Perspective

Microchemical Systems: Status, Challenges, and Opportunities

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Microfabrication techniques and scale-up by replication have fueled spectacular advances in the electronics industry, and they are now creating new opportunities for reaction engineering. The term "microreactor" typically meant a small tubular reactor for testing catalyst performance. However, with the widening use of microfabrication technologies in many fields of chemistry, "micro" increasingly designates chemical systems fabricated with techniques originally developed for electronic circuits. Such systems have feature sizes in the micron to hundreds of micron range, and reaction components are usually integrated with sensors and actuators. The reduction in size and integration of multiple functions create structures with capabilities that exceed those of conventional macroscopic systems and add new functionality while potentially making low cost, mass production possible. Existing examples include nucleic acid synthesis and detection, microchemical analysis, combinatorial synthesis of drugs, and microchemical reactors for on-demand synthesis (Manz and Becker, 1998).

These developments build, in part, on advances in MicroElectroMechanical Systems (MEMS) (Wise, 1998). The field, started by using fabrication techniques developed for microelectronics to construct sensors and actuators, now encompasses a wide range of materials and microfabrication methods. MEMS devices are now found in a broad spectrum of automotive, aircraft, health care, printing, and optical applications. The research investment made in MEMS has enabled the fabrication of microchemical reaction systems. Many of the components (e.g., valves, pumps, flow sensors, mixers, and separation devices) needed in integrated chemical systems have been demonstrated in various metals, ceramics, and polymers (Ehrfeld et al., 1998a,b; Wise, 1998). Miniaturization of chemical analytic devices in "micro-total-analysis-systems" (μTAS) (van den Berg and Harrison, 1998) represents a natural extension of MEMS technology to chemistry and biology with obvious application in combinatorial chemistry, high throughput screening, and portable analytical measurement devices.

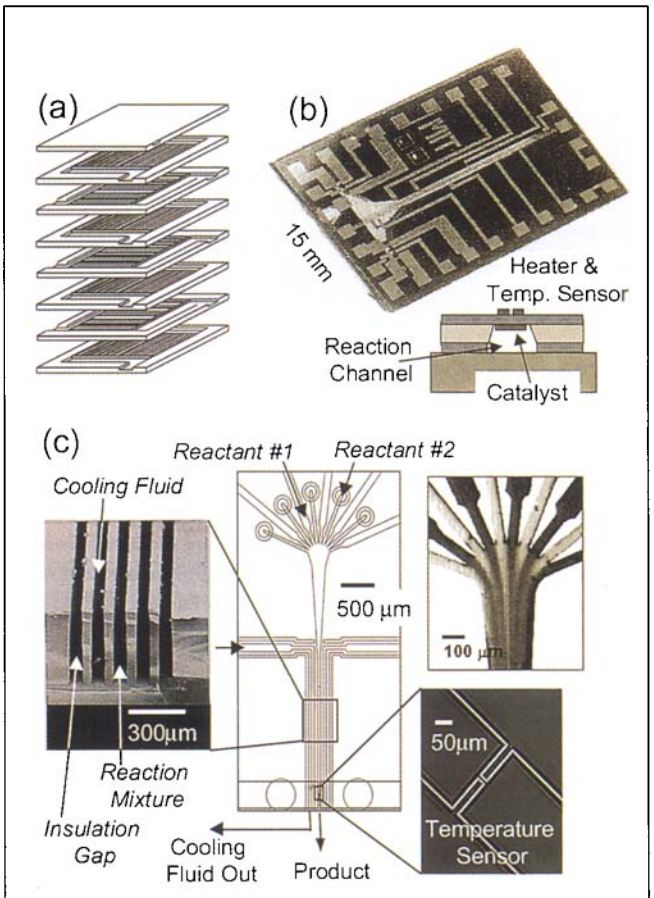

Figure 1. Examples of microreactors. (a) Microchannel-based reactor (Tonkovich et al., 1998); (b) thin wall reactor (Srinivasan et al., 1997); (c) liquid-phase reactor with lamination of fluid streams (courtesy of T. Floyd, MIT). Heat exchangers and temperature sensors in downstream reaction zone. Upper righthand insert shows mixing of acid-base mixture in gray tone image of indicator color.

Advantages of microfabrication

Microfabrication offers many advantages. It not only reduces consumption of expensive reagents, fluidic components with small dead volumes, but also improves separation resulting from higher surface-to-volume ratios, integration of sensors and actuators, parallel screening, and mass fabrication of multiple units by replication. Chemical engineers often use small reactors, but are faced with bench top analytical equipment and large panels of complex fluid handling manifolds. With the continual advances in μTAS and microfabricated reactors, these macroscopic test systems could eventually be replaced by PC-card sized microchemical systems consisting of integrated microfluidic, sensor, control, and reaction components.

Such systems would clearly require less space and utilities, and produce less waste. They would enable high-throughput screening of catalysts and process chemistries under realistic conditions, which has proven difficult in current combinatorial approaches. Moreover, the small dimensions imply laminar flow, making it feasible to fully characterize heat and mass transfer and extract chemical kinetic parameters from sensor data.

Application of microreaction technology

Microreaction technology is also expected to have an impact on chemical production (Ehrfeld et al., 1998a; Lerou et al., 1996). The high heat- and mass-transfer rates possible in microfluidic systems could allow reactions to be performed under more aggressive conditions with higher yields than achievable with conventional reactors. More importantly, new reaction pathways deemed too difficult in conventional microscopic equipment, e.g., direct fluorination of aromatic compounds (Chambers and Spink, 1999), could be pursued. Even if a microreactor failed, the small quantity of chemicals released accidentally could be easily contained. Moreover, the presence of integrated sensor and control units could allow the failed reactor to be isolated and replaced while other parallel units continued to produce. These inherent safety characteristics suggest that production scale systems of multiple microreactors should enable distributed point-of-use chemical synthesis of chemicals with storage and shipping limitations, such as highly reactive and toxic intermediates (e.g., cyanides, peroxides, azides). As a demonstration of these concepts, DuPont has synthesized a number of potentially hazardous chemicals, including isocyanates, in a microreactor formed by bonding silicon wafers patterned to form channels, preheaters, and catalytic reactor sections (Lerou et al., 1996).

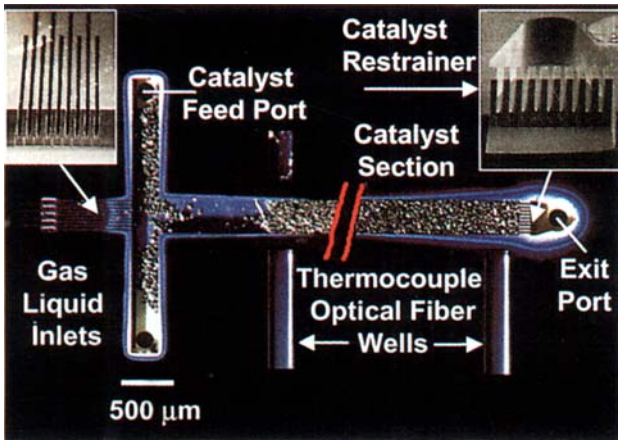

Figure 2. Multiphase packed-bed reactor with active carbon catalyst (Courtesy of M. Losey, MIT). Gas-liquid inlet sections on the left, catalyst support grid and exit on the right. Catalyst is introduced through the large wing sections. The vertical lines are wells for thermocouples and optical fibers for temperature and species monitoring, respectively. The color photograph (by Felice Frankel) is a digital composite of two separate images in both ends of the reactor. The red sketched lines indicate the long mid-section not photographed. The channel is 625 μm wide and 20 mm long. Alignment marks were digitally removed. Right- and lefthand micrograph inserts show inlet and exit sections, respectively. The openings are 30 μm wide and 300 μm deep.

Scale-up to production by replication of microreactor units used in the laboratory would eliminate costly redesign and pilot-plant experiments, thereby shortening the development time from laboratory to commercial production. This approach may be advantageous particularly for the fine chemical and pharmaceutical industries where production often is as small as a few metric tons per year. The strategy would also allow for scheduled, gradual investment in new chemical production facilities without committing to a large production facility from the outset. Ultimately, the large-scale manufacturing of individual components and subsequent integration, as done in the electronic and automotive industry, could challenge the traditional centralized economy of scale (that is, a few large plants) practiced in the chemical industry.

The reduced consumption of expensive reagents, fast response time, and integration of sensors and actuators inherent in microfabricated systems are attractive particularly for screening of biological samples. Recent DNA detection units are essentially microchemical systems that combine reagent dosing, controlled reaction, separation, and detection. For example, the integrated silicon and glass microfluidic device developed by Burns et al. (1998) meters reagents and DNA-containing solutions, mixes these solutions, and then amplifies or digests DNA in a temperature controlled reaction chamber. The reaction products are subsequently separated by electrophoresis and detected by fluorescence using an on-chip photodiode. Such devices have obvious applications in gene sequencing, medical diagnostics, and biohazard detection. The "pharmacy-on-a-chip" device is another example of integration of microfabrication, chemistry, and electrical signals to achieve a specific objective (Santini et al., 1999). In this case, an electrical current drives electrochemical reactions leading to dissolution of a membrane—with a resulting controlled release of a defined volume of reagents from a microfabricated reservoir.

Microreactor research over the past few years has demonstrated a widening range of chemical applications, increasingly sophisticated designs, and expanding levels of integration. Gas-phase reactors tend to be based on microchannel plates (Figure 1a) or freestanding thin walls from silicon based MEMS fabrication (Figure 1b). Microchannel systems exploit the high heat-transfer rate made possible by the small dimensions (Ehrfeld et al., 1998a) and have the additional advantage of higher chemical productivity per unit volume than MEMS-based devices. Similar to conventional ceramic monolith reactors, however, they suffer from lack of sensing and active control within the microchannel assembly. Stacking microchannel plates with different reaction and heat exchanger functions provides the potential for energy integration (Tonkovich et al., 1998).

Thin wall reactors offer the opportunity for integration of flow and temperature sensors on the external side. The micron-thick wall provides good thermal contact with the catalyst in the interior (see Figure 1b). Energy transfer in the active reactor wall may be manipulated by adjusting the thickness of the wall and choosing materials of different thermal conductivity. Thermal isolation is useful when using the thin-wall reactor as a calorimeter, but also creates the potential for multiple steady states for highly exothermic reactions. Increased heat conduction out of the catalyst removes the multiplicity and opens mild reaction conditions typically not accessible in conventional reactors. The integrated heaters and temperature sensors combined with the low thermal mass of the wall has the

further advantage of fast thermal response times. The use of a permeable membrane, instead of the thin wall, allows the integration of separation with chemical reaction, as in macroscopic membrane reactors. For example, the integration of a submicron-thick palladium membrane makes a high-efficiency hydrogen purification device and provides the potential for conducting hydrogenation and dehydrogenation reactions (Franz et al., 1999).

The small dimensions in microreactor channels guarantee laminar flow so that mixing occurs primarily by diffusion. This characteristic becomes both a challenge and an advantage for liquid-phase reaction systems (Burns and Ramshaw, 1999). To accelerate mixing, most liquid-phase reaction systems rely on splitting and recombination of the fluid streams several times so that a laminated fluid is created with an increased fluid interface and shortened diffusion path (Ehrfeld et al., 1999). Alternatively, the liquid feed can be introduced to produce a laminated stream (Figure 1c). The choice of design becomes a trade-off between mixing speed, pressure drop, volume flow, and the feasibility of microfabrication. The relatively slow mixing phenomenon can be exploited in phase transfer reactions, separation devices, and nucleation studies, as well as in novel microfabrication schemes (Brody et al., 1996; Kenis et al., 1999).

The high surface-to-volume ratios attainable in microfabricated structures, controlled reactant distribution and contacting pattern, improved thermal management, and fast mass-transfer rates suggest that a microfabricated multiphase system also could have performance advantages relative to conventional macroscopic systems. Figure 2 shows a multiphase packed-bed reactors fabricated using deep reactive-ion etch technology and standard photolithography tools. The reaction chamber holds porous catalyst particles in place by a microfabricated filter as reactants are fed continuously in a cocurrent fashion. The gas and liquid reactant streams are brought into contact by a series of interleaved, high-aspect ratio inlet channels designed to increase gas-liquid mass transfer.

Outlook

These microreactors (Figures 1a–1c and 2) represent a small fraction of the many possible designs for microreactors. The ability of microfabrication to reproduce complex designs in a parallel fashion should invigorate the innovative nature of reactor design and lessen the tedium of stirred tanks, and tubular and trickle bed reactors. In developing microreaction technology, it will be essential to be focused on systems where microfabrication can provide unique process advantages. Such advantages could be derived from increased mass and heat transfer leading to improved yield and safety for an existing process. The real value of the miniaturization effort, however, would be in exploring new reaction pathways and finding economical and environmentally benign solutions to chemical manufacturing.

It is important to exploit characteristics resulting from the small dimensions beyond the high transport rates, specifically forces associated with high surface-to-volume ratios. For example, Orchid Biocomputer uses capillary valves and pressure to control fluid deliveries and well volume consistency across multiple reactor wells in combinatorial synthesis (DeWitt, 1999). In preparing fluids for its "genechips," Affymetrix uses surface tension differences along fluid channels to precisely meter fluids and pressure to move the resulting fluid packets around on the microfluidic chip (Anderson et al., 1998). Strategically placed permeable gas membranes allow gas to pass through but stop the fluids at specific locations. In general, chemical systems rely on large surface areas for separations or reactions. Surface-to-volume ratios can be increased by microfabricating internal structures. Such schemes have been exploited in making separation columns for proteomics, immobilizing enzymes, and size selective catalysis (He et al., 1999; van den Berg and Harrison, 1998).

The need to develop novel structures with controlled surface characteristics suggests that microreactor fabrication must go beyond classical micromachining and silicon MEMS techniques. Microfabrication in glass already forms the foundation for many biological devices because of the need for an insulating substrate for electrophoresis. Fabrication in plastics using embossing and injection molding techniques is rapidly expanding (Ehrfeld et al., 1998b; van den Berg and Harrison, 1998). The family of chemical self-assembly and microfabrication techniques, "soft lithography," developed by Xia and Whitesides (1998) further provide unique opportunities for microfabrication and chemical tailoring of surfaces to particular applications. Its strengths include the ability to transfer patterns onto nonplanar surfaces, formation of microstructures, and compatibility with a wide range of materials (polymers, metals, and ceramics). These techniques have already produced unique microstructures and capabilities that could further advance microchemical systems (Kenis et al., 1999).

To move beyond the laboratory into chemical production, microreactors must be integrated with sensors and actuators either on the same chip or through hybrid integration schemes. It was the integrated circuit that created the microelectronics revolution, not the transistor itself. The integration of chemical systems with sensors in μTAS is already a rapidly expanding field, and cross-fertilization with microreactors for chemical synthesis will result in integrated chemical processors. The packaging of multiple reactors presents significant challenges in fluid handling, and local reactor monitoring and control, which have not been previously addressed in traditional design of chemical plants. Thus, the realization of microreaction technology offers tremendous multidisciplinary research opportunities across biology, chemistry, materials, and electronics, as well as in the traditional chemical engineering subdisciplines of catalysis, transport phenomena, reaction engineering, and systems.

Acknowledgments

The author thanks Prof. Martin A. Schmidt, the MIT microreactor group, and collaborators at DuPont for stimulating research interactions and the DARPA MicroFlumes Program for financial support.

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