
Gayle De Maria

GAYLE DE MARIA
Chimica Oggi – Chemistry Today / TKS Publisher

Sixth Symposium on Continuous Flow Reactor Technology for Industrial Applications

After the really big success of the first five symposia held in Madrid, Paris, Como, Lisbon and Pisa, Chimica Oggi/ Chemistry Today, TKS Publisher, organized in Budapest the sixth symposium on "Continuous Flow Reactor Technology for Industrial Applications". The symposium was held on September 23-26 and had a new improved format.
A one day training session for beginners, two days conference with workshops discussions and a practical session.
The teachers of the training session - Paul Watts (Nelson Mandela Metropolitan University) and Peter Poechlauer (DPx Fine Chemicals Austria) - were able to put together a really interesting agenda focusing on basic principles, equipment and application. The participation was strong: new people coming also from new emerging countries. The two days agenda chaired by Laurent Pichon (MEPI) provided a presentation of case studies focusing on scale up synthesis for Pharma and Fine Chemicals Industries, on work-up solutions and an overview on Emerging countries.
Three contemporary workshops held by Robert Ashe - AM Technology, Oliver Kappe - University of Graz and Peter Poechlauer – DPx Fine Chemicals Austria, Paul Watts - Nelson Mandela Metropolitan University, addressed all the doubts and questions of attendees and implemented a strong discussion and networking.

A practical session organized at ThalesNano facility on the last day, open to a small group of participants, was very much appreciated especially from beginners.
An exhibition area with companies showcasing their equipment and services completed the offer of the event.
Below a summary of the lectures, vendor communications, posters and workshops.

LECTURES

C. Oliver Kappe - Institute of Chemistry, University of Graz
Running hazardous chemistry in Flow – Application towards API synthesis

Diazomethane (CH_2N_2) is one of the most valuable and versatile C1-building blocks in organic chemistry. It is a potent methylation agent for carboxylic acids, phenols, alcohols and a plethora of other nucleophiles, such as nitrogen and sulphur heteroatoms. It is also essential for Arndt-Eistert homologation chemistry via α-diazoketones, and for ring-expansion or homologation of ketones. Unfortunately, CH_2N_2 is a volatile, highly irritating, poisonous and carcinogenic compound (the boiling point of diazomethane is -23°C). Furthermore, diazomethane is exceedingly heat-, light- and shock sensitive and tends to decompose explosively. The hazardous properties of diazomethane have in the past severely limited its widespread use in laboratories and industry.
Oliver described a process in which generation,

separation, and chemical transformations of diazomethane are integrated in a robust, commercially available tube-in-tube reactor. In this process diazomethane is generated in a way that avoids the handling of pure gaseous diazomethane but instead uses membrane technology whereby diazomethane generated in an aqueous environment diffuses through a semipermeable membrane into an anhydrous organic solvent. He demonstrated that the generated anhydrous diazomethane using this protocol can be used for an efficient and atom economic synthesis of key intermediates in the synthesis of a number of antiretroviral APIs such as Atazanavir. This method eliminates the need to store, transport or handle diazomethane and produces the key α-haloketone building blocks in a multistep system without racemization in excellent yields. Scale-up strategies and further chemistries of diazoalkanes in continuous flow were discussed.

Andrea Adamo - Massachusetts Institute of technology; Zaiput Flow Technologies

Flow chemistry tools for integrated API synthesis

Scenarios involving pharmaceutical shortages, providing pharmaceuticals in hard to access areas, streamlining of supply chain of pharmaceuticals would all benefit by the availability of a transportable system for making them on demand. The Pharmacy on Demand (POD) project aims to develop a compact pharmaceutical plant able to synthesize, purify and formulate up to 1000 doses/day of a pharmaceutical of choice. A flow chemistry based approach was selected as an enabling tool for this project. After briefly describing the POD and its technical challenges, the talk focused on novel reactors, in line separation devices, pressure regulators and other tools that were developed to address the POD design. Additionally, examples of applications of the new tools library were provided including the synthesis of fluoxetine. In the talk Andrea highlighted the role that a POD type of setup could play in the pharmaceutical manufacturing industry for i) lowering production cost of low volume drugs, ii) as a way to address drug shortages, iii) as a tool for flexible production schemes where scaling up is achieved by scaling out, iv) as modular system for delocalized/portable production. Finally, Andrea shared his thoughts on his equipment selection process as well as a description of the tools he has developed for the project and their expected impact on practical applications.

Paul Watts - Nelson Mandela Metropolitan University, South Africa

The application of flow chemistry to develop new markets in emerging countries

When micro reactor technology was first introduced it was seen as being a research and development tool suitable only for small scale production. However the most topical examples discussed in the literature include the Ritter reaction performed on an industrial scale by DSM (Austria) which has to date generated over 4000 tonnes of product and the synthesis of nitroglycerine in China. The key driver in these examples being safety, where the excellent mixing and heat transfer characteristics of micro structured reactors

enables these highly exothermic reactions to be safely performed. Nevertheless there is now a plethora of commercial reactors on the market, which means that most companies are investigating this technology to rapidly screen reactions utilizing continuous flow, leading to the identification of reaction conditions that are suitable for use at a production level. Furthermore the inherent safety associated with the use of small reactor volumes enables users to employ reaction conditions previously thought to be too hazardous for use within a production environment; such as extreme reaction conditions or the use of hazardous compounds. One challenge in South Africa is that chemicals are often imported from other countries, increasing the cost of research and production. It is envisaged that by developing small production platforms, at point of need, chemicals and drugs can be manufactured within the country.

Dirk Verdoes - TNO Sustainable Chemical Industry

Achievements and challenges for highly selective, modular separations

We firmly believe that decentralized, flexible production is a key element/enabler in the transition that the European chemical industry will make in the coming decade. The drivers behind are the expected shift from bulk chemicals to higher added value fine and specialty chemicals, the use biomass as feedstock and the trend towards sustainability which will stimulate the use of waste streams as raw material as well as the increasing use of green electricity.
The big challenge for establishing decentralized, flexible production plants is their disadvantageous economy of scale. The personnel costs can be minimized by using continuous processes with advanced on-line sensors and analytical tools enabling remote controlled production. The use of modular unit operations will spread the investment risks and strongly reduce the time-to-market. Different types of modular continuous reactors have been developed and successfully demonstrated during the last decade. Their technical advantages have been clearly demonstrated, but a (further) decrease of the costs of the reactors will be necessary.
The availability and applicability of modular separation technologies for decentralized, flexible production is much less advanced. TNO focuses on the development and use of separation modules that can be operated continuously with a high selectivity and a low energy consumption. The challenges and possible solutions for providing ready-to-use separation modules were discussed. Illustrative examples were given for modular crystallization, extraction and

evaporation processes that could further fill the toolbox with modular unit operations for decentralized, flexible production.

Xiong-Wei Ni - NiTech Solutions Ltd
Continuous processing and crystallization

Flow chemistry technologies play a key role in process intensification drives to improve manufacturing in the chemical and pharmaceutical industries, through more efficient use of reagents, solvents and energy while minimizing side reactions, unwanted products and waste materials. Flow technologies come with different sizes and shapes from micro, meso through to macro scales, each has some unique features as well as some shortfalls, for example, while micro/meso reactors offer extremely high heat transfer rate, but are poor in dealing with solids. In his presentation, Xiong-Wei explained why crystallization environment is critical for nucleation and growth of crystals, how continuous crystallization and reaction would be implemented; Xiong-Wei used real industrial case studies to demonstrate that significant step change benefits can be achieved using this type of plug flow technology in lab, pilot and industrial scales.

Gilda Gasparini – AM Technology
Improving sustainability of multiphase reactions using dynamic mixing: 2 examples

Mechanically stirred reactors are the most practical solution for gas/liquid reactions at the plant scale since such processes generally require efficient mixing for extended periods. The Coflore reactors are mechanically stirred flow reactors with a reactor channel divided into multiple stages. This ensures good reaction time control and effective separation of reactants and products.
Common drivers for switching from batch to continuous include smaller equipment, better process control, reduced thermal mass of equipment (reduced energy waste) and elimination of high peak loads on the utilities (heating/cooling utilities are sized for peak loads). For many applications, flow reactors can also deliver improved yield/ purity. Moreover, the advantages of flow reactors for hydrogenation reactions are particularly compelling given the high cooling demand and the presence of flammable gas at elevated pressure.
Two challenging processes were considered: a biocatalytic oxidation and a neat hydrogenation. They both involve three phases systems but also have different extra challenges: long reaction time the first, feeding slurries at pressure the latter.
Set up including feeding system and benefits were discussed in details showing the different savings that running in continuous can bring.

Osman M. Bakr - King Abdullah University of Science and Technology (KAUST)
Flow reactors: a platform for the rapid optimization and scale-up of high-quality nanoparticles

Metal and semiconductor nanocrystals play a major role in catalysis and optoelectronics. However, the utility and activity of nanocrystals, to large a degree, is dictated by their size, faceting, and morphology. Obtaining monodisperse nanocrystals of a desired shape and size - an important milestone towards their practical utilization and commercial application - entails exquisite control over their nucleation and growth kinetics. Yet those kinetics are extremely sensitive to temperature and concentration, as well as the fact that nucleation and growth should ideally occur at substantially different temperatures in order to achieve uniform particle size and shape distributions. Unfortunately, these constraints mean that most nanocrystal syntheses are difficult to scale-up in traditional batch reactors, without severely compromising product quality, due to chemical and thermal gradients in the reactor, as well as the difficulty of rapidly, and uniformly, changing the reaction temperature.
In this work, Osman demonstrated a strategy to realize a variety of high quality nanocrystals using a continuous-flow dual-temperature-stage reactor system of narrow channel coils. By employing two temperature-stages, Osman and his group were able to mostly separate the nucleation and growth steps of nanocrystal formation, and thus obtain highly monodisprese nanoparticles via a scalable and automated method. A kinetic model was used to explain and optimize the nucleation and growth processes within the reactor stages.
Considering that the flow-regime allows rapid screening of synthetic parameters, automation, and low reagent consumption during optimization, this study provides a platform for the speedy investigation and optimization of emerging nanoparticle systems.

Laurent Pichon - MEPI
Process intensification survey 2014

A marketing survey on the perception of flow chemistry was first disclosed in 2012 at the 4th Symposium on Continuous Flow Reactor Technology for Industrial Applications in Lisbon. This analysis was refreshed with inputs from a new survey realized in 2014 and presented in Budapest.
The panel of 25 companies interviewed is essentially European and represents mainly large and medium size companies in pharmaceutical, fine chemicals and specialty chemicals sectors.
The results show that the interest in flow chemistry is increasing, and the understanding on how this new principle works, and what added value it could bring, are also progressing.
The willingness of implementing flow chemistries is reinforced.
The specialty chemicals sector is very active with the recent introduction of larger capacity flow reactors, while the fine chemical sector behavior is more volatile.
The main slowing down factor of the activity is the ability of the players to invest in new technologies in a slow reacting European market overfed with free batch capacities, while Asia remains very active. This may change in a near future with business coming back from Asia, due to local regulatory or environmental concerns issues.
While process safety was ranking nr 1 among the speeding up factors in 2012, this year shows a change with competitiveness being the most sought parameter. A 30 % in cost saving seems commonly required for a technology change.
The combination of the two factors is paving the road to route scouting, simplifying the multi-step processes by using

more challenging chemistries in a now recognized secured environment.
In addition, newcomers are entering the flow chemistry arena: nanoparticles production, nutraceuticals, as well as continuous mixing operations for paints, cosmetics…
Nevertheless, the flow chemistry sector is still driven by a technology push approach, and the expected turn to a market pull boost is not there yet, despite very encouraging signs.

VENDOR COMMUNICATIONS

Patrick Kaiser - Sigma-Aldrich
Handling highly exothermic reactions in flow

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. The increased flow capabilities by unit number and scale required the development of a concept to enable safe and efficient development and scale-up of flow processes.
The characterization of the flow equipment and the adequate control of the flow processes are essential parts of this concept. The identification of the critical parameters and the required flow unit specifications and characteristics is the key to turn a chemical reaction of interest into a stable flow process on the required scale and quality level. Furthermore, it enables a smooth scale-up or process transfer within Sigma-Aldrich, or between Sigma-Aldrich and its customers.
Sigma-Aldrich has designed a multi-purpose medium scale flow plant at its site in Switzerland, which allows the implementation of flow processes handling critical materials or reaction conditions 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).
Sigma-Aldrich uses flow chemistry as enabling technology to make new classes of products accessible. In this case study the experiences dealing with a highly exothermic sulfide oxidation were presented. The process enables the synthesis of sulfonic acids and its salts as salt formation or IPC reagents. The handling of reaction energies of approx. 1 Mega Joule/mol in a solvent free process is the main challenge. This challenge is specially addressed in a concept for the process development and scale-up. The characterization of the flow equipment as well as the reaction properties is essential to establish a safe and adequate flow process. The case study highlighted the aspects of scale-up and presented the requirements of a properly designed product transfer from one production site to another.

Stephanie Peschke - Ehrfeld Mikrotechnik BTS GmbH
Process intensification with Flow Chemistry: Modular. Scalable. Efficient.

Flow Chemistry tools are one puzzle piece to complete future laboratory and production concepts by adding a valuable contribution to process intensification. For the right choice of these tools, different aspects have to be taken into account to succeed finally with their introduction in lab, pilot and production scale. First of all, equipment for highly sophisticated process tasks should be as modular as possible and should also be easily implementable for various conditions and applications in branches like Fine and Specialty Chemicals, Pharma, Food or Cosmetics, but also in the Polymer and Petrol Industry. Second condition is the scalability of micro- and millireactors as well as of small micro mixers for the lab without big deviations for the process conditions applied. Starting with different channel design, the scale-up is done in different ways, but up to a low ton scale range, structures or whole reactor parts will be increased and/or multiplied. Last but not least the efficiency by applying high performance devices is the key point, why decision makers have to be convinced. This technology will change the mindset of the people involved with and will lead to other ways in working and scaling-up reactions. To overcome the hurdles of implementation, there are some important points: master the complexity, dispel conservative doubts, support the education of young scientists and stimulate interdisciplinary team work.

Yi Jiang - Corning Inc.
Innovation drives green growth: advanced flow reactor technology - industrial production made real

Corning Incorporated is the world leader in specialty glass and ceramics. Drawing on more than 160 years of materials science and process engineering knowledge, Corning creates and makes keystone components that enable high-technology systems for consumer electronics, mobile emissions control, telecommunications and life sciences. In the last 12 years, Corning has brought to chemical process industry with 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. 1000x improvement in heat transfer, 10-100x enhancements in multiphase mixing, x/1000 reduction in chemical holdup and reaction time comparing with conventional stirred batch reactors enable cleaner, safer, and more efficient manufacturing reality, which are crucial to today global pharma, fine and specialty chemical industry.
This communication discussed how Corning AFR have been successfully applied in a variety of flow-chemistry process developments, and shared the stories of seamless transfer of flow processes from lab quick-feasibility-tests (QFT) directly to x1000 ton/yr industrial productions in China and Europe respectively, and also to highlight the latest AFR innovation: G1 microchannel photoreactor devoting to highly effective and scalable photochemical synthesis.

Yashwant Kulkarni - Sigma-Aldrich, USA
Continuous flow manufacturing applications: synthesis from gram scale to tons

Since the inception of flow chemistry efforts in its R&D labs, Sigma-Aldrich has focused on developing continuous flow reactors employing in-house chemistry and engineering expertise. This focus has allowed Sigma-Aldrich to develop simple, yet highly efficient reactor systems which are versatile, modular and readily customizable for applications in a wide

variety of fields. These systems are also capable of functioning under a wide array of parameters that include temperature extremes (from -80 to +300° C) and the ability to handle slurries.
The presentation focused on Sigma-aldrich approach to developing Continuous Flow Manufacturing (CFM) as a viable manufacturing platform, applications to process scale-ups and its offers in this space.

Stéphane Varray - Lonza Ltd
Continuous flow chemistry and FlowPlate® microreaction technology

Lonza, a world leader in the development of flow chemistry processes for the manufacture of chemical APIs, is launching two new licensing options for its Microreaction Technology (MRT) Platform. This is the latest addition to the award-winning MRT offering, which includes Lonza's FlowPlate® Reactors. The reactors are available in four sizes, with innovative milli- and micro-channel designs. This technology has already been used to develop multiple small-molecule and peptide products.
The key benefits of the new Research Evaluation Agreement (REA) include access to Lonza's extensive know-how and process patents in microreaction technology, in addition to the FlowPlate® Reactors. Customers will receive the FlowPlate® platform processes for set-up, scale-up, and system operation, along with world-class technical support. These platform protocols will support faster initial process development and ultimately shorten the time to large-scale production.

Charlotte Wiles - Chemtrix BV
Scalable flow chemistry: A flexible tool for the research, development and production of Pharmaceuticals, Fine and Specialty Chemicals

Reactions are conventionally executed under non-ideal conditions in order to gain control over the process; this can include the use of large volumes of solvent, cryogenic conditions, the use of stoichiometric reagents and long dosing/reaction times. Subsequent product isolation is then time consuming and results in the generation of large quantities of waste. Time is then lost when a target is identified as the synthetic route must be redeveloped in order to be suitable for up-scaling to the target production quantities.
Compared to stirred vessels, continuous flow reactors have significant processing advantages which include improved thermal management, enhanced mixing control and access to larger operating windows enabling the development of safe, efficient, robust and sustainable production processes – with benefits not only harnessed for the reaction steps, but also in cost and waste reduction when considering that increased product purities require less downstream processing. Applicable at both the lab and production scale, continuous flow reactor technology has the ability to benefit both early stage researchers and process development chemists/engineers in the exploitation of sustainable synthetic processes. Proven benefits of this technology include access to novel processing windows, increased process safety and reduced costs.

In addition to Customer examples, the CoRIAC (demonstration of Continuous Reactors with In-line Analytics for fine Chemical production) project, which started in July 2010, with the goal of removing barriers to the transition to continuous flow for fine chemical and pharmaceutical producers, culminating in the construction of two pilot-plant demonstrators to put the technology developments into practise were also discussed.

POSTERS

Olivier Vorlet - Ecole d'ingénieurs et d'architectes de Fribourg
Synthesis of gold nanoparticles in a continuous-flows microreactor : a step towards upscalable modular production

A continuous-flow microreactor and a conventional batch reactor were compared to the synthesis of gold nanoparticles (AuNPs). This project was a partnership between the Institute of Chemical Technology of Fribourg (ChemTech) and the laboratory of Bionanomaterials at the Adolphe Merkle Institute (AMI) for the purpose of scale-up nanoparticles synthesis.
Synthesis of spherical AuNPs were carried out by reduction of gold (III) chloride complex ions with L-ascorbic acid (H2Asc) as reducing agent in presence of polyvinylpyrrolidone (PVP) used as a stabilizing agent. AuNPs are characterized by transmission electron microscopy (TEM), UV-VIS spectroscopy, depolarized dynamic light scattering (DDLS) and nanoparticle tracking analysis (NTA). Batch syntheses was performed in an EasyMax® reactor. The microreactor device is built with two syringe pumps, standard PTFE tubes 2mm ID and Y-shaped connector. Complex and expensive micromixer device is replaced with a thermostated ultrasonic bath. The reaction was chemically quenched by adding 2-methyl-propanethiol.
In batch condition, a temperature rise present a decrease of the mean radius, respectively an increase of polydispersity index (PDI). The ratio of concentrations (Au / H2Asc) has an unstable effect on the properties of nanoparticles.
In continuous-flow microreactor, reactants ratio have a poor effect on the PDI. However, the geometry of the microreactor (tube length) and the residence time, have a significant effect. In continuous mode it is possible to significantly reduce the polydispersity index compared with a batch mode. Continuous process have many advantages in terms of flexibility in comparison to batch process. The cost and simplicity of the process-flow equipment can facilitate the process scale-up simply by increasing the number of reaction channels.

Christophe Allemann - University of Applied Sciences Western Switzerland
Pitfalls in the design of a cheap continuous reactor for photo-oxidation using oxygen as oxidant

After decades of development of photochemical reactions, industrial applications remain very limited to date. Batch reactors are not appropriate for photochemistry at large scale due to photon transfer limitation. Continuous reactors offer an opportunity to widespread photochemical reactions at industrial scale; however, several challenges still have to

be solved, especially for gas/liquid reaction where mass transfer is challenging. Photochemical oxidation of a-pinene in a plug flow reactor using oxygen as oxidant gives pinocarvone and/or verbenone with very poor conversion, unless the mixture is highly diluted. The challenge of this reaction is the poor solubility of oxygen in organic solvents (e.g. dichloromethane). Several options to increase the a-pinene conversion into pinocarvone and/or verbenone by increasing its concentration in dichloromethane failed to deliver a scalable process. Among these options, we have tested i) oxygen saturation of the reaction mass, ii) parallel feed of oxygen and use of a static mixer, iii) a combination of i and ii, iv) varying the residence time. The poster discussed this specific issue.

Frédéric Toussaint - UCB Pharma SA
Development and optimization of a free-radical racemization in Continuous Flow Reactor

The racemization of enantiomers is a useful chemical transformation in the pharmaceutical industry given the widespread use of chiral separation technologies in the industry. However some substrates prove to be a challenge for racemization process such as non-activated aliphatic amines. Based on the literature, the racemization of these compounds is achieved by the action of an alkanethiol in the presence of AIBN as radical initiator. However this kind of reaction is usually not performed in industrial batch scale for the potential safety issues of AIBN. The poster described the development and the optimization of a robust, safe and scalable racemization process in continuous mode and compared to a process in batch mode. This study was performed using a DoE approach and different types of microfluidic systems (micro-reactor) were evaluated.

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. Batch to continuous -Economic drivers and obstacles
Robert Ashe – AM Technology

The attendees were asked to fill in a questionnaire covering key issues such as adoption drivers, equipment capability, equipment cost, know-how and ultimately sentiment. The group was made of industrial end users, research organizations and equipment suppliers with various levels of existing experience in flow.
The results were then discussed with the wider audience of the symposium reaching some interesting general conclusions.
Higher purity, lower operating costs and safety were all considered strong drivers, with lower capital costs not scoring as high. It was also pointed out that there are strong region variations in terms of drivers and ultimately the return on investment is what needs to be demonstrated.
The perception is also that the flow reactor market is well served, however peripherals and especially other flow equipment (i.e. for work up) are not. This is also reflected on the perception of the cost of these items. Flow reactors are considered fair value for money but other equipment are considered very pricey. Interestingly it was highlighted how well established analytical equipment are also expensive but are deemed essential for the job. This is the goal for flow equipment. Moreover, it is expected that as the technology gets established the cost will drop following an economy of scale.
The strongest barrier identified during this workshop was in the know-how. Both new graduates and senior people in process development are considered not well trained in working in flow. It was highlighted how flow chemistry requires a more inter-disciplinary approach which may not be available in all companies. This gap can also be filled through process development outsourcing.
Finally, the workshop participants were asked whether they agreed or not with the following statement: "Right now manufacturing experts from the 1950s would easily recognise processes today. In 25 years these same processes will be obsolete……..Adoption of continuous manufacturing will cause this change." (Janet Woodcock, Director of the Center for Drug Evaluation and Research FDA, 2011). In general there was an agreement with flow being an essential part of future manufacturing, with various opinions on whether 25 years is a realistic time or not.
The wisdom of crowds shows an overall positive outlook for the future of flow chemistry. This is also confirmed in a separate survey performed in the US by the company Sentinel Process Systems. An overwhelming majority of the industrial end users interviewed are inclined to look more closely at developing some of their processes utilizing flow and 72% of them are already working in this area.

2. Hazardous reactions and their implementation in production
Oliver Kappe - University of Graz- and **Peter Poechlauer** – DPx Fine Chemicals Austria

Oliver Kappe of University of Graz and Peter Poechlauer of DPx Fine Chemicals Austria discussed various aspects of hazardous reactions. They started by asking: "when do we call a reaction hazardous?"
In some cases extreme reaction conditions (high temperature, high pressure), coined "new process windows" may cause a hazard. In other cases the rate and amount of energy released by a chemical reaction renders it hazardous. Finally, properties of chemicals themselves may be called "hazardous", if they are for example explosive or toxic.
"Hazard is always related to the amount of hazardous material, and to the level of control we can exert on a system", they concluded. In fact, process control and process understanding are primary reasons to perform chemical reactions in a continuous way: temperature and reaction time are under strict control. This allows speeding up the reactions, and minimizing the amount of material sitting inside a reactor.

Kappe then expanded on the link between temperature and reaction rate: While this link may have been known for a long time (the Arrhenius equation describes it), we tend to miss opportunities arising from it: a reaction taking 9 weeks to completion at ambient temperature will be finished within 3 minutes at 200°C and within 1 second at 270°C.
"Why then", he asked, "did we not make use of this before?" First reason: A conventional reactor cannot heat or cool a reaction mixture at the required rate. A state-of-the-art flow reactor can. Second reason: classical analytics could not monitor the reaction progress. State-of-the-art online analytics can. Poechlauer showed how these considerations, if applied to conventional batch recipes, quickly lead to simple designs of equivalent flow processes, with the benefit of maintaining strict control of exothermic reaction mixtures. The primary reason for this strict control is the high surface-to-volume ratio in tubes of a flow reactor, which may be more than 100 times higher than in batch vessels.
Remains the issue of hazardous reagents. "People frequently had to re-design their chemistry and fit it into the vessels they had available in their plant" Poechlauer explained. "Flow chemistry allows using typical lab reagents such as diazo compounds on production scale. In other cases it allows using equipment that has been developed for continuous processes in other industries – extruders, for example.
"Hazardous" does not mean: "cannot handle", they concluded. The ability to handle hazardous chemicals frequently shortens synthetic pathways and improves the environmental balance of a synthesis.
And: The ability to apply hazardous reaction conditions becomes affordable if small-structured equipment is used. This opens up new chemistries for large-scale synthesis.

3. How to educate the new generation of researchers and engineers in flow chemistry

Paul Watts - Nelson Mandela Metropolitan University

The participants of this workshop were a mix of academics and industrialists. The discussion firstly focussed on how to better integrate flow chemistry training into University education. It was identified that flow chemistry is an interdisciplinary topic which lies in the middle of chemistry and chemical engineering, and consequently neither community is really teaching it. Furthermore, because of the interdisciplinary nature of the topic, communication and language between the disciplines is not straightforward, making it harder for newcomers to the field. Chemistry and chemical engineering departments need to work together to develop new courses in this area.
The debate then addressed how academics are attempting to train flow chemists. It was clear that everyone's biggest concern was the equipment availability and cost, however it was highlighted that some of the equipment vendors are providing educational resources for their equipment which in principle makes it easier for universities to use the equipment in teaching laboratories. Nevertheless the discussion highlighted that all teaching labs need support from a group of academics and unless everyone wishes to implement new technology change is difficult to implement, as it is often easier for academics to leave courses as they have always been. It was felt that the technology has only really been effectively introduced at postgraduate level to date in most universities. Given that the cost of commercial equipment seemed to be a major obstacle it was noted that the use of homemade reactors was the most feasible mechanism to introduce practical applications at undergraduate level. In any case, it should still be possible to introduce some element of theoretical training.
The question was then posed as to whether industry need 'short courses' to train their employees. This was very much the case, however it was clear that ideally such short courses should be held within industry to get greatest attendance, as it was felt that this would help enormously as all staff could be introduced to the benefits of the technology more effectively. It was noted that amongst the delegates that it was felt that a 'champion' is needed in order to drive the technology at all companies and that a critical mass of staff are needed in order to integrate chemists, engineers and analysts into one strategic group.
The questioned however remained about how one could address some of these issues most effectively. One option that was highlighted was exchange programmes between industry and academia; students with experience in the technology could work within a company or untrained industrialists could conduct a sabbatical at a University. It was evident that developing network between industry and academia would help. Regarding training courses it was clear that further activities are needed and a better way of facilitating these would help.

The training session attracted really a lot of new people interested in entering the Flow chemistry market. Young researchers from Academia and Chemical companies enjoyed learning the basic principles but also the applications of this technology.
Great discussion took place especially during the Vendor presentations and Workshops. The results of the latter were displayed to all the audience with the help of the chairman and moderator Laurent Pichon.
The exhibition as usual helped people to interact and understand better the equipment involved in flow chemistry. A small group of people had moreover the possibility to participate to a practical session at ThalesNano facility and perform specific reactions (Hydrogenation, Swern oxidation, N-alkylation).
The networking which started at the show continued as usual in the evening during Budapest city tour and cruise dinner: an informal way to get to know each other and enlarge the "flow chemistry community".

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. Please visit our event website:
www.flowchemistrytks.com

ACKNOWLEDGEMENTS

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