
Gayle De Maria

GAYLE DE MARIA
Chimica Oggi - Chemistry Today
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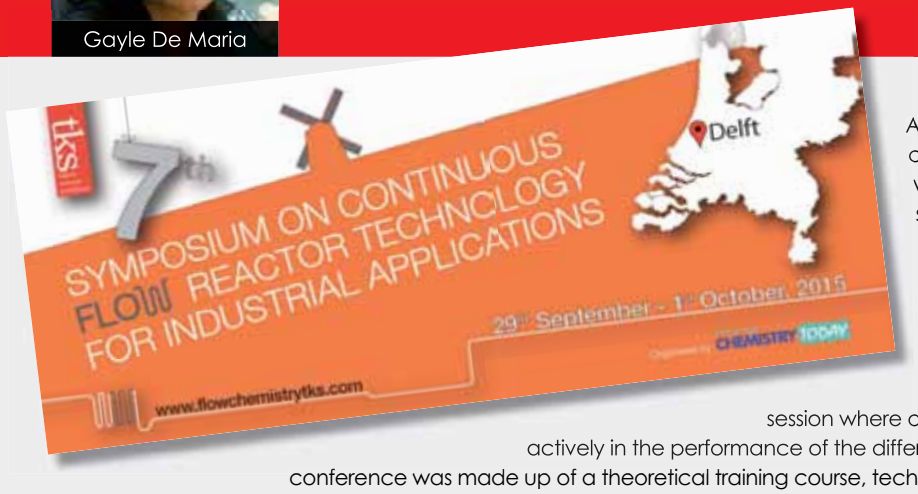
7th Symposium on Continuous Flow Reactor Technology for Industrial Applications



Almost as a yearly tradition – for the 7th consecutive year - we are now ready to share with our readers information concerning our latest symposium on "Continuous Flow Reactor Technology for Industrial Applications" which was held in Delft (The Netherlands) on September 29 – October 1, 2015.

Due to the positive feedback on the practical session performed in Budapest, TKS team organized in Delft a half day of "hands on" session where a limited number of people could participate actively in the performance of the different reactions. The remaining part of the conference was made up of a theoretical training course, technical and commercial presentations, workshops and a final Roundtable. The teachers of the training session – Kerry Gilmore (Max Planck Institute) and Peter Poechlauer (DPx Fine Chemicals Austria) – based their inputs on the training session of the year before and added new important data especially on the application side.

The participation was really strong thanks also to the strategical geographic area where many companies are involved in flow chemistry or are looking at this technology with great interest. The two days agenda were chaired by Jean Marie Bassett (Chem4Chem, formerly TNO) and provided presentations of case studies both on Pharma and Fine Chemicals Industries, of work-up solutions and analytical technologies. Two contemporary workshops, held by Ernie Hillier (Waters Corporation) and Mark Roeland (TNO), entered into details of analytical technologies and downstream processing. A final roundtable summarized the most important issues raised during the event and saw the participation not only of the speakers but also of participants. An exhibition area with companies showcasing their equipment and services completed the offer of the event.

Below a summary of the Practical session, lectures, vendor communications, posters and workshops.

PRACTICAL SESSION

People were divided into groups and took part in the demonstrations held by five companies. Please find the details below.

Viktor Gyollai - AM Technology

Efficient liquid-liquid extraction using Coflore dynamically mixed flow reactor

The Coflore® mixing technology has been shown to give high mixing intensity independent of fluid velocity for both homogenous and multi-phase systems. Strong mixing is beneficial to mass transfer limited reactions but also to work up steps such as extraction. Moreover, the ability to have two streams flowing in counter current can bring significant advantage in terms of extraction efficiency and reduction in solvent use. The Coflore ACX block fits into the same flanges and shaking platform as the Coflore ACR reactor and it can be heated to drive the separation. It comprises of up to 8 mixing cells and separate channels for the light and heavy phases. The fluid with higher density is injected at the second top cell of the block through the side port while the lighter phase is injected via the side port at the second cell from the bottom. The raffinate and the extracts come out from the bottom and top outlets respectively. The extractor performance is dependent on efficient mixing of immiscible fluids and good phase disengagement.

During the practical session the solution of an acid-base indicator in aqueous acetic acid was extracted using petroleum ether. The intense red solution lost its colour gradually as it travelled down the extractor.

The participants also had the opportunity to have a closer look at the ACR block to be able to quickly understand why the mixing is so efficient in the Coflore reactors.

Charlotte Wiles - Chemtrix

A safe and efficient method for the preparation of organic azides under continuous flow

Looking to the chemical industry, we see that the use of

flow reactors is increasing for small molecule production, specifically where increased process control is required – this can be for reasons of reaction selectivity, but also process safety. In addition to the ability to operate under high temperatures and pressures, a significant advantage of flow reactors is their low hold-up volume and absence of a headspace – facilitating the development of synthetic routes for challenging chemistries.
Whilst the azide functional group offers the chemist a facile route to the installation of synthetically interesting motifs – the production of organic azides is however problematic due to their thermal instability and the risk of HN3 build-up in the headspace of reactors. During the practical session, the concept of rapid reaction screening and the performance of conventionally hazardous reactions was demonstrated via the azidation of an alkyl mesylate using Labtrix Start – exploring reaction temperatures of 100 to 195 C!

Alessandra Vizza, Guillaume Gauron - Corning
Let the light flow
The proposed reaction was based on the redox chemistry of iron, which can be induced with 405 nm.
The reaction equation is:

$$MB + nFe^{3+} \underset{dark}{\overset{light}{\rightleftharpoons}} (S + L) + nFe^{3+}$$

In this case MB is methylene blue, which was transformed into color less S (Semiquinone) and L (leuco methylene blue).

Rafael Kuwertz, Stephanie Peschke - Ehrfeld
Process development made easy: automated variation of parameters for a neutralisation reaction in a modular lab plant
The use of micro-/millistructured reactors in the continuous flow technology benefits from a high surface to volume ratio. Chemical reactions which require a rapid heat exchange, rapid mixing or a defined residence time with a narrow distribution can be conducted in the Modular MicroReaction System (MMRS) of Ehrfeld Mikrotechnik BTS. Due to the small channels the hold-up in the reactor is significantly reduced leading to a faster response time, enhanced safety and hence an easier control of the reaction. The combination of scalable interface modules with the MMRS technology enables a fast and easy pathway from R&D to production using high performance flow reactors.
During the practical session two concepts of the continuous flow technology were presented with a neutralization reaction as example reaction. The first concept showed the transfer from batch to continuous flow using micro mixer. Whereas the second concept used a scalable integrated reactor/mixer system of the FlowPlate® Lab technology. In addition the application of several sensors (pressure, temperature, pH, optical cell) with the automation and control unit LabManager® as well as an auto sampler AutoSam® demonstrated the easy, flexible and fast automation of this technology.

Richard van Someren, Marc Crockatt, Dirk Verdoes - TNO
Multi-Phase Flow Chemistry
TNO has implemented and demonstrated several multi-phase chemical reactions in flow chemistry over the last few years. This concerns continuous slurry processes with a variety of solid particles in a liquid medium with or without a gas phase. A demonstration of such a process was given in a bench-scale continuous flow rig that was developed specifically for this purpose.

LECTURES

Fabrice Odille - SP Process Development
From laboratory to pilot plant – learning by doing
Flow reactor is a technology with great potential to increase effectiveness in a process. A lot can be accomplished with such reactor and the lead time for the development can be shorter. Many data point can be gathered in a simple experiment. This case study demonstrated the scalability of a fast and exothermic reaction using micro reactor and meso reactor. In the scope of this study it was exemplified how issues with precipitation can be handled to be able to produce large quantity of material. The case study was based on a Grignard type reaction to produce selectively a ketone from a ester. The importance of mixing and heat transfer was presented. The development was performed in either a Sigma Aldrich glass chip reactor and in an ART PR37. The large scale manufacture was performed using different plates of different volume of the ART PR37. How to cope with reaction being heat sensitive when going in up in scale was demonstrated.

Massimo Bertoldi - La Mesta
Examples of process intensification in Raptor at production scale
The concept and the performances of the proprietary continuous tubular reactor named Raptor were presented. In the plug flow reactor, the fluid is moving through a cylinder (the reactor geometry) as a series of thin "plugs" in the axial direction. Each plug has an uniform composition but different composition from the ones before and after it. The key assumption is that the fluid is perfectly mixed in the radial direction but not in the axial direction. Each plug is considered as a separate entity. The heat and mass transfer are maximized. La Mesta has designed and developed a plug flow reactor to intensify the process parameters for multiphase reactions. The small reactor volume facilitates the easy handling of hazardous compounds, instable materials and highly exothermic reactions in very safe conditions. The process control, the safety, the environmental, product quality and economical aspects for the plug flow reactor versus the batch reactor for different types of reactions were considered. Practical examples of carbonylation (CO at high pressure in corrosive solvent), hydrogenation (heterogenous and homogeneous catalysts at high hydrogen pressure and temperature), phosgenation (COCl2 used in stoichiometric amount), multi-steps (the reaction control: thermodynamic versus kinetic equilibrium), hazard (uncontrolled onset CO2 gas evolution) and cryogenic reactions (possible to work economically at -90°C with high flexibility) were disclosed in details to demonstrate the real advantages of this intensified process

technology. 5 plug flow reactors (3 at production scale and 2 at pilot scale) are working at La Mesta site. A continuous plug flow reactor with an inner volume around 1 liter can produce up to hundred kilograms of a fine chemical per day.

Gareth Alford - GSK

Small, Agile Factories: How to deliver the precision of Continuous Processing, with the Agility Required for Pharmaceutical Manufacture

Batch Processes have and will continue to fulfill an important role in the manufacture of Active Drug Substance; they allow multiple recipes to be executed in the same core equipment. However, the compromise is, batch fails to deliver the precision, speed of manufacture and intensification of a flow process.
Here, Gareth presented how at GSK, they are modularising a library of flow and batch unit operations to allow to execute different recipes, quickly, in a Flow mode. They expect that this approach not only changes the way the Factory looks, and costs, but how it is built, deployed and operated.
They are starting applying these approaches with API manufacture, but also thinking about how they may bridge to alternative formulation technologies.
They believe this will allow GSK to deliver more medicines of value to patients, both in affordability and function.

Christopher Hone - University of Leeds (*in cooperation with AstraZeneca*)

Process Intensification for Reaction Kinetics using Continuous Flow Reactors

Continuous processing technology is transforming the way that fine chemicals are manufactured. Currently there is no defined scale-up path for flow technologies within high value manufacturing environments which is a major barrier to the uptake of continuous processing. Statistical approaches, such as Design of Experiments and numerical self-optimising systems, identify a single set of optimal operating conditions that maximises yield or other reaction metric. These techniques optimise well in the equipment used for the optimisation, but do not reveal an explanation as to why a response is dependent on a particular input.
The primary focus of the methodology described in this presentation is to generate models which describe the rate-limiting kinetics utilising continuous flow technology.
The approach can be applied with small material quantities and reflects that there is limited time and resource available for process development. Scale-up using such models significantly reduces the risk compared to directly transferring laboratory conditions to the pilot plant scale. The methodology has been implemented for the rapid generation of kinetic models using sequential experimentation of process-relevant design space. Small scale experiments were conducted using a small scale automated coil flow reactor to collect data. The models were used to explore the design space and identify the optimal operating region. Subsequently, the reactions were successfully scaled-up to a different reactor for chemical manufacture. The approach has been applied to a series of industrially relevant reaction case studies.

Wouter Stam - Flowid

Butyl Lithium reaction executed at room temperature

The SpinPro Reactor, based on patented rotor-stator spinning disc technology, has been used for the production of a pharmaceutical product via a lithium-halogen exchange with n-butyl lithium. This process is traditionally carried out at very low temperatures between -70°C and -20°C. In bulky batch processes, these cold conditions are required to prevent runaway of this highly exothermic reaction. Major drawbacks of these near-cryogenic conditions, however, are the significantly reduced reaction rates, lowered productivity, and very high cooling costs.
In the SpinPro reactor, heat transfer is so high that runaway of the reaction and potentially hazardous situations can be avoided, even at near ambient temperatures. Moreover, given the very low hold-up of reactant materials in the compact reactor, the process is inherently safer.
It was found that at very moderate reaction temperatures between 0°C and 20°C, productivity dramatically increases compared to the traditional batch process. In addition, the very high degree of mixing in the reactor prevents the formation of hotspots, giving a high degree of control over product selectivity.
The experimental results obtained with the lithium-halogen exchange reaction in the SpinPro using n-butyl lithium have thus proven three things: productivity can be raised, selectivity can be increased, and cooling costs can be reduced.

Markus Wysshaar - Erbo Spraytec AG

Continuous Fluidized Bed Spray-Technology: A Novel, New Microencapsulation Method for Large-Scale Production of Food and Feed Ingredients

As a toll- manufacturer, Erbo Spraytec AG runs two fluidized-bed multiprocessor production plants of the newest technology for microencapsulation of food and feed ingredients in large scale (500- 3500 kg/hour). The spouted- bed PP 500 plant is designed to encapsulate active substances in water soluble matrices, whereas the fluidized-bed top-spray plant, MP 11, is designed for coating and matrix encapsulation with fats and lipids.
For R&D- work Erbo Spraytec AG runs two pilot plants with analogue technology. Developed new processes and products can be up-scaled in-house. Quality control of raw materials and finished products can be conducted in the laboratory in-house on state of the art analysis instruments.
The diversified technology permits an extraordinary variability with regard to the raw materials as well as to the properties of the end products. By combining different starting materials and processes it is possible to produce tailor-made powder products with defined and specific properties, as e.g. protection against environmental influences, taste masking, controlled release of active ingredients, etc. The specific properties can partially even be combined in the same product. If requested, also the logistics for the raw materials and finished products as well as the filling in variable and customer-specific packaging solutions can be organised.
Technology and processes were explained in the presentation on examples of applications for food, feed and cosmetics, i.e. odor-masking of natural extracts, encapsulation of omega-3 rich fish oils, controlled release of feed ingredients, spray-granulation of hygroscopic materials.

Ernie Hillier - Waters Corporation

Enabling Comprehensive Process Understanding in Continuous Flow Reactions with Online UPLC Analysis

Flow chemistry offers many well-understood advantages

over batch processing, such as thermal stability, optimal material usage and product quality, minimal waste, and minimal facility footprint and requirements.
With the combination of lab scale continuous flow reactors and appropriate sensitive and selective analytics, reaction kinetics can be well understood in early development with minimal cost and time. Of interest in today's current climate, and with recent regulatory changes regarding impurities analysis and reporting, is the understanding of the pathways promoting their formation. This is of particular interest for impurities that are known to be difficult to clear in downstream process steps or are known to be genotoxic.
PATROL UPLC methods can be used in the early development for reaction understanding and optimization. Studies can be performed rapidly, with the analytical output from the Empower software dictating the next experiments in rapid succession. The automation of sample analyses and transfer of analytical information can further streamline developments, leading to quicker decision making, and ultimately more patent life profitability. Additionally, the same analytical methods can be used in the scale up and commercial operations for monitoring of CQA's and for closed-loop process control.
With the combination of these evolving technologies and techniques businesses can achieve goals of increased efficiencies that drive product quantity and quality, with the added benefit - of beating competitors in Time to Market.

Mark Roelands - TNO
Recent developments in multi-phase flow chemistry at TNO, applying process system engineering methodology
To enable the implementation of modular flexible plants in fine-chemical industries to produce high added value product, TNO has identified various areas where breakthroughs can be realized to further decrease the investment and operating costs. In the introduction Mark presented a number of the envisioned breakthroughs.
In the last decade many show cases for different types of modular continuous reactors for flow chemistry have been demonstrated at lab scale. In TNO's view there will not be "a one size fits all solution" that can cover the whole area of flow chemistry. Within the flow chemistry domain, TNO focuses on development and demonstration of equipment for multi-phase flow processes, with a special interest in processes involving solid compounds. TNO's most important aim is to find and implement the optimal process and therefore they not only use and test reactors from TNO's own portfolio, but also use reactors from external suppliers. A few examples of recently tested combinations of reactors and processes were presented.
Furthermore, they foresee that holistic process models will become more and more important for the development and scale-up of process systems combining different equipment modules in one system. Ideally, such a process model includes all relevant aspects needed to model, predict and control the process. Examples of aspects are kinetics and equilibria of chemical reactions, heat and mass transfer and flow behaviour. With the development of validated process models TNO aims to accelerate and to improve the development at lab scale as well as to streamline the design and construction of decentralized, flexible production plants.

André H.M. de Vries - DSM Chemical Technology R&D BV
Flow chemistry, how to bring it to industrial scale?
Flow reactions are now becoming accepted in the fields of pharmaceutical manufacture, agrochemicals, flavours and fragrances, and fine chemicals where smaller production amounts are required. The advantages of flow have been extolled by many and include a greener plant, for example by the use of reduced amounts of solvent, improved energy efficiency, and the ability to run hazardous reactions in a safer way. The use of a flow reaction also moves the implementation of a reaction from having a plant and adapting it, and the chemistry to fit. Flow allows the equipment to be more suited to the chemistry required.
Many companies now sell flow reactors, some with specific requirements in mind, such as electrochemistry and photochemistry. Even for a reaction that does not need this specialized equipment, there is still some adaption necessary to fit the chemistry to the reactor. Of course, a dedicated plant could be built but this is a financial risk and volume predictions have to be good to make it efficient and cost effective.
One approach DSM has been using of late is to design a flow reactor to fit the chemistry. This allows the use of mesoreactors rather than microreactors and addresses such issues as mixing. The goal has been to make flow reactors that will be optimal for the desired transformation yet cheap enough that they can dedicated to that use. If GMP is required, the reactor is discarded after use and a new one used.
The manufacture of these reactors has been achieved by the use of 3D laser metal printing; a technique that has been available for some time but not used in this context. Pumps and work-up equipment still needs to be added to the system, but for the reactor itself there is now no need to make the chemistry fit the plant. Examples were given.

Charlotte Wiles - Chemtrix
Exploring Novel Process Windows for API & Complex, Expensive Molecule Production – Flow4API
The presentation focused on the observations made during a public-private initiative called Flow4API (exploring novel process windows for API – and other complex/expensive molecules – production (and intermediates thereof) in continuous flow systems). The consortium comprised of 4 members - ISPT, TNO, Synthon and Chemtrix and focused on evaluating the challenges and advantages associated with the continuous manufacturing of API's together with complex molecules with typical values of 1000's Euro/kg and annual production volumes of < 1 kg/y. With common processes selected for evaluation, the goal was to develop learnings that could be generally applied to the production of pharmaceuticals, flavours, fragrances, veterinary products and fine chemicals – extensions to this project was also described.
By combining continuous flow reaction screening with design of experiment and process analytical tools the group were able to rapidly short list suitable processes for further detailed optimisation and scale-up. The result being a series of telescoped processes operating with improved yields and in some cases reduced reagent stoichiometry when compared to the starting batch reactions. Examples were given of the transformations assessed and the lessons learnt.

VENDOR COMMUNICATION

Stephanie Peschke - Ehrfeld

Promising application fields with flow reactors: batch-to-conti and scale-up

In the past, chemists and engineers were not aware of which great benefit may bring the use of micro- and milli reactors for their daily challenges. Also their managers were not aware of the cost savings arising from the implementation of flow equipment. There is still a lack of attractive applications and the related benefits for exactly these examples, especially for the use of flow technology equipment in production scale. Ehrfeld has investigated 3 attractive fields and showed how beneficial the use of the technology platform micro- and milli-reactors can be. They selected promising examples from the following application scope:

- Peroxide synthesis – explosive reactions
- Sulfonations/Alcoxylations (Ethoxylations) – very fast reactions
- AI/API – multistep synthesis (pathways in one process step); fast reactions like Organometallic reactions (Lithiations, Grignard reactions), Nitrations, etc.

Each example showed a short analysis of the product market, a short introduction into the application, the challenges for the conventional synthesis compared to the process in flow, the approach of turning the reaction from batch-to-conti and the idea of a lab plant set-up, which is further scalable to production scale.

Alessandra Vizza - Corning SAS

Corning® Advanced-Flow™ Reactors: Customized solutions to meet chemical processing challenges

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.
In last 12 years, Corning has brought to the chemical process industry with a powerful process intensification platform: Corning® Advanced-Flow™ Reactor (AFR) and their application technologies, which cover from "fast" lab-scale flow process development to "seamless" scale-up of flow process to commercial production.
Transferring chemical synthesis from traditional batch technology to continuous flow may bring significant advantages in the reduction of cost, complexity and safety that are usually associated with process scale-up. In the pharmaceuticals and fine and specialty chemicals industries products quality and requirement becomes today crucial parameters. With traditional batch technology, it is often not possible to maintain optimum product quality when scaling up a process in a short period of time. However, seamless scale-up can 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.
Scaling up processes using Corning AFRs is faster than with traditional batch process and the time to market is drastically reduced. In addition, this technology reduces development and production costs.
Corning® Advanced-Flow™ Reactors have been successfully applied in a variety of flow-chemistry process developments. This presentation communicated about the cases of seamless transfer of flow processes from lab size directly to industrial productions in China and Europe respectively.

Petteri Elsner - Lonza

A Toolbox Approach for the Pharmaceutical Production in Flow

Several reaction types that are being conducted batch or semi-batch wise within the pharmaceutical and fine chemical industry would potentially benefit from continuous flow operation in terms of economy and environmental impact. Moreover, process development and scale-up would be facilitated by the adoption of continuous flow reactors in the initial stages of molecule discovery and synthesis. Depending on the characteristics of the chemistry, different operating scenarios would be favored as compared to batch or semi-batch processing. Flow regimes and the nature of the process stream play an even more vital role when micro- or milli-dimensioned reactors are used for chemical manufacturing. Reaction rates and phases will dictate which type of equipment is suited best for the development of a continuous process. Based on their experience, a combination of several equipment pieces along the reaction axis leads to the most intensified process in terms of throughput and quality. A toolbox approach where a limited amount of modules and micro-structured plates are combined to account for a large space of chemical characteristics was presented.

Andrea Adamo - Zaiput Flow Technologies

Integrated Liquid-liquid Separator and its Uses in Flow Chemistry

Successful implementation of flow chemistry based processes requires the availability of adequate tools for in-line chemical work-up. During the speech Andrea presented a liquid-liquid separator designed for flow chemistry applications. The separator exploits surface forces to achieve separation of immiscible liquids, an integrated pressure controller ensures that adequate separating conditions can be maintained during operation. Andrea first discussed in detail its principle of operation, its properties and typical performance. Then he provided some examples of practical applications of the device drawn both from his own work and current literature. The example covered cases of extraction, multistep synthesis and solvent switch. As multistep example discussed the synthesis of fluoxetine that involves 3 reactive and 3 extractive steps all integrated in one single continuous process.

Viktor Gyollai - AM Technology

COFLORE – Continuous Manufacturing Technology for Speciality Chemicals Production

For some time now, the high value chemical manufacturing industry has expressed an interest in flow processing. This has now become a real desire to move the development of flow

processing out of the laboratory and research environment and implement it in the plant arena to gain commercial benefit from the technology.
This shift requires the flow equipment to cope with the demands of:

- Flexibility – different reaction times, different phases
- Versatility – synthesis step, work up steps
- Scalability – reproducible results from lab to production.

The Coflore mixing technology has been shown to give excellent plug flow across a wide range of fluid velocities. This enables the Coflore reactors to offer the versatility of a batch reactor with the efficiency advantages of continuous processing. The same reactor can be used to run different processes which require different residence times by changing the flow rate rather than having to change the flow path or length of the reactor. This also results in very predictable scale up and our active mixing enables the processing of multi-phases, including mixed gas-liquid-solid systems.
One key area of interest is hydrogenation. On top of the capital and running cost reductions, the reduction in reactor footprint greatly improves the safety of this process. Used as a development tool, it is possible to test various operation conditions in the Coflore reactor leading to a smaller, more efficient system.
Another area of interest is biocatalysis. The Coflore has demonstrated consistent advantages over batch or other continuous systems for processes such as oxidations, esterifications and reductions with reaction rates up to 20 times faster than small batches. Thanks to its design, the faster reaction rate is maintained during scale up.
Apart from synthesis, the Coflore can be used for counter current reactions or extractions. Counter current reduce the amount of solvent required and can be plugged in series with the continuous reactor. The mixing intensity can be tuned to suit the process. Effective counter current extraction can be achieved also for problem systems with tendency to emulsify and small density difference.

Miguel A. Bañares - Instituto de Catálisis y Petroleoquímica, CSIC
Real-time Raman monitoring during heterogeneous catalyzed reaction, the acetalization of glycerol using acid catalysts
The acetalization of glycerol with acetone produces solketal (2,2-dimethyl-1,3-dioxolane-4-yl methanol) with total selectivity. Glycerol acetals and ketals are widely used in industry as bases, pharmaceutical intermediates, additives, flavors, and scents. They also enhance the viscosity and cold properties of biodiesel; optimize flash point and oxidation stability; and reduce the emissions of carbon monoxide and hydrocarbons, among others.
This reaction demand acid sites and the group investigated several mesoporous catalysts with different acidic properties, in order to assess the role of porosity on the interaction between glycerol and acetone and the role of the nature and number of acid sites (Brønsted and Lewis) on the reactoin rate, selectivity and mechanism.
Real-time Raman monitoring during reaction is used to study the influence of all these catalyst parameters, to probe the reaction mechanism, and to assess the role of intermolecular interactions (1). The molecular information provided by this technique leads to a more complete process understanding, which in turn is an enabling technology for implementing process analytical technologies (PAT).
The progress of the acetalization reaction was monitored following the variation in intensity of characteristic Raman bands and using chemometric analyses. The results obtained by real-time Raman monitoring illustrate the interaction between glycerol and acetone forming an adduct and the progressive formation of solketal. Raman spectra illustrate the formation of 3-(2- hydroxypropan-2-yloxy) propane-1,2-diol intermediate species. Raman monitoring enables real-time control of the reaction, thus enabling the optimization of reaction conditions for a more efficient reaction.

Pierre-Baptiste Flandrin - University of Bath
Improving mixing in different flow reactors by CFD simulation with a view to production scale-up
A range of different CFD (computational fluid dynamics) simulations have been employed aimed at increasing the efficiency of mixing inside various geometries of flow reactors, intended for use in upstream chemical self-assembly and downstream crystallization and formulation processes. In industry, Design and Simulation software packages are used to deliver better design and manufacture improved products. This approach allows the prediction of product behaviour, testing of innovative concepts and optimization of designs early in the design and engineering process. It also provides the capability to validate and better understand the implications of design choices before manufacturing.
Analyses were made using Ansys Fluent Software with different UDF (user defined functions), giving insight into flow behaviour in an initial set of reactor geometries. Turbulent flow was studied in the continuous reactor geometry of a COBC (Continuous Oscillatory Baffled Crystallizer) and in a Scalable BTR (Baffled Tube Reactor) at the University of Brunel as well as segmented flow in the KRAIC bespoke flow crystallizer at the University of Bath. The set of performed experiments showed that, for the COBC and BTR, the oscillations between each baffle have a complex flow structure (turbulence which depends on the frequency and the amplitude of the signal given by the pump). For segmented flow different pipe geometries (T, Y and K-pieces) and internal diameters (0.5, 1, 2, 3 and 4 mm) were simulated showing different resultant slug sizes. The comparison between simulation and experiment proves that CFD simulations are able to predict accurately the flow behaviour in multiple situations. These reactors are designed for the purpose of scaling-up lab scale batch reactions to production scale without loss of reaction selectivity whilst maximising yield.

Javier Guerra - Crystal Pharma SAU
Macromolecular Ruthenium catalyst in flow photochemistry. In-situ recovery through size-exclusion nanofiltration
Organic photochemistry is in its renaissance as flow

photoreactors become the solution for the limited light penetration through the reaction medium. This drawback was the main limitation for industrial applications of organic reactions mediated by light. The millimeter scale of the channels allows for an intense and homogeneous photon flux leading to fast and clean reactions. In addition, duration of the light exposure can be accurately controlled by the system flow rate, thus avoiding side products from the overirradiation of the reaction mixture.
The group reported the use of a macromolecular photocatalyst based on $[Ru(bpy)_3]^{2+}$ units anchored to a second generation polyamidoamine (PAMAM) dendrimer in different flow photochemical reactions. $[Ru(bpy)_3]^{2+}$ is a powerful single-electron-transfer (SET) agent that makes possible redox reactions catalyzed by light under environmentally benign reaction conditions. Visible light is a clean energy source and its use fulfills the requirements in the search of sustainable chemical processes.
Three model reactions were chosen to perform this study: Appel reaction in the absence of phosphines as reducing agents, reductive opening of chalcone epoxide and azide reduction. These reactions have successfully been performed by this catalyst under visible-light irradiation (450 nm) by means of LEDs leading to results that are in agreement with those published in the literature with the monomer $Ru(bpy)_3Cl_2$. As reported, the translation of the above mentioned photochemical reactions into flow continuous processes led to severe time reductions compared to batch chemistry.
The novelty in this work lies on the recycling of the catalyst that facilitates its *in-situ* reuse. Current works are addressed to find the right conditions to perform continuous nanofiltration through a modified Zaiput liquid-liquid separator system.

Svetlin Isaev - Brunel University London
A Novel Continuous Flow Reactor for Automated Product and Process Design
Reactor configuration and characteristics take an important role in many industrial applications involving chemical synthesis and processes and design and optimisation. The requirements of modern synthetic chemistry are currently undergoing a transformation from traditional batch processes to continuous flow processes. The group presented a novel continuous flow reactor that allows the rapid design and optimisation of scalable processes for a range of materials in liquid or mixed phases. The flow reactor it is predominantly a Continuous Oscillatory Baffled Reactor (COBR) but due to its modular design is easy to manufacture, scale and maintain. It comprises a cylindrical tube containing a series of orifice baffles placed at specific distance. An oscillation mechanism and measurement probes directly integrated into the flow channels for in situ measurements enable close – loop process optimisation and control. The performance and characteristics of the reactor were presented together with a series of case studies including bioprocess for biofuel production, small drug for molecule synthesis and optimisation and beverage formulation.

Takashi Ouchi - Takeda Pharmaceutical Company Limited
Process Intensification for the Continuous Flow Hydrogenation of Ethyl Nicotinate
A particular challenge that has not been fully met is how to move rapidly and safely to scale up reactions in research laboratories from mgs to kgs. It is precisely under these circumstances where new tools can greatly assist the process. Indeed, by definition, process intensification is the "strategy for making dramatic reductions in the size of a chemical plant so as to reach a given production objective". Accordingly, this approach can involve shrinking the size of individual pieces of equipment or by cutting the number of unit operations or devices involved. In addition, interest in greater sustainability through more selective processes, often under heterogeneous conditions, has become an attractive goal. Nevertheless, working with and scaling up of hydrogen gas reactions brings with it well recognized issues (i.e. safety assessment, mixing and H2 solubility), which are the subject of keen interest due to the importance of the reductive process in fine chemical manufacture. One such process involving precious metal catalyzed hydrogenation of substituted pyridines is of interest due to the importance of the functionalized piperidine products as intermediates in the preparation of many biologically active molecules. A process intensification study for the selective, partial and full hydrogenation of ethyl nicotinate using a trickle bed reactor for meso-flow transformations (HEL FlowCAT) was reported. The process achieved a throughput of 1219 g/d (space-time yield of 78 g/h of product per g of active catalyst) for the partial hydrogenation to ethyl 1,4,5,6-tetrahydropyridine-3-carboxylate, whereas the productivity for the full hydrogenation process reached a 1959 g/d of throughput (space-time yield of 408 g/h of product per g of active catalyst) on this laboratory scale flow chemistry platform.

J.-C. Remigy - Toulouse University
Catalytic Polymeric Membranes: Competitive microreactor for sustainable chemistry?
Catalytic membranes have several applications due to their advantages like catalyst immobilization or the intensification of the contact between reactants and catalyst. Most catalytic membranes are based on inorganic materials due to their high resistance, but inorganic membranes cannot attain the high packing density offered by polymeric hollow fibre membranes which can reach up to 10,000 m^2/m^3 at low cost.
Metallic nanoparticles are particularly interesting in catalysis due to their unique physicochemical properties but also from the massive increase of surface area upon reduction of scale in comparison with classical heterogeneous catalysts. However their use as suspended solids presents some drawbacks like the necessary recycling step. Stabilization of suspended nanoparticles is also an important problem to avoid aggregations which results in a decrease of the catalytic activity.
Since 2006, this research group has been producing polymeric catalytic membranes using palladium nanoparticles. The nanoparticles are in-situ generated on a polymer layer grafted at the surface of polymeric membranes. The grafted layer is a polymer gel where nanoparticles are homogeneously dispersed in a non-aggregative way. The nanoparticle's diameters are around 2 nm and nanoparticles are close together (d~2nm) leading to a high local concentration (~10^{14} NP/mm^3). The nanoparticles are entrapped in the grafted layer, without observing palladium leaching.
Suzuki–Miyaura cross-coupling was performed in a continuous way using such membranes by filtering a reactants solution in ethanol at 60 °C. Full conversion has been obtained for a residence time around 10s, only giving the desired cross-

coupling product. The scale-up of such results to industrial hollow fibre modules at constant flux density is only done by multiplying the membrane surface area. Production capacity up to 10,000 ton/(year.m^3) are achievable like such obtained with microreactors. Thus, the catalytic HF modules will be microreactors operating at low temperature with high efficiency, leading to a sustainable chemistry.

Karen Robertson - University of Bath

Precipitation Reactions in a Flow Environment

Flow chemists have used microfluidics to impart an unparalleled control over reactions yielding outstanding optimisation and process intensification. The major caveat to microfluidics is that precipitation reactions are limited to nanoparticles thus excluding a wide range of chemistries that could benefit from the unique environments offered in flow. By increasing the internal dimensions of the reactor solids may be permitted but at the cost of desired fluid dynamics and amount of reagents required to operate the reactor. Segmented flow offers a compromise between reactor size and reagent cost whist retaining many of the characteristics of microfluidics.

A benchtop flow reactor (KRAIC) was presented which uses liquid-segmented flow to achieve the control necessary to satisfy the challenges of flow crystallisation enabling access to environments not achievable in standard batch chemistry methods:

1. Many compounds are known to produce high yields only on the small scale. By encapsulation into discrete slugs in a segmented flow environment a series of micro batches (~0.5 ml) are effectively deployed thus allowing a high yield, high volume of product to be obtained through a flow environment without the need to set up individual crystallisation experiments.
2. Fast precipitation reactions are difficult to control and often lead to crystalliser failure through blockages when performed in flowing environments. By creating slugs of the two solutions and combining these slugs in a controlled manner within a segmented environment the mixing ratio of reactants can be carefully controlled. The segmented flow environment prevents adhesion of the particles to the mixer preventing blockages.

Laurentiu Vladuceanu - Fuji-Techno Pumps - Motor Technology Ltd

Pulse free metering pump for continuous flow production

Tremendous amount of work done today to develop new leading edge technologies in food, pharmaceutical, polymers, chemistry etc., brought to life new critical requirements in terms of processing parameters that needs to be fulfilled in order to succeed.

For increasing process yield and product quality in a continuous flow application it is crucial to have a pump capable to feed continuously, non-pulsating and accurately even under varying parameters conditions, capable to work any type of continuous flow microreactors, skids, etc., to meet high demanding processing conditions: high pressure, critical temperature, wide range of discharging flow rate, accuracy and pulsation free as well as low shearing effect.

Fuji Techno's Super Metering Pumps (SMP) have been created, designed and manufactured to fit all types of continuous flow applications (microreactors, skids) achieving best possible results in this respect:

- Best discharge flow accuracy (better then ±0.1%), which is more accurate than flowmeter, throughout a specified rate range.
- Unrivalled constant flow rate even under varying discharge pressure;
- Pulsation free;
- Perfectly proportional flow rate to pump speed and lack of adjusting lapse time.

Super Metering Pumps produced by Fuji Techno Industries are currently used in wide range applications, lab or industrial scale, in various industry like pharma, chemistry, food, oil, etc. by large number of industry leading companies for over 30 years because of their unique performance:

- Injection urethane or additives into extruder;
- Cosmetic, pharmaceutical, explosives and film manufacturing;
- Precision coating, spraying, spray dryer and combustion;
- Chromatographic analysis, food processing, accurate mixing;
- Semiconductor washing.

Fulfilling all requirements without compromise Super Metering Pumps helped customers and partners to achieve consistently increased yield and surpass all processing barriers in continuous flow process in supercritical conditions of temperature, pressure and flow rate.

Participants were divided into two groups and each group had a topic to discuss. Each group had a facilitator who managed the exchange of opinions and draw the conclusions.

Ernie Hillier - Waters Corporation

Analysis - Choosing analytical techniques that maximize process understanding and response

The goal of this session was to understand the needs of flow chemistry in combination with existing technologies and the potential of incorporating new technologies. Do all these technologies deliver the qualitative and quantitative results in a timely manner?

1. What are the needs for each measure
2. Appropriate analytical techniques
2.1. FTIR, NMR, LC/UV, LC/MS
2.1.1. Capabilities and requirements for use
3. Measurement - continuous real-time or endpoint testing
3.1. Post process testing vs QbD
4. How to connect the data output to the process control
4.1. Data interpretation, visualization, and use
4.1.1. Trending plots, MVDA, Predictive models, DCS comms (feedback/feedforward control)

Group Discussion:

Which criteria an analytical method would have to meet to serve the needs of a continuous process, and, which

analytical methods would qualify for.
A. Product/intermediate analytics
Participants talked about chromatographic methods
- about different methods (GC; HPLC; UPLC etc.) and methods of detection.
- their time demand
- their potential for automation
- their limit of detection / quantification
- ...

As scientists - with always the desire to fix a problem a 'design' discussion evolved.
Where they wanted to have a non-disruptive 'sensors' that would sit outside of the flow reactor and through being positioned over the glass as specific points to be able to provide readouts - while not coming in contact with the sample/reaction - so as not to have an impact on the 'flow'.

Then the group sketched up a small flow plant and continued the workshop by asking which methods / control strategy would qualify for.
B. Process control
We talked about spectroscopic and generic methods
- Where/how to control basic parameters such as flow/ pressure/temperature
- Where/how to perform spectroscopic analyses e.g. to determine the degree of conversion or by-product formation.
- How to ensure process safety
- …

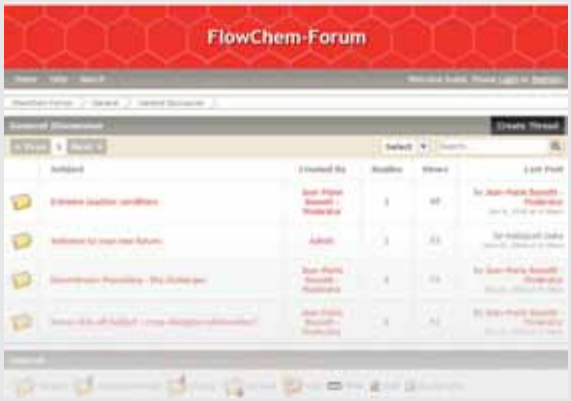
The group was sufficiently small to be highly interactive: moderators asked questions / provided statements and asked the attendants for their experience or their feedback. To some, the exercise was new and reflected the fact that continuous process design is distinctly different from batch process design.

Final comments/observations:
The group consisted of ~30 scientists who were all fully engaged in these discussions. Structurally based on lessons learned from this session. In preparation have reference documents for the groups review to help in guiding the discussion. Also a questionnaire that is filled out prior to meeting to help in structuring the review. In addition to session leader have a moderator to assist with discussion and note taking or add 3rd person to help with this task.
Many thanks to Dr. Peter Poechlauer for his leadership, guidance, notes, and assistance during this session.

Mark Roelands - TNO
Downstream processing - Current status of downstream processing in continuous flow processing: benefits, gaps and needs
In this workshop the position of downstream processing in continuous flow chemistry was assessed. Furthermore the availability of continuous separations was evaluated: for some types of separations continuous flow equipment is already commercially offered while other types of separations still need further development . The objective was to discuss in a stepwise approach benefits and challenges for different kinds of separation technologies. Additionally, some novel opportunities (e.g. telescoping) arising from the introduction of continuous separations was given.

CONCLUSIONS

The symposium ended with a Roundtable on ***Protocols for upscaling*** moderated by Peter Poechlauer, Kerry Gilmore and Jean-Marie Bassett. The topics discussed where: how to start/approach flow chemistry; how to transfer a reaction from batch to flow; which reaction should one test; what needs to be considered before putting a reaction into flow; what equipment should one buy and why; what peripherals (pumps, sensors, separation methods). Many other topics came up during the discussion and made us understand that this new field of applied science is fast-moving and thus demands other, more frequent, means for interaction to bridge the gap between our annual events.



In considering these current developments, we have decided to extend our role to providing a **web-based forum** for exchanging ideas, discussing challenges and opportunities and the launching of initiatives. We therefore invite participants from all sections of the Flow Chemistry community to use this forum to make their ideas and cases (successful and unsuccessful) known. A lively discussion on all topics, not just reactors, but also in-line analytics and downstream processing can be a benefit for us all. For those interested please go to:
http://flowchem-forum.freeforums.net/.

Tekno Scienze staff is already working on the next symposium; therefore I would like to invite those who are interested in our next event to stay tuned and watch out for announcements. Any kind of suggestions on how to improve the event are also welcome.

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S-adenosyl methionine	29908-03-0	Ursodeoxycholic acid	128-13-2
L-ergothioneine	497-30-3	Acarbose	56180-94-0
Pyrroloquinoline quinone	72909-34-3	Androstenedione	63-05-8
Glucosamine	3416-24-8	Sirolimus	53123-88-9
Docosahexaenoic Acid	6217-54-5	Daunorubicin	20830-81-3
Nicergoline	27848-84-6	Spinosad	168316-95-8
Mupirocin	12650-69-0	Vanillin	121-33-5
Glutathione	70-18-8	Virginiamycin	11006-76-1
Daptomycin	103060-53-3	Avilamycin	11051-71-1
Polymyxin B	1404-26-8	Enramycin	11115-82-5
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