation was not clear, the presence of small amounts of water in the filtration cake seemed to promote the transition of form I into the stable form II. Now, NIR spectroscopy obviously provides a means of investigating and understanding the key parameters involved in the solid processing and to optimize the final quality.

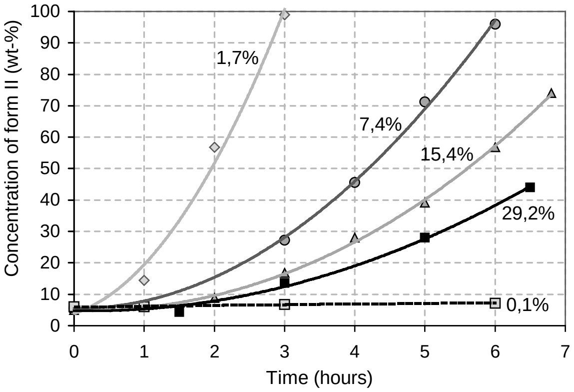

Fig. 8. Transition kinetics at 20 °C, time variations of the concentration of form II as a function of the moisture content of the suspension, measured using NIR spectroscopy.

Five isothermal experiments were performed as described above, with different amounts of solvent in the filtration cake. The temperature was set to 20 °C and the amount of seed form II crystals was 2%. The mass percentage of solvent in the cake was determined by using a moisture analyzer, as described previously, except for the experiment performed with 0.1% solvent. In this latter case, given the low liquid content, the sample of suspension was placed at 50 °C in a drying oven with ventilation, for 10 h. The moisture contents measured for the five experiments in question are given in Fig. 8.

As one can easily see, the experimental results are rather contradictory since the rate of transition is found to increase with decreasing moisture content of the suspension, except with very small amount of solvent. In this latter case, the rate of transition is almost equal to zero. To understand such results, one should remember that the solvent content in the drying filter was fixed through filtration under vacuum which, of course, extracts pure acetone rather than the residual water present in the liquid. Consequently, low moisture contents in the cake are likely to correspond to higher water concentrations, except with 0.1% solvent where almost no solvent remains. Now, the API in question is much more soluble in water than in acetone, which tends to suggest a solvent-mediated phase transition process. Such mediation is fully consistent

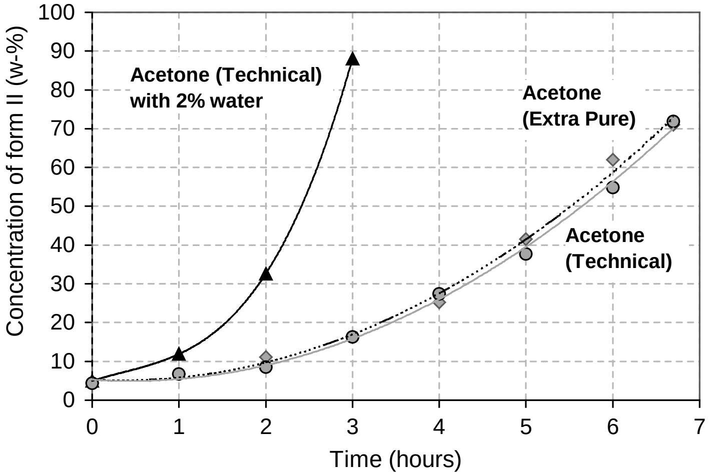

Fig. 9. Transition kinetics at 20 °C with 16% liquid in the filtration cake: NIR spectroscopy time variations of the concentration of form II for three different grades of solvent.

with previous results concerning the specific area of seeds. This is why the hypothesis of the key role of small amount of water in the transition was set.

In order to confirm the role of water, three additional experiments were performed at 20 °C, with a constant mass of solvent in the filtration cake: 16 wt.%. Three solvents were used: acetone of extra pure grade, acetone of technical grade and acetone of technical grade containing 2% distilled water. Fig. 9 clearly demonstrates that the rate of transition does not depend on the purity of the solvent, but on trace amounts of water in acetone which, probably, significantly promote the phase transition process. One can therefore reasonably consider that water is the reason why, as outlined above, the rate of transition is higher in the industrial mother liquors than in pure acetone.

5. Conclusion and perspectives

Many difficulties encountered in the monitoring and control of crystallization reactors and subsequent unit operations arise from the lack of efficient on-line sensors, but IR spectroscopic techniques and more specifically NIR technologies associated with fiber-optic probes are really promising.

The aim of the present paper was to assess the performances of fiber-optic NIR spectroscopy for the monitoring and optimization of the cooling crystallization and filtering of SaC, an API subject to polymorphic transitions. An interesting issue was also to demonstrate that the need for rigorous calibration and measurement procedures, which is often considered as a significant obstacle for industrial development of monitoring strategies, is not a definite constraint: coarse calibrations can also allow valuable information to be obtained and analyzed. From this latter point of view, the NIR spectra were found to be sensitive to the polymorphic composition of the solid, and a PCR technique was satisfactorily used for the calibration—using few off-line data—of the measurements of polymorphic composition.

Several features of the solid processing process were also investigated. NIR spectroscopy was shown to provide highly valuable information on the kinetic of polymorphic transitions involved during the filtration step. In particular, the effect of small amounts of water in the solvent was demonstrated to be a determining factor of the rate of polymorphic transition, its control is therefore essential for the mastery of the final composition of the API.

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