Gayle De Maria

5TH Symposium on Continuous Flow Reactor Technology for Industrial Applications

GAYLE DE MARIA
Chimica Oggi – Chemistry Today / TKS Publisher

Chimica Oggi-Chemistry Today organized for the 5TH consecutive year the symposium on "Continuous Flow Reactor Technology for Industrial Applications" on 11-12 September 2013 in Pisa, Italy, attracting experts from all around the world, including the far away Australia. A keynote lecture and a case study on process intensification opened the agenda which displayed other case studies on catalysis, critical compounds, specialty chemicals and pharmaceuticals. The presentations were interchanged with vendor communications, discussions, companies' exhibition and poster sessions. Three contemporary workshops were arranged on the morning of the second day to deepen specific topics and allow fruitful exchange of ideas. Below a summary of the lectures, vendor communications, posters and workshops.

LECTURES

Andrzej Stankiewicz - Delft University of Technology
Towards more industrial implementations of process intensification: The significance of knowledge and technology transfer

The chemical process industry today faces tremendous challenges concerning materials and energy efficiency, environmental burden and operational safety. Market pressures and cost competitiveness of the developing economies in the East provide an additional challenge that the European chemical industry has to face in the coming years. Meeting all these challenges requires focusing on development of innovative equipment, novel processing methods and new chemistries that would drastically increase the efficiency of chemical and biochemical manufacturing. Stirred tank, the workhorse of chemical industry since the Middle Ages, will eventually have to make room for much more efficient devices. Process Intensification (PI) clearly addresses the above challenges and provides new technologies which combine substantial increase in cost competitiveness with material and energy savings, improved safety and environment-friendly processing. An important example of such technologies are continuous flow reactors.

In order to increase the number of commercial-scale implementations of PI-technologies by the industry, efficient ways of knowledge and technology transfer are needed. This has been clearly recognized both by the European Roadmap for Process Intensification (2007) and by the European chemical industries who in 2008 established the European Process Intensification Center (EUROPIC).

EUROPIC is a unique, fully industry-driven platform, which creates interfaces between academia, end users, engineering companies and technology providers. Paying special attention to the quality and reliability of the supplied information, EUROPIC provides its members with unlimited access to the world's largest Process Intensification databases. It performs new technology scouting, benchmarking and trend analyses, issues position papers and provides its members with worldwide consulting services, as well as courses and trainings.

Peter Poechlauer - DSM ChemTech Center
The role of Process Intensification in Sustainable Manufacture of Fine Chemicals

"In pursuing our sustainability goals, we have to work not only on environmental issues or social issues, but a combination that allows for reduced negative environmental impact, positive societal impact and corporate financial and economic health. Therefore DSM is dedicated to balancing social, environmental and economic needs globally and across generations", stated Peter.

DSM's "ECO+ solutions" are products and services that, when considered over their whole life cycle, offer clear ecological benefits compared to the mainstream solutions they compete with. These ecological benefits can be created at any stage of the product life cycle – from raw material through manufacturing and use to potential re-use and end-of-life disposal. "With our aspiration of making 80% of our pipeline and 50% of our existing business "ECO+", improvement of our production processes are in the focus of our development activities", added Peter.

The development of production processes for active pharmaceutical ingredients and their intermediates has classically been driven by development speed and product

quality. Lately further criteria such as volume and properties of waste, and the potential to reduce production cost have been added. Both the chemistry (better catalysts, benign solvents) and the process technology (better reactors) contribute, and ideally their close connection ("the right reaction in the right reactor") allows reaching the required improvements. So the classical "route scouting" has to be enlarged to "process scouting". Options to intensify a process add to its sustainability:
Process intensification, defined as "driving a chemical reaction from the limits of the equipment to the limits of chemistry and physics", goes in parallel with thorough process understanding, and this allows reliable correlation of product quality attributes with a parameter space. This in turn allows adapting a process over its life cycle to different boundary conditions, and thus enables both continuous process verification and continuous improvement.

DSM has developed a number of continuous intensified processes, and the above principles are detailed by several examples of different chemistries and process technologies. Many of these chemistries, while being eco-efficient, have classically been "forbidden" for scale-up because of high reaction energies or appearance of unstable or toxic intermediates. The tight control of reaction conditions in intensified processes has allowed considering such reactions for full-scale production. "This has led us to the task of defining suitable reactors at the required scale, and we have configured modular reactors specifically for the required reaction as part of the scale-up activities. Strategic partnerships with manufacturers of reactors have helped us to share tasks and profit mutually from experience, but also to broaden our offer to our business partners", concluded Peter.

Mike Hawes - Syrris Ltd
Recent advances in flow chemistry technology
In the last 10 years flow chemistry has evolved from obscurity to the most rapidly developing synthetic chemistry process. Chemists are now able to perform a wider range of faster, cleaner, safer chemistry. This presentation specifically looked at how specific areas of flow chemistry have developed over the last 2-3 years, both from the chemistry and technology viewpoints.
Applications covered included: reaction optimisation, focussed library synthesis and subsequent scale up of pharmaceutically relevant heterocycles (including Pyrrole-3-carboxylic Acid derivatives, imidazo derivatives and thiazole derivatives), all in a continuous flow environment; nanoparticle synthesis offering controllable particle size and narrower particle size distribution (including gold nanoparticles, iron nanoparticles and nikel nano crystals) and the comparison of biocatalytic processes in batch and in flow. Historically, in flow chemistry, vast excesses of catalysts have been used and then residence time and yield quoted. In a production sense, this is only part of the picture therefore this presentation assessed the throughput per gram of biocatalyst.
A major technology development in the last few years is the advancement of electrochemistry in flow. Flow plus electrochemistry is an exciting combination due to high surface areas and small electrode distances. It can offer unique activation of chemical reactions enabling selectivity and transformations not possible by other techniques, a reduction in the quantities of toxic and hazardous oxidising/reducing reagents used (a catalytic amount can be used and continually reactivated) and rapid oxidations and reductions (even up to 6 electron oxidation).This presentation looked at developments in the technology and demonstrated chemistry.

Leon Geers – TNO
Demonstration of a heterogeneously catalyzed five phase reaction in continuous flow
TNO and ISPT have organized a program called CoRIAC, in which 11 partners from chemical industry (DSM, Janssen Pharmaceutica, P&G), equipment manufacturers (ESK, Chemtrix, Mettler Toledo, Bronkhorst HighTech), a pilot plant builder (Zeton), and academia (Eindhoven University of Technology) actively work together to develop and benchmark different reactor designs and analytical tools for a number of specific industrial chemical processes on a small scale (1-10 kg/hr). A particularly challenging case was the debromination step in the synthesis of a complex pharmaceutical compound. Traditionally, this was done in a batch stirred tank reactor with a residence time of over 17 hours. In addition, a solvent switch was necessary after the debromination to accommodate the next step in the process. It was demonstrated that the reaction step could be executed in a continuous flow Helix reactor in a bench scale test rig. By using a different solvent, the solvent switch could be eliminated, but this seriously limited the solubility of both reactants and products leading to a five phase process (3 solids, liquid solvent, and gas formed as a byproduct). "With a residence time of 30 minutes, we were able to achieve a stable conversion of 50%, without optimizing the reaction conditions. This work gave enough confidence to scale up the process to a 10 times higher throughput, for which a pilot scale rig is being developed", stated Leon.

Patrick Kaiser - Sigma-Aldrich
Handling critical compounds in flow processes - flow chemistry beyond reactor design
In 2004, Sigma-Aldrich started to use micro- and meso-reaction technology to broaden its product portfolio. First, the flow technology was only applied for lab scale development and syntheses. In the last years it was focused more on medium and large scale production.
Sigma-Aldrich has designed a multi-purpose medium scale flow plant at its site in Switzerland, which allows the implementation of critical flow processes in an industrial manufacturing environment. The modular concept of the plant facilitates

product changeover and the integration of specialized modules (gas handling, flow work-up). Technical features enable a safe handling of starting materials and process streams together with a high product quality level.
Sigma-Aldrich uses flow chemistry as enabling technology to make new classes of products accessible. Critical product properties such as thermal stability or extreme stench challenge a production in conventional batch equipment on a multi kg scale. Case studies were presented where the manufacturing of such compounds were realized on Sigma-Aldrich's medium flow plant.
Technical and quality aspects of the manufacturing processes were addressed. The challenge related to starting material handling, downstream processing and filling of critical substances at a regulated quality level were highlighted.
A brief overview over available continuous downstream processing techniques and examples of their application in the process were given.
The presentation addressed also common challenges and practical aspects related to the operation of multi-purpose flow plants in an industrial environment.

Dominique M. Roberge - Lonza AG
From Microreactors to Continuous Flow, and to Plant Design
The development of a flow process as opposed to batch was often linked with a longer development time and a need of more resources. This situation has changed in recent years from the use of standardized tools such as a modular microreactor system including a plug and play process control.
A powerful methodology for developing flow processes is based on 3-stages approach: a proof of concept (1), an optimization and modeling analysis (2), and a long run study in a mini-plant (3).

The proof of concept is the initial stage where the solubilities and concentrations are fixed, taking into account the rough kinetics or the mass transfer understanding. The proof of concept shall be seen as an accelerated stage where a batch process might be transposed into a continuous one and a rapid decision is seek for a go / no-go decision into the next stage.
It is followed by an optimization stage where for Type B/C reactions (kinetically controlled reactions) a complete kinetic analysis including activation energy is searched to model the reaction under various conditions. The highest yield is not always the sole driver and economic targets are often more appropriate. For mass transfer limited reactions (Type A reaction), a statistical design of experiments is the method of choice for this optimization including mass transfer factors such as the flow rates and type of micro-structures.
The long run study is often associated with a mini-plant where all the advantages of flow technology can be demonstrated. The mini-plant will operate a microreactor at the heart to control a key reaction but will also be implemented with work-up unit operations in flow. The approach is extremely powerful as it enables the study at laboratory scale of all the features that are inherently associated with a pilot plant namely: stability over time on stream, solvent recirculation, model prediction, and robustness. The outcome will lead to highly intensified mini-plant processes that will be the basis of the "Factory of tomorrow".

Jaeyon Yoon - SK Life Science
Continuous process for pharmaceutical chemicals
SK Life Science'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. 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 process under cGMP environment with full validations and waiting for regulatory inspections. For the fixed bed catalytic application is; hydrogenation dehydrogenations, acid/base catalyzed 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. For the Suzuki coping reaction, SK is currently developing fix bed, heterogeneous catalyst which potentially impacts economic; high productivity, catalyst recovery, and higher turnover. SK has unique position to produce custom made in-house fixed bed catalyst for specific application, by manipulating catalyst loading, pore size, shape and metal combinations. Also applications in continuous process equipment were presented such as continuous extraction and distillation etc.

John Tsanaktsidis - CSIRO Materials Science and Engineering
Continuous Flow Processing in CSIRO: from monomers to polymers
Continuous flow processing (CFP) using tubular reactors represents an emergent paradigm shift in chemical processing that is poised to change the way chemicals and polymers are manufactured. Benefits include more sustainable (green) manufacturing processes, a shift away from resource dependence and unacceptable waste generation, to cleaner production and enduring resource use. In his presentation John outlined CSIRO's capability in CFP and provided representative examples in polymer synthesis, including the synthesis of well-defined polymers using RAFT polymerisation technology.

Gabor Rozipal – ThalesNano
Utilizing flow chemistry to create novel compounds for industry
Industrial synthesis practices require smart production techniques that have long term economic viability. Processes have to be delivering the desired products not only in the required quality and quantity, but they have to be in accordance with a keep growing set of other development guidelines too. An extended parameter space, however, enabled by flow chemistry may potentially increase the development stages' degrees of freedom. By doing so, not only a wider window is opened to novel compound synthesis quests, but whole synthetic procedures may comply with the process development guidelines better too. At ThalesNano experts have investigated performing several highly exothermic and endothermic chemistries in an extended temperature range from -70°C up to 450°C in order to demonstrate the improved safety and efficiency of their novel flow devices. In Gabor's presentation, examples were given of various cost effective and sustainable C-H activation methodologies, low temperature novel scaffold syntheses from explosive intermediates, and high temperature scaffold syntheses that can be of interest especially for pharmaceutical industry that is suffering from a significant deficit of novel bioactive chemotypes.

VENDOR COMMUNICATIONS

Andrew Fallows - Motor Technology
The pump solution for demanding Continuous Flow Reaction processes
Fuji Techno manufactures Pulse Free, High Accuracy (deviation <±0.1%) and High Stability displacement pumps. To maximise yield and product quality, it is essential to provide a non-pulsating flow of liquid, at high accuracy and high stability, even with variation in the discharge pressure.
This vendor communication explained the operating principles and performance of the pump, as well as some applications, in which the pumps are being used.
– Dakin reaction (Hydrogen peroxide, Sodium hydroxide).
– Anionic block copolymerization (Styrene, Alkyl methacrylate).
– Halogen and organic lithium exchange reaction.

Joe Lambert - Parr Instrument
Flow chemistry: variations on a theme
From the early days of petroleum refining, the use of continuous flow reactors has progressed to encompass even the needs of small volume production schedules as seen in today's pharmaceutical industry. Reasons for shifting from batch reactors to flow reactors include economy of scale, heat dissipation, rapid and flexible changeovers, and higher throughput. This presentation showed the variety, similarity, and interchangeability of three-phase reactor styles used to accomplish these goals.

Viktor Gyollai - Ubichem Pharma Group
Reactions in Continuous Flow
The economical synthesis of certain organic molecules may bring about the use of dangerous or aggressive reagents and unique process technologies. Intensification of chemical processes is an efficient tool in these cases and Ubichem is devoted to explore these unique technologies. High pressure high temperature continuous flow reactors are highly suitable for those syntheses that require high temperature and, contrary to the conventional methods, relatively volatile solvents can also be used as reaction medium thanks to the shift in boiling point at high pressure. Some examples of the potentially useful reactions include: ring-closures leading to various heterocycles, transition metal-catalyzed carbon-carbon cross-coupling reactions, esterifications in alcohols as solvents without catalysts, addition of water to multiple bonds without catalysts, nucleophilic aromatic substitutions, pericyclic reactions. Tubular falling-film reactors, on the other hand, can be utilized for those reactions in which gas-evolution or foaming is expected, such as decarboxylations, retro Diels-Alder reactions or the Wolff–Kishner reaction. Highly exothermic reactions can be carried out safely in a low-temperature continuous flow reactor. The scale-up of these processes tend to be easier due to the more efficient heat transfer. Among many others, two very important reactions fall into this class: lithiation and ozonolysis. Practical examples selected from the above methods were presented in details.

Roland Guidat - Corning Reactor Technologies
What customer expect from a flow reactor company
In conventional batch industry, feeding the reactor with the requested raw material (piping, gaskets, pump), is part of the know-how of the customer. In continuous flow reactor, pumps are specific (low flow, high pressure), and not very common yet; gasket type used (O ring) is not currently the most popular in production plant; conventional piping resistant to corrosion are widely used, but the smallest internal diameter available is 15 mm. Besides the reactor, the vendor has to provide / develop / assess the availability and reliability of piping, gaskets, pumps, flow meters. Since more than 150 years, Corning is focused on the quality and reliability of its products and services. This high

quality requirement has been put in place many years ago in the AFR Business, where the testing and reliability group is a significant and important part of the staff. Corning has tested many gaskets in various conditions, developing a wide internal databank. Has developed and tested metal free connectors with a wide range of operating temperature and pressure. "We have currently plenty of dosing lines available for test at customer site, and we tested many different types of pump, to be in a position to select the best available technology according to the fluid properties. Ultimately, we are in a position to provide not only the most versatile continuous flow reactor, but the best available global solution for continuous flow chemistry", stated Roland.

Tomoya Inoue - AIST on behalf of TECNISCO

Flow chemical devices for multiphase heterogeneous catalytic reactions

TECNISCO is a member of DISCO Corporation, and a specialist of microprocessing technology based on Cutting, Grinding, Polishing, Metalizing, and Bonding. With these technologies, precision Glass Micro Reactors have been manufactured. Tecnisco also provide processing service for precision components, including medical devices industries. In this symposium, Tomoya introduced brand new reactors designed by AIST, and manufactured by Tecnisco. As described in AIST poster, AIST went successful in designing microfluidic devices suitable for multiphase heterogeneous catalytic reactions and have demonstrated that it is highly efficient for the direct synthesis of hydrogen peroxide from hydrogen and oxygen in terms of acquired hydrogen peroxide concentration and the reaction condition. It includes reactor design suitable for multiphase reactions, namely gas-liquid- reactions with packed bed catalyst, and how to load / unload catalyst in the micro packed bed. "Through our demonstration we would like to convince the audience that our flow chemical devices are suitable for conducting multiphase- and heterogeneously catalyzed reactions", said Tomoya.

POSTERS

Dusan Boskovic, Alexander Mendl, Tobias Tuercke, Stefan Loebbecke -Fraunhofer-Institute for Chemical Technology ICT

Save kilogram-scale production of nitrate esters in a continuous pilot plant comprising microstructured reactors

We report on the use of microreaction technology for the safe synthesis and processing of different energetic materials, namely nitrate esters, in the liquid and liquid/liquid phase regime. The hazardous potential of these reactions often arises from both the huge reaction exothermicity and a certain thermolability of the reaction products or intermediates. Continuously run microstructured reactors have been used for both lab-scale experiments and production of energetic materials in the kilogram scale since they offer numerous technical advantages compared to classical processing. Accumulation of strong reaction heats and hot spots, which result in unwanted side, subsequent and decomposition reactions, can be successfully suppressed in microreactors and moreover, continuous processing permits flexible production capacity and also short residence times, which can be precisely adjusted. Consequently, the use of microreactors greatly reduces the hazardous potential associated with reactions that are highly exothermic or potentially explosive. The Fraunhofer-Institute has developed a fully automated and remote controlled multipurpose plant employing specially designed microstructured reactors initially for the synthesis and subsequent downstream processing of trinitroglycerin. Today the multipurpose plant is particularly used for the production of different energetic liquid compounds such as ethylene glycol dinitrate (EGDN), triethylene gycol dinitrate (TRENO), methyl nitrate (MN), trinitroglycerin (NGL), and others. The plant has a wide range of safety features and every aspect is controlled and monitored remotely. It comprises two main process units: a continuously operated synthesis unit and a continuously operated unit for the raw product work-up. The plant is mostly used for campaign-wise production providing up to 150 g

purified product per minute. The final products fulfill all necessary specifications with respect to purity as well as thermal, impact and friction stability.

P. Biessey[1,2], M.O. Piepenbrock[1], F. Herbstritt[1], F. Schael[1], J. Heck[1], M. Grünewald[2] - 1. Ehrfeld Mikrotechnik BTS GmbH; 2. Ruhr-University Bochum

A versatile reactor for intensified multiphase reactions and downstream processes

Currently microreactors or, perhaps more appropriately, reactors with micro- and milistructured components generate an ever growing interest in the chemical industry. Due to these small dimensions microreactors offer an extremely high surface to volume ratio over conventional reactors and present themselves as potential solutions for all processes where efficient heat transfer and/or mass transfer is required. Especially with the current trend of modularization and decentralization of chemical processes and production as for example demonstrated in the F3 Factory Project (funded by the European Union within the FP7 framework) the need for process intensified equipment opens up great opportunities for microreactors. However, in order to realize this potential ways of reactor design have to be developed to take microreactors away from the laboratory scale and transfer their inherent benefits to the pilot and ultimately to the production scale. In the present contribution we present a reactor concept that allows for easy scale up from laboratory application all the way to production. The design of this class of apparatus focuses on optimal heat transfer through rectangular channels and efficient mass transfer by static mixing elements providing efficient mixing for 1-phase systems and high interface area for multi-phase processes. The benefits of the apparatus are discussed by extensive characterizations of heat transfer, and residence time distributions in 1-phase and 2-phase systems. Finally the versatility of the equipment is demonstrated by looking at its applications in intensified downstream processes exemplified by evaporation.

K. Skowerski[1], S. J. Czarnocki[1], P. Knapkiewicz[2] - 1. Apeiron Catalysts; 2. Wrocław University of Technology

Tube-in-tube reactor for continuous flow olefin metathesis

The history of olefin metathesis has started from industrial processes for production of simple olefins under continuous flow (CF). The synthesis of more complex molecules promoted by well-defined complexes under continuous flow mode remains underdeveloped and seems to be far away from industrial applications. This is especially true for transformations in which ethylene is evolved. For such reactions much lower TONs were obtained in CF setups than in batch reactors (BR). It has been proved that ethylene has negative influence on efficiency of well-defined ruthenium complexes (1). In order to avoid issue related with ethylene two setups were developed, namely circulating flow reactor equipped with degasser (2) and continuous stirred tank reactor (3). Although successive both these solutions suffer from lack of versatility. The authors reported on tube-in-tube reactor (PFR-V) which allows more efficient hetero- and homogeneous olefin metathesis under continuous flow mode owing to possibility of continuous removal of ethylene. The results of RCM and CM reactions obtained in this new reactor were compared with those observed in BR and under CF without removal of ethylene (PFR).

Mohammed Alotaibi, Stephen Haswell - University of Hull

Development of a monolith based immobilised lipase microreactor for biocatalytic reactions in a biphasic mobile system

The production of a stable enzyme functionalised silica monolith was presented for flow reaction chemistry. The macroporous silica-monoliths were prepared from two precursors, tetramethoxysilane (TMOS) and tetraethyl orthosilicate (TEOS) to produce a range of surface areas 222 m^2/g to 529 m^2/g which were subsequently functionalised with commercially available Candida antarctica lipase (CAL). To evaluate the lipase activation, the hydrolysis of 4-nitrophenyl butyrate was performed in flow mode using a mobile water-decane biphasic system. To evaluate the performance of the immobilised lipase and free lipase reactions were also carried out. Both free and immobilised lipase reactions were evaluated at over extended run times and elevated temperatures. The kinetic studies performed for the homogeneous catalyst showed that the initial velocity was increased linearly with increasing the amount of free lipase. The amount of CAL immobilized was calculated to be in the range 8.16 mg to 9.2 mg. A comparison kinetic study between homogeneous lipase and immobilized lipase was carried out. The results obtained showed that the affinity of free lipase to the substrate is much higher than the affinity of immobilized lipase to the substrate for all the catalysts which was expected. However the turn over number of immobilized lipase in some cases was higher by three times than the homogeneous catalyst. It was found therefore that microreactors (silica monolith) with small average pore diameter 1.15 µm gives higher activity than the homogeneous catalyst. An important application for the methodology developed is the production of enzyme catalyzed biodiesel production. The efficiency of immobilized lipase microreactor in transesterification of tributyrin with methanol to yield methyl butyrate has also been examined and the conversion of tributyrin was monitored using gas chromatography and gas chromatography-mass spectrometry. Initial results for the conversion of tributyrin with methanol to yield methyl butyrate were presented in the poster.

Tomoya Inoue - UMEMSME-AIST

Flow chemical devices for multiphase heterogeneous catalytic reactions

Since the last decade, flow chemical technology has offered an alternative opportunity to handle chemical processes safely and efficiently. Still, compared with monophasic reactions, multiphase reactions had sometimes suffered insufficient reaction performance than expected, mainly due to maldistribution of reaction fluids, even compared with conventional reactor technologies in which fluid handling technologies had already established. Also, heterogeneous catalysts have been less incorporated into the flow chemical technology; once it is fully incorporated, we can enjoy advantages of flow chemical technologies with varieties of reactions.

Hydrogen peroxide has various kinds of application. On-demand production is preferred for small scale applications, and the direct process from hydrogen and oxygen is favourable rather than downsizing petrochemical anthraquinone process. So far, efforts to realize the process have been challenged by the safety and efficiency issues; the process is not only reacting hydrogen and oxygen that causes explosion, but also handling mass transfer for its three phase reaction, gas (hydrogen and oxygen), liquid (water and hydrogen peroxide itself).

Even though AIST already demonstrated the concept nearly a decade ago, hydrogen peroxide productivity had been insufficient because of gas-liquid maldistribution as well as un-optimized reaction conditions. Now they successfully produced aqueous hydrogen peroxide using originally designed glass-fabricated flow chemical devices, with newly designed gas / liquid distribution structure. Parallel catalyst packed bed operation was also enabled, by proper fluidic device designs. Combined with catalyst development and parallel reactor operation AIST has successfully developed the process

capable of 10 wt% hydrogen peroxide production with 1 kg/d throughput. The reaction pressure is 1 MPa, less than these required for the direct process developed so far (5-10 MPa). AIST believes that the flow chemical technology they developed makes a breakthrough in not only hydrogen peroxide production but also other heterogeneously catalyzed multiphase reactions, especially challenging oxidation processes.

Yvonne Wharton - C-Tech Innovation

MiFlow Reactor: demonstration of scale up of ionic liquid synthesis using a microwave flow approach

C-Tech Innovation has developed a large scale continuous flow microwave reactor (MiFlow) that is capable of producing >10 kg of product per day. The reactor has been trialled using a wide range of reactions that are applicable to a variety of industrial sectors and demonstrated a significant reduction in reaction times and increase in reaction yields. Using a microwave flow reactor for large scale chemistry is faster, cleaner, greener and safer than using a batch approach. The MiFlow project is being carried out in collaboration with Solvionic, who manufacture ionic liquids, and aims to demonstrate the benefits that microwave flow chemistry can bring to their industrial scale up processes. There is a real need for better controlled processes of ionic liquid synthesis, since their uses in emerging applications like electrochemical storage requires a high degree of purity. Because batch production is not adapted to giving colourless and high quality products supporting solvents and washing steps have to be used. The use of organic solvents in large quantities produces waste and is not in line with the 12 Principles of Green Chemistry. In this context, the use of microwave flow reactors is a very promising alternative that will eliminate or minimise environmental damage, while also reducing waste and energy consumption. The cost of ionic liquids is still high, mainly because their production volumes are still very low compared to molecular organic solvents. If high added value industrial applications based on ionic liquids start, the production of larger volumes will lead to costs falling. Moreover the development of continuous flow processes for ionic liquid production will decrease production costs, thanks to better yields and reduction of waste and energy consumption associated with low investment. This poster presented the development of the MiFlow reactor and described the early results from the scale up of the ionic liquid processes.

WORKSHOPS

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

1. *How to design an excellent flow process – driver evaluation, identification of critical parameters and tool selection*

Dirk Kirschneck - MicroInnova

Development methodology was intensively and controversy discussed in the workshop lead by Dirk Kirschneck, Managing Director of Microinnova Engineering. It was agreed the methodology is a key success factor. Flow processing can provide a much better control of parameters or enable new strategies impossible in batch. The knowledge is not available directly for example in a book. All major development teams have a theoretical evaluation at the beginning. No ranking in the drivers could be found, but there was agreement in the group that it makes sense to concentrate on not more than two drivers to keep the focus. The theoretical phase is followed by batch testing phase afterwards. The batch phase can be substituted by microwave testing. Some teams have their main focus on the design of a single step and optimize this. Others concentrate on the design of more direct synthesis routes for example by using hazardous

chemistry. Each chemical reaction has its own difficulties which occur in terms of bottlenecks. The fundamental root causes needs to be solved. The tools are wide spread. Microreactors are only one tool from a long list of tools and strategies. It was agreed that maximum number of different tools ("toys") is one of the success factors. Typical developers are chemists in rare cases with engineering support although the reaction technology knowledge is of importance. Training is typically happening on the job, by visiting conferences and self-studies.

2. *What technologies challenges remain for the field of flow chemistry? What are the strategies players are adopting?*
Charlotte Wiles – Chemtrix

The participants of this workshop were a diverse mix of academics and industrialists with users and non-users joining what proved to be an interesting and lively discussion. Whilst focus on *what technology challenges remain?* centred on the need for lab to plant solutions – considering the process from feed solution preparation to product isolation and purification. Significant time was spent discussing the need for increased robustness and choice for flow reactor peripherals which include pumps, valves, tubing and process analytical tools – with a clear message that 'the reactor is only part of the solution!'
The discussion deviated to discuss '*what challenges remain for flow chemistry?*' with the largest being cultural acceptance of innovation – with it widely acknowledged that with time the technical challenges can be overcome. Part of this discussion centred on a need for clarity regarding regulatory affairs, with topics of concern including definition of cleaning protocols, what is a batch and what process data is required? How to deal with this facet of process development also links to a general reticence within industry not to be the first to implement such a technology – it was felt that more case studies are needed to give a more general feel on the advantages at the production scale with regards to safety, cost & time savings. With this in mind, the group concluded that where there is no option to perform in batch, processes are assessed in flow but where the risk/reward ratio is not big enough, often the lab-scale flow data is used to improve the existing batch process – with 'chemists wanting to find a chemical solution not an innovative one' commented upon. A well-made point was that 'batch is often problematic it is just that we are familiar with solving the challenges associated with 6m3 batch vessels'.
The workshop concluded with the *strategies players are adopting* and revealed that those who are actively pursuing flow chemistry are taking two approaches, the first group (largely in the fine chemical sector) stated that they prefer to use flexible, modular skid based systems which give freedom for multiple processes and reduce the risk of redundancy if a particular product contract is only awarded for a limited timeframe, whereas dedicated equipment could be seen as a solution within the pharma industry where product lifetimes for the Company can be inherently longer.

Culturally, round table/consortia/training activities were seen as a positive way to reduce the feeling of risk and insecurity within a Company. Knowledge sharing within the Community, through the promotion of both successes and challenges, together with access to less expensive equipment is also required. A closing remark was 'invest at the lab to enable processes to be pulled through the R&D then on to production.

3. *Commercial adoption of flow reactors - economic drivers and obstacles*
Laurent Pichon – MEPI

The third workshop was composed of 20 actors from the flow chemistry world, who had to discuss about the commercial adoption of flow reactors, emphasizing economic drivers and obstacles.
The first acknowledgment was to admit that the flow chemistry market growth expected 5 years ago is no there. Despite the obvious benefits gained from continuous processes on safety, quality, impact on environment, and competitiveness, the business model is currently dominated by a technology push, which is always slower than a market pull strategy. The offer is very rich but its visibility is still limited. There are still some technology limitations (high viscosity, S/L media...).
The financial benefits expected from a flow chemistry implementation is difficult to predict on a global basis, as it is very varying a lot from one

considered project to another. It always needs to be double-checked with preliminary studies. In addition, there is no long term return on experience so far.
However, the response of the market is quite heterogeneous when technology, locations and applications are observed in more details.
While it seems the micro reactors for laboratory / university market has reached maturity, the commercial challenge remains huge for the milli / meso units.
If the competition against fully paid back batch vessels in Europe is very hard and leads to a quiet market place, those new technologies are spreading rapidly on the emerging Asian markets!
If opportunities on the drug segment remain strong, its development is slow. The fine chemical market is complicated due to the layers of intermediates up to the final client. Cosmetics and specialty chemicals markets remain attractive with growth and cash flow available. Finally a switch from technology push to market pull is strongly expected and the sooner, the better. Advertising on a coming "success story" would be a wonderful catalysis of the flow chemistry business.

Strong discussions took place during the presentation of the workshops results and carried on by the chairmen David Ager of DSM Innovative Synthesis and Jean-Marie Bassett of TNO Sustainable Chemicals Industry. The exhibition area made up of 13 booths with companies displaying their equipment and 5 posters implemented the networking and exchange of ideas which started and continued during the social events organized for the evening of the two days. The day before the opening of the conference, participants enjoyed a visit of the medieval village VicoPisano and the Brunelleschi Rocca, and an olive oil tour (tasting different kind of oils) plus dinner in a typical Tuscan countryside farmhouse (il Frantoio of Vicopisano). Olive oil, wine and music entertainment helped to create a familiar atmosphere without forgetting flow chemistry issues. Networking continued on the evening of the first day with a tour of Pisa and of its most important monuments, ending with a dinner in a typical Tuscan restaurant (Locanda Sant'Agata). These kind of extra activities have the aim to promote information exchange and stimulate fruitful collaborations in a serene environment.
The symposium ended with the idea that events like this one are a useful tool for the diffusion and acceptance of flow chemistry technology: the most important thing is in fact to share successes to pave the way to this business.
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 locations or on how to improve the event are also welcome.

ACKNOWLEDGEMENTS

I would like to thank the speakers and the workshops facilitators for their inputs and suggestions which have been inserted in this article.

Learn, Innovate, Partner, Promote

26-27 February 2014, Sofitel Munich Bayerpost, Munich, Germany

HPAPI World Congress is the region's leading high potency production and manufacture congress that brings together decision makers, influencers and end users from across industry.

Your congress, your way. Explore all elements of high potency API production and manufacture – through keynote sessions, practical clinic presentations and discussion, interactive roundtables and dedicated networking sessions; HPAPI World Congress gives you the opportunity to learn on a number of different levels to achieve your goals.

Speakers include:

Marvin Faber
Senior Director, Global Head EH&S
Patheon Inc.

Dr Holger Rauter
Director R&D
Heraeus Precious Metals GmbH & Co.

Dr Sobia Nayyar
Global Market Segment Manager, Small Molecules
SAFC

Register now to secure your place.

Register now – on your phone!

Scan this QR pattern with the camera on your smartphone to register for the HPAPI World Congress 2014. Don't have a QR reader app? You can download one for free from the App Store. Don't have a smartphone? You can also register online by clicking register now on our website: www.terrapinn.com/HPAPI14

The earlier you book, the more you save. Don't forget your special code to claim your Early Bird discount: **AD1**

HPAPI WORLD CONGRESS 2014

www.terrapinn.com/HPAPI14

2014 sponsors

SAFC® AMRI GLOBAL SMARTSOURCING EXCELLA PHARMA SOURCE fermion FPS FOOD PHARMA SYSTEMS

Heraeus MICRON TECHNOLOGIES novasep When purity is key. Patheon Performance the World Over