REVIEW ARTICLE

Pharmaceutical Manufacturing Continuous Crystallization Procedures: A Review

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Abstract

This academic publication provides an overview of constant crystallization of solutions in the pharmaceutical industry. The comparison of continuous versus batch crystallizers, their construction benefits and drawbacks, and the addition of solid form framing to create a constantly focused interaction between digital advanced process technology technologies and chemical manufacturing functionalities were all covered in detail because of the broad key knowledge spectrum of precipitation. In-depth discussion was also given to mechanistic multiscale modeling, whose comprehension is crucial for the creation of future control applications. Process simulation and crystallizer optimization are also covered in the multiscale modeling section describes the model-based provided, which also addresses the intensifying method. Techniques the last section, is taken into consideration. The reader can become familiar with research pieces and their outcomes, which have thus far created different emerging viewpoints, by reading the unique articles on a particular theme that is gathered, talked about, and contrasted in the aforementioned primary categories. The pharmaceutical sector places a lot of emphasis on crystallization, and readers may already discover literature on continuous crystallization. However, due to the increasing trend towards the synthesis of items with special features that cannot be produced using conventional methodologies, the current study has placed a greater emphasis on the construction of automatic control for the generation of certain fine chemicals. Continuous crystallization may also allow for intensification techniques, modeling for optimization, "on-demand" production, and MPC. A classification study examines the literature.

Key words: Continuous crystallization process, intensification, mechanistic multiscale modeling, medicinal industrial production, model-based predictive control

INTRODUCTION

With applications ranging from very generic to very specific compounds, crystallization is a common method of material separation. It also has a huge impact on the pharmaceutical industry of pharmaceuticals because more than 90% of the ingredients in medications (active pharmaceutical ingredients [APIs]) are produced in a similar to crystal products. Although continuous manufacturing is a kind of production that is more time and cost effective, over the past two decades, the quantity of investigations on a constant crystallization has quickly expanded. Mixed suspended mixed item removal crystallizers, but also rod-shaped or plug flow crystallizers (PFC), also known as coiled segmented or slug flow crystallizers, crystallizers with laminar-flow tubular technology (LFTC), flow inverters (CFI), and variable oscillatory baffled crystallizers, are by far the most widely utilized pharmacy industry processes that are ongoing (COBC).

One of the control methods, design predictive control, necessitates the development of a mathematical model. In addition, planning, optimization, monitoring, and scaling up of crystallization processes are all done using mathematical models. As a result, mathematical modeling has improved our comprehension of crystallization. Regardless of its complexity, crystallization is now seen as a procedure that is more integrated, intensive, and clever.[1] Since the authors believe that mathematical modeling and MPC are crucial for the further development and application of technologies in the industry, this work gives a lot of attention to these two factors of continuous crystallization.

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Although crystallization has long been a part of industry, such as the sugar business, some parts of it are still unknown and cannot be generalized.[4-7] Because of this, crystallization is frequently referred to as a form of art rather than science. Before this, this document was created to provide a quick summary of scientific papers on the constant crystallization within the chemical sector, particularly the pharmaceutical industry. The following sections make up the paper: comparison of pressure and constant approaches and their benefits and drawbacks, in addition to the moving of the crystallization and the procedure of production running for continued flow; incorporating the constant recrystallization into the constant drug manufacturing[13] and the introduction of "on-demand" manufacturing; integration of PAT on the internet; mechanical multiscale modeling, computation, but instead optimization; and model-based. The division of nonetheless is not covered in this research.[2]

THE RESULT OF THE OPERATING MODE

Regarding procedures and product attributes: To Continuous Processes with Group Although batch-wise crystallization is still the most typical kind of crystallization within the pharmaceutical sector, it has some well-known negatives, including numerous scale-up problems, high production and upkeep fees, possible product inconsistency, and crystallization currently happening under non-uniform circumstances as they change over time.[3] However, recently, the United States Food and Drug Administration (USFDA) demonstrated significant support for continuous manufacturing,[8] which should spur a growing interest in developing and utilizing continuous systems for manufacturing.[9,10]

The drug maker center for continuous manufacturing's continuous crystallization facility, which already has been utilized using mathematics modeling, design, and process control improvement, is one of the most well-known instances in the industry.[11] The soluble information, metastable sector widths, and rate parameters were all previously acquired with a batch method, but many authors that performed research utilizing continuous crystallizers used this data instead. Furthermore, batch techniques are required for suspension and seed preparation.[12]

According to the research of Siddique *et al.*, an exchange method from a group mode as for such a constant flow, a transfer procedure was divided into three parts. Initially, basic physical information as an example soluble as well as solvent screening was gathered in a batches crystallizer. The following step is was to collect kinematic information MSZW, growth, and dissolution kinetics, as and seed loading are a few examples. OBC using the batch oscillatory baffled crystallizer. This allowed for a more accurate determination of the kinetic parameters because cooling rate, which varies greatly depending on the type of crystallizer, is a factor in crystallization kinetics as well.

All of the studies taken into consideration in this section are briefly summarized in Table 1.

A DOWNSTREAM UNIT OPERATING MODEL FOR CRYSTALLISATION

In the pharmaceutical sector, as well as other industries where a finished product is required isolated derived from the last broth or a greater level of there must be purity attained, purification and division stages may of utmost importance.

The experiments that used continuous crystallization in conjunction with other separations or immediately upstream are included in this chapter.

Table 2 provides a general summary of all studies taken into consideration in this section.

Coupling of the crystallization process using just a single additional downstream or upstream method

In some research, a process of constant crystallization has been closely linked with an additional stream or upstream process. This method is more commonly used when studying the impact of one process's output on another, or the impact of crystallization's output on another process. Yang *et al.*[26] developed a research of a continuously operating process in which tests were carried out on three distinct setups: (1) An MSMPR in the absence of a damp mill; (2) an MSMPR such a mill that is wet operating in a recycling; and (3) an MSMPR with a loop such A moist one kraft pulp performed downstream to be a segregator. According to a steady state data, the addition is both wet mill and the dry mill can be improved the system's particle properties, as well as startup time. When the mill was employed for downstream processing, it had been found that smaller crystals (55 m) having a homogenous dispersion were produced, especially whenever a mill tip speed and per turnover residency. The stakes were enormous at the time. In this case, crystal growth was dominated by secondary nucleation and breaking.

A reasonably high super saturation might create further issues in the filtration in situations where its thermodynamic balance in the clarifier is not attained; new crystals may develop on the filter mesh, resulting in obstruction. As a result, a crystallization process should be planned to produce products with improved filtration time and efficiency. The research conducted by Acevedo *et al.*[14] It was demonstrated how the product attributes of benzoic acid and paracetamol, both obtained using an MSMPR, affected continuous filtration. Small crystals formed during paracetamol's crystallization process had a detrimental impact on filtering. Larger block chord lengths (110 m) were attained inside the crystallization benzoic acid is a kind of acid. Larger crystals are known to be simpler to filter.[27] But when benzoic acid crystallized,

Table 1: Compares batch crystallization systems with continuous methods for forming crystals. A quick summary of the studies taken into account inside this section[15-25]

Contrast between	The different types of crystallization	Substances	Findings
PFC and batch	Cooling	L-alanine	Smaller median size and a narrower CSD were both found in the PFC.
CPCMSMPR, single stage PFC, linked PFC, phase (CPC and CPC- D),	Enantiomers that form conglomerates are cooled or separated.	D-/L-threonine	The paired PFC produced the most output; the CPC, CPC-D, and connected PFC produced the highest yields.
Batch OBC, and batch COBC	Chilling	Milk sugar	In the COBC, bigger crystals with a more compact CSD were produced.
Oscillatory flow that is continuously and batch-operated a micro-reactor	Cooling	Paracetamol	The constantly operating system produced a smaller mean size.
Multi-segmented MSMPR, batch, and MSMPR	Ant solvent and cooling	Paracetamol	The batch technique created the largest crystals, with the highest yields equivalent.
Multi-segmented and batch tubular slug flow crystallizer	Precipitation that is chilling	Lysozyme	The flow field tubular crystallizer produced smaller crystals; it did not produce any amorphous formation.

PFC: Plug flow crystallizers, MSMPR: Multistage mixed suspension mixed product removal

two distinct morphological forms – stiff plates and needles – were produced. There was a substantial influence on filtering, especially depending on the humidity levels, in which were markedly larger inside. This example (45 wt%) was higher than paracetamol (22.2 wt%), as well as on the clogging of screen pores that lowered the amount of filtrate that was produced. Liu *et al.*,[28] additionally used a COBC to crystallize and filter paracetamol and benzoic acid. It is clear from the in their investigation, the researchers used FBRM measures. Median chord length (weighted squarely) and particle count when it comes to benzoic acid changed before the test. This filtered result of benzoic acid had a high MC, as in the prior investigation, which was caused by a heavily agglomerated product. Given that no globules form during the crystallization of benzoic acid, the presence of globules the filtration process was responsible for.[29] According to the yield results, the filter and continuous crystallization techniques were determined to be appropriate for the manufacturing of APIs. Nevertheless, research showed indicated.

An investigation into the creation of acetylsalicylic acid (ASA) describes the linking of the constant reaction with crystallization.[30]

Continuous API production from start to finish

Another study was created to investigate how automated control loops and PAT tools can be used to generate steady-state conditions. This research was based using the same API and integrated continuous production process. The yield of the procedure and the qualities of the final product were significantly influenced by the reagent, which was continually injected into the first reaction crystallizer. As a result, with adequate control, desirable crystal characteristics and yields (91.4%) were obtained. The return loop of level control was used to keep up appropriate residency hours as influenced by the Kinetics of crystallization during cooling crystallization in the second MSMPR. Consequently, a fairly narrow CSD was attained. In recent years, there has been a rise in fascination with commercialization of laboratory fume hoods (LHC), as the industry has needed to adapt quickly to sudden and major shifts in the product requirements as well as to new processes to reduce the time required for cleaning verification and cleaning itself.[31,32]

This is extremely useful when there are unexpected alterations needed and/or demands, as an example during a viral or perhaps a pandemic outbreak. LHC systems are much less expensive and easier to adapt to different assembly lines or manufacturing scenarios than batch procedures.[31]

In addition, LHC technologies are less expensive to set up as opposed to batch fabrication, and despite their modest size, they can achieve larger overall efficiencies than batch production because continuous production allows for the use of solutes at higher concentrations (near solubility). As a result, less waste and solvent are required.[31] LY2886721 was synthesized using an LHC processing system. The LHC was equipped with a reacting MSMPR distillation unit with a circulating loop that could generate the desired product without the need for grinding or additional to pH cycles increase the aspect ratio of crystals. Furthermore, In comparison to batch crystallization (5–10% per mass),

Table 2: Crystallisation that is ongoing implementation into constant operation: A quick summary of the studies investigated in this section

Material	Constant synthesis mechanism	Crystallization	Findings
Connection of the crystallization process with just one additional downstream or upstream technique			
Paracetamol	(1) Wet milling for crystallization	cooling crystallization in a MSMPR	The (2) method produced smaller crystals; wet mill implementation produced more uniform CSDs in these situations.
	(2) Wet milling for crystallization		The (1) strategy resulted in the greatest yield and the fastest start-up time.
(1) Paracetamol	Filtration of crystallization	(1) MSMPR cooling crystallization; (2) MSMPR ant solvent crystallization	In the first example, smaller crystals with uniform morphology were obtained; in the second case, larger crystals with irregular morphology were obtained.
(2) The benzoic acid	Filtering and washing of crystallization	(1) Cooling crystallization seeded; (2) antisolvent crystallization seeded	The (1) scenario was shown to be very suited for the studied downstream processing; agglomerates were found in the (2) system; and acceptable yield was reached in both situations.
ASA	Reaction - crystallization - filtration (batch)	Cooling crystallization in a tubular crystallizer	Immediately filtering had a detrimental influence on product characteristics since the response remained intact during crystallization. Higher temperatures resulted in narrower CSD.
Nicardipine hydrochloride; ciprofloxacin hydrochloride; neostigmine methyl sulfate; rufinamide	Too numerous to mention (information can be found in the reference)	MSMPR antisolvent crystallization (maximum two steps)	The yield obtained in the (2) instance was 32%; the purity gained in the subsequent steps of the (3) case was insufficient, therefore the process was done within a single-batch system; the purity and yield that were produced with in (4) incident became 99.4% with 65%, respectively.
The amino acids L	Evaporation - crystallization - filtering - washing	Cooling crystallization seeded in a CFI	A better yield prediction model should be created; homogeneous flow was not attained.
ASA	Reaction crystallization filtering drying homogenization tableting	MSMPR antisolvent crystallization	The greatest quantity had been achieved at the lowest humidity, with no effect from residence time. The highest temperature produced the largest median size; residence duration had no effect. At the greatest temperature and slowest residence time, the lowest MC was attained; enough flow ability was obtained.

PFC: Plug flow crystallizers, MSMPR: Multistage-mixed suspension mixed product removal, ASA: Acetylsalicylic acid

lesser seed (1.3% per mass) was required. On the basis of the current system, scale-up research was also carried out. The system underwent two scale-ups: First, testing plays on a 1 kg scale, and second, testing experiments upon a 10 kg spectrum. It was discovered that the crystallizer's the final scale-up was very successful. Because it generated crystals with the necessary size (131 m; the highest was 200 m) and with good productivity (92.7%). Adamo *et al.* also created a refrigerator- plug-and-play size production line for upon request synthesis, segregation, and purification.[31] Because a batch crystallization approach was employed, this study does not interest us from the perspective of our paper.

Two MSMPR crystallizers were added to the system by Zhang *et al.* to enhance it. (1) Nicardipine hydrochloride, (2) Doxycycline hydrochloride, (3) Ammonium methyl sulfate, and (4) Rufinamide were all synthesized using the system; however, only the last three APIs were produced using a continuous method because (1) had a tendency to oil-out. Antisolvent crystallization with MSMPR was employed

in the synthesis of (3) as a key downstream step, much like it was in the processing of (2). The yield in this instance was 85% and was attained after two crystallizations. The sample was unavailable treated within the batch reactor for attain the desired quality and output of 90%; however, it purity was insufficient. In addition, (4) was crystallized in the MSMPR, at which point a crystalline end-product was produced. Thus, a 350 ml vessel may be used in place of the existing MSMPR vial (60 ml) and still flow into the thoughtful system. As a result, production would increase to 1200 dosages/day. Hohmann *et al.*[33] created the downstream microplant for separation and purification isolation for acidic substances, when the CFI unit was installed fitted, in contrast to other research reported in this order, for what MSMPR systems were employed to carry out the precipitation procedure's downstream processing. MSMPR crystallizers, on the other hand, predominate in end-to-end. Research because they often permit longer retention times, as well as a higher yield.[34]

On their latest publication work on continuous end-to-end manufacturing, Domokos *et al.*[35] demonstrate how product characteristics directly affect the caliber filtering and the filtered output. Hydrochloride, as a model material, was used, then to single-stage MSMPR was utilized to carry out the ant solvent cooling crystallization. It was discovered that when temperature decreased, the yield rose (41.88% on 25°C vs. 59.74% on 0°C). In addition, crystals having a median width of 601 m at 25°C were found as opposed beyond 400 m at 0°C. They discovered that ASA crystals larger than 250 m had existed.

IMPLEMENTATION OF ONLINE TECHNOLOGIES MAKE IT POSSIBLE TECHNOLOGY (PAT)

As a result of the intricacy of crystallization, it is essential to not only to be able to follow and command the procedure however, to gather specific information, such as equilibrium information that can be utilized for additional research as well as process improvement. The Food and Drug Administration released a PAT guideline in September 2004 to encourage the utilization and advancement of this technologies in the pharmaceutical sector.

The advent of PAT has increased the precision, resilience, and sturdiness of in-line measurement techniques, despite its drawbacks, such as limited dependability in some situations, the impact of numerous factors on the veracity of the measurements produced, fouling, etc.[36-38]

FBRM, accelerated total reflection, the most commonly used PAT tools in the continuous pharmaceutical sector are spatial infrared (attenuated total reflectance-Fourier transform infrared [ATR-FTIR]), ultraviolet/visible (ATR-UV/vis), spectrometry, and PVM.[39] The primary applications of FBRM include chord length assessment, particle counting, chord length distributions determination, steady-state estimates.[40,41] kinetic estimation[42,44], and polymorphism determination.[45] According to the inline estimation (microscope) of crystal, distribution, and crystal morphology, chord length and centerline dispersion can be turned into crystal size and CSD.[43] Because of the relationship between the peak heights in the related absorption spectra and the concentration, spectroscopy techniques such as ATR-FTIR and ATR-UV/Vis are primarily often used to monitor the concentrations of solutes.[46-48] additionally, steady-state and kinetics calculations can be made using this data.[42,49]

Supersaturation

The acquired data were combined with an FBRM technique for steady-state determination (count number and chord length). According to benzoic acid's rapid kinetics, its stability in a PFC was attained after 15 s using both approaches. Employing FTIR and/or FBRM devices in continuous systems might be difficult because the tip of the probe needs to be 45° away from the flow.

Size, distribution, and morphology of crystals

It came to be that this method was not appropriate for evaluating the kinematics in this case, as the FBRM considerably underestimated the percentage of crystals smaller than 1 mm. CSDs collected in a steady state were utilized to assess nucleation and growth rates. It was discovered that this substance exhibits growth rate distribution or size-independent growth; hence, information on particles of different sizes in smaller ranges is also necessary to simulate the growth kinetics.

Powell *et al.*[47] investigated the cooling crystallization liquid paracetamol in a multistage crystallizer and discovered that the addition for nucleation and regulation had an interesting effect on crystal shape.

Polymorphic form

More than 50% of APIs contain many polymorphic forms, and since many API product attributes depend on polymorphs, it is typically desirable to manufacture a specific form. To achieve the desired form, it is, therefore, absolutely essential to monitor and manage the process. The cooling crystallization of L-glutamic acids in an MSMPR was studied in the work by Lai *et al.*,[42] and the polymorphism was investigated. A Raman spectrometer was used for a subjective online measurement, and for a quantitative measurement, it was paired with just an offline X-ray particle diffractometer. It was found that regardless of residence time; only the form was formed at lower

temperatures (25°C). The desired shape was produced at a higher temperature (45°C). Therefore, in the system that ran at 25°C, the seed of the form was implemented. As a result, the production of form polymorphs should not be possible in any of these circumstances when the super saturation of processes falls below the nucleation limit. However, all crystals changed to the more stable form after a set amount of time. It is evident that the polymorphic change in this investigation was driven by kinetic rather than thermodynamic forces. To obtain the desired form and a better yield, more research based on this article on the polymorphism durability of L-glutamic acidity in MSMPR devices needs to be done. Acevedo *et al.*[50] described a technique for determining carbamazepine's quality in an MSMPR clarifier using Raman spectroscopy. In their independent tests, they discovered that a polymorphic peak ratio of 0.900 0.01 implies that the suspension only contains the only form that is stable at 25°C (form III). Since there was only one clear solution present at the start of the continuing study, the average maximum ratio was approximately 1.[39] A comparatively stable peak value of a product was attained following 8 residence times (0.986). The fact that this number was still greater than the peak ratio that had been previously established (0.900 0.01) suggests that the metastable forms (form II) were still present. However, the off-site X-ray diffraction technique verified that the result solely included form III. Conclusion: Raman spectroscopy's sensitivity is affected by operating settings, a proper system, solute concentration, and other factors.

Model-free predictive control

To regulate CQAs in continuous processes, a model-free technique or a fractional (PID) approach is frequently utilized and is focused on the direct use of PAT. Because no mathematical model is required, the model-free technique is easier to implement than the model-based approach. Direct nucleus control (DNC)[51] and concentration feedback control (CFC) are the two most popular PID strategies. The goal of the first strategy is to maintain a constant number of crystals; as a result, larger crystals emerge when the maximum count of crystals is low and smaller crystals when the overall number of particles is high. In the second strategy, the process dynamics are managed by maintaining a constant super saturation; hence, a system must be fitted. Besenhard *et al.*[52] used a DNC to investigate the ongoing seeded cooling crystallization of salicylate in an LFTC. Crystal growth and agglomeration were the main mechanisms in this particular system. As the flow velocity of the seed dispersion decreased, the rate of both pathways rose (fewer seeds). At seed slurry flow rates <4.5 ml/min, agglomeration was found to be insignificant, allowing for extremely strong crystal size adjustment. Agglomeration, however, made the control less effective but still allowed for process control. A similar methodology was used in Yang *et al.*[53] study, which involved the continuous seeded cool crystallization of paracetamol in up to two MSMPR condensers paired sequentially. Both MSMPRs were used to measure the temperature and the number, size, and dispersion of chords using Pt100 thermocouples and an FBRM probe. The final crystal number and size of paracetamol are dependent on the amount of nucleus generated because the process of crystallization is nucleation-dominant. The practical oriented the constant more quickly when automated direct maturation control (ADNC) was used in one or two MSMPRs than it did when it was not because ADNC initiated nucleation with a quicker and higher cooling rate. Smaller grains were dissolved, nucleation was enhanced, and smaller crystals were grown if a smaller finite particle size was needed.

The same authors conducted a second study based on ADNC.[54] In this investigation, an MSMPR crystallizer was equipped with a wet mill autonomous direct nucleation control (WMADNC). As in earlier projects, the process was tracked and managed using an FBRM probe. Two alternative set-ups were utilized, which are similar to the study[26] that was addressed in the preceding subsection. A wet mill was utilized to create nuclei in the first case, while a limit crystal size adjustment method was used in the second. In contrast to the previous investigation, it was found in this one that the WMADNC implementation did not speed up start-up times. However, once a steady-state was reached, where this strategy proved effective, the WMADNC's benefit became more apparent.

MECHANISTIC MULTISCALE MODELLING, SIMULATION, AND OPTIMISATION

Despite the fact that crystallization has been presented in industry for many decades now, the mathematical modeling of crystallization is still rather unclear and not uniform due to its complexity. In the past, many studies based on crystallization modeling of simple inorganic substances in batch systems have been performed, but since organic substances are more interesting for the pharmaceutical industry, the number of crystallization studies of more complex organic substances in batch systems has also increased in recent years.[55] Calculating kinetics, creating systems, optimizing processes, scaling up operations, conducting theoretical simulations, and performing parameter sensitivity analysis are all common uses of mathematical modeling.[56-58] In addition, it has been applied to model-based control loops, which are discussed in greater detail in the section that follows. The biggest advancement in this field has been the addition of the populace equation given (PBE) to the crystallization process modeling [Table 3].

Modeling using dedicated mathematical software

Because of the complexities of a crystallization system, mathematically characterizing it can be difficult and time-consuming at times.

Table 3: Provides a basic overview[59-63]

Type of crystallizer	Type of crystallization	Substance	Modeling approach	Crystal growth	Findings
Multi-segmented MSMPR (up to three)	Cooling and antisolvent	NS (API)	NS	Size independent	Lower yield and significantly smaller attainable range of mean sizes were achieved if the SIK was implemented (single-stage); Simulations showed that half smaller attainable range of mean sizes is achieved if the SIK is implemented (two and three-stage).
COBC	Cooling and antisolvent	Paracetamol	MoM	Size independent	Higher percentage of the antisolvent in the in-flow caused higher E-factor values but increased costs of production.
PFC	Antisolvent	Benzoic acid	MoM, HF-FVM, and MoC	Size independent (RF and CCG dispersion)	The best results were obtained with a mathematical model, which includes CCG dispersion mechanism; Developed model can be used for validation
Two-stage MSMPR	Cooling	Paracetamol	MoM	Size independent	Optimization was used for process conditions determination; Experimentally validate.
Multisegmented PFC	Antisolvent	Paracetamol	MoM and HF-FVM	Size independent	Optimization of the system resulted into higher mean size; More multimodal CSD can be obtained with the approach described in the third case.
MSMPR-HT	Cooling	L-glutamic acid	HF-FVM (for PBE discretization); FEM (for solving PBE/CFD in COMSOL	Size dependent	Validation based on experimental results gave comparable results; Developed model can be used on other systems.

PFC: Plug flow crystallizers, MSMPR: Multistage-mixed suspension mixed product removal, ASA: Acetylsalicylic acid

Mathematical models obtained by numerical solving

In the previously described study, the parametric study of non-solvent crystallization in a cortex was also demonstrated.

MODEL-BASED PREDICTIVE CONTROL ANDPROCESS INTENSIFICATION

Model-based predictive control

Batch crystallization has already been very thoroughly documented in terms of model-based predictive control.[64] The amount of research applying brand predictive control (MPC) to continuous systems is still relatively modest, but it has greatly expanded over the past 20 years. Even more complicated problems can be solved effectively and quickly thanks to increased processing power and a greater understanding of mathematical models.

Model-free predictive control (MPC)-controlled systems respond to changes more slowly than MPC-controlled systems, which can also manage multivariable, sensitive, non-minimum phase, and non-minimum phase systems.[65,66]

The most popular MPC strategies include observer-based feedback control, non-linear control, and linear control

design.[67] A process is typically controlled by changing process parameters that are similar to model-free control.[68]

Process intensification

The pharmaceutical industry, which generates high-quality goods, is a very economically robust sector (3 trillion dollars). The industry has consistently been challenged to modify its manufacturing to become more efficient due to rising generic market competition, higher research and development expenses, the need for more production, etc.

As was seen in the preceding part, effective control can boost output by speeding up the process's ability to attain steady state, boosting productivity, etc. However, process intensification is specifically highlighted in this section, where several recently established research that brought a system drive approach to continuous crystallization are presented shows the design approach for a transferable, sophisticated temperature-based process control. Adapted from Tahir *et al.*,[69] in Control Eng. Pract., vol. 3, advanced management of an ongoing. As previously stated, continuous processing allows for a reduction in the overall amount of downstream processing (telescoping).[70] In addition, the proper crystallization strategy can reduce additional steps like milling and granulating and make other processes easier, such as filtration and drying, in addition to enabling the creation of goods with desirable qualities. These methods could be considered intensification. A two different MSMPR unit for benzoic acid was developed in the study[71] to produce only spherical particles and effectively isolate nucleation and crystal development from the agglomeration process.[72-76]

CONCLUSION

This review article looked at the continual crystallization of (mainly) APIs. It is well known that a continuous method can be used to produce some more desirable crystalline features (narrow CSD, specific polymorph, etc.). Based on this, the switch from such a batch to a continuous flow was initially proposed, as enhanced product qualities can significantly affect an API's efficacy and have an impact on other downstream processes.

The application of continuous crystallization in fully continuous downstream and upstream processes was therefore researched and presented. PAT (FBRM, FTIR, etc.) has made process monitoring, data collecting, and control possible in crystallization processes. The recreation of a process is possible with the use of mathematical modeling, which itself is based on equations for population imbalance, gravimetric balance, and energy balance. Without additional experiments, optimization and scale-up can be done using the resulting simulations. To ensure the developed model is accurate, it is suggested that independent trials be used to validate it. In addition, model-based predictive control is designed using mathematical models. The crystallization process can be made more intelligent, intense, and integrated by incorporating the MPC. According to the research that has been conducted, the MPC outperforms model free control by a wide margin.

REFERENCES

1. Nagy ZK, Fujiwara M, Braatz RD. Modelling and control of combined cooling and antisolvent crystallization processes. J Process Control 2008;18:856-64.
2. Wood B, Girard KP, Polster CS, Croker DM. Progress to date in the design and operation of continuous crystallization processes for pharmaceutical applications. Org Process Res Dev 2019;23:122-44.
3. Simon LL, Pataki H, Marosi G, Meemken F, Hungerbühler K, Baiker A, *et al.* Assessment of recent process analytical technology (PAT) trends: A multiauthor review. Orga Process Res Dev 2015;19:3-62.
4. McGlone T, Briggs NE, Clark CA, Brown CJ, Sefcik J, Florence AJ. Oscillatory flow reactors (OFRs) for continuous manufacturing and crystallization. Org Process Res Dev 2015;19:1186-202.
5. Besenhard MO, Neugebauer P, Scheibelhofer O, Khinast JG. Crystal engineering in continuous plug-flow crystallizers. Cryst Growth Des 2017;17:6432-44.
6. Neugebauer P, Khinast JG. Continuous crystallization of proteins in a tubular plug-flow crystallizer. Cryst Growth Des 2015;15:1089-95.
7. Hohmann L, Greinert T, Mierka O, Turek S, Schembecker G, Bayraktar E, *et al.* Analysis of crystal size dispersion effects in a continuous coiled tubular crystallizer: experiments and modeling. Cryst Growth Des 2018;18:1459-73.
8. Yang X, Acevedo D, Mohammad A, Pavurala N, Wu H, Brayton AL, *et al.* Risk considerations on developing a continuous crystallization system for carbamazepine. Org Process Res Dev 2017;21:1021-33.
9. Lee SL, O'Connor TF, Yang X, Cruz CN, Chatterjee S, Madurawe RD, *et al.* Modernizing pharmaceutical manufacturing: From batch to continuous production. J Pharm Innov 2015;10:191-9.
10. Allison G, Cain YT, Cooney C, Garcia T, Bizjak TG, Holte O, *et al.* Regulatory and quality considerations for continuous manufacturing. May 20-21, 2014 continuous manufacturing symposium. J Pharm Sci 2015;104:803-12.
11. Mesbah A, Paulson JA, Lakerveld R, Braatz RD. Model predictive control of an integrated continuous pharmaceutical manufacturing pilot plant. Org Process Res Dev 2017;21:844-54.
12. 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;39:1268-80.
13. 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;19:1871-81.
14. Acevedo D, Peña R, Yang Y, Barton A, Firth P, Nagy ZK. Evaluation of mixed suspension mixed product removal crystallization processes coupled with a continuous filtration system. Chem Eng Process Process Intensif 2016;108:212-9.
15. Dave K, Luner PE, Forness C, Baker D, Jankovsky C, Chen S. Feasibility of focused beam reflectance measurement (FBRM) for analysis of pharmaceutical suspensions in preclinical development. AAPS PharmSciTech 2018;19:155-65.
16. 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 Intensif 2015;89:41-53.
17. Su M, Gao Y. Air-liquid segmented continuous crystallization process optimization of the flow field, growth rate, and size distribution of crystals. Indust Eng Chem Res 2018;57:3781-91.
18. Jiang M, Papageorgiou CD, Waetzig J, Hardy A, Langston M, Braatz RD. Indirect ultrasonication in continuous slug-flow crystallization. Cryst Growth Des 2015;15:2486-92.
19. Jiang M, Braatz RD. Designs of continuous-flow pharmaceutical crystallizers: Developments and practice. Cryst Eng Comm 2019;21:3534-51.
20. Steendam RR, Keshavarz L, Blijlevens MA, de Souza B, Croker DM, Frawley PJ. Effects of scale-up on the mechanism and kinetics of crystal nucleation. Cryst Growth Des 2018;18:5547-55.
21. Mou M, Li H, Yang BS, Jiang M. Continuous generation of millimeter-sized glycine crystals in non-seeded millifluidic slug flow. Crystals 2019;9:412.
22. Gigliobianco MR, Casadidio C, Censi R, Di Martino P. Nanocrystals of poorly soluble drugs: Drug bioavailability and physicochemical stability. Pharmaceutics 2018;10:134.
23. Cruz P, Rocha F, Ferreira A. Effect of operating conditions on batch and continuous paracetamol crystallization in an oscillatory flow mesoreactor. Cryst Eng Comm 2016;18:9113-21.
24. Majumder A. Modeling and simulation studies of a novel coupled plug flow crystallizer for the continuous separation of conglomerate-forming enantiomers. Processes 2018;6:247.
25. Li S. Residence time distribution and flow models for reactors. In: Li S., editor. Reaction Engineering. Ch. 5. Boston: Butterworth-Heinemann; 2017. p. 213-63.
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;15:5879-85.
27. Perini G, Salvatori F, Ochsenbein DR, Mazzotti M, Vetter T. Filterability prediction of needle-like crystals based on particle size and shape distribution data. Sep Purif Technol 2019;211:768-81.
28. Liu YC, Domokos A, Coleman S, Firth P, Nagy ZK. Development of continuous filtration in a novel continuous filtration carousel integrated with continuous crystallization. Org Process Res Dev 2019;23:2655-65.
29. Morris G, Power G, Ferguson S, Barrett M, Hou G, Glennon B. Estimation of nucleation and growth kinetics of benzoic acid by population balance modeling of a continuous cooling mixed suspension, mixed product removal crystallizer. Org Process Res Dev 2015;19:1891-902.
30. Rimez B, Septavaux J, Scheid B. The coupling of in-flow reaction with continuous flow seedless tubular crystallization. React Chem Eng 2019;4:516-22.
31. Adamo A, Beingessner RL, Behnam M, Chen J, Jamison TF, Jensen KF, *et al.* On-demand continuous-flow production of pharmaceuticals in a compact, reconfigurable system. Science 2016;352:61-7.
32. Zhang P, Weeranoppanant N, Thomas DA, Tahara K, Stelzer T, Russell MG, *et al.* Advanced continuous flow platform for on-demand pharmaceutical manufacturing. Chem A Eur J 2018;24:2776-84.
33. Hohmann L, Löbnitz L, Menke C, Santhirakumaran B, Stier P, Stenger F, *et al.* Continuous downstream processing of amino acids in a modular miniplant. Chem Eng Technol 2018;41:1152-64.
34. Orehek J, Teslic D, Likozar B. Continuous crystallization processes in pharmaceutical manufacturing: A review. Org Process Res Dev 2020;25:16-42.
35. Domokos A, Nagy B, Gyürkés M, Farkas A, Tacsi K, Pataki H, *et al.* End-to-end continuous manufacturing of conventional compressed tablets: From flow synthesis to tableting through integrated crystallization and filtration. Int J Pharm 2020;581:119297.
36. Kessler RW, Kessler W, Zikulnig-Rusch E. A critical summary of spectroscopic techniques and their robustness in industrial PAT applications. Chem Ing Tech 2016;88:710-21.
37. Korasa K, Hudovornik G, Vrečer F. Applicability of near-infrared spectroscopy in the monitoring of film coating and curing process of the prolonged release coated pellets. Eur J Pharm Sci 2016;93:484-92.
38. Simone E, Zhang W, Nagy ZK. Application of process analytical technology-based feedback control strategies to improve purity and size distribution in biopharmaceutical crystallization. Cryst Growth Des 2015;15:2908-19.
39. Kacker R, Regensburg SI, Kramer HJ. Residence time distribution of dispersed liquid and solid phase in a continuous oscillatory flow baffled crystallizer. Chem Eng J 2017;317:413-23.
40. 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.
41. Li J, Trout BL, Myerson AS. Multistage continuous mixed-suspension, mixed-product removal (MSMPR)

crystallization with solids recycle. Org Process Res Dev 2016;20:510-6.
42. Lai TT, Ferguson S, Palmer L, Trout BL, Myerson AS. Continuous crystallization and polymorph dynamics in the L-glutamic acid system. Org Process Res Dev 2014;18:1382-90.
43. Zhao Y, Kamaraju VK, Hou G, Power G, Donnellan P, Glennon B. Kinetic identification and experimental validation of continuous plug flow crystallisation. Chem Eng Sci 2015;133:106-15.
44. Kutluay S, Şahin Ö, Ceyhan AA, İzgi MS. Design and optimization of production parameters for boric acid crystals with the crystallization process in an MSMPR crystallizer using FBRM® and PVM® technologies. J Cryst Growth 2017;467:172-80.
45. Gao Z, Wu Y, Gong J, Wang J, Rohani S. Continuous crystallization of α-form L-glutamic acid in an MSMPR-Tubular crystallizer system. J Cryst Growth 2019;507:344-51.
46. 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.
47. 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;20:626-36.
48. Liu YC, Dunn D, Lipari M, Barton A, Firth P, Speed J, *et al.* A comparative study of continuous operation between a dynamic baffle crystallizer and a stirred tank crystallizer. Chem Eng J 2019;367:278-94.
49. 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 Intensif 2015;97:180-6.
50. Acevedo D, Yang X, Mohammad A, Pavurala N, Wu WL, O'Connor TF, *et al.* Raman spectroscopy for monitoring the continuous crystallization of carbamazepine. Org Process Res Dev 2018;22:156-65.
51. Acevedo D, Jarmer DJ, Burcham CL, Polster CS, Nagy ZK. A continuous multi-stage mixed-suspension mixed-product-removal crystallization system with fines dissolution. Chem Eng Res Des 2018;135:112-20.
52. Besenhard MO, Neugebauer P, Ho CD, Khinast JG. Crystal size control in a continuous tubular crystallizer. Cryst Growth Des 2015;15:1683-91.
53. Yang Y, Song L, Nagy ZK. Automated direct nucleation control in continuous mixed suspension mixed product removal cooling crystallization. Cryst Growth Des 2015;15:5839-48.
54. Yang Y, Song L, Zhang Y, Nagy ZK. Application of wet milling-based automated direct nucleation control in continuous cooling crystallization processes. Indust Eng Chem Res 2016;55:4987-96.
55. Trampuž M, Teslić D, Likozar B. Crystallization of fesoterodine fumarate active pharmaceutical ingredient: Modelling of thermodynamic equilibrium, nucleation, growth, agglomeration and dissolution kinetics and temperature cycling. Chem Eng Sci 2019;201:97-111.
56. Schall JM, Capellades G, Mandur JS, Braatz RD, Myerson AS. Incorporating solvent-dependent kinetics to design a multistage, continuous, combined cooling/antisolvent crystallization process. Org Process Res Dev 2019;23:1960-9.
57. Porru M, Özkan L. Simultaneous design and control of an industrial two-stage mixed suspension mixed product removal crystallizer. J Process Control 2019;80:60-77.
58. Sulttan S, Rohani S. Coupling of CFD and population balance modelling for a continuously seeded helical tubular crystallizer. J Cryst Growth 2019;505:19-25.
59. Afsi N, Bakir T, Othman S, Sheibat-Othman N, Sakly A. Estimation of the Mean Crystal Size and the Moments of the Crystal Size Distribution in Batch Crystallization Processes. In: 2016 4th International Conference on Control Engineering and Information Technology (CEIT). United States: IEEE; 2016. p. 1-6.
60. Porru M, Özkan L. Monitoring of batch industrial crystallization with growth, nucleation, and agglomeration. Part 2: Structure design for state estimation with secondary measurements. Indust Eng Chem Res 2017;56:9578-92.
61. Ruan C. Kinetics and morphology of flow induced polymer crystallization in 3D shear flow investigated by Monte Carlo simulation. Crystals 2017;7:51.
62. 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;19:1859-70.
63. Jolliffe HG, Gerogiorgis DI. Process modelling, design and technoeconomic evaluation for continuous paracetamol crystallisation. Comput Chem Eng 2018;118:224-35.
64. Szilagyi B, Eren A, Quon JL, Papageorgiou CD, Nagy ZK. Application of model-free and model-based quality-by-control (QbC) for the efficient design of pharmaceutical crystallization processes. Cryst Growth Des 2020;20:3979-96.
65. Jha SK, Karthika S, Radhakrishnan TK. Modelling and control of crystallization process. Resour Efficient Technol 2017;3:94-100.
66. 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.
67. Ghadipasha N, Romagnoli JA, Tronci S, Baratti R. A model-based approach for controlling particle size distribution in combined cooling-antisolvent crystallization processes. Chem Eng Sci 2018;190:260-72.
68. Onel M, Beykal B, Wang M, Grimm FA, Zhou L, Wright FA, *et al.* Optimal chemical grouping and sorbent material design by data analysis, modeling and dimensionality reduction techniques. ESCAPE 2018;43:421-6.
69. Tahir F, Krzemieniewska-Nandwani K, Mack J, Lovett D,

Siddique H, Mabbott F, *et al.* Advanced control of a continuous oscillatory flow crystalliser. Control Eng Pract 2017;67:64-75.
70. Orehek J, Teslic D, Likozar B. Continuous crystallization processes in pharmaceutical manufacturing: A review. Org Process Res Dev 2020;25:16-42.
71. 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;15:4225-36.
72. Peña R, Oliva JA, Burcham CL, Jarmer DJ, Nagy ZK. Process intensification through continuous spherical crystallization using an oscillatory flow baffled crystallizer. Cryst Growth Des 2017;17:4776-84.
73. Li H, Yang BS. Model evaluation of particle breakage facilitated process intensification for Mixed-Suspension-Mixed-Product-Removal (MSMPR) crystallization. Chem Eng Sci 2019;207:1175-86.
74. Köllges T, Vetter T. Polymorph selection and process intensification in a continuous crystallization-milling process: A case study on l-glutamic acid crystallized from water. Org Process Res Dev 2019;23:361-74.
75. Benitez-Chapa AG, Nigam KD, Alvarez AJ. Process intensification of continuous antisolvent crystallization using a coiled flow inverter. Indust Eng Chem Res 2019;59:3934-42.
76. Hussain MN, Baeten S, Jordens J, Braeken L, Van Gerven T. Process intensified anti-solvent crystallization of o-aminobenzoic acid via sonication and flow. Chem Eng Process Process Intensif 2020;149:107823.

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