Review

First-principles and direct design approaches for the control of pharmaceutical crystallization

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Abstract

Crystallization is the main separation and purification process for the manufacturing of drug substances. Not only does crystallization affect the efficiency of downstream operations such as filtering, drying, and formulating, the efficacy of the drug can be dependent on the final crystal form. Advances in simulation and control algorithms and process sensor technologies have enabled the development of systematic first-principles and direct design approaches for the batch control of crystallization processes. These approaches address different challenges associated with pharmaceutical crystallization control. This paper provides an overview of recent technological advances in the in situ control of pharmaceutical crystallization processes. Implementation of the first-principles and direct design approaches are compared, and their relative merits are explained. Areas of future opportunities for application of advanced control strategies in pharmaceutical crystallization are presented.

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1. Introduction

The global pharmaceutical and biotechnology industries are facing increased pressure to improve process efficiency and reduce time to market. Reducing time to market extends the length of time before patent expiration, and improving process efficiency is important in the manufacture of generic drugs and when large quantities of drugs are needed for life-threatening diseases (like AIDS) in poor countries. In the biotechnology industry, where the production cost is very high, there is a strong incentive to reduce cost. Technologies involved in drug discovery, such as combinatorial chemistry and high-throughput screening, are shortening the evaluation time of potential drugs and have received much attention recently [1]. Technological advances in the pharmaceutical manufacturing processes have not been as thoroughly discussed, but are also valuable in reducing the time to production as well as increasing profitability, efficacy, and safety of the drugs.

Most pharmaceutical manufacturing processes include a series of crystallization processes to achieve high purity and to produce the desired final crystal form. The operating conditions of the crystallization process determine the physical properties of the products such as the crystal purity, size, and shape distribution. These properties determine the efficiency of downstream operations, such as filtration, drying, and formulating, and the product effectiveness, such as bioavailability and shelf-life. For pharmaceuticals that exhibit various polymorphs or stereoisomers, the crystallization process also affects the polymorph produced and the extent of chiral separation. The solid-state phase and purity of the product affect the drug dissolution and toxicity, which are important from a consumer and regulatory point of view [2]. Therefore batch-to-batch uniformity and consistency are required. Improved control of crystallization processes offers possibilities for better crystal product quality, shorter process times, and the reduction or elimination of compromised batches.

Recent trends in the early stage development of pharmaceutical crystallization processes include the use of smaller size crystallizers, automation of lab reactors, and running experiments in parallel using multiple small reactors [3]. This is motivated by limited availability of pharmaceutical and higher throughput desired during the development stage. Real-time analysis using in situ sensors are essential as sampling becomes highly undesirable with smaller size crystallizers. Various spectroscopic instrumentation are available for in situ monitoring during the operation of crystallization processes (see [4,5] and references cited therein). Attenuated total reflection-Fourier transform infrared (ATR-FTIR) spectroscopy enables the accurate measurement of solution concentrations for crystallization processes [6-12], including the multi-solvent multi-solute organic systems commonly encountered during pharmaceutical crystallization [13]. ATR-FTIR spectroscopy has also been applied to the detection of the metastable limit, monitoring during polymorphic transitions, and evaluation of impurity concentrations during crystallization [12,14]. Both near-IR spectroscopy [15] and Raman spectroscopy [16,17] coupled with fiber optics have been used for the in situ detection of various polymorphs. Raman spectroscopy has also been used for monitoring solution concentration during protein crystallization [18,19].

Laser backscattering, also known as Focused Beam Reflectance Measurement, is widely used in the pharmaceutical industry to measure changes in the crystal size and shape [4]. It measures the chord length distribution (CLD), which is a close function of the crystal size distribution [20]. Laser backscattering has been applied to the detection of nucleation [12,21,22] and the monitoring of fines dissolution [23] during crystallization processes. Other techniques capable of online particle size characterization during crystallization include ultrasonic spectroscopy [24] and laser diffraction [25,26]. As a complement to particle size characterization techniques, process video microscopy is used to image the crystals as they grow in solution, to visualize the extent of agglomeration and changes in crystal size and shape [4,27]. In recent years most of these techniques have been used to design new pharmaceutical crystallization processes and to troubleshoot problems with existing processes.

Even with these advances in in-process sensors and a better understanding of the crystallization mechanisms at the molecular level, as exemplified by improved crystal shape predictions [28], pharmaceutical crystallization processes can be challenging to control due to variations in solution thermodynamics and kinetics induced by contaminants, complex nonlinear dynamics associated with nonideal mixing and dendritic growth, and unexpected polymorphic phase transformations [29]. Most crystallization processes in the pharmaceutical industry are
designed and controlled based on trial-and-error experimentation, which can be time consuming and expensive. Recently in-process sensors have enabled the development of systematic first-principles (model-based) and direct design (measurement-based) approaches for the control of industrial crystallization processes. This paper describes these approaches and efforts toward automation and the integration of various systems techniques to achieve the rapid development of pharmaceutical crystallization processes. Since many of the fundamental mechanisms for the crystallization of pharmaceuticals are similar to those for biochemicals and proteins [30,31], the concepts presented here are also applicable to the crystallization of industrial enzymes and biopharmaceuticals.

2. First-principles approach

The fundamental driving force for crystallization from solution is the difference in chemical potential between the solution and the solid phase; however, it is more convenient to write the driving force in terms of the supersaturation, which is the difference between the solution concentration and the saturation concentration. Supersaturation is typically created by cooling, evaporation, and/or addition of antisolvent, including changing the pH by addition of acid or base (see Fig. 1). The limited temperature stability of most pharmaceuticals precludes the use of evaporation and limits the temperature range that can be used during cooling crystallization. For the crystallization of biochemicals and biomolecules, such as amino acids and proteins, supersaturation is created by similar methods used for pharmaceuticals [30,31]. It is important to control the extent of supersaturation during crystallization since the size, shape, and solid-state phase of the product crystals are dependent on the supersaturation profile achieved during the crystallization process.

The first-principles approach to crystallization control is the most widely studied [4,32], where a model constructed from material and energy balances are used to optimize some function (e.g., mean crystal size) of the crystal size distribution. An overview of the first-principles approach is described below. For a detailed review of model development for solution crystallization, the readers are referred to review articles on this subject [32,33]. The population balance equation describes the material balance that accounts for the distribution of different size crystals in the crystallizer. To simplify the model, most batch crystallization studies in the literature only consider nucleation and growth kinetics (e.g., no agglomeration, no dendritic growth), ignore shape changes, and study the optimization of the temperature profile for a cooling crystallizer. A simplified population balance equation for a well-mixed batch process is

\[
\frac{\partial f}{\partial t} + \sum_{j=1}^{n} \frac{\partial}{\partial r_j} (G_j(r_j,S,T;\theta_b)f) = B(f,S,T;\theta_b) \prod_{j=1}^{n} \delta(r_j) \]  

(1)

where \( T \) is the temperature, \( S \) is the supersaturation, \( f(r_1,\ldots,r_n,t) \) is the crystal size distribution, \( r_i \) is the \( i \)th characteristic growth dimension, \( G_i = dr_i/\partial t \) is the growth rate along \( r_i \), \( B \) is the nucleation rate which is typically some integral function of \( f \), \( \delta \) is the Dirac delta function, \( \theta_b \) is a vector of growth kinetic parameters, and \( \theta_n \) is a vector of nucleation kinetic parameters. The nucleated crystals are assumed to have zero size, which is reasonable because the distribution is not significantly affected if the actual size of a nucleus is used.

Although software is available for simulating these equations (e.g., see review [4]), a simplified moments model is typically used for identifying the kinetic parameters. This model is obtained by multiplying both sides of (1) by powers of \( r_i \) and integrating [34]. For crystals with one characteristic growth dimension and size-independent growth, these moment equations are:

\[
\frac{d\mu_l}{dr} = B(\mu_b,S,T;\theta_b) 
\]

(2)

\[
\frac{d\mu_j}{dr} = jG(S,T;\theta_b)\mu_{j-1}, \quad j = 1,2,\ldots 
\]

(3)

where the moments

\[
\mu_j(t) = \int_0^\infty r^j f(r,t) \, dr 
\]

(4)

are related to physical properties of interest such as crystal number, length, area, and volume. The value of \( k \), in Eq. (2), is typically 2 or 3. The number of moments needed to describe the crystallization process depends
on the nucleation mechanism that is dominant in the crystallizer. Assumptions are typically made so that the moment equations are closed, that is, there exists an integer \( j \) such that derivatives of the lower order moments do not depend on the higher order moments. This enables the integration of a small finite number of lower order moment equations without requiring the integration of the equations for the higher order moments. Hence a small number of sparse ordinary differential equations are solved instead of the partial differential equation (1). The model is completed by a material balance on the solute and an energy balance for the multiphase system; these are integrodifferential equations that can be written in terms of low order moments [35].

A data-efficient method for model identification is an iterative procedure involving optimal experimental design, automated batch experiments, parameter estimation, and model selection (see Fig. 2). This procedure is repeated until the model parameters are accurate enough for use in dynamic optimization and control [35,36]. The procedure has been applied to various crystallization processes including those with shape change [35,37,38], and to pharmaceuticals [39]. The following describes the model identification process in more detail with respect to pharmaceutical batch crystallization.

2.1. Experimental design and data collection

The experimental design variables for batch crystallization can include mixing speed, mass and distribution of seed crystals, temperature and solvent addition profiles, and the final batch time. The initial batch experiment for the model identification process shown in Fig. 2 is designed using initial estimates of the model parameters and some experimental design objective such as minimizing the uncertainties in the model parameters [40]. Initial estimates may come from prior experience with the pharmaceutical to be crystallized. Alternatively, the initial estimates of kinetic parameters may come from the application of parameter estimation to data collected during the determination of the metastable zone [22,41]. When initial estimates are not available, the first batch experiment can be designed using engineering judgment on how to excite the dynamics of the system.

The temperature, solution concentrations, and crystal moments or ratios of moments, which is a function of particle size distribution, are measured during the batch experiment. These data are used for estimation of kinetic parameters [42,43] as described in the next section. In the pharmaceutical industry, using ATR-FTIR spectroscopy to measure the solution concentration has become commonplace [7,11,12,44]. For the determination of the crystal moments, a particle characterization technique, such as laser backscattering, and an appropriate computational method is used. The crystal moment data can be estimated from weighted normalization of the laser backscattering data [20] or by using chemometrics to relate laser backscattering data to moments [45] (see Fig. 3). The weighted normalization is easy to apply and has been used in industry but does not give the highest accuracy. Correlating laser backscattering to moments using chemometrics, on the other hand, is not very practical as this requires a large amount of calibration experiments. The most theoretically justified method to extract moments is inverse geometric modeling, which uses analytical geometry and optimization to compute moments from the laser backscattering data [46,47]. The theory behind this method requires many assumptions including that the particles perfectly backscatter light at all angles and that all particles have a known shape. More work is warranted to generalize geometric modeling methods to the complex crystal shapes typical in pharmaceutical crystallization.

![Fig. 2. Iterative procedure for model identification and optimal control design: \( u \) is a parameterization of all experimental design variables (e.g., initial conditions, processing conditions, sensor locations), \( y \) is a vector of measurements, \( \theta \) is the vector of model parameter estimates and \( E_\theta \) is the confidence region for the \( i \)th hypothesized mechanism, \( \hat{\theta} \) is the vector of selected parameter estimates and \( E_{\hat{\theta}} \) is its associated confidence region, and \( \hat{u} \) is the optimal control policy (including initial conditions, equipment specifications, operating conditions, actuator and sensor locations, etc.). Software implementing these steps is available for download [78].](image-url)
2.2. Parameter estimation and hypothesis mechanism selection

Improved estimates of the model parameters and associated uncertainty descriptions are computed from the dynamic data collected from the batch experiments. The model identification procedure shown in Fig. 2 considers that there may be multiple hypothesized models for the kinetic mechanisms. This is especially true for secondary nucleation processes, common in the seeded batch crystallization of pharmaceuticals, in which nuclei may be produced by particle–particle collisions, particle-mixing blade collisions, or interactions between particles and turbulent eddies. Each of the hypothesized mechanisms uses a different model structure for the kinetics [32, 48, 49]. Maximum likelihood or Bayesian estimation is used to compute the parameter estimates from the input $u$ and output $y$ data, for each of the $i$ hypothesized models. The uncertainty in the model parameters for the $i$th candidate model, $E_i$, is quantified using multivariate statistics and used by a model selection procedure to determine the most likely model [37, 38]. A common method is to select the model with the smallest uncertainties.

Subsequent batch experiments in the model identification procedure are designed to either produce data that are likely to minimize the magnitude of the parameter uncertainties for the most likely hypothesized model or to maximize the ability of the experiment to distinguish between multiple hypothesized models.

Model parameters obtained from the iterative model identification procedure shown in Fig. 2 are much more accurate than estimates obtained from data collected from trial-and-error experimentation. Accurate model parameters are typically obtained with 2–4 batch experiments for crystallization processes dominated by nucleation and growth. The model-based experimental design approach applied to a batch cooling crystallization of a proprietary pharmaceutical obtained nucleation and growth parameters in two experiments [39].

2.3. Batch optimal control

Once the model is sufficiently accurate, it is used by a dynamic optimization algorithm to compute the physical design variables, initial conditions, startup procedures, setpoints to lower level feedback control loops, and the feedback control system. Traditionally the stopping criterion for model accuracy has been based on engineering guesswork. Since small model uncertainties can have a large effect on the crystal size and shape distribution of the product crystals [50], a more rigorous stopping criterion is warranted. An example of a rigorous stopping criterion for the model identification procedure is a bound on the expected effect of parameter uncertainties and disturbances on the product quality (see [51] and references cited therein).

Optimal control has been widely recommended to improve batch crystallization operations [32]. Performing the open-loop optimization off-line with nominal values of the model parameters and then implementing the optimal trajectory is the approach used most frequently. This approach has been applied to the crystallization of a proprietary pharmaceutical to maximize the crystal size and minimize the coefficient of variation (which is the width of the distribution over its mean) [39]. The optimal recipe was predicted to reduce nucleation by more than 50% compared to industrial practice.

The benefits of the nominal open-loop optimal control, however, can be lost due to errors in the model parameters as observed in a study of paracetamol crystallization [41]. Several optimal control algorithms have been developed to provide robustness to parameter and control implementation uncertainties. Approaches that incorporate modern robustness analysis techniques in...
model-based controller design have been proposed (see [52] for an overview and extensive list of references). Most of these techniques minimize the worst-case deviation of the performance index due to uncertainties (often referred to as the minmax or minimax approach), or solve a weighted optimization where one term in the objective quantifies nominal performance while another term accounts for robustness (e.g., as measured by the worst-case deviation or the variance of the product quality). The resulting optimal control trajectory is the outcome of the tradeoff between the nominal performance and robustness objectives. These techniques can be used to compute the robust open-loop optimal control trajectory or formulated as a closed-loop robust optimal control strategy by repeatedly solving the optimization on-line. This has resulted in improved robustness of the optimal performance in simulated batch crystallization processes [51,52]. Fig. 4 shows the benefits of robust optimal control in the simulated batch crystallization of paracetamol in water, for the unseeded system described in [41]. Applying the robust optimal control trajectory obtained using worst-case minimization leads to a factor of two reduction in the worst-case deviations of the mean crystal size at the end of the batch, with only a small degradation in the nominal mean crystal size. This illustrates the tradeoff between nominal performance and robustness.

2.4. Challenges of pharmaceutical crystallization control

The first-principles approach requires a model with accurate crystallization kinetics. Data analysis for in situ sensors has improved in recent years due to the use of multivariate statistics for correlating spectral data [5] and the development of better algorithms for estimating particle size distribution based on improved understanding of the operational physics of the sensors [47,53]. However, agglomeration, dendritic growth, polymorphism/
3. The direct design approach

The metastable zone specifies the default region for operating an industrial crystallization process to avoid uncontrolled nucleation. The metastable zone is bounded by the solubility curve and the metastable limit, which can be determined experimentally in an automated laboratory system [12,22]. The vast majority of pharmaceutical crystallization processes are designed so that the desired operation is within the metastable zone. Operation close to the metastable limit (high supersaturation) results in excessive nucleation, lower purity, and higher filtration times. Operation close to the solubility curve (low supersaturation) leads to slow growth and long batch times. The setpoint supersaturation profile is the result of the compromise between the desire for fast crystal growth that occurs near the metastable limit and low nucleation rate that takes place near the solubility curve (see Fig. 5).

The most common practice in the pharmaceutical industry is to use trial-and-error to experimentally determine an operating profile that lies within the metastable zone and gives acceptable crystals. A much more efficient approach is direct design, which uses feedback control to follow a setpoint supersaturation curve in the metastable zone (see Fig. 5) [12,56–58]. The closed-loop control strategy used to implement direct design, shown in Fig. 6, is most accurately referred to as concentration-control (C-control) although it is commonly called supersaturation-control, since the supersaturation is not directly measured, but is calculated from the in-process solution concentration measurement and a previously measured saturation concentration. A direct measurement of the supersaturation during the crystallization process would be preferred since the saturation concentration can vary due to feed impurities. However, there is no sensor for direct supersaturation measurement that has been accepted by the pharmaceutical industry, although prototype supersaturation sensors have been developed [59]. Two control trajectories resulting from application of the direct design approach to the paracetamol–water system is shown in Fig. 7.

This C-control strategy is very different from industrial practice in the pharmaceutical industry, which implements the setpoint trajectory as a function of time. In C-control, the setpoint is state-dependent instead of time-dependent. More specifically, the setpoint in C-control is a desired dependency between two states—the solution concentration and the temperature. The feedback control structure is implemented so that its objective is to provide the desired interrelationship between the two states.

The setpoint concentration-temperature trajectory is suboptimal, in the sense that it does not optimize a performance objective defined as an analytical function of the crystal size distribution. Instead, this approach provides a nearly constant tradeoff between the need to
avoid excessive nucleation (keep the nucleation rate $dN/dt$ small, where $N$ is the number of crystals nucleated and $t$ is time) and to avoid overly long batch times (keep the growth rate $dr/dr$ large, where $r$ is a characteristic dimension of the crystals). If the tradeoff between the nucleation and growth rates is represented in terms of minimizing their ratio $(dN/dt)/(dr/dr) = dN/dr$, then a constant tradeoff would be represented by $dN/dr$ equal to a constant. If the nucleation and growth rates are functions only of supersaturation, then a constant tradeoff would correspond to constant supersaturation.

For many pharmaceutical crystallization processes, the lack of an explicit performance objective in terms of the crystal size distribution is not much of a drawback. Although there are empirical expressions that relate many performance objectives such as filtration time to the crystal size distribution [60], these expressions do not take into account the crystal shape and other factors important for pharmaceutical crystals, and suitable expressions are unavailable for critical drug-specific objectives such as the ability to form stable tablets when compacted with excipients. Without these expressions, first-principles optimization-based approaches use a surrogate objective such as maximizing the mean crystal size or minimizing the amount of nucleated crystal mass, as discussed in several review papers [4,32]. The value of globally optimizing a performance objective is clearly lower when a surrogate objective is used.

The direct design approach does not require the derivation of first-principles models and the associated determination of crystallization kinetics. This is a significant advantage for crystallization processes where phenomena such as dendritic growth occur, for which parametrized descriptions appropriate for parameter estimation are not available. The metastable zone determination and C-control strategy can be easily implemented and even automated using an FTIR spectrometer, an ATR-FTIR probe, a glass vessel, a thermocouple, a cold/hot water source, valves, a chemometrics software package for relating the infrared spectra to the solution concentration, and flexible software such as Visual Basic [12,56,58]. Batches can be run with various agitation speeds and seed types, amounts, and sizes [56] and for several operating curves in the metastable zone [58], to determine the conditions that produce the best product crystals. Such automated crystallizers are expected to become standard in industrial pharmaceutical crystallization laboratories.

4. Comparison of T- and C-control strategies

To simplify the presentation, the subsequent discussion focuses on batch cooling crystallization, although similar considerations hold for antisolvent crystallization.

Current industrial operation of pharmaceutical crystallizers is to follow a batch or semibatch recipe that specifies seed mass, seed time, and a temperature trajectory to follow as a function of time. This temperature trajectory is the setpoint to a lower level “slave” proportional-integral feedback controller that manipulates a valve on flow of cooling fluid to a jacket on the crystallizer. The weakness of this approach is that the concentration–temperature relationship can shift widely due to changes in the kinetics and phase equilibria, which are not directly taken into account in temperature control.

New control strategies have become possible due to recent developments in sensor technologies such as ATR-FTIR spectroscopy that provide in-process measurement of solution concentrations. This has opened up the opportunity to design control systems with much lower sensitivities to the crystal product quality to model uncertainties and process variations. A detailed simulation and experimental study has shown that controlling concentration versus temperature gives much lower sensitivities to most practical disturbances and to variations in the nucleation and growth kinetics [41]. An example where C-control is more robust than T-control by a factor of two is shown in Fig. 8.

Although the above discussion describes C-control in the context of the direct design approach and T-control in the context of the first-principles approach, it is actually possible to implement either approach using C-control or T-control. This is illustrated in the flowchart in Fig. 9. First consider the case where the direct design approach is used to design a T-control system. Batch recipes for current manufacturing-scale pharmaceutical crystallizers are written in terms of temperature versus time setpoints, rather than in terms of solution concentration. While ATR-FTIR spectroscopy has become widely used in pharmaceutical process development laboratories, it has not yet had widespread use at the manufacturing scale.

![Fig. 8. Sensitivity of mean crystal size as a function of variation in the nucleation kinetic exponent $b$, with nominal nucleation and growth kinetics and solubility curve experimentally determined for the crystallization of paracetamol in water. The nominal mean size was 109 µm.](image-url)
Although recent changes in the US Food and Drug Administration’s process certifications and improvements in infrared instrumentation designed for the plant-scale are expected to result in more manufacturing facilities using solution concentration measurements, some pharmaceuticals companies may be reluctant to move away from using batch recipes given in terms of temperature setpoints. In this case, the direct design approach with C-control could be used in the development laboratory, with a concurrent measurement of the temperature and addition rate. If the same localized mixing and cooling could be achieved in the industrial-scale crystallizer, then using these measured temperature and addition rate profiles in the industrial-scale crystallizer with the same seeding procedure and the same seed characteristics (including the same seed mass per unit volume) would produce similar product crystals as in the laboratory-scale crystallizer. Unfortunately, it is usually difficult to achieve the same localized mixing and cooling in an industrial-scale crystallizer, as it has very different heat transfer characteristics and mixing behavior than at the laboratory scale. Furthermore, implementing temperature or addition rate profiles at the industrial scale will not have the reduced sensitivity to disturbances achieved by C-control.

Now consider the case where the first-principles approach is used to design a concentration-based controller instead of a temperature control system. The parameterization of the optimal control trajectory in terms of temperature can just be replaced by a parameterization in terms of the concentration–temperature setpoint and the feedback controller parameters that implement that setpoint. This type of implementation will provide much greater robustness than the optimal temperature control schemes commonly described in the literature.

In a rigid implementation of T-control, the batch time is fixed from run to run. An interesting aspect of C-control is that it allows the batch time to vary, since time is not explicitly considered by the feedback control system. The C-control system is an automated method to compensate for changes in the crystallization kinetics by varying the cooling rate, which changes the batch time. Certainly variability in batch time is preferred over variability in product quality.

The operation of other batch and semibatch processes would benefit from employing a similar operating strategy as C-control, where the dependencies between physically or chemically defined states are used as setpoints. This is more than just the well-known ability of a well-designed state feedback control to suppress the sensitivity of the outputs to disturbances. In crystallization the phase equilibria, the kinetics, and the constraints (being in the metastable zone) are parameterized in terms of a low number of important states with physical meaning. The idea of C-control is to design a state feedback controller with the goal of forcing the control trajectory to operate within the space dimension defined by this low number of states (in this case, concentration and temperature). This physics-based control strategy is natural from the point of view of thermodynamics and kinetics, and it allows the design of robust control systems without requiring highly accurate first-principles models. This type of strategy should be considered whenever a chemical process is to be controlled.

5. Future opportunities

The vast majority of papers on crystallization control have investigated the control of some characteristic (e.g., weight mean size) of the crystal size distribution. However, there has been a rapid growth of experimental literature devoted to the study of polymorphism [61,62], with the desired objective being to produce one polymorph while avoiding others. Unexpected or undesired polymorphic transformation of pharmaceutical is a well-known phenomenon observed during manufacturing processes including crystallization [63]. Because different polymorphs of the same drug compound can have different properties, a thorough evaluation of polymorphism is included in the New Drug Application to demonstrate control over the manufacturing process [2,64].

To ensure consistent production of the desired polymorph, better control over the crystallization process is needed. Strategies for obtaining the desired polymorphs include seeding, choice of solvents, and crystal engineering (see [65–67] and references therein). Although the theoretical framework for solvent-mediated polymorphic transformation [68] is available, it is still difficult to predict and control during pharmaceutical crystallization [29]. In a high-throughput evaluation of various crystallization conditions for paracetamol polymorphs, some irreproducibility was observed, consistent with the known
intractable nature of the polymorphic transformation [69]. For the efficient design of robust and reliable crystallization processes, a more integrated approach based on underlying physical mechanisms is desired rather than trial-and-error. We believe that controlling polymorphic transformation during pharmaceutical crystallization is an area where the implementation of more advanced modeling and control strategies can have a large impact.

Another area where modeling and control strategies can be beneficial is macromolecular crystallization. Due to recent developments in genomics and proteomics, there has been an increasing demand in protein crystallization for structure-based drug design. For faster protein structure determination, high-throughput approaches including microfluidics have been developed for rapid screening of numerous crystallization conditions that result in protein crystal formation [70–72]. Because many of the protein crystals produced this way are not of diffraction quality, there is a need for optimization of high-throughput protein crystallization process to produce large high-quality crystals for structural analysis [73]. It has been shown that larger crystals of several model proteins, such as lysozyme and aprotinin, can be obtained by controlling the supersaturation level by changing the temperature or the ionic strength of the solution [19,74,75]. This strategy or a more advanced control strategy could be used in combination with high-throughput techniques to improve protein crystal growth.

Protein crystallization is also important in the manufacture of biopharmaceuticals. Therapeutic proteins require different crystal characteristics, where small uniform crystals with a narrow distribution are preferred [76]. Also, therapeutic proteins are produced at a much larger scale than proteins for structural studies. In this respect, a better understanding of issues associated with scale-up, such as the effect of mixing on protein crystallization, is desired. Currently, insulin is the only therapeutic protein commonly produced in crystalline form [77]. Recently it was observed that some crystalline proteins exhibit increased stability compared to the amorphous form, suggesting that an increasing number of therapeutic proteins may be produced in the crystalline form in formulation [77]. These recent developments in drug delivery and biotechnology open many opportunities to apply advanced control strategies in the crystallization of proteins and other biomolecules.

6. Conclusions

Systematic approaches to control crystallization processes is desired to reduce time to market, increase the efficiency of drug manufacturing, and improve product consistency. The stability of the pharmaceutical product, its pharmacokinetics, and efficiency are determined by the size distribution and the solid-state phase of the crystals. Recent developments in sensor technologies have enabled the design and implementation of advanced control strategies to pharmaceutical crystallization processes.

This paper described some pharmaceutical crystallization processes that have been controlled using the first-principles approach, and some that have been controlled using the direct design approach. Efforts were summarized that explicitly consider parameter uncertainties and nonidealities in the model assumptions in the first-principles approach. The direct design approach circumvents these modeling issues by using in situ concentration measurements and engineering understanding of the constraints posed by the solubility curve and metastable limit, and the need to follow a control trajectory that trades off the rates of nucleation and growth. Either approach can be implemented with concentration-vs-temperature or temperature-vs-time setpoints, with these implementations having very different sensitivities to disturbances such as deviations in seed characteristics and changes in the contaminant profiles in the feed streams. These types of studies provide recommendations on which control strategy is most appropriate for a particular solute(s)–solvent(s) system.

Potential applications of advanced control to pharmaceutical crystallization include the production of desired crystal polymorphs and protein crystals.

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