CORNING

Advanced-Flow™ Reactors

Continuous Flow Processing Technologies from Lab Feasibility to Industrial Production

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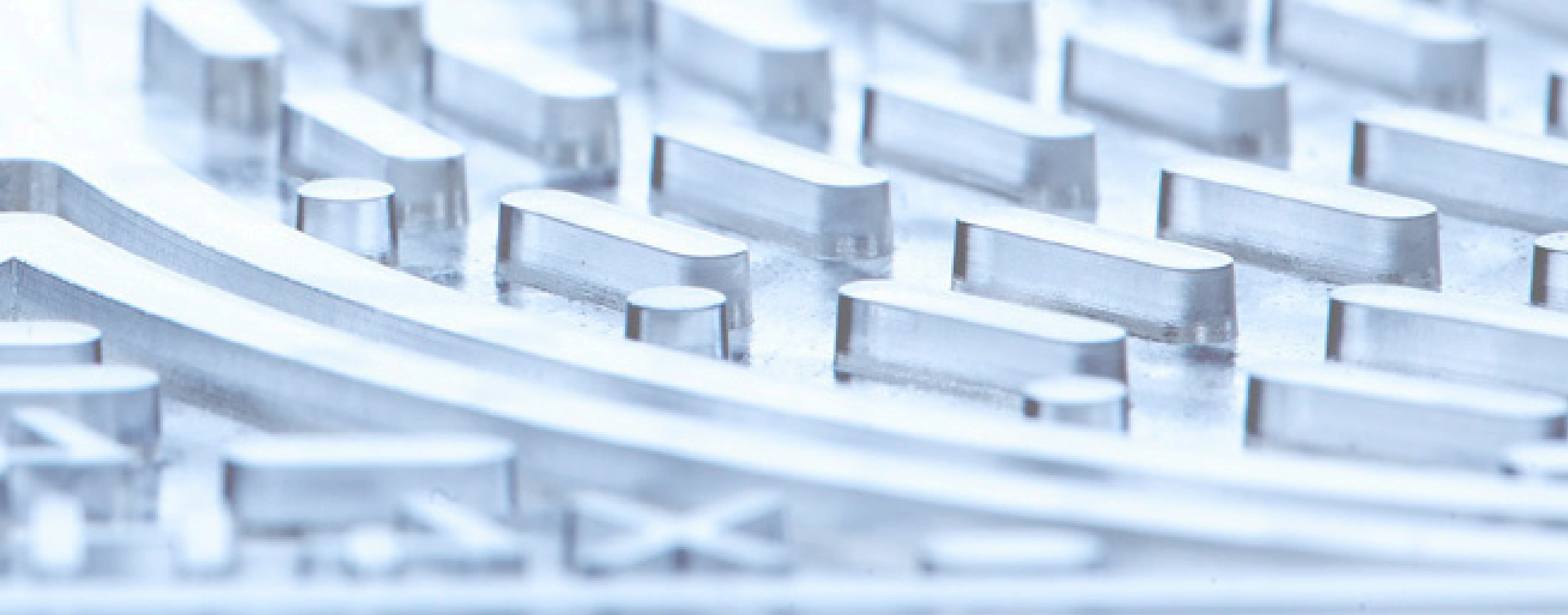
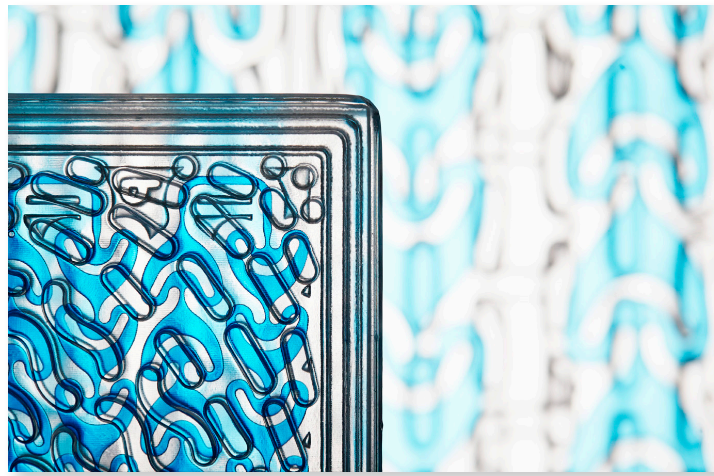


Corning® Advanced-Flow™ Reactors

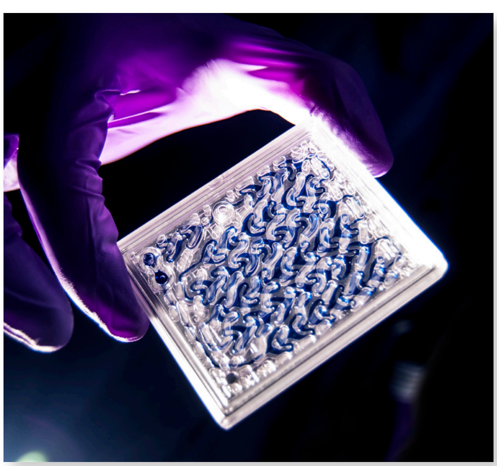
As environmental and safety regulations become more stringent, the chemical manufacturing industry is increasingly looking to continuous flow processing[1] as a less risky, more efficient, and less costly alternative to traditional batch processing.



Long used in other trades like the petroleum refining and petrochemical industries, continuous flow methods have gained steady adoption in the production of fine chemicals, agrochemicals, and active pharmaceutical intermediates (APIs), etc., over the past five to ten years, largely thanks to the pioneering work of Corning Incorporated and Corning Advanced-Flow Reactor (AFR) Technology.

Corning Advanced-Flow Reactors are continuous flow processing technologies that address a wide range of applications in pharma and fine chemical manufacturing. Every reactor in Corning's product line is built around the same keystone component – the integrated fluidic module, a uniquely designed and meticulously engineered reactor plate made of either specialty glass or specialty silicon carbide – which allows for rapid and seamless scale-up from lab scale to commercial production, as well as improved heat transfer, mass transfer, and mixing. Compared to traditional batch reactors, Corning's reactors offer dramatic savings in space, cost, and time while also enhancing purity, increasing yields, and improving safety; they are also inherently safer, more efficient, and more durable in corrosive conditions than other continuous flow reactors on the market today.

BACKGROUND



In the early 2000s, Corning saw an opportunity to leverage its expertise in glass science to build a better microreactor for pharmaceutical applications. At the time, microreactors were being used for lab-scale molecule discovery, but the transition from bench-top to commercial production posed a challenge for drug companies. Furthermore, most incumbent microreactors were made with metal, which was corrosion-prone and unsuitable for certain reaction types. Perceiving a need for more robust materials, better reactor design, higher throughput, and greater ease of scale-up, Corning scientists began developing the integrated fluidic module.

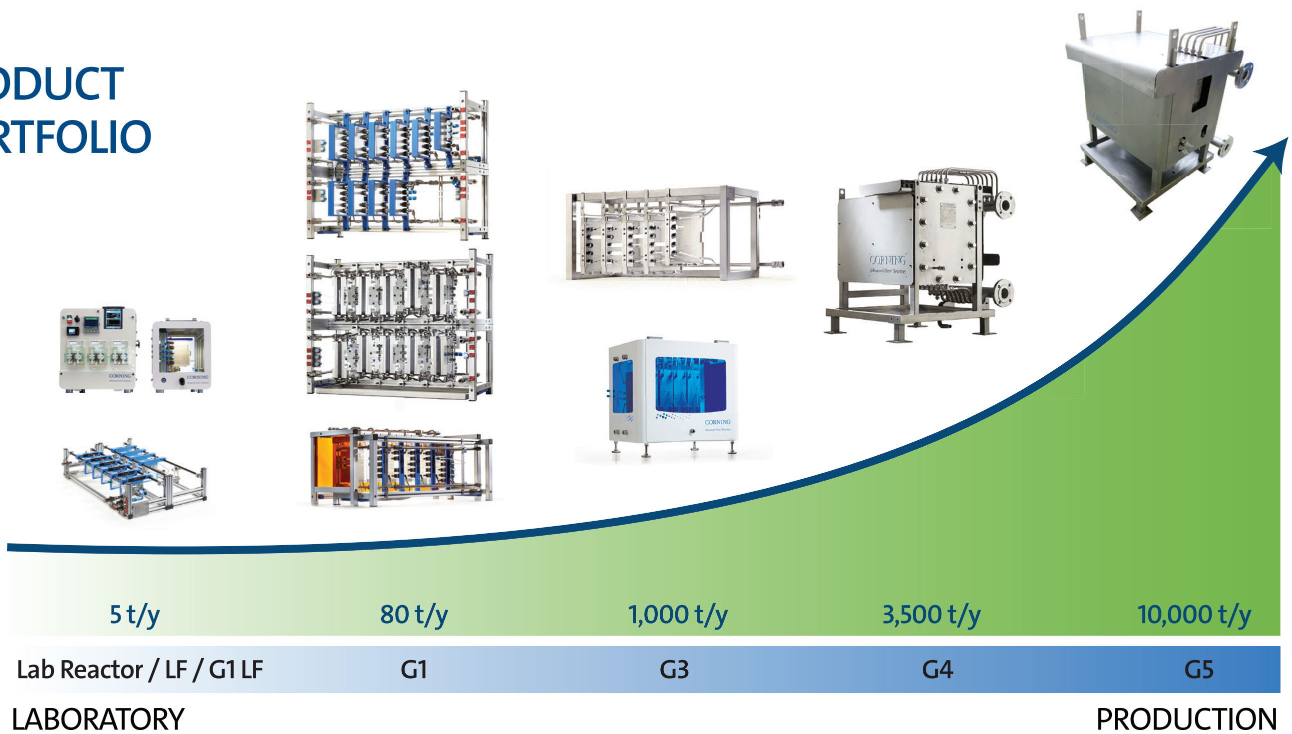
[1] For the purposes of this article we are defining 'continuous' to mean continuous unit operations, focused mainly on the chemical transformations that occur inside Corning Advanced-Flow Reactors, from the input of raw materials to the output of intended product; downstream processes should be considered separately and on an application-by-application basis.

Although Corning initially intended to sell these fluidic modules alone, they soon realized that they could better serve their potential customers by offering a complete product and released their first full reactor – the G1 – in 2006. Over the next four years, driven by market demand for greater reaction capacity, they developed and commercialized several higher-throughput models as well, collaborating closely with manufacturers and university labs to fine-tune the specifications. These advances were embraced by customers, who continued to press for even higher-capacity options.

For their industrial-scale reactor, the G4, Corning sought to accommodate high-temperature caustic applications and reactions involving fluorine by making the fluidic modules out of a material with even better corrosion resistance than specialty glass: silicon carbide (SiC)[1]. By using high-quality SiC and integrating both SiC and stainless steel into their reactor design, Corning achieved superior thermal conductivity and system thermal shock resistance, leading to higher throughput with no change in heat transfer and mixing performance. Corning has since released a full line of SiC reactors.

Corning continues to expand its product portfolio with a variety of innovative offerings, including photoreactors, low-flow reactors, lab reactor systems, auxiliary equipment, and more.

PRODUCT PORTFOLIO



There have been more than 500 installations of Corning reactors since the first G1 reactor debuted in 2006, and adoption of this technology continues to grow steadily.

VALUE PROPOSITION

Corning® AFR™ Technology offers four key benefits over traditional batch processing:

1. *Inherently safer technology*
2. *Better and more consistent product and process quality*
3. *Lower OPEX and CAPEX*
4. *Reduced environmental impact*

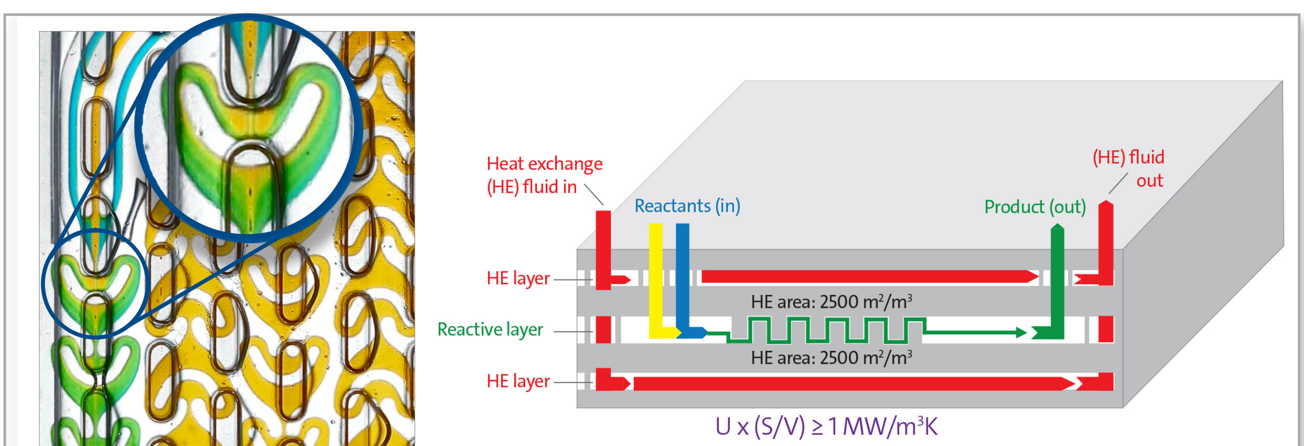
These benefits are enabled by the:

- ***continuous and small-scale nature***, which allows for much lower reaction volumes (holdups) than batch reactors and is compatible with real-time, in-line monitoring.
- ***design of the fluidic modules***, which facilitate better mixing, narrow residence time distribution, and superior heat and mass transfer than both batch reactors and other continuous flow reactors, and can be readily reconfigured to meet the needs of thousands of different reactions at multiple scales.
- ***configuration of the reactors*** themselves, which are optimized to limit the potential impact of catastrophic events.
- ***quality of Corning's materials***, which are more resistant to corrosion and thermal shock than competitive materials.

ADVANTAGES OF CORNING'S FLUIDIC MODULE DESIGN

Patented "HEART" Cell Design

Integrated, Multi-layer Structure



Corning's "Heat Exchange and Advanced Reaction Technology" (HEART) facilitates 100x better mass transfer than batch processors, and 2-4x better mass transfer than benchmarked flow reactors.

Corning's SiC is up to 300x more corrosion-resistant than market-grade SiC.

"Sandwich structure" of tightly integrated heat exchange and reactive layers facilitates 1000x better heat transfer than batch reactors, accommodating highly exothermic reactions.

1. INHERENTLY SAFER TECHNOLOGY

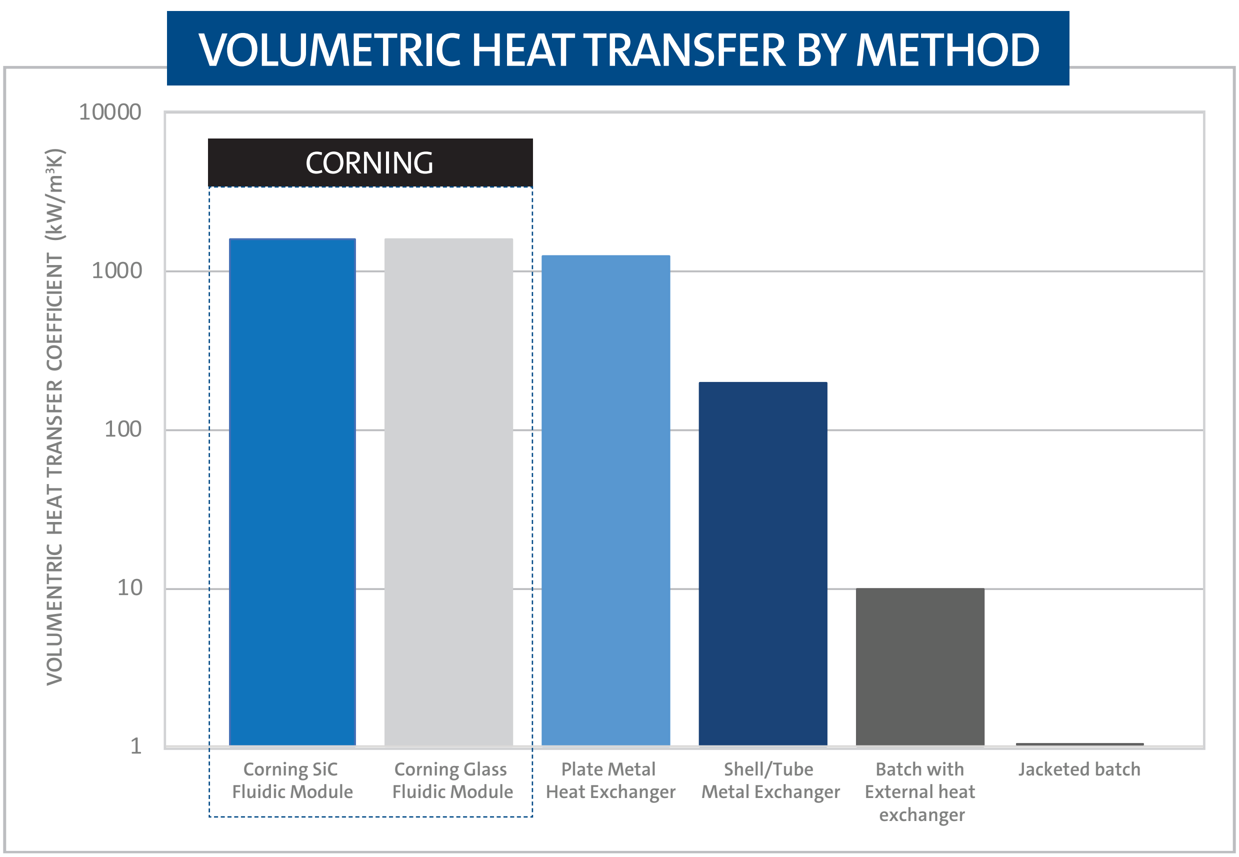
Corning's reactor technologies are inherently safer than batch processing, largely because the reaction volumes (holdups) required for several fluidic modules operating continuously in series are much lower than those used in a single batch reactor. A Corning G4 reactor with a throughput of 2000-3500 tons/year uses holdups of 1-3 L, whereas a batch reactor with comparable throughput requires 3000-6000 L of holdup.[2] The continuous nature of this process can also reduce accumulation of unstable intermediates, thereby limiting inventories of hazardous materials. In addition, the multi-layer design of Corning's fluidic modules provides ~1000x higher volumetric heat transfer than batch processing, allowing these systems to accommodate highly exothermic reactions that would otherwise be difficult, costly, or dangerous.[3]

Furthermore, Corning's materials and overall reactor design have been engineered to reduce the risk of catastrophic events, particularly at industrial plant scale.

The intrinsic properties of Corning's SiC material and the thermal design of their fluidic module enable more efficient heat transfer to keep the reaction under control and avoid any thermal runaway that could lead to an explosion of the reactor.

In addition, the small hold up joint with efficient mechanical design of the reactor can reduce the consequences of an explosion if it may happen (i.e., reduce shockwave and missile emission).

In a round of testing conducted at the French National Institute for Industrial Environment and Risks (INERIS), sensors located less than a meter away from a production-scale G4 reactor during a forced explosion registered no harmful shockwave.[4]



2. BETTER AND MORE CONSISTENT PRODUCT AND PROCESS QUALITY

The seamless scalability of Corning's reactor products ensures highly consistent product quality from lab bench to industrial production. This scalability limits downtime needed for process adjustments, which can in turn accelerate time to market and reduce capital investment risk.[5]

Development Time: Corning Advanced-Flow Reactors versus Batch Reactors

Corning's reactors don't just improve product consistency across multiple scales, they also increase product conversion and selectivity, and produce better yields.[5]

The high selectivity of the processes performed in Corning reactors is driven primarily by the unique design of the fluidic modules, which dramatically improves heat transfer and mass transfer. The narrow residence time distribution (RTD) associated with the continuous nature of this process further increases selectivity by limiting the opportunity for side reactions, promoting plug flow behavior and ease of system clearing, which results in even higher purity output.[6]

100x *Better Mass Transfer**

1000x *Better Heat Transfer**

1000x *Lower Reaction Volume**

50x *Better Residence Time Distribution**

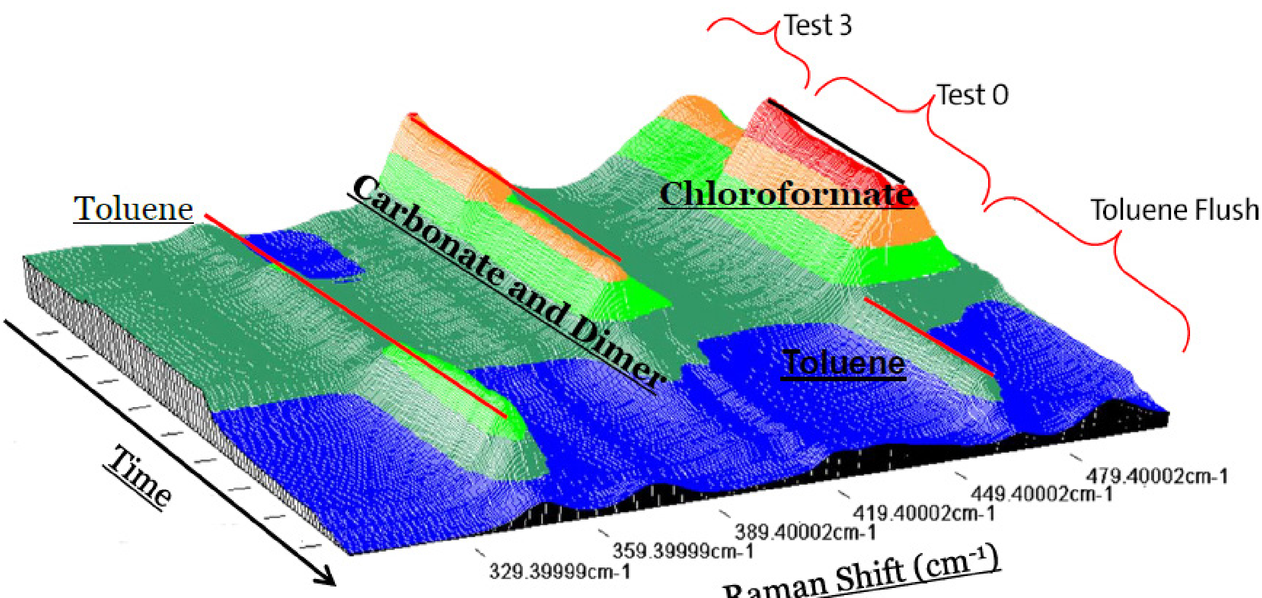
* compared to traditional batch reactors

PROCESS ANALYTICAL TECHNOLOGY (PAT)

Another benefit of the continuous nature of Corning's reactor products is their compatibility with in-line, real-time monitoring and adjustment, which facilitates process automation.

Most manufacturers who use batch methods can only test quality after the completion of the entire process, at which point there is little to no opportunity to adjust or recover a bad batch. The Corning Advanced-Flow Reactor process can be tracked and modified before a large amount of out-of-spec product is produced.[7]

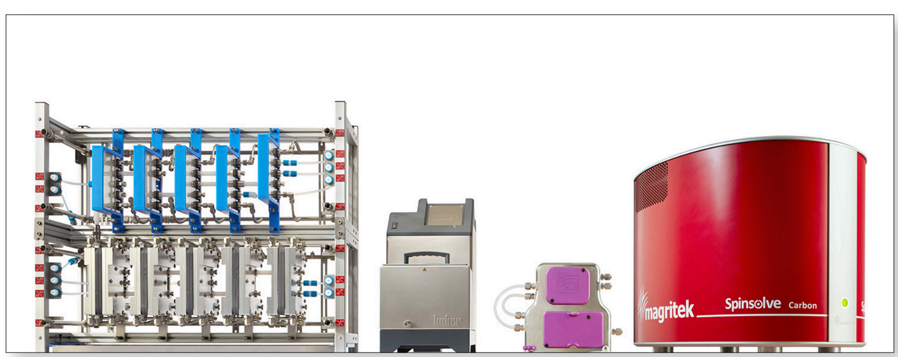
In this two-step reaction below, organic acid chloride first reacts to create organic carbonate. The organic carbonate then reacts with the organic acid chloride to form the dimer, or desired product. This highlights how online analysis enables close monitoring of the process in real time to maximize the formation of the final product while minimizing the remaining intermediate.



Courtesy Center for Process Analytical Chemistry (CPAC)

UPSTREAM & DOWNSTREAM EQUIPMENT

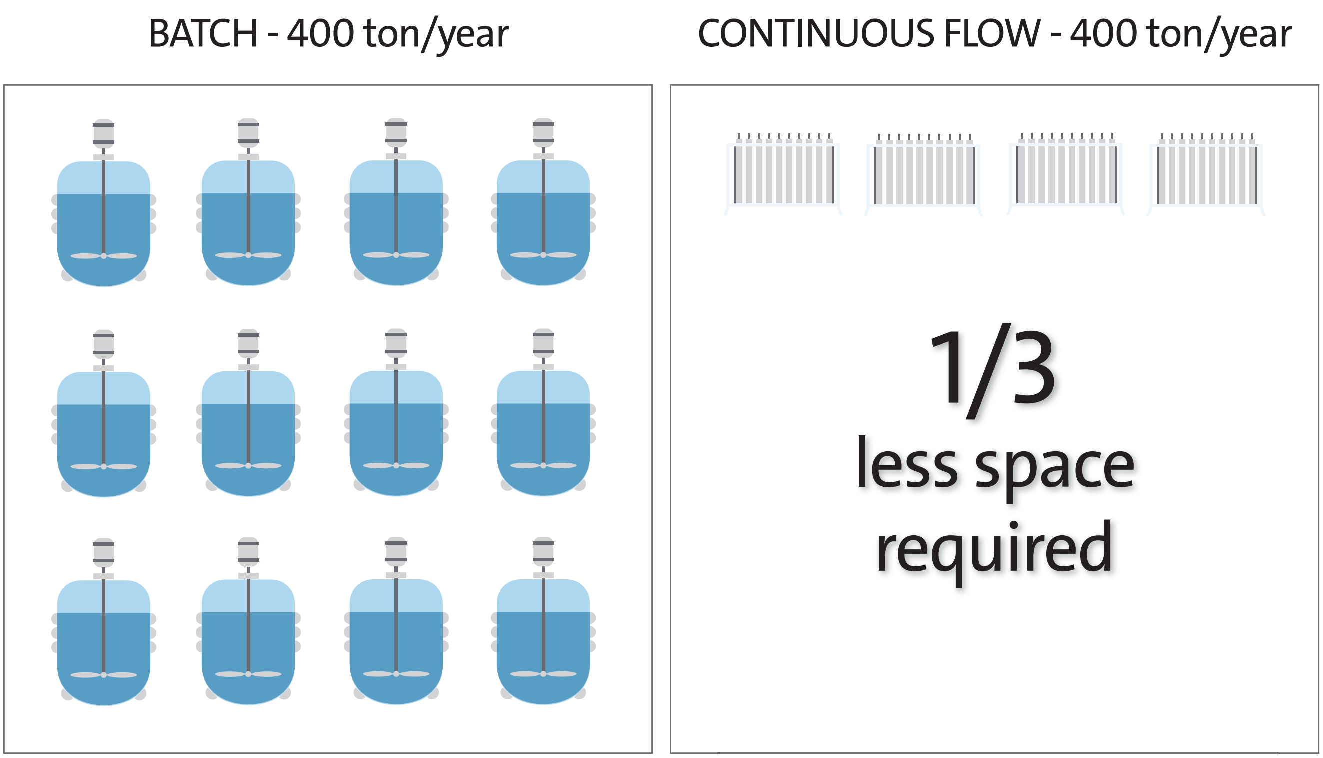
Corning collaborates with other companies to implement inline analytical techniques – sometimes referred to as Process Analytical Technology, or PAT – and also works with auxiliary equipment suppliers to help customers pair material dosing lines (e.g., pumps, flow meters) and temperature controllers (e.g., chillers, heat exchangers) with the correct Corning Advanced-Flow Reactor model.



3. LOWER OPEX AND CAPEX

Higher yields resulting from more consistent, higher purity output are just one of many ways in which Corning's reactors can reduce OPEX (operating expense) for manufacturers who currently use batch reactors. For example, thanks to their high coefficients of heat and mass transfer, Corning's reactor products can accommodate more concentrated reactions, which enables reduced reaction time – in some cases, from 10 hours to less than 10 seconds – and decreases the volume of required solvents and/or catalysts (along with the associated line item). By limiting the amount of solvent and producing higher purity output, AFR technology also limits the need for (and expenses related to) certain downstream distillation and purification steps. Overall, the process is more efficient, uses less energy, and reduces cycle times from weeks to days by eliminating time-consuming operations associated with batch processing (e.g., stirring, dosing, reworking, cooling, cleaning, etc.).

Corning's reactors can also lead to lower CAPEX (capital expenditure), particularly in greenfield projects, by massively reducing manufacturing footprint and infrastructure compared to batch processing. The footprint of the system itself is much smaller than that of a conventional batch reactor, and the continuous nature of the process – along with its high yield – can enable a 1000x reduction in material inventory (e.g., solvents and catalysts, unstable intermediates, machinery needed for now-redundant downstream separation processes, etc.), which can in turn reduce overall facility size by 70-90%.



Finally, the superior inertness afforded by Corning's materials reduces maintenance costs and enables much improved product lifetimes compared to both batch reactors and other continuous flow reactors by increasing resistance to corrosion and fouling.

Other potential economic benefits include accelerated development timelines due to seamless scale-up, option value associated with versatile equipment, and reduced investment risk.

4. REDUCED ENVIRONMENTAL IMPACT

The space-saving, energy-conserving, and waste-reducing benefits of Corning AFR Technology may help companies meet “green” targets by reducing the environmental impact (in terms of energy, waste, land, etc.) of their manufacturing business. The Green Chemistry R&D Act of 2007 reflected a major push by the U.S. and the EU to ensure use of safer and more sustainable products.

Reduction in or elimination of solvent use is a particularly significant environmental benefit associated with Corning’s reactor products.

HIGH PRIORITY USE CASES

Because of its superior safety characteristics, Corning AFR Technology is particularly suitable for reactions that:

- ***Involve unstable intermediates/products*** (e.g., peracids, chloramines, etc.) ***or toxic materials*** (e.g., cyanides, phosgene, etc.)
- ***Are rapid and highly exothermic*** (e.g., oxidation, nitration, acid-base, etc.) ***and/or have runaway hazards*** (e.g., cycloaddition, transposition, nitration, etc.)

Corning AFR Technology is also well suited for reactions where conditions related to process exothermicity, concentrations, mixing, etc., make batch processing difficult or impossible; where mass transfer is limiting (e.g., non-homogenous liquid-liquid, gas-liquid, gas-liquid-solid); and/or where residence time distribution has a direct impact on final quality (e.g., nanoparticles, microparticles, high-grade and technical polymers, etc.)

SUCCESSFUL INDUSTRIAL INSTALLATIONS OF CORNING AFR TECHNOLOGY

Over the last three years, there has been a significant increase in the number of Corning Advanced-Flow Reactor installations for large-scale chemical manufacturing in China, which is the leading global market for flow reactor application technologies. By the end of 2019, the Corning AFR team had successfully designed and installed four projects each with more than 10,000 metric tons annual throughput. In fact, one of these installations has maintained steady operations since August 2017, and demonstrated consistent high quality product output with minimal maintenance required, resulting in significant profit for the company while also helping to reduce their environmental impact.

BARRIERS TO ADOPTION

Despite numerous successful applications, some manufacturers have been reluctant to apply Corning AFR Technology to their processes. Hesitancy is understandable. Process engineering groups are highly familiar with their (often fully depreciated) batch operations and do not want to risk their reputation or manufacturing operation on a new technology to which they are not accustomed.

However, Corning's AFR sales and support teams are committed to providing expert application development support and ongoing maintenance services to ensure a smooth transition from batch processing to inherently safer, more cost-efficient, and more durable continuous flow processing.

Photo courtesy Angelini Pharma Inc.

All Corning AFR installations are customized to meet specific user requirements, and include three to six months of set-up support to ensure successful deployment of the technology. Knowledgeable technicians are available if customers require maintenance or other assistance post-installation, whether in-person or on the phone.

Corning is not new to the chemical processing industry. We entered the chemical industry through our organic silicon invention that became Dow Corning, which helped build our knowledge base in chemistry and materials science. We leveraged our market access and chemistry know-how to create Corning Advanced-Flow Reactors, which changed and disrupted how the industry thinks about chemical processing. We have been working on this technology since 2002 and have become the market leader in flow reactors. Corning also has a track record of more than 165 years of developing category-defining products that transform industries and enhance people's lives. Customers can feel secure knowing that Corning is committed to this product and its application services.

Corning's reactors are far more flexible than conventional batch reactors and can be configured to accommodate an estimated 30-50% of currently practiced batch processes.

Most of the non-addressable processes involve solids, which pose challenges for all continuous flow processes, including Corning AFR Technology. However, many customers have learned to manipulate the solubility parameters of their solvent systems to eliminate the formation of precipitates altogether, while others have modified reaction conditions to accommodate particle formation or catalyst use. Generally speaking, Corning AFR products can process particles up to ~200 microns in diameter and has demonstrated success in applications such as catalytic hydrogenation with Pd/Carbon powder catalyst from the lab to commercial production.

While continuous flow processing offers clear OPEX improvements over batch processing, the existence of excess and/or fully depreciated batch capacity for existing production demand may limit the CAPEX advantages associated with converting operations. A detailed ROI examination should be undertaken to determine if the ROI for switching from batch to continuous process meets corporate expectations for capital investments. Corning can assist in these assessments.

The improved efficiency of Corning AFR Technology versus batch reactors sometimes puts pressure on down-stream processing resources, but there are usually engineering solutions that can be covered by the savings from deploying Corning's reactor technologies. Corning collaborates with several engineering firms to help with the integration process for customers in need of assistance.

POSITIVE INDUSTRY TRENDS

There are clear industry trends toward adoption of Corning AFR Technology, particularly in China, the active pharmaceutical intermediates (API) segments, and in many diverse fine, and specialty chemical segments, usually involving the manufacture of unstable, hazardous intermediates.

- Attendance is rising at conferences that are focused on the development and application of continuous flow technology, moving continuous flow technology from a niche market to mainstream chemical engineering.

- The U.S. Department of Energy (DOE) has created an Institute called RAPID (Rapid Advancement in Process Intensification Deployment), whose objective is to double U.S. energy productivity by 2030.[8] Continuous flow processing is expected to play a major role.

- The U.S. Food and Drug Administration (FDA) recently published guidance on quality considerations for continuous manufacturing of small molecule, solid oral drug products regulated by the Center for Drug Evaluation and Research (CDER).[9]

- Many universities are now teaching continuous flow processing as part of their chemical engineering curricula to familiarize young engineering graduates with the technology so that they will be able to help corporations adopt it. Professor Klavs Jensen and his graduate students at MIT have made particularly significant contributions.[10]

- Historically, most of the fundamental continuous flow technology has been developed and adopted in Europe and the U.S., but is beginning to see much more widespread adoption in China.

Corning Advanced-Flow Reactors offer significant advantages over both traditional batch reactors and other continuous flow reactors. Our patented fluidic module design provides vastly improved mixing, very narrow residence time distribution, and superior heat and mass transfer, which in turn enables faster, inherently safer reactions that produce better yields of higher purity output. At a time when industry regulations are tightening, Corning AFR Technology offers an attractive solution for manufacturers concerned with safety and environmental impact, and Corning is committed to working closely with customers to ensure that they see the most value possible from their adoption of this breakthrough technology.

To learn more, visit:
www.corning.com/reactors

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