Emerging Microreaction Systems Based on 3D Printing Techniques and Separation Technologies

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The past three decades have seen increasing progress in the integration and process diversification of microfluidic systems for use in chemistry, biochemistry, and analysis. Here we summarize recent achievements in microreaction modules and microseparation units. We look into recent developments of microreaction systems fabricated by various 3D printing techniques for chemical synthetic applications. Moreover, we take a look at the recent achievements of newly developed microseparation technologies with enhanced separation efficiency realized by adopting single or hybrid principles as well as novel device concepts. Emerging technologies of 3D printing have potential to realize a vertically stacking the microchannels and miniaturization of bulky microreaction accessories. When the advanced microreaction systems are integrated with newly developed microseparation technologies, automated synthesis of industrial compounds, such as pharmaceuticals which need multiple types of salification chemistry, will be almost completed. Many opportunities are open to developing innovative microreaction systems with these techniques that can also be highly durable under harsh conditions.

Keywords: Microfluidics, 3D printing, microreaction, separation

1. Introduction

Microfluidics has become increasingly attractive in many fields including chemistry, biochemistry, and analysis, since its advent approximately three decades ago [1, 2]. In particular, microfluidic system integration and process diversification have greatly enhanced the system performance for continuous-flow chemistry [3].

Among the microfluidic components, microreaction modules and microseparation units are the major components that can dramatically alter the overall performance of the entire system. Recently, there has been a surge of new types of microreactors and microseparators, some of which resulted from combining the available techniques but more importantly some from new concepts. It is, therefore, meaningful to offer a perspective on new technologies for fabricating microreactors and microseparators for continuous-flow chemistry.

Fabricating the microfluidic system has strongly been dependent on molding and lithographic approaches with photoresists and polydimethylsiloxane (PDMS) [4]. However, these routes need complex steps and skillful hands, and difficult yet to realize sophisticated design of microfluidic devices [5]. Therefore, three-dimensional (3D) printing techniques as an additive manufacturing technology draws much attention due to its relatively facile way of fabricating monolithic bodies several micrometers to centimeters in size. The 3D printing techniques enable printing of microfluidic devices in one step [6] and provide high throughput with no well-trained skills [7]. Moreover, fast modification of design is possible by revising computer-aided design (CAD) software with desktop computers, making it suitable for the prototype design of microreactor for specific chemical process. With these advantages, it is well worth looking into recent developments of microreactor systems for chemical synthetic applications other than biological use, which are fabricated by various 3D printing techniques.

Separation of various mixtures is essential for the synthesis and analysis in a continuous-flow system. Basically, the usual separation principles are also applicable to microseparator such as diffusion, extraction, distillation, solubility, and wettability. In addition, phase separation in mixed phases such as gas and liquid is also involved in microchemical process. Furthermore, single compound separation in a single phase of mixed compounds is also essential to establish the microchemical processes. Therefore, it is meaningful to take a look at the recent achievements of newly developed microseparation technologies with enhanced separation efficiency. These achievements realized by adopting single or hybrid principles as well as novel device concepts are described and compared with the conventional separation.

2. 3D-Printed Microfluidic Systems

2.1. 3D Printing Techniques and Materials.

To build three-dimensional structures with 3D printers, the designs are drawn with CAD software (e.g., Rhinoceros 3D, Autodesk Inventor). The printer fabricates three-dimensional structures by layer-by-layer approach according to the design of CAD file [13]. The 3D printing techniques and various resourcing materials for microreactor applications are grouped into two categories: light-induced process and photo-curable materials, and heat-induced process and thermostoﬁng resins and metals.

2.1.1. Light-Induced Process and Photo-Curable Materials.

Three types of 3D printing techniques, stereolithography apparatus (SLA), digital light projection (DLP), and multiple jet modeling (MJM), utilize ultraviolet (UV) lights and photo-curable resins with low viscosity to build three-dimensional structures (Table 1).

The SLA type of 3D printers fabricates structures by a focused laser beam or light-emitting diode (LED) lights (Figure 1 (a)). This type of 3D printer was commercialized around late 1980s and is recently making rapid advances in the hardware [14]. The resolution of the printed three-dimensional structures depends on the spot size of the laser beam and the absorption spectra of photo-curable resins. The highest resolution is ~27 × 27 × 0.25 (x, y, z axis) micrometers [8]. Alternatively, two-photon absorption SLA lithography (TPA-SLA) with infrared femtosecond laser (~780 nm wavelength) can fabricate 3D structures a few hundreds of nanometers in size, offering the highest resolution out of available 3D printing techniques [15]. However, this TPA-SLA lithography technique takes a long time even to print
objects millimeters in size. The DLP type of 3D printers, a recently developed system, is similar to the SLA type in terms of principle and working concept. Projection methodology is the difference between the two. The DLP type projects the UV light to the photo-curable resin to crosslink the whole layer polymerization (Figure 1 (b)). This layer-by-layer approach enables a faster building speed than the point-by-point approach of the SLA type. The parameters that affect building time are the layer thickness and the required exposure time, and not the length of X and Y axis of the model [16]. The resolution of printed structures depends on the size of the projected pixel. The highest resolution as reported is 27 × 27 × 0.25 μm (SLA) and 50 × 50 × 50 μm (DLP) for the SLA and DLP types of 3D printers, respectively.[8,9] Both SLA and DLP types of 3D printers strike a balance between the resolution, equipment cost, and printing performance [17]. The SLA or DLP types are similar in price around thousands of dollars, but the DLP type is a bit cheaper than the SLA type. Currently, these printing systems use mostly a single type of photopolymer resin in a single resin vat, which makes it difficult to build multimaterial-based structures. Choi et al. have reported an SLA printing with multiple resin vats [18]. However, the process is rather complicated and it takes longer process steps (e.g., washing uncured resin and changing vat) compared to single-material printings.

The MJM type of 3D printer is an advanced type of inkjet printer, but it jets photo-curable resin and wax one at a time (Figure 1 (c)). The photo-curable resin is solidified by UV light and remains as an actual desired structure. The easy-resolution, equipment cost, and printing performance [17]. The SLA or DLP types are similar in price around thousands of dollars, but the DLP type is a bit cheaper than the SLA type. Currently, these printing systems use mostly a single type of photopolymer resin in a single resin vat, which makes it difficult to build multimaterial-based structures. Choi et al. have reported an SLA printing with multiple resin vats [18]. However, the process is rather complicated and it takes longer process steps (e.g., washing uncured resin and changing vat) compared to single-material printings.

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Table 1. Summary of 3D printers’ features applied to microfluidic fields

| Type of 3D printer | Materials | Resolution (x × y × z) μm | Advantages | Disadvantages |
|-------------------|-----------|--------------------------|------------|--------------|
| SLA, DLP          | Photo-curable polymers containing acrylate and/or epoxy functional groups | 27 × 27 × 0.25 [8] (SLA) 50 × 50 × 50 [9] (DLP) | Low price of 3D printers High resolution | Limited material selection High price of resin Low viscosity of resin required Poor solvent resistance |
| MJM               | Proprietary photoresins; Formlabs, Watershed, Somos, Ormocer, Fototec, etc. | 34 × 34 × 16 [10] | Higher resolution than other 3D printing techniques Easy to print complex features Multimaterial printing is possible as open-source | Limited material selection High price of resin and printers Low viscosity of resin required Poor solvent resistance Low resolution Need post-treatment for smooth surface |
| FDM               | Thermosoftening plastics; ABS, PLA, PP, PMMA, PET, PDMS, etc. | 100 × 100 × 80 [11] | Diverse selection of thermoplastics Multimaterial printing is possible Low price of 3D printers | |
| SLS               | Metals; stainless steel, titanium, cobalt-chrome, aluminum, nickel, etc. Ceramics; yttria, zirconia, alumina, SiC, etc. | 30 × 30 × 20 [12] | Superior resistant and mechanical strength of metal and ceramics | High price of 3D printer Need long process time |

*aHighest resolution reported as microfluidic application.
*Reported highest resolution on web page.

Figure 1. Four 3D printing configurations. (a, b) SLA type 3D printer and DLP type 3D printer. Adapted with permission from Ref. [14], Copyright 2016 The Royal Society of Chemistry. (c, d) MJM type 3D printer and FDM type 3D printer. Adapted with permission from Ref. [17], Copyright 2016 The Royal Society of Chemistry.
melted or dissolvable wax part works as a support and prevents the collapse and deformation of photo-curable resin parts during printing process. The MJM type gives a rather high resolution that is about 34 × 34 × 16 (x, y, z axis) micrometers [10]. However, the MJM type is more expensive, approximately 5 to 10 times higher than other 3D printing devices such as DLP type.

Photo-curable materials are usually used for SLA, DLP, and MJM type printings. Many photo-curable polymeric resins contain acrylate and/or epoxy functional groups as cross-linkable units. As with the conventional 2D printers and specialty chemicals, most of photo-curable resins are proprietary chemicals that are exclusively supplied by 3D printing companies with non-disclosed chemistry to end users. Insufficient diversity of resins limits broad applications of polymer-based 3D printing technology. In addition, the transparent resin slightly turns dark or yellowish after the curing. In practice, the optically transparent resin needs monitoring even after curing to monitor the chemical or physical change inside the microfluidic channel.

The resins are mixed with photo-initiators to form radicals or cations upon exposure to a UV light. The photo-initiators usually contain phenone groups or phosphine oxide groups. Absorbers or organic dyes are also added to the resins to control curing depth. Although the optimized cocktail formulation of these additives is highly critical for optimizing the curing kinetics and 3D printing performance, the formulated composition of the chemical additives is not open to users. Conventional photoresists (e.g., SU-8) used for soft lithography require a few minutes to solidify over tens of micrometers of curing depth. However, 3D printing resins demand faster curing kinetics due to the shorter light exposure time of several seconds to cure the desired layer a few tens of micrometers deep.

As reported [8, 19], some biocompatible and photo-curable resins are being used for diverse biochips and cell chip applications. In contrast, applications involving polymeric microreactors are not as diverse because of much harsher reaction conditions involved. Low durability of the 3D-printed polymeric microreactors is a critical drawback for chemical synthesis even under ordinary reaction conditions. In particular, the poor solvent resistance to organic solvents severely limits the utility of 3D-printed polymeric microreactors. It is, therefore, needed to improve or develop photo-curable resins with robust chemical and thermal stability for actual microchemical applications. Development of the resistant resins such as silicone-based inorganic polymers [20] would provide a breakthrough toward fabricating durable microreactors for broad industrial applications.

### 2.1.2. Heat-Induced Process and Thermosoftening Materials

To build three-dimensional structures with thermosoftening materials, 3D printer uses heat to melt thermoplastics and shape the desired structure with the softening resin, followed by solidification to form the mechanically rigid structures. Fused deposition modeling (FDM) is a well-known heat-induced process for fabricating three-dimensional systems [17]. The FDM type of 3D printers uses a filament shape of thermoplastic feed to build three-dimensional structures. The printer's nozzle melts the filaments into a viscous liquid and extrudes the liquid resin at the desired locations to fabricate 3D structures (Figure 1 (d)). The resolution depends on the printer's nozzle size. The highest resolution reported in microfluidic devices is about 100 × 100 × 80 (x, y, z axis) micrometers [21] and ordinary resolution is over 150 micrometer, which is relatively inferior to that of the light-induced 3D printers. The price of 3D printers varies with the resolution of the three-dimensional structures but many FDM type 3D printers can be purchased around one thousand dollars or less for laboratory use. Also, many inexpensive FDM 3D printers are commercially available as a do-it-yourself (DIY) kit that is assembled by end users. Unlike the light-induced 3D printing techniques, the FDM printing technique does not need post-print steps such as removing the uncured resin or post-UV curing. However, the structure formed needs an extra finishing process for smoothing the external surface roughness, due to low resolution.

Various thermoplastics resins are utilized for this 3D printing, and they are mostly open-source materials such as acrylonitrile butadiene styrene (ABS), polyactic acid (PLA), polypropylene (PP), poly(methyl methacrylate) (PMMA), polyethylene terephthalate (PET), etc. Generally, these printing materials are rather cheaper than the photo-curable resins. Most of thermoplastics have hydrolytic stability but varying organic solvent resistance depending on the resins.

### 2.1.3. 3D-Printed Glass, Metal, and Ceramic Materials

Glass is a widely used material due to transparency, chemical and thermal stability, and mechanical strength. Glass, however, requires a high temperature up to 1200 °C to melt and is difficult to cast for shaping structures [22]. Due to the low thermal

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**Figure 2.** (a) DLP 3D printed fused silica glass microchannel (inset scale bar, 200 μm). Adapted with permission from Ref. [23], Copyright 2017 Macmillan Publishers Limited. (b) FDM 3D printed glass structures. Inset scale bar of upper left corner is 5 mm and bottom right corner is 250 μm. Adapted with permission from Ref. [24], Copyright 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
conductivity, fast and local melting can cause possible cracks upon shaping and cooling. These intrinsic shortcomings have made glasses unsuitable for 3D printing.

Recently, however, two approaches have been reported for building glass microfluidic structures using resins containing silica particles. In one approach, a mixture of silica particle and photo-curable polymeric binder was used. Kotz [23] reported utilization of amorphous silica nanoparticles dispersed in UV curable resins (hydroxyethylmethacrylate [HEMA], tetraethyleneglycoldiacrylate [TEGDMA]). The silica–resin composite was shaped by a DLP printer (Figure 2 (a)). This polymer–silica composite was then sintered at 1300 °C to remove the polymer binder and to get the object of fused silica glass.

The other approach is to extrude the silica-filled polymer [24]. The silica–polymer composite is shaped by positioning the extruding nozzle (Figure 2 (b)). Hydrophilic fused silica nano-particles are contained in a polymeric ink (mixture of tetraglyme, PDMS) and shaped with 3D printer. The silica–polymer composite was dried and heat-treated to remove solvent at 100 °C, burn out the organics at 600 °C, and sinter at 1500 °C. Polymers containing fused silica particles enable 3D glass printing, which is an advance toward hard-to-print materials.

Metal has good mechanical strength and chemical resistance. Stainless steel, titanium, alumina, and zirconia are commonly used for 3D printing. The metal 3D printings are based on metal-powder melting process. Powder bed fusion (PBF) such as selective laser sintering or selective laser melting techniques is a typical process in 3D-printed metal systems. The PBF type of 3D printers forms three-dimensional structures by directly melting and sintering the fine metallic powder via laser or electron beam. The diameter of the metallic particles is under 100 micrometers, with the resolution depending on the size of the metallic powder. Carbon dioxide laser (CO2 laser), an infrared laser with 9–12 micrometers of wavelength, is mainly utilized to sinter the powder. By PBF technique [25], the highest resolution is about 30 × 30 × 20 (x, y, z axis) micrometers (Figure 3) [12]. Binelli et al. reported a concept of 3D printed microreactor with aluminum alloy (AlSi10Mg) powder [26]. In this research, microreactor was printed as separated part, housing structure and microchannel plate, and the microchannel plate was composed with 3D parallel channels with width of 0.5 mm, height of 0.25 mm, and channel length of 50 mm.

Gupta et al. reported a PBF-printed metal microchannel with titanium alloy for a liquid chromatography application [27]. The fabricated microchannel, 0.9 mm in diameter and 0.6 m in length, was utilized as a chromatography column to be packed with a porous polymer monolith to separate intact proteins and peptides from complex mixtures. Metal 3D printing could be the most reliable and promising approach for microreactor applications, as evidenced by various uses of commercial metal microreactor systems in the market [28] that are fabricated by conventional and highly expensive machining and bonding technique.

Ceramics are also a highly durable material with excellent resistance to heat and chemicals. The material has excellent mechanical strength. Conventionally, ceramics have been printed by PBF techniques [29]. Recently, ceramic 3D printing with light-induced process such as SLA technique was reported, in which photo-curable preceramic polymers were used as precursors of oxide and non-oxide ceramics [30, 31]. The reported 3D printing techniques shaped the preceramic polymers in a way similar to the SLA process, followed by high temperature pyrolysis [32]. Eckel et al. used (mercapto-propyl)methylsiloxane with vinylmethoxysiloxane as a preceramic polymer, and Zanchetta et al. used commercially available silicone resin (SILRES MK) mixed with an organically modified silicon alkoxide, 3-(trimethoxysilyl)propyl methacrylate. In both cases, the 3D printed ceramic polymers were pyrolyzed at 1000 °C to convert the preceramic resin to ceramics. These results showed SiOC ceramic cellular structure. There has been no report on the fabrication of 3D printed ceramic microreactor yet, except for the Al2O3 ceramic microreactor made by conventional mold casting of the powder slurry [33]. The SLA of preceramic polymers could lead to opportunities for complex-shaped, high temperature, and chemical-resistant ceramic structure systems ranging in size from microscale to macroscale.

2.2. Performance of 3D-Printed Microreactors. Three-dimensional structures can be fabricated easily by 3D printing without resorting to complicated lithographic processes. The microfluidics community, however, has been quite slow in adopting the technique for fabricating the devices with functional design concepts. Microreactors need unique channel design tailored to specific chemistry and good resistance to heat and solvent to perform various reactions. The 3D printing techniques as discussed allow fabrication of complex channel design at a low cost. On the other hand, the material selection is still narrow owing to printability and material stability.

Although there are only a limited number of reports on the microreactors fabricated by 3D printing, we nevertheless examine and evaluate 3D-fabricated microreactors, simple microreactors first followed by microreactors with multiple channels.

2.2.1. Simple Microreactors. Shallan et al. built microfluidic device, mixer, gradient generator, and droplet generator by a DLP type of 3D printer [34]. In this work, a commercial acrylate-based resin was used with the channel dimension of 500 × 500 micrometers in height and width. To demonstrate the capability of the 3D-printed microfluidic devices, the authors fabricated a microfluidic device for continuous optical monitoring of nitrate in water using the Griess test, which is a color changing reaction with N-(1-naphthyl)ethylenediamine (Griess reagent) and nitrate ion.

Kitson et al. built milli- and micro- “reactionware” devices with the FDM printer using PP thermoplastic material, demonstrating the versatility of 3D-printed reactors by performing organic reaction and inorganic synthesis (Figure 4 (a)) [35]. Reductive amination of benzaldehyde with benzylamine was performed, and various Mo clusters were synthesized in the presence of 1 M of HCl acid. Scotti et al. connected the FDM-printed PP microreactor to a mass spectrometer, which facilitated to customize the reactor applications for online analysis of Diels–Alder and retro Diels–Alder reactions (Figure 4 (b)) [36].

Bishop et al. reported Prussian blue nanoparticle synthesis in a 3D-printed microreactor built by FDM [37]. The reactor was fabricated with ABS and PET resins. In this report, the 3D

![Figure 3](image-url). Commercially available PBF 3D printed stainless steel metal microreactor. The inner volume of 3D printed metallic reactor is 1–8 mL. Detailed information of 3D printer which built this model was not open to public. Adapted with permission from Ref. [28]
printed microdevice with $400 \times 400 \times 200$ ($x$, $y$, $z$ axis) micrometers of channel dimension was used to monitor the produced amount of H$_2$O$_2$ by utilizing the Prussian blue nanoparticles.

In yet another work, a 3D-printed catalytic reactor was fabricated using an acetoxy-silicone polymer that is commercially available as a bathroom sealant, LOCTITE W 5366, which was cured in ambient humidity (Figure 4 (c)) [38]. The polymer was printed by open-sourced FDM 3D printer, Fab@Home platform assembled at the laboratory. Pd/C catalyst was dispersed in the silicon resin, and it was used to build a 3D-printed catalytic reactor. With the reactor, catalytic hydrogenation of styrene to ethylbenzene was studied using Et$_3$SiH as the hydrogen source.

2.2.2. Microreactors with Multiple Channels. 3D printers can be utilized to fabricate microreactors with multiple channels in a reproducible manner, contrasting the conventional fabricating techniques that strongly depend on skills.

Anderson et al. reported fabrication of a 3D-printed fluidic system with parallel multiple channels by MJM process [39]. The device utilizing a commercial resin, Objet Vero® White Plus, which contains epoxy and acrylate monomers, was fabricated with a membrane on top of the channel in order to transport drug into endothelial cells of the upper chamber. This device has 8 parallel channels, each of which is 3 mm wide and 1.5 mm high.

Riche et al. fabricated an SLA-printed microfluidic device as a parallel droplet generator using a commercial photo-curable resin, Somos® WaterShed XC 11122 (Figure 4 (d)) [40]. The droplet generator with channels 250 micrometer wide and high was used to synthesize platinum nanoparticles in an ionic liquid solvent system, which produced droplets of uniform size that is invariant to changes in flow. Femmer et al. showed that 3D printed parallel droplet generators could uniformly generate droplets in high-throughput (Figure 4 (e)) [41]. The droplet generator was fabricated with a methacrylate based photo-curable resin by a DLP type 3D printer.

3. Recent Advances in Microseparation Technologies

The advent of 3D printing has made fabrication of complex structures an easy task. Similar to the fabrication of microreactor with 3D printing, the capability of new technologies bodes well for transforming the traditional separation techniques such as extraction, distillation, diffusion, and others to those suitable for microfluidic separation, or "microseparation" in short.

Other avenues for microseparation include configuration of the microfluidics for efficient separation and membrane-based separation. Membranes have extensively been utilized for
Figure 5. Separation materials with small pore sizes (0.2–2.0 nm) for inter-gas separations in conventional microseparators. (a) MMM hollow fibers of MOF and polyimide for separation of hydrogen from other gases. Adapted with permission from Ref. [50], Copyright 2010 American Chemical Society. (b) Sulfur-doped SOD zeolite membrane or hydrogen separation from carbon dioxide under harsh condition. Adapted with permission from Ref. [51], Copyright 2013 AIDIC Servizi Srl. When a specific gas compound is separated from a gaseous mixture (we call this “inter-gas separation”), various membrane materials with microporosity (pore size of 0.2–2.0 nm) are used to induce selective permeability owing to different diffusion rate of the compounds. Hu et al. reported mixed-matrix membrane (MMM) hollow fibers of MOF and polyimide for separation of hydrogen (H2) from other gases by exploiting the fact that the pore size of the MOF is around 0.7–0.8 nm (Figure 5 (a)) [50]. Günther et al. reported that sulfur-doped sodalite (S-SOD) zeolite membrane with 0.29 nm pore diameter separates H2 from carbon dioxide (CO2) under harsh conditions (~800 °C and ~40 bar), which showed different diffusive mobility between the gases, as the pore size approaches the kinetic molecular diameter of H2 (Figure 5 (b)) [51].

These studies showed simple ways to separate gas molecules with similar kinetic diameters. However, the diameter of hollow fibers is relatively too large (millimeter scale), for example, to be embedded into integrated microfluidic system. Further work is needed to take full advantage of continuous-flow microfluidics.

For the separation of only gaseous compounds from liquids (we call this “gas–liquid separation”), porous membrane with macroporosity (pore size of 1–10 μm) has been used to conduct the phase separation. Lochovsky et al. reported in-plane trapping and removal of gas bubbles in microfluidic systems with gas permeable PDMS wall (Figure 6 (a)) [52]. The PDMS is known to have a pore size of few microns, which allows gas molecules to permeate through while blocking liquid phase. Liu et al. reported a nozzle-type passive microfluidic debubbler system (Figure 6 (b)) [53], for which polytetrafluoroethylene (PTFE) venting membrane with 5 μm pore size is the key for the separation. These simple and powerful methods for continuous separation of gas from liquid phase are derived, in particular PDMS, from facile fabrication processibility. However, inherent vulnerability of the PDMS membranes limits its use only to mild operating conditions in terms of chemicals, temperature, and pressure.

A distinct difference in polarity has been exploited for the membrane separation of a mixture of two or multiple liquid compounds (we call this “inter-liquid separation”). For the selective wettability, membranes with large pores (size, >10 μm) are needed to allow the exclusive penetration of highly polar or non-polar liquid. Bannock et al. reported the use of a porous and hydrophobic PTFE capillary with 15–25 μm pore size for separation of liquids with different affinity (Figure 6 (c)) [54].

Recently, new microseparation systems and processes have emerged for efficient separation in the integrated chemical processes. Rather than relying solely on the porosity of separating materials, they utilize alternative unique properties or phenomena such as wettability of separating materials [52–56]. This
approach also gives clues to the solution of fouling problem that generally plagues the entire separation process. In addition, novel device concepts as in the prototypes of liquid membranes have been advanced [55, 56]. These emerging microseparation technologies provide excellent performance not only for both binary (e.g., gas–liquid) and multiphase (e.g., gas–liquid–solid, gas–water–oil) mixtures but also for single-phase mixtures (e.g., inter-gas, inter-liquid) with simpler principles. We first look into the single-phase mixtures.

3.1. Membrane-Assisted Microseparations. Weeranoppanant et al. reported a multistage counter-current liquid–liquid extraction which integrates segmented flow mixing and membrane-based phase separators in microfluidic system (Figure 7 (a)) [57]. The system is composed of a self-tuning pressure control element and a membrane-based microseparator of embedded hydrophobic membrane that allows only oil phase to flow through in segments of water and oil. However, the conventional membrane-based microseparator might cause incomplete penetration of oil phase or excessive breakthrough of water phase under inappropriate flow conditions. Thus, the integrated diaphragm valve could dynamically open and close to control the amount of flow in each outlet. The modified microseparator with diaphragm valve permits to robustly operate multistage liquid–liquid extraction even for separation steps in series of different mixtures with relatively low interfacial tension, as in the extraction of acetone between toluene and water and the extraction of acetic acid between water and ethyl acetate.

Breisig et al. reported a droplet microfluidics for liquid–liquid extraction in capillary membrane system (Figure 7 (b)) [58]. An organic phase with a good affinity to capillary tube wall becomes a continuous medium while an aqueous phase with a poor affinity to capillary tube forms the droplet. The solute is extracted into the liquid that has a higher solubility for the solute. Eventually, the difference in wettability allows the phase separator to split the organic and aqueous phase. A notable feature is that phase inversion is easily achievable during the phase separation stage. By combining two capillary membranes with different affinities, the droplet systems of organic and aqueous phases can be inverted. For instance, the organic phase in the first hydrophilic membrane capillary forms

![Figure 7](image-url) Newly developed microseparators for inter-gas separations. (a) Interfacial catalyzed separation of carbon dioxide from other gases with superamphiphobic silicon nanowires repellent both to water and oils. Adapted with permission from Ref. [57], Copyright 2016 The Author(s). (b) Dynamic liquid membrane with recycling liquid film for separation of carbon dioxide from methane. Adapted with permission from Ref. [58], Copyright 2016 Elsevier B.V.

![Figure 8](image-url) Newly developed microseparators for inter-liquid separations. (a) Counter-current liquid–liquid extraction with diaphragm valve system. Adapted with permission from Ref. [59], Copyright 2017 American Chemical Society. (b) Capillary membrane-based liquid–liquid extraction and its phase inversion version. Adapted with permission from Ref. [60], Copyright 2017 Elsevier B.V.
droplets in aqueous continuous phase, and in the second hydrophobic membrane capillary, the organic phase can become continuous phase and water can form droplets.

3.2. Membrane-Free Microseparations. A superamphiphobic structure, a selective liquid membrane, droplets, and segmented mixing and phase separation have been utilized to effect separation for the single-phase mixtures.

Vishwakarma et al. reported an integrated process of selective capture of CO$_2$ from its mixture with the aid of an interfacial catalyst (Figure 8 (a)) [59]. A superamphiphobic silicon nanowire structure repelling both water and oil separates the liquid flowing above the nanowires from the gas flowing through the silicon nanowires. The CO$_2$ in a gaseous mixture of CO$_2$–CH$_4$ is selectively dissolved into the upper liquid phase. This inter-gas microseparator performs the separation with the distinct solubility principle in a membrane-free system with no physical barrier, which enhanced the efficiency by ~50% in less than 1/6 of the residence time needed by the dual-channel separator with a membrane barrier [60]. In the study, a natural gas containing 2.95% CO$_2$ flows into silicon-nanowires-embedded microsystem while liquid reactants flow above the silicon nanowires. Selective CO$_2$ absorption by liquid reactants occurs at the tips of silicon nanowires where the ionic liquid catalysts are immobilized.

The intimate contact among the three phases that consist of nature gas, liquid reactants, and interfacial catalyst enhances the efficiency of CO$_2$ separation from the natural gas owing to the promoted mass transfer. The membrane-free system based on the superamphiphobic surface can be extended, in general, to other CO$_2$ separation systems, with other more wetting CO$_2$ absorbents such as sodium hydroxide.

Setnickova et al. reported a new type of membrane system named “dynamic liquid membrane” (DLM) for separation of gas mixture (Figure 8 (b)) [55]. The DLM is formed by continuously feeding a recycling liquid film down a steel underlay along the parallel wires aligned with 6-mm interval. The liquid film as a wall of permeation cell contacts the gas mixture (CO$_2$ + CH$_4$) feedstock. The water film, possessing a 30 times higher solubility of CO$_2$ than CH$_4$, allows CO$_2$ to selectively permeate through the water film, resulting in the removal of CO$_2$ from the mixture gas. The system as reported is relatively large (membrane area of 276 cm$^2$). Note that an improvement in separation efficiency can be realized by miniaturizing such a system into a microfluidic system.

A micro-total envelope system, junctions involving anisotropic wetting, and a liquid-gated membrane have been advanced for microseparation of binary or multiphase mixtures.

Singh et al. reported an automated total process for generation, purification, and utilization of carcinogenic gaseous reagent in a totally enveloped microsystem named "micro-total envelope system" (μ-TES) that includes a unique microseparator based on silicon nanowires (Figure 9 (a)) which play a key role to separate carcinogenic gaseous reagent without vulnerable membrane [61]. A strongly carcinogenic compound of chloromethylmethyl ether (CMME), a useful reagent for synthesis of drugs and natural products, is generated in situ from its less toxic precursors. Then, the volatile CMME gas is separated from the non-volatile byproduct liquid with high boiling point in the distillation microseparator of superamphiphobic silicon nanowire that possesses a much better chemical resistance than polymer membrane separator. The microseparator exhibits a 96% CMME separation efficiency at optimized flow rate. The condensed CMME was used for subsequent chemical process in the continuous-flow system.

Wang et al. reported a microfluidic gas–liquid separation system involving a morphology-patterned anisotropic wetting surface (Figure 9 (b)) [62]. The system consists of a Y-shaped microchannel as the upper part and a stripe pattern as the lower part. The stripe pattern is prepared either by photolithography or reactive-ion-etching in such a way that water droplets spread anisotropically. As a result, the contact angle in the perpendicular direction is different from that in the parallel direction.

The Y-shaped microchannel consists of one inlet and two outlets, and the outlets form an included angle of 90°. When the stripe pattern is adjusted to be parallel to one branch of the Y-shaped microchannel, the other branch of the microchannel becomes perpendicular to the stripe pattern. When a liquid flows, it does only along the branch parallel with the stripe pattern. However, gas segments in the liquid can be separated along the branch perpendicular to the strip pattern. Thus, gas and liquid can be successfully separated without any membrane and with the combination of anisotropic wetting and microfluidic pattern.

3.3. Liquid-Gated Membrane Microseparation. Hou et al. reported “liquid-gated membrane” (LGM) that mimics micro- and nanoscale pores in living organisms that control the movement of gases, liquids, and solid particles [56]. The key concept of LGM lies in gating a pore of a membrane by liquid configuration (Figure 10 (a)). Membranes with any kind of pore size and surface chemistry, such as hydrophobic PTFE, polypropylene, and hydrophilic nylon, can be converted to LGM.

When the pores of a membrane are filled with a strongly wetting liquid that coats the pore surface intimately, other gases and liquids could flow through without contacting the solid wall if they have a penetration pressure higher than a flow-through pressure (critical pressure). By integrating LGM into microfluidic system, a continuous separation of

![Figure 9](image-url). Newly developed microseparators for gas–liquid separations. (a) Automated system for separation of carcinogenic CMME from byproducts. Adapted with permission from Ref. [61]. Copyright 2016 The Author(s). (b) Separation of gas–liquid segments on morphology patterned surface. Adapted with permission from Ref. [62]. Copyright 2016 American Chemical Society.
Multiphase mixtures was realized. The system consists of a microchannel that is connected with the surface of LGM and another outlet microchannel flowing on the opposite side of the LGM (Figure 10 (b)). The LGM has a critical pressure for gas flow ($P_{\text{critical(gas)}}$) and also for liquid flow ($P_{\text{critical(liquid)}}$) that is higher than $P_{\text{critical(gas)}}$. When the flow pressure (pressure difference applied for the flow) is lower than $P_{\text{critical(gas)}}$, the binary mixture flows only along its original microchannel. When the pressure difference is higher than $P_{\text{critical(gas)}}$ but lower than $P_{\text{critical(liquid)}}$, the gas segments in the binary mixture are separated from the liquid and flow through the LGM and subsequently the outlet microchannel.

Moreover, a binary mixture of solid and liquid that is immiscible with the gating liquid can flow through without triggering fouling problems, which is a major hindrance in microseparation. The LGM prevents any material from sticking to pores and clogging the system because of the pore surface that is always wetted by a liquid (Figure 10 (c)).

Multiphase mixtures with immiscible phases such as air, water, and oil could also be separated (Figure 10 (d)). In this case, the critical pressure for oil to flow through is higher than that for water. Thus, with increasing flow pressure, they can be separated in the order of gas, liquid, and then oil. Almost every membrane system can be converted to LGM by adding a liquid that is energetically matched to the pore surface, which makes LGM attractive as one of the most powerful microseparators.

4. Conclusions

We have presented a summary of recent achievements of microfluidic systems for the microreaction components fabricated by 3D printers and the microseparation components developed by new device concepts, prospecting the future direction of microreactors and microseparators.

An emerging technology of 3D printing can replace tedious lithographic processes to build microfluidic devices, and computer-aided fabricating steps can ensure reliability and reproducibility of the fabricated microfluidic devices. The polymeric resins for 3D printing techniques are quite inadequate because of the inherent instability of the resins with respect to heat and chemicals. Therefore, advances in the resin material would provide breakthroughs for microreactors. Glass, metal, and ceramic are promising materials for 3D printers to fabricate diverse types of microreactors for industrial applications. In fact, the conventional fabrication technologies have long utilized these materials to manufacture microreactors.

Vertical stacking of microchannels by 3D printing would be a leap forward for high productivity. To the best of our knowledge, there has been no report on multilayered microreactors fabricated by vertically stacking the microchannels using 3D printing techniques.

Another issue that can be dealt with by 3D printing is miniaturization of microfluidic systems. Despite the advances in flow chemistry, the microfluidic system still needs a set of bulky accessories, which makes the entire system large. Integrated microfluidic systems with compact configuration should be possible with 3D printing and with adaptation of latent potential of existing device concepts.

Microseparation is an integral part of any microfluidic system. Microseparating technologies are critically customized to specific synthetic and analytical purposes in microchemical processes. A series of these customized separation steps need
to be integrated for automated synthesis of industrial compounds. A case in point is the pharmaceutical synthesis where the multiple types of salification chemistry are appropriately implemented to separate and recover drug intermediates produced from different liquid mixtures at various points in series under flow conditions [63]. It is fortunate that many opportunities are open for us to develop innovative microseparation technologies by adopting multifunctional physical and chemical phenomena of newly developed nanomaterials and nanostructures [64], including microseparators that are highly durable even under harsh conditions.

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