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WHITEPAPER

Continuous Manufacturing: A Novel and Enabling Tool to Overcome API Batch Manufacturing Limitations

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While batch processing remains the primary approach in pharmaceutical manufacturing, recent years have seen a significant shift toward continuous flow processes. This trend is particularly evident in certain chemical processes involving hazardous reactions. The shift is primarily driven by enhanced safety, quality, and sustainability that are inherently associated with continuous flow processes. On the other hand, advancements in flow chemistry technology, increased awareness of flow reactor designs and types, availability of commercial flow reactors and more importantly availability of flow reactor spares to build custom-designed lab-scale reactors, have further accelerated the adoption of flow chemistry in the industry. As a result, many industries have begun establishing their own flow process R&D facilities.

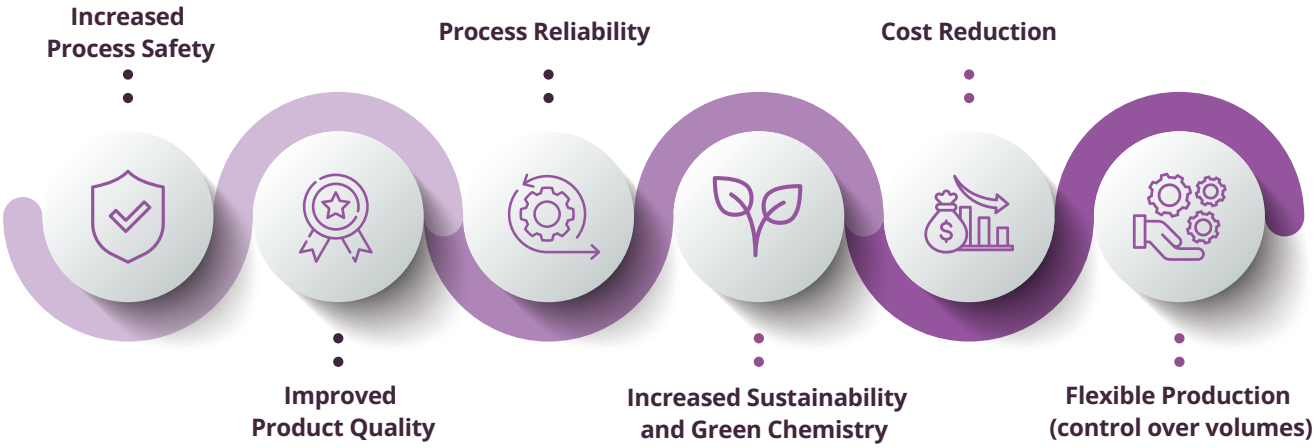
Introduction

Flow technology is a modern tool that is gaining increasing attention from process organic chemists and the pharmaceutical industry for API manufacturing. Transforming batch processes into continuous flow processes is based on the principle of enabling reactions to occur on a micro-scale in a continuous manner. Unlike the batch approach—where unit operations are conducted in discrete steps, each carried out in a single large batch—flow chemistry involves carrying out reactions continuously in small tubular reactors (or small stirred tanks) until the desired production volume is achieved.

Although flow chemistry began more than two decades ago in academia, in recent years the industry has been adopting this technology at an exponential rate. Academic research has demonstrated that many reactions are amenable to flow processing, with numerous interesting publications available on the subject.

In this white paper, we outline the benefits of flow chemistry, general strategies for successful implementation, and examples of reactions that have been successfully adapted to flow at commercial production scale.

Advantages of flow process over the batch process



Increased process safety

Increased process safety is one of the key factors driving the adoption of flow chemistry in manufacturing. Particularly for reactions involving high-energy intermediates, such as azides, diazo compounds, nitro compounds, or pyrophoric reagents like organometallics, conducting on large scale in batch mode poses significant risks, including the potential for runaway reactions.

Flow chemistry offers a safer alternative in such cases for two main reasons:

- High energy reagents/intermediates can be generated in micro-scale continuously with better heat exchange and continuously separating them out from the reaction pool.
- There is a possibility of converting high-energy intermediates into next stage stable products, thus eliminating the risk of accumulation of high-energy intermediates, e.g. generation of azides in flow and subsequently converting it to triazole.

In general, reactors used in flow chemistry have a smaller footprint than batch reactors. This minimizes potential damage in the rare event of a runaway reaction. Smaller reactor volumes also enable the use of real-time monitoring technologies that can quickly detect anomalies. Additionally, flow systems are typically automated, allowing for rapid shutdown procedures if needed. Since reaction volumes are much lower compared to batch systems, chemistries involving hazardous reagents that would be too dangerous in batch mode can be safely carried out in flow.

Improved product quality

Drug safety depends on API quality. Regulatory bodies insist pharmaceuticals meet strict quality standards. The U.S. Food and Drug Administration (FDA) requires that APIs meet specific purity standards and that manufacturers implement systems for managing quality at each stage of production.2 Although batch processes have been used traditionally to make APIs and meet such requirements, flow chemistry offers better control over consistency of production of quality APIs. For example, in batch syntheses, raw materials must be discharged from each process before being transferred to the next. These delays mean reactants can overreact and products can degrade, potentially reducing the quality of the final product or creating waste.

Continuous manufacturing avoids such problems with below advantages:

- **Possibility of In-line Monitoring:** Unlike in batch processes, parameters in a flow system can be adjusted during operation with minimal disruption. Any product affected by out-of-specification conditions can be easily separated from the product stream while the reaction continues. This allows for rapid adjustments to maintain product quality and minimize waste.

- **Automated shutdown:**Furthermore, because continuous flow systems utilize automated control mechanisms and in-line monitoring technologies, any deviations that could impact API quality can be quickly detected and corrected.

NOTE: In the flow process, we call the time taken for complete (maximum) conversion residence time. It is important to note that reaction time (or residence time) in flow is several orders of magnitude less compared to batch process reaction time. So, for example, if a batch hydrogenation takes 8 hours for good conversion, the same reaction in a flow process would need only a few minutes. Having said that, in the batch process, a product formed in the first half of the required reaction time stays in the reactor until the fixed acceptable conversion is achieved. This is one of the main causes for side-products (impurities) in the batch process. This problem is eliminated in the flow process as the products are continuously isolated from reaction conditions (no chance of by-product formation) to yield very high-quality products.

Process reliability

Due to the small size of the reactors, there is significantly enhanced control over several process parameters as explained below:

- **Homogeneous Mixing:** By ensuring efficient mixing of reactants, uniform distribution and contact between reactant molecules are achieved. This minimizes the formation of localized hotspots or cold spots, reducing the risk of incomplete reactions and ensuring consistent product quality.

- **Efficient Heat Transfer:** Flow reactors typically offer a high surface area-to-volume ratio, facilitating efficient heat transfer and accurate temperature control. This improves thermal management, reduces the risk of thermal runaway, and enhances overall process reliability.

- **Consistency Throughout the Flow Process:** Flow chemistry systems enable precise control over key reaction parameters such as pressure and residence time. This ensures reactions are conducted under consistent conditions, resulting in reproducible outcomes and improved process robustness.

Overall, flow chemistry enhances process reliability by providing consistent reaction conditions and improved control over process parameters. Continuous flow is a key technology for the manufacture of pharmaceutical products, as it helps ensure uninterrupted supply chains. These advantages make flow chemistry a reliable and robust approach for chemical synthesis and manufacturing.

Increased sustainability and green chemistry

Flow chemistry facilitates the implementation of green chemistry principles, including the use of safer solvents and the minimization of by-products. By enabling precise control over reaction parameters and allowing rapid process optimization, flow chemistry supports the development of more sustainable synthetic routes as explained below:

- **Energy Efficiency and Lower Carbon Footprint:** : As mentioned above, the reaction time (or residence time) in flow chemistry is significantly shorter compared to batch processes. As a result, flow processes, especially in tubular or microreactors, drastically reduce energy consumption. Additionally, the high surface area-to-volume ratio in flow reactors ensures efficient heat exchange, minimizing energy waste. The use of back-pressure regulators (BPRs) allows reactions to be conducted at temperatures well above the atmospheric boiling point of solvents, further improving energy efficiency.

  For example, high-temperature reactions such as those at 350 °C often yield less than 20% in batch processes, requiring large amounts of energy to produce multi-kilogram quantities. In contrast, the same reactions in flow systems can be carried out at temperatures below 200 °C with much higher conversions. This makes flow chemistry an ideal choice for high-temperature reactions.

- **Reduced Environmental Impact:** Due to improved heat transfer and superior mixing, flow processes typically require smaller quantities of reagents, solvents and catalysts compared to batch processes. This directly contributes to waste reduction and lowers the environmental impact. Moreover, flow reactors are well-suited for telescoping multiple reaction steps, eliminating the need for intermediate work-up, extraction, concentration and solvent switching. These advantages collectively result in significantly reduced waste, making flow chemistry a more environmentally friendly choice for API and fine chemical manufacturing.

- **Smaller Footprint:** Continuous manufacturing significantly reduces reactor size, thereby minimizing the overall footprint of manufacturing facilities. This not only reduces infrastructure costs but also lessens the environmental burden on land resources, contributing to more sustainable production practices.

Cost reduction

- **Capital Expenditure:** In batch process, huge reactor vessels with high footprint contribute to huge capital costs. But, in flow process, smaller tubular or micro reactors can be employed which reduces capital expenditure cost for both the reactor and manufacturing facilities.

- **Operational Expenditure:** Also, as explained above, energy consumption in flow process is much less compared to batch process which contribute significantly to operating cost savings.

Flexible production (control over volumes)

On demand production is a great advantage of continuous manufacturing. In this rapidly changing market, an introduction of a new API in the market or sudden surge in the demand of a product can affect the volume demand. Continuous manufacturing gives great flexibility to either upscale or downscale with little impact on capex.

Handling extreme reaction conditions and handling hazardous reagents

Another unique advantage of flow chemistry is its ability to handle some extreme reactions conditions. For example, certain reactions involve handling high energy intermediates or extreme high temperatures of >300 °C. In such cases, batch process becomes a big “no go” and thereby missing the opportunity to bring some APIs into the market. Flow chemistry offers a safer way to carry out reactions that involve extreme reaction conditions because there is greater control with intrinsic enhanced process safety features.

Some practical challenges in developing flow technology

While flow chemistry offers many advantages over batch process, optimization of chemical reactions in flow process is not a straightforward exercise.

- Not all chemical processes are amenable to flow process. Flow chemistry traditionally involves liquids flowing through pipes. Certain processes involving slurries, such as solid precipitation during the reaction, solids addition, solid-solid mixing, or even highly viscous liquids, pose challenges. However, new technologies have evolved to handle some of these scenarios under flow conditions.

- There is no universal flow reactor that is suitable for evaluating all types of reactions. Lab-scale, custom-designed prototypes must often be developed to demonstrate proof-of-concept, which can later be translated to a pilot scale and eventually to commercial scale manufacturing.

- Optimizing a chemical reaction in flow process typically involves several trial-and-error iterations. It necessitates coordinated, multidisciplinary efforts from process chemists, chemical engineers, and mechanical engineers.

To develop a successful flow process for both existing and new batch processes, one must learn how to evaluate whether a particular chemical process can be transformed into a flow process. Developing a flow process starts with the design of a custom-designed prototype with the type of reactor, pumps, connectors and other flow spares that are compatible with the selected chemical process. This requires a team of subject matter experts in flow technology. Only a suitable and compatible flow reactor design ensures successful adaptation of batch process into a flow process.

Types of reactors

- **Plug Flow Reactors (PFRs):** Plug flow reactors typically have a cylindrical or tubular geometry (e.g., coil reactors). These systems enable efficient mixing and heat transfer, making them ideal for fast and exothermic reactions. Notably, PFRs have been successfully used to achieve complete conversions within seconds, especially in "flash chemistry" applications where high reaction rates are essential. Numerous examples of such implementations can be found in the literature.

- **Column Reactors:** Column reactors are packed with solid materials that act as catalysts or stoichiometric reagents. They are often designed to operate under elevated pressures and have significant considerations for downstream processing. These reactors offer excellent control over reaction parameters and can be tailored for a variety of chemistries. Representative case studies are available in the literature.

- **Gas Flow Reactors:** Using gaseous reagents poses handling and safety challenges in traditional batch systems. Flow chemistry addresses these issues with specialized gas flow reactor designs that improve safety, mass transfer, and overall efficiency. These systems enhance the robustness of gas-phase reactions and are well documented in scientific publications.

- **Slurry-Compatible Reactors:** Reactions involving the formation of solids or requiring solid reagents often lead to slurries, which are difficult to handle in micro- or meso-fluidic systems. Recent advancements have enabled the continuous processing of slurries through specially designed reactors that minimize clogging and ensure consistent flow.

- **Photochemical Flow Reactors:** Flow photochemistry has opened new avenues for performing light-driven reactions efficiently and safely. These reactors are relatively easy to configure and scale, supporting both small- and large-scale synthesis without major complexity. They provide excellent light penetration and temperature control.

- **Trickle Bed Reactors (TBRs):** TBRs are ideal for conducting triphasic reactions, involving solid catalysts, gas, and liquid phases simultaneously. The fixed bed, usually containing the solid catalyst, is continuously fed with liquid and gas streams. These reactors are widely used in both research and industrial applications, with well-documented case studies available.

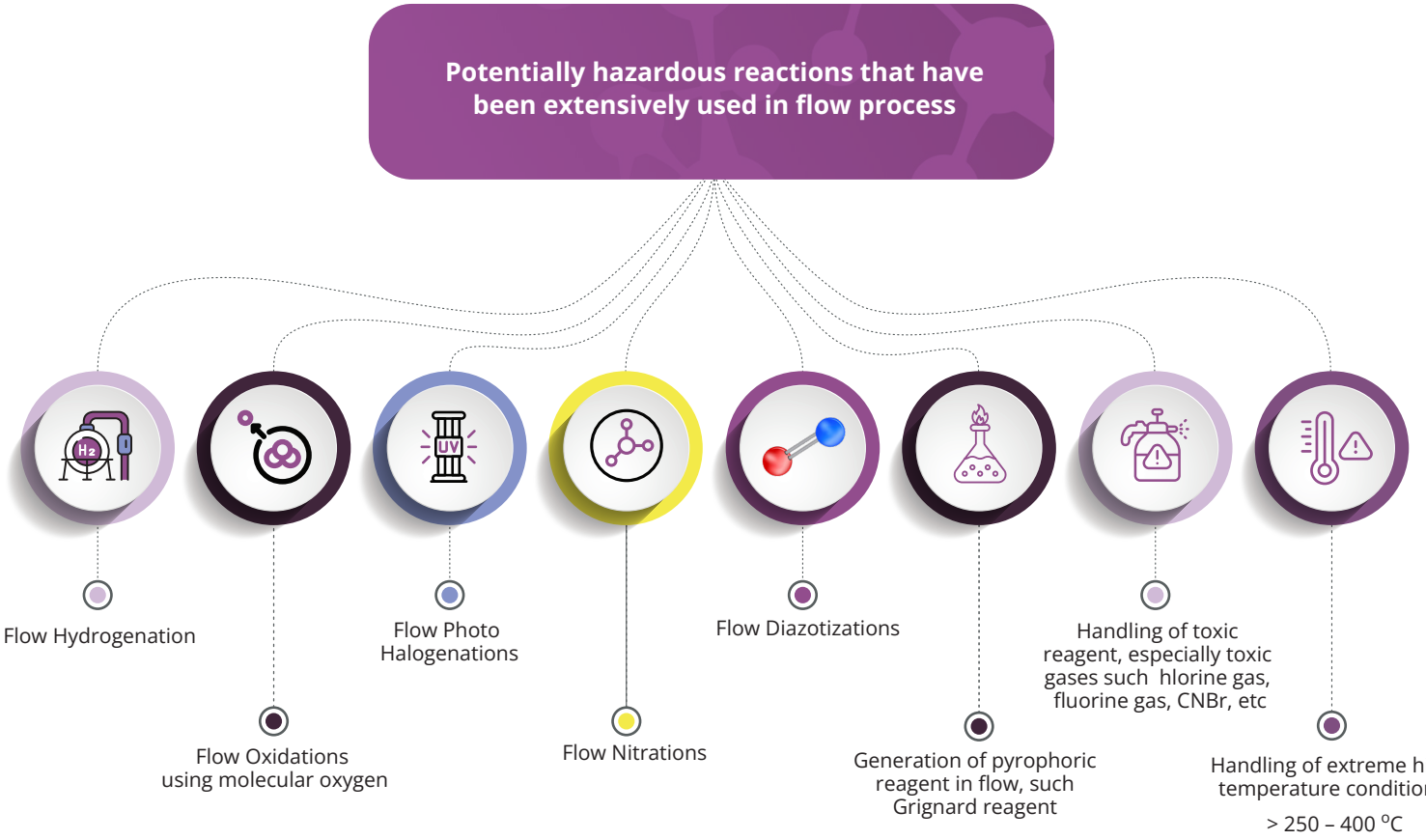
Key applications of flow chemistry

Over the past fifteen years, continuous flow and microreactor technology have proven to be powerful tools for the safe and controllable use of hazardous or highly reactive reagents in organic synthesis. The small channel dimensions characteristic of microreactors ensure a very high heat exchange efficiency that suppresses the formation of hotspots, temperature gradients, or accumulation of heat. Thus, high reaction selectivity and enhanced safety can be achieved even for very fast and highly exothermic reactions. The excellent heat and mass transfer characteristics of microreactors, together with the fact that the reaction is resolved along the length of the reaction channel, enable precise control of the residence time of the intermediates or products by a thermal or chemical quench of the solution. Highly reactive, toxic, or explosive intermediates can be generated in situ and consumed within the reactor loop by combining multiple reagent streams. Thus, the synthesis of API that was previously not possible to perform by batch process are now possible to handle in a safe and controlled manner.

In recent years, several different types of reactions have been performed using continuous flow chemistry in the pharmaceutical, fine chemical, green chemistry, and other catalytic process industries. Much of this adoption is driven by chemical processes that are challenging or unsafe to scale up using traditional batch processes.

- Flow chemistry offers enhanced safety for handling hazardous or toxic reactants, making it especially valuable for reactions involving materials that pose risks to human health. It is also increasingly used to control stereochemistry, as flow systems allow precise adjustment of reaction parameters to minimize issues like epimerization.

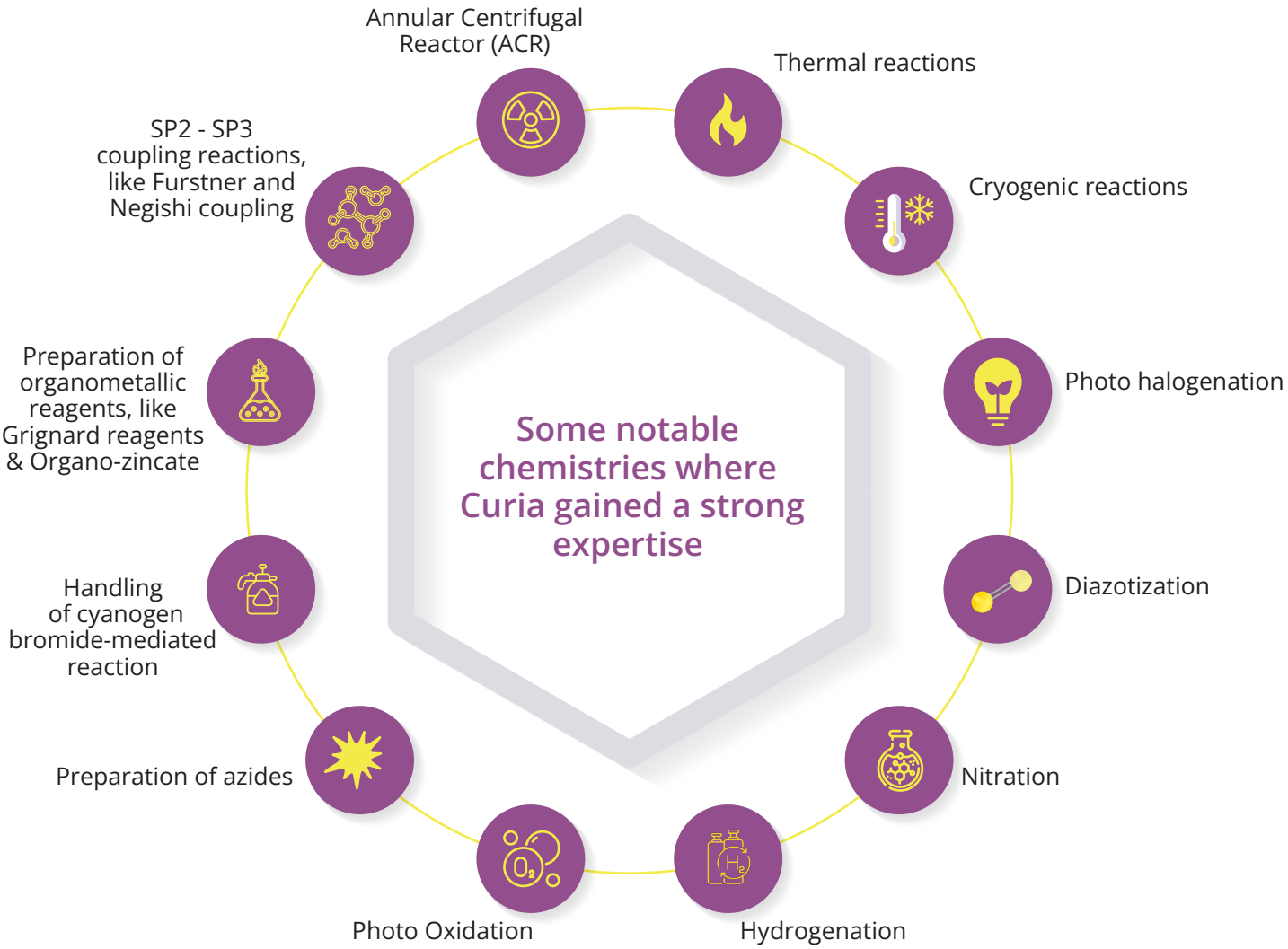
- Additionally, flow chemistry is ideal for situations where starting materials are limited or expensive, as it enables efficient small-scale synthesis with minimal waste.



Flow chemistry capabilities at Curia

Curia's chemical development team actively embraced flow technology. Curia's flow chemistry expert team believes that there is no universal flow instrument that can offer all flow chemistry solutions. Each chemical reaction is unique and needs a customized flow reactor set-up. Curia has adopted a custom design approach "Build-it-yourself". Curia takes each chemical transformation independently, evaluating, designing & developing a suitable customized flow reactor. Curia's flow chemistry team comprises of strong synthetic chemists, expert chemical engineers & mechanical engineers who work closely with local expert engineering & fabrication companies to build prototype reactors based on initial lab-scale trails. After a successful demonstration on kilo scale using pilot reactor, a manufacturing scale reactor will be built incorporating all safety features with ATEX compliance and CE rated European safety features Curia constructed a state-of-art flow chemistry lab at Curia's Hyderabad site (non-GMP) while Curia's Bon-Encontre site provides GMP pilot-scale to large scale manufacturing capabilities.

Curia's Hyderabad site has successfully developed many lab-scale flow reactors using this custom design approach as a proof-of- concept on a variety of reactions (see below) and delivered materials from gram to kilo scale to different customers.

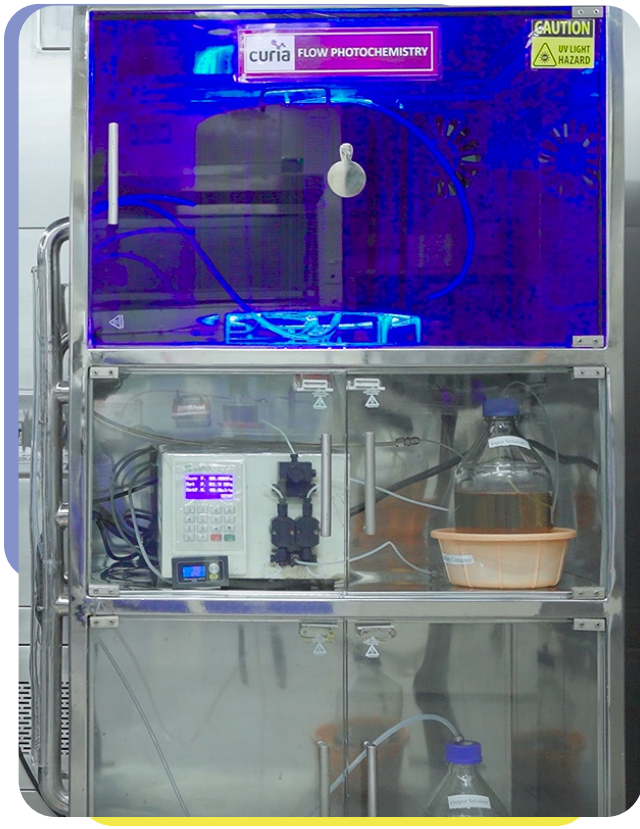


The Curia team took some of these lab-scale reactors to pilot scale reactors and even manufacturing scale reactors by leveraging the expertise of engineering & fabrication companies available locally. Using pilot scale reactors, we delivered materials to various customers from >10 kg, 100 kgs and ton level manufacturing scale. Curia's Hyderabad and Bon Encontre sites worked closely with each other to take the lab-scale reactor to the next manufacturing stage by building a manufacturing scale flow reactor-based plant with tech transfer.

Discover our success stories

Curia has successfully developed many lab-scale flow reactors as a proof-of-concept to scale up reactors for large-scale synthesis.

Photo halogenation



Although photo bromination offers an excellent low-cost and greener solution for various bromination processes, traditional batch photo bromination using Hg and Xe lamps suffers from several inherent issues, such as formation of undesired by-products, consuming high energy, and loss of efficiency due to a decrease in intensity as light travels through the reactor (Beer–Lambert Law). Most of these shortcomings were addressed using flow photo reactors designed by several scientists across academia and industry. We developed a unique and first-of-its-kind flow photo reactor using circularly sandwiched LEDs. This design not only takes care of all of the shortcomings described above in batch photo reactors, it also uses low-energy LEDs and offers uniform light intensity. Moreover, the annular shape of the reactors ensures that all emitted light is utilized, as light emitted at different angles

Curia's Bon Encontre site needed a photo flow reactor where the volume requirement was at least a ton/month. Curia's team tried many models available in the literature. However, we couldn't achieve desired residence times of <5 mins (on our chemical problem) to meet the required volume. As, we were getting 20-30 mins residence time with literature available models and LED light sources. Such high residence time couldn't meet our ton/month production requirement.

Then, Curia's team came up with the unique design of "Circularly Sandwiched Continues Photo Reactor," where the tubular reactor is placed in between the two (cylindrical) high intensity LEDs in sandwich manner. The LED lights used were high intensity power and robust LEDs. These were embedded on LED panels designed with proper heat sinks to avoid overheating of LEDs and provide long lasting capacity (approximately one year) for LEDs with diminished intensity. After validation of proof-of-concept in a small-scale reactor, Curia built a pilot scale and installed the reactor Curia's Bon Encontre site with tech transfer where the production went successfully.

Main Features Curia Photo Flow Reactor

- Unique Circularly Sandwiched Continuous Photo Reactor (CSCPR), a first-of-its-kind.
- Robust reactor design with high-intensity long-lasting LED lights embedded with heat sinks.
- Modular design with HMI (automation).
- Wattage can be adjusted from 200W to 1200W with the wattage modulated switch.

Reactor technical achievements

- Significantly increased reaction speed
- High efficiency with high quantum yields more energy efficient!
- High throughput, ~ 40 Kg/day. Can produce bromination product of approximately 1 tons/month
- Amenable to scale up. A simple 5x scaled-up reactor can produce approximately 5-10 tons/month

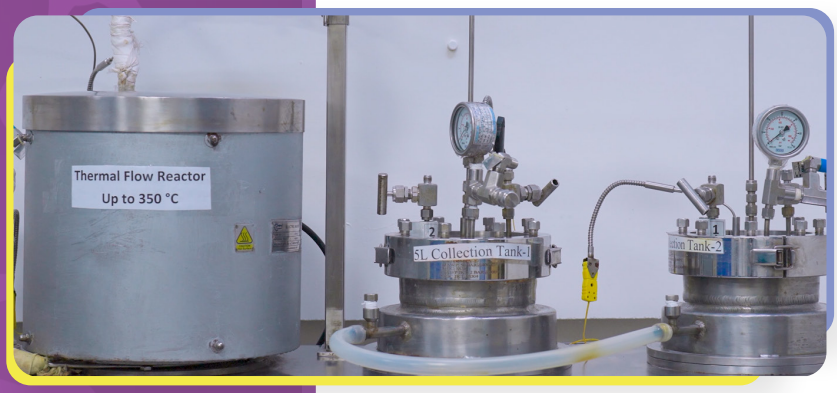
Thermal reactions

Batch thermal reactions face several challenges, primarily related to controlling temperature and maintaining product consistency due to non-uniform conditions within the reactor. These challenges can lead to safety concerns like thermal runaways and difficulties in scaling up from lab to industrial production. Batch reactors, especially larger ones, can have poor heat transfer characteristics. The volume to surface area ratio makes it difficult to remove heat generated by exothermic reactions, potentially leading to temperature gradients and hot spots. Batch reactors exhibit non-linear behavior, meaning their properties change throughout the reaction. This makes it difficult to design a single control system that can handle all stages of the reaction effectively. As the reaction progresses, conditions like temperature, concentration, and viscosity can change significantly, leading to variations in reaction rates and product quality across the batch. Irregularities in particle nucleation or other factors can cause inconsistencies in product properties from one batch to another. Exothermic reactions, particularly in batch reactors, can produce heat faster than it can be removed, leading to a runaway reaction where temperature increases uncontrolla- bly, potentially causing explosions or other hazards. Scaling up from a lab-scale batch reactor to a larger industrial reactor often requires significant redesign of the equipment and process to maintain heat transfer and mixing efficiency. Controlling batch reactors, particularly with exothermic reactions, requires sophisticated control strategies that can adapt to changing conditions.

In one example, Curia needed to carry out a reaction at 300 °C. Batch reaction became very challenging yielding poor conversion (<10%) even at longer reaction times. The Curia flow chemistry team tried various thermal flow chemistry designs and successfully identified a couple of designs where the reaction can carry at even as high 350 °C safely in a flow reaction. Unlike the high temperature batch reactions, the high-temperature flow reaction was clean with no or traces of decomposition (by-product) formation, with conversions at almost >90%. With this success, the Curia team worked with a local engineering company to build a pilot scale thermal flow reactor which was used to safely carry out our different high-temperature chemistry.

Curia's custom-designed thermal reactor

- Using 320 °C, delivered 10 Kgs of product to a customer
- Using 180 °C, delivered 3 Kgs of product to a customer
- Using 220 °C, working on developing a flow process for a commercial-scale business opportunity.



Hazardous reagents

Handling hazardous reagents in batch mode presents several challenges, primarily due to the potential for runaway reactions, mischarging errors, and the inherent risks associated with large-scale chemical processes. These challenges can lead to safety hazards, production disruptions, and compliance issues. The safe management of hazardous reagents is a key part of the transition from medicinal chemistry syntheses to pilot scale processes. During the past decade, continuous flow and microreactor technology have been shown to be powerful tools for the safe and controllable use of hazardous or highly reactive reagents in organic synthesis.

In one example, Curia needed to use large volumes of CN-Br (300 Kgs) to produce KSM. Reaction in batch was found to be highly exothermic and quite fast. This combination of exothermicity and quick reaction nature is deadly combination that can become a potential run-away reaction. Moreover, because of the exothermicity, a color impurity was generated in the batch. Considering a 3 Kg batch size restriction recommendation from the Process Safety Assessment (PSA) Team, the reaction would need 100 batches to convert 300 Kg of CNBr, which was taking several months to complete the work. Curia's team quickly developed a microreactor design which enabled us to carry out the reaction in flow with 30 seconds residence time. The microreactor design nicely contained the exothermicity as volumes in the microreactor were quite small (< 10 mL). Also, as product (reaction mixtures) came out of the microreactor quite fast and gets quenched spontaneously (< 1 min), there was no decomposition and product quality was significantly high.

Curia jacketed microreactor achievements

- Produced high quality material (light yellow & off-white) in good yields.
- Achieved 25 Kg/day
- Delivered multiple batches of over 200 kg.

Hydrogenation

Hydrogenation reactions are often exothermic and can be sensitive to temperature fluctuations. Maintaining safe operating conditions, especially at larger scales, requires careful control of temperature and pressure. Efficiently removing the heat generated during hydrogenation is crucial to prevent runaway reactions and ensure product quality. Batch reactors can struggle with heat transfer, especially in larger volumes, potentially leading to temperature gradients and inconsistent reaction outcomes. Batch hydrogenation often requires handling large quantities of catalyst, including its addition, removal, and disposal. This can be a labor-intensive and potentially hazardous process, especially with pyrophoric catalysts (those that can ignite upon contact with air). Scaling up batch hydrogenation processes can be difficult due to the challenges in maintaining consistent conditions and achieving efficient heat and mass transfer at larger volumes.

To support Curia's two European manufacturing sites to convert existing batch hydrogenation processes, the task was given to Curia's Hyderabad team to develop fixed bed hydrogenation technology. Curia's flow chemistry team looked at various designs, came up with their own requirements, and enlisted the help of a local engineering company to build a pilot scale Fixed Bed Hydrogenation Reactor (FBD). With an in-build lab-scale reactor and pilot scale FBD reactor, Curia can validate many batch hydrogenation reactions into flow hydrogenation processes. Currently, Curia's flow chemist team is working on two customer projects to support Curia's Bon Encontre site to shift the existing batch hydrogenations manufacturing process to continuous hydrogenation using FBD. In another separate project, Curia is working on developing a flow hydrogena- tion technology to support other Curia sites to convert existing large scale batch hydrogenation manufacturing to a flow hydrogenation process.

Conclusion

Continuous flow chemistry offers quality, innovation, and safety advantages for early and late phase API synthesis. Advantages offered by flow chemistry justify the investment needed for specific processes for commercial production. Developing the flow processes requires a deep understanding of synthetic chemistry. Scaling up such processes requires engineering expertise. Doing both efficiently requires a full-service CDMO with the infrastructure to support complex projects and the know-how to innovate. At Curia, we have a dedicated facility with the necessary equipment and an expert flow chemistry team comprised of strong synthetic chemists, and skilled chemical engineers & mechanical engineers.

References:

1 A Survey of Pharmaceutical Companies and Contract Manufacturing Organizations. J. Christopher McWilliams, Ayman D. Allian, Suzanne M. Opalka, Scott A. May, Michel Journet, Timothy M. Braden Org. Process Res. Dev., 2018, 22, 1143-1166

2 Continuous-Flow Technology—A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients. Bernhard Gutmann, David Cantillo, C. Oliver Kappe. Angew. Chem., Int. Ed., 2015, 54, 6688–6728.

3 Continuous flow chemistry: where are we now? Recent applications, challenges and limitations. Faith M. Akwi and Paul Watts, Chem. Commun., 2018, 54, 13894-13928

4 Flow Chemistry: Recent Developments in the Synthesis of Pharmaceutical Products Riccardo Porta, Maurizio Benaglia, and Alessandra Puglisi, Org. Process Res. Dev., 2016, 20, 2−25.

5 A Perspective on Continuous Flow Chemistry in the Pharmaceutical Industry. Marcus Baumann, Thomas S. Moody, Megan Smyth, and Scott Wharry
Org. Process Res. Dev.,2020, 24, 1802-1813.

6 Photochemistry in Pharmaceutical Development: A Survey of Strategies and Approaches to Industry-wide Implementation. Eric G. Moschetta, Gemma C. Cook, Lee J. Edwards, Michael A. Ischay, Zhen Lei, Frederic Buono, François Lévesque, Jeffrey A. O. Garber, Maura MacTaggart, Melda Sezen-Edmonds, Kevin P. Cole, Matthew G. Beaver, Jaika Doerfler, Suzanne M. Opalka, Wenli Liang, Peter D. Morse, and Naomi Miyake Org. Process Res. Dev., 2024 28, 831-846

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