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3D Printing of PEEK Reactors for Flow Chemistry and Continuous Chemical Processing†

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Chemically resistant parts for flow chemistry, with integrated mixing elements have been produced using the 3D printing process of fused filament fabrication, from poly(etheretherketone). Poly(etheretherketone) has greater chemical resistance than common fused filament fabrication materials such as acrylonitrile butadiene styrene, polypropylene, or even high-performance plastics like poly(etherimide), in addition to having superior thermal resistance and excellent mechanical strength. Printed reactors were demonstrated to be suitable for liquid-liquid extraction and flow chemistry and to be capable of withstanding pressures of at least 30 bar allowing superheated solvents to be used. Burst tests in simple geometries of 20 minute duration have indicated that increased operating pressures of up to 60 bar could be accommodated in future reactor designs. The ability to use fused filament fabrication for these reactors allows highly customisable, cost effective flow reactors and equipment to be fabricated on relatively inexpensive benchtop scale printers. X-ray microcomputed tomography was utilised to non-invasively image and verify the internal structure of the prints to ensure fidelity in reactor fabrication. This non-invasive method of equipment validation shows potential in helping to demonstrate regulatory compliance for bespoke additively manufactured components, for example in continuous pharmaceutical manufacturing where the methods and printer used in this work should be sufficient to produce, (continuous) manufacturing scale equipment.

1. Introduction

Additive manufacturing (AM), more commonly termed 3D printing (3DP), has been previously used by several groups to fabricate chemical reactors. Some of these have been batch reactors,[1,2] while others have been designed for use in flow chemistry.[3–5] The use of additive manufacturing theoretically allows for customised parts with as many inlets, mixers and spectroscopic monitoring points[6] as required, for the same cost as a simple block. In practice however, there are still limitations on the print resolution, part dimensions, and materials, which vary by AM technique.

Printing of metal parts has been demonstrated with simple, single inlet – single outlet[7] and more advanced multiple inlet reactors with integrated cooling jackets,[8] usable with chemicals that would destroy most plastics. Custom reactors produced by selective laser melting (SLM) are also offered by several companies.[9] Hybrid printing techniques such as ultrasonic additive manufacturing (UAM), which laminates metal foils and removes material with integrated computer numeric control (CNC) milling are also available, allowing mixed metal parts to be produced.[10] While AM has been used successfully to fabricate parts exhibiting with good chemical resistance and excellent heat transfer properties, a significant drawback of metal printing techniques however is the substantially higher cost of equipment and materials compared to other AM methods.

Printing techniques used to fabricate flow chemistry parts have predominantly been stereolithography (SLA) and fused filament fabrication (FFF). The chemical compatibility of reactors produced with these techniques is typically poor for polymers such as acrylonitrile butadiene styrene (ABS), polylactic acid (PLA), polycarbonate (PC) and polyamide (PA), with destructive swelling caused by contact with aldehydes and ketones in many cases and near uniformly poor tolerance of chlorinated solvents.

Printing by SLA or multi-jet modelling (MJM) may results in uncured resin or support material that must be removed once the print is complete, a process that is often difficult and may be near impossible for internal tubing of any great length. This

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difficulty is further enhanced by the integration of internal elements such as static mixers. The same issue is encountered with powder fusion techniques such as selective laser sintering (SLS) and SLM where unfused material remains in hollow spaces.

Improvements in the design of FFF printers along with the filament materials has facilitated the fabrication of leak tight chemical reactors. Rao *et al.* at UCL for example, demonstrated that FFF could produce polypropylene flow reactors that, while not pressurised, were stable under heating up to 150 °C.[11] Microfluidic chips in PLA have also been produced using FFF and also shown to tolerate up to 20 bar of pressure,[12] and using an inert atmosphere during the print allowed NMR 'cuvettes' for reaction monitoring to be printed from polyamide, as it allowed the nozzle temperature to be increased, leading to better layer adhesion and parts that could withstand 10 bar of pressure.[13] Commercial platforms for the manufacture of microfluidic chips are available, and claim to produce parts capable of withstanding up to 20 bar of pressure.[14] However, the cyclic olefin copolymer (COC) used is still limited in terms of chemical compatibility and temperature range.

Poly(etheretherketone) (PEEK) is a high-performance plastic with excellent mechanical strength, a high melting point and excellent chemical resistance. Many parts currently used in flow chemistry and analytical chemistry such as tubing, unions and wetted components within pumps are manufactured from PEEK. PEEK is also bio-compatible, allowing it to be utilised for applications such as cell culture or bioassays. Previously the use of additively manufactured parts, primarily with photocurable resins, for biological applications has encountered issues with cell toxicity.[15]

Additive manufacturing of PEEK parts has been previously performed using SLS[16] resulting in good mechanical strength. However, SLS tends to result in porous material suitable only for medical implants or non-wetted parts. In contrast to powder fusion techniques FFF can leave hollow spaces in parts with no post processing being required to remove residual material. The need for support structures within a build can be eliminated through careful design or choice of build orientation. This is particularly true for parts intended for laboratory scale flow chemistry which have only narrow diameter sections of 0.1-3 mm. This therefore allows for more complicated internal channels than would be possible with fusion or curing additive manufacturing techniques.

PEEK was first 3D printed using FFF by Valentan *et al.* in 2013.[17] It is a difficult polymer to 3D print with due to its high melting temperature and high viscosity.[17–19] Common FFF materials such as PP and ABS have printing temperatures between 220 °C and 260 °C, which is significantly lower than the 370 to 430 °C printing temperatures of PEEK.[18] Warping and delamination of layers is common in PEEK FFF parts due to thermal stresses as a result of the high printing temperatures. However, it has been shown that warping and layer delamination of the part due to these thermal stresses can be reduced by printing PEEK in a heated chamber with a high temperature (>150 °C) build plate.[18,20,21] This research has led to the production of printers with heated chambers specifically used to print high performance engineering plastics such as PEEK and PEI, though the number of these printers available is still limited and are considerably more expensive than standard FFF printers.

This study investigates the performance of FFF printed PEEK components incorporating integrated mixing elements capable of performing flow chemistry while under increased pressure and continuous purification *via* liquid-liquid extraction.

2. Experimental

2.1 Flow equipment

The pumps utilised for all tests were LD class dual piston HPLC pumps with 36 mL heads and a Hastelloy flow path (Teledyne Scientific Systems Inc., State College, PA, USA).

2.2 Part production

Flow reactor parts were designed in Autodesk Fusion 360 (Autodesk, San Rafael, USA) and printed using 1.75mm diameter PEEK filament on a Funmat HT FFF printer (Intamsys, Shanghai, China), according to the manufacturer instructions. This system has a build volume of up to 26 x 26 x 26 cm. The printed parts are subject to an annealing step after the print has completed, reducing inhomogeneity in the crystallinity of the PEEK and allowing strain relief, improving the mechanical strength of the pieces. Annealing was carried out following the printer manufacturer recommendations; the samples were placed in a furnace at 150°C for 1 hour, this was then increased

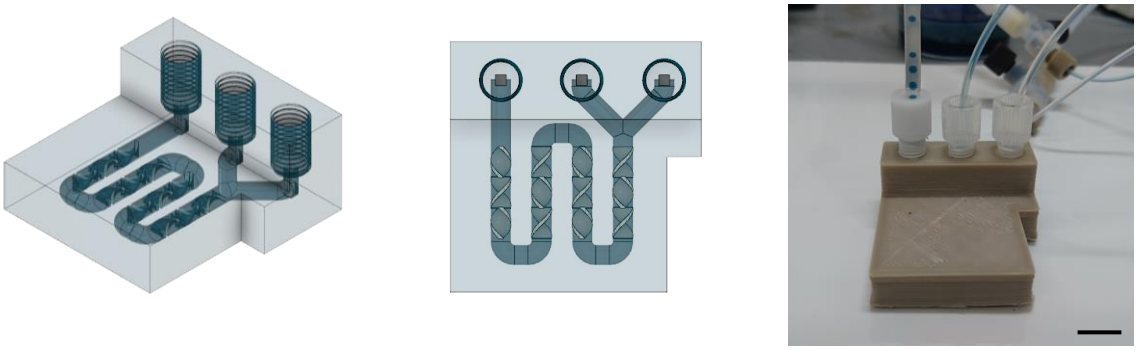

Figure 1. CAD image of the designed part and final printed piece. (Left) Orthographic view (Centre) Top view showing channel and mixer geometry (Right) Printed part. Scale bar is 10 mm.

to 250°C for 2 hours and the subsequently reduced again to 150°C for 30 minutes. The samples were then left to cool to room temperature. The pieces were designed with two inlet streams meeting at a Y shaped interface before encountering the mixing elements and exiting through a single outlet (Figure 1). The inlet ports were printed with 1/4”-28 unified fine thread (UNF) ports for connection with common flow chemistry fittings. These were cleaned with the appropriate tapping tool to remove artefacts. The printing of threads is important to avoid the production of large quantities of swarf generated during thread cutting, which can lead to blockages within the channels. The cutting of threads into FFF parts also places strain on the layers, potentially causing separation and damage.

The orientation of the inlet ports is also crucial due to the stress generated when fittings are tightened. For example, if printed layers are being laid down in the xy plane then the profile of the ports should also be in this plane, otherwise the part can split at the layers rendering the piece useless. This was encountered in initial designs and prompted the switch in inlet geometry (Figure 2).

The integrated mixers are of a helical, Kenics type design, fully joined to the tube wall. This design allows laminar mixing across a wide range of Reynolds numbers compatible with multi-phasic flows through by alternating blending of fluid in both the direction of helical elements through 180 ° turns in their initial alignment with every mixer element (Figure 3), and a pitch (mixer length/tube diameter) of 1.5. This arrangement exhibits excellent mixing efficiencies with low pressure drops and is widely utilised.[22,23] An FFF extrusion nozzle of 0.4 mm diameter was initially used first to produce mixer elements, with profiles of 0.42 and 1.2 mm. Examination of the mixers using an optical microscope demonstrated a high quality surface finish was obtained using the 1.2 mm profile, however some printing artefacts were noticed with the 0.42 mm profile (Figure 3). This is because the mixers were printed using a single extruded line, due to the diameter of the nozzle, whereas a mixer with a profile of 1.2 mm involved fabrication using three lines of material. These problems were largely resolved when the parts were printed with a smaller nozzle diameter, as the resolution of the mixers greatly improved.

Parts of up to 260 mm in the XYZ directions can be printed with this desktop based printer, which would be capable of direct fabrication of flow reactors compatible with manufacturing scale throughput for flow chemical processes in low volume applications, for example continuous pharmaceutical production.

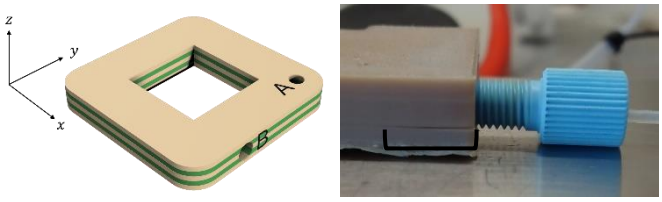

Figure 2. (Left) For the print orientation shown holes located at the position indicated by port B will resulted in layer separation on insertion of the threaded screw, this was not found when port A positioning with design shown in figure 1 was used. (Right) The effect of ports printed with a perpendicular profile to the build plane (extent of crack in reactor wall indicated).

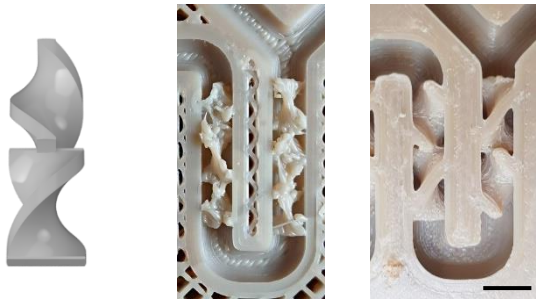

Figure 3. (Left) Intended internal mixer design (Centre) Printed mixer elements with 0.4 mm nozzle, 0.42 mm profile, 3 mm diameter (Right) Printed mixer elements with 0.4 mm nozzle, 1.2 mm profile, 4 mm diameter. Scale bar, for images in centre and right of figure only, is 5 mm.

2.3 X-ray micro computed tomography

X-ray Micro computed tomography (µCT) was used as a non-destructive method to examine the internal structure of the reactors after 3D printing. Scans were carried out at the UCD X-ray CT facility using the nanotom-m nanoCT system (Phoenix X-ray, GE Measurement and Control, Wunstorf, Germany). A voltage of 70 kV and a current of 100 µA were used, no filters were required and maintained to achieve a voxel size of 2.88 µm was achieved. Scan time was 9 mins and 1079 projection images were generated. Images were analysed reconstructed using VGStudio MAX 3.2 (Volume Graphics GmbH, Heidelberg, Germany).

2.4 Mixer performance

To test the mixer was achieving efficient mixing with multiple liquid phases a simple continuous flow liquid-liquid extraction (LLE) was performed at a range of flow rates. A 1.6 mM solution of benzoic acid in water was pumped, meeting an equal flow rate of ethyl acetate. Output from the mixer was collected and allowed to separate, with care taken not to allow further mixing within the collection vial. Aliquots from each phase were then immediately diluted with ethanol and the subsequent partitioning of benzoic acid into the aqueous and organic phases measured by UV spectrophotometry using a Shimadzu UV-1800 spectrophotometer (Shimadzu corp., Kyoto, Japan). A 3DP part of 4 mm channel diameter with 8 mixing elements (1 mL internal volume) were compared to a Y-mixer and a T-mixer of 4 mm I.D. without mixing elements to show the effect of inlet geometry. The length of tubing following these simple mixing junctions was the same as a printed part.

After this initial analysis two further iterations of the device were printed, with smaller channel diameters of 3 and 2 mm to allow a larger number of mixing elements (12 and 16, and 0.70 and 0.26 mL internal volume respectively) with the same pitch. These versions were tested at faster flow rates only to determine the effect of mixing element number on extraction efficiency at low residence times. More detailed analysis of multiphasic liquid contacting with static mixers has been conducted in literature.[24]

2.5 Pressure testing

A 4 mm channel part was tested for pressure resistance by pumping deionised water through though the PEEK reactor at 0.5 mL/min and spring-based back pressure regulators (BPR), to generate pressure in the system. Additional smaller test pieces were also tested throughout the development of the reactor with integrated mixers, these smaller pieces consisted of a single inlet and outlet either side of a short length of tubing within a printed block. For a successful print no leaks can occur from between the PEEK layers when the reactor is pressurised, this allows the heating of solvents significantly above their boiling points in a flow reactor, allowing optimal reaction choices to be made. In general, when making connections the port threads had PTFE tape added to ensure a leak tight seal. The flow rate out of the part was measured to ensure no internal leaks were present.

2.6 Flow chemistry test

To demonstrate the suitability of the part for performing flow chemistry the S_NAr reaction of 2,4-difluoronitrobenzene with morpholine was carried out (Figure 4), using methanol as the solvent and a reaction temperature of 80 °C. A 100 psi back pressure regulator was installed after the reaction chip. The reaction chip was a 4 mm channel reactor with 8 mixing elements as it had the largest internal volume at 1 mL.

Not all of the reaction products are necessarily observed, with the ortho and bis species predominating. The reactor output was met with a stream of equal parts ethyl acetate and water in a second printed mixer part to quench and workup the reaction before analysis of the resulting organic layer. The printed reactor was heated by submersion in a water bath or a custom aluminium heating block that sits on a standard laboratory hotplate (Figure 5). The printed workup section was at room temperature.

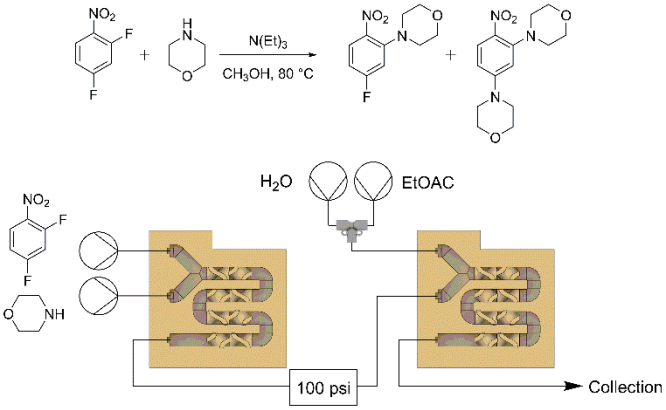

Figure 4. Reaction of 2,4-difluoronitrobenzene with morpholine with telescoped liquid-liquid extraction

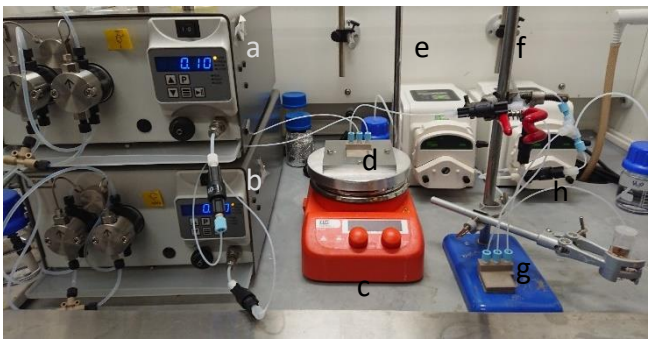

Figure 5. Custom aluminium heating block and wider experiment setup for temperature control of 3DP reactor; a) reagent 1 pump b) reagent 2 pump c) hotplate for reactor heating d) heating block with printed reactor chip e) ethyl acetate pump f) deionised water pump g) printed workup chip h) system outlet for collection.

3. Results and Discussion

3.1 X-ray micro computed tomography

Figure 6 shows the 3D model of the reactors reconstructed and image slices from the µCT scans. The infill structure, channel walls and mixers can be clearly seen in each reconstructed image. Some roughening of the PEEK surface was observed on the internal structure of the 4 mm channels (Figure 6 left); however, the mixers appear to be of high resolution. Some of the mixers of the 3 mm channel part (Figure 6 centre) appear to be of a lower resolution. Overall, the 3 mm channel reactor was visually found to exhibit reduced surface roughness at the channel walls and no pores were observed. The 2 mm channel reactor (Figure 6 right) mixers appear to be well defined and the internal walls of the channels show no surface texture, apart from the layers caused by the 3D printing process. The reactor/mixer scales of operation were chosen to test the resolution possible with developed PEEK printed methods, and as such, are considered to be of suitable quality given they are compatible with small lab scale equipment in terms of typical flow chemistry development scales. Quantitative methods/metrics for part accuracy can also be developed from this µCT approach.

Overall the use of µCT was found to be a powerful and convenient tool to non-invasively and non-destructively verify print geometry and quality. Given the criticality of complex internal elements for enhancement of heat transfer and mixing which in turn can control critical process and product attributes such as reaction selectivity, product purity, yield and productivity, this could be a useful approach in incorporating

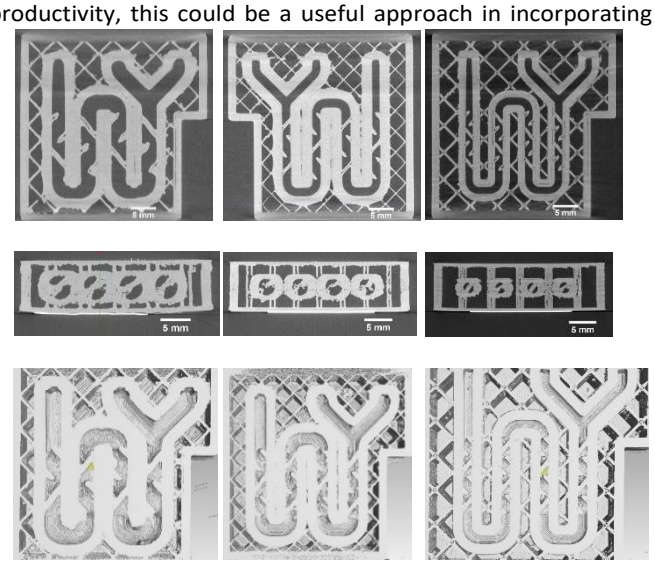

Figure 6. Top and side image slices and 3D reconstruction of (left) 4mm channel, (centre) 3mm channel and (right) 2mm channel reactor CT reconstruction

bespoke additively manufactured reactors and equipment in chemical processes. For example, in continuous pharmaceutical production where quality and regulatory considerations are of the utmost importance.

3.2 Mixer performance and design considerations for 3D-printed static mixers

Figure 7 (top) shows the extraction efficiency of benzoic acid from aqueous to organic phases in each one of the mixers investigated, at thermodynamic equilibrium the extraction efficiency of this system would be anticipated to be > 99%. The range of flowrates used in each of the investigated mixers remains well within the laminar flow regime for an equivalent pipe flow section (Re < 100) in all cases, and so any reduction in contacting time between the aqueous and organic phases is not offset by increased mixing due to turbulence. As would be expected due to the absence of further mixing elements the T- and Y- mixers show significantly reduced extraction efficiency compared to the printed Kenics type mixers at equivalent flow rates. At flow rates of 1 mL/min the printed mixers have extraction efficiencies of > 90 % compared to 86 and 82 % for the Y and T mixers (Figure 7). The extraction efficiency for the Y- and T- mixers dropped to 58 % by 4 mL/min whereas the printed mixers were still at least 80 %, with the 2 mm ID variant at nearly 95 %.

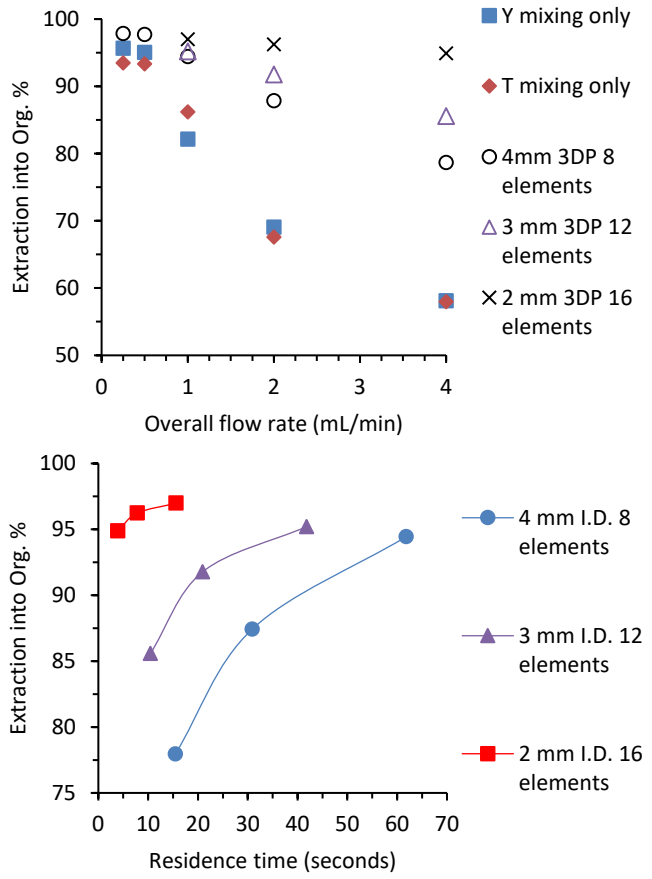

Figure 7 (Top) Influence on extraction efficiency with of flow rate (Bottom) Influence of mixture residence time at three tube/mixer diameters shown.

In the case of the Kenics type static mixer the degree of mixing for single phase laminar flow is related almost exclusively to the number of mixing elements the flow has passed through, largely independent of scale of operation, due to the geometric folding based mixing method utilised.[25] In the case of multi-phase flows the degree of mixing of the immiscible liquids is more complex as complete meso and micro mixing cannot occur to give a single homogeneous phase due to the interfacial tension between the phases. As such it would be expected that the number of elements the flow passes through and overall contacting time between the immiscible phases would be primary factors affecting extraction efficiency.[22] This was found to be the case, as can be seen in Figure 7 (bottom), that as the channel diameter is scaled down the reduction in residence time is more than made up for by the increase in mixing elements. For example, an approximate 95% extraction efficiency required 4 s, 42 s and 94 s of mean residence time with the 16, 12, and 8 element sections respectively.

The Kenics mixer provides efficient mixing even at very low Reynolds numbers and is suitable for high viscosity fluids while only generating low pressure drops across the static mixer.[25,26] Given the relative openness of the structure, compared to a design like the SMX mixer, it is more accommodating of solids[22] and so resistant to blockages, for example due to low level unintended precipitation often experienced in flow chemistry applications. Where a more uniform residence time distribution is critical, increased numbers of Kenics laminar mixing elements within a longer channel will approximate idealised plug flow over a wide range of flow rates, scales and Reynolds numbers due to the geometric nature of the laminar mixing processes.[27] FFF printing techniques will offer advantages compared to powder bed fusion techniques such as SLM, where long channels and internal elements can exacerbate problems with clearing unfused powder from inside the reactor.[8]

Residence time distribution (RTD) experiments were conducted by injecting an acetone tracer into one inlet of the 4 mm I.D. 3DP mixer with 8 elements and compared to tubing of the same diameter and volume with only an initial T-mixer. Narrower profiles were achieved for the printed mixer at all flow rates compared to the T-mixer (see ESI for details). Profiles are as expected based on the presence of mixed and unmixed (inlets and turns) laminar flow segments in the mixer and in-line with literature for Kenics type mixers.[27]

However, it should be noted that the Kenics mixer geometry represents just one of many static mixer designs, the most suitable of which will depend on the mixing time and heat transfer requirements of a given reaction, desired Reynolds number and composition of the streams. Furthermore, different mixing element designs can easily be combined within a single channel, taking advantage of the flexibility derived from using printed reactors to provide a bespoke mixing solution for a given reaction.

When near the limits of printer resolution, as in this study, mixer choice considerations intersect with limitations for the print resolution. For example, it is not possible that the blades of a 9 element SMX mixer could be printed in the 2 mm channel with the available nozzles on the printer. Therefore, despite the SMX

being a more efficient mixer design on a per element basis,[25] more Kenics type elements per unit residence time could be utilised. In practice, a balance between robustness to blockage, single or multi-phase mixing efficiency and scale can be sought for a given application. With the Kenics mixer and alternate mixer designs particularly SMX mixers,[25] a significant literature exists characterizing the residence time distribution,[27] pressure drop,[26] mixing time scales,[28] and multiphasic contacting[29,30] allowing selection of the optimal mixer conformation. Furthermore, improvements in additive manufacturing and multiphasic computational fluid dynamics (CFD) simulation capabilities, may enable direct computational design approaches and novel laminar mixer geometries that are less intuitive and amenable to traditional manufacturing to emerge and proliferate.

3.3 Pressure testing

The 4 mm channel was shown to hold held a pressure of 500 psi (34 bar) for at least 20 minutes with no sign of leakage from the material layers. This pressure rating and chemical resistance would allow for example the superheating of acetonitrile to 200 °C while maintaining a good safety margin. Additional pressure tests were conducted during the development of the printed reactor systems with simplified tubular geometries, shown in the supporting information. In these tests pressure was increased until failure was observed, prints were found to be stable up to 60 bar for 20 minutes with leaking from threaded inlet observed at 72 bar operating pressure. As such it is likely that further increases in operating pressure for flow chemistry above those demonstrated in the printed flow reactor should be achievable.

3.4 Flow chemistry test

The reaction in figure 4 was performed with separate feeds of the aromatic substrate and the nucleophile being pumped at 0.1 mL/min each, giving a residence time of 5 minutes. A 100 psi back pressure regulator was installed after this mixer. The outlet stream from this reactor was then routed to a second printed mixer to meet a stream of equal parts ethyl acetate and water with a combined flow rate of 1 mL/min and a workup residence time of < 1 minute. The separate layers were allowed to settle and then analysed by HPLC on a C18 column. The use of ethyl acetate and methanol would preclude the use of ABS or PLA parts and poly(etherimide) (PEI) is expected to have more limited resistance to bases. Titanium and stainless steel do not offer significant advantages for chemical compatibility, with typically lower resistance to bases than PEEK. Hastelloy, with its excellent chemical tolerance, would be ideal, however printing *via* SLM often leads to cracking within parts during the print due to rapid heat and cool cycles, requiring modification to the alloy composition for this to be significantly reduced.[31]

Performing the reaction at room temperature gave a small amount of the ortho substituted product (2.4 % by peak area) which increased to 31.5 % upon heating to 80 °C. The measured internal temperature of the part, 5 mm from the surface, was 65 °C, while the temperature 2 mm from the bottom of the part

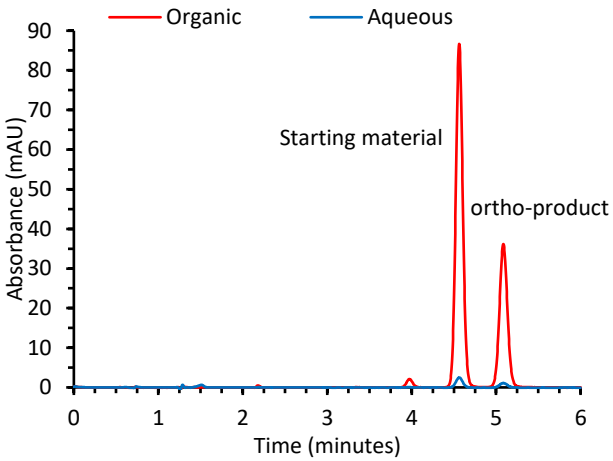

Figure 8. HPLC data showing the high extraction efficiency for the telescoped workup step.

was 77 °C. This difference in values could be improved through a layer of insulation on top of the piece, alternatively printed jacketed section for heat transfer could be utilised. The efficiency of the telescoped extraction was high, with 97 % by peak area percentage of the product in the organic phase after the workup step (Figure 8).

4. Conclusions

Strong and chemically resistant flow reactors have been printed from PEEK *via* FFF with material costs less than the off-the-shelf cost of an injection moulded PEEK tubing union. The printed reactors have been shown to withstand high pressures of 500 psi and are capable of performing chemistry at increased temperatures, allowing solvents to be superheated. The integrated Kenics type mixing elements were of good resolution and shown to improve reagent mixing and allow the performance of continuous flow liquid-liquid extractions. We believe that the ability to produce customised reactors with tailored geometries and properties approaching those of metal parts, as and when required by chemists, is highly valuable to both chemistry education and to research and manufacturing. Furthermore, the use of μCT for quality assurance with bespoke reactor design and fabrication may provide a suitable level of compliance for adoption in regulated production environments for example in the case of GMP products.

Conflicts of interest

There are no conflicts to declare

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