Second Symposium on Continuous Flow Reactor Technology for Industrial Applications

Chimica Oggi / Chemistry Today organized a second symposium on “Continuous Flow Reactor Technology for Industrial Applications” on 3-4 October just before CPhI, in Paris, obtaining a success even bigger than the previous event [1]. In coordination with the symposium partner, Corning SAS, Chemistry Today brought together twenty speakers from industry and academia to discuss the most recent applications and experiences from the world of continuous flow chemistry. Thanks to last year’s experience and to the participants’ feedback, the presentations were focused more on equipment, auxiliary equipment, process analytical technologies, regulatory and safety issues.

A workshop on economic evaluation sponsored by Lonza entered into details of the economical benefits brought by this technology.

Two panel discussions helped the audience to make the point at the end of each day by managing useful and provocative statements/questions coming from all the participants. The implemented exhibition area moreover hosted fifteen exhibitors which led to important and helpful networking.

Let’s enter into details of the lectures and get to know more about the speakers and their experience.

Xiong-Wei Ni.
NiTech Solutions Ltd
Speech: Continuous crystallisation is right here and right now

Slowly but surely, continuous manufacturing is beginning to make significant inroads into the pharmaceutical and process industries, and crystallisation is one of the key manufacturing steps that is predominantly still operated as a batch process. GlaxoSmithKline has very recently set a target to cut waste in its factories around the world from 100kg of raw materials for every 1kg of drug produced to 30:1 by 2015, continuous manufacturing and crystallisation will play a significant role in this drive. In this presentation Dr Ni highlighted the underlying science governing solution crystallisation; outlined the challenges in transferring knowledge learnt from lab batch crystallisation to industrial operation; introduced the novel continuous crystallisation technology, the continuous oscillatory baffled crystallizer (COBC), which offers near plug flow conditions under laminar flows with excellent heat transfer coefficient, provided controllable temperature profiles that cannot be achieved in large batch operations, allowing well-defined continuous crystallisation. He then used real examples of industrial crystallisation in COBC to demonstrate the significant benefits obtained, e.g. consistent crystal morphology and size; better filterability; significantly reduced crystallisation time, space usage, utility and energy consumption. Dr Ni’s aim was to convince the audience that continuous crystallisation is right here and right now.

Laszlo Ürge.
ThalesNano Inc.
Speech: Scale-up of flow hydrogenations from discovery to pilot-plant

Once a clinical candidate has been discovered, the difficulty lies in scaling up the synthetic route. At this stage, medicinal chemistry meets process R&D, and examines a variety of synthetic routes and conditions based on the initial laboratory protocol in order to produce the clinical candidate in kg or higher quantities. In most cases, the typical batch lab protocol needs to be re-optimized for scale-up due to the different vessels, heating and cooling methods, separation and purification techniques, parameter control, sampling etc. used in medicinal chemistry and GMP production. This optimization procedure significantly delays
the drug development process causing millions in lost revenue. Continuous processes offer an efficient solution for the rapid transfer of the synthetic procedure from discovery to development without time-consuming adaptation and optimization of the methods from the laboratory to GMP production scale. The scale up of catalytic hydrogenation is especially difficult due to the extreme safety requirements particularly in real large scale processes. ThalesNano has developed flow hydrogenation reactor series from bench top to pilot plant systems, covering mg to kg scale that makes difficult and dangerous reactions safe and effective. The scale-up of several heterogeneous hydrogenation reactions using flow reactors was presented. In addition the application of the systems for other homogenous and heterogeneous reactions was also discussed.

**Peter Poechlauer**, DSM
Speech: Process intensification in development and efficient production of pharmaceuticals

Process intensification - a set of principles to allow a chemical reaction “to proceed as fast and selective as possible” allows improving the development and production of pharmaceuticals in a number of ways:

- It allows establishing a viable parameter space for process conditions in shorter development times to design new, more efficient processes.
- It allows shortening synthetic pathways by making so far hazardous reagents and reaction conditions accessible.
- It helps in using the raw materials of a process more efficiently and thus improves its waste balance and environmental footprint.

DSM focuses on new methods of sustainable chemicals production and uses systematic approaches to constantly improve the environmental balance of a number of existing processes. We apply principles of process intensification early in processes development as well as in the improvement of existing processes. The number of different unit operations replaced by “intensified” equivalents is constantly increased. Their stepwise implementation is part of our “continuous improvement” process and allows a smooth transition from conventional technologies to more advanced equivalents. The principles and DSM’s approach were illustrated by several examples.

**Fabrice de Panthou**, AETGroup
Speech: New development with continuous Raptor® technology

The Raptor® technology was developed by AETGROUP a few years ago for process intensification and continuous manufacturing. The specificities of this technology are the high throughput and the efficiency of the stirring system for mass transfer.
High throughputs are necessary to avoid number-up issues and for production costs. Efficient mixing allows process intensification, particularly in heterogeneous reactions. Indeed, the Raptor® technology is recommended when a process involves solid/gas/liquid compounds. Safety improvements are often a major reason for taking the decision to manufacture in continuous. It may avoid the main batch risks like unstable intermediates, risk of accumulation and implementation of hazardous reagents. Real case examples illustrated the specificities of this technology already used for manufacturing at industrial scale.

Carsten Damerau,
HNP Mikrosysteme GmbH
Speech: How to Select a Suitable Pump

A short overview of functional principles of the most common pump types were given. The relevant properties were outlined using the example of micro annular gear pumps. The focus of the presentation was set on performance, precision and pulsation. In chemical processes, pumps are part of a complex setup of interacting components. As there is no one-size-fits-all pump, special challenges result from selecting the most suitable pump type and its configuration. In consequence pump manufacturers need a deeper understanding of the customer’s application and depend on complete information. The influence of liquids’ compositions, viscosities, pressure conditions and flow rates was demonstrated.

Hervé Lucas,
Kaiser Optical Systems
Speech: The Applicability of Raman Analyzers for in-situ Studies in Small-Volume Reactors

Raman Spectroscopy was first reported in 1928 but it remained a relative underutilized technique until the 1960’s when the development of the laser, multi-stage monochromators, and electronic detectors led to a resurgence of interest. Following these instrumental advances the feasibility of many applications were demonstrated in the research laboratory but only in the last 15 years has Raman spectroscopy emerged as a viable in situ analytical and process control tool. The early years of this period were dominated by improvements in Raman spectrometer components including the development of high power, small footprint NIR lasers, high performance holographic laser rejection filters, and low-noise CCD arrays detectors. The later years have seen a significant increase in the type and quantity of published application successes. At the core of this emergence has been developments in sampling and sampling interfaces. The ability to flexibly configure the optical sampling interface using fibre-optic delivery allows Raman analyzers to be integrated to reactors ranging from the micro-scale to large volume manufacturing reactors. In this presentation example of improvements in sampling for both liquid and gas-phase Raman applications was shown as well as applications of Raman spectroscopy for the study of small reactor systems including sealed microwave systems, continuous flow reactors, NeSSI platform devices, and small volume thermal reactors.

Jürgen Grebner,
LAUDA DR. R. WOBBER GMBH & CO. KG
Speech: Temperature control for continuous flow micro reactors

A lot of efforts need to be spent to optimize a chemical process for a continuous flow reaction. Different to the “classical” batch reaction in double jacket reactors chemists have a much better possibility to improve selectivity and yield by optimization of the reaction temperature for continuous flow reactions. Due to the design of micro reactors a very constant and fast heat removal is possible. However this requires the choice of a thermostat which offers sufficient heating or cooling power as well as a good possibility to connect this thermostat with continuous flow micro reactors and which allows an easy programming of the total system. Over the past years LAUDA became a very important supplier of high dynamic process thermostat systems to be used together with continuous flow reactor technology. An extreme wide temperature range and rapid temperature changes are two main advantages of the LAUDA Integral XT product range. Also the standard maximum pump pressure of up to 2.9 bar can even be increased to 5.8 bar using an additional high pressure pump. This allows a reasonable and constant heat transfer for high exothermic or endothermic reactions even with heat exchange channels having a very small inner diameter. The available range of interface modules (e.g. RS 232/485, analogue module, Profibus ...) guarantees that the control fits to the chemists requirement and also enables the easy transfer of documentation of temperature profiles from one laboratory to the other. Specially designed adaptors allow the easy connection of temperature control systems with continuous flow micro reactors. Due to the fact that LAUDA covers the range from laboratory instruments up to customized industrial systems with some hundred kW heating or cooling power it also is possible to support chemists and engineers during the transfer from laboratory / pilot scale to the production process. This makes LAUDA a valued partner for all users of the encouraging technology of continuous flow reactors around the world.

Frank Gupton,
Virginia Commonwealth University
Speech: Heterogeneous Catalysis In-Flow

Palladium-catalyzed cross-coupling reactions are of strategic importance in organic synthesis and have been widely used for the assembly of complex organic molecules in pharmaceutical applications. These reactions have typically been performed under homogeneous conditions employing a ligand to enhance the catalytic activity and selectivity for specific applications. However, the issues associated with homogeneous catalysis remain a challenge to pharmaceutical synthesis due to the lack of recyclability and potential contamination from residual metals in the reaction
Recent advances in catalyst support systems have provided the opportunity to carry out these reactions under ligand-free heterogeneous reaction conditions. Due to the unusually high turnover numbers, these catalysts can be readily incorporated into continuous flow systems, which provide significant operational as well as environmental advantages. These catalysts have been successfully employed in-flow for Suzuki-Miyaura, Heck and Sonogashira reactions with excellent yields and high throughput.

Volker Hessel, IMM
Speech: Micro Processing for Intensifying Fine Chemistry and as Gateway to Novel Process Windows

Micro Process Technology as is A manifold offer for microreactors is on hand. Process intensification is demonstrated for the initial stage of reaction; novel purification devices are missing apart from some laboratory prefigurations. Production feasibility in fine chemistry has been reported for scaled-out microstructured reactors run in demonstration pilot plants in short performance trials, often at industrial site, but the picture on the use for business is vague and scattered. These micro-reactor based pilot plants were dedicated and home-made; just recently some commercial modular plants have been launched.

Micro process technology and process intensification are breakthrough technologies with step-change nature, but address a traditional industry used to incremental changes. "Such entirely new concepts are far from our daily experience, which is advantageous to enable step-change improvements and disadvantageous for introduction in real-life business both for technical and soft human factor reasons. Accordingly, a judgement on the cost and ecological impacts is needed – not only 'after process', but also 'ex-ante' – to account for the holistic view and to envision the whole process chain," stated Hessel.

Novel Process Windows
Micro Process Technology speeds up heat and mass transfer; Novel Process Windows speed up reaction kinetics. Microreactors are apparatus made for millisecond- and second-processing. A hand-in-hand design of the reactors and processes is demanded to enable fast chemistry rather than subduing chemistry around the reactor. Often the process windows suited for microprocessing are very different and remote from the classical process sheets – shifted to harsher conditions for process intensification (higher temperature, higher pressure, higher concentration/solvent-free, explosive or thermal runaway regime) and utilizing process integration in time and space (all-at-once, direct route, one flow-multi-step, transform to catalytic) – named here Novel Process Windows. Via such intensification, the productivity of the reactor can be increased by orders of magnitude. The integration of reaction and processing steps gives room for new chemical transformations.

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FLOW CHEMISTRY

Yi Jiang
Coming SAS
Speech: Advanced Flow Reactors for Multiphase Pharma & Fine Chemical Applications

This presentation highlighted the breakthrough technology of continuous flow reactors in the area of multiphase pharma and fine chemical synthesis applications in terms of intensifying multiphase mass and thermal transports through detailed millimeter-scale microchannel designs. Conventional “batch” synthesis with mixing and reactions done in bulky meter-scale 3D vessels often generates by-products, may even represent a safety issue when dangerous processes or highly toxic reagents are involved. Refined millimeter-scale “2D” design of channel reactor allows significant specific area for thermal transfer and superior mixing for reducing overall multiphase mass transfer resistance. All these open wide window of opportunity for accurate and easy control of multiphase reaction kinetics, and removes the scale-up barriers of traditional multiphase reactors. This presentation summarized several applications of multiphase continuous flow reactors including a continuous 2-step synthesis related to bio-fuel additives. It demonstrated how effectively apply advanced flow glass reactors consisting of millimeter-scale microchannel modules to overcome the limitation of reaction equilibrium and to enhance heterogeneous reactions involving dangerous chemicals, where a precise control of the reaction conditions offered by advanced flow reactor has crucial impact on the selectivity. A robust, green and safer industrial-scale process was also described.

Sophie Walton
Centre of Process Innovation Ltd
Speech: Disks, baffles and glass flows – expectations, pitfalls and step changes in economics!

CPI is a public/private pilot scale process development house in the North East of England. Having invested 36 million pounds in a range of “plug and play” pilot assets, CPI now trials third party processes and chemistry on many different types of continuous reactor system. Having designed, built and operated both bespoke and also “off the shelf” reactor systems at different scales and specifications for a huge variety of different applications Dr Walton presented some of CPI’s experiences with its collaborators. From spinning disks, COBR’s and advanced flow reactor systems CPI tackles chemistries ranging from sulphonation, nitration, slurry hydrogenation and radio labelled metabolite chemistry. Dr Walton explained the issues they encountered and how these were overcome. Walton also explained what they have learnt to be some of the critical factors for success on these projects and discussed how collaborative approach can help with delivery on complex single and multi partner projects.

Derek Atkinson
Oxford Catalysts
Speech: Microchannel reactor architecture enables clean synthetic fuels

Microchannel process technology offers process intensification, in the form of enhanced heat and mass transfer, to a wide range of chemical reactions. This presentation described the application of microchannel technology to the production of ultra-clean synthetic fuels. These fuels, which are one-to-one replacements for petroleum derived fuels, are produced by passing synthesis gas, a mixture of carbon monoxide and hydrogen, over a cobalt catalyst: a process known as Fischer-Tropsch (FT) synthesis for its German inventors. Although, any carbonaceous material can produce synthesis gas, the most efficient path is the conversion of natural gas via steam methane reforming (SMR). Both the SMR and FT benefit from the process intensification offered by microchannel technology, resulting in smaller, less costly processing hardware; thus, enabling cost effective production of synthetic fuels from smaller scale facilities, appropriate for biomass and offshore natural gas resources. The products from FT based processes can be upgraded into a diesel blend or synthetic paraffinic kerosene, or simply blended with associated crude oil for transport to the world market.

Carmine Raffa
Ehrfeld Mikrotechnik BTS GmbH
Speech: High Performance Devices for Flow Chemistry

Ehrfeld Mikrotechnik BTS GmbH (EMB), a subsidiary of Bayer Technology Services GmbH, is a leading company for services and products related to micro reaction technology. EMB provides Micro Reactors and High Performance Devices like mixers, micro heat exchangers and micro reactors and also complete reaction units in various materials and for a wide application range. Together with customer support like training, feasibility studies and customer project services, EMB acts as supplier for complete and holistic solutions. In the last years, Micro Reaction Technology has been well established in R&D, process research and process intensification. The Modular Micro Reaction System MMRS of EMB plays a major role in this area. A large number of worldwide acting companies and research institutes use the benefits of this labtool with great success. With the request of scalability of the present devices to production scale applications, a new and important challenge is rising these days. EMB faces this request with two new product groups. With Miprowa® production scale reactors for chemical production scale and Lanza® Micro Reactors for pharma production, EMB offers a reliable and cost-effective way for the scale-up of processes from laboratory to (large-scale) chemical and API production. Special interface modules based on the lab tool MMRS allow to transfer the R&D experience to production units with a minimum of work and time. MMRS, Lanza® and Miprowa® Micro Reactors open a new and powerful way to the industrial application of high performance flow devices.
FLOW CHEMISTRY

In particular it illustrated the value of PAT in a continuous flow context, looking at on-line probes (such as FTIR) as well as pseudo on-line such as gas chromatography, for helping to drive automatic optimisation of techniques in the laboratory and then enable real-time control in the plant.

Continuous flow chemistry presents unique challenges for process development and optimization. The very nature of flow chemistry – that it is flowing – and that reaction times are short due to vastly improved mixing characteristics creates the critical need to have a correspondingly fast return of analytical information to ensure success. A non-optimized process or a process out of compliance is potentially generating a continuous waste stream, or at best delivering a volume of unreacted material that requires further processing.

**WORKSHOP ON ECONOMIC EVALUATION**

**Dominique Roberge, Lonza**

*Speech: The Impact of Flow Processes in Redesigning Chemical Routes: Microreactor Technology and Beyond*

The key concept behind the utilization of flow is to achieve extreme process intensification. The intensification process enables inherently safer conditions that lead to the development of new processes, so-called “Flash Chemistry,” that could otherwise never be performed under batch conditions. In a microreactor it is possible to perform highly energetic reactions, work with unstable intermediates, employ more reactive reagents, and use more active catalysts that enable new, out-of-the-box chemistry. In addition, the workspaces can be designed for high temperature and high pressures reactions; a new domain for a typical chemist. A microreactor will be at the heart of flow processes to control the “Flash Reaction” but will be implemented in parallel with other flow unit operations such as liquid-liquid extraction, distillation and crystallization. The outcome will lead to highly intensified mini-plant processes, so-called “Flash Chemistry,” that could otherwise never be performed under batch conditions.

**Sergio Pissavini, Corning SAS**

*Speech: Micro-reactor Flow Chemistry: Impact on plant economics, guidelines and cases review*

The economics of the integration of the continuous flow reactor technology in industrial production are related to the correct evaluation of the different elements of the value proposition and by the correct engineering choices for a rational integration. The value proposition for two different frames, grass root and integration in existing plant, were evaluated together with a discussion on the possible engineering approach and solution for an effective implementation. A typical common reaction and relevant test data was used as base for the discussion.

**Berthold Schenkel, Novartis Pharma Ltd**

*Speech: Continuous Manufacturing: Technologies and the Economical Benefit*

Reactions in continuous mode are becoming more important in chemical development and manufacturing of APIs in pharmaceutical industry and Novartis, which is still dominated by batch manufacturing. Recently developed continuous reactions, the requirements in pharmaceutical development and the benefits of continuous reaction mode was presented. Approaches how to transfer continuous reactions from lab into production scale were shown. The economic benefit of continuous operation mode is the key for success in the pharmaceutical industry. Based on case studies the potential to reduce the production cost was summarized.
The use of real-time in situ FTIR analytics provides instantaneous feedback on changes in continuous flow process conditions such as residence time and reagent flow rates. In a production environment, in situ FTIR can be used to ensure that the process effluent is maintained with acceptable quality attributes and allows real-time information about any unexpected process upsets such as pump failure. Several case studies will be presented that will illustrate the value of having highly molecular specific chemical information provided instantaneously through the use of real-time in situ mid-IR technology.

Melvin V. Koch,
University of Washington
Speech: The Benefits of Real-Time Measurement and Sampling to Enhance the Performance of Advanced Flow Reactors

There has been significant advancement in measurement tools that support efforts in improving process monitoring and control. A key part of these advances has been in miniaturization technology, as micro-analytical tools, combined with improvements in process sampling and sensor platforms which are proving to be valuable approaches for implementing Process Analytical Technology (PAT). Recently a program was initiated to demonstrate the value of an advanced flow reactor platform in conjunction with micro-analytical tools and modular sampling systems components to improve process understanding and control. The program is a collaboration between the US Food and Drug Administration (FDA), Corning, Kaiser Optical Systems, Parker Hannifin, and CPAC (Center for Process Analytical Chemistry). Results from initial experiments show significant progress towards the ultimate goal of Process Understanding and a future path towards Process Control. Implementation of this approach will have a large impact on the possibility to obtain a competitive edge and to also demonstrate that green chemistry is achievable.

Mark Hoyle,
AstraZeneca
Speech: Addressing Potential Chemical Reaction Hazards for Flow Chemistry Operations

The chemical industry has been seeking alternatives to stirred-tank reactors for many years and continuous processing (process intensification) is an area of significant increased industrial interest, particularly in the pharmaceutical industry. One of the major benefits lauded around the technology is that of safer operation. The lower inventories involved obviously give credibility to this claim and without a doubt the massive heat removal ability of tubular reactors are beneficial for highly energetic reactions. However, the inherent instabilities of certain materials should not be over-looked and slow reactions (with potential side-reactions/secondary reactions) will need to be addressed appropriately in the design of the complete operating system, i.e., from feed vessel through to collection/isolation vessels. As is paramount with all chemical manufacture, the early consideration of chemical reaction hazards allows appropriate system design and therefore safe operating conditions to be prescribed. Failure to carry out such studies can lead to potentially serious consequences regardless of the technology being used.

Using case studies from pharmaceutical process development for continuous flow chemistry operation this speech showed the methodology by which chemical reaction hazards were addressed prior to operation. Chemistries considered cover the ideal scenario of fast energetic reactions (but with potentially unstable products) through to potentially undesirable slow reaction involving a rapid and energetic secondary reaction just above the desired reaction temperature.

Interesting and in some cases provocative discussions took place during the two panel discussions held by Dr William Heggie, Scientific Officer in Hovione’s company. Participants were invited before and during the event (via email / post it) to address questions on specific topics related to flow chemistry and participate actively to the discussion. The questions were grouped in 6 categories: Handling of Solids/Slurries; Heterogeneous Reactions; Range of reactions; Development/Scale Up; Equipment/Reliability; Analysis; GMP Implications. The majority of the questions pertained to equipment issues and to specific reactions and some of them also to regulatory issues. Unfortunately FDA answers were not available but Dr Heggie together with some speakers managed to give at least an overview of the regulatory situation but some good questions remained without a feedback. Evaluation forms were sent to all the participants to obtain positive and negative comments to work on for the next event and surely Regulation will be a must topic. The event drew accolades from attendees: “This symposium was a good mix of talks about new equipment and talks about new methods for continuous flow chemistry”, said Martin Cohen, Senior Research fellow, Cytec Specialty Chemicals. “It was very informative, attractive and well organized”, said Emmanuel Gheerbrant, researcher at Sanofi Aventis.

The response of this second conference was very positive: 130 people representing 90 organizations and 19 countries participated actively to the networking. “The success of this symposium is not due to Flow Chemistry per se, because this technology is not a novelty. The novelty is in the transposition from other chemical fields to specialty chemicals and Fine Pharma”, stated Sergio Pissavini, business director of the advance flow reactor group, Corning SAS.

Closing the symposium Sergio Pissavini expressed his satisfaction for an event which was able to answer to questions and suggestions which came from the audience of the previous year and evinced the intention to organize once again in partnership with Teknoscienze (Chimica Oggi / Chemistry Today publisher) a third symposium. So keep tuned and follow our press releases.
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