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Review

Green microfluidics in microchemical engineering for carbon neutrality

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ABSTRACT

The concept of "carbon neutrality" poses a huge challenge for chemical engineering and brings great opportunities for boosting the development of novel technologies to realize carbon offsetting and reduce carbon emissions. Developing high-efficient, low-cost, energy-efficient and eco-friendly microfluidic-based microchemical engineering is of great significance. Such kind of "green microfluidics" can reduce carbon emissions from the source of raw materials and facilitate controllable and intensified microchemical engineering processes, which represents the new power for the transformation and upgrading of chemical engineering industry. Here, a brief review of green microfluidics for achieving carbon neutral microchemical engineering is presented, with specific discussions about the characteristics and feasibility of applying green microfluidics in realizing carbon neutrality. Development of green microfluidic systems are categorized and reviewed, including the construction of microfluidic devices by bio-based substrate materials and by low carbon fabrication methods, and the use of more biocompatible and non-destructive fluidic systems such as aqueous two-phase systems (ATPSs). Moreover, low carbon applications benefit from green microfluidics are summarized, ranging from separation and purification of biomolecules, high-throughput screening of chemicals and drugs, rapid and cost-effective detections, to synthesis of fine chemicals and novel materials. Finally, challenges and perspectives for further advancing green microfluidics in microchemical engineering for carbon neutrality are proposed and discussed.

1. Introduction

Since China has pledged that it should become carbon–neutral by 2060 according to the draft outline of the 14th Five-Year Plan (2021–2025) for China's national economic and social development, "carbon neutrality" has evoked intense echoes all over the country, especially in the field of chemical engineering. Carbon neutrality refers to net-zero carbon dioxide (CO_2) emissions which can be attained by counterbalancing a measured amount of carbon released with an equivalent amount sequestered [1–3]. As an important link between natural raw materials and downstream end consumer products, chemical engineering industry contributes 16.7% of the total industrial carbon emissions and around 6% percent of the total energy carbon emissions in China, with annual emissions approaching 1.5 billion tons per year [4]. Therefore, the concept of carbon neutrality poses a huge challenge for chemical engineering, a switch of such kind will be difficult for the entire industry. On the other hand, it also brings great opportunities for boosting the development of innovative technologies to realize carbon offsetting and reduce emissions. Novel strategies, such as microchemical engineering technology, have been well recognized as one of the most economic and feasible ways in chemical engineering to achieve energy conservation and carbon emission reduction [5–7]. Microchemical engineering utilizes integrated and miniaturized microchannel equipment as the core, through mixing and dispersion at micron-level in the microchannels, the heat and mass transport and reaction can be intensified, realizing the generation of products with high controllability, improved yield, inhibited by-products formation and lower energy consumption. It has intrinsic attributes of high efficiency, safety and energy-saving and is a promising method for chemical engineering process intensification towards carbon neutrality [8,9].

As one of the core technologies in microchemical engineering, microfluidics has attracted extensive scientific interests for realizing highly efficient and controllable processes [10,11]. Microfluidics processes and manipulates tiny fluids (1×10^{-9} L – 1×10^{-18} L) in microchannels with dimension of tens of micrometers, where flows are non-turbulent and highly ordered [12]. The influence of microfluidics has been expanded from early applications in the analytical chemistry [13] and ink-jet printing to the syntheses of fine chemicals and novel materials, high-throughput

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assays [14], and the simulation of cellular and intracellular systems [15]. While significant progresses are being achieved, the current development of microfluidics in microchemical engineering towards carbon neutrality is mainly at an infant stage and far from completion. It is important to note that not only the construction of microfluidic devices and the fluidic systems, but also the existing applications are not adequate to fully satisfy the requirements of carbon neutrality. For instance, conventional microfluidic device fabrication processes rely on standard microelectromechanical system (MEMS) fabrication techniques, including photolithography, micromachining, and chemical etching. These time-consuming multistep procedures require highly trained personnel and resource intensive facilities, thus greatly increasing the carbon emissions [16,17]. Moreover, the substrate materials for microfluidic device are mainly petroleum-derived polymer and plastics materials like polydimethylsiloxane (PDMS), acrylics and polycarbonate [18,19]. Glass is also another type of important materials [20]. The use of these materials is accompanied by high petrochemical energy consumption as well as toxic and corrosive waste, therefore leading to significant increase of carbon emissions and prohibiting carbon offsetting [21–23]. Furthermore, the typical fluidic systems in microfluidics involve the use of non-biocompatible and destructive organic solvents, whose production and disposition rely on large consumptions of petrochemical energy and results in huge carbon dioxide emissions. Besides, current situation of the applications of microfluidics is also somewhat contradictory to carbon neutrality. For example, when applying microfluidics in the syntheses of materials and the separation and purification of chemicals, the speed and efficiency are still not enough to reduce the energy cost [24]. Further, unfavorable components, such as non-biodegradable ingredients, are always used, increasing the costs and subsequently turns the whole process not environmentally friendly [25]. Therefore, developing high-efficient, low-cost and eco-friendly microfluidics towards carbon neutrality is around the corner. Such kind of "green microfluidics" would contribute greatly to the realization of carbon offsetting and the reduction of carbon emissions for microchemical engineering industry. It is worth noting that green microfluidics is one of the major areas that contribute greatly to green chemistry, like reducing the use of hazardous materials, decreasing waste generation, and improving biocompability and biosafety. Therefore, apart from carbon neutrality, green chemistry should also be one of the merits that green microfluidics can offer. While in this review, we aim at offering a whole scene of applying green microfluidics for achieving carbon neutrality. Though there are still large gaps between green microfluidics and CO_2 emission reduction, this review is intended to spark inspirations for researchers who try to shift their work towards carbon neutrality by summarizing recent advances in achieving CO_2 emission reduction with green microfluidics. Therefore, we hope this review can work as a heuristic guidance for applying microfluidics in carbon neutrality and inspire more fantastic works that can authentically link green microfluidics with carbon neutrality in the future.

Herein, we summarize up-to-date progress in green microfluidics for microchemical engineering towards carbon neutrality, as illustrated schematically in Fig. 1. First, strategies for developing green microfluidic systems are interpreted. The construction of microfluidic devices by bio-based substrate materials and by low carbon fabrication methods are introduced. The use of more biocompatible and non-destructive fluidic systems such as aqueous two-phase systems (ATPSs) is also highlighted. Then, emerging low carbon applications benefit from green microfluidics are reviewed, covering aspects include separation and purification of biomolecules, high-throughput screening of chemicals and drugs, rapid and cost-effective detections, and synthesis of fine chemicals and novel materials. The challenges and perspectives for further advancing green microfluidics in microchemical engineering for carbon neutrality are proposed and discussed in the end.

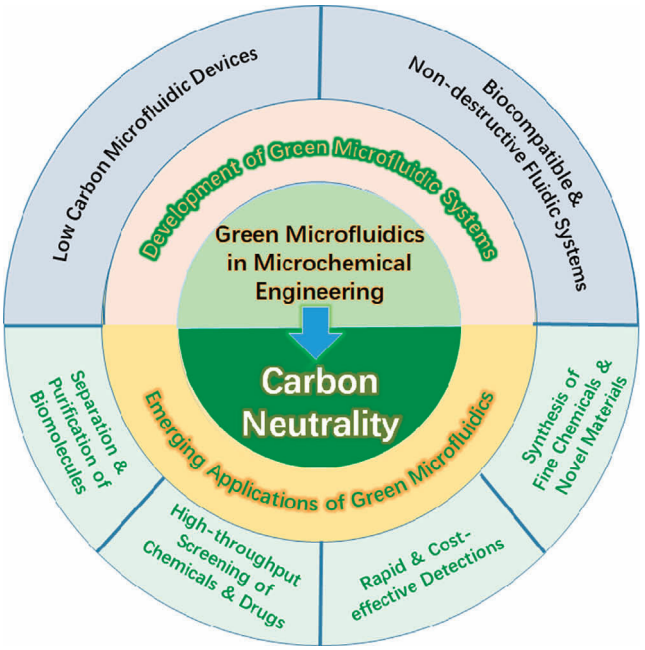

Fig. 1. An overview illustrating the key points of green microfluidics in microchemical engineering towards carbon neutrality.

2. Development of Green Microfluidic Systems

2.1. Construction of low carbon microfluidic devices

When embarking in the design of new microfluidic devices towards carbon neutrality, the choice of the substrate material is of fundamental importance and relevance. Currently, the substrate materials for conventional microfluidic devices are mainly petroleum-derived polymer and plastics materials. Polydimethylsiloxane (PDMS), poly(methyl methacrylate) (PMMA), polycarbonate (PC), and cyclic olefin copolymer (COC) are all representative materials that consumed in relatively large quantities. Various microfluidic devices based on these materials have been constructed and applied in multiple areas with remarkable achievements accomplished. However, the use of these petroleum-derived materials, along with the concomitant waste and disposition problems, should be taken into account when aiming at carbon neutrality. Glass is another type of commonly used substrate materials, whose production also requires large amounts of petrochemical energy and is accompanied by huge carbon dioxide emissions [26]. Therefore, proposing low carbon materials as novel substrate materials for green microfluidic devices are highly desired. Bio-based polymers and plastics, such as polylactic acid (PLA), poly(DL-lactic-co-glycolide) (PLGA), polyglutamic acid (PGA) and proteins, are materials produced from biomass, which can reduce the consumption of petrochemical energy [27,28] (as shown in Table 1). Moreover, they can be completely decomposed by environmental microorganisms after being used and discarded, and finally become inorganic and be a part of the carbon cycle in nature [39,40]. Multiple achievements have been made about adopting these bio-based materials for the construction of green microfluidic devices [35,38,41–43].

PLA is a natural derived polyester material, which can be molded, extruded, 3D-printed and laser-cut. All the current manufacturing facilitates used to construct microfluidic devices can be

Table 1
Typical bio-based materials used for constructing green microfluidic device

Type	Species	Ref.
polylactic acid (PLA)	biodegradable synthetic polymer	[29]
poly(DL-lactic-co-glycolide) (PLGA)	biodegradable synthetic polymer	[30]
polyglutamic acid (PGA)	biodegradable synthetic polymer	[30]
poly(glycerol sebacate) (PGS)	biodegradable synthetic polymer	[31]
silk fibroin	natural protein	[32]
gelatin	natural protein	[33]
alginate	natural polymer	[34]
zein	natural protein	[35]
chitosan	natural polymer	[36]
agarose	natural polymer	[37]
shellac	natural protein	[38]

rapidly applied to PLA by adjusting the manufacturing parameters, such as temperature, pressure and speed. For instance, a PLA microfluidic device with flow focusing junctions has been developed through extrusion based 3D printing, as shown by the digital microscopic images in Fig. 2(a) and (b). The developed device has a good transparency (92% transmittance) and a surface roughness of about 0.04 μm. Therefore, the direct observation of the fluid flow within the PLA devices can be achieved through the use of semi-transparent PLA with sufficiently thin walls. Moreover, the surface properties of the PLA substrate can be well adjusted by an alkaline hydrolysis approach, as shown in Fig. 2(c). The developed PLA microfluidic devices are more bio-inert, do not show absorption of small molecules, and are compatible with most chemical and biological protocols. Besides, PLGA is also a commonly used, prototypical, and biodegradable material, which can be used as the substrate materials for constructing green microfluidic device [44]. For example, a robust multilayered PLGA microfluidic device with extruded inlets and outlets has been developed, as shown by the images in Fig. 2(d). The PLGA networks are found to be readily perfused without leaks, occlusions, or interchannel cross-talk over a large-area device, demonstrating its great potential for conducting continuous generation of products with high controllability, improved yield, and inhibited by-products formation. Though PLA and PLGA show great promises for the construction of green microfluidic devices, some drawbacks still exist. One of the major drawbacks is their prices are always higher than that of conventional petroleum-derived polymer and plastics materials, which hinders their wide applications. Therefore, novel cost-effective synthetic methods for PLA and PLGA are highly desired and will promote the development of green microfluidic systems undoubtedly.

Apart from synthetic polymers, proteins are also promising candidates for constructing green microfluidic device. For instance, zein, a prolamin of corn, is a potential low-cost bio-based material of agricultural origin. Zein comprises of 50% hydrophobic amino acids including alanine, proline and leucine. It is biodegradable in nature and has been approved by U.S. Food and Drug Administration (FDA) as a nontoxic material. Thus, it can perform as low carbon substrate materials for constructing microfluidic devices. Zein can be bonded easily and quickly to different kinds of material without requiring expensive equipment such as oxygen plasma generator. As illustrated in Fig. 2(e) and 2(f), zein-based microfluidic devices have been successfully developed using standard soft lithography and stereo lithography techniques, which show distinct permeability to small molecules enable diffusive exchange between fluid flows and bulk zein microfluidic channels. Due to

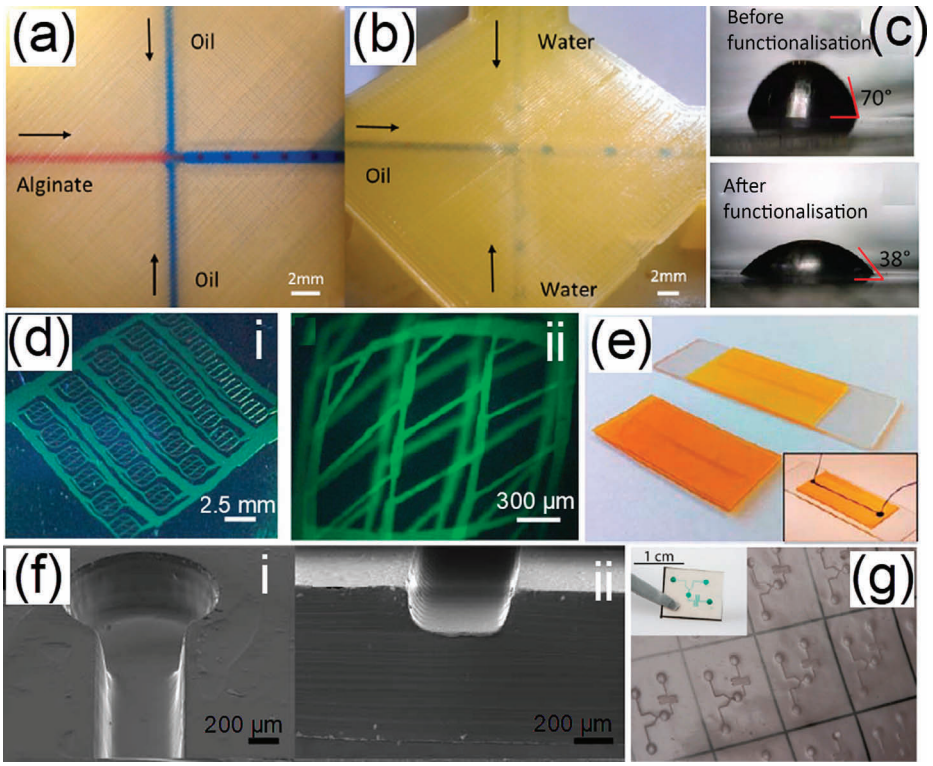

Fig. 2. Construction of low carbon microfluidic devices by bio-based materials. (a) Alginate droplets generated in sunflower oil in the PLA microfluidic device. (b) Mineral oil droplets generated in water in the PLA microfluidic device. (c) Tuning the surface properties of the PLA substrates. (d) PLGA as the substrate for microfluidic device. (e) Zein microfluidic devices. (f) Scanning electron microscopic (SEM) images of zein device. (g) Shellac as the substrate for microfluidic device. ((a, b) Reproduced with permission [29]. Copyright 2016, Public Library of Science. (c) Reproduced with permission [31]. Copyright 2018, Chemical and Biological Microsystems Society. (d) Reproduced with permission [30]. Copyright 2004, Wiley-VCH. (e, f) Reproduced with permission [35]. Copyright 2011, Royal Society of Chemistry. (g) Reproduced with permission [38]. Copyright 2016, American Institute of Physics.)

its biocompatibility, biodegradability and renewability, the developed zein microfluidic device demonstrates sufficient strength to facilitate fluid flow in a complex microfluidic design that shows no leakage under high hydraulic pressure, therefore has the potential to be used as fluid manipulator that can be coupled with other functional components for more complicated biochemical reaction and analysis applications. Besides, shellac, an excretion of *Kerria lacca*, is also biodegradable and renewable protein and has insulating properties and capabilities to form smooth surfaces, therefore has also been used for constructing green microfluidic device [45]. As illustrated in Fig. 2(g), shellac microfluidic device has been successfully fabricated through hot embossing technique, which enables low processing temperatures and therefore little energy consumption. Further, the good wettability, low water uptake, and simple structuring process of shellac microfluidic device renders it a promising platform in microchemical engineering. The bioactivity of protein is sensitive to the surrounding environment and inclined to be denatured [46]. Therefore, investigations over the preservation of protein bioactivity in protein-based microfluidic devices are important, especially for using as functional components towards biochemical reaction and analysis applications. However, current studies always have neglected the preservation of protein bioactivity and more attentions should be paid in this aspect to further verifying the utility of protein-based green microfluidic devices.

Time-consuming multistep procedures like photolithography, micromachining, and chemical etching are always involved in the conventional microfluidic device fabrication processes. Alternative fabrication methods have been proposed since late 1990s, such as soft-lithography, rapid-prototyping, print-and-peel technique, and scaffold-removal mold technique [47–51]. However, these approaches have different limitations, including the generation of chemical waste, still long processing time, and high startup and operating costs of the process due to the need for a high-resolution 3D printer. Therefore, the need for green and accessible fabrication methods to boost microfluidics development gave rise to novel techniques. Recently, a green, low-cost, user-friendly, and elastomeric (GLUE) rapid-prototyping method to fabricate microfluidic devices has been proposed, as illustrated schematically in Fig. 3 [52]. The GLUE method uses water-soluble nontoxic white glue as the patterning material and can achieve minimum tested feature widths of 200 μm, with tunable heights. Moreover, the intrinsic low cost of the GLUE method coupled with the use of nontoxic materials or cleanroom facilities can contribute to the elimination of most barriers imposed by conventional microfabrication methods, accelerating the development of green microfluidic devices in a low carbon manner. Though green and accessible fabrication techniques, like GLUE rapid-prototyping method, have been developed, the substrate materials used are still conventional petroleum-derived polymer and plastics materials. Whether these promising techniques can be applied with bio-based materials for the construction of green microfluidic devices is worth investigating, and the integration of bio-based materials with green and accessible fabrication techniques will prosper the development of green microfluidic systems in a more efficient manner.

2.2. Biocompatible and non-destructive fluidic systems

Fluidic systems in microfluidics are composed of immiscible liquids which can form interfaces between each other. Typically, water–oil emulsions are used as the fluidic systems, and organic solvents like long-chain alkane, liquid paraffin, dichloromethane, and dimethylsulfoxide (DMSO) are adopted as the oil phase [53–56]. Moreover, to stabilize the water–oil interfaces, various surfactants are added in the fluidic systems, such as Span 80, EM 90 and Dow Corning 749, most of which are petroleum-derived [57–59]. The production of these surfactants requires the use of organic solvents, such as n-hexane, tetrabutylammonium hydroxide and benzoic acid, which inevitably increases the carbon emissions in turn [60]. Therefore, more biocompatible and non-destructive fluidic systems with less reliance on organic solvents and surfactants are also important for the development of green microfluidic systems.

One of the promising fluidic systems is aqueous two-phase systems (ATPSs). ATPSs, also known as all-aqueous systems, are formed by dissolving two incompatible additives in water, such as two incompatible polymers or one polymer and other salts, above the critical concentrations for phase separation, as illustrated in Fig. 4(a) [61]. These incompatible additives can redistribute in water and form immiscible aqueous phases, when the entropic contribution that favors mixing becomes smaller relative to the enthalpic penalty that opposes it [64]. ATPSs contain a significantly large amount of water, typically over 80% (mass), imparting distinct properties beyond those of traditional water–organic solvent systems, such as biocompatibility and the recyclability. Moreover, the construction of ATPSs does not require any surfactant. Thus, ATPSs represents the most feasible fluidic systems in establishing green microfluidics that can reduce carbon emissions from the source of raw materials. Representative pairs of ATPSs for green microfluidics are summarized in Table 2. Among all the pairs, dextran and polyethylene glycol (PEG) are the most recognized additives due to their intrinsic biocompatibility, extensive source and low-cost.

Apart from biocompability and recyclability, another important feature of ATPSs is the ultralow interfacial tension. Particularly, the interfacial tensions between two immiscible aqueous phases are often in the range of $\sim 5 \times 10^{-4}$ – 0.5 mN·m^{-1} [65]. For instance, the typical interfacial tension for dextran/PEG ATPSs is only 0.07 mN·m^{-1} when the concentration of dextran and PEG is 8 and 6%(-

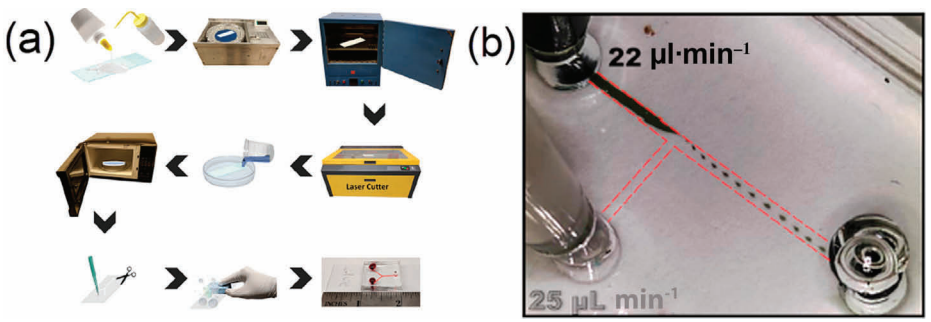

Fig. 3. (a) Schematics illustrating the GLUE rapid-prototyping method to fabricate green microfluidic devices. (b) Droplet generation in the microfluidic device by GLUE method. Reproduced with permission [52]. (Copyright 2020, American Chemical Society.)

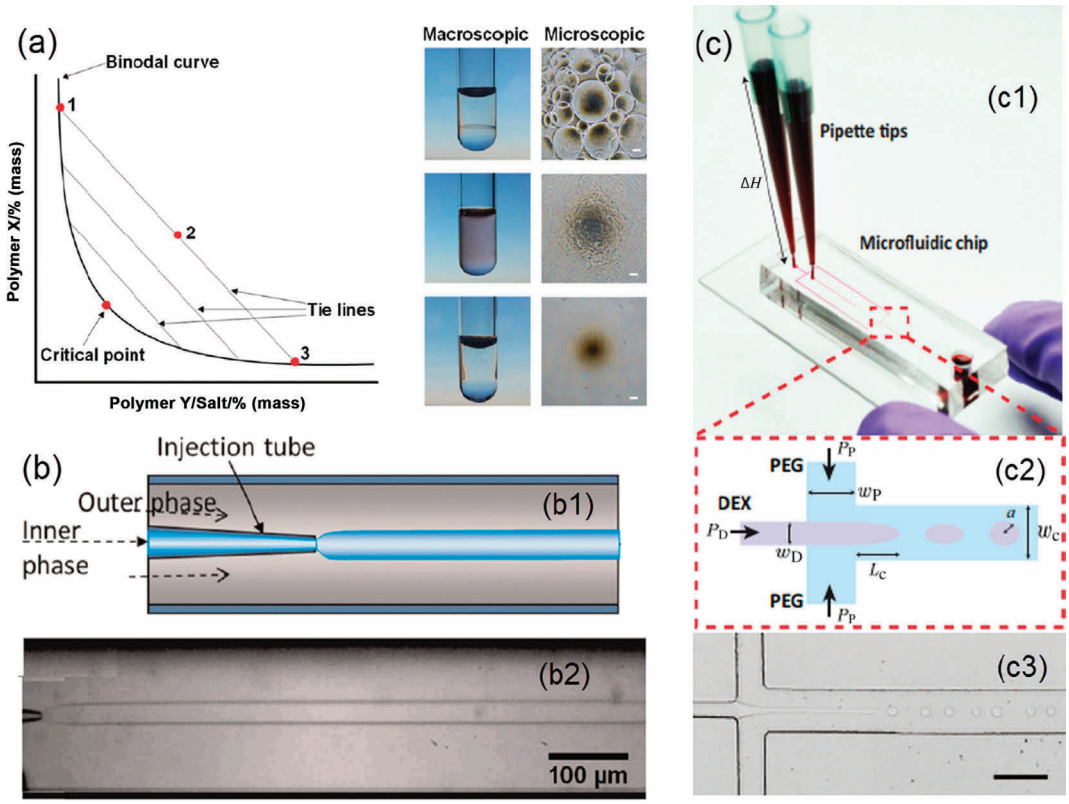

Fig. 4. (a) Phase diagram of a typical ATPS: The binodal curve separates the phase diagram into two regions including a single-phase region below the binodal curve and a two-phase region above the binodal curve. The two end points (1, 3) of tie lines correspond to the final compositions of the two immiscible aqueous phases after complete phase separation of the aqueous mixture (2). Left images showing three different states of polymer mixtures: (top) Supercritical (two phases), (middle) critical, and (bottom) subcritical (one phase) states. Scale bars are 100 mm. (b) Stable ATPSs jets formed in microfluidic channels. (c) ATPS droplets formation in green microfluidics by the gravity-driven hydrostatic pressure: (c1) Digital image of the microfluidic device; (c2) Schematic of the generation of droplets; (c3) Microscopic image of the generation of droplets in microfluidic channels. ((a) Reproduced with permission [61]. Copyright 2017, Wiley-VCH. (b) Reproduced with permission [62]. Copyright 2012, American Institute of Physics. (c) Reproduced with permission [63]. Copyright 2016, American Chemical Society.)

Table 2
Representative ATPSs for green microfluidics

Pair I	Dextran	PEG	K_2HPO_4	Starch
Pair II	PEG	Dextran	PEG	PEG
	Polyvinyl alcohol (PVA)	Starch	2-propanol	Locust bean gum
	Polyvinyl pyrrolidone (PVP)	PVA	Ethanol	Guar gum
	Methylcellulose	PVP	Ionic liquids	Xanthan
	Gelatin	Tripotassium phosphate (K_3PO_4)		Casein
		Monopotassium phosphate (K_2HPO_4)		
		Sodium citrate		

mass), respectively, which is around four hundred times smaller than that of oil–water interfaces (in the range of 30 $mN{\cdot}m^{-1}$) [66]. The ultralow interfacial tension turns ATPSs into a physically active system that is extremely sensitive to external influences. Specifically, the ATPSs interfaces are inclined to deform even subjected to tiny external vibrations, therefore the creation of new liquid–liquid interfaces only consume very little energy [67]. This offers great convenience for applying ATPSs in developing green microfluidics, allowing the production of droplets and jets with designable structures and tailored sizes. Several excellent reviews have been done to offer comprehensive descriptions of ATPSs in microfluidics [68,69], herein, we focus our discussion on controlling ATPSs in microfluidics in an energy efficient and "green" manner. For instance, manipulation of ATPSs jets in microfluidic devices has been shown to be a critical tool in the separation and purification of biomolecules, and controllable ATPSs jets can be achieved by optimizing the viscosity and external vibrational effects, as shown in Fig. 4(b) [62]. Moreover, various strategies have been proposed to facilitate the control formation of ATPSs droplets in microfluidic channels. Mechanical vibrator and piezoelectric actuator are used to hydrodynamically perturb ATPS to form droplets [70]. Electrospray is also applied with the gravity to facilitate the jet breakup into droplets [71]. All of these strategies involve external energy inputs, such as mechanical energy and electric energy, which is opposite to the requirement of energy conservation for carbon neutrality. Recently, a completely "green" method has been developed, which utilizes the gravity-driven hydrostatic pressure to generate ATPSs droplets in microfluidic channels, as shown in Fig. 4(c) [63]. Specifically, the fluid to be injected in microfluidic device is filled in pipette tips as fluid columns at the inlets, which introduces low speed flows to the flow-focusing junction device. The low flow speeds from the fluid-column-induced weak hydrostatic pressures help controllably form ATPSs droplets. The resulting droplet size can be con-

trolled by adjusting the interfacial tension and viscosity of two aqueous phases (dextran/PEG), as well as by varying the height of the fluid column at the inlets.

3. Emerging Low Carbon Applications of Green Microfluidics

3.1. Separation and purification of biomolecules

Extraction in ATPS has long been used both on laboratory and industrial scales for separation and purification of biomolecules, including recombinant proteins and protein-based drugs. Specifically, PEG/salt two-phase systems are widely used in largescale operations, providing good yields and high selectivity for desired proteins in the PEG-rich phase, while rejecting the majority of contaminants (cell wall debris, nucleic acids, and unwanted enzymatic activities) into the salt-rich phase. Moreover, extraction in ATPS is well-suited for continuous operation on microfluidic chips, as low Re-number flows enable facile and reproducible generation of stable interfaces and two-phase flow, making it straightforward to establish a stable interface without surfactants or special surface treatments. Green microfluidics can significantly improve the separation and purification efficiency of biomolecules due to the short diffusion distance as well as the large surface area-to-volume ratio of the phase boundary inside the microchannels. Various biomolecules have been collected and enriched by green microfluidics, include simple protein fractionation, fractionation of live and dead cells, and electrophoretically-enhanced protein extraction, as summarized in Table 3. For instance, the separation and purification of bovine serum albumin (BSA) and β-galactosidase can be efficiently achieved by utilizing a PEG/salt ATPSs microfluidics, where BSA (green signal) and β-galactosidase (red signal) can be almost entirely separated at the downstream, as illustrated in Fig. 5(a) [77]. Besides, high purity and recovery rate of bacteriorhodopsin (integral membrane protein found in the Archaea cell membrane, mainly in *Halobacteria species*) has also been achieved by utilizing a PEG/salt ATPSs microfluidics, as illustrated schematically in Fig. 5 (b) [80]. Moreover, with the high efficiency of separation and purification by green microfluidics, remarkable intensification of enzymatic reactions can be achieved. For instance, a continuous-flow process based on a suitably designed ATPSs parallel-laminar flow in a microfluidic device using for enzymatic catalysis has been developed, as illustrated schematically in Fig. 5(c) [82]. In the urease reaction, PEG and dextran solutions are selected as the two aqueous phases, in which the enzymes settle mainly in the dextran phase while the products partition mainly to the PEG phase within short residence time. Characterized by rapid mass transfer base on the large specific surface area, micron-scale diffuse distance and fast surface renewal rate, the proposed ATPSs microfluidics exhibits the remarkable intensification of enzymatic reaction with biotransformation rate 500 times higher than that of a conventional beaker system. Furthermore, the reaction yield can be significantly improved by the numbers of reaction cycles and the length of the microchannels. For example, the enzymatic reaction rate of the four-cycle reaction can be increased by about 4 times, which only takes 0.72 s. It is worth noting that the flow channels of microfluidic devices are narrow, and large-scale applications need to be amplified. Currently the scale-up of microfluidics relies mostly on massive parallelization, which is to manipulate hundreds of microfluidic channels simultaneously. Scaling up by parallelization to the desired product volumes appears to be technologically feasible, but it will be a great engineering challenge with respect to device material and design as well as robust operation. This process is somewhat tedious, resource intensified, energy-consuming and on the contrary of carbon neutrality. Novel strategies are highly desired for the scale-up of microfluidics for separation and purification. For instance, integrated thousands of micromechanical valves on a single microfluidic chip have recently been established and demonstrated that the control of the fluidic networks can be simplified through multiplexors [83]. This enabled realization of highly parallel and automated fluidic processes with substantial advantages. Moreover, the fabrication of these devices by microfluidic large-scale integration (mLSI) is reliable and hence can contribute to the carbon neutrality [84].

3.2. High-throughput screening of chemicals and drugs

High-throughput screening, the automated mining of compound libraries for active chemicals and drugs, has been the primary tool for discovering novel chemical matter [85–87]. Recently, green microfluidics has been proposed as a valid platform for high-throughput screening due to their properties of low sample consumption, low analysis cost, easy handling of nanoliter-volumes of liquids and being suitable for cell based assays [88,89]. Significant achievements have been made by applying green microfluidics, especially droplet microfluidics, in high-throughput screening of chemicals and drugs [90–94]. Two representative types are ATPSs microfluidics and cell-based microfluidics [95–97]. For instance, due to its intrinsic biocompatibility and recyclability, ATPSs droplets in microfluidics are particularly suitable for the screening of bioactive chemicals. The concept of performing ATPSs droplet-based high-throughput screening is illustrated schematically in Fig. 6(a), including four integral steps of droplets library generation, storage, mixing, and optical detection based on commercially available cross-junctions and optical fibers [98]. Specifically, droplet library is defined as a collection of monodispersed droplets with hundreds of different reagents encapsuled in each separate droplet, which are necessary for microfluidic applications including combinatorial chemical synthesis, DNA-encoded libraries, and massively multiplexed PCR. As

Table 3
Biomolecules separated and purified by ATPSs microfluidics

Type of biomolecules	ATPSs	Ref.
BSA	Dextran/PEG; $(NH_4)_2SO_4$/PEG; Potassium phosphate buffer/PEG	[72,73]
GFP	Dextran/PEG; $(NH_4)_2SO_4$/PEG; Potassium phosphate buffer/PEG	[72,73]
Immunoglobulin G (IgG)	Potassium phosphate buffer/PEG	[74,75]
Genomic DNA	Dextran/PEG; Potassium phosphate buffer/PEG	[76]
β-galactosidase	Dextran/PEG	[77]
α-Amylase	K_2HPO_4/PEG	[78]
Insulin	Dextran/PEG; $(NH_4)_2SO_4$/PEG; Potassium phosphate buffer/PEG	[72,73,77]
Ovalbumin	Dextran/PEG	[79]
Bacteriorhodopsin	Potassium phosphate buffer/PEG	[80]
Mycotoxin ochratoxin A	$(NH_4)_2SO_4$/PEG; Potassium phosphate buffer/PEG	[81]
Ammonium carbonate	Dextran/PEG	[82]
Urease	Dextran/PEG	[82]

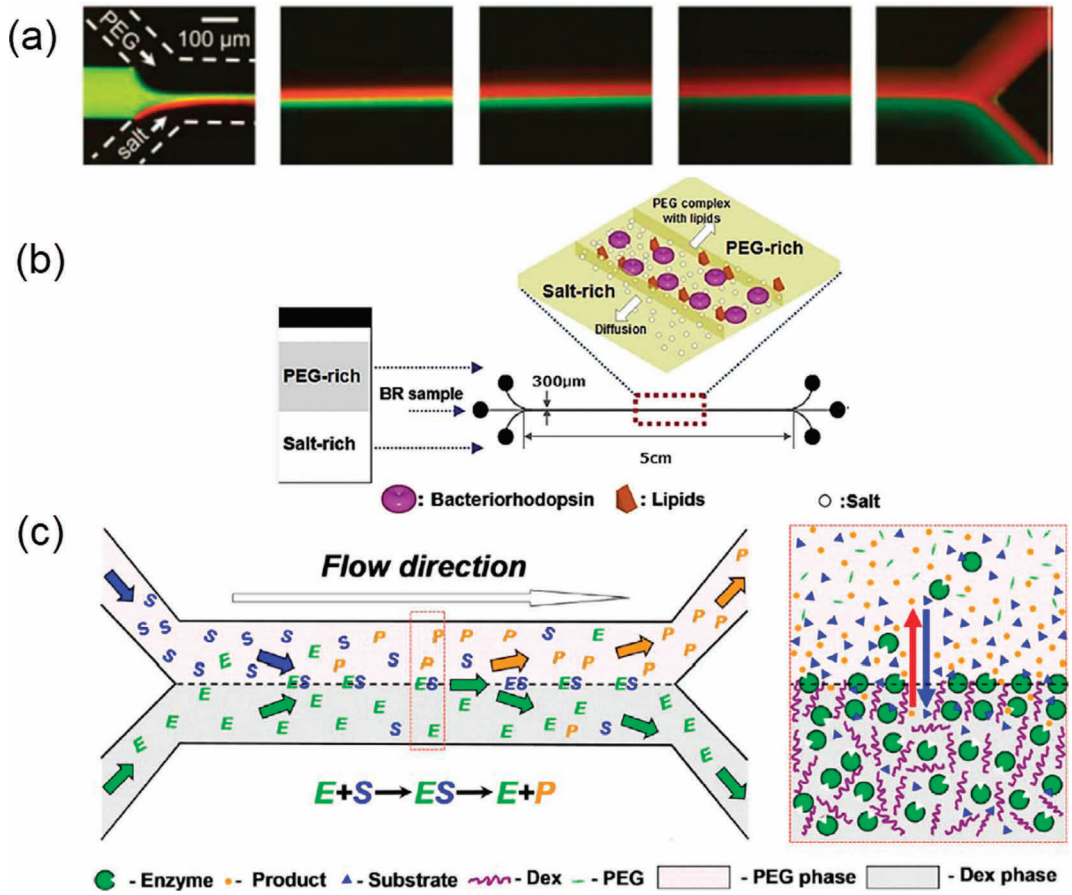

Fig. 5. (a) Fluorescence microscopic images showing the separation and purification of BSA (green signal) and β-galactosidase (red signal) by green microfluidics. (b) Schematic representation of green microfluidics applied on the purification of bacteriorhodopsin. (c) Schematic illustration of the enzymatic reaction and product separation in green microfluidics. ((a) Reproduced with permission [77]. Copyright 2008, Royal Society of Chemistry. (b) Reproduced with permission [80]. Copyright 2010, American Institute of Physics. (c) Reproduced with permission [82]. Copyright 2018, Elsevier.)

shown in Fig. 6(a), for the establishment of the droplet library, the optimal range of conditions for drop generation in the microfluidic channels are first determined over a range of tubing diameters and flow rates, then the generated droplets are collected and stored by wrapping a flexible capillary tube around a spool. This approach can accommodate drop assays with volumes ranging from 2 nl to 2 ml, and storage densities ranging from 300 to 3000 drops per metre tubing. Generation rates are up to 200 drops per second and merging rates are up to 10 drops per second. The simplest and most common used "mix and read" assay can be well performed, with the cost of the entire system less than 20 USD and the assembly time less than 10 minutes. Furthermore, the ATPSs droplets can also perform as platforms for fabricating cell-encapsulated hydrogel beads. The cells can be captured in alginate solutions and crosslinked by $BaCl_2$ at a T-junction. The cells inside the tubing can be simultaneously cultured with high viability, sufficient for cell-based screening of drugs. Cell-based microfluidic high-throughput screening is of great importance for the discovery of novel pharmaceutically valuable compounds. To date, different components for microfluidic cell-based high-throughput screening platforms have been developed, including cell culture [100–102], introduction and transportation of samples [103,104], and characterization of cell viability [105,106]. For example, a complete microfluidic droplet screening workflow for high throughput cytotoxicity screening of single mammalian cells has been successfully developed, as illustrated schematically in Fig. 6(b) [99]. The screening workflow is comprised of 4 steps: (1) the drug library is formatted using the library generation chip into a droplet emulsion with each member uniquely coded with an optical label; (2) each droplet library member is combined with a cell-containing droplet on a merge chip; (3) the combined emulsion is incubated for cell treatment; and (4) the emulsion is reinjected into the assay chip, where each droplet's fluorescence is measured for both assay and drug coding readouts. The developed system can achieve drug screening at a frequency of more than 100 Hz. The cells can be encapsulated in individual aqueous droplets, and merged with optically-coded droplets from a library enabling to identify drug composition and drug concentration in each droplet. After 24 hours off-chip incubation, the droplets are then reinjected in the chip and merged with fluorescent dye droplets for staining live/dead cells to investigate the cytotoxicity of the drug. Drugs with desired pharmaceutical efficacies can be screened in a fast and energy efficient manner.

3.3. Rapid and cost-effective detections of biomolecules

The development of new detection capabilities based on more sustainable technologies is essential to make the detection process carbon neutral and closer to the principles of green analytical chemistry, including reducing and eliminating the use of solvents, direct detection without sample pretreatment, miniaturization of analysis systems, and more efficient determination with lower energy consumption and analysis time [107–109]. Realization of the concept of green microfluidics by integrating microfluidic devices with miniaturized functional components and detection systems show great potentials in achieving rapid and cost-

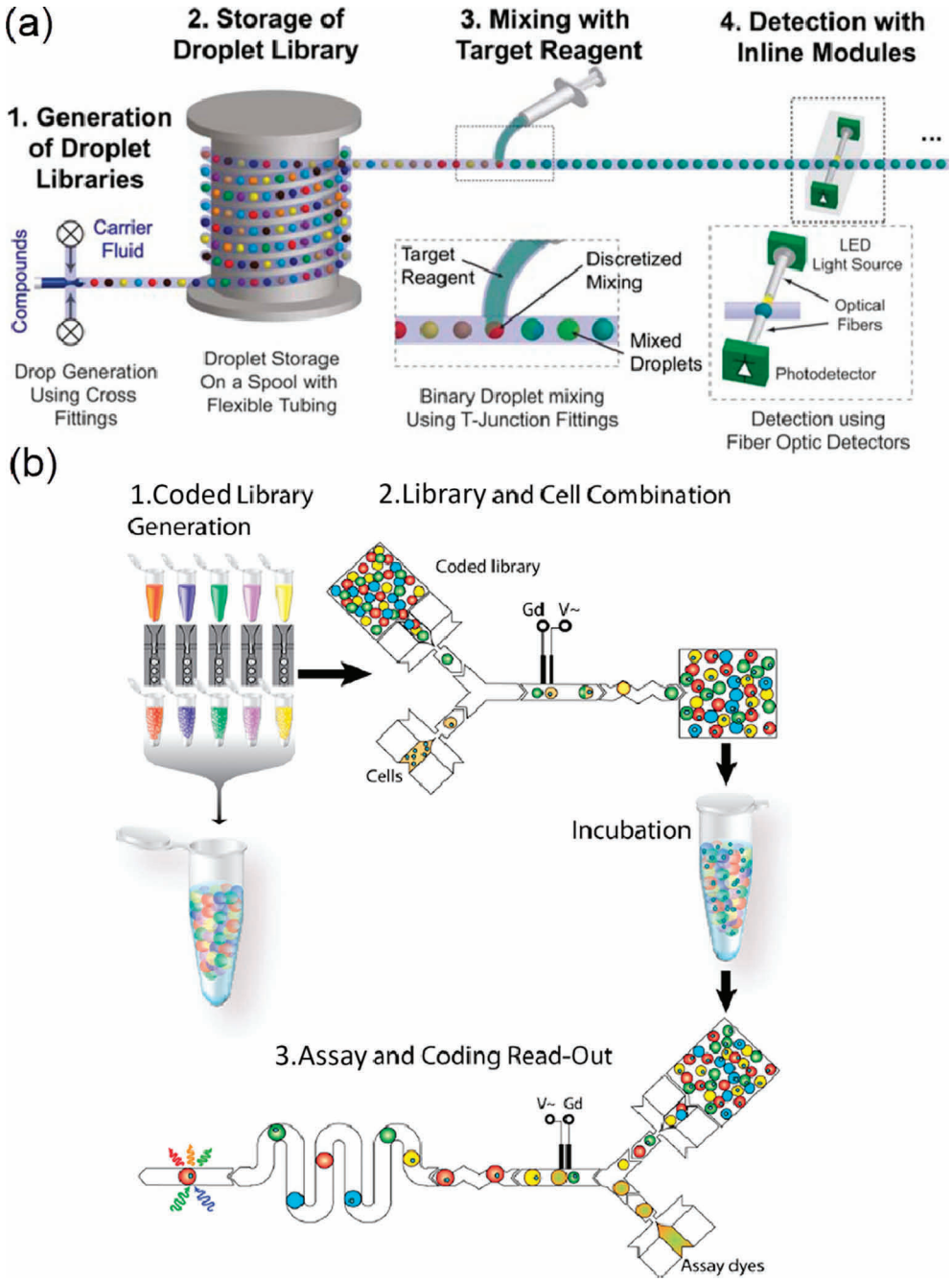

Fig. 6. (a) Conceptual schematics of performing ATPSs droplet-based high-throughput screening, including: 1. generation of droplet libraries, 2. storage of droplet libraries, 3. Mixing with targeted reagents, 4. detected with incline modules. (b) Workflow of microfluidic cell-based high-throughput screening of drugs, including: 1. coded library generation, 2. library and cell combination, 3. assay and coding read-out. ((a) Reproduced with permission [98]. Copyright 2010, Royal Society of Chemistry. (b) Reproduced with permission [99]. Copyright 2009, National Academy of Sciences.)

effective detections [110]. For instance, a green microfluidic system based on fully integrated cotton threads to perform high-efficient and low-cost electrochemical detections has been developed [111]. Particularly, due to their intrinsic features such as high availability, low cost, biodegradability and flexibility, cotton threads present a suitable type of green materials with the possibility of the creation of detection regions, by simple deposition or incorporation of compounds in the threads, such as conductive materials that can be used as electrodes in electrochemical detections. Hydrophilic cotton threads containing carboxylic groups are miniaturized and integrated in microfluidic devices, which allows the chromatographic separation of ascorbic acid (AA) and dopamine (DA) through an ion exchange mechanism with subsequent highly efficient detection of the compounds, as illustrated in Fig. 7(a) and 7(b). The detection limits of AA and DA can be lowered to 2.89 $\mu mol \cdot L^{-1}$ (for AA) and 4.41 $\mu mol \cdot L^{-1}$ (for DA), respectively. The detection can be performed at a low cost (less than 0.01 dollars for the cost of certain materials rather than the cost of the whole detection), and with a small volume of waste generated (107.1 μl). The proposed green microfluidic system has been employed to determine the levels of AA and DA present in the tears of healthy volunteers without sample pretreatment, demonstrating its feasibility for the performance of greener electrochemical detections through a simple, inexpensive and eco-friendly method-

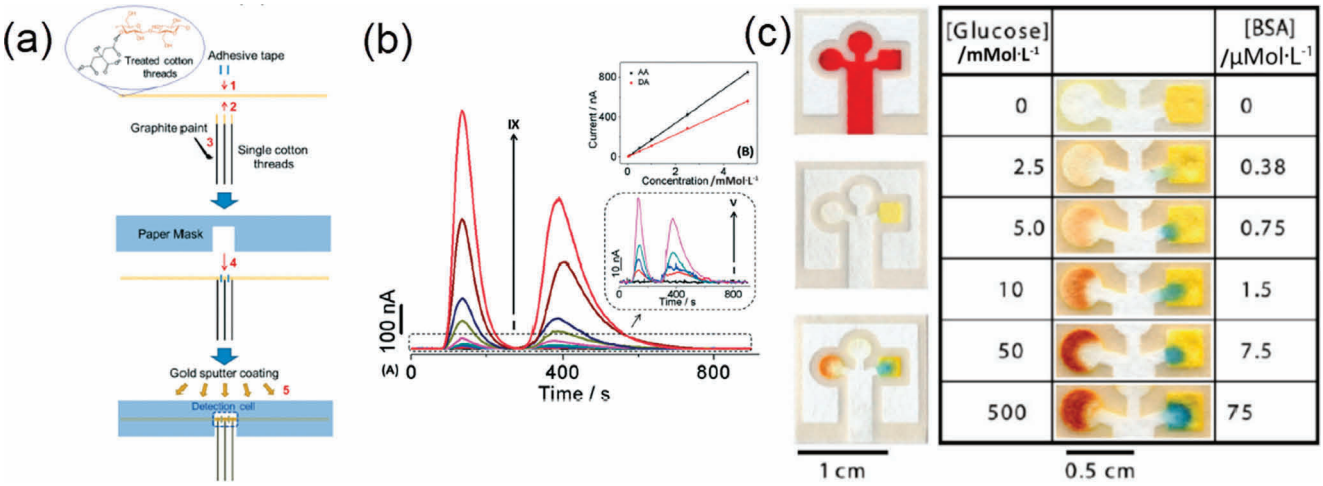

Fig. 7. (a) Manufacturing process of the proposed separation system showing the steps of the main microchannel preparation with the formation of the detection cell through gold deposition and the assembly of the system with the integration of all necessary components. (b) Typical chromatograms obtained with the proposed system for the separation and detection of solutions containing mixtures of AA and DA in acetate buffer pH 3.8 with the following concentrations of both species: (I) 0.00, (II) 0.025, (III) 0.050, (IV) 0.10, (V) 0.25, (VI) 0.50, (VII) 1.00, (VIII) 2.50 and (IX) 5.00 mmol·L^{-1}. The insert shows the signals for the lowest concentrations (I–V). (B) Linear relationship between oxidation current values (n = 3) and AA and DA concentrations in the range of 0.025–5.00 mmol·L^{-1}. Interval time: 100 ms; applied potential: 0.6 V; injected volume: 2.0 µl. (c) Paper-based microfluidic device for the simultaneous detection of glucose and BSA in urine. (left top) Patterned paper after absorbing 5 L of Waterman red ink by capillary action. The central channel absorbs the sample by capillary action and the pattern directs the sample into three separate test areas: (left middle) Complete assay after spotting the reagents. The square region on the right is the protein test and the circular region on the left is the glucose test. The circular region on the top was used as a control well and was spotted with either iodide but no enzyme solution, or with enzyme solution but no iodide; (left bottom) Positive assay for glucose (left) and protein (right) using 5 L of a solution that contained 550 mmol·L^{-1} glucose and 75 mol·L^{-1} BSA in an artificial urine solution. (right) Glucose and protein detection assays using varying concentrations of glucose and BSA. ((a, b) Reproduced with permission [111]. Copyright 2018, Royal Society of Chemistry. (c) Reproduced with permission [112]. Copyright 2007, Wiley-VCH.)

ology. Furthermore, a discussion of green microfluidic-based detection, especially in the context of low-resource settings, is not complete without mentioning paper-based microfluidics, which uniquely offer the potential for truly disposable, self-contained, and low-cost detections [113–115]. For instance, a paper-based microfluidic device for simultaneously detecting glucose and BSA in 5 µl of urine is developed, as shown in Fig. 7(c) [112]. The detection limits of glucose and BSA can be optimized as 2.5 mmol·L^{-1} (for glucose) and 0.38 µmol·L^{-1} (for BSA), respectively, which are lower than that of commercial dipstick assays without microfluidics. The developed green microfluidic system is small, disposable, inexpensive, portable, and requires no external equipment, reagents, or power sources, that is favor for the realization of carbon neutrality.

3.4. Synthesis of fine chemicals and novel materials

Taking advantages of various fluidic structures and intrinsic characteristics, green microfluidics can be used to synthesize fine chemicals and novel materials spanning the nano- to millimeter scales [116]. For instance, the use of segmented flow, multi-step chemistry, and rapid mixing of integrated separation steps make microfluidics a powerful platform for the green synthesis of various fine chemicals, whose properties can be controlled with unparalleled precision [117]. Green synthesis is a bionanotechnology evolution that helps to eradicate harmful chemistry by synthesizing fine chemicals using natural plant extracts [118,119]. By applying microfluidics with green synthesis, the complexity in the conventional synthesis process and the economic and environmental load on chemical development can be reduced significantly, thus reduce the carbon emissions as a result. Recently, a microfluidic-based green synthesis of silver nanoparticles (AgNPs) has been developed [120]. Aqueous leaf extracts from the medicinal plant *Ipomea quamoclit* L. are used to react with silver nitrate ($AgNO_3$) in the microfluidic channels to produce AgNPs, as shown in Fig. 8(a). The leaf extract is shown to be used as a bio-reducing agent to produce AgNPs without harmful compounds. Moreover, unlike conventional synthetic methods, no harmful and toxic chemicals that are neither economical nor eco-friendly are used [126]. The whole process is simple, viable, dependable, cost-effective and eco-friendly, thus is beneficial to the achievement of carbon neutrality. Besides, green microfluidics have also been applied widely in the synthesis of different biomaterials in a low carbon manner. Particularly, ATPSs microfluidic droplets and jets have proved an important stepping stone to the fabrication process. For example, ATPSs microfluidic droplets can be solidified by chemical or physical crosslinking to form spheroidal particles, Janus particles, and particles with a socket shape, as shown in Fig. 8(b) [121,122,127]. Moreover, ATPSs microfluidic droplet interfaces have been employed as 2D templates for the fabrication of complex vesicles composed of a few macromolecular layers, including liposomes, polymersomes, and colloidosomes, as shown in Fig. 8(b) [123–125,128]. The fabricated architectures can be used as artificial membraneless organelles for biomedical applications and bioreactors for microchemical engineering, as demonstrated in Fig. 9 [129,130]. Additionally, ATPSs microfluidic jets have been applied as important templates in fabrication of biomaterials, such as hydrogel fibers and woven fabrics, which have great potentials in fields of tissue engineering scaffolds, implantable hydrogel device and biosensors, as well as wearable electronic devices [131–134].

4. Challenges and Perspectives

Reducing carbon emissions from the source of raw materials and realizing green and clean production processes through microfluidics are the "green power" for the transformation and upgrading of traditional chemical engineering industries. Advances in green microfluidics, including the development of green microfluidic systems by bio-based substrate materials, low carbon fabrication methods and the use of more biocompatible and non-destructive fluidic systems, have enabled the realization of carbon

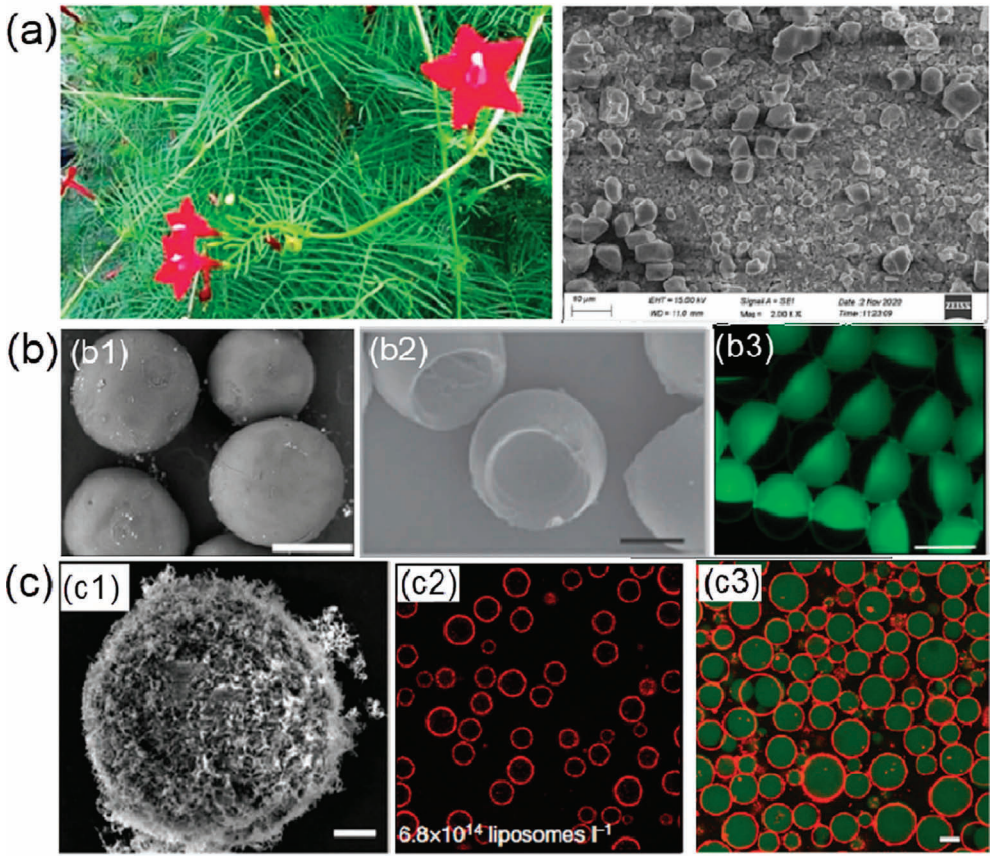

Fig. 8. (a) Microfluidics-based green synthesis of AgNPs by aqueous leaf extracts from the medicinal plant *Ipomea quamoclit* L.. (b) ATPSs microfluidic droplets based spheroidal particles (i, scale bar: 400 μm), particles with a socket shape (ii, scale bar: 30 μm), and Janus particles (iii, scale bar: 20 μm). (c) ATPSs microfluidic droplet interfaces based colloidosomes (i, scale bar: 2 μm), liposomes (ii), and polymersomes (iii, scale bar: 10 μm). ((a) Reproduced with permission [120]. Copyright 2021, Springer Nature. (b) Reproduced with permission [46]. Copyright 2016, Royal Society of Chemistry [121]. Copyright 2012, Wiley-VCH [122].Copyright 2015, Wiley-VCH. (c) Reproduced with permission [123]. Copyright 2016, Springer Nature [124]. Copyright 2014, Springer Nature [125]. Copyright 2010, Elsevier.)

offsetting and the reduction of carbon emissions for microchemical engineering, and demonstrated diverse applications ranging from separation and purification of biomolecules, high-throughput screening of chemicals and drugs, rapid and cost-effective detections, to synthesis of fine chemicals and novel materials. Despite these compelling and exciting achievements, there remain significant opportunities to better understand green microfluidics and to further leverage their unique characteristics in the development of microchemical engineering industry.

4.1. Design and discovery of new green microfluidics

Although significant achievements have been made for the development of green microfluidic systems, the strategies are still not enough and deserve more investigations. For instance, current species of substrate materials suitable for green microfluidics are limited, the source of raw materials should be further broadened. Compared with synthetic polymers, materials of natural origins, such as proteins and natural polymers, are more promising due to their independence of petrochemical resources, biocompability and more widely availability in nature. Future investigations are suggested to pay more attentions for verifying the potentials of more natural original materials as substrate materials. Besides, though ATPSs show great viabilities in green microfluidics, the high osmolality associated with the concentrated salt-rich aqueous phase in ATPSs is harmful to cells and biomolecules [135]. Therefore, there remains a need to find new compositions of ATPSs that can mimic the cytoplasmic environments. To address this issue, components of natural origins, such as enchylema that extracted directly from cells with proper purifications and separations, can be direct applied as suitable component of ATPSs to mimic the cytoplasmic environments and facilitate bio-based applications.

4.2. New applications towards carbon neutrality

Some achievements have been obtained by using materials fabricated by green microfluidics. For instance, adsorbing materials, like porous particles, have been demonstrated as efficient platform for carbon capture [136,137]. However, these achievements are not enough and far from completion. There still leaves large gaps for realizing carbon neutrality by using different materials fabricated by green microfluidics. For instance, novel materials with specially designed physical structures and chemical compositions for carbon capture are highly desired. And the fabrication of these novel materials by green microfluidics deserves systematic investigations. Hopefully prosperous results using green microfluidics to fabricate novel materials for capturing CO_2 in a more efficient way can be achieved in the near future.

4.3. Realization of industrialization and commercialization

The creation of an integrated and miniaturized laboratory has long been a dream of the chemical engineering community. However, the industrialization and commercialization of microfluidics is far from completion, rather than establishing an integrated and miniaturized system, most experiments still involve connecting a

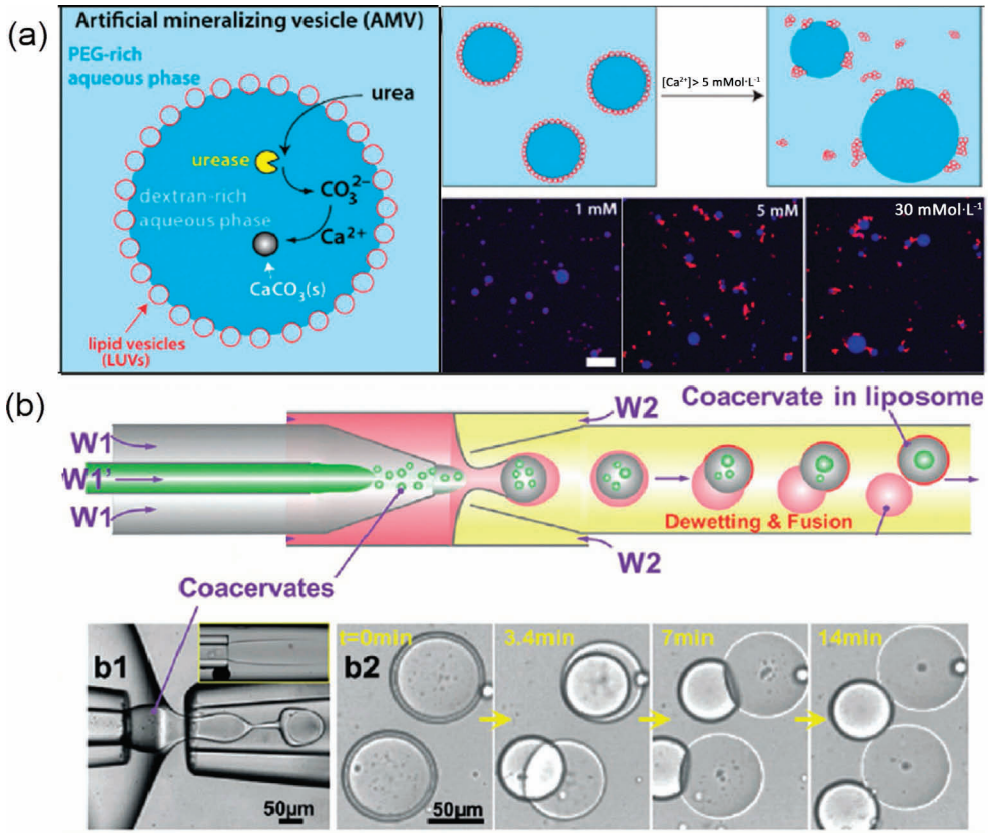

Fig. 9. (a) (left) Schematics of enzymatic production of $CaCO_3$ mineral within liposome-coated ATPS vesicles. (right) (upper line) Schematics of the experiment, in which the effect of adding Ca^{2+} to a sample of liposome-coated ATPS vesicles is evaluated. At 5 mM Ca^{2+} and above, the interfacial layer of liposomes is disrupted. (bottom line) CLSM images of liposome-coated ATPS vesicles with different amounts of added Ca^{2+} as indicated in each panel. Scale bar: 10 μm. (b) Microfluidics-based green synthesis of artificial nucleoid-like membraneless organelles: (top) Schematics; (bottom) optical microscope images of the microfluidic preparation of emulsion templates with coacervates as well as relevant dewetting transition and fusion process to form liposome-coated ATPS droplets. ((a) Reproduced with permission [129]. Copyright 2015, American Chemical Society. (b) Reproduced with permission [130]. Copyright 2017, Wiley-VCH.)

small microfluidic device with complicated instruments, or interfacing it with macroscale control architectures. Truly integrated and miniaturized green microfluidic systems are highly desired to be realized and, more importantly, commercialized [138,139].

Declaration of Competing Interest

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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Supplementary Material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cjche.2022.01.014.

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