Electronic Supplementary Material (ESI) for Lab on a Chip

Design and Additive Manufacture for Flow Chemistry
Supplementary Information

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General Considerations

1.1 Data Analysis

All ^{1}H and ^{13}C spectra were measured at 400 and 100 MHz respectively using a Bruker DPX 400 MHz spectrometer. The solvent used for NMR spectroscopy was chloroform-d_1 (δ 7.26, ^{1}H; δ 77.0, ^{13}C) using TMS as the internal reference. Chemical shifts are reported in ppm and *J* values are reported in Hz. All flow reactions were carried out using a FlowSyn continuous flow system. All chromatographic manipulations used silica gel as the adsorbent. Reactions were monitored using TLC on aluminium backed plates with Merck TLC 60 F_{254} silica gel. TLC visualised by UV light at a

wavelength of 254 nm, or stained by exposure to an ethanolic solution of vanillin (acidified with concentrated sulphuric acid), followed by charring where appropriate. Purification by column chromatography using Apollo ZEOprep 60/ 40-63 micron silica gel.

1.2 Computer Aided Design

CAD drawings were produced using the commercially available software NX 7.5 (Siemens Industry Software), and converted to .STL file format for visualisation in MiniMagics 2.0 (Materialise).

1.3 Additive manufacturing equipment

Selective Laser Melting (SLM) – SLM parts were produced using a Renishaw AM250, Renishaw MTT 100 or a Realizer SLM 50

Stereolithography Apparatus (SLA) – SL parts were produced using a 3D Systems Viper si2 SLA system.

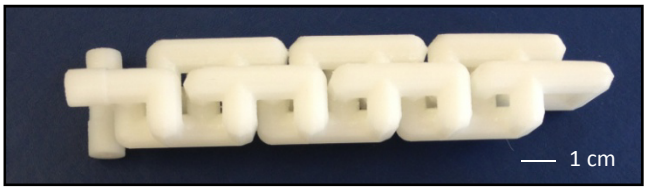
Multi-Jet Modelling (MJM) – MJM parts were produced using a 3D Systems ProJet 3000Plus 3D Printer.

Selective Laser Sintering (SLS) – SLS parts were produced using an EOS FORMIGA P 100 and an EOS EOSINT P 390 system.

Fused Deposition Modelling (FDM) – FDM parts were produced using a Stratasys Dimension 3D Modelling Printer.

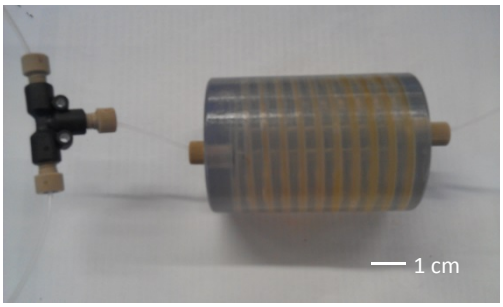
2. Reactors

2.1 RD1



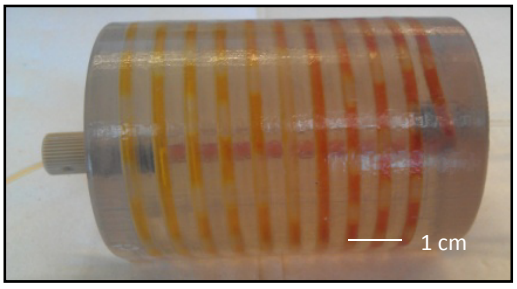
Reactor design 1 was manufactured via FDM from acrylonitrile butadiene styrene (ABS) to external dimensions of approximately 150x30x30mm. The reactor had two inlets joining at a t-piece connected to an outlet by a continuous tube of length 510 mm, diameter 3 mm and a total volume of 3.6 mL, contained within a wall thickness of 5 mm. The flow path has a split-and-recombine (SAR) mixer geometry.

2.2 RD2



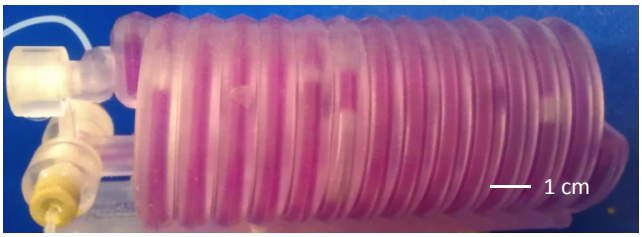
Reactor design 2 was manufactured via SL from Accura 60 resin to external dimensions of approximately 70x50x50mm. The reactor had a single inlet connected to an outlet by a continuous tube of length 3300 mm, diameter 3 mm and a total volume of 23mL.

2.3 RD3



Reactor design 3 was manufactured via SL from Accura 60 resin to external dimensions of approximately 70x50x50mm. The reactor had two inlets joined at an internal t-piece, connected to an outlet by a continuous tube of length 3300 mm, diameter 3 mm and a total volume of 23mL.

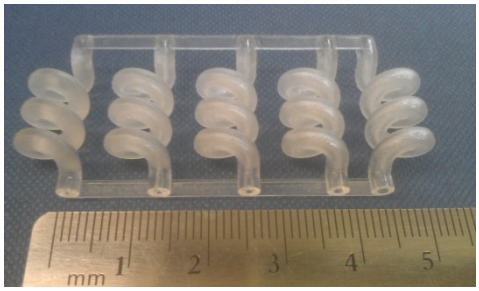
2.4 RD4



Reactor design 4 was manufactured via SL from Accura 60 resin to external dimensions of approximately 140x50x50mm. The reactor had two inlets joined at an external T-piece, connected to an outlet by a continuous tube of length 2320 mm, diameter 3 mm and a total volume of 16.4mL. The

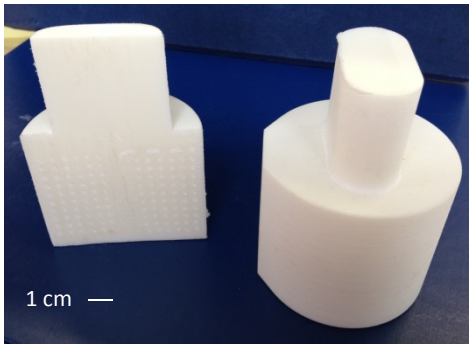
flow path has an initial split-and-recombine (SAR) mixer geometry (internal, not visible), followed by a continuous tube wrapped around the outside.

2.5 RD5



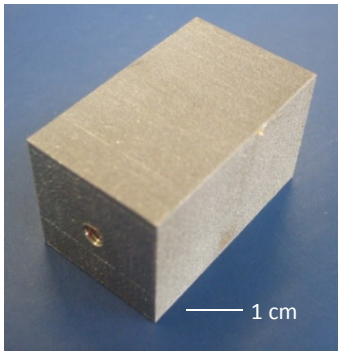
Reactor design 5 was manufactured via SL from Accura 60 resin to external dimensions of approximately 55x25x5mm. The build had a series of tubes of length 70mm, with channel diameters of 0.25, 0.375, 0.5, 0.625 and 0.75mm.

2.6 RD6



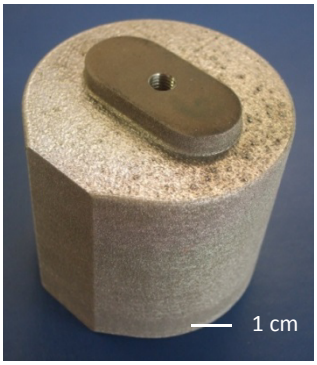
Reactor design 6 was manufactured via SLS from nylon-12 to external dimensions of approximately 70x50x50mm. The reactor had two inlets joined at an internal T-piece, connected to an outlet by a continuous tube of length 13200 mm, diameter 2 mm and a total volume of 41mL.

2.7 RD7



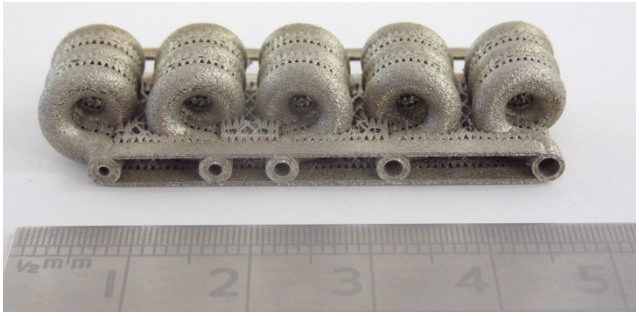
Reactor design 7 was manufactured via SLM from stainless steel to external dimensions of approximately 55x30x30mm. The reactor had a single inlet connected to an outlet by a continuous tube of length 300 mm, diameter 3 mm and a total volume of 2.1mL.

2.7 RD8



Reactor design 8 was manufactured via SLM from stainless steel to external dimensions of approximately 55x60x60mm. The reactor had a single inlet connected to an outlet by a continuous tube of length 4210 mm, diameter 3 mm and a total volume of 13.2mL.

2.7 RD9



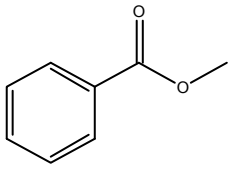
Reactor design 9 was manufactured via SLM from stainless steel to external dimensions of approximately 55x25x5mm. The build had a series of tubes of length 70mm, with channel diameters of 1, 1.25, 1.5, 1.75 and 2mm.

3. Chemical Syntheses

3.1 Oxidation of Aldehydes to Methyl Esters

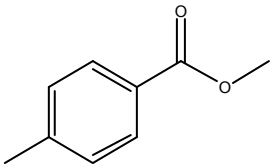
An aldehyde (4mmol, 1 equivalent) and tetra-butyl ammonium bromide (132mg, 0.4mmol, 0.1equivalents) were dissolved in methanol (1.65mL, 40mmol, 10 equivalents) and made up to 5mL with ethyl acetate. The solution was transferred to a small glass vial. To a second glass vial sodium hypochlorite (5mL, 12.5% solution in water) was added. The two solutions were flowed through the reactor RD2 at 0.38 $mLmin^{-1}$ giving a t_R of 30 minutes. Reactant products were collected and extracted using ethyl acetate (3x25mL) and distilled water (25mL). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated to dryness under vacuum. Samples were analysed using NMR spectroscopy.

Methyl Benzoate



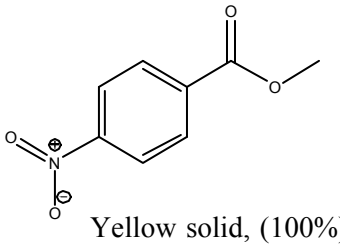
Clear colourless liquid (93%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.92 (s, 3H, CH_3), 7.42-7.64 (m, 3H, Ar-H), 8.05 (m, 2H, Ar-H) ppm.

Methyl p-Toluate



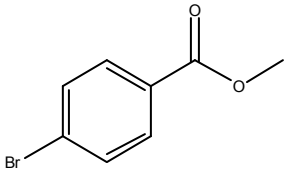
Colourless solid, (54%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.39 (s, 3H, CH_3), 3.89(s, 3H, CH_3) 7.21-7.23 (d, J = 8.0 Hz, 2H, Ar-H), 7.92 (d, J = 8.0 Hz, 2H, Ar-H).

Methyl p-Nitrobenzoate



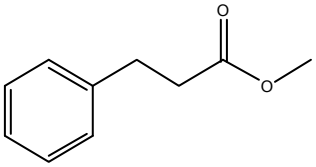
Yellow solid, (100%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.99(s, 3H, CH_3) 7.22 (d, J = 11.2 Hz, 2H, Ar-H), 7.92 (d, J = 10.8 Hz, 2H, Ar-H) ppm.

Methyl p-Bromobenzoate



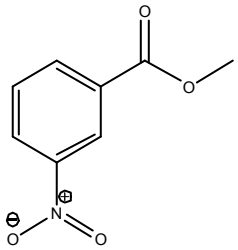
White solid, (100%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.92(s, 3H, CH_3) 7.57-7.59 (m, 2H, Ar-H), 7.89-7.91 (m, 2H, Ar-H).

Methyl 3-phenylpropionoate



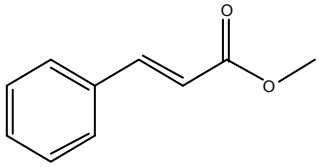
Colourless Liquid, (100%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.61-2.66(t, J = 4 Hz, 2H, CH_2), 2.80-2.81 (t, J = 4 Hz, 2H, CH_2), 7.11-7.54 (m, 5H, Ar-H) ppm.

Methyl 3-Nitrobenzoate



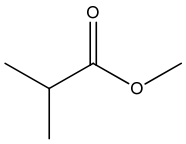
Yellow solid, (99%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.00(s, 3H, CH_3), 7.45-7.69 (t, J = 7.8 Hz, 1H, Ar-H), (dt, J = 1.4, 7.9 Hz, 1H, Ar-H), 7.92 (ddd, J = 0.8, 2.0, 8.0 Hz, 2H, Ar-H), 8.87-8.89 (t, J = 5.6 Hz, 1H, Ar-H) ppm.

Methyl trans-cinnamate



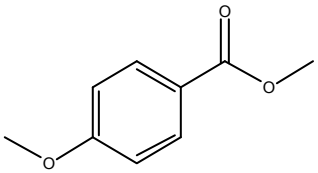
Yellow solid, (17%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.83(s, 3H, CH_3), 6.70-6.72 (d, J = 7.6 Hz, 1H, CH), 6.74-6.76 (d, J = 7.6 Hz, 1H, CH), 7.26-7.60 (m, 5H, Ar-H) ppm.

Methyl isobutyrate



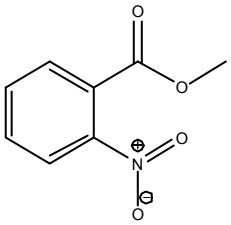
Colourless oil, (100%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.18-1.20(d, J = 5.2 Hz, 6H, CH_3), 2.57-2.62 (sept, J = 6.7 Hz, 1H, CH), 4.40 (s, 3H, CH_3) ppm.

Methyl anisate



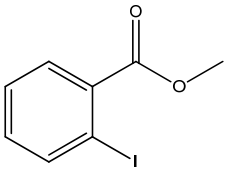
Yellow Oil, (5%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.90(s, 3H, CH_3), 6.52-6.53 (dd, J = 1.6, 3.6 Hz, 1H, CH), 7.18-7.19 (dd, J = 1.6, 3.6 Hz, 1H, CH), 7.58-7.59 (dd, J = 1.6, 3.6 Hz, 1H, CH_3) ppm.

Methyl o-Nitrobenzoate



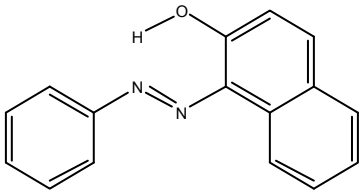
Yellow liquid, (56%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.92 (s, 3H, CH_3), 7.64-7.92 (m, 4H, Ar-H) ppm.

Methyl o-Iodobenzoate



Yellow liquid, (22%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.93 (s, 3H, CH_3), 7.12-7.98 (m, 4H, Ar-H) ppm.

Procedure for the Production of Sudan 1 Dye



A solution of aniline (0.2mL, 0.204g, 2.19mmol), hydrochloric acid (10M.,0.35mL), water (2mL) and N,N-dimethylformamide (4mL) was prepared and pumped at 0.195 mL/min^{-1} . A solution of sodium nitrite (0.75g, 10.9mmol), water (4mL) and N,N-dimethylformamide (2mL) was prepared and pumped at 0.195 $mLmin^{-1}$. The two streams intercepted at a t-piece and were pumped together at 0.39 mL/min^{-1} through SLA reactor RD3, giving a residence time of 30 minutes. After 30 minutes the stream was intercepted by a solution of β-napthol (0.3g, 1.04mmol), sodium hydroxide solution (10%, 6 mL), water (3mL) and N,N-dimethylformamide (3mL) being pumped at 0.39 mL/min^{-1} giving a residence time of 15 minutes. Reactant products were collected and extracted using diethyl ether (3x25mL) and water (25mL). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated to dryness under vacuum. Samples were analysed using NMR spectroscopy. Red Solid, (17%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.87-6.89 (d, J = 8.0, 1H, Ar-H), 7.11-7.78 (m, 9H, Ar-H), 8.56-8.58 (d, J = 8.0 Hz, 1H, Ar-H), 16.28 (s, 1H, OH) ppm.

Procedure for the persulfate-iodide reaction

A solution of 0.5M potassium iodide (20mL, 1.66g) was prepared and pumped at rates ranging from 18-40 $mLmin^{-1}$ through inlet A. A second solution of 0.01M potassium persulfate (20mL, 0.05g), 0.01M sodium thiosulfate (10mL, 0.02g) and 5 drops of starch indicator was prepared and pumped at rates ranging from 18-40$mLmin^{-1}$ through inlet B. The inlets were joined at a t-piece before passing into SLA reactor RD4. The flow stream was visually monitored, with the time being recorded at which the reaction changed colour from colourless to a vibrant blue. The reaction conditions were repeated using commercially available PTFE tubing as the flow path.

Solvent Compatibility Data

SLA: Accura 60

Due to the lack of available solvent compatibility data for the Accura 60 resin, we opted to undertake our own basic study. 1cm^3 cubes of Accura 60 resin were manufactured via stereolithography before being subjected to a range of solvents. Each cube was weighed before and after exposure to solvents for the specified time period, with the weight gain/loss through swelling being quantified. Notes were also added where any visual observations were made. Variations in dimensions due to swelling were also recorded. Initial variations in weights are a reflection of the effectiveness of the support structure removal process, rather than the accuracy of the build.

Solvent	Weight of Accura Cube	Weight-30 minutes solvent exposure	Weight Change (%)	Weight-2 hour solvent exposure	Weight Change (%)	Weight-24 hour solvent exposure	Weight Change (%)	Dimensional Changes Due to Swelling (+/- mm)
Ethyl Acetate	1.2632	1.2636	0.03	1.2676	0.35	1.2826	1.54	0.09
Diethyl Ether	1.2651	1.2646	0.04	1.2652	0.01	1.2712	0.48	0.09
Toluene	1.2729	1.2733	0.03	1.2721	0.09	1.2740	0.09	0.14
DCM	1.2687	1.3047	2.83	Slight degradation	N/A	Complete degradation	**N/A**	N/A
THF	1.2623	1.2715	0.73	1.2928	2.42	Slight degradation	**N/A**	N/A
Petrol	1.2832	1.2828	0.03	1.2820	0.09	1.2820	0.09	0.09
Methanol	1.2673	1.2788	0.91	1.3021	2.75	Slight degradation	N/A	N/A
IPA	1.2625	1.2622	0.02	1.2632	0.06	1.2740	0.91	0.07
Hexane	1.2773	1.2774	0.01	1.2767	0.05	1.2771	0.01	0.08
Butan-1-	1.2739	1.2739	0.00	1.2720	0.15	1.2765	0.20	0.11

ol								

To determine whether any material leaching had occurred into the solvent, we weighed the contents of the vial both before and after the experiment. The vial weights were equal, both before and after the experiments, showing that there was no detectable level of leaching into the solvent from the Accura 60 solvent.

SLM: Stainless Steel

Stainless steel is a chemically robust material due to the stable metal oxide layer coating its surface. Full solvent stability data can be found on the Cole-Palmer website (http://www.coleparmer.co.uk/Chemical-Resistance). Physical observations of the part during use showed no sign of any chemical degradation of the parts, including removal of any partially sintered steel particles from the surface.

SLS: NYLON-12

The amide linkage on NYLON-12 makes it chemically susceptible to a range of chemicals typically including strong acids and nucleophiles. No chemistry was undertaken using NYLON-12 parts and therefore no leaching effects have been observed. Full solvent stability data can be found on the Cole-Palmer website (http://www.coleparmer.co.uk/Chemical-Resistance).

FDM: ABS

ABS is chemically susceptible to a range of reagents typically including strong acids and nucleophiles, as well as a range of general organic solvents. It is also prone to large degrees of swelling in these conditions. Full solvent stability data can be found on the Cole-Palmer website (http://www.coleparmer.co.uk/Chemical-Resistance). No chemistry was undertaken using NYLON-12 parts and therefore no leaching effects have been observed.

Build Resolutions

Detailed electronic calliper measurements were taken of each of our parts to determine whether theoretical build resolution is comparable to the resolution we actually achieved for our builds.

Reactor Design	AM Manufacturing Process	Description of Measurement Taken	Measurement Taken (mm)	Corresponding CAD Measurement (mm)	Resolution (+/- mm)
RD1	FDM	External tube circumference (cylinder)	9.92	10.00	-0.08
		External tube width (hexagonal)	9.08	9.00	+0.08
RD2	SLA	Circumference	52.04	52.00	+0.04
		Length	75.06	75.00	+0.06
RD3	SLA	Circumference	52.06	52.00	+0.06
		Length	75.03	75.00	+0.03
RD4	SLA	External tube circumference (cylinder)	14.95	15.00	-0.05
		External tube width (hexagonal)	9.47	9.50	-0.03
		Base plate width	27.46	27.50	-0.04
RD5	SLA	Tube circumference	2.99	3.00	-0.01
RD6	SLS	Reactor circumference	62.12	62.00	+0.12
		Entrance port width	20.29	20.00	+0.29

		Entrance port length	40.07	40.00	+0.07
RD7	SLM (Renishaw 250)	Reactor length	49.91	50.00	-0.09
		Reactor width	30.35	30.25	-0.10
RD8	SLM (Renishaw 250)	Reactor circumference	62.22	62.00	+0.22
		Entrance port width	20.12	20.00	+0.12
		Entrance port length	40.14	40.00	+0.14
RD9	SLM (Realizer 50)	Tube 1 internal diameter	1.77	1.75	+0.02
		Tube 2 internal diameter	1.52	1.50	+0.02
		Tube 3 internal diameter	1.25	1.25	0
		Support frame width	3.49	3.50	-0.01

FDM parts were built within +/- 0.1mm of the exact designed dimensions of the built parts, demonstrating a significant improvement over theoretical build resolutions.

SLA parts were built within +/-0.05mm of the exact designed dimensions of the built parts, demonstrating the scope of accurate builds possible when using SLA.

SLS parts were built within +/-0.3mm of the exact designed dimensions of the built parts, showing that theoretical build resolutions are often not achieved without precise build parameter optimisation for each individual part.

SLM parts were built within +/-0.22mm of the exact designed dimensions of the built parts using the Renishaw AM 250, however using the Realizer 50 resolution was improved dramatically to +/-0.02mm