Real-time Product Morphology Monitoring in Crystallization Using Imaging Technique

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Many speciality organic chemical products, such as pharmaceuticals are crystals that exhibit multiple morphological forms and habits that are of critical importance not only to the end use properties of the products, but also to their downstream processing, such as in filtration and handling and in transport and storage. It is known that minor changes in operating conditions, such as cooling rates and supesaturation can have significant impact on the product leading to batch-to-batch variation. As a result, precision manufacture of crystalline products demands on-line techniques for real-time measurement of crystal morphology. The use of a non-invasive on-line imaging technique in a batch reactor for monitoring cooling crystallization of (L)-glutamic acid which exhibits two polymorphs, alpha and beta is described. The technique was found to allow real-time observation of some temporal moments that are critical in the crystallization process, in particular the crystallization onset and transformation between the two polymorphs. For validation and benchmarking purpose, an off-line system for particle characterization, the PharmaVision 830, and photo-microscope were also used in the study in parallel with the on-line imaging system. © 2005 American Institute of Chemical Engineers *AIChE J,* 51: 1406–1414, 2005

Introduction

High value-added speciality chemicals, such as pharmaceuticals are often manufactured in batch crystallization processes. For a product in crystalline form, morphology often represents a critically important property not only to the end-use functional properties, but also to downstream processing and handling of the product. It is known that certain crystal morphological forms and habits have been related to difficulties in dissolution rate, process hydrodynamics, handling and storage or in milling and grinding processes. The ability for a substance to crystallize in more than one crystal structure, that is, polymorphism, has been the subject of many previous theoretical studies, which led to the development of some software systems, such as HABIT[1, 2] and CERIUS2[3]. These software systems calculate the attachment energies and the relative growth rates associated with the crystal faces. However, they have not been able to consider all the engineering factors that might affect the crystal morphology. It is known that minor changes in supersaturation, cooling rates, reactor hydrodynamics, pH and impurity in the feed can have significant impact on the crystal product. In addition, there are unexpected factors which

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can become deterministic, such as the wall effect on heat transfer, baffles, and impeller materials and types[4]. For these reasons, there is a genuine need to develop on-line techniques for real-time measurement of crystal morphology from nucleation through crystal growth until completion of a batch run.

Various techniques have been studied previously for in-line crystallization process monitoring. These include attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) for concentration measurement[5-7], X-ray diffraction (XRD) and Raman spectroscopy for crystallographic structure[8, 9], and laser diffraction[10], acoustic spectroscopy[11], and light scattering techniques[12] for crystal size distribution measurement. In contrast, there have been only a few publications on monitoring crystal morphology.

Laser diffraction techniques were investigated previously for recognition of nonspherical particles, but only have achieved limited success. The main difficulty has been in obtaining a single-particle pattern in mixtures due to problems associated with partial scattering of the particles[10, 13, 14]. Mougin[15] attempted to interpret the ultrasound attenuation spectra in order to identify dynamic changes in morphology during the crystallization of an organic compound. A correct interpretation was found possible although some additional information needs to be provided which is not always readily available. Studies have also been made to produce crystals with different size and shape properties through supersaturation control using ATR FTIR[5, 16]. Modification of temperature to maintain supersaturation values during nucleation and crystal growth helps produce uniform size and shape properties. This practice requires concentration and supersaturation models for the compound to crystallize obtained from calibrations, and the temperature range for control may be limited.

In laboratory studies, photo-microscopy has been the most widely used method for analyzing crystal morphology. Samples are taken periodically from the reactor and observed using a photo-microscope imaging system. Software systems are also often available for quantitatively analyzing the images. Patience and Rawlings[17] reported an interesting approach for automating this process using a flowcell in a laboratory study of the crystallization of sodium chlorate. The flow through the cell was periodically stopped to allow a photo-microscope capturing images after settling down of the crystals at the bottom of the flowcell. In this way, the crystals of the compound were lying on a habit face and showing a particular shape to be characterized by a commercial image analysis software. They also developed an automatic control system by manipulating the impurity in the feed. The system has some limitations. First, the sampling period is from 20 to 30 seconds, whereas significant morphological events in crystallization might take only a few seconds. In addition, the use of a flowcell is clearly not ideal for many industrial processes. The flowcell configuration requires a pump to circulate the solution, which might cause crystal breakage, as discovered by Mougin[15]. Lasentec, Inc, USA developed a particle vision measurement (PVM) probe which can be used for visualization of the process *in situ*. The PVM uses a charged coupled device camera with light sources fitted into the probe[12, 18]. Barrett and Glennon[18] used the PVM probe to visualize the crystals in the determination of the meta-stable zone of an inorganic compound. Patience[19] made an attempt to use the PVM probe in the crystallization of sodium chlorate. He encountered difficulties in the analysis of the images using a commercial image analysis software tool.

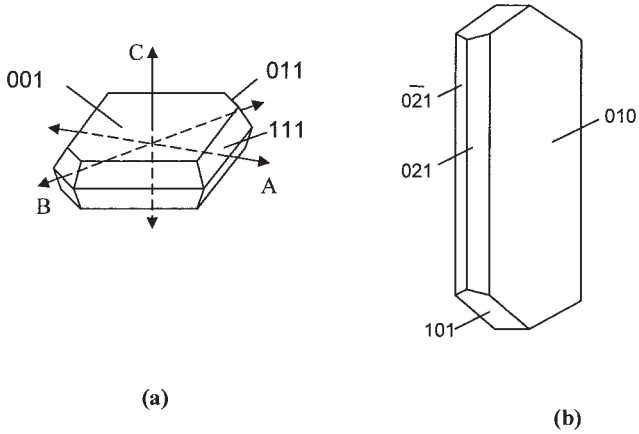


Figure 1 Morphology of L-glutamic acid α- (a), and β-form (b)[20,21]

The purpose of this work is to study the use of a noninvasive on-line imaging prototype developed by scientists at the pharmaceutical manufacturer GlaxoSmithKline, for monitoring in real-time the crystallization of an organic compound, (L)-glutamic acid, which exhibits two polymorphic forms. The focus of discussion is on using the technique to monitor some critical temporal phenomena during the process, in particular the onset and the dynamic transition between two polymorphs. An off-line imaging system, the PharmaVision 830 of Malvern Instruments, Ltd., and optical microscopy are also used to validate and benchmark the findings with the on-line system. The imaging system has the advantage of being able to take images at a high speed (up to 30 images per s). In addition, it is noninvasive because it does not need samples to be taken or reply on the circulation of the slurry through a flowcell.

The rest of the article is organized as follows. In section 2, the theory of crystal growth for (L)-glutamic acid will be briefly introduced, in particular the mechanism of growing into either α or β form. The third section describes the experimental set up. The results and their discussion will be presented in section four, and conclusions and plan for future work is presented in section five.

Crystal growth from solution for (L)-glutamic acid

The chemical selected for the study, glutamic acid, $C_5H_9NO_4$, is an amino acid used by the body to build proteins. It has two known polymorphs[20, 21], the prismatic α and the needle-shaped β forms, as shown in Figure 1. The solubility curves, for the α and β forms are given in Figure 2. The mechanism for L-glutamic acid to grow toward either polymorphic form, and to different shapes is not yet fully understood and, therefore, has been the subject of some experimental and theoretical studies[20, 22].

It was understood that once a nucleus is formed, the crystal growth often involves four steps[15]: transport of solute molecules from the bulk of the solution toward the boundary layer surrounding the crystal surface; diffusion of solute molecules through the boundary layer toward the adsorption sites; adsorption itself of solute molecules onto the crystal surface; and interfacial diffusion,

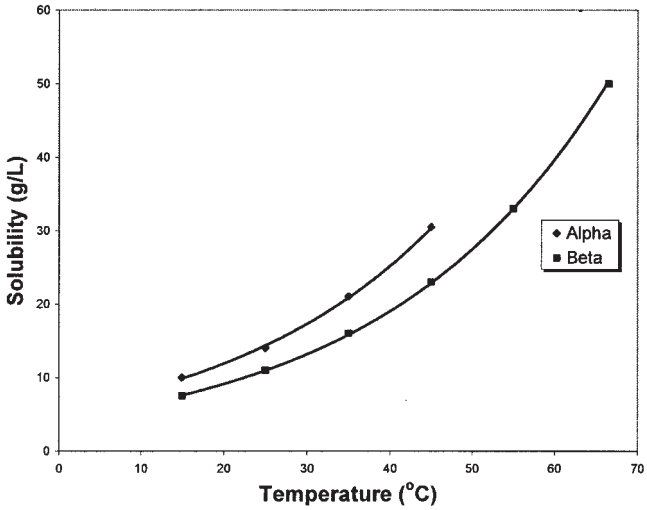


Figure 2 Solubility curves of (L)-glutamic acid in α and β forms[22]

whereby the adsorbed molecules migrate toward the optimum incorporation site and undergo a variable degree of desolvation. Any of these four steps can potentially be rate-limiting and can be affected by changes in the operating conditions (for example, solvent, supersaturation). The surface properties of the growing crystal impose constraints on the mechanism of growth. Generally speaking a smooth surface at the molecular scale makes the integration of a growth unit more difficult. The surface structure can be characterized by the surface roughness[23, 24] and depending on its value, the growth can be described by either continuous or layer growth models[25].

The shape or habit of a crystal can be controlled either thermodynamically or kinetically. While the rougher surfaces grow quicker, the kinetic shape of a crystal is determined by the rate-determining step of growth of the slow growing faces unless an impurity adsorbs on the faster growing faces reducing dramatically the rate of growth on one of these faces. The shape can also be controlled by varying the conditions, such as supersaturation or impurities - the so-called *crystal engineering*.

Prediction of crystal polymorph and morphology through molecular modeling has been the subject of study of some previous work. Crystal polymorph prediction can be based on high-throughput experiment and screening techniques[26-28]. On the other hand, morphological modeling research has led to some software systems, such as HABIT[1] and CERIUS2[29]. However, it needs to point out that these systems have not been able to fully consider the engineering operating conditions, such as cooling rates on the shape, and, therefore, it is still open for research[30]. As a result, on-line measurement of morphology can partially compensate the inability to simulate the morphology and shape. On the other hand, being able to measure morphology on-line in real-time will no doubt provide a tool that can help the development and validation of new and more sophisticated shape prediction models

The Experiment

System setup

Experiments were carried out using a glass jacketed reactor of 500 mL, a data interface board, and a PC running WinISO process control software provided by Hazard Evaluation Laboratory, Ltd. To control the temperature, a Julabo FP50-HD thermostated bath was employed. Due to the operated temperatures, a condenser was used to circulate water at 6°C to prevent loss of solvent. Reactor stirring was provided using a pitched blade stirrer rotating at a constant speed of 200 rpm. The temperature was measured using a platinum resistance thermometer (PT100), and the turbidity was measured with an in-house-built turbidimetric fiber-optic probe system. Both signals along with pH values were logged onto the computer system. Observation and recording of the process operation were conducted in real-time using the on-line imaging system. For the image analysis in the PVS830, a pipette was used to take samples from the reactor solution at several instants during the experiment. The samples were quickly placed on the sample glass slide of the PVS830 previously calibrated and covered, and then images were grabbed and analyzed. The time from taking a sample until the image analysis was from 10 to 20 s.

The on-line imaging system employed in the experiments is a prototype system developed by research scientists at Glaxo-SmithKline, UK[31], the system is depicted in Figure 3. A CCD camera fitted with Navitar Precise Eye/Mitutoyo optics is employed for image acquisition with a maximum frequency of up to thirty images per second with a pixel resolution of 640 x 480 and a field of view from 140μm to 16mm dependent on calibrated lenses employed. The camera is situated just outside the reactor wall and an imaging window is attached to the external reactor wall to minimize convexity effects on the images. To provide illumination, a xenon strobescopic light source is used and the light is conducted using a fiber optic guide. Camera acquisition and "strobe" are synchronised to freeze the moving particles by using a camera interface box developed by the GSK researchers. The captured images are sent to a PC running Video Savant® software (IO Industries, Inc.) for acquisition, storage and management of the frames. To enhance the contrast of particles from the image background, two fiber optic light guides could be used, both are adjustable in angles and distances from the camera. The system allows to visualize and record in real-time every event occurring throughout the complete batch crystallization run.

The PharmaVision System 830 (PVS830) from Malvern Instruments, Ltd. is an automatic vision system for analysis of

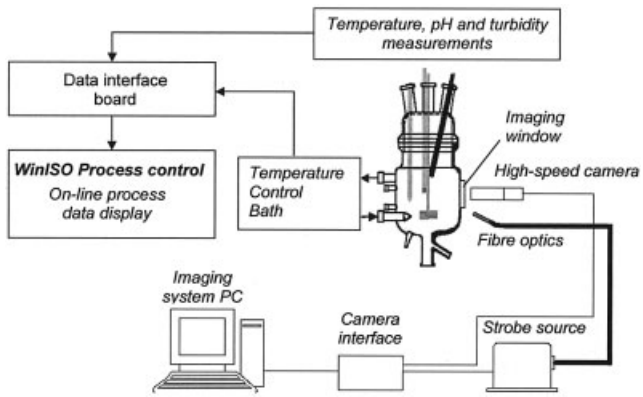


Figure 3 Experimental system with the on-line imaging system.

the size and shape of particles[32]. A zoom lens allows analyzing particles between 0.5 and 2,000 μm. The instrument automatically calibrates itself prior to an analysis by the measurement of both light intensity and precision grating with a known number of lines per mm. To perform analysis, the sample is placed on a sample tray under a CCD video camera. A linear actuator connected to a PC moves the camera across the sample tray and the camera takes digitized video images. Particles from the images are automatically segmented by embedded computer software obtaining a variety of shape parameters, such as length, width, mean diam. and roundness, supported by images of all particles for further visual understanding. The performance of the instrument is verified by reference slides certified and traceable to the National Institute of Standards and Technology standards.

Solutions of 33.3 g of L-glutamic acid (purchased from Aldrich Chemicals) dissolved in 500 mL of fresh distilled water were prepared. The solutions were heated up to 95°C and kept constant at this temperature until everything was dissolved, then linearly cooled down to 15°C keeping this temperature until the end of the experiment. Different linear cooling rates of 1, 0.5 and 0.25°C/min were investigated in the study. The concentration and temperatures of the experiments were chosen to be near to those used in an industrial scale operation.

Results and discussion

The on-line imaging system enables the temporal polymorph properties to be observed in real-time throughout the process of a batch run. In this article, we mainly present the results showing the dynamic transformation between the two polymorphs, as well as identifying the onset of the crystallization, because they are known to be the critical moments for the process.

Polymorphic transformation of (L)-glutamic acid

The three crystallization experiments correspond to three linear cooling rates of 1, 0.5 and 0.25°C/min, respectively. For the experiment employing a cooling rate of 0.25°C/min, the images revealed that the crystals were at first growing with a rhombic shape, α-form (Figures 4a and 4b). Transformation into β-form was observed at the temperature of 60°C as illustrated in the real-time image of Figure 5a. For the experiment using a cooling rate of 0.5°C/min, α-form crystals were also first found and the transition to β form was also observed, but at the much later stage corresponding to the temperature of 30°C. No transition from α to β was observed when a cooling rate of 1°C/min was used.

The kinetic effect is evidently detected on the images with the observation of the metastable α form, before the thermodynamically stable β form. In addition, the result also shows that the polymorphic phase transition into the β-form is better promoted when the crystallization takes place at a high-temperature, that is, when a slower linear cooling rate was used. The observed phenomena are consistent with the previous analysis in literature that α-crystals in fact provide the surface for the nucleation of β-crystals[33-35].

Shape dimension values of the crystals during the polymorphic transition were calculated using the PVS830 software, as demonstrated in Figure 5b for a sample.

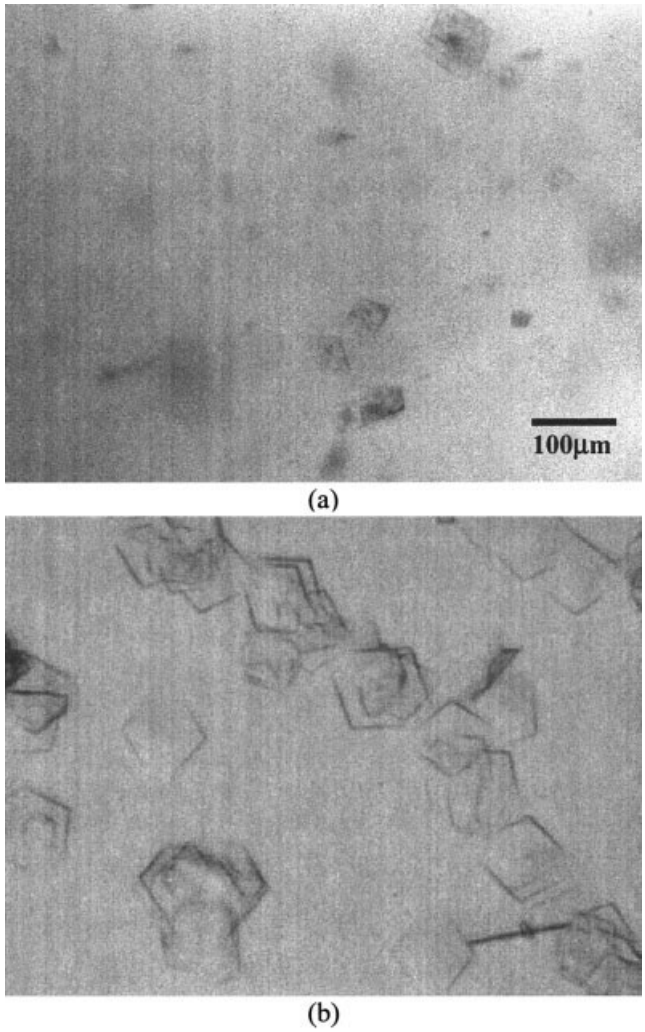


Figure 4 Observed crystals at 63°C and cooling rate 0.25°C/min in real-time (a), and in the PVS830 (b).

To benchmark the observations, samples were also taken for inspection under optical microscope. In Figure 6a, the microscope image shows the observed sample at the moment when the rhombic crystals were present. Similarly, the optical microscope image of Figure 6b shows mixed α and β forms, indicating an instant during which the polymorphic transition was taking place.

Crystal evolution

The growth rate of the crystallographic faces with respect to supersaturation for the α and β polymorphs of (L)-glutamic acid has been investigated previously[20, 21]. The results of these studies indicated that the fastest growing directions in β-crystals correspond to the face (1 0 1) (please refer to Figure 1b), whereas in the α-form only in the directions B and C different growth rates were observed under different conditions, with no significant changes in growth rates for other faces. In our experiments, special attention was given to monitoring these changes of the crystallographic faces and their influence on the overall morphology of the crystals by following the crystalli-

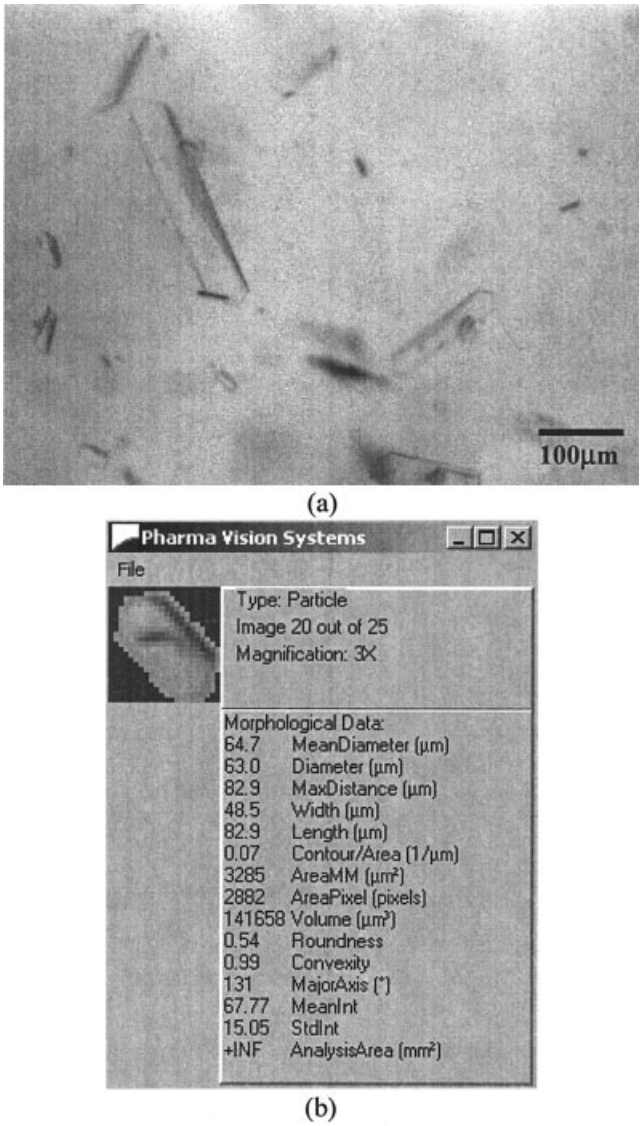


Figure 5 Real-time image for the cooling rate 0.25°C/min at 60°C (a), and shape dimension obtained by the PVS830 from a sample at 60°C (b).

zation processes with the on-line imaging system, together with comparisons of the crystal evolution at several temperatures for the three cooling rates used in the experiments.

Here we only present the results for two experiments of the cooling crystallization from 95°C to 15°C, one with a cooling rate of 0.25°C/min, and the other 0.5°C/min. All other conditions are kept the same. The difference of images for the two experiments at two instants will be compared in the paper, that is, when reaching 55°C, and 30°C. Figures 7a and b show the real-time images of the crystals at 55°C corresponding to the two experiments of cooling rates 0.25°C/min and 0.5°C/min, respectively. It can be seen that for the experiment of 0.25°C/min, at 55°C, the crystals are already predominantly in β form. In contrast, when reaching the same temperature, for the experiment of 0.5°C/min cooling rate, the crystals are still mainly in α form. It is worth re-calling that at the beginning of both experiments, crystals were all in α form.

When the temperature reaches 30°C, for the experiment adopting 0.25°C/min cooling rate, the crystals have almost completely transformed into β form, as demonstrated by Figure 8a; while for the experiment using a cooling rate of 0.5°C, the transition from α to β is still taking place, as evidenced by Figure 8b.

Figure 9 shows an image taken using the off-line PVS830 system during the experiments, and the quantitative size and shape information calculated for an isolated crystal using the built-in software of the PVS830. It demonstrates that quantitative and more detailed analysis can be made for these images. As an example, we compare Figure 5b and Figure 9b, the

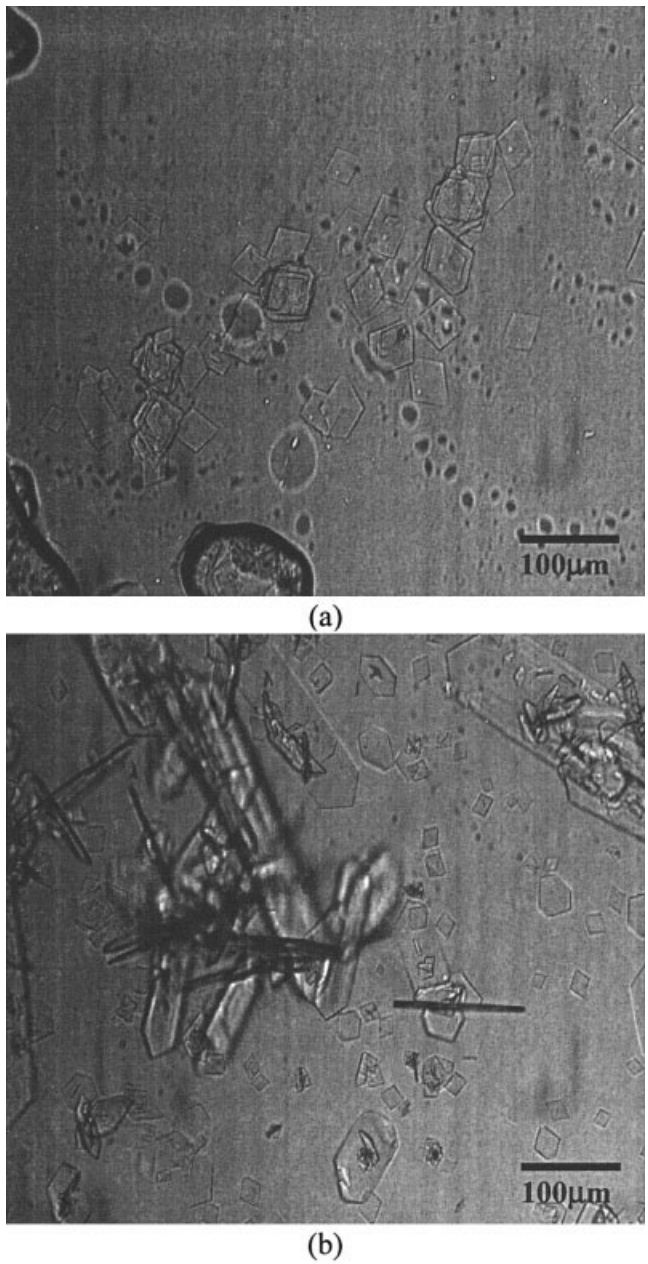


Figure 6 Optical microscope images for the cooling rate 0.25°C/min with the first observed crystals (a), and during the polymorphic transition (b).

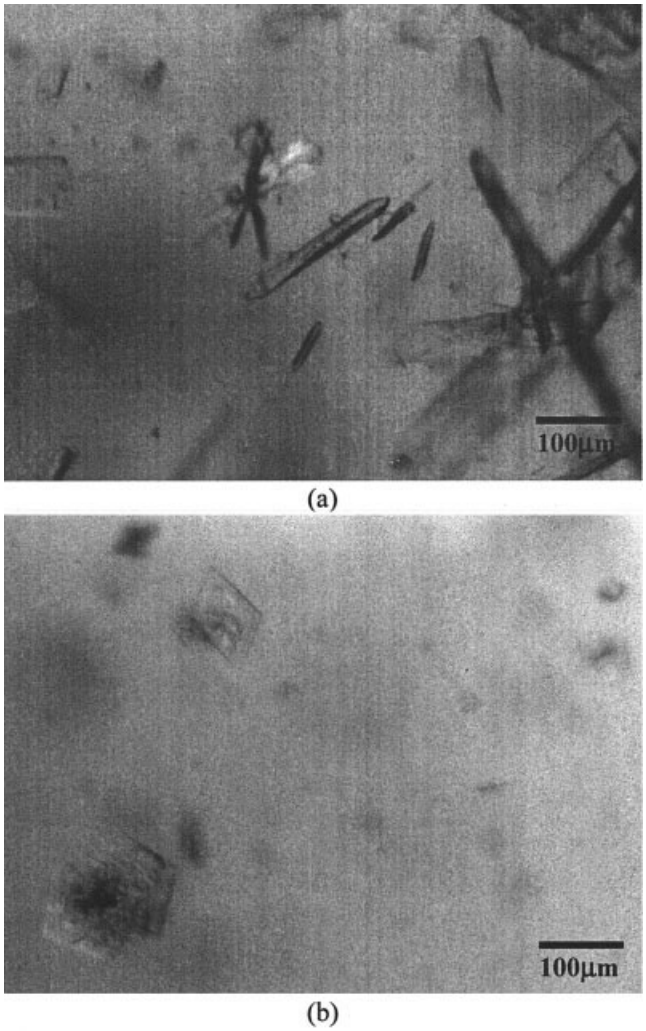


Figure 7 Real-time images at 55°C for cooling rates 0.25 (a), and 0.5°C/min (b).

former is about the dimensional information for a crystal at 60°C for the experiment of 0.25°C cooling rate which has the length of 82.9 μm and width 48.5 μm, and the latter is for a crystal when reaching 15°C for the same experiment which has the dimension of 262 μm in length and 55.6 μm in width. In other words, the length/width ratio changed from 1.7 to 4.7 when the operating temperature is dropped from 60°C to 15°C, indicating faster growth rate in the length, reflected in the (1 0 1) face, than in the width. This is consistent with the findings in literature[21, 22]. Although the two crystals in Figure 9b and 5b were not for the same crystal, they represent the sizes of typical crystals for those moments. The information can be made more accurate if the mean dimensional information is used.

For the cooling rate 0.5°C/min, changes on the crystal habit of the α-form were observed between 40 and 35°C. In Figure 10a and b, quantitative values are provided reflecting the changes in crystal size and morphology, notably due to changes on the growth of the face (0 1 1). The information confirms that for α form, the growth rates for the faces responsible for prismatic shape are not significantly different.

Discussion

As supersaturation is the driving force of crystallization, it is expected that crystals grow faster when the level of supersaturation is higher. The driving force will continue to exist until the concentration in the solution reaches the value corresponding to the solubility. It was expected that, with high supersaturation, the crystals will exhibit rough surfaces and grow fast, which was consistent with the observations in experiments. It needs to stress that high growth rate may not always mean big crystals, because higher supersaturation at the nucleation stage encourages the formation of more nuclei, leading to a large amount of particles with smaller size. As a result, through manipulating the supersaturation level at the nucleation and crystal growth stages, the crystal size can be controlled. For instance, in order to obtain smaller crystals, a feasible strategy is to create high supersaturation at the early stage, followed by low supersaturation at the crystal growth stage. On the other hand, one should keep a low supersaturation level during nucleation and increase it during the crystal growth stage if big crystals are desired. For (L)-glutamic acid, due to the existence of more than one solid phase, to produce a desired size of a desired polymorph, α or β, both the effect of cooling rate which defines

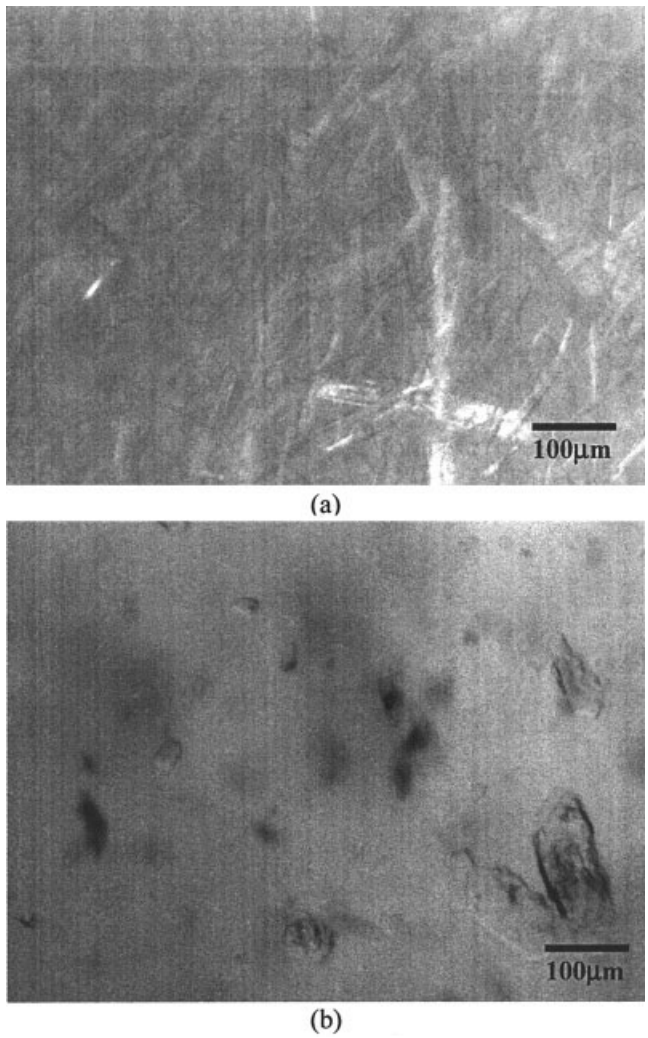
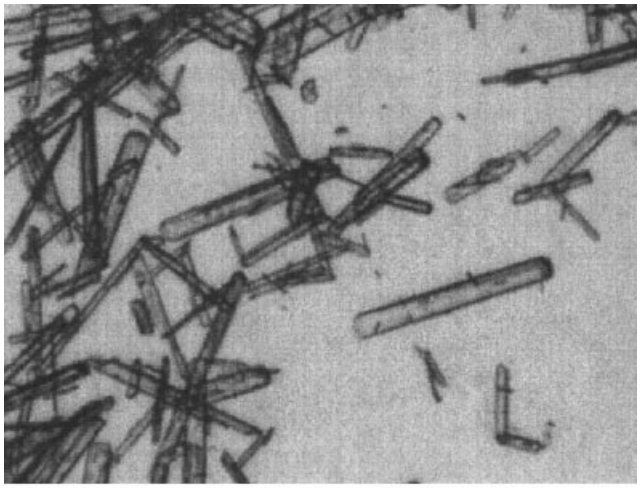
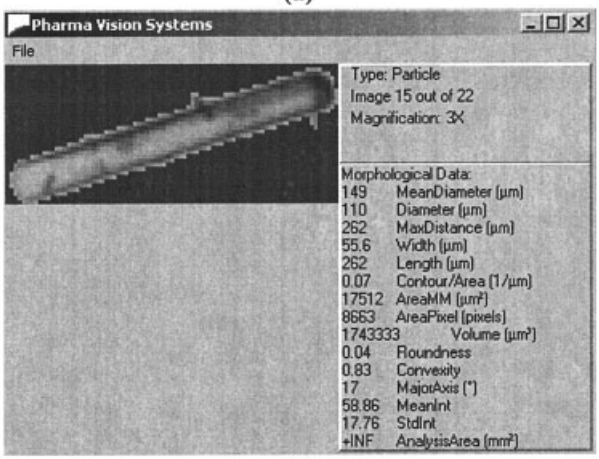


Figure 8 Real-time images at 30°C for cooling rates 0.25 (a), and 0.5°C/min (b).



(a)



(b)

Figure 9 Crystal image and shape quantification at 15°C and 0.25°C/min by the PVS830.

the supersaturation and the nucleation temperature, and the solubility of the polymorphs need to be considered.

The phenomenon observed that a slow cooling rate is in favor

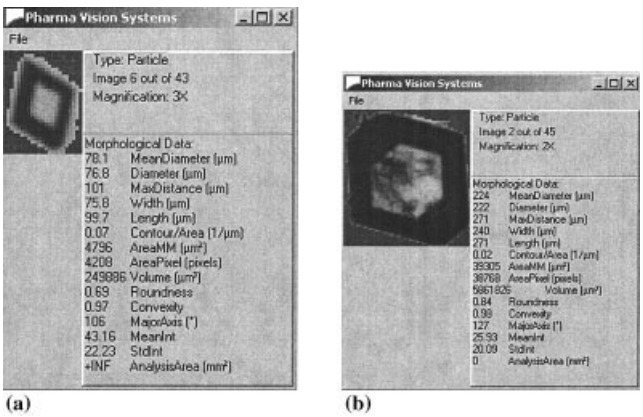


Figure 10 Shape quantification obtained by the PVS830 from a samples at 45°C (a), and 35°C (b) with cooling rate 0.5°C/min.

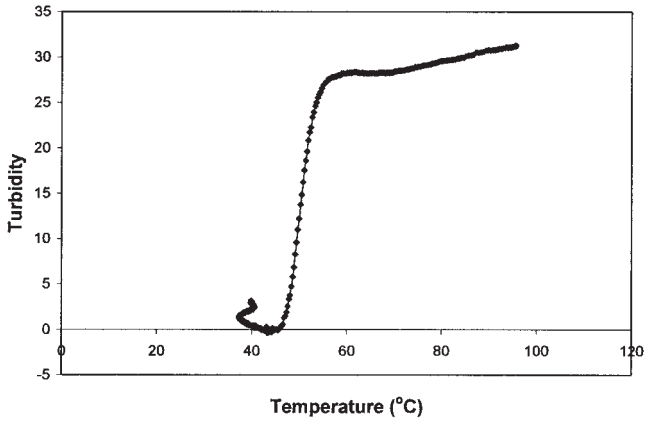


Figure 11 Turbidity curve for the cooling rate 1°C/min.

of a faster transformation into the β-form is in fact related to the solubility of the α-form and the onset temperature. Because the slow cooling rate has a high-temperature for the crystallization to start, and the subsequent reduction in solution concentration will rapidly reach the point where the α-form can no longer stay as a solid form, but due to the still existing supersaturation with respect to the β-form, the α-form crystals will dissolve and transform into the β-form. When a fast cooling rate is used, a lower onset temperature and higher supersaturation is achieved, leading to longer periods of growth for α-crystals before the polymorphic transformation occurs. Garti and Hadassa[35] used an ice-bath to quickly cool down a solution of glutamic acid to 45°C. By X-ray analysis they showed that for approximately one hour initially no β-form was present, and after this period transformation into β form was observed at a concentration near to the solubility of the α-form. Mougin et al.[36] employed a cooling rate of 0.4°C/min also observed the transformation of α into β near to the solubility concentration of the α-form, and using a cooling rate of 0.1°C/min they observed only the β-form. The reason can be attributed to the fact that crystallization occurred at 38°C (identified from turbidity) with a concentration of 20g/L and this point is located between the solubility curves of α and β forms (see Figure 2), that is, the nucleation could only promote the production of the β form. We can conclude that whether α form is observed or not depends primarily upon whether it is thermodynamically possible, that is, whether at the onset the supersaturation is sufficient for the α form to exist, or if only the β form is supersaturated, hence, this form will be observed. The high supersaturation levels reached using fast cooling rates not only provide longer periods of growth for α-crystals, but also increase the growth rate, contributing to producing bigger α-crystals and in shorter periods from the onset observing changes in morphology due to growth of the slower face (0 1 1).

During the onset stage, the crystallization experiments were carefully followed by the on-line imaging system. The onset point is said to occur when the first few crystals start to appear in the solution, which is sometimes called the "cloud point". In measurements using optical turbidity, time lag detection from the beginning of nucleation is in fact involved as a result of the instrument sensitivity and as the crystals grow to a detectable size. Looking at the real-time images, we were able to identify a number of first appearing particles instants before the fiber-optic turbidity probe could show a pronounced reduction in

light transmittance at the cloud point (Figure 11). The fiber-optic turbidity probe requires a certain number of small particles to be present in the solution in order to detect a reduction in the light transmitted. We could observe that this stage occurs as a period of time rather than as a sudden event. In Figure 12a, a real-time image illustrates the instants when the few first particles appeared As a comparison, Figure 12b shows an image before onset occurring. The temperature at onset points obtained by on-line imaging corresponding to the three cooling rates are summarized in Table 1.

Table 1. Crystallisation Onset Values Obtained from OnLine Imaging

Cooling Rate	Temperature Onset	Cooling Time
1°C/min	54.10°C	42 min
0.5°C/min	59.74°C	55 min
0.25°C/min	69.95°C	47 min

Conclusions

The use of an on-line imaging technique for real-time monitoring a 0.5 Liter batch crystallization reactor for an organic compound, (L)-glutamate acid that exhibits two polymorphic forms is described. Three batch runs were investigated which correspond to three linear cooling rates, 1, 0.5 and 0.25 °C/min. In order to validate and benchmark the observations using the on-line system, an off-line particle characterization system and a photo-microscope were used in parallel. The on-line system was found to be able to capture instantly the first few particles formed during the crystallization onset before depletion in light transmittance by optical-turbidity measurement.

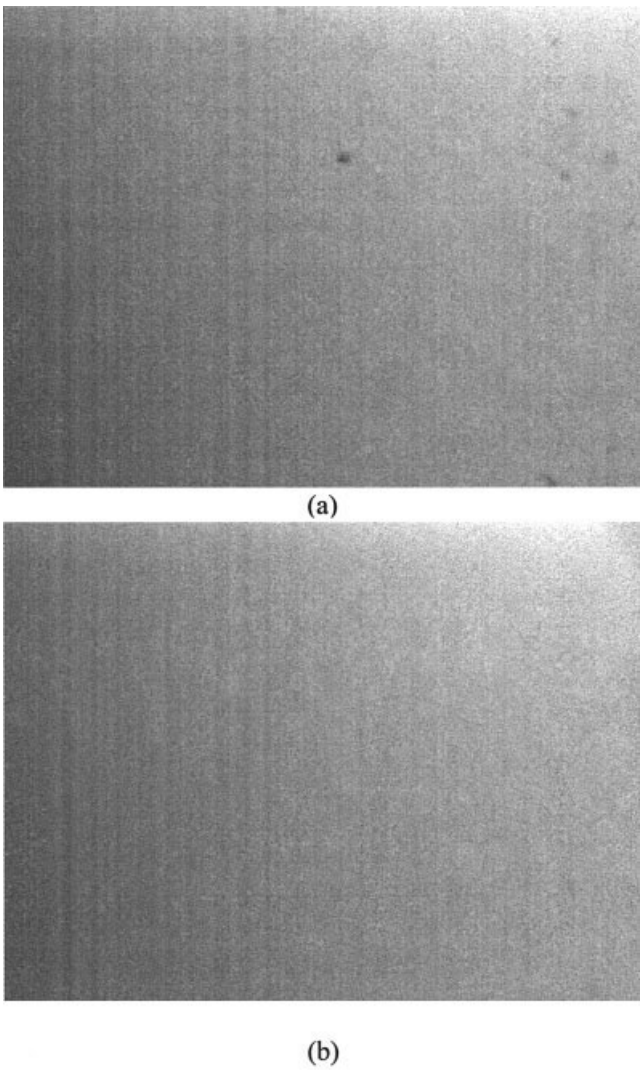


Figure 12 Real-time image showing the onset stage of the crystallization at cooling rate 1°C/min. (a) first few particles, and (b) clear solution.

For all the three batch runs under three different linear cooling rates, it was observed that crystals in α-form were first formed, which was followed by transformation into β-form for the two batch runs of 0.25°C/min and 0.5°C/min cooling rates. No polymorphic transformation was observed for the batch run under the cooling rate of 1°C/min. In the slowest cooling rate, 0.25°C/min, α-crystals appeared only for a very short period of time before the polymorphic transition. This period of existence of the α-form is so short that the later predominance of crystals in β-form might lead to the misperception that only β-form has ever appeared.

An off-line particle characterization instrument, the PharmaVision System 830 of Malvern Instruments, Ltd. was also used in the study in parallel with the on-line system which analyses the samples taken from the reactor. The PharmaVision System 830 validated some of the observations obtained using the on-line system, and in addition provides quantitative values of shape descriptors. It was observed that at high supersaturation levels, bigger α-crystals are obtained with particular growth on the (0 1 1) face. For β-crystals on the other hand, the crystallographic face (1 0 1) shows the fastest growth rate leading to longer needles at low supersaturation levels.

The future work will include investigating image analysis techniques to obtain quantitative information of the 2-D images, and developing a methodology for constructing the 3-D structure from information obtained from 2-D. The latter is being undertaken in collaboration with Heriot-Watt University.

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