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Progress of Pharmaceutical Continuous Crystallization

Dejiang Zhang [a,b], Shijie Xu [a,b], Shichao Du [a,b], Jingkang Wang [a,b], Junbo Gong [a,b,*]

[a] School of Chemical Engineering and Technology, State Key Laboratory of Chemical Engineering, Tianjin University, Tianjin 300072, China
[b] Collaborative Innovation Center of Chemical Science and Chemical Engineering, Tianjin University, Tianjin 300072, China

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ABSTRACT

Crystallization is an important unit operation in the pharmaceutical industry. At present, most pharmaceutical crystallization processes are performed in batches. However, due to product variability from batch to batch and to the low productivity of batch crystallization, continuous crystallization is gaining increasing attention. In the past few years, progress has been made to allow the products of continuous crystallization to meet different requirements. This review summarizes the progress in pharmaceutical continuous crystallization from a product engineering perspective. The advantages and disadvantages of different types of continuous crystallization are compared, with the main difference between the two main types of crystallizers being their difference in residence time distribution. Approaches that use continuous crystallization to meet different quality requirements are summarized. Continuous crystallization has advantages in terms of size and morphology control. However, it also has the problem of a process yield that may be lower than that of a batch process, especially in the production of chirality crystals. Finally, different control strategies are compared.

1. Introduction

Crystallization, which can be used to determine numerous product properties in the solid-liquid separation process, is not only a separation and purification process but also a refining process in the pharmaceutical industry [1–3]. Of active pharmaceutical ingredients (APIs), 90% are crystals of small organic molecules [4]. At present, most crystallization processes in the pharmaceutical industry are performed in batches [5]. Although batch crystallization has been widely studied, the problems of batch-to-batch variability and processing inefficiency are still present [6]. As a means of dealing with these problems, continuous crystallization has received increasing attention due to its characteristics of constant conditions at the steady state and high product efficiency [7–9]. Continuous crystallization is a unit operation in which the mother liquid is continuously flowed in, and the slurry is continuously withdrawn. According to an analysis by Schaber et al. [10], the continuous crystallization process can save 9% to 40% of the production cost. In this review, we discuss how to meet the different pharmaceutical quality requirements using continuous crystallization, and outline the different control strategies that are used in continuous crystallization.

2. Comparison between two types of continuous crystallization

There are two main types of continuous crystallizer: the mixed-suspension mixed-product removal (MSMPR) crystallizer and the continuous tubular crystallizer [11]. Fig. 1 shows a schematic diagram of the two general types of crystallizer.

The residence time distribution in the MSMPR crystallizer is relatively wide and long, compared with the tubular crystallizer, in which it is relatively narrow and short. Table 1 [6] provides a comparison of these two types of crystallizers.

3. General requirements for crystal products

Numerous studies have been carried out on converting batch

* Corresponding author.
E-mail address: junbo_gong@tju.edu.cn

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crystallization processes into continuous crystallization ones [6,11,12]. In order for a continuous crystallization process to substitute for a batch crystallization process, the quality of the continuous products should meet the quality that is achievable in batch products [13].

As shown in Fig. 2, the general quality requirements for pharmaceutical crystallization are yield, purity, size, morphology, polymorphism, and chirality [11]. However, the process of continuous crystallization is different from a batch process [14], and must be carefully designed and controlled. In general, two problems must be solved in order to employ a continuous process in pharmaceutical crystallization: The first is the design problem, which determines whether a new designed crystallization process is able to produce the desired crystals; and the second is the control problem, which determines whether a continuous crystallization process can produce the desired crystals in a stable manner. In the past few years, a certain amount of progress has been made to allow the products of continuous crystallization to meet the abovementioned requirements. The following sections discuss this progress from a product engineering perspective.

4. Continuous MSMPR crystallizers in pharmaceutical crystallization

The MSMPR crystallizer is one of the most commonly used continuous crystallizers. In general, the MSMPR crystallizer is assumed to be well-mixed. In this crystallizer, supersaturation, which is created by means of processes such as cooling, evaporation, or a reaction, is the driving force for nucleation and growth. A high degree of supersaturation will accelerate the nucleation and growth rate, and will consequently increase the total crystal surface in the crystallizer. In turn, a large total crystal surface will accelerate the supersaturation consumption rate, thus creating a feedback loop. The MSMPR crystallizer will eventually achieve a steady state, except under special circumstances.

Many studies have been performed on the MSMPR crystallizer, and this type of crystallizer has been used to produce inorganic salts. Since inorganic salts are relatively simple, issues of polymorphism and chirality may not exist or may not be important for their crystallization. In addition, the requirements of inorganic crystals, such as crystal size distribution, purity, and yield, may differ from the requirements of pharmaceutical crystallization. Therefore, the design and control processes in pharmaceutical continuous crystallization are often different from those in the continuous crystallization of inorganic salts.

4.1. Using MSMPR crystallizers to meet purity and yield requirements in pharmaceutical crystallization

Purity and yield are the basic requirements for a crystallization process, since they directly influence the process economy. However, as a characteristic of continuous crystallization, the process must be operated at a certain degree of supersaturation [15]; hence, the yield of a single pass of a continuous crystallization process is lower than the yield of a single batch process. To overcome this problem, many researchers have modified MSMPR crystallizers into different forms. Table 2 [7,13,15–18] compares different approaches for increasing product yield.

In order to reduce the residual supersaturation, the simplest approach is to extend the residence time [11,16,17,19]. The attainable yield can be calculated according to the population and mass balance equations. However, this method would lead to low productivity. In addition, a long residence time may lead to a low purity. As shown in Ref. [16], given a long enough residence time, a maximum yield can be achieved, but the purity is then at its lowest, at about 97.6%.

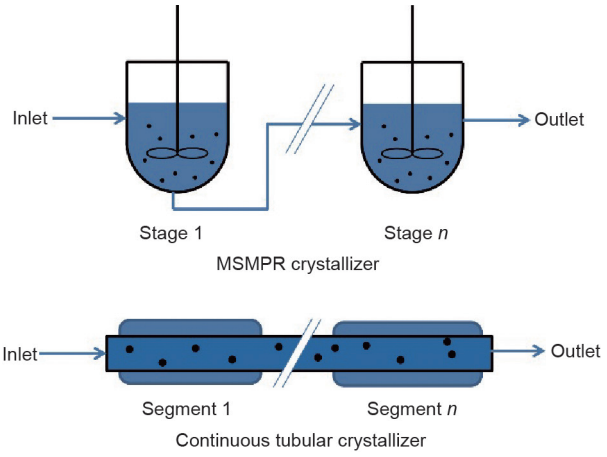

Fig. 1. Schematic diagram of two types of continuous crystallizer: the MSMPR crystallizer and the continuous tubular crystallizer.

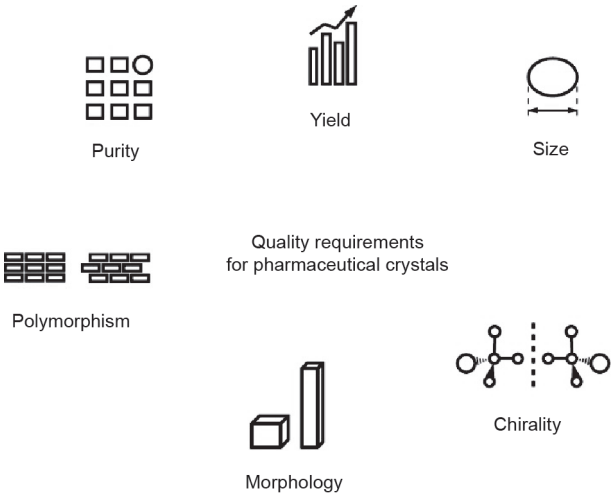

Fig. 2. General quality requirements for pharmaceutical crystals.

Table 1
Comparison of the MSMPR and tubular crystallizers [6].

Type	Advantages	Disadvantages
MSMPR crystallizer	• Easier to convert from batch crystallizer	• Less efficient than tubular crystallizer
	• Lower maintenance cost	• May lead to non-stable behavior
	• Equipment is simpler	• Startup process may be relatively long
	• Easier maintenance	• Relatively hard to scale up
Tubular crystallizer	• Higher efficiency than an MSMPR crystallizer of the same volume	• Maintenance is expensive and complex
	• Narrow residence time distribution	• Easier to cause fouling
	• Easier to scale up	• Equipment is relatively complex

Another widely used method to improve the yield is mother liquid recycling. In mother liquid recycling, the slurry is concentrated after filtration and then returned to the crystallizer. Alvarez et al. [15] used mother liquid recycling to improve the cooling crystallization yield of cyclosporine. They were able to increase the yield from 74% to 87%, compared with the yield of a batch process. However, the purity decreased from 95% to 94%. They also established an empirical impurity distribution model. Using this model in conjunction with the population and mass balance equations, Alvarez et al. [15] were able to simulate the effect of the operating conditions on the production purity and yield. In their work, they used a distribution coefficient (DC) to characterize the impurity concentration distribution. The DC can be defined as shown in Eq. (1):

$$\mathrm{DC} = \frac{\left(C_{\mathrm{imp}}/C_{\mathrm{CycA}}\right)_{\mathrm{solid}}}{\left(C_{\mathrm{imp}}/C_{\mathrm{CycA}}\right)_{\mathrm{liquid}}} \quad (1)$$

where C_{imp} is the concentration of impurity and C_{CycA} is the concentration of the host.

According to those authors' results, the DC is a linear function of the impurity ratio of the starting solution. Alvarez et al. [15] experimentally measured the relationship between the DC and the impurity ratio of the starting solution. They concluded that the third-stage temperature was the primary control variable for the final purity and yield. Based on this work, they transformed the crystallization of aliskiren hemifumarate into a continuous reactive/cooling crystallization process [16], and were also able to determine the relationship between the operating conditions and the product quality. Zhang et al. [17] developed two-stage anti-solvent/cooling crystallization, and compared the addition of the anti-solvent in each stage in order to determine which resulted in a better quality. Their results showed that it was preferable to add the anti-solvent in the second stage. In later work, Wong et al. [18] simplified the cyclosporine multistage MSMPR crystallizer into a single-stage MSMPR crystallizer by continuously concentrating and recycling the mother liquid, thereby achieving better purity and yield (94.3% and 91.8%, respectively). In the continuous anti-solvent/cooling crystallization of deferasirox [18], the recycled mother liquid was evaporated, mixed with anti-solvent, and then re-refluxed into the crystallizer. The maximum yield and minimum impurity concentration were 89.1% and 0.2 ppm, respectively.

Mother liquid recycling is an effective method of enhancing the yield. However, this method still has three weaknesses [13]. First, it cannot deal with a case in which the APIs are sensitive to temperature, and especially when they are sensitive to high-boiling-point solvents. Second, mother liquid recycling may modify the solution composition in the crystallizer, especially during anti-solvent crystallization. Third, the recycle ratio is limited by impurity buildup. To overcome these problems, Ferguson et al. [13] applied an organic solvent nanofiltration membrane in order to preferentially concentrate the API (deferasirox) and purge the limiting impurity (4-hydrazinobenzoic acid) from the mother liquid recycling stream. Using this method resulted in a dramatic increase in crystallization yield without sacrificing purity (the yield was 98.7% and the impurity was 0.15 ppm); it also reduced the energy consumption. Another method, proposed by Li et al. [7], uses solid recycling to improve the yield of two-stage cyclosporine continuous crystallization. In the work by Li et al. [7], the crystals were recycled to the crystallizer after filtration. This method was mainly used in a system in which the crystal growth rate was relatively low. Increasing the crystals in the crystallizer provides more crystal surface to consume the solution concentration, hence increasing the yield. The maximum yield obtained by this method was 79.8%.

In general, simultaneous improvement in both yield and purity is a somewhat paradoxical concept, unless a new method is used. The relationship between purity and yield that is established by the DC is useful for designing a continuous process. A smaller size distribution results in a larger total crystal surface area, making it easier for impurities to adhere to the surface [20]. However, although crystal size distribution is often considered to have an effect on crystal purity, this factor was not considered in that study, as far as the authors know. In the future, it may be possible to consider the effect of particle size on purity. In addition, it is always desirable to find a new method that can simultaneously improve purity and yield.

4.2. Using MSMPR crystallizers to meet size requirements in pharmaceutical crystallization

Crystal size is another important property of crystal products, since it can significantly affect the physicochemical characteristics of the API [21–23]. Multiple factors have an impact on crystal size distribution, including but not limited to residence time, temperature, and impurities.

This study outlines two main directions that may be followed in order to use MSMPR crystallizers to produce a desired crystal size distribution. The first method is to obtain a small crystal size distribution [24–26]. This mainly causes the drug to have a faster delivery rate. The second method is to obtain a large crystal size distribution [27,28]. This mainly enhances the efficiency of downstream operations. The population balance model is the basic model that is used to predict crystal size distribution.

In multistage MSMPR crystallization, the general operating variables are temperature, residence time, and anti-solvent addition rate. For a given operating condition, it is possible to calculate the attainable maximum and minimum size distribution, based on the population and mass balance model. Vetter et al. [29] constructed an attainable region of mean particle sizes versus the total residence time for three different pharmaceutical MSMPR cascades (paracetamol cooling crystallization, *L*-asparagine anti-solvent crystallization, and aspirin cooling/anti-solvent). As shown in Fig. 3, increasing the number of MSMPR crystallizers in the cascade results in a larger attainable region and in diminishing returns for the attainable maximum crystal mean size. In a later study, Vetter et al. [30] took the uncertainty in kinetic parameters into consideration and construct-

Table 2
Different approaches for increasing product yield.

Approach	Yield (wt%)	Purity (%)	Compound	Ref.
Extend residence time	93.6	97.6	Aliskiren hemifumarate	[16]
	91.0	91.6	Compound A	[17]
Mother liquid recycling	87.0	94.0	Cyclosporine	[15]
	91.8	94.3	Cyclosporine	[18]
	89.1	—	Deferasirox	[18]
Solvent nanofiltration membrane	98.7	—	Deferasirox	[13]
Solid recycling	79.8	96.0	Cyclosporine	[7]

ed a more reasonable attainable region for the paracetamol cooling MSMPR cascade crystallization. However, in some cases, it may not be easy to attain the operating conditions required to obtain the maximum or minimum size; for example, the residence time may be too short for the heat transfer. Power et al. [31] took the energy balance constraint and operating volumes constraint into consideration and constructed another attainable region for the paracetamol cooling MSMPR cascade crystallization. In general, the attainable region can be regarded as a guide when designing a crystallization process, as it helps the designer to avoid aiming for an unfeasible case [32].

In some cases, the minimum attainable mean size of MSMPR crystallization is still too large for the requirement; thus, some improvement should be employed to deal with this problem. Instead of a fine crystal elimination operation, Griffin et al. [24] proposed a large-crystal dissolving operation mode in order to obtain a small mean crystal size. Using this method made it possible to reduce the particle size of the product of aspirin continuous crystallization at a plant scale. In this way, the volume-weighted mean crystal size was reduced from 224.2 μm to 60 μm, for a cut size of 120 μm. However, when using this method, caution is necessary in order to avoid non-stable behavior and the possibility of fouling, due to the increase in supersaturation. Another method that can reduce crystal size was proposed by Yang et al. [25,26], who added a wet mill operation to the continuous crystallization process. It is interesting to note that different locations of the wet mill were shown to have different impacts on the particle size. In their work, Yang et al. compared the effect of different configurations of the integration of a rotor-stator wet mill with MSMPR on the crystal size distribution. When the wet mill was located upstream, it served as a seed generator and may have resulted in a larger mean size. When it was downstream, it served as a continuous size-reduction tool (decreasing the square-weighted mean chord length from 71 μm to 55 μm). In addition, the use of a wet mill operation was shown to narrow the particle size distribution, regardless of the position of the mill. Narducci et al. [33] coupled ultrasound with an adipic acid MSMPR crystallizer. In the presence of ultrasound, the crystal size of adipic acid was much smaller (about 60 μm) than with MSMPR alone (about 500 μm). Compared with ultrasound, residence time has little effect on crystal size. Powell et al. [34] investigated the morphology change of paracetamol continuous crystallization products in the presence of the additive hydroxypropyl methylcellulose (HPMC). The product crystals were tabular and small, compared with a range of different morphologies that occurred when no HPMC was added. Finally, the mother liquid recycling method mentioned in Section 4.1 can also reduce the particle size.

In some cases, it is desirable to obtain a large crystal size that is infeasible according to the attainable region. To achieve this purpose, the fine crystal dissolving approach is widely used [35,36]. However, care must be taken when using this method, since it may result in non-stable behavior in continuous crystallization. Su et al. [27] and Powell et al. [28] described a periodic flow method to increase the residence time distribution and hence the crystal size. In glycine continuous crystallization, they shifted the MSMPR into novel periodic flow crystallization. The residence time distribution clearly increased and blocking in the pipe was avoided. The volume-based mean particle size D_{43} increased from 342.16 to 696.76, compared with the same operation without periodic flow. Finally, the solid recycling method mentioned in Section 4.1 can also increase the particle size.

To achieve the desired crystal size in continuous crystallization, the attainable region can be a helpful guideline. If, according to the attainable region, manipulating the operation conditions (i.e., temperature and residence time) do not permit meeting the crystal size distribution requirements, then the problem can be solved by adding an operation (i.e., wet milling, fine crystal dissolving, or

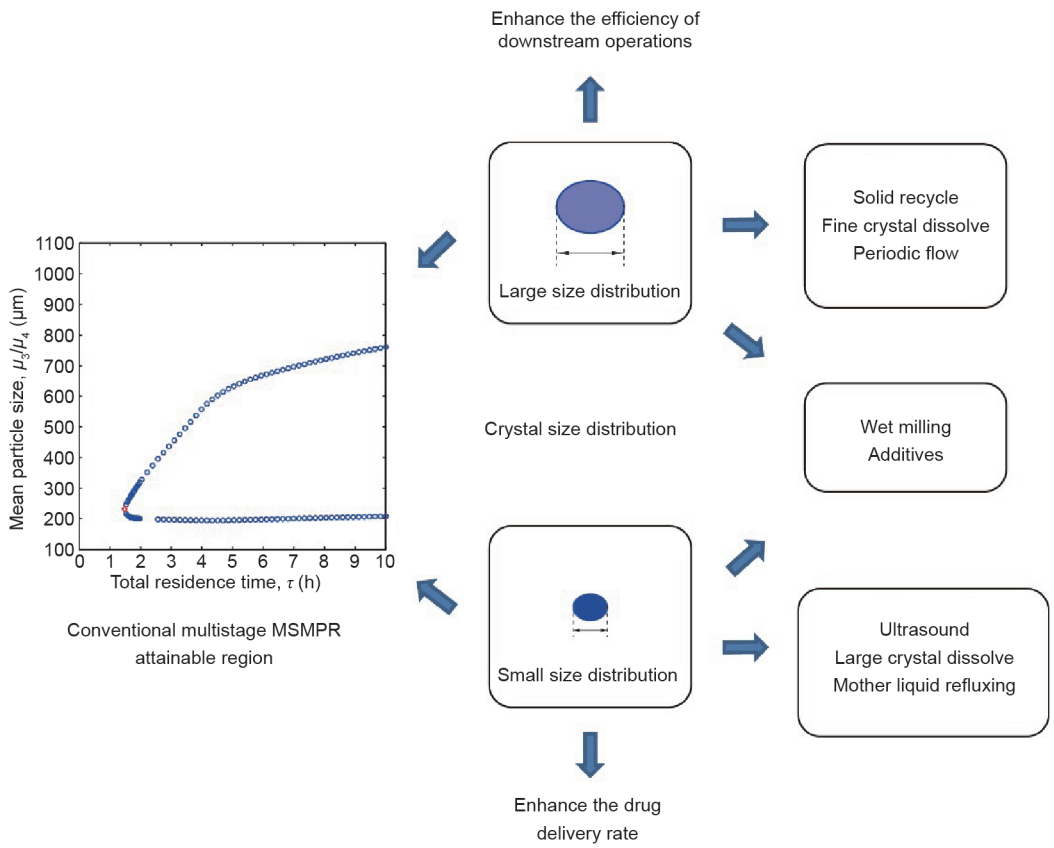

Fig. 3. Using MSMPR to meet the size requirements in pharmaceutical crystallization.

ultrasound) or modifying the operation mode (i.e., through periodic flow).

4.3. Using MSMPR crystallizers to meet morphology requirements in pharmaceutical crystallization

Differences in crystal morphology result from the growth rate difference between different crystal faces [37]. Producing the desired pharmaceutical crystal morphology in MSMPR crystallization is more complex than producing the desired size, since it involves dealing with coupling problems such as shape evolution, multidimensional population balance, and mass balance. Simulating crystal morphology in MSMPR is easier than morphology modeling in batch crystallization, in that the supersaturation in the continuous process is constant and in a steady state.

Borchert et al. [37] have simulated the evolution trajectory of the single crystal shape. Because the supersaturation is constant, the crystal morphology changes according to the same evolution trajectory, as shown in Fig. 4. The difference in morphology can be thought of as the difference in the crystal age in the crystallizer. The steady-state crystal age distribution in the MSMPR crystallizer is equal to the residence time distribution in the well-mixed vessel. Next, the morphology distribution in the continuous crystallization process can be solved iteratively by coupling the crystal age distribution with the mass balance and multidimensional population balance. Kwon et al. [36] coupled MSMPR with a fines trap in order to control the shape distribution of tetragonal hen-egg-white (HEW) lysozyme crystals. They simplified the crystal shape evolution as a change in the crystal aspect ratio. A kinetic Monte Carlo simulation, coupled with heat balance and multidimensional population balance, was used to model the crystallization process. The desired crystal could be obtained by an appropriate adjustment of the jacket temperature. However, unlike batch crystallization, controlling crystal morphology by adding additives is rarely done in continuous crystallization. Gerard et al. [38] added calcium-based additives to the sodium bicarbonate crystallization in a MSMPR reactor. The method mentioned above that was used to change crystal size by adding HPMC in a paracetamol continuous crystallization was also found to change the crystal morphology.

The sphere is an attractive crystalline morphology. Because of the resulting good flowability and handling properties, producing crystals with a spherical shape can improve the downstream processing efficiency [39]. However, many factors can influence the quality of spherical crystals [40]. The operating conditions for continuous crystallization at a steady state are constant. Therefore, some researchers have attempted to produce spherical crystals using continuous crystallization.

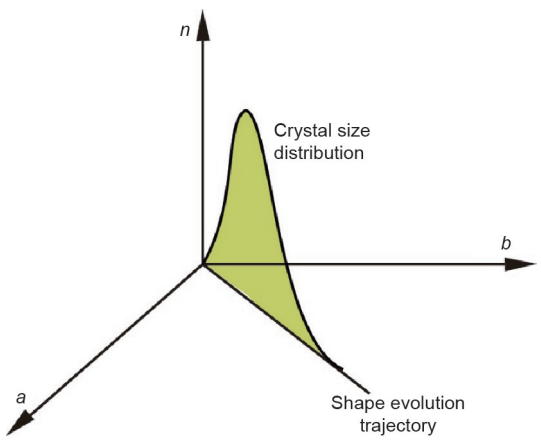

Fig. 4. Crystal morphology distribution in continuous MSMPR.

Tahara et al. [41] used a single-stage MSMPR crystallizer to produce spherical crystals of albuterol sulfate. Water was used as the solvent and an ethyl acetate/emulsifier (Pluronic L-121) mixture was used as the anti-solvent. Because of the large amount of solvent used in spherical crystallization, Tahara et al. used a continuous solvent-recovery process to improve the economics of the process. They found that a relatively low emulsifier concentration (2%), a small crystallizer volume (50 mL), and a long residence time (60 min) resulted in a large particle size. Peña and Nagy [42] divided the continuous spherical crystallization of benzoic acid into two steps. The first step was the nucleation and growth-dominant stage, which was done in the first crystallizer with ethanol as the solvent and water as the anti-solvent. The second step was the agglomeration dominant stage, which was done in the second crystallizer with toluene as the bridging liquid. This operation had the obvious advantage of separating the different processes and thereby improving the controllability of the process. Using this process, Peña and Nagy were able to continuously obtain spherical crystals with a diameter of about 1 mm.

A great deal of work remains to be done regarding crystal shape control in pharmaceutical continuous crystallization. Because the crystal shape evolution trajectory is the same in the MSMPR crystallizer, it is possible to reduce the multidimensional population balance to a one-dimensional population balance, thus simplifying the design and control process.

4.4. Using MSMPR to meet polymorphism requirements in pharmaceutical crystallization

Controlling the polymorphism of pharmaceuticals is one of the key objectives in the pharmaceutical crystallization process, since different polymorphs can have a great impact on the physical and chemical properties of a compound [43]. In batch crystallization, numerous approaches can be used to control the polymorphism of a pharmaceutical product [44,45]. However, since some operating conditions are completely different for batch versus continuous crystallization, it may be infeasible to apply batch polymorph control strategies in a continuous process [46]. To the best of our knowledge, few studies have focused on controlling polymorphism in a continuous process. In order to transition pharmaceutical manufacturing from batch processes to continuous processes, this problem cannot be avoided.

Lai et al. [46] demonstrated that it is possible to produce the desired *L*-glutamic acid polymorphs in a continuous process by manipulating the crystallizer temperature and residence time. They concluded that if the endpoint temperature in a single-stage MSMPR is 25 °C, in order to obtain pure stable β polymorph, the residence time should be 900 min, which is not realistic for the continuous crystallization process. Another important finding was that the initial seeding strategies cannot control the polymorph; rather, the major factors that control the polymorph are the relative nucleation and growth kinetics between two polymorphs. In addition, Lai et al. stated that it may be difficult to achieve the desired polymorph and the desired yield simultaneously. In later work, Lai et al. [47] expanded their research in single-stage MSMPR to cascade MSMPR. Using a cascade MSMPR, they were able to control the polymorphism of enantiotropic *p*-aminobenzoic acid while maintaining a high yield. Based on the kinetic parameters they obtained, they established a polymorph population balance model for continuous crystallization. Using this model, they then simulated continuous crystallization under different operating conditions. Using the simulation results, they were able to obtain the desired polymorph by adjusting the operation conditions.

Motivated by the abovementioned research, Farmer et al. [48] performed a remarkable work analyzing polymorphism under steady-state conditions, and modified the population balance model

into a non-dimensional form. Using this non-dimensional model, two non-dimensional numbers could be used to determine which polymorph was obtained, as shown in Fig. 5 [45,46,48]. Farmer et al. concluded that dissolving the unsteady polymorph has no effect on the steady-state polymorph. They systematically analyzed the effect of operating conditions on the polymorph during continuous crystallization, and obtained simulated results that agreed with the experimental data from Lai et al. [47].

Co-crystallization is a method to improve drug quality. Pharmaceutical co-crystals are multicomponent molecular systems that are typically formed through the hydrogen bonding of a co-former molecule with the API [49]. Powell et al. [49] used a novel periodic MSMPR crystallizer to produce the urea-barbituric acid co-crystal, and compared the effect of different operating conditions on the co-crystal form. Their results showed that the pure crystal form I could be obtained using optimal crystallization conditions. However, the pure crystal form III was not easy to obtain. Lee et al. [50] used continuous co-crystallization to separate vanillin. This technology separated vanillin by adding phenazine to form 1:2 co-crystals of phenazine-vanillin. The co-crystals were then recrystallized in acetone to obtain the α form of the vanillin crystals. The use of continuous operation in this process was mainly due to the fact that if the residence time of the continuous operation is short, the degree of supersaturation of the system will be large, thus facilitating the nucleation and growth of the co-crystal. The process yield was about 51.2%.

In general, the main differences between batch and continuous crystallization are: ① Seeding cannot control polymorphism in continuous crystallization; ② the main approaches used to control polymorphism in continuous crystallization are relative nucleation and growth kinetics between two polymorphs; and ③ dissolving the unsteady polymorph has no effect on the steady-state polymorph in continuous crystallization. Although the technical application of continuous crystallization to achieve desired polymorphs and co-crystals is still lacking for most polymorphic drugs, this method is gaining increasing attention.

4.5. Using MSMPR to meet chirality requirements in pharmaceutical crystallization

The separation of conglomerate-forming enantiomers is another requirement in the fine chemical industry, especially in drug production [51,52]. Preferential crystallization is an attractive process for gaining pure enantiomers from racemic mixtures [53]. However, conventional MSMPR cannot deal with this problem, so modification must be done in order for it to achieve the requirements for this process. There are three types of ternary phase diagrams of enantiomeric systems: ① diagrams for conglomerate-forming systems, ② diagrams for racemic compound-forming systems, and ③ diagrams for solid solution-forming systems. The phase diagrams of most organic molecules that can contain *R* and *S* enantiomers depict conglomerate-forming and racemic compound-forming systems [54].

The first research in transitioning preferential crystallization from batch process to continuous process was published by Qamar et al. [53]. In that study, an MSMPR with continuous seeding and with a fine-dissolving operation was used to continuously produce a preferential enantiomer. Continuously seeding the preferential enantiomer crystals maintained the solution concentration within the metastable zone in which spontaneous primary nucleation could be suppressed. Because the counter-enantiomer concentration could not be consumed, the operation needed to be carefully designed. The highest yield of this process was 6.6%. Based on this work, Qamar et al. [55] performed a theoretical investigation of continuous preferential crystallization in a coupling crystallization. In their operation mode, two ideally mixed coupled crystallizers were connected through exchange pipes and equipped with fines dissolution units. The two crystallizers continuously exchanged crystal-free liquid. Simultaneously, each crystallizer was seeded separately with one of the two enantiomers. Using this new operation mode, the productivity, yield, and purity were significantly increased. Chaaban et al. [56] applied the continuous separation of enantiomers to *DL*-asparagine monohydrate crystallization using coupled crystallizers, and studied the effect of the initial seed quality. Using seed crystals with a lower average particle size and smoother surface structure was observed to improve the productivity, yield, and purity. However, due to the low crystal growth rate, the productivities were still unsatisfactory. Galan et al. [57] also used this mode to produce *D*-/*L*-threonine, and were able to continuously separate enantiomers with purities > 99%. Because continuous seeding is too complex for industrial application, Vetter et al. [51] added suspension mills to the continuous preferential crystallization (Fig. 6). Crystals were continuously milled in order to provide sufficient surface for crystal growth. Another important advantage was that the presented process was robust. As long as the processing parameters were correctly chosen, even if counter-enantiomer crystals appeared, the process

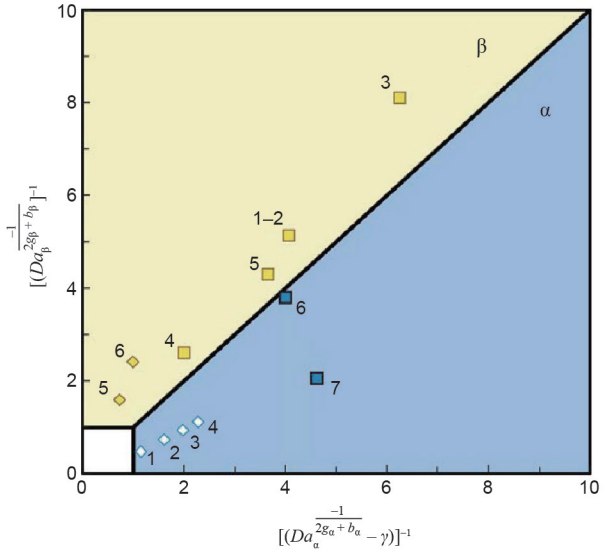

Fig. 5. Three stability regions for polymorphic continuous crystallization [48]. Diamond-shaped data points correspond to Ref. [45], and square-shaped data points correspond to Ref. [46]. (Copyright © 2016, Wiley Online Library, Ltd.)

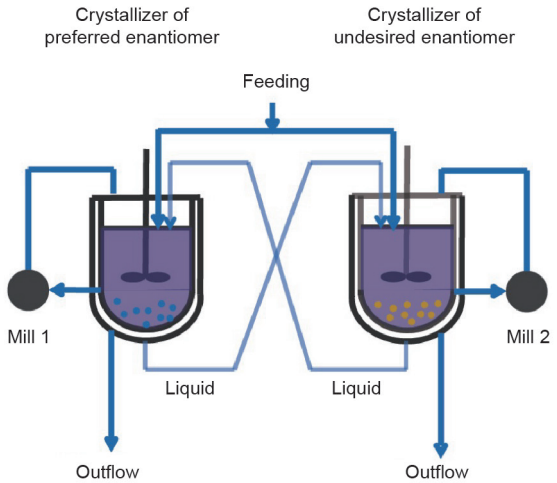

Fig. 6. A novel process flow sheet used for continuous preferential crystallization [51]. (Copyright © 2015. Wiley Online Library, Ltd.)

was able to recover.

Temmel et al. [58] provided an equilibrium model for continuously separating the substances in solid-solution-forming systems. In later work, Temmel et al. [54] introduced a counter-current process to separate solid solution compounds.

In general, in order to produce the desired chirality, the main idea is to suppress homogeneous nucleation. However, such approaches often result in low yields. The review article by Rougeot and Hein [59] provides an overview with further details about continuous preferential crystallization.

5. Continuous tubular crystallization in pharmaceutical crystallization

Continuous tubular crystallization is another commonly used continuous crystallization. In the tubular crystallizer, the solution is fed at the inlet and moves through the tube. Crystallization is caused by supersaturation generated by cooling or anti-solvent addition, and the product crystals are withdrawn at the outlet. In theory, a cascade consisting of an infinite number of MSMPR crystallizers is mathematically equivalent to a continuous tubular crystallization [29].

In cases that have high conversions with a short residence time, the continuous tubular crystallizer is preferable [6]. Depending on the operation mode, continuous tubular crystallization can be broadly classified as plug flow crystallization, segment flow crystallization, or oscillatory baffled crystallization, as shown in Fig. 7. Compared with an MSMPR crystallizer, a tubular crystallizer has the advantages of a narrow residence time distribution and a relatively simple scale-up process [60]. However, it suffers from the disadvantages that the continuous tubular crystallizer may not be easy to control [6], and that the system can be easily blocked [61]. These characteristics cause research into tubular flow crystallizers to focus mainly on size control. To the best of our knowledge, the use of tubular flow crystallizers to meet other requirements is still limited [62].

5.1. Using tubular crystallizers to meet size requirements in pharmaceutical crystallization

Because of the narrow residence time distribution, in theory, crystal size is relatively easy to control in a tubular crystallizer. As mentioned above, having a propensity for blockages and being difficult to control are the two major problems in a tubular crystallizer. Blockages are mainly caused by fouling and particle sedimentation. The control problem has two main reasons: First, supersaturation, temperature, and mixing are not easy to control in a tubular crystallizer; and second, it is difficult to sample and difficult to use process analysis technology (PAT) in a tubular crystallizer.

5.1.1. Plug flow crystallizer

The plug flow crystallizer is a common type of continuous tubular crystallizer. Unlike an MSMPR crystallizer, a plug flow crystallizer has no crystal surface to consume supersaturation at the tubular crystallizer inlet. Therefore, many studies seed the tubular crystallizer at the inlet, which can decrease the fouling rate and control the product size. In addition, multi-segment cooling and multi-addition have been used in plug flow crystallizers to control size distribution.

In the work by Eder et al. [62], a suspension of acetylsalicylic acid seed mixed with acetylsalicylic acid mother liquid was continuously pumped into a plug flow crystallizer. Eder et al. investigated the effect of flow rate on the final crystal size distribution, and concluded that a high flow rate resulted in a low volume mean diameter, and that blockages in the pipe could be avoided by manipulating the seed flow rate. In this way, they achieved a volume mean diameter of 325 μm. In their later work, Eder et al. [63] investigated the effect of seed loading and multistage cooling on the final acetylsalicylic acid mean size. To control nucleation without seeding, Majumder and Nagy [64] applied a fines dissolution process in plug flow crystallization. In their experiments, plug flow crystallization was divided into several segments. Some segments cooled the slurry, while other segments heated the solution to dissolve the fines. Majumder and Nagy established a population balance model coupled with nucleation and the growth and dissolution kinetics, and systematically studied the key factors that determine fines dissolving. They determined that fines removal could be achieved when the larger crystals grow faster than the smaller ones, and when the smaller crystals dissolve faster than the larger ones.

In order to simplify seeding operations, many researchers use various strategies to produce uniform seeds. According to research

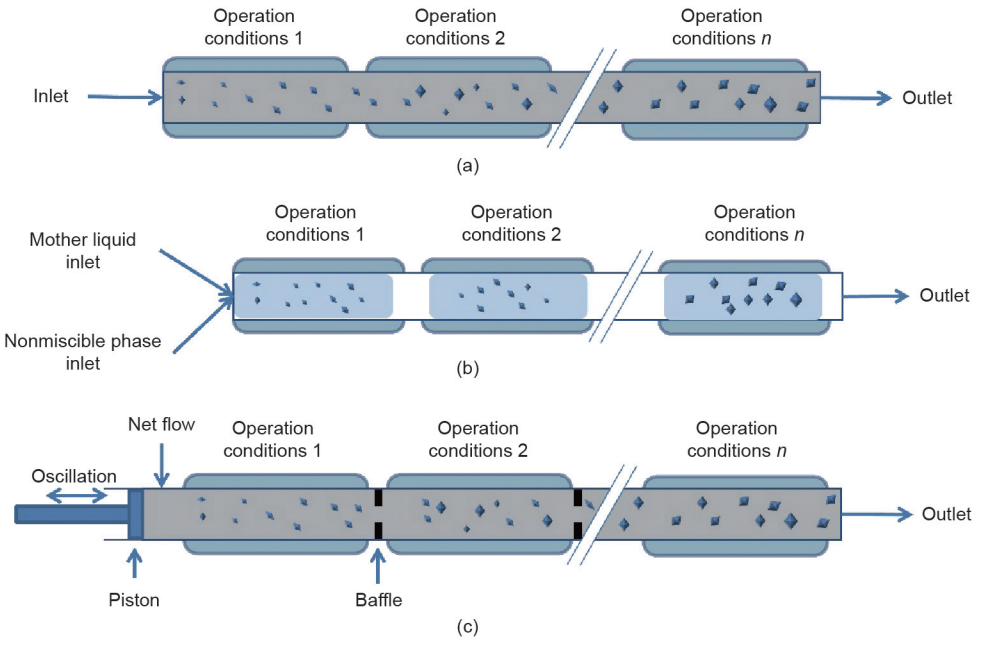

Fig. 7. Schematic diagrams of (a) a plug flow crystallizer, (b) a segment flow crystallizer, and (c) an oscillatory baffled crystallizer.

[65], contact secondary nucleation can produce seeds of uniform size. Wong et al. [66] applied a contact nucleation device to generate uniform seeds; the size of the seeds could be controlled by supersaturation and by the residence time of the seeds in the nucleation device. Cui et al. [67] systematically studied the relationship between nucleation rate and seed size versus contact force, area, and frequency. They concluded that, within a certain range, the nucleation rate was linearly related to all three factors and the seed size appeared to be independent from these factors. Ultrasound is another method of separating nucleation and growth, as demonstrated by Furuta et al. [60], who applied ultrasound in plug flow crystallization. Their results showed that the crystal size decreased remarkably when using this method (down to 1–7 μm).

The residence time distribution in plug flow crystallization is similar to that in batch crystallization; however, unlike the typical crystal size control operation in batch crystallization, curve cooling is difficult to use in plug flow crystallization. Hohmann et al. [68] applied a coiled flow inverter design with counter-current air cooling in a continuous tubular crystallizer. With this device, the plug flow crystallizer could operate under linear or curve cooling with a narrow residence time distribution. The size of the produced crystals was about 20–80 μm.

The attainable regions for crystal size in conventional plug flow crystallizers can be calculated using population and mass balance [29]. However, this model mainly aims at determining the ideal mixture. For crystallization with relatively large anti-solvent ratios, it is possible to encounter non-ideal mixing. To deal with this problem, Ferguson et al.[69] applied a Roughton-type vortex mixer to enhance the mixing efficiency. With this device, the square-weighted chord length was reduced from 152 μm to 52 μm.

Ridder et al. [70] developed the population balance model to optimize the multi-segment multi-addition plug flow crystallizer (MSMA-PFC). Unlike the corresponding model in the batch process, the population balance model in a plug flow crystallizer is with respect to length into the crystallizer. A multi-objective optimization was carried out to determine the anti-solvent addition rate in each segment that would maximize the crystal size distribution while minimizing the coefficient of variation. It was found that the typical optimization of anti-solvent addition involved maintaining the solution shifts between growth-dominated and nucleation-dominated regimes. Based on this work, Su et al. [71] optimized the total number, location, and distribution of anti-solvent additions in the MSMA-PFC.

5.1.2. Segment flow crystallizer

Another type of tubular crystallizer that is widely used is the so-called segment flow crystallizer. Fig. 7 provides a schematic diagram of the segment flow crystallizer. Unlike plug flow crystallization, the fluid in segment flow crystallization is divided into many individual droplets. Due to this feature, the residence time distribution in segment flow crystallization is narrow [72]. Another feature of this operation mode is that the crystals are fixed in the droplets, which allows the upper limit of the crystal size to be controlled by controlling the size of the droplets [73].

Neugebauer and Khinast [74] investigated using this type of crystallizer to produce protein crystals, and were able to obtain enzyme lysozyme crystals with sizes that ranged between 15 μm and 40 μm within 113.4 min. Jiang et al. [61] used the same type of crystallizer to continuously produce *L*-asparagine monohydrate. In their research, nucleation and growth were separated in order to enhance the individual control of each phenomenon. By manipulating the gas and liquid flow rates and adjusting the mixing approach of hot and cool fluids that was used for seed generation, Jiang et al. were able to obtain crystals with a maximum size of 588 μm within 5 min. In later work, Jiang et al. [75] used ultrasonic nucleation devices instead of the original nucleation device. Using indirect ultrasonication, Jiang et al. produced crystals with a size of 321 μm within 8.5 min. Rossi et al. [76] used ultrasonication in droplet-based microfluidic crystallization, and were able to produce adipic acid crystals with a small mean size (15 μm) at a high product rate and with a narrow distribution. In addition, many researchers use segment flow crystallizers to investigate the crystallization mechanism.

5.1.3. Oscillatory baffled crystallizer

Another type of continuous tubular crystallizer that is widely studied is the continuous oscillatory baffled crystallizer (COBC). Fig. 7 provides a schematic diagram of an oscillatory baffled crystallizer. Compared with the segment flow crystallizer, the diameter of the oscillatory baffled crystallizer is relatively larger, which can result in greater productivity. The oscillatory baffled crystallizer can operate at a relatively lower net flow rate of mother liquid than a continuous plug flow crystallizer, without plugging concerns. The oscillatory operation can also lengthen the residence time of the crystals with a relatively short crystallizer length.

The operation of an oscillatory baffled crystallizer is more complex than the operation of the other two types of tubular crystallizer. Both the frequency and the amplitude of the oscillation have an effect on the product. In general, during continuous operation, the maximum oscillatory velocity is at least double the net velocity of the fluid flowing [77].

Lawton et al. [78] investigated the use of COBC in pharmaceutical crystallization. Using COBC, they achieved a crystal chord length of about 150 μm. Brown et al. [79] used COBC in an anti-solvent crystallization of salicylic acid. However, due to an imbalance of flow rates in the mixer, they were unable to obtain crystals of constant size. Siddique et al. [80] used COBC combined with ultrasound to produce α lactose monohydrate. Ultrasound was used as an induced nucleation approach. The size of the produced crystals was about 1500 μm within 4 h. The review by McGlone et al. [77] provides further detail about COBC.

5.2. Using tubular crystallizers to meet other requirements in pharmaceutical crystallization

With the aim of producing the desired morphology, Sang-Il Kwon et al. [81] investigated the crystal shape of tetragonal HEW lysozyme crystals that were produced via continuous plug flow crystallization.

To produce the desired yield, Cogoni et al. [82] applied mother liquid recycling in paracetamol plug flow crystallization. They systematically studied the effects of the extraction position and recycling ratio on the yield and final mean size. Plug flow crystallization with a recycling ratio of about 30% mother liquid resulted in a yield of about 50%. This yield could be further increased by increasing the recycle ratio.

To produce the desired polymorph and co-crystals, Briggs et al. [83] investigated the *L*-glutamic acid polymorphic form using COBC, and estimated the effects of the initial solution concentration and the seed-loading ratio on the product polymorph. Their results showed that supersaturation is the main control variable for the polymorphism of the products. Supersaturation below 3 resulted in a thermodynamically stable β polymorph, whereas a mixed phase of the β form and the metastable α form was obtained when supersaturation was between 3 and 8. Zhao et al. [84] used COBC to produce α-lipoic acid-nicotinamide co-crystals, and achieved a productivity of 350 $g \cdot h^{-1}$ with a purity of 99%.

6. Control strategy in continuous crystallization

Process control has always been an important issue in crystallization. The advantage of continuous crystallization is that all oper-

ating parameters (temperature, residence time, concentration, etc.) are constant and in a steady-state condition, making the control of continuous crystallization relatively easier than the control of batch crystallization [85].

There are two main types of control approach: the model-based approach and the model-free approach. The model-based approach has three main components. ① The *process model* is used to describe the crystallization process and to predict the quality of the product; this model usually consists of a series of equations (the population balance equation, mass balance equation, heat balance equation, solubility expression, and crystallization kinetic expression). ② The *observer* is used to estimate whether the real state of the system is consistent with the set point. ③ The *optimizer* is used to optimize the operation variables such that the system can reach the set point at the lowest cost. The model-free approach is a proportional-integral-derivative (PID) control approach that is based on the direct use of PAT.

The overall objective of continuous crystallization process control is to stably produce crystals in accordance with the requirements. Yang and Nagy [32] compared the PID control approach with the nonlinear model predictive control (NMPC) approach. Based on the predicted future behavior of a system, the NMPC approach is a control method that uses online measurement data combined with a mathematical model to optimize the operating conditions. Although developing the NMPC approach is relatively complex, this approach can considerably enhance the performance, as compared with the PID control approach. Using a continuous two-stage MSMPR cascade crystallizer, the results showed that the PID control approach was not a convenient way of controlling crystal size and product yield due to the nonlinearity of the process. In contrast, the NMPC approach showed good performance in both servo control and regulatory control.

Yang et al. [85] proposed a model-free automated direct nucleation control (ADNC) approach. The development of this approach was based on the development of PAT. The ADNC approach uses total counts, which are measured by focused beam reflectance measurement (FBRM), to create feedback for the control process conditions. This approach is mainly used to control processes that have crystal size distribution as their objective. Yang et al. [85] used this approach for particle size control in paracetamol continuous crystallization. When the residence time and feed concentration of a continuous crystallization process are consistent, the steady-state product particle size should only be a function of the number of particles. Therefore, if the number of particles below the set point is known, the product size should remain the same for that set point, as long as the number of particles in the system can be kept within the set number. The final operating conditions are given by the control results when the system enters a steady state. This approach can be thought of as a quality-by-control (QbC) concept. In their later work in single-stage paracetamol continuous crystallization, Yang et al. [25] applied wet milling in an ADNC approach. The wet-milling speed serves as another operating condition and can be used to separate the crystal growth and nucleation phenomenon. The upstream addition of wet milling can be considered as a primary nucleation control approach, and the downstream addition of wet milling can be considered as a secondary nucleation control approach. Su et al. [11] applied a concentration control approach to maintain the paracetamol continuous crystallization system at the set point. By regulating the anti-solvent addition and fresh slurry, the system could keep the anti-solvent mass fraction and supersaturation at set points.

For particle size control in a plug flow crystallizer, Besenhard et al. [86] developed a model-free feedback controller to control the size of cooling crystallization acetylsalicylic acid products. By manipulating the rate of seeding, the particle size of the crystal was stabilized at 90–140 μm.

Another control problem in MSMPR is startup optimization. A continuous crystallization system is in fluctuation before it reaches the steady state. This results in an inconsistent product quality. Yang and Nagy [87] compared the effect of different startup policies on the startup duration. Their results showed that using an appropriate startup policy can achieve a reduction of approximately 50% of the startup duration time in the two-stage anti-solvent/cooling continuous crystallization of aspirin.

Encrustation is an important problem in continuous crystallization. Because the solution in continuous crystallization is supersaturated, encrustation will continue to grow. Without an anti-fouling operation, encrustation leads to an increase in thermal resistance, reduces the residence time, and may even cause an unplanned shutdown of the process. Majumder and Nagy [88] proposed a mathematical model that combines the population balance model with the encrustation model in order to simulate the effect of encrustation on the process supersaturation, temperature, and crystal size distribution. The dynamic behavior of the thickness of the encrustation over time is also given. Based on this model, Koswara and Nagy [89] proposed an anti-fouling control approach that operates by means of a heating and cooling cycle. A continuous plug flow crystallizer was divided into two symmetric regions. In each region, an operation was performed to periodically heat and dissolve the crystals and then to cool the crystals. According to the model, both encrustation and dissolving led to a reduction in crystal size. Therefore, if the crystal size dropped below a set point, the operation was switched.

PAT can be used to obtain *in situ* information about the solution, which is important for the simulation and control of the crystallization process. A number of commercial PATs have been used for crystallization [32,85,90], including the FBRM, particle video microscope, attenuated total internal reflectance Fourier-transform infrared spectroscopy, and attenuated total reflectance/ultraviolet spectroscopy. In addition, there is a significant amount of PAT under development, including ultrasound measurement [91] and image-based measurement [92–95]. Depending on the development of PAT, crystallization process development can be shortened remarkably and the robustness of the system can be enhanced.

7. Conclusions

Pharmaceutical continuous crystallization carries the advantages of controllability and productivity. Due to an increase in research in this field, continuous crystallization technology can now be used to produce several desired pharmaceutical crystals. Compared with the batch process, the continuous crystallization process offers potential economic advantages. However, not every process is suitable for continuous crystallization thus far. For example, in the production of chiral crystals, the yield from continuous crystallization still low. In addition, suitable processes for an MSMPR crystallizer are not the same as those for a tubular crystallizer. For example, the MSMPR crystallizer is preferred when larger crystals are desired. For the control of continuous crystallization, PAT and model-based control strategies have been used, albeit mainly for size and concentration control. In the future, the field of pharmaceutical continuous crystallization could benefit from efforts in the following areas: ① advanced process control technology (such as the neural network model); ② continuous crystallization combined with other unit operations (such as nanofiltration); and ③ the development of integrated process models (such as the purity prediction model).

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Compliance with ethics guidelines

Dejiang Zhang, Shijie Xu, Shichao Du, Jingkang Wang, and Junbo Gong declare that they have no conflict of interest or financial conflicts to disclose.

References

[1] Childs SL, Chyall LJ, Dunlap JT, Smolenskaya VN, Stahly BC, Stahly GP. Crystal engineering approach to forming cocrystals of amine hydrochlorides with organic acids. Molecular complexes of fluoxetine hydrochloride with benzoic, succinic, and fumaric acids. J Am Chem Soc 2004;126(41):13335–42.
[2] Vishweshwar P, McMahon JA, Bis JA, Zaworotko MJ. Pharmaceutical co-crystals. J Pharm Sci 2006;95(3):499–516.
[3] Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Deliv Rev 2007;59(7):617–30.
[4] Alvarez AJ, Myerson AS. Continuous plug flow crystallization of pharmaceutical compounds. Cryst Growth Des 2010;10(5):2219–28.
[5] Sen M, Rogers A, Singh R, Chaudhury A, John J, Ierapetritou MG, et al. Flowsheet optimization of an integrated continuous purification-processing pharmaceutical manufacturing operation. Chem Eng Sci 2013;102(15):56–66.
[6] Chen J, Sarma B, Evans JMB, Myerson AS. Pharmaceutical crystallization. Cryst Growth Des 2011;11(4):887–95.
[7] Li J, Trout BL, Myerson AS. Multistage continuous mixed-suspension, mixed-product removal (MSMPR) crystallization with solids recycle. Org Process Res Dev 2016;20(2):510–6.
[8] Leuenberger H. New trends in the production of pharmaceutical granules: Batch versus continuous processing. Eur J Pharm Biopharm 2001;52(3):289–96.
[9] Anderson NG. Using continuous processes to increase production. Org Process Res Dev 2012;16(5):852–69.
[10] Schaber SD, Gerogiorgis DI, Ramachandran R, Evans JMB, Barton PI, Trout BL. Economic analysis of integrated continuous and batch pharmaceutical manufacturing: A case study. Ind Eng Chem Res 2011;50(17):10083–92.
[11] Su Q, Nagy ZK, Rielly CD. Pharmaceutical crystallisation processes from batch to continuous operation using MSMPR stages: Modelling, design, and control. Chem Eng Process: Process Intens 2015;89:41–53.
[12] Byrn S, Futran M, Thomas H, Jayjock E, Maron N, Meyer RF, et al. Achieving continuous manufacturing for final dosage formation: Challenges and how to meet them. J Pharm Sci 2015;104(3):792–802.
[13] Ferguson S, Ortner F, Quon J, Peeva L, Livingston A, Trout BL, et al. Use of continuous MSMPR crystallization with integrated nanofiltration membrane recycle for enhanced yield and purity in API crystallization. Cryst Growth Des 2014;14(2):617–27.
[14] Myerson AS, Krumme M, Nasr M, Thomas H, Braatz RD. Control systems engineering in continuous pharmaceutical manufacturing. J Pharm Sci 2015;104(3):832–9.
[15] Alvarez AJ, Singh A, Myerson AS. Crystallization of cyclosporine in a multistage continuous MSMPR crystallizer. Cryst Growth Des 2011;11(10):4392–400.
[16] Quon JL, Zhang H, Alvarez A, Evans J, Myerson AS, Trout BL. Continuous crystallization of aliskiren hemifumarate. Cryst Growth Des 2012;12(6):3036–44.
[17] Zhang H, Quon J, Alvarez AJ, Evans J, Myerson AS, Trout B. Development of continuous anti-solvent/cooling crystallization process using cascaded mixed suspension, mixed product removal crystallizers. Org Process Res Dev 2012;16(5):915–24.
[18] Wong SY, Tatusko AP, Trout BL, Myerson AS. Development of continuous crystallization processes using a single-stage mixed-suspension, mixed-product removal crystallizer with recycle. Cryst Growth Des 2012;12(11):5701–7.
[19] Wierzbowska B, Hutnik N, Piotrowski K, Matynia A. Continuous mass crystallization of vitamin C in *L*(+)-ascorbic acid ethanol water system: Size-independent growth kinetic model approach. Cryst Growth Des 2011;11(5):1557–65.
[20] Mersmann A. Crystallization technology handbook. 2nd ed. New York: Marcel Dekker Inc.; 2001.
[21] Wu C, Xie Y. Controlling phase and morphology of inorganic nanostructures originated from the internal crystal structure. Chem Commun 2009;(40):5943–57.
[22] Yang H, Sun C, Qiao S, Zou J, Liu G, Smith S, et al. Anatase TiO_2 single crystals with a large percentage of reactive facets. Nature 2008;453(7195):638–41.
[23] Variankaval N, Cote AS, Doherty MF. From form to function: Crystallization of active pharmaceutical ingredients. AIChE J 2008;54(7):1682–8.
[24] Griffin DW, Mellichamp DA, Doherty MF. Reducing the mean size of API crystals by continuous manufacturing with product classification and recycle. Chem Eng Sci 2010;65(21):5770–80.
[25] Yang Y, Song L, Zhang Y, Nagy ZK. Application of wet milling-based automated direct nucleation control in continuous cooling crystallization processes. Ind Eng Chem Res 2016;55(17):4987–96.
[26] Yang Y, Song L, Gao T, Nagy ZK. Integrated upstream and downstream application of wet milling with continuous mixed suspension mixed product removal crystallization. Cryst Growth Des 2015;15(12):5879–85.
[27] Su Q, Rielly CD, Powell KA, Nagy ZK. Mathematical modelling and experimental validation of a novel periodic flow crystallization using MSMPR crystallizers. AIChE J 2016;63(4):1313–27.
[28] Powell KA, Saleemi AN, Rielly CD, Nagy ZK. Periodic steady-state flow crystallization of a pharmaceutical drug using MSMPR operation. Chem Eng Process: Process Intens 2015;97:195–212.
[29] Vetter T, Burcham CL, Doherty MF. Regions of attainable particle sizes in continuous and batch crystallization processes. Chem Eng Sci 2014;106:167–80.
[30] Vetter T, Burcham CL, Doherty MF. Designing robust crystallization processes in the presence of parameter uncertainty using attainable regions. Ind Eng Chem Res 2015;54(42):10350–63.
[31] Power G, Hou G, Kamaraju VK, Morris G, Zhao Y, Glennon B. Design and optimization of a multistage continuous cooling mixed suspension, mixed product removal crystallizer. Chem Eng Sci 2015;133:125–39.
[32] Yang Y, Nagy ZK. Advanced control approaches for combined cooling/antisolvent crystallization in continuous mixed suspension mixed product removal cascade crystallizers. Chem Eng Sci 2015;127:362–73.
[33] Narducci O, Jones AG, Kougoulos E. Continuous crystallization of adipic acid with ultrasound. Chem Eng Sci 2011;66(6):1069–76.
[34] Powell KA, Saleemi AN, Rielly CD, Nagy ZK. Monitoring continuous crystallization of paracetamol in the presence of an additive using an integrated PAT array and multivariate methods. Org Process Res Dev 2016;20(3):626–36.
[35] Lakatos BG, Sapundzhiev TJ, Garside J. Stability and dynamics of isothermal CMSMPR crystallizers. Chem Eng Sci 2007;62(16):4348–64.
[36] Kwon JSI, Nayhouse M, Christofides PD, Orkoulas G. Modeling and control of crystal shape in continuous protein crystallization. Chem Eng Sci 2014;107:47–57.
[37] Borchert C, Nere N, Ramkrishna D, Voigt A, Sundmacher K. On the prediction of crystal shape distributions in a steady-state continuous crystallizer. Chem Eng Sci 2009;64(4):686–96.
[38] Gerard A, Muhr H, Plasari E, Jacob D, Lefaucheur CE. Effect of calcium based additives on the sodium bicarbonate crystallization in a MSMPR reactor. Powder Technol 2014;255:134–40.
[39] Garg J, Arora SKS, Garg J. Spherical crystallization: An overview. Int J Pharm Technol 2014;4(1):1909–28.
[40] Kovacic B, Vrecer F, Planinsek O. Spherical crystallization of drugs. Acta Pharm 2012;62(1):1–14.
[41] Tahara K, O'Mahony M, Myerson AS. Continuous spherical crystallization of albuterol sulfate with solvent recycle system. Cryst Growth Des 2015;15(10):5149–56.
[42] Peña R, Nagy ZK. Process intensification through continuous spherical crystallization using a two-stage mixed suspension mixed product removal (MSMPR) system. Cryst Growth Des 2015;15(9):4225–36.
[43] Lee AY, Erdemir D, Myerson AS. Crystal polymorphism in chemical process development. Annu Rev Chem Biomol Eng 2011;2:259–80.
[44] Hermanto MW, Chiu MS, Braatz RD. Nonlinear model predictive control for the polymorphic transformation of *L*-glutamic acid crystals. AIChE J 2009;55(10):2631–45.
[45] Yang X, Sarma B, Myerson AS. Polymorph control of micro/nano-sized mefenamic acid crystals on patterned self-assembled monolayer islands. Cryst Growth Des 2012;12(11):5521–8.
[46] Lai TTC, Ferguson S, Palmer L, Trout BL, Myerson AS. Continuous crystallization and polymorph dynamics in the *L*-glutamic acid system. Org Process Res Dev 2014;18(11):1382–90.
[47] Lai TTC, Cornevin J, Ferguson S, Li N, Trout BL, Myerson AS. Control of polymorphism in continuous crystallization via mixed suspension mixed product removal systems cascade design. Cryst Growth Des 2015;15(7):3374–82.
[48] Farmer TC, Carpenter CL, Doherty MF. Polymorph selection by continuous crystallization. AIChE J 2016;62(9):3505–14.
[49] Powell KA, Bartolini G, Wittering KE, Saleemi AN, Wilson CC, Rielly CD, et al. Toward continuous crystallization of urea-barbituric acid: A polymorphic co-crystal system. Cryst Growth Des 2015;15(10):4821–36.
[50] Lee T, Chen HR, Lin HY, Lee HL. Continuous co-crystallization as a separation technology: The study of 1∶2 co-crystals of phenazine-vanillin. Cryst Growth Des 2012;12(12):5897–907.
[51] Vetter T, Burcham CL, Doherty MF. Separation of conglomerate forming enantiomers using a novel continuous preferential crystallization process. AIChE J 2015;61(9):2810–23.
[52] Lorenz H, Seidel-Morgenstern A. Processes to separate enantiomers. Angew Chem Int Ed 2014;53(5):1218–50.
[53] Qamar S, Peter Elsner M, Hussain I, Seidel-Morgenstern A. Seeding strategies and residence time characteristics of continuous preferential crystallization. Chem Eng Sci 2012;71:5–17.
[54] Temmel E, Wloch S, Müller U, Grawe D, Eilers R, Lorenz H, et al. Separation of systems forming solid solutions using counter-current crystallization. Chem Eng Sci 2013;104:662–73.
[55] Qamar S, Galan K, Peter Elsner M, Hussain I, Seidel-Morgenstern A. Theoretical investigation of simultaneous continuous preferential crystallization in a coupled mode. Chem Eng Sci 2013;98:25–39.
[56] Chaaban JH, Dam-Johansen K, Skovby T, Kiil S. Separation of enantiomers by

continuous preferential crystallization: Experimental realization using a coupled crystallizer configuration. Org Process Res Dev 2013;17(8):1010–20.
[57] Galan K, Eicke MJ, Elsner MP, Lorenz H, Seidel-Morgenstern A. Continuous preferential crystallization of chiral molecules in single and coupled mixed-suspension mixed-product-removal crystallizers. Cryst Growth Des 2015;15(4):1808–18.
[58] Temmel E, Müller U, Grawe D, Eilers R, Lorenz H, Seidel-Morgenstern A. Equilibrium model of a continuous crystallization process for separation of substances exhibiting solid solutions. Chem Eng Technol 2012;35(6):980–5.
[59] Rougeot C, Hein JE. Application of continuous preferential crystallization to efficiently access enantiopure chemicals. Org Process Res Dev 2015;19(12):1809–19.
[60] Furuta M, Mukai K, Cork D, Mae K. Continuous crystallization using a sonicated tubular system for controlling particle size in an API manufacturing process. Chem Eng Process: Process Intens 2016;102:210–8.
[61] Jiang M, Zhu Z, Jimenez E, Papageorgiou CD, Waetzig J, Hardy A, et al. Continuous-flow tubular crystallization in slugs spontaneously induced by hydrodynamics. Cryst Growth Des 2014;14(2):851–60.
[62] Eder RJP, Radl S, Schmitt E, Innerhofer S, Maier M, Gruber-Woelfler H, et al. Continuously seeded, continuously operated tubular crystallizer for the production of active pharmaceutical ingredients. Cryst Growth Des 2010;10(5):2247–57.
[63] Eder RJP, Schmitt EK, Grill J, Radl S, Gruber-Woelfler H, Khinast JG. Seed loading effects on the mean crystal size of acetylsalicylic acid in a continuous-flow crystallization device. Cryst Res Technol 2011;46(3):227–37.
[64] Majumder A, Nagy ZK. Fines removal in a continuous plug flow crystallizer by optimal spatial temperature profiles with controlled dissolution. AIChE J 2013;59(12):4582–94.
[65] Reyhani MM, Parkinson GM. Source of nuclei in contact nucleation as revealed by crystallization of isomorphous alums. In: Botsaris GD, Toyokura K, editors Separation and purification by crystallization. Washington, DC: American Chemical Society; 1997. p. 28–35.
[66] Wong SY, Cui Y, Myerson AS. Contact secondary nucleation as a means of creating seeds for continuous tubular crystallizers. Cryst Growth Des 2013;13(6):2514–21.
[67] Cui Y, Jaramillo JJ, Stelzer T, Myerson AS. Statistical design of experiment on contact secondary nucleation as a means of creating seed crystals for continuous tubular crystallizers. Org Process Res Dev 2015;19(9):1101–8.
[68] Hohmann L, Gorny R, Klaas O, Ahlert J, Wohlgemuth K, Kockmann N. Design of a continuous tubular cooling crystallizer for process development on lab-scale. Chem Eng Technol 2016;39(7):1268–80.
[69] Ferguson S, Morris G, Hao H, Barrett M, Glennon B. *In-situ* monitoring and characterization of plug flow crystallizers. Chem Eng Sci, 2012;77:105–11.
[70] Ridder BJ, Majumder A, Nagy ZK. Population balance model-based multiobjective optimization of a multisegment multiaddition (MSMA) continuous plug-flow antisolvent crystallizer. Ind Eng Chem Res 2014;53(11):4387–97.
[71] Su Q, Benyahia B, Nagy ZK, Rielly CD. Mathematical modeling, design, and optimization of a multisegment multiaddition plug-flow crystallizer for antisolvent crystallizations. Org Process Res Dev 2015;19(12):1859–70.
[72] Eder RJP, Schrank S, Besenhard MO, Roblegg E, Gruber-Woelfler H, Khinast JG. Continuous sonocrystallization of acetylsalicylic acid (ASA): Control of crystal size. Cryst Growth Des 2012;12(10):4733–8.
[73] Dombrowski RD, Litster JD, Wagner NJ, He Y. Crystallization of alpha-lactose monohydrate in a drop-based microfluidic crystallizer. Chem Eng Sci 2007;62(17):4802–10.
[74] Neugebauer P, Khinast JG. Continuous crystallization of proteins in a tubular plug-flow crystallizer. Cryst Growth Des 2015;15(3):1089–95.
[75] Jiang M, Papageorgiou CD, Waetzig J, Hardy A, Langston M, Braatz RD. Indirect ultrasonication in continuous slug-flow crystallization. Cryst Growth Des 2015;15(5):2486–92.
[76] Rossi D, Jamshidi R, Saffari N, Kuhn S, Gavriilidis A, Mazzei L. Continuous-flow sonocrystallization in droplet-based microfluidics. Cryst Growth Des 2015;15(11):5519–29.
[77] McGlone T, Briggs NEB, Clark CA, Brown CJ, Sefcik J, Florence AJ. Oscillatory flow reactors (OFRs) for continuous manufacturing and crystallization. Org Process Res Dev 2015;19(9):1186–202.
[78] Lawton S, Steele G, Shering P, Zhao L, Laird I, Ni XW. Continuous crystallization of pharmaceuticals using a continuous oscillatory baffled crystallizer. Org Process Res Dev 2009;13(6):1357–63.
[79] Brown CJ, Adelakun JA, Ni Xw. Characterization and modelling of antisolvent crystallization of salicylic acid in a continuous oscillatory baffled crystallizer. Chem Eng Process: Process Intens 2015;97:180–6.
[80] Siddique H, Brown CJ, Houson I, Florence AJ. Establishment of a continuous sonocrystallization process for lactose in an oscillatory baffled crystallizer. Org Process Res Dev 2015;19(12):1871–81.
[81] Sang-Il Kwon J, Nayhouse M, Orkoulas G, Christofides PD. Crystal shape and size control using a plug flow crystallization configuration. Chem Eng Sci 2014;119:30–9.
[82] Cogoni G, de Souza BP, Frawley PJ. Particle size distribution and yield control in continuous plug flow crystallizers with recycle. Chem Eng Sci 2015;138:592–9.
[83] Briggs NEB, Schacht U, Raval V, McGlone T, Sefcik J, Florence AJ. Seeded crystallization of β-*L*-glutamic acid in a continuous oscillatory baffled crystallizer. Org Process Res Dev 2015;19(12):1903–11.
[84] Zhao L, Raval V, Briggs NEB, Bhardwaj RM, McGlone T, Oswald IDH, et al. From discovery to scale-up: α-lipoic acid: Nicotinamide co-crystals in a continuous oscillatory baffled crystalliser. CrystEngComm 2014;16(26):5769–80.
[85] Yang Y, Song L, Nagy ZK. Automated direct nucleation control in continuous mixed suspension mixed product removal cooling crystallization. Cryst Growth Des 2015;15(12):5839–48.
[86] Besenhard MO, Neugebauer P, Ho CD, Khinast JG. Crystal size control in a continuous tubular crystallizer. Cryst Growth Des 2015;15(4):1683–91.
[87] Yang Y, Nagy ZK. Combined cooling and antisolvent crystallization in continuous mixed suspension, mixed product removal cascade crystallizers: Steady-state and startup optimization. Ind Eng Chem Res 2015;54(21):5673–82.
[88] Majumder A, Nagy ZK. Dynamic modeling of encrust formation and mitigation strategy in a continuous plug flow crystallizer. Cryst Growth Des 2015;15(3):1129–40.
[89] Koswara A, Nagy ZK. Anti-fouling control of plug-flow crystallization via heating and cooling cycle. IFAC-PapersOnLine 2015;48(8):193–8.
[90] Ferguson S, Morris G, Hao H, Barrett M, Glennon B. *In-situ* monitoring and characterization of plug flow crystallizers. Chem Eng Sci 2012;77:105–11.
[91] Razavi SM, Callegari G, Drazer G, Cuitino AM. Toward predicting tensile strength of pharmaceutical tablets by ultrasound measurement in continuous manufacturing. Int J Pharm 2016;507(1–2):83–9.
[92] Tachtatzis C, Sheridan R, Michie C, Atkinson RC, Cleary A, Dziewierz J, et al. Image-based monitoring for early detection of fouling in crystallisation processes. Chem Eng Sci 2015;133:82–90.
[93] Brown CJ, Ni XW. Determination of metastable zone width, mean particle size and detectable number density using video imaging in an oscillatory baffled crystallizer. CrystEngComm 2012;14(8):2944–9.
[94] Brown CJ, Ni XW. Evaluation of growth kinetics of antisolvent crystallization of paracetamol in an oscillatory baffled crystallizer utilizing video imaging. Cryst Growth Des 2011;11(9):3994–4000.
[95] Brown CJ, Ni X. Online evaluation of paracetamol antisolvent crystallization growth rate with video imaging in an oscillatory baffled crystallizer. Cryst Growth Des 2011;11(3):719–25.