In recent years, we have observed a trend away from designing microreactors towards designing chemical processes with microreactors. Concerning the latter, plant concepts, fluidic and electronic interfaces and platforms, sensory and analytical devices, and process automation have come more and more to the fore, as well as economic cost-calculations.

MICROREACTORS VERSUS MICROSTRUCTURED REACTORS

Stemming from MEMS (MicroElectroMechanical System) developments, designs and fabrication technology, packaged microfluidic chips – used first for biological and chemical analysis (μTAS, Micro Total Analysis Systems) – were modified to perform chemical syntheses (1). In addition, chip devices for the mixing of miscible or immiscible fluids offered a novel means for the processing of this unit operation.

The typical construction materials for chips are silicon, glass and polymers such as polydimethylsiloxane. While most microfluidic chips operate at throughputs in the ml/hour-range or below, microstructured stainless steel devices provide a much larger capacity owing to the somewhat larger internal dimensions, the sometimes higher degree of parallelisation and the use of robust feeding schemes, for example, using industrial high-pressure pumps (1). These steel devices are assembled in a 3-D manner, for example, with plate stacks inserted in the recesses of housings. They somehow fill the gap between tiny microfluidic chips and the smallest conventional equipment, such as static mixers or other process-intensification tools. Indeed, throughputs as high as 3.5m³/hour liquid flow at pressures of only a few bars can be achieved for some microstructured devices and for selected operations (see Figure 1) (3, 4). More devices are available for flows in the 100l/hour-range, and it should be feasible to perform even combined operations – such as mixing-reaction-quenching – with at this capacity using today’s microstructured devices.

Concerning the remarks above, chips may be more adequately termed ‘microreactors’; the 3-D architecture apparatus represents a ‘microstructured reactor’, with volumes sometimes as high as several tens of litres and weighing several tens of kilograms (1).

PROCESS AND PLANT ENGINEERING DESIGN

It has been realised, though, that microreactor design on its own is not sufficient to achieve industrial
There have been extensive and comprehensive reports on the factors driving the use of microreactor technology, and several comparisons with conventional technology have been made. Some examples of how the technology is being used in industry are given below.

**Laboratory Molecular Discovery and Process Development**

At the laboratory level, microreactors are gaining acceptance in producing new materials and developing processes for scale up. In the pharmaceutical industry, drug discovery has been speeded up by using modern implementation of the technology. Process engineering, and plant erection and control, are just a few of the other processes which have to be solved downstream of industrial laboratory-testing with microreactors. Depending on the application, we can identify at least two different scenarios for plant concepts with microstructured devices. More or less complete ‘micro and mini plants’ are made by integration of small-sized micro-devices, which are equipped with smart sensors and analytical devices within one entity. This includes speciality platforms like the MicroChemTec Backbone, the FAMOS Breadboard, and the NeSSI Backbone stations, as well as table-top plants like the CYTOS, SEQUENOS, MICROSYN II and AuMuRes systems (see Figure 2). The latter represent more of an entire miniature plant ready for ‘plug-and-play’ use, while the docking stations are made more for flexible, custom-made plant construction.

A very different approach from these ‘micro plants’ is provided when only one microstructured reactor is inserted as part of a complete industrial pilot or production plant (5). The process control and fluidic environment here is governed by conventional, mostly large-sized tools, and the microstructured reactor has to be adapted to this layout, while in the table-top plants, this is typically the other way around. In this way, quite large plants with microstructured reactors have been realised in recent times. Among them is a pilot plant at a Degussa site, with a microstructured reactor of more than two storeys in size (about six metres in length) for the production of propylene oxide (plant engineering by Uhde). Also, fuel-processing plants in the 5kW-plus range, which are currently operated at IMM, belong to this category. In the latter case, although the size of the microstructured reactor is no larger than a shoebox, the whole plant may measure several metres in each dimension.

While we expect chiefly new functionality from the chip systems and table-top plants at the laboratory scale (even if this is only the speed of information improved by an order of magnitude), the hybrid plants within conventional industrial-site environments are ruled by the typical laws of economics for the chemical and pharmaceutical industries. Here, the microstructured reactor has to demonstrate a quantifiable added value, and this can only mean higher margins for the plant in terms of, for example, savings in energy or raw material costs or ‘capex’ investment, or a better safety or environmental balance.

**APPLICATIONS OF MICROREACTOR TECHNOLOGY IN INDUSTRY**

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**Figure 1:**

a) SuperFocus – an off-the-shelf microstructured mixer with a liquid-flow of up to 300l/hour (at ~10 bar).

b) StarLam3000 – an off-the-shelf microstructured mixer with a liquid-flow of up to 3500l/hour (at ~0.5 bar). In front of the StarLam3000 is the small-sized version, StarLam300, with a flow of ~300l/hour.

Source: IMM (both)

**Figure 2:**

a) Microchemtech Backbone with nine assembled micro or miniature devices connected.

b) Microsyn II table-top system.

Source: a) IMM, b) mikroglas chemtec AG
screening techniques; the same holds true for catalyst combinatorial chemistry. Microreactors offer the opportunity to further improve drug discovery and process development with virtually the same tools, and to then transfer this to the production stage with analogue equipment at low – but not negligible – scale-up ratios, having quite similar defined flow conditions. Already at the discovery stage, preparative quantities for further analytical characterisation can be isolated.

Chip reactors with parallel reactant flows – which cross in a complex, typically multi-levelled network – allow continuous-flow organic synthesis to be performed, offering an alternative processing with novel features to the established titer-plate batch-processing common in drug development. The advantages are, for example, minimum inventory (particularly important with regard to valuable samples), the conduct of multi-step syntheses in one format with a small footprint, and the ability to vary process parameters in a short time-scale (1). The latter enables quench-flow (6) or improves in a similar way electrospray ionisation mass spectrometry (ESI-MS) (7) analyses to be performed in the millisecond range and to extract kinetic data from there. Other types of kinetic measurement may also be performed, such as transient operation in pulses – with all the benefits of such analyses.

Researchers at the University of Tokyo (Japan) prepared a small (2x2) library in a chip microreactor by reacting 3-nitrobenzoyl chloride and 3,5-dinitrobenzoyl chloride, each with DL-1-phenylethylamine and 4-amino-1-benzylpiperidine using a phase-transfer reaction (8). In a similar fashion, GlaxoSmithKline (GSK) generated a (2x2) library for a domino reaction which consisted of a Knoevenagel condensation giving an intermediate which immediately underwent an intramolecular hetero-Diels-Alder reaction with inverse electron demand (9). As aldehydes, commercially available rac-citronellal and a synthesised aromatic aldehyde were selected, as well as two commercially available 1,3-diketones, 1,3-dimethylbarbituric acid and Meldrum’s acid. By generating 2 x 2 combinations of these reactants, four different cyclo-adducts were generated; libraries of a more extended size were also realised. Again, GSK published the synthesis of a 3x7 library using the Knorr reaction of diverse 1,3-dicarbonyl compounds and hydrazines under ring-closure to pyrazoles (10) (see Scheme 1). The Knorr synthesis is of interest for drug applications as products with a wide range of biological activity can be generated in this way.

For the serial screening of homogenous catalysis under multi-phase conditions, not only were libraries of similar size achieved, but the extraction of kinetic data and modelling was performed for asymmetric syntheses, increasing the depth of information gathered. Steric, solubility and electronic effects on reactivity were monitored for a substrate library for the isomerisation of allyl alcohol derivatives conducted, as a liquid/liquid operation (11, 12). For the gas/liquid hydrogenation of Z-(ct)-acetamidocinnamic methyl ester, a detailed benchmarking of the continuous microkinetic test versus the traditional batch kinetic apparatus was conducted; this clearly showed benefits in terms of consumption of precious materials containing catalyst and solvent consumption, test-throughput frequency and ease of automation (12, 13). The work was partly done for the purpose of creating new materials for the Rhodia Company.

In the field of heterogeneous-catalyst screening, computational evaluation methods via genetic algorithms and neural nets have the potential to extract information buried in a tangled mass of data. Today, this is more of a vision and needs to be explored in the future – but it is certainly a key to the proper use of micro-devices at the discovery level. Micro-devices allow the integration of much functionality on a small footprint and the monitoring of data in-line and in real time, as for example recently demonstrated for in-line FTIR, Raman and NMR techniques. So far, these investigations have been only to prove feasibility; they wait to be implemented in, for example, self-optimising systems, cycle-loop operation and computer-assisted discovery, as mentioned above.
**Process Intensification**

We naturally know much more about laboratory investigations with microstructured reactors, since this is the domain of universities and institutes, and typically is not considered as strongly protected, proprietary industrial know-how. Nevertheless, it is becoming evident that testing is moving more and more in the direction of microreactor pilots. Even in this respect, it is often difficult to establish from the rare examples officially reported whether a process is really being performed at the production level – and thus of commercial value to the company – or is still at the pilot stage.

Most of the known pilot processes in the field of fine chemicals use a microstructured mixer, with connected tubing or micro heat exchanger, for engineering reasons similar to those for when conventional static mixers replaced batch equipment – that is, compactness and low capital cost, low energy consumption and other operating expenses, negligible wear and no moving parts, thereby minimising maintenance (14). Further advantages include the lack of penetrating shafts and seals (providing a closed-system operation), a short mixing time and well-defined mixing behaviour, a narrow distribution residence-time, and a performance independent of pressure and temperature. In particular, it is the combination of high mass transport (that is, large conversion) and excellent thermal management (that is, high selectivity) that renders microreactors attractive for the production engineer.

As an example, Merck has successfully run a production process involving a organometallic reaction using five miniature mixers for about five years – until the lifetime of the fine chemical product ended (15). The yield was increased by about 20% compared with a former batch production process. It was, in particular, remarkable that a former cryogenic process could now be conducted at room temperature without any loss in selectivity.

Recently, the Clariant Company published work on production of an azo pigment with micro-mixers (16). Owing to the improved mixing characteristics, better pigment products could be synthesised – that is, having better optical properties in terms of brightness, colour-strength or transparency. This is as a result of the smaller particles precipitated in the microreactor. For its ultimate application as a dye, this may mean that less pigment needs to be incorporated into the commercial dye matrix so that the profit margin on the process can be increased. The Clariant example represents the first industrial transfer of microreactor results with regard to particulate formations; others – showing clear benefits at the laboratory scale for powders or encapsulates – await commercial exploitation.

The Clariant Company also established a pilot process for the synthesis of phenyl boronic acid by a Grignard reaction (17). This reaction has many side and consecutive reactions which lead to an extremely high sensitivity to changing local concentration profiles and thermal overshooting. A mismatch in feed, mixing or temperature control can easily decrease the yield of this cryogenic process down to 10-20%, while the best batch performance barely exceeds 65%. Using a microstructured mixer, the yield can be increased to about 90%. No loss in yield was reported for the scale-up from a laboratory-scale micro-mixer to a pilot microstructured mixer. As in the Merck case, the formerly cryogenic process (around -50°C) could now be performed at room temperature – in fact, providing an even better performance. This considerably reduced the energy costs of the process (see Figure 3).

A further gain in energy saving was achieved by facilitating downstream purification, since the much improved product purity of the microreactor process (92% pure raw product, as compared with 80% in the batch case) eliminated the need for energy-consumptive distillation. The clean final product could now be isolated simply by precipitation or extraction.

**Scheme 1:** 3 x 7 pyrazole library, generated by the Knorr reaction of diverse 1,3-dicarbonyl compounds and hydrazines in a microfluidic chip with parallel processing (10)

**Novel Processes and Routes**

These examples demonstrate that microreactor processing can intensify existing chemical processes in industry, and even lead to first revenue streams from the technology. However, there are disadvantages to microreactor technology and,
in conversation, reports abound of unsuccessful trials by industry. In this context, maybe the best strategy is to use microreactors for processes which are desirable, but not currently feasible given the limitations of today’s equipment. For such novel processes and routes, microreactors provide an enabling technology.

A good example of this kind of application is the direct hydrogen-peroxide process developed by IMM at the laboratory scale using UOP’s proprietary catalyst and process know-how, and which is now being investigated on a pilot-scale level at UOP (2). The direct synthesis of hydrogen peroxide from the basic elements has the potential to replace the anthraquinone process – but has suffered so far from the fact that nearly all approaches reported in the patent literature have been associated with a risk of explosion. When using microstructured reactors, a quenching of the radical chain can be achieved due to the high surface-to-volume ratio – thus providing a kind of inherent safety, at least at the reactor level.

The key to a high selectivity towards hydrogen peroxide is to have a noble-metal catalyst in a partially oxidised state (2). Otherwise, only water is formed, or no reaction is achieved. Peroxide testing at IMM used such an H₂O₂ selective catalyst, placed within a mini-trickle bed reactor equipped with a micro-mixer. Using UOP process specifications, a space-time yield of 2.0 g H₂O₂/(gCAT h) was achieved which exceeds values reported in the literature (see Table 1). Furthermore, the reaction was carried out at only 30 bar (considerably lower than for published processes), and involved smaller O₂/H₂ ratios, saving valuable raw materials. The maximum H₂O₂ weight concentration achieved so far is 1.7%.

It could be clearly shown that improved selectivity and conversion was given at explosive O₂/H₂ ratios. UOP then carried out pilot-scale tests at still higher pressures in a fully automated explosion cell, to reproduce vendor work and study conditions and kinetics. A selectivity as high as 85% at 90% conversion has been achieved so far (O₂/H₂ ratio of 3). An economic calculation, as well as basic engineering, of the production process has been performed, aiming at large-scale production of about 100,000 tonnes per annum. The new H₂O₂ site is planned to be realised within the next few years.

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References


| Table 1: Specifications of the Direct Hydrogen Peroxide Microreactor Process – Comparison with Published Processes |
|---------------------------------------------------------------|---------------|---------------|
| Pressure, bar | Published | UOP Test |
| Temperature, ºC | 35 | 50 |
| O₂ : H₂ | 6.8 | 3.0 |
| ‘Space velocity’, g H₂/(gCAT h) | 2.6 | 1.8 |
| H₂O₂ concentration (max), wt% | 5.2 | 1.7* |
| Yield, g H₂O₂/(gCAT h) | 1.5 | 2.0 |
| * Not optimised. |

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