

Micro-players edge microreactors into the mainstream



Microreactors are demonstrably able to produce commercial chemicals efficiently and quickly. Now, the long-awaited move from lab to product line for EOF-based reactors is being expedited by a new multi-disciplinary alliance; David Appleyard reports

WIDELY known as 'lab on a chip' systems, microreactors are essentially a series of interconnecting channels formed in a planar substrate and may be fabricated from glass, quartz, ceramics, polymers, and metals. Reagents are brought together within these channels to deliver a high purity product and, today, a large range of reactions has successfully been demonstrated in such devices, among them many famous and industrially-relevant organic processes.

The main advantage associated with the miniaturisation of chemical synthesis is the increased reactor control resulting from predictable thermal and mass transportation properties. In traditional large reactor vessels, fluctuations in temperature, for example, are difficult to correct promptly, whereas changes on the micro-scale are observed almost immediately. Decreasing the reactor dimensions also gives an inherently high surface-to-volume ratio and therefore heat generated by exothermic reactions can be dissipated rapidly, reducing the likelihood of thermal runaway or hot-spot formation.

Improved reactor control yields other advantages too, in typical bulk systems, synthesis is perhaps some 70% of the theoretical efficiency, while on the micro-scale this figure can rise to a favourable 90% or higher. The ability to optimise the reaction process within as little as five minutes is another key advantage of the microreactor system. Current bulk technology is based on the scale-up of successful lab-scale reactions. However, at each stage of the scale-up, reactor modifications result in changes to the surface-to-volume ratio, which in turn has a profound effect on the thermal and mass-transport properties of the reaction. As a result of these variations it is often necessary to re-optimize the process at each stage

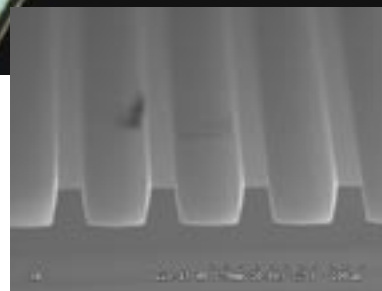
of the scale-up process, a route both costly and time consuming. When using micro-fluidic systems, conversely, a reaction is first optimised using a single microreactor. To increase production volume, the number of reactors is simply increased using an approach referred to as scale-out or numbering up. Consequently, a reaction is only optimised once and all subsequent reactors are controlled using the same operating conditions. This approach is therefore cost-effective, time-efficient, and flexible, enabling changes in production volume by simply increasing or decreasing the number of reactors employed.

The possibilities promised by micro-fluidic systems and the benefits of reduced consumption of reagents, shorter temperature cycling times, faster mixing, and the high degree of automation possible compared to conventional equipment systems have not only interested scientists, but have also sparked the interest of industrial players, especially those in the areas of life sciences and fine chemistry.

from cupboard to commerce

The latest research at Hull University's Chemistry department in the UK has thrown up a number of commercial reactions that are of interest to big pharma. For example, the peptides and peptide-related molecules that form the basis of a multitude of pharmacological compounds have recently been synthesised by a team led by Paul Watts in a borosilicate glass micro-reactor at Hull, where a conversion of up to 100% for a dipeptide was demonstrated.

Uniquely, the research on microreactors at Hull is based on electro-osmotic flow (EOF) and while examples of pressure-driven systems are known, EOF has the clear advantage of simplicity. EOF requires no mechanical



A glass microreactor chip suitable for two-stage synthesis; the glass is 35 mm x 20 mm

parts, enables pulse-free flow, and generates minimal backpressure. Previous work has successfully demonstrated the ability to synthesise a range of compounds within an EOF-based micro-reactor, including stilbene esters, peptides, 1,3-diketones and unsaturated carbonyl compounds, demonstrating both reduced reaction times and enhanced conversions compared to those observed in batch processes.

Nonetheless, while many decision makers now acknowledge the performance of microreactors and no longer consider the technology to be immature, a complete picture of the process, including detailed engineering designs and economic calculations, is required before large-scale investment and roll-out of the technology can be achieved. Questions regarding the impact of other processing operations – such as separation – energy efficiencies, consequential costs for equipment, process controllability and safety, overall profitability of the process and multipurpose flexibility are raised. Each chemical process and each company demands unique profiles and specifications. In addition, the data set is far from being complete. Direct evidence of pilot plant operation and production with chemical micro-processing apparatus is consequently limited, but the growing number of industrial patents, the number of industrial participants at microreactor conferences, and the increasing sales of supplier companies in the field indicate a growing interest within the industry.

However, while Hull's research expertise in EOF reactors has proven that the technology has benefits in a range of typical industrial reactions, academic research in single reactors is not enough to make industry invest in the technology. Why should industry invest in developing reactions that exploit microreactors when there are no production scale devices available to provide a return on investment?

micro-fluidics prompt micro-moves

While current research in microreactors, notably in Japan, Europe and the UK, is aimed at further improving yields and safety, reducing waste or performing chemistry that is impossible in batch production, the industry at large has adopted a 'wait and see' approach. Consequently, the drive to commercialisation is being pioneered by those seeking to capitalise on first mover advantage, such as the UK/Dutch alliance that is building on Hull University's groundbreaking research.

Lionix, a Netherlands-based commercial operation with expertise in microreactor micro-technology processes, is involved as a partner for the production of the reactor vessels, having developed the key technology to make reactors and experience in the route to volume production through their "design for manufacturing" approach.

In this case the substrate of choice for the reactors is glass and although hydrofluoric acid (HF) etching is the usual process, it has dimensional constraints. Lionix, however, is also developing the deep reactive ion etching (DRIE) process in a large Eureka-funded project with Adixen/Alcatel. DRIE is much more controllable and precise than HF and can consequently make repeatable, rectangular structures in the 10–300 µm range. This offers large design freedom for the microreactors, which have to be designed specifically for a specific reaction (class). They can also integrate platinum electrodes and seal the troughs by diffusion bonding with glass to make wafers of multiple reactors that include manifolds. Fabrication of the reactor by etching and bonding technologies is relatively low cost in a mass production foundry and makes it suitable as a disposable product. Lionix and Olivetti I-Jet have entered into an agreement to combine the expertise of both companies in the area of design and development for volume production in the field of micro-systems, opening significant opportunities for the high volume

manufacture of microreactors that would be required to move the technology into the mainstream chemicals and pharma industry.

Moreover, Lionix has developed a modular integration technology platform which enables the (hybrid) integration of micro-sensors in a complete miniaturised subsystem. The sensors for important process parameters such as temperature, pressure and flow can be added to every single microreactor in a cost-effective way.

With Hull University providing the reactor design to suit the chemistry and Lionix making the reactors and the micro subsystem integration, the final piece of the puzzle is the control and system integration that addresses the technical challenges of repeatability, scale and applicability to the production environment. The Cambridge Design Partnership, with expertise in systems integration and control, as well as experience of project management and technology transfer, aims to achieve just that. Overcoming the multidisciplinary engineering challenge of bringing together research scientists, technology suppliers, and a system integrator to produce a commercial, reliable, controlled and cost effective manufacturing system is the next step.

In discussions with potential customers, Cambridge Design Partnership has defined a goal of a 1 t/y system as a target for pharmaceutical and fine chemical production. The vision is for a revolution in pharma manufacturing, a self-contained stand-alone system controlled by a PC that is a continuous flow system with around 1000 reactors operating in parallel.

The plans will see wafers containing 20–50 individual reactors and which are subsequently stacked into groups of 50 wafers, each being built into a self-contained subsystem that is electronically controlled. Each of these sub-units is fed with fluids, power and control information by the system, which commands the operation of each reactor and logs its performance for quality assurance. This architecture ensures reliability and scalability so one system can easily be reconfigured for a number of reactions to ensure the end user can achieve a return on capital investment. However, a number of technical barriers remain before this can be achieved. For instance, pressure, temperature, voltage and current control are all key factors within the microreactor environment. Similarly, each reactor



must be individually controlled and its output monitored to ensure that a single reactor failure does not contaminate the high quality, high value product. By monitoring current in each individual channel, a single stream can be stopped to prevent this and will form part of a series of mechanisms delivering feedback and control.

Initially, development is directed at achieving a lab system that uses a standard architecture and communications protocol that can be easily scaled and reconfigured for alternative chemistries and production volumes. The communications protocol will establish rules for different control elements to talk to themselves and the PC, and will be hidden from the human interface, which will simply be a PC that is easy to understand and flexible to use.

an emerging market

Progress in micro-system technology, micro-fluidics and analysis is making it possible to build complete chemical 'plants' in a desktop format, enabling R&D on chemical processes on the micro-scale with unique features, such as extremely low reagent consumption, fast mixing, and optimal control of process conditions.

It is evident that volume production of these fine chemicals could then be established by numbering up of the micro-reactor units. Certainly, development of the EOF microreactor system is a cutting edge project, and some industry observers estimate the microreactor market to be worth of the order of \$100m over the next few years. However, unlike in Japan, UK sponsorship of such development is only just appearing. Consequently, this promising and emerging technology in the fine chemicals sector is being speculatively funded by the partners. Within the year, Cambridge Design Partnership and its partners fully expect to have a working lab system capable of delivering a few kg of product per month.

How much more might be achieved if the partners were themselves able to number up? ■

Cambridge Design Partnership's integrated microreactor production system (IMPS)

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