Microreaction technology

Microreaction technology may not mean new chemistry - but it does mean better chemistry.

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In recent decades - in the race towards developing finer structures - computer chips have become smaller and smaller, and yet more powerful with each product generation. At the same time, methods have been developed to produce these microstructures in various materials.

These methods have allowed the development of what is generally called microsystem technology. Miniaturisation is no longer exclusive to microelectronics. Mechanical, optical, thermal and fluid microdevices are now part of our life and can be found, for example, in laser heads for CD-players, microsensors in the automotive industry, ink-jet printer heads and minimum-invasion surgical instruments.

More than 20 years ago, the first ideas were mooted as to whether it would be possible to perform chemistry in these small dimensions. The motivating force was the minimal amounts of material that would be required; indeed since then, a booming market has emerged in the form of " analysis on a chip" and "diagnosis on a chip". High-throughput synthesis and screening techniques also make use of miniaturised systems, and are now ubiquitous in the life science industry.

What are microreactors?

Microreaction technology is not new. It had already been suggested in the early eighties and the idea resulted in several pioneering patents (1). The first international meeting was held in 1996, and prototypes have been built throughout the past decade (2).

Microreactors are defined as miniaturised reaction systems, fabricated by microtechnology and precision engineering. They enable chemical reactions to be conducted in a continous way instead of batch processing. Microreactors have to perform three basic functions:

- To initiate and facilitate a reaction through mixing of the reactants,
- To provide the time and volume necessary to allow the reaction to finish (residence time), and
- To provide or remove heat (heat exchange).

Continuous processing of reactions in the small capacity volumes of microreactors allows the rapid equilibration of concentration gradients and narrow temperature distributions. The reactors usually consist of several stacked plates containing the microstructures in the sub-millimeter range. They can be constructed as components to perform single-unit operations such as mixing, heat exchange and separation, or as integrated microreaction systems.

Examples of functional systems have been reported by research institutes such as Forschungszentrum Karlsruhe (FZK, Germany), the Institute for Microtechnology (IMM, Mainz, Germany), and the Technische Universitaet (Ilmenau, Germany). Cellular Process Chemistry (CPC) was the first company in the world to provide a commercially available, fully integrated microreaction system.

Advantages of microreaction technology

Miniaturisation has a number of fundamental advantages in performing chemistry. Microreactors offer a much improved control of reaction parameters, such as temperature and relative concentrations, and thus allow for higher yields, smaller amounts of by-products and higher selectivities.

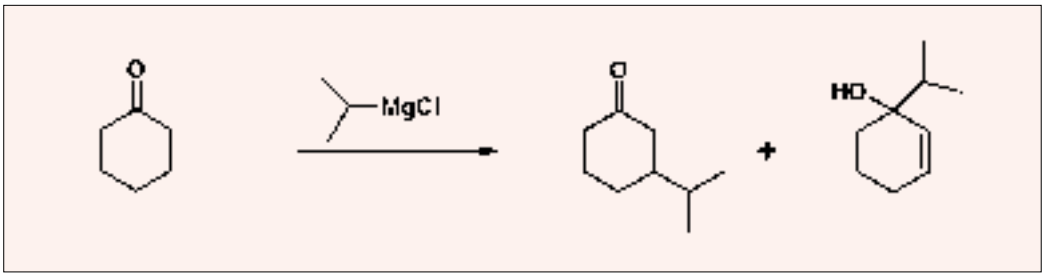

Figure 1. A Grignard reaction of cyclohexenone with isopropyl magnesium chloride.

By using a continous process instead of batch processing, they (microreactors) can be applied to synthesise kilogram or even ton amounts, particularly in parallelised arrays

Better mixing Mixing by diffusion in conventional vessels would take too long; for this reason, mass transfer is achieved by turbulence and vigorous agitation. Undesired concentration gradients, particularly during the dosing process, are unavoidable.

Laminar flow dominates in microchannels, compared with vessels. With a channel width of less than 0.1mm, it is hardly possible to produce turbulence. Under these conditions, mixing by diffusion becomes very fast. Provided the geometry of the reactant flows is suitable, perfect mixing is achieved in fractions of a second. And due to the constant flow of the reactants, their relative ratios are constant.

Better heat exchange Another problem encountered when scaling up a reaction is the provision or removal of the reaction heat, particularly with fast and/or highly exothermic reactions. This may lead to hot spots, resulting in side reactions or unfavourable selectivities. As a result of their much improved surface-to-volume ratio, microreactors have a heat exchange capability that is orders of magnitude better than conventional vessels. This is regardless of the material of construction as, with small-wall diameters, it does not matter whether the microreactor is made of steel, glass, silicon or ceramics.

Comparison with conventional processing Conventional process R&D, scale-up and batch processing of organic reactions are usually tedious and time-consuming procedures. Several process limitations have to be considered. These include:

- Operating temperature range,
- Reaction control,
- Mass transfer and agitation, and
- Safety (highly exothermic reactions, runaways and other hazards).

In many cases, process engineers would be reluctant to conduct potentially hazardous reactions at larger scales. The process often has to be adapted to the available equipment or, if this is not viable, significant investments may be necessary for the installation of special equipment.

It is important to mention that, although microreactors contain microstructures, they are not meant to perform small-scale chemistry. By using a continous process instead of batch processing, they can be applied to synthesise kilogram or even ton amounts, particularly in parallelised arrays.

"Numbering-up" replaces scale-up With just one reactor and flow rates of between 1 and 100 ml per minute, between 100mg and 10g of product can be synthesised per minute. In one hour, this would represent between 6g and 600g; in one day, this would amount to between 144g and 14kg!

With 10-fold or 100-fold parallelised arrays, one can imagine that syntheses in the multi-kilogram or ton range are easily achievable; this can be done step-wise and with little effort. Since the very same process that was used to produce a couple of grams is also used to synthesise larger amounts, no tedious scale-up studies are required. Once a process has been established in a microreactor in the laboratory, production can immediately be started in parallelised arrays. This results in huge time-savings and much improved productivity.

Safety The capacity of one microreactor usually lies in the range of a few milliliters. This, combined with the flame-arresting effect of the small channels, means that microreactors are inherently safe tools for laboratories, pilot plants and production sites. Potentially hazardous reactions can be handled much more easily because of the vastly reduced amounts of dangerous reactants and solvents.

Applications

Organic synthesis Microreactors do not provide new chemistry; they do, however, provide the opportunity for better chemistry.

Temperature (hot spots) and concentration gradients, and other disturbances caused by limited reaction control, can prevent optimal results from being obtained using conventional vessels. This

can lead to frustration - particularly at larger scales. The key advantage of microreactors lies in the ability to control precisely the temperature, relative concentration and reaction time. This can significantly improve both the quality and reproducibility of the chemistry. The chemistry may not be new, but it is certainly better.

Numerous applications have been cited as "proof of principle". Microreactors have been used in commodity syntheses, for example, ethylene oxide (3) and the preparation of HCN (4), and have also been used in polymerisations. In all, more than 60 reactions from different reaction classes have been performed successfully in CPC standard microreaction systems (5). In most cases, a positive effect can be detected in terms of yield and/or selectivity. The suitability of the system was successfully put to the test with the full adaptation of the synthesis of a blockbuster pharmaceutical (Ciprofloxazin®) to the microreactor (6).

Process optimisation Microreactors are also very useful in the optimisation of chemical processes. As a result of the continuous operation of microreactors, a parameter scan on the reaction can be performed very quickly. Actually, in many cases, it is possible to drive the reaction to the limits of its inherent potential; this information can then also be used as a benchmark for traditional scale-up studies.

An overview of the possible variables includes the following:

- Rapid screening of reaction parameters,
  - temperature,
  - time,
  - relative concentrations,
  - pH,
- Reagent screening,
- Potential for online-analysis, and
- Software-supported optimisiation of reaction variables (factorial design).

The example of a Grignard reaction of cyclo-hexenone with isopropyl magnesium chloride is shown in Figure 1. The initial yield was 49% and the isomer ratio was 3:2; the optimised yield was 78% and the isomer ratio was 19:1. The optimisation run with 14 different reaction conditions was completed within six hours.

The sequential synthesis of research compounds and their intermediates is another useful application of microreactors. Together with an autosampler and a fraction collector, this can be done in an

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automated fashion. Specific advantages over conventional parallel synthesisers are:

- Flexibility of reaction conditions,
- Use for demanding chemistry,
- Higher amounts, and
- Synthon synthesis.

Microreactors are also versatile tools for reagent screening or the synthesis of compound libraries.

Benefits for the life science industry

Microreactors will become a standard tool for chemists - not to replace but to supplement existing technology

The chemical industry is currently undergoing significant change in terms of consolidation and refinement of internal processes to react to market pressures.

Drug development times and costs in the life science industries are considered to be extremely high. This has led top pharmaceutical companies to set ambitious goals, such as bringing up to five new products per year onto the market, increasing R&D throughput by a factor of ten and cutting back development time to five years. Time-to-market is the most crucial factor. An estimation of the global pharmaceutical market indicates that gains of about 15 billion dollars could be achieved by decreased development times and increased productivity.

Microreaction technology can significantly help to achieve these goals. The fast production of sufficient quantities of drug candidates for all R&D phases - ranging from preclinical research to later stages of clinical phases and even to manufacturing - creates a huge value for this segment. Microreactors lead to the output of more new drugs as a result of shorter development times and increased R&D efficiency.

Summary and outlook

Microreaction technology is already inducing a paradigm shift by demonstrating the advantages of continuous processing over batch processing - even for small-scale chemistry. The following advantages are evident:

- Better chemistry
  - by better mixing,
  - better heat exchange, and
  - safer handling of hazardous conditions.
- Faster development
  - by fast optimisation, and
  - numbering-up instead of scale-up.
- Higher R&D throughput
  - by faster transfer of research results,
  - more flexibility towards market demands, and
  - broad applicability.

Microreactors will become a standard tool for chemists - not to replace but to supplement existing technology. They will have a significant impact on all situations where chemistry is a critical factor. The value of this technology for the industry is tremendous. In a world where globalisation is putting a great deal of pressure on margins and reducing the life-cycle of pharmaceutical products, time to market is becoming crucially important.

The existence of young companies with the goal of developing ready-to-use microreaction systems demonstrates that the shift from specific developments to standard systems has already started.

Dr Axel Kleemann is Executive Vice President of CPC Cellular Process Chemistry GmbH, with responsibility for key account customers. He received a PhD degree in organic chemistry in 1991 at the Johann-Wolfgang-Goethe-University of Frankfurt, Germany. He then joined the German subsidiary of Shell Research Ltd to work on the discovery and development of crop protection products. Over the next three years, he held various positions in Germany, the UK and the Netherlands. Following the takeover of the Shell agrochemical business by American Cyanamid in 1994, Dr Kleemann was appointed Senior Scientist at the US facilities; in 1996, he returned to Germany as a Group Leader in the discovery department. In 1999, he co-founded CPC Cellular Process Chemistry GmbH, a company engaged in the design and manufacturing of microreaction systems.

Note: CPC - Cellular Process Chemistry GmbH is a company engaged in the design and fabrication of integrated microreaction systems and their application in a wide variety of synthetic organic reactions.

References

1. Appeldoorn et al., US 3701619, 1970, Akzona. Ashmead et al., US 5534328, 1993, Du Pont. Löhder et al., DD 246257, 1986, Akademie der Wissenschaften der DDR.
2. Manz A and Becker H (eds) (1998). Topics in Current Chemistry, Volume 194, Microsystem Technology in Chemistry and Life Science, Springer Heidelberg.
3. Kerstenbaum H, Lange de Oliveira A, Schmidt W, et al. (1999). Proceedings of the 3rd International Conference on Microreaction Technology, Frankfurt am Main.
4. Hessel V, Ehrfeld W, Golbig K, Wörz O (1999). GIT, 10, 1100.
5. CPC Cellular Process Chemistry GmbH. Website: www.cpc-net.com.
6. This process has been applied for patent by CPC.