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# Reflecting on barriers to continuous pharmaceutical crystallization

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This Comment explores why continuous crystallization, despite its success in other industries, remains underutilized in pharmaceutical manufacturing. Among other challenges, we highlight two core issues: the lack of off-the-shelf small-scale equipment with integrated monitoring tools, and the absence of compatible continuous downstream units for filtration and drying, both of which limit practical implementation.

Crystallization is a separation and purification step that generates solid crystalline material, typically in suspension, and is usually followed by filtration and drying steps[1]. Owing to its cost-effectiveness relative to other methods such as chromatography, crystallization is a key unit operation across manufacturing of bulk chemicals, food, agrochemicals, explosives and pharmaceuticals. Crystallization processes can be operated in batch or continuous modes; however, while the bulk chemical industry favors continuous operations, at least for large volume products where the benefits of continuous processes more clearly outweigh the costs, the pharmaceutical industry still predominantly employs batch processes[1]. This Comment examines the underlying factors driving these industry-specific preferences and outlines research opportunities aimed at overcoming the barriers to a wider adoption of continuous crystallization in pharmaceutical manufacturing.

The past two decades have seen a considerable increase in research efforts toward the investigation and application of continuous manufacturing of active pharmaceutical ingredients. Major initiatives, such as the Novartis-MIT Center for Continuous Manufacturing and the Continuous Manufacturing and Advanced Crystallization hub centered at the University of Strathclyde, alongside continuous process development at many pharmaceutical companies, have shown several potential benefits of continuous processes[2]. For example, a higher space–time yield enables smaller process volumes, which in turn enhance safety, particularly in highly exothermic, explosive or toxic processes[2]. Continuous systems also improve process controllability through augmented heat- and mass-transfer rates. In addition, the quasi-steady-state operating conditions typical of continuous crystallization schemes grant access to multiple regions within the phase diagram (for example, tanks in series), an advantage that is difficult or impossible to achieve in inherently transient batch processes. Such features ultimately lead to improved product quality through steady-state operation, greater scalability with much smaller scale-up increments, heightened efficiencies, improved sustainability and elimination of batch-to-batch variability[2]. Regulatory bodies such as the US Food and Drug Administration and the European Medicines Agency also actively support continuous manufacturing, as reflected in the guidance provided by the International Council for Harmonization. Overall, the effort has been successful to the extent that continuous synthesis is now regarded as a viable alternative to batch processing within the pharmaceutical industry. Despite successful proof-of-concept examples[3–7] and various early-adopter implementations, continuous crystallization remains far from seeing widespread adoption.

## Continuous crystallizers

Among the various types of continuous crystallizer that have been developed, the (multistage) mixed-suspension mixed-product removal (MSMPR) formalism stands out as the most advanced from an operational standpoint and is the most widely studied (see examples in refs. 4–6,8). These crystallizers operate by continuously mixing the suspension in one or more stirred tanks while removing both the solid (crystals and/or precipitates) and liquid phases from the system. However, tubular plug flow crystallizers, including segmented flow[9] and continuous oscillatory baffled[10] crystallizers, have emerged as alternative designs (typically with a lower energy input per volume). However, although these systems are studied, technical and operational challenges such as fouling, clogging, particle settling and down-scaling currently limit their broader industrial adoption. In contrast, MSMPR crystallizers can be operated at steady state (ensuring constant kinetics, usually growth dominated) with high solids concentrations and there is a broad experience base regarding their scale. In combination with particle formation equipment such as wet mills (see, for example, ref. 6), the need for a high nucleation rate in the crystallizer can be bypassed. This extends the operating range of MSMPR crystallizers to conditions that minimize the chance of fouling, promote slow-growth-dominated kinetics, and ensure that the system remains 'well seeded' at all points throughout the operation, making the system more stable against process disturbances.

## Continuous crystallization challenges

Several barriers to the adoption of continuous crystallization have been discussed in the literature; one representative source is cited here for brevity[2]. These include technical and operational issues such as clogging, encrustation and size-based classification. While some of these issues are due to the heterogeneous solid–liquid flow streams involved, some issues have their roots in the complex solution-phase behavior exhibited in some pharmaceutical systems (for example, oiling out and gelation). Such physicochemical oddities of solution-phase behavior are not typically observed in the bulk chemical industry. In addition, industry-specific factors unique to pharmaceutical manufacturing

**Table 1 | Overview of the perceived challenges for continuous crystallization in the pharmaceutical industry and the evaluation of these challenges**

| Type of challenge | Perceived challenges | Current state and evaluation |
|---|---|---|
| Technical/operational | Clogging of tubular systems (transfer lines and plug flow crystallizers) | Addressed by intermittent transfer at high flow rates (for example, through pressure-driven control) and proper process design. |
| | Fouling or encrustation of equipment | May be mitigated by implementing effective process control strategies (low supersaturations, temperature cycling) and incorporating proactive clean-in-place protocols. |
| | Level control (that is, maintaining a consistent liquid level) | Advanced control strategies to manage fluctuations and maintain stability. |
| | Size-based classification | Intermittent transfer at high flow rates to ensure isokinetic particle withdrawal; integration of size control measures (for example, mills, ultrasound) to maintain consistent size distribution at reduced particle size. |
| | Leakages | Intrinsic to continuous operation but usually manageable. |
| Industry specific | Regulatory differences and time-to-market pressure | Continuous crystallization at the drug-substance level is considered a higher regulatory risk than batch crystallization owing to the absence of approved commercial examples. However, when addressed proactively during development, regulatory uncertainty has not been shown to delay approval timelines or market entry. In addition, reduced scale-up requirements inherent to continuous crystallization offer potential to streamline process development. |
| | Small production volumes and high product values | Lower cost sensitivity at small scale limits the economic advantage of continuous crystallization, but scale-dependent challenges still influence process selection. |
| | Product molecular complexity | More precise control and more narrow processing conditions should improve crystallization of complex molecules. Requires methods to adequately characterize and understand the various undesirable phase boundaries to narrow down and choose the processing conditions better. |
| | Manufacturing flexibility and agility | In principle, continuous crystallization offers significant flexibility, but there are a limited number of examples within the pharmaceutical industry owing to the maturity of the technology. |
| | Material traceability | No physical separation of product material in continuous processing can be overcome through residence time distribution characterization, advanced process monitoring, process tracking and steady-state operation. There are also strategies that can be used to segregate lots of varying input materials (such as using a standby feed-vessel arrangement). |
| | Manufacturing culture | Can be a barrier, especially if the advantages are not clearly understood or communicated. |
| | Lack of downstream integration | Can be a barrier because it negates some of the potential economic benefits of continuous systems, but not strictly necessary to exploit advantages of continuous crystallization. |
| | Replacement of installed equipment | Installed equipment base and excess capacity often makes it such that investing in new equipment with high capital expenditure is a challenge. |

further complicate implementation, such as stringent regulations, high-value products (for example, US$500–100,000 $kg^{-1}$ for pharmaceuticals versus US$0.1–1 $kg^{-1}$ for bulk chemicals) with intense time-to-market pressure due to short patent protections, and typically low production volumes (for example, 10 kg per day for pharmaceuticals versus 1–10 tons per hour for bulk chemicals).

Some of the challenges in adopting continuous crystallization for pharmaceuticals are less significant than perceived (Table 1 and Fig. 1). Especially challenges related to process development that can be overcome through an effective workflow. In practice, the lack of laboratory-scale continuous crystallization equipment that allows scalable process characterization with minimal material use (for example, ≤100 g) limits the ability to fully exploit continuous crystallization advantages, keeping most development confined to the batch mode. This issue extends beyond pharmaceuticals. Even in the bulk chemical industry, where large-scale production relies on continuous crystallization, laboratory development and data based on batch processes are used to design continuous crystallization processes. This methodology often leads to poor process understanding and, in turn, troublesome scale-up (particularly owing to scale-dependent slurry behavior) and transfer to continuous. Nonetheless, batch experiments combined with process modeling can still be used to understand system kinetics and to inform continuous development[4]. Accessing such benefits, however, requires specialized personnel. In addition, continuous crystallization development often involves building a custom set-up, which requires extensive optimization and characterization. This absence of standardization leads to variations in continuous crystallization across different sites. This contrasts with the typical across-industry equipment similarity, where different-sized batch equipment is readily available at both pilot and production scales. These differences contribute to the perception that continuous crystallization is inflexible, time-consuming, difficult to operate, resource intensive and challenging to scale up.

Furthermore, the pharmaceutical industry lacks a clear economic incentive to adopt continuous crystallization, unlike bulk chemical processes[7]. This is partly because continuous processes often operate under kinetic control, yielding lower throughput without recycling than thermodynamically controlled batch processes. However, operation under kinetic control is not necessarily a strict requirement. Continuous processes can be adapted to optimize yield and stability by operating at longer residence times or by equilibrating the suspension

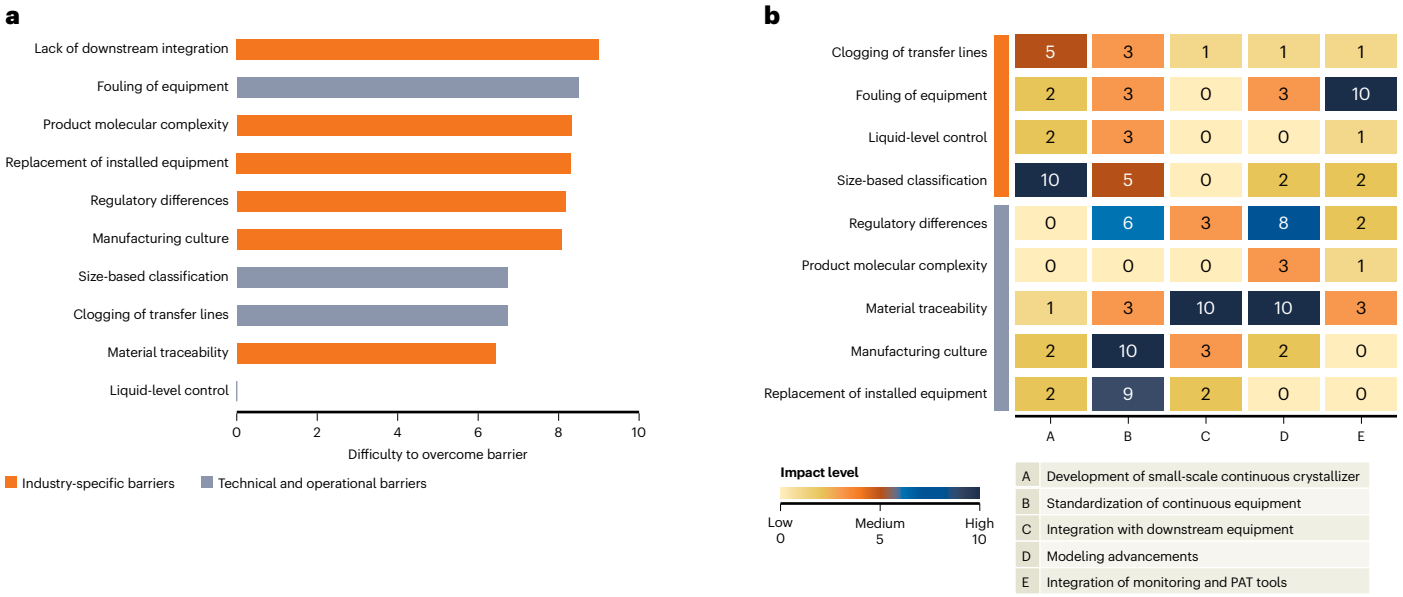


**Fig. 1 | Assessment of various barriers to adopting continuous crystallization in the pharmaceutical industry, categorized into industry-specific and technical and operational barriers, along with key research directions.** Rankings are based on anonymous assessments by the authors of this work and are calculated first as *Z* scores and then scaled using min–max normalization to a 0–10 scale. **a**, Ranking of the perceived ease of overcoming key barriers, where higher scores indicate barriers that are more difficult to overcome. **b**, Heatmap illustrating the relationship between identified barriers and future research directions and mitigation strategies, where higher scores indicate research directions that are particularly important for overcoming the associated barrier.

to the most stable polymorph, effectively making the process less constrained by kinetic limitations. This flexibility represents a technical advantage of continuous crystallization. Despite these advantages, the economic challenges persist. Continuous crystallizers operate at supersaturated steady states, making thermodynamic equilibrium unattainable and often requiring lower slurry densities than batch processes to facilitate transfer. These operational factors can reduce process efficiency compared with batch systems. Moreover, transitioning to continuous crystallization demands the installation of dedicated equipment or adaptation of existing systems. Unlike batch processes, where crystallizers, filters and dryers are campaigned over weeks or months for each product, continuous crystallization allows for alternative operational models. One potential approach involves smaller, product-dedicated equipment operating over extended periods. While this approach helps contain additional costs, it does not eliminate the economic burden of overcoming the lock-in effect created by the industry's past reliance on batch-based infrastructure, contributing to the hesitation of many companies to adopt continuous crystallization. Batch crystallization equipment aligns more easily with existing isolation and drying infrastructure. Continuous crystallization leads to hybrid batch–continuous set-ups that introduce operational complexity that offset some of its benefits. Overcoming this bottleneck will require not only technical advances in continuous filtration, washing and drying but also a shift in organizational culture and greater familiarity with continuous process control[2].

## Potential research directions

The lack of off-the-shelf small-scale continuous crystallization equipment (with about 1–200 ml crystallizer volume, about 0.1–25 ml $min^{-1}$ flow rate and about 10–1,000 min residence time) stems from the technical challenges related to reducing the size of crystallization equipment without compromising performance and scalability. While new technologies are typically optimized at smaller scales, where experimentation is more manageable before complexity increases, for continuous crystallization the reverse is true. Medium-scale (200–2,000 ml) and larger-scale (>2 l) crystallizers handle the technical and operational difficulties related to heterogeneous flow (Table 1) more effectively, owing to greater inertia and reduced sensitivity to disturbances. Any approach that can improve the stability of small-scale continuous crystallization equipment should be explored. Another challenge is integrating process analytical technology (PAT) into small-scale equipment, as limited space can hinder installation and potentially disrupt hydrodynamics when not carefully configured. In addition, in situ probes are prone to fouling[11], and the lack of standardized mitigation strategies further complicates their use, underscoring the importance of thoughtful PAT and sensor integration. Efforts are underway to address these limitations of small-scale continuous crystallization[12,13] but have not yet reached technological maturity. Advances in crystallization modeling, including physics-based (mass, energy, population balance) and data-driven (machine learning) advances, as well as hybrids of the two, enable dynamic predictive design, adaptive control or optimization (such as Bayesian optimization), and reduced reliance on experimentation. Modeling, especially when coupled with PAT and sensors, is a key enabler for continuous crystallization[14]. Ongoing academic progress, especially focusing on mechanistic understanding of crystallization, provides a strong foundation for industrial translation; however, improving usability and robustness continue to be important.

Furthermore, lacking off-the-shelf small-scale continuous crystallizers creates a self-reinforcing paradoxical institutional challenge that has reduced market draw for continuous crystallization. On the one hand, small- and medium-sized pharmaceutical companies and contract development and manufacturing organizations are hesitant to

make investments in such dedicated continuous manufacturing equipment as early adopters; on the other hand, companies that do want to invest miss commercially available validated small-scale crystallizers to characterize and develop their processes. While several promising technologies are now emerging[12,13], further validation, particularly demonstrations of robust slurry handling and scalability, is necessary to initiate adoption. This is compounded by the fact that, while the advantages of continuous crystallization are compelling, they are often less clear-cut than those of continuous flow synthesis, as outlined above. One of the major drivers of continuous crystallization in the pharmaceutical industry is precisely the success of upstream continuous synthesis. At its core, this is a coordination problem: without broad alignment between technology developers and decision-makers, no single stakeholder is willing to absorb the risk of early adoption. This misalignment suppresses visible market demand, even when there is an underlying benefit.

Off-the-shelf continuous crystallizers remain an untapped opportunity. Compared with flow chemistry, crystallization offers high potential for standardized continuous equipment owing to its intrinsically higher process uniformity (that is, a similar sequence of process steps) and narrower process condition range (for example, temperature, stirring rates and supersaturation). Flow chemistry is characterized by a much broader diversity of reactions and operations, each with its own unique requirements for materials, conditions and reactor design.

Small-scale continuous crystallizers would also address the common trade-off in early pharmaceutical development: sacrificing scalability by avoiding full-scale studies or compromising process development owing to limited material availability. This trade-off is particularly mitigated when combined with process modeling, which benefits from the inherently more stable, time-invariant nature of continuous crystallization, making it easier to model and generate high-quality data compared with batch processes. As synthesis increasingly occurs at smaller scales and in parallel with crystallization process design, such equipment helps strike a better balance, enabling scalable process development with low material input.

Therefore, the crystallization community must continue to advance continuous crystallization efforts. The development of scalable, small-scale crystallizers integrated with suitable PAT and sensors should be a research priority. Development of effective continuous small-scale filtration and dryer units, to isolate the crystalline product, preferably with operational containment and easy solid product collection, must follow suit to harness the full potential of continuous manufacturing. Ideally, these downstream units also account for potential differences in residence times with continuous crystallization. While examples of such filtration and dryer systems exist in the literature[15], only a few have reached commercial maturity. Institutional support should focus on recognizing and understanding the benefits of continuous crystallization, investing in small-scale systems and initiating workforce development initiatives.

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