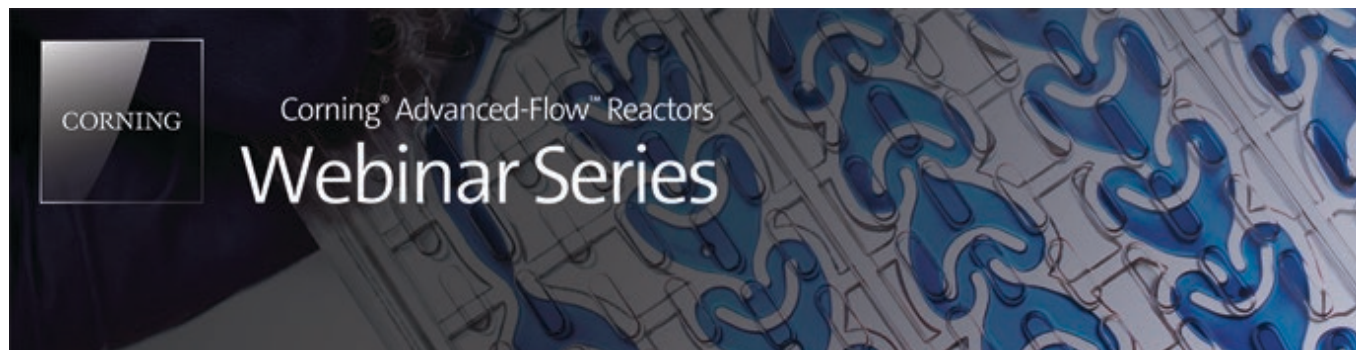


Webinar 2: “Stepping into Corning® Advanced-Flow™ Reactor Technology: How to Analyze Your Batch Process Data to Transition from Batch to Flow”

Session 1: Tuesday, Dec. 8 – 11am Eastern Standard Time

Session 2: Thursday, Dec. 10 – 10am Central European Time



Questions & Answers

Q1: Are such findings (order of adding reagents, premixing etc.) accidental or is there a good way to see in which case such clever combinations could be beneficial?

A: There is always serendipity in research. However, a quick analysis beforehand could be helpful. You have to:

- a) capitalize on chemical knowledge to first assess combination; and
- b) check the stability of your feeds, make a mixing reagent combination in a small batch and analyze them overtime (hours/days) and compare the analysis results with dissociated samples

Q2: How often is it necessary to perform design of experiments (DoE) for optimization in flow?

A: Performing DoE in flow is much easier than in batch because you can generate data faster. In a good day of work you can probably go up to 30 different sets of parameters, which could mean completion of a DoE within a week. Other factors such as performing your tests in a planned and smart way can also help minimize the time spend in the lab, the amount of samples to analyze, and the consumption of starting material.

Q3: Nice talk. I was doing the experiment in the same manner as you have explained; however, we encountered a clogging problem during the reaction in the first step. Did you observe the same kind of problem? If so, how did you overcome?

A: If the first step involves diazonium, it can precipitate. A good hint in the paper is when the use of mechanical stirrer is mentioned. In this case, the idea is to do the reaction as diluted as possible and see the behavior. A high dilution saves material and can help focus on the reactivity first. In addition, it is very important as well to monitor the pressure over time. After the diluted system has been optimized, working at higher temperature or concentration can be investigated.

Also, we have observed the order of addition can be important to avoid clogging as some of the feeds are not compatible. Additionally, the control of pH may also be critical in this step.

Q4: Thanks for the presentation, very helpful. I appreciate your feedback and experience regarding aqueous work-ups (with phase separation) when there are some particles in the media. Are membrane separators suitable?

A: The use of membranes will depend on the type of solid and on its behavior toward the membrane. The phase could be kept with the solids and the other phase will go through the membrane to avoid clogging the membrane itself. In such case, the solid should not have any affinity toward the membrane, which avoids accumulation that could clog the membrane. We suggest contacting Zaiput Technologies (support@zaiput.com), the manufacturer of membrane separators. They are a great resource to provide answers on this topic.

Q5: In brief...based on any existing batch reaction, what could be the quick way to identify if it is the candidate for flow reaction?

A: Flow chemistry is usually suitable for fast, exothermic and/or hazardous reactions going from seconds up to a few minutes that do not involve solids (at any stage). Solids can sometimes be used in flow, but some other parameters have to be considered.

Our next webinar will give general advice and hints that will help you decide if flow chemistry is a good fit for your process. Visit our website, www.corning.com/AFRwebinars to learn more and register.

Q6: Can a so-called slow reaction > 600s be converted to < 600 secs by enhanced mixing/heat transfer in flow reactor?

A: In many cases, when talking about slow reaction in batch, we include in the reaction residence time – not only the reaction kinetics but also the time needed for the mixing of the reactant and for the heat removal. In batch, it is not uncommon to have a residence time of hours because one of the reactants is slowly added in order to efficiently remove

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the heat and to avoid a runaway reaction. In flow, you will be able to optimize the heat transfer and the mixing of the reactants, and the global process residence time will be mainly related to the reaction kinetics. You will also be able to minimize the kinetics time by working at a higher temperature (up to 200°C) and higher concentration, which can be easier to control in flow than in batch. The chemistry itself can be evaluated for possible use of more active reagents, as they may be easier to control in flow.

Q7: How do you use flow chemistry to scale up to kg scale or tons scale? Does it require high flow rate and high concentration? Is that a good way to follow?

A: To scale up a process in flow, the optimized, and already intensified process conditions (e.g., temperature, concentrations, ratios, reaction time, heat exchange capacity, mixing quality, etc.) need to be maintained constant while increasing the throughput. This can be achieved by increasing the volume of the reactor by the same factor as the throughput (a 100 times higher throughput requires a 100 times larger reactor to maintain the same residence time). To achieve continuous production capacities of kilograms per week a throughput of around 10 ml/min is needed (10 ml/min times 1 440 min per day = 14,4L per day). With 10 L/min running 7 000h per year, capacities of up to 4 200 T/y may be achieved.

For additional information on our seamless scale-up approach to maintain critical processing parameters constant whatever the scale, we will hold a dedicated Webinar in March. Visit our website at www.corning.com/AFRwebinars to learn more and register.

Q8: How fast is development in flow compared to batch?

A: Our reactors adjust quickly from lab to large scale processes because, once the process is optimized at lab scale, the reaction conditions are unlikely to change at production scale. The scale up is carried out by increasing the reactor volume, or the number of reactors used in parallel, and does not require additional process development, except for some minor adjustments, as the heat and mass transfer performance are consistent throughout all the development stages.

This results in a general much shorter process development time as compared to typical batch process development.

Moreover, Corning® Advanced-Flow™ Reactor (AFR) technology offers high flexibility in terms of reactor configuration at lab/pilot scale, that several process conditions can be tested quickly and easily in a development campaign. This shortens the duration of the process feasibility phase.

Q9: Any advice for switching from batch to flow for long reactions (5h) and low stability of the product?

A: Flow chemistry is usually suitable for fast reactions going from seconds up to a few minutes. It is important to understand why your reaction is slow in batch. For example, is the slow reaction related to the kinetics or the overall process that includes also the mixing of the reactants and the heat transfer or to the kinetics? In flow reactions, mixing and heat transfer can be optimized and thus the reaction time will be given by the kinetics. If a reaction is slow due to long time needed for a good mixing or for heat transfer, flow reactions can decrease the time needed for the reaction. If the kinetics is slow, the reaction can be accelerated by increasing the temperature and the concentration. With kinetics data, the reaction speed at different temperatures can be calculated.

Low stability products are easier to control in flow due to improved temperature control and the use of a chemical quench.

Q10: Do you recommend multiple phase reactions to be performed in continuous mode? How do you increase required turbulence and facilitate mass transfer in the best way?

A: Yes, a continuous mode system with high mixing is usually superior to a batch system. The ability to work under pressure and with a high heat exchange can allow reactions to perform more smoothly. The turbulence is increased by adding static mixers in the system. Corning uses its patented HEART-shape design in its systems to enable a state-of-the-art mixing capability and help the system make the most of the reactivity.

Many examples exist of multiphase system (liq/liq, liq/gas and even liq/gas/sol) which greatly benefit from flow technology. To give you a sense of how our mixer performed, you can check related articles available on our website

(<https://www.corning.com/worldwide/en/innovation/corning-emerging-innovations/advanced-flow-reactors.html>).

Q11: How to calculate the retention time to know complete reaction? Is that try and error testing?

A: By knowing the flowrate from the pumps and the volume of the reactor, the residence time can be measured (with some calculation). With gas (vanishing or being formed), it is slightly different as the gas volume varies over time, in which case approximations have to be carried out and such approximations can influence the system.

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Trial and error can be used to reach the right residence time, but DoE (Design of Experiment) or AI-assisted chemistry could also provide some improved estimation and thus reduce the number of experiments to be run. One of the most reliable methods includes performing a study on the kinetics of the reaction to get robust data and a model of the process that ideally includes intensified process conditions like higher temperatures and concentrations. Traditional tools like the RC1 from Mettler Toledo generate data that can be easily used in flow to make a first assessment on the needed residence time.

Q12: What about chemistry with equilibrium? How do you deal with that sort of issue where you can't remove waters continuously as the system is closed?

A: This challenge can be addressed in two ways. By adding separation steps into the reaction path, thus removing stepwise one of the products, or knowing the thermodynamic of the equilibrium and making use of the extended process window available through flow chemistry to work at process conditions (high temperature and pressure) where the equilibrium will be pushed towards full conversion even without removing one of the components. Both solutions are not necessarily straight forward and chemical reactions with equilibrium remain a challenge in flow chemistry, requiring some special attention and expertise.

An interesting example describing such an approach was published a few years ago:
<https://doi.org/10.1016/j.biortech.2011.07.007>

Q13: Could you comment what is the potential to automate chemistry with Corning? E.g. can your devices be easily integrated with other flow equipment?

A: Flow reactors are ideally suited for automation because of the ease of sensor and control element integration. Our engineering department is able to provide modular turn-key installations on request. Flow reactors can easily be combined with a batch vessel and/or other equipment 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. Additionally, a wide range of suitable Process Analytical Technology (PAT) tools are already available from different suppliers. Care has to be 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.

Customers are already using our G5 technology (<https://www.corning.com/worldwide/en/about-us/news-events/corning-advances-flow-reactor-technology-for-industrial-chemical-production.html>) in an automated plant for initial mixing followed by other equipment and then switch to a tubular reactor to provide

enough residence time with lower pressure drop. Hybrid solutions can also be considered when needed.

Q14: Do you have any tips to identify catalyst induction issue before transferring into flow chemistry? (that cannot be detected in batch reactor?)

A: Usually catalyst induction can be deducted from the batch protocol. It can be the reason why a reaction runs for many hours. In this case, kinetic studies are the way to find this out. On the other hand, a number of catalysts can be activated in flow easily by heating them at high temperature (or adding an activator) before the now active catalyst is mixed with the substrate. There are cases with Pd being activated for a Hydrogenation reaction.

Q15: Does AFR use a CSTR or PFR reactor model?

A: The global hydrodynamic behavior of chemical reactors is often characterized by the Residence Time Distribution (RTD). RTD corresponds to the time necessary for different elements of fluid to pass through the reactor and determines if the reactor behavior is close to a perfect stirred tank or to a plug flow reactor. Corning Advanced-Flow Reactors were characterized by the RTD method and it was shown that for the recommended flowrate the behavior is of plug flow type.

Q16: Is it possible to control polymer molecular weight using a flow system? Is there an online device to measure molecular weight of obtained polymer?

A: Yes, it is possible to improve control of polymer molecular weight using flow chemistry. As the reaction conditions and exact ratio of species are more precisely controlled, polymer chains can grow more accurately. In particular, the plug flow behavior and narrow residence time distribution allow good control on the chain length.

PAT like Raman, FTIR spectroscopy or light scattering detectors can be integrated in-line using a suitable flow cell to follow the polymerization. Other technologies like automated sampling coupled with traditional offline analysis can also be used to monitor the molecular weight of the obtained polymer.

Q17: What is thermal quench?

A: Thermal quench basically relies on cooling down the whole reactive stream to such a low temperature that it essentially stops the reaction. This can either deactivate the catalyst or the reaction. On the other hand, it may not necessarily stop the reaction, just

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slow it. Therefore, control of the sample conditions has to make sure the reaction does not start again.

Q18: How do you manage to pump slurry?

A: Pumping a slurry requires adequate pumps that are designed for the application. Additional considerations include the slurry concentration and solvent nature, which each or both can have a strong impact on pump performance.

Working with slurry requires a good system, and proficiency at controlling the conditions. Initial mixing of the starting solution is important as well.

Q19: How do you correlate retention time from Batch to Flow?

A: Reaction time in batch is always a combination from multiple factors. Where in flow it is mainly the pure expression of the kinetic.

A good question to have in mind is: why do we have such reaction time in batch? For example, is it because of the long addition of one of the reagents? Is it because of a slow addition to manage heat release? Or maybe, it is due to bad mass transfer behavior? As most of those parameters will be better handled in flow, residence time (reaction time in flow) will be mainly linked to the kinetics of the reaction.

If it is not possible to correlate directly reaction time to residence time, literature examples could provide guidance.

Q20: How do you manage to do reactions where gas generates?

A: As a flow reactor is a closed system, an outlet may be required to allow the gas to be removed. Examples of outlets include a gas/liquid separation device to keep everything continuous or a simpler system like collecting in a batch and letting the gas be released.

Gas release 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 should not have a direct impact on the pressure as a flow reactor can provide better control of pressure; however, , the relationship between residence time and kinetics should be considered. For example, the kinetics may not be fast enough compared to the residence time available with the gas.

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.

Q21: What about reactions where gases are evolved (like CO₂)? Is there any restriction on the application of this reactions to Flow Chemistry?

A: See answer to the previous question for reference. Addressing gas generation is achievable despite challenges. The main challenge may be due to the kinetics of the reaction. If it is too low, it will be difficult to simultaneously maintain a high mixing and a long residence time.

Q22: How can we calculate the pressure drop from pump to output so that we can get the exact residence time and desired flow rate?

A: Corning reactors have been characterized and pressure drop can be estimated for the different type of fluidic modules. When only liquids are used, residence time can be easily calculated from the total flow rate and internal volume of the reactor.

For Gas/Liquid applications, the installation of a back pressure regulator at the reactor output to increase the global pressure of the system is highly recommended in order to increase the residence time, as the real gas flow rate is pressure and temperature dependent.

However, various phenomena make this residence time difficult to estimate: the gas may be consumed if it's a reactant, pressure gradient along the reactor, vaporization phenomenon, sliding factor between gas and liquid phase. Thus, another way to estimate residence time could be the apparent residence time, considering only the liquid flow rate.

Q23: Can you share examples which have scaled up economically using flow chemistry?

A: Such examples have been shared during our Webinar #1 Stepping into Corning® Advanced-Flow™ Reactor Technology: An Industrial Overview. The recording is available on our website.

Q24: It is interesting to mention that we are not wizards. For some people flow still looks like magic, can you share why it is not?

A: Flow Chemistry is a different approach to the same goal, that can help improve, sometimes dramatically, the reaction results. Any reaction has two factors: chemical kinetics (Activation Energy, Enthalpy...) and physical kinetics (mixing, heat exchange). All remain valid but the latter can be improved using flow chemistry tools.

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Q25: You have mentioned that old chemistry can be still done, how to look at literature with a flow approach?

A: Once a reaction is identified, check it has been done in flow. If not, the first thing is to check if the reaction involves solid at any stage (starting material, product, intermediate). Then, check the conditions are compatible with the equipment (pressure/temperature, etc.). Then, ideally check for kinetic data (reaction time, energy) to check if it sounds possible. Finally, I would recommend a quick test with tubing and a T-connector. This will help give a first insight.

Q26: Do you have any viscosity restrictions? How do you manage viscosity in the transition to flow?

A: The limitation will come from the combination of viscosity, duration of the reaction and throughput. As a rule of thumb, applications with viscosities of 50 to 100 cPo can be run if the reaction time does not exceed a few 10th of seconds. Working with solvents and higher temperatures may help to mitigate the problem.

A high viscosity can 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 improved control of the reactions conditions, enabling exothermic and multiphase polymerizations with excellent results. In particular, the narrow residence time distribution allows for improved control on the chain length. Corning’s flow reactors can also be used for radical polymerizations initiated by various means, like temperature, pH or even light.

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