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A Microcapillary Flow Disc Reactor for Organic Synthesis

Christian H. Hornung,[†] Malcolm R. Mackley,[†] Ian R. Baxendale,[‡] and Steven V. Ley*[,‡]

Department of Chemical Engineering, University of Cambridge, Pembroke Street, Cambridge CB2 3RA, UK, and Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK

Abstract:

This paper reports proof of concept, development, and trials for a novel plastic microcapillary flow disc (MFD) reactor. The MFD was constructed from a flexible, plastic microcapillary film (MCF), comprising parallel capillary channels with diameters in the range of 80−250 μm. MCFs were wound into spirals and heat treated to form solid discs, which were then capable of carrying out continuous flow reactions at elevated temperatures and pressures and with a controlled residence time. Three reaction schemes were conducted in the system, namely the synthesis of oxazoles, the formation of an allyl-ether, and a Diels−Alder reaction. Reaction scales of up to four kilograms per day could be achieved. The potential benefits of the MFD technology are compared against those of other reactor geometries including both conventional lab-scale and other microscale devices.

Introduction

Most organic chemistry performed in research laboratories is currently conducted batch-wise in glass apparatus. However, the emergence of micro- and meso-fluidic devices presents the opportunity to carry out continuous or semi-batch reactions for small quantities of product in a fully confined and controlled environment.[1,2] Current microreactor technologies include chip-based devices made from glass, metal, silica, polymers or ceramics, individual or bundled capillaries, micro-mixer units, micro-falling films, microbubble columns, single-/tri-channel thin-film microreactors, or lab-scale packed bed assemblies.[3−9] A key benefit of microreactors for pharmaceutical applications in particular is the ability to increase the reactor through-put by a simple numbering-up of the basic flow components, as opposed to a classical scale-up approach, which often requires several design steps, starting from normal laboratory scale via a pilot plant to the final production scale. The scale-up of flow reactors can either be an internal numbering-up, having for example, a series of microchannels in one device, or externally, by running several devices in parallel. A crucial problem occurring during flow reactor scale-up is the unequal or maldistribution of feed streams into large numbers of microchannels. This problem in combination with other practical issues when processing larger fluid streams results in some microreactor designs being more suitable for larger scale than others.[10]

This paper describes a novel plastic microcapillary reactor that can be used for organic synthesis and that also shows good potential for process scale-up due to the presence of a large number of microchannels per device (19 at present) and the simplicity of arranging several of these devices to function in parallel. The reactor is made from a thermosetting plastic film which is manufactured by a continuous extrusion process.[11] The manufacturing costs are low, offering the potential to use these microreactors as disposable or recyclable units. This is a key benefit, particularly in applications where cross contamination between samples needs to be avoided. Furthermore, issues relating to cleaning and sterilisation of microfluidic components are eliminated, thus removing what is usually a time-consuming and complex procedure. In this paper both the design of the apparatus and its performance during three chemically different reactions are described.

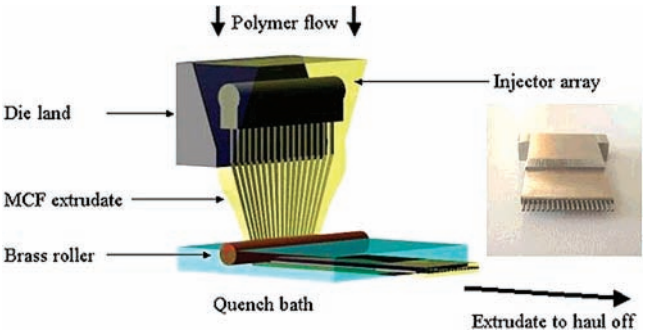

Figure 1. **Schematic diagram of an MCF extrusion line.**

Manufacture of a Microcapillary Flow Disc (MFD) Reactor

MFDs are made from a plastic microcapillary film (MCF) which is manufactured by an extrusion process called gas-entrained polymer extrusion.[11] Here a polymer melt is extruded over an array of injectors that are placed near the exit of a rectangular extrusion die. Figure 1 shows a

* To whom correspondence should be addressed. E-mail: svl1000@cam.ac.uk.
† Department of Chemical Engineering.
‡ Department of Chemistry.

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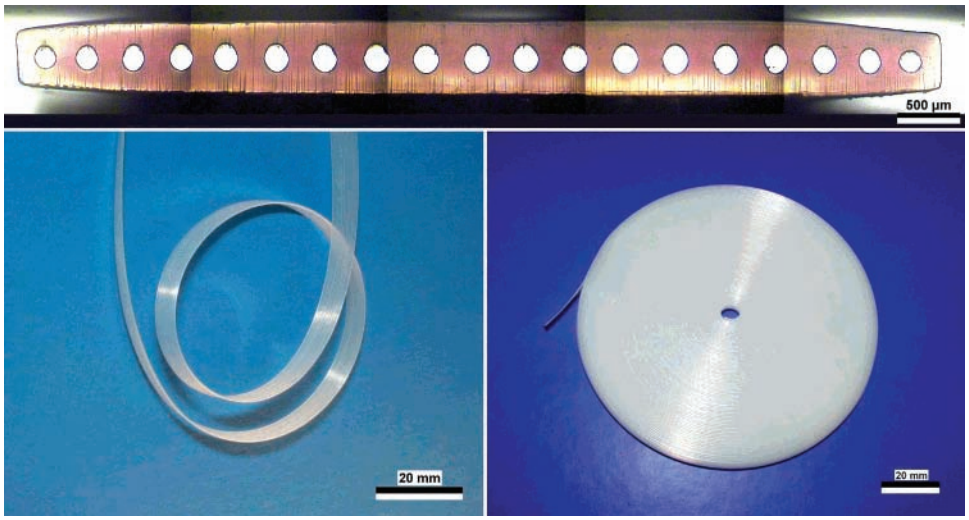

Figure 2. **Photographic images of an MCF containing 19 capillaries: microscope image of MCF cross section (top), side view of a single film (bottom left), and single spiral MFD (bottom right).**

schematic diagram of the end of the extrusion line.

The injectors are connected to ambient air conditions, and the flow of polymer melt over the injectors causes air to be entrained into the polymer, thus forming an array of continuous capillaries. The extrudate leaving the die passes either through a quench bath or over a set of chilled rollers to solidify the polymer melt. The quenched extrudate is then drawn away from the process by means of a haul-off device. Such postprocessing enables a significant degree of variation to be defined for the final capillary channel diameters matching the device dimensions to the final application.

A wide range of thermoplastic materials are suitable for this extrusion process. To date, MCFs have been successfully manufactured from polymers such as linear-low-density polyethylene (LLDPE), polypropylene (PP), polyurethane (PU) and poly(vinylalcohol) (PVA) amongst others.[11,12] The heat-transfer performance of MCFs has been characterised in earlier work,[13] and heat-transfer coefficients were found to be as high as 1.4 kW m^{-2} K^{-1} (per unit area) or 34.7 MW m^{-3} K^{-1} (per unit volume), despite the thermal conductivity of the polymer matrix being roughly 1000 times lower than those of good heat-conducting metals. This allows good temperature control of any continuous-flow chemical reaction to be carried out inside MCFs. Within the scope of this work, MCFs fabricated from LLDPE and having channels between 180 and 220 μm in diameter were tested. The thickness of such a film is 0.58 mm, its width 1.38 mm. For these capillary diameters the flow within each channel will be essentially laminar.[13]

The MCFs are coiled to form MFDs, which have a suitable reactor length (typical length between 5 and 40 m) to carry out liquid-phase organic synthesis with reaction times of between a few minutes and several hours. Figure 2 shows a microscope image of an MCF cross section, the film from the side, and an MFD. Using a hot press and a brass/aluminium mold the MFD is heat melded at temperatures

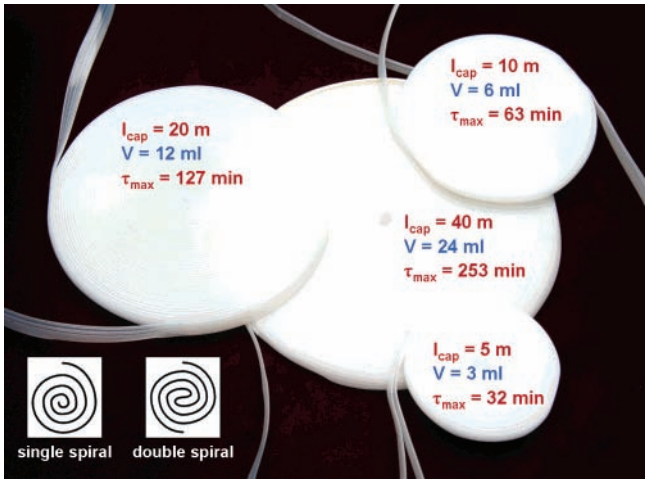

Figure 3. **Different sized, double-spiralled MFDs including specifications: capillary length l_{cap}, volumetric hold-up V, maximum residence time at a flow rate of 0.1 mL/min τ_{max}. (Bottom left) Schematic illustration of two different configurations, single and double spiral.**

close to the melting point of the polymer (for LLDPE, at 116 °C) to form a solid, compact disc. The operating temperature for this process had to be chosen carefully in order to get sufficient bonding between adjacent layers of MCF without melting the capillary microstructure. The MFD can be wound up into different configurations, illustrated in Figure 3, a single or a double spiral. In the first of these arrangements the reaction mixture enters the disc radially at the circumference and exits at the centre as a single concentric spiral (see Figure 2). For the double helix disc, both inlet and outlet are radially positioned (see Figure 3). A set of differently sized MFDs are shown in Figure 3.

A simple way of combining two liquid reaction feed lines outside the MFD is to use a commercially available T-mixing piece. The three reaction case studies reported in this paper employed this configuration to mix two solvent streams carrying the reagents and their feed into the MFD. An alternative way of mixing two feed lines using an MCF

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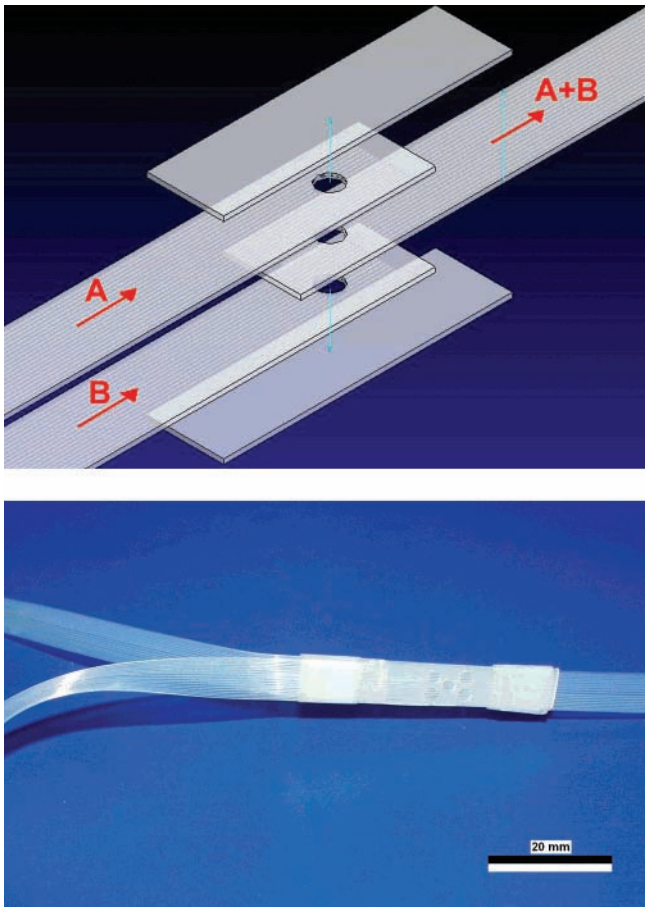

Figure 4. **Schematic diagram and photographic image of an MCF mixing cell (A and B are representing the two feed lines).**

mixing cell is shown in Figure 4; this approach has also found application in different chemical processes within our laboratories.

The MCF mixing cell is made up of three films which are heat melded together, with their central capillaries being connected. The mixing cell is manufactured in five steps. First the entrances of three MCFs are heat sealed by melting up the final 1−3 mm at the cut phase of the film. In a second step these three films are heat pressed at a controlled temperature for 5 min. This creates a solid gapless joint between the flat surfaces of the MCF, without melting-up or deforming the capillaries inside the films. After cooling, one or a series of holes are punched into the unit perpendicular to the capillaries, connecting the central microchannels in all three MCFs. In a second heat treatment, blanks are layered on the top and bottom of the mixing holes, using the same settings as in the first layering step. In a final step, a piece of heat-shrink tubing, made from polyolefin, is shrunk over the whole unit to seal the system. The mixing cell represents a space-optimised solution of joining two fluid streams together and feeding them into one MCF, minimising the fluidic pathway between the mixing point of two phases and the entry into the reactor channels, and with a minimal use of material.

The connection between an MFD and standard microfluidic tubing or pumps is made up of a four-part assembly. Figure 5 shows an MFD reactor with eight discs operating in parallel. The fluid distributor and the MFD inlet connectors are shown in detail.

The inlet connectors are made up of standard microfluidic fittings. The end of the MCF coming from the disc is turned into a cylindrical geometry, which is placed between a male nut and a male−female adapter and sealed at the circumference with a ferrule (see Figure 5 top left). The cylindrical MCF end is prepared in two heat-melding steps. First the MCF is wrapped helically around a polyolefin cylinder, which has a lower melting point than that of the LLDPE of

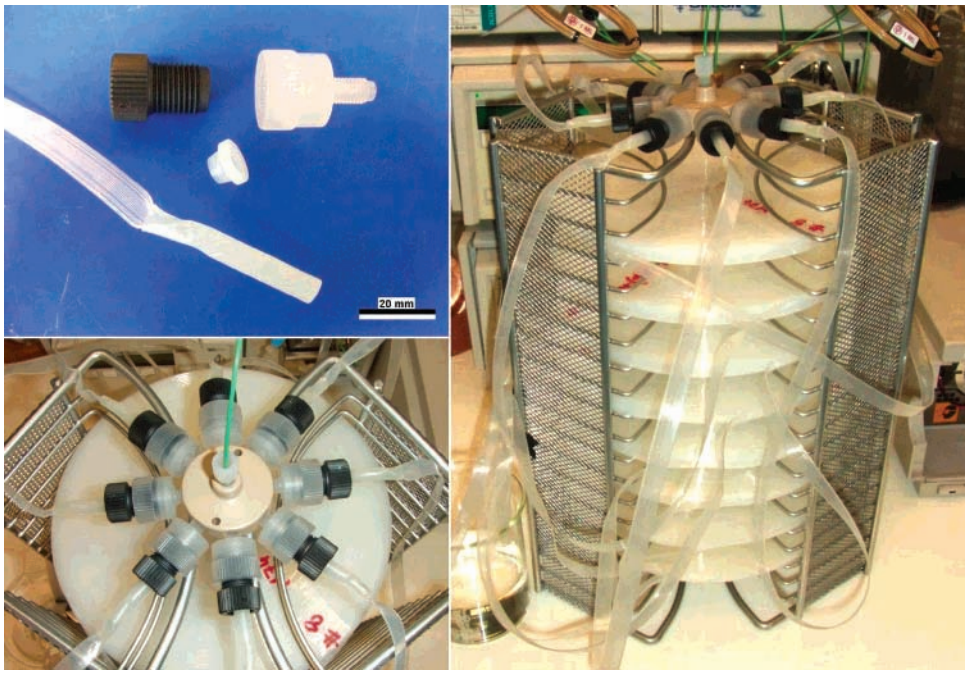

Figure 5. **MFD reactor operating eight discs in parallel. MCF connector at the inlet of each disc, consisting of a cylindrical MCF inlet unit, two plastic fittings, and a plastic ferrule (top left), side view of the MFD reactor (right), eight-fold manifold acting as fluid distributor on top of reactor (bottom left).**

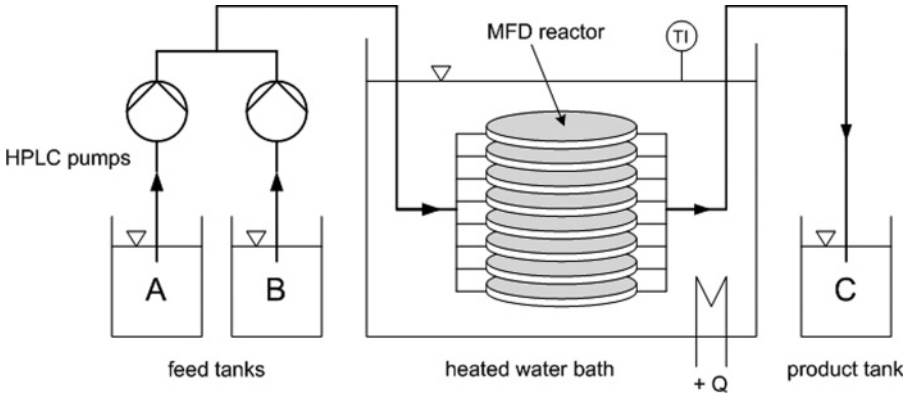

Figure 6. **Experimental set-up of an MFD reactor for organic synthesis (constant-feed mode).**

the MCF, and is heat treated at 116 °C for 5 min. The operating temperature of the second step was chosen to be in a range below the melting point of the MCF (∼120 °C) and above the shrinking temperature of the heat-shrink tubing (∼100 °C) and melting temperature of the inner core (∼115 °C). This guarantees that a nearly cylindrical unit with sufficient homogeneity is formed when the heat-shrink tubing compresses the other two components to the point where the molten inner core creeps into the gaps between the helical coils of the MCF. After cooling, the unit is cut with a razor blade perpendicular to its middle axis, creating a front face which contains the openings to all 19 capillaries in a concentric ring around the middle axis.

Eight of these connectors are screwed into an eight-fold fluid splitter. The discs are mounted in a rack, with the eight outlets being bundled and leading to a collection reservoir. The reactor assembly can be submerged into a heated water bath in order to regulate the reaction temperature in the MFDs. The maximum flow rate is 41 mL/min (2.5 L/h), only limited by the pressure build-up inside the MFDs. In the experiments presented in this work, the maximum operating pressure was restricted to 20 bar, although the MCFs can have a pressure rating in excess of 50 bar (depending on the channel diameter and the amount of polymer matrix surrounding the capillaries). Figure 6 shows a flow diagram of the MFD reactor arrangement.

Two feed solutions, A and B, are pumped from reservoirs using Gilson 307 HPLC pumps fitted with 10-mL heads and are mixed in a T-piece, which is situated inline after the pumps. The reaction temperature is controlled via the water bath temperature. Due to the relatively small flow rates through the microcapillaries, the reaction mixture achieves the temperature of the water bath quickly after entering the discs, which means the reactor operates quasi-isothermally.

The reactions can be run in two different modes: (1) continuous feed mode or (2) "slug flow" mode. In the first case, both feed solutions are fed simultaneously into the reactor as a continuous stream until the experiment is stopped and the pumps are switched off. Afterwards the reactor is flushed with pure solvent. In the second case, a slug of each feed solution (usually 1 mL of each) is injected with a Gilson 819 injection module into a constant solvent stream which is provided by the HPLC pumps. The slugs are mixed in the T-piece, travel down the reactor, and are collected at the outlet. Only the reaction mixture is collected. The solvent that emerges before and after the reaction plug is separated. The latter mode is used when processing small analytical quantities or testing reaction conditions, using only one MFD at a time.

Results and Discussion

Three different, but commonly used, reactions were chosen to validate the MFD technology. These included heterocyclic ring formation, simple phenolic allylation, and a Diels−Alder reaction. The reactions were performed on different scales ranging from a test run, equivalent to 0.5 kg per day, through to a full capacity of 4 kg per day. The objective in these reactions was to achieve both high conversion and purity of the product in a reliable fashion using a device capable of operating across a broad range of scales.

In the first of these reactions, the formation of 4,5-disubstituted oxazoles was investigated since these heterocyclic rings are prevalent in many drug substances and agrochemicals.[14] This system was also selected as its feasibility had already been shown in the preparation of a small collection of oxazoles using a modular flow reactor[15] whereby acid chlorides were reacted with enolisable methylene isocyanides.[14] In these experiments reagents were mixed on a microfluidic 1-mL glass chip with a serpentine microchannel at 60−100 °C followed by base-catalysed cyclisation and scavenging of excess starting material with immobilised reagents placed in prepacked glass tube reactor cartridges (packed bed columns). In work reported here a single 19-capillary MFD with a channel length (l_{cap}) of 40 m and a flow rate of 0.15 mL/min using acetonitrile as solvent was optimised to react ethyl isocyanoacetate **1** with 3- or 4-substituted benzoyl chlorides **2** to give an intermediate *C*-alkylated product **3** at ambient temperature over a 2-h residence time. The intermediate was not isolated but was allowed to pass through a polymer-supported base (PS-BEMP, 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene) in the form

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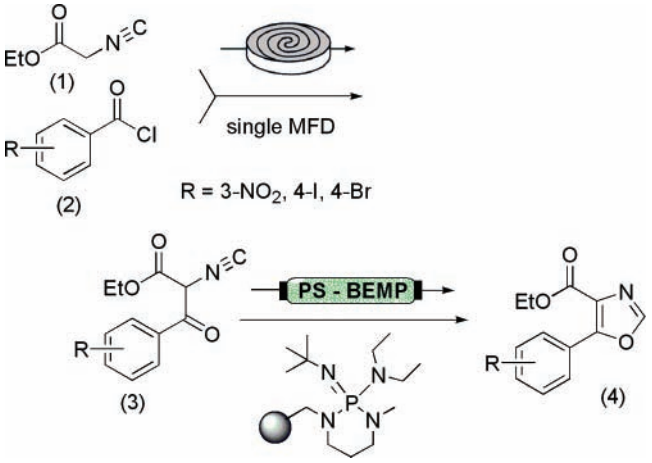
Scheme 1. **Formation of 4,5-disubstituted oxazoles**

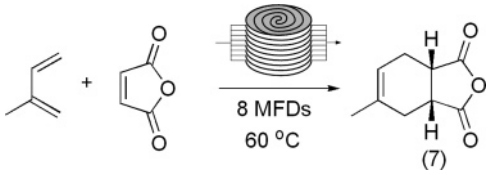


of a packed glass tube cartridge to effect cyclisation to the oxazoles **4** (Scheme 1). The conversion for this transformation was between 74 and 100%, and product work-up simply consisted of a solvent removal step. To achieve similar conversion rates on a glass chip with a total volumetric hold-up of only 1 mL, and therefore a limited residence/reaction time of ~10 min (using the same fluid delivery system) the system had to be heated up to 60 to 100 °C,[15] whereas the MFD could be operated at ambient temperature.

For the second series of experiments using MFD reactors a typical alkylation reaction was employed. There is an inherent toxicity associated with alkylating agents; also their reactions often occur with an exotherm in batch reactors, thus necessitating careful containment and temperature control. However, in flow mode using an MFD both containment and heat-transfer difficulties are minimised. A medium-scale flow reactor using eight MFDs (l_{cap} = 40 m) running in parallel at 4 mL/min gave an overall output of 0.365 g/min or an aggregated 0.526 kg/day of final product following aqueous extraction and solvent removal. Salicylaldeyhde **5** was alkylated with allyl bromide using DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as a base to remove HBr, thus giving the ether adduct **6** (Scheme 2). The rapid heat transfer from the MFDs by simple natural convection in air easily contained the exothermic process by operating at room temperature without any cooling system. In batch mode this reaction rapidly led to reflux of the volatile and toxic alkylating agent allyl bromide which therefore needed special containment. The product work-up consisted of an aqueous wash in order to extract the base out of the product phase. This was carried out either in batch, using standard lab glassware, or continuously, by using Syrris FLLEX flow liquid−liquid extraction unit. After solvent removal, the final product was isolated with a >99% conversion in quantitative yield.

Finally, we studied a Diels−Alder reaction using again eight parallel MFDs (l_{cap} = 40 m) running at 60 °C. Temperature was controlled by simple emersion of the MFDs in a heated water bath. This reaction was selected owing to its usefulness in synthesis programs, leading as it does to reasonably complex architectures by a concerted process from simple chemical inputs. In this experiment the volatile diene, isoprene, was reacted with maleic anhydride as the dienophile to give the product **7** (Scheme 3). The conversion for this process using eight parallel MFDs was >93%; in isolated yields, between 85 and 98%. This could be achieved using flow rates between 2 and 6 mL/min. When the reactor was working to full capacity, namely eight parallel discs running at a flow rate of 6 mL/min, an output of 2.73 g/min or 3.93 kg/day of the final crystalline product **7** following solvent removal was readily achieved. In comparison to these experiments, the reaction was carried out in a batch glass vessel with the same concentrations and under the same conditions. Here, conversion rates of 91−96% and a yield of 89−90% were achieved.

Scheme 3. **Diels−Alder reaction**

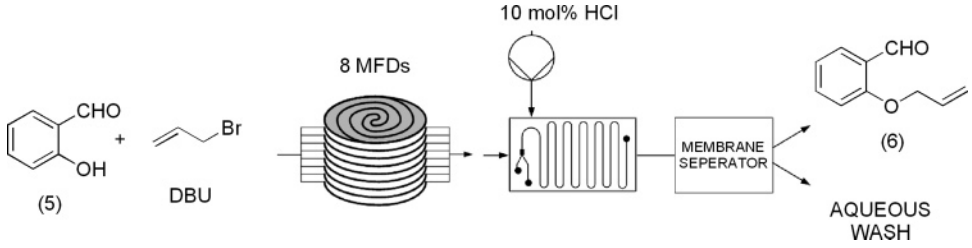


Summary and Conclusions

Within this paper we have demonstrated that plastic microcapillary films (MCFs) can be simply manufactured into microcapillary flow discs (MFDs) that form an effective platform for a range of continuous flow reactions. Each MFD had 19 parallel channels, and in one reactor configuration, eight MFDs were operated in parallel, constituting 152 capillaries with a combined length of over 6 km, providing chemical outputs of up to 4 kg per day. It is worth highlighting that this number of discs is not the limit of the current system, and both lower and higher volumetric throughputs could easily be achieved.

MFDs provide a potentially low-cost solution for micro- and mesoscale flow chemistry.[16] With the proof of concept reactions carried out in this work we have demonstrated the viability of plastic MFDs for use in organic synthesis.

Scheme 2. **Synthesis of an allylic ether using eight parallel MDFs and with continuous aqueous extraction**



Additionally, the low manufacturing cost of the device provides the option to use it as a disposable component, despite the fact that the MFDs exhibited sufficient robustness to enable extended and repeated usage. MFDs are able to operate at elevated pressure, provide excellent temperature control and fast heat transfer, and can offer a controlled residence/reaction time between seconds and hours.

MFDs can sustain higher pressures than standard laboratory glassware reactors. The small dimensions of the system mean that pressurised flows within the MFD can be generated due to the high flow resistance of the microchannels, thus yielding beneficial effects in terms of higher boiling points, greater solubility, and higher diffusion rates. The high surface/volume ratio has the potential to be exploited in reactions using functionalised capillary walls, ideal for the immobilisation of reagents, catalysts, and scavengers.[17] The melt-extrudable polymers, polyvinyl alcohol (PVA) and polystyrene (PS), are suitable materials for the preparation of MFDs with functionalised capillary surfaces. Their development is currently under investigation. The use of polymers such as polyethylene (PE), fluorinated ethylene propylene (FEP), or perfluoroalkoxy polymer resin (PFA) which are relatively opaque to microwave irradiation would enhance flow microwave chemistry applications. Preliminary experiments using LLDPE MCFs as a continuous-flow system within a focused laboratory microwave unit (Emrys Optimizer) have shown promise. However, a disadvantage of MFDs is their low thermal stability. The fact that they are made from thermoplastics will inevitably limit the temperature range of application for reactions at typically below 150 °C. Solvent resistance of the MCF matrix might also be an issue for certain polymers. However, tests with LLDPE films, which were used within the three case studies of this paper, have shown a good resistance to many commonly used solvents, such as ethers, alcohols, acetonitrile, DCM, and toluene. MFDs made from fluorinated polymers, such as PFA or FEP, would offer sufficiently high solvent stability for almost all organic processes.

With the experiments described in this article, we have shown that MFD technology has certain strategic advantages over other microreactor designs such as longer reactor length (leading to longer reaction times) and its low manufacturing costs. Although in the above experiments all the parallel capillary tubes have been used to process the same chemical inputs, in principle each capillary could function as an independent reactor. We believe that the evolution of such a system is poised to have a considerable impact on chemistry synthesis programs in the future.

Experimental Section

Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without further purification. ^{1}H NMR spectra were recorded on a Bruker Avance DPX-400 spectrometer with residual chloroform as the internal reference ($\delta = 7.26$ ppm).

Oxazole Formation 4. Three sets of feed solutions were prepared for the synthesis of three different oxazoles: (a) 4-(3-nitro benzyl)-5-(ethylaceto)oxazole ethyl isocyanoacetate **1** (0.1 mol/L in MeCN), 3-nitrobenzoyl chloride **2** (0.125 mol/L in MeCN); (b) 4-(4-bromobenzyl)-5-(ethylaceto)oxazole ethyl isocyanoacetate **1** (0.5 mol/L in MeCN), 4-bromobenzoyl chloride **2** (0.5 mol/L in MeCN); and (c) 4-(4-iodobenzyl)-5-(ethylaceto)oxazole ethyl isocyanoacetate **1** (0.1 mol/L in MeCN), 4-iodobenzoyl chloride **2** (0.1 mol/L in MeCN). A 1-mL sample of each solution was simultaneously injected into the two feed lines, mixed in a T-piece, and fed into the MFD. An Omnifit 0.34 mL-glass tube cartridge was filled with 0.3 g of PS-BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene) and put in line following the MFD. The total flow rate through the reactor was set to 0.19 mL/min, resulting in residence times on the MFD of 119 min. The reactor set-up was operated at ambient temperature. The product solution which was collected at the outlet of the packed-bed column was removed on a VapourTech V10 solvent evaporator. ^{1}H NMR spectra were taken of the white crystalline product using d_3-chloroform as a solvent, leading to the following conversions and yields: (i) 4-(3-nitrobenzyl)-5-(ethylaceto)oxazole: quantitative conversion, 99% yield; (ii) 4-(4-bromobenzyl)-5-(ethylaceto)oxazole: 75% conversion; and (iii) 4-(4-iodobenzyl)-5-(ethylaceto)oxazole: quantitative conversion.

Salicylaldehyde Allyl Ether 6. Two feed solutions were prepared, (1) salicylaldehyde **5** (73.26 g; 2 mol/L) and DBU (185.16 g; 4 mol/L) in a total volume of 300 mL of MeCN and (2) allyl bromide (145.20 g; 4 mol/L) in a total volume of 300 mL of MeCN. The two feed solution streams were pumped into the reactor and continuously mixed in a T-piece before being fed into the eight MFDs running in parallel. The total flow rate through the reactor was set to 2 and 4 mL/min, resulting in residence times on the MFD of 113 and 57 min, respectively. The reactor was operated at ambient temperature. An aqueous extraction was carried out on the product solution in order to remove salt and excess base from the product stream. This was either carried out in batch, using standard laboratory glassware, or in continuous mode, using a flow liquid−liquid extraction set-up. For the latter, the organic product solution was mixed on a glass microreactor chip (Syrris 274 μL) with an equal amount of aqueous HCl (10 mol %) and then fed into a membrane separator (Syrris FLLEX) to separate both phases again. Two HPLC pumps (Knauer K-120) provided the flow for this set-up. The flow rates were set to a maximum of 1.5 mL/min for each line in order to achieve a sufficiently good separation. Afterwards the solvent was removed on a VapourTech V10 solvent

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evaporator. ^{1}H NMR spectra were taken of the solvent-free liquid product using d_3-chloroform as a solvent, leading to the following conversions, yields, and outputs: (i) reaction run at 2 mL/min: 99% conversion, in quantitative yield, 0.183 g/min equating to 0.263 kg/day output and (ii) reaction run at 4 mL/min: 99% conversion, 0.365 g/min equating to 0.526 kg/day output.

Continuous Flow Process: 3a,5,7a-Trimethyl-3a,4,7,-7a-tetrahydro-isobenzofuran-1,3-dione (7). Two feed solutions were prepared: (1) maleic anhydride (264.76 g; 9 mol/L) in MeCN (300 mL) and (2) isoprene (245.24 g; 18 mol/L) in MeCN (200 mL). The two feed solution streams were continuously mixed in a T-piece and then fed into one MFD or the full complement of eight MFDs running in parallel. The total flow rate through the reactor was set to either 2, 4, and 6 mL/min, resulting in residence times on the MFD of 113, 57, and 28 min, respectively. The reaction temperature was set to 60 °C by immersion of the MFD unit in a heated water bath. Afterwards the solvent was removed on a VapourTech V10 solvent evaporator. ^{1}H NMR spectra were taken of the solvent-free crystalline product using d_3-MeCN as a solvent, leading to the following conversion rates, yields, and outputs: (i) reaction run at 2 mL/min: 93% conversion, 85% yield, 0.73 g/min equating to 1.05 kg/day output, (ii) reaction run at 4 mL/min: 93% conversion, 90% yield, 1.50 g/min equating to 2.16 kg/day output, and (iii) reaction run at 6 mL/min: 93% conversion, 98% yield, 2.73 g/min equating to 3.93 kg/day output.

Batch Process: 3a,5,7a-Trimethyl-3a,4,7,7a-tetrahydro-isobenzofuran-1,3-dione (7). Maleic anhydride (4.41 g), isoprene (6.13 g) in MeCN (10 mL) (the same concentrations as for the continuous process) were stirred in a 20-mL glass vial at 60 °C. Samples were taken after 30, 60, and 120 min and analysed as described earlier. From the ^{1}H NMR spectra, the following conversion rates and yields could be determined: (i) after 30 min, 91% conversion, (ii) after 60 min, 96% conversion, and (iii) after 120 min, 96% conversion, 89% yield.

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