Panel Discussion on Flow Chemistry

Commentary article

GIANVITO VILÉ
Group Leader of the Innovation Lab for Sustainable Process Intensification & Professor in Flow Chemistry, Politecnico di Milano

In June 2002, a research article containing for the first time the words "continuous flow chemistry" in the title was submitted and accepted in a peer-reviewed journal. After 18 years, it is now time to look back at the developments and celebrate the success of flow chemistry and continuous manufacturing in bringing industrialization and automation, major drivers in most of the modern branches of industry, into the chemist's dictionary. Flow chemistry is today an established enabling technology that can drastically improve the safety of hazardous chemicals, reducing handling of highly energetic intermediates, enhancing yield, reducing solvent and other raw material inputs, and lessening the environmental impact of a pharmaceutical process. This is key for a sector that has been historically suspected of generating the highest amount of waste and pollution. In particular, flow technology has advanced substantially from library synthesis to manufacturing, and it is not surprising that high temperature/pressure reactions, hazardous chemistries, flash methods involving organometallics, polymerizations, photochemical or electrochemical reactions, and multistep syntheses of APIs can all be accomplished effortlessly. Besides, novel process windows have facilitated the conduction of reactions which could not be traditionally done in batch due to safety concerns. This has widened the IP space and, from the answers of this year panelists, it emerges clearly that this has made possible that 5 drugs approved by the FDA could be manufactured in flow under GMP conditions. Panelists mention that it is difficult to predict whether this trend will continue to increase, but current evidences suggest that there is now a great number of molecules in the pipeline relying on at least one flow chemistry step during manufacture. Some panelists have highlighted that the trend seems to correspond to the increasing number of CMOs and CDMOs supporting today large pharmaceutical companies with efficient and cost-effective continuous processes at commercial scale.

While the field continues to gather importance, it has also started to embrace new technologies. According to this year panelists, machine learning can have a tremendous impact to assist experimentalists in predicting conditions and proposing reaction schemes. Complemented with DoE tools for process development, it can enhance the power of feedback-based optimization and validation methods. In addition, the now widespread use of real-time, non-invasive methods, such as IR and NMR, help triggering commands when parameters go out-of-range, saving significant material of high cost. 3D-printing is now becoming essentially important with regard to rapid prototyping of novel reactor geometries. The outstanding work done by some of the panelists in creating novel 3D-printed photoreactors has shown the true power of additive manufacturing to accelerate the design of reactors with optimal fluid-dynamic characteristics. As correctly stated, such novel technologies can help today improving product and process understanding, based on new scientific evidences, with the overall aim of expanding the use of micro- and millireactors while ensuring a safe drug supply to the consumer and improve manufacturing performance.

At industrial scale, a trend remains in preferring flow chemistry due to the small-scale nature of the systems compared to traditional batch reactors. This seems to change the perspective of producers, since there is no longer a need to build large facilities to accommodate batch vessels. Such reduction of the manufacturing footprint can enable manufacturers to respond on demand to production needs. And, in the age of pandemics, this aspect is key. It is, in fact, dangerous to rely on international trade only, and localized (European) production can become increasingly important to ensure local production facilities. All panelists agree that this can happen only embracing flow chemistry.

An important aspect which has emerged from this year answers concerns sustainability. As policy makers continue to apply pressure towards sustainability, the eventual carbon footprint of processes may well push chemical development in the direction of continuous manufacturing. Flow chemistry can in fact contribute significantly to achieving a zero-waste target.

In this issue we have foreseen a Panel discussion on Flow Chemistry involving some of the most important Key Players in the field. Some of the hot topics discussed: Future perspectives on Drug approvals; Benefits & challenges to implement Machine Learning; Potential for localised manufacturing; zero-waste target; The importance of courses in education.
Enjoy the reading.

Finally, transitioning from batch to flow requires a broad mind-set change. And this can only be done with education. It is, thus, wonderful to see that all panelists have stressed the importance of having "flow chemistry" and "process intensification" courses in the chemistry and chemical engineering curricula. Theoretical and practical trainings on these industrially-relevant topics are fundamental and should be a mandatory part of undergraduate education. In fact, failure to be aware of the opportunities that continuous manufacturing brings, means that those entering the workplace only consider age-old toolbox options. Politecnico di Milano, the Eindhoven University of Technology, the University of Graz are offering already flow chemistry courses; and we expect that this trend will increase in the years to come, as more professors will establish independent groups in academia. By teaching the next generations the skills required to transform batch processes into flow mode can help challenge the status quo, leading to a wider implementation of this unique technology.

ABOUT THE AUTHOR

__Gianvito Vilé__ studied Chemical Engineering at Politecnico di Milano and obtained his PhD at ETH Zurich. From 2016 to 2019, he was a Lab Head at Idorsia Pharmaceuticals, coordinating R&D activities to transform batch pharmaceutical processes into continuous mode. In 2020, he moved back to Italy, accepting a faculty position at Politecnico di Milano funded by Bracco. He is developing novel flow processes to increase the sustainability of the pharmaceutical industry.

Panelists

Franz Amann, Senior Scientist Development and Samuel Bourne Scientific Specialist - **CARBOGEN AMCIS**

Martin Elliott, Chief Commercial Officer - **Centillion Technology Limited**

Charlotte Wiles, CEO - **Chemtrix BV**

Stephen Houldsworth VP, Global Platform Management & Marketing - **CordenPharma International**

Alessandra Vizza, Regional Business Director Corning Reactor Technologies - **Corning**

Hannes Gemoets, Head of R&D - **Creaflow**

Srividya Ramakrishnan, Head - API Process engineering and **Rakeshwar Bandichhor**, Head of Chemistry, API, PR&D - **Dr Reddys**

Anne Kaaden, Head of Marketing and **Joachim Heck**, Managing Director, **Ehrfeld Mikrotechnik**

Timothy Noel, Associate Professor, **Eindhoven University of Technology**

Michael Nonnenmacher, Senior Project Manager, Innovation Management, Business Line Health Care - **Evonik Nutrition & Care GmbH**

Rui Loureiro, Process Chemist Development - **Hovione**

Dirk Kirschneck, Strategic Director, **Microinnova**

Xiong-Wei Ni, FIChemE, FRSC, Founder and CSO - **NiTech® Solutions Ltd**

David Lovett, Managing Director - **Perceptive Engineering**

Johannes Khinast, Professor at University of Graz and CEO / Scientific Director of **Reseach Center - Pharmaceutical Engineering**

Bill Dubay, Global Head of R&D and Olivier Dapremont, Process Technologies AMPAC Fine Chemicals, an **SK pharmteco company**

Mark Muldowney, Head of Technology and Innovation - **Sterling Pharma Solutions**

FRANZ AMANN[1], SAMUEL BOURNE[2]
1. Senior Scientist Development
2. Scientific Specialist
CARBOGEN AMCIS

DO YOU SEE CHALLENGES WITH THE CLEANING VALIDATION OF CERTAIN TYPES OF FLOW REACTORS, FORMULATION AND TABLETING STEPS ETC FOR PHARMA APPLICATIONS?

A general challenge associated with cleaning flow reactors is the limited ability to visually inspect small tubes and other internal structures. Identifying parallel flows or dead spots within fittings and valves is critical and can be considered during the initial design of the reactor. If classical rinsing is insufficient due to the type of deposits or any geometrical complexities then most reactor modules can be easily disassembled to perform an initial gross decontamination; however, this is ideally avoided as it requires additional time and requires specialist knowledge of the equipment.

WHAT ARE YOUR RECOMMENDATIONS FOR THE FURTHER INCLUSION OF FLOW CHEMISTRY IN ACADEMIC CHEMISTRY EDUCATION?

Over the past 15 years there has been a steady increase in flow chemistry related research and a corresponding increase in publications from academia. The use of lab flow chemistry equipment should be part of the practical undergraduate education. Not necessarily in special courses but as one tool within synthetic chemistry. Accordingly, the general theoretical education, especially at the universities, should give some insight to basic concepts of chemical engineering including flow chemistry as an established technique.

THERE CURRENTLY ARE 5 PHARMACEUTICALS APPROVED BY THE FDA WHICH UTILIZE FLOW CHEMISTRY UNDER GMP. HOW MANY NEW API APPROVALS UTILIZING CONTINUOUS PROCESSES DO YOU EXPECT THE NEXT 10 YEARS?

It's difficult to put an exact number on this; although, the evidence suggests that there are now a great number of molecules in the pipeline that rely on at least one flow chemistry step during their manufacture. The trend is clear - as the pharmaceutical industry, particularly CMOs and CDMOs, move towards more efficient and cost-effective processes for commercial manufacture, the number of filings that contain flow chemistry steps will continue to rise.

BENEFITS AND CHALLENGES TO IMPLEMENT MACHINE LEARNING ALGORITHMS WITHIN THE PHARMA INDUSTRY – COMPARISON WITH TRADITIONAL QUALITY BY DESIGN (QBD) METHODOLOGIES

The advent of machine learning is clearly new to many industries and the advantages for the chemical industry are yet to be fully realised. For the time being, QbD and DoE continue to be the most effective tools for process development, optimisation and validation at CARBOGEN AMCIS. However, it is possible to envision more AI based approaches being used across the industry in the near future as relevant applications of the technology are developed and perfected.

HOW DO CONTROL STRATEGIES FOR CONTINUOUS MANUFACTURING DIFFER TO THOSE USED IN BATCH & WHAT OPPORTUNITIES DOES CM BRING?

The control strategy for a continuous process also differs very little from the control strategy of a batch process. The final critical quality attributes of the API must be met and the robustness must be demonstrated using the specified equipment over a series of runs or batches. The greatest advantage of continuous manufacturing is the availability of real-time parameter data and in-line analysis using non-invasive methods such as IR, UV/Vis and NMR. The ability to automatically trigger a divert to waste command if any parameters go out-of-range or in the event of an equipment failure gives ultimate control over the quality of product included in a run or batch. In contrast, an equipment failure during a batch manufacturing process can easily result in the loss of significantly more material at much greater cost.

WHAT ROLE CAN FLOW CHEMISTRY PLAY IN REDUCING THE HEALTH, SAFETY AND ENVIRONMENTAL CONSIDERATIONS OF MANUFACTURING SOME OF THE MOST HAZARDOUS MATERIALS?

Flow chemistry can dramatically improve the safety of hazardous chemicals by means of the make-and-consume principal; whereby the inventory of highly energetic intermediates is reduced by continuously forming then destroying them in the subsequent chemical transformation. Many well suited reactions also benefit from improvements in yield; as a result, energy, solvent and other raw material inputs can be reduced, lessening the environmental impact of the process.

THE ROLE OF FLOW CHEMISTRY IN HELPING COMPANIES ACHIEVE THEIR SUSTAINABILITY OBJECTIVES, PARTICULARLY WITH REGARDS TO CARBON FOOTPRINT.

The pharmaceutical industry is beginning to take small steps towards sustainability but there is still a long road ahead. By improving the efficiency of reactions, flow chemistry techniques can reduce the carbon footprint of a process through reduced raw material and solvent consumption. Intelligently designed continuous processes can reclaim chemical energy and recycle solvents. Such processes already exist but they are rarely, if yet, to be applied to complex pharmaceutical synthesis and have only limited potential for cost saving but bear a certain risk of contamination. As policy makers continue to focus in on sustainability the efficiencies offered up by flow chemistry will make the technology even more attractive.