XUNLI ZHANG
CHARLOTTE WILES
SARAH L. PAINTER
PAUL WATTS
STEPHEN J. HASWELL

Microreactors as tools for chemical research

ABSTRACT

The unique operational characteristics of microreactors are described in this article, with particular reference to their use as tools for chemical synthesis. With reference to the future automation, an example is presented to illustrate how microreactors can be readily integrated into current HPLC systems, to enable fully integrated chemical synthesis and product analysis to be performed.

INTRODUCTION

A microreactor is generally defined as a device consisting of a number of interconnecting micro channels in which small quantities of reagents are manipulated, mixed and allowed to react for a specified period of time. The movement of fluids within such a device can be achieved in a number of ways with the most common being mechanical micropumping and electroosmotic flow (EOF) which may include electrophoresis separations (1, 2). The typical cross-sectional dimensions of such micro channels are in the range of 10–500 μm and are normally fabricated on the planer surface of substrates such as glass, polymers, ceramics, and metals. Depending on the material selected, a range of fabrication methods can be used for the production of micro channels including photolithography and wet-etching, powder-blasting, hot embossing, injection moulding and laser micromachining (2).
A number of recent reviews have described the development of microreactors, based on the so-called "Lab-on-a-Chip" technology and outlined the relevance of such techniques to the field of organic synthesis (3-12). In this article, the fundamental and practical advantages associated with microreactor technology are related to the current needs of the chemical industry, who are constantly searching for controllable, informative, high-throughput, environmentally friendly processes whilst retaining a high degree of chemical selectivity. Specific examples are also presented in order to illustrate the intrinsic advantages associated with micro reaction technology, together with an illustration of how these devices can be integrated into existing automated instrumental systems so enabling new synthetic methodology to be coupled with an analytical finish.

CHARACTERISTICS OF MICROREACTORS

The unique operating characteristics of microreactors, compared to conventional batch reactors, include a high surface area to volume ratio, enhanced heat transfer, diffusion dominated mass transfer, spatial and temporal control of reagents and products, the generation of concentration gradients and the opportunity to integrate processes and measurement systems in an automated manner.

High surface area to volume ratio

When scaling a conventional centimetre sized reactor down to the micron scale, the surface to volume ratio significantly increases to the point where the container walls can effectively become an active or influential part of the reaction or process occurring in the fluidic channel. Clearly this attribute of microreactors can be viewed in a positive way and leads to the opportunity of exploiting surface dependent performance. A relatively simple, but important example, of this effect is where the surface charge of the capillary is neutralised by the solution contained within it to form a charged double layer, which under the influence of an applied electric field leads to the electroosmotic mobilisation of the solution. In more chemical applications the surfaces could be represent reagents, catalysts or even physical molecular imprinted structures.

Enhanced heat transfer

The high surface to volume ratio can also significantly improve thermal transfer conditions within micro channels in two ways; firstly, the convective heat transfer which takes place at the solid/fluid interface, is improved via an increase in heat transfer area per-unit-volume and secondly, heat transfer within a small volume of fluid takes a relatively short time period to occur enabling a thermally homogeneous state to be reached quickly. The improvement in heat transfer can certainly influence overall reaction rates and, in some cases, product selectivity. Perhaps one of the more profound effects of the efficient heat transfer property of microreactors is the ability to carry potentially explosive or highly exothermic reactions in a safe way, due to the relatively small thermal mass and rapid dissipation of heat.

Mass transfer dominated by diffusion

It is well known that the flow within microchannels is restricted to diffusive mixing under laminar flow conditions. Based on Fick's law (13), the relationship between the travel distance (L) of a molecule by diffusion and time (t) can be simplified as

$$L = (2D \cdot t)^{1/2} \qquad (1)$$

where D is diffusion coefficient.
From Eq. (1) it can be seen that by scaling down the dimension in which diffusive mixing occurs, a significant reduction in the time taken to achieve complete mixing is achieved. For example, a water molecule takes 200 s to diffuse across a 1 mm wide channel, but only takes 500 ms to cross a 50 μm wide channel (where the self-diffusion coefficient of water at 25 °C is 2.30×10^{-9} $m^2 s^{-1}$)

Aldehyde	Activated Methylene	Applied Field (V cm^{-1})	Flow Rate (µl min^{-1})	Conversion (%)
Benzaldehyde	Ethyl cyanoacetate	333	0.5	99.1
4-Bromobenzaldehyde	Ethyl cyanoacetate	333	0.3	99.5
3,5-Dimethoxybenzaldehyde	Ethyl cyanoacetate	333	0.3	94.7
4-Benzyloxybenzaldehyde	Ethyl cyanoacetate	333	0.5	95.1
Benzaldehyde	Malononitrile	167	1.0	96.9
4-Bromobenzaldehyde	Malononitrile	167	0.5	96.3
3,5-Dimethoxybenzaldehyde	Malononitrile	167	0.7	97.8
4-Benzyloxybenzaldehyde	Malononitrile	167	1.0	99.7

Table 1. Summary of the results obtained for the synthesis of α-, β-unsaturated compounds in a miniaturised flow reactor.

(14). This significant reduction in mixing time is beneficial for controlling reaction progress, in particular for initiating or quenching reactions in a controlled manner, enabling improvements to be made in product selectivity.

Spatial and temporal evolution of reactions

Under such diffusive laminar flow conditions, the ability to add reagents at specific locations or time leads to the unique ability to control and monitor the spatial and temporal domain of dynamic chemical processes. This attribute has some analogies with the control exerted on biochemical reactions by the micron-scale structures of living cells. Exploitation of this effect, such that a reaction well occurs in a position where the local concentration of a key intermediate is high, is a potentially valuable approach towards controlling the yield and selectivity of reactions.

System integration and automation

Each of the properties of a microreactor outlined above do not have to be exploited independently but can be combined to provide multiple functionality within one microreactor. In this way, multi-step processes, combining a range of physical and chemical steps, can be performed in a controlled and reproducible way. In addition, the integration of *in-situ,* real time or end of line analytical measurements can be effectively realised using microreactor technology, leading to rapid automated methodology. A combination of these two features will clearly create tools for the pharmaceutical and fine chemical industries, where high throughput and information rich techniques are constantly sought for the rapid evaluation of reaction arrays.

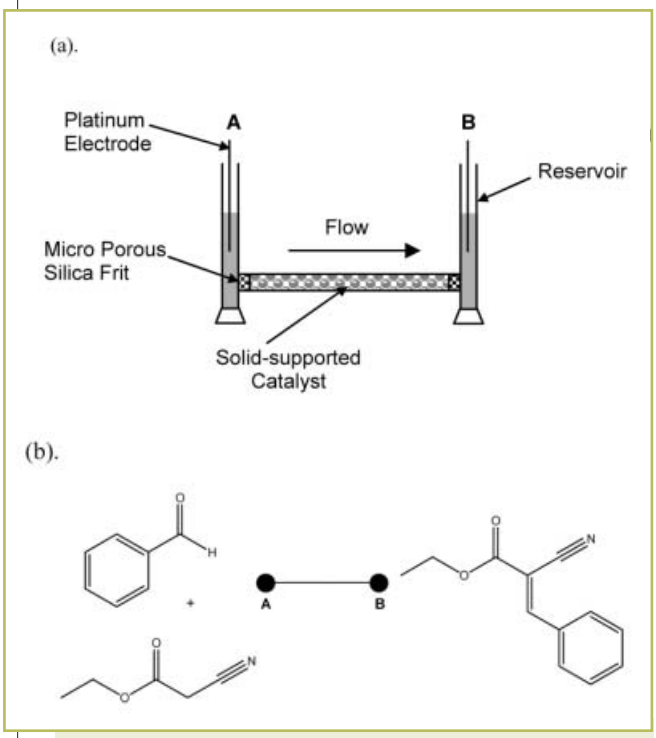

Fig. 1. Schematic illustrating the (a). reaction set-up used for the evaluation of solid-supported catalysts in miniaturised flow reactors and (b). reaction manifold used for the synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester.

EXPLOITING THE HIGH SURFACE TO VOLUME PROPERTIES OF MICROREACTORS

Although the rapid growth of microreactor technology has led to the transfer of many common synthetic reactions from batch to "chip" (15-19), little attention has been paid to the problems associated with the continuous purification of these reactions products. To tackle this, the incorporation of solid-supported catalysts within miniaturized flow reactors has been investigated, leading to the synthesis of analytically pure compounds and aiding the development of efficient multi-step processes. By way of example, we describe here the use of supported catalysts held within a borosilicate glass capillary (500 mm (i.d) x 3.0 cm (length) in which solvent and reagents are pumped under electroosmotic conditions (Figure 1). The supported catalyst was dry packed into the reactor and held in place by micro porous silica frits (20). The packed capillary was primed with MeCN to remove any air, ensuring the formation of an electrical circuit; a leak-tight connection between the capillary and reagent reservoirs was achieved using PTFE thread seal tape. To mobilise reagents by EOF (from reservoir A through the packed-bed to reservoir B), platinum electrodes were placed within the reservoirs and voltages applied using a high voltage power supply (0 to 1000 V DC); typical applied fields of 167 to 333 and 0 V cm^{-1} were employed.

In order to benchmark the technique against traditional stirred/shaken reactors, the base-catalysed Knoevenagel condensation of 8 α,β-unsaturated compounds was used (Table 1) (21); this was followed by the acid-catalysed protection of 15 aldehydes as their respective dimethyl acetal (22). In all cases, high run-to-run reproducibility (< 0.9 percent RSD) was demonstrated along with excellent product purity and isolated yields (> 94.7 percent). As an extension to this investigation, the incorporation of multiple supported catalysts (a polymer-supported acid and a silica-supported base) into the aforementioned reactor was examined to demonstrate the two-step synthesis of 20 α,β-unsaturated compounds; again all products were obtained in excellent yield (> 99.1 percent) and analytical purity (> 99.1 percent). Furthermore, when performing the two-step reactions, Amberlyst-15 was recycled over 200 times and silica-supported piperazine over 1000 times, with no sign of degradation.

This technique has been demonstrated to be a simple and efficient approach for the incorporation of solid-supported catalysts into miniaturised flow reactors, resulting in a system suitable for the continuous flow synthesis of analytically pure compounds. Compared to

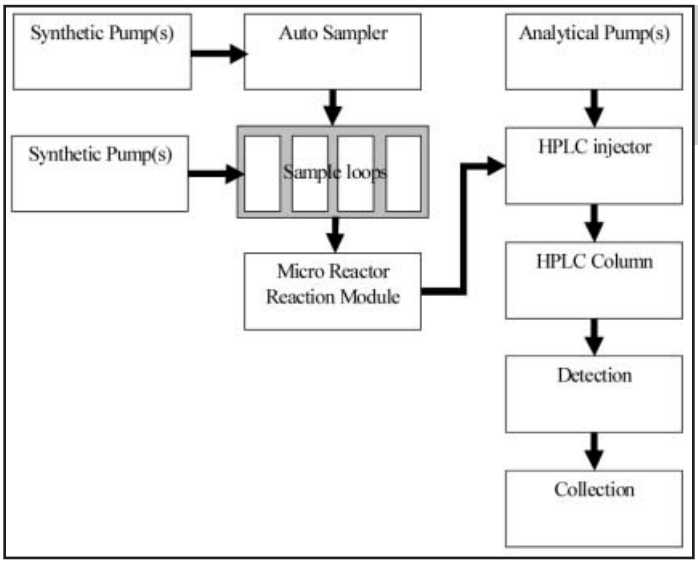

Figure 2. Schematic illustrating the automated reagent selection, micro reaction and HPLC analysis set-up developed

independently optimise the flow in all three sections of the process, is also important with respect to reagent integrity, reaction efficiency and chromatographic separation. Clearly, the system described has additional applications beyond that of a quality control technique for chemical synthesis, for example it would be relatively simple to incorporate biological processing and/or couple the reactor set-up to other analytical instrumentation. In summary, the automated system described allows the rapid evaluation of an array of reaction conditions such as reaction time, temperature and reagent stoichiometry, enabling the production of combinatorial libraries with ease.

Figure 3. Illustration of the automated reagent introduction, reaction and analysis set-up developed

traditional batch techniques, the application of miniaturised flow reactors proved advantageous, as it is possible to synthesise compounds in high yield and purity without the use of extended reaction times (min cf. > 24 hr). Additionally, the ease with which supported catalysts are recycled provides a reaction reproducibility unparalleled in traditional stirred or shaken reactor vessels. Consequently, whether milligrams of a compound are required for biological evaluation (single reactor) or tonnes for the production of fine chemicals (multiple reactors), the flexibility associated with micro reaction technology enables these differences in scale to bridged with ease.

INTEGRATION AND AUTOMATION OF CHEMICAL SYNTHESIS WITH ANALYTICAL DETECTION

The ability to generate a large quantity of chemical reaction information through automation represents an important capability of microreactor systems, with this in mind, the following example describes the use of a modified HPLC system for automated reagent selection, microreaction and chromatographic analysis (Figure 2 and 3).
Figure 3 shows a multi valving system, located between two syringe pumps shown in the foreground, used in combination with an HPLC autosampler to allow the introduction of multiple reagents onto the microreactor. Due to the low diffussional distances obtained in this system, compared to the use of reagent slugs, this approach is amenable to the individual introduction of a large number of reagents onto the microreactor. Hence the rapid loading of sample introduction loops can be performed without compromising either the reaction or analytical flow rates, offering time efficiency whilst ensuring that concentration of the sample is not reduced by excessive diffusion into the carrier solvent. In addition, high flow rates can be maintained for the chromatographic separation which would be difficult to achieve if the exit stream of the microreactor was directly coupled to the analytical column. The ability to

CONCLUSIONS

It has been demonstrated that microreactors offer many advantages over conventional macro-scale reactors, particularly with respect to achieving controllable, information rich, high-throughput, environmentally friendly and automated processes capable of generating large quantities of product with a high degree of chemical selectivity. These advantages can be attributed to the dramatic reduction in scale leading to unique operating conditions such as the spatial and temporal reagent control obtained under a non-turbulent, diffusive mixing regime and a high surface to volume ratio. There is no doubt that microreactor technology can be used as a platform for a wide range of applications such as chemical and biological analysis, chemical synthesis, materials chemistry and biotechnology – to name but a few.

REFERENCES AND NOTES

1. P. D. I. Fletcher et al., *Tetrahedron*, **58**, pp. 4735-4757 (2002)
2. T. Laurell et al., *8th International Conference on Miniaturized Systems for Chemistry and Life Sciences (MicroTAS 2004)*, pp. 26-30 (2004) Malmö, Sweden, September
3. T. Schwalbe et al., *Chimia*, **56**, pp. 636-646 (2002)
4. C. J. Cullen et al., *Curr. Opin. Drug Discov. Dev.*, **7**, pp. 798-806 (2004)
5. H. Pennemann et al., *Org. Process Res. Dev.*, **8**, pp. 422-439 (2004)
6. M. Brivo et al., *Lab Chip*, b510856j (2006)
7. K. Jahnisch et al., *Angew. Chem. Int. Ed.*, **43**, pp. 406-446 (2004)
8. V. Hessel, H. Lowe, *Chem. Eng. Technol.*, **28**, pp. 267-284 (2005)
9. P. Watts, S. J. Haswell, *Chem. Eng. Technol.*, **28**, pp. 1-12 (2005)
10. P. Watts, S. J. Haswell, *Chem. Soc. Rev.*, **34**, pp. 235-246 (2005)
11. J. Yoshida et al., *Chem. Eng. Technol.*, **28**, pp. 259-266 (2005)
12. P. D. I. Fletcher et al., *Dekker Encyclopedia of Nanoscience and Nanotechnology*, **2**, pp. 1547-1564 (2004)
13. A. Fick, *Ann. Phys. Chem.*, **94**, pp. 59-86 (1855)
14. R. Mills, *J. Phys. Chem.*, **77**, pp. 685-688 (1973)
15. S. J. Haswell et al., *Lab Chip*, **1**, pp. 164-166 (2001)
16. E. Garcia-Egido et al., *Lab Chip*, **2**, pp. 31-33 (2002)
17. C. Wiles et al., *Org. Process Res. Dev.*, **8**, pp. 28-32 (2004)
18. K. Jahnisch et al., Angew. *Chem. Int. Ed.*, **43**, pp. 406-446 (2004)
19. C. Wiles et al., *Tetrahedron*, **61**, pp. 10757-10773 (2005)
20. P. D. Christensen et al., *Anal. Commun.*, **35**, pp. 341-344 (1998)
21. C. Wiles et al., *Tetrahedron*, **60**, pp. 8421-8427 (2004)
22. C. Wiles et al., *Tetrahedron*, **61**, pp. 5209-5217 (2005)

XUNLI ZHANG, CHARLOTTE WILES, SARAH L. PAINTER, PAUL WATTS AND STEPHEN J. HASWELL *

***Corresponding author**
The University of Hull
Department of Chemistry
Hull, HU6 7RX, United Kingdom