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IDENTIFICATION OF PHARMACEUTICAL CRYSTALLIZATION PROCESSES

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Abstract: A key bottleneck in the production of pharmaceuticals is in the formation of crystals from solution. The control of the crystal size distribution can be critically important for efficient downstream operations such as filtration and drying, and product effectiveness (e.g., bioavailability, tablet stability). This paper provides an overview of recent developments in the identification of pharmaceutical crystallization processes. This includes descriptions of recent activities in sensor technologies, model identification, experimental design, and robustness analysis of pharmaceutical crystallization processes. *Copyright ©2002 IFAC*

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1. INTRODUCTION

A key bottleneck in the production of pharmaceuticals is in the formation of crystals from solution. For efficient downstream operations (such as filtration and drying) and product effectiveness (e.g., bioavailability, tablet stability), the control of the crystal size distribution can be critically important. Also important are the crystal purity and the crystal shape. The crystal size and shape affect the dissolution rate, which is important in most pharmaceutical applications. In the pharmaceutical industry, the relative impact of drug benefit versus adverse side effects can depend on the dissolution rate. Control of crystal size and shape can enable the optimization of the dissolution rate to maximize the benefit while minimizing the side effects. Poor control of crystal size and shape can result in unacceptably long filtration or drying times, or in extra processing steps, such as recrystallization or milling. Purity is especially important in the food and pharmaceutical industries, in which the crystals will be consumed.

Fig. 1. Photograph of paracetamol crystals taken from a batch crystallizer (paracetamol is the active ingredient in Tylenol).

Figure 1 shows the variability in crystal shape that can occur at a single time instance in a pharmaceutical crystallizer. This particular drug, paracetamol (also known as acetaminophen), can have three different crystal morphologies when grown from a paracetamol-water solution (Finnie *et al.*, 1999).

The fundamental driving force for crystallization from solution is the difference between the chemical potential of the supersaturated solution and

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that of the solid crystal face (Kim and Myerson, 1996; Mullin and Sohnel, 1977). It is common to simplify this by representing the nucleation and growth kinetics in terms of the supersaturation, which is the difference between the solute concentration and the saturated solute concentration. Supersaturation is typically created in pharmaceutical crystallizers by cooling and/or by adding a solvent for which the solute has a lower solubility.

The challenges in the processing of pharmaceutical crystals are significant. First, there are significant uncertainties associated with their kinetics. Part of the difficulty is that the kinetic parameters can be highly sensitive to small concentrations of contaminating chemicals, which can result in kinetic parameters that vary over time. Also, many pharmaceutical crystals are sufficiently fragile that the crystals break after formation, or the crystals can agglomerate or have erosion or other surface effects that are difficult to characterize. Another significant source of uncertainty in industrial crystallizers is associated with mixing. Although crystallization models usually assume perfect mixing, this assumption is rarely true for an industrial-scale crystallizer.

Crystallization processes are highly nonlinear, and are modeled by coupled nonlinear algebraic integro-partial differential equations. The very large number of crystals is most efficiently described by a distribution (e.g., see Figure 2). For the case of distribution in shape as well as overall size, there are at least three independent variables in the equations. Simulating these equations can be challenging because the crystal size distribution can be extremely sharp in practice, and can span many orders of magnitude in crystal length scale (0.01 nm to 200 μm) and time scale (20 μs to 200 min). The short time scales are especially relevant in impinging jet crystallizers, in which crystal nuclei are formed directly from solution under conditions of very high supersaturation.

Another challenge in crystallization is associated with sensor limitations. The states in a crystallizer include the temperature, the solution concentration, and the crystal size and shape distribution. The solution concentration must be measured very accurately to specify the nucleation and growth kinetics. Obtaining an accurate measurement of the full crystal size distribution (CSD) is even more challenging. Hence it is desirable to estimate the states from the noisy measurements that are available.

This paper reviews efforts towards the control of pharmaceutical crystallization processes. A description of the current status of sensor technologies is followed by a description of an approach for model identification and experimental design.

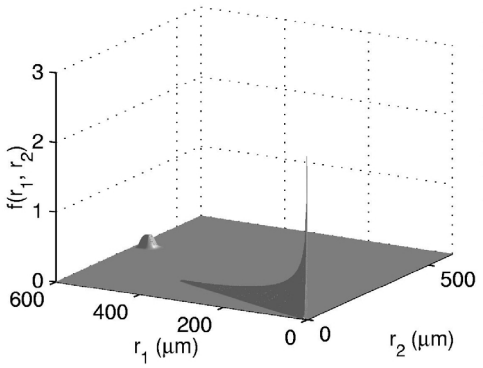

Fig. 2. The crystal size distribution for prism-like crystals with two characteristic length scales (r_1 and r_2) and nucleation and growth kinetics identified from laboratory data (Braatz *et al.*, 2002).

Next, recent advances are discussed in the robustness analysis of nonlinear distributed parameter systems, focusing on applications to crystallization processes.

2. SENSOR TECHNOLOGIES

Measurements of both the solution concentration and the crystal size distribution are necessary for effective estimation and control.

2.1 *Solution Concentration Measurement*

The nucleation and growth rates are strongly dependent on the solution concentration, making its measurement necessary for estimating kinetic parameters and highly useful for feedback control. A significant advantage of attenuated total reflection (ATR) Fourier transform infrared (FTIR) spectroscopy over most other methods for solution concentration measurement is the ability to provide simultaneous measurement of multiple chemical species. The feasibility of ATR-FTIR spectroscopy for the *in situ* measurement of solution concentration in dense crystal slurries has been demonstrated (Dunuwila *et al.*, 1994; Dunuwila and Berglund, 1997; Lewiner *et al.*, 1999; Lewiner *et al.*, 2001). In ATR-FTIR spectroscopy, the infrared spectrum is characteristic of the vibrational structure of the substance in immediate contact with the ATR immersion probe. The crystal of the ATR probe is selected so that the depth of penetration of the infrared energy field into the solution is smaller than the liquid phase barrier between the probe and solid crystal particles. Hence when the ATR probe is inserted into a crystal slurry, the substance in immediate contact with the probe will be the liquid solution of the slurry with negligible interference from the solid crystals.

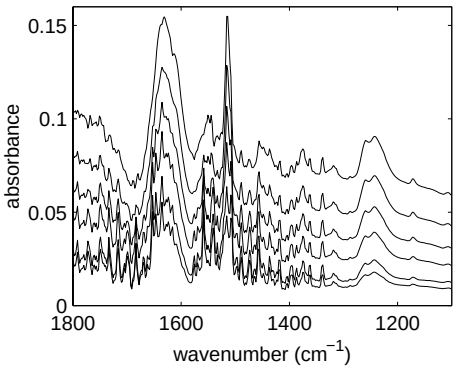

Fig. 3. ATR-FTIR spectra for paracetamol-water solution at different concentrations and temperature, in ascending order: 0.010 g/g water (33°C), 0.015 g/g water (38°C), 0.020 g/g water (43°C), 0.025 g/g water (48°C), 0.030 g/g water (53°C), and 0.035 g/g water (58°C).

The combination of ATR-FTIR spectroscopy with advanced chemometrics analysis can measure solution concentrations with accuracy as high as ±0.1 wt% in dense crystal slurries (Togkalidou *et al.*, 2000; Togkalidou *et al.*, 2001*b*). The absorbances measured in the mid-infrared range using ATR-FTIR are usually linearly related to the solution concentration, so nonlinear chemometrics analysis such as used in near-infrared spectroscopy (Amrhein *et al.*, 1996) is usually unnecessary. The ATR-FTIR approach has been applied to a number of complex pharmaceutical compounds in academic and industrial laboratories. This includes applications to several polymorphic crystal systems with multiple solvents and solutes at Merck (Togkalidou *et al.*, 2002). Figures 3 and 4 show the ATR-FTIR spectra and solubility curve for the paracetamol-water system (Fujiwara *et al.*, 2002), which is an especially challenging system due to the relatively low solubility of paracetamol in water. The reliability and consistency of this approach are expected to result in even more applications to pharmaceutical crystallization processes in future years, both in academia and industry.

2.2 *On-line Crystal Size Distribution Measurement*

Our laboratory crystallizer is equipped with a laser backscattering device and a video microscope which are used to measure the crystal size distribution *in situ*. A significant advantage of this approach is the ability to take measurements in slurries with high crystal solids density, as occurs in operations typical of the pharmaceutical industries.

The laser backscattering approach is based on inserting a probe directly in the crystallizer, focusing a laser beam forward through a window in the

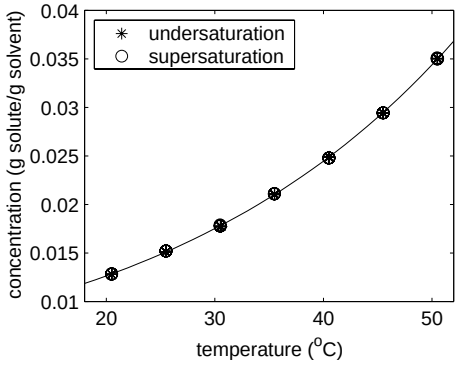

Fig. 4. Solubility curve for paracetamol in water constructed from ATR-FTIR spectroscopy and advanced chemometrics analysis.

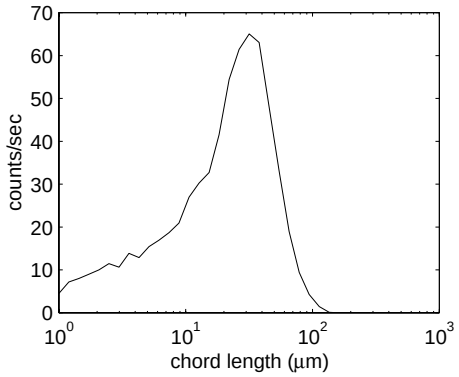

Fig. 5. Chord length distribution of paracetamol crystals in water collected from a Lasentec FBRM M400L.

probe tip, and collecting the laser light scattered back to the probe. The updated version of the instrument, the Lasentec *Focused Beam Reflectance Measurement* (FBRM), has been applied to numerous pharmaceutical crystallizers (Togkalidou *et al.*, 2001*c*).

Like any laser-based method applied to a crystal slurry, a transformation is required to relate the collected laser light to the crystal size distribution. The FBRM instrument measures the chord length distribution (e.g., see Figure 5) as the laser beam emitted from the sensor randomly crosses two edges of a particle, with this distance being the chord length. There have been efforts to relate the chord length distribution to the crystal size distribution, both by the Lasentec company and by some independent researchers (Ruf *et al.*, 2000; Tadayyon and Rohani, 1998). This relationship is dependent on a large number of operating variables, whose effects are not easy to model theoretically, especially for dense crystal slurries (Monnier *et al.*, 1996; Monnier *et al.*, 1997). Chemometrics methods have been used to relate the chord length distribution to the crystal size distribution (Togkalidou *et al.*, 2001*a*) and to other variables such as the filtration resistance (Johnson *et al.*, 1997; Togkalidou *et al.*, 2001*c*).

A weakness of the laser backscattering and related laser-based sensors is that the distribution of crystal shape cannot be directly determined. For example, a collection of rod-like crystals are characterized mathematically by a two-dimensional distribution (one dimension being the length, and the other dimension being the breadth), but the light scattering instruments only provide one-dimensional distributions. It is impossible to uniquely determine a two-dimensional distribution from a one-dimensional distribution. The shape information is averaged out to obtain a one-dimensional distribution.

An alternative method for measuring the crystal size distribution is through periodic sampling, video microscopy, and image analysis (Puel *et al.*, 1997; Rawlings and Patience, 1999). Sampling can be problematic in an industrial environment. A commercial instrument that has become available is the Lasentec Particle and Vision Measurement (PVM) system, in which images of crystals in solution are obtained using a probe inserted directly into the dense crystal slurry. This video microscope can collect 10-30 images a second, providing two-dimensional snapshots of the crystals in real time. On-line video microscopy can image crystals as small as 5-15 microns (Pacek *et al.*, 1994), not as small as obtained by laser scattering instruments. However, the quality of the images for most dense crystal slurries limits the ability of imaging software to automatically identify individual particles and quantify the characteristics of these particles (e.g., maximum axis, minimum axis, aspect ratio). An advantage of on-line video microscopy is the direct observation of the crystals, which allows shape information to be obtained. Also, the PVM in particular is a rugged instrument suitable for use in industrial applications. The main use of on-line video microscopy today is for qualitative troubleshooting, with only some researchers using the images for quantitative prediction (Baier and Widmer, 2000). Recently, the on-line estimation of characteristics of the crystal shape distribution has been demonstrated, using a combination of the PVM, the FBRM, and robust chemometrics (Togkalidou *et al.*, 2001*a*). Given the importance of crystal shape in pharmaceutical applications, and that progress becomes easier as computers continue to increase in speed, the accuracy of such predictions can be expected to improve in future years.

3. ITERATIVE MODEL IDENTIFICATION AND EXPERIMENTAL DESIGN

In the past two years iterative model identification and experimental design has been applied to several crystallization processes, including for

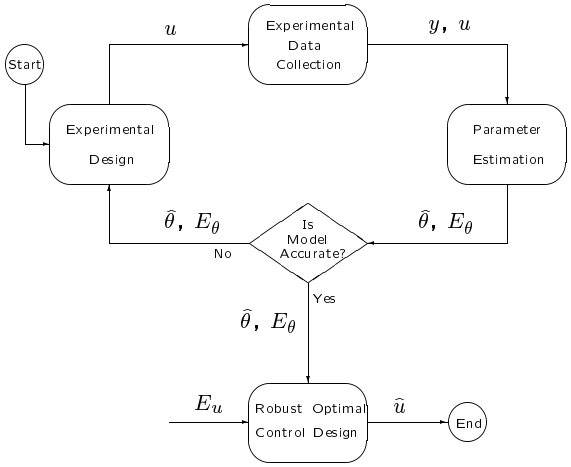

Fig. 6. Iterative model identification and experimental design

crystals with different rates along different growth axes (Gunawan *et al.*, 2002). Our approach is similar to approaches used for linear lumped parameter systems, except generalized to the nonlinear distributed parameter equations needed to model pharmaceutical crystallizers (see Figure 6). A model selection step (not shown in the figure) is used to select among different model structures, which correspond to different nucleation and/or growth mechanisms.

The overall closed loop crystal product quality can be used as the objective of the experimental design (Ma and Braatz, 2002), instead of the commonly used D-optimal experimental design objective (Box *et al.*, 1978; Miller and Rawlings, 1994), which focuses on the uncertainty in the model parameters. Experimental design variables that have been optimized between each batch experiment include the temperature profile, antisolvent addition rates, and various characteristics of the seed distribution (Chung *et al.*, 2000). Accurate model parameters are typically obtained with as few as four batch crystallization experiments. A typical comparison between model predictions and measurements are shown in Figure 7, where the moments μ_{10} and μ_{01} are closely related to the average length and width of rod-like crystals in the slurry. The moments were computed by weighted normalization of the FBRM data (Tadayyon and Rohani, 1998). We have applied this approach to several pharmaceutical crystallization processes, including to the crystallization of paracetamol (Fujiwara *et al.*, 2002). It is expected that it will become increasingly common for pharmaceutical companies to identify models for use in scaling up the crystallization process.

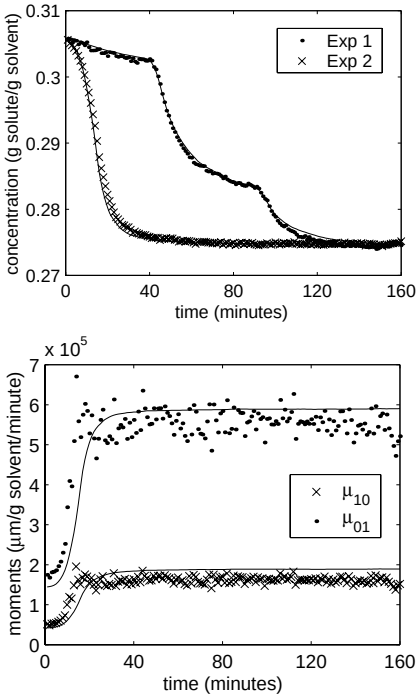

Fig. 7. (top) The measured solution concentrations for two experiments and (bottom) the measured moments (μ_{10} and μ_{01}) in the second experiment along with the model predictions (solid lines).

4. ROBUSTNESS ANALYSIS

Crystallization processes can have a very high sensitivity to model parameter variations (Ma *et al.*, 1999*a*). The iterative model identification and experimental design procedure relies heavily on the ability to quantify the effect of model uncertainties on the crystal product quality. We developed an approach to quantify the impact of such variations on the product quality without exhaustive simulation of all possible process conditions (Ma *et al.*, 1999*b*; Ma and Braatz, 2001). The approach is applicable to finite-time nonlinear distributed parameter systems. The knowledge of the worst-case model parameters are used to determine where experimental effort should be focused to improve model accuracy.

Robustness analysis with regard to control implementation uncertainties can guide the selection of the control instrumentation, by determining where high precision sensing and actuation are required. The computation of the worst-case external disturbances determines which disturbances significantly affect the product quality. This robustness analysis has been applied to several batch crystallizers, both in simulations and in experiments (Ma *et al.*, 1999*a*; Ma and Braatz, 2002). Robustness estimates are provided with reasonable computational requirements.

5. CONCLUSION

The pharmaceuticals industry is continuing to grow faster than most other industries, and most pharmaceuticals must undergo multiple crystallization steps before arriving at the final product. Advances in measurement technologies are removing the main bottleneck that limited progress in the 1970s-1980s.

Model identification and experimental design algorithms are being applied to pharmaceutical crystallization processes. Pharmaceutical crystallization processes have all the characteristics that make an interesting control problem—partial differential equations, nonlinear dynamics, significant uncertainties, unmeasured state variables, significant disturbances, sensor noise, etc. Crystallization processes pose a rich array of control problems that are expected to keep control engineers engaged for some time.

6. ACKNOWLEDGMENTS

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