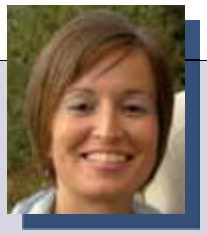

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Third Symposium
on Continuous Flow Reactor Technology for Industrial Applications

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Chimica Oggi / Chemistry Today organized a third symposium on "Continuous Flow Reactor Technology for Industrial Applications" on 2-4 October 2011 at Cernobbio, Lake Como, Italy, achieving a growing interest from international experts. Together with the symposium partner, Corning SAS, Chimica oggi / Chemistry Today organized an agenda with a keynote speaker, a representative of FDA and 15 experts from industry to discuss case studies, manufacturing solutions, process analytical technologies and regulatory issues related to continuous flow chemistry. The conference was accompanied by a poster / exhibition area where 23 companies and 5 Universities had the chance to display their equipment and results. An important moment of the day in fact was the conference time-breaking where people could network and implement their acquaintance. The final panel discussion moreover was characterized by a lively discussion between speakers and participants and gave good ideas for a future event.
Let's enter into details of the lectures.

Conference facility - Grand Hotel di Como- Spazio Como

Ian Baxendale – University of Cambridge
"Chemical synthesis and processing using flow reactors"

During the last decade there has been a steady growth in interest within the chemical community for flow chemistry approaches to synthetic targets due to inherent benefits such as automated and telescoped reaction sequences, quick reaction optimisations and in-line work-ups and purifications. Consequently, flow chemistry addresses both environmental and economic drivers. However, conducting flow chemistry requires changes in synthesis planning and execution and so one should be careful to determine the true the benefits and assess the worth of altering current working practice. This talk focused on some of the benefits that can be realised using flow chemical processing using examples conducted in Baxendale's laboratories.

Giorgio Borghi - Matric Europa
"The advantages of continuous production of specialty chemicals enabled by flow chemistry"

In the last 2 decades the world market share of countries which were leaders in production and export of APIs and specialty chemicals, Italy and Spain in particular, has shrunk considerably due to the growth of competitors from the BRIC community, especially India and China. Manpower accounts for a large share of the production costs; continuous processes is able to reduce the incidence of manpower on the unit product costs, and when linked to on-line real-time analytical platforms enable maintaining the process parameters in an operating window which ensures conformity of product quality to the required specification. Particular interest has been devoted in the last few years to those enabling technologies which aim at transforming batch processes into continuous processes and take advantage of the advances made in the field of PAT and integrated process control for production of API and specialty chemicals. Other "enabling technologies" are being explored with the aim of linking them and making the complete processes continuous. Of particular interest are filtrations on selective membranes which are used both for purification of the product and to shift the reaction equilibrium by continuously removing the product, and utilization of reactive membranes with immobilized catalysts and enzymes.

Franz Amann - Dishman Group
"Ozonolysis in a micro reactor system"

Dishman (Innovative Ozone Systems/Carbogen Amcis) is working with a proprietary device for continuous ozonolysis based on a micro reactor set-up. Although the reactions are run under pressure the flow chemistry approach delivers safety advantages due to the prevention of accumulation of ozonides. The technical set-up and several chemical examples were discussed. In most cases, the ozonolysis itself works satisfactory but the ozonide processing in semi-batch mode had to be adapted to the requirements of the continuous device. Continuous and batch wise production gave comparable results with regard to yield and quality.

Gilda Gasparini - AM Technology
"Scaling up flow reactors - (Biotech case study)"

Unlike batch reactors, the output of a flow device can be changed without altering the hardware or set-up conditions. This flexibility saves time and cost in development. The improved control capabilities

of flow systems can also deliver better yield and productivity. However, the use of flow reactors in bio applications are still limited. Traditionally, flow systems have been considered unable to handle multiphase systems and long reaction time efficiently. Three UK technology companies, C-Tech Innovation, Ingenza and AM Technology are collaborating to develop new flow process techniques for bio manufacturing. The project will integrate all aspects of bioprocess development from catalyst discovery and engineering, to process design, through to small footprint manufacturing of high value products. The objectives of this project is to design a compact flow reactor for continuous bio processing and develop improved process design techniques to accelerate the introduction of new bio-manufacturing processes for a variety of product types such as unnatural amino acids and chiral amines. Results were shown based on the biocatalytic oxidase of the D-amino acid giving a mixture of L-amino acid and the a-ketoacid using wild-type D-amino acid oxidase. This is a multi-phase reaction (G/L/S) with a reaction time in batch of over 24 hours. Tests on the optimization from batch to continuous at the lab scale have already shown a reduction in reaction time from 24 to 3 hours and the following production scale up study results were shown and discussed.

Oliver Kappe - University of Graz
Roman Morschhäuser - Clariant Produkte Deutschland GmbH
"Challenges and opportunities in large scale microwave flow chemistry"

High-speed microwave synthesis has attracted a considerable amount of attention in recent years. Since the first reports on the use of microwave heating to accelerate organic chemical transformations by the groups of Gedye and Giguere/Majetich in 1986, more than 5000 articles have been published in the area of microwave-assisted organic synthesis (MAOS). Not only is direct microwave heating able to reduce chemical reaction times from hours to minutes, but it is also known to reduce side reactions, increase yields and improve reproducibility. For many years it has been attempted to transfer MAOS into a commercially relevant scale. Apart from missing technological concepts, the relatively low efficiency in terms of energy conversion from microwave radiation into heat is a major hurdle which has so far prevented up-scaling of this promising technology. Well known but undesired up-scaling effects like thermal runaways, corrosion of pipe work and the reliability of continuous flow systems causes severe problems for any engineer dealing with highly pressurized systems at temperatures of 250°C and above. Nevertheless, the possibility of performing chemical reactions close to "borderline" conditions for most transformations can open up interesting novel process windows. Even in the absence of a "specific microwave effects", the potential of volumetric heating can be significant and should become even more visible with increasing scale. By using several model transformations the group demonstrated the good scalability of various synthetic organic transformations under microwave conditions on a multi kg/hour scale. Data of energy efficiency were presented for some standard reaction types including amidations and esterifications. An outlook on the technological potential of continuous microwave-heated flow systems and future targets for further development were given.

Sunday dinner - Lido di Lenno

Wenting Chen - Beijing Laviana Pharmatech Co., Ltd
"Continuous flow reactor: A platform toward the green manufacturing"

Applying continuous flow technology in manufacture process can improve the economic efficiency of current process by improving the reaction yield, minimizing the solvent use, reducing the waste generated, expanding the safety margin as well as achieving energy saving and process consistency. The process developed in house using micro reactor in Laviana for ongoing CMO projects showed that the purity of crude products increased, the solvent use can be reduced or eliminated, and the overall process can be automated to eliminate the chance of error. The micro reactor technology provides a unique platform to develop applications in making chemical manufacture greener, to access an easy and quick scalable methodology in bulk chemical manufacture, and to make the in-lab manufacturing of bulk chemical possible.

Barry Johnson - Alfa Laval Ltd
"Achieving production scale flow chemistry"

Alfa Laval has embarked upon a demonstration programme for Plate Reactors at large scale in order to contribute to the case for continuous process plants in the Fine and Pharmaceutical Industry. Reactions which utilize reagents and chemistries common in the industry are chosen to address the issues of operating with real materials. The study is aimed primarily at developing scale up guidelines, but will also, inevitably, give lessons on process startup and shutdown, economics and equipment (both reactor and ancillaries) performance. In this presentation Johnson presented his experience from 2 reactions, a TEMPO catalysed oxidation and an organometallic synthesis / reduction. These reactions introduce different and common processing challenges including immiscible phases, competing byproduct reactions, sensitive reagents and highly energetic materials. Studies are performed at a number of different reactor sizes and throughputs culminating with operation in a ART® Plate Reactor PR49 at the 50 to 100 L / hr range. At each scale the reaction yield is assessed with regard to the reactor operation and performance. Adaptions to the operating scenario and to the reactor for operation at the next larger scale are determined and implemented.

Peter Poechlauer - DSM Fine Chemicals
"From batch to continuous: a 'quality by design' approach to handle hazardous materials in API manufacture"

After some reluctance the pharmaceutical industry has started to embrace concepts of continuous manufacturing and in the meantime various pharmaceutical intermediates and APIs are manufactured using partially or fully continuous synthetic routes. This has opened further options in the way manufacturers of pharmaceuticals secure the quality of their products: authorities are supportive of these new developments, as they both streamline production processes, and allow a better process understanding. DSM focuses on new methods of pharmaceutical

fine chemicals production and uses systematic approaches to analyze processes for improvement options based on continuous manufacturing. DSM has implemented several continuous processes for API manufacture. The presentation exemplified the translation of "batch" recipes into continuous flow recipes following "quality-by-design" principles.

Nigel A. Fletcher - Foster Wheeler Energy Ltd
"Successful achievement of regulatory compliance and continuous pharmaceutical processing"

The talk started by looking at the key regulatory issues facing the designer and the operator of a pharmaceutical continuous processing plant. It continued with a short review of the background to continuous processing and some of the recent output of the US FDA and other leading regulatory agencies to understand what challenges must be met. The speech then moved on to a case study for a multiproduct continuous plant and reviewed how the multiproduct aspect added new challenges to the design. The case study described some of the features of the plant that the project team designed introduced to address instrumentation and control, cleaning and other 'normal' GMP issues together with all the 'new' regulatory concerns. Finally Fletcher looked at some of the lessons learned, what has happened since the unit came into operation and how the owner is now using the plant.

Christine Moore - FDA
"Continuous manufacturing -FDA perspective on submissions and implementation"

Continuous manufacturing is a technology actively being explored for pharmaceutical manufacturing, both by academia and industry. With its lower equipment size and higher throughput, continuous manufacturing has the potential to provide economic and safety benefits. From a quality perspective, the online monitoring and control used in continuous manufacturing can lead to increased product quality assurance and implementation of real-time real testing (RTRT) approaches. The speech discussed the regulatory implications of continuous manufacturing from a US FDA viewpoint. Both scientific and regulatory considerations were provided for developing and implementing a continuous manufacturing process.

David Ager – DSM
"Doing the reaction isn't everything"

There are many examples of reactions performed in a flow regime, especially when hazardous or high-energy intermediates are involved. In many cases, a batch method is used to isolate the desired product and this can be economical as it fits into an existing plant. An alternative is to isolate the product in a continuous manner and this was the focus of this presentation. In particular the use of centrifugal contact separators was described. In addition to being a method to continuously separate immiscible liquids, the equipment can also be used to perform reactions at the same time.

Yi Jiang - Corning SAS
"Continuous flow reactors: right platforms for CRO/CMO"

The presentation highlighted some recent technology breakthroughs in continuous flow reactors, and how these advancements can enhance the flexibility in process development and the scalability in cost-effective production. Searching for better "efficiency" and "flexibility in Big Pharma has led to significant growth in CRO/CMO business today. Globally CRO has undertaken 1/3 of drug development, with annual market expansion rate of 20-25%. Asia pacific becomes a crucial region crowed with a significant number of CRO/CMO competing with quality, cost, and service reputation. Besides the nature of this cost-conscious business, dedicated CRO/CMO must provide fast response to customer's need, combined with their flexible, reliable, and competitive specialist approaches. The presentation summarized how module-based advanced flow reactors have been applied for effective flow-chemistry process development of multipurpose, and why they could quickly meet the product demands in competitive and dynamic ecosystem. As the providers of this new technology platform, how important to help CRO/CMO recognize the potentials of this technology and delivery values of this technology applications.

Dirk Kirschneck - Microinnova
"Manufacturing solutions for microreactors and continuous flow chemistry"

Flow chemistry in combination with process intensification tools as microreactors offers a lot of new possibilities in development and manufacturing of chemicals. Advantages as reactions in novel process windows, higher safety or better product quality are important drivers to switch from batch to continuous processing and to integrate intensification technology. With this new approach also plant technology has to be reconsidered. Highly automated continuous microfluidic systems displace flasks in laboratory, flow mini-plants replace the conventional pilot plant systems and high efficient and flexible manufacturing systems are doing the manufacturing process instead of batch vessels. This change brings a lot of challenging tasks for plant technology and devices, as required pressure and temperature ranges are much higher and dimensions of the equipment often need to be much smaller. Flexibility is a key of successful design and the need of GMP-compliant design makes the topic even more difficult. Microinnova has worked out plant solutions which fit in this new approach of development and manufacturing and meet perfectly the demand of efficiency and flexibility. Kirschneck entered into details of the "modular multipurpose plant" platform which delivers a performance of a continuous plant mixed with the flexibility of a batch vessel.

Pietro Delogu – Serichim
"Continuous flow processes: a multiproduct modular approach"

The use of continuous processes for pharma products and intermediates is going to be more and more popular. Resistance to the introduction of this "new" approach in the industrial practice has progressively been overcome, as the valuable advantages in terms of yields, product quality, safety and production costs have become evident. As this technology is leaving the phase of its infancy, innovation efforts should be devoted to increase operability and to better define the criteria for qualification of equipment and validation of processes. Systems able to afford the continuous operation advantages, at the same time retaining the flexibility typical of the batch plants have to be designed and offered to the pharma industry. The speech discussed two topics: first, how scaling up can be carried

out in order to guarantee results independently from the reactor size for the plant reaction section (when a conventional reaction system, based on plug flow reactors, is used); second, a typical sequence of unit operations, able to effect the production of several APIs, was presented and proposed as a continuous multiproduct unit. According to Delogu the multiproduct plant approach should be considered a very interesting requisite in order to allow productions in campaigns based on continuous processes.

Ikenna Ngene - TNO Science & Industry
"How to develop continuous intensified separations for fine-chemical industry?"

The conventional way to carry out processes in fine-chemical industries is in batch operation in stirred tank reactors. These are not only used for chemical reactions but also for subsequent separations like evaporation, extraction, stripping and crystallization. However, stirred tank reactors are not efficient for these tasks because of mass and heat transfer limitations. "Intensification" of reactors and separations is an opportunity for fine-chemical industries to improve product quality, to lower processing cost and to achieve more sustainable processes. Over the last decade major steps forward were made in the development of continuous micro-structured reactors. The next step is the introduction of continuous micro-structured separation equipment that has a similar performance on separation efficiency. For separation the major challenge is to scale down the volume of the equipment while maintaining productivity by controlling mass and heat transfer over interfaces (droplets, bubbles, particles and films). TNO has developed two technologies for widely applied separations: extraction using intensified contactor technology and flash distillation using micro-evaporator technology.
TNO's objective is to accelerate the development of these technologies by showing that the desired Volumetric Productivity is achievable for real industrial cases. Additional challenges to bring this promising technology into reality are: multi-purpose applicability, chemically resistant materials, modular construction for flexible capacity and cost-effectiveness.

Ayman Allian – Abbott
"In situ FTIR monitoring for continuous chemistry"

The successful transformation of batch processes to flow chemistry relies on two foundations. First, good understanding of the reaction rates of the process at hand as it dictates both the choice of the flow setup and flow rates to be used during the continuous process. Second, there is a need to detect process upsets to ensure highest degree of product quality and yield during continuous processing, which can be performed using robust online PAT tools. In this study, the use of in situ FTIR spectroscopy as a powerful tool that allowed seamless adaptation of highly energetic ozonolysis chemistry to flow was demonstrated. In situ FTIR provided a wealth of information on ozone mass transfer, the required ozone-to-substrate ratio, and other key factors that are critical for a successful continuous process. During continuous operation, the same in situ FTIR was used as PAT tool to monitor the process and eliminate the need for offline analysis. This understanding provided by FTIR allowed the development of a continuous ozonolysis apparatus utilized to generate 2.5 kg of product with only a two week lead time.

Steven Ferguson - Solid State Pharmaceutical Cluster Ireland, University College Dublin
"PAT based design of continuous plug flow crystallizations"

The study presented the development of a plug flow crystallization (PFC) platform consisting of a vortex mixer combined with a tubular reactor. Process analytical technologies (FBRM, PVM, FT-IR) were applied in-situ in order to characterize and optimize crystallizations via the use of novel flow cells. In addition to this a new calibration free method for concentration monitoring was successfully utilized. These techniques permit significant reductions in process development time and could also be applied to in situ monitoring and control of continuous industrial crystallizations. The results of this characterization indicate that plug flow crystallizers provide a robust and impressively productive crystallization methodology. Supersaturation was found to be depleted extremely rapidly within the reactor volume allowing for the maximum potential system yield to be obtained. This meant that despite the small size of the crystallizer (~40 ml) it was capable of producing approximately 50 kg of product per day. In addition to this, vortex type mixers have demonstrated the ability to maintain mixing efficiency at unequal flow rate ratios. This presents obvious operational advantages when compared to conventional confined impinging jet (CIJ) mixers, allowing larger anti-solvent additions relative to product feed. This facilitates the generation of higher supersaturation and resulted in the reduction in final product particle size below 10 µm, highlighting the potential of such crystallizer configurations to eliminate the need for milling operations to reduce particle size.

As usual a very interesting panel discussion moderated by Sergio Pissavini, Process Intensification Consultant, former business director of the Advance Flow Reactor Group of Corning SAS, and by Michele Maggini, professor of Organic Chemistry at the University of Padova, closed the event. The audience was pleased with FDA statements which helped in explaining the regulatory current situation. A very high interest was expressed on the economic benefits given by this technology and surely this will be a must topic for future events. Talking with the participants I had the feeling that the event was really appreciated both from a scientific and social / networking point of view. The boat trip on Lake Como and the Gala dinner on Comacina Island helped people in socializing and deepen their acquaintance in front of a good glass of wine and beautiful sceneries. The response of this third conference was very positive: 130 people representing 78 organizations and 20 countries. "*The quality of the presentations, the number of questions and the subsequent discussions made it clear that the Symposium was very successful again this year. Of course there is always room for improvement, but when asked via a show of hands how many of this year's participants would plan to attend a similar meeting next year, the overwhelming majority of hands were raised. This was obvious testimony to the value the participants believed they received from the Symposium. We are looking forward to incorporating the improvement suggestions into next year's meeting*", stated Robert J. (Bob) Ritchie, Ph.D., Vice President, New Opportunity Development, Corning Incorporated, closing the Symposium. ■