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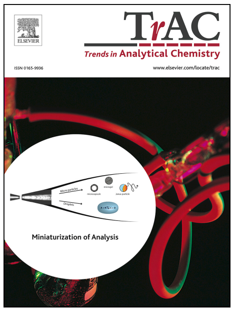

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Recent advances of 3D printing in analytical chemistry: focus on microfluidic, separation, and extraction devices

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Abstract

3D printing has attracted the attention of analytical chemists. 3D printing possesses the merits of fast and low-cost fabrication of geometrically complex 3D structures and has been employed in the fields of microfluidic devices, electrochemical sensors and biosensors, separation sciences, sample pretreatment, and wearable sensors. We focus on the applications and materials of 3D printing in microfluidic devices, separation sciences, and extraction over the last three years and we offer outlook. It is clear that the 3D printing in separation science is here to stay and with new materials development, to develop to on demand fabrication of separation tools.

Keywords: 3D printing; Microfluidic devices; Separation science; Extraction

1. Introduction

Recently, three-dimensional (3D) printing, also called “additive manufacturing,” has become a widely used tool for the construction of different devices in analytical chemistry [1]. 3D models are usually created directly by computer-aided design (CAD) and then printed based on layer-by-layer addition [2]. Compared with traditional manufacturing methods, 3D printing has various merits, including fast, low-cost, and fabrication with minimal waste generated [3,4]. Nowadays, 3D printing is an important tool in manufacturing and prototyping [5-7]. Various technologies for 3D printing have been used consisting of fused filament fabrication (FFF), stereolithography (SLA), selective laser melting (SLS), inkjet and Polyjet printing, and laminated object manufacturing (LOM) [8–11]. The techniques of 3D printing have been well-introduced in several reviews [12–14], thus they will not be covered here in detail.

3D printing was first introduced about 40 years ago [15]. Research in 3D printing has exhibited a rapid growth for printing functional parts, such as biomaterials, nanomaterials, metals, and ceramics as well as polymers [16–18]. 3D printing ~~is~~ has been extensively used in the fields of analytical chemistry, environment sciences, biology, medical devices, and other manufacturing fields [19–22]. In analytical chemistry, the main research fields include microfluidic devices, electrochemical sensors and biosensors, separation sciences, sample pretreatment, wearable sensors, and others [23]. A review of 3D printing applications in sensors and biosensors has been published by our group as well as several reviews published in the special area of analytical chemistry [24–27]. A recent comprehensive review on the broader implications for analytical chemistry was published by Spence *et al.* in 2017 [12]. This review mainly focuses on using 3D printing in the areas of microfluidic devices, separation sciences, and extraction over the last three years, putting in perspective the application of rapidly developing field of printable materials in connections to analytical chemistry applications (Fig. 1). We discuss recent developments for past 3 years and we provide outlook and future directions. Future impacts and challenges of 3D printing in these areas will be discussed. We hope that the review will guide analytical scientists to further explore 3D printing techniques in order to realize its potential applications in analytical chemistry.

2. Microfluidic devices in analytical chemistry

Microfluidic devices have the ability to control fluid samples in channels with micrometer widths [28]. Microfluidic techniques have evolved from simple devices to multi-functional integration, such as those used for cell or tissue incubation control, micropumps, and microvalves, and are generally referred to as "micro total analysis systems" [29,30]. Compared with traditional techniques, microfluidic techniques have many merits, including low cost and a small footprint leading to portability, fast analysis speed, small sample consumption, and component integration. Based on these merits, these integrated techniques are considered as important tools in analytical chemistry [31].

The materials used in the manufacture of microfluidic systems have evolved to fulfill the requirements of their various applications. Glass or silicon materials are often used for construction of traditional microfluidic systems. Soft lithography, using poly(dimethylsiloxane) (PDMS) materials, was introduced for the preparation of low-cost microfluidic devices two decades ago [32,33]. PDMS-based microfluidic devices have the advantages of simplicity of fabrication, rapid prototyping, and low cost. Many microfluidic devices are still made by PDMS materials [34–36]. However, PDMS materials based microfluidic devices also show some drawbacks, such as absorption of small molecules, cumbersome user interfaces, and limited manufactured ability [37]. Despite the limited resolution of 3D printing technology, 3D printing has been explored as promising complementary technology due to their superior merits of low-cost, minimum waste and easy to design different modules. In analytical chemistry, 3D-printed techniques in microfluidic devices have been widely used in the areas of environment analysis, disease diagnosis, cell analysis, chemical analysis, and so forth [38-40]. Table 1 summarizes some applications, techniques, materials, printed objects, analytical details, and advantages of 3D printing techniques in the field of microfluidic devices. We will elaborate on particular applications in the following sections.

2.1 Environment analysis

Environment analysis and monitoring are critical in the field of environment protection [41–45]. Many methods are currently available for the analysis of pollutants, including spectrophotometry, atomic absorption spectrometry, and chromatographic methods [46]. However, these methods require costly and complex machines, and lack the ability to obtain on-site and real-time measurements [47,48].

3D-printed microfluidic devices can solve these problems as a result of their intrinsic advantages. Examples of microfluidic devices used in environment analysis over the last three years are summarized as follows.

Breadmore *et al.* used Y-shaped microfluidic devices made by FFF for the colorimetric detection of iron in water (Fig. 2A) [41]. In the same group, a porous membrane integrated 3D-printed microfluidic device was constructed by FFF and used for the detection of nitrate in soil. Three different materials, including polylactic acid (PLA), acrylonitrile butadiene styrene (ABS), and Lay-Felt were chosen for preparation of the device (Fig. 2B) [42]. A 3D-printed flow system was developed using poly(methyl methacrylate) (PMMA), which enhanced the portability, simplicity, and low cost determination of lead in natural waters [43]. 3D printing has also been used for the preparation of more complex device structures. The 3D SLA-printed technique was employed for the construction of fourth generation microflow injection analysis system. The device was then employed for the detection of trace metal and glucose in complex samples, and other application cases (Fig. 2C) [44]. Recently, Breadmore *et al.* integrated multi-materials on a 3D-printed microfluidic device in order to detect ammonium in environmental water samples (Fig. 2D) [45].

2.2 Disease diagnosis

Important method for disease diagnosis is the detection of disease markers [49–52]. Lately, several 3D microfluidic diagnostic devices have been designed for the detection of various disease markers. Urinary tract infections ~~are~~ were considered one of the most common bacterial infections and mainly caused by *E. coil*. Microfluidic capillaric circuit was constructed by stereolithographic 3D printing technology and replicated into PDMS for rapid and facile detection of *E. coil* [49]. Boutelle *et al.* constructed a microfluidic device that integrated electrochemical biosensors to detect changes of glutamate, glucose, and lactate concentration. This device was further utilized for online detection of brain injury in patients in an intensive care unit [50]. A polymerase chain reaction (PCR) 3D-printed microfluidic device was fabricated for the determination of microRNA-21 levels in cancer cells and subsequently used for breast cancer diagnosis [51]. Tseng *et al.* used CuO nanoparticles and PLA composite materials for the preparation of a 3D-printed flow reactor to monitor living rat brain extracellular glucose [52]. Recently, SLA 3D printing technology was chosen by Frascella's group to construct the lab-on-a-chip platform for detection of early cancer biomarkers [53].

2.3 Cell analysis

Compared with traditional multiwell plate platforms, 3D-printed microfluidic devices can provide a 3D microenvironment for *in vitro* and *in vivo* cell analysis [54,55]. These 3D-printed devices have been utilized in the fields of single-cell analysis, cell culture and cancer cell invasion assays owing to the merits of low-cost, ease of use, biological compatibility, and facile integration with other devices [56–59].

Martin *et al.* presented a new method of 3D cell culture that is integrated with online detection modules. Endothelial cells were used as test cells for cell adhesion experiments on the inserts, and macrophages were also cultured and stimulated under different conditions [56]. In the same group, a 3D cell culture model connected to 3D-printed flow housings was prepared to culture PC 12 cells and then for separating and detecting the release of dopamine and norepinephrine [57]. Serex *et al.* employed extrusion-based 3D printing technology to integrate micro-concentrators in the microfluidic device, which led to an increase of cell concentration [58]. Recently, executing cell apoptosis and intracellular cross-talk was realized on a mixed 3D-printed and paper-based microfluidic device [59].

2.4 Others

Other applications using 3D-printed techniques in microfluidic devices include DNA analysis and chemical analysis [60–63]. Gale *et al.* used 3D printing to prepare an inexpensive and rapid microfluidic device for visualizing various fluid phenomenon, including DNA melting, fluorescent imaging analysis, and interfacial dynamics [60]. An FFF-synthesized glass microreactor was demonstrated by Raman spectroscopy, which was further employed for online mass spectrometric analysis of synthetic reactions [61]. Nordin *et al.* used stereolithographic 3D printer for construction of various high density microfluidic devices including valves, pumps, multiplexer and mixer, which showed lower volume valves and improved durability than previous work (Fig 3A). The 3D printing technology ~~makes~~ made it possible to fabricate and test a new multiplexer within one day [62]. In addition, an excellent 3D-printed microfluidic chip was put forward by Chen *et al.*, which was used for determining the inhibition of cancer cells according to survival concentration and the evaluation of efficiency in multi-drug combinations (Fig. 3B) [63].

3. Separation science

Separation science plays a central role in analytical chemistry. 3D printing techniques have attracted great attentions in the fields of high-performance liquid chromatography (HPLC), capillary electrophoresis (CE), and others [27]. Many detailed devices for separation science have been constructed by 3D printing including separation columns, stationary phases, samples preprocessing devices, detectors, interface devices, *etc*. [64]. The fields, techniques, materials, printed objects, analytical details, and advantages of 3D printing for separation science are summarized in Table 2.

3.1 High-performance liquid chromatography

High-performance liquid chromatography (HPLC) is a common and powerful separation tool that has been widely utilized in various fields [65]. HPLC column and stationary phase materials are the most important part of the instrument. 3D printing is capable of producing complex geometrically and defined materials, which offers a new range of tools for the design of different column structures and stationary phase materials. Here, we summarize the recent advances using 3D printing in the field of HPLC.

Fee *et al.* used SLA-printed technique to design various stationary phases with particles of different shapes including icosahedra, tetrahedral, octahedral, triangular bipyramid, and stellar octangular (Fig. 4A-E). They showed that tetrahedral particles owned the lower plate height than other types of particles. Hence, 3D printing can regulate the shape, position, and orientation of stationary-phase particles [66]. Except for shapes of porous beds, column shapes also can be designed by 3D printing. In Fig. 4F-H, different shapes of polymerized monoliths were prepared by selective laser melting 3D printing to evaluate the effect of column geometry in chromatographic separation. These column shapes included 3D spiral, 2D serpentine, and 3D serpentine with the same length. The 3D serpentine column exhibited a high theoretical plate number, peak capacity, and less analytical time for the separation of small molecules and proteins. 3D printing provides a novel idea for the design of high-efficiency HPLC columns [67].

3.2 Capillary electrophoresis

In addition to HPLC, capillary electrophoresis (CE) is also considered a fundamental analytical technique in various fields. 3D printing technologies can be used to print electrophoretic separation devices. Martin *et al.* integrated electrode materials and capillary into microfluidic devices during the print process using PolyJet 3D printing technology, which was further used for the detection of catechol and nitric oxide (Fig. 5A-D) [68]. A novel thread-based microfluidic device was prepared by FDM 3D printer for capillary electrophoresis separation and further used for the determination of ions in diet soft drinks (Fig. 5E-G) [69]. To date, 3D printing has been also been applied to the building of detection and interface devices among the CE field. Macka *et al.* employed FFF to fabricate a photometric detection body for the analysis of Cu^{2+} and Zn^{2+} complexes by CE. In addition, the system was chosen for the analysis of river water [70]. The interface technique is very important for connecting the CE and mass spectrometer (MS). The FFF technique was utilized by

Lago *et al.* for printing the cartridge in order to improve the interface between the CE instrument and the MS. Heat dissipation was studied by separating thermally unstable species, which demonstrated that the 3D-printed cartridge had better properties than the original cartridge [71]. Recently, a light-emitting diode (LED)-induced fluorescence detector for CE was built by FFF. The device has two detectors in a CE system, which carried out dual-detector functions: Taylor dispersion analysis (TDA) and CE-TDA. The system was used to monitor the reaction between fluorescein isothiocyanate and protein [72].

3.3 Others

3D printing also has certain applications in gas chromatography (GC) and membrane separation. Lucklum *et al.* used SLA 3D printing to design and fabricate miniature gas chromatography (GC) columns with an improved packing density and separation capabilities. These 3D-printed GC columns were then used as sensors of ethylene gas [73]. In the same group, a stacked spiral GC column was designed and printed by the same method. The system could detect ethylene with ambient air and the detection limit was found to be 2.3 ppb [74]. Spence *et al.* used the Polyjet technique to create a membrane separation device with the ability to measure binding constants between Zn^{2+} and human serum albumin (HSA). The device can be fully customized and the user can choose any membrane for the dialysis test. Hence, the 3D-printed membrane separation device is considered as a very important tool in equilibrium dialysis [75].

4. Extraction

Extraction is an important sample preparation method used to improve the selectivity and sensitivity of analytical samples [76,77]. Solid-phase extraction (SPE) and liquid-phase extraction (LPE) are the two most widely used extraction techniques [78,79]. Recently, new materials and techniques used in extraction have emerged as a research hotspot, and are now widely used in the fields of biomedical, pharmaceutical, forensic, and environmental research [80-83]. 3D printing techniques (especially FFF and SLA techniques), consisting of the many merits mentioned above, also have aroused the attention of scientists in the extraction field. Here, we mainly focus on the application and materials of 3D printing used in the extraction field. In addition, Table 3 summarizes the current fields, techniques, materials, printed objects, analytical details, and advantages of 3D printing for extraction.

4.1 Solid-phase extraction

Solid-phase extraction (SPE) is used to extract target compounds from a liquid or gaseous sample. 3D printing can be utilized to prepare different SPE sorbent configurations consisting of fibers, particles, blades, and tubes for online analysis. These 3D-printed extraction devices have been used in the fields of pharmacy, environment, medicine, biology and chemistry. Some detailed examples for the application of these SPE devices are described as follows.

FFF 3D printing and the composite material thermoplastic elastomer and poly(vinyl alcohol) (PVA), called “LAY-FOMM 60,” were employed by Bączek *et al.* for preparation of tube-shaped adsorbents (Fig. 6A). Application of the 3D-printed device was confirmed by extracting glimepiride from water, then desorption by methanol, water, or a mixture of both, followed by analysis by LC-MS [84]. In the same group, FFF 3D printing and the same material were further used to fabricate sorbents for the extraction of steroids from human plasma [85]. Su *et al.* used SLA 3D printing and resins containing a mixture of TiO_2 nanoparticles materials to build a demountable mini-column as an SPE device (Fig. 6B). The device demonstrated the high selective extraction of inorganic As and Se species, followed by analysis by ICP-MS. As and Se species can be extracted and analyzed with low detection limits and high sensitivity. 3D printing displays the advantages of simple manufacture of analytical components and the ability to design smart multifunctional devices [86]. Maya *et al.* fabricated a disk-based automated SPE device by SLA 3D printing and used a clear photoactive resin as the printed material (Fig. 6C). The automated SPE system was used for the quantification of iron in water. The limit of detection, sensitivity, and reproducibility were improved by the novel 3D-printed system [87]. In addition, their group designed an SLA 3D-printed rotating disk adsorptive extraction device (RDSE) for the synchronous extraction of 14 metals from complex samples (Fig. 6D) [88]. A microflow injection analysis was developed by Miró *et al.* by SLA printing technology and used to determine organic emerging contaminants from human saliva and urine samples [89]. Recently, 3D printed microfluidic devices with formed monoliths were used for extraction of different biomarkers. Woolley et al. developed a reversed-phase lauryl methacrylate-based monolith, which formed in 3D printed microfluidic devices and was used for the extraction and determination of preterm birth biomarkers (Fig. 6E) [90]. In addition, the group also prepared a 3D printed microfluidic device with monolith for immunoaffinity extraction of preterm birth biomarkers (Fig. 6F) [91].

4.2 Liquid-phase extraction

Liquid-phase extraction (LPE) is another important sample preparation method that has recently applied by 3D printing [92,93]. Maya *et al.* printed different phase separators with an SLA 3D printer using a clear photoactive resin material. This is the first report of 3D printing used in dispersive LPE to concentrate organic phases under an automated function. The automated microextraction system was used to extract parabens in various real samples that were then further separated by liquid chromatography. The method showed high stability, reproducibility, and sensitivity for the extraction [92]. SLA 3D printing is also used for the construction of automated nanostructured hollow-fiber supported microextraction. The application of the device was used to identify nonsteroidal anti-inflammatory drugs (NSAIDs) in urine samples, which showed low limits of detection and high relative recovery [93].

5. Conclusions and future perspectives

Compared with traditional fabrication techniques, 3D printing undoubtedly shows many advantages in analytical chemistry, such as on-demand fabrication of the devices [94,95]. In this review, the applications and materials of 3D printing in microfluidic, separation science, and extraction devices, and the advantages of this evolving technology were summarized. Despite the advantages and wide applications of 3D printing, there are some constraints, especially for low resolution, which limit further development of 3D printing in analytical chemistry [96]. It is expected that with new technologies of 3D printing, this problem will be solved fairly rapidly.

As a future perspective, improving the resolution will become a research theme in the field of 3D printing. Currently, the most cost-effective 3D printers face some difficulties when constructing micro-scale structures. With the continued development of 3D printing techniques, it is confident that the resolution will enhance by the procedural modification, the development of printable materials, the improvement of manufacturing technology of 3D printers, the selecting of smaller nozzles, *etc*. Moreover, the exponential growth in publications of 3D printing research shows the application potential of this fabrication technique.

Type of 3D-printed materials also play an important role in the development of 3D printing. Many materials have been widely employed in the field of analytical chemistry such as PLA, ABS, resins, and paraffin wax. In future, there are two main aspects to improve 3D-printed materials. One is the improvement of material activities or properties, such as using more types of printable materials, or the incorporation of other active materials (such as graphene, nanomaterials, and metal oxides) with existing ones. With the development of additive manufacturing and the importance of environmental protection, the other aspect is considered to be the preparation of environmentally friendly materials for 3D printing by using biodegradable and recyclable materials.

Most studies on 3D printing ~~have~~ used only simple applications in analytical chemistry; thus, expanding the scope of application to more challenging analytical problems is another important future perspective of 3D printing. For example, with the improved resolution of additive manufacturing, micro-scale HPLC and SPE stationary phase materials can be prepared based on the uniformity and reproducibility of the technique, which will replace most other manufacturing techniques. 3D printing can also design connectors to combine different parts or instruments, such as connecting preparation devices to separation machines, and combining separation devices with detectors. 3D printing methods also can be utilized for the preparation of fit-for-purpose devices, which will expand their application in remote locations or in difficult places, *e.g.*, *in vivo* detection or wearable sensor devices. Thus, the future perspectives of 3D printing in analytical chemistry should be focused on the improvement of techniques and materials, and expanding the scope of applications.

Conflicts of interest

The authors declare no competing financial interest.

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1 **Tables:**

2 **Table 1** Recent advances of 3D printing in microfluidic devices

Applications	Techniques	Materials	Printed Object	Analytical Details	Advantages	Ref.
Environment analysis	FFF	Veroclear-RGD 810, ABS	Y-shaped device	Isotachophoresis and colorimetric detection of iron in river water	The same device with different applications	[41]
	FFF	Poly-lactic acid (PLA), ABS, and Lay-Felt	Integrated porous membrane	Analysis of nitrate in soil	Low-cost flexible method	[42]
	SLA	Poly(methyl methacrylate) (PMMA)	Multi pumping flow system	Determination of lead in natural waters	Portability, simplicity, and low cost	[43]
	SLA	FLGPCL2 Clear	Lab-On-Valve fluidic platforms	Determination of trace metal and glucose in complex samples	Fast, inexpensive prototyping and with unique versatility	[44]
	FFF	Graphene PLA, ABS, Microdiamond-ABS	Microfluidic reactor	Determination of ammonium in natural waters	Greater temperature control and accuracy	[45]
Disease diagnosis	SLA	Not mentioned	Microfluidic capillaric circuits	Detection of bacteria	Rapid and simple prototyping	[49]
	3SP and Polyjet techniques	“ABS white” and VeroClear (RGD810)	Hard microfluidic chip; electrode holder	Detection of biomarkers such as glutamate, glucose, and lactate	High time resolution	[50]
	Multi-jet technique	Visjet® M3 build materials and Visjet® S300 support materials	Droplet-based PCR microfluidic chip	Detection of breast cancer	Easy and rapid to validate	[51]
	FFF	Poly(lactic acid) with copper oxide nanoparticles	Flow reactor	Detection of glucose	Simplified procedure and improved sample throughput	[52]
	SLA	Acrylic acid	Lab-on-a-chip	Detection of cancer biomarkers	Easily customized	[53]

Cell analysis	Polyjet technique	Full Cure 720	Cell culture devices	Cell culture and analysis	New and versatile way to culture cells	[56]
	Polyjet technique	Full Cure 720 and 705	3D-printed housings	Detection of dopamine and norepinephrine release	Close-to-real-time analysis of multiple molecules	[57]
	Extrusion-based 3D printing	Different colored resins	Microchannels	Cell concentration	Rapid microfluidic switching and high-resolution	[58]
	SLA	Transparent resin	Paper-based microfluidic platform	Investigating cell apoptosis and intracellular crosstalk	Simple, fast, and low-cost	[59]
Others	FFF	PLA, Nylon	Glass-like layers	DNA analysis	Low-cost and rapid	[60]
	FFF	Glass	Glass microreactors	Analysis of synthesis reaction; measurement of drugs	Custom manufacture and rapid	[61]
						[62]
	Polyjet technique	Visijet S300	Microfluidic gradient generator	Multi-drug combinations for screening appropriate drugs	Easy-to-use, one-step, and high-throughput	[63]

Table 2 Recent advances of 3D printing in separation science

Fields	Techniques	Materials	Printed Objects	Analytical Details	Advantages	Ref.
HPLC	STL	Urethane-based oligomer	Particles	Comparison of plate height of different particle shapes	Convenience of controlling packing configuration and shape	[66]
	Selective laser melting (SLM)	Titanium alloy (Ti-6Al-4 V) build material	Columns	Separation of small molecules and proteins	Providing new method for designing high-efficiency HPLC columns	[67]
CE	PolyJet	Liquid support	Microfluidic device	Detection of catechol and nitric oxide	Directly incorporate electrode in the printing process	[68]
	PDM	ABS	Thread-based microfluidic device	Separation and detection of ions	Low-cost	[69]
	FFF	PLA	Photometric detector body	Separation of Zn^{2+} and Cu^{2+} complexes	Affordability and flexibility	[70]
	FFF	ABS	Cartridge	Separation of a thermally unstable species	Easily positioned and improved control of temperature	[71]
	FFF	ABS	Fluorescence detector	Dual-detection TDA and CE−TDA analyses	Low cost	[72]
Others	SLA	Acrylic polymer	Miniature GC columns	Detection of ethylene	High-resolution	[73]
	SLA	Acrylic plastic	GC columns	Detection of ethylene	High-resolution	[74]
	Polyjet technique	VeroClear and Tangoblack	Dialysis base plate	Measure the binding affinity of Zn^{2+} to HSA	Customizable	[75]

Table 3 Recent advances of 3D printing in extraction

Fields	Techniques	Materials	Printed Objects	Analytical Details	Advantages	Ref.
SPE	FFF	LAY-FOMM 60	Sorbents	Extraction of glimepiride from water sample	Low-cost and customizability	[84]
	FFF	LAY-FOMM 60	Sorbents	Extraction of steroids from human plasma	Cost-effective, efficient, and repeatable	[85]
	SLA	BV-007 resin and TiO_2 NPs	Column holders	Extraction of As and Se species from high-salt-content samples	Simple and can design smart multifunctional devices	[86]
	SLA	Clear photoactive resin	Disk-based SPE	Quantification of Fe in water samples	Highly robust and simply designed	[87]
	SLA	Clear photoactive resin	Extraction disks	Extraction of 14 trace metals	Easily adapted and increase extraction capacity	[88]
	SLA	Colorless Clear Resin (FLGPCL02)	Stator	Extraction of antimicrobials in biological specimens	Producing the smoothest surfaces	[89]
	SLA	Resin	Microfluidic extraction monolith	Extraction of preterm birth biomarkers	Quickly, inexpensive	[90]
	SLA	Resin	Immunoaffinity monolith	Extraction of preterm birth biomarkers	Quickly, inexpensive	[91]
LPE	SLA	Clear photoactive resin	Phase separators	Extraction of parabens	High reproducibility, stability, and sensitivity	[92]
	SLA	FLGPCL02 resin	Extraction chamber	Determination of acidic drugs	Optimization of physicochemical variables	[93]

Figures:

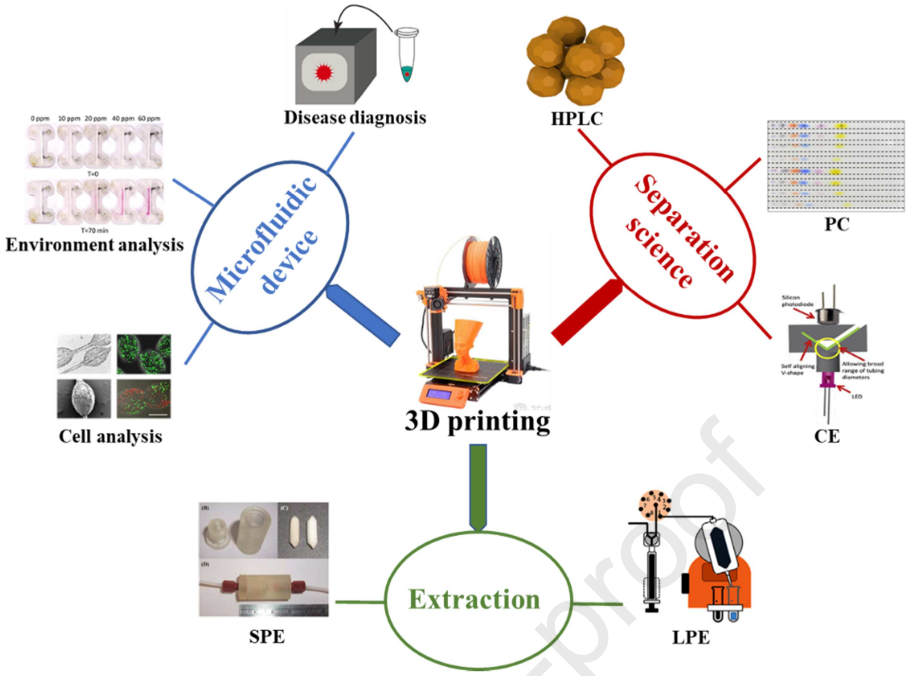

Figure 1. Schematic diagram of 3D printing used in microfluidic, separation science, and extraction devices.

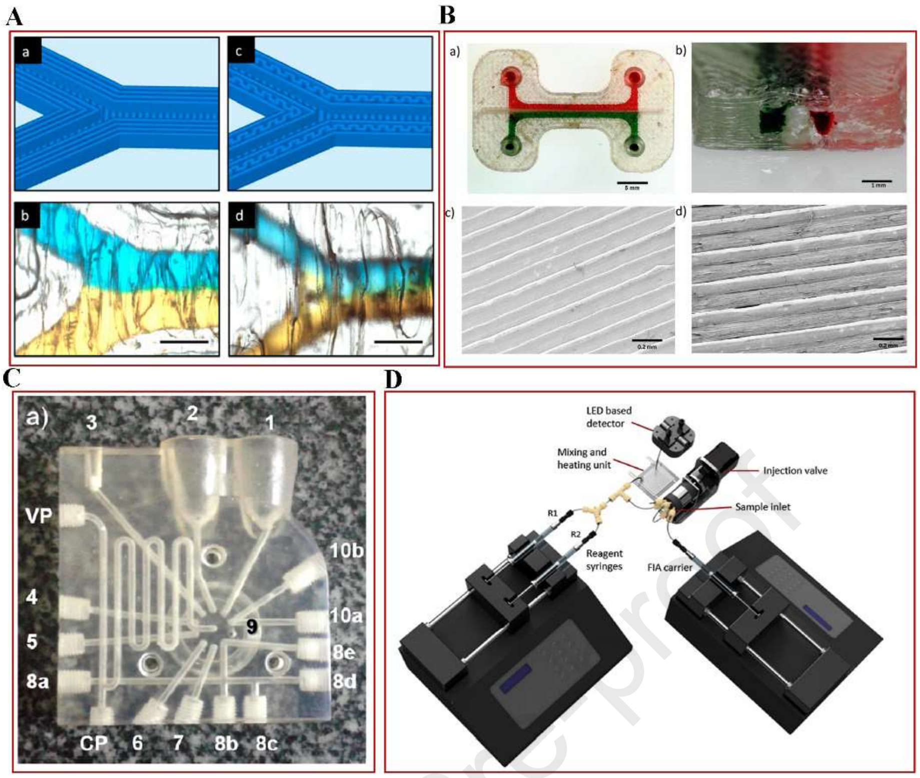

Figure 2. (A) Comparing the construction of 3D-printed microchip employing four loops (a, b) and two loops (c, d). **(B)** (a) Integrated microchip with membrane by 3D printing. (b) Imaging the cross section of microchip. SEM photographs of (c) unwashed and (d) washed Lay-Felt. **(C)** Feature of the SLA technique printed manifold for multiply in-valve (bio)chemical experiments and sample automatic handling methods. **(D)** Diagram of flow injection analysis system integrating 3D printed mixing and heating unit and connecting with LED detector (reproduced with permission) [41, 42, 44, 45].

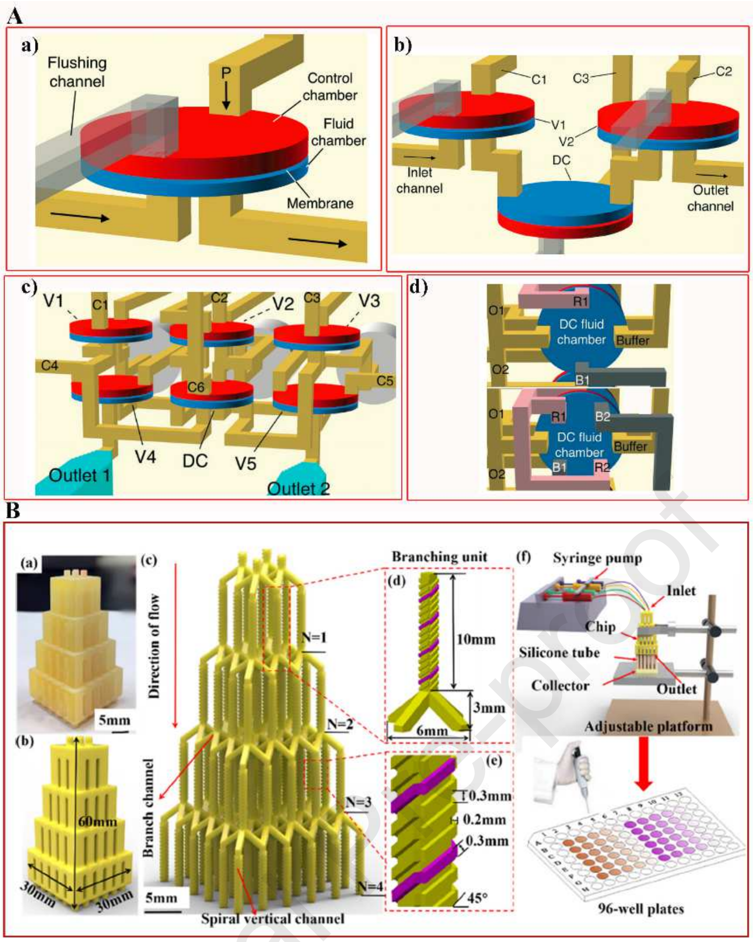

Figure 3. A) CAD design of 3D printed (a) membrane valve, (b) pump, (c) multiplexer and (d) mixers. B) Photographs of (a) 3D-printed prototype and (b) CAD model of microchip, (c) interconnected 3D-printed multi-drug combination microfluidic channel network structure with (d) tree-shaped branch and (e) helical channel, and (f) 3D-printed microfluidic device with syringe pump was used for cytotoxicity analysis (reproduced with permission) [62, 63].

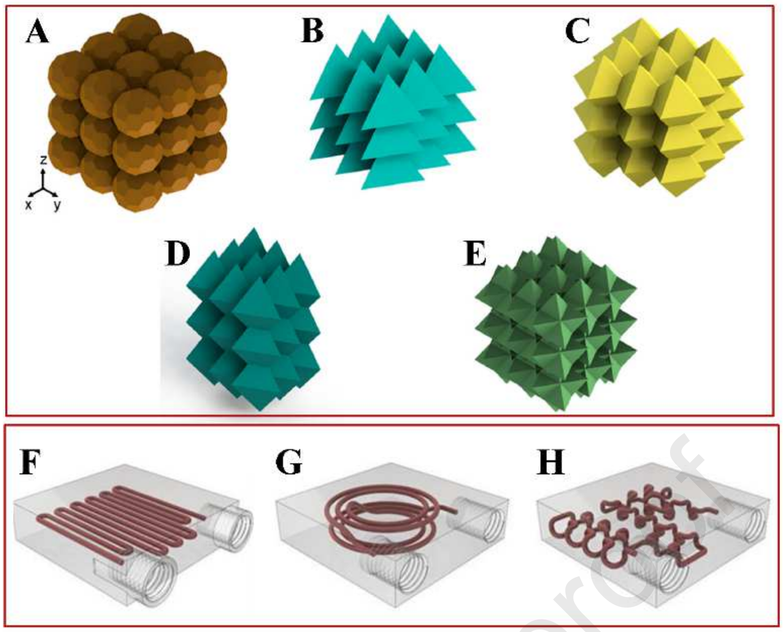

Figure 4 CAD models of stationary-phase particles utilized in the research: **(A)** icosahedra, **(B)** tetrahedra, **(C)** octahedra, **(D)** triangular bipyramids, and **(E)** stella octangulae; Shapes of **(F)** 2D serpentine, **(G)** 3D spiral, and **(H)** 3D serpentine columns (reproduced with permission) [66, 67].

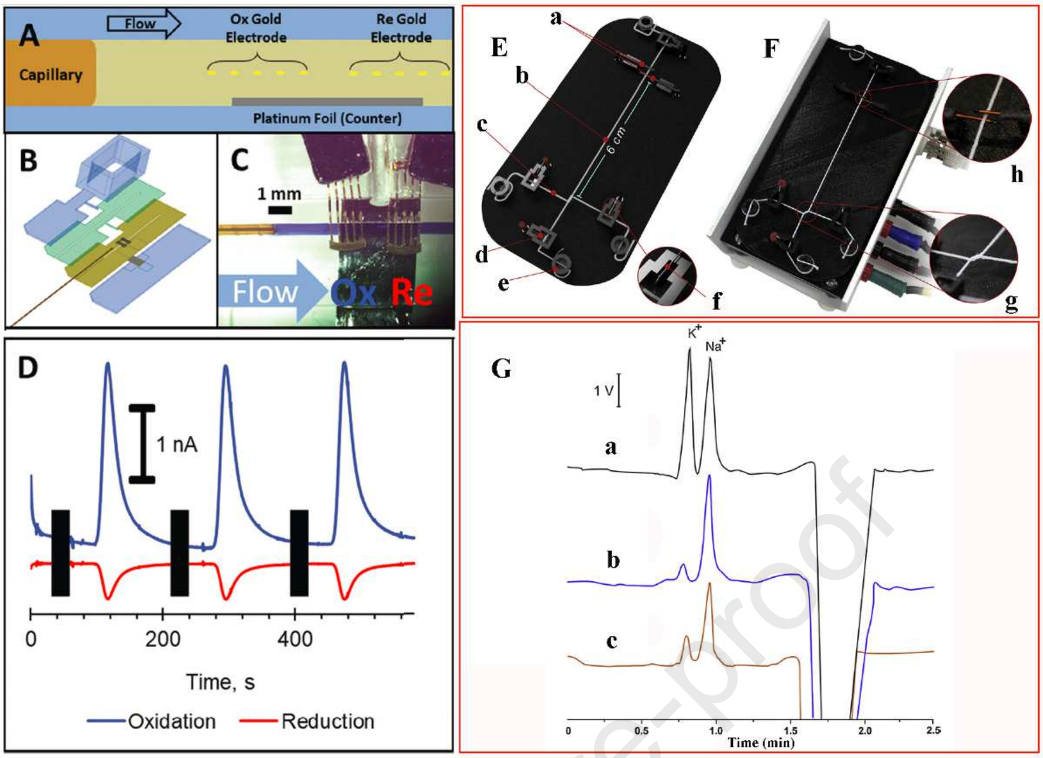

Figure 5 (A) Schematic of two working electrodes in the middle of channel and one platinum counter electrode at the bottom of channel. **(B)** CAD design process for the stacking of three models. **(C)** Optical image of dual working electrode arrays with the platinum counter electrode. **(D)** Amperometric trace responsive of oxidation of catechol and reduction of quinone. **(E)** Schematic of the paper-based microfluidic analytical device. **(F)** Image of the platform in an aluminum cage. **(G)** Electropherograms of (a) standard ions solution, (b) lemon, and (c) cola soft drinks (reproduced with permission) [68, 69].

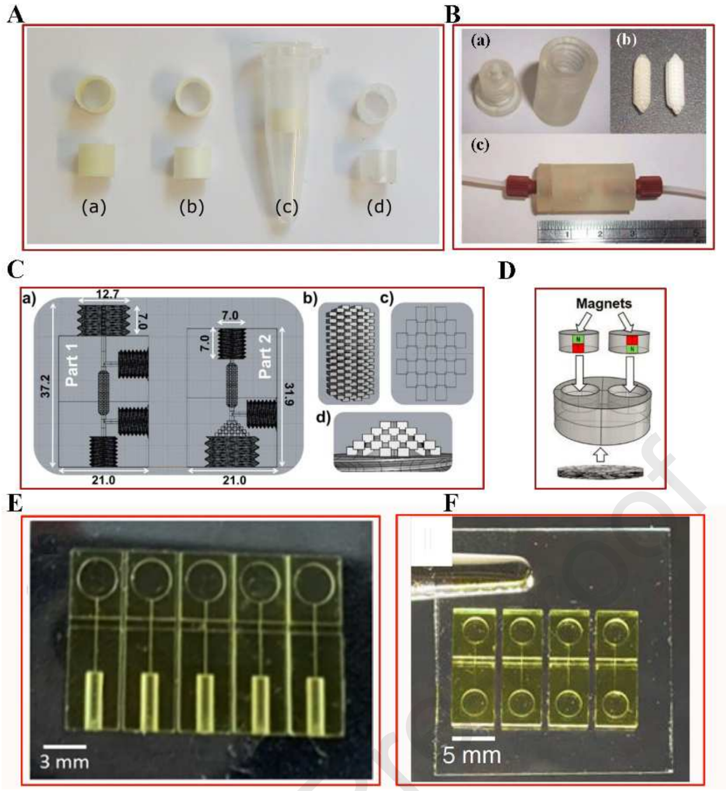

Figure 6 (A) Diagrams of 3D-printed sorbent with similar tube shape (a) before and (b) after elution, (c) the sorbent put in the Eppendorf tube, and (d) the negative control tube. **(B)** (a) Diagram of the male holder manufactured by raw resin incorporated with TiO_2 NP (left) and the hollow chamber (right). (b) Diagram of the cuboid-stacked packing prepared by resin (left) and TiO_2 NPs mixed resin (right). (c) Diagram of the final assembled minicolumn. **(C)** 3D-printed device for SPE. (a) Parts of the extraction device, detail of (b) the mixers of extraction device, (c) single-layer cubes of a mixer, and (d) sorbent disk support. **(D)** Diagram of 3D-printed RDSE devices. **(E)** Photography of 3D-printed microfluidic extraction device with reversed-phase lauryl methacrylate-based monolith. **(F)** Photography of 3D-printed microfluidic extraction device with immunoaffinity monolith (reproduced with permission) [84, 86, 87, 88, 90, 91].

Highlights:

- 3D printing techniques show attractive merits in analytical chemistry.
- Applications of 3D printing in microfluidic, separation sciences and extraction devices were summarized.
- Materials for 3D printing in analytical chemistry were highlighted.
- Future perspectives of 3D printing in analytical chemistry were discussed.

Authors declare no conflict of interests.