Process Intensification through Microreactor Application

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Review
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Dedicated to the memory of Professor Dr. Valentin Koloini

A substantial amount of publications each year demonstrate how through the application of microprocess engineering significant benefits can be obtained concerning product yield, purity and time needed for chemical transformations, compared to the equivalent bulk reactions. Microreactors clearly hold the potential to revolutionize chemical synthesis, but scarce articles demonstrate specific suggestions for possible replacement of existent industrial processes. The focus of this review is to assess whether significant advances have been made for the implementation of microstructured devices into existent industrial processes or their complete replacement. The papers are reviewed in light of particular beneficial microreactor characteristics with potential for process intensification.

Key words:
Microreactor, process intensification, integrated micro-unit operations

Introduction

Process intensification based on micro-devices is a new concept in chemical engineering which aims at reducing capital and energy costs along with the environmental impact by reducing the size of the chemical plant. With the decrease of equipment size by several orders of magnitude, substantial economical benefits, improvement of intrinsic safety, and reduction of environmental impact can be achieved.[1] In addition, the small scales used reduce exposure to toxic or hazardous materials, and the enclosed nature of the microreactors means greater ease of containment in the event of a runaway reaction. The benefits of moving from batch to continuous processing, utilizing intensive reactor technologies with high mixing and heat transfer rates and the possibilities of providing flexibility in a multiproduct environment are being explored. The tendency toward higher added-value chemicals, with increased product purity presents one of the major challenges of a chemical engineer.

These new directives have lead to the development of microprocess engineering, which utilizes chemical reactors with internal dimensions of less than one millimeter.[2] Because of the small amounts of chemicals needed and the high rate of heat and mass transfer, microscale systems are especially suitable for reactions with highly flammable, toxic and explosive reactants, for the elimination of by-products, for achieving maximum conversion and energy utilization.[3] Microreactor technology can enable new reaction pathways such as solvent free reactions, hazardous reactions[4] and control of particular reactions such as oxidation and fluorination.[5] Because of the high surface to volume ratio in microchannels, heat transfer is very efficient and reaction temperatures in microreactors can be regulated by very effective heat removal or application. The small length scale of microreactors reduces transport limitations, giving nearly gradientless conditions desirable for the determination of reaction kinetics and also allows us to carry out reactions under more precisely controlled conditions than with conventional macroscale reactors, leading to a possibility of improved selectivity and yield of the desired products. Roberge *et al.*[6] claim that 50 % of reactions in the fine chemical or pharmaceutical industry could benefit from a continuous process based mainly on microreactor technology, and for the majority (44 %), a microreactor would be the preferred reaction device. Higher capacities can be achieved by simple multiplication of each microstructured unit (so-called 'numbering-up') instead of expensive and sometimes extremely difficult scale-up. Continuous operation is uninterrupted with the replacement of the failed microreactor, while the other parallel units continue production.[7] One of the main motivations for the use of microreactor technology are the gain in yield and safety.

Several reviews have been published up to date on microreactor technology which cover the areas of process miniaturization for catalytic reactions,[8,9]

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design principles for multiphase microsystems,[10] microstructured mixer devices and their mixing principles,[11] droplet microfluidics,[12–14] intensification of photocatalytic processes,[15] fabrication of microfluidic systems,[16,17] application of enzymatic microreactors in chemistry and biochemistry,[18–21] miniaturization of chemical synthesis,[22–25] multiphase organic synthesis[26] and on-chip integration of multiple reactions in a combinatorial mode.[27] In this paper, the benefits of the application of microreactor technology were explored with specific industrially relevant examples of superior microreactor performance over traditional methods. The papers are reviewed in light of particular beneficial microreactor characteristics with potential for process intensification. Only articles, in which a clear comparison of microreactor performance to classical methods was made, were reviewed and categorized in the way of the beneficial characteristics responsible for improved operation.

Impact on research and development

Microreactors have been recognized as versatile tools for rapid optimization of reaction parameters,[28] as reliable instruments for kinetic research and have been found particularly useful in combination with high-throughput methods.[29] It has been shown that the continuous microreactor is an ideal tool for parameter screening which can be performed much faster in continuous mode than in batch mode. They are also a highly efficient tool for combinatorial chemistry and for rapid catalyst screening in the area of catalytic chemistry.[30] Geyer *et al.*[25] have described them as a valuable alternative to the roundbottomed flask. With the ability to fine-tune the mass transfer contributions, impose temperature profiles, monitor the progress of extraction and reaction, together with the excellent accessibility for process modeling, they are becoming indispensable in research and development laboratories engaged in translating processes from 'concept to commercialization'.

Heat transfer improvements for temperature regulation

Most synthetic transformations performed in microreactors have involved ambient or low-temperature conditions in order to safely conduct highly exothermic reactions. Razzaq *et al.*[31] developed a high temperature/high-pressure microtubular flow unit for processing homogeneous reaction mixtures. Stainless steel coils were used that could be directly heated across their full length by electric resistance heating to temperatures up to 350 °C. The pressure could be set and stabilized in the range of 50–200 bar, while standard batch microwave systems operate at 20 bar. Rapid heating and cooling of the reaction mixture was possible because of efficient heat transfer through the thin steel reactor coil. They showed how the long reaction times for Diels-Alder reaction of 2,3-dimethylbutadiene and acrylonitrile to provide the cyclohexene adduct could be reduced to merely 20 minutes. They also noted the particularly important advantage of direct scalability, which is a critical problem in microwave-assisted batch transformations.

Waterkamp *et al.*[32] worked on a process intensification study of the synthesis of ionic liquids in microreactors. A microstructured mixer along with reaction tubes was utilized and a production rate of 9.3 kg [BMIM]Br per day was achieved. The strongly exothermic alkylation could be thermally controlled even at elevated temperatures leading to high reaction rates and product purity above 99 %. A more than twentyfold increase of the volumetric production rate compared to a conventional batch process was the result of process intensification. Similarly, Renken *et al.*[33] investigated the use of a microstructured reactor system for the production of ethylmethylimidazole ethylsulfate ionic liquid. Their results showed that heat management during the reactor operation is a crucial point leading to high quality ionic liquid product and avoiding thermal runaway. They reported specific reactor performance of about 4 kg m^{-3} s^{-1}, which was around 3 orders of magnitude higher as compared to traditional reactors.

Microreactor processing for the aqueous Kolbe-Schmitt synthesis of hydroquinone and phloroglucinol was studied by Hessel *et al.*[34] Temperature limitations of classical batch synthesis, which is set by reflux conditions, were overcome by the use of a few microstructured components at high pressure and high temperature. Consequently, a favorable speed-up of the chemical reaction was achieved at temperatures normally outside the useful range for organic synthesis. A high yield of 50 % of phloroglucinol converted to the corresponding carboxylic acid was accomplished, which is about 20 % higher than for a laboratory batch synthesis. Process intensification was achieved by reducing the reaction time from 2 hours for the batch synthesis to 50 seconds for the microreactor system.

Lorner *et al.,*[35] argued that for certain systems of highly exothermic reactions, a considerable reduction of the operational time compared to a semi-batch stirred tank could be achieved. They described possible intensification of industrial production by means of using a continuous microreactor in which mixing and heat transfers are augmented. For the case of the Grignard reaction, a reduction of the operation time from 5 hours to less than 10 seconds was demonstrated. The use of five reactors in paral-

lel was proposed in order to reach industrial productivity of the stirred tank reactor.

The Moffatt-Swern oxidation of different alcohols in a continuous flow microreactor system was performed by van der Linden *et al.*[28] The microreactor process was shown to offer significant advantages over the batch process. Due to the small reactor volume, accumulation of trifluoroacetoxydimethylsulfonium salt and alkoxydimethyl-sulfonium salt was minimized. Secondly, because of the short residence times, which can be applied in the microreactor, the exothermic Pummerer rearrangement of the unstable intermediate was limited. The process could therefore be operated at remarkably high temperatures in comparison with a batch reaction, at 0–20 °C instead of –70 °C. A continuous flow microreactor system was optimized using reactors of different volumes allowing modulation of the residence times of labile intermediates. The microreactor was tested for reliability by running the system for several hours. For testosterone, the system was in process for 1.5 h without any problems, resulting in an 4-androstene-3,17-dione production rate of 64 g h^{-1}.

Solid catalyzed hydrogenation in a Si/glass microreactor using supercritical CO_2 as the reaction solvent was performed by Trachsel *et al.*[36] A packed bed microreactor was used for the hydrogenation of cyclohexene and the results were compared with the same reaction conducted in three phase gas-liquid-solid state and larger scale reactors using s.c.CO_2 as the reaction solvent (Fig. 1). The results indicate that high pressure microreactors are favorable for exothermic reactions because of the good heat removal due to the small reactor dimensions. One order of magnitude increase of the volumetric production rate was achieved compared to larger scale systems. The development of hot spots inside the channels was avoided because of the large microreactor surface-to-volume ratio, combined with the good thermal conductivity of Si, which led to an increased heat removal from the exothermic reaction.

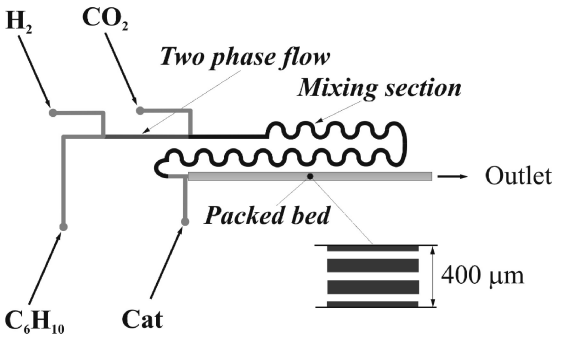


Fig. 1 – *Packed bed microreactor[36] – schematic of the channel design*

Ehrfeld *et al.*[37] prepared hydrogen cyanide in a microreactor via the Andrussow route. The rapid cooling of the products by a micro heat exchanger prevented hydrolysis of HCN to ammonia.

The CYTOS system from CPC (Cellular Process Chemistry Systems) is an integrated processing microreactor system, which can be applied to a wide range of chemical reactions (Fig. 2). Due to its ability to handle highly exothermic reactions, positive effects on the yield and selectivity were detected. Substances can be synthesized in the scale of 144 g to 14 kg d^{-1}. Singh *et al.*[38] used the CYTOS system for a continuous flow procedure for copper(II)-mediated N- and O-arylation of a range of compounds with arylboronic acids. Yields from 56–73 % were obtained and a continuous generation of compounds was possible which could lead to efficient scalability avoiding scaling-up procedures. Microreactor technology could be efficiently used for the copper(II)-mediated N- and O-arylation of various compounds with arylboronic acids. Under conventional conditions, the reactions in dichloromethane require 12–72 h and in the microreactor, these took only 2 hours.

Kestenbaum *et al.*[39] conducted ethylene oxide synthesis in a microreactor and compared the results to an existing industrial process (Fig. 3). The

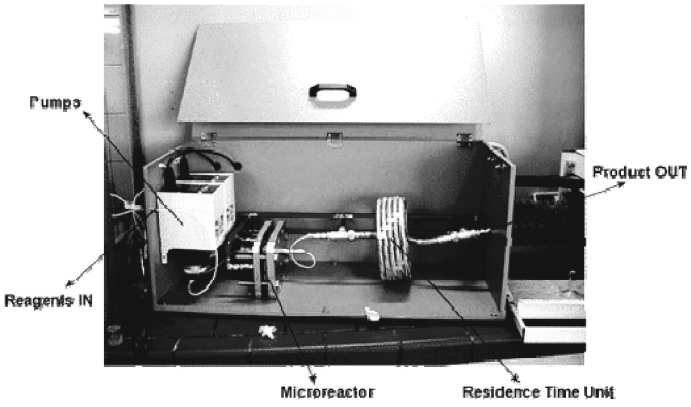


Fig. 2 – *CYTOS College System. Reprinted with permission.[38]*

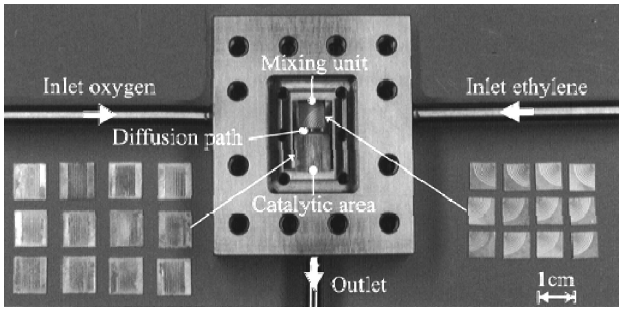


Fig. 3 – *Microreactor ethylene oxide synthesis. Reprinted with permission.[39] Copyright (2002) American Chemical Society.*

microreactor was used due to the very good heat transfer characteristics which avoided the formation of hot spots. Apart from that, because of the inherent safety in dealing with explosive substances, 15 % ethylene in pure oxygen could be used, which is in the middle of the explosive regime and cannot be used in the industry. Higher volumetric production rates of 0.14–0.78 t h^{-1} m^{-3} were achieved in comparison to 0.13–0.26 t h^{-1} m^{-3} in the case of an industrial reactor.

High surface to volume ratio

In a review by van Gerven *et al.*[15] on the intensification of photocatalytic processes, microreactors have been investigated in performing photochemical and photocatalytic reactions. The main advantage described is the high surface to volume ratio, which in the case of photochemical reactions leads to efficient illumination. This permits efficient catalytic exposure to radiation, and in addition also leads to maximized reagent – catalyst contact. A much better control over variables such as temperature and flow rates was possible due to the fast heat and mass transfer. The microreactors currently implemented in industry can produce up to 5,000 or even 20,000 ton y^{-1}. Values as high as 23 g L^{-1} TiO_2 were reported, which is 11 times more catalyst per unit of volume than in a conventional batch reactor. The catalyst area-to-reactor volume of almost 14,000 m^2 m^{-3} was achieved, while this value in a work by Takei *et al.*[40] reached 250,000 m^2 m^{-3}. They found a 70-fold increase in the reaction rate compared to a slurry reactor with the same selectivity and yield. Li *et al.*[41] reported a 60 (using a 530 μm diameter capillary) to 160-fold (using a 200 μm diameter capillary) increase in reaction rate compared to a slurry reactor.

Biodiesel was produced at a rate of 61 kg m^{-3} min^{-1} by Kraii *et al.*[42] This result compares well with the 42 kg m^{-3} min^{-1} reported for typical batch processes. The process in the microreactor is much more efficient, since there is no distinct separation step, and cleaning of the reactor between batches can be omitted. They also showed that it is advantageous to perform chemo- and biocatalytic conversions continuously (specifically lipase catalyzed esterification of oleic acid with butanol). With the current low-cost equipment used, which can be situated in a fume cupboard, they have been able to produce 100 kg amounts of chemicals in a matter of days.

Chen *et al.*[43] conducted catalytic dehydration of bioethanol to ethylene over TiO_2/γ-Al_2O_3 catalysts in microchannel reactors. The reaction results indicate that the catalysts doped with TiO_2 have high ethanol conversion of 99.96 % and ethylene selectivity of 99.4 %. Ethylene yield of 26 g g^{-1}_{cat} h^{-1} can be achieved, which is favorable for the process intensification and miniaturization of the ethylene production process using bioethanol. In another work, Chen *et al.*[44] studied the performances of a methanol steam microreformer, constructed of CuZn metal foam and coated by CuZnAlZr catalyst. The improved external and internal mass transfer resulted in a methanol conversion increase of about 10 % in microreformer compared with packed-bed.

Akay *et al.*[45] prepared microporous polymers (with porosity up to 90 %) with a well-prescribed internal microstructure in monolithic form to construct a flow-through microbioreactor. Phenol-degrading bacteria were immobilized on the walls of the microchannels and it was shown that at comparable initial substrate concentration, the volumetric utilization in the microreactor was at least 20-fold more efficient than the packed bed. This enhanced efficiency was attributed to the reduction of the diffusion path for the substrate and nutrients and enhanced availability of the bacteria for bioconversion in the absence of biofilm formation as well as the presence of flow over the surface of the monolayer bacteria.

Using a system of five continuous flow microreactors, the Suzuki reaction has been carried out on an industrial scale by Merck in Germany, where researchers found improvements over conventional batch reactors.[46] Microreactors offer a convenient and highly efficient means to optimize reaction conditions and the performance of catalysts. In the case of the reaction of 3-bromobenzaldehyde with 4-fluorophenylboronic acid, 90 % yields were reported for the microreactors, compared with 50 % in stirred flasks.

The Baylis-Hillman reaction in a microreactor environment was considered by Acke and Stevens.[47] A first continuous production process of Baylis-Hillman adducts was developed and optimized for use under microreactor conditions. After optimization, the reaction could be performed continuously and approximately 30 % faster compared to batch conditions.

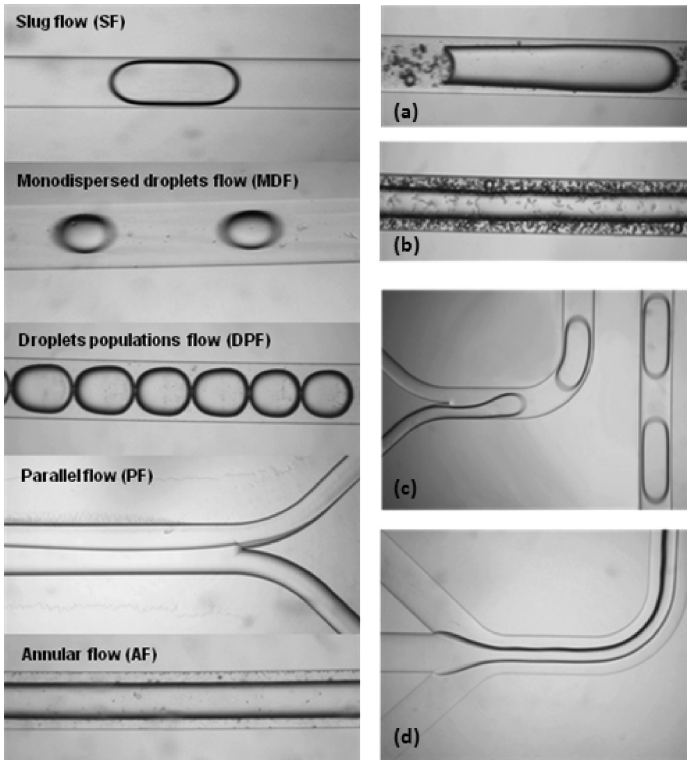
Larger interfacial area for multi-phase systems

The details of the transport phenomena for multiphase processes in microstructured devices are still not completely understood. It is known that miniaturization could greatly increase mass and heat transfer efficiency and minimize amount of fluids resulting in shorter reaction times and reducing the cost of research and development. However, in order to optimize the design and the operation of multiphase processes in the microreactor, we have

to predict and accurately control the existing flow patterns to achieve optimal conditions for a specific chemical process. The representative photographs of stable flow patterns for two immiscible fluids in the Y-shaped microchannel (width/depth = 220/50 μm) are presented in Fig. 4. Slug flow, monodispersed droplets flow, droplets populations flow, parallel flow and annular flow are the most common flow patterns of two-phase microfluidics.

In a work by Žnidaršič-Plazl and Plazl,[48] parallel flow was successfully utilized for lipase-catalyzed synthesis of isoamyl acetate. The flow rates of the aqueous and organic phase were set so the interface was positioned in the middle of the microchannel, which allowed direct separation at the exit of the microreactor. Esterification occurred at the interface between the phases and the study revealed orders of magnitude faster reaction rates as reported for classical batch esterifications. In another work that has been accepted for publication,[49] lipase-catalyzed synthesis of isoamyl acetate was studied using 1-butyl-3-methylpyridinium dicyanamide/*n*-heptane two-phase system. A 2.8 fold increase in the reaction rate was obtained while using a continuously operated microreactor, compared to a vigorously mixed batch experiment. Effective mixing throughout the microreactor system, due to the formation of slug flow (Fig. 4c), provided a large interfacial area for the reaction and for simultaneous product extraction. Two mechanisms govern mass transport, convection through internal circulation and diffusion between the two phases. The thickness of the interfacial boundary layer is reduced, which augments diffusive penetration. Internal circulation, which is stimulated within the slugs by their passage along the channel, is responsible for a large enhancement in the interfacial mass transfer and the reaction rate.[50] Furthermore, the amphiphilic property of the enzyme causes it to bind itself to the interface and causes a decrease in the interfacial tension which causes the severance of small droplets of the organic phase (Fig. 4a). An intense emulsion is formed which further increases the interfacial area for the reaction and product extraction (Fig. 4b).

Huang *et al.*[51] developed a microreactor system to enhance the oxidation of dibenzothiophene (DBT) and 4,6-DMDBT for deep desulfurization with the oxidant of hydrogen peroxide. A T-junction microchannel was used for the formation of aqueous slug flow. DBT conversion of 97 % was achieved with a residence time of 1.3 min at 60 °C and 4,6-DMDBT was also successfully oxidized to 97 % at 70 °C. The authors claim that a microchannel reactor is far superior to conventional equipment in terms of providing more interfacial area with much less power input. Apart from that,



F i g . 4 – *Flow patterns for two immiscible fluids*

the increased mass transfer is vital in reducing resistance. Energy input in a mixer-setter per cubic meter of liquid is 150–250 kJ, while the liquid-liquid slug flow takes only 0.2–20 kJ.[52]

Perhaps one of the best known microreactors is the falling film microreactor for gas/liquid contacting developed by Institut für Mikrotechnik Mainz (IMM). Liquid films of a few tens of micrometer thickness[53] and interfacial areas of up to 40,000 m^2 m^{-3} can be obtained.[54] Jahnisch *et al.*[54] conducted direct fluorination of toluene using elemental fluorine and compared the results to the performance of a laboratory bubble column. Yields of up to 28 % of monofluorinated ortho and para products for a degree of toluene conversion of 76 % were obtained, which was the same order as described for the industrially applied Schiemann process. The volumetric production rates however were orders of magnitude higher than those of the laboratory bubble column. Their experiment also demonstrated how very explosive mixtures could be handled safely.

The separation process of liquid – liquid extraction in a variety of contactors was performed by Kashid *et al.*[55] Liquid – liquid slug flow in a capillary was presented as an alternative to conventional equipment. A microextractor was shown to provide superior performance and greater efficiency. The interfacial area in conventional contactors is often poorly defined, because of the complex hydrodynamics involved, and the intensity of mass transfer

is limited by the constraints imposed by the underlying buoyancy or gravitational effects. Liquid-liquid microextractor-reactors were shown to offer superior performance and greater efficiency in comparison to conventional equipment, with very large specific interfacial areas in comparison with other contactors, which enhances the mass-transfer and heat-transfer rates. Moreover, the internal circulation in the slugs also improves the mass-transfer rate by surface renewal at the phase interface. Calculations of the interfacial area and power requirement show that the slug flow capillary microreactor is far superior to conventional equipment in terms of providing more interfacial area with much less power input.

Kobayashi *et al.*[56] developed a microfluidic device for conducting gas-liquid-solid hydrogenation reactions. Products were obtained within 2 minutes for a variety of substrates. Extremely large interfacial areas (10,000–50,000 m^2 m^{-3}, as opposed to only 100 m^2 m^{-3} for conventional reactors) provided effective interaction between hydrogen, substrates, and a palladium catalyst. Another improvement was due to the short path required for molecular diffusion in the very narrow channel space. A solid catalyst was immobilized on the wall of the microchannel and the liquid and gas were pumped into the channel. The flow was well controlled, and the gas was passed through the center of the channel and the liquid along the inner surface of the channel. The volumetric production rate obtained was 140,000 times higher than those produced by ordinary laboratory flasks.

De Mas *et al.*[57] investigated the possibilities of increasing productivity of microreactors for fast gas-liquid reactions. Direct fluorination of toluene in acetonitrile was selected as a model reaction and was performed at room temperature in microchannels formed in a silicon substrate (Fig. 5). The throughput of a single-channel microreactor was increased by up to one order of magnitude relative to previously published results by simultaneously increasing the superficial gas and liquid velocities. By operating at faster gas and liquid velocities the contacting between the two phases was enhanced, thus outweighing the reduced liquid residence time.

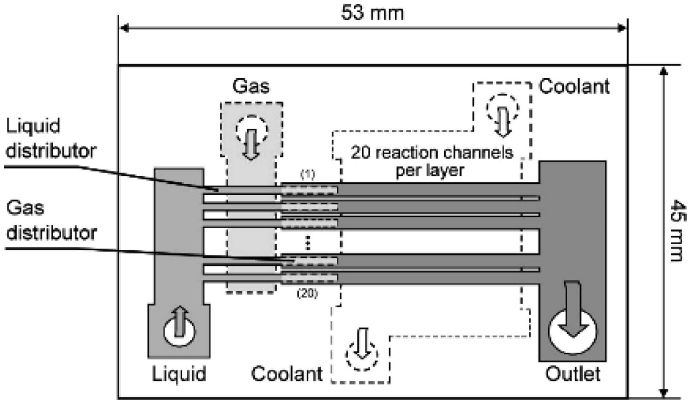


Fig. 5 – *Microreactor for fast gas-liquid reactions. Reprinted with permission.*[57]

A continuous flow glass microreactor was used for the esterification reaction of phthalic anhydride with methanol. Benito-Lopez *et al.*[58] evaluated different temperatures and pressures up to 110 bar with supercritical CO_2 as a co-solvent, which was generated inside the microreactor. Substantial rate enhancements were obtained, a 53-fold increase at 110 bar and 60 °C. Supercritical CO_2 as a co-solvent gave rise to a 5,400-fold increase, with respect to batch experiments at 1 bar at the same temperature.

Efficient mixing

A process optimization of a catalyzed bleach oxidation for the production of functionalized aldehydes using microreactor technology was done by Ferstl *et al.*[59] A catalyzed oxidation of 2-butoxyethanol to 2-butoxyacetaldehyde was performed and the original batch process was successfully replaced by a continuous microreaction process to provide better control on the suppression of unwanted subsequent oxidation to 2-butoxyacetic acid. By improving the mixing quality in the microreactor, the macroscopic reaction rate was increased compared to the lab-scale batch process.

The installation of a StarLam 3000 microreactor in an existing production plant was reported by Kirschneck and Tekautz.[60] The StarLam 3000 is a large-capacity microstructured mixer (with a throughput of about 3 m^3 h^{-1}), which creates a finely-dispersed injection of two fluid streams. The aim was to double the capacity of a running two step batch process and was achieved by installing a microreactor for the first reaction step. A higher reaction rate made it possible to reach overall throughputs of 3.6 tons per hour. In addition, energy savings were achieved.

Integrated microchemical systems

Techniques for integrating micro-unit operations (MUOs) in a multiphase flow network are being developed for constructing microsystems where a sequence of consecutive operations will be fabricated on one chip. This micro-integration methodology is termed continuous-flow chemical processing (CFCP)[27,61] and will simplify downstream operations and accelerate sample analysis time. The integration of fundamental MUOs, such as mixing and reaction, two- and three-phase formations, solvent extraction, solid-phase extraction, heating, and cell culture has been successfully integrated a

F i g . 6 – *Scheme of an integrated microchemical system representing a consecutive reaction, extraction and phase separation*

chemical system on a microchip by Tokeshi *et al.*[61] Žnidaršič-Plazl and Plazl[62] utilized a microreactor system by combining two MUOs for simultaneous extraction and phase separation. Their system served as a successful tool for steroid extraction at the micro-scale and further integration of other downstream steps was proposed for the development of an independent self-sufficient process. In Fig. 6 a schematic example of such a system shows how reaction, extraction and phase separation can be unified in one microfluidic set-up.[49]

Conclusions

Microstructured reactors represent a highly effective means for process intensification for specific processes. The benefits of employing microreactor technology include enhanced heat and mass transfer, safety, environmental impact, distributed production, high portability, remote (on-site) applications and flexible nature of the technology. Reactions in microreactors are performed under precisely controlled conditions providing improved yields and product quality compared to the batch procedures. Novel techniques are deployed in order to improve the technology to a cleaner, smaller and more energy efficient technology. Miniaturization of chemical processes means that only small quantities of reagents are required and allows for high-throughput screening of reaction conditions in a highly controlled manner. They are an ideal tool for high throughput experimentation, and can speed up process research and development with the ability to maintain the high level of control and selectivity. Promising results will initiate more research toward the adaptation of microsystems to industrial-scale processes and the development of integrated systems with integrated sensor and control units which will replace existing production. One set-back which still has to be overcome for translating the potential of the novel techniques into an economical advantage is finding numbering-up solutions for increasing production capacities.

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