JEAN-MARIE BASSETT
Chem4Chem. TKS Scientific Advisory Board

The 9th Symposium on Continuous Flow Reactor Technology for Industrial Applications,

November 14-16, 2017 Barcelona, Spain

Following the international tradition of previous symposia, November 2017 saw us this time in Barcelona, the venue being hosted by the University of Barcelona, Faculty of Chemistry. As regular participants already know, Teknoscienze with its journal Chemistry Today has been instrumental in raising the awareness amongst chemists, chemical engineers and development scientists of the benefits of using flow reactor technology in the fine chemicals arena.

Simply said, batch processing technologies developed 150 years ago are being examined in the light of increasing business demands and regulatory pressures for more efficient processes. The results of this examination and the ensuing experimental work form the content of this symposium. We have been taken on a journey that started in Madrid in 2009, passing through Paris, Lake Como, Lisbon, Pisa, Budapest, twice in Delft to end up in Barcelona! A lot has been learnt on the way. The culmination of this journey will be our celebrating the 10th anniversary of this tone-setting conference.

At this 9th Symposium, we were fortunate in attracting a large number of high quality speakers, not only from leading academic establishments, but also from innovation-oriented companies that are discovering the benefits of a flow chemistry approach to making speciality and fine chemicals. We had 31 speakers coming from 11 different countries, reflecting a truly international symposium composed of about 140 delegates drawn from 24 countries world-wide. We were impressed that our symposium attracted delegates from as far away as Japan, S. Korea and Australia on the one hand, and from Argentina and the USA on the other. Irrespective of our speakers' home languages, all gave clear presentations in very good English. Such was the interest from the audience that all speakers needed to field questions, either directly after their talk, or during the breaks over coffee and lunch.

Marking a departure from previous symposia, it was decided to try a new approach to showing practical demonstrations of flow chemistry technology. The availability of an audio-visual link with a specially equipped laboratory permitted everyone to see live demos from the comfort of their auditorium armchair. In this way the crush of a cramped lab space was avoided.

The symposium benefitted strongly from the contribution of Prof C. Oliver Kappe, who kindly agreed to lead the round-table discussion at the end of the third day. A particular focus in this discussion were the demos given by individual commercial enterprises and the posters submitted by academics. Vapourtec, Ehrfeld, Corning, Zaiput and Innosyn were able to demonstrate their increasingly familiar equipment, either in simulation mode, or using live chemical reactions. YPSO-FACTO, pioneering a new software package to simulate and evaluate chemical processes, was able to demonstrate the underlying principles of their new product, and at the same time appeal for beta-testers.

In general lectures offered more references to the increasing collaboration between chemists and chemical engineers in achieving successful process development in flow chemistry. However, despite this there were only sporadic mentions of items from fluid dynamics principles (e.g. Dean Vortices) that govern fluid behaviour in tubular reactors. This is regrettable. Many argued that advances in the use of production-scale flow chemistry depend upon the adoption of physical chemistry and engineering approaches. In this sense, our symposium of "Continuous Flow Reactor Technology for Industrial Applications" needs a conscious reminder that flow reactor technologies are not accidental in their conception. They are the result of an understanding of physics, chemistry, fluids behaviour, materials science to name but a few. It would even be valid to say that pumping (with, for example, a HPLC pump) a reaction mixture through a narrow, coiled PTFE tube is not flow chemistry technology at all. Such an approach can give results fortuitously without needing to know anything about reaction kinetics and how these influence production rate. But the real advances in Industrial Applications are made when chemical reactions are studied more closely and the link is made between reactor design and the properties of the intended reaction process. Noticeable during this symposium were more presentations addressing the downstream part of a flow process, therefore answering the question : what happens after the flow reactor? This development was very welcome and indicated a progression towards more integrated continuous flow chemistry.

LECTURES

Tyler McQuade, VIRGINIA COMMONWEALTH UNIVERSITY

Machine-Chemist Partnerships: Automating Flow
The list of session speakers was headed by Tyler McQuade, from Virginia Commonwealth University, who introduced the topic of Machine-Chemist Partnerships, whereby the interface between chemists and automation was explored. Interesting examples were shown that take our perception one stage further than simply the cooperation between chemists and chemical engineers.
As the saying goes, "necessity is the mother of innovation." The necessity to enable chemists to produce more per unit time and the drive to lower critical medicine manufacturing costs are two themes that have more in common than one might expect at first glance.
Dr. McQuade divided the presentation into three chapters:

1. progress combining artificial intelligence with automated synthetic capabilities;
2. recent advances from the Medicines for All Initiative – a program to develop low cost medicine manufacturing to address developing World needs; and
3. the common lessons that were learned from both of these activities. The presentation intersected the wonderful worlds of complex pharmaceutical synthesis, advanced synthetic chemistry and chemical engineering.

Jesus Alcazar, JANSSEN-CILAG RESEARCH & DEVELOPMENT DIVISION

On demand preparation or organometallic reagents by metal insertion reactions in flow: accessing new chemical space for drug discovery
In this lecture a detailed explanation for the in-situ generation of these classes of reagents using flow chemistry was disclosed. These flow approaches are currently having an impact at all levels of the Drug Discovery process in Janssen, from Hit to Lead to Late Lead Optimization. Dr Alcazar explained the advantageous use of flow chemistry techniques in the performance of Grignard and organo-zinc reactions in exploratory chemistry for drug discovery. In this way he was able to exert strong control on the progress of key reactions.

Walter Linhart, MICROINNOVA ENGINEERING

Continuous manufacturing – More than exothermic reactions in small scale reactors
In Microinnova's presentation case studies showed some new possibilities, including the handling of solids or slurries as well as downstream process capabilities. A special focus was on the client's drivers and on the technical solutions. Walter Linhart was able to show that Microinnova has now evolved further than merely providing equipment for hazardous reactions. Ways of handling solid-phase reactants and products were described, including continuous crystallisation.

Peter Hermsen, INNOSYN

Flow chemistry delivers: fast scale up of challenging chemistry
In this presentation, several cases were presented in which the application of continuous flow chemistry enabled the application and scale up of challenging chemistry: low temperature organometallic reactions and catalytic oxidation with air and how current flow chemistry technologies, in particular that of Innosyn, can enable a fast scale-up to commercial production. The launching of Innosyn as an independent company spin-out from DSM underlines advances made by DSM in the manufacture of flow reactors by 3D printing.

Christof Aellig, LONZA

The benefits of using flow for multiphase reactions
Dr Aellig elaborated on Lonza experiences with the use of plate and coiled-tube reactor designs for multi-phase reactions. Special attention was given to reactions with Ozone and also reactions involving nano-particle Palladium

(obtained from Pd(OAc)2). Taking account of engineering factors, such as mass transfer and Dean vortices, played a key role in this work.

Arne Askildsen, GE HEALTHCARE

Synthesis of X-ray contrast agents – continuous processing
Some general considerations and challenges by going from batch to continuous were discussed.
A study of a chemical reaction was highlighted, where it was discovered that it was possible to operate at a significantly higher temperature in a plug-flow reactor than in a batch reactor. In the latter technology, degradation of one of the reagents in the reaction is a problem at high temperature.
Attention was given to how investment decisions on the conversion of batch processing to continuous flow chemistry need to be carefully prepared and supported. In the case of GE Healthcare, production of an X-ray contrast agent had been carrying on for already a long time, now reaching the limits of existing capacity. Development work has shown significant savings can be achieved using flow chemistry. These data will be important for decision making.

Charlotte Wiles, CHEMTRIX

Flow Chemistry - From concept to implementation
A thorough overview was presented of a number of cases where Chemtrix has played a key role in executing a chemical reaction in their flow reactor technology. Special attention was given to the deployment of Chemtrix reactors of different sizes in maintaining the achieved performance advantage all the way through scale-up. This presentation highlighted how manufacturing companies, using continuous flow techniques, have approached the transition from 'idea to reality' and the typical timelines for this transfer. Examples were selected to demonstrate the translation of existing processes from batch to flow, whilst others demonstrated how the technology was used to develop production protocols that enable manufacturing to be brought back in house or outsourced to CMO's.

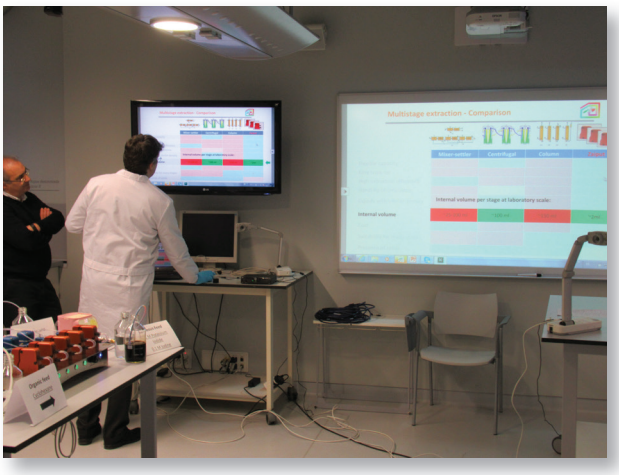
Christian Hornung, CSIRO

Continuous flow hydrogenations using novel catalytic static mixers inside a tubular reactor
The use of 3D printing to make reactor and catalytic static mixers was described. In the use of continuous flow reactor systems the hydrogenation of olefins, reductive aminations and reduction of nitro groups were performed with good results.

Viktor Gyollai, AM TECHNOLOGY

Hydrogenation in flow
Heterogeneous catalytic hydrogenation could be used in a counter-current mode to achieve efficient reductions of e.g. carbohydrates, without blockage or significant deteriorations. Sustained continuous hydrogenation requires a flow pattern where liquid and catalyst flow down through the reactor and hydrogen flows up. This ensures uniform distribution of gas, liquids and solids and can operate for days or weeks without interruption. It also presents formidable technical challenges relating to pumps, gas disengagement, flow control and pumping. These problems however are solvable using novel hardware solutions and this presentation covered development work and lab studies which have been in progress for over 5 years.

Wouter Stam, FLOWID



The benefits of using spinPro for multiphase reactions
Flowid develops continuous reactor solutions, from process development services to the realisation of skids. Flowid's SpinPro reactors are known for their high mass and heat transfer. They give unique control over the most demanding multiphase, exothermic chemistry including precipitation and emulsification. Flowid solutions are easily scalable from lab to full-scale production. Examples given included the production of cyanoacrylate (monomer for super-glue), and examples of nitration, halogenation and other exothermic reactions. It was explained that there should be no confusion with a thin film spinning disc reactor.

Wim Dermaut, AGFA MATERIALS

Bromination reaction at pilot scale using flow technology
This was a follow-up presentation to the one given at the 2016 8th Symposium, in Delft. Essentially the use of elemental bromine is hazardous. The lecture explained that in a flow reactor system, the generation of hypobromite in-situ (sodium bromide + hypochlorite) is a perfectly adequate substitute without the drawbacks of using bromine itself. The whole process development trajectory was described, including speculation about the fluid dynamics behaviour, mentioning Dean Vortices as being potentially responsible for enhanced mixing.

Bertrand Gallet, CORNING SAS

"Move into industrial production with Corning® Advanced-Flow™ Reactors"
A convincing overview of Corning's offer of Advanced-Flow® plate reactors was produced. Emphasis was given to the design of channels to promote efficient mixing at all scales from micro-flow to Advanced Flow® (up to pilot and production scale). Being made of glass, Corning reactors are also amenable for use in photochemistry. However, seamless scale-up was shown to be achieved via straight-forward methodology due to the consistent performance of Corning AFR: 1000x improvement in heat transfer, 10-100x enhancements in multiphase mixing, x/1000 reduction in chemical holdup comparing with conventional stirred batch reactors.

Massimo Bertoldi, LA MESTA

Continuous flow processing: the factory of tomorrow
The "Factory of Tomorrow" is today a reality as a result of La Mesta's internal development efforts. Based upon proprietary Raptor Technology, a continuous plug-flow mini-reactor, continuous downstream processing has been added to achieve a fully integrated continuous process technology with GMP status. Five reactions both in cGMP and non cGMP were considered in details: isomerization reaction of a double bond, the formation of a carboxylic acid with CO at high pressure in corrosive solvent, carbonate synthesis with phosgene from an alcohol, cyclization of an amino thioalcohol with phosgene and the chlorosulfonyl controlled hydrolysis to make the sulfamoyl chloride. More than 130 Tons have been manufactured in continuous mode over this period.

Peter Poechlauer, PATHEON

Linking the manufacture of pharmaceutical ingredients to their work-up and formulation
The lecture explained how, in implementing various continuous flow processes, Patheon has learned to tackle questions related to health, safety, environment and questions of regulatory compliance. Not only through mastering purely technical matters such as process safety, cost and product quality, Patheon has been successful through uniting competencies in continuous API synthesis and continuous drug product manufacture. Patheon is therefore well positioned to serve the needs of quick synthesis method development and reliable cGMP manufacture of both APIs and drug products.

Akira Matsuoka, KOBE STEEL

Large capacity micro channel reactor (SMCR®) and the industrial applications
The use of numbering-out can lead to large capacity production using micro-channel reactors originally designed for small-scale development work. Explanations were given on how robust multi-channel reactors can be made using ceramic plates through the use of diffusion bonding, and where desirable, constructed in a way that enables dismantling for cleaning. The channel structure of SMCR mentioned above can achieve precise fluids injections for each channel. Therefore, SMCR enables large flow rate processing and bulk chemical applications even though the raw materials react immediately after their confluence and/or immiscible fluids have to be contacted at a given volume flow rate by slug flow and annular flow.

Gareth Jenkins, BRITEST

Techno-Economic decision making tools for batch to continuous evaluation
A comprehensive overview of tools for Techno-Economic Decision Making was presented. The focus here was the commonly-faced dilemma of whether to convert a batch process to a continuous flow-chemistry process and the resulting investment decision. Essential step-wise use of criteria for evaluating each process was examined. Flow-charts mapping the decision-making process were introduced, showing at each stage which options needed to be considered, and how these eventually affect the investment decision. As well as techno-economic considerations, other factors, especially sustainability drivers, can be incorporated. Benefits include better management of the level of data required for decision making through different stages of the development lifecycle, clarity in capturing data gaps and requirements, and clear articulation to stakeholders of the justification for decisions taken regarding process strategy. The use of these evaluation

tools were demonstrated through relevant case studies.

Rudi Oliveira, HOVIONE

Process development in Flow Chemistry using kinetic modelling

The use of kinetic modelling in flow chemistry process development was examined. Initially describing all the possible drivers that govern the choice between flow chemistry and batch processing, examples were shown of how a study of the reactions kinetics could determine both the technical as well as the economic feasibility of a process. Data generated could be verified experimentally and fed back to refine the model.

Bashir Harji, CAMBRIDGE REACTOR DESIGN

The design and operation of a continuous cooling crystalliser

Focussing on the downstream processing area, with particular attention was given to crystallisation as part of a continuous flow process. This is an area that is the most difficult to execute in the production of a well-formed crystalline product. Examples described were adipic acid in the commodities area, but more specifically antibiotics and other APIs where morphology is a key property for a useable pharmaceutical. Intrinsic to this new technology are all of the other considerations relating to crystalline materials for example isomorphs and polymorphs, crystal habit and crystal imperfections.

Anne Kaaden, EHRFELD MIKFOTECHNIK

Small is the new Big: Millireactor in multi-tonne production application

This presentation showed the implementation pathway of the worldwide first visible millireactor in production application. Based on an integrated scale-up concept, the path from bench scale development towards multi-ton production was described. Describing how a small-scale milli-reactor process can be scaled up to multi-tonne production, the development procedure was shown to involve different perspectives: chemical, technological and economic. Using ethylene oxide to make polyethylene glycol as an example, conversion of a batch process to a fully developed continuous flow process took 8 months and realised significant savings in manufacturing costs.

Roger-Marc Nicoud, YPSO-FACTO

Adapting process engineering to (bio)chemists for the development of smarter processes

A spirited presentation was given on how misconceptions between chemists and chemical engineers, within the same company, can lead to failed process development at the most extreme, but more commonly lead to a sub-optimum use of resources and an inefficient process. Indeed, process engineering appears very well suited for fields needing an optimized process at an early development stage while it

Posters

1	ON-DEMAND ON-SITE CONTINUOUS PROCESSING – THE CONCEPT OF "CHEMICAL GENERATORS" IN MODERN PHARMACEUTICAL AND FINE CHEMICAL MANUFACTURING *Bernhard Gutmann (University of Graz)*
2	A 3D PRINTED STAINLESS STEEL REACTOR FOR A FAST MULTISTEP, MULTIPHASE CONTINUOUS PROCESSING *Bernhard Gutmann (University of Graz)*
3	PRODUCTION OPTIMIZATION AND SCALE-UP OF SMART MATERIALS USING CONTINUOUS FLOW REACTORS *Pierre-Baptiste Flandrin (University of Bath)*
4	CONTINUOUS SYNTHESIS MEETS PURIFICATION: HANDLING PARTICLES IN CONTINUOUS FLOW *Heidrun Gruber-Wölfler (Graz University of Technology)*
5	FLOW REACTOR SYSTEM FOR PHOSGENE REACTIONS *Hiroaki Yasukouchi (Kaneka)*
6	AN EFFICIENT APPROACH FOR CHEMICAL PROCESS DEVELOPMENT USING KINETIC MODELING IN BATCH AND CONTINUOUS MODE *Marianna Katz (Hovione)*
7	CROSS-COUPLING OF ORGANOZINC REAGENTS IN FLOW *Ananda Herath (Genomics Institute of the Novartis Research Foundation)*
8	ADVANCED PROCESS CONTROL BASED ON SPATIALLY RESOLVED IN-LINE SPECTROSCOPY *Calogero Piscopo (Fraunhofer-Institute for Chemical Technology ICT)*
9	USING ADVANCED AUTOMATION TO FULLY EXPLOIT CONTINUOUS MANUFACTURING SYSTEMS *John Mack (Perceptive Engineering Limited)*
10	IN-SITU ON-DEMAND CONTINUOUS GENERATION OF ANHYDROUS DIAZOMETHANE *Doris Dallinger (University of Graz)*
11	METERING PUMP SYSTEM WITH VERSATILE CONTROLLER *Harry Morikawa (Fuji Techno Industries Corporation)*
12	FABRICATION OF DUAL FOCUSING MICROFLUIDIC FILM DEVICE EMBEDDED WITH ELECTRODE FOR ELECTROPORATION APPLICATION *Se-Jun Yim (Pohang University of Science and Technology)*
13	THE DESIGN AND OPERATION OF A CONTINUOUS COOLING CRYSTALLIZER *Bashir Harji (Cambridge Reactor Design)*
14	CONTINUOUS FLOW SYNTHESIS OF AN AGROCHEMICAL INTERMEDIATE VIA A TELESCOPED NITRATION/HYDROGENATION/CYCLIZATION SEQUENCE *David Cantillo (University of Graz)*
15	A FLOW-ASSISTED SEQUENTIAL ISOMERIZATION: REACTIONS OF O-LITHIATED ARYL ETHERS *Hyune-Jea Lee (Pohang University of Science and Technology (POSTECH))*

seems far less efficient to address typical issues faced by the fine chemicals companies, such as the requirement to produce samples very fast and to have the flexibility to handle expected production targets that may vary by orders of magnitude. Technological solutions can then be proposed and studied to remove such obstacles, while going gradually towards an increasingly detailed analysis making it possible to reach a secured and optimized process with great agility and with important savings of time and experimental resources.

Alain Rabion, SANOFI

One step continuous flow synthesis of a WHO essential medicine using fluorine gas

The process described involved fluorination using elemental fluorine, performed successfully in a Boostec or a Corning silicon carbide plate reactor system. Initial fluorination reaction conditions were defined using a steel tube flow reactor at milli-liter scale. Development and pre-industrialization studies have been performed using a pilot scale silicon carbide flow reactor at liter scale. Two commercially available flow reactors were tested and validated in order to produce the desired quality of crude Flucytosine. Key achievements were the execution of a hazardous reaction in a flow chemistry process that led to important cost reductions. This enabled the API to be marketed by the WHO for 3rd world use.

ACADEMIA CORNER

Short presentations were given by Pierre-Baptiste Flandrin of Bath University on production optimisation for smart materials; by Heidrun Gruber-Wölfer (Graz University of Technology) on solids handling involving purification in flow; and also by Berhard Gutmann (University of Graz) on "Chemical Generators" in on-demand on-site continuous processing.

ROUND-TABLE DISCUSSION

The meeting was completed by a round-table discussion, led by Prof O. Kappe, on the merits of various Demos presented at the symposium. There still appeared to be divergent opinions on the meaning of "flow" as compared with "continuous". In essence this 9th Symposium has underlined that fact that there is now a community committed to exploring and applying different flow systems, starting in exploratory chemistry and going all the way to full commercial implementation.

SUMMING UP

We all now look forward to the coming 10th Symposium on Continuous Flow Reactor Technology for Industrial Applications. This 10th anniversary will surely display a consolidation of many experiences collected during the last years, amid growing awareness of the benefits of new ways to perform chemical processes! ■

ABOUT THE AUTHOR

***Jean-Marie Bassett**, born in the London area, is half-British/half-French, but now living in The Netherlands, (so fairly European), graduated in Chemistry at London University. At TNO, the Dutch Applied Research organisation, he has been active in setting up the business in innovative technologies for chemicals processing. Now Jean-Marie is an independent consultant operating under the name Chem4Chem. Jean-Marie has published about 20 articles in organometallics and later in technology development.*