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Recent Developments in the Crystallization Process: Toward the Pharmaceutical Industry

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ABSTRACT

Crystallization is one of the oldest separation and purification unit operations, and has recently contributed to significant improvements in producing higher-value products with specific properties and in building efficient manufacturing processes. In this paper, we review recent developments in crystal engineering and crystallization process design and control in the pharmaceutical industry. We systematically summarize recent methods for understanding and developing new types of crystals such as co-crystals, polymorphs, and solvates, and include several milestones such as the launch of the first co-crystal drug, Entresto (Novartis), and the continuous manufacture of Orkambi (Vertex). Conventional batch and continuous processes, which are becoming increasingly mature, are being coupled with various control strategies and the recently developed crystallizers are thus adapting to the needs of the pharmaceutical industry. The development of crystallization process design and control has led to the appearance of several new and innovative crystallizer geometries for continuous operation and improved performance. This paper also reviews major recent progress in the area of process analytical technology.

1. Introduction

The considerable developments in the crystallization process in the pharmaceutical industry have been accelerated by several high-profile cases over the past few decades. For example, thalidomide was marketed as a sedative or hypnotic in the late 1950s and early 1960s and was used by many pregnant women as an anti-nausea agent. However, while (*R*)-(+)-thalidomide served as a sedative, its optical isomer (*S*)-(−)-thalidomide was tragically found to act as a teratogen, resulting in the malformation and death of thousands of infants [1,2]. Another example occurred in 1998, 18 months after the new commercial product ritonavir was launched. A new stable polymorph (form II) was identified in supplies of the drug [3], which greatly reduced ritonavir's solubility compared with the original crystal form, leading to an oral bioavailability problem [4]. In another example in 2008, rotigotine (Neupro) was recalled in the United States and in Europe because of the unexpected appearance of a new polymorph during storage. The topic of maintaining the stability of a solid-state drug in a dosage form has attracted increasingly significant attention in order to ensure product quality [5–7]. Different forms of solid state can lead to variations in product performance, such as a reduction of solubility and dissolution rates or an increase in tablet hardness. Therefore, crystallization technology, as a core technology, was selected as a means of controlling the factors that impact solid-state phase transformations [8]. The US Food and Drug Administration (FDA) and other regulatory agencies have set strict standards to ensure the safety and stability of pharmaceuticals. Further top-down supervision has put forward higher requirements for medicine production, and particularly for the crystallization process. Based on these practices and on advances in nucleation and growth theory at the molecular level [9–12], crystallization is developing from an empirical science to an evidence- and theory-based science.

Because the requirements for improving the efficiency and

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properties of drugs are becoming more stringent, the pharmaceutical manufacturing sector is considering implementing process automation and launching continuous production facilities [13–15]. Precise control of batch processes and the design of continuous processes lead to more reliable products and to a higher production rate. Significant progress has been made in the control of crystallization processes, leading to improvements in different aspects of crystalline product quality including the crystal size distribution (CSD), polymorphic form, morphology, purity, tap density, flowability, compactibility, solubility, and dissolution rate [16–19]. The development of population balance models of crystallization systems has provided a better understanding of the effects of major process variables, such as agglomeration, breakage, additives and impurities, and process control strategies, on the quality of the crystalline material [20]. Two factors promote the research and application of crystallization process control: first, advances in the understanding of the crystallization mechanism; and second, the advent of process analytical technology (PAT) [20–23].

In recent years, continuous crystallization has attracted increasing interest for crystal production. Mixed-suspension mixed-product removal (MSMPR) crystallizer is the most widely used type of continuous crystallizer; it can be coupled with different control strategies, including model-free and model-based approaches [24,25]. The recently developed plug flow crystallizer (PFC), slug flow crystallizer (SFC), microfluidic crystallizer, airlift crystallizer, and impinging jet mixer crystallizer have shown promising results for optimizing crystal qualities. The oscillatory baffled crystallizer (OBC) also exhibits prospects for practical applications [26–29]. In addition, the coupling of other unit operations with the crystallization process and the incorporation of novel designs have enhanced the process efficiency [30–33].

In this review paper, the factors that contribute to the development of the pharmaceutical crystallization process are grouped into two categories: crystal engineering, and advanced solution crystallization process design and control.

2. Crystal engineering

The concept of "crystal engineering" was first proposed by Schmidt [34] in 1971. Today, crystal engineering is a powerful tool for designing pharmaceutical solids with desirable physicochemical properties [35]. The diverse structures in pharmaceutical solids, as highlighted by Cherukuvada and Nangia (Fig. 1) [36], provide considerable maneuverability for optimizing product quality. Various intermolecular interactions and packing modes can be used at the molecular level in order to fine-tune the crystal structure with desired physical and chemical properties [34,37]. "Fine-tuning" includes introducing guest molecules to form multiple-component crystals, screening the crystallization condition for different packing arrangements and/or conformations, and promoting preferred crystal nucleation and growth via tailor-made additives and a solid-liquid surface.

2.1. Polymorphism

After the issue with ritonavir in 1998 served as a warning to pharmacists and crystal engineers [3], polymorphism became increasingly important in both fundamental research and intellectual property rights. In addition to its effect on drug safety, polymorphism is an important factor in the testing of generic drugs, a huge expansion of which has occurred following the expiration of many patents of original drugs.

The question of how to screen the new polymorphs using a systematic approach rather than by chance has become an important one. Llinàs and Goodman [38] summarized the time scale of different crystallization experiments. The rapid crystallization process is more likely to form metastable polymorphs (Fig. 2) [38]. Mirmehrabi and Rohani [39] developed a method based on atomic electronegativity for selecting a suitable solvent in the preparation of a desired polymorph. Hydrogen-bonding ability can be predicted by calculating the partial charge distribution of solvent and solute molecules. A comprehensive database was explored by Allesø et al. [40], containing 218 organic solvents and 24 property descriptors. Principal component analysis and self-organizing map analyses enable the convenient and rapid selection of diverse solvents. Besides the organized solvent database, high-throughput crystallization platforms such as CrystalMax (TransForm Pharmaceuticals, Inc.) and Crystal16™ (Avantium Technologies, Inc.) were developed to help

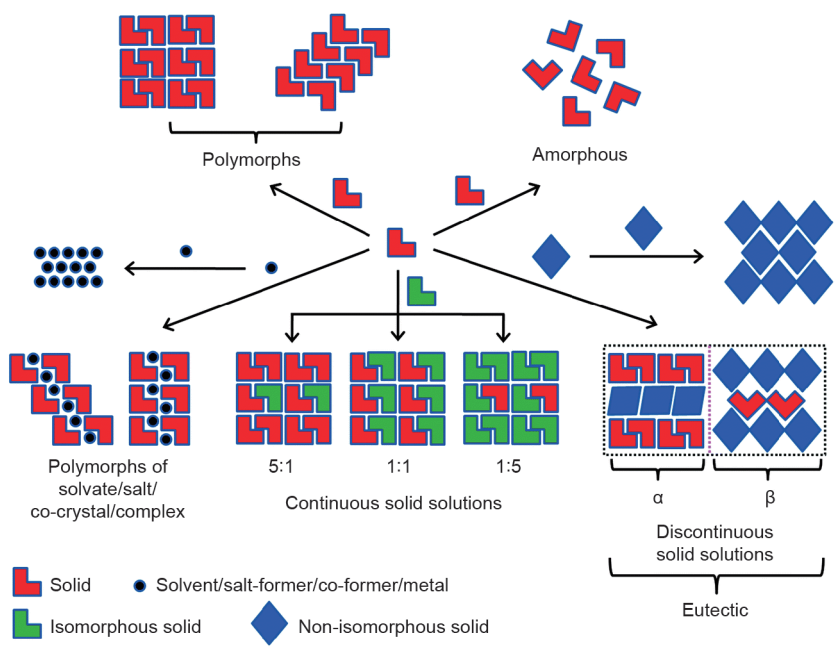

Fig. 1. Structural diversity of pharmaceutical solids. (Caption and figure reprinted with permission from Ref. [36])

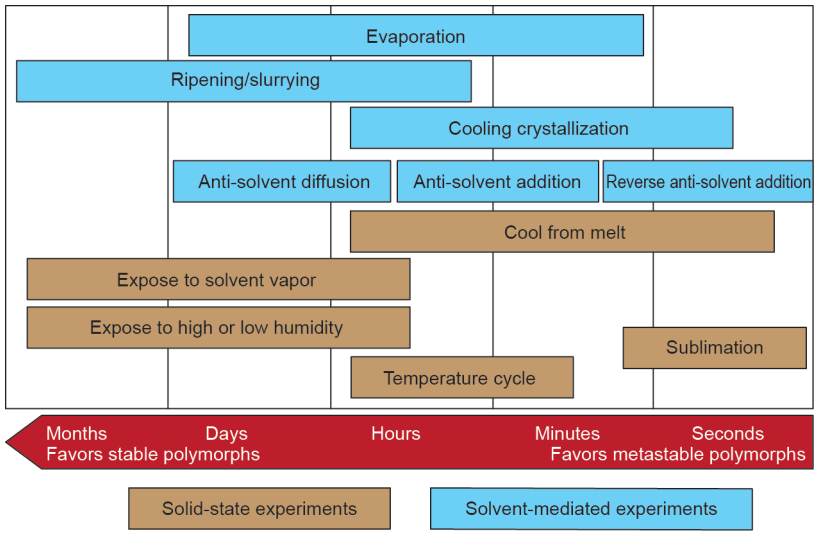

Fig. 2. Crystallization experiments showing the timescales that can be employed to favor stable or metastable polymorphs. (Caption and figure reprinted with permission from Ref. [38])

screen the polymorphs of a given active pharmaceutical ingredient with high efficiency. Pfund and Matzger [41] created a high-density-format polymer-induced heteronucleation (PIHn) platform, in which 288 distinct polymers act as crystallization directors for obtaining novel solid forms. Advances in comprehensive polymorphic screening based on solvent selection and high-throughput platforms have paved the way toward the ultimate goal of harvesting the desired polymorphs. The development of a multivariable control system (i.e., controlling solvent, temperature, and supersaturation) coupled with high-throughput powder X-ray diffraction (PXRD) or Raman detectors in an automated fashion is highly desirable for the pharmaceutical industry [41,42]. By comparing medicinal qualities based on all possible solid forms, the best drug candidate can be selected for further development.

The transformation between different forms of pharmaceutical ingredients has attracted considerable attention in recent years as researchers seek to produce or maintain the stability of a specific crystal form. Much research has been conducted to study the mechanisms and conditions of transformation. Two kinds of mechanisms of polymorphic transformation that affect the specific form produced and drug stability—solvent-mediated and solid-state—have been studied in the pharmaceutical industry. Driven by differences in solubility, solvent-mediated transformation is generally divided into three steps: ① the dissolution of the unstable phase, ② nucleation, and ③ the growth of the stable form [43]. In the past few years, modeling and *in situ* composite sensor arrays have helped researchers to understand mechanisms and optimize the conditions in various systems [44–46]. Temperature, stirring speed, solvent type, pH, seeding, and other variables have been emphasized by researchers, with the nucleation rate or the growth rate of the new crystal form usually being specified as the rate-determining step. Takeguchi et al. [47] successfully obtained the desired high-purity polymorph in the first step during a scale-up manufacturing process. Through solvent- and temperature-screening experiments, higher temperature and hydrogen-bond-donating solvents that promote the formation of hydrogen bonds were found to be preferable in the optimization and designing process. In solid-state transformation, polymorphic transformation can happen during the formulation and storage processes. Influential factors include drying, milling, granulation, and tabletting, as well as temperature and humidity changes during the storage period. Extensive research on these factors provides guidelines on the stability of the metastable form during formulation and storage. Additives and some excipients have exhibited inhibiting effects on polymorphic transformation, indicating a promising method of stabilizing the metastable crystal form.

As the study of "polymorphism" suggests, an amorphous phase can be treated as a special kind of polymorphic phase [48]. The development of an amorphous pharmaceutical lies in the competition between the advantages gained in the solubility and dissolution rates, and the disadvantage of enhanced instability. Developing an amorphous drug is an attractive method to improve the oral delivery of poorly water-soluble drugs, as shown in Fig. 3 [49–52]. Numerous cases have been successfully developed to date, and the solubility enhancement can be assessed using measured thermodynamic quantities [53,54]. However, there is a challenge of instability due to higher thermodynamic activity in the amorphous state. To inhibit the inherent tendency of the amorphous phase to recrystallize, processing and storage conditions as well as various newer polymers and excipients have been exploited. Amorphous solid dispersions can be stabilized by stabilizers, which can potentially modify the glass transition temperature or form non-covalent interactions, thus impacting the rate of crystallization [55]. As a single-phase blend, co-amorphous formulations can be produced by using low-weight co-formers, which can significantly reduce the amount of stabilizers compared with polymer and mesoporous silica [56,57].

2.2. Modification by guest molecules

By introducing guest molecules, crystal engineering provides a number of routes to optimize the properties of active pharmaceutical ingredients (APIs) and may also be used as a strategy to extend (or avoid) patent protection in the development of new drugs. Guest molecules such as salt-formers, co-formers, and solvates can occupy the crystal lattice to remedy the deficiency of the original crystals without changing the chemical identity or biological activity of the API. Properties of interest include the crystal size, shape, stability, and especially the aqueous solubility, because up to 90% of new API candidates under development are poorly water soluble [57].

2.2.1. Salt

Salt formation is widely used with ionizable drugs, and over half of the APIs approved by the FDA are pharmaceutical salts. Ionized APIs usually have greater solubility and dissolution rate, which are achieved by forming a corresponding salt or by modifying the

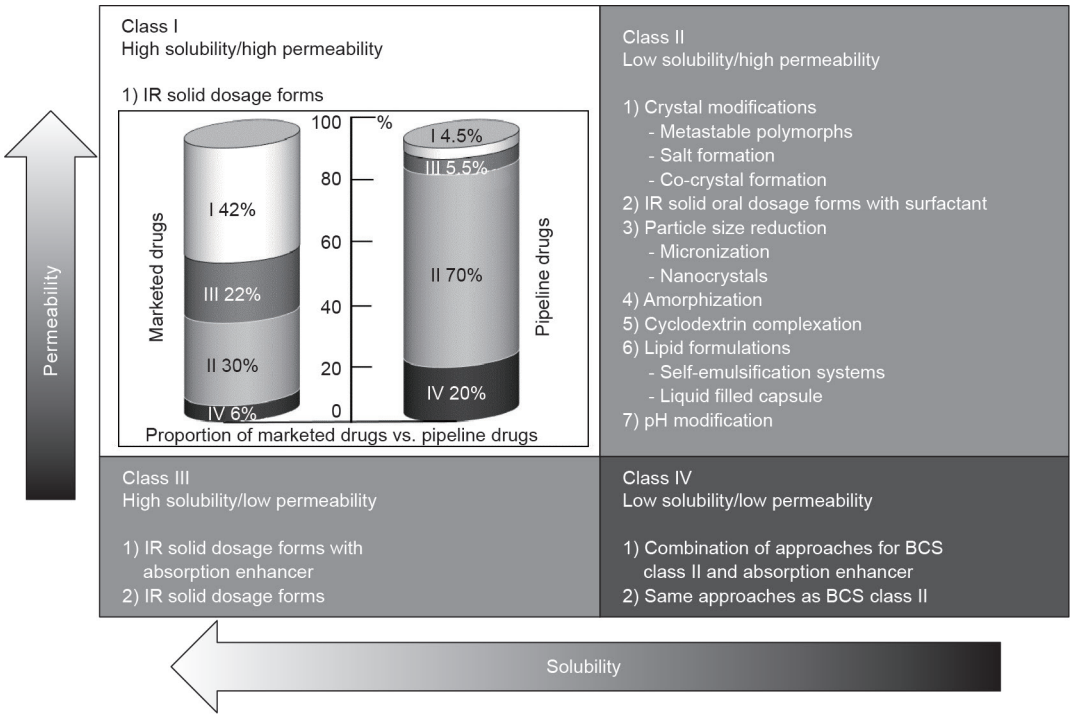

Fig. 3. The biopharmaceutics classification system (BCS), as defined by Amidon et al. [51], divided into four classes of solubility. Viable formulation options based on the BCS and the proportion of marketed drugs versus pipeline drugs (insert column chart). (Adapted from Refs. [49,52])

solution pH. More and more applications of salt drugs have been developed in order to improve solubility and stability, as well as to extend intellectual property protection [58–62]. The presence of a two-unit difference in pK_a between APIs and acid/bases to ensure proton transfer is a well-known screening principle. High-throughput technologies have been exploited for this purpose. Consideration should also be given to safety and to the common ion effect. Typical examples show the existence of common ions that may suppress the dissolution of a salt and decrease its solubility. Thackaberry [63] reviewed the non-clinical toxicity of counter ions in pharmaceutical salts. Additional research to provide examples of typical counter ions, especially commonly used anions/cations, would help to optimize salt-formers and formulation methods in the future.

2.2.2. Co-crystals

Starting with the first introduction of co-crystals into the pharmaceutical industry in the early 2000s, and through to the launch of the first commercial product, Entresto (Novartis), in 2015, great progress has been made in the development of pharmaceutical co-crystals, and hundreds of case studies have been published [64–66]. We now know that co-crystals are single-phase crystalline solids that include two or more different molecules and/or ionic compounds in a stoichiometric ratio [67]. The FDA recently released a paper outlining standards and guidance for the development of pharmaceutical co-crystals and providing specifications for how to develop and test co-crystal drugs [68]. Various co-crystal model compounds have demonstrated improved physicochemical performance that could benefit the pharmaceutical industry. Improvements have been reported in solubility/dissolution rate, stability, bioavailability, melting point, mechanical properties, permeability, and so forth [69–73].

In general, there are three main steps in the development of a new co-crystal drug, prior to final approval: ① the design and selection of the co-former and experimental screening; ② an evaluation of the solid properties and preclinical performance; and ③ formulation and process scale-up [74]. Table 1 [74,76,77] lists recently developed co-former selection methods and experimental screening technologies. Lin et al. [75] developed a differential scanning calorimetry Fourier-transform infrared (DSC-FTIR) technique, which can realize a one-step screening and qualitative detection procedure for co-crystal formation in real time. A process that involves theoretical prediction combined with a high-throughput and/or quick one-step method is being developed to accelerate co-crystal formation.

Research on multidrug co-crystals has boosted the development of effective therapeutic hybrids [76]. As more co-crystals appear in the open literature and in patents publications, they present challenges regarding the large-scale synthesis and stability of these drugs in the presence of excipients.

2.2.3. Solvates

When a solvent molecule is crystallized with a host molecule in the same crystal lattice, whether stoichiometrically or non-stoichiometrically, a new solid phase called the solvate is formed. The solvate usually exhibits different physicochemical properties than the original solid phase. Hydrates are the most important kind of pharmaceutical solvate because of their nontoxic and stable properties [78]. These properties are due to the excellent ability of water molecules to form hydrogen bonds, in comparison with other organic solvents. A growing number of studies have focused on the solvent-molecule interactions that trigger solvate formation, and have tried to establish principles for solvate screening, preparation, and storage. The main factors involved in solvate formation are considered to be the hydrogen bond acceptor and donor abilities and the polarity of the solvent [79]. Two challenges remain in solvate drug development: ① The screening and exploration of the formation, transformation, and storage conditions of a solvate take a great deal of time and carry a high cost [80]; and ② it is difficult to distinguish between stoichiometric and non-stoichiometric solvates when the solvent content is similar. These challenges leave considerable

Table 1
Co-former selection methods and experimental screening technologies for co-crystal preparation. (Summarized from Refs. [74,76,77])

	Selection/screening methods	Key notes
Co-former selection methods	Supramolecular compatibility	Based on Cambridge Structural Database or Hansen solubility parameter prediction
	Shape and polarity analysis	Based on shape and polarity of co-former and API
	Lattice energy calculation	Based on lattice energy minimization methodology
	Virtual co-crystal screening	Based on molecular electrostatic potential surfaces
	Conductor-like screening	Fluid-phase thermodynamics theory conductor-like screening model
Experimental screening technologies	Solvent evaporation	The most widely used, cost-efficient method
	Solution co-crystallization	Cooling, anti-solvent, slurry, ultrasound-assisted, and microwave-assisted crystallization
	Mechanical grinding	Neat solvent/polymer-assisted grinding
	Supercritical fluid technology	Co-crystallization with supercritical solvent
	DSC-FTIR micro spectroscopy	Simultaneous DSC-FTIR micro spectroscopic system
	High-throughput technology	Using *in situ* Raman microscope and a multi-well plate, high efficiency
	Spray drying	A promising method for large-scale co-crystal generation
	High-shear granulation	High-shear wet granulation

room for controversial issues in patents and in the development of solvate drugs [78].

2.3. Crystal structure prediction

Crystal structure prediction (CSP) methods can provide a microscopic perspective to supplement experimental studies on thermodynamic stability and polymorphism, and to guide the course of experimentation. Substantial progress has been made in the computed crystal energy landscape over the past decade, combined with the results from industrial crystallization processes [81,82]. A series of blind tests of CSP that deal with flexible molecules have been performed since 1999, hosted by the Cambridge Crystallographic Data Center (CCDC) [82]. The prevailing consensus is that the experimental results analysis and computational optimization are based on close packing, conformation preferences, and intermolecular interactions between API molecules and guest molecules. CSP can provide reliable guidance in identifying the most stable form of conformation through the lattice energy gap. However, several bottlenecks hinder the progress of CSP as an accurate method for solid-form screening: ① The vast number of potential crystal structures poses a challenge for computational work when dealing with crystal cell parameters and flexible torsion angles; ② there are differences between the real crystal free energy and the calculated lattice energy at 0 K; and ③ there is a lack of kinetic knowledge of crystal nucleation and growth, and of the combination of thermodynamic and kinetic simulation [83].

2.4. Other developments in crystal engineering

Researchers have continued to explore the theory and applications of crystal nucleation and morphology over the past decades. Two-step nucleation theory and crystal morphology prediction were developed in recent years, and have been applied in various practices [84,85]. Tailor-made or functional additives and nanoporous templates have been developed that permit the selective nucleation and growth of a specific crystal form, thus significantly affecting the crystallization process and the product properties [86,87]. Diao et al. [88,89] conducted a systemic study on the role of surface chemistry and the morphology of various polymeric substrates on heterogeneous nucleation. Ultrasound- and microwave-assisted crystallization have also shown considerable prospects for intensifying the nucleation and growth processes [90]. Recent studies reported on the gel formation or jelly-like phase-mediated crystallization of inefficient crystallization systems, which provides a new method of producing crystals [91,92]. However, challenges still remain regarding undesired phenomena such as liquid-liquid phase separation, jelly-like phase formation, and highly viscous systems.

3. Solution crystallization process control and design

Prior to the 1990s, solution crystallization process control was limited because of a lack of sufficiently accurate *in situ* sensors (i.e., to monitor concentration, CSD, and polymorphic nature) and a lack of understanding about the processing factors of crystallization [23]. Advances in crystallization process design and control have occurred over the last couple of decades, based on the development of real-time monitoring and on emerging commercial software for the crystallization process, such as the gCRYSTAL®, DynoChem®, and COMSOL Multiphysics® software. Process-modeling software permits more effective design and operation of crystallizers, and facilitates the optimization of seeding, operation profiling, and scaling up. For example, computational fluid dynamics (CFD) simulations help researchers to understand the hydrodynamics and crystallization kinetics that occur during the scale-up process, and can be used to guide scale-up strategies. In addition, PAT enables better control and design of pharmaceutical processes; its goals of quality-by-design (QbD) and quality-by-control (QbC) help to improve efficiency and regulate risk in the pharmaceutical industry.

3.1. Process analytical technology

The PAT concept was proposed by the FDA in 2004 to ensure final product quality by the timely monitoring, analyzing, and controlling of process parameters. During the last decade, a wide usage of *in situ* monitoring technologies, including attenuated total reflectance Fourier-transform infrared (ATR-FTIR) spectroscopy, focused beam reflectance measurement (FBRM), Raman spectroscopy, and particle vision measurement (PVM), has helped to improve data quality and agility, as well as process reliability and performance. ATR-FTIR enables accurate monitoring and control of the solution concentration. Its accuracy and agility have been improved by purging the background and using chemometrics techniques on multiple wavenumbers in order to correlate spectral intensity and solution concentration. The use of fiber optics has improved flexibility and promoted wide application of the PAT concept in both academia and the industry. The continuous tracking of particle count and size distributions by FBRM has made quantitative calculations available for the development of accurate crystallization models. The newest generation of FBRM has overcome the probe-fouling problem, which required frequent cleaning during the monitoring period [93]. As a

well-developed technology, Raman spectroscopy has been used to identify differences in polymorphism and to test solvent-mediated polymorphic transformation, solution concentration, and the polymorphic ratio of the solid mixture [94]. PVM can track the real-time visualization of particles in progress and can provide image-based particle trending, crystal growth, polymorphic transformation, agglomeration, and oiling out in crystallization processes. Combined with Raman spectroscopy and FBRM, image-based tracking can help to monitor and control crystal form, size, and shape [94]. Based on these technologies, the *in situ* monitoring of the properties of both the liquid and solid phases has become possible.

In recent years, attempts have been made to develop PAT-based high-performance sensors as well as monitoring and control methods. Ref. [95], a multi-author review paper, clearly presents the state-of-the-art progress and current trends of PAT from a multi-disciplinary perspective. The basic principles of different PAT sensors can be divided into imaging, spectroscopy, acoustic signals, and electronic signals. Spectroscopy is the most widely used PAT in practice, and image-based monitoring and analysis technology has shown potential applications. Simon et al. [96] introduced endoscopy/stroboscopy-based technology, which is usually used in medical diagnosis, for use in the crystallization process; this technology can be used to acquire richer information such as particle color, transparency, shape, and size. El Arnaout et al. [97] used an in-line imaging probe with an automated analysis algorithm to provide high-quality information on particle shape, size, and counts. However, challenges still exist regarding image recognition (particle overlapping) and mathematical modeling for particle feature analysis. Coupling ultrasonic velocity and attenuation, a new ultrasound technique has shown some success in simultaneously monitoring solution concentration, particle size, and suspension density [98]. Acoustic emission (AE) was developed as a non-contact in-line technology to track both the liquid and solid phases in suspension [99]. AE has the advantages of pre-nucleation acoustic signals and real-time crystal purity measuring during the crystallization process.

PAT-based manufacturing has shown the ability to regulate process variability and final product quality. However, PAT development faces certain challenges, including: ① the integration of signals from different PAT sensors, which would require chemometrics analysis and would affect control strategy; ② the development of high-accuracy multicomponent monitoring systems for multicomponent suspensions, in the presence of other species and impurities; ③ high-quality solid-phase characterization and analysis, especially at high-suspension density; and ④ the application of multiple sensors in the emerging continuous crystallization process.

3.2. Solution crystallization process control

3.2.1. Model-free control strategy

Model-free control strategy is carried out by means of a predefined temperature or solvent/anti-solvent ratio trajectory. It is actually a feedback control strategy that is based on the difference between the set points and the real-time measurements of factors such as concentration/supersaturation, particle counts, temperature or concentration (T/C) control, direct nucleation control (DNC), or their combinations. Temperature control uses a predefined temperature trajectory to control nucleation and growth processes. However, this strategy can be seriously influenced by uncertainties in the operation optimal trajectory and by disturbances during the process [100]. Concentration control was developed in the past decade and has benefited from progress in real-time and accurate concentration measurement (e.g., ATR-FTIR, ATR-UV/Vis). Chemometrics and calibration-free strategies for ATR-FTIR were successfully developed in order to construct the operating zone, which is usually confined between the solubility curve and the metastable limit [17,101]. In comparison with the liquid-phase measurement of T/C control, DNC directly measures the counts of solid particles and controls nucleation and dissolution through a feedback control strategy [102]. DNC has shown promising applications in fines removal, continuous seed preparation, mitigating the effects of breakage, and producing more uniform crystals. Yang et al. [25] first implemented the feedback DNC method in single-stage and two-stage continuous MSMPR crystallization processes; they achieved the desired CSD and were able to effectively suppress disturbances. The combination of DNC and T/C control methods has an advantage over DNC in the nucleation process and over T/C control in crystal growth, although such a combination inevitably increases the complexity of the system.

3.2.2. Model-based control strategy

By combining crystallization process modeling and control with optimization algorithms, model-based control strategies can be developed to provide tight quality control in the presence of uncertainties and disturbances, while requiring fewer experiments. Fig. 4 [103] provides a comparison of the frameworks of the model-based and model-free approaches. Model-based optimization can be fulfilled by means of a dynamic optimizer, by calculating the optimal trajectory based on real-time sampled data.

Model-based optimization is subject to the constraints of the system. To ensure consistency of the process model, especially for the model predictive control (MPC) strategy, a state observer/estimator can be used to estimate the internal states of the real crystallization process, using a limited quantity of input and output data from the real system. The objective functions of model-based optimization include increasing the product yield and mean crystal size, or reducing batch/residence time and narrowing the width of the CSD. Attempts have been made to better understand process mechanisms, constraints and the effect of disturbances, process uncertainties, and model/process mismatches. Mesbah et al. [104] developed a model-based approach to control the growth rate below a constrained value. The growth rate was correlated with the measured CSD through an extended Luenberger-type observer, and effective control was implemented, thus improving yield and product quality. The solute concentration can also be controlled by using a phase diagram assisted by an analytical CSD estimator [105], or by using the concentration control strategy in a hierarchical structure [106]. Trifkovic et al. [107] proposed a novel way to directly calculate the nucleation and growth rates from the moments of particle population density obtained by FBRM. By combining the crystallization model with the population and mass balances, the optimal anti-solvent flow rate was obtained using both a single- and multi-objective optimization algorithm. The nucleation rate was suppressed and the growth rate was minimized. Continuing this line of investigation, Sheikhzadeh et al. [108] implemented a real-time optimization of those objectives. MPC strategy has demonstrated advantages for multivariable control systems [109,110]. In future, the analysis of multiple variables will have higher requirements; systematic analysis methods of statistical process control have shown potential application in this field [20].

3.3. Design of innovative solution crystallization processes

3.3.1. Solution process design based on APIs

Conventional crystallization technologies are mainly classified as solution crystallization, melt crystallization, or reaction crystallization. New types of crystallization processes have also been proposed, including membrane crystallization and supercritical fluid crystallization. The selection of a specific type of crystallization process mostly depends on the features of the model compound. For example, sodium chloride is prone to evaporation crystallization due to the limited sensitivity of solubility versus temperature;

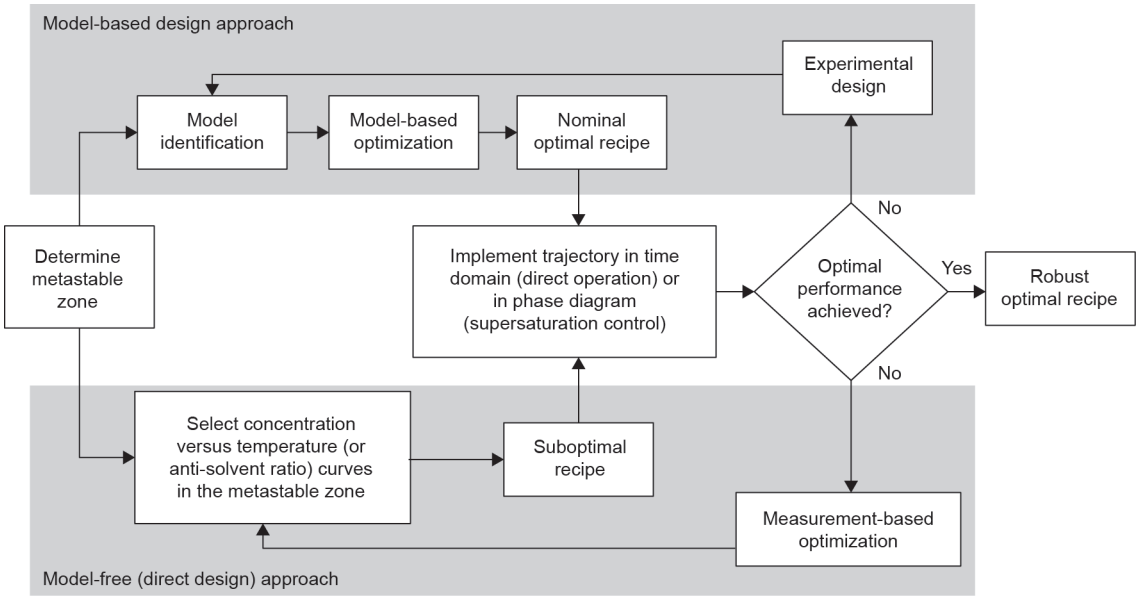

Fig. 4. Schematic representation of the model-based and model-free approaches for crystallization systems. (Caption and figure reprinted with permission from Ref. [103])

in contrast, APIs are more likely to require cooling crystallization, or a combination of cooling and anti-solvent crystallization, due to thermal sensitivity. Specific operational strategies have been developed to optimize the process and product, such as seeding, fines removal, use of an optimal cooling rate or evaporation rate, and use of a reactant/anti-solvent addition rate. However, various properties of APIs can lead to difficulties during the process of crystallization, such as oiling out, the gelation phenomenon, and so forth.

Oiling out is usually considered to be an undesirable phenomenon in the crystallization process [111]. De Albuquerque and Mazzotti [112] developed a robust process to avoid oiling out in a vanillin and water system. By using thermodynamic modeling and a phase diagram, and designing the operational trajectory, the crystallization yield and crystal purity were maximized. It is interesting to note that Takasuga and Ooshima [113] designed oiling-out crystallization in order to control crystal size, and resolved the problem of the low recovery of crystal product that occurred in a single-phase crystallization process. The crystal size can be controlled by changing the oil droplet size, which can be affected by the agitational speed and composition. In fact, gelation can completely break off the crystallization process. Yin et al. [114] reported the reason for gelation and evaluated the polarity and Hanson solubility parameters for the gelation process. Bao et al. [91,92] developed a gel-mediated crystallization process for cefotaxime sodium and valnemulin hydrogen tartrate that produced the desired crystals.

Even though crystal size and shape can be optimized by the process control method, some crystal properties are still determined by the crystal's molecular structure. For example, the crystals of cephalosporins cannot usually grow larger than 100 μm. To avoid crystals with a small size and with needle- or flake-like shapes, spherical agglomeration and spherical crystallization were used to successfully optimize the product properties of cephalosporins. Yang et al. [115] realized a spherical growth strategy using gelatin as an induced polymer to overcome the disadvantages of the flake-like shape of *L*-tryptophan. The introduction of an induced polymer and the optimization of concentration and temperature greatly improved the bulk properties of *L*-tryptophan particles, such as particle size distribution, bulk density, and flow property. Choosing process design considerations that were specific to the features of the model compounds played an important role in improving the product quality and efficiency of the process.

3.3.2. New types of crystallizers

Crystallization operations can be classified into batch and continuous processes, both of which have advantages and disadvantages. Continuous crystallizers such as the Oslo-type crystallizer are suitable for fragile crystals because they permit crystals to grow without intense mechanical attrition. The details of other types of crystallizers, such as forced-circulation (FC) crystallizers, draft tube baffle (DTB) crystallizers, and so forth, have been reviewed by Rohani [111] and Paroli [116]. This section highlights several newly developed crystallizer types and discusses their advantages and disadvantages.

The recently developed microfluidic crystallization technology has the advantages of being able to adapt to trace amounts of sample and good mass/heat transfer performance, and also shows high efficiency and accuracy in experiments. A typical microfluidic crystallizer is shown in Fig. 5(a) [117], with channels ranging from tens to hundreds of micrometers. Crystallization takes place in the defined nanoliter volumes. This method permits high efficiency and accuracy in screening crystallization conditions, measuring solubility, and measuring the kinetics of nucleation and growth [118–120]. It offers the potential to grow large single crystals and to study the mechanism of crystallization, while suffering from limited scale-up potential for industrial applications. In addition, using micro mixing, the impinging jet crystallizer can effectively mix the solution and anti-solvent or reactants together, and achieve a uniformly highly supersaturated solution. This method has been shown to be promising for producing small particles with narrow CSD [121,122]. Recently, Liu et al. [123] presented an impinging jet mixer-batch-tubular crystallizer for reactive crystallization; this technology can run continuously and is easy to scale up. To narrow the CSD, microwave-/ultrasound-assisted crystallizers and airlift crystallizers have been designed to reduce fine crystals [31,90,124–126]. Microwaves can quickly dissolve fine particles and reduce the heating cycles that are needed to remove fine crystals in batch crystallization [90]. Ultrasound can effectively trigger nucleation and narrow the CSD and metastable zone width [124]. Thus, both microwave- and ultrasound-assisted crystallization can effectively reduce batch time and improve product quality. Instead of using an impeller in conventional stirred crystallizers, or moving internal parts in Oslo-type crystallizers, an airlift crystallizer (Fig. 5(c)) [127] can effectively reduce crystal collisions using air mixing and can suppress secondary nucleation [31].

Compared with batch operation, continuous processes offer high production efficiency and can reduce product variability without interruptions. The continuous manufacture of Orkambi (Vertex) and the conversion of the Darunavir (Janssen) manufacturing process from batch to continuous were approved by the FDA in July 2015 and April 2016, respectively. PFCs facilitate the crystallization process along the length of the crystallizer, resulting in a time that is similar to that of a batch process. The back-mixing in a PFC is eliminated or minimized, effectively decreasing agglomeration and secondary nucleation and leading to a narrower CSD. Because of the lower mixing intensity, methods to induce nucleation must be considered. Raphael and Rohani [26] used Kenics static mixers to promote mixing at the entrance of a tubular crystallizer. Alvarez and Myerson [27] combined Kenics static mixers with a multiple-points anti-solvent strategy to optimize the CSD. Eder et al. [128] developed a Kenics continuously seeded process for the production of APIs in a tubular crystallizer. An idea has been presented to combine an anti-solvent tube with a Kenics static mixer in order to promote homogeneous mixing in a double-jacketed tubular crystallizer, as shown in Fig. 6. Unlike a PFC, an OBC, as shown in Fig. 5(b), uses periodically spaced restrictions to produce oscillatory mixing. The advantages of the OBC include enhanced heat and mass transfers, reduced induction time and residence time, and narrower metastable zone width and CSD [29,129]. Commercialized crystallizers from NiTech Solutions (Scotland) have contributed to propelling forward the application of the continuous OBC in industry.

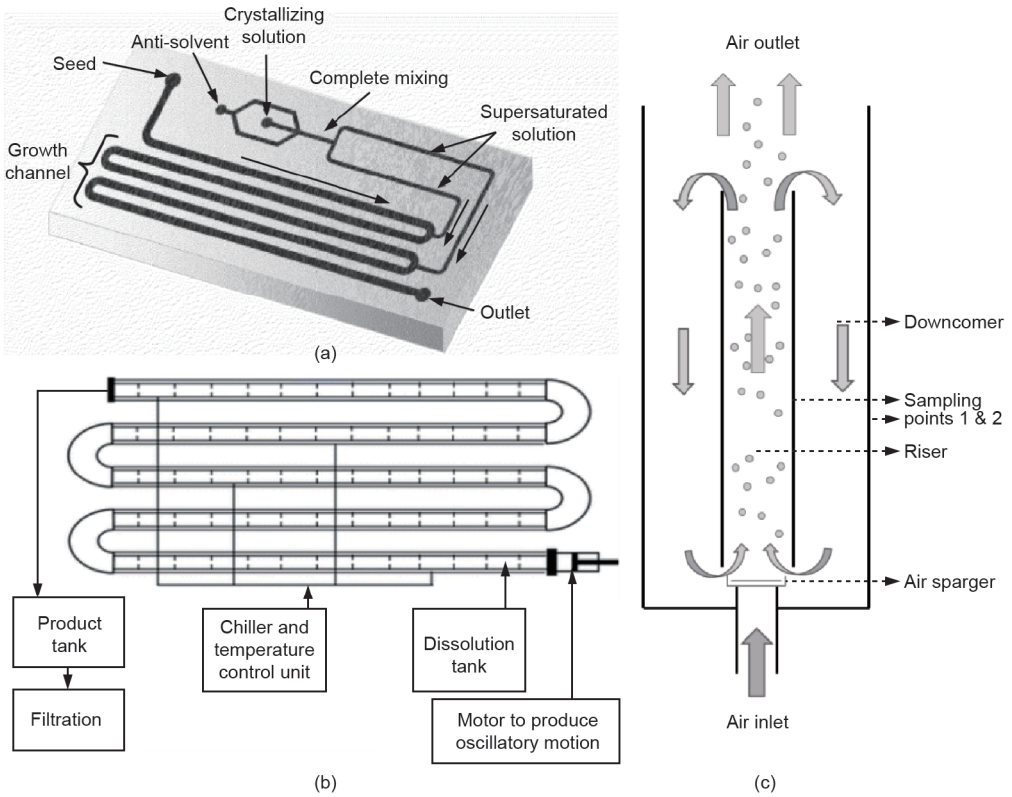

Fig. 5. Schematic drawings of (a) a typical microfluidic crystallizer, (b) a continuous oscillatory baffled crystallizer, and (c) an internal circulation airlift crystallizer. (Parts (a) and (b) are adapted from Refs. [117,129])

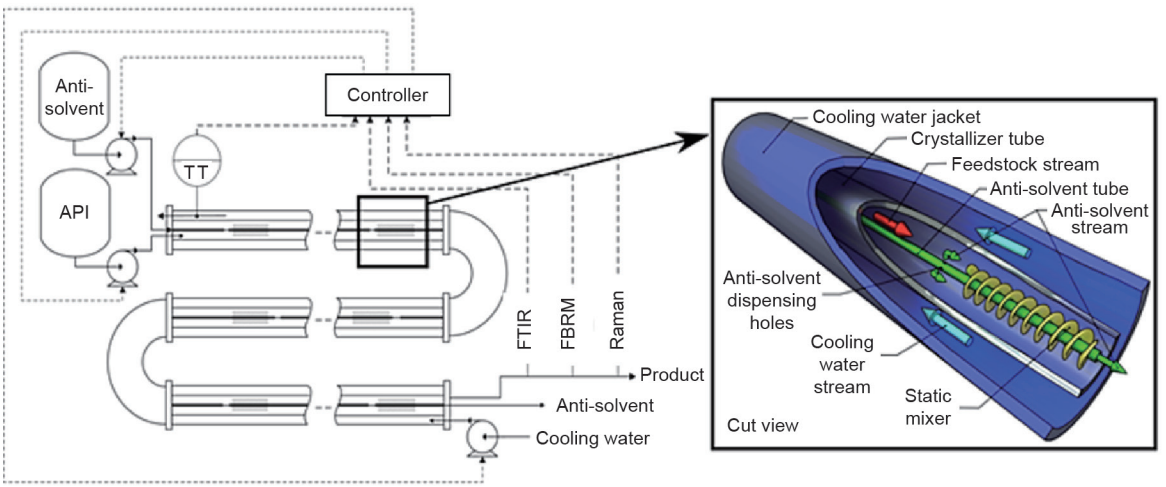

Fig. 6. Schematic diagram of a double-jacket tubular crystallizer with an anti-solvent tube and a Kenics static mixer inside to promote homogeneous mixing. TT: temperature transmitter.

4. Conclusions

This paper highlighted recent developments in the crystallization of pharmaceuticals in industry, with a focus on crystal engineering and on crystallization process design and control. Advances in our current understanding of crystal engineering and in the design of novel crystallizers and crystallization processes have helped to develop scientific methods for polymorphic screening and product properties optimization. However, challenges remain: There is a need for high-throughput technologies for the *in situ* screening and testing of new crystals and the prediction of crystal structures. Other challenges involve dealing with oiling out and undesired gelation phenomena. In crystal engineering, remaining challenges involve understanding and controlling the nucleation of desired forms and polymorphic transformation through the use of solvents and additives. Although thousands of studies on co-crystals have been published, further challenges remain in bringing co-crystals to market in a safe and well-regulated way. In addition, the robustness of a product's quality and of the production of co-crystals is a bottleneck in practical application. The flexibility and economics of batch crystallizers can be enhanced through different control strategies, but continuous crystallizers are preferable due to their higher process efficiency and constant product quality. Differences in lab-scale and industrial-scale crystallization pose scale-up challenges in areas such as hydrodynamics, heat and mass transfer performance, and so forth. Scaling up can lead to changes in nucleation, growth, breakage, and agglomeration, and will affect crystal qualities. Operational strategies such as seeding, use of a cooling rate, use of an anti-solvent addition rate, and establishing a mode are vitally important during the scale-up process. Opportunities and challenges exist in the novel design of crystallization processes and crystallizers, which will help researchers to achieve the objective of precise process control, constant product quality, and robust and efficient process operation.

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Compliance with ethics guidelines

Zhenguo Gao, Sohrab Rohani, Junbo Gong, and Jingkang Wang declare that they have no conflict of interest or financial conflicts to disclose.

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