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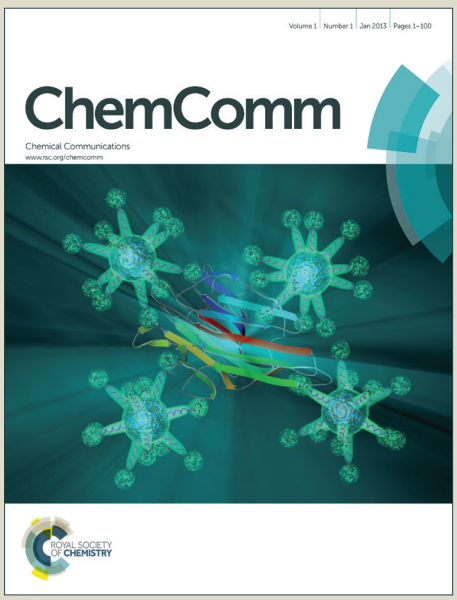

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Novel Microfluidic Approach for Extremely Fast and Efficient Photochemical Transformations in Fluoropolymer Microcapillary Films

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The unique optical properties of the fluoropolymer microcapillary film (MCF) material combined with the extremely fast photoinactivation of Herpes HSV-1 virus, and photodegradation of dye, diclofenac and benzoylecgonine in the MCF array photoreactor, demonstrate a new flexible and inexpensive platform for rapid photochemical transformations, high-throughput process analytics and photochemical synthesis.

Photochemical transformations including the treatment of fluids with ultraviolet light especially of wavelength lower than 280 nm (UVC) has been in practice for many decades, with the first publication reported by NIH in 1949.[1] Since then, several studies have shown that UVC is very effective in e.g. the inactivation of bacterial cells and viruses particles,[2] the photodegradation of pharmaceuticals and other contaminants of concern,[3] and the photochemical synthesis of species.[4] However, the range of commercial products and applications to be found nowadays based on photochemical transformations is very limited. We believe that this is due to limited understanding of photoreactor design, unclear scale-up methods, the optical limitation of the reactor materials and the very short light penetration depth in opaque fluids. The reported photoreactor designs vary from e.g. thin-film or falling film reactors, bubble columns with concentric lamps and tubular reactors[3,5] based on large-bore (> 5 mm in diameter) glass or plastic tubing. In all cases, the radiation field across the fluid is highly heterogeneous and the region with intense light irradiance is usually limited to a very thin region close to the transparent wall of the photoreactor.[6] To mitigate this effect, current design requires methods for promoting significant radial mixing e.g. by promoting turbulence using mixers[7] or Dean vortices.[8] Consequently, *current photoreaction systems are intrinsically flawed* since fluid-dynamics and radiation field are highly heterogeneous and photochemical processes are difficult to predict and to scale-up.

In this study, we present a novel microfluidic system for controlled, extremely fast, and efficient photochemical transformation of chemical and biological species. The microcapillary film (MCF) photoreaction system (Fig. 1) is made of a flat fluoropolymer ribbon containing an array of microcapillaries running along it, usually in the range of 10 μm up to 1 mm internal diameter, which are irradiated by a source of light. The MCF was produced by Lamina Dielectrics Ltd (Billingshurst, West Sussex, UK) from Teflon® FEP (Dupont, USA) using a novel melt-extrusion process.[9]

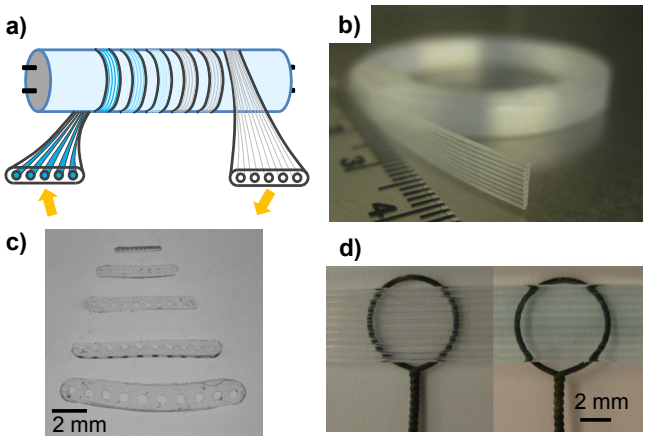

Fig. 1. Overview of fluoropolymer MCF microfluidic technology. a) One possible setup for use in photodegradation of fluids using a tubular lamp and small bore MCF material wrapped around the bulb. b) Flexible MCF, showing a parallel array of microcapillaries embedded in continuous flat plastic film. c) Microphotograph of the cross-section of 10 bore MCFs produced from Teflon® FEP, having a range of mean hydraulic diameters from 103 ± 7 μm (top) to 494 ± 7 μm (bottom). d) Outstanding optical transparency of fluoropolymer MCF.[10] The left hand image shows capillaries filled with air, with background image optically distorted as a result of the significant difference in refractive index between air and the wall material. The right image show capillaries filled with a blue dye dissolved in water and no image distortion.

Six unique properties are exemplified in the MCF: (i) The MCF is fully transparent to visible and UV radiation, including UVC; (ii) The flat surface of the film (Fig. 1b) combined with the excellent optical transparency and low refractive index of fluoropolymers

(Fig. 1d) allows the irradiation of the entire volume of the fluid flowing in the microcapillaries with straight incident photon rays, without wall refraction effects (such effect is not realized in glass/quartz tubular photoreactors); (iii) The small capillary diameters permit operation under low optical thicknesses[11] (less than 0.1) with uniform irradiance of the flowing fluid (even for fluids that in conventional reactors appear to be opaque) and the capillary diameters can be fine-tuned to the incident light and its penetration depth (Fig. 1c); (iv) Fluid behaviour approaches the plug flow regime allowing a tight fluid residence time distribution at the reactor exit, and in consequence (in conjunction with (iii)), high reactants conversions and high products yield and selectivity; (v) The small capillary volumes results in extremely rapid photo-transformations of substrates which are complete in a matter of seconds, a result until now not attainable in other practical photoreactors; (vi) The flexible nature of the MCF make it easily scalable. We demonstrate these capabilities with a range of applications, including the fast photoinactivation of a highly contagious enveloped Herpes HSV-1 virus particles, the fast decolourization of a dye and the photodegradation of contaminants of emerging concern including a pharmaceutical compound (diclofenac) and a class I drug metabolite (benzoylecgonine, BLG). Microstructured reactors and microphotoreactors have been shown in literature to perform photochemical transformations and to outperform classical photoreactor designs,[12] but none of them could accomplish collectively the six unique properties of the MCF photoreaction system described here.

We have measured the fluid behaviour in a 10 bore Teflon® FEP MCF with different mean hydraulic diameters (d_h) as shown in Fig. 2a and 2b (materials and methods are detailed in ESI). The residence time distributions were performed by injecting a step of 1000 mg/l Blue Dextran 70 at a flow rate of 0.5 ml/min, and measuring real-time the absorbance in the whole set of 10 microcapillaries with an Actipix UV microfluidic monitor (Paraytec, York, UK) equipped with a 214 nm dichroic filter. The measured cumulative F-curves were remarkably sharp at high superficial flow velocity of u_{mean} = 42.0-100.0 mm/s for the whole array of microcapillaries in MCFs with distinct d_h. The dimensionless axial dispersion coefficient, *uL/D* estimated by fitting the experimental data to plug flow with axial dispersion model with open-open boundaries[13] ranged from 13.1 to 136.4 for a MCF with d_h = 103 μm, and between 14.0 and 42.0 for the larger bore MCF with d_h = 159 μm as summarized in Table 1.

Table 1 Axial dispersion coefficients measured on individual MCF microcapillaries. A value of *uL/D* of 50 and over shows near plug flow behaviour, with molecular dispersion sufficient to promote radial mixing and deliver narrow ranges of UVC exposure times

	uL/D	
Capillary	d_h = 103 ± 7 μm	d_h = 159 ± 12 μm
C1	51.8	14.0
C2	84.7	34.4
C3	130.2	40.4
C4	136.4	40.4
C5	134.1	37.3
C6	134.1	38.9
C7	122.3	42.0
C8	80.4	41.8
C9	22.6	38.4
C10	13.1	25.7

In general, the flow behaviour approached that typical for a plug flow reactor, with maximum values of *uL/D* about 3.2-fold larger in the smaller bore MCF. This is linked to the shorter time for radial diffusion in smaller diameter capillaries,[14] being proportional to the square of the distance according to the Stokes-Einstein equation for molecular diffusion.[15] The square of the d_h ratios between the two MCFs is ~3.4, therefore similar to the increase in *uL/D*, which reveals the importance of using small diameter capillaries in respect to consistent fluid flow performance. The broad distribution in *uL/D* values in particular at the edge capillaries is linked to the small variation in d_h for each microcapillary across the film; with pressure drop being proportional to d_h^4 small variations in d_h result in significant variations in flow distribution and mean residence time of the liquid across the whole set of microcapillaries. This effect can be minimized by improving the melt-extrusion process.

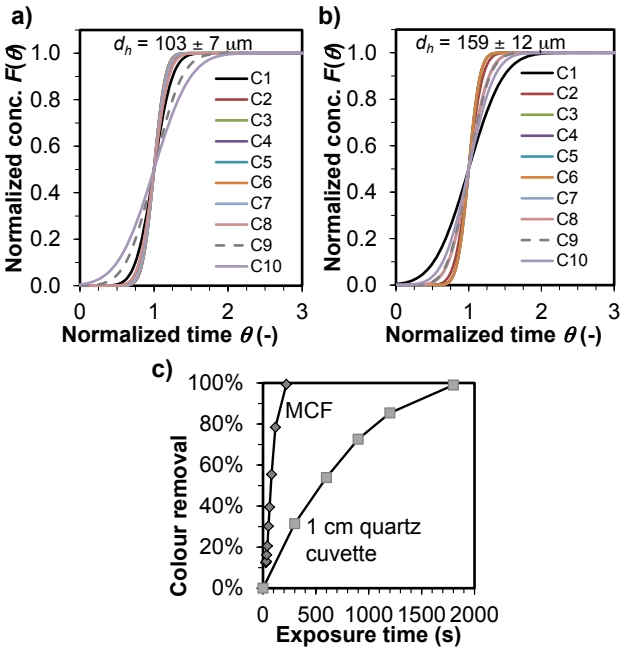

Fig. 2. Fluid hydrodynamics and colour removal in the MCF. In a) and b) the radial molecular diffusion distance in the MCF is very short, therefore the fluid reveals essentially plug flow behaviour as shown by the large normalized axial dispersion numbers, *uL/D* summarized in Table 1 for a) a 10 bore MCF with d_h = 103 ± 7 μm and b) a 10 bore MCF with d_h = 159 ± 12 μm. c) The small internal diameter of the microcapilllaries allows to fully irradiate all fluid streamlines in the whole volume of the fluid, consequently the UVC photobleaching in a 10 bore MCF with d_h = 192 ± 12 μm yields a 10-fold increase on the rate of removal of 20 mg/ml indigo carmine (k = 0.0155 s^{-1}, R^2 = 0.9777) compared to a 1 cm thick quartz cuvette (k = 0.0016 s^{-1}, R^2 = 0.9879) based on a lamp irradiance of 17.9 mW/cm^2 for both MCF and quartz cuvette. The exposure time for the MCF in (c) was adjusted by varying the flow rate between 0.2 and 2.0 ml/min.

The UVC photobleaching of indigo carmine dye in the MCF was 8.1-fold faster than in a 1 cm width quartz cuvette (Fig. 2c), although the incident photon flux was identical (17.9 mW/cm^2) in both reactors. A linear plot of $\ln(C/C_0)$ versus time returned a 10-fold increase in the first-order kinetic constant, k. The absorption coefficient at 254 nm of the 20 mg/l indigo carmine aqueous solution was 42.5 cm^{-1}, yielding a light penetration distance of 47 μm for 1 $\log_{10}$ unit (i.e. 90%) reduction in transmitted UV-light through the solution. Consequently, in the 1 cm width cuvette a large fraction of the fluid volume was not irradiated at one time, and consequently the volumetric reaction rate dramatically decreased. This is a common occurrence in conventional photoreactors. In the MCF with the small diameter capillaries the entire volume is successfully irradiated,

consequently the photodegradation reaction rate significantly increased.

We further applied the MCF to demonstrate the extremely fast photodegradation of a range of molecules and inactivation of biological material. Firstly, we spiked a 10% fetal calf serum (FCS) with ~10^7 PFUs of highly infective Herpes virus, HSV-1, and infused the infected opaque solution (Abs_{254} = 13.9 cm^{-1}) through a 10 bore MCF. A 3 seconds exposure to UVC from a 5W PL-S5 TUC compact 253.7 nm germicidal lamp (Lamp Specs, Tolworth, UK), arranged longitudinally parallel to the MCF resulted in ~3 log_{10} units reduction factor (RF) in virus titre, and a maximum of 3.4 log_{10} units with less than 10 s exposure, corresponding to 99.96% of virus particles effectively inactivated. The plateau in data in Fig. 3a is linked to the tailing effect associated with aggregation or resistance virus subpopulations.[16]

We further investigated the kinetics of UVC bleaching of indigo carmine at a high concentration (100 mg/l, Abs_{254} = 212.6 cm^{-1}) with MCFs of different bore diameters wrapped around a 8 W 253.7 nm tubular germicidal lamp (Germicidal G8T5, GE Lighting, Northampton, UK) (Fig. 1a) and found that MCF with smaller d_h outperformed those with larger d_h (Fig. 3b). In these experiments, the internal volume of the different MCFs in Fig. 3b was kept constant at 0.15 ml, by fixing the different exposed length, L to 1800, 756 and 518 mm for the large, medium and small bore MCFs, respectively. This is associated with more effective light penetration in smaller bore microcapillaries but also to sharper residence time distribution and smaller reactor volumes.

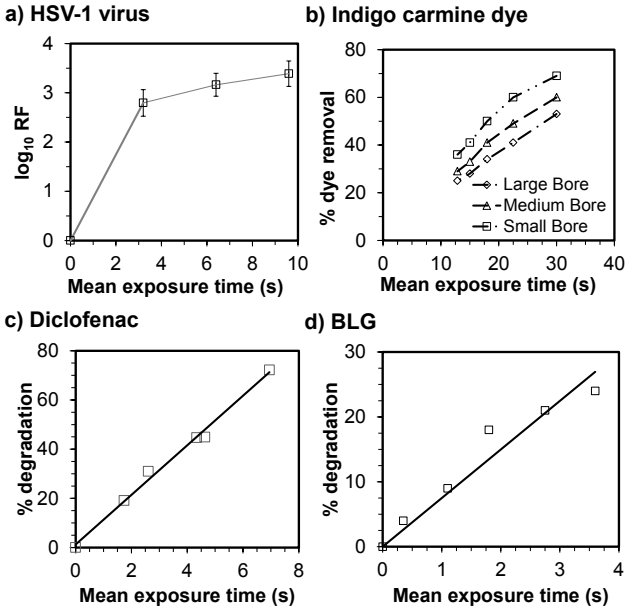

Fig. 3. UVC photodegradation processes in a 10 bore fluoropolymer MCFs. a) inactivation of enveloped Herpes HSV-1 virus particles in an optically thick solution in a MCF with d_h = 192 ± 12 μm, showing up to 3.4 log_{10} units of reduction factor (RF) in virus titre with less than 10 s exposure to UVC. b) Removal of 100 mg/l indigo carmine in water using MCFs with d_h = 192 ± 12 μm (large bore), d_h = 159 ± 12 μm (medium bore) and d_h = 103 ± 7 μm (small bore). c) Photodegradation of a pharmaceutical, diclofenac in a 192 ± 12 μm i.d. MCF. d) Removal of a contaminant of emerging concern, BLG with UVC and H_2O_2 in a 192 ± 12 μm i.d. MCF at pH 5.9 and H_2O_2:BLG molar ratio of 17.4. All experiments shown in a) to d) were carried out at a fixed u_{mean}, and the mean exposure time varied by changing the exposed length L of the MCF.

An area of increasing concern is water quality[17] and in consequence we investigated the photodegradation of selected contaminants of emerging concerns including diclofenac (a pharmaceutical, Fig. 3c) and BLG (the main phototransformation product of cocaine in water, Fig. 3d). As a result of the microfluidic approach adopted here, these compounds degraded in a matter of seconds, which is unprecedented in literature. By increasing the H_2O_2:BLG molar ratios up to 700, BLG conversions up to 95% were recorded within a mean exposure time of less than 2.5 s (results not shown). Complete degradation of BLG can also be obtained at smaller H_2O_2:BLG molar ratios by increasing the reactor length, although pressure drop increase would need to be considered. The photodegradation processes shown in Fig. 3b-3d revealed a first order kinetics, in theory typical of photochemical processes, however in practice often difficult to measure or obtain with current photoreactor designs because of the intrinsic dependence of reaction kinetics with secondary mixing, radiation field and fluid-dynamics. The inherent flexibility of the MCF material is ideal for fitting tubular or other light sources on a range of scales or for direct exposure to sources of radiation (e.g., sunlight).

We believe that this disruptive and inexpensive microreaction platform technology will provides new breakthroughs in the fields of analytical chemistry, photochemistry and photobiology since it minimizes the intrinsic volumetric heterogeneity of the radiation and fluid-dynamics fields encountered in conventional photoreaction systems, therefore allowing a higher degree of control of photochemical transformations. The MCF photoreactor opens new frontiers for studying phototransformations of emerging contaminants and controlled substances,[18] identifying transformation by-products, for the photochemical synthesis of chemical species,[4] and for designing photochemical units or disposable modules for downstream processing of biopharmaceuticals and plasma derived products. This is particular relevant for studying phototransformations (kinetics, reaction mechanisms, quantum yields) from very small volumes of highly-priced chemical compounds, metabolites or intermediates, which are currently unrealizable using other photo-irradiation systems. The liquid volumes used in the MCF are of the order of fractions of ml. This combined with improved reaction efficiency, products yield and selectivity results in reduced treatment cost, increased speed and safety.

The MCF photoreactor can also be easily scaled-up to suit the typical throughput of high added value biomanufacturing products, by increasing the internal diameter (Fig. 1c) and/or the number of microcapillaries. The photosynthesis, photodegradation and photoinactivation processes become fully scalable as the reaction kinetics of the photoprocess is decoupled from the radiation field (often invariant across the capillary cross section at optical thicknesses < 0.1, which are easily attainable in the MCF) and fluid-dynamics. The light penetration and fluid flow through the plastic MCF is fully predicted and governed by well-defined radiation and fluid-dynamics laws, in particular the flow is laminar, therefore the fluid velocity profile parabolic, and the radiation field (irradiance) fully described by Lambert-Beer' law. In addition, with small diameter microcapillaries, typically 1 mm or less and preferably 500 μm or less, molecular diffusion becomes significant further promoting the radial mixing of the fluid resulting in narrow range of residence time distributions across the fluid streamlines. Collectively, the above factors contribute to delivering superior photoreaction transformation products or efficient contaminant removal, which vastly exceeds the specifications of any other photoreactor design.

In summary, the unique optical properties of fluoropolymer MCF material combined with the extremely fast inactivation of HSV-1

virus particles, and photodegradation of dye, diclofenac and BLG herein reported in the MCF array photoreactor provides a breakthrough to explore the advantages of non-invasive and efficient phototransformations of uncommon and regulated substances in a simple, flexible and scalable microreactor format, with multiple applications from small scale kinetic characterization to full scale manufacturing using a single-affordable and semi-disposable microfluidic platform. For large-scale applications we envisage in near future extruding wider MCF films containing hundreds or thousands of microcapillaries embedded in a single fluoropolymer plastic sheet. When the MCF is coupled with advanced analytical mass spectrometry techniques, new frontiers in photochemistry and environmental science can be explored.

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Notes and references

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