Emerging trends in flow chemistry enabled by 3D printing: robust reactors, biocatalysis and electrochemistry

Victor Sans[a]*

[a] Institute of Advanced Materials (INAM), Universitat Jaume I, Avda. Sos Baynat s/n, 12071, Castellon, Spain

e-mail address: sans@uji.es

Key words: flow chemistry, continuous-flow, 3D printing, additive manufacturing, biocatalysis, electrochemistry

Abstract

This contribution reviews the state of the art in the employment of additive manufacturing for the development of continuous-flow reactors, highlighting their potential for developing green and sustainable chemical processes. Additive manufacturing, commonly known as 3D printing has an untapped potential for the design and development of sustainable chemical processes. The integration of multiple enabling technologies is facilitated by the freedom of design inherent to these techniques. In this way, safer and efficient processes with integrated capabilities can be realised in a simple and cost-effective fashion. This relatively young field is evolving towards more robust and functional devices. Two trends are discussed here. First, the employment of robust materials, including metal and ceramics for the fabrication of the reactors. Secondly, the integration of flow reactors with biocatalysis and electrochemistry, both of them key technologies for the sustainable synthesis of chemicals and fuels.

Introduction

Continuous-flow manufacturing, also known as flow chemistry is a core technology for the development of green and sustainable chemical processes.[1]Flow chemistry technologies contribute to the development of green chemistry and engineering in a

number of ways, including improved safety, faster reactions, reduction in the use of solvents, waste generation and energy needs.[2] Optimal mixing of the reagents in single or multiple-phase reactions and better contact of substrates with catalysts, heat-exchanging units, etc. eliminates heat and mass transfer limitations ensuring the transformations take place with maximum efficiency.[3-4] This is particularly suited for fast, highly exothermic reactionsThe employment of flow chemistry conditions facilitates the digitisation of the synthetic processes,integrating analytical tools and machine learning techniques to improve the quality, reproducibility, efficiency and sustainability of the synthetic processes.[5] Furthermore, flow chemistry can be combined with other enabling technologies, including catalysis, biocatalysis,[6] microwave dielectric heating,[7] electrochemistry or photochemistry.[8]

Additive manufacturing (AM), commonly known as 3D printing (3DP), are a set of manufacturing techniques characterised by fabricating parts by adding materials, typically in a layer-by-layer fashion.[9] These techniques enable a big degree of freedom of design and the possibility to generate tailored complex geometries that would not be possible, or would be very expensive, with traditional manufacturing techniques. AM techniques have been introduced in the literature[10-13] and therefore a brief introduction of the relevant techniques will be done. Extrusion techniques include Fused Deposition Modelling (FDM) and Direct Ink Writing (DIW). A thermoplastic polymer is extruded through a hot end in FDM, while the platform and nozzle move along XYZ axis. DIW extrudes a paste through a thin needle, allowing the processing of relatively dense and viscous materials compared to other AM techniques. However, DIW typically offer limited spatial resolution. Powder bed techniques include selective laser sintering (SLS), selective laser melting (SLM) and electron beam melting (EBM).[10] In these techniques a powder bed of granular material (metal or polymer) is solidified layer-by-layer with a laser or an electron beam as energy sources. The powder layer is renewed by employing a rake or a roll. In vat photopolymerisation, a liquid monomer formulation is deposited in

a bath and selectively polymerised employing a laser, known as stereolithography (SLA); a projector, digital light processing (DLP) or a liquid crystal display (LCD). The UV light selectively polymerises a layer of the monomeric formulation, then the stage adjusts the position and the process is repeated.

The employment of 3DP to manufacture continuous flow reactors was first reported by Kitson *et al.*[14] The field has rapidly grown to develop a broad range of applications in the synthesis of chemicals, materials[15] and crystallisation processes.[16] The digitalisation of the manufacturing process allows advanced design, where simulation of properties (e.g. flow, electric fields, pressure drop) enables the fabrication of optimised reactor geometries.[17-19] There are several excellent reviews which showcase the developments in the field.[13, 19-21] The focusing of this contribution is on recent trends identified in the literature which represents areas of potential growth for continuous-flow green and sustainable process development.

Robust materials for 3DP reactors

Early examples in 3DP devices employed polymers with limited chemical and thermal resistance. Most FDM commercial printers are limited to temperatures <300 °C. The use of polypropylene (PP) considerably improved the chemical stability and offer a window of temperature slightly over 100 °C. Flow reactors manufactured with 3DP have been demonstrated in PP.[14,22,23]. Commercial low cost printers can be employed to 3DP PP, thus enabling the development of a broad range of budget applications.[24, 25]

Polyether ether ketone (PEEK) is a thermally and mechanically robust polymer and resistant to a broad range of chemicals. It is very challenging to print by FDM due to its high melting point.[26] Typically, high thermal stresses result in excessive warping and delamination problems. Recently, the use of specialised printers with heated chamber and thermally resistant parts have been employed to print flow reactors in PEEK at high temperatures (>350 °C). A relatively simple reactor with two inlets and a mixing structure

have been reported by Harding *et al*.[27] The ability to withstand a pressure of 34 bar and the wide range of temperatures enable the employment of superheated solvents and to couple the reaction with a telescoped liquid-liquid separation. The reaction of 2,4-difluorobenzene with morpholine in MeOH at 80 °C, coupled to a liquid-liquid extraction was demonstrated under flow conditions. The authors tested the printed parts up to failure, acknowledging that 60 bar could be achieved without signs of failure, which occurred at 72 bar. Under these conditions, there is a good scope to superheat solvents while maintaining safe operating conditions.

The use of metal printed reactors facilitates heat transfer and the development of chemically resistant reactors, enabling challenging reaction conditions in terms of temperature, pressure and chemicals employed. Employing selective laser melting (SLM), Gutmann *et al*. designed and manufactured a stainless-steel (SS) millifluidic reactor with optimised flow patterns by CFD (Figure 1A-D). This was corroborated with tracer experiments, which demonstrated limited axial dispersion. This is relevant, since powder bed fusion techniques, like SLS or SLM, have associated a rough finishing derived from the granular nature of the starting materials. The resulting reactor was employed for a difluoromethylation reaction employing nBuLi as a base and fluoroform as a fluorine source (Figure 1E), which can be regarded as a green fluorinating agent since it is non-toxic and ozone-friendly. The transformation is highly exothermic and fast even at low temperatures, but the reactions were carried out in 2 minutes of residence time with excellent results.[28]

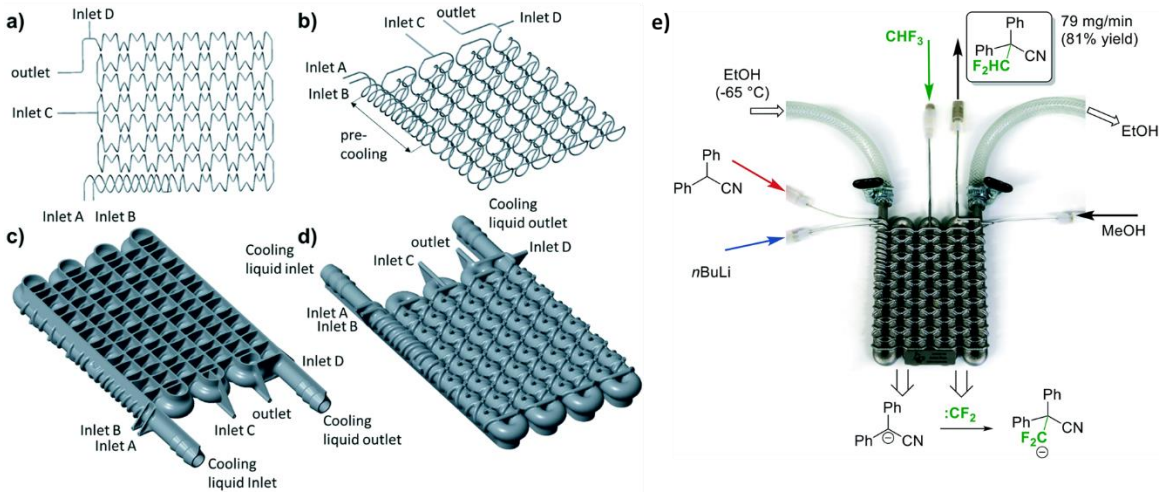

Figure 1 Stainless steel 3DP reactor manufactured with SLM. a-d) represent the CAD design files. a) Top view of the channel design. Total channel length is ca. 4 m, corresponding to 1.89 mL reactor volume. b) Perspective view of the channels. c) Bottom view of the reactor including cooling channel and support structure. d) Perspective view from the top part of the design, including holes to remove excess powder trapped in the channels during printing. E) Schematic representation of the fluorination reaction undertaken in the flow reactor. Adapted from reference [28] - Published by The Royal Society of Chemistry.

More recently, the same groups reported SS 3DP reactors with embedded in-line oxygen sensors for the oxidation of Grignard reagents. A split and recombine flow reactor and a cascade micro CSTR reactors were manufactured.[29] The resulting systems were employed for the aerobic oxidation of chlorophenylmagnesium bromide with oxygen, which is a green oxidant due to its low cost, high atom economy and lack of by-products. The optimal mixing generated in the printed reactors led to higher selectivity compared to a control coil reactor made with PFA tubing. Lee *et al.* demonstrated an increased control over the surface finishing employing high resolution SLM, enabling the development of 3D printed microfluidic reactors.[30] The increased resolution was achieved by controlling the laser focusing (λ = 1064 nm, 30 μm laser spot) and the particle size of the SS powder. The authors demonstrated that a tailored channel geometry and arrangement led to a very good control over the selectivity of an ultrafast

(residence times of 0.333 ms) Fries rearrangement reaction of o-iodophenyl diethyl carbamate, employing PhLi to activate the halide.

Ceramics are harder materials to manufacture with precision due to the requirement of post-manufacturing thermal treatment to transform the green body into finished structures. In most reported examples, structured reactors are created with robocasting, also known as direct ink writing. Very recently, ceramic microreactors made of SiCN, manufactured with DLP have been reported.[31] Silane based polymers with a controlled composition were printed into the corresponding shapes and thermally treated up to 1000 °C to generate the ceramic structures. An isotropic shrinkage of a 20% in weight and size allowed for an accurate design of microstructured pillars. After immobilisation of a Ru catalyst by impregnation, the cracking of ammonia into H_2 and N_2 was efficiently demonstrated in a broad range of temperature (500-1000 °C).

Integrating functionality in 3DP flow reactors

Another area with a huge growth potential is the integration of multiple enabling technologies. Here, recent advances in the integration of 3DP of flow reactors with biocatalysis and electrochemistry will be discussed.

Biocatalysis in flow is an area of growth in green chemistry, since it combines the efficiency of flow transformations with the unparalleled selectivity and mild conditions achieved with biocatalysts.[32, 33] The efficient immobilisation of enzymes enables the development of continuous-flow applications,[6, 34, 35] enabling the development of single step and cascade bio-transformations.[36]

The development of bioreactors fabricated with 3DP has a big potential to contribute to this field. The post-modification of printed devices is an attractive approach to achieve this goal. Peris *et al.* reported the first example of enzyme immobilisation in a 3DP reactor fabricated with FDM in nylon.[37] After surface modification, free aldehyde groups were employed to immobilise enzymes, via imine formation with lysine groups from the protein

surface. A screening of immobilisation surfaces and enzymes was undertaken in 3D printed devices, which rapidly led to the translation of optimal combinations of immobilisation strategies and enzymes to a flow reactor. The enzyme maintained a comparable activity to its free state for *ca.* 100 h under stream for the kinetic resolution of benzylamine. A similar strategy was recently reported for the post-printing chemical etching of polylactic acid fabricated with FDM.[38] The use of piranha solution for the etching, followed by hydroxylation and sililation afforded active surfaces for enzyme immobilisation. The nature of the silane offered flexibility for the mechanism of immobilisation (e.g. an amino silane was employed to immobilise glutaraldehyde). A design of experiments approach enabled the optimisation of the protocol conditions. A series of enzymes (penicillin G acylase (PGA), protease, glycosidase and lipase) were immobilised to demonstrate the versatility of the approach. PGA was employed for the synthesis of amoxicillin under batch conditions only. However, the approach seems feasible for flow conditions.

The printing of agarose based hydrogels containing enzymes employing direct ink writing enabled the generation of disks which could be stacked to form multienzyme flow reactors for cascade transformations (Figure 2A).[39] Despite the limited spatial resolution inherent to DIW, this modular approach can be employed to print devices containing thermostable enzymes. Simple disks with linear orifices were manufactured containing a ketoisovalerate decarboxylase (KIVD) modified by directed evolution to increase the temperature stability to withstand the printing conditions (Figure 2B). The same protocol was employed with an alcohol dehydrogenase (ADH) enzyme. The decarboxylation reaction of ketoisovalerate to isobutaraldehyde and subsequently to isobutanol employing a stack of disks containing both enzymes (Figure 2C). Leaching of enzyme was detected, which might explain the decay in activity over time in the flow experiments (Figure 2D). Shortly after the same group expanded the protocol to a range of phenyldecarboxilases and demonstrated a chemoenzymatic synthesis by combining

the decarboxylation of p-coumaric acid to 4-vinylphenol with a Heck C-C coupling catalysed by $Pd(OAc)_2$.[40]

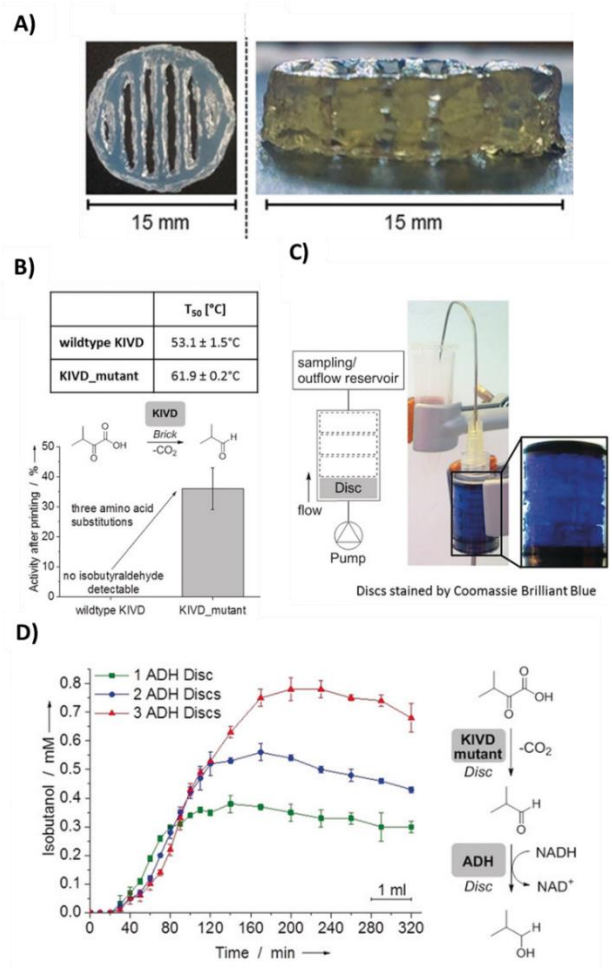

Figure 2. A) Images of the 3D printed scaffold disks employed to support the enzymes. B) Directed evolution of KIVD enzyme of wild-type KIVD and the KIVD-mutant to increase thermal resistance and resist the printing process. Only the mutant enzyme showed activity after printing. C) Detail of the fluidic system. The enzyme-loaded discs were stained with a blue dye for better visualisation of the set-up. D) Concentration of iso-butanol in the outlet as a function of time and the combination of one KIVD-mutant disc with ADH disks. Adapted from reference [39] with permission from Angewandte Chemie International Edition, ed. John Wiley and sons.

The same manufacturing technique was employed by Schmieg *et al.* to manufacture small hydrogel structures with immobilised enzymes, namely b-galacticosidase, benzoylformate decarboxylase, O-Nitrophenyl-β-D-galactopyranoside and ADH.[39] They shaped the hydrogels in cubic grids of 13x13x3 mm and packed the structures in FDM printed microreactors. All the enzymes were stable under continuous flow. Thorough kinetic studies revealed important mass transfer limitations, which severely affected the performance of the biocatalytic reactors. This is probably due to the fact that

the enzymes were trapped within the hydrogel matrix, obviously hindering the mass transfer of substrates and products to the catalytic centres. An increase in surface area would lead to an improved performance due to better contact between reagents and enzymes. Another strategy is to functionalise the surface of the support to avoid mass transfer limitations.[37]

Electrochemical flow reactors are gaining interest for the development of sustainable chemical transformations. Redox processes can be efficiently carried out electrochemically, reducing the need for oxidant and oxidising species. There are several examples in the literature of employing 3DP for the development of electrolyser cells.[41, 42] In synthetic chemistry, the main advantages offered by electroreactors are the need of low or no support electrolyte, due to the short distance between the electrodes and a high electrode surface to volume ratio, which improves mixing and shortens reaction times compared to traditional batch reactors.[43] The low distance between electrodes reduces the ohmic losses and facilitates mass transfer, even though in many cases mass transfer of reagents and products to and from the electrodes limits the overall performance.[44] Hence, typically, the electrochemical reactors are limited to microfluidic or parallel plate configurations. In an early example, 3DP has been employed to generate the spacers of electrochemical reactors to accurately control the distance between electrodes.[45] The employment of 3DP facilitates the development of parts of electrochemical devices that can fit in with commercially available equipment (e.g. stirring plates), which facilitates the development of simple and efficient synthetic protocols.[46]

The intensification of the electrochemical processes by improving mixing can have positive effects on activity and selectivity, particularly when working with fast reactions or with chemicals that can degrade by redox processes. Lölsberg *et al.* demonstrated the improved mass transfer properties of 3DP electrochemical mixing electrodes.[47] They employed electron beam deposition to generate CFD optimised electrodes with a

titanium-aluminium-vanadium alloy. Similarly, Bita *et al.* fabricated electrodes in a similar fashion and coated them with a Pt layer via electrodeposition.[48] In the assembled flow cell, the 3DP parts were employed as working electrodes in axial flow cells configurations and tested in the fast electrochemical reduction of $[Fe(CN)_6]^{3-}$ at different concentrations. Under diluted conditions, more heavily affected by mass transfer limitations, the reaction occurred 30-45 times faster compared to no flow conditions. Mo *et al.* demonstrated that gas diffusion layered electrodes fabricated with EBM offered less ohmic resistance in proton electron membrane electrolysers, which translated to an 8% efficiency increase compared to traditionally woven gas diffusion layers.[49] Marquez-Montes *et al.* developed a filter-press electrochemical reactor, where critical components to optimise mass and charge transfer were fabricated with 3DP (Figure 3C-D).[50] The design of the flow distributors, turbulence promoters was supported with CFD calculations (Figure 3A-B). Nafion was employed as a membrane to separate the half-cells. LSV curves for the reduction of 1 mM $K_3Fe(CN)_6$ at 5 mV s^{-1} in the a benchmark configuration without turbulence promoters (CPM in Figure 3A), showed mass transfer limited reactions (Figure 3E). When turbulence promoters were added, residence time distribution studies indicated low axial dispersion and higher mass transfer coefficients were observed for the reduction of $[Fe(CN)_6]^{3-}$ (Figure 3F). The filter press configuration makes this an interesting approach, since it is easily scalable.

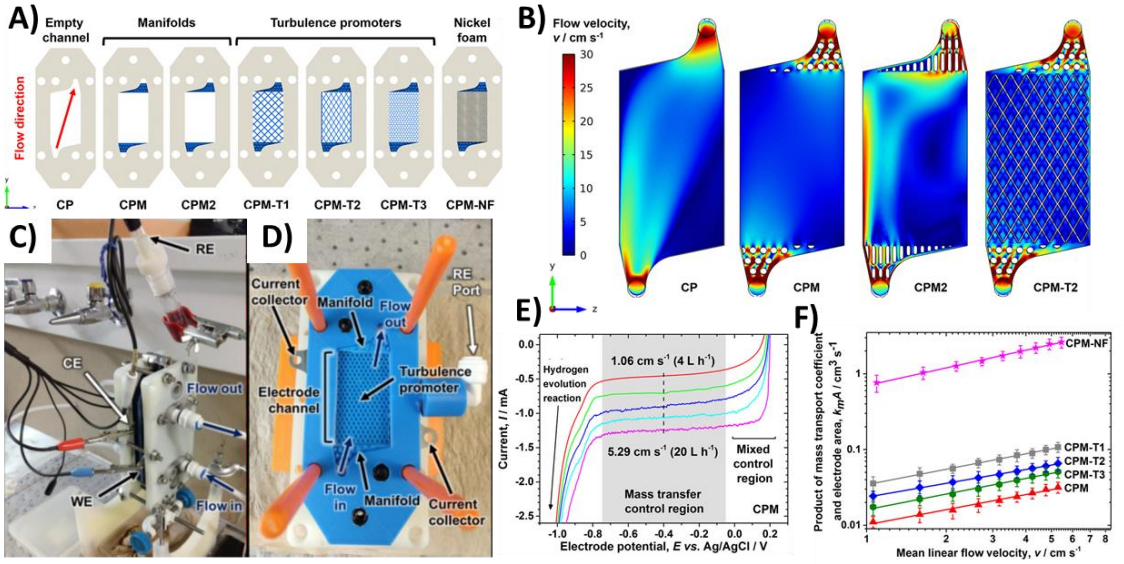

Figure 3. A) Channel configurations studied, including 3D printed manifolds and turbulence promoters. B) Flow velocity contour simulated with CFD at 15 L h^{-1}. C) Image of the assembled filter-press electrochemical reactor. D) Image of the printed flow layer. E) LSV results for the cathodic reduction of ferricyanide 1mM at 5 mV s^{-1} in the benchmark CPM configuration. F) Mass transfer coefficients of the different channel configurations assayed. Adapted with permission from reference [50]. Copyright 2020 American Chemical Society

Electrochemical flow cells manufactured with 3DP have also found applications in the synthesis of nanomaterials.[51] The combination of CAD design, finite element simulation and 3D printing was applied to manufacture a flow cell. The simulation of the flow and electrical distribution along the cell enabled an optimised design of the reactor with parallel plate reactors and was employed for the synthesis of Fe_3O_4 nanoparticles.

Conclusions and future directions

3D printing has a big potential for the development of sustainable flow process. The digitalisation of the manufacturing process facilitates the integration of design with powerful tools, such as CFD, which allows the development of optimised mixing structures. These can be easily fabricated with different 3DP techniques and implemented to reduce heat and mass transfer limitations and to add functionality to the reactors by integrating enabling technologies.

Emerging trends in the field include the development of more robust reactors, employing metal and ceramics. Besides, the integration of multiple technologies, including electrochemistry, chemo- and biocatalysis are areas with a huge growth potential. There

is no limitation in further integrating multiple technologies to perform multiple transformations, telescoping separation, analytics, etc.

A big challenge ahead in the field is to address issues related to scalability. Currently, the technology is limited to relatively small-scale machines and with slow manufacturing processes. Large scale 3D printing is mostly limited to extrusion methods,[52] but the integration of robots is opening new avenues, which can translate into developing large-scale applications with different types of materials and additive manufacturing techniques.[53] This is necessary to increase the industrial uptake of these technologies.

Circular economy aspects related to the recycling and disposal of reactors, catalysts and materials at the end of their use is another area of development.[54] There is a lot of potential for optimisation in the recycling and disposal at the end of life of the reactors and materials employed for reactor manufacturing. Comprehensive life cycle assesments will help selecting materials and manufacturing techniques to minimise environmental impacts.[55]

Conflicts of interest

No conflicts of interest are declared

Acknowledgements

The Generalitat Valenciana is gratefully acknowledged for funding (CIDEGENT/2018/036).

References

[1] S.V. Luis, P. Lozano, J. Alcazar, K. Mizuno, T. Wirth, L. Vaccaro, I.R. Baxendale, A.A. Kulkarni, M.V. Gomez-Almagro, J. Sánchez-Marcano, **Flow Chemistry: Integrated Approaches for Practical Applications**, Royal Society of Chemistry, 2019.
[2] D. Dallinger, C.O. Kappe, **Why flow means green – Evaluating the merits of continuous processing in the context of sustainability**, *Current Opinion Green Sustain. Chem.* 2017, **7**:6–12
[3] S.G. Newman, K.F. Jensen, **The role of flow in green chemistry and engineering**, *Green Chem.* 2013, **15**: 1456-1472.
[4] R.L. Hartman, J.P. McMullen, K.F. Jensen, **Deciding whether to go with the flow: evaluating the merits of flow reactors for synthesis**, *Angew. Chem. Int. Ed. Eng.* 2011, **50**: 7502-7519.
[5] V. Sans, L. Cronin, **Towards dial-a-molecule by integrating continuous flow, analytics and self-optimisation**, *Chem. Soc. Rev.* 2016, **45**: 2032-2043.
[6] L. Tamborini, P. Fernandes, F. Paradisi, F. Molinari, **Flow Bioreactors as Complementary Tools for Biocatalytic Process Intensification**, *Trends Biotechnol.* 2018, **36**: 73-88.
[7] T.N. Glasnov, C.O. Kappe, **Microwave-assisted synthesis under continuous-flow conditions**, *Macromol. Rapid Commun.* 2007, **28**: 395-410.
[8] Y.H. Su, N.J.W. Straathof, V. Hessel, T. Noel, **Photochemical Transformations Accelerated in Continuous-Flow Reactors: Basic Concepts and Applications**, *Chem. Eur. J.* 2014, **20**: 10562-10589.
[9] N. Guo, M.C. Leu, **Additive manufacturing: technology, applications and research needs**, *Frontiers Mech. Eng.* 2013, **8**: 215-243.
[10] L.E. Murr, S.M. Gaytan, D.A. Ramirez, E. Martinez, J. Hernandez, K.N. Amato, P.W. Shindo, F.R. Medina, R.B. Wicker, **Metal Fabrication by Additive Manufacturing Using Laser and Electron Beam Melting Technologies**, *J. Mater. Sci. Technol.* 2012, **28**: 1-14.
[11] W.E. Frazier, **Metal Additive Manufacturing: A Review**, *J. Mater. Eng. Perform.* 2014, **23**: 1917-1928.
[12] S.C. Ligon, R. Liska, J. Stampfl, M. Gurr, R. Mulhaupt, **Polymers for 3D Printing and Customized Additive Manufacturing**, *Chem. Rev.* 2017, **117**: 10212-10290.
[13] N. Bhattacharjee, A. Urrios, S. Kanga, A. Folch, **The upcoming 3D-printing revolution in microfluidics**, *Lab Chip.* 2016, **16**: 1720-1742.
[14] P.J. Kitson, M.H. Rosnes, V. Sans, V. Dragone, L. Cronin, **Configurable 3D-Printed millifluidic and microfluidic 'lab on a chip' reactionware devices**, *Lab Chip.* 2012, **12**: 3267-3271.
[15] O. Okafor, A. Weilhard, J.A. Fernandes, E. Karjalainen, R. Goodridge, V. Sans, **Advanced reactor engineering with 3D printing for the continuous-flow synthesis of silver nanoparticles**, *React. Chem. Eng.* 2017, **2**: 129-136.
[16] O. Okafor, K. Robertson, R. Goodridge, V. Sans, **Continuous-flow crystallisation in 3D-printed compact devices**, *React. Chem. Eng.* 2019, **4**: 1682-1688.
[17] S. Bettermann, F. Kandelhard, H.-U. Moritz, W. Pauer, **Digital and lean development method for 3D-printed reactors based on CAD modeling and CFD simulation**, *Chem. Eng. Res. Des.* 2019, **152**: 71-84.
[18] M. Bracconi, M. Ambrosetti, O. Okafor, V. Sans, X. Zhang, X. Ou, C.P. Da Fonte, X. Fan, M. Maestri, G. Groppi, E. Tronconi, **Investigation of pressure drop in 3D replicated open-cell foams: Coupling CFD with experimental data on additively manufactured foams**, *Chem. Eng. J.* 2019, **377**.
[19] C. Parra-Cabrera, C. Achille, S. Kuhn, R. Ameloot, **3D printing in chemical engineering and catalytic technology: structured catalysts, mixers and reactors**, *Chem. Soc. Rev.* 2018, **47**: 209-230.
[20] S. Rossi, A. Puglisi, M. Benaglia, **Additive Manufacturing Technologies: 3D Printing in Organic Synthesis**, *ChemCatChem.* 2018, **10**: 1512-1525.
[21] A.J. Capel, R.P. Rimington, M.P. Lewis, S.D.R. Christie, **3D printing for chemical, pharmaceutical and biological applications**, *Nat. Rev. Chem.* 2018, **2**: 422-436.

[22] V. Dragone, V. Sans, M.H. Rosnes, P.J. Kitson, L. Cronin, **3D-printed devices for continuous-flow organic chemistry**, *Beilstein J. Org. Chem.* 2013, **9**: 951-959.
[23] Z.X. Rao, B. Patel, A. Monaco, Z.J. Cao, M. Barniol-Xicota, E. Pichon, M. Ladlow, S.T. Hilton, **3D-Printed Polypropylene Continuous-Flow Column Reactors: Exploration of Reactor Utility in SNAr Reactions and the Synthesis of Bicyclic and Tetracyclic Heterocycles**, *Eur. J. Org. Chem.* 2017, **2017**: 6499-6504.
[24] J.M. Neumaier, A. Madani, T. Klein, T. Ziegler, **Low-budget 3D-printed equipment for continuous flow reactions**, *Beilstein J. Org. Chem.* 2019, **15**: 558-566.
[25] M.R. Penny, Z.X. Rao, B.F. Peniche, S.T. Hilton, **Modular 3D Printed Compressed Air Driven Continuous-Flow Systems for Chemical Synthesis**, *Eur. J. Org. Chem.* 2019, **2019**: 3783-3787.
[26] B. Valentan, Z. Kadivnik, T. Brajlih, A. Anderson, I. Drstvensek, **PROCESSING POLY(ETHER ETHERKETONE) ON A 3D PRINTER FOR THERMOPLASTIC MODELLING**, *Mat. Tehnol.* 2013, **47**: 715-721.
[27] M.J. Harding, S. Brady, H. O'Connor, R. Lopez-Rodriguez, M.D. Edwards, S. Tracy, D. Dowling, G. Gibson, K.P. Girard, S. Ferguson, **3D printing of PEEK reactors for flow chemistry and continuous chemical processing**, *React. Chem. Eng.* 2020, **5**: 728-735.
[28] B. Gutmann, M. Köckinger, G. Glotz, T. Ciaglia, E. Slama, M. Zadravec, S. Pfanner, M.C. Maier, H. Gruber-Wölfler, C. Oliver Kappe, **Design and 3D printing of a stainless steel reactor for continuous difluoromethylations using fluoroform**, *React. Chem. Eng.* 2017, **2**: 919-927.**
[29] M.C. Maier, R. Lebl, P. Sulzer, J. Lechner, T. Mayr, M. Zadravec, E. Slama, S. Pfanner, C. Schmölzer, P. Pöchlauer, C.O. Kappe, H. Gruber-Woelfler, **Development of customized 3D printed stainless steel reactors with inline oxygen sensors for aerobic oxidation of Grignard reagents in continuous flow**, *React. Chem. Eng.* 2019, **4**: 393-401.*
[30] H.J. Lee, R.C. Roberts, D.J. Im, S.J. Yim, H. Kim, J.T. Kim, D.P. Kim, **Enhanced Controllability of Fries Rearrangements Using High-Resolution 3D-Printed Metal Microreactor with Circular Channel**, *Small.* 2019, **15**: e1905005.
[31] K.-W. Gyak, N.K. Vishwakarma, Y.-H. Hwang, J. Kim, H.-s. Yun, D.-P. Kim, **3D-printed monolithic SiCN ceramic microreactors from a photocurable preceramic resin for the high temperature ammonia cracking process**, *React. Chem. Eng.* 2019, **4**: 1393-1399.
[32] J. Britton, S. Majumdar, G.A. Weiss, **Continuous flow biocatalysis**, *Chem. Soc. Rev.* 2018, **47**: 5891-5918.
[33] P. Lozano, S. Nieto, J.L. Serrano, J. Perez, G. Sanchez-Gomez, E. Garcia-Verdugo, S.V. Luis, **Flow Biocatalytic Processes in Ionic Liquids and Supercritical Fluids**, *Mini Rev. Org. Chem.* 2017, **14**: 65-74.
[34] J.M. Bolivar, F.L. Gallego, **Characterization and evaluation of immobilized enzymes for applications in flow-reactors**, *Current Opinion Green Sustain. Chem.* 2020, doi.org/10.1016/j.cogsc.2020.04.010
[35] M. Romero-Fernández, F. Paradisi, **Protein immobilization technology for flow biocatalysis**, *Current Opinion Chem. Biol.* 2020, **55**: 1-8.
[36] M.L. Contente, F. Paradisi, **Self-sustaining closed-loop multienzyme-mediated conversion of amines into alcohols in continuous reactions**, *Nat. Catal.* 2018, **1**: 452-459.
[37] E. Peris, O. Okafor, E. Kulcinskaja, R. Goodridge, S.V. Luis, E. Garcia-Verdugo, E. O'Reilly, V. Sans, **Tuneable 3D printed bioreactors for transaminations under continuous-flow**, *Green Chem.* 2017, **19**: 5345-5349.*
[38] J. Ye, T. Chu, J. Chu, B. Gao, B. He, **A Versatile Approach for Enzyme Immobilization Using Chemically Modified 3D-Printed Scaffolds**, *ACS Sustain. Chem. Eng.* 2019, **7**: 18048-18054.
[39] M. Maier, C.P. Radtke, J. Hubbuch, C.M. Niemeyer, K.S. Rabe, **On-Demand Production of Flow-Reactor Cartridges by 3D Printing of Thermostable Enzymes**, *Angew. Chem. Int. Ed. Eng.* 2018, **57**: 5539-5543.*

[40] M. Peng, E. Mittmann, L. Wenger, J. Hubbuch, M.K.M. Engqvist, C.M. Niemeyer, K.S. Rabe, **3D-Printed Phenacrylate Decarboxylase Flow Reactors for the Chemoenzymatic Synthesis of 4-Hydroxystilbene**, *Chem. Eur. J.* 2019: 5.
[41] G. Chisholm, P.J. Kitson, N.D. Kirkaldy, L.G. Bloor, L. Cronin, **3D printed flow plates for the electrolysis of water: an economic and adaptable approach to device manufacture**, *Energy Environ. Sci.* 2014, **7**: 3026-3032.
[42] J.R. Hudkins, D.G. Wheeler, B. Peña, C.P. Berlinguette, **Rapid prototyping of electrolyzer flow field plates**, *Energy Environ. Sci.* 2016, **9**: 3417-3423.
[43] A.A. Folgueiras-Amador, T. Wirth, **Perspectives in flow electrochemistry**, *J. Flow Chem.* 2017, **7**: 94.
[44] C.A. Paddon, M. Atobe, T. Fuchigami, P. He, P. Watts, S.J. Haswell, G.J. Pritchard, S.D. Bull, F. Marken, **Towards paired and coupled electrode reactions for clean organic microreactor electrosyntheses**, *J. Applied Electrochem.* 2006, **36**: 617.
[45] A.A. Folgueiras-Amador, K. Philipps, S. Guilbaud, J. Poelakker, T. Wirth, **An Easy-to-Machine Electrochemical Flow Microreactor: Efficient Synthesis of Isoindolinone and Flow Functionalization**, *Angew. Chem. Int. Ed.* 2017, **56**: 15446-15450.
[46] C.G.W. van Melis, M.R. Penny, A.D. Garcia, A. Petti, A.P. Dobbs, S.T. Hilton, K. Lam, **Supporting-Electrolyte-Free Electrochemical Methoxymethylation of Alcohols Using a 3D-Printed Electrosynthesis Continuous Flow Cell System**, *ChemElectroChem.* 2019, **6**: 4144-4148.
[47] J. Lölsberg, O. Starck, S. Stiefel, J. Hereijgers, T. Breugelmans, M. Wessling, **3D-Printed Electrodes with Improved Mass Transport Properties**, *ChemElectroChem.* 2017, **4**: 3309-3313.*****
[48] B. Bayatsarmadi, M. Horne, T. Rodopoulos, D. Gunasegaram, **Intensifying Diffusion-Limited Reactions by Using Static Mixer Electrodes in a Novel Electrochemical Flow Cell**, *J. Electrochem. Soc.* 2020, **167**: 063502.
[49] J.K. Mo, R.R. Dehoff, W.H. Peter, T.J. Toops, J.B. Green, F.Y. Zhang, **Additive manufacturing of liquid/gas diffusion layers for low-cost and high-efficiency hydrogen production**, *Int. J. Hydrogen Energy.* 2016, **41**: 3128-3135.
[50] R.A. Marquez-Montes, V.H. Collins-Martinez, I. Perez-Reyes, D. Chavez-Flores, O.A. Graeve, V.H. Ramos-Sanchez, **Electrochemical Engineering Assessment of a Novel 3D-Printed Filter-Press Electrochemical Reactor for Multipurpose Laboratory Applications**, *ACS Sustain. Chem. Eng.* 2020, **8**: 3896-3905.*****
[51] I. Lozano, C. López, N. Menendez, N. Casillas, P. Herrasti, **Design, Construction and Evaluation of a 3D Printed Electrochemical Flow Cell for the Synthesis of Magnetite Nanoparticles**, *J. Electrochem. Soc.* 2018, **165**: H688-H697.
[52] H. Al Jassmi, F. Al Najjar, A.-H.I. Mourad, **Large-Scale 3D Printing: The Way Forward**, *IOP Conference Series: Materials Science and Engineering.* 2018, **324**: 012088.
[53] P. Urhal, A. Weightman, C. Diver, P. Bartolo, **Robot assisted additive manufacturing: A review**, *Robot. CIM-Int. Manufact.* 2019, **59**: 335-345.
[54] M. Sauerwein, E. Doubrovski, R. Balkenende, C. Bakker, **Exploring the potential of additive manufacturing for product design in a circular economy**, *J. Clean. Prod.* 2019, **226**: 1138-1149.
[55] V. Gonçalves Maciel, D. J. Wales, M. Seferin, V. Sans, **Environmental performance of 3D-Printing polymerisable ionic liquids**, *J. Clean. Prod.* 2019, **214:** 29-40.