JEAN-MARIE BASSETT
Chem4Chem

Scientific Advisory Board Member


Jean-Marie Bassett

8th SYMPOSIUM on Continuous Flow Reactor Technology for Industrial Applications

OVERVIEW

Over the last 7 years we have seen a step by step development in the content and format of the annual Symposium on Continuous Flow Reactor Technology for Industrial Applications. More and more companies, supported by academia and innovation organisations, are turning to the use of flow reactors and associated technologies for the performance of flow chemistry processes in real industrial environments. With exciting results!
The **8th Symposium on Continuous Flow Reactor Technology for Industrial Applications,** is now a true forum for sharing experiences and philosophies distilled from actual practice.
On the innovation side, increasingly we see small companies being created and starting up in the commercial supply of novel equipment, be it flow reactors, in-line analytical systems or technology items for downstream processing. In this sense, we see a welcome stimulus for business that is seemingly unstoppable!
This year, the Symposium spanned 3 days in Delft, the first day being the now well-established practical session, this time hosted by both TNO and the Delft University of Technology (TUD).

In all, **11 companies** were able to display their equipment in operational mode, performing in most cases actual chemical reactions.
Of the roughly **130 delegates** who attended the symposium, about 62 took part in the practical session. Such a large number needed careful organisation, division into groups and good time-keeping. This allowed each exhibitor a fair chance to explain what they wanted to show and permitted delegates sufficient time to understand, ask questions and generally absorb all the information.
We were fortunate in attracting a large number of high quality speakers, from not only 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.
Our **21 speakers** came from 9 different countries reflecting a truly international symposium composed of delegates drawn from 18 countries world-wide. 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.

The symposium was structured to provide a distinct **Pharma Session** and also a separate **Analytics Session**. The latter was co-chaired by Brian Marquardt who kick-started it by giving a keynote lecture on in-line analytics.
It was noticeable throughout the symposium that the theme of interdisciplinary collaboration came up time and time again. Expressed as the injection of engineering principles into the domain of fine chemicals production, now a necessity by virtue of the adoption of continuous flow chemical processing, implied a working collaboration between chemical engineers and chemists.
Together with Chemistry Today I am delighted to provide you, dear Readers, with a summary of the lectures and presentations, hoping that you will find them interesting for your job.

LECTURES

ANDRZEJ STANKIEWICZ
Delft university of Technology

Green Electricity-Based Processing and Flow Chemistry
Professor Stankiewicz opened up the symposium with his keynote lecture. He offered an exciting overview of the diverse ways of using electricity-based energy forms to initiate and perform chemical reactions. These included: electric fields, magnetic fields, induction, microwaves, plasmas, ultrasound and light.

Prof Stankiewicz explained that the long-term vision on the future of intensified chemical processes encompasses the utilisation of renewable ("green") electricity as primary energy source for those processes. With electricity becoming the most widely available, versatile energy form on Earth, electricity-based methods will play an important role in the development of flexible, distributed production units for clean manufacturing of fuels and chemicals in various environments. In this context the lecture addressed the thermodynamic domain of process intensification and reviewed recent advances in the utilization of various electricity-based forms of energy to intensify chemical reactions at the molecular level. The focus is on using electric, electromagnetic and acoustic fields to influence the orientation, alignment and activation of molecules. The challenges of implementation of the resulting novel reactor concepts were discussed. To realise the above-described vision, more symbiotic research between catalysis, physics and chemical engineering was postulated. Better understanding of the underlying phenomena and interrelations between the catalysis and various energy forms is a prerequisite here. The concurrent development of tailored, energy-responsive catalysts and novel reactor concepts with enhanced field control will lead to a new quality in chemical processing. Micro- and millistructured flow chemistry systems will be an essential element of that development.

We were extremely grateful to Prof. Stankiewicz for facilitating our use of the Delft University of Technology, Process Technology Institute laboratories for the practical session, and the use of the University Aula for the symposium itself.

ALAIN MERSCHAERT
UCB Pharma

Challenges and Successes in Implementation of Flow Chemistry
The last few years UCB Pharma has significantly developed its enabling technologies capabilities with a particular focus on continuous flow synthesis. The presentation emphasized the technical challenges as well as initial successes and the current strategy for increased application of continuous manufacturing in particular for the early stages of chemical process development.
While outlining strategies and decision making processes used by UCB in the development of a flow chemistry approach to API manufacture, many issues were dealt with. Amongst others was the need to maintain pace with the timescale set by Clinical Trials, and the simultaneous requirements for a verifiable process and production of the necessary quantities. The reactions that benefitted the most from the flow chemistry method were in fact low temperature organometallic reactions, and high temperature reactions with corrosives. Several illustrative case studies were also discussed.

PETER MCDONNELL
Sanofi - Industrial

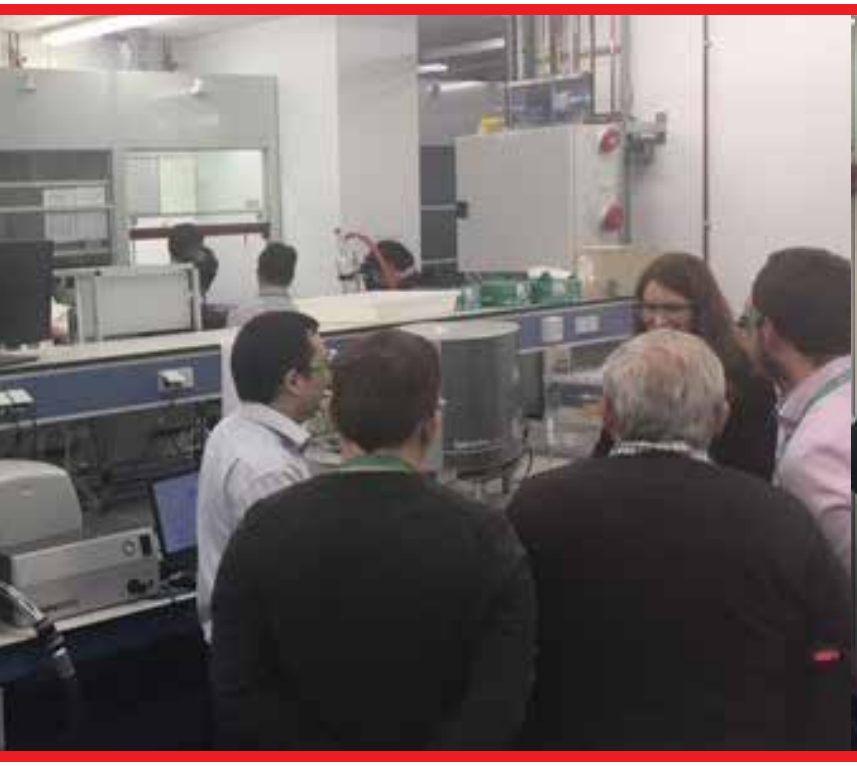
Experiences with the Implementation and Regulatory Impact of Continuous Flow Processes
For many years Sanofi has been exploring the benefits of continuous manufacturing of APIs in both chemical and biotechnology applications. The advantages and disadvantages of batch and continuous technologies were presented, including experience through many regulatory inspections. Approaches to validation and the use of appropriate PAT were described. Some reflections on the barriers to adoption of continuous processing were itemised, as well as potential solutions to such challenges. Important conclusions were shown, including the avoidance of a special DMF filing, even after 8 FDA inspections.
Sanofi had made an inventory of "for and against" factors in adopting flow chemistry for both chemical and biologicals manufacturing processes. A key item, as others have found, was the need to fully understand the process in terms of kinetics, thermodynamics, mixing and solids handling. This is a distinct departure from methodologies using batch processing.

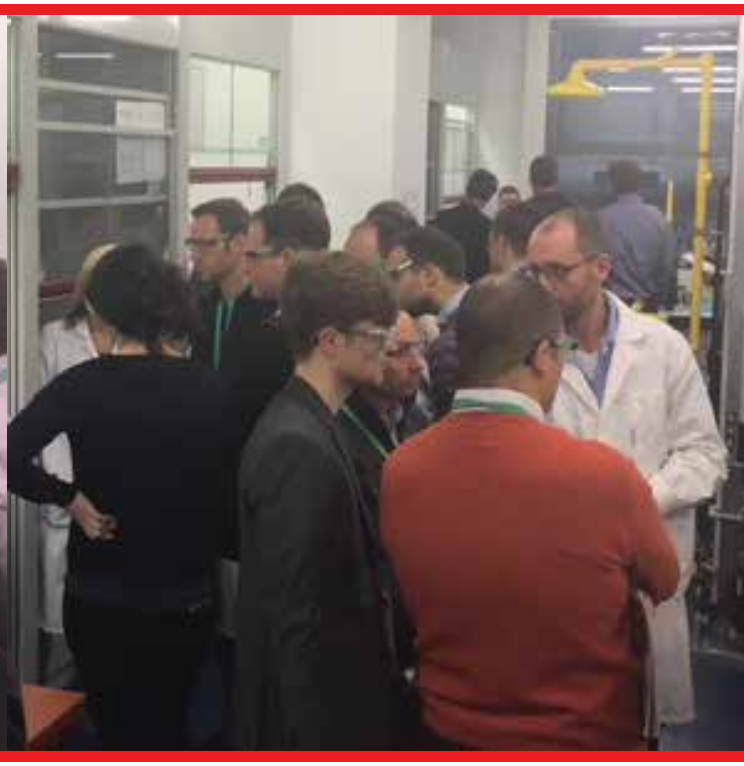
SARAH HUNTER
GlaxoSmithKline

Flow Chemistry Process Design for Organometallic Exothermic Reactions
A review of the design methodology applied to a continuous pharmaceutical process using organometallic reagents was presented. Process design was undertaken by evaluation of the kinetic parameters of the desired reaction and subsequent degradation of the reaction products. Simulation of a reaction model, developed in silico, was used to specify acceptable process parameters to optimise product quality and simplify the operating model. In silico design allowed the process to operate outside of the cryogenic, addition rate controlled systems normally applied to organometallic chemistry. The optimised process operates under assumed adiabatic reaction conditions at ambient temperatures, with microsecond mixing times and sub second residence times. The process has been demonstrated as a small scale replica, maintaining the scale independent parameters at the anticipated pilot plant production rate.
A key message derived from the presentation was the need to perform accurate simulations before embarking upon experimental work for upscaling.

BRIAN J. MARQUARDT
MarqMetrix

Development of Process Analytical Solutions for Real-Time Monitoring of Continuous Flow Reactors
Continuous Flow Reactors (CFRs) are flow cells that are optimized for the continuous production of a target chemical compound. Compared to batch reactors, CFRs have greater energy efficiency due to their superior mixing schemes and heat transfer properties. As a result of this efficient heat transfer, reactions that require cryogenic temperatures in batch, such as the Swern oxidation, can frequently be performed at much milder temperatures in CFRs, significantly reducing temperature control costs. An example reaction included a four reagent sampling system interfaced to a continuous low-flow reactor to enable real-time reaction monitoring using a four channel process Raman spectrometer. This allowed for optimization, minimizing the production of "off spec" product and removing the need for off-line quality control analytics. Real-time chemical modelling was performed to determine product quality using multivariate statistical methods. Results from these experiments demonstrated that the oxidation can be performed at cost effective temperatures in continuous flow, avoiding cryogenics. This presentation effectively demonstrated the use of process analytical tools for the optimization and control of CFR production systems across a number of reactions.





WOUTER STAM
Flowid

Spinning Disc Technology: No More Limits in Chemical Industry
Spinning disc technology harvests the effect of high shear and centrifugal action for the intensification of chemical processes.
The discs, of about the size of a DVD, rotate at thousands of revolutions per minutes while the distance between the discs and the encasing are typically only a millimetre. By almost completely removing limitations of heat and mass transfer in chemical processes, spinning disc technology opens up operating windows at process-intensified conditions that were hitherto unfeasible. Exotic, highly exothermic, or slow multiphase processes can now be performed in a safe and economical way in devices the size of a cookie jar at full industrial scale. The focus was on the operating principle behind spinning disc technology and how this lies at the heart of the most important types of equipment such as spinning disc reactors, extractors, crystallizers, evaporators, etc.

ROGER-MARC NICOUD
Ypso-Facto

From Batch to Continuous Processes: a good answer, but what is the question?
Most industries switched to continuous processes decades ago and major successes are known for continuous chemical processes. The pharmaceutical, biopharmaceutical and fine chemical industry express a genuine interest in the field. Even regulatory bodies, like the FDA, encourage the switch from batch to continuous. Yet, batch remains the widely accepted standard in this industry and the steps taken toward continuous remain somewhat shy. A paradox? Dr. Nicoud proposed a fresh look at the question through the chemist's eyes but with process engineer googles. A rational approach to process selection was detailed, starting from general considerations and basic concepts of chemical engineering. Different types of reactors were compared and practical examples were presented as an illustration, including several reaction cases (first order, catalytic, etc.), liquid-liquid extraction, and chromatography. Additional constraints often arise from the reaction nature: the specificities associated to chemical processes and biochemical processes were also investigated.

C. OLIVER KAPPE
Institute of Chemistry, University of Graz.

Towards the Continuous Manufacturing of Opioid-Derived Active Pharmaceutical Ingredients
Continuous flow (micro-) reactor technology offers the unique possibility to perform gas-liquid multiphase chemistry with unparalleled efficiency and process safety. In batch, the interfacial area is low and poorly defined, thus leading to prolonged reaction times. Due to the small characteristic dimensions of micro-reactors, large and well-defined interfacial areas are observed, typically orders of magnitudes higher than in traditional batch environments. These large interfacial areas lead to efficient mass transfer between the two phases. In this lecture several industrially relevant gas-liquid transformations involving pure oxygen were demonstrated. These are often associated with severe safety risks and process challenges, even using micro-reactor technology. An example in this lecture was a Pd-catalysed *N*-demethylation of an opioid derivative performed with 100% oxygen in an elevated temperature/pressure regime. Combined with hydrolysis/hydrogenation steps the overall three-step process directly leads to noroxymorphone, a key intermediate in the preparation of many opioid-based APIs.
Prof Kappe has been a pioneer in bringing back to life "forgotten" and hazardous chemistry through the use of continuous flow techniques. This lecture re-affirmed his position of authority in this area, but also highlighted the benefits of performing the scale-up in collaboration between university, pharma company supplier and CMO.

KAREN ROBERTSON
University of Bath

Flow Chemistry and Crystallisation – a Match Made in Harmony
The lecture presented an overview of how crystallisation can form an obstacle to the use of continuous flow processing. Flow chemistry and crystallisation have been separate worlds since their inception. Flow chemists use narrow bore (micro) reactors that can achieve unparalleled mass and heat transfer conditions but are inaccessible to flow crystallisation scientists due to blockage issues. Here were presented the development and optimisation of a new small bore (meso) crystalliser (KRAIC) that can be used as a combined flow chemistry and crystallisation apparatus or directly coupled to a preferred flow chemistry set-up.
Examples included instant precipitation reactions, where the combination of two solutions produces an immediate precipitate. In batch conditions it is very difficult to control the mixing of solutions that result in an array of polymorphs. Here the presentation described the use of flow technology to tightly control the mixing conditions and ensure segmented flow to prevent blockages of the flow crystalliser.

MARK ROELANDS
TNO

Advances in Development of Multi-Phase Flow Chemistry at TNO: Continuous Halogenation
Agile manufacturing systems that are automated, modular and flexible (feedstock, product, capacity, point-of-use) are nowadays being introduced into the fine chemical industry. Currently, different types of continuous reactors for flow chemistry have been demonstrated. Within the flow chemistry domain, TNO focuses on development and demonstration of equipment for multi-phase flow processes. TNO's objective is always to find and implement the optimal process and therefore not only use and test reactors from TNO's own portfolio, but also use reactors from external suppliers. As an example of TNO's work, the Flow4API project demonstrated how the halogenation of carboxylic acids with halogenation agents worked in continuous flow (See Scheme 1), furnishing the corresponding acyl halide. These reactive intermediates are generally important intermediates in organic chemistry, rather than products themselves, and are utilised in a myriad of organic reactions. Extended to Grignard chemistry in flow, the process was able to suppress Fittig-Wurtz coupling and deliver high quality product.

JOHAN TER HARMSEL
Zeton

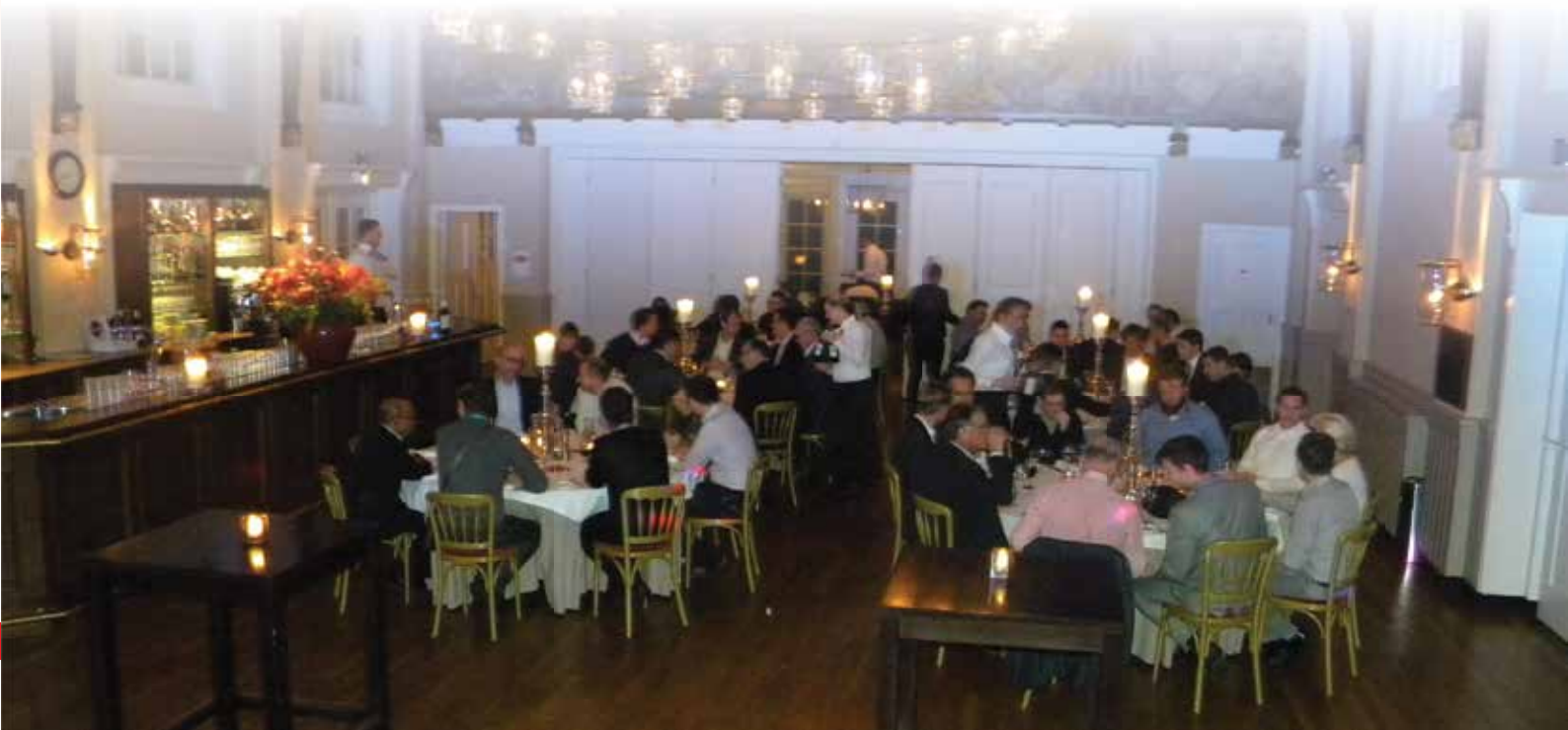
Flow Chemistry – Teamwork Creates Success
Already for about two decades, efforts have been made to enable the entry of flow chemistry in environments which were until recently dominated by batch-wise operations.
The initial doubts and reservations within these markets were difficult to counter. Consequently entrepreneurs of new reactor concepts had difficulties to gain momentum for a thorough introduction of their products into these markets. Recent interest by industry indicates a transfer from technology push to market pull for technologies facilitating continuous manufacturing with flow reactors. Manufacturers of reactors and auxiliary equipment together with service providers lead the way to innovative solutions that can further give a boost to safety, efficiency, flexibility and product quality in the production of a variety of chemical intermediates and products.
The presentation explained that strategic co-operations and commitment between manufacturers, full-service providers and (fine) chemical or pharmaceutical companies will accelerate further developments.

JAEYON YOON
SK Biotek

Flow Process for Pharmaceutical Chemicals – Commercial Production under cGMP
SK Biotek's continuous process program was initiated more than 15 years ago with idea originated from petrochemical industry which is SK's main business. SK's continuous process covers wide range of applications; static mixer type, fixed bed, continuous extraction and continuous distillation etc. These applications are in not only lab scale but also in commercial scale. Currently several commercial pharmaceutical products are produced using continuous process, some products are produced under validated cGMP condition. For the static mixer type applications are; fast exothermic and hazardous chemistry are good fit, such as organometallic reactions (Organo lithium coupling and Grignard), azide (Curtius rearrangement etc), hydrogen peroxide, tetrazole and nitro compounds. SK successfully developed low temperature organometallic processes under cGMP environment with full validations and waiting for regulatory inspections. Fixed bed catalytic applications are: hydrogenation dehydrogenations, acid/base catalysed reaction as well as Suzuki couplings. Fixed bed catalyst is usually more efficient than that of batch, easy to recover the catalyst, higher turnover, selective, and easy to work up (no need to separate catalyst from the product). Also these fixed bed reactors can handle extreme conditions, 300 atm and 600°C, which can perform exotic reactions that conventional batch reactors cannot handle.

WIM DERMAUT
Agfa Materials

Quick Wins using Flow Chemistry for Fine Chemicals Synthesis
The advantage of using flow chemistry for certain demanding chemical syntheses has been described extensively in the literature lately, often driven by research in large pharmaceutical companies. There is already a high level of expertise present when it comes to lab scale testing and even reports on commercial scale synthesis using flow chemistry are getting more and more common. This might strengthen the belief, mistakenly, that flow chemistry solutions for chemical synthesis are by definition complex and highly engineered. By an in-depth discussion of two actual case studies, the Agfa presentation clarified its approach to first focus attention on the identification of short-term achievable quick wins. Two case studies were described, one where the use of a standard pump configuration enabled a substantial gain in process safety by avoiding the handling of a very dangerous reagent, and another where a significant simplification of the process was obtained by flow processing. Lab scale research on these two processes was discussed, the optimization of the applicable process parameters, the design and characterization of the flow reactor used. This led to the first scale-up to pilot scale, processing several kilograms of product per day.



VENDOR PRESENTATIONS

CHARLOTTE WILES
Chemtrix

Application of Process Intensification to Fine Chemical and Pharmaceutical Production

Whilst chemical engineers are trained to think of continuous processing as being an efficient route to the development of safe and controllable processes, synthetic chemists have received largely the same training for centuries – which is based on the use of stirred reaction vessels. Consequently, within medicinal chemistry and development laboratories, focus is on the speed of compound preparation and not on the process or route employed to obtain the material. Looking to how reactions are conventionally performed, they are often executed under non-ideal conditions in order to gain control over the process; this can include the use of large volumes of solvent, cryogenic conditions, the use of stoichiometric reagents and long dosing/reaction times. Subsequent product isolation is then time consuming and results in the generation of large quantities of waste. The essential conclusions from Chemtrix were:
"Remove silos across business units to maximise benefits, look to the process as a whole –not just the part that you are responsible for and, finally, be open to different approaches!"

BRIAN WITTKAMP
Mettler-Toledo

Analytics in Flow Chemistry

In this talk the technology of in-situ mid-infrared for real time monitoring and optimization of continuous flow chemistries was presented.
Case studies included: G/L Homogenous Catalysis, Continuous Process for Alkene Ozonolysis, Vilsmeier-Haack Transformation and Stereoselective Mannich Reaction.
Current challenges associated with off-line analysis and how these were overcome with mid-infrared were discussed.

ANNA GERDOVA
Magritek

Developments in Bench-Top NMR Spectroscopy

NMR spectroscopy is one of a large number of techniques used to understand the behaviour of molecular materials. However the development of instrumentation for NMR spectroscopy has followed a very different path compared with that followed by most other chemical analysis techniques. The presentation discussed why these differences occurred, and how recent developments have enabled the introduction of benchtop, meso-field NMR spectrometers, which provide new tools to assist chemists and chemical engineers in understanding chemical processes. The current capabilities and performance of benchtop NMR spectrometers was described, and the use of benchtop NMR for continuous reaction monitoring was introduced.

BRUNO LENAIN
Kaiser Optical Systems

Raman spectroscopy as a process analytical instrument in continuous processing, monitoring, and control

Raman spectroscopy is an established tool in research analytical laboratories because of its sampling versatility, minimal sample preparation, and compatibility with aqueous systems.
Raman spectroscopy has excellent scalability, model transferability, and compatibility from microreactor to production settings. These features can be exploited to control flow processes involving gases, solids, or liquids in real time. For the past 20 years, Kaiser Optical has applied the measurement principles of Raman spectroscopy in a manufacturing environment for understanding, monitoring, and controlling continuous processes or unit operations. Continuous manufacturing is commonly used in chemical and petrochemical industries. Examples were shown of Raman spectroscopy as a tool to monitor flow reactions in microreactors, in secondary processing of pharmaceuticals, synthesis of dispersed polymers, and bioprocessing.

ANDREA ADAMO
Zaiput Flow Technologies

Continuous Efficient Multistage Extraction

Liquid-liquid extraction is a very common workup strategy in pharmaceutical production due to its high selectivity and large capacity at relatively small energy consumption. In many cases, multiple extraction stages are required to achieve a high degree of separation. Current industrial approaches have the disadvantages of excessively large footprint, limited flow capacity and, importantly, are difficult to scale-up.
A multistage counter-current liquid-liquid extraction at the ml/min scale was presented. The setup is essentially composed by a cascade of extraction steps; at each extraction step two immiscible phases are first contacted for mass transfer and then separated with membrane based liquid –liquid separators; after each stream proceeds to its subsequent extraction step.

GUILLAUME GAURON
Corning Advanced Flow Reactors

Corning® Advanced-Flow™ Reactors: Industrial Production Made Real

Corning Incorporated is the world leader in specialty glass and ceramics. Drawing on more than 160 years of materials science and process engineering knowledge, Corning creates and makes keystone components that enable high-technology systems for consumer electronics, mobile emissions control, telecommunications and life sciences. This talk highlighted how Corning® Advanced-Flow™ Reactor had been successfully applied in a variety of flow-chemistry processes, and communicated cases of seamless scale up from laboratory scale directly to industrial production units. Examples of industrial installations were presented to demonstrate that the industrial production is a reality.

VIKTOR GYOLLAI
AM Technology

Efficient Modelling of the Temperature Profile in Coflore Reactors

Controlling the temperature of an n^{th} order reaction in flow can be achieved with multiple heat transfer zones operating at different temperatures. The disadvantage of this set up is that it requires multiple heater-chillers which add cost and complexity. The Coflore ACR reactor uses actively mixed heat transfer cells which decouples heat transfer performance from HTF flow rate. This allows precise tuning of the jacket temperature with a single supply of heat transfer fluid by changing the flow rate of the HTF according to the values calculated by the prediction software.

ALAIN GEORG
Fluitec

Modular Process Technology for Continuous Chemical Reactions

For more than 2 decades, Fluitec has specialised in converting batch processes to continuous operation. A reactor concept based on the familiar mixer/heat exchanger was recently developed by the company for converting semi-batch processes to continuous reaction processes and in doing so combining a very high conversion rate with reliable control of exothermic reactions. This presentation gave an insight in how to convert an (exothermic) reaction process to continuous operation using an innovative mixer/heat exchanger. It explained how to test the process concept on lab/pilot plant scale and how to convert it to full production size. Topics covered included: process approach, reactor concepts, scale-up possibilities and examples.

We are pleased to announce that the 9th edition of the Symposium on Continuous Flow Reactor Technology for Industrial Applications

will be held in November 2017

Dates and venue will be disclosed soon

Stay tuned!

Posters

1	NON-PULSATING METERING PUMPS *Haruyuki Morikawa - Fuji Techno Industries*
2	TARGETING PARTICLE SIZE OF SPIN CROSSOVER COMPOUNDS WITH TUBULAR FLOW REACTORS *Pierre-Baptiste Flandrin - Bath University*
3	AN ATTEMPT TOWARDS RATIONAL FULL DESIGN OF FLOW REACTOR SETUP *Frédéric Toussaint - UCB Pharma*
4	BRIDGING ACADEMIA AND INDUSTRY WITH ENABLING TECHNOLOGIES *Claudio Battilocchio - Cambridge University*
5	CONTINUOUS FLOW RUTHENIUM-CATALYSED OPPENAUER-TYPE OXIDATION OF SECONDARY ALCOHOLS *Ricardo Labes - Cambridge University*
6	CATALYTIC HOLLOW TUBES FOR FLOW REACTORS *Haruo Sawa - Nippon Kodoshi Corporation*
7	FLOWPLATE® GEOMETRIES FOR MULTI-PHASE APPLICATIONS *Elsner Petteri - Lonza*
8	A NOVEL CONTINUOUS FLOW REACTOR FOR AUTOMATED PRODUCT AND PROCESS DESIGN *Harris Makatsoris, Samet Isaev, Ioannis Alissandratos - Cranfield University*
9	INTENSIFICATION AND OPTIMISATION OF REACTIONS WITH DIAZOMETHANE BY IMPLEMENTATION OF FLOW TECHNOLOGY *Joachim Hayen - UC Leuven-Limburg*