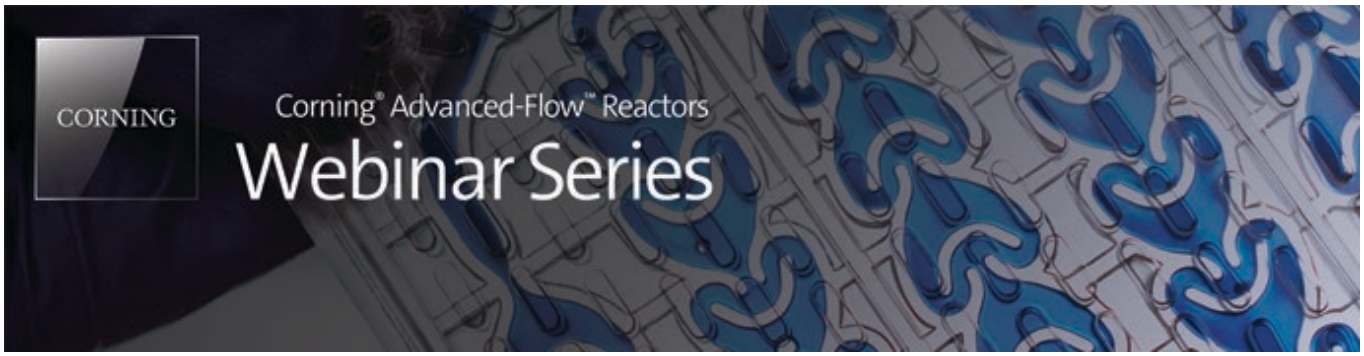
Webinar 1: "Stepping into Corning® Advanced-Flow™ Reactor Technology: An Industrial Overview"
Session 1: Tuesday, Dec. 1 – 10am Central European Time
Session 2: Thursday, Dec. 3 – 11am Eastern Standard Time



Questions & Answers

Q1: Could you state pressure and temperature limitations of the reactors?

A: Max pressure is 18 bar and temperature -60°C – +200°C

Q2: Can you explain, again, the reactor model? I mean, the heat exchanges and reactor working?

A: The reactor has a three layer sandwich design. Two layers of heat exchanger liquids run around the reaction pathway, ensuring excellent heat exchange control. In the middle layer, the reagent solution runs in the HEART-shaped channel, benefitting from the excellent mixing capabilities of the equipment. Metering Pumps continuously feed the reagents into the reactor.

Q3: Can you comment on possibility to use a single industrial AFR for different processes (multi-purpose use)? It is often said that the main advantage of batch is that it is more multi-purpose vs flow, can you comment?

A: The reactor configuration can be easily modified by the customer, on demand to deliver the most suitable synthetic design. Using basic tools at the laboratory scale, it can still be performed on the industrial scale reactor. Medichem mentioned publicly their use of a Corning G4 reactor for 3 unrelated reactions in their chemical portfolio.

We used to consider batch processing more versatile as we accept as a prerequisite the batch limitations in terms of mixing and heat exchange. And a lot of work has been done over the past years to better understand such limitations and find solutions to overcome them during scale-up. Flow reactors can require more work to be customized to each specific chemistry, but with a real focus on optimizing the chemistry without the usual batch limitations. Just considering the reactor equipment is a too narrow point of view of the question. You need to consider not only the equipment but your process globally to

estimate if the additional work needed for configuring a flow reactor is worth the added value it may provide to your chemistry.

Q4: Any example with polymer chemistry?

A: A high viscosity can quickly become a limitation for the throughput when using flow reactors so the applications in polymer chemistry will be limited to products with low to moderate viscosity, either with short chain length or used in solvents. Flow reactors provide very good control of the reactions conditions, enabling exothermic and multiphase polymerizations with excellent results. In particular, the narrow residence time distribution allows for good control on the chain length. Our flow reactors can also be used for radical polymerizations initiated by various means, like temperature, pH or even light.

Q5: Do you have any viscosity restrictions? We run solution polymers in batch and wish to investigate Continuous Flow.

A: The limitation will come from the combination of viscosity, duration of the reaction and throughput. As a rule of thumb, we consider that applications with viscosities of 50 to 100 cPo can only be run if the reaction time does not exceed a few 10^{th} of seconds.

Q6: How is this flow technology usability in high exothermic reaction which need a high degree of temperature controls?

A: Corning AFR fluidic modules are specifically designed to ensure efficient heat exchange transfer. The two heat exchange layers and the uniform heat exchange fluid distribution of our fluidic modules ensure an accurate temperature control and a uniform temperature distribution, enabling more efficient heat transfer to keep the reaction under control and avoid any thermal runaway. The typical volumetric heat transfer coefficient achieved using AFR technology is in the range of $1MW/m^3.K$.

Q7: Do you have similar photochemistry examples which can be shared?

A: There are several examples of photochemical reactions available in the literature at larger scale. In addition, some of our customers prefer us not to disclose any chemistry detail in the photochemical field. In 2020, two papers from Professor Kappe (OPRD 2020, 24, 10, 2208) and Professor Monbaliu (RCE, 2020,5, 1224) disclose reactions on Corning's G3 Photo Reactor; respectively on a bromination reaction and nanoparticles synthesis.

Q8: How are regulatory agencies responding to flow chemistry in pharma?

A: Regulatory agencies are responding very well. The U.S. Food and Drug Administration (FDA) has been a strong supporter of continuous manufacturing technology for many years. The FDA has already approved a few continuous flow processes, and the latest draft of the guidance document (February 2019) is clearly in favor of it. Also as shown during the webinar, the AIFA (Italian Health agency) has approved Angelini dossier very quickly and without any major comment. Regulatory agencies are ready to provide their support for continuous manufacturing. They should be informed as soon as possible in the regulatory process in order the get the best support from them.

Q9: Was scale up to production also done with biphasic (or more) mixtures so far? What are the challenges compared to miscible fluids?

A: Yes, we have customers that are using a multiphasic system at production scale. Mainly liquid/liquid and a few gas/liquid.

There is no particular challenge compared to miscible fluids. The general rule to follow when scaling up using our technology is to keep the same residence time per plate, ensuring the mixing and heat exchange capacity will remain the same whatever scale is used. When dealing with gas, the challenge will be the design of the auxiliaries and the startup and shut down activities. As it requires a very good understanding and control to avoid any back flush in the gas line.

Q10: You mentioned that multiple G4 units running in parallel at the site in China are running continuously with maintenance approximately every 6 months?

Do you know what process controls they have in place to indicate potential equipment failures? If not, what sort of controls would Corning typically implement?

A: The most critical piece of equipment that requires maintenance is the membrane pump. The lifetime of membranes installed into the pump is about 8000hrs, according to the experience data shared by the vendor. We suggested the customer replace the membrane every 6 months. Some customers are then taking advantage of this system stop to perform maintenance every 6 months, and check the system, in particular the status of the gaskets in the reactor to help avoid potential issues and emergency failures.

Data like pump flow rate, dosing system pressure, and system temperature are recorded in the DCS (Distributed Control System) and the customer can get all the

historical data on a regular basis. Our customers are also using DCS data analysis to make decisions regarding maintenance. The frequency of data analysis and maintenance depends on projects and customers procedures. Normally, the data analysis is applied monthly. Then customers will find some regularity after the system runs for a few months. Corning can assist customers to complete the procedure for maintenance by providing training based on our experience in other projects.

The most critical parameter to follow in a flow installation is the pressure at the pressure side of the pump head as any change of the pressure indicates a change of the system downstream. Quick changes will usually indicate a change in the process conditions, while a slow evolution usually indicates a change on the equipment, like fouling or corrosion.

Q11: Can you comment on why this technology is the today solution for chemical industry?

A: I won't say flow technology is THE solution, but more is A solution. Flow chemistry won't match all chemistries as solids and equilibrium handling remain challenging. But in a wide range of chemical reactions, such as reactions involving highly exothermic steps or hazardous and unstable intermediates, this technology is clearly a solution the industry should take in consideration as it provides clear added value in terms of manufacturing costs, safety, quality, process intensification and process control.

Q12: Is FC consuming more solvents if compared to batch? If yes, has any integrated system been developed to recover and recirculate into the plates?
A:

During development you tend to use more chemicals but mainly because you are going to produce much more samples and data.

In production, from our experience, you will normally use less solvent than in batch for two reasons. You tend to work with higher concentration in flow. Most of the time dilution is used for the exothermicity control and not really for the chemistry itself. As flow technology allows much better control of the temperature, you can push your chemistry to the limit and even sometimes get rid of the solvent.

Also speaking about cleaning, as the flow reactor internal volume is lower than a batch, you will use up to ten times less solvent for the same results.

Additionally, you can use any common industrial system for the solvent recovery and then recirculate it in the reactor. We can imagine a system where you adjust your concentration at the inlet with a solvent feed directly coming from the outlet recovery system.

Q13: Can you help me getting the hydraulic diameter of G1SiC? And heat transfer coefficient for the reactors?

A: The hydraulic diameter of G1 SiC is around 1.1 mm (the values can slightly vary between the different designs and depending on which position in the channel is considered). Corning can provide pressure drop calculation for your specific parameters.

Corning Advanced-Flow Reactors have a volumetric heat exchange coefficient in the range of 1 $MW/m^3.K$ for each fluidic module. The fluidic modules were designed to keep comparable heat exchange performance for all scales.

Q14: What are the main difficulties encountered during the scale-up?

A: Typically, a scale-up entails a larger piece of equipment. Traditionally, the surface to volume ratio changes, impacting the heat exchange transfer capability of the system. The mixing properties tend to be strongly impacted as well. Corning reactors have been designed to keep both parameters identical across all reactors, ensuring a fast-pace scale-up process. In the scale-up phase, some parameters can be slightly tuned, but typically they do not involve a new optimization, hence a swift scale-up.

Q15: How is gas generation in a reaction handled? Is the gas removed in any way or it simply will increase the total pressure, thus limiting the equipment?

A: As a flow reactor is a close system, you will need to reach an outlet to allow the gas to be removed. For that you have various possibilities, like using a gas/liquid separation device to keep everything continuous or to use a more simple system like collecting in a batch and letting the gas be released.

This can be more challenging than injecting a gas as the gas released will occupy space inside the reactor and lower the global residence time. This will not have a direct impact on the pressure as you can better control it with a flow reactor, but in another way, this still have a risk of limiting the use of it. Mainly, if the kinetic is not fast enough compared to the residence time available with the gas.

Still one advantage of dealing with gas release in flow is the limited volume compared to a batch process and avoiding its accumulation. Even if collected at the outlet, it is easier to dilute and flush it compared with conventional technology.

Q16: Can we combine this technology with other technologies in a plant?

A: Yes, flow reactors are one piece of equipment among many others that are necessary to perform a chemical synthesis. They can easily be combined with a batch vessel to perform an additional chemical step, with plug flow reactors, heat exchangers or CSTR (Continuous Stirred Tank Reactors) to extend the residence time, or with any continuous separation steps that are already a standard in the industry. Care has to been taken during the engineering phase to ensure that all equipment is designed according to the same flow parameters and that the interfaces are well defined.

Q17: Can we do heterogeneous reactions in AFR?

A: Traditionally, heterogeneous reactions can either mean gas/liquid or liquid/solid reaction. The first case benefits from Corning's high mixing capability. On the other hand, dealing with solids depends on many parameters, including the size of the solid. This is reaction dependent although the main trend is that these types of reactions may not be the best for flow reactors if solids tends to be big, concentrated or eager to aggregate.

Q18: How many different raw materials can be fed into one reactor system?

A: In principle, as many as you want. Each fluidic module could be a mixing one and so having two inlets. Meaning you can add one more inlet for each fluidic module of the reactor configuration. In other words, for a 10 fluidic modules reactor, you could have up to 11 inlets.

But the idea is to try to lower this number as much as possible. As for each inlet this means one solution delivery system. This increases cost and risk of failure.

Q19: Can you please share any published articles in journals, about the design and working of corning AFR?

A: You can find a list of AFR-related publications on our website (https://www.corning.com/media/worldwide/Innovation/documents/AFR/AFR%20Publications%20Nov.%202020_v2.pdf). The first part of our publication list is dedicated to the design and characterization of our technology.

Q20: How does the pressure drop with these reactors compare with a plug flow reactor?

A: If by a plug flow reactor we refer to tubing, the Corning reactor will present a higher pressure drop. This is related to the internal design of a plate that ensures not only plug flow but also a very good mixing. Pressure drop calculations can be provided for your specific application.

Q21: Does Corning plan to increase its expertise to develop electrochemistry reactors such as you did for photochemistry?

A: For the time being, no such expansion is envisioned. We are always happy to discuss with customers about specific challenges and see how to address them. Do not hesitate to contact us at reactors@corning.com.

Q22: Is there a leading motivation for adopting flow (i.e. safety vs. seamless scale-up etc.) or all of them are equally important?

A: All motivations are important and strongly depend on the process and the market where it is applied. A main focus is the inherent safety and scalability of dangerous reactions on the industrial scale, but pharma tends to focus more on increasing quality and efficiency as product costs are higher. This depends on the process involved. In addition, once the technology is present, its multi-purpose ability can be used for other projects based on other motivations.

Q23: How about the Capital Investment compared to batch?

A: Initial investment at lab scale is usually higher than with batch as it require more equipment. From our customers' experiences, at production scale you will usually get an average 30% saving compared to batch.

This savings is really linked to the process and where the technology brings value. Cost savings can come from many different point as reducing safety cost, avoiding separation or purification steps, reducing waste and a high level of automation.

Q24: In the examples mentioned, what type of online analysis was used to control the process?

A: In the examples most of the analytical work was still done offline as dedicated equipment and setup is required for online analysis. Optical analytical methods (Raman, IR, UV, Vis, …) are easy to implement in flow using an appropriate flow cell. Numerous

examples have been published and equipment is available from different suppliers. Work up free analytical methods, where samples are directly injected into an instrument without further treatment, but results will come with a delay, can also be used in combination with a sampler. This gives access to the traditional methods like HPLC, UHPLC, GC. A new generation of benchtop NMR are gaining in popularity and are also suitable for use in line with a flow reactor. There are a variety of solutions but all have their limitations and sometimes they need to be combined with separation steps. By-phasic streams, in particular are often a challenge for the analytical equipment. Qualitative analytics is very easy online while quantitative analytic requires a lot of work on calibration.

Q25: Is the high mixing really needed for a solution reaction beyond the initial addition of reactants?

A: This is again process dependent. For multiphase reactions the continuous mixing dramatically increases the mass transfer and the overall kinetic of the reaction. Homogenous reaction rates depend on intrinsic properties (activation energy…) and the ability for molecules to meet each other. The latter parameter is influenced by the high mixing and it helps to ensure a fast reactivity. In addition, a high mixing can allow a better and more even energy heat transfer distribution.

A number of reactions are instantaneous, such as many acidic-basic reactions, so they do not need such high mixing in itself, but this will help in the temperature control.

We also have customers cases, such as the G5 example (https://www.corning.com/worldwide/en/about-us/news-events/corning-advances-flow-reactor-technology-for-industrial-chemical-production.html) which use our technology for the initial mixing and then switch to a tubular reactor to provide enough residence time with lower pressure drop. Hybrid solutions should be considered when needed.

Q26: What are the most important reactor features/aspects to ensure successful seamless scale-up?

A: The most important thing is to have the same residence time per plate in order to keep the same mixing and heat exchange capacity at larger scale. If the residence time per plate of a lab scale reactor was 10 seconds, then the flow rate in a production scale reactor should also be 10 seconds per plate. Additionally, one has to ensure working at the steady state where the conditions are reproducible. This means steady conditions (pressure, flowrate, etc.…). Once these parameters are established and checked, scale-up is no issue.

Additionally, it is important to work in the reactors specifications to ensure seamless scale-up (plug flow system so within the specified flowrate range).

Q27: Can we use flow chemistry for herbal extracts or natural products?

A: The high mixing and energy could be envisioned to extract a molecule from one phase to another. Our reactor was used to extract minerals from asteroids: https://linkinghub.elsevier.com/retrieve/pii/S0009250920303067). The only requirement entails either a liquid extract or very thin particles which do not aggregate in the reactor.

Q28: How has pressure drop been taken care at scale? As at scale up flow rates are high, do we need high pressure pumps?

A: The reactors have been designed so that the fluidic modules have the same behavior at all scales (including the industrial scale) and the same maximum pressure limitation of 18 bar. Therefore, the pumps that are needed for any scale should be in this range of pressure.

Q29: Are there any studies on how density of process fluids, specifically high-density fluids, affect Corning reactor performance (conversion, heat transfer efficiency, etc.)?

A: Few studies have addressed this topic from an experimental point of view. Among the most recent is the following describing the flow pattern and mass transfer observed when using two none miscible high viscosity, high density liquids:

https://linkinghub.elsevier.com/retrieve/pii/S0009250920303067

The heat transfer will be impacted by the different flow regime but only an experimental study conducted with the specific liquids will allow to quantify the heat transfer efficiency.

Q30: What are the usual residence times applied in your reactors?

A: Residence time varies significantly. The reactors are best for fast reactions (seconds) and up to a few minutes (maximum 10 minutes). The actual limiting factors limiting the addition of extra module fluidic is the pressure drop. Reactions in viscous media are more limited in term of residence time. An alternate solution when reactions are too high, is to use a "hybrid solution". In such cases Corning reactors are used to ensure a high control during the initial mixing phase, then tubular reactors are added to provide higher residence time with lower pressure drop.

Q31: Flow is enabling, but any sense of the minimum value of a product that will justify the capital costs vs existing batch reactors?

A: The cost of investment has to be taken into account as well as the product. It depends if the process intensification can save solvent or reagent, smoothen conditions, simplify the extraction, have a better impurity profile, and/or speed up scale-up process. In addition, reactors are versatile so can be multi-purpose and help handle processes safely. The quantity to produce is also an important factor to consider as the higher the quantity, the lower the value of the product needs to be. At large scale, even low savings generate enough return in cash for the Capex. Good examples can be found in the bulk, fine and specialty chemistry industry where a lot of low value products are manufactured at large scale in flow. All of this has to be taken into account to estimate the investment. Some customers have their return on investment within an average of 1.5 years, and not all of them work in pharma.

Q32: If reaction is completed with flow chemistry, even after that workup process will we still need batch setup?

A: Batch and flow are just different tools. Some processes are less suitable for flow (e.g. solid handling) while others are less suitable for batch (hazardous, mixing and temperature sensitive, highly exothermic processes). Both technologies can complement each other or even be used together (most of the exotherm released in a flow reactor and the end of the conversion being performed in a batch for longer).

Very nice example of fully end-to-end continuous process are available (GSK, MIT-Novartis consortium, etc.) but we saw also a lot of customers using flow chemistry only when it's required and doing the other steps with conventional batch reactor.

Q33: What methodology can be used to determine the footprint improvement of flow chemistry?

A: Public examples show a clear earning in the footprint use compare to batch (see Eli Lilly's public communication). We don't have specific methodology to evaluate the footprint improvement as this is strongly linked to the final process. But to still provide some guideline and basic information, a flow reactor is usually less than 1m² for production capacity up to about 1mT/h of solution. Then dosing lines to feed your system is also about 1m² footprint and you may need 2 to 5 (average is around 3). Obviously you also need the feeding tank and a collecting vessel, but those are generally already installed in the plant.

An example on the impact on a nitration plant economics, including footprint, can be found here:

https://depts.washington.edu/cpac/Activities/Meetings/Satellite/2011/Presentations/Monday/3%20-%20Sergio%20-%20Corning%20-%20CPAC%20Rome%202011.pdf

Q34: Do you have method to detect (anticipate) fouling issue from the lab scale?

A: Fouling tends to occur if the system is not at a real steady state, where something more than the desired reaction occurs. In this case, usually, it is possible to detect it early by monitoring the pressure and notice slow but steady variations. Otherwise, temperature or product quality change can help it. Lab scale equipment, because of their smaller dimensions, are more sensitive to fouling so potential fouling issues will be seen very quickly during lab trials as a pressure increase will occur sooner in the small channels, allowing to directly identify process conditions limiting when not completely avoiding such issues at production scale.

Q35: If I have additional technical questions about your units, who can I contact?

A: Yes, of course, our technical teams of Application Engineers or our sales teams will be more than happy to discuss with you. If you want to discuss a specific process, we can also protect it via NDA. Any questions can be sent to reactors@corning.com.

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