Overcoming Challenges to Continuous Processing with Solids

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Expanding the Role of Solids in Flow Processing

Flow chemistry offers clear advantages over traditional batch reactions, particularly with respect to controlling key reaction parameters like mixing, temperature, and pressure. These tighter controls not only boost efficiency but also make it possible to safely run highly exothermic or otherwise hazardous reactions that would pose risks in conventional batch setups.

Despite these proven benefits, flow chemistry in small molecule drug manufacturing has mostly been limited to reactions where all components stay dissolved in liquid phase and residence times are less than 30 minutes. However, many of the same advantages — enhanced heat and mass transfer in smaller, well-controlled reactors — also apply when solids are involved. Continuous slurry and solids-handling systems can leverage these same physical principles, though they require more sophisticated engineering to do so reliably. These fully soluble reactions, however, account for only about 17–19% of all pharmaceutical processes. The majority of reactions (>63%) involve solid starting materials, generate solid by-products, or produce solid products.1 When solids are part of the picture, the process becomes more complex, shifting from simple liquid flow to managing slurries (mixtures of solids suspended in liquids), which demands more sophisticated engineering and equipment.

Because continuous processing in pharma is still relatively young, few companies have tackled these extra layers of complexity. This hesitation is rooted less in impossibility than in the technical challenges of managing solids in flow and the shortage of personnel with the training and experience to operate such systems effectively. Other industries have long adopted assembly-line style continuous manufacturing, reaping consistent gains in cost, quality, and sustainability, benefits that pharma manufacturing stands to reap in equal or greater measure. Regulators like the U.S. Food and Drug Administration (FDA) actively encourage this shift, having endorsed continuous manufacturing for years as a proven path to faster, more reliable, and higher-quality drug production.

Despite regulatory support, many drug makers still confine flow chemistry to the easiest, fully soluble reactions while leaving more complex or solids-heavy steps in batch mode. This restricted approach undermines the potential of continuous manufacturing to transform entire supply chains. For companies building new greenfield facilities, however, the economics are clear: replicating outdated batch infrastructure makes little sense when continuous systems can deliver the same output faster, more economically and safely, and with less waste.

One of the biggest barriers now is talent, as the primary challenges in operating continuous systems that handle slurries and solids are as much about workforce training as equipment. Without investing in both, drug makers risk falling short of the business and patient needs of modern pharma and ultimately fail to deliver the speed, quality, cost, and sustainability that the market demands.

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Putting the Business Case First

For any drug substance or finished drug product, the business case is key when designing the manufacturing process. The goal should always be to deliver high-quality medicine to patients as quickly as possible, at a sustainable cost and with minimal waste. Any approach that achieves this should take precedence, whether that means sticking with conventional methods or adopting advanced flow chemistry, including reactions that involve solids.

Too often, companies shy away from managing solids in flow because they see it as technically daunting or assume the learning curve is too steep. But in practice, avoiding these challenges usually means leaving speed, cost savings, and quality gains on the table.

Some early adopters understand this reality. They recognize that the full potential of continuous processing means expanding from straightforward liquid-phase reactions into more complex heterogeneous flow processes. To get there, they are taking a phased approach: building know-how on simpler systems first and then progressively adding the equipment, skills, and confidence to handle solids and slurries as an integral part of their flow operations.

Others, however, remain stuck in old modes of thinking. By clinging to batch manufacturing for solids-heavy steps, these companies prop up outdated infrastructure and protect institutional inertia at the expense of sound business sense. This reluctance ignores a simple truth: the economics of drug manufacturing today do not reward excuses for inefficiency. Companies that fail to modernize their approach and continue to avoid flow processes for solids will find themselves struggling to keep up as competitors deliver better products, faster and more sustainably.

Why Telescoping Falls Short

Some manufacturers that see the benefits of flow chemistry but want to dodge the complexities of solids handling often resort to telescoping — pushing all solids-related steps to the very end of the process and then performing those steps in batch mode. In this shortcut, steps like crystallization, filtration, and drying are bundled together at the finish line under the assumption that a single, final crystallization will purify the product completely.

The problem is that this approach undermines one of the most important principles in modern drug manufacturing: building quality into every stage of production. A robust process should not wait until the last step to clean up impurities. Instead, it should monitor and manage them as they arise, actively purging them at multiple points. This stepwise approach is not only more scientifically sound, but it is also what regulators expect when evaluating process robustness. Relying on one final crystallization to remove all impurities introduces unnecessary technical risk and regulatory uncertainty, a point echoed in both industry best practices and recent FDA guidance.

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Telescoping also compounds impurities rather than controlling them, leaving a heavier burden on the final step and increasing variability. In contrast, continuous processes that manage solids step by step minimize risk, ensure consistency, and deliver higher-quality outcomes.

Tackling Solids Processing from the Outset

Expanding continuous processing for small-molecule drugs demands more than flow chemistry for simple liquids; it requires proven solutions for handling solids from the start. Achieving this at scale means having technologies that can reliably manage reaction slurries, crystallizations, filtrations, and drying as integrated, continuous operations.

CONTINUUS Pharmaceuticals' Integrated Continuous Manufacturing (ICM) platform was built as a solution to do exactly that. Originating at the Novartis–MIT Center for Continuous Manufacturing, the ICM platform reflects more than a decade of development focused on mastering the solid-handling steps that often deter companies from going fully continuous. From its earliest days, the team's mandate was clear: tackle each unit operation, including solids handling, and design practical, robust equipment that keeps the whole system moving in flow.

This vision for the ICM brought together diverse expertise, including organic and analytical chemists, process engineers, crystallization scientists, and experts in solids handling, to collaborate to develop proprietary tools for continuous filtration, crystallization, drying, and downstream finishing. On the drug product side, specialists in extrusion, injection molding, and tableting extended the continuous mindset all the way to the final dosage form.

One early test case illustrates the stakes. Metformin, one of the world's most prescribed — and lowest-cost — diabetes drugs, is notoriously challenging to scale. The batch reaction runs at high concentration as a slurry, generates heat rapidly, and takes about 14 hours to complete. By-products build up during the reaction and must be controlled continuously, while incoming raw materials can carry solid impurities that must be removed upfront. CONTINUUS developed and patented a continuous polish filtration unit operation to purify the feedstock and then engineered a flow process to manage heat and limit unwanted by-products. Continuous crystallization, filtration, wet milling, drying, and other unit operations were integrated to complete the line.

In another project, the ICM platform was used to transform a four-step batch process, for another approved medication — in which each step involved solids — into a streamlined two-step continuous line. What once required a year to produce the active ingredient and several months more for tableting was compressed into just over two days from start to finished tablets. Such time savings illustrate the real value of handling solids in flow: faster delivery, lower cost, and better control.

These and other projects have shaped the ICM platform into a practical, end-to-end solution for continuous small molecule manufacturing. Its proprietary technologies have proven robust,

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and because the system was developed with insights from the FDA through a collaboration in 2016–2017 and USP in 2018, it aligns with current regulatory expectations, giving manufacturers confidence that fully embracing continuous processing is a feasible and compliant path forward.

Integrating the Right Technologies to Make Flow Work

Beyond the industry's hesitancy to adopt transformative manufacturing technologies, another roadblock to broader adoption of continuous flow chemistry is the limited supply of practical, affordable reactor systems built for small molecule production. Many specialized flow reactors remain expensive and are tied to narrow supply chains, which adds cost and risk for manufacturers looking to scale up.

CONTINUUS Pharmaceuticals avoids these constraints through its integrated approach. The ICM platform combines standard, proven equipment with proprietary technologies to handle flow chemistry reliably, whether the reaction stream is a simple liquid or a complex slurry of solids. This includes practical reactor designs like plug flow reactors and stirred tanks in series, which are flexible, easy to source globally, and straightforward for operators to understand and maintain.

A centralized user interface coordinates every stage of the process. Solid starting materials can be fed continuously and precisely. Reactions, workups, and crystallizations flow seamlessly into continuous filtration and drying, all designed to handle slurries without blockages or breakdowns.

Take crystallization: the ICM platform uses a series of temperature-controlled tanks to guide particle formation under stable conditions, minimizing fouling on vessel walls and producing crystals with tight size distributions. The resulting slurry moves directly to filtration, where the wet cake remains thin (just millimeters thick), which keeps flow rates steady and avoids the common pressure drop and channeling issues seen in traditional batch filters where cakes can grow a foot deep. For drying, CONTINUUS's proprietary drum dryer creates a thin film that evaporates solvent rapidly under vacuum, delivering better heat transfer than bulky agitated dryers and protecting the crystal structure. When very fine particles are needed, continuous wet milling is also available, keeping the entire line integrated.

This modular, integrated approach facilitates the integration of upstream API production with downstream continuous formulation and drug product production. This is supported by global regulatory bodies' inclusion of continuous manufacturing into ICH Q13.

Take formulation and tableting: CONTINUUS's proprietary drug product system integrates twin-screw extrusion with injection molding for a system that directly addresses the challenge of ensuring content uniformity in traditional powder blending. Both the API and an excipient blend are gravimetrically fed at the appropriate drug loading rates into a twin-screw melt extruder, where they are blended. Formulations may be designed to maintain the crystallinity

of the API. In-line PAT continuously monitors and controls content uniformity and crystallinity. The resulting extrudate is injection molded into tablets of any shape desired. The entire process is automated and has a residence time of ~5 minutes.

Every element of this system was shaped by rigorous collaboration between chemists and engineers, who defined the performance needs for each unit operation and tackled the real-world challenges of integrating them. The result is an end-to-end continuous line for manufacturing small molecule drugs at scale that saves time and cost without compromising on quality: a practical solution that sets the ICM platform apart from other flow chemistry offerings still limited by equipment gaps or unrealistic custom designs.

Equally important, the ICM platform extends beyond API synthesis to encompass continuous drug product manufacturing under a unified framework of end-to-end manufacturing and control (EMC). By integrating API production with downstream formulation and tableting, all coordinated through a centralized control strategy, the system delivers not just a continuous line but a true end-to-end solution. This ensures consistent quality across both substance and product, aligning with regulatory expectations for integrated continuous manufacturing and demonstrating the full scope of the platform's capabilities.

Sidebar: Tackling Real-Time Monitoring Challenges

Real-time monitoring of key process parameters is essential for making continuous manufacturing work as intended. Process analytical technologies (PAT) play a central role during development, providing the deep insight needed to lock in a robust process that runs reliably at steady state.

However, when solids enter the picture, monitoring becomes more complex. Many common PAT tools for flow chemistry, such as mid-infrared (mid-IR) spectroscopy, are designed to track molecules in solution but cannot see solid particles suspended in a slurry. This limits their usefulness for reactions where solids are part of the chemistry or form along the way.

To close this gap, CONTINUUS has explored and applied a wider range of tools. Raman spectroscopy, for example, can detect many solid phases, provided they do not fluoresce under the laser. Focused beam reflectance measurement (FBRM) offers a practical solution for real-time particle sizing, capturing changes as crystals form and grow.

Just as important, basic sensors often do more for continuous control than is widely recognized. Inline probes for flow rate, pH, temperature, pressure, conductivity, and density provide immediate, actionable data across multiple unit operations. For crystallizations or filtrations involving solids, they help ensure that slurries flow smoothly and that critical parameters stay within tight limits. Even simple color or reflectance sensors can flag subtle shifts in process conditions before they affect quality.

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Once the design space is well defined, these straightforward sensors, particularly temperature and flow rate monitors, become the backbone of a stable continuous process. By combining smart use of advanced PAT where needed with practical, durable probes, CONTINUUS ensures that flow chemistry involving solids remains predictable, consistent, and fully under control.

Delivering on the Promise of Continuous Manufacturing

The argument for continuous manufacturing of small-molecule drugs is undeniable. Companies that have embraced flow chemistry, even for individual steps, have demonstrated real gains in speed, cost, and quality. Now, early adopters are beginning to bring continuously manufactured drugs to market, setting new benchmarks for efficiency.

To meet this shift, Western contract manufacturers have built flow chemistry capabilities into their service models. In response, contract manufacturers in China and India are also moving to offer flow-based solutions, with mixed levels of technical maturity so far. But piecemeal adoption is not enough. The pharmaceutical industry must move beyond simple reactions and tackle the more representative processes that include solids and slurries in order to fully realize the cost savings, sustainability, and quality benefits of continuous processing.

The ICM platform makes this possible. It has been built for the full spectrum of real-world chemistry, including the solid handling steps that most often hold companies back. CONTINUUS has shown that flow chemistry with solids is both practical and scalable, not the insurmountable hurdle many still imagine.

Companies can apply the ICM system flexibly: from upgrading a single unit operation to overhauling an entire end-to-end line. The greatest value comes when all parts work together as an integrated flow of reactions, separations, crystallizations, filtrations, drying, and finishing dosage forms, controlled through a unified platform. For companies ready to compete on speed, cost, and quality, ICM offers a direct way to deliver on the strongest business case the industry can make: to provide better medicines to patients, faster and more sustainably.

References:

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