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Mesure de la distribution de taille de cristaux aciculaires par analyse d'images d'une sonde video in situ

Measuring the size distribution of acicular crystals by image analysis from in situ video probe

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Résumé

La cristallisation discontinue d'oxalate d'ammonium (OA) a été étudiée en vue de la mise au point d'un modèle dynamique du procédé en solvant pur ou contaminé par des impuretés dissoutes. La concentration en soluté a été mesurée par spectroscopie ATR FTIR in situ, tandis que la phase solide dispersée était suivie par une sonde vidéo CCD immergée permettant l'acquisition d'images. En vue d'évaluer la distribution des tailles de particules (DTP), un algorithme de traitement des images vidéo bidimensionnelles des cristaux d'OA a été mis au point. Cet algorithme vise à assurer une mesure fiable de la taille des cristaux ; la spécificité du système étudié ici étant essentiellement liée à la forme aciculaire des cristaux. En particulier, une difficulté majeure du traitement provient du grand nombre de particules superposées qui doivent être différenciées avant la mesure de leur taille. Après segmentation, l'identification des particules a été essentiellement basée sur une technique de détection des coins, permettant ensuite une reconstruction du périmètre des cristaux. L'efficacité de la méthode a ensuite été évaluée par comparaison du traitement automatique avec celui effectué manuellement par un opérateur humain. Plus de 80% des particules d'OA en suspension ont été évaluées de façon satisfaisante, même les cristaux présentant une image floue on été identifiés, à condition que leurs coins soient intacts.

Abstract

The batch cooling crystallization of ammonium oxalate (AO) in water was investigated in order to design a dynamic model of the process in both pure and impure solvent. The solute concentration was measured using in situ ATR FTIR spectroscopy while the solid dispersed phase was monitored through in situ image acquisition, using an immersed CCD video probe. In order to evaluate the particle size distribution (PSD) an algorithm for the processing of video 2D images of AO crystals was developed. The algorithm is intended to enable reliable crystal size measurements; the specificity of the system under investigation being related to the acicular shape of AO crystals. In particular, a major difficulty arises from the many overlapping particles which have to be differentiated prior to their size measurement. After segmentation, the identification of particles was mostly based upon a refined method for the detection of corners followed by the reconstruction of the crystals perimeters. The efficiency of the method was evaluated through comparison between the automatic image processing measurements and measurements performed by a trained human operator. More than 80% of AO particles are satisfactorily detected in suspension, even fuzzy crystals, provided that their corners are unbroken.

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Mots-clés : Cristallisation industrielle, distribution de taille de particules, technologies analytiques de procédés (PAT), analyse d'images, contrôle des procédés.

Key-words : Industrial crystallization, Particle size distribution, Process Analytical Technologies (PAT), Image analysis, Process Control.

1. Introduction

Solution crystallization processes are widely used as industrial separation and purification unit operations, notably in the pharmaceutical industry where batch processes are expected to yield solids with desirable properties (e.g., ability to downstream processing, chemical purity, nice particle shape and size distribution, specific area, reduced fines content, etc.) In particular, as far as the pharmaceutical industry is concerned, the size and the shape of crystals are known to have considerable impact on the final properties of drugs (i.e. bioavailability, stability on storage, ease of processing, etc.)

In the pharmaceutical market where the increasing use of generic medicine leads to an obvious hard economical competition, the quality requirements for industrial crystallized products are becoming more and more demanding. The latter competition also results in the pressure imposed by both the international regulatory agencies and the consumers.

As far as measuring the Crystal Size Distribution (CSD) is concerned, it is well established that conventional monitoring techniques, such as Laser Diffraction (LD), Ultrasonic Attenuation Spectroscopy (UAS) or focused-beam reflectance measurement (FBRM), do not provide reliable in-line estimates. For example, major difficulties arise from the use of in situ laser diffraction techniques requiring highly diluted samples and rather "ideal" particles shapes. Ideal means here that the particles, in order to fit the theoretical models used to process LD measurements, should be as close as possible to spheres, and exhibit rather simple distributions (i.e. multimodal distributions are really difficult to analyze). The main disadvantage of UAS is that it requires a large set of accurate physical data related to the liquid and solid phases. And finally, the main disadvantage of FBRM is that it does not actually measures the CSD but the Chord Length Distribution (CLD) (Kermpkes et al., 2008, Hukkanen and Braatz., 2003).

This is why image analysis appears as a promising sensor for measuring the CSD. Should they be developed, efficient methods would have no major limitation in terms of particles shapes, refractive index, features of the size distribution, etc. As compared to other existing methods, the technique also offers the invaluable advantage that human operators have always the possibility of looking at the particles and evaluate, for example, possible changes or disturbances during the process.

However, in the field of crystallization monitoring, three major difficulties still make the development of image analysis difficult. Firstly, it is impossible today to clearly identify the crystal shapes and sizes in dense slurries. Secondly, to the best of our knowledge, no "universal" method exist. In practice, consequently, various specific processing methods have to be developed depending on every particular case (i.e., in terms of 2D and 3D shapes, size distribution and range, quality of recorded images, illumination, etc. Thirdly, due to the difficulty of mathematical and numerical image processing, the many problems raised by CSD measurements can be very complex and computer-time consuming, so that advanced hardware and software tools are required.

Following a previous study devoted to the characterization of rather spherical but fuzzy particles (i.e., CSD measurements of citric acid particles dispersed in water), the present work aims at measuring the size of oxalate ammonium particles. As shown in Fig.1b, in contradiction with the previous study, the particles exhibit very clear outlines and rather perfect acicular shapes but the difficulty lies here in the necessity of separating superimposed crystals.

2. Experimental setup

The experimental setup of the batch crystallization process of Ammonium Oxalate crystals was conducted in pure water (Gherras & Févotte 2011a, 2011b). Fig.1.a illustrates the materials and the imaging system of the experiment. The reactor is a 2L, double-jacketed, glass vessel provided by a condenser. The stirring device is a 3 blades, profiled pale, propeller (Mixell TT) driven by a motor at 300 rpm which is sufficient

to obtain a homogeneous suspension. The temperature of the crystallizer is controlled by a heating/cooling bath provided with an external Pt100 temperature sensor in a feedback control way.
The in situ imaging system consists of a probe (EZProbe sensor) developed at the university Lyon 1 (Presles et al. 2010) equipped with a CCD monochrome camera with resolution up to $4\mu m^2$ per square pixel, and 640×480 pixels per image. The video images are acquired by a frame grabber with a rate of 25 fps. Images of particles are formed using a transmitted light conducted within the probe by optical fibers from the light source.
Figure 1.b displays an example of in situ image of Ammonium Oxalate crystals obtained during the batch cooling experiments.

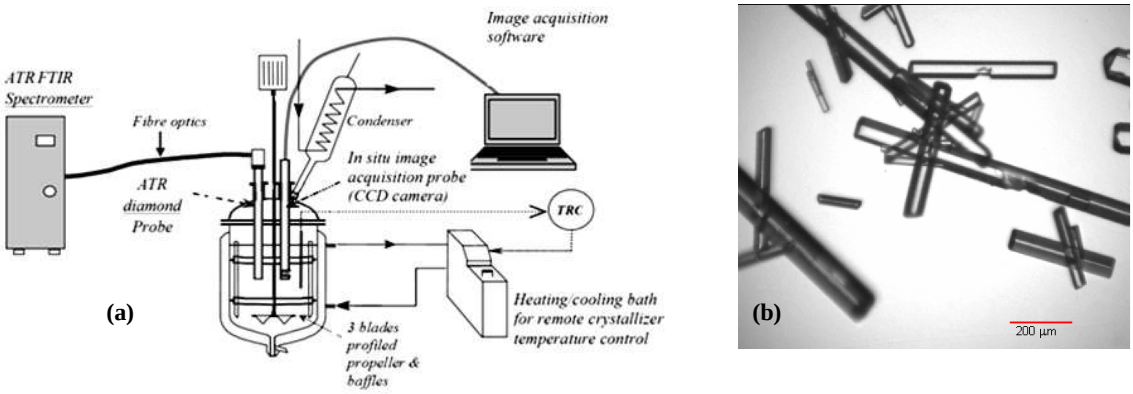

Figure 1. (a) Experimental setup of batch crystallization process. (b) Example of grey level image of Ammonium Oxalate crystals in pure water.

3. Image analysis method

A method based on the geometric properties of the particle shapes has been developed (Ahmad et al. 2011a, 2011b) to detect the overlapped rectangular and regular/irregular prismatic crystals by the assumption that each particle can be constructed from grouping three of their correspondent salient corners that belong to the same particle.

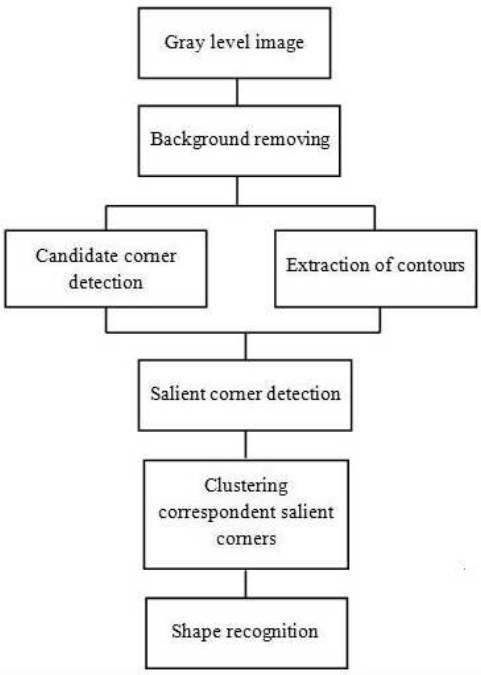

Figure 2. Schematic diagram of the image analysis based method

As displayed in Figure 2, the method is divided into two main steps involving the detection of salient corners from the gray scale image, and then recognizing the shape by clustering the correspondent salient corners that satisfy certain geometric conditions.
The software was developed in Matlab® and would clearly take less time after being rewritten in other specific real time languages. A computer simulation process has been developed in order to validate the method before experiments were implemented on the real images.

4. Experimental results

4.1 Segmentation results

The proposed method was applied on 150 video images acquired during a typical batch cooling crystallization operation of ammonium oxalate performed in water at different periods of crystals density and aggregation (low, intermediate and solids concentrations successively). Figure 3 shows successive images together with the results of the proposed processing. It should be noticed that every crystal sticking out the frame of pictures is withdrawn from the counting process as its size cannot obviously be estimated.

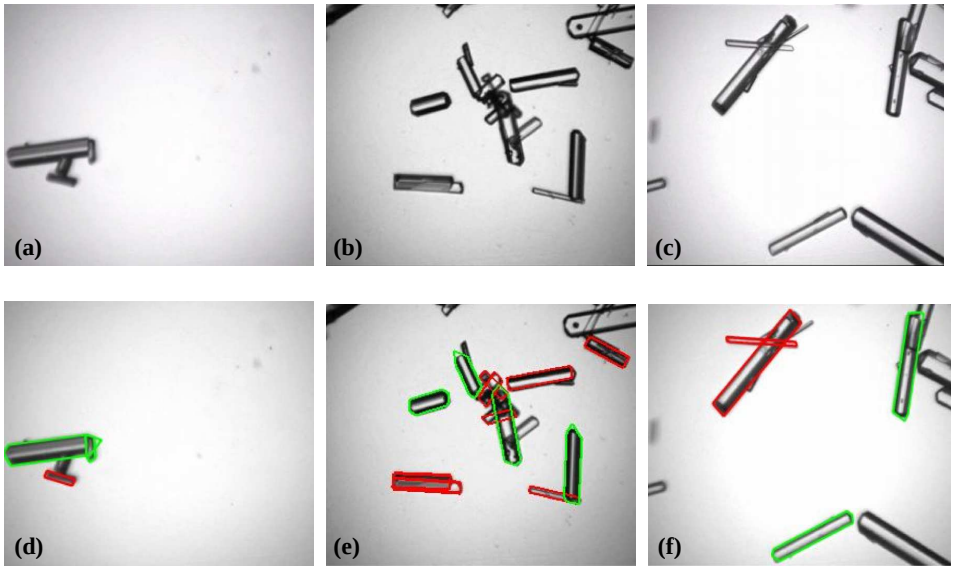

Figure 3. Examples of in situ images of ammonium oxalate crystals during crystallization experiment. (a) Real image acquired from the middle of the experiment. (b)& (c) Real images at the end of the experiment. (d), (e), (f) Results of the proposed method.

According to their shapes, the particles are classified into two categories: rectangles and regular/irregular prismatic particles. It is worth noting that he possibility of performing such sorting of the particle shapes is also a major advantage of the technique and is quite impossible with other marketed sensing devices. In figure 3, the boundaries of the recognized prismatic particles are marked by a green color and the rectangular ones are marked by a red color.

4.2 Particle size distribution measurements

Following the segmentation process, the particle size distributions are performed for three sets of video sequence images, with low, intermediate and high solids concentrations. Each set contains 50 images. Thus, 150 images were used to perform the size distribution. Firstly, the length and width of each detected crystal is calculated for all image sets and then the size distributions are evaluated by histogram method (Scott, 1979) for illustrating the frequency of each length and width parameters of the crystals during the experiment. Typical examples of the resulting histograms are displayed in Figure 4.

The results show that the particles have a tendency to exhibit a prismatic shape for high solids content, whereas smaller particles observed at the beginning of the crystallization process exhibit a more rectangular shape. The quantitative analysis of the crystals is very important for characterizing the flow properties, dissolution rate, agglomeration tendencies, mixing and demixing properties, filterability, etc (Allen, 2003).

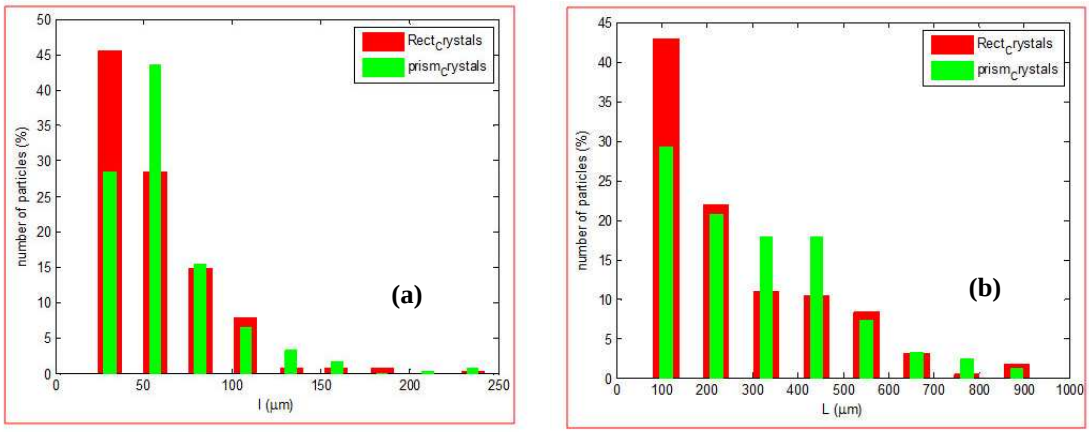

Figure 4. Particle length and width distributions. (a) Particle width distribution of prismatic and rectangular crystals (b) Particle length distribution of prismatic and rectangular crystals

4.3 Comparison with manual sizing

In order to validate the accuracy and the efficiency of the method, a quantitative comparison between automatic and manual sizing was performed. The cumulative distribution function (CDF) was estimated by both methods, as shown in figure 5. The normalized error was calculated for both length and width cumulative distributions:

$$Err = \sum \frac{|CDF_M - CDF_A|}{CDF_M} \tag{1}$$

where CDF_M and CDF_A are the cumulative distributions of manual and automatic sizing, respectively.

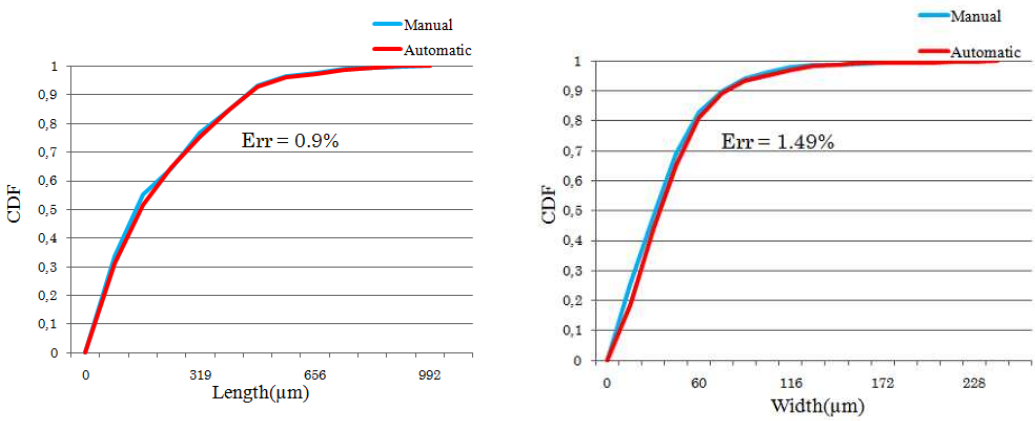

Figure 5. Comparison of cumulative distribution functions (CDF) of particles length and width for 150 in-situ images. (a) Comparison of particles width distributions. (b) Comparison of particles length distributions.

The results are quite satisfactory as the difference between the two estimated distribution remains very low (less than 2%). One can therefore consider that the proposed image analysis based method could be used for analyzing automatically the particle size distributions for monitoring industrial crystallization processes.

5. Conclusion

The problem raised by the monitoring of well-shaped acicular ammonium oxalate crystals generated in suspension through batch cooling crystallization was addressed in this paper. The batch cooling solution crystallization of ammonium oxalate in water was selected as a model-system. An algorithm was developed, that allowed computing the size distribution of crystals form image acquired in situ, using a immersed video sensor. A specific method was developed and satisfactorily validated through a comparison with estimates obtained by human visual expertise.

Two interesting features of the technique can be outlined: the method is shown to allow monitoring two different specific crystal shapes (rectangular and prismatic) and, more than 80% of the particles in suspension are successfully detected, which is quite satisfactory. However, prior to its possible use in real-time, a significant effort should now be focused on the reduction of the computation time required by the method.

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