Applications of Process Analytical Technology to Crystallization Processes [1]

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Abstract

Crystallizations of pharmaceutical active ingredients, particularly those that posses multiple polymorphic forms, are among the most critical and least understood pharmaceutical manufacturing processes. Many process and product failures can be traced to a poor understanding and control of crystallization processes. The Food and Drug Administration's Process Analytical Technology (PAT) initiative is a collaborative effort with industry to introduce new and efficient manufacturing technologies into the pharmaceutical industry. Process Analytical Technologies are systems for design, analysis, and control of manufacturing processes. They aim to assure high quality through timely measurements of critical quality and performance attributes of raw materials, in-process materials, and final products. Implementation of PAT involves scientifically based process design and optimization, appropriate sensor technologies, statistical and information tools (chemometrics), and feedback process control strategies working together to produce quality products. This review introduces the concept of Process Analytical Technology and discusses its application to crystallization processes through review of several case studies. A variety of in situ analytical methods combined with chemometric tools for analysis of multivariate process information provide a basis for future improvements in modeling, simulation, and control of crystallization processes.

Key words: Process Analytical Technology, polymorphism, crystallization, in situ,

Contents

1 Introduction

Historically, pharmaceutical production involves the manufacture of the finished product using batch processes, followed by laboratory testing and analysis to verify its quality. This approach has been successful in providing quality pharmaceuticals to the public. Modern process engineering and manufacturing science achieves high levels of quality through the use of online process monitoring and control. Adoption of these methods offer the pharmaceutical industry the opportunity to lower manufacturing cycle times and end-product

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variability, which can result in a shorter time-to-market and a reduced likelihood of product failures. The Food and Drug Administration's Process Analytical Technology (PAT) initiative is a collaborative effort with industry to facilitate the introduction of new and efficient manufacturing technologies into the pharmaceutical industry[1].

Process Analytical Technologies are systems for design, analysis, and control of manufacturing processes, based on timely measurements of critical quality and performance attributes of raw and in-process materials and products, to assure high quality of products at the completion of manufacturing. PAT includes scientifically based process design that identifies key measures of product quality and the critical process variables that affect them, appropriate measurement devices, statistical and information technology tools, and feedback process control strategies that work together to ensure production of final products with the desired quality.

There are many current tools and measurement devices that enable scientific pharmaceutical development, manufacture, and quality assurance. When these tools are used within a PAT system, the information they collect can be used to facilitate process understanding, develop risk-mitigation strategies, achieve continuous improvement, and share information and knowledge. In the PAT framework, these tools can be categorized as:

- Multivariate data acquisition and analysis tools
- Modern process analyzers or process analytical chemistry tools
- Endpoint monitoring and process control tools
- Knowledge management tools

An appropriate combination of some, or all, of these tools may be applicable to a single-unit operation, or to an entire manufacturing process and its quality assurance.

A goal of the PAT initiative is to encourage the application of process engineering expertise in pharmaceutical manufacturing and regulatory assessment. The results of PAT are a depth of process knowledge leading to optimized operation with control systems that ensure quality outcomes. Models analyzing the information obtained from process measurements provide a framework for representing process knowledge. With PAT these measurements and modeling can be performed in real-time and on-line and thus be used for process control. Quality control using PAT is based on in-process electronic data rather than laboratory testing on a subset of the final product, thus essentially the entire production run may be evaluated for quality control purposes. PAT thus holds the promise of improving efficiency and quality.

Some of the potential benefits of pharmaceutical manufacturing based on PAT include:

- enhancing process understanding and reducing process failures
- ensuring quality through optimal design, continuous monitoring, and feedback control
- reducing cycle time to improve manufacturing efficiency
- identifying the root causes of process deviations
- basing regulatory scrutiny on process knowledge and scientifically based risk assessment

The present article is an introduction to the application of PAT to crystallization processes. It will describe how some of the important PAT concepts such as identification of critical variables, real time process monitoring, process control, and chemometrics are applied to crystallization. Through several case studies we will attempt to illustrate PAT's utility to crystallization processes, especially those involving crystal polymorphism, in the pharmaceutical industry.

2 Applying Process Analytical Technology to Crystallization

Traditionally, pharmaceutical crystallization processes have been developed empirically; thus there is much advantage to be gained in applying PAT to these systems. We will describe how aspects of PAT including the identification of critical variables, sensor technologies to observe these variables, chemometrics tools to manage and interpret data, and process control schemes are applied to crystallization.

2.1 Critical Variables in Crystallization Processes

The main measures of the quality of the outcome of a crystallization process are the crystal size distribution, crystal shape, and polymorphic form. The size and shape of the crystals formed will have a strong effect on the processability, with smaller particles and non-spherical particles being more difficult to flow, filter, and process. Fine particles have much higher surface area and can collect impurities at the surface. The solubility of different polymorphic forms can differ and dissolution rates will also depend on crystal size and polymorphic form. The critical variables that affect the final quality can be divided into thermodynamic and process variables.

The influence of thermodynamics on the outcome of a crystallization process can be summarized through a phase diagram like that in Fig. 1. On this plot of solute concentration against temperature, the curves C_1 and C_2 correspond to the solubility of two possible polymorphic forms. Above temperature T_1,

form I has the lower solubility and is the more thermodynamically favored (it has the lower free energy). Below T_1, form II is the more stable solid phase.

Full characterization of the phase diagram identifies the most stable crystal form at any operating condition. Fig. 2 illustrates the relative free energy at point A in Fig. 1; the free energy of the solution is the highest followed by form II and then form I. At temperatures below T_1 the relative stability of forms I and II will change. Enantiotropic polymorphs have a temperature, like T_1, where the relative stability of two forms changes. In monotropic systems the relative stability of the two forms is the same at all temperatures. However the relative stability does not determine the rate of formation or the rate of growth of the different polymorphic forms.

The key thermodynamic variables that affect the kinetics of nucleation and growth are the supersaturation, S, and the interfacial tension, γ, between the solid and the liquid. The supersaturation is

$$S = \frac{C - C^*}{C^*}, \tag{1}$$

where C is concentration at a point on the phase diagram and C^* is the solubility at the same temperature. The supersaturation is a measure of the thermodynamic driving force toward a solid phase. We should recognize that the true thermodynamic driving force is the difference in chemical potential between solution and crystal[2].

$$\Delta\mu = \mu_s - \mu_c = RT \ln \frac{\gamma_a C}{\gamma_a^* C^*}. \tag{2}$$

This chemical potential difference is only equivalent to S when the deviation from an ideal solution (represented by activity coefficients, γ_a) is negligible and S is small,

$$\frac{\Delta\mu}{RT} = \ln \frac{C}{C^*} = \ln(1 + S) \approx S. \tag{3}$$

At point A on the diagram both the supersaturation and interfacial tension are different for the two possible polymorphic forms. The important question is from a liquid at point A, what form, I or II, will be observed? This will be determined by the nucleation and growth rates of each polymorphic form. In crystallization processes there are two mechanisms for nucleation: homogeneous and heterogeneous. In homogeneous nucleation spontaneous fluctuations in density in the liquid allow the formation of a more stable solid phase. Heterogeneous nucleation is triggered by impurities or surfaces in contact with the

liquid. For most industrial processes heterogeneous nucleation is the dominant mechanism with the rate of nucleation given by[3]

$$J = N_0 \nu \exp\left(\frac{-\Delta G^* \Phi}{kT}\right), \tag{4}$$

where the free energy barrier to nucleation of a sphere is

$$\Delta G^* = \frac{16\pi v^2 \gamma^3}{3(\Delta\mu)^2}. \tag{5}$$

N_0 is the number density of solute molecules, v is the molar volume of solute molecules, Φ is a function of the contact angle between the solvent and the impurity or surface triggering the nucleation, and ν is the transport rate of solute molecules to the interface. We can also consider the nucleation rate as depending on an empirical constant A that contains all of the process condition variation (such as mixing rate, solvent viscosity, and impurity effects in Φ) and the remaining thermodynamic factors

$$J = N_0 A \exp\left(\frac{-\Delta G^*}{kT}\right). \tag{6}$$

Homogeneous nucleation has the same dependence on the free energy barrier but a different prefactor that has no dependence on Φ.

To compare nucleation rates of two polymorphic forms we examine the two free energy barriers:

$$\Delta G_1^* = \frac{16\pi v^2 \gamma_1^3}{3S_1^2} \qquad \Delta G_2^* = \frac{16\pi v^2 \gamma_2^3}{3S_2^2} \tag{7}$$

At point A, $S_1 > S_2$ favors the stable polymorph while $\gamma_1 > \gamma_2$ favors the unstable polymorph. As these two factors have opposite effects on the nucleation rate the competition between the two will determine which polymorph nucleates faster.

The rate of growth of different polymorphic forms also depends on a similar combination of kinetic and thermodynamic variables[4]

$$R = k\frac{(\Delta\mu)^n}{\gamma} \tag{8}$$

where k is a constant that depends on process variables and growth mechanism. The presence of γ shows that different crystal faces can have different growth rates that will lead to non-spherical crystals.

As represented in Ostwald's law of stages, the usual situation is that the least stable polymorph is formed first. This suggests that the interfacial tension is the more important variable. Whether the favored polymorph is based on faster nucleation or faster growth cannot be easily distinguished. The role of interfacial tension is indicated by the fact the changing the solvent can alter which polymorph is formed. Interfacial tension of crystalline solids also differs between crystal faces suggesting that surface-active agents that bind preferentially to a particular face will alter the rate of formation of particular polymorphs.

The key aspects of a crystallization process are the rates of nucleation and growth of the crystals. The connection of these rates to the thermodynamic variables is well established. However both of these rates contain factors that depend on the flow, mixing, heat and mass transfer, and uniformity of a process situation in an unknown manner. Impurities and additives can have a significant effect on these rates by altering the interfacial energy of particular crystal faces. Especially with respect to the process variables and role of solvent, impurities, and additives the development of models capable of connecting measurement to final process outcomes is still a topic of current research[4,5].

2.2 Sensor Technologies for Crystallization Processes

Process analytical technology can involve application of continuous monitoring and control of industrial processes so that they adjust themselves to reach the desired or optimum states. This requires sensor technologies that are able to measure both indications of product quality and critical process variables.

We can identify several locations for process measurement:

- off-line: analysis laboratory at separate site
- at-line: analysis laboratory at manufacturing site
- on-line: measurements on a diverted sample stream which may be returned to the process after measurement
- in-line: integrated real-time measurement without sampling, but the process stream may be disturbed (for example, a probe may be inserted).
- non-invasive: integrated real-time measurement where the sensor is not in contact with the material and the process stream is not disturbed

Problems with off-line and at-line measurements include time delays for analysis, statistical sampling errors, where the sample analyzed is not representative, and physical sampling errors, in which the process of sampling changes the material. Thus non-invasive sensors are the most desirable technology. Recent scientific advances in the area of process analytical chemistry have pro-

vided many measurement options. Among the instrumental techniques that are promising and have gained prominence are NIR, Raman and chemical imaging technology. More details on the application of these technologies are found in recent review articles[6,7]. Many of these tools have been utilized in other chemical industries; therefore the pharmaceutical industry can leverage this experience with emerging technology to streamline their processes and manufacturing operations[8].

To gain the full benefit of PAT in crystallization processes, sensors that can measure key process variables such as supersaturation and desired quality endpoints such as size, shape, and polymorphic form are required. Recent advances have provided methods that can address many of these needs [9].

2.2.1 Supersaturation

There are non-invasive methods that can determine supersaturation by inferring solution concentrations from measured spectra. Attenuated Total Reflectance-Fourier Transform Infrared (ATR-FTIR) spectroscopy measures spectra in the mid infrared range. Compared to near infrared spectra, these spectra show greater chemical selectivity. The reflectance sampling allows this technique to be used for solids in their native state without any sample preparation and be applied in situ to processes. Although ATR-FTIR has been used to measure polymorphic form offline[10,11], its main in-line process application has been to the solution phase and not the solid phase as it measures the properties of the material in direct contact with the probe[12]. After calibration using chemometrics methods such as partial least squares, this technique can provide information about liquid phase concentrations and thus the supersaturations non-invasively, even in multicomponent mixtures with an example given in Fig. 3[13,14]. NIR methods can also be used to measure solution concentration[15].

2.2.2 Particle Size

Traditional methods for determining a particle size distribution, such as dynamic light scattering, require removal of a sample from the process. However, there are several methods that have the potential to characterize the particle size distributions in situ. These include diffusing wave spectroscopy (DWS)[16], turbidity[17], and frequency-domain photon migration (FDPM)[18] that rely on the multiple scattering of light (useful for any non-transparent suspension), methods that correct for multiple scattering (cross-correlation dynamic light scattering)[19], and methods that use time variance of reflectance to measure a chord length distribution (Focused Beam Reflectance Measurement or FBRM)[20]. Other physical properties that can be related to particle

size include acoustic attenuation of sound waves (signal is proportional to the density difference between particles and solvent)[21], electroacoustic effects[22], and spectroscopic methods such as NIR that are sensitive to particle size and chemical composition[23].

Essentially all indirect measurements of particle size measure a signal that is an integration of a size dependent weighting function over the particle size distribution. A reported particle size distribution only results from solution of an inverse problem to find the optimal distribution. Alternatively the result of the measurement can be considered as a fingerprint of a particular size distribution. For online monitoring in a process, this level of accuracy maybe sufficient as the measurement can be compared with that of a desired state through a calibration process. Chemometric methods can be employed to build correlations of signal with process conditions or outcomes. Where direct imaging of the process is possible, the direct determination of a size distribution is preferable.

2.2.3 Particle Shape

Essentially the only way to obtain complete information about the particle shape is by direct observation. Currently there have been demonstrations of in process video to provide online assessment of particle shape. These techniques require complex image analysis to translate two-dimensional images into a quantitative measure of the shape. Image analysis is limited to particles large enough to be visualized and in-process observation is limited to the surface if the suspension does not allow penetration of light. An example commercial implementation is Lasentec's PVM products[20]. Most of the techniques for particle size analysis provide a signal that depends on particle shape, but there are no current methods to invert that signal to determine the shape from the signal. Again these methods could be used in fingerprint mode or with chemometric analysis to develop a correlation with desired or undesired process outcomes.

2.2.4 Polymorphic Form

A number of methods are currently employed for characterizing pharmaceutical solid polymorphs. The definitive evidence for the existence of polymorphism is via the demonstration of a nonequivalent crystal structure by single crystal X-ray diffraction. Other methods including X-ray powder diffraction (XRPD), microscopy, thermal analysis (e.g., differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), hot-stage microscopy), and spectroscopy (e.g., IR, Raman, solid state NMR) are used for further characterization and for routine off-line testing of polymorphic form. Recent advances

in instrumentation; particularly those in vibrational spectroscopy and X-ray diffraction has made it possible to monitor kinetic processes of polymorphic systems in real-time.

Raman and near-infrared spectroscopy (NIR) measure fundamental vibrational modes and these techniques can be used to provide distinguishing fingerprints associated with each polymorphic form[24]. These spectroscopic techniques complement one another with Raman measuring vibrational modes that change in polarizability and NIR measuring vibrational modes that change in dipole moment. A distinguishing feature arising from the complementary nature of these two spectroscopic techniques derives from the differing intensities associated with the water vibrational peak(s). While in infrared spectroscopy, water produces a very intense absorption band often obscuring the other peaks of interest, in Raman spectroscopy, water is a poor scatterer resulting in a weak signal that is easily subtracted from the spectrum. For this reason, Raman is often used advantageously when monitoring aqueous processes. Nonetheless, both Raman and near-IR have been used to monitor polymorphic transformations during slurry turnover of a crystallization solution. In both of these instances, the vibrational spectra were obtained by interfacing the spectrometer with a fiber optic immersion probe inserted into the reactor vessel (Fig. 4). Linear regression or principal component analysis were used to deconvolute these spectra from which the level of each polymorphic form in real-time were determined.

Although Raman and NIR spectroscopies can be used to provide a wealth of information on polymorphic form, vibrational spectroscopy does not provide information on crystal structure directly. For vibrational spectroscopy, the observations on crystal form must be first "qualified" by X-ray diffraction. Recent advances in X-ray diffraction have enabled investigators to monitor polymorphs in crystallization both "directly" and in real time. Energy-dispersive X-ray diffraction and scattering using high-energy synchrotron radiation has enabled investigators to monitor polymorphs in crystallization slurries, including TNT[25], glutamic acid and citric acid[26]. The BedeMonitor^{TM}is a recently developed instrument for real time X-ray diffraction and does not require a synchrotron X-ray source. This commercially available instrument utilizes a high intensity X-ray source and a linear detector to collect a wide 2-theta range simultaneously. On-line measurement of a crystallization process is achieved by recirculating a sample of the crystallization slurry through a specially designed and thermally regulated flow cell, through to the X-ray measurement zone and back to the crystallizing vessel as in Fig. 5. In this manner XRPD data can be collected from the crystallization process without disturbing the conditions of the crystallization[27].

Traditionally automated process control has not been a major concern in a pharmaceutical manufacturing environment dominated by small batch processes. Process adjustment or improvements are difficult for a validated and approved process.

In the chemical industries, process control is an essential part of the design and operation. A control scheme must actively keep a process operating within specification; the safety and economic impact of an out of control process are unacceptable. Almost all chemical processes involve some sort of feedback control with much current interest in model predictive control (MPC) that integrates process knowledge into the control plan to provide an optimal control strategy[29]. Also of current interest in the engineering community is Multivariate Statistical Process Control(MSPC)[30,31]. Traditional process control monitored one variable at a time, but advances in sensor technology make it possible to measure multiple process and quality variables at once. Through the use of chemometrics methods such as PCA or PLS, multivariate data is reduced in dimension and correlated with final product quality. This information can then be used for control or fault detection. A recent example illustrates the application of MSPC to a batch polymerization process[31].

As we saw in section 2.1 the location on the phase diagram sets the supersaturation and affects both nucleation rate of new crystals and the growth rate of the existing crystal, but a process does not operate at a fixed position on the phase diagram. As a batch process proceeds, crystallization of solid causes the liquid concentration to change with time.

In most processes the temperature is not dropped immediately to the final value because of concern about the supersaturation. If the supersaturation is too large, unstable polymorphs become more likely and the nucleation rate increases which favors the formation of smaller crystals and a broader size distribution. The metastable line in Fig. 6 shows the approximate supersaturation where nucleation will begin at a significant rate. Some supersaturation is necessary to cause crystallization to commence and to avoid the economic cost of longer process times. It is also common to avoid nucleation by seeding the liquid with crystals of the desired polymorphic form, which will then grow[32].

Application of this method to polymorph control is shown in Fig. 7 where path 1 enters into a region where a less stable polymorph could possibly form. ATR-FTIR provides process monitoring that could be used along with control of the temperature to avoid the region of the phase diagram where formation of an undesired polymorph is possible.

The rate of cooling along this path is also an important process variable. Over time the crystals will continue to grow so the length of the process affects the maximum size of the crystals. Also there can be interconversion of polymorphic forms from the less stable to more stable form. The rate of interconversion depends on both the thermodynamics (supersaturation and temperature) as well as process variables. Process variables that can affect the quality of the final product are primarily related to the mixing and fluid mechanics of the process, which affects the rates of all growth processes occurring. We know the least about the effect of these variables and they are also the ones that most complicate the scale-up of crystallization processes.

There are several possible control strategies that have been applied to crystallization processes[33]. In the most common approach, a fixed path in the temperature and concentration phase diagram is selected based on process knowledge. Its drawback is that because it is not adjusted during the process it cannot respond to unexpected events. Any fluctuation, for example a temperature spike or mixing disturbance can lead to an out of specification batch. A second control strategy includes an online measurement of a process stopping point. Examples include continuing mixing until the mean particle size increases to the target value or until there is a polymorph interconversion. This type of control allows recovery from unforeseen events and can ensure that a batch meets specification. One drawback to this strategy is if you wait you are not guaranteed to reach the specification. Finally a third approach which most fully applies the PAT vision is to have an active control scheme that changes process conditions based on measurements to achieve the desired quality endpoint.

2.4 Chemometrics

Chemometrics is defined as the use of multivariate data analysis and mathematical tools to extract information from chemical data. Modern in-line or on-line sensors are capable of collecting huge amounts of data from chemical processes. The application or development of chemometric tools to this wealth of process data is termed "process chemometrics" and seeks to provide additional insights into the chemical process through monitoring, modeling, and control[9]. Process chemometrics has matured and gained acceptance within chemical process modeling, simulation, and control. There is no doubt that process chemometrics will ultimately be adopted and utilized in pharmaceutical manufacturing processes.

Chemometrics tools are useful in both the design stage of crystallization processes when experimental design methods aid in the optimization of the many operating variables and in the interpretation of the multivariate data collected

by process sensors.

2.4.1 Chemometric Modeling

Most chemometric tools derive a mathematical relationship between various properties and activities of a chemical (or combination of chemicals). A typical approach is to clearly define a property of interest (e.g., crystal size distribution) and then create a list of contributing variables likely to affect that property (e.g., solvent, degree of supersaturation etc.). The values of these variables are generally obtained by doing experiments.

Next a training set must be selected. This is a set of conditions for which the desired responses as well as the contributing variables are well quantified. The training set serves two important purposes. First, it establishes the chemical space in which we can work. For example, if we use degree of supersaturation as one of our contributing variables, then the degree of supersaturation in our training set provide an allowable range for conditions being tested. Conditions falling outside our chemical space may fail to be adequately modeled. Second, the training set provides the data upon which the model is built.

The final step in building a chemometric model is to use a multivariate regression method to establish the needed correlation between the desired property and the measured variables. Current methods include multiple linear regression (MLR), principle component regression (PCR), and partial least squares(PLS)[34,35]. There are numerous software packages that employ these and other methods. Although non-linear versions of these techniques are increasingly available[36,37], the usual implementations of these methods are generally linear in scope.

Before a chemometric model is used, it must be validated. One method of validating such a model is to reserve a randomly chosen portion of the training set from model development, and determine how well the model functions on the omitted samples. A popular method is "leave-one-out" cross validation which omits only one test sample, uses the rest to create the model, and tests the one remaining sample and then repeats for each sample separately. A model that frequently yields erroneous output may be the result of insufficient input. Then we must consider whether we have overlooked factors that contribute to the property being studied. We may need to consider variables that seem only marginally related to the property of interest. The magic of chemometric techniques is that they frequently discover hidden relationships between contributing factors and corresponding variables.

After a model has been validated, it may be used to examine the set of unknowns. It is assumed that each unknown falls within the chemical space defined by the test set, and that each contributing variable can readily be

measured for the unknowns. Thus chemometrics involves two critical components: experimental design and multivariate data analysis.

2.4.2 Experimental Design

The traditional approach to experimental design has been to change one variable at a time with the goal of isolating the effect of that factor. This is not the most efficient approach to obtaining information about a complex process in which there are strong interactions between variables.

The objective of experimental design is to plan and conduct experiments in order to extract the maximum amount of information from the collected data in the smallest number of experimental runs. The basic idea is to change all relevant factors over a set of planned experiments and then connect and interpret the results using chemometrics. For example, in a crystallization process one would like to known the rate of nucleation of different polymorphic forms at each location on the phase diagram. Relevant variables include the choice of solvent, the temperature and supersaturation (concentration), the rate of mixing, the concentration of excipients or impurities, the available surface area (process size), and the amount of seed crystals present.

The range of interest of all these variables would be determined and then experiments conducted. A full factorial design would perform an experiment at the extreme values for each variable and at the average value of all variables. This would lead to 2^k experiments if there were k variables. For values of $k > 5$ it is often not practical to perform all of these experiments. As some of the variables relevant to crystallization are not continuous (solvent, excipients) the number of experiments will increase even faster. Chemometrics provides several strategies for reducing the number of experiments while providing optimal coverage of the process variable space. Fractional factorial design removes a subset of the experiments while ensuring a uniform converge of the variable space. Evolutionary optimization designs perform a small set of experiments and then use this information with a simplex method to choose new experimental conditions that are nearer to the optimal outcome[38].

An example applying fractional factorial experimental design to crystallization optimization is given by Togkalidoua et al.[39] who varied six operating variables, (seed type, seed amount, temperature, solvent ratio, addition time, and agitation intensity) in an attempt to minimize the filtration resistance of the final product. Chemometric methods were applied to relate process observations to the final product while these variables were being altered.

The advantage of careful consideration of experimental design is illustrated by the characterization of polymorphs of ritonavir[40] by Morissette et al.[41]. They used high throughput screening to perform more than 2000 experiments

under a variety of conditions including variable solvents. They covered the solvent space by characterizing solvents by their physical properties such as Hildebrand and Hansen solubility parameters, log P, hydrophile-lipophile balance, boiling point, and melting point while preparing mixtures from a 24 solvent library to sample the space in a efficient manner.

The main challenge in applying these concepts to crystallization processes is that the outcome of process depends on how all the above variables change with time. A different time-dependent path through the space of variables provides a different process outcome. Another concern is applying experimental design methods to choose parameters without consideration of a process model. For example, if process variables that affect scale-up are not included in the experimental space, then all that may result are optimum condition for laboratory scale crystallizations and not optimum conditions for the final process.

2.4.3 Multivariate Data Analysis

Chemometric techniques are most valuable for problems with an excessive number of variables. For example, chemometrics techniques have been applied to near-infrared (NIR) spectra of solid drug products. In this case, the absorbance at each measured wavelength is a variable, and there may be hundreds of them. The goal is to connect these many measured variables with the desired property. Examples of possible output variables include:

- Qualitative analysis to identify the sample
- Quantitative analysis to measure concentration of a component
- Quantitative correlation of a quality measure (size distribution, shape, polymorphic form) with the spectra

The most straightforward multivariate data analysis is a multiple linear regression (MLR) in which the variable to be modeled is described as a linear combination of the dependent variables.

$$y = a_1 x_1 + a_2 x_2 + a_3 x_3 + \ldots \tag{9}$$

In the NIR example, the x_i would be the absorbance at each wavelength while y would be the desired property, for example the concentration of the drug product. The coefficients a_i are chosen to find the best fit of the data, usually by minimizing the sum of the square of the error at each point.

Another technique, principle component analysis (PCA), allows for a refinement of MLR. PCA does not use the original variables of the model, but rather uses the techniques of linear algebra to derive a new set of variables

- each a linear combination of the original variables. These derived variables (also called latent variables or principle components) are determined based on variability in the data - the first latent variable accounts for the majority of the variability in the system, and the second latent variable accounts for most of the remaining variability, and so on[38].

A modeler will then apply MLR to the latent variables, choosing sufficiently many latent variables to account for nearly all of the variability. This may be 90%, 95%, or more of the variability, based on the needs of the model. This combination of PCA and MLR is called Principle Component Regression (PCR). By constructing and using such latent variables, PCR is more efficient than MLR and more likely to incorporate most sources of variability into the model. However, these same latent variables make it difficult to identify specifically the important (i.e., variability-inducing) components in the original model.

PLS is another technique that combines features from PCA and multiple regression. It can be used to predict a set of dependent variables from a (very) large set of independent variables. The difference between PLS and PCR is that in PLS the choice of the latent variables is adjusted to obtain the best possible fit of the property to the measured variables. In PCR the principle components are determined only by the variance of the measured variables and are independent of the property you are trying to fit.

An example application of chemometrics is the use of Raman spectroscopy to identify and quantify the amount of different polymorphic forms present in a solid mixture of ranitidine hydrochloride[42]. The need for multivariate data analysis arises because the two polymorphic forms are chemically identical and thus will have many spectroscopic peaks in common.

PCA identified the features from the data in Fig. 8 that showed the most discrimination between the two polymorphic forms. Based on three principle components, a correlation was developed that could quantify the amount of each polymorph present in a solid mixture across the entire concentration range.

3 Crystallization Case Studies of PAT

Three important quality measures of a crystallization process are the size, shape, and polymorphic form. Here we present case studies that illustrate the use of the PAT concept to control each of these aspects of product quality.

3.1 Control of Crystal Size Distribution

The final size distribution of a crystalline product will affect the processability with smaller particles being much more likely to aggregate and more difficult to flow and filter. Properties of tablets, such as hardness and dissolution rate, manufactured from these crystals will depend on the crystal size distribution. For this reason there are has been much interest in using online crystal size measurements to control the final size distribution.

Matthews and Rawlings[43,44] demonstrated how to choose the optimum cooling path and seeding protocol to obtain easily filtered crystals. The parameters for a kinetic model of crystal growth were fit to data obtained by in situ measurement of particle size via turbidity and supersaturation. The model was then used to design a cooling and seed crystal introduction schedule. Tests of the final product showed a 25% lower resistance to filtration.

Fujiwara et al.[45] used the combination of process monitoring, chemometrics, and process control to optimize the size distribution of paracetamol crystals formed in a batch process. Small crystals of paracetamol tend to agglomerate and form a substandard final product with highly variable dissolution rates. They used chemometrics methods to develop a calibration for in situ ATR-FTIR measurements of concentration. The critical variables for this process were the solubility curve and the degree of supersaturation that corresponded to spontaneous nucleation of small crystals (metastable limit). ATR-FTIR mapped the solubility curve and FBRM measurements of particle size identified the onset of nucleation. Fig. 9 shows size measurements for two seeded crystallization runs; the first run followed a preset cooling profile that crossed the metastable limit, while the second run was actively controlled to avoid nucleation. In the controlled run the number of smaller crystals was much less and agglomeration was not observed.

3.2 Control of Crystal Shape

In the crystallization of sodium chlorate, the presence of an additive, sodium dithionate, blocks the growth of one particular crystal face thus changing the morphology from cubic to tetrahedral[46,47]. The processing properties of the final product such as flowability and filterability are altered by the distribution of the different shapes.

Process video microscopy provided online data about the shape, but the raw images do not provide quantitative information to control the process. The instrument provided measures of aspect ratio or boxed area, but these were not able to distinguish the shapes. By a chemometrics analysis, a method com-

bining the information from the different measures of aspect ratio and boxed area was developed that could distinguish between the two crystal shapes. This measure was then used in a control scheme to adjust the concentration of the additive to get the desired distribution of shape in the final product[48,49].

This type of control scheme is very important for polymorph control as it shows the importance of solution-crystal interactions, which also determine growth rates of different polymorphic forms. Interactive control of an additive designed to prevent the growth of a particular face could be used for selection of a particular polymorph.

3.3 In-Situ Monitoring of Polymorphic Form

Many pharmaceutical solids can exist in different polymorphic forms. These polymorphs differ in internal solid-state structure and possess different chemical and physical properties, which may have an impact on drug substance processability and drug product quality/performance, such as stability, dissolution, and bioavailability. For this reason pharmaceutical manufacturers often select a drug substance polymorphic form that has the desirable characteristics that will aide in the manufacture of the drug product formulation. Hence, it becomes critical to have a robust crystallization process that consistently produces the desired polymorphic form of the bulk pharmaceutical active ingredient.

For systems that can exist in several possible polymorphic modifications, thermodynamic data is generally useful to determine which polymorphic modifications will likely arise during crystallization but kinetic considerations will also be critical as well. Real time monitoring of polymorphs would be advantageous for several reasons. During development in-situ monitoring would provide kinetic data on the process and would enable a manufacturer to develop a robust crystallization process that consistently produces the desired crystalline form. In-situ monitoring during routine production would also be useful in the determination of crystallization endpoint and would optimize operation time to an efficient minimum. This would minimize the probability of allowing an unconverted or "out of specification" batch. In addition, in-situ polymorph monitoring would allow the manufacturer to identify and quantify undesirable polymorphs and enable one to take appropriate remedial action, such as extending crystallization times or seeding with the desired crystalline form. Finally, in-situ measurements would minimize possible data artifacts associated with sample isolation and preparation (e.g. evaporation of solvent) that may alter the crystalline form. Over the recent years, numerous powerful analytical techniques including Raman, near-IR and X-ray diffraction have been developed which have been utilized for monitoring polymorph

transformations in real-time. The examples from the recent literature illustrate the potential of in-situ polymorph monitoring during crystallization of bulk pharmaceuticals.

3.3.1 Progesterone

In-situ Raman spectroscopy has been used to monitor progesterone polymorphs. Progesterone is known to exist in five polymorphs with Forms I and II being the two relevant forms in the crystallization studies. Raman spectra (Fig. 12) of the two modifications reveal differences in the peak attributed to the progesterone carbonyl (1662 cm^{-1} for Form I and 1667 cm^{-1} for Form II) and the observed peak position was used to correlate the concentration of each crystalline form. By using in-situ Raman spectroscopy and the above peak correlation, kinetic data was obtained for a crystallization process proceeding in accordance to Ostwald's law of successive stages. The polymorph transformation that was monitored in this study was for a post-crystallization slurry where Form II is the kinetically favored polymorph formed during isothermal crystallization and where Form I is the thermodynamically favored polymorph generated following stirring of the crystalline slurry (Fig. 13). Turnover kinetics for this polymorphic transformation were obtained under various conditions and over a wide range of temperatures and was used in Pharmacia to specify process parameters and cycle times that enable the manufacturer to consistently and reliably produce either of two desired progesterone polymorphs[50].

3.3.2 MK-A

MK-A, a compound under development at Merck Research Laboratories is initially isolated during "crude" crystallization as a "semi-pure" form. This is compromised of various crystalline forms including the anhydrous forms A and C, the hemihydrate and the dihydrate. As a final step, a slurry turnover process in isopropyl acetate was developed to transform the various polymorphs into a single Form A. During initial development, thermodynamic data was obtained on this system where process boundaries were defined which would assure that Form A would be the most stable crystalline form.

The Raman spectra (Fig. 14) of the various crystalline forms were obtained and revealed distinct features in their spectra in terms of both peak position and peak width. This was used to build a correlation between the spectra and the concentration of each crystalline form. By using in-situ Raman spectroscopy, studies were conducted to elucidate the turnover kinetic of two polymorph transformation pathways: hemihydrate $\rightarrow$ Form C and Form C $\rightarrow$ Form A. The dihydrate form was not monitored as it was unstable under the defined conditions and is shown to readily dehydrate to Form A. The kinetics of the

hemihydrate to Form C transformation (Fig. 15a) was monitored and exhibited the characteristic sigmoidal profile during solid phase turnover and was greatly accelerated by Form C crystals. The turnover rate for Form C to Form A transformation (Fig. 15b) was also monitored under various conditions (e.g. moisture levels and temperature) and was shown to be approximately one third of the rate of the hemihydrate to Form C transformation.

This example elegantly demonstrates in a complex polymorphic system how thermodynamic data may be used to define process boundaries and how kinetic data may be used to define appropriate cycle times that will assure adequate polymorph turnover. Based upon both thermodynamic and kinetic information, a highly robust slurry turnover process was developed that consistently generated MK-A in the desired polymorphic form[51].

3.3.3 Trovafloxacin Mesylate

Trovafloxacin mesylate is prepared by hydrolysis of the ethyl ester with methanesulfonic acid in tetrahydrofuran and is initially isolated as a metastable crystalline modification (Form I). When this unstable polymorphic form is heated in various solvents it converts to the thermodynamically most stable Form II. In this system in-situ near infrared spectroscopy (NIR) was used at Pfizer to follow the turnover of these polymorphs to determine the required process times to reach the steady state energy minimum. By using principal component analysis the NIR spectra were deconvoluted to determine relative levels of Forms I and II during slurry turnover (Fig. 16)[28].

3.3.4 Glutamic Acid

Glutamic acid is known to exist as two polymorphic modifications (α and β). The α form exhibits characteristic X-ray diffraction peaks at 3.34Å and 3.74Å, while the β form exhibits diffraction peaks at 4.02Å and 4.14Å. These characteristic peaks were used to monitor the kinetics of crystallization slurry turnover from the unstable α form to the more stable β form (Fig. 17). Real-time monitoring by X-ray diffraction was achieved by using high intensity dispersive synchrotron radiation and a specially designed crystallizer cell to maximize the weight fraction of the particle suspension in order to generate a suitable X-ray signal[26].

3.3.5 Glycine

The commercially available Bede-Monitor^{TM} has been used to monitor the crystallization of glycine from an aqueous solution via X-ray diffraction. Glycine in this example was dissolved in water at 60° and was slowly cooled. The X-

ray data collected with the BedeMonitor^{TM} shows that under these conditions crystallization generates uniquely the α form and that this occurs at temperatures below 15° (Fig. 18).

4 Critical Analysis of Case Studies

We can review these representative case studies and examine how aspects of PAT are implemented in crystallization processes in the pharmaceutical industry with a special focus on polymorphism.

There appears to be very little use of process modeling and optimization in the pharmaceutical processes outlined. We choose two case studies from chemical engineering research groups to illustrate how model based design and control could be applied to crystallization processes. Most of the examples focused on one aspect of quality at a time, for example the polymorphic form was monitored but size distribution was not. Chemometrics provides many methods for dealing with multivariate information, but its full potential is not being used. Existing techniques for statistical design of experiments are not extensively used to optimize operating conditions in a systematic manner. Although the role of thermodynamic variables in crystallization is well defined, connecting process variables to quality outcomes will likely require sophisticated data mining.

The most widespread adoption of PAT concepts is in the use of sensors for process monitoring. Our examples show that there are several analytical techniques that can measure polymorphic form in situ. The advantage of real time process monitoring is widely recognized and essential to each example. At the present time, advanced chemometrics techniques are calibrating and interpreting results from many of the online sensors. For example, in section 3.3.3 PCA was used to build correlation between NIR spectra and polymorphic form.

Process control applications to polymorph control have been limited to locating process end points such as the correct polymorphic form or the correct particle size. Based on other examples of crystallization processes one can envision future processes that couple online measurement of polymorphic form with measurement of other variables (supersaturation, mixing, particle size), use chemometrics to find correlations between process conditions and desired polymorphic form, and control the process to reach the desired end point in an optimal manner.

5 Conclusions and Future Directions

The manufacturing of high valued-added pharmaceutical active ingredients often involves final or intermediate production of the solid form, where crystallization plays a key role as a separation and purification unit operation. The quality and properties of the final product are primarily determined by their shape, size, and polymorphic form. This article introduced PAT and discussed its utility in controlling these measures of quality. Although PAT has been widely used in chemical industry, its application in pharmaceutical industry is at its infant stage. It is expected that we will observe more and more applications of PAT to pharmaceutical manufacturing processes. Our case studies illustrate that a variety of promising in situ analytical methods, combined with chemometric tools for analysis of multivariate process information, provide a basis for future improvements in modeling and control of crystallization processes within the framework of PAT.

Pharmaceuticals will have an increasingly prominent role in the health care of the future. Pharmaceutical manufacturing will need to utilize innovation, cutting edge scientific and engineering knowledge, and the best principles of quality management to respond to the challenges of new discoveries and new ways of doing business such as novel drug products involving nanotechnology, individualized therapies, or genetically tailored treatments. Regulation of the future will also need to meet these challenges, by incorporating new scientific information into regulatory standards and policies. Both industry and regulatory practices will need to be informed by the best techniques of risk assessment and management.

Pharmaceutical manufacturing continues to evolve with increased emphasis on science and engineering principles. Effective use of the most current pharmaceutical science and engineering principles and knowledge, throughout the life cycle of a product, can improve the efficiencies of both the manufacturing and regulatory processes. FDA's PAT initiative is designed to do just that by using an integrated systems approach to regulating pharmaceutical product quality. The approach is based on science and engineering principles for assessing and mitigating risks related to poor product and process quality. Thus the desired future state of pharmaceutical manufacturing may be characterized as:

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- Product and process specifications based on mechanistic understanding of how formulation and process factors impact product performance
- Continuous real-time assurance of quality
- Regulatory policies and procedures tailored to recognize the current level of scientific knowledge

- Risk-based regulatory scrutiny that recognizes
  - the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance
  - the capability of process control strategies to prevent or mitigate the risk of producing a poor quality product

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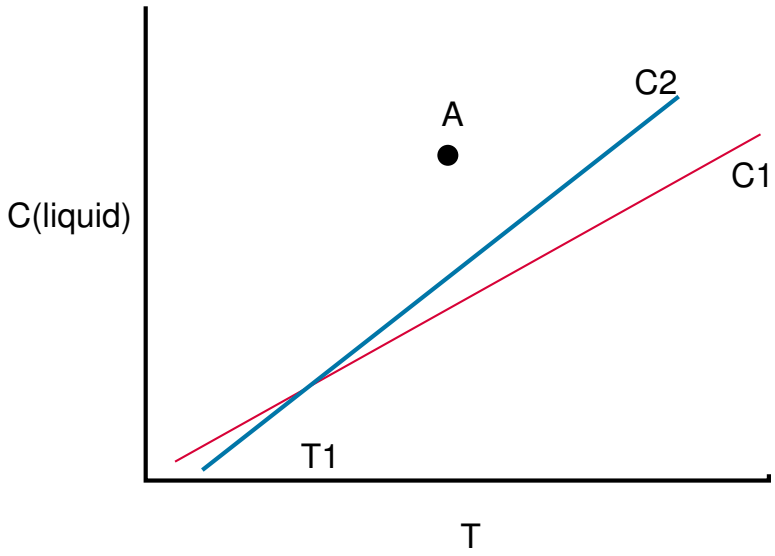

Fig. 1. Example phase diagram showing the solubility curves of two polymorphic forms.

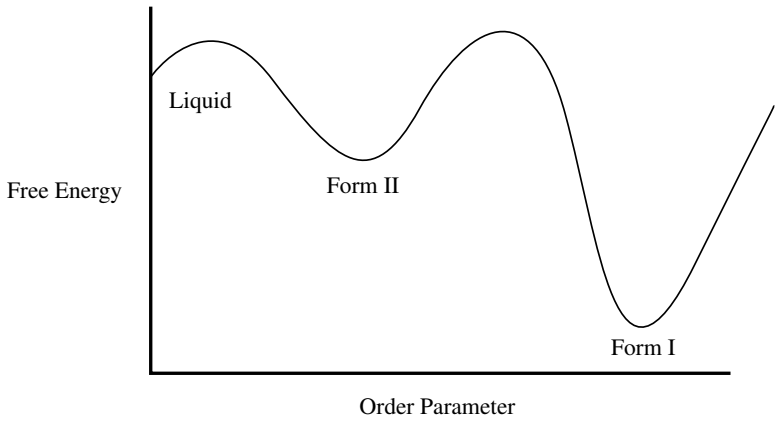

Fig. 2. Relative free energy at point A from Fig. 1.

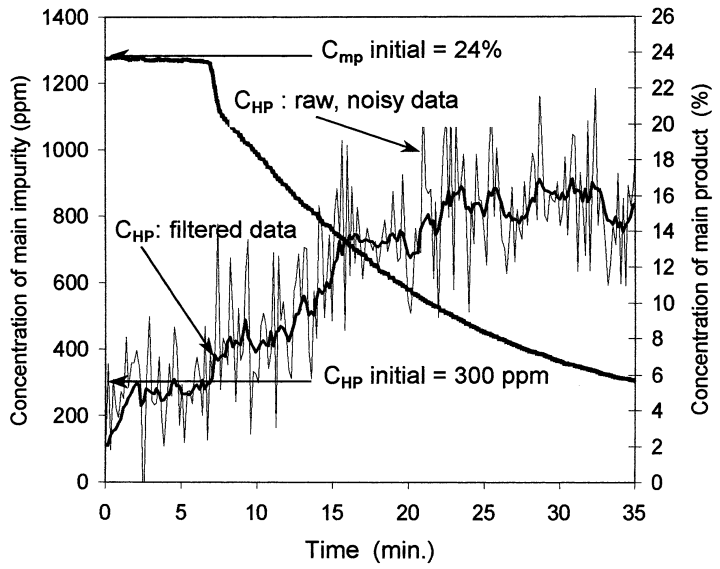

Fig. 3. Time trace of concentration of solute and impurity as measured by ATR-FTIR.C_{MP} is the concentration of the main product in the solution; it is diminished as the crystallization occurs. C_{HP} is the impurity concentration. Both concentrations are measured in a single FTIR measurement([13], reproduced with the permission of Elsevier Science).

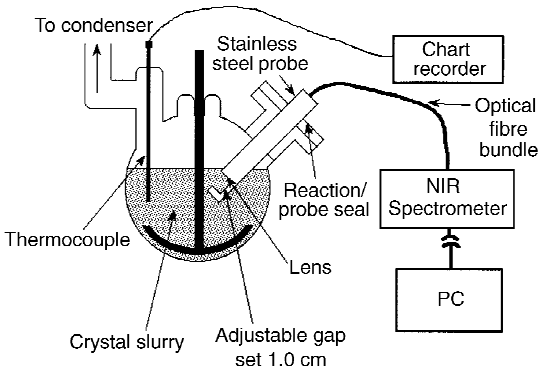

Fig. 4. Near-IR probe to monitor polymorphs in crystallization slurries ([28], reproduced with the permission of The Royal Society of Chemistry).

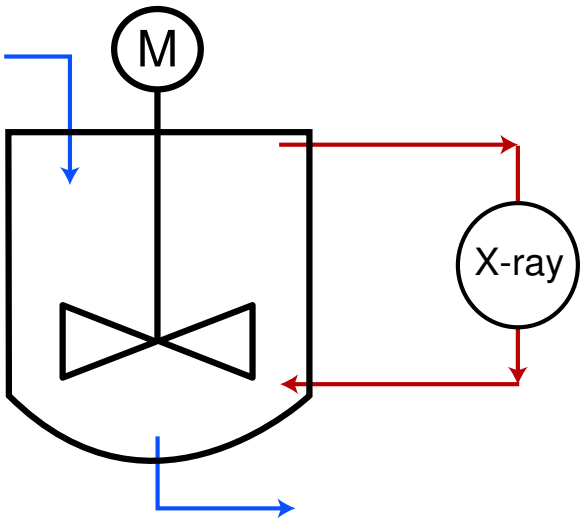

Fig. 5. Schematic of the BedeMonitor^{TM}.

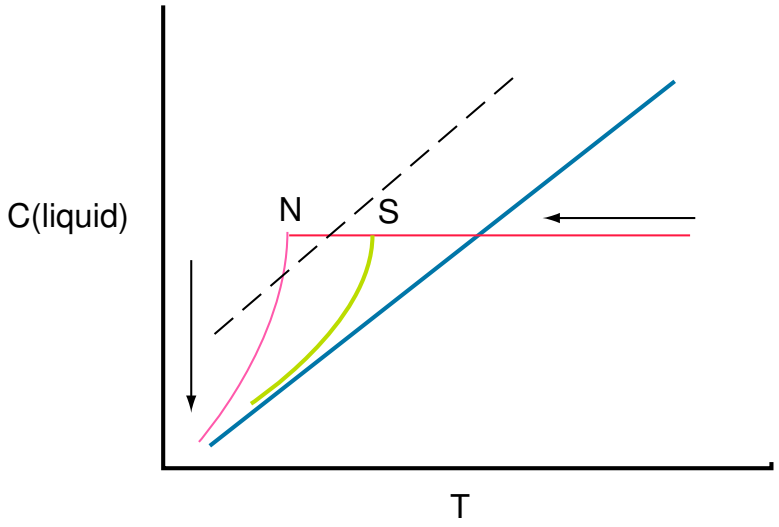

Fig. 6. Path for a crystallization process. The dashed line is the metastable limit where nucleation will begin immediately.

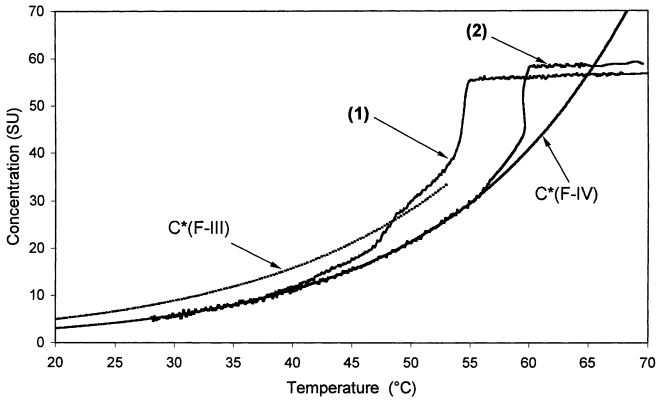

Fig. 7. Concentration profile obtained via ATR-FTIR for unseeded(1) and seeded(2) operation ([13], reproduced with the permission of Elsevier Science).

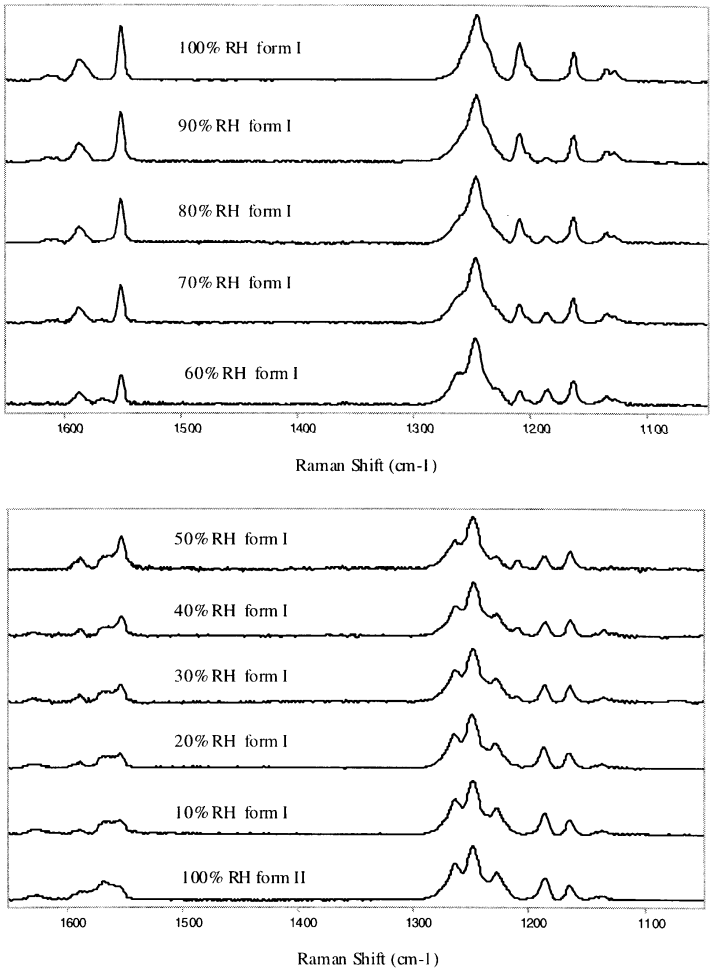

Fig. 8. Raman spectra of mixtures of Ranitidine hydrochloride (RH) polymorphic forms ([42], reproduced with the permission of Elsevier Science).

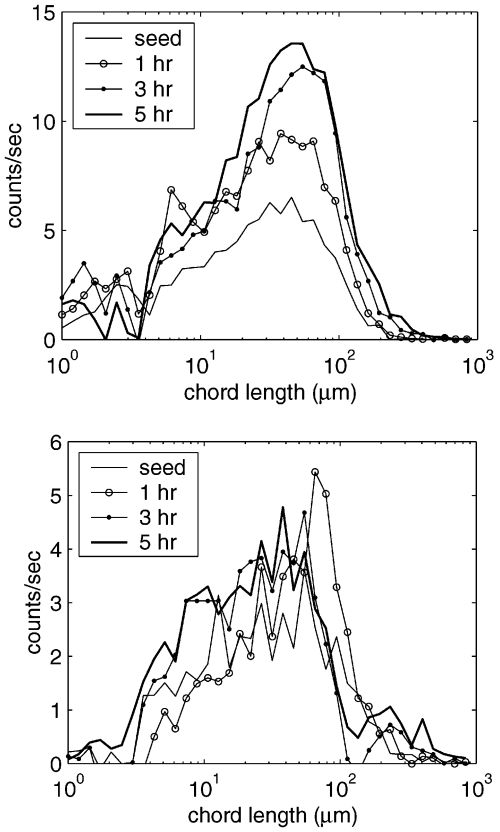

Fig. 9. Size measurement for uncontrolled (top) and controlled (bottom) crystallization of paracetamol ([45], reproduced with the permission of the American Chemical Society).

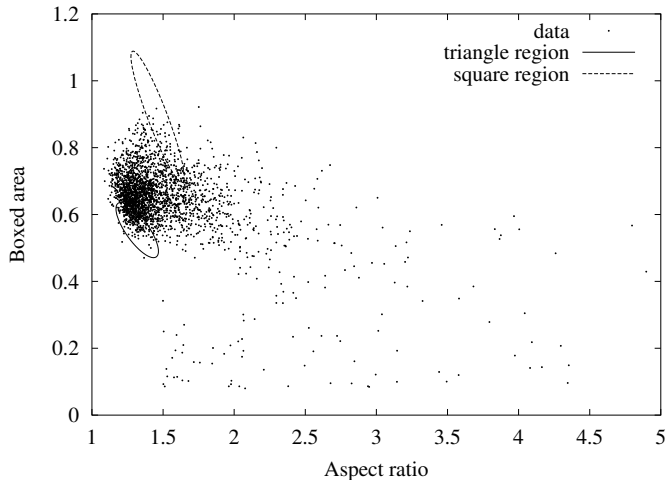

Fig. 10. Aspect ratio versus boxed area showing the regions where triangle and squares can be distinguished ([49], reproduced with the permission of the American Institute of Chemical Engineers).

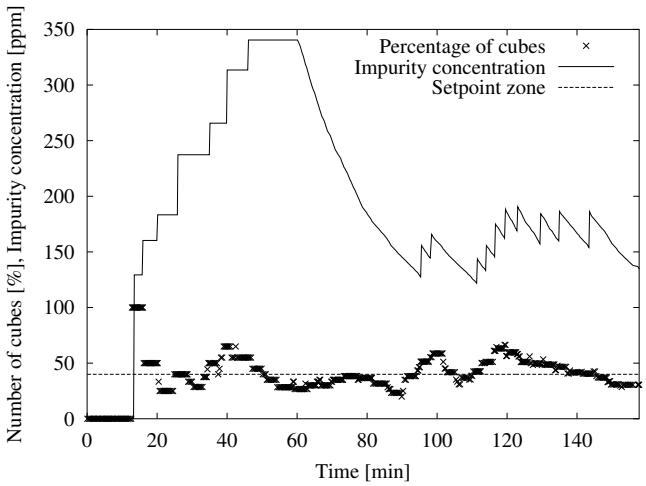

Fig. 11. Concentration of additive and cubic crystals as a function of time([49], reproduced with the permission of the American Institute of Chemical Engineers).

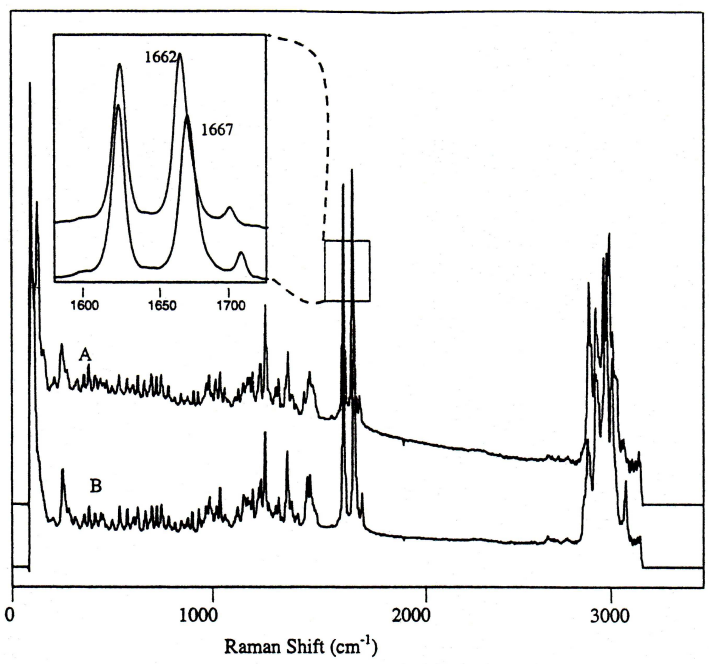

Fig. 12. Raman spectra of progesterone polymorphs: (A): Form I and (B): Form II ([50], reproduced with the permission of the American Chemical Society).

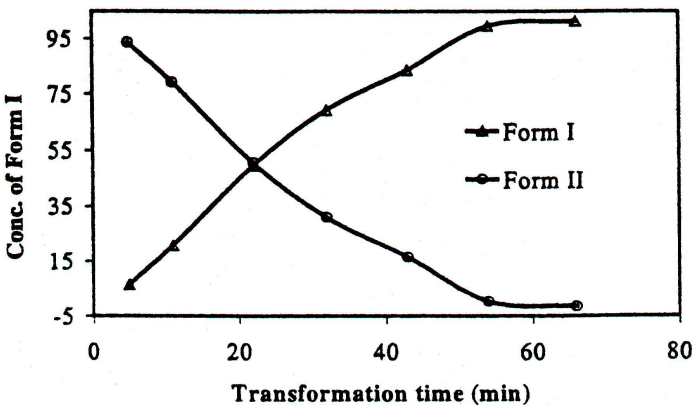

Fig. 13. Progesterone polymorph conversion profile ([50], reproduced with the permission of the American Chemical Society).

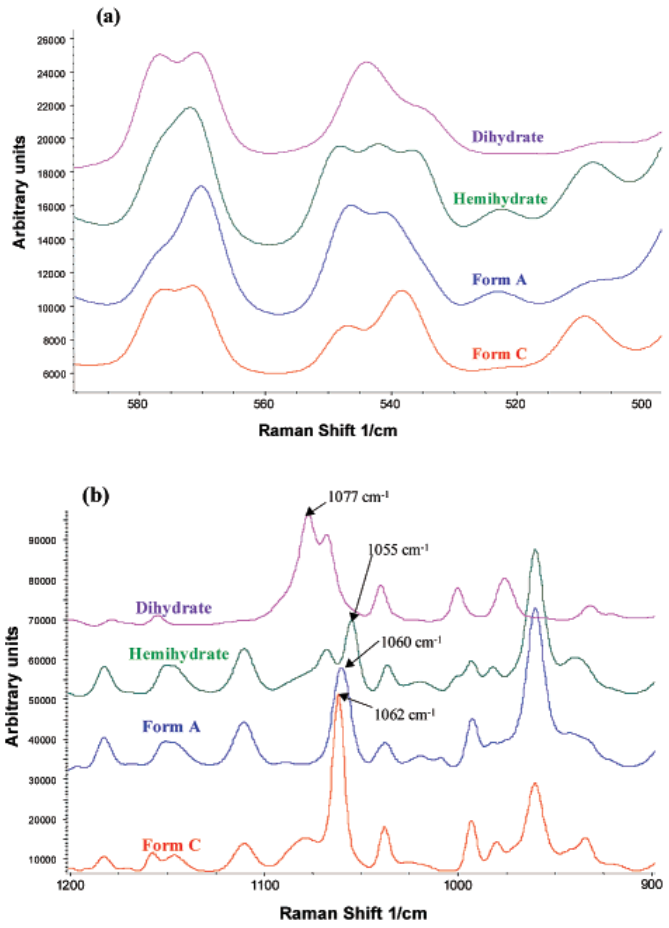

Fig. 14. Raman spectra of MK-A polymorphs ([51], reproduced with the permission of the American Chemical Society).

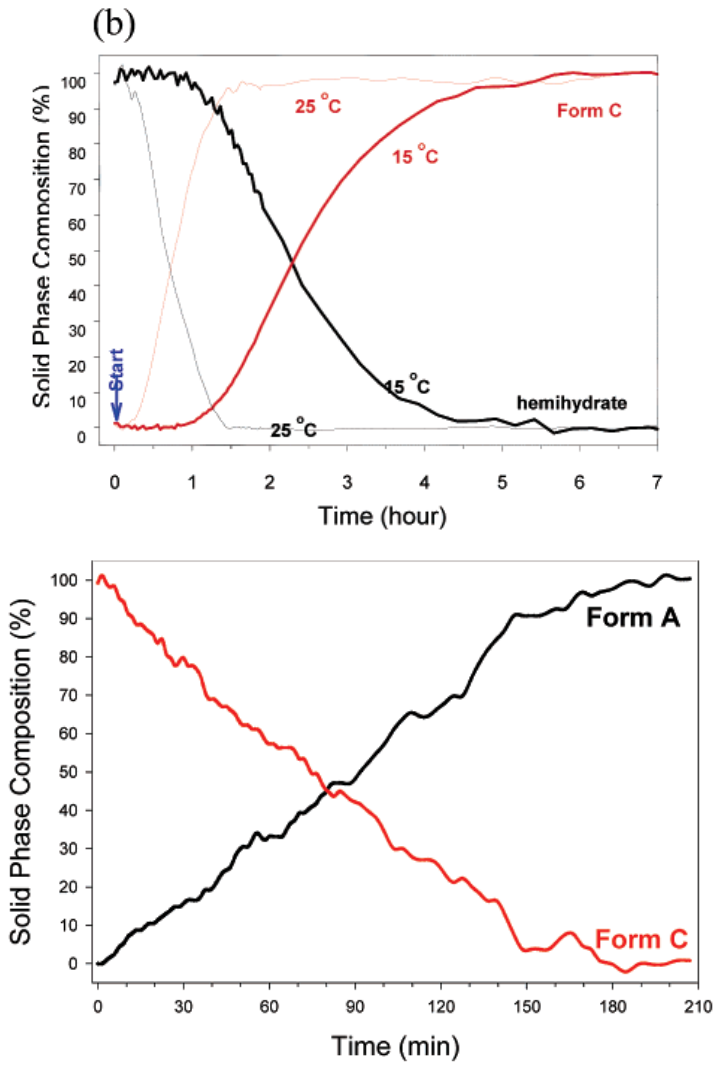

Fig. 15. a) Hemihydrate → Form C turnover, b) Form C → Form A turnover ([51], reproduced with the permission of the American Chemical Society).

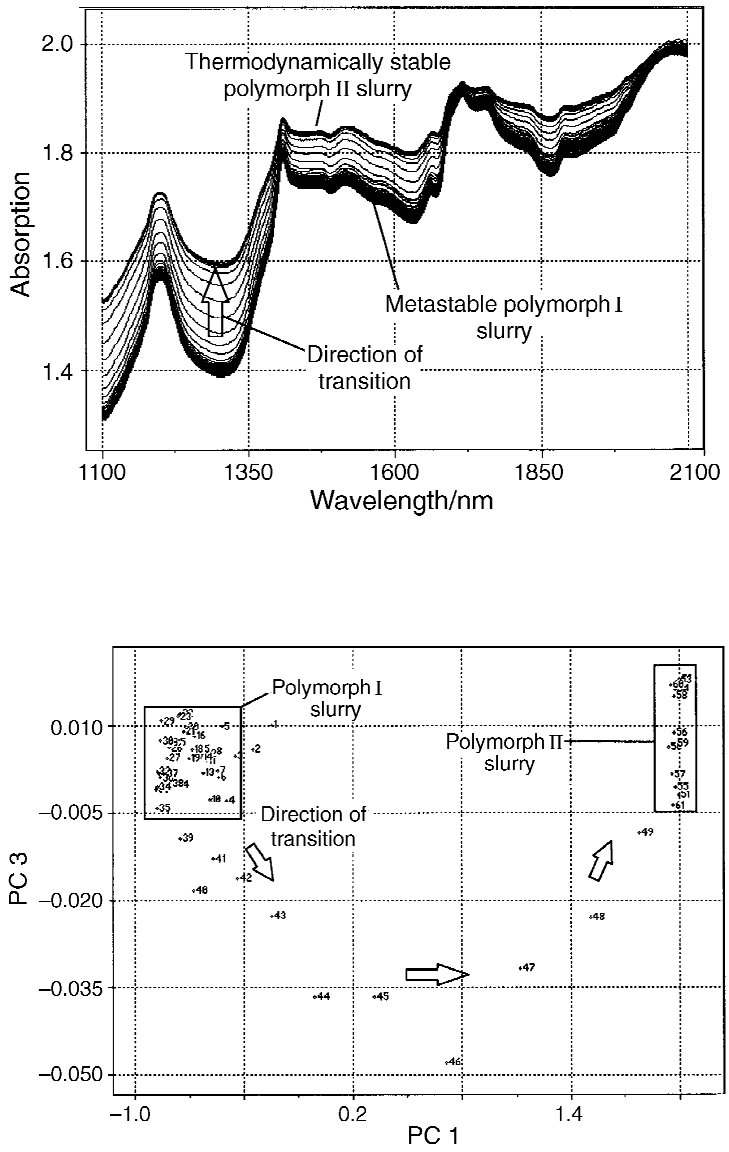

Fig. 16. PCA of near-IR spectra of trovafloxacin mesylate during polymorph conversion ([28], reproduced with the permission of The Royal Chemical Society).

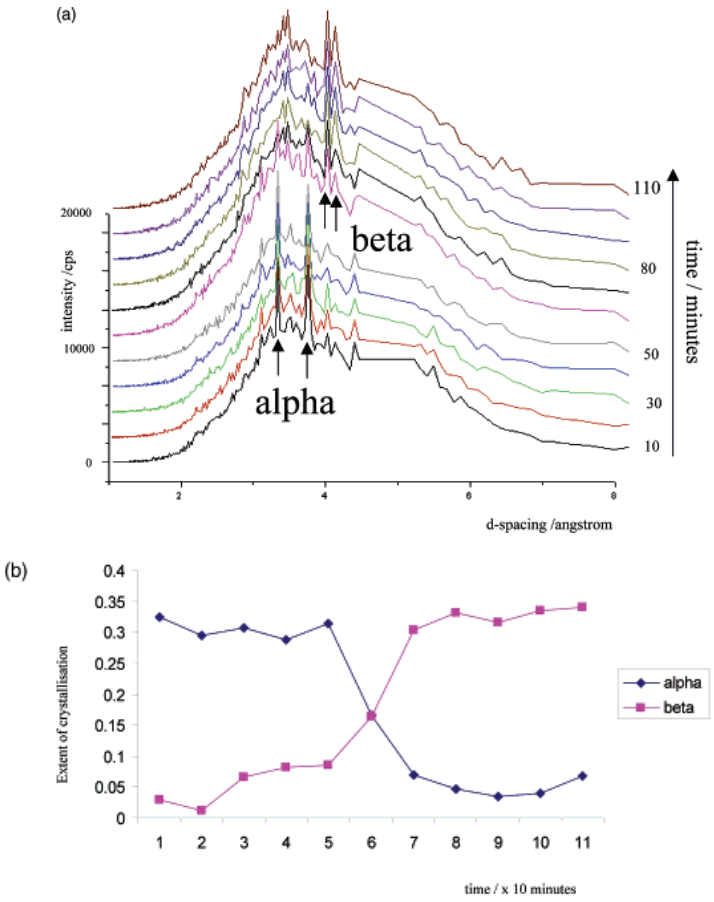

Fig. 17. X-diffraction to monitoring of glutamic acid polymorph conversion ([26], reproduced with the permission of the American Chemical Society).

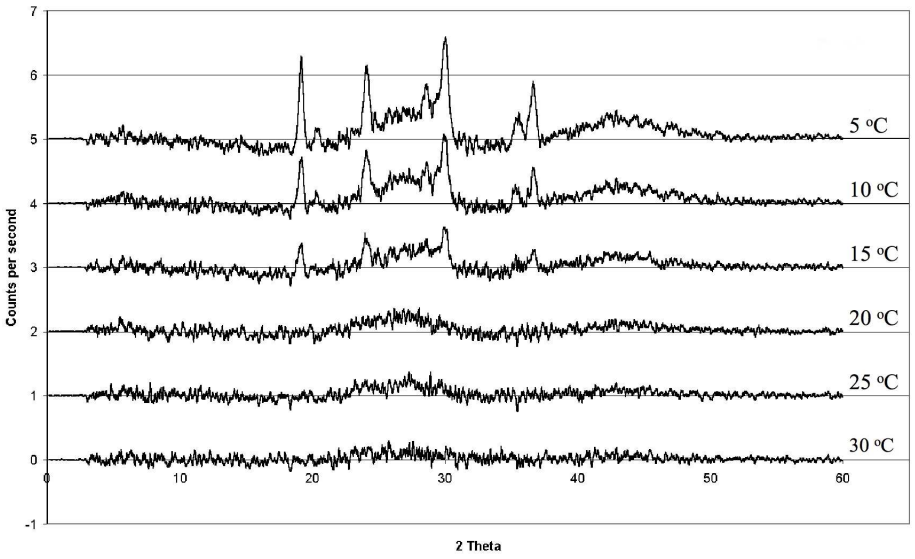

Fig. 18. Monitoring the crystallization of α-glycine with the BedeMonitor^{TM}([27], reproduced with the permission of Bede).