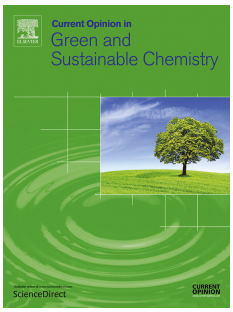

Recent Advances in 3D Printing for Continuous Flow Chemistry

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Recent Advances in 3D Printing for Continuous Flow Chemistry

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Abstract

Continuous flow processes have distinct advantages over batch chemistry when it comes to long-term sustainability in the chemical industry, and they are widely acknowledged as being a greener approach to synthesis. However, despite this, the high costs and complexity of current commercial systems act as barriers to entry in this key technology for new entrants, stymieing chemists transition to continuous flow. In this overview, we discuss how 3D printing has emerged as a transformative force for chemists seeking to move into continuous flow. Alongside the physical equipment and microreactors, recent reports on incorporation of catalysts into 3D-printed reactors offers great promise for recyclability and environmental sustainability and the combined convergence of 3D printing and catalysis represents a transformative shift towards environmentally conscious, efficient, and standardized chemical processes in continuous flow.

Introduction

The synthesis of small molecules and the scale-up syntheses of these are a key component of the United Nations Sustainable Development Goals (SDGs), to develop a more sustainable global future by 2030 [1]. As the chemistry community confronts an escalating demand for environmentally friendly solutions, innovative methodologies such as flow chemistry have emerged as transformative chemical processes over batch syntheses [2]. Unlike conventional batch processes, flow chemistry involves the continuous flow of reactants through a reactor [3], and offers improved safety, efficiency, and scalability while reducing environmental costs and waste production on a large scale. In accordance with the twelve principles of green chemistry outlined by Anastas and Warner, these attributes have positioned flow chemistry as an key tenet of sustainable chemical synthesis [4].

The introduction of 3D printing in the 1980s was a significant development for a range of scientific disciplines and is swiftly changing the way scientists carry out their

research. 3D printing involves the layer by layer building of physical objects from a digital computer aided design (CAD) model. With easily accessible modelling software, these objects can be rapidly accessed by anyone using low-cost devices, with little to no knowledge of the printers themselves [5]. Laboratories worldwide have rapidly realised the potential of 3D printing as an invaluable tool for rapid prototyping and creating complex laboratory apparatus that were previously challenging or costly to produce using traditional manufacturing methods. In recent years, the integration of 3D printing with flow chemistry has driven innovation in reactor design and catalysis by leveraging the additive manufacturing precision to create custom flow reactors and system set ups tailored to the reaction requirements [6,7].

The progress in 3D printing technologies, including Fused Modelling Deposition (FDM), Stereolithography (SLA), and Selective Laser Sintering (SLS), have facilitated the development of different types of reactors using a wide range of materials such as polymers, metals, and ceramics, making it possible to tailor specific reaction conditions to the required reactors [7–12]. This flexibility in material selection not only expands the possibilities for designing highly efficient and selective flow reactors, but also contributes to the development of greener chemical processes. Further advancements in this area have seen the incorporation of catalysts into 3D printed reactors for flow catalytic reactions [13]. The precision offered by 3D printing technology allows for the strategic placement of catalysts within the reactor, optimizing the interaction between reactants and catalysts. Exploiting the adaptability of this technology and the different ways in which a catalyst can be embedded within a 3D print has been crucial for developing catalytic systems that can withstand a wide range of operating conditions, whilst maintaining stability and activity.

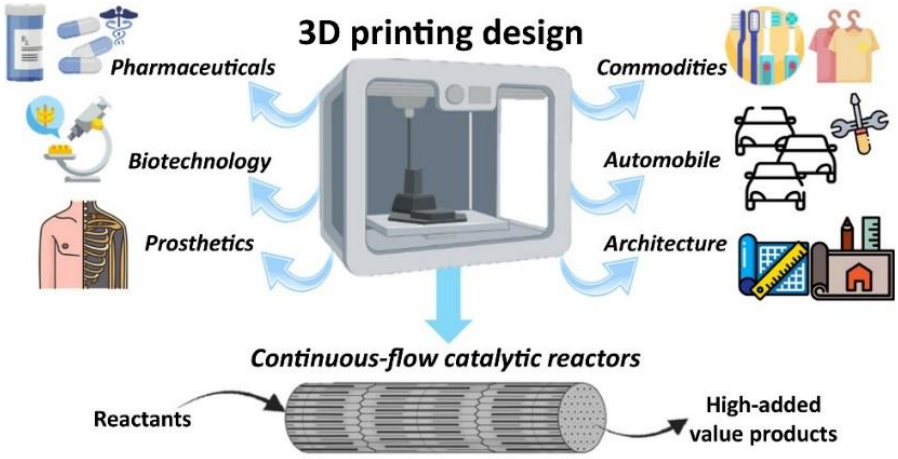

Figure 1: Applications of 3D printing [14]

This review explores the most innovative advancements in this interdisciplinary field over the past two to three years, highlighting some of the ongoing impactful and diverse contributions of 3D printed reactors applications to catalytic processes. It illustrates how the convergence of 3D printing and catalysis is reshaping the research landscape, not only by facilitating the swift prototyping of flow reactors but also by driving the creation of customised catalytic systems and greener catalytic processes.

Chemical catalysis

While traditional methods like fixed-bed reactors and continuous stirred-tank reactors have been widely used for catalytic reactions in flow, they face constraints regarding design flexibility and the time-consuming process of catalyst recovery from the final product [15,16]. Customized 3D printed reactors can overcome these limitations, leading to higher catalyst performance and selectivity in flow chemical reactions [14,17]. 3D printed monoliths have garnered considerable attention for catalytic reactions owing to their distinctive features, encompassing tailored pore size, customized pattern design and improved heat and mass transfer capabilities [18–22]. However, despite these advantages, achieving optimal efficiency and higher conversion rates compared to conventional packed bed and batch processes requires the optimization of the internal structures, as underscored by several authors [22–24].

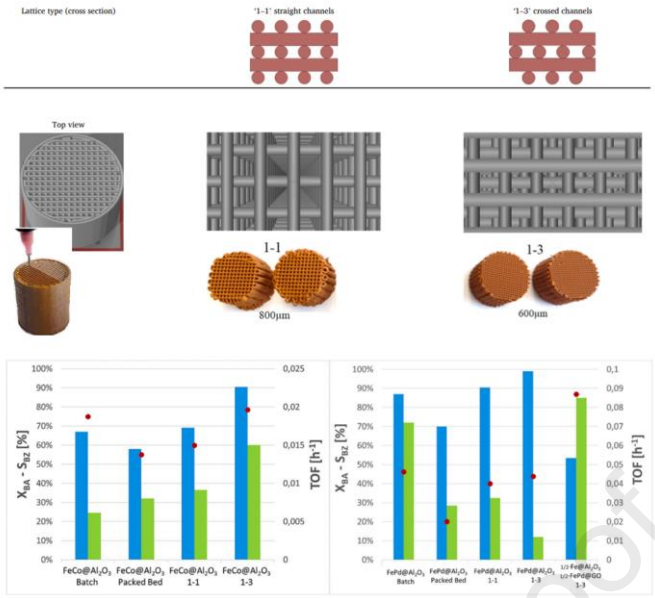

Figure 2: Upper Section: Fabrication of Fe-containing supported monolithic catalysts using the micro-extrusion-based direct-write 3D technique. Lower Section: Comparative assessment of the performance between 3D printed monoliths and their packed bed counterparts in the continuous flow reactor and batch reactor for the oxidation of benzyl alcohol [23]

Beyond structural optimization, the selection of materials used in 3D printing and the reaction conditions significantly influence the performance of the flow reactors in catalytic applications and its environmental footprint [25]. The synergy between structural design and material choice is essential for attaining the desired catalytic outcomes. A study by Jaquot reported an improved sustainable monolith formulation in the oxidation of benzyl alcohol into benzaldehyde by substituting Cobalt and Palladium metals with less active but more environmentally abundant iron metal (Figure 2) [23]. This modification not only showcases the impact of material selection on catalytic performance but also exemplifies a shift towards more sustainable practices in catalysis. Significant enhancements were observed with the FePd@Al_2O_3 configuration in XBA conversion, showcasing a 20% increase during the transition from a traditional packed bed reactor to 3D printed stacked monoliths reactor, along an improved Turnover Frequency (TOF) performance from 0.02 h^{-1} to 0.04 h^{-1}. Moreover, molecular oxygen was utilized alongside an aqueous solvent, contributing to a greener process. The use of water as a solvent for catalytic reactions further contributes to the overarching goal of sustainability, as recently exemplified by Vega [24] and Zhakeyev [18]. Incorporating water as a solvent not only aligns with green chemistry principles but also contributes to the reduction of organic solvents, which are often associated with environmental and health concerns [26].

The functionalization of 3D printing material with a catalyst through 3D printing technology, whether through preloading or post-loading, enhances the recyclability of catalysts [27]. SLA 3D printing, in particular, facilitates the preloading of catalysts with polymerizable functional groups into the resin [28]. Zhakeyev demonstrated how vinyl groups within the St-BTZ photocatalyst can react with acrylate resin during the SLA photomolymerization process, enabling successful integration and the direct creation of functional catalysts in the resin matrix [29]. In an initial attempt to 3D print SLA microfluidic reactors [18], the authors encountered suboptimal irradiation to the reaction solution due to external surfaces containing photocatalyst, compromising the device effectiveness. Consequently, the challenge was addressed through the design of monolithic structures, enabling direct irradiation of the active surface for the photosensitisation of singlet oxygen. While pre-functionalization is a straightforward technique when embedding catalysts within reactors prior to initiating the SLA 3D printing process, the compatibility of certain catalysts presents limitations to its widespread application. In this context, Pellejero [30] applied the Au@POM/TiO_2 photocatalyst through dip-coating onto the ABS mold before the polymer casting process. Subsequently, the catalyst was assessed for its effectiveness in the reduction of 4-nitrophenol to 4-aminophenol, achieving a conversion rate exceeding 90%. These examples stand as promising techniques, not only in overcoming the challenges of irradiation encountered in photocatalytic processes but also in contributing to environmental wastewater remediation. Furthermore, recent publications in the field have also enhanced the use of 3D printed flow reactors for wastewater treatment and pollutant degradation [19,31–34].

Biocatalysis

In the search for sustainable and environmentally benign chemical processes, biocatalysis has also emerged as a transformative new approach to continuous flow [35]. Using enzymes as natural catalysts, biocatalysis represents a green and effective alternative to metal-based catalysis in the production of APIs and fine chemicals, showcasing high activity under mild conditions and substrate specificity [36,37].

The exploration of enzyme immobilization has arisen as a response to challenges related to stability and reusability of enzymes in solution. Novel methods and designs

for enzyme immobilization to bioreactors have recently been investigated, contributing to the ongoing enhancement of their applicability to industrial processes [38–40]. Noteworthy advancements include surface modifications of 3D printed objects using FDM, achieved through coating methods. Examples of such innovations include Mussel-inspired polydopamine coating, as demonstrated by Sriwong for the immobilization of GcAPRD on a polypropylene (PP) reactor [41], and chitosan coating for immobilizing laccase on a poly-lactic acid (PLA) reactor, as explored by Shen [42]. Other methodologies encompass co-entrapment of two different enzymes in agarose gel by Croci [43] and the covalent binding of a decarboxylase into ceramic supports by Valotta [44].

Standardization of 3D printed Reactionware

On-demand prototyping has been a remarkable development that has accelerated the rapid design of flow chemistry reactionware. This dynamic capability has significantly reduced the time and effort traditionally required for designing and iterating reactionware, allowing researchers and engineers to swiftly explore novel configurations in a cost-effective manner. This design flexibility has enhanced the development and optimization of greener chemical processes, particularly in research and development settings [45].

Over the last decade, numerous papers have showcased the widespread adoption of 3D printing to fabricate diverse components to integrate into the flow chemistry process [46]. These demonstrated the adaptability of 3D printing across various aspects of chemical synthesis, including the development of syringe pumps for controlled reagent delivery, customized flow reactors and mixers tailored to specific reaction conditions, and the successful integration of sensors for real-time monitoring of crucial parameters [7,47,48]. While these advancements in 3D printing have undoubtedly contributed to their success, reproducibility of reactions still remains a critical concern. The lack of comprehensive documentation regarding experimental setup, light source, or reaction parameters, poses a hurdle in achieving consistent and reliable outcomes across different laboratories and studies, especially in the domain of photochemistry [49–52]. Accurate reporting and monitoring of these, are essential for ensuring reproducibility, given their direct influence on the reaction rate and yield

(Figure 3). Addressing this challenge is pivotal for harnessing the full potential of 3D printing in advancing flow chemistry methodologies on a broader scale.

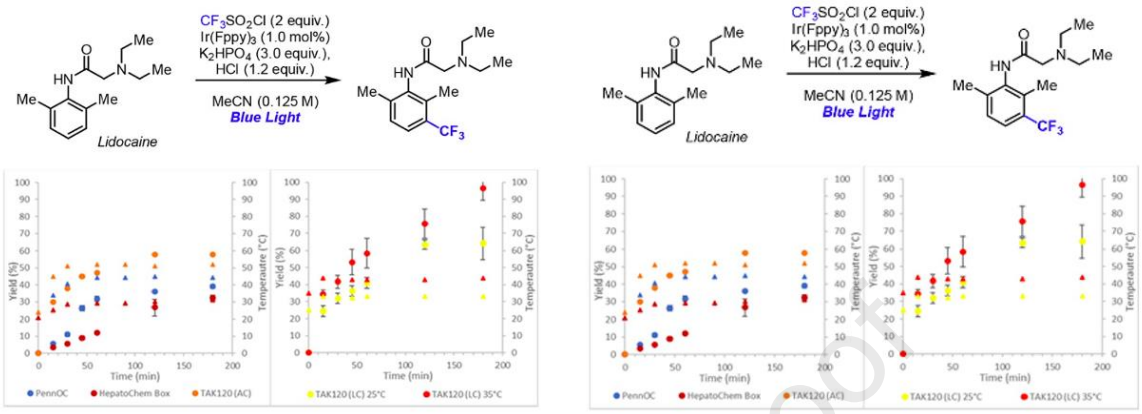

Figure 3: Performance comparison of two photocatalytic reactions across four different photoreactors and set-ups over time, monitoring the reaction yields (%, dots) and reaction temperature (ºC, triangle). [52]

Photochemical reactions have gained relevance as a sustainable approach due to their potential to drive chemical transformations using visible light as an abundant and renewable energy source [53]. This process offers numerous benefits such as reduced reliance on non-renewable energy sources, minimized environmental impact, and the ability to carry out reactions under mild conditions [54]. Therefore, it is crucial to establish standardized protocols to ensure the reproducibility of photochemical reactions, in order to continue promoting sustainable and greener chemistry practices [55]. Standardization presents significant challenges due to the wide range of light sources and array of experimental setups that have been used. Variations are caused by factors such as differences in heat emitted by lamps leading to reaction reproducibility problems, necessitating a standard for optimal distance between the lamp and reactor and accurate temperature control and monitoring. To address this, Schiel recently developed a simple and reproducible PETG 3D printed photoreactor and setup characterized by its ability to maintain a controlled temperature range between -20°C and +80°C through the insertion of thermoelectric coolers (TECs) into the chamber walls [56]. Furthermore, the reactor design incorporates an electronic control unit based on an Arduino microchip to ensure precise monitoring temperature control. The simplicity of this design addresses the limitations encountered in batch processes such as limited light penetration and temperature fluctuations associated with LED lights.

Fused modelling deposition (FDM) is a widely used additive manufacturing technique that is particularly well-suited for creating intricate and functional flow reactor designs. FDM involves heating and extruding thermoplastic materials layer by layer to build up the desired 3D structure. These polymers are chosen for their ability to withstand the chemical and thermal conditions present in photochemical reactions while offering durability and cost-effectiveness [7]. To address the challenges of a lack of reproducibility and standardization of continuous flow chemistry, the Hilton group developed a 3D printed PLA flow system and selected polypropylene as their primary material for developing standardized flow and photochemical flow reactors [57,58]. Initially, stereolithography was used for development of photochemical reactors due to the clear appearance of the final prints. However, challenges related to heat led to the transition to the use of PP, which is also transparent to UV light. The dimensions of the reactor internal channels were optimised along with the distance of the lamp from the reactor in order to develop a standard housing for LED lamps that could be utilized in conjunction with 3D printed flow photochemistry (Figure 4).

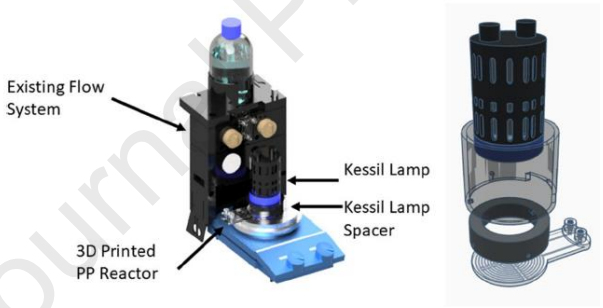

Figure 4: Proposed continuous flow photochemistry system designed to work seamlessly with existing Kessil lamps (depicted on the left). A detailed view (shown on the right) provides an illustration of the suggested lamp setup positioned above the 3D-printed reactor [57].

The system developed by the group was further commercialized in partnership with IKA in 2021 enabling the readily adoption by laboratories and industries worldwide and incorporates 3D printed polypropylene and PVDF reactors at its core demonstrating the potential of 3D printing of commercial reactors [63]. The effectiveness of the system was first demonstrated in the bromination of various toluenes, achieving a productivity of 75 mmol h^{-1}. The 3D printed PP photoreactors were further adapted by the group in order to gain an understanding of temperature fluctuations over time and its correlation with the distance of the lamp and light intensity [59]. These studies enabled greater standardisation over the photochemical reaction and led to the

development of a low cost fully automated 3D printed flow chemistry system for real-time monitoring of key reaction parameters through a PC-interface platform [60]. Recent advancements in the utilization of this system have been published for the development of a novel synthetic pathway aimed at synthesizing heterocycles containing CHF_2 through intramolecular oxy-difluoromethylation of alkenes [61]. The adoption of the flow system facilitated a substantial reduction in reaction time, decreasing it from several hours to 20 minutes. A range of products were synthesised resulting in yields ranging from moderate to excellent with favourable stereo- and regioselectivity. Furthermore, the scalability of this method was successfully demonstrated, maintaining consistent yields as the reaction was scaled up from 42 mg to 0.186 g. The IKA flow system has also been recently used for the rapid modification of nucleosides via Suzuki-Miyaura coupling, resulting in significant reductions in both reaction time and solvent usage, alongside column-free product isolation [62]. This methodology was applied to the synthesis of Brivudine, an antiviral drug, achieving an isolated yield of 85%. The synthesis was conducted in a one-pot procedure without intermediate isolation, employing milder reaction conditions and reducing the time required from 2 days to just 3 hours compared to conventional processes. These recent developments represent a noteworthy step forward in achieving a more standardized flow chemistry approach with 3D printed systems, contributing to improved optimization and increased efficiency.

Conclusion

In summary, the integration of 3D printed reactors in catalytic processes has emerged as a transformative force, significantly enhancing the development of greener chemical processes. As further research and development continues, it is evident that these reactors allow for precision and customization, optimizing the overall efficiency of catalytic reactions. By tailoring the design of the reactors, incorporating green solvents, optimizing the loading of catalysts, and standardizing the reaction setup, 3D printed reactors are driving the evolution towards a more environmentally conscious and efficient future in chemical processes.

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Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Stephen Hilton reports a relationship with IKA that includes: consulting or advisory and funding grants. Dr Stephen Hilton is the inventor of the IKA FLOW that was developed in conjunction with IKA If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.