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10th International Symposium on Continuous Flow Reactor Technology for Industrial Applications

Continuous being implemented for pharmaceutical manufacturing with advantages in EHS, quality and cost

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Introduction

The 10th International Symposium on Continuous Flow Reactor Technology for Industrial Applications was held at the Ramada Plaza Milano Hotel Conference Centre, Milan, Italy from Tuesday 13th November to Thursday 15th November 2018. The event had 160 delegate attendees, mostly from equipment suppliers including: AM Technology, UK; Chemtrix, The Netherlands; Corning, USA; Ehrfeld Mikrotechnik, Germany; Flowid, The Netherlands; HNP Mikrosysteme, Germany; Kaneka Corporation, Japan; Kobe Steel, Japan; Magritek, New Zealand; Microinnova Engineering, Austria; Parr Instrument Company, USA; Syrris, UK; ThalesNano, Hungary; Uniqsis, UK; Vapourtec, UK and Zaiput Flow Technologies, USA. There were also attendees from contract manufacturing organisations (CMOs) including: Angelini, Italy; Asymchem, USA; Cambrex, USA; La Mesta Chimie Fine, France; Snapdragon Chemistry, USA and from academia including: University of Strathclyde, UK; University College London, UK; University of Milan, Italy and University of Bath, UK. Attendees from the agrochemical, fine chemical and pharmaceutical industries were also present, including: Syngenta, Switzerland; GlaxoSmithKline (GSK), UK and Merck, USA.

The event was organised by Tekno Scienze Publisher, Italy and consisted of presentation sessions, poster, exhibition and networking sessions and concluded with a roundtable discussion. There was a large exhibition session. Most of the exhibitors were reactor based but other vendors (for example, pumps), analytical equipment and CMOs were also present.

King Kuok (Mimi) Hii (Imperial College London, UK) was the Chair for the entire event and this was unusual in the fact that normally the chairperson is changed for a different session or theme. This article includes a short summary of the talks and the roundtable discussions.

Progress and Challenges

Alastair Florence (Continuous Manufacturing and Crystallisation (CMAC), University of Strathclyde, UK) was the first presenter giving a keynote talk on 'Progress and Challenges for Continuous Manufacturing Research'. He highlighted the recent talk by Janet Woodcock (US Food and Drug Administration (FDA), USA) (1) and the Convention on Pharmaceutical Ingredients (CPhI) Annual Industry Report 2018 (2). He presented examples that showed continuous manufacturing (CM) was becoming more established such as the FDA approving tablet production on the continuous manufacturing line at Janssen Pharmaceutica, Belgium, and mentioning a range of processes:

wet granulation, roller compaction or direct compression where CM is used to produce the final formulated product. He did highlight that although 90% of companies see CM as important, only 17% see their strategy for continuous as mature. CM is still at the exploratory stage. The pace is increasing, the FDA approved 112 new chemical entities (NCEs) since 2014 and four were approved CM products. He highlighted the companies which are adopting continuous (for example GSK (Singapore), Lilly (Ireland)). The role of data and digital would be important. His case studies were in the area of continuous crystallisation where a digital crystalliser was highlighted using software such as COMSOL Multiphysics® (COMSOL Inc, Sweden) gPROMS Formulated Products (Process Systems Enterprise, UK) and Unity (Unity Technologies, USA). The opportunities were process simplification and intensification. The challenges were in reduction of material and experimental overheads for development, improvement equipment robustness and lack of examples of integrated CM for drug substances.

Laurent Pichon (MEPI, France) gave a talk on the 'Evolution of the Adoption of Flow Technologies: Facts and Future'. He showed a slide (**Figure 1**) which indicated that between 2008 and 2018 there was a technology push (raising awareness, curiosity and learning). From 2018 there would be more industrialisation leading to a market pull. This looked to be implemented first in China and India, with Europe, USA and Japan following. Pharmaceuticals would be leading the pull followed by specialty chemicals, fine chemicals (CMO) then agrochemicals and cosmetics (**Figure 2**). He highlighted several vendor technologies: NiTech® Solutions, UK (for example continuous cooling crystallisation of active pharmaceutical ingredients (APIs)); Corning; CSIRO, Australia; Microinnova Engineering; Uniqsis; Vapourtec; Syrris (electrochemistry in flow and Titan being the first turnkey system for large scale continuous processing with dedicated flow pumps (250 ml min^{-1} and 20 bar) and numerous large volume reactors). The use of continuous for crystallisation, liquid-liquid or liquid-gas extraction and filtration was mentioned with several companies advocating their technology for liquid-liquid or liquid-gas extraction. The issues being addressed for continuous were solid handling, high viscosity, gas introduction or generation at meso scale, slow reactions and decision process (culture, training, speed).

Gerardo de Leon Izeppi (Microinnova) gave a talk on 'Economic Driven Technology Selection at Early Stages of a Project'. He talked about estimation

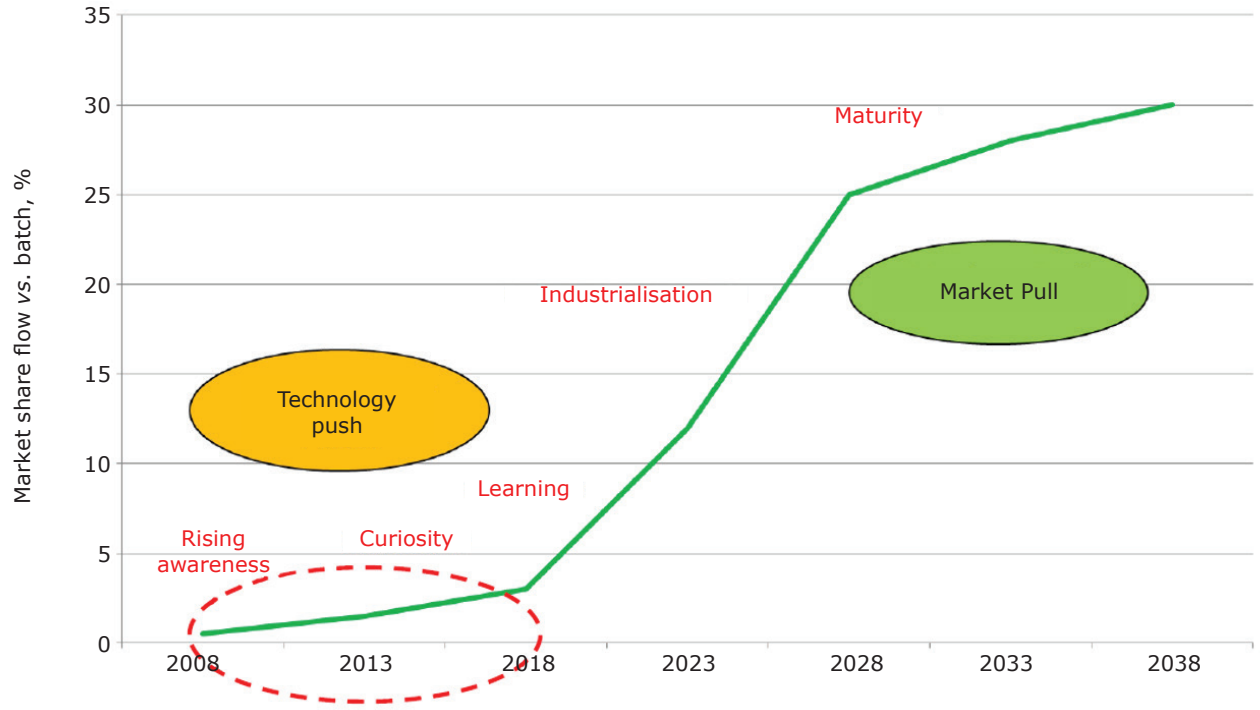

Fig. 1. Ten years of flow chemistry. Reproduced with permission from (3). Copyright (2016) Teknoscienze

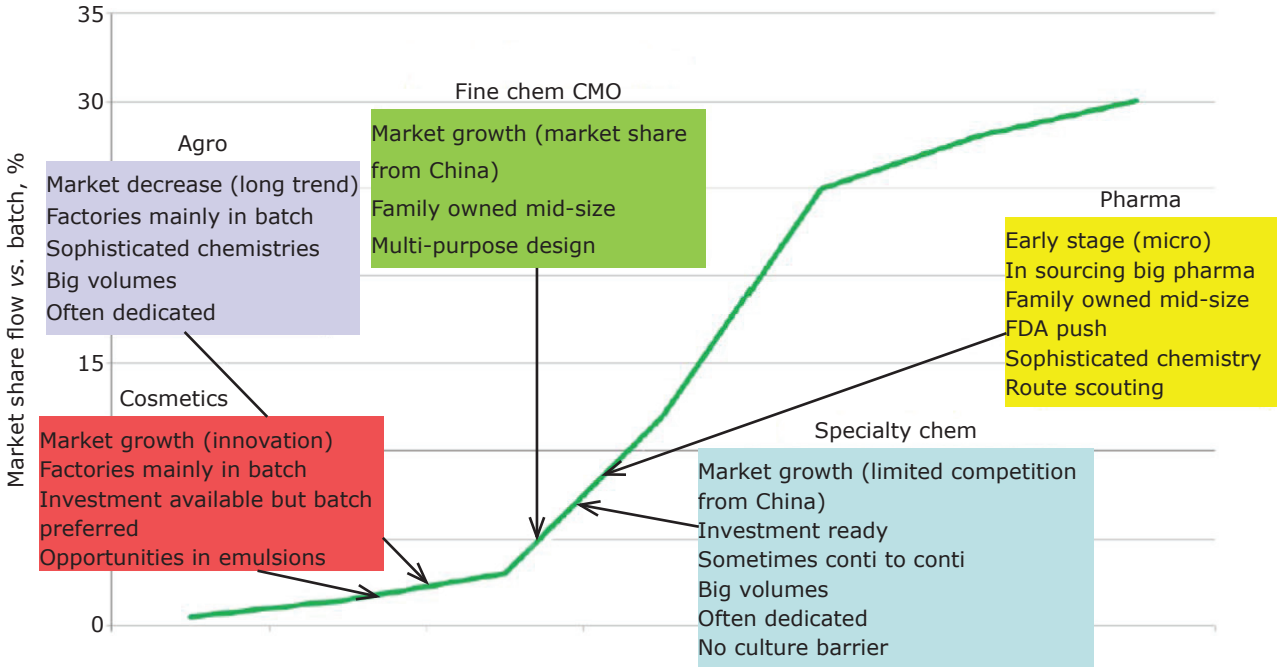

Fig. 2. Market trends (applications). Reproduced with permission from (3). Copyright (2016) Teknoscienze

of capital costs (capacity factored, parametric models, equipment factored models) and the importance of operational costs. His case study was for a polymer plant (batch *vs*. continuous manufacture), where CM would be more profitable where the biggest savings came from labour costs and capital costs would have the lowest impact on the profitability.

Anne Kaaden (Ehrfeld Mikrotechnik) gave a talk on the 'Economic Perspective on Micro- and Millireactors – The Pathway of Being Established As Process Technology'. Ehrfeld Mikrotechnik is a spin-out from the Fraunhofer Institute for Microengineering and Microsystems (IMM, Mainz, Germany) by Professor Ehrfeld who is a pioneer in this area. She highlighted the challenges in implementation of the technology (missing or unpublished references in production scale) and used the lighthouse project as a reference. This is a millireactor in production for which Ehrfeld Mikrotechnik designed, manufactured and supplied a Miprowa® production reactor for Shaoxing Eastlake Biochemical, China, with a production capacity of up to 10,000 tonnes year^{-1} for a highly exothermic alkoxylation reaction. The Miprowa® millireactor has a throughput of about 1 m^3 h^{-1}, has a nominal width of 400 mm, length of 7 m and contains about 150 rectangular reaction channels with exchangeable static mixers. The commission took place in September 2016 and replaced a batch process (*ca.* 20 batch reactors, volume *ca.* 50 m^3). The advantages were significant: capacity increase, yield enhancement, higher product quality, safety enhancement and reduction of energy consumption and footprint. The reactor was inspected six months after start-up and no fouling or sedimentation in the channels or static mixers was found. The unit has been running in continuous operation since September 2016. A recent press release stated that Shaoxing Eastlake Biochemical has started to implement two more millireactors of the same size, thus tripling production capacity at its Shaoxing site to 30,000 tonnes year^{-1} (4).

Charlotte Wiles (Chemtrix) gave her presentation on '10 Years of Flow Chemistry – From an R&D Concept to Examples of Implementation at an Industrial Scale'. Ten years ago, microchannel reactors (10 ml reactors with 100 µm channel dimensions) were widely used which allowed for gram to kilogram production under flow conditions. Scaling up in the early 2000s was proposed by numbering up reactors which was economically unfeasible. Chemtrix's approach therefore was to increase channel dimensions (100 µm to 1–5 mm) and maintain the key properties (efficient mixing, high thermal control and suitable material of construction). The fundamentals of flow chemistries

were discussed and the equipment used, for example LABTRIX® for reaction screening (Suzuki-Miyaura cross coupling), PROTRIX® flow reactor for kilogram scale (for example, Dakin oxidation) and PLANTRIX® industrial flow reactor (for example nitration, API and intermediates). For successful implementation of flow chemistry, she concluded that a cultural change was needed, management support and education was required and that a team was required (for example chemists, chemical engineers, quality assurance (QA), EHS and regulatory affairs).

Hiroaki Yasukouchi (Kaneka Corporation) gave a presentation on 'Continuous Flow Synthesis for Pharmaceutical Intermediates'. Kaneka Corporation's flow reactor facilities are in Singapore and Japan. He highlighted the use of phosgene in its flow processes with the associated enhancement in process safety. Examples included a chloroformate reaction in flow where excellent yield was claimed compared with batch reaction (5). Other examples included synthesis of pharmaceutical intermediates such as imidapril, relebactam and solifenacin. A deacylation reaction in flow with a packed bed system was highlighted and excellent yield and scale-up processes were established. In conclusion its flow facilities were applicable to multi-purpose usage, good manufacturing practice (GMP) production and large-scale production.

Process Development

Matthew Bio's (Snapdragon Chemistry) presentation was on 'Automation of Experimentation: Chemical Process Development in the Era of Industry 4.0'. He commented that with a batch process, you design the chemistry to fit the reactor, with flow you can design the reactor to fit the chemistry. A key element in moving from laboratory reactors to productions in flow was analysis (at-line) and control strategy. He highlighted the importance of automation. For fast reaction process development, he used the Matteson reaction as a case study and showed evidence of how poor mixing can occur for fast reactions and how to optimise reaction parameters. Pump pulsation could be a problem in this respect. He also showed a production reactor setup which could fit inside a fume cupboard. The strategy employed was reaction design (route and reagent, kinetic analysis, heat flow analysis) to laboratory reactor (optimisation of reactor and process and characterisation of process) to production reactor (confirm design space, set control space for GMP manufacture).

Flavien Susanne's (GSK) talk was on 'Industrialisation of Continuous Processes: The Place of Process Simulation'. Flow chemistry and continuous processing within GSK has been an up-and-down adventure over the last ten to fifteen years. The company spent a lot of time developing its first flow plant, which was installed about ten years ago in Stevenage, UK (now the site of one of GSK's global R&D hubs). GSK's first commercial process came out of that pilot plant and it has built a lot of expertise there. GSK has made a commitment to move toward continuous processing, the idea is to apply as much continuous processing as possible to new drug filings and thus during the last three years, GSK has installed a continuous process in its Global Manufacturing & Supply (GMS) facility in Singapore, which is now up and running. He outlined how it was using process simulation by the use of Dynochem® (Scale-up Systems, Ireland) for kinetics and process development then Aspen (Aspen Technology, USA) or gPROMS (Process Systems Enterprise, UK) and then process design. A system-based approach was at the centre of its process development.

Massimo Bertoldi (La Mesta Chimie Fine) spoke on 'Flow Chemistry: The Future is Today'. La Mesta Chimie Fine does multistep organic chemistry for sophisticated products in markets such as pharma intermediates and API, agrochemical intermediates, flavour and fragrances, cosmetics, photography industry and fine chemicals. The plant in the French Riviera has a total capacity of 138 m^3 batch (plus a continuous facility). The plant has pilot scale: 100–200 l reactors and industrial manufacturing scale: 2000–27,000 l batch reactors which are stainless steel, glass lined or Hastelloy. The reactors can be operated at high pressure, up to 100 bar (2000 l) in batch or semi batch. The plant can also perform distillations (batch, continuous and short path) in glass lined or stainless vessels, up to 60 plates/1 mbar/250°C. The facility also has filter dryers (up to 5000 l) filters, centrifuges, dryers and ovens. It can produce phosgene at 12 kg h^{-1} in multipurpose continuous flow workshops (500 l h^{-1}). A range of organic reactions can be performed including heterogenous catalytic hydrogenation. It uses a continuous flow reactor: RAPTOR® Technology. RAPTOR® is a tubular continuous agitated reactor, equipped with heating/cooling jacket and a longitudinal shaft having several impellers; temperature range (-100°C to 300°C), pressure (300 bar), heat exchange (150 m^2 m^{-3}), residence time (10 seconds to a few minutes), flow rate (5–500 l h^{-1}) and stirring (1500 rpm). He

claimed that RAPTOR® is a plug flow mini-reactor in different sizes. One version is equivalent to 70 perfectly stirred mini-reactors with reaction mass moving from one side to the other with the flow. Heat and mass exchanges are due to the stirring system: mixing is always the same and does not change with the rate of introduction nor does it allow any back flow. Examples of continuous manufacture included mesylate, isocyanate decarboxylation and API synthesis.

Reactions in Flow

Elizabeth Farrant (New Path Molecular Research, UK) gave a talk on 'Libraries, Screening and Therapeutic Peptide Synthesis: The Power of Automated Flow Chemistry'. Peptides are of importance as they play a role in human physiology. Since 2000 there have been 28 new non-insulin peptide drugs. As of 2016, there are more than 50 peptide drugs worldwide with sales of more than US$1 trillion. She outlined the challenges and why flow chemistry could be advantageous. The initial aim of continuous was to separate steps in the synthesis such as activation and coupling. She showed the flow system (bench-top unit). The benefits of flow were efficient synthesis, more control over chemistry and scale (can be scaled linearly).

Mimi Hii (Imperial College London) stepped in to replace a keynote speaker and spoke about 'Homogeneous Catalysis in Flow'. She highlighted several areas from her research group in the field of homogeneous catalysis at the interface of organic and inorganic chemistry. The group is interested in developing selective catalysts for C–C or C–X bond formations for organic synthesis. A particular area of interest was aerobic oxidations in flow where molecular oxygen is the greenest oxidant for redox reactions, yet aerobic oxidation is one of the most challenging to perform with good chemoselectivity, particularly on an industrial scale. She detailed several reactions such as a safe, practical and selective process for the aerobic oxidation of alcohols to aldehydes and ketones developed using a ruthenium catalyst in a continuous flow reactor (6). The reactor was a commercially available X-Cube™ reactor (ThalesNano) where the catalyst is loaded in one or two cylindrical cartridges which can be heated and pressurised. In a typical experiment, a solution of the alcohol is pumped to a gas mixer where it was pre-mixed and saturated with the gaseous reactant (oxygen or air) before it was passed through the catalyst bed (6). The product stream can then be collected as separate fractions (for single-pass experiments) or, if desired, re-circulated in continuous flow (low conversion per pass) until reaction is complete. A variety of primary and secondary alcohols can be converted to their corresponding carbonyl compounds in good yields and excellent selectivity, with the exception of primary aliphatic alcohols, which gave only moderate conversions. For certain reactions, oxygen can be replaced with air without noticeable decrease in catalyst activity.

Claudio Battilocchio (Syngenta) spoke about 'Continuous Multistep Processes for the Preparation of Active Ingredients'. One of the advantages of using flow chemistry is the reduced risk from using toxic reagents (particularly if produced *in situ* using flow and then consumed in a subsequent step). Dihaloformaldoximes are highly versatile and reactive intermediates that can be used to prepare interesting building blocks for organic synthesis. However, dichloroformaldoximes were originally classified as warfare agents (for example, phosgene oxime) and the underlying toxicity and safety issues make the production and use on a large scale challenging. He described flow set-ups using aqueous streams of glyoxylic acid with hydroxylamine aqueous solution converting to hydroxyiminoacetic acid. The reaction was exothermic and so a thermal imaging camera was used to monitor temperature and design a process where careful migration of the hazard was achieved by using internal heat exchangers. He spoke about the assembly of a fully integrated continuous process, generating dichloroformaldoximes on demand. The advantages claimed were: (a) use of bench-stable starting material feeds; (b) generation and direct use of highly energetic intermediates; (c) improved process robustness and reliability over the batch mode, on a large scale (*ca.* 100−500 g) and (d) high productivity, using a small footprint system, equating to kilogram amounts of product per day.

Elin Stridfeldt (EnginZyme, Sweden) gave a presentation on 'EziG™ – Enabling Flow Applications in Packed-Bed Reactors for Enzyme Catalysts'. EnginZyme's remit was making biocatalysis suitable for industry. She detailed the advantages and disadvantages associated with using enzymes for catalysts in reactions. The immobilisation (cross-linking, encapsulation, binding to carrier) of enzymes was attractive but has many limitations (for instance activity loss, time consuming, not general for all enzyme types). A simple solution to immobilise enzymes in industry was required. Its solution was EziG™ which is used for immobilisation

of His-tagged™ enzymes, performed in a single step from cell lysate (intracellular expression) or cell-free culture supernatant (extracellular expression). Binding by the His-tag enriches the enzyme in the immobilisation process and offers a non-destructive binding which results in high retention of catalytic activity. The carrier material is inert and suitable for organic solvents as well as aqueous media. It also has excellent fluid properties which minimises diffusion limitations, to give an effective heterogeneous biocatalyst which is suitable for use in batch reactions and flow chemistry applications. The enzyme can be stripped off and the support reused. Examples were given where EziG™-lipase in flow outperforms the commercially available catalyst (7–10).

Advantages and Challenges of Flow

In a slight change Alessandra Vizza (Corning Reactor Technologies), Andrea Adamo (Zaiput Flow Technologies) and Jürgen Kolz (Magritek) spoke about 'Integrating Continuous Processes: Reaction, Separation and Analytics'. The chemical reaction demonstrated was a biphasic system with a phase transfer catalyst which integrated Corning's G1 SiC reactor to allow for a high mixing capacity and chemical compatibility. The phase separator from Zaiput Flow Technologies was installed at the outlet of the G1 reactor to separate the organic phase from the aqueous phase. A Spinsolve® benchtop NMR spectrometer from Magritek was then used on a stop flow mode to quickly analyse the chosen layer. Within ten seconds, the ^{1}H-NMR spectrum was obtained which allowed for an accurate monitoring of the reaction processing.

Wouter Debrouwer (Creaflow, Belgium) talked about the 'The HANU-reactor: Development of a Continuous Flow, Pulsating Plate Photoreactor'. In recent years photochemistry has seen a revival thanks to the advent of photoredox catalysis, development of irradiation sources and continuous flow reactors. The HANU-reactor is a unidirectional continuous flow plate reactor equipped with static mixing elements and is scalable by widening the process channel. The reactor has a borosilicate or quartz window and can operate up to 80°C and 10 barg using split and recombine + pulsatile flow. Case studies for intramolecular [2+2] cycloaddition (Cookson's diketone and Paternò-Büchi) and thiol-ene reaction were presented. A pilot scale version of the HANU-reactor has been installed at Ajinomoto Bio-Pharma Services in Wetteren, Belgium. The unit will enable scale-up of photochemical processes that were developed and optimised in the laboratory HANU-reactor. Full implementation of the pilot reactor in a GMP environment will follow in 2019.

André H.M. de Vries (InnoSyn, The Netherlands) gave a talk on 'Flow Chemistry at Industrial Scale: Enlarging Operating Windows and Increasing Productivity'. InnoSyn has a range of innovative technologies (falling film photoreactor, cryogenics, continuous flow reactors and mixers, three-dimensional (3D) metal printed assets) for challenging chemistries (catalytic hydrogenations, catalysed deuterations, enzymatic resolutions, asymmetric transformations, preferential crystallisations, photochemistry (racemisation of quaternary carbon centre) and organometallics). 3D printing using a selective laser melting process produces homogenous metal objects directly from 3D computer aided design (CAD) data, by selectively melting fine layers of metal powder with a laser beam. He showed 3D printed flow reactors and static mixers with intricate details possible in mm sized channels giving full flexibility. He gave several examples (for instance, Matteson reaction) where flow reactors were used from laboratory to full scale demonstration.

Jonathan Knight (Cambrex) gave his presentation on 'Challenges and Advantages of Moving from an Industrial Batch Operation to an Industrial Continuous Flow Operation'. He outlined some of Cambrex's commercial flow operations such as nitration (nitrobenzene derivatives), liquid-liquid extraction and oxidations using nitric acid. This was continuous oxidation in a tube reactor at temperatures up to 200°C and pressure up to 40 bar, capacity 8 tonnes day^{-1}, annual production 2000 tonnes, recycling of NO into dilute nitric acid and differently substituted aromatics can be oxidised. He gave details of its mounted CaMWave™ KiloLAB Flow Reactor which is a skid unit which can do temperature up to 200°C, pressure up to 20 bar, flowrate up to 200 ml min^{-1}, 10 l per single run, classical heating or heating *via* microwaves through flow through quartz glass section in microwave cavity (**Figure 3**). The system can be adapted to use a plate reactor and perform heterogeneous reactions (up to 10 wt% solids). In-house reactor design was demonstrated for continuous stirred tank reactors (CSTR) which had been designed to optimise heat transport, >30% solids in feed, reaction and product slurry, handle exothermic reactions generating 5 kW, high shear mixers both in feed tank and reaction vessels to ensure homogeneous slurry and high

Fig. 3. CaMWave™ KiloLAB reactor

mass and heat transfer and reactor jacket design for optimised cooling capacity. Computational fluid dynamics (CFD) modelling for the intense mixing in the agitation zone was shown. He gave other examples of flow operation and companies (for example Lilly, GSK and Vertex Pharmaceuticals, USA) who are incorporating continuous into manufacturing operations.

Akira Matsuoka (Kobe Steel) gave a presentation on 'Practical Case Studies on How Large Capacity Micro Channel Reactor (SMCR®) Promotes Industrialisation of Flow Chemistry'. Kobe Steel has a flexible SMCR® demo unit with a processing volume of 30 ml, channel length 1 m to 3 m, installed heat exchanger, with an operating temperature of 200°C and pressure up to 3 MPa for €50k. He gave examples of rare metal recovery (liquid-liquid extraction with reduced processing compared to mixer settler), homogeneous liquid-liquid reaction and mentioned gas to liquids for gas-liquid-solid reactions.

John Tsanaktsidis (CSIRO) gave a presentation on 'Continuous Heterogeneous Catalysis Using CSM Technology'. He talked about CSIRO's facility for developing flow chemistry solutions for the chemical manufacturing industry. The capabilities include liquid-liquid, gas-liquid processes, catalysis (homogeneous and heterogeneous processes), solid-liquid (slurry) and downstream processing. The FloWorks facility will be a 410 m^2 industry-facing facility for flow chemistry due for completion by the end of November 2018. The facility will house up to eight researchers and is intended to be a collaborative space for chemists and engineers from academia and industry to facilitate technology transfer solutions for continuous chemical manufacturing. The catalytic static mixer (CSM) technology was shown as a tubular reactor system with static mixer inserts. The static mixers were produced using additive manufacturing techniques and were design optimised (CFD and engineering fluid dynamics (EFD)) for surface area, fluid flow (pressure drop) and heat and mass transfer. The surface morphology of the static mixers was developed by cold-spray, electrochemical and chemical coating techniques (wash-coating, carbonisation). A prototype reactor was used for continuous hydrogenation showing selective hydrogenation of vinyl acetate to ethyl acetate. Nitro reductions were also highlighted, for example linezolid (first oxazolidinone drug) leading into the second generation synthesis of linezolid by Pfizer, USA (11). He showed that no (or negligible) leaching of the metal from the static mixer occurred. He showed the combination of CSM with photocatalysts.

Wouter Stam (Flowid) gave his presentation showing the 'The benefits of Using SpinPro for Multiphase Reactions'. The SpinPro Reactor is a continuous reactor that allows chemical reactions to take place in seconds in a highly controlled and safe manner. The claim is that it performs reactions under process intensified conditions resulting in high energy and resource efficiency, improved product quality and flexibility in production and development. He did emphasise that the SpinPro Reactor is not to be confused with a 'thin film spinning disc reactor'. The SpinPro Reactor is another type of spinning disc reactor (rotor-stator type). Significantly large shear rates in the gasses and liquid can be induced, which in turn leads to a much larger interfacial area available for mass transfer and a higher degree of turbulence and micro mixing. In addition, the volume of the reactor is completely filled with liquid. The SpinPro technology is well suited for multiphase chemistry, liquid-gas, liquid-liquid or combinations. Furthermore, it can handle precipitation reactions and controlled emulsifications.

Integration of Flow

Miguel Gonzalez (Asymchem, USA) gave a talk on 'A Continuous Journey of Flow Chemistry Integration into the Global Business of Manufacturing

Intermediates and API's'. Asymchem's chemical engineering laboratory was set up in 2009, mainly for flow chemistry research. Its services include assessment of flow reaction feasibility, design of prototypes, process definition and optimisation, equipment design and validation and technology transfer to production. It has developed different types of equipment to support a wide range of reaction types and implemented processes on a wide range of scales. Flow chemistry capabilities include ozonolysis/ozonation, reactions with diazomethane, nitration, electrochemistry, Curtius rearrangement and continuous catalytic hydrogenation.

A bit of a diversion was supplied by Carsten Damerau (HNP Mikrosysteme) who gave a talk on 'Pumps – Enabling Continuous Flow Chemistry'. To the dismay of the audience he announced that there was a range of pump types for liquid and gas and there was no universal pump system that covered all applications. He showed the consequences of a pulsating feed producing erratic stoichiometric conditions in static mixers and capillaries, unwanted reactions and therefore lower yield of desired product (12). Selecting a pump with the lowest pulsatile effects was advocated and the use of two or more pumps giving hydraulic interaction was shown. He did give solutions such as flow meters in a closed loop control. He advocated the use of micro annular gear pumps of the hermetic inert series giving high chemical resistance against oxidising and reducing media, acids and bases. They are hermetically sealed, long service life, wear-resistant, ultra-hard materials giving precise dosage (low pulsation) *via* rotary micro annular gear technology with no valves. He illustrated the use of pumps for feed modules and modular plants showing the example of a system used by GSK for an API production system made by Zeton, Canada.

Ernie Hillier (Waters, USA) finished the presentation session by talking about 'PAT/CM A 10 Year Journey – Starting with Collaboration, Lessons Learned, Partnerships – Where We Are Today'. He talked about the development of high-pressure liquid chromatography (HPLC) and how Waters had developed a system to cut analysis time from about 30 min to <1 min using the ACQUITY UPLC system. He showed examples of peptide analysis for HPLC, where analysis time was reduced and the quality of data was improved using the UPLC system. For continuous manufacture the requirements of at-line analysis require fast decision making. He showed Waters' PATROL system which had been employed in a few continuous processes in collaboration with Pfizer, Merck and Lilly and advocated the merits of collaboration.

Round Table Discussion

Oliver Kappe (University of Graz, Austria) led a round table discussion in the last hour on 'How has Flow Chemistry Impacted on Chemistry in the Last 10 Years?'. The panel included the speakers with questions and comments from the audience. A recent publication was highlighted: 'Continuous Processing in Pharmaceutical API' which looked at a survey of pharmaceutical companies and CMOs (13). There was agreement about the statement in the article that continuous processing at scale has primarily been about enabling reaction chemistry, while postprocessing and analytical remain in the very early stages of development and implementation. Digital and process analytical technology (PAT) were mentioned in this context as well as auxiliary equipment and supply chain issues. Data and control systems will be key as well as standardised systems, i.e. modules within modules (one pump for one chemistry, change to another manufacturer for different chemistry, pump control system must integrate). There were many stories regarding flow chemistry from the last ten years with more examples. Companies seem to be sharing more so there is 'less competition', indeed an example is highlighted above where vendors are collaborating to produce an overall package for a customer. Pharmaceutical companies appear to be using CMOs more (big pharma is risk averse and CMOs have teams working on continuous). A big talking point was that many of the realised industrial processes employing continuous are based in China, while few were in Europe. This could be due to factors such as existing assets and the risk averse nature of the industry. A discussion point was also training, for example education for chemists (undergraduate courses still rely on batch systems for practical training, can we have continuous examples in synthesis for undergraduate or graduate chemists?). A theme that most of the panel agreed with was culture and integration of skills (education requirement; use of teams: analytical chemists, organic chemists, process safety, mechanical and chemical engineers to work together). The mood of the panel was optimistic in that the last ten years had seen a shift towards continuous (flow) and although there was still learning required, more implementation of flow (continuous) chemistry by industry would be realised in the near future.

Conclusions

The key messages from the event:

- The main key advantage that the speaker(s) advocated for the use of flow chemistry (or continuous processing) was environment, health and safety (EHS). This was emphasised in the majority of the talks
- The next ten years for flow chemistry is going to be crucial. There was optimism that flow is going to happen. A few speakers mentioned that Woodcock (US FDA) had recently presented (October 2018) at the 3rd International Symposium on Continuous Manufacturing of Pharmaceuticals on 'Modernizing Pharmaceutical Manufacturing: FDA View' (1). Her key statement from that talk was "the technology is available and used in other sectors and the regulators were on board and will continue to support". The CPhI Annual Industry Report 2018 (published in October 2018) also highlighted in that there was a "warning to pharma manufacturers that don't invest in continuous manufacturing that they will be forced out of the market" (2)
- There are a few examples of flow in commercial production. This is more evident in China than Europe and there was a feeling that the pace would accelerate if examples from Europe are publicised. CMOs also commented that they were sometimes not allowed to publicise the route (i.e. continuous) by the customer
- Although equipment vendors highlighted their technology solutions regarding continuous, it was felt that auxiliary equipment was one of the factors that hampered implementation (for example pumps)
- Vendor companies are collaborating (not competing) in different areas of the process, playing to strengths i.e. process chemistry in flow with downstream process in flow.

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The Reviewer

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