Article:
Zhang, F, Shan, B, Wang, Y et al. (3 more authors) (2021) Progress and Opportunities for Utilizing Seeding Techniques in Crystallization Processes. Organic Process Research and Development, 25 (7). pp. 1496-1511. ISSN 1083-6160

https://doi.org/10.1021/acs.oprd.1c00103

Progress and Opportunities of Seeding Technique in Crystallization Processes

Fangkun Zhang[a,*], Baoming Shan[a], Yinglong Wang[b], Zhaoyou Zhu[b], Zaiqun Yu[c], Cai Y. Ma[d],

[a] *College of Automation and Electronic Engineering, Qingdao University of Science & Technology, Qingdao, 266061, P. R. China*

[b] *College of Chemical Engineering, Qingdao University of Science and Technology, Qingdao, 266061, P. R. China*

[c] *Institute of Chemical & Engineering Sciences, Agency for Science, Technology and Research (A*STAR), 1 Pesek Road, Jurong Island, Singapore 627833*

[d] *Centre for the Digital Design of Drug Products, School of Chemical and Process Engineering, University of Leeds, Leeds, LS2 9JT, United Kingdom*

** Corresponding author. E-mail: f.k.zhang@hotmail.com or f.k.zhang@qust.edu.cn*

Abstract: Seeding is a significant but challenging task in optimizing crystallization process operation, product quality, and process efficiency. With the development of modern crystallization technology, there has been considerable advancement in the seeding technique in recent years. This article reviews the seeding techniques as well as their main progress, challenges and opportunities in the field of crystallization processes. This review summarized the key seeding parameters and desired product quality attributes, clarified the qualitative connection between seeding parameters, state variables and product quality attributes based on a variable-based causal graph (VBCG), and analyzed various possible factors that resulted in seeding technique failure by an Ishikawa diagram. Combing with these factors, the recent development on studies of seeding technique and existing issues were discussed from six aspects, i.e. seed loading, seed quality, seeding condition, seed preparation, seed storing and seeding mode. The challenges and opportunities for seeding technique are analyzed based on research accomplishment, and the potentially valuable topics and directions on seeding technique are presented in improving crystallization.

Keywords: Seeding technique, seed preparation, design and optimization, crystallization

---

1. Introduction

Crystallization has been widely used for product separation and purification in the fields of food, pharmaceutical and chemical industry[1, 2]. In addition to high purity and yield, for crystal products with precise control of crystal size and crystal size distribution (CSD), the requirements for various product quality attributes are also increasing. It is also necessary to control crystal polymorph, chirality, morphology, quality and even crystal shape distribution. These product quality attributes can be affected or manipulated by different operating variables, including supersaturation, temperature profile, seeding, stirring and so on. During these variables, seeding has become one of the most effective means in improving crystallization behavior, process efficiency, and product quality. Seeding is regarded as a more important role than other factors such as cooling profile and supersaturation in improving product CSD and quality[3, 4]. Some argue that the seed's importance to crystallization can never be overemphasized[5].

Undoubtedly, seeding has been an effective technique to separate growth from nucleation and to stabilize crystallization processes, which can not only greatly reduce the crystallization time and complexity, but improve the controllability of crystallization system[6-8]. In the past 20 years, seed effects have been widely studied and much progress in improving seeding efficiency has been made in crystallization field[7, 9]. Seeding was commonly treated as an technique to provide a template for the assembly of molecules to produce crystals according to a certain structure[10]. The template provides growing points for molecular deposition/integration on the seed surfaces, hence reducing the difficulty of phase transformation from solution to solid during crystallization. Therefore, the growth of seed crystals is independent of spontaneous nucleation, which can effectively separate crystal nucleation and growth during crystallization processes. If the solution for crystallization is supersaturated, crystallization process will be aroused by added seeds. The added seeds not only induce the crystallization solution to grow into the desired crystal form (e.g., metastable polymorph) when nucleation is hard[11], but also reduce inclusion or occlusion during crystallization and maximize the rejection of impurities as much as possible[5, 12].

Traditionally, seed crystals were added from an external source, generally from a milled crystals or from previous batch products. This seeding mode is powerful and multifunctional, but the abrupt introduction of seed will also destroy the stable environment in crystallizer, hence increasing the probability of inducing the explosive nucleation and introducing impurities and bacteria into crystallizer[13]. Moreover, seed preparation is sometimes complex, costly and time-consuming if high-quality seed is required[14], and the exact dosage is hard to calculate[15]. This paper focuses on the systematic analysis of these issues and further sort order in development and application of the seeding technique in crystallization.

In order to study the seeded crystallization process scientifically (in contrast to pure trial-and-error approaches), significant efforts have been undertaken in recent two decades to understand the effects of various seeding parameters[16, 17], and the application of new technologies has also opened up broader space for developing new seeding techniques[18, 19]. Our goal is to bring the reader up to date with some of those activities and further realize the potential of seeding technique in optimizing crystallization. This review article mainly focuses on the techniques of adding homogeneous seeds in crystallization processes. Readers can refer to literature for other closely related topics such as the addition of heterogeneous seeds (see e.g., Javdani and coworkers[20]) and heterogeneous nuclei as seeds in protein crystallization (e.g., Zhou and coworkers[21]).

2. How do seeds affect crystallization processes?

Seeding is a powerful but complex step for industrial crystallization process, which includes many parameters that should be taken into account commonly when designing and implementing a seeding strategy. The key seeding parameters and desired production targets affected by the seeding parameters are summarized in Table 1. In the past two decades, how these parameters affect crystallization processes and product quality attributes have been widely studied by many scholars[7, 14, 17, 22-24], which will be discussed in detail in the following sections.

To clarify the effect of changing seeding parameters on the crystallization process and production targets, a variable-based causal graph (VBCG) is used to show the qualitative connection between seeding parameters, state variables and production targets, as shown in Figure 1. It shows the most direct effects of changing each seeding parameter on key crystallization phenomena and consequently on the objectives. In the VBCG, the most important state variables of the system are supersaturation σ and size distribution n_i, which are connected by the crystallization phenomena describing in the population balance equations and the total crystal surface area in a feedback loop[24]. The key seed attributes of the CSD are emphasized to illustrate the qualitative effect of the phenomena on the CSD of product. For a fixed operational policy, the main pathways that are followed in the VBCG depend on initial seed attributes and operational conditions at seeding point, which largely determines the whole crystallization behavior and the final product attributes. Therefore, seeding technique is critical to the crystallization success. The seeding technique is not only influenced by factors mentioned above, but also influenced by factors that difficult to describe by mathematical variables such as the seed surface property $R_{a,s}$, as shown in Figure 2.

Not only that, there are many unquantifiable factors easy to be ignored may cause seeding failure in actual industrial crystallization processes, e.g. seed activity. All possible causes for

seeding failure are summarized here by an Ishikawa diagram in Figure 2, in which these factors are roughly classified into six aspects: (1) seed loading; (2) seed quality; (3) seed preparation; (4) seeding condition; (5) seed storage; (6) seeding mode. Of these factors, the first three aspects are prerequisite to ensure product quality and consistency, which closely related to seed quality, quantity, and property. The latter three aspects are crucial to guarantee the effectiveness of seed and give full play to the advantages of seeding technique, among which the seeding conditions were vital and widely studied by researchers[25-28]. If there is no suitable seeding environment, the desired product quality attributes, e.g. crystal polymorph, for seeding crystallization are hardly achievable.

2.1 Seed loading

Typically, seed loading is a general designation for the seed mass, size and size distribution, which is a group of important parameters used to quantify the added seeds in the crystallization[29, 30]. Seed mass is sometimes called seed load, or seed weight in the literature[31, 32], which usually refers to the mass of seeds to be added in the crystallization process, while the seed loading rate (SLR) shown in equation (1) is also frequently used to have a unified quantization[6, 29, 33].

$$\eta = \frac{M_s}{M_p - M_s} \tag{1}$$

Where η is defined as SLR, M_s and M_p are seed mass and product mass, respectively. The seed size was generally referring to the characteristic length of the seed, which includes number mean size (d_{10}), Sauter mean diameter (d_{32}), and weight mean crystal size (d_{43}) for the bulk of seeds. The seed size distribution was usually described by the number CSD or volume CSD, which was also commonly approximated by Gaussian distribution, log-normal distribution, gamma distribution, or a combination of them in the references[3, 34]. The used SLR can vary from as low as 0.1% to as high as 10%, which is dependent on the seed size and product requirement[35].

To determine the right seed quantity, many researchers[36-40] have investigated the effects of seed loading on product yield, mean size, coefficient of variation (CV), and CSD for different crystallization processes by simulations and experiments. The research work are mainly summarized as the following three aspects: (1) Seed loading effects on products; (2) Nucleation inhibition; (3) Seed recipe design and optimization.

(1) Seed loading effects on products. Regarding the quantitative study on seed loading, the mass-balance equation (2) is widely used to calculate the amount of seeds for specified size according to the expectant product mass and size, which is simple, then particularly embraced in experimental research and industrial applications. The equation is commonly expressed as follows,

$$\bar{L}_s = \bar{L}_p \left(\frac{M_s}{M_{th} + M_s} \right)^{1/3} \tag{2}$$

where $\bar{L}_s$ and $\bar{L}_p$ are the number mean sizes of the seeds and final products, respectively, while M_s and M_{th} are the mass of added seeds and theoretical product. This equation is derived from the mass balance with several assumptions: (1) McCabe's ΔL law (see the references[16, 41]); (2) seed growth only, i.e., the seed growth is dominant while nucleation is negligible[10, 42]; (3) seeds and products have the same volume shape factor. The contribution of the equation (2) is the use of a simple form to construct the relationship between seeds and products based on mass balance, which has practical guiding significance for industries. However, there are some problems when this function was used in practice. It is not all the crystals follow the ΔL raw, and it can be seen that the function is simple and rough. At the same time, it is impossible that both the seeds and products have the same volume shape factor. Besides, the actual crystallization process is coupled with crystal breakage, agglomeration, and nucleation. Therefore, more and more scholars are dedicated to the study of seed loading effects for specific case in different crystallization systems. Lewiner et al.[43] studied the effects of seeding in the batch cooling crystallization of an organic weed killer, in which seeding was proved to be efficient in reducing the batch-to-batch variations and in increasing the average size of the final particles. The results also showed that there was an optimal seed amount in the range of low seed loading, giving the maximum mean crystal size of the products. Patience et al.[37] investigated the effects of seed mass and seed size on product yield and product mean size based on size-independent growth model simulations, found that increasing seed mass can be used to increase final product yield and reduce batch time. The effects of seeds on the final CSD of ammonium sulfate were studied in a batch cooling crystallizer, it was found that the mean crystal size will gradually reach a steady value irrespective of the seeding if the batch time is sufficiently long[44]. The impact of seed surface area on the product CSD was investigated in a glycine batch cooling system[38], and the results indicated that the product CSD could be effectively regulated if the seed surface area is over a specific value. It was found by experiments that a proper choice of SLR could result in a unimodal distribution of crystal products[16]. Besides, it was demonstrated that increasing seed mass could effectively decrease the nucleation rate and therefore stabilize the growth kinetics during crystallization[40]. To find an appropriate seed mass, the seed size was often approximated by the mean size of seeds. However, some scholars believe that that seed activity reduces with size, if the seeds below a certain threshold size will fail to grow[45, 46]. The seeds should also be not too large as the required seed mass can be uneconomically large for the process yield. Furthermore, large seed crystals can be the source of the secondary

nucleation due to attrition. Lung-Somarriba et al[38] proposed that the seed size should be one-quarter of the maximum achievable crystal size of the product to avoid attrition. For a higher seed loading ratio, it was observed that the increased number of particles consumed the supersaturation much faster and the product size distribution followed very closely to that of the seed particles. Similarly, for a constant seed load, when particles with smaller size were used, the difference between seed and product crystal sizes reduced considerably with a similar size distribution profile[17].

(2) Nucleation inhibition. Increasing seed mass has been known as an attractive option in inhibiting nucleation, but the key issue is how many seeds should be added to suppress nucleation effectively as more seeds mean high cost. A generally accepted criterion for determining seed loading is to maximize the growth of seeds while minimizing the growth of newly nucleated crystals[40]. Kubota and Doki et al[30, 42, 47] discussed the critical SLR to effectively suppress nucleation, and therefore developed a function to chart the relationship between the critical seed size and the SLR based on experimental studies of two crystallization systems. They also pointed out that, if enough seeds were loaded over the critical SLR under well-mixed conditions, no scale-up effect on CSD was observed[42]. However, it is still uncertain whether increasing the seed load can always be applied to suppress nucleation, or whether this method only works in some special cases. As pointed out by Tseng and Ward[29], smaller seeds are more effective in suppressing nucleation than the larger seeds, after investigating the critical SLR for seeding batch crystallization by simulations based on 43 systems. Meanwhile, they highlighted that there is a great deal of variability in the critical SLR, and a single correlation is inadequate to describe the relationship between critical SLR and seed size. It was noted that smaller seeds can more easily lead to seed agglomeration with purity decreasing[48], and smaller seeds may be inactivated when they reach a certain size. Coles and Threlfall[46] indicated that many examples of a critical seed size are probably nothing to do with size but with surface effects, the repeated failure of small seeds to grow is related to their surface features rather than their size. To successfully suppress nucleation though achieving the growth-dominated process by seeding, an exorbitant seed load is always applied or suggested in practice. It is worth noting that crystal growth is not the only factor determining the reproducibility of seeded crystallization process. At a very high seed mass, the results often become almost independent of the cooling profile, and the mean size of the product crystals will decrease. In addition, increasing seed mass often leads to an increase of crystal aggregation, especially for small seed sizes[16, 49, 50]. Possibly the best suitable choice is only when the seed loading is designed or optimized according to the desired product quality attributes.

(3) Seed recipe design and optimization. Concerning the seed recipe design and optimization, several researchers[3, 22, 33, 51-53] have devoted to the design and optimization of seed loading. Chung et al[22] first studied the optimization of seed distribution (seed mass, seed mean size, and the width of the seed distribution) based on a batch crystallization process. It was found that optimizing the seed size distribution (SSD) can have a larger effect on the particle size distribution (PSD) than optimizing the supersaturation by simulations based on three optimization objectives, namely weight mean size, CV, and the ratio of the nucleated crystal mass to seed crystal mass. The SLR on crystallization kinetics was studied by Huang et al[54], and found that increasing SLR could facilitate the growth kinetics together with a more uniform size distribution of crystal products. In order to obtain the desired product CSD, a novel framework of optimal seed recipe design for batch cooling crystallization systems was presented by Nagy et al[3]. The framework was based on the analysis of standard sieve to optimize the composition of seed mixture. They also proposed a systematic design for shaping CSD combined supersaturation with seed recipe optimization by a dynamic seeding method[55]. The best objective function for seeded batch crystallization was studied by simulations based on size-independent growth and nucleation model[51], indicating that the width of the PSD can be controlled much more effectively by manipulating seed properties than by adjusting the supersaturation trajectory.

2.2 Seed quality

Seed quality is the reflection of the physical and chemical properties of seeds, which is closely related to crystal purity, form, lattice strain, surface roughness and so on. Seed quality has a critical impact on crystallization behavior, crystallization kinetics, and final product form and quality. Many factors can affect seed quality, and the most significant of which is seed origin.

Seed may come from milled crystals, pretreated crystals, product slurry and primary nucleus (or via anti-solvent addition), so they have different purity, lattice strain, surface property, and polymorph, which can significantly impact seed growth trajectory and final product quality and CSD[31, 56-58]. Kardum et al[57] demonstrated that seed origin can cause different supersaturation trajectory and product CSD, while product crystal polymorph depends on the added seed structure regardless of the crystal form used for preparing the solution. Seeds are often directly from crystallized products, but they can also be produced via a variety of means such as milling or other offline methods in order to obtain a narrow SSD more suitable for seeding. In the case of the high purity of active pharmaceutical intermediates (APIs), the seeding-by-nucleation technique often is preferred to avoid the entrainment of impurities from added seeds.

In terms of seed purity, the seed crystals should not only be chemically pure, but also polymorphically pure. Otherwise, seeding desired polymorph will fail with a mixture of

polymorphs [58, 59]. For instance, Maher et al.[58] indicated that the root causes of piroxicam batch failure were the seed polymorph contamination. Today, seeding has been developed to be a key technique for crystal polymorph control over the last decades[12, 60, 61], which has moved on from a mysterious process to one that there are some ways that may be used to attack this central problem in crystallization field. Stable polymorphs are commonly preferred for product development as they avoid the risk of crystal form transformation and subsequent quality issues. However, the metastable polymorphs are sometimes selected for product development when they exhibit superior quality attributes such as higher solubility, bioavailability and product handling properties[17]. In addition, it is possible to obtain a bonus by seeding the mixed polymorphs. Beckmann et al.[62] produced the desired metastable polymorph products exclusively by using the pure metastable polymorph as seeds in the abecarnil crystallization; meanwhile, they obtained a polycrystalline product containing a mixture of both polymorph solids by seeding two mixed crystal polymorphs. For the crystallization of enantiomers, Muller and coworkers[63] highlighted the importance of identifying the transition temperature and devised a seeding strategy that involved seeding at low supersaturation below the transition temperature to manufacture the desired stable solid form consistently. Sometimes seeding may fail in crystallizing the target polymorph. Yu and coworkers[64, 65] demonstrated that seeding one polymorph can nucleate a different crystal form despite the thermodynamic stability in seeded melt crystallization of D-mannitol and D-sorbitol. However, seeding failed to obtain the desired polymorphic outcome because of cross-nucleation occur for other crystallization systems[66, 67].

Except the seed purity (chemical and polymorphic purity) above, seed surface properties such as roughness and regularity are very important to seed quality[33, 68], which may affect the crystal morphology and quality of products, e.g. rough surfaced seeds are more easily lead to crystal aggregation. Generally, seed surface properties are determined by the seed origin and previous process, e.g. seed preparation.

2.3 Seed preparation

Seed is usually crystallized products produced before to avoid complicated seed preparation in industry, however, this does not always meet the requirements to seed size, lattice strain and surface property. Therefore, additional processing and handling processes such as milling and sieving are frequently used to prepare a narrow SSD for a uniform product with a narrow CSD[16]. Other means such as washing, dissolution and aging are often combined together to improve SSD and quality[14, 33]. Table 2 summarized the recent studies on seed preparation by using different combinations of various processing methods based on different crystallization system. It is seen from Table 2 that the seed was mainly prepared by wet and dry recrystallized products, previous

batch products and direct commercial products. Dry milling and wet milling are the primary processing approach used to obtain desired small seeds with a narrow size distribution. Table 3 compared the advantages and disadvantages of dry milling and wet milling.

Dry milling is widely applied to prepare dry seeds in the early phase of drug development since dry milling operations consume fewer resources for process development[5]. However, there are many drawbacks with dry milling as shown in Table 3. Dry milling could melt or form a compacted layer for some materials within the mill chamber, which cause the hydrates dehydrated or the solvates desolvated, and make the crystals lose their crystallinity and become amorphous[5, 33]. The milled particles can interact with the mill metal surface. In addition, the mechanical rotor could cause defective seeds with lots of fine crystals. In most cases, sieving is combined with the dry milling to achieve a narrow or specified size range of seeds, as shown in Table 2. However, there are many disadvantages associated with the seeds after dry milling and sieving. The sieved seeds are difficult to achieve exact seed size distribution according to the sifter fraction due to the seed particle agglomeration and the clogging of mesh. The edges and faces of seeds are fractured or defective and the crystal dust often adheres to seed surfaces, both of which might result in multiple crystal growth leading to particle agglomeration or other undesired growth effects[17]. To solve these problems, seed preparation has been optimized by several groups by using a combination of advanced process analytical technologies (PATs) and multiple operations[14, 33]. Aamir et al.[14] designed several different seeds prepared by combining milling, sieving, and washing to investigate the effects of seeds based on the batch cooling crystallization processes of potassium dichromate. They found that the experimental results can be in good agreement with the model-based CSD prediction if the seed quality was good with less fine particles. In contrast, the product size distribution would be over predicted by the model if the seeds contained fine particles or crystal dust. Zhang et al.[33] studied the effects of three types of seeds prepared by using different methods of milling, sieving and washing based on the experiments of β-L-glutamic acid (β-LGA) batch cooling crystallization by using the Electron Microscope, in-situ ATR-FTIR, Focused Beam Reflectance Measurement (FBRM), and online imaging system. They discussed the effects of seed loading ratio, seed mean size, and seed size variance on the product yield and CSD based model simulation, respectively. We proposed a seed preparation method to ensure seed quality for seed recipe design and implementation, and highlighted the importance of washing seeds by the solvent. Figure 3 shows the microscopy images of three seed crystals prepared by using different methods with a combination of milling, sieving and washing, and their corresponding size distributions analyzed by in-situ image system[33]. It is seen that the washed seed crystals (Figure 3 (b) and (c))

by the solvent help remove the fine crystals and smooth the seed surface, thereby improving the final product quality and CSD.

Wet milling is a preferred approach for seed preparation to reduce seed crystal size in many crystallization processes. It is robust, easy to use, widely applicable, and offers both financial and product property advantages than dry milling. The advantages of wet milling for crystallization mainly include smaller crystal seeds, tunable seed size and amount, controlled seed crystal form, as well as the robustness of scale-up[5], as summarized in Table 3. Kougoulos et al.[75] investigated the effects of various particle engineering techniques including sonocrystallization, high shear wet milling(HSWM), and dry hammer milling on product uniformity and stability based on a conventional API batch cooling crystallization. They indicated that the use of dry hammer milling will increase fine particle formation resulting in reduced content uniformity of both 5% w/w and 30% w/w API capsule blends compared to sonocrystallization and non-optimal HSWM, which should be avoided in API production. In recent years, integrated wet milling and crystallization technologies have been broadly developed to intensify crystallization processes[70, 72-75, 79-82]. Engstrom et al.[70] proposed a scaling approach for API particle size reduction by introducing a toothed rotor-stator wet milling based on cooling crystallization. Yang et al.[72] proposed an in situ seed generator using by integrating the upstream application of a high shear rotor-stator wet milling with the continuously mixed suspension mixed product removal crystallization (MSMPRC), and significantly reduced startup duration and enhanced the product yield. The high shear rotor-stator wet milling is popular in reducing particle size, which allows for a reduction of particle size down to ~10-15 μm, thereby improving scalability[74, 79]. Due to lack of the breakage mechanism knowledge, wet milling may lead to less-than-ideal overall robustness of the wet milling operation. On the basis of the work by Engstrom et al.[70] and Harter et al.[79], Luciani et.al. [81] investigated the significance of different scale-up factors to predict milling performance by a model-aided approach and discovered a very good correlation between the breakage rate and shear number. Ahmed et al.[82] highlighted the importance of coupling wet milling and advanced inline measurement technologies with crystallization to engineer desirable particle attributes. The wet milling seeded crystallization with PATs was coupled to investigate to reduce particle surface energy through interchanging the rotor-tooth configuration and operating the rotational speed, which demonstrated integration of wet milling technologies particularly rotor-stator devices can effectively avoid common issues encountered with traditional dry milling units[82]. We believe wet milling combined with crystallization has considerable potential to enhance crystal seed attributes control.

However, it is also noted that some post-processing processes can make the seeds ineffective. For instance, Sung et al.[83] found out that the washed seeds of magnesium sulfate heptahydrate were ineffective when they were used to seed crystallization solution below a supersaturation of 2.3 °C. Seed activation can be sometimes necessary, as crystals exposed to environmental conditions may not grow at low supersaturation, which may be due to surface contamination. Seed activation can be achieved by washing or wet grinding with a solvent before addition[62]. Additionally, seed slurries are often prepared and settled for hours to avoid agglomeration and solvent entrapment[84].

2.4 Seeding condition

In the past two decades, many researchers have confirmed that seeding condition within crystallizer is vital for crystal evolution and product quality for seeded crystallization processes. The effects of various seeding conditions have been reported in the literature, mainly including seeding supersaturation[26, 85, 86], temperature[87, 88], seeding point[27, 86], seeding time[32, 50, 89], metastable zone width(MSZW)[8, 90], material of stirrer and crysatllizer[26] and hydraulic property[32, 91] in crystallizer. During these studies, supersaturation, temperature and location at seeding are the most preferred factors due to their direct and serious influences on product quality attributes. Figure 4 shows a schematic diagram of solution concentration-temperature phase, which is divided into three zones: stable zone, metastable zone (MSZ) and unstable zone. The stable zone is an undersaturated zone wherein seeds will be fast dissolved, e.g. seeding point SP_0 and SP_5, thus the seeds in general are not be added in this zone unless intentionally for partial seed dissolution. The unstable zone is a supersaturated zone where spontaneous nucleation will happen, e.g. seeding point SP_4 and SP_9, thus it will make meaningless by adding seed strategy unless you want to seed by nucleation.

Seeding are usually carried out in the MSZ, e.g. SP_2 and SP_7 as illustrated in Figure 4, to avoid seed dissolution and nucleation, because MSZ is one area that without spontaneous nucleation and dissolution, but in which crystallization can be induced by adding seeds[46]. However, choosing an appropriate location in MSZ to add seeds is not easy, since it is largely dependent on the knowledge of MSZW. For convenience, seeding was commonly performed at a low supersaturation so as to avoid nucleation[35]. In some cases, in order to improve seed quality and size distribution, the seeds were added in the unstable zone but close to the solubility curve so that it can partially dissolve fine crystals and smooth seed surface[58, 89]. Therefore, the solubility curve and the MSZW should be established before a suitable supersaturation and temperature profile can be set. A general rule of thumb is to add seeds midway between the solubility curve and the super-solubility curve[10]. The point of seeding can be derived either from the knowledge of solubility and super-solubility,

fixing the point was advised to near to the solubility line and to a maximum of 1/4 to 1/2 into the MSZ (like the yellow region as shown in Figure 4) or by trial-and-error[50]. Online measurement by PATs can be a critical aid in detecting the right seeding point[92]. Measurement of solution concentration by, e.g., Attenuated total reflectance-Fourier transform infrared (ATR-FTIR) spectrometry, Near Infrared (NIR), UV/vis or Raman spectroscopy can be very effective in detecting seeding points. After seeding, in order to ascertain the effectiveness of seeding, particle count and size distribution can be measured by an in-situ/on-line particle size and counting instrument, e.g., FBRM, online imaging, and Ultrasound.

Supersaturation, together with the amount of available crystal surface area provided by seeds, largely defines both crystals' growth rate and their quality[93]. If supersaturation is higher or closer to the upper limit of MSZ, an explosive nucleation, avalanche or shower of crystals can occur, thereby further inducing secondary nucleation, crystal breakage and agglomeration. In addition, high seeding supersaturation can cause higher crystal breeding, subsequent outgrowth of secondary nucleation and agglomeration[8]. Warstat and Ulrich hold that seeds should preferentially not be added at a higher supersaturation than 30-40% of the MSZ[49]. It was generally recommended to add crystal seeds at lowest possible supersaturation[76], but a lower seeding supersaturation might be responsible for seed dissolution[74]. Moreover, the supersaturation at seeding time is also related to seed mass, seed size and solution temperature, a suitable supersaturation should keep seeds growth but without dissolution and secondary nucleation occurrence[73]. However, identifying a suitable seeding temperature is not easy, because the temperature effects are commonly coupled with supersaturation, seed loading and following temperature profile[17, 94]. Nevertheless, some studies[32, 85, 87] found that seeding temperature was crucial on crystal form, shape, and even final product quality. The same seeds could evolve into different crystal shapes under the different seeding temperatures[88]. For cooling crystallization process, the temperature was commonly manipulated to keep supersaturation within MSZ to avoid inadvertent secondary nucleation while maintaining growth. A superior temperature profile for seeded crystallization was deemed to keep supersaturation constant by a model-based or model-free feedback control[55, 95]. Moreover, seeding time and location are also important operating parameters[7, 27, 96]. Generally, the seeding location should be a point where seeds were well dispersed, e.g., close to stirrer to add seeds[50]. Once the seeds were added, an isothermal condition was generally maintained for some time for seeds to be dispersed into the solution and to consume the initial supersaturation[17]. Sullivan et al. suggested that the first 15-30 minutes following seed addition were the most critical period in ensuring the effectiveness of seeding[9].

Besides above main influencing factors, the material of stirrer, baffle and crystallizer[26], size and shape of agitator and hydraulic properties[32, 91] in a crystallizer were also found to affect the seeding effectiveness to some extent, thereby affecting the product form, size, and quality. In addition, it should be noted for evaporative crystallization, that hot surfaces of the heat exchanger might lead to the partial dissolution of seeds[12]. This often happens in evaporative crystallization processes, especially when the damaged crystals have a higher solubility and a slower growth rate.

2.5 Seed storage

Seed storage is often ignored in lab research because it is not a problem to prepare a handful of seeds whenever necessary. A great quantity of seeds is generally prepared in advance to avoid the whole crystallization process to shut down, especially for the continuous seeded crystallization, thus seed storage becomes particularly important. Seed storage may encounter several issues. Contamination and agglomeration of seed particles are major concerns since they may seriously affect seed quality, which result in seeding failure, and yield low-quality products. The crystal seed surface can be easily poisoned, even by exposure to ambient air. The poisoned surface may hamper seed growth or result in crystal monstrous growth[50].

How to maintain seed quality and prevent seed agglomeration is a challenge to seeded crystallization process. The seed sizes commonly are mostly distributed among 1-200 μm, which easily lead to particle agglomeration. Typically, the seed slurry was stored temporarily in a pre-equilibrated solution with preset concentration and temperature. Figure 5 shows a typical seed slurry vessel used for seed storage, which includes a vessel with an agitator, a temperature control system, and a pump for subsequent seed slurry transport. The temperature control apparatus is used to maintain the vessel constant temperature because if the solution for seed storage is not suitably pre-equilibrated, the seeds may dissolve or grow. To avoid temperature gradient within the vessel, and the pre-equilibrated solution is held at a constant temperature. Another potential process risk factor is settling of seeds, thus proper stirring is generally essential to ensure seed dispersion. It found that the seeds were preserved in a slurry for several weeks without showing degradation or change of particle size or shape[97].

In addition, seeds are sometimes stored in an anti-solvent liquid (for instance, sugar seeds in propyl alcohol) with a certain mass to avoid damp and aggregation[98]. However, one potential question is that the way may lead to seed contamination, even result in inactivation. A possible solution is making the seed particles suspend among the crystallization solution before seed addition to remove impurities and clean the growth faces. It is better to activate the seed surface to dissolve the contaminated outer layer by a prepared solution[12, 99].

2.6 Seeding mode

Traditionally, seed particles were added from an external source, initially as a dry powder, but more generally as a slurry in a saturated solution of mother liquor or an appropriate anti-solvent[9]. Although seed can be well prepared beforehand and seeding condition can also be optimized, maintaining the quality and dispersity of seeds in the crystallizer is more important. Therefore, the seeding mode becomes a critical step. The seeds can be added as a dry powder or as a wet slurry. One seed generation approach is dry milling, in which the pin mill and jet mill are two common types of dry mill methods depending on the seed size specification[5]. However, dry powder is prone to particle clumping or aggregation if not properly processed, and the hydrophobic seed particles are susceptible to agglomeration due to strong polar or non-polar interactions. In contrast, seed slurry is a more preferred method in practice, as it can overcome the above drawbacks by dispersing the seeds in a small volume of liquid before their addition into the solution. The slurry could be prepared in a saturated solution of the same solvent or a different solvent as in anti-solvent crystallization. In addition, seed slurry allows healing of processed seed particles by smoothing the fractured faces and edges of the seed particles through growth and Ostwald ripening.

After preparing the seed slurry from the vessel, the next question is how to transport the suspension into the crystallizer. The transport of seed slurry may meet several problems, especially for continuous seeding crystallization[100]. Clogging and settling of solid particles are major concerns since they may fully stop flow in the tubing, force the process variables out of their design space, and even oblige the whole production to shut down[5, 100, 101]. Moreover, the heat loss to the environment can cause seed growth and nucleation happening on the tube wall during transfer, hence resulting in either clogging/settling in the tube or a lot of fine crystals[102]. How to maintain a consistent flow of the seed suspension and prevent clogging/settling is a challenge for seed slurry transfer especially in the continuous seeding crystallization. In order to avoid these risks, it can take the following methods: remove unnecessary fittings, cut down the tubing as short as possible, enlarge tubing inner diameters, increase the heat preservation, increase flow velocity, selecting material of tubing inner walls, etc. However, enlarging tubing diameters will decrease the flow velocity of suspension and cause settling of seeds if the total flow is kept constant. Through process design, increase heat preservation, avoid seed dissolution or growth, strengthen pipeline design, reduce the risk of blockage and settlement, so as to improve the sowing mode. Overall, these possible risks mentioned above during the addition of seeds should be considered in the process design for safety and product quality.

3. Challenges and opportunities

Although significant progress has been made over the past two decades, many elements regarding the design, optimization and control of seeding with more accurate description remain enigmatic. Current prominent issues are highlighted as follows:

- Seed is commonly simplified into one-dimensional size with an overwhelming use of the mean seed size and coefficient of variation for operation design and optimization, which is oversimplified and the crystal shape distribution is lost, resulting in inaccurate or unrepeatable products.
- Seed is generally assumed as an initial variable, then the model-based optimization strategies often perform suboptimally owing to the uncontrollable operating disturbances by the abrupt seed introduction.
- Seeding technology lacks systemic design and evaluation methodology of seeding technique including seed preparation and loading.

In view of the above problems, the potentially valuable topics to improve seeding technique are summarized from the following several aspects.

3.1 Seed measurement and monitoring

The seeding technology development is largely dependent on the measurement technology, which lies in the research of the sensor, signal transmission and measure instrument. One of the most important enablers of modern crystallization technology might be the FBRM, which extended the concept of seeding and realized the real-time online measurement of crystal characteristic size. With the use of FBRM, online monitoring and controlling methods have been greatly developed in crystallization processes. As the FBRM only measures the one-dimensional chord length of crystals, which is difficult to apply the model-based control, and the accurate CSD from chord length distribution (CLD) is almost impractical by the existing transformation methods[103, 104]. Many other measurement methods have also been developed for inline or online measurement of crystals, such as online imaging, microscopy, Raman spectroscopy, and ultrasound, as reviewed in the papers[18, 105, 106].

Unfortunately, few people pay attention to the online detection of seeds in past research. On the one hand, it was lacking of feasible equipment for seed online measurement, mostly the seeds were taken as an initial variable and measured by offline methods. Therefore, seed measurement results by the online measurement apparatus are open to question, because few works discussed the measurement precision and accuracy of the measuring equipment while used for seeds. On the other hand, it is more difficult for seed measurement owing to seed size is much smaller, which asks for higher requirements on the software and hardware of measuring apparatus and transducers. The measurement accuracy will be reduced largely when the seed size is very small, which is more

challenging for two-dimensional and three-dimensional measurement and monitoring of such small crystals. However, monitoring particle dimension and count in real-time enables the seeds to evolve as expected in the process and allows for direct feedback control of the seed morphology to target final products of a specific crystal shape distribution with desired downstream and quality properties. In addition, mapping seed behavior through inline/online measurement and monitoring can significantly increase the probability of success and minimizes the need for additional scale down experiments for improved understanding and optimization due to unexpected process behavior. Predictably, online measurement of dynamic micro crystals will become one of the most promising and anticipated directions for revolution in the crystallization field.

3.2 Operation design and optimization

The idea of quality-by-design (QbD) has already been accepted extensively and widely used to improve product quality attributes in the field of crystallization industry. Some researchers tried to present a framework or general rules for designing or optimizing seed recipe. It is worth mentioning that 20 empirical rules were proposed by Ulrich and co-workers for designing seeding of batch crystallization process that takes into consideration of the MSZW, growth rate, agglomeration tendency, and secondary nucleation[8]. The proposed rules can be used to aid the selection of near-optimum process conditions for specified product properties. It's proposed that seeding should be implemented at moderate supersaturation (30-40% of the MSZW). These rules are easy to implement and contribute to the selection of seed size and the alleviation of agglomeration. Some made endeavors to optimize seeding protocol and found that optimizing seed recipe could obtain a better result than optimizing the supersaturation[3, 4], as mentioned above. Nagy et al.[3] presented a QbD framework for optimal seed recipe design for batch cooling crystallization, which can achieve a target product CSD by optimizing the amounts of seeds from various sieved seed fractions. Moreover, they investigated the effects of seed quality prepared using different methods and provided an evaluation method based on experiments and simulations[14]. Industrial practitioners may find it difficult to put the strategy into practice because sieving operation and collection of different sieve fractions necessitate a host of GMP procedures. Furthermore, the desired seed size distribution may be inaccessible via sieve in practice, especially for fragile needle-like crystals.

One question is whether the existing seed preparation scheme is a feasible solution for industrial applications at present. Whether the seeding strategy is the simplest and effective method should be assessed according to certain performance indicators. However, the systematic evaluation methodology is desperately lacking, and the methods of seeding design and optimization are very limited, which are restricting the promotion and application of seeding technique. In

practice, the seeding process is a complicated system engineering. It is difficult to give a general evaluation method due to lots of variables coupling to each other. In our experience, The reasonable decomposition of design process is a method to reduce the influence of various coupling factors under the guidance of system engineering methodology. Another question worth thinking about is how to precisely control seed loading? According to the authors' knowledge, previous studies generally considered seed loading as uncertainties rather than controlled variable for the control of the product CSD and quality. The systematic strategy for optimizing product quality attributes by controlling seed loading is rare. The systematic strategy to precisely control the shapes of CSD in real time by continuously adding seeds should be of concern. Furthermore, designing seeding policy by coupling with other auxiliary equipment such as mixers to continuously seeding can be a potential, which can provide extra freedom for design and optimization of crystallization. Real-time continuous seeding technology should be further developed.

3.3 Seed action mechanism

Although the seed adding technique has been widely applied in the field of crystallization, the mechanism of seed action is not well understood and the optimal seeding policy is still in debate. Seeding control is still unclear and empirical, which commonly adopted a semi-empirical correlation to describe the seeding process simplistically. Due to the inadequate understanding of seed action mechanisms, and the influences of impurities, additives, and solvents on the growth rate of individual crystal faces, the model-based control always remained poor and unsatisfying. There are still many unexplained phenomena, such as inert crystals, the invalidity of crystals[46], the failure of seed crystals smaller than a certain size to grow[90], whether there are inactive seeds existed owing to the seed itself is incomplete or process damage, and literature data were sometimes contradictory[43]. Seed growth by primary nucleation and secondary nucleation is also unresolved[46]. Moreover, the shape of seeds can be modified by both chemical and physical methods (e.g., the use of solvents, additives, pH, and temperature cycling)[107]. The first-principles understanding of the effect of each of these methods is required to engineer crystal shape according to their functional applications. Therefore, a full understanding of the seed assisted crystallization mechanism still requires vast research. Some crystal growth models[107] provide a better understanding of the mechanism of growth and shape evolution. The models can help to design more efficient experiments by reducing the size of the parameter space to be explored. Molecular simulation may be one useful tool in providing mechanistic insight into the various kinetic processes involved in the growth of individual crystal faces from a molecular perspective[108-110].

In addition to using the homogeneous seeds and additives, the heterogeneous seeding could be a promising means to better understand and control the nucleation and crystal growth processes[20, 111]. However, the mechanism of heterogeneous seeding is more complicated.

4. Conclusions

In this paper, a critical overview of the major developments related to the seeding technique in crystallization research over the past two decades is reviewed, and the challenges and opportunities faced by crystallization research are revealed. The main developments occurred in the application of the traditional seeding technique are deep understanding of effects of various seeding parameters, rules of thumb for seed loading, and quantitative seed recipe design and optimization. However, kinds of problems existed in currently seeded crystallization described in the paper indicate that the potential of seeding technique is worthy of expectation. With the development of seeding technology, there is no doubt that new and more effective methods are needed to improve the seeding efficiency and practicability. One common issue of the current seeding technique is costly and time-consuming for seed preparation. Therefore, the novel seeding technique should be valued to solve the issues and to improve the availability and controllability of seeding technique. Many recent trends can be distinguished in the literature regarding the development of new seeding techniques and methods to crystallization processes. Without the sake of completeness, the following three topics of interest can be considered as a potential to develop new technologies:

- Multiple-pass seeding technique is a potential alternative to control seed loading with different size and shape distribution, which can be used to deploy seed recipe with different size and mass according to the optimized control strategies, and then treat seeding as a processing variable with adjustable degree of freedom, so as to realize real-time seeding control.
- New design strategies integrating seeding technique with auxiliary technologies, such as ultrasound, mixer, and gassing, should be developed to improve seeding effectiveness. We believe there will be some surprises if appropriate auxiliary technology is chosen to assist or couple with the seeding technique.
- Automation technologies are extremely urgent to improve the control level of the seeding technique, improve process safety and overcome the uncertainties of process operation. In addition, new seed generation modes such as anti-solvent, additives and inducer

should be extended, and new methods to meet specific requirements are expected to be developed.

In addition, most of the designs of the industrial crystallizers lack effective actuators meet the desired control objectives, e.g., producing a product with a defined CSD[112]. Moreover, the effectiveness of the available actuators is generally quite limited. It is worth noting that improper use of the process actuators can have detrimental effects similar to those caused by deliberate process disturbances. Eliminating the negative effects is often impossible as many actuating techniques have an irreversible action. To intensify the safety and effectiveness, the automatic seeding actuator should be developed to effectively track the control objectives.

The challenges and opportunities for seeding technique discussed above do coexist, which also point out the directions for further research and improvement of seeding technology. With the development of new technologies and new methodologies, the seeding technique is moving from an artistic status to a scientific plateau, and it is becoming increasingly important and will be brilliant in the field of industrial crystallization.

Declaration of Competing Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements: This work was supported by the National Natural Science Foundation of China (Grant No. 61903213), Natural Science Foundation of Shandong Province (Grant No. ZR2019BF039) and by the Talent Introduction Foundation of Qingdao University of Science & Technology (Grant No. 010022888). The authors additionally thank Prof. Zoltan K. Nagy from Purdue University for fruitful discussions.

Abbreviations

API	Active pharmaceutical intermediate
ATR-FTIR	Attenuated total reflection-Fourier transform infrared
CLD	Chord length distribution
CSD	Crystal size distribution
CV	Coefficient of variation
DIJM	Dual impinging jet mixer
DNC	Direct nucleation control
GMP	Good manufacturing practice
FBRM	Focused beam reflectance measurement

HSWM	High shear wet milling
IC	Initial condition
LGA	L-glutamic acid
MSMPRC	Mixed suspension mixed product removal crystallization
MSZ	Metastable zone
MSZW.	Metastable zone width
SLR	Seed loading rate
SSD	Seed size distribution
PAT	Process analytical technology
PSD	Particle size distribution
QbD	Quality-by-Design
VBCG	Variable-based causal graph

Greek

η	Seed loading rate
σ	Relative supersaturation

Nomenclature

B	Breakage
C	Solution concentration
C_s	Solution concentration at seeding point
C^*	Solubility
CV	Coefficient of variation
D	Crystal dissolution rate
G	Growth rate
$I_{i,AG}$	Agglomeration rate constant component i
J	Nucleation rate
L	Crystal size
M	Mass
$m_{i,j}$	j^{th} moment of CSD of component i
N	Number of crystals
n	Crystal size distribution
P_{AM}	Production rate amorphous solid
$R_{A,s}$	Seed surface property
SP	Seeding point
t	Time
T	Temperature
w	Molar lattice strain
Z	Crystal purity

Subscripts

50	Median
A	Surface
AG	Agglomeration
AM	Amorphous phase
C	Crystalline phase
HX	Heat exchanger/Foreign surface
i	Component i
P	Product
PN	Primary nucleation
S	Seeds
SN	Secondary nucleation
th	Theoretical

References

[1] Zhang D, Xu S, Du S, Wang J, Gong J. Progress of pharmaceutical continuous crystallization. Engineering. **2017**, 3(3)**:** 354-364.

[2] Jiang M, Braatz RD. Designs of continuous-flow pharmaceutical crystallizers: developments and practice. CrystEngComm. **2019**, 21(23), 3534-3551

[3] Aamir E, Nagy ZK, Rielly CD. Optimal seed recipe design for crystal size distribution control for batch cooling crystallisation processes. Chemical Engineering Science. **2010**, 65(11)**:** 3602-3614.

[4] Ward JD, Yu CC, Doherty MF. A new framework and a simpler method for the development of batch crystallization recipes. AIChE Journal. **2011**, 57(3)**:** 606-617.

[5] Tung HH. Industrial perspectives of pharmaceutical crystallization. Organic Process Research & Development. **2013**, 17(3)**:** 445-454.

[6] Kubota N, Doki N, Yokota M, Sato A. Seeding policy in batch cooling crystallization. Powder Technology. **2001**, 121(1)**:** 31-38.

[7] Yu ZQ, Chew JW, Chow PS, Tan RBH. Recent advances in crystallization control an industrial perspective. Chemical Engineering Research and Design. **2007**, 85(7)**:** 893-905.

[8] Ulrich J, Jones MJ. *Seeding Technique in Batch Crystallization*. Wiley-VCH Verlag GmbH & Co. KGaA, 2012.

[9] O'Sullivan B SB, Baramidze G. Recent advances for seeding a crystallization process. Mettler Toledo Auto-Chem. **2012:** 1-13.

[10] Mullin JW. *Crystallization, fourth ed.* Butterworth-Heinemann: Oxford, 2001.

[11] Mousaw P, Saranteas K, Prytko B. Crystallization improvements of a diastereomeric kinetic resolution through understanding of secondary nucleation. Organic Process Research & Development. **2008**, 12(2)**:** 243-248.

[12] Beckmann W. Seeding the desired polymorph: Background, possibilities, limitations, and case studies. Organic Process Research & Development. **2000**, 4(5)**:** 372-383.

[13] Zhang CT, Wang HR, Wang YL. Internally generated seeding policy in anti-solvent crystallization of ceftriaxone sodium. Chemical Engineering & Processing Process Intensification. **2010**, 49(4)**:** 396-401.

[14] Aamir E, Nagy ZK, Rielly CD. Evaluation of the effect of seed preparation method on the product crystal size distribution for batch cooling crystallization processes. Crystal Growth & Design. **2010**, 10(11)**:** 4728-4740.

[15] Wang H-Y, Ward JD. Seeding and optimization of batch reactive crystallization. Industrial & Engineering Chemistry Research. **2015**, 54(38)**:** 9360-9368.

[16] Yu ZQ, Chow PS, Tan RB. Seeding and constant-supersaturation control by ATR-FTIR in anti-solvent crystallization. Organic Process Research & Development. **2006**, 10(4)**:** 717-722.

[17] Parambil JV, Heng JYY. *Seeding in Crystallisation*, 2017.

[18] Nagy ZK, Fevotte G, Kramer H, Simon LL. Recent advances in the monitoring, modelling and control of crystallization systems. Chem Eng Res Des. **2013**, 91(10)**:** 1903-1922.

[19] Kleetz T, Scheel R, Schembecker G, Wohlgemuth K. Cooling Crystallization: is gassing competetive to seeding? Crystal Growth & Design. **2018**, 18(9)**:** 4906-4910.

[20] Javdani A, Ahmadpour J, Yaripour F. Nano-sized ZSM-5 zeolite synthesized via seeding technique for methanol conversions: A review. Microporous Mesoporous Mater. **2019**, 284**:** 443-458.

[21] Zhou RB, Cao HL, Zhang CY, Yin DC. A review on recent advances for nucleants and nucleation in protein crystallization. Crystengcomm. **2017**, 19(8)**:** 1143-1155.

[22] Chung SH, Ma DL, Braatz RD. Optimal seeding in batch crystallization. The Canadian Journal of Chemical Engineering. **1999**, 77(3)**:** 590-596.

[23] Kubota N, Doki N, Yokota M, Jagadesh D. Seeding effect on product crystal size in batch crystallization. Journal of Chemical Engingeering of Japan. **2002**, 35(11)**:** 1063-1071.

[24] Lakerveld R. Development of a task-based design approach for solution crystallization processes. Ph.D thesis, Universiteit Delft, 2010.

[25] Bergfors T. *Succeeding with seeding: some practical advice*. Springer Netherlands, 2007.

[26] Ni X, Liao A. Effects of mixing, seeding, material of baffles and final temperature on solution crystallization of L-glutamic acid in an oscillatory baffled crystallizer. Chemical Engineering Journal. **2010**, 156(1)**:** 226-233.

[27] Kim CM, Kim SR, Ahn JH. Development of auto-seeding system using image processing technology in the sapphire crystal growth process via the Kyropoulos method. Applied Sciences. **2017**, 7(4)**:** 371.

[28] Codan L, Sirota E, Cote A. Improving the filterability of particles by healing the seed particles. Organic Process Research & Development. **2018**, 22(9)**:** 1131-1142.

[29] Tseng YT, Ward JD. Critical seed loading from nucleation kinetics. AIChE Journal. **2014**, 60(5)**:** 1645-1653.

[30] Doki N, Kubota N, Yokota M, Chianese A. Determination of critical seed loading ratio for the production of crystals of uni-modal size distribution in batch cooling crystallization of potassium alum. Journal of Chemical Engingeering of Japan. **2002**, 35(7)**:** 670-676.

[31] Ferguson S, Morris G, Hao HX, Barrett M, Glennon B. Automated self-seeding of batch crystallizations via plug flow seed generation. Chemical Engineering Research and Design. **2014**, 92(11)**:** 2534-2541.

[32] Malwade CR, Qu HY. Cooling Crystallization of Indomethacin: Effect of Supersaturation, Temperature, and Seeding on Polymorphism and Crystal Size Distribution. Organic Process Research & Development. **2018**, 22(6)**:** 697-706.

[33] Zhang F, Liu T, Chen W, Ma CY, Wang XZ. Seed recipe design for batch cooling crystallization with application to L-glutamic acid. Industrial & Engineering Chemistry Research. **2019**, 58(8)**:** 3175-3187.

[34] Salvatori F, Mazzotti M. Manipulation of particle morphology by crystallization, milling, and heating cycles-a mathematical modeling approach. Industrial & Engineering Chemistry Research. **2017**, 56(32).

[35] Kalbasenka AN. Model-based control of industrial batch crystallizers: experiments on enhanced controllability by seeding actuation. Ph.D thesis, Technische Universiteit Delft, **2009**.

[36] Fevotte G. New perspectives for the on-line monitoring of pharmaceutical crystallization processes using in situ infrared spectroscopy. International Journal of Pharmaceutics. **2002**, 241(2)**:** 263-278.

[37] Patience DB, Dell'Orco PC, Rawlings JB. Optimal operation of a seeded pharmaceutical crystallization with growth-dependent dispersion. Organic Process Research & Development. **2004**, 8(4)**:** 609-615.

[38] Lung-Somarriba BLM, Moscosa-Santillan M, Porte C, Delacroix A. Effect of seeded surface area on crystal size distribution in glycine batch cooling crystallization: a seeding methodology. Journal of Crystal Growth. **2004**, 270(3)**:** 624-632.

[39] Liu JJ, Ma CY, Hu YD, Wang XZ. Effect of seed loading and cooling rate on crystal size and shape distributions in protein crystallization-A study using morphological population balance simulation. Computers & Chemical Engineering. **2010**, 34(12)**:** 1945-1952.

[40] Long BW, Yang HT, Ding YG. Impact of seed loading ratio on the growth kinetics of mono-ammonium phosphate under isothermal batch crystallization. Korean Journal of Chemical Engineering. **2016**, 33(2)**:** 623-628.

[41] Canning T, Randolph A. Some aspects of crystallization theory: Systems that violate McCabe's delta L law. AIChE Journal. **1967**, 13(1)**:** 5-10.

[42] Doki N, Kubota N, Sato A, Yokota M, Hamada O, Masumi F. Scaleup experiments on seeded batch cooling crystallization of potassium alum. AIChE Journal. **1999**, 45(12)**:** 2527-2533.

[43] Lewiner F, Fevotte G, Klein JP, Puel F. Improving batch cooling seeded crystallization of an organic weed-killer using on-line ATR-FTIR measurement of supersaturation. Journal of Crystal Growth **2001**, 226 348-362.

[44] Hojjati H, Rohani S. Cooling and seeding effect on supersaturation and final crystal size distribution (CSD) of ammonium sulphate in a batch crystallizer. Chemical Engineering & Processing Process Intensification. **2005**, 44(9)**:** 949-957.

[45] Shimizu K, Kubota N. A note on the minimum size of crystals that can produce secondary nuclei. Journal of Crystal Growth. **1986**, 78(1)**:** 177-180.

[46] Coles S, Threlfall TL. A perspective on a century of inert seeds in crystallisation. CrystEngComm. **2014**, 16(21)**:** 4355-4364.

[47] Doki N, Yokota M, Sasaki S, Kubota N. Size distribution of needle-shape crystals of monosodium L-glutamate obtained by seeded batch cooling crystallization. Journal of Chemical Engingeering of Japan. **2004**, 37(3)**:** 436-442.

[48] Funakoshi K, Takiyama H, Matsuoka M. Influences of seed crystals on agglomeration phenomena and product purity of m-chloronitrobenzene crystals in batch crystallization. Chemical Engineering Journal. **2001**, 81(1-3)**:** 307-312.

[49] Warstat A, Ulrich J. Seeding during batch cooling crystallization-An initial approach to heuristic rules. Chemical Engineering & Technology. **2006**, 29(2)**:** 187-190.

[50] Lafferrère L, Hoff C, Veesler S. In situ monitoring of the impact of liquid−liquid phase separation on drug crystallization by seeding. Crystal Growth & Design. **2004**, 4(6)**:** 1175-1180.

[51] Hsu CW, Ward JD. The best objective function for seeded batch crystallization. AIChE Journal. **2013**, 59(2)**:** 390-398.

[52] Zhang DJ, Liu LD, Xu SJ, Du SC, Dong WB, Gong JB. Optimization of cooling strategy and seeding by FBRM analysis of batch crystallization. Journal of Crystal Growth. **2018**, 486**:** 1-9.

[53] Qian HL, Dai L, Jiang F, Shi YQ, Wang ZX, Liu W, *et al.* Quantitative design of seed load based on model identification of nucleation and crystal growth stages without transmittance data. Powder Technology. **2018**, 335**:** 11-17.

[54] Huang D, Liu W, Zhao S, Shi Y, Wang Z, Sun Y. Quantitative design of seed load for solution cooling crystallization based on kinetic analysis. Chemical Engineering Journal. **2010**, 156(2)**:** 360-365.

[55] Nagy ZK, Aamir E. Systematic design of supersaturation controlled crystallization processes for shaping the crystal size distribution using an analytical estimator. Chemical Engineering Science. **2012**, 84(84)**:** 656-670.

[56] Kalbasenka AN, Spierings LCP, Huesman AEM, Kramer HJM. Application of seeding as a process actuator in a model predictive control framework for fed-batch crystallization of ammonium sulphate. Particle & Particle Systems Characterization. **2007**, 24(1)**:** 40-48.

[57] Kardum JP, Hrkovac M, Leskovac M. Adjustment of process conditions in seeded batch cooling crystallization. Chemical Engineering & Technology. **2013**, 36(8)**:** 1347-1354.

[58] Maher A, Hodnett BK, Coughlan N, O'Brien M, Croker DM. Application of new technology to a mature piroxicam crystallization process to gain process understanding and control, via industrial-academic collaboration. Organic Process Research & Development. **2018**, 22(3)**:** 306-311.

[59] Lee AY, Erdemir D, S.Myerson A. Crystal polymorphism in chemical process development. Annual Review of Chemical and Biomolecular Engineering. **2011**, 2**:** 259-280.

[60] Mangin D, Puel F, Veesler S. Polymorphism in processes of crystallization in solution: A practical review. Organic Process Research & Development **2009**, 13**:** 1241-1253.

[61] Bucar DK, Lancaster RW, Bernstein J. Disappearing polymorphs revisited. Angewandte Chemie-International Edition. **2015**, 54(24)**:** 6972-6993.

[62] Beckmann W, Nickisch K, Budde U. Development of a seeding technique for the crystallization of the metastable: A modification of Abecarnil. Organic Process Research & Development. **1998**, 2(5)**:** 298-304.

[63] Müller M, Meier U, Wieckhusen D, Beck R, Pfeffer-Hennig S, Schneeberger R. Process development strategy to ascertain reproducible API polymorph manufacture. Crystal Growth & Design. **2006**, 6(4)**:** 946-954.

[64] Yu L. Nucleation of one polymorph by another. Journal of the American Chemical Society. **2003**, 125(21)**:** 6380-6381.

[65] Chen S, Xi H, Yu L. Cross-nucleation between ROY polymorphs. Journal of the American Chemical Society. **2005**, 127(49)**:** 17439-17444.

[66] Kitamura M, Hayashi Y. Secondary nucleation behavior and the mechanism in antisolvent crystallization of Thiazole derivative polymorphs. Industrial & Engineering Chemistry Research. **2016**, 55(5)**:** 1413-1418.

[67] Maddar FM, Perry D, Unwin PR. Confined crystallization of organic materials in nanopipettes: tracking the early stages of crystal growth and making seeds for unusual polymorphs. Crystal Growth & Design. **2017**, 17(12)**:** 6565-6571.

[68] Ostermann MC, Termuhlen M, Schembecker G, Wohlgemuth K. Growth rate measurements of organic crystals in a cone-shaped fluidized-bed cell. Chemical Engineering & Technology. **2018**, 41(6)**:** 1165-1172.

[69] Hermanto MW, Phua A, Chow PS, Tan RB. Improved C-control of crystallization with reduced calibration effort via conductometry. Chemical Engineering Science. **2013**, 97(6)**:** 126-138.

[70] Engstrom J, Wang C, Lai C, Sweeney J. Introduction of a new scaling approach for particle size reduction in toothed rotor-stator wet mills. International Journal of Pharmaceutics. **2013**, 456(2)**:** 261-268.

[71] Abu Bakar MR, Nagy ZK, Rielly CD. Seeded batch cooling crystallization with temperature cycling for the control of size uniformity and polymorphic purity of sulfathiazole crystals. Organic Process Research & Development. **2009**, 13(6)**:** 1343-1356.

[72] Yang Y, Song L, Gao T, Nagy ZK. Integrated upstream and downstream application of wet milling with continuous mixed suspension mixed product removal crystallization. Crystal Growth & Design. **2015**, 15(12)**:** 5879-5885.

[73] Acevedo DA, Kamaraju VK, Glennon B, Nagy ZK, Acevedo DA, Kamaraju VK*, et al.* Modeling and characterization of an in situ wet mill operation. Organic Process Research & Development. **2017**, 21(7).

[74] Kalbasenka AN, Spierings LCP, Huesman AEM, Kramer HJM. Application of seeding as a process actuator in a model predictive control framework for fed-batch crystallization of ammonium sulphate. Particle & Particle Systems Characterization. **2007**, 24(1)**:** 40-48.

[75] Kougoulos E, Smales I, Verrier HM. Towards integrated drug substance and drug product design for an active pharmaceutical ingredient using particle engineering. AAPS PharmSciTech. **2011**, 12(1)**:** 287-294.

[76] Lakerveld R, Kalbasenka A, Kramer HJ, Grievink J, Jansens PJ. The application of different seeding techniques for solution crystallization of ammonium sulphate. Proceedings of European Congress of Chemical Engineering (ECCE-6); 2007; Copenhagen; 2007.

[77] Adi H, Larson I, Stewart P. Use of milling and wet sieving to produce narrow particle size distributions of lactose monohydrate in the sub-sieve range. Powder Technology. **2007**, 179(1-2)**:** 95-99.

[78] Johnson B, K, Tung H, Hsin, Lee I, Midler M, Cote A, Starbuck C. Processes and apparatuses for the production of crystalline organic microparticle mompositions by micro-milling and crystallization on micro-seed and their use. U.S. Patent 063785, 2009-1-26

[79] Harter A, Schenck L, Lee I, Cote A. High-shear rotor–stator wet milling for drug substances: expanding capability with improved scalability. Organic Process Research & Development. **2013**, 17(10)**:** 1335-1344.

[80] Rajagopalan AK, Bötschi S, Morari M, Mazzotti M. Feedback control for the size and shape evolution of needle-like crystals in suspension. III. wet milling. Crystal Growth & Design. **2019**.

[81] Luciani CV, Conder EW, Seibert KD. Modeling-aided scale-up of high-shear rotor–stator wet milling for pharmaceutical applications. Organic Process Research & Development. **2015**, 19(5)**:** 582-589.

[82] Ahmed B, Brown CJ, McGlone T, Bowering DL, Sefcik J, Florence AJ. Engineering of acetaminophen particle attributes using a wet milling crystallisation platform. International Journal of Pharmaceutics. **2019**, 554**:** 201-211.

[83] Sung C, Estrin J, Youngquist G. Secondary nucleation of magnesium sulfate by fluid shear. AIChE Journal. **1973**, 19(5)**:** 957-962.

[84] Barrett P, Smith B, Worlitschek J, Bracken V, O'Sullivan B, O'Grady D. A Review of the use of process analytical technology for the understanding and optimization of production batch crystallization processes. Organic Process Research & Development **2005**, 9(3)**:** 348-355.

[85] Widenski DJ, Abbas A, Romagnoli JA. A model-based nucleation study of the combined effect of seed properties and cooling rate in cooling crystallization. Computers & Chemical Engineering. **2011**, 35(12)**:** 2696-2705.

[86] Gross MB, Kind M. Comparative study on seeded and unseeded bulk evaporative batch crystallization of tetragonal Lysozyme. Crystal Growth & Design. **2017**, 17(6)**:** 3491-3501.

[87] Seki H, Furuya N, Hoshino S. Evaluation of controlled cooling for seeded batch crystallization incorporating dissolution. Chemical Engineering Science. **2012**, 77**:** 10-17.

[88] Zhang F, Liu T, Huo Y, Guan R, Wang XZ. Investigation of the operating conditions to morphology evolution of β-L-glutamic acid during seeded cooling crystallization. Journal of Crystal Growth. **2017**, 469(1)**:** 136-143.

[89] Qamar S, Elsner MP, Hussain I, Seidel-Morgenstern A. Seeding strategies and residence time characteristics of continuous preferential crystallization. Chemical Engineering Science. **2012**, 71**:** 5-17.

[90] Threlfall TL, De'Ath RW, Coles SJ. Metastable Zone Widths, Conformational Multiplicity, and Seeding. Organic Process Research & Development. **2013**, 17(3)**:** 578-584.

[91] Ting HH, and Warren L. McCabe. Supersaturation an crystal formation in seeded solution. Industrial & Engineering Chemistry. **1934**, 26(11)**:** 1201-1207.

[92] Zhou GX, Fujiwara M, Woo XY. Direct design of pharmaceutical antisolvent crystallization through concentration control. Crystal Growth & Design. **2006**, 6(4)**:** 892-898.

[93] Ma CY, Wang XZ. Closed-loop control of crystal shape in cooling crystallization of L-glutamic acid. Journal of Process Control. **2012**, 22(1)**:** 72-81.

[94] Trampuz M, Teslic D, Likozar B. Crystallization of fesoterodine fumarate active pharmaceutical ingredient: Modelling of thermodynamic equilibrium, nucleation, growth, agglomeration and dissolution kinetics and temperature cycling. Chemical Engineering Science. **2019**, 201**:** 97-111.

[95] Nagy ZK, Chew JW, Fujiwara M, Braatz RD. Comparative performance of concentration and temperature controlled batch crystallizations. Journal of Process Control. **2008**, 18(3-4)**:** 399-407.

[96] Tung H, Paul E, Midler M, McCauley J. Crystallization of organic compounds: An industrial perspective. Wiley, Hoboken, NJ; **2009**.

[97] Eggers J, Kempkes M, Cornel J, Mazzotti M, Koschinski I, Verdurand E. Monitoring size and shape during cooling crystallization of ascorbic acid. Chemical Engineering Science. **2009**, 64(1)**:** 163-171.

[98] Mersmann A. *Crystallization technology handbook*. CRC Press, 2001.

[99] Narducci O, Jones AG, Kougoulos E. Crystal product engineering in the seeded cooling crystallization of Adipic acid from aqueous solution. Organic Process Research & Development. **2011**, 15(5)**:** 974-980.

[100] Yang X, Acevedo D, Mohammad A, Pavurala N, Wu H, Brayton AL, *et al.* Risk Considerations on developing a continuous crystallization system for carbamazepine. Organic Process Research & Development. **2017**.

[101] Giri G, Yang L, Mo Y, Jensen KF. Adding crystals to minimize clogging in continuous flow synthesis. Crystal Growth & Design. **2019**, 19(1)**:** 98-105.

[102] Majumder A, Nagy ZK. Dynamic modeling of encrust formation and mitigation strategy in a continuous plug flow crystallizer. Crystal Growth & Design. **2015**, 15(3)**:** 1129-1140.

[103] Worlitschek J, Hocker T, Mazzotti M. Restoration of PSD from chord length distribution data using the method of projections onto convex sets. Particle & Particle Systems Characterization. **2005**, 22(2)**:** 81-98.

[104] Li H, Kawajiri Y, Grover MA, Rousseau RW. Application of an empirical FBRM model to estimate crystal size distributions in batch crystallization. Crystal Growth & Design. **2014**, 14(2)**:** 607-616.

[105] Ma CY, Liu JJ, Wang XZ. Measurement, modelling, and closed-loop control of crystal shape distribution: Literature review and future perspectives. Particuology. **2016**, 26(3)**:** 1-18.

[106] Emmerich J, Tang Q, Wang Y, Neubauer P, Junne S, Maaß S. Optical inline analysis and monitoring of Particle Size and shape distributions for multiple applications: Scientific and industrial relevance. Chinese Journal of Chemical Engineering. **2019**, 27(2)**:** 257-277.

[107] Dandekar P, Kuvadia ZB, Doherty MF. Engineering crystal morphology. Annual Review of Materials Research. **2013**, 43**:** 359-386.

[108] Liang S, Duan X, Zhang X, Qian G, Zhou X. Insights into polymorphic transformation of L-glutamic acid: a combined experimental and simulation study. Crystal Growth & Design. **2015**, 15(8)**:** 3602-3608.

[109] Anwar J, Boateng PK. Computer simulation of crystallization from solution. Journal of the American Chemical Society. **1998**, 120(37)**:** 9600-9604.

[110] Agrawal SG, Paterson AHJ. Secondary nucleation: mechanisms and models. Chemical Engineering Communications. **2015**, 202(5)**:** 698-706.

[111] Hayles-Hahn C. Nanoseeds for pharmaceutical batch crystallisation. **2013**.

[112] Chianese A, Kramer HJM. *Industrial Crystallization Process Monitoring and Control*. Wiley-VCH Germany, 2012.

Tables and Figures

Table 1. Key seeding aspects and desired production targets

Seeding aspects	Production targets
● Seed attributes ① Mass ② Size distribution ③ Polymorph ④ Lattice strain ⑤ Surface properties ● Operational aspects at seeding point ① Supersaturation ② Temperature ③ Mixing during insertion ④ Location of insertion ⑤ pH ⑥ Hold time ⑦ Solvent ratio(Anti-solvent)	● Product attributes ① Product purity ② Product yield ③ CSD of products • Maximize mean • Predictable • Uni-modal • Narrow ④ Polymorph fraction ⑤ Crystalline fraction ⑥ Product shape ⑦ Reproducibility ● Operational attributes ① Scale-up behavior

Table 2. Summary of the studies on seed preparation

System	Seed source	Dry or wet	Mechanism	Milling or grinding	Sieving	Aging	Washing or dissolution	Filtering & drying	Process type	Reference
Ceftriaxone sodium+ acetone	Re-crystallized product	Dry	Milled anti-crystallization product	√	√	—	—	—	Offline	[13]
Potassium dichromate + water	Re-crystallized product	Dry	Ball milling	√	√	—	√	√	Offline	[14]
Indomethacin + ethanol Indomethacin + acetone	Re-crystallized product	Dry	No milled crystals	—	√	—	—	—	Offline	[32]
L-Alanine + water	Re-crystallized product	Dry	No milled crystals	—	√	—	√	√	Offline	[68]
Potash alum + water Ammonium oxalate + water	Re-crystallized product	Dry	Milled crystals	√	√	√	√	√	Offline	[69]
API+ ethanol	Re-crystallized product	Wet	Teethed rotor-stator milling	√	—	—	—	—	Offline & inline	[70]
Sulfathiazole+ n-Propanol	Re-crystallized polymorph product	Dry	Cooling crystallization	—	—	√	√	√	Offline	[71]
Paracetamol + ethanol	Re-crystallization product	Wet	Rotor-stator wet milling	√	—	—	—	—	In-situ	[72]
Triethanolate + ethyl acetate/ethanol/ water	Previous batch products	Dry	Seed healing	—	—	√	√	√	Offline	[28]
Paracetamol +water and isopropyl alcohol (IPA)	Previous product	Wet	Wet milling	√	—	—	√	√	In situ	[73]
Ammonium sulphate + water	Product & Previous product slurry	Dry & wet	High speed rotor milling	√	√	√	√	√	Offline	[74]

Continued Table 2

System	Seed source	Dry or wet	Mechanism	Milling or grinding	Sieving	Aging	Washing or dissolution	Filtering & drying	Process type	Reference
Benzoic acid + ethanol	Commercial product	Dry	Jet mill	√	√	—	—	—	Inline	[31]
L-glutamic acid + water	Commercial product	Dry	Ball milling	√	√	—	√	√	Offline	[33]
Mannitol + isopropyl alcohol/water	Commercial product	Dry & Wet	Wet and dry milling & ultrasound	√	√	—	√	—	Off line& In-line	[75]
Ammonium sulphate + water	Commercial product	Dry & wet	Ball milling	√	√	√	√	√	Offline& inline	[76]
Lactose + propan-2-ol/1-butanol	Commercial Lactose	Dry	Fluid energy mill	√	Wet sieving	—	√	—	Offline	[77]
API	Commercial product	Wet	Ball milling	√	√	√	√	√	Offline	[78]
Aspirin and three additional development compounds	Commercial product	Wet	Rotor-stator milling	√	—	—	—	—	Inline	[79]
Monosodium L-glutamic acid monohydrate + hydrochloric acid & D-mannitol + ethanol	Commercial product & Re-crystallized product	Wet	Wet milling & Previous products	√	—	√	√	√	In situ	[80]
1-Butanol+water n-Heptane/Methyl Isobuty Ketone	Commercial product & Re-crystallized product	Wet	High-Shear Rotor−Stator Wet Milling	√	—	—	—	—	In-situ	[81]
Acetaminophen + 2-propanol	Commercial product	Dry & Wet	Ball mill & rotor-stator milling	√	√	√	—	—	Off line& In-line	[82]

"√" indicates the processing method was used in seed preparation, while "—" indicates the processing method was not adopted or not mentioned in the reference.

Table 3. Comparison of advantages and disadvantages of dry milling and wet milling

Processing technique	Advantages	Disadvantages
Dry milling	• Simple and practicable • Increase batch reproducibility • Improve controllability • Change lattice strain • Form new growth points and improve crystal activity • Consume less resource for process development	• Change crystal form, structure and crystallinity • Contaminated or poisoned during milling • Cause seed agglomeration and poor seed quality with numerous fine crystals • Need multiple steps for post-processing with time-consuming • Uncontrollable seed size distribution
Wet milling	• Produce smaller seeds • Controlled seed crystal form • Tunable of seed size and amount • Robust for scale-up • High efficiency& uniform particles	• Increasing secondary nucleation • Potential power consumption and cost to remove solvent • Breakage mechanism is unclear • Solvent entrainment • Requiring extra unit operation

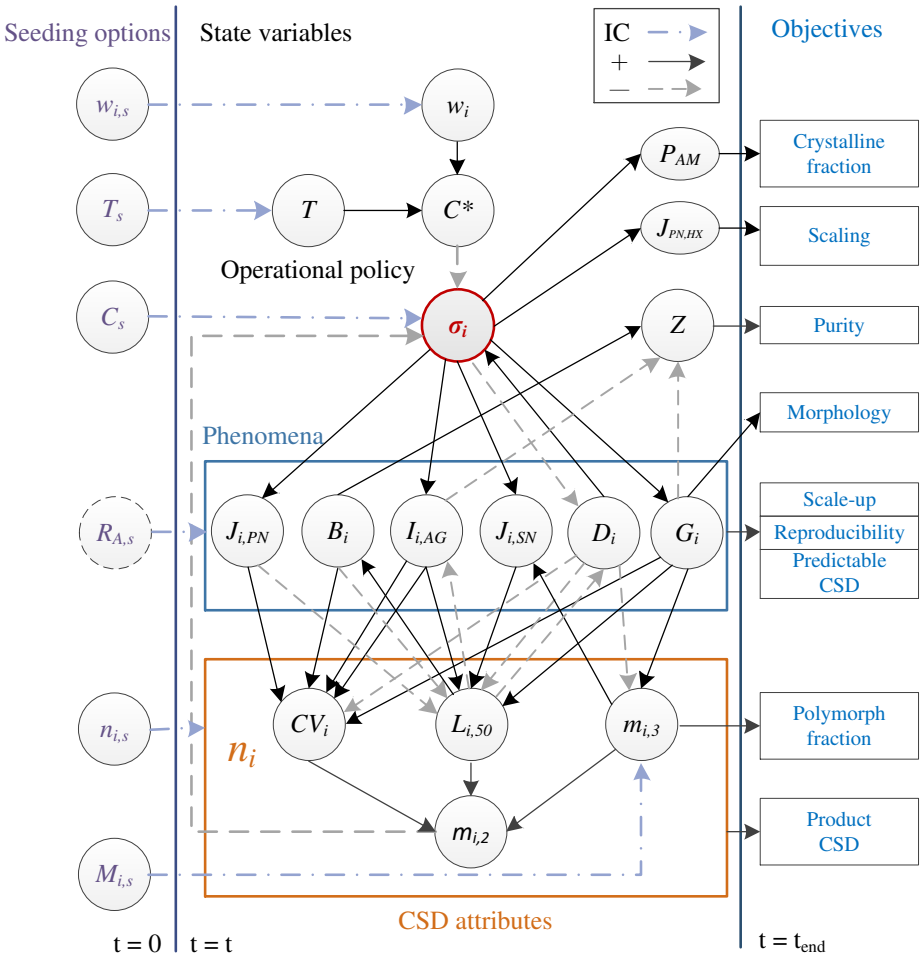

Figure 1. Seed VBCG for batch cooling crystallization[24]. Abbr. IC means initial condition. '+' and '–' indicate that the cause and effect variables tend to change in the same and opposite direction, respectively.

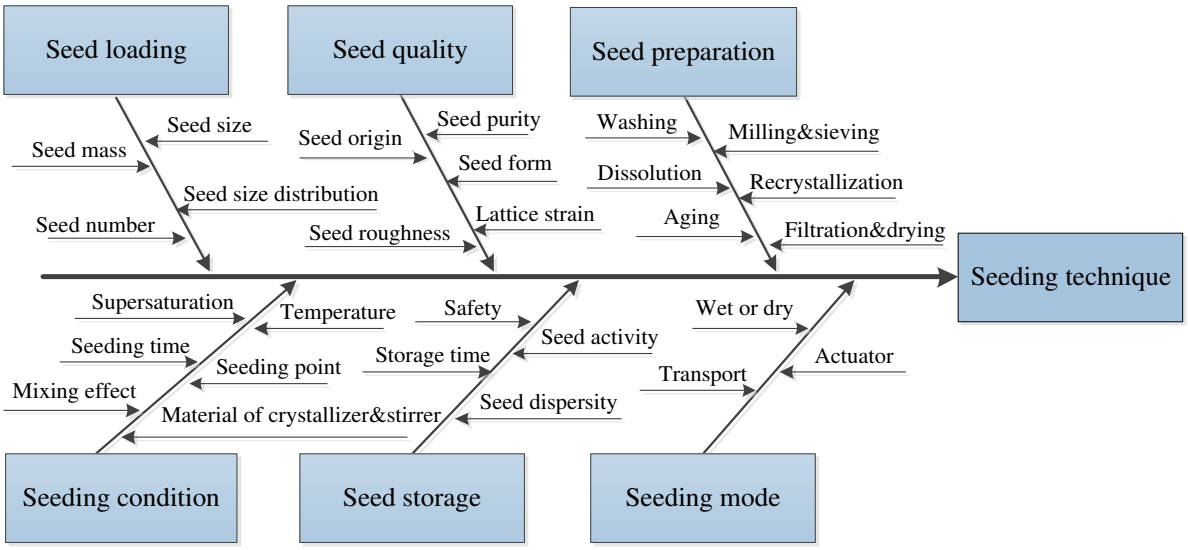

Figure 2. Ishikawa diagram illuminating possible causes for seeding failure in crystallization processes

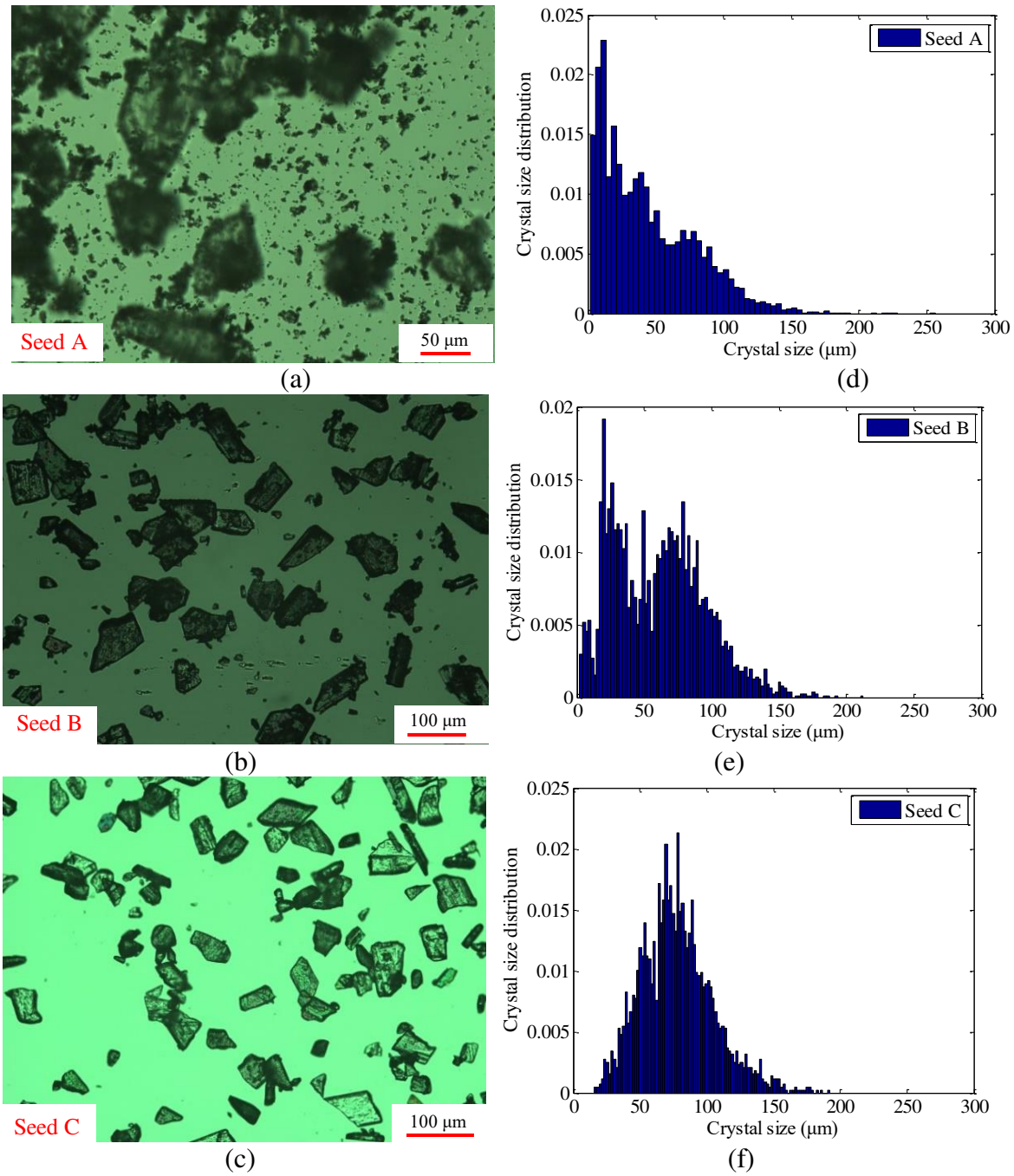

Figure 3. Microscopy images of seeds prepared by three different operating conditions and the corresponding size distributions measured by a non-invasive imaging system[33]

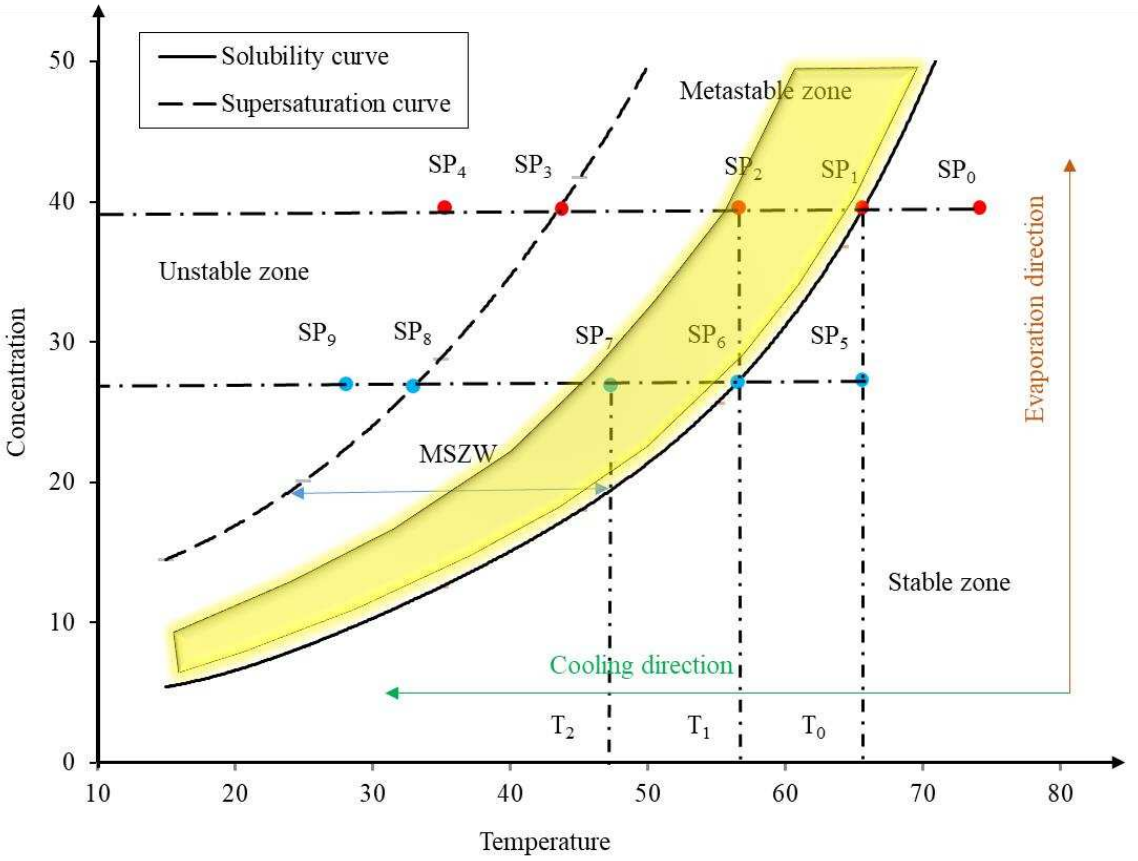

Figure 4. Schematic diagram of seeding point distribution

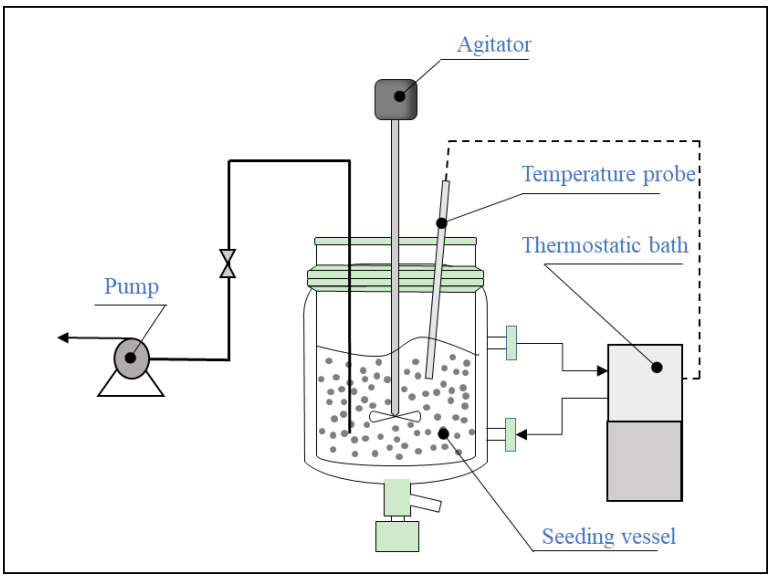

Figure 5. Typical seed slurry vessel used for seeded crystallization

Table of Contents (TOC) Graphics