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Biodegradable Polymers for Micro Elastofluidics

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Micro elastofluidics is an emerging research field that encompasses characteristics of conventional microfluidics and fluid-structure interactions. Micro elastofluidics is expected to enable practical applications, for instance, where direct contact between biological samples and fluid handling systems is required. Besides design optimization, choosing a proper material is critical to the practical use of micro elastofluidics upon interaction with biological interface and after its functional lifetime. Biodegradable polymers are one of the most studied materials for this purpose. Micro elastofluidic devices made of biodegradable polymers possess exceptional mechanical elasticity, excellent bio compatibility, and structural degradability into non-toxic products. This article provides an insightful and systematic review of the utilization of biodegradable polymers in digital and continuous-flow micro elastofluidics.

1. Introduction

Polymer is one of the most important materials in modern society. Polymers are macromolecules consisting of chains with repeating subunits called monomers. Each polymer has its own unique properties due to their diverse molecular characteristics and types of chemical bonds. Polymers are generally classified as synthetic and natural polymers. A synthetic polymer is the more dominant group in terms of availability. Synthetic polymers such as polyesters have been the pillars of many industries for decades, playing an essential role in everyday life. Common synthetic polymers feature high performance and adaptability in vast ranges of applications due to their mature manufacturing processes. Typical examples of successful commercial synthetic polymers are polyethylene terephthalate (PET), polyethylene (PE), and polypropylene (PP). On the other hand, natural polymers found in plants, animals, and microorganisms have been extracted and studied for a range of applications since the dawn of humanity. As such, natural polymers have become critically important to many industries including paper, textile, food, cosmetics, and pharmaceutics. Common natural polymers are cellulose derived from wood, chitosan derived from crustaceans, animal-based DNAs, and proteins.[1–3]

Microfluidics is a multi-disciplinary field involving well-controlled manipulation of extremely small amounts of liquids. The emergence of microfluidics enables researchers to implement chemical processes in a significantly reduced scale with apparent advantages such as less reagents, less waste, and reduced operation cost. To date, microfluidic devices have been used for a wide range of applications in the fields of chemistry, biology, and biomedical engineering.[4] Based on how the fluid is manipulated, microfluidics is classified into two main areas: continuous-flow microfluidics and digital microfluidics. In continuous-flow microfluidics, liquid is manipulated and transported continuously in microchannels without disruption. Continuous liquid flow is maintained through external components such as micropumps, or on-chip utilizing electrostatic, magnetic, or capillary forces. Continuous-flow microfluidic devices have been utilized for micro- and nanoparticles separation,[5] cell sorting,[6] separation of cancer cells,[7] and concentration of bioparticles.[8] Digital microfluidics focuses on handling discrete liquid droplets. In contrast to continuous-flow microfluidics, the design of a digital microfluidic system is relatively straight forward due to the absence of tubes, microchannels, valves, or pumps. In addition, digital microfluidics offers distinct advantages such as the ability to perform different operations at the same time, minimum sample consumption, and faster reaction rate.[9,10] Due to these exciting features, digital microfluidics has been applied for a variety of biomedical applications such as chemical and biological assay, protein analysis, or clinical diagnostics.[11,12] In addition, digital microfluidics can be combined with analytical techniques such as Raman spectroscopy, electrochemiluminescence, and colorimetry. These combinations further extend the utilization of digital microfluidics beyond biomedical fields, reaching analytical chemistry, environmental analysis, or food processing.[13]

Miniaturized flexible and stretchable devices have been becoming increasingly important due to the rise of wearable and implantable devices, leading to thriving research toward biomedical applications such as on-skin sensors, cardiac pacemakers or nerve stimulators.[14–16] However, current research only focuses on physical interfaces to the body via electric signals. A

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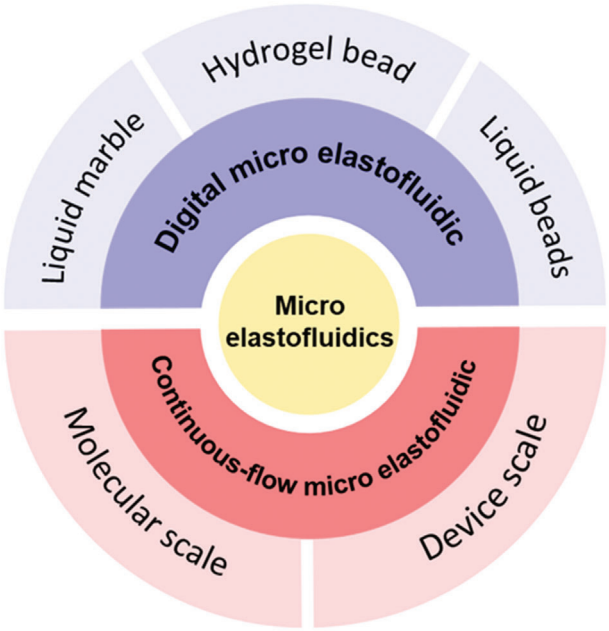

Figure 1. The overall concept of micro elastofluidics.

chemical interface would allow for assessing body fluid and delivering drugs in real time. Microfluidic devices are prospective candidates for the implementation of this chemical interface. The ability to handle and manipulate fluid at micro-scale enables microfluidic devices to perform a wide range of fluid-based operations, such as controlled delivery of drug molecules and extraction of biofluids for sensing,[17–19] which are challenging to achieve with conventional wearable and implantable devices. However, a gap still exists between conventional microfluidics and wearable, implantable devices. There is a lack of theoretical understanding of the interaction between fluid flow and flexibility and stretchability. Hence, it is necessary to fill this gap with further advancement of microfluidics toward applications in reliable and biocompatible systems. Recently, Nguyen coined the term micro elastofluidics, which defines the research area focusing on the manipulation of fluid based on fluid-structure interaction inside flexible, elastic microscale devices. The interactions between stationary or moving fluids with surrounding deformable structures are the fundamental backbone of micro elastofluidics.[20] Micro elastofluidics is expected to play a key role in future development of hybrid wearable and implantable devices, which include microfluidics, electronics. and biological subsystems. In terms of classification, similarly to conventional microfluidics, micro elastofluidics are also categorized into digital and continuous-flow micro elastofluidics. **Figure 1** provides an overview of the concept of micro elastofluidics.

Digital micro elastofluidics focuses on the fabrication, manipulation, and applications of discrete microscale, liquid-containing solid-like systems to safely encapsulate and transport liquids. The flexibility and elasticity of the polymeric container allow digital micro elastofluidic systems to be handled independently like a solid particle without the need for an external handling platform with electrodes or magnets as in the case of conventional digital microfluidics. A fundamental understanding about possible interactions between encapsulated liquid and surrounding solid matrix or solid shell is essential for the construction of digital micro elastofluidics platforms. The simplest form of elastic liquid encapsulation system is a liquid marble. A liquid marble is formed by coating a liquid droplet with a layer of micro- or nanoparticles. Liquid marble possesses similar characteristics of a liquid droplet on a hydrophobic surface such as non-wetting, deformability under applied mechanical force, and mobility on both liquid and solid surfaces without rupturing. With these unique features, liquid marble is considered a digital micro elastofluidic platform. Our team has conducted extensive research on liquid marble with promising outcomes regarding their fabrication, handling, and practical applications.[21-28] Nevertheless, the rapid evaporation of a liquid marble due to its porous shell severely limits its applicability. On the other hand, liquid beads consist of a solid polymer shell and a liquid core. Compared to liquid marbles, liquid beads retain its content for a longer duration because of the mechanically stable and relatively non-permeable shell. Recently, our team successfully synthesized core-shell microparticles with a trimethylolpropane trimethacrylate (TMPTMA) shell and a core of fluorinated oil or water. Thermal and mechanical analyses showed that these microparticles can potentially find application in digital polymerase chain reaction (PCR).[29,30] Another notable form of liquid encapsulation is hydrogel bead. Hydrogel is a solid material with 3D, cross-linked network that contains a large amount of water. Hydrogel beads have tunable mechanical properties such as elasticity, flexibility, and porosity. Changing the type and the degree of polymeric crosslinking can tune these properties.[31] In addition, the rates of water retention and release of hydrogel beads are adjustable to suit their applications.

Continuous-flow micro elastofluidics encompasses the studies at molecular and device scale of a microfluidic device that contains flexible and elastic elements. At the molecular scale, the major research focus is on the dynamic behavior of moving fluids with elastic characteristics inside microchannels. At the device scale, it is all about designing flexible, stretchable microfluidic components and devices that utilize the interactions between liquid flow and their deformable component for new or enhanced functions. Viscoelastic fluid is typical example of molecular-scale micro elastofluidics. Viscoelastic fluids exhibit both viscous and elastic characteristics. Compared with water or the so-called Newtonian fluids, the behavior of viscoelastic fluids inside microchannels is much complex, depending of the shear rate. The fluid-channel wall interaction and effects of fluids on the migration patterns of suspended biological cells or particles in the microchannels are some notable microfluidic applications related to viscoelastic fluids. Meanwhile, the development microfluidic devices with flexible and stretchable components have attracted a great attention from the research community in the recent years. Flexibility and stretchability allow these devices to be potentially used in wearable sensing and drug delivery devices. Our team acknowledged this emerging trend by devising the term flexible microfluidics in a recent article.[32] The advent of flexible microfluidics would help to establish a common framework for further discoveries and investigations into flexible and stretchable microfluidic devices. Regarding microscale fluid-structure interactions, currently there are only a few published papers discussing this phenomenon in the context of flexible

microfluidic devices with deformable microchannels. The lack of fundamental understanding about FSI is the main reason why novel micro elastofluidic device concepts have not yet been reported.

Material selection is one of the most important steps for the design of a microfluidic device. The choice of material can impact its performance and functionality. For conventional microfluidics, a range of materials is available for device fabrication: inorganic compounds, polymers, paper, hydrogels, or even composite materials.[33] In micro elastofluidics, the range of qualified materials is narrowed down due to the requirement for flexibility and stretchability of the final device. In addition, due to the intrinsic differences between digital and continuous-flow micro elastofluidics, it is necessary to consider material selection for each of them separately. For digital micro elastofluidics, a wide range of polymers has been reported for synthesizing the shell of liquid marbles, liquid beads, or hydrogel beads.[34–36] For continuous-flow micro elastofluidics, only specific polymers are used for preparing viscoelastic fluids. However, various materials including silicon, silicon-based compounds, thermoplastics, elastomers, liquid metals, cellulose-based papers, and textiles have been adopted for the fabrication of flexible microfluidic devices.[37–39] Non-degradable and biodegradable materials are both considered, depending on the fabrication methods of the platforms and the targeted applications. Biodegradable materials, particularly biodegradable polymers, have been attracting significant attention from the scientific community. In addition to flexibility and elasticity, biodegradable polymers are also known for their exceptional biocompatibility and biodegradability—the ability to be structurally decompose by microorganisms or body's immune system into non-toxic by-products. These features allow biodegradable polymers to be a more sustainable alternative material to their non-degradable counterparts.

This paper provides a comprehensive review on current biodegradable polymers for the fabrication of digital and continuous-flow micro elastofluidics. The review begins with the introduction and classification of biodegradable polymers, followed by a discussion about the use of biodegradable polymers in digital micro elastofluidics. Previous studies incorporating biodegradable polymers for liquid marbles, liquid beads, and hydrogel beads are highlighted. Next, we explore the utilization situation of biodegradable polymers in continuous-flow micro elastofluidics. This section summarizes recent works in characterizations of viscoelastic fluids (molecular scale) and fabrication of flexible, stretchable microfluidic devices (device scale). It should be noted that fluid-structure interaction is not within the scope of the device sub-section. The paper concludes with future perspectives on the role of biodegradable polymers in micro elastofluidics.

2. Biodegradable Polymers: Overview and Classification

Biodegradable polymer is a class of polymers that degrades naturally into by-products such as gases, water, biomass, and inorganic salts at the end of their lifetime. Biodegradable polymers are highly compatible with biological interfaces. In addition, structural characteristics and functionalities of biodegradable polymers are inherently customizable due to their unique chemical compositions and the presence of reactive groups on the polymer backbone. Both chemical and mechanical techniques have been used to convert raw biodegradable polymers into processable forms such as fibers, particles, pellets, and films that can be manufactured into end products or transformed into functional materials. Recently, biodegradable polymers find extensive use in practical applications such as packaging, agriculture, chemical analysis, drug delivery, and tissue engineering.[40,41] Like other polymer classes, biodegradable polymers are categorized as synthetic and natural biodegradable polymers. **Table 1** lists the key properties and applications of representative biodegradable polymers.

Synthetic biodegradable polymers are produced via polycondensation or hydrolysis of functional groups. Besides biodegradability, synthetic biodegradable polymers are known for their highly ordered structure, ease of processing, and low immunogenicity. Among synthetic biodegradable polymers, polyester is one of the most prominent groups. Most biodegradable polyesters have aliphatic backbones that are prone to hydrolytic degradation. However, structural degradation rates differ depending on the stability of the ester function groups. Currently, biodegradable polyesters are mainly used for biomedical applications such as scaffolds for tissue engineering, surgical suture, long-term implants, and targeted drug delivery.[42,43] Particularly, some biodegradable polyesters such as PLA, PGA, and PLGA are approved by US Food and Drug Administration for commercial clinical use. Another group of biodegradable synthetic polymers is water-soluble biodegradable synthetic polymers such as polyvinyl alcohol (PVA) and polyethylene glycol (PEG). Their water solubility is attributed to the active hydroxyl groups on the backbone that readily form stable hydrogen bonds with water molecules. The resulting water-based polymeric solution can be processed further to yield elastomeric films or hydrogels with high transparency. In addition, these water-based biodegradable synthetic polymers serve as crosslinkers or plasticizers that offer tunable mechanical properties. These polymers have been widely adopted in sectors such as textile, paper, and food packaging an in biomedical applications such as wound dressings and drug delivery.[44,45]

Natural polymers are formed via addition or condensation polymerization reactions that occur within living organisms. Condensation natural polymers are created from the combination of monomer units, with water as the second reaction product. Additional natural polymers are formed without any by-products by combining the monomer units that make up the polymer directly. Natural polymers are known for their abundance, mechanical tunability, high biocompatibility, and water retention ability. Polysaccharide is one of the major natural polymer groups. Polysaccharides obtained from different sources have varying structural stability and hydrophilicity. These versatile polymers have been used in a wide range of applications such as textile, paper processing, food, biomedical, building, and construction, as well as oil spill cleaning.[46–49] In addition, high surface activity enables polysaccharides to be converted into hybrid synthetic-natural polymers with functional properties.[50] Proteins or protein-based polymers are another important group of natural polymers synthesized from amino acids. Proteins perform critical biological functions in biological systems. For

Table 1. Overview of some common biodegradable polymers.

Polymers	Type	Common processing form	Modulus of elasticity [MPa]	Solubility in aqueous solution	Common applications
Poly(1,8-octanediol-co-citric acid) (POC)	Synthetic biodegradable polyester	Film	0.92–16.4	Not soluble	Tissue engineering
Poly-L-lactide (PLLA)	Synthetic biodegradable polyester	Film	2270	Not soluble	Sutures, bone filling, drug delivery, medical devices
Poly(lactic-co-glycolic acid) (PLGA)	Synthetic biodegradable polyester	Film	2000–6000	Not soluble	Tissue engineering, drug delivery
Polycaprolactone (PCL)	Synthetic biodegradable polyester	Fiber/film	3700	Not soluble	Sutures, drug delivery, biomedical implants
Poly(glycerol sebacate) (PGS)	Synthetic biodegradable polyester	Film	0.025–1.2	Not soluble	Tissue engineering, drug delivery
Ecoflex (from BASF)	Synthetic biodegradable polyester	Film	500	Not soluble	Food packaging
Polyethyleneglycol (PEG)	Synthetic water-soluble polymer	Film	-	Soluble	Drug delivery, dispensing agent, plasticizing agent
Polyvinylalcohol (PVA)	Synthetic water-soluble polymer	Film	707.9	Soluble	Textile, paper industry, food packaging, wound dressings
Cellulose fibers	Polysaccharide	Fiber	13200	Not soluble	Paper industry, wound healing, tissue engineering, oil spill cleaning
Chitosan	Polysaccharide	Film	14.2–64	Soluble	Food industry, textile, drug delivery, wound healing
Gelatin	Polysaccharide	Film	35–50	Soluble	Food industry, cosmetics, forensics
Starch	Polysaccharide	Film	117–295	Soluble	Adhesive in papermaking industry, tissue engineering, drug delivery
Sodium alginate	Polysaccharide	Hydrogel	27.81	Soluble	Wound healing, drug delivery, tissue engineering
k-Carrageenan	Polysaccharide	Film	1510	Soluble	Drug delivery, tissue engineering
Silk	Protein	Fiber	14000–36000	Soluble	Sutures, cell culture, tissue engineering, drug delivery

example, enzymes catalyze chemical reactions; antibodies form an integral component in our immune system; whereas collagen, keratin, and silk are used in tissue engineering and drug delivery.[51,52]

3. Biodegradable Polymers in Digital Micro Elastofluidics

Digital micro elastofluidic platforms include liquid marbles, liquid beads, and hydrogel beads. **Figure 2** depicts the general structures of these platforms. Liquid marbles and liquid beads are similar in terms of their distinct layered structure, whereas hydrogel bead is a crosslinked matrix that traps water. The material choice of the encapsulating shell is determined by the application. Nevertheless, utilizing raw materials with biodegradability is the optimal choice to achieve a balance between performance and environmental friendliness. In addition, many biodegradable polymers possess extra bio-friendly features such as edibility (safe to be consumed) and bioresorbability (safe to be absorbed) by the body after dissolution. The following sub-sections discuss how biodegradable polymers are handled to make liquid marbles, liquid beads, and hydrogel beads.

3.1. Liquid Marble

Liquid marbles are prepared by rolling a droplet across a powder bed. Owing to high porosity and non-wetting characteristics of the coating layer, liquid marble finds application in biosensors, microreactors, and droplet-based sample handling.[53] **Figure 3** summarizes the fabrication method and important properties of a liquid marble.

To date, most liquid marbles are made of non-degradable powder such as polytetrafluoroethylene (PTFE), polyvinylidene fluoride (PVDF), carbon black, graphite, etc.[54] Biodegradable polymers were reported as feasible candidates for liquid marble preparation. Matsukuma et al. used polylactic acid (PLA) as the base material to fabricate mechanically-stable water-based liquid marbles through solvent vapor exposure.[55] In another report, Schmücker et al. successfully utilized polylactic acid (PLA)

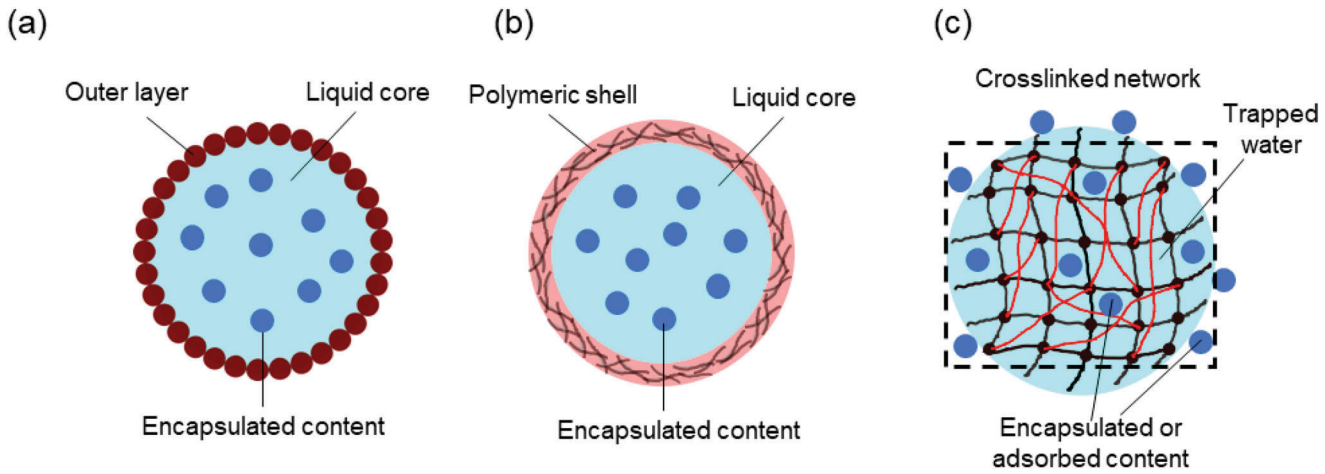

Figure 2. General structures of digital micro elastofluidic platforms: a) liquid marble; b) liquid bead; c) hydrogel bead.

and polycaprolactone (PCL) as individual or blended powder beds to synthesize liquid marbles encapsulating aqueous urea solution, serving as fertilizer carriers.[56] In another approach, instead of using natural hydrophobic biodegradable polymers, Ihara et al. attempted to form liquid marbles encapsulating cobalt chloride solution from hydrophobically modified cellulose powder. Plasma treatment, followed by the deposition of tetramethylcyclotetrasiloxane (TMCTS) was carried out to transform cellulose from naturally hydrophilic state into hydrophobic state, prior to the formation of a liquid marble.[57]

On the other hand, biodegradable polymers in fibrous form have been investigated to form the coating layer of liquid marbles. For instance, inspired by how animals and vegetables encapsulate liquid within their fibrous membrane, Mele et al. devised an innovative method to coat water droplets with a matrix of electrospun nanofibers consisting of fluoroacrylic copolymer and cellulose acetate (CA)—a derivative of cellulose. The ease of surface functionalization of nanofibrillar outer layer and high stability of water core enable this composite liquid marble to be used in drug delivery and bioreactors.[58]

3.2. Hydrogel Bead

Hydrogel bead is a small spherical or quasi-spherical solid with densely crosslinked network. Thousands of polymer strands are physically or chemically joined together through the gelation process to form the 3D body of hydrogel bead. In most cases, metallic ions are introduced to serve as crosslinking nodes between polymeric chains for a higher degree of crosslinking which enhances mechanical robustness. Hydrogel beads are known for their excellent adsorption of a variety of molecules such as drugs, dyes, or agrochemicals due to the presence of numerous microscopic pores within the matrix and on its surface. **Figure 4** illustrates a common fabrication method and typical properties of a hydrogel

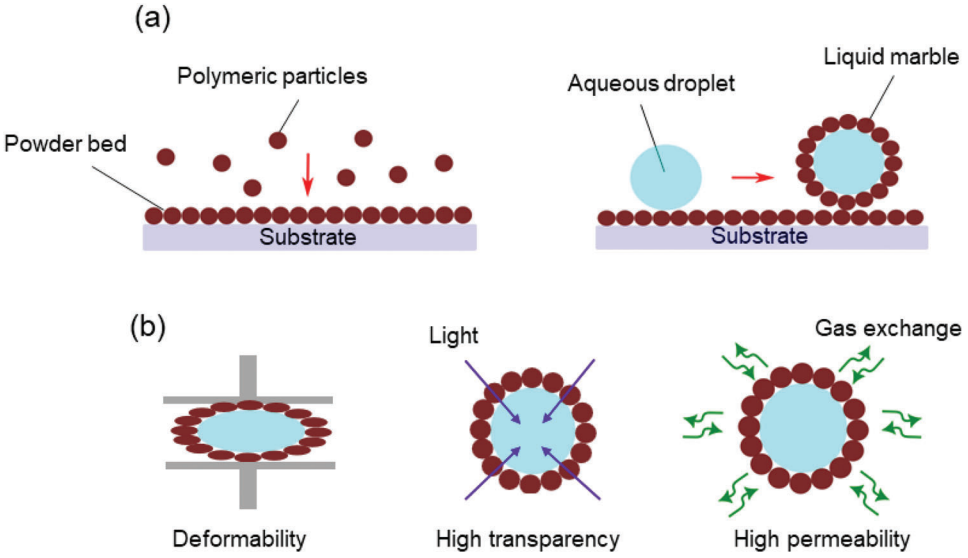

Figure 3. Liquid marble as a micro elastofluidic platform: a) fabrication of liquid marble by rolling of an aqueous droplet on polymeric powder bed; b) important properties of liquid marble.

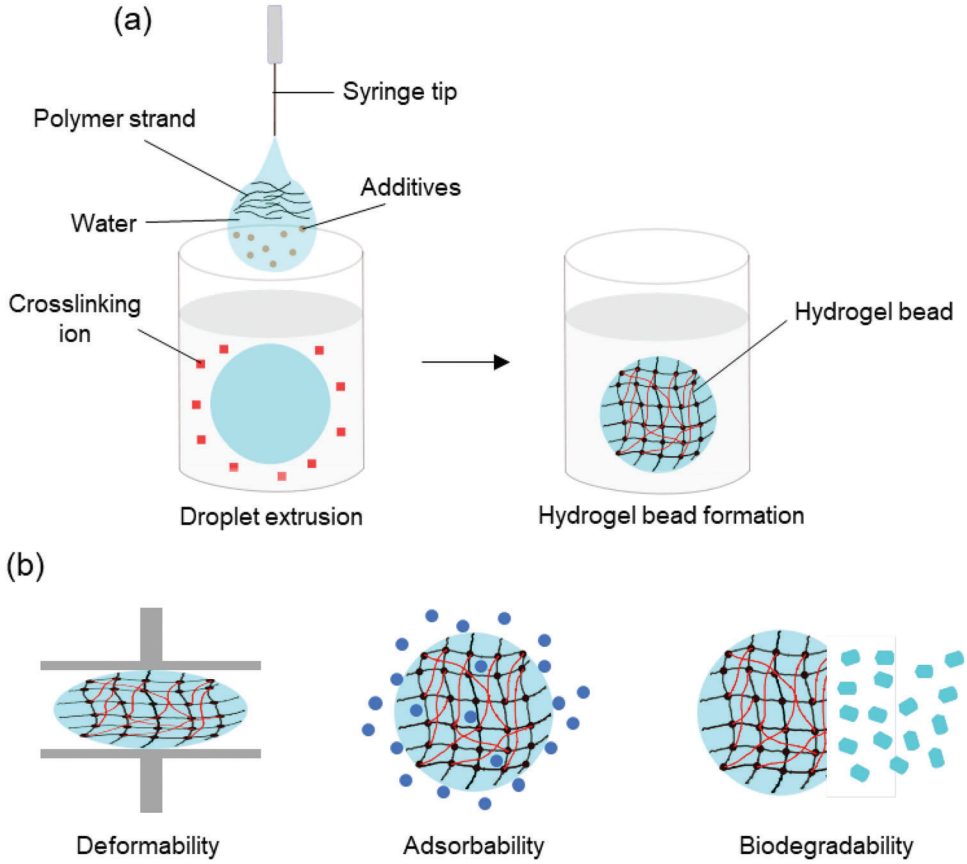

Figure 4. Hydrogel beads: a) formation of hydrogel beads by extrusion method; b) typical properties of hydrogel beads.

bead. In this section, we discuss notable works on hydrogel beads fabricated from biodegradable polymers focusing on wastewater treatment, cell culture, and controlled release applications.

3.2.1. Wastewater Treatment

Hydrogel beads have been long considered as a prospective candidate for pollutant removal from wastewater. Thanks to the highly porous network, hydrogel beads are able to capture and store pollutants within their structure.[59] Hydrogel beads synthesized out of biodegradable polymers are known not only for their excellent retention capabilities by forming stable complex with pollutant, but also for being eco-friendly without generating any harmful by-products to the water during and after wastewater treatment.[60,61]

Dye is one of the most common organic pollutants which is removed from wastewater through adsorption. Biodegradable polymeric hydrogel bead has been emerging as an inexpensive and effective dye absorbent. The removal of methylene blue (MB), a popular cationic dye, is heavily investigated due to its toxicity and carcinogenicity.[62] Polysaccharides such as sodium alginate, cellulose, and chitosan are chosen for forming hydrogel-based dye adsorbents due to their high surface area and excellent affinity to organic molecules.[63] For instance, Hu et al. developed a facile process to synthesize tannic acid-polyvinylalcohol/sodium alginate (TA-PVA/SA) hydrogel beads using a rapid gelation method. Natural organic compound tannic acid (TA) was added for the purpose of enhancing adsorption efficiency and thermal stability. Adsorption test showed that the composite beads are able to hold a large amount of MB, up to 147.06 mg g^{-1} at 30 °C.[64] Benhalima et al. utilized carboxymethyl cellulose (CMC) as the main polymeric material to form polysaccharide hydrogel beads by ionotropic gelation in a solution containing Al^{3+}, with sodium dodecyl sulphate (SDS) as pore-forming agent for improving adsorption performance. MB molecules migrate to the surface of hydrogel beads and attach to the carboxylate group of CMC polymer strands via electrostatic attraction. Following three sorption cycles, the CMC hydrogel beads achieved a maximum adsorption capacity of 350 mg g^{-1}.[65] Besides MB, blue dye 4 is another type of dye that is investigated for their potential removal from wastewater. Galan et al. fabricated chitosan-based beads crosslinked by glutaraldehyde to extract the reactive blue dye 4 from an aqueous wastewater solution. The team claimed that the adsorption mechanism of hydrogel beads is attributed to the opposite charges between chitosan and reactive blue dye 4, which leads to the binding of dye molecules onto the hydrogel surface.[66]

Heavy metal ion is another pollutant that can be effectively extracted from wastewater using polymeric hydrogel beads. Cellulose and its derivative such as CMC have been employed as raw materials for making biodegradable hydrogel beads with high

surface area and high sensitivity to ions. Yang et al. prepared CMC hydrogel beads crosslinked with epichlohydrin (ECH) in wax suspension with promising adsorption efficiency. Results of Langmuir adsorption model demonstrated that the hydrogel beads can absorb considerate amount of Cu (II), Ni (II), and Pb (II) ions at neutral pH level, up to 6.49, 4.06 and 5.15 mmol g^{-1}, respectively.[67] Polysaccharide hydrogel beads fabricated from chitosan are also good candidates for heavy metal removal. Due to the presence of abundant active groups on the surface, chitosan-based hydrogel sequesters and adsorbs a wide range of heavy metal ions. For example, Rahmi et al. successfully fabricated chitosan/gelatin composite hydrogel beads with spherical shape using the inverse suspension method. By examining the adsorption efficiency of hydrogel beads for different metal ion solutions, Rahmi et al. reported that the beads exhibited high adsorption capacity for Hg (II) ion in a single metal ion solution (>50%), and good adsorption efficiencies for all metal ions (54%–95%) in a multiple metal ion solution containing Pb(II), Cd (II), Hg(II) and Cr(II).[68]

3.2.2. 3D Cell Culture

Conventional cell culture is conducted on flat surfaces such as culture flasks or petri dishes. This method produces cells with monolayer distribution which does not reflect the actual interaction between cell layers or between cells and the surrounding extracellular environments. 3D cell culture has been developed to address this issue. A 3D cell culture enables cells to grow and interact with the surroundings in an artificial matrix-based environment. Hydrogels have been a subject of interest in 3D cell culture due to the similarities of its structure and properties with extracellular matrix (ECM). Particularly, hydrogel beads made of alginate are favored for cell culture due to their ease of gelation, high porosity of gel network for diffusion of nutrients, exceptional transparency for cell observation, and gentle dissolution for cell extraction.[69] Allallam et al. prepared alginate hydrogel beads using the gentle ionotropic gelation method to preserve three types of human cancer cells. The authors reported that their alginate beads maintained living cells up to 4 weeks without culture media replacement.[70] Apart from alginate-based hydrogel beads, non-alginate hydrogel beads have also been explored for 3D cell culture. Wieduwild et al. utilized multi-channel microfluidic design to fabricate robust hydrogel beads from peptide–polyethylene glycol conjugates and oligosaccharides using a noncovalent crosslinking mechanism. The authors used human neonatal dermal fibroblasts (HDFn) as the cell sample. High survival rates of HDFn cells under conventional culturing conditions confirmed the effectiveness of this hybrid hydrogel bead in 3D cell culture.[71] Piatkowski et al. synthesized chemically crosslinked chitosan beads using a microwave-assisted fabrication method. The extracellular hydrogel beads exhibited adjustable morphology, antioxidant effect, resulting in high proliferation rate of mouse fibroblasts L929 cells.[72]

3.2.3. Controlled Release of Content

Besides storage, hydrogel beads can be modified to release its content in a controlled manner. Target molecules enter the hydrogel bead rapidly during the encapsulation stage and then gradually diffuse out of the matrix at the desired location. Numerous studies on the fabrication of biodegradable polymeric hydrogel beads with controlled release have been reported, mainly for capturing and delivering agrochemicals and drugs.

Designing an effective drug-loaded system requires careful selection of carrier type and base materials. Hydrogel bead is a particularly appealing type of delivery system that is widely used in the biomedical field. Due to the stringent requirement for in vivo compatibilities, drug-loaded hydrogel beads are mostly made of biodegradable polymers. Owing to the tunable properties and physiochemical interactions with drugs, biodegradable polymeric hydrogel bead can function like a "smart" platform that is capable of storing and releasing drug contents in a configurable manner.[73] Depending on the drug incorporation method and properties of the hydrogel matrix, the loaded drug can be released from hydrogel beads via diffusion-controlled, swelling-controlled, or chemically-controlled mechanisms.[74] Natural hydrogel systems based on polysaccharides are excellent platforms for drug delivery. Cellulose, chitosan, k-carrageenan, alginate, and pectin have been used to fabricate hydrogel beads for delivery of drugs such as therapeutic proteins, anaesthetics, antibiotics, and antihyperglycemics.[75–80] These works investigated the drug-capturing phenomenon, polymer-drug interaction and release behavior. In addition, studies suggest that polysaccharide-based biodegradable polymers can be formulated with nanoparticles to create hybrid hydrogel beads for improved properties. Azizi et al. devised an ex situ synthesis procedure that combines k-Carrageenan and silver nanoparticles to generate bionanocomposite beads. The team used silver nanoparticles as a study model for drug capturing and release, **Figure 5**. The resultant hydrogel beads showed fascinating antibacterial and antimicrobial effects in addition to its drug release feature.[81] Yadollahi et al. prepared nanocomposite hydrogel beads from chitosan and zinc oxide (ZnO) nanoparticles via in situ reaction method. Their results revealed that the nanocomposite beads had higher swelling capacities and longer drug release time compared to pure chitosan beads.

Besides serving as a vehicle for drug transport, hydrogel beads can be used as agrochemicals carrier for precision agriculture. Agrochemicals are essential to crop growth, but they tend to be toxic to the environment and human health. Conventional immediate-release methods impart excessive chemicals to large areas.[82] Hence, controlled release approaches have been studied extensively to deliver agrochemicals in a safe and controllable manner whilst minimizing environmental impact. The simple, inexpensive, and versatile polysaccharide hydrogel beads can be utilized to accurately deliver agricultural chemical products to soil or plants. Alginate hydrogel bead is a typical example of a cheap, effective biodegradable carrier system. Alginate hydrogel bead served as the carrier with controlled-release for a wide range of pesticides and fertilizers such as urea, cypermethrin, thiram, imidacloprid, nitrogen, and phosphate-based salts. Besides, the introduction of alginate-based substances promotes plant growth and enhances productivity.[83] Alginate can be used as a sole material to make hydrogel beads or used in conjunction with other polysaccharides such as gelatin, starch, chitosan to enhance the overall mechanical stability of beads in soil.[84–87] Similar to drug delivery applications, inorganic fillers are

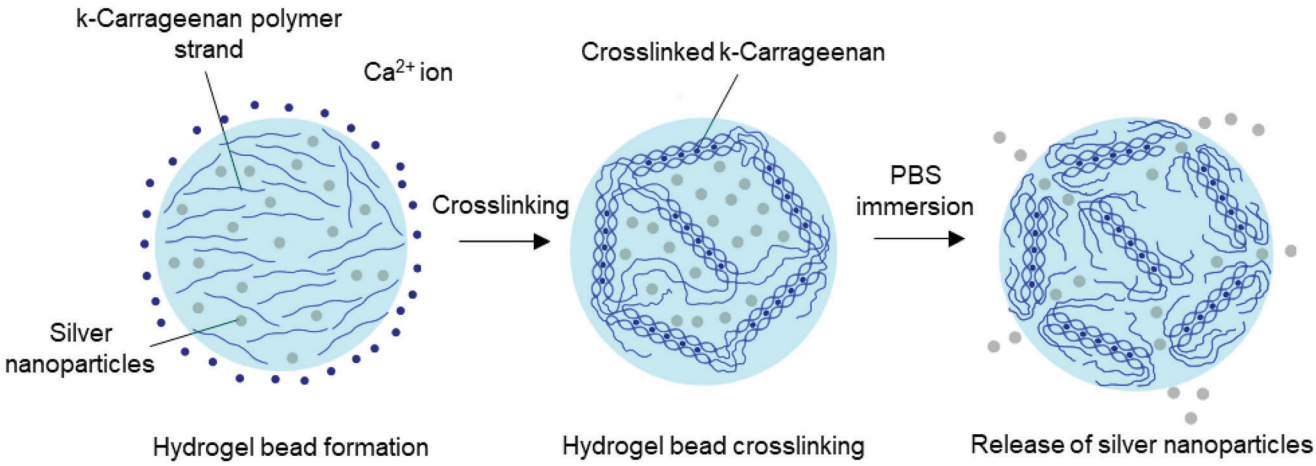

Figure 5. Formation of crosslinked hydrogel bead as a platform for capturing and releasing silver nanoparticles as a drug study model.

incorporated into polymeric hydrogel beads as enhancers. For instance, Singh et al. utilized hollow cenosphere, a by-product from coal-firing power plants as an additive for their chitosan-coated alginate beads to improve loading capacity of imidacloprid. The authors demonstrated that the modified beads have excellent encapsulation efficiency and good controlled-release profile in different pH levels.[88]

3.3. Liquid Bead

Liquid beads possess similarities to liquid marbles in terms of their distinct core-shell structure. However, while the outer part of liquid marbles consists of micro- or nanoparticles that are loosely held together by capillary and van der Waals forces, the shell layer of liquid beads is formed through stable interaction with the core. In many cases, elastic shell is further crosslinked via chemical or physical crosslinking methods to enhance shielding effect for the liquid core and overall mechanical robustness of the liquid beads. **Figure 6** depicts typical properties of liquid beads, and common techniques for the generation of liquid beads, such as polymerization, droplet extrusion, coaxial electrospinning, microfluidic droplet formation.[36,89] This section looks into the state of the art of using biodegradable polymers for making liquid beads by reviewing some of the successful works in biosensing, drug delivery, and cell culture applications.

3.3.1. Biosensor

A biosensor is a quantitative or semi-quantitative analysis tool that includes signal transduction and biometric identification components. Bioactive compounds produce a signal, which is then sent via a converter to a physical and chemical detector. Biomolecular detection, object recognition, and signal translation are major steps in every biosensor process, regardless of the sensing technology.

Considerable efforts have been devoted to creating biosensing platforms based on liquid beads with complete biodegradability. The general concept is to blend micro- or nanosensors with the core solution, prior to formation of final liquid beads with a protective polymeric shell. In this way, the tiny, immobilized sensors perform its sensing function when liquid beads are exposed to the medium that contains biomolecules to be detected and analyzed. For instance, Xie et al. employed polyethylene glycol diacrylate (PEGDA)–a polymeric derivative of PEG–to synthesize liquid beads for enclosing two separate types of nanosensors, quantum dots (QDs) and gold nanorods (NRs) using glass capillary microfluidic device. This permeability of PEG-based shell was engineered to specifically detect biomolecules such as glucose and heparin, while at the same time preventing nano sensors from leaking out, **Figure 7**. The authors used sodium alginate as another biodegradable polymer to coat the shell, forming the second outer layer to promote safe contact with biological system. Interestingly, sensing efficiency of alginate-coated biosensors remained the same as the uncoated one.[90] In another effort, Watanable et al. managed to form liquid beads with tetra-polyethylene glycol (tetra-PEG) as hydrogel shell and dextran-rich aqueous core, using aqueous two-phase system (ATPS) droplet formation method. The shell was formed and stabilized via two stages: (i) internal phase separation of tetra-PEG upon formation of droplets, which leads to migration of tetra-PEG molecules; (ii) transformation of shell into hydrogel-like structure by cross-end coupling reaction between tetra-PEG monomers. The liquid beads were also fabricated using a capillary microfluidic device. The team claimed that their liquid beads can be potentially used as a stable biosensing platform with fascinating structural characteristics such as swelling-deswelling behavior, deformation resistance, and semi-permeability.[91,92]

3.3.2. Drug Delivery

Similar to hydrogel beads, liquid beads with core-shell structure can be functionalized to capture and release drugs at a desirable rate. However, due to the presence of a polymeric shell, drug delivery using liquid beads is more beneficial. By varying the polymer shell's mesh size and thickness, the drug release cycle of liquid beads can be tailored. In addition, large interior core volume allows liquid beads to retain a larger amount of drug. In terms

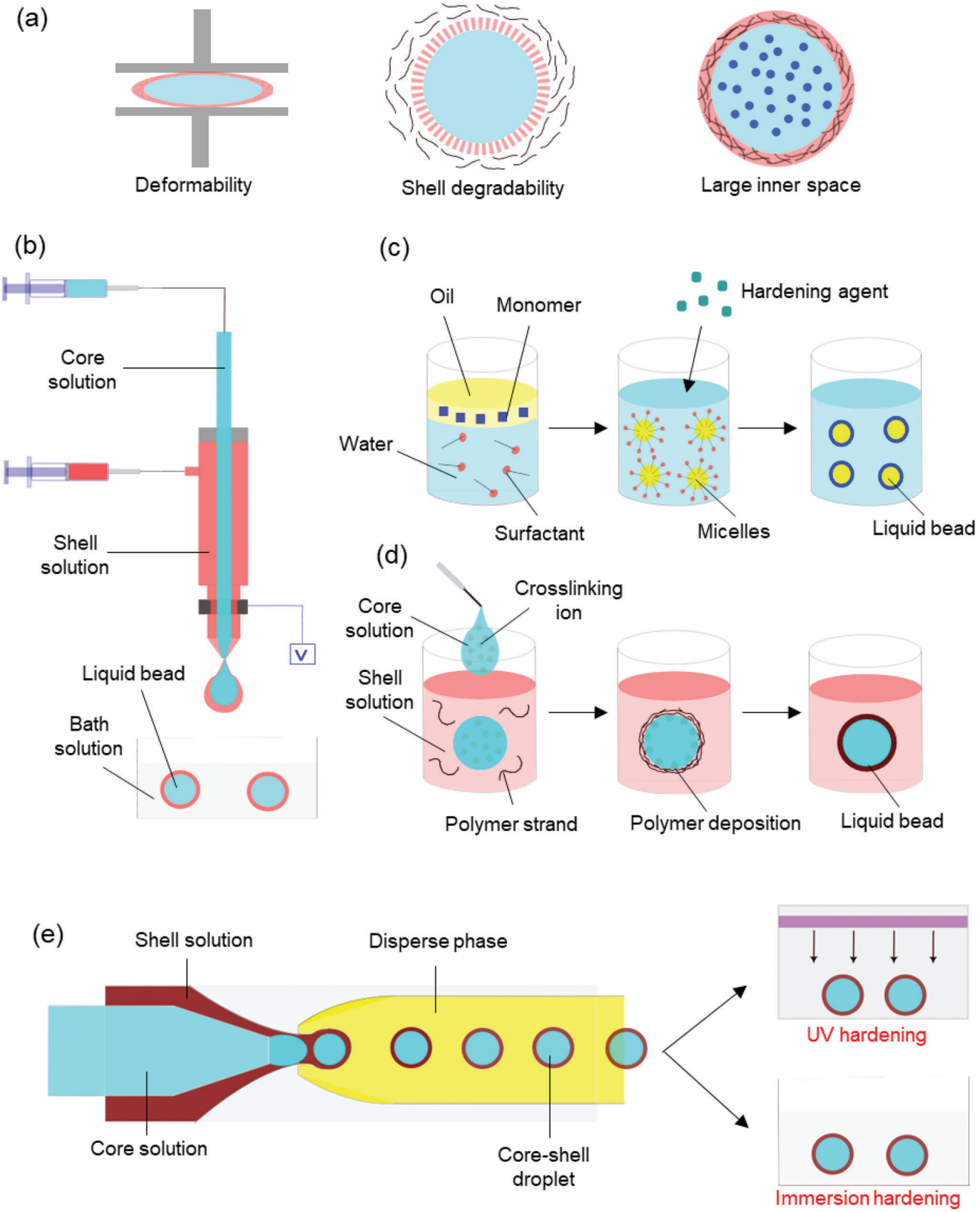

Figure 6. Typical properties and different fabrication methods of liquid bead: a) properties of the liquid bead; b) coaxial electrospinning fabrication method; c) polymerization fabrication method; d) droplet extrusion fabrication method; e) coaxial-flow microfluidic droplet formation fabrication method.

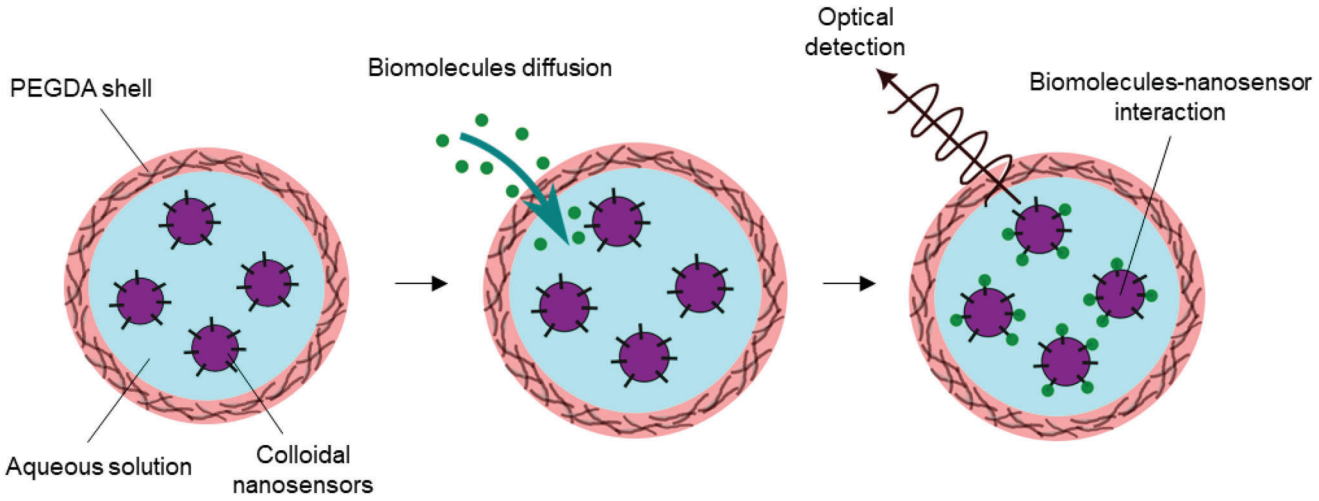

Figure 7. Liquid bead with an aqueous core and PEGDA shell for biosensing of glucose and heparin molecules.

of release mechanism, the encapsulated drugs can either be released through molecular diffusion or stimuli-responsiveness of the shell.

Polysaccharides such as chitosan and alginate are widely employed for shell formation of drug carrier based on liquid beads due to their short processing time, ease of shell crosslinking, low immunogenicity, and good bio adhesion. The majority of polysaccharide-based drug-loaded liquid beads are fabricated using the microfluidic flow-focusing method to yield monodisperse droplets prior to shell formation. For instance, Li et al. reported a strategy to synthesize core-shell chitosan liquid beads for acid-triggered burst release of stomach-specific drug via a two-step process. Oil-in-water-in-oil (O/W/O) emulsions were first formed using a microfluidic device. Subsequently, the water-based shell was hardened via interfacial crosslinking reaction. Experimental results showed that decomposition rate of chitosan shell depends on the environmental pH value. The lower the pH value, the faster degradation of chitosan shell, allowing burst release of drug into the surrounding medium.[91] Yu et al. employed a microfluidic approach to generate uniform liquid-filled core-shell alginate particles for encapsulating and releasing ovalbumin protein. Ex situ and in situ crosslinking techniques were used simultaneously to maintain the spherical shape of particles. Sustained release and pH-triggered release of ovalbumin are two drug release modes that were investigated. To further prolong the release time of ovalbumin, the authors utilized delta inulin as a pore-blocking agent and chitosan or poly(ethylenimine) as additional coating layer to slow down the escape of protein from liquid bead.[92]

Synthetic biodegradable polyesters such as PLA, PLGA, and PCL have been utilized for entrapment and release of drugs. Regarding the core of polyester-based liquid beads, both water-based and oil-based systems were investigated. Due to the ability to generate stable water-in-oil-in-water (W/O/W) emulsion with well-controlled droplet size, microfluidic droplet formation is commonly used to generate liquid beads with hydrophobic biodegradable polyester shell and drug-loaded aqueous core. Biodegradable polyesters are dissolved in solvents to form the oil phase, which subsequently turns into a shell-like structure upon interfacial contact with the aqueous phase in the microfluidic device. Many successful attempts have been made to synthesize and investigate hydrophilic drug loading and releasing behavior of biodegradable polyesters-based liquid beads. Hydrophilic substances such as Congo Red dye, Nile Red dye, bovine serum albumin (BSA) have been used as drug models for the studies.[93–95] On the other hand, research into encapsulation of oil-based drug has also been carried out. Martins et al. conducted a series of studies into the formation of PLA-based liquid beads using coacervation method with different oily cores such as thyme oil, thymol, and p-Cymene. First, oil-in-water (O/W) emulsion is formed and stabilized with surfactant, following with dropwise addition and precipitation of PLA to form shell layer, which is eventually hardened by octamethylcyclotetrasiloxane (OCMTS). High encapsulation efficiency and controllable release rate of oily cores prove that PLA-based liquid beads can be potentially used as active oil-based drug protection and delivery systems.[96,97]

3.3.3. 3D Cell Culture

Besides hydrogel beads, liquid beads have also been utilized for encapsulation and culturing cells. Nevertheless, core-shell liquid bead offers better gas transfer efficiency and larger internal storing space for cells due to its higher surface-to-volume ratio. In a liquid bead, the polymeric shell acts as a permeable barrier, which protects cells from the surrounding environment and allows inward diffusion of gas molecules to facilitate cell growth. Alginate is predominantly chosen as the raw material to form the shell layer of liquid beads due to the ease of formation and low cost of base material. Various types of cells have been successfully encapsulated and grown within alginate-based liquid beads. For instance, Nebel et al. employed a simple inverse gelation approach to synthesize alginate liquid beads containing mesenchymal stem cells (MSCs). Two other polysaccharides, CMC and xanthan gum (XG) were used as thickeners to regulate the shape of the core. Excellent cell proliferation was demonstrated by 2.5-fold increase in cell numbers after four days of cell cultivation.[99] In another study, Rao et al. prepared alginate

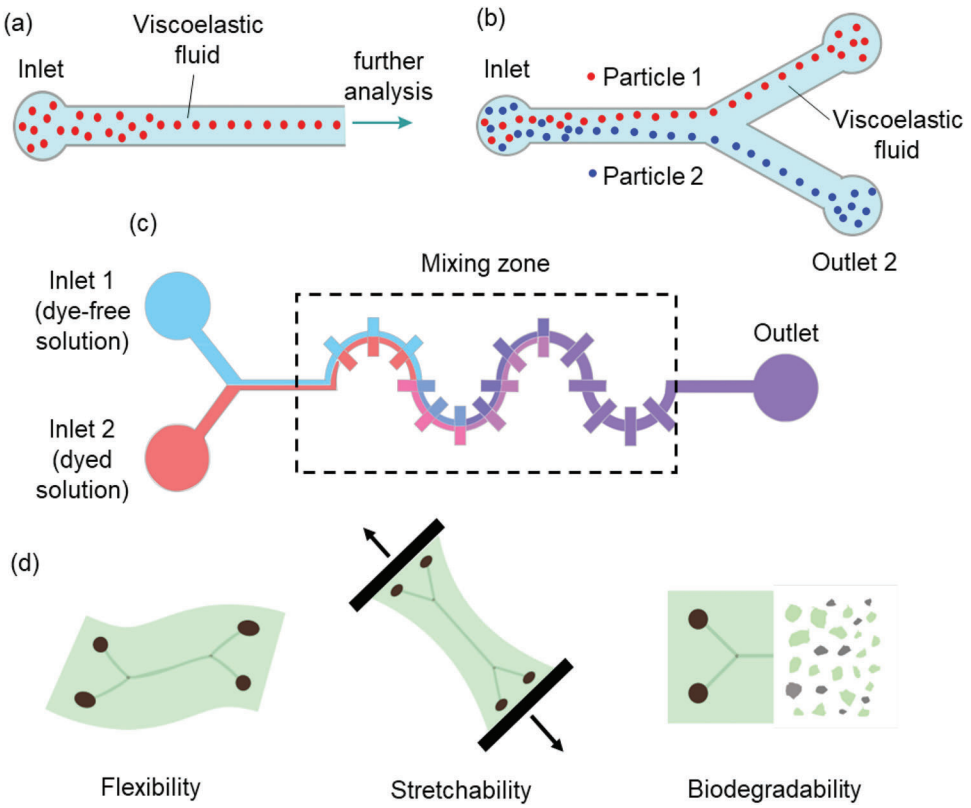

Figure 8. Schematic of continuous-flow micro elastofluidics: a) molecular scale: focusing of single particle type suspended inside viscoelastic fluid flowing in a straight microchannel); b) molecular scale: separation of two particles with different properties suspended in viscoelastic fluid flowing in a straight microchannel; c) mixing enhancement between dyed and dye-free solutions (both are viscoelastic fluids) by integration of a modified serpentine microchannel as a mixing zone, after Hong et al.[102]; d) typical properties of micro elastofluidic devices with biodegradable polymeric substrate.

liquid beads using coaxial electrospray method to grow prostate cancer cells inside the aqueous core. The results demonstrated that it took only 2 days for the initially limited amount of cancer cells to be enriched into the same number of cells with a conventional culturing method, which normally needs 10 days.[100] Besides alginate, researchers have been investigating biodegradable polyesters with low immunogenicity such as PLA or PLGA to form 3D cell culture platform. Both microfluidic and coaxial electro-spraying techniques were used to form polyester-based liquid beads with an aqueous core. Promising results of survival and proliferation of yeast cells and NIH3T3 fibroblasts cells were achieved.[101,102]

4. Biodegradable Polymers in Continuous-Flow Micro Elastofluidics

As mentioned above, continuous-flow micro elastofluidics utilizes flexibility and elasticity for new functions at molecular and device scale. Biodegradable polymers have been employed for research at both scales. In the molecular scale sub-section, we highlight the use of biodegradable polymers for viscoelastic effects toward enhancement of mixing, focusing, and separation of particles. In the sub-section on device scale micro elastofluidics, we outline the utilization of biodegradable polymers in the fabrication of flexible, stretchable microfluidic devices with respective applications in wearable electronics and tissue engineering. **Figure 8** presents the general schematic of this section.

4.1. Molecular Scale

Viscoelastic fluid is a class of non-Newtonian fluid that exhibits both viscous and elastic behaviors. These unique rheological properties are attributed to the presence of long-chain polymeric molecules. Water or glycerol is used as the media for dissolution of these polymers. The alignment and orientation of polymers produce normal stresses that act perpendicularly to the flow direction, resulting in viscoelastic properties of the fluids.[104] To characterize the fluidity of viscoelastic fluids, dimensionless numbers such as Reynolds number (*Re*), Deborah number (*De*), or Weissenberg (*Wi*) number are used. The ratio between *Wi* and *Re* is termed elasticity number (E), which is also the ratio of elastic stress to inertial stress. Since these two stresses normally exist simultaneously in a continuous flow of viscoelastic fluid, both of them can exert their synergetic elasto-inertial effect on the trajectories of suspended particles or other fluids flowing in a confined microchannel. This unique effect of viscoelastic fluid has been leveraged in microfluidics for efficient focusing and separation of microparticles or mixing improvement between two or more fluid types.

Commonly, viscoelastic fluids exist either in the form of biological fluids such as saliva, DNA solutions, mucus, or synthetic polymer-based solutions.[104] Currently, only a few types of polymers can be used to prepare synthetic viscoelastic fluids for microfluidic applications. They are polyethylene oxide (PEO), polyvinyl pyrrolidone (PVP), hyaluronic acid (HA), and polyacrylamide (PAA). Although all of these polymers are biocompatible, only PEO and HA are considered biodegradable polymers.[105,106] Hence, PEO and HA possessed a high level of environmental friendliness compared with PVP and PAA. PEO is a synthetic macromolecule, which consists of multiple long and highly flexible polymer chains, resulting in the viscoelasticity of PEO solution. PEO can also be referred to as the high molecular weight version of PEG since both polymers are constituted from ethylene oxide monomer with the same fundamental structure. Meanwhile, hyaluronic acid is a naturally occurring disaccharide that is found in the human body, particularly in the skin, joints, and eyes. When dissolving into water, hydrophilic hyaluronic acid polymer chains connect with other to form a gel-like network, giving the elasticity effect to the final solution. Both PEO and HA-based solutions exhibit shear-thinning effect, a non-Newtonian fluid behavior, where the viscosity of a fluid decreases as the shear rate increases.[107,108] The following sub-sections discuss PEO and HA-based viscoelastic fluids for particle manipulation and mixing enhancement.

4.1.1. Particle Manipulation

Particle manipulation is a key task in microfluidics. Many published articles focused on both fundamental research and practical applications. Compared to macro-scale manipulation, microfluidic-based techniques offer advantages such as lower operation cost, reduced sample volume, and higher manipulation efficiency.[109,110] Particle manipulation based on viscoelastic fluids is the simplest and most versatile passive method, which can be applied for a broad range of particle sizes and flow rates. Particle focusing and separation are the two most common types of particle manipulation using viscoelastic fluids. Flow-induced forces resulting from viscoelasticity including lift and drag forces are the main acting forces on suspended particles in viscoelastic fluids.[111] Lift forces, including inertial lift force and elastic lift force, play a major role in lateral migration and positioning of particles. The final focusing and separation behavior of particles is determined by the difference in magnitude between these forces, especially in a straight microchannel. In curved microchannels, particle positioning is additionally affected by drag force, which arise due to imbalance of pressure and velocity gradient at the channel cross-section. Controlling flow rates, channel geometries, and the concentration of polymer in the viscoelastic fluids can tune the balance between the flow-induced forces for high-throughput focusing and separation of particles with different sizes, shapes, and structures.[112,113]

Particle focusing in microfluidics refers to the process of concentrating particles in a fluid into one or more narrow streams as they pass through a microchannel, which finds application in flow cytometry and cell sorting.[114] Viscoelastic fluids enable the precise and highly controlled focusing process, where particles are forced into consistent single or multiple lines due to the inertial-elasto effect. PEO and HA-based viscoelastic fluids have been thoroughly investigated for steady focusing of microparticles. For instance, Yang et al. investigated the effects of various PEO concentrations on focusing behavior of polystyrene (PS) particles. The authors found that at a relatively high PEO concentration (3500 ppm), PS particles were focused in a single line, whereas double line focusing was observed at a low PEO concentration (1500 ppm). The authors explained that depending on the elasticity number adjusted by PEO concentration, focusing of particles can occur in either single or double line.[115] Holzner et al. utilized aged PEO solution (500 ppm) as viscoelastic fluid for robust center-line focusing of mammalian cells (HL-60 and Human B-ssssssslymphoid cells) and bacterial cells (*E.coli* cells) using a straight rectangular microchannel. The focused stream of bacteria was then successfully adopted for cell characterization using imaging flow cytometry with rapid cell counting and analyzing speed.[116] In another attempt, Lim et al. leveraged the turbulent drag-reducing effect of HA-based viscoelastic fluid for efficient focusing of human blood cells (WBC) at high flow rates (up to 50 mL min^{-1}) in an unexplored flow regime with high Reynolds number ($Re \approx 10\,000$). The authors envisioned that their study could inspire future development of high-throughput sorting system for bioparticles suspended in a large fluid volume.[117]

Particle separation in microfluidics is the process of separating particles from an original mixture into different groups based on their geometries, physical properties, mechanical properties, electrical properties, or labels (fluorescent or magnetic tags). This process is crucial for a wide range of applications such as diagnostics, cell analysis, and environmental assessment.[5,118–120] Particle separation using viscoelastic fluids is highly efficient since the presence of lift and drag forces allows two or more types of particles with different geometries or properties to be separated. In addition, particle separation is further supported by elasto-inertial focusing, which occurs simultaneously with separation. The focusing process enables particles to position themselves firmly in their individual streams without diffusing or migrating to other areas in the microchannel, ensuring the high efficiency of particle separation.[121–123] Both PEO and HA solutions have been used for the synergetic focusing and separation of a wide range of bioparticles. For instance, Shi et al. used PEO-based viscoelastic fluid for a two-stage size-selective separation process of cancer cells from a biofluid called malignant pleural effusions, using a two-inlet microfluidic device with contraction-expansion array microchannels. The analysis showed that the concentration of PEG strongly affected the lateral movement and positioning of cells in the microchannel, and 150 ppm was the optimal concentration for effective cell separation. Regarding application, the authors successfully utilized their rapid separation process to improve the accuracy of a cell smear method.[124]

Yuan et al. utilized PEO water-based solution with PEO concentration of 2,000 ppm to effectively separate microalgae *Chlorella* from contaminating bacteria *Bacillus Subtilis* in a simple straight microchannel. Regarding flow behavior, the authors observed that large microalgal cells migrated to the channel walls, whereas small bacterial cells focused in the center of microchannel. This difference in trajectories resulted in extremely high separation efficiency, where 92.97% of bacteria were isolated from the initial microalgae-bacteria mixture.[126] Nam et al. developed a continuous cell separation process based on HA

solution to isolate and detect extremely rare candida cells. The results revealed that the candida cells were separated with high efficiency (≈ 99.1%) with a high purity of cells (97%), which further strengthened the suitability of HA-based viscoelastic fluid for the process.[119]

4.1.2. Mixing Enhancement

Micromixing is another attractive microfluidics-based research topic, which finds applications in chemical and biological fields, such as chemical synthesis, chemical extraction, DNA analysis.[126–129] A wide range of active and passive methods have been used for enhancing the mixing efficiency of different fluid streams flowing in the microchannel. Compared with other methods, passive mixing enhancement based on viscoelastic fluids presents critical advantages such as simplicity of device setup, low cost of operation, and compatibility with various microchannel geometries. The flow instabilities of viscoelastic fluids resulting from elasto-inertial effects of viscoelastic fluids can be utilized to induce chaotic flow motion, which facilitates mixing enhancement between different types of fluids flowing in microchannels. PEO solution is the most commonly used viscoelastic fluids for mixing enhancement in microchannels with different geometries.[128–130] For example, Hong et al. utilized PEO-based viscoelastic fluid to promote efficient mixing between ethanol-tetraethyl orthosilicate (TEOS) solution and ethanol-ammonia solution in a modified serpentine microchannel, leading to successful synthesis of silica particles.[102] The authors observed that by adding PEO solution (500 ppm) into the ethanol-ammonia solution stream, irregular and unstable vortices were generated inside the side-wells of the microchannel, and enhanced mixing between two fluid streams was achieved. Hua et al. used PEO-PEG co-solution as the crucial component to generate and maintain unstable flow patterns inside a microchannel with integrated rhombic structures. Experimental visualization revealed that by increasing the elasticity of the viscoelastic fluid, mixing between two model solutions (one is fluorescently-labeled and one is fluorescence-free) was dramatically enhanced.[129]

4.2. Device Scale

Currently, research into microfluidic devices with flexibility and stretchability is emerging to match with the recent trend in developing wearable and implantable electronic devices for biomedical applications. For this type of device, all of device components such as microchannels, microvalves, or micropumps are flexible and stretchable. The use of rigid materials such as glass or silicon is declining, whereas elastomers such as polydimethylsiloxane (PDMS) are heavily adopted for making flexible and stretchable microfluidic devices. However, PDMS is non-degradable. Thus, PDMS-based microfluidic devices might not be suitable for some implantable applications that require the substrate to safely degrade inside the body. In the search for potential replacements, recently researchers are increasingly attracted by biodegradable polymers due to its processability, biodegradability, and exceptional mechanical properties. Both synthetic and natural biodegradable polymers have been investigated for suitability in making sophisticated flexible and stretchable devices with integrated micro components. Biodegradable polymers can be used as the sole device material, or as one part of a composite material to construct the device substrate, which normally exists in the form of hydrogels, papers, or polymeric film. The final device can be fully biodegradable or partially biodegradable, depending on the proportion of biodegradable polymers.

Regarding fabrication methods, several techniques have been used for making biodegradable microfluidic devices, such as soft lithography, etching, molding, engraving, and 3D printing. Soft lithography and 3D printing are two most common fabrication methods due to their applicability to a wide range of polymeric materials. Soft lithography is a multi-step technique based on photolithography to create microscale patterns on the surface of a polymeric substrate. High resolution of micropatterns and rapid device prototyping are two significant advantages of soft lithography, leading to its popularity in microfabrication.[131,132] Compared to conventional soft lithography, 3D printing has been emerging as a more versatile and cost-effective method. The advent of 3D printing has a potential to revolutionize the microfluidics field, by enabling a wider range of materials for fabricating microfluidic devices with lower processing costs and higher degree of automation.[133–135] In this sub-section, we provide a review of biodegradable polymer for making hydrogel-based, paper-based, and polymeric film-based flexible and elastomeric microfluidic devices, with strong emphasis on device applications toward wearable or potentially implantable systems.

4.2.1. Hydrogel-Based Devices

As mentioned in the previous section on digital micro elastofluidics, hydrogel is solid with 3D matrix structure, which possesses unique physical and mechanical properties. For making microfluidic devices, various types of biodegradable polymers have been processed into hydrogel with well-define shapes and embedded microchannels to serve as a device substrate. Natural polymers such as sodium alginate, gelatin, and silk fibroin have been employed extensively for this purpose due to their high solubility in water and simple gelation process. However, bare hydrogels based on natural polymers usually exhibit inadequate mechanical robustness for handling or applying to a physical surface. Thus, natural polymers are normally used in conjunction with one or more synthetic polymers with good elastomeric properties to promote te overall flexibility and stretchability of the microfluidic device.[136–138] For instance, Liu et al. successfully fabricated a hydrogel-based substrate with laser-engraved microchannels based on sodium alginate and polyacrylamide (PAAm) via a series of ionic crosslinking, thermal crosslinking, and UV-polymerization. The authors conducted trials on both human and animals to verify the effectiveness of their highly stretchable microfluidic device (up to 550% elongation without liquid leakage) as a sensing platform for different human motions and also as a near-field communication (NFC) system. Positive results from the trials demonstrated that the all-hydrogel microfluidic devices can be used as wearable and potentially implantable bioelectronics for wireless monitoring of motional and physiological parameters.[139] Guo et al. utilized 3D printing to fabricate an

artificial skin with integrated electronics and microchannels based on polyurethane—silk fibroin (PU-SF) hydrogel composite. The excellent stretchability of the PU-SF artificial skin was validated by the stretch-and-recovery measurement. The authors applied the PU-SF artificial skin on human's wrist to evaluate its capabilities in detecting wrist motion as well as electro and optical sensing. Excellent conformation to the wrist during the test and positive electromechanical measurements validated the great potential of the artificial skin as a low-cost wearable device for motion sensing and biochemical analysis.[140]

4.2.2. Paper-Based Devices

Paper-based microfluidics is an emerging branch of biodegradable devices, which uses paper from cellulose fibers as the sole substrate. This type of microfluidic device is fabricated by applying micro-scale patterns onto the porous surface of paper to form microchannels that wick liquids by capillary action without the need for external pumping systems. Besides exceptional flexibility, low cost of fabrication, ease of operation, and disposability after usage are the most considerable advantages of paper-based microfluidic devices.[141–143] Many researchers utilized filter paper with superior wicking capabilities and inherent flexibility to fabricate flexible paper-based microfluidic devices for sweat analysis, which has the potential to evolve into complete wearable sweat sensors.

Fiore et al. fabricated a novel microfluidic device from filter paper using a combination of wax printing and laser-cutting techniques. The authors successfully integrated paper-based microfluidic devices as a crucial component into their electrochemical immunosensor for cortisol analysis in sweat.[144] In another attempt, Mogera et al. used chromatography-grade filter paper as a base to fabricate their paper-based microfluidic device, which was used for accurate detection and analysis of uric acid in sweat. Simple paper cutting tool was used to create serpentine shape for the paper microchannel, which was attached to another paper part with plasmonic properties. The authors used PDMS as the encapsulation layer to further improve the flexibility of the device, also protecting the microchannel from contamination and minimizing evaporation of sweat.[145]

4.2.3. Polymeric Film-Based Microfluidic Devices

Besides hydrogel and paper, polymeric thin film is another type of substrate that has been studied for making biodegradable microfluidic devices. Several synthetic polymers such as PGS, POC, PCL, or Ecoflex (from BASF) are engineered to possess film-forming abilities, which have been utilized by researchers in both academia and industries to create film-based products for various biomedical applications.[146–149] Recently, researchers have been making attempts on using these polymers to form flexible and elastic films with thicknesses between 100 µm and 2 mm for housing microchannels. Casting into a patterned mold following by crosslinking is the most common process adopted to produce polymeric films with integrated microchannels.[150–152]

For instance, Ye at al. fabricated a biodegradable micro vessel scaffold with embedded perfusable microchannels by volumetric casting of PGS onto a patterned silicon wafer and subsequent curing to yield an elastomeric substrate. Promising results from both in vitro and in vivo experiments indicated that this scaffold can be used as an implantable and biodegradable platform for vascular support of tissue.[153] Salvatore et al. successfully constructed a biodegradable microfluidic device based on Ecoflex substrate with integrated sensor array for flow mapping. The authors utilized simple drop casting technique of Ecoflex solution on a Teflon negative mold, which was then sealed with another Ecoflex layer to form the film-based microfluidic device. In addition, a top layer of Ecoflex can also be used to encapsulate the microfluidic device for prolonging stable electrical performance while connecting the sensors to a Bluetooth module, enableing potential applications of the device in food tracking and post-surgery medical monitoring.[154]

5. Conclusions and Future Perspectives

Due to the growing demand for sustainable solutions for health monitoring and environmental waste management, research into environmental and biological-friendly platforms has been gaining attention from researchers. Microfluidics is an ideal technology for producing cost-effective and scalable miniaturized systems which can be effectively used in biomedical and environmental applications. Since the fabrication of the first lab-on-a-chip device in the mid-1970s, microfluidic technology has evolved rapidly with numerous remarkable achievements. However, most of the conventional microfluidic platforms including digital microfluidics and continuous-flow microfluidics are operated without taking many considerations of environmental or biological compatibility. The concept of micro elastofluidics is devised to extend the usability of conventional microfluidics to those applications requiring direct contact with environmental waste or biological interface. The first step toward the creation of a micro elastofluidic system that can satisfy the stringent environmental and biological criteria is to select the right device materials. Biodegradable polymer is the most suitable candidate because of its high flexibility, biocompatibility, and most importantly its biodegradability, which occurs either naturally or in a controllable manner. In addition, by-products resulting from biodegradation process of biodegradable polymers are generally non-toxic. Hence, by using biodegradable polymers as part of a micro elastofluidic platform, the concern of detrimental effects that the platform might cause to surroundings at the end of its life cycle is eliminated.

This review provides an overview on biodegradable polymer for digital micro elastofluidics including liquid marbles, liquid beads, hydrogel beads, and continuous-flow micro elastofluidics. For digital micro elastofluidics, biodegradable polymers have been used to form the shell of liquid marbles and liquid beads, or the entire 3D matrix structure in the case of hydrogel beads. These biodegradable miniaturized solid systems have been exploited for various environmental and biomedical applications such as wastewater treatment, precision agriculture, biosensing, drug delivery, 3D cell culture. In continuous-flow micro elastofluidics, biodegradable polymers such as PEO or HA have been utilized to make viscoelastic fluids to improve focusing, separation of bioparticles or enhance mixing between fluid streams in microchannels. At the device scale, both natural and synthetic biodegradable polymers were adopted for fabrication of flexible

and stretchable microfluidic devices, which found their ways in various wearable and potentially implantable biomedical applications.

With the proven capabilities, biodegradable polymer is expected to play an integral part in the further development of micro elastofluidics. We expected that the fusion of biodegradable polymers and micro elastofluidics will promote the connection between physics, electronics, and environmental as well as biological systems. Regarding the development of digital micro elastofluidics, further studies into the ability to form liquid marbles should be carried out with a wider range of biodegradable polymers. The future prospects of liquid marbles are tremendous due to their simple, energy-free fabrication process as well as a variety in functionalization or manipulation schemes. Hence, it is necessary to intensify research efforts toward biodegradable liquid marbles, which would open new avenues for low-cost commercial platform for critical applications such as drug delivery. Hydrophobic polymers discussed in this review such as PCL or PLA should be adopted in future research for further comprehensive characterizations, whereas trials for formation of liquid marbles using unexplored polymers such as PGS, POC should be carried out. For continuous-flow micro elastofluidics, the interaction between Newtonian or non-Newtonian fluids (such as viscoelastic fluids) with their surrounding such as deformable structures and microchannels could be a major research focus. Comprehensive research of fluid-structure interaction could be a challenging task due to its complex physics and multi-disciplinary nature. One of the crucial FSI phenomena to be studied is elastocapillarity, which refers to the deformation of elastic solid caused by capillary action of liquid. Initial studies into the effect of elastocapillarity on microchannels have been carried out, indicating that this fluid-structure interaction might have some influences on the flow velocity or capillary rise.[158,159] We expect that theoretical and technical investigation into essential fluid-structure interaction phenomena such as elastocapillarity would facilitate the practical applications and emergence of micro elastofluidic devices.

Conflict of Interest

The authors declare no conflict of interest.

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biodegradable polymers, flexible and implantable devices, hydrogel bead, liquid bead, liquid marble, micro elastofluidics

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