Curiosity, Disillusionment, Persistence, Success

Finally, Flow Chemistry is Establishing as Green, Sustainable and Profitable Process Technology

Around 1995, the path of the microreaction technology platform began when Wolfgang Ehrfeld, then professor and head of the Institute of Microtechnology in Mainz, Germany, was driven by the question: If the topic of „micro" has led to enormous performance increases and innovations in electronics, why should this not be possible in the field of process technologies?

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Segments like pharmaceuticals, fine and specialty chemicals, agrochemicals, and chemical ingredients for consumer care products and food and beverages have emerged as particularly attractive for the application of microreaction technology.

Microreaction technology means channel dimensions in the micro and millimeter range with significantly improved surface-to-volume ratios compared to established process technologies and shorter mixing times. For fast, highly exothermic reactions, there is considerable potential for improving product quality, product yield, raw material and energy requirements, process safety and manufacturing costs and EBIT, with attractive capital payback times.

Advantages of microreaction technology are fast and good mixing and excellent heat transfer performances, enabling higher selectivities and yields while lowering raw material requirements. Besides, the number of by-products and the energy demand for their separation (downstream processing) is reduced. About 70% of energy costs correspond to the separation of by-products. In terms of safety, fast, explosive, and highly exothermic reactions involving toxic substances can be run in much smaller reactor volumes compared to batch reactors.

Developing New Synthesis Pathways

However, micrometer-scale channel dimensions are not suitable for use in production because they are too prone to clogging, do not meet the robustness requirements of a production operation and allow only relatively small throughputs. For production, therefore, a scale-up to the millimeter scale is necessary, which retains the advantages of microtechnology in terms of heat transfer performance and mixing speed. In the scale-up process, the transition of channel geometries from the micrometer to the millimeter scale already takes place in the laboratory. Conversions, yields, process parameters and product qualities determined in this way in laboratory can be transferred directly to conditions in production reactors with same channel geometries. A scale-up step on a pilot scale is no longer necessary, although of course pilot tests with real raw material qualities from production to investigate fouling, cleaning procedures and longtime stability of the process cannot be dispensed with. The integrated scale-up concept leads to a quick scale-up to production.

From our point of view, a few segments have emerged as particularly attractive for the application of microreaction technology: pharmaceuticals, fine and specialty chemicals, agrochemicals, and chemical ingredients for consumer care products and food and beverages.

In many industries in Europe and the US, postponing of innovation is quite common, the pharmaceutical and fine chemicals industries included. However, continuous optimization is and will remain an increasingly important issue for companies in order to keep up with the current pace of technological evolution and to be innovative. Redesign of a chemical process is mandatory for a transfer from a batch to a continuous process. It is probably due to this time effort that people fall back on the original manufacturing method instead of running processes continuously and thus more efficiently, sustainably and safely. Continuous approaches can contribute to developing new optimized synthesis pathways. However, the priority of the pharmaceutical industry is the ontime delivery of life-saving drugs.

Increasing Flexibility and Sustainability

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Active pharmaceutical ingredients (APIs) are usually produced in multistep synthesis processes due to the very often complex structure of the molecules. Take lithiation as a simple two-step example: In a batch process, the addition reaction step proceeds very slowly because the unstable and highly reactive intermediates decompose rapidly. The reaction must be run at extremely low temperatures (-48°C) while the continuous process can be run at room temperature because of the excellent heat exchange, effective mixing and precise control of process. This results in less by-product formation and therefore higher yields, making the process safer and „greener". Besides, energy savings due to avoiding cryogenic conditions make the continuous process highly cost effective.

Additionally, manufacturers are dependent on effective supply chain processes. This has become much more apparent after the outbreak of the Covid pandemic. Critical delays in the supply of raw materials can have a significant impact on projects. Pandemic-related disruptions of transportation links have been a major challenge for many chemical companies. Producing key raw materials instead of sourcing them is becoming more essential for companies and definitely more profitable under companies' perspectives. Microreaction technology can be the key to success right here, as required quantities can be produced selectively and sustainably in a short time with low hold-up and space requirements.

> "Continuous approaches can contribute to developing new optimized synthesis pathways."

Sustainability can be viewed from two sides here, from an environmental perspective and from an economic perspective. The environmental aspect of flow chemistry/microreaction technology combines two factors:

the lower formation of by-products—which leads to higher yields and smaller amounts of raw materials—and the abdication of additional solvents—which do not have to be separated later in cost-intensive steps. Process reliability also plays a major role. The much smaller internal volumes of the micro and millireactors, do not have to be filled or emptied like batch reactors, what prevents the risk of explosions and fires. From an economic point of view, cost savings can be established through improved product quality, raw material savings, reduced space requirements, sustainable plant safety, lower energy consumption, and, in consequence, more favorable CO_2 balances.

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Miprowa production reactor with 154 reaction channels and static mixing inserts.

Making the Transition

Thus, the principles of Green Chemistry can be perfectly met by the application of flow chemistry/microreaction technology. Flow chemistry applications are inherently safer because they require comparably smaller reaction volumes and lower amounts of solvents and chemical substances. The risk of environmental exposure from chemical substances is almost non-existent, and processes can be scaled up easily and quickly without the need for the optimization of reaction conditions.

Considering these advantages suggests the question: why is flow chemistry, and in particular microreaction technology, not already established process technology? The answer is multilayered.

Developing continuous processes requires significant financial investment for most companies. Therefore, direct evidence of the return on investment (ROI) is critical for a company to make the transition. Drivers for moving from batch to flow processes include reducing capital expenditures (CAPEX) and operating expenses (OPEX), as well as significantly increasing process safety and product quality.

Any development cycle consists of the following phases: curiosity, disillusionment, persistence and success. At the very beginning, microreaction technology was known as a „panacea“ for all process engineering problems, whereupon curiosity led to the integration of the technology, which quickly turned into the disillusionment phase. At that time, the technology was still far from being ready to survive, especially in production. New developments take an average of about 30 years to be established in the market. Now, we are in the persistence phase, whereby transition to the success phase has already started in some cases. Given the challenges the pharmaceutical industry is facing—secure material supply, reduce operation cost and increase flexibility, enhance sustainability and safety, innovate and reduce time-to-market—the question regarding the breakthrough of flow chemistry is: if not now, when?

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Flow Chemistry

Key Technology for Sustainable Processes

Continuous Manufacturing (CM)—also called Flow Chemistry or Micro Reaction Technology (MRT)—is a technique that has been gaining global importance over the past decade as a result of improved process control and reduced operating costs, leading to increased manufacturing profits and a competitive edge. Recent years have shown that the reason for a company to change from "batch" to "flow" have been varied, often depending on the sector, process type of interest and scale of operation. Supply chain security and improvements in process sustainability are strong emerging drivers for the adoption of CM.

With the product key, the infrastructure needed varies greatly and depends on the available chemistry, cost of goods, volumes required and the hazard profile of a transformation. The modularity and flexibility of continuous flow set-ups enables the development of small, agile production plants that can be used for the manufacture of multiple products—with easy re-configuration allowing for rapid product changeover.

Following on from this, the ease of replicating these small footprint systems represents an opportunity for manufacturers to develop a process and subsequently deliver production units across multiple countries to serve the local product demands. This is in stark contrast to the current approach of a single large-scale plant, with warehousing used to manage supply chain disruptions.

With all of these benefits, a logical question follows: Why the slow adoption of MRT?

CHEManager asked executives and industry experts to share their views on drivers as well as barriers for the use of flow chemistry and the prospect for this technology in their industry sector. We proposed to discuss the following aspects:

- In your opinion, what are the strongest drivers (success factors) of the implementation of flow chemistry processes?

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- Which barriers are slowing down or impede the implementation of flow chemistry processes?
- What does it need for flow chemistry to be implemented more widely?

Read the insightful answers of the experts on pages 12/13.