1
Principles of Microprocess Technology

Wladimir Reschetilowski

1.1
Introduction

The microreactor technology is nowadays the key technology for process intensification. Manufacturers of microreactor systems bring their products to market with slogans like "A Chemical Factory in a Briefcase" or "Lab-on-a-chip." Due to the small dimensions of microstructures, which do not exceed 1 mm, microreactors contribute to the minimization of material in terms of production as well as raw material and energy consumption during exploitation. Moreover, due to the intensification of heat and mass transfer, the productivity of plants with microreactors is in a number of cases significantly higher than that with classical batch reactors applied in industry.

Extensive research efforts have been made incessantly in this field during the past few years. Recent advances in the design and fabrication of microreactors, micromixers, microseparators, and so on show that they represent a cheap alternative for the production of special fine chemicals by a *continuous* process to observe simpler process optimization and rapid design implementation. It is possible to predict that in the near future chemical, pharmaceutical, and biological laboratories will change radically toward considerable improvement of process and synthesis efficiency at essential miniaturization of reactor devices.

One of the key moments in the microprocess technology is the effective way to increase the process productivity by the so-called reproduction (numbering-up) of continuous microreactor systems, that is, a series of continuous reactors works simultaneously. Hereby the dimensions of microreactors and their efficiency in heat exchange do not change, when transferring processes from laboratory to pilot and production scales. Due to the facility to change the process parameters (temperature, pressure, flow velocity, ratio of reagents, use of catalysts, etc.) rapidly and accurately, the microreactor systems can be predestined as an ideal tool for effective and fast optimization of investigated reactions. The full automation of such systems interfaced with integrated analytical devices in real time (online analytic) gives an opportunity to receive high-grade information about optimal parameters of multistage reactions within only a few hours.

Up to now different reactions of the preparative organic chemistry, such as Wittig reaction, Knoevenagel condensation, Michael addition, Diels–Alder reaction, or Suzuki coupling, have been successfully carried out in microreactors with predominantly improved conversion and selectivity. In addition, modern developments and benefits of microreactor technology are mentioned for heterogeneous reaction systems, which may differ by their nature and run in various types of microreactors: synthesis of organic polymers and inorganic nanoparticles, heterogeneous catalysis, and bio-, electro-, and photocatalysis. Therefore, it is very important to outline these aspects from the point of view of the preparative feasibility of chemical reactions to make it attractive for the chemical industry.

1.2
History

Since the times of alchemy, experiments in chemical laboratories were carried out in flasks and test tubes. Chemists begin research works in scales from a milliliter to several liters, spending a lot of time and energy to find the optimum reaction conditions. Furthermore, it is difficult to scale the processes for pilot and production plants.

Early studies with the detailed description of the so-called microstructured reactors (microreactors) are dated 1986; however, theoretical calculations of scientists of the former GDR were not put into practical application [1]. A patent of that time describes, very generally, a miniaturized chemical engineering apparatus and systems made by simple fabrication methods. A stack-like arrangement of platelets carrying microchannels and fluid connecting structures was also proposed.

The first microreactors that have confirmed huge potential of a new approach were designed and placed in operation in 1989 in Karlsruhe (Germany) at the Karlsruhe (Nuclear) Research Centre. Mechanical micromachining techniques were used to produce a spinoff from the manufacture of separation nozzles for uranium enrichment [2]. Wide development of this technology started in late 1995 after the workshop on microreaction technology in Mainz (Germany), organized by AIChE, DECHEMA, IMM, and PNNL. The 1st International Conference on Microreaction Technology (IMRET) at the DECHEMA, Frankfurt am Main, took place in early 1997 and was focused on studying and introducing microreactor technology. It is held regularly till date with the last one being IMRET 12.

In addition to these conferences, recent progress on microcomponents, microprocesses, and mathematical modeling is described in a number of excellent review articles [3–7] and various monographs [8–12]. In 2001, German scientists and companies created a platform to study the advances of manufacturing and application of the microsystems at industrial scale (MicroChemTec).

The miniaturization of continuous processes has been of increasing interest in the past few decades. During this time, the microreaction technology and flow

chemistry have moved from academic and industrial research to commercial applications. With industry taking up such innovations, this trend is also reflected in the patenting behavior of companies active in this area [13]. It is noted that during the past few years the number of patent publications in the field of microreactor engineering has increased steadily and seems now to approach a more constant level.

Today, microstructured devices are commercially available and are offered by different manufactures and engineering companies such as BTS Ehrfeld, CPC, IMM, Mikroglas, Microinnova, Little Things Factory, and so on. Using engineering techniques from the semiconductor chip production, such as lithography technology in combination with plasma or micromechanical structurization as well as laser technology, it is possible to design microstructures and, in particular, microreactors on the base of stainless steel, silicon, glass, ceramics, or even polymers [14–16]. Stainless steel is the favorite material for construction of microreactors that are applied in pilot plants and for the purpose of chemical production with a battery of microreactors running in parallel. Glass is the most customary material used for the manufacturing of equipment for chemical processes due to its resistance toward various solvents, acids, bases, and other reagents. Silicon shows optimal thermal conductivity and heat transfer capacity and therefore is much employed in reactions conducted at both high and low temperatures. Microreactors manufactured from polymers have restricted performance due to the low tolerance (the most used polymer) toward most of the reagents and solvents.

Based on the unequivocal advantages of microprocess technology, a lot of companies started to study microstructured devices as tools for process intensification [14]. BASF, Bayer, Clariant, Degussa, DSM, Lonza, and Merck are among them and have also published some studies they had performed to investigate the applicability of microstructured devices for chemical production [17–20]. Several pilot- and production-scale applications of microreactors have also been reported. There are about 20 plants published in the literature and 30–40 plants estimated to be installed worldwide [21].

1.3
Basic Characteristics

What are the reasons that microreactors in many cases produce better results than conventional reactors? In order to provide an optimal progress of a chemical reaction, different conditions must be fulfilled in the reactor: First, a nearly ideal mixing of the reactants should be ensured, linked with the generation of an extended phase interface in multiphase reactions. Afterward, the required response time must be guaranteed by a residence time with preferentially narrow residence time distribution. Finally, the reactor heat necessary for the reaction must be supplied or carried off. In this connection, control of temperature, pressure, time of reaction, and flow velocity in reactors with small volume is carried out much

easily and more effectively. The main conclusive advantages of microsystems are safety of carrying out strongly exothermic reactions and dealing with toxic or explosive reactants, as a whole essentially reducing research costs, introduction, and scaling of chemical processes.

Otherwise so-called "microeffects" have been intensively discussed, which should cause unexpected potentials of microreactors [22]. Meanwhile, it is known that microeffects are scaling down effects that are relevant or dominant on the microscale (from 100 µm to 1 mm). These effects are held responsible for (i) intensified mass transport toward the smaller dimensions, (ii) intensified heat transport toward the smaller dimensions, and (iii) intensified surface phenomena by higher surface area-to-volume ratios as a result of the smaller dimensions.

1.3.1
Microfluidics and Micromixing

The main difference of microstructured reactors from the classical continuous-flow reactors consists in a laminar flow regime of the fluids (liquid and gases). The laminar flow regime is defined by dimensionless number, that is, the Reynolds number Re (Equation 1.1), which depends on the velocity u, the density ρ, the traveled length L, and the viscosity η of the fluid:

$$Re = u\rho L/\eta. \tag{1.1}$$

Skilled data show that by fluids having standard values of density and viscosity and reactor channel diameters from 1 µm to 4 mm the Reynolds number always remains under the critical value ($Re = 2300$) on the border between a transition region and laminar flow is possible [23]. It is necessary to note that the laminar flow regime in microstructures is characterized by Reynolds numbers in the range between 10 and 500. The reason lies in the fast lateral diffusion, causing intensive mass transfer between layers and thus providing convergence of residence time. Microfluidics of multiphase systems are even more difficult, as different structures of a flow depend on the conditions of phase dosage or on the geometry of mixers. The most important flow types are so-called slug flow and annular flow. The formation of a highly specific surface of the phases, thus arriving at a favorable mass transfer in a liquid phase, and also the suppression of coalescence are important conditions of an effective processing in multiphase systems. This state can be achieved especially in a liquid phase in the case of slug flow in which, under the influence of flow layer friction led back to the walls of the microchannels, so-called Taylor whirls are formed, increasing mass transfer coefficients. Proceeding from it, the use of microchannels predetermines almost ideal mixture of reagents caused by molecular diffusion [24]. Equation 1.2 shows the approximation for molecular diffusion within a microchannel, where t_D is the diffusion timescale, L is the length over which the diffusion must occur, and D is the diffusion coefficient:

$$t_D = L^2/D. \tag{1.2}$$

Consequently, a facile technique used to increase the rate of diffusive mixing should employ narrow, high aspect ratio reaction channels, hence increasing the interfacial surface area [25].

Opposed to the turbulent mixing on a macroscale, turbulence is not induced when using mechanical or magnetic stirrers on the microscale. Moreover, the laminar flow almost completely inhibits formation of gradients of concentration and temperature in volume and time. The channel diameters of microreactors for the production of chemicals lie typically in the range from 1 mm to about 100 μm. It follows that the diffusion timescale of gases should be less than 1 s, and in the case of channel diameters under 100 μm even less than 1 ms [22]. In liquids, the diffusion timescales lie, however, often in the range of minutes or seconds; thus, lateral diffusion may appear as a limiting factor if liquid reactions proceed very fast. In this case, it is necessary to reduce diffusive barriers by connecting preliminary lamellar micromixing for an intensification of mass transfer [26]. This leads to a clear reduction of response time and increases space–time yield. Ideal diffusive micromixing gives rise to high productivity and sharp selectivity of reaction and, as a result, considerable decrease in the formation of by-products.

Although many different types of micromixers have been reported in the literature [27], one of the most popular approaches involves an increase in contact area between reagent flows by so-called lamination. An example of this is described by Bessoth *et al.* [28]: the two reagent flows are split into thin "laminae" and subsequently brought back together to allow a greater degree of diffusive mixing at the point of confluence, leading to complete mixing in 15 ms. Consequently, with the ability to efficiently mix reagent flows, reactions performed in such miniaturized systems are limited only by the inherent reaction kinetics.

1.3.2
Temperature and Pressure Control

Temperature is the most important parameter influencing kinetics and qualitative characteristics of the reaction products. The deviation from optimal reaction temperature involves uncontrollable change of reaction rate, negatively influencing selectivity of chemical processes. The exact control of temperature, also due to reasons of heat exchange, is the central factor to find out the ideal process parameters. In traditional large-scale reactors, fluctuations in reaction temperature are difficult to correct because any alteration requires time to have an effect on the whole system. In comparison, changes on the microscale are observed almost immediately. The flow regime obtained within microfluidic devices is laminar; therefore, time taken to enable thermal mixing across a microchannel can be approximated according to molecular diffusion theory [22]. To describe the heat transfer to laminar flow of fluids, normally the Nusselt number *Nu* (Equation 1.3) is used. It depends on the convective heat transfer coefficient α, characteristic length L, and the thermal conductivity of the fluid λ and can also be described as a dimensionless gradient of the temperature

on a surface:

$$Nu = \alpha L/\lambda. \tag{1.3}$$

Increasing the rate of thermal mixing and decreasing the channel diameter result in an inherently high surface area-to-volume ratio, which exceeds the contact area in traditional reactors – from 10 000 to 50 000 m^2/m^3 compared to conventionally 100 m^2/m^3 – and enables the rapid dissipation of heat generated during the reaction (silicon channels: 41 000 $W/(m^2 K)$; glass: 740 $W/(m^2 K)$) [6]. Equation 1.4 shows the approximation for the heat transfer within a microchannel, where t_w corresponds to the heat timescale, L is the traveled length of the fluid, and a is the thermal diffusivity coefficient:

$$t_w = L^2/a \quad \text{with} \quad a = \lambda/\rho c_p. \tag{1.4}$$

By means of the heat timescale, it is possible to show the difference between microreactors and conventional ones: with transition from the diameter in centimeters (and turbulent flow) to the microreactor with microchannels (and laminar flow), the value of this characteristic time increases by a factor of 1000 as a result of a much higher heat transfer coefficient as well as a higher surface area for heat exchange [22].

The rate of heat exchange is directly proportional to the surface area. Therefore, in microstructured reactors it is some orders of magnitude higher than that in usual reactors. The heat removal in the case of strongly exothermic reactions represents the most serious problem when scaling processes. The factor of heat exchange is inversely proportional to the diameter of the channel. In microreactors, it reaches values of up to 10 W/m, much higher than that in traditional heat exchangers. In this case, the most effective heat exchange enables instant heating and cooling of reaction mixtures, which supports isothermal reaction conditions at all points of the microreactor system.

Until recently, the temperature control of highly exothermic reactions using the microreaction systems was mainly based on the removal of heat in order to prevent hot spot formation and thermal runaway [29]. More recently, however, research has focused on techniques that enable microreactors to be heated because they can efficiently dissipate the heat. If a microheat exchanger is integrated into a microreactor, both effects can be combined, that is, either enabling fast heat supply in the reactor or heat removal from the reactor [30]. In practice, strongly exothermic reactions such as nitration, oxidation, chlorination, and even fluorination with elementary fluorine (in microreactors made of nickel) can be carried out in microreactor systems under nearly isothermal conditions [31].

Another important parameter of the chemical process is the reaction pressure. In the case of cylindrical vessels, the most admissible pressure is inversely proportional to the diameter of a capillary. Thus, the microsize of capillary provides the chance to use such reactors at high pressure. Despite attained pressures of 400 bar and above, reactions in microreactors can be carried out more safely compared to large-scale reactors. Considering high temperatures

and pressures, microreactor systems are ideal reactors for carrying out reactions under supercritical conditions [32,33].

The above-mentioned parameters, that is, the surface area, the heat exchange, and the reaction temperature and pressure, all influence the reaction kinetics. The inherent advantages of microstructured devices allow to considerably reduce the required time of reaction and to increase productivity in comparison to traditional reactors on the macroscale. However, before the use of microreactors in the production also other effects need to be investigated, for example, the pressure loss with higher throughputs, which can lead to a restriction of the flow per microreactor module. As a matter of fact, this problem can be avoided by numbering-up of many single microreactor modules. Connecting microreactors of the same proven dimensions to operate in parallel or in series, higher capacities can be reached and compact microplants can be built up [34]. Nevertheless, nowadays microreactors are adapted rather for the production of small and medium amounts in the field of special and fine chemicals or pharmaceutical substances.

1.3.3
Safety and Ecological Impact

One of the main aspects of modern chemistry is the safety of the chemical processes. It is easy to see that the volume of a batch reactor must be some orders of magnitude higher than that of the continuous-flow microreactor to reach the identical quantity of final products (using equal amounts of reactants). The small quantity of reactants in the reactor minimizes the potential of thermal explosion by dangerous reactions. Indeed, explosion or depressurization of reaction systems with hazardous substances in the continuous microreactors leads only to insignificant technical problems or to a minimum leakage of chemicals, as opposed to the scales of explosions or leaks in standard reactor volumes. Microreactors, with their narrow channel dimensions, hold such a small quantity of reaction fluid that a mechanical failure in one reactor requires merely a temporary shutdown and subsequent replacement.

The implementation of hazardous (particularly explosive) reactions in a microreactor is also safer because of the high surface area-to-volume ratio, which increases the heat transfer rate from the reaction zone. For example, the effect of miniaturization on the explosion limits of an H_2/O_2 mixture in the high-temperature catalytic microreactor was described by Veser [35]. At ambient pressure conditions for a conventional reactor with 1 m diameter, explosive behavior sets in upon crossing the third explosion limit around $T = 420\,^{\circ}C$. When decreasing the reactor diameter to 1 mm, explosion occurs at substantially higher temperatures ($T = 750\,^{\circ}C$) by crossing the second explosion limit. If the reactor diameter is reduced from 1 mm to 100 μm, the explosive reaction regime can be pushed further toward higher pressures and temperatures, so that even the first ignition limit is raised above ambient pressure conditions and explosive behavior can generally be excluded; that is, the reaction becomes inherently safe.

Health and environment are the key factors for operability in the chemical industries. Not only the processes need to be safe, but also it has now economic sense to decrease the impact of processes on the health of workers and the surrounding community. This aims at either eliminating the emissions of chemical products or minimizing the amount of waste being disposed. In this connection, continuous-flow reactors in the chemical production often provide the global solution to the environmental problems (green chemistry) [36,37]. Besides processes safety, the considerable reduction of reagent amounts plays a major role both in the course of laboratory research and during scale-up to the pilot plant or large-scale production. Switching production to a small continuous process can significantly reduce the amount of waste associated with the process and ultimately improve its economics. For these reasons, small quantity processing in micro-reactors may be in the future more favorable than using multipurpose batch production processes.

1.4
Industrial Applications

In spite of all proven advantages, microreactors are nowadays found only occasionally in the production. On part of the chemical industry, the microreactor arrangements were developed at last for production scaling purposes and are tested presently under production conditions. Now a number of well-known European, American, and Asian chemical and pharmaceutical companies actively introduce the new advanced technology in practice. Some examples have been published within the past few years showing the potential when an accurate plant design and development is carried out [21,38,39].

The first and up to now most often mentioned example for microreactor process engineering is the DEMiS project in Germany (Degussa, Uhde, TU Chemnitz, TU Darmstadt, MPI Mülheim), in which a microstructured reactor was used for the epoxidation of propylene to propylene oxide using H_2O_2 on a TS-1 zeolite with a production capacity of approximately 5–10 t/year. Other examples of industrial microreactor applications are the synthesis of azo pigments (Clariant, Frankfurt, Germany, CPC, 80 t/year), the synthesis of nitroglycerol (Xi'an Chemical Industry Group, China, IMM, 130 t/year), and the radical solution polymerization of acrylate resins (Siemens Axiva, Frankfurt, Germany, 2000 t/year).

DSM Fine Chemicals GmbH (Linz, Austria) installed a microstructured reactor in an existing production plant for the manufacture of a high-value intermediate for the polymer industry. The reactor was designed and fabricated at the Institute for Micro Process Engineering (Karlsruhe, Germany) and dimensioned for throughput of 1700 kg/h. Microinnova KEG (Graz, Austria) also installed a microstructured reactor designed by IMM (Mainz, Germany) in an existing plant for the production of fine chemicals. This installation and the associated speedup of the first reaction step in a running two-step batch process led to a doubling of the throughput.

Evonik Industries together with partners from industry (BASF) and research groups (IMM) developed the ozonolysis reactions in a falling film microreactor in a large scale of 120 t/year in the frame of BMBF-funded project (µ.Pro. Chem). Lonza has carried out investigations to check whether the innovative microreaction technology could contribute to the process intensification in the production of its products. The investigation results proved that continuous microreactors suit for 50% of 22 examined production processes. Recently, in cooperation with the Ehrfeld Mikrotechnik BTS (EMB) and Bayer Technology Services Company, the compact microreactor Lonza FlowPlate™ with flexible design for continuous production of fine chemicals and pharmaceuticals was developed.

After several years of experience in application of microreaction technology in R&D and production, Sigma–Aldrich decided to assemble its own microreactor system that is now offered as Microreactor Explorer Kit 19979 for the broad applications. This research work enables the development of new pharmaceutical processes with low energy and material consumption. Meanwhile, also Merck KGaA in Darmstadt, Germany, reported about the operation of a number of microreactor plants for diverse reactions. The production costs are typically reduced by 20% compared to traditional batch or semibatch processes. The new technology is intruded very intensively by other pharmaceutical companies such as Novartis AG (Switzerland), F. Hoffmann-La Roche AG (Switzerland), Abbott (USA), Nycomed (Denmark), which transfer available batch processes in continuous-flow microreactors. It remains to be seen how this exciting area of process intensification will develop. Many novel, potentially important applications of microreactor technology for production of fine chemicals, bioproducts, nanoparticles, and other industrial products are presented below.

1.5
Concluding Remarks

Microreactors exhibit numerous practical advantages when compared to traditional, conventional reactors. The small dimensions of the microchannels (submicrometer and submillimeter size) allow usage of minimal reagent amounts under precisely controlled conditions, providing the basis for reaction screening conditions as well as improving the overall safety of the process.

They exhibit excellent mass and heat transfer, shorter residence time, and smaller amounts of reagents, catalyst, and waste products, when compared to macroscale reactors. Moreover, lightweight and compact system design, laminar flow, effective mixing, short molecular diffusion distance, better process control, and small energy consumption are just some of the microsystem advantages. In addition, they can be easily coupled with numerous detection techniques together with the pretreatment of the samples on a single chip. Having in mind all these benefits, one of the main motivations for the use of microreactor technology is the gain in economy, safety, and ecology.

According to the experts in the field of chemical synthesis, it is more preferable to use continuous process in microreactors for up to 70% of all chemical reactions [19]. Today, a lot of homogeneous reactions in liquid–liquid systems are investigated because they can be simply carried out in microreactors. Heterogeneous reaction systems, both liquid–liquid and gas–liquid, in microreactors are more and more intensively studied and find practical application. Special attention is given to catalytic processes as they dominate in chemical technology.

The full development and potential of the microreaction technology as an alternative to already established chemical processes will only be revealed if the future user can learn its special features during education, that is, as a student at university. In this connection, practical training is necessary and can be very helpful. Therefore, respective contributions in the further chapters of this book about the application of the microreaction technology in different areas of the preparative chemistry will be completed by verified laboratory experiments ready to be put into practical application. These experiments have the potential to be used in curricula of chemistry and chemical engineering as well as in process technology and bioengineering for the continuing education.

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