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Microgels for 3D Biofabrication

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ABSTRACT

While traditional bulk hydrogels have been widely used in 3D bioprinting for tissue engineering, engineered cell-loaded scaffolds still fall short of expectations because their nanoscale molecular networks impede cell function. Microgels, as micron-sized hydrogel materials, offer significant advantages in enhancing mass transport and tissue permeability, while concurrently promoting cellular proliferation, migration, and differentiation. Incorporating microgels as bioinks into 3D bioprinting enables customization of shape, mechanical properties, and functionality, significantly expanding the applications of hydrogel materials and addressing diverse bioprinting needs. Hierarchically porous scaffolds formed by microgel assembly leverage dual-scale porosity: nanoporosity inherent in the material and microporosity originating from the assembly. This unique structure promotes tissue regeneration and facilitates microtissue assembly. This review provides an overview of microgel fabrication techniques, describing their role as carriers for cells and biomolecules, as well as their applications in 3D biofabrication. Notably, we throughout present the application of microgels in 3D biofabrication. Finally, we provide an outlook on the potential applications of microgels in biomedical engineering and their integration with emerging printing technologies.

1 | Introduction

3D bioprinting refers to the process of shaping bioinks, which are composed of cells, biomolecules, and hydrogel materials, into specific structural forms based on predefined designs [1]. This technique is widely applied in tissue engineering and regenerative medicine, offering diverse printing methods to meet various biomedical and laboratory research needs [2, 3]. 3D bioprinting techniques can be divided into three categories: inkjet-based bioprinting, extrusion-based bioprinting, and vat polymerization bioprinting. With advancements, various 3D bioprinting techniques have emerged as a predominant technique for fabricating hydrogel scaffolds. The nanoporosity of available bulk hydrogel scaffolds has imposed limitations in recruiting surrounding cells or transferring signaling cues and nutrients to encapsulated cells [4]. Microgels have drawn considerable attention as versatile carriers for cells and drugs, which is highly promising for emerging bioink candidates. Microgel normally refers to micron-level granular hydrogel from 1 to 1000 μm. It can be generated in a variety of morphologies according to application requirements under different strategies.

Ting Xie, Huaibin Wang, and Jieting Li contributed equally to this work.

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Microgels have been widely applied in the fields of tissue engineering and regenerative medicine. It can be fabricated from various natural or synthetic materials, with their size and shape precisely controlled through multiple fabrication methods [5]. Common fabrication technologies for microgels include mechanical fragmentation [6], emulsification [7], microfluidics [8], electrospraying [9], and centrifugation [10]. In response to growing demand for highly biocompatible strategies, newer approaches have emerged, such as gas shearing [11], aqueous two-phase emulsions [12], lithography [13], and 3D printing [14, 15]. In general, microgel fabrication technology has evolved from producing irregular, polydisperse particles to achieving precise control over morphology and size with high monodispersity.

Microgels represent a promising alternative to conventional bulk hydrogels in 3D bioprinting, owing to their highly tunable structural design and versatile functional payload integration. When assembly into bulk hydrogels, microgels offer flexible integration via physical entanglement, chemical crosslinking, or bio-specific interactions [16]. This capability overcomes limitations associated with conventional hydrogels, particularly concerning structural complexity and uniformity of cell distribution [17–20]. Notably, their particulate nature enables two complementary cellular engineering strategies: surface functionalization for cell attachment or direct cell encapsulation within individual microgel units. This dual approach not only preserves structural integrity during printing but also enhances physiological relevance by improving oxygen/nutrient permeation depth [21].

The inherent granular flow characteristics and shear-thinning behavior of microgels position them as exceptional bioink candidates, enabling synergistic integration of mechanical robustness and self-healing capabilities through engineered dynamic crosslinking between particles [22]. More importantly, it addresses the ongoing challenge of balancing excellent printability and biocompatibility in traditional materials [23]. Microgels can also be formulated as a suspension support medium for printing [24], providing physical support for printed structures and inhibit ink diffusion, thereby improving resolution [25]. Figure 1 summarizes the key characteristics, advanced manufacturing and current applications of microgels and their aggregates, highlighting their versatility and potential in biomedical and biotechnological fields.

Here, we comprehensively review prevailing microgel fabrication techniques and their compatibility in biofabrication. Their tunable properties, biocompatibility, and exceptional capacity to encapsulate cells and biologically active molecules render them ideal materials for fabricating complex tissue structures. We subsequently summary breakthroughs in microgel-based bioinks, focusing on their applications in 3D biofabrication and tissue regeneration.

2 | Fabrication of Microgels

Research and technological advancements are expanding microgel fabrication options. Methods include mechanical fragmentation, batch emulsions, precipitation polymerization, gas-shearing methods, electrospray technology, lithography, centrifugation, and 3D printing (Figure 2). Each method has advantages and limitations, making selection crucial based on application, performance, and cost. This section highlights their strengths and challenges in biofabrication.

2.1 | Mechanical Fragmentation

The mechanical fragmentation method employs intense mechanical shearing forces to fragment bulk hydrogels into micron-scale particles. It stands out for its simplicity, low cost, and high production efficiency, making it the most straightforward approach for microgel fabrication (Figure 2A). This method involves physically breaking preformed bulk gels into microgels using a mixer or homogenizer. The final shape of the microgels is determined by the geometric shape and size of the sieve pores [26]. Surman et al. [27] utilized sieves of specific sizes to produce microgels, which were then mixed with chondrocytes for bioprinting. The resulting bioprinted microgel scaffolds demonstrated high chondrogenic potential.

However, the fundamental principles of this method inherently present significant limitations: low microgel precision, poor uniformity, and the risk of high shear forces compromising cell viability. Besides, cells are usually mixed after the formation of microgels due to the high mechanical shearing forces, and the cells remain only on the surface of the microgels [6]. While postprocessing steps such as centrifugal sorting or filtration can isolate microgels of specific sizes, they potentially reduce overall biofabrication efficiency and quality. Such limitations severely constrain the biofabrication potential of microgels, particularly in applications requiring precise cell–microgel integration or viability-sensitive tissue constructs.

2.2 | Microfluidics

Microfluidics has become one of the most commonly used manufacturing techniques. Within microfluidic channels, an aqueous hydrogel precursor solution is sheared by an oil phase to form monodisperse droplets, which are subsequently solidified via photo- or chemical crosslinking (Figure 2B) [8, 28]. Compared with the mechanical fragmentation method, the unique flow characteristics within microfluidic channels, coupled with the precision of these devices, provide opportunities for generating hydrogels with controlled characteristics. Advances in microfluidic device design have facilitated the fabrication of complex microparticles, including rod-shaped, core–shell, Janus, and crescent morphologies, which significantly broaden the applications of microgels [29, 30]. These structures have been successfully applied in drug delivery [31], drug evaluation [32], and tissue engineering [8].

Most microfluidic systems rely on oil and surfactants to generate droplets. However, oil-based methods pose challenges in postprocessing removal, and the required washing steps can compromise cell integrity and viability [11]. Furthermore, the microscale channels often necessitate low flow rates to maintain droplet uniformity, inherently limiting production throughput. To increase the microsphere productivity, a study employed high-throughput step emulsification microfluidic technology to fabricate porous microgels, serving as the basic building blocks

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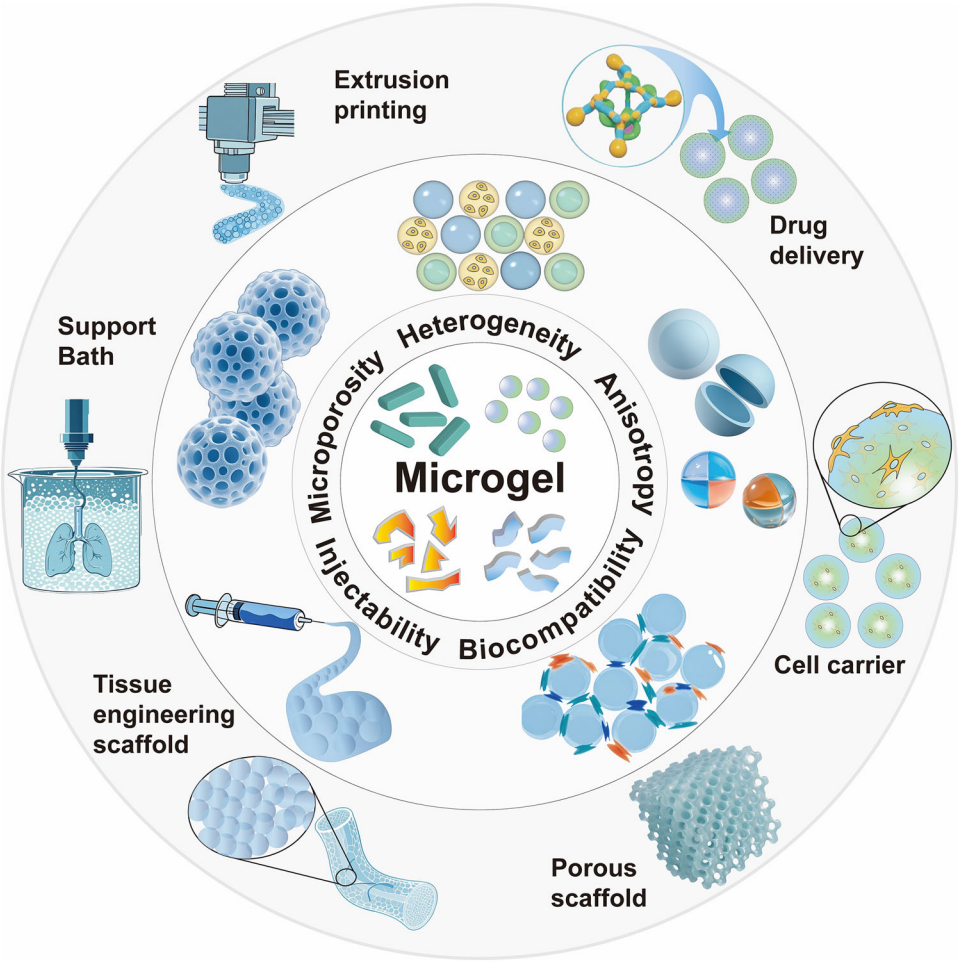


FIGURE 1 | An overview of properties, advanced manufacturing, and applications of microgels.

of porous hydrogel scaffolds [4]. Similarly, Kamperman et al. [33] reported a parallelized microfluidic device, which was made up of five radially arranged parallel flow-focusing units. The production scale can be further expanded by increasing the number of droplet generators in parallel [34].

To ensure droplet stability during microchannel flow, the addition of surfactants is typically required. Therefore, the development and exploration of low-toxicity dispersed phases and surfactants are critically important for microfluidic biofabrication of microgels. Furthermore, microchannel devices are usually designed and manufactured by photolithography, which increases the complexity and cost of this method. The current efforts are only applicable to the laboratory environment. The potential in industrial applications needs to be further tapped.

2.3 | Batch Emulsions

Batch emulsions represent one of the earliest methods for microgel fabrication (Figure 2C). This method involves mixing the aqueous gel precursor solution with an oil phase to form droplets under stirring, followed by the formation of microgels through photopolymerization or thermal curing [26]. The size of the droplets can be controlled by the degree of stirring and surfactants that can alter the surface tension between the two phases. The resulting droplets can be transformed into microgels through photopolymerization or thermal curing.

Compared with microfluidics, the batch emulsions method is relatively straightforward to operate and does not require precise devices. However, challenges remain in controlling the shape and monodispersity of microgels [7]. The combination of emulsification technology and microfluidics enhances the monodispersity and dimensional accuracy of microgels. Due to its excellent encapsulation properties, ease of operation, wide applicability, and scalability, this method is widely used in drug delivery [35–37].

Batch emulsions method can also be combined with 3D bioprinting technology to achieve advanced biomanufacturing. For instance, Wang et al. [38] proposed a one-step microgel bioprinting method using aqueous two-phase emulsion bioresins to prepare porous hydrogels. The resulting interconnected pores facilitated cell guidance and growth on the microgel surfaces. However, this method is difficult to control the morphology of microgels. Zarzar et al. [39] demonstrate that droplet geometries can be alternated between core–shell structure and Janus configurations by varying the interfacial tensions using hydrocarbon

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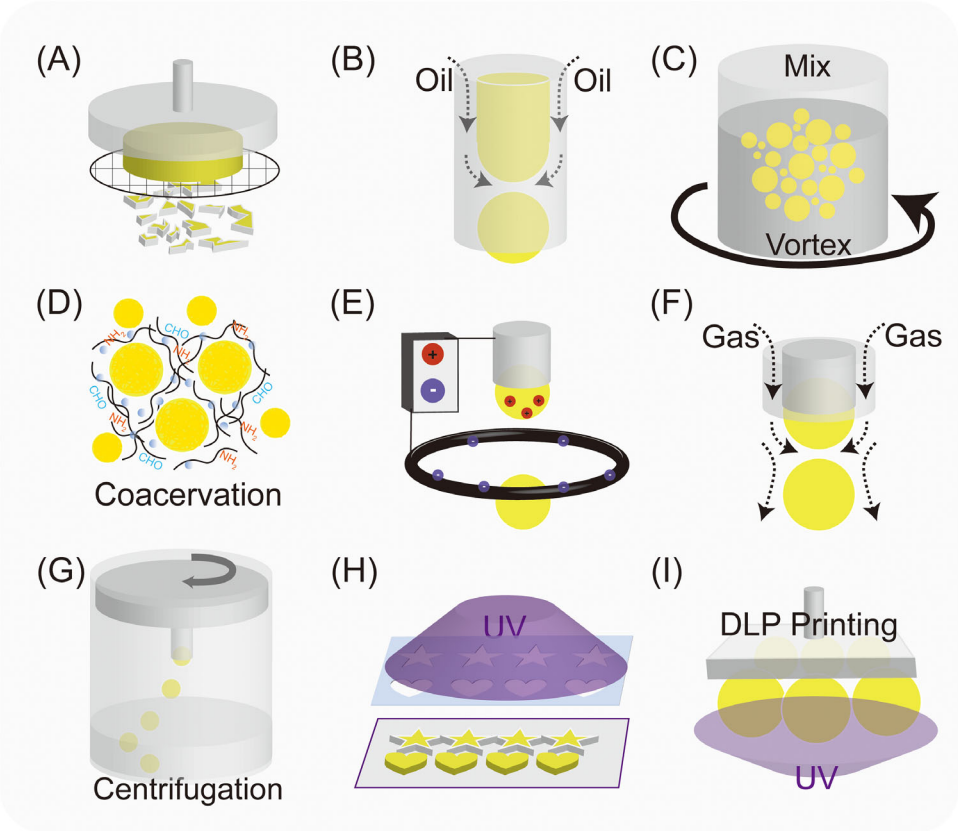


FIGURE 2 | Schematic representation of different fabrication methods of microgels. (A) Mechanical fragmentation: the preformed bulk hydrogels are broken down into microscopic particles by mechanical force. (B) Microfluidic technology: in which two immiscible liquids flow through microfluidic channels, forms droplets of one phase under the action of interfacial tension and shear forces. (C) Batch emulsions: in which immiscible liquids are mixed together to generate droplets that can be crosslinked to form hydrogel microparticles. (D) Complex coacervation: in which two water-based gels with opposite charges are mixed together, forming droplets through phase separation, and then solidified into particles by crosslinking. (E) Electrospray technology: high voltage is applied to a liquid, causing it to form simple particles under the action of an electric field. (F) Gas shearing: using a coaxial needle, gas is used as the shearing force, the liquid of the inner needle is cut into droplets, and then the particles are crosslinked. (G) Centrifugation: the hydrogel precursor solution is loaded in a rotating microfluidic channel and droplets are generated by centrifugal drive. (H) Lithography: in which masks are used as templates for hydrogels at the microscale. (I) DLP printing: microgels are formed by depositing a hydrogel solution layer by layer via light curing. This technique enables the customization of microgel shapes according to specific requirements.

and fluorinated surfactants. However, the biocompatibility of this approach remains unverified.

Nevertheless, emulsion systems are usually unstable and prone to demulsification, which can lead to microgel aggregation and homogeneity. Precise control over factors such as emulsifier type, dosage, and stirring speed is essential. Furthermore, in emulsification processes utilizing organic solvents as dispersants, residual solvent can be potentially harmful to cells. Therefore, further optimization of the process and material selection is necessary to enhance performance and broaden the application range.

2.4 | Precipitation Polymerization

Precipitation polymerization involves dissolving the monomer or initiator in the solvent and promoting the precipitation of the insoluble polymer into microgel particles (Figure 2D) [40–42]. Functional monomers, such as temperature-sensitive, pH-responsive, or light-responsive variants, can be incorporated during synthesis, imparting tailored functionalities to meet diverse application requirements.

Traditionally conducted under batch conditions, this method typically yields particles ranging from 100 nm to 1 μm. Notably, recent advances employing temperature ramp and fed-batch strategies have successfully expanded particle sizes to 1–5 μm, bridging part of the gap between nanoscale (<1 μm) and microfluidic-scale (>10 μm) particles [43, 44]. Furthermore, innovations like photo-crosslinking-assisted continuous precipitation polymerization [44], comonomer-induced self-assembly [45], and charge-driven coprecipitation [46] now enable precise regulation of microgel topology, anisotropy, and functionality. For instance, Xie et al. [47] recently prepared mechanically contractile and biochemically functional core–shell microgels via precipitation polymerization. These demonstrated efficacy in rapid wound closure and functional reconstruction during chronic diabetic wound treatment.

In biomanufacturing, precipitation polymerization offers distinct advantages: surfactant-free production yielding pure products,

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straightforward scalability, and monomer design flexibility to impart multiresponsive properties (e.g., temperature, pH, or light sensitivity). Unlike microfluidics, which demands precise flow control devices, this method requires no specialized devices, reducing costs while achieving higher yields. However, microfluidics surpasses precipitation polymerization in producing monodisperse, shape-controlled particles. Relative to emulsion polymerization, precipitation avoids emulsifier residues though exhibits relatively less precise particle size control. Consequently, its operational simplicity and customizable functionality establish precipitation polymerization as one of the mainstream technologies for constructing smart microgel platforms.

2.5 | Electrospray Technology

Electrospray technology utilizes high-voltage electrostatic fields to prepare microgels. In 1964, Taylor's research on the conical shape formed by droplets under the influence of an electric field laid the foundation for the physics of electrospray [48]. In this process (Figure 2E), a microgel precursor solution is sprayed through a nozzle onto either a solid collector or conductive liquid reservoir [9, 49]. At the nozzle outlet, surface tension and electrostatic forces shape the solution into Taylor cones. Subsequent cone-jet fragmentation under intense electric fields generates progressively finer droplets, which solidify upon collection to form microgels. Recent advances include coaxial needle designs that diversify microgel morphologies [50]. Integration with 3D printing enables extrusion-based fabrication of microgel fibers with filamentary resolution at cellular scales, guiding directional cell growth and alignment [51].

This method eliminates the need for potentially harmful substances such as oils, organic solvents, or surfactants, thereby better preserving the biological activity of biomolecules. As a result, it holds great promise for biomedical applications, including cell encapsulation and drug delivery [9, 52, 53]. However, several parameters influence microgel formation, including voltage, ambient humidity, solution concentration, conductivity, and flow rate. Similar to microfluidic techniques, challenges remain in scaling up the process to meet industrial production requirements.

2.6 | Gas Shearing

The gas-shearing method employs precisely regulated pneumatic forces to fragment hydrogel precursor solutions into micron-scale particles (Figure 2F) [54]. In this process, microgel size is modulated by adjusting two key parameters: gas flow rate and hydrogel solution feed velocity. This dynamic control mechanism enables the generation of particles within defined dimensional ranges while maintaining high-throughput production capacity—a critical advantage for scalable microgel manufacturing. This system is relatively simple and easy to assemble, offering advantages of biofriendly, high throughput, and relatively low cost [11]. By changing the configuration of the needle system and gas flow in the spray ejector device, multicompartmental microgels with two to eight compartments can be designed [54]. This configuration holds potential for encapsulating multiple active agents within a single microgel. Multicompartmental microgels have already demonstrated utility in multidrug delivery systems [55], multienzyme cascade reactions [56], and the creation of multifunctional encoded materials [57].

Nevertheless, this methodology continues to present certain technical challenges in the production of smaller microgels with satisfactory monodispersity. Generally, an increase in gas flow rate corresponds to a decrease in microgel size, However, this also results in heightened droplet instability.

2.7 | Centrifugation

In the centrifugation method, under centrifugal force, liquid within the capillary is ejected through the nozzle as droplets that subsequently solidify into microgels upon crosslinking in external containers (Figure 2G). Centrifugation has undergone a transition from yielding polydisperse to monodisperse particles and from homogeneity to heterogeneity. Diverse microgel morphologies, including fibrous, tear-shaped, Janus-type, and microcapsule configurations, can also be engineered through centrifugal parameter optimization and capillary channel design [10, 58].

However, excessive centrifugal forces may induce membrane damage in sensitive cells (stem cells or primary cells). Systematic optimization of centrifugation parameters could potentially mitigate cellular stress, thereby enhancing the methodology's applicability in biomanufacturing applications. Furthermore, as the quantity of microgels increases during centrifugation, the rising liquid meniscus height in the reservoir causes microgel deformation, limiting production efficiency. This limitation can be addressed by incorporating a waste liquid box adjacent to the collection reservoir [59].

Due to its relative biocompatibility, centrifugation has become a widely adopted preparation platform. It has been utilized for various applications, including cell encapsulation and drug delivery [10]. However, it remains challenging to meet the demands of high-throughput biofabrication required for industrial-scale production.

2.8 | Lithography

Lithography, initially developed for the microelectronics industry, is now used in various biomedical applications. It leverages the property of photosensitive materials to polymerize under light exposure, using photomask techniques to fabricate microgels at the microscale (Figure 2H) [60–62]. The advantage of this method is the precise control over the shape and size of microgels, even enabling complex three-dimensional structures.

Lithography's evolution spans distinct development phases: traditional lithography, flow lithography [13] (including continuous-flow [63] and stop-flow variants [64]), holographic lithography [65], and two-photon lithography [66]. Cumulative advances across these stages have systematically overcome limitations in resolution, material compatibility, and biocompatibility.

Flow lithography integrates lithographic principles with microfluidics, enhancing resolution but requiring synchronization of droplet flow rates with polymerization kinetics.

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Subsequently, holographic lithography eliminates physical masks by employing multibeam interference principles, directly projecting 3D patterns onto photosensitive materials through linear optical phenomena, thereby enabling complex volumetric fabrication.

Two-photon lithography, the latest nanoscale 3D printing technology based on nonlinear optical effects, enables localized polymerization of photosensitive materials within the focal volume through ultrafast laser excitation. This approach overcomes the resolution limitations of conventional lithography, though fabrication efficiency remains relatively low. Furthermore, its near-infrared light offers deep tissue penetration and causes minimal cellular damage, allowing for direct printing of live cell-encapsulating structures [67–69].

Collectively, lithography outperforms alternative technologies for fabricating submicron-scale architectures, albeit with higher equipment costs. Critical limitations include material transparency requirements and photodamage risks: high-energy UV/exposure may induce DNA lesions or cellular apoptosis. Future development priorities involve optimizing photoinitiator wavelengths, developing low-toxicity initiators, and decoupling throughput from resolution constraints.

2.9 | 3D Printing

3D printing technology can precisely control the shape, size, and internal structure of the printed model, and even construct complex microgel structures, including gradient structures and multimaterial composite structures. This capability holds significant promise for advancing personalized medicine [70, 71], drug delivery systems [72, 73], and tissue engineering [74, 75]. With the continuous advancement of 3D printing technology, the printing resolution of some technologies can reach the micrometer level. For example, DLP (Figure 2I) has enabled the successful fabrication of 400 μm microgels [76]. Notably, DLP-printed stem cell-laden microgels demonstrate exceptional biocompatibility and multidirectional differentiation potential [76–78]. Furthermore, the integration of microfluidics/emulsion techniques with 3D printing combines precise microscale manipulation capabilities with spatial orchestration, establishing a robust technological platform for multimaterial, gradient, and compartmentalized biomanufacturing [78–80].

3D bioprinting technology enables the integration of living cells and bioactive components into bioinks, facilitating the fabrication of functionally customized microgels and their hierarchical assembly, thereby broadening applications in biomanufacturing while ongoing technological advancements promise innovative solutions to meet escalating biomedical demands for precision-engineered microgels.

3 | Microgels Use for 3D Biofabrication

Microgel-based bioinks represent a promising alternative to traditional bioinks due to their unique rheological properties, which confer distinct advantages in 3D printing applications [81]. Microgels' high porosity and biocompatibility make them one of the ideal choices for cell encapsulation and tissue engineering applications [82, 83]. Their highly porous structure provides ample space for cell growth and migration while facilitating nutrient transport and metabolic waste clearance, crucial for maintaining cell viability and promoting tissue regeneration [84–86].

The physical properties of microgels, such as mechanical strength and elasticity, can be adjusted by altering their chemical composition and crosslinking density, offering flexibility in designing printed structures with specific mechanical requirements [87]. Furthermore, the modular design of microgels allows for the creation of multimaterial print inks by mixing populations with different functions, offering new avenues to simulate the complex structures of natural tissues for advanced tissue engineering [88, 89].

3.1 | Microgels-Based Bioink

Extrusion-based bioprinting is one of the most widely used printing methods. Bioinks for extrusion printing require three key characteristics: high viscosity, shear-thinning properties, and self-healing capabilities. The viscosity of hydrogels is critical for printing performance, closely related to mechanical strength and structural stability. While higher viscosity improves interlayer adhesion and stability, it may require higher printing pressures, potentially affecting cell viability [2]. Conversely, low-viscosity bioinks risk structural collapse, interlayer delamination, reduced print accuracy, and issues like cell sedimentation and poor uniformity [90]. Thus, hydrogel concentration and viscosity must be carefully optimized based on specific printing requirements and application goals.

Currently, the materials available for bioprinting via extrusion are relatively limited, which restricts the development of extrusion-based printing techniques. The main reason for this limitation is the poor printability of many hydrogel materials. However, converting these materials into microgels can significantly improve their printability. In a quiescent state, densely packed microgels exhibit solid-like behavior under low strain due to interparticle friction and physical associations. When subjected to external pressure (high strain), these interactions induce shear-thinning, resulting in fluid-like flow. This reversible solid-to-fluid transition makes microgels ideal as extrusion bioinks or injectable materials [91, 92].

Nevertheless, successful printing of microgel based bioinks depends on factors such as particle size, as well as the shape and dimensions of the printing nozzle. As shown in Figure 3A, Xin et al. [93] compared the extrusion behaviors of particles with different sizes using nozzles of varying diameters. For monodisperse microgels, continuous extrusion is only achievable when the nozzle diameter exceeds twice the microgel dimensions. In contrast, polydisperse microgel systems require nozzle diameters at least three times larger than the maximum microgel size to ensure successful extrusion. However, this dimensional scaling inevitably results in reduced printing resolution, as increased nozzle size directly compromises structural fidelity and feature definition during the deposition process. Furthermore, during the extrusion process, microgels are further compressed, which

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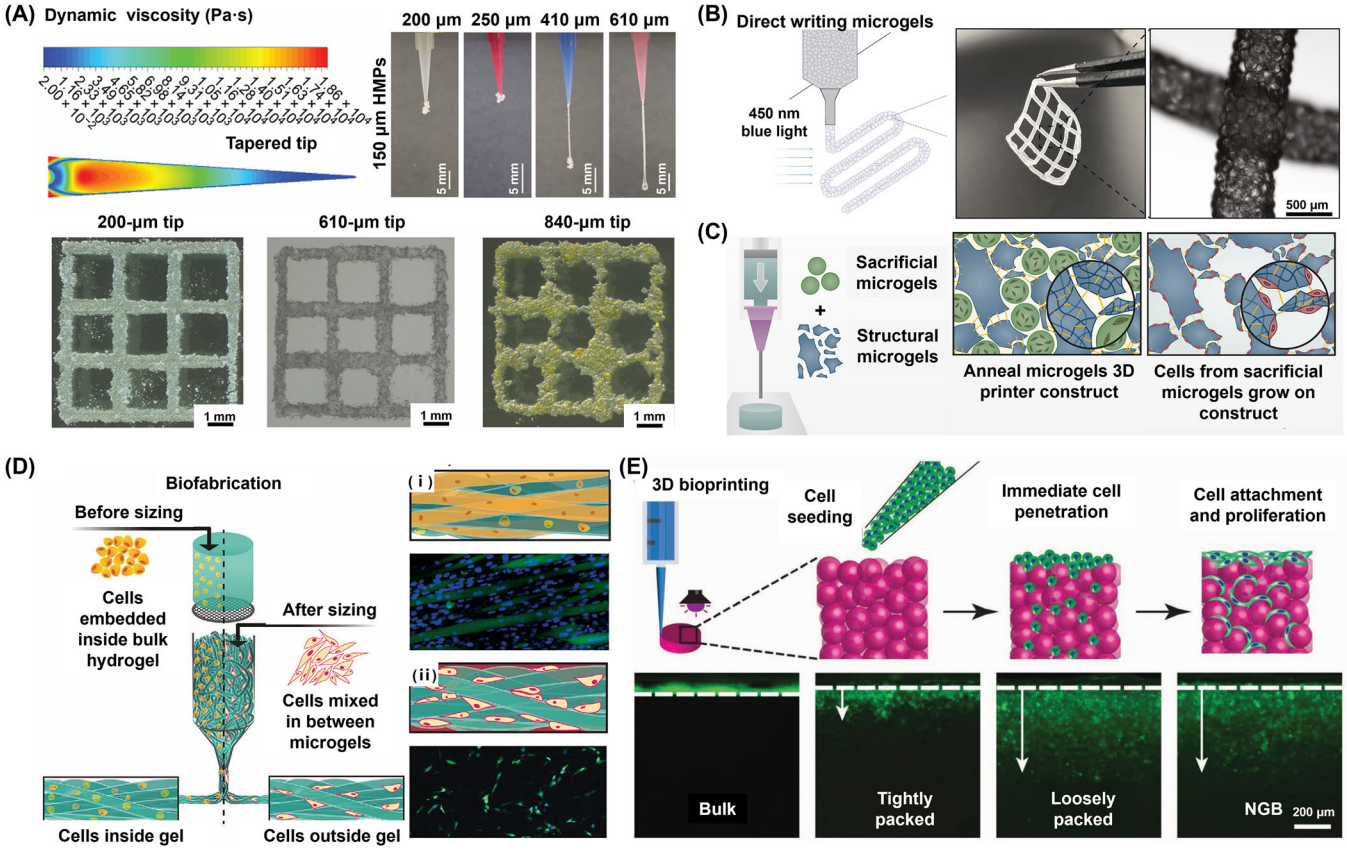


FIGURE 3 | Extrusion bioprinting of microgel bioink. (A) Continuous extrusion of HMP bioinks requires large opening in the syringe and low resistance [93]. Copyright 2021, American Association for the Advancement of Science. (B) Direct ink writing of jammed microgels via extrusion printing [94]. Copyright 2023, Springer Nature. (C) Design of granular inks composed of structural, UV-crosslinkable and sacrificial, cell-containing microgels to enable direct bioprinting and void fraction [95]. Copyright 2023, Royal Society of Chemistry. (D) The 3D biomanufacturing of microfibers can guide the direction of cell growth [17]. (i) Schematic and fluorescence images of cell-laden entangled microgels bioink; (ii) schematic and fluorescence images showed high viability of cells after the printing process and cells adhering to the outer surface of entangled microgels. Copyright 2020, WILEY-VCH. (E) 3D printing of microgel microporous scaffolds capable of seeding and culturing cells on demand [18]. Copyright 2022, Wiley-VCH.

enhances interparticle adhesion, allowing the structure to remain stable after extrusion and facilitating subsequent crosslinking (Figure 3B) [94].

The crosslinked structures are often porous due to the microscale spaces between the microgels. For printing structures that require higher porosity, sacrificial microgels can be mixed to form composite microgel materials that can be removed after printing (Figure 3C) [85, 95]. Spherical particles possess inherent isotropy, whereas the use of nonspherical particles can introduce anisotropy into the printed structures, enabling the fabrication of heterogeneous and complex architectures. Research has shown (Figure 3D) that during extrusion, fibrous hydrogels can form an ordered network of microstrands, resulting in enhanced stability postextrusion and the ability to guide cell alignment according to the direction of the entangled chains [17]. What is more, cells can either be pre-encapsulated within the hydrogel or seeded after printing, allowing them to migrate and grow along the microporous gaps (Figure 3E) [18].

For cell-laden inks, a balance must be achieved between extrudability and cellular compatibility under low shear forces. The particle properties of microgels and the larger gaps between particles can balance extrudability and the protective effect on cells during injection. Microgels based on chemical crosslinking or enzyme crosslinking usually have good mechanical properties, but are often unsuitable for extrusion bioprinting. Extrusion requires overcoming higher yield stresses, leading to elevated shear stresses and increased cell damage. In contrast, reversible dynamic crosslinking between microgels maintains injectability without sacrificing mechanical integrity.

Dynamic covalent bioinks, utilizing mechanisms like host–guest interactions, hydrazone, and boronate ester crosslinking, exhibit essential shear-thinning and self-healing properties while preserving cell compatibility [22, 96, 97]. For instance, Burdick et al. [96] developed hyaluronic acid microgels with dynamic covalent interparticle crosslinking, enabling direct printing of stable structures that support cell invasion in vitro (Figure 4A). Adamantane and cyclodextrin (AC) host–guest interactions, which exhibit mechanical sensitivity, have been developed to fabricate stress-relaxing hydrogels [98]. Morley and his colleagues [99] introduced AC bonds into hyaluronic acid microgels, encapsulating neural stem cells within the microgels. Under shear stress, the AC bonds break, allowing the microgel to pass through the nozzle. Once the force is removed, the AC bonds rebond, facilitating the stable existence of the extruded structure (Figure 4B). Similarly,

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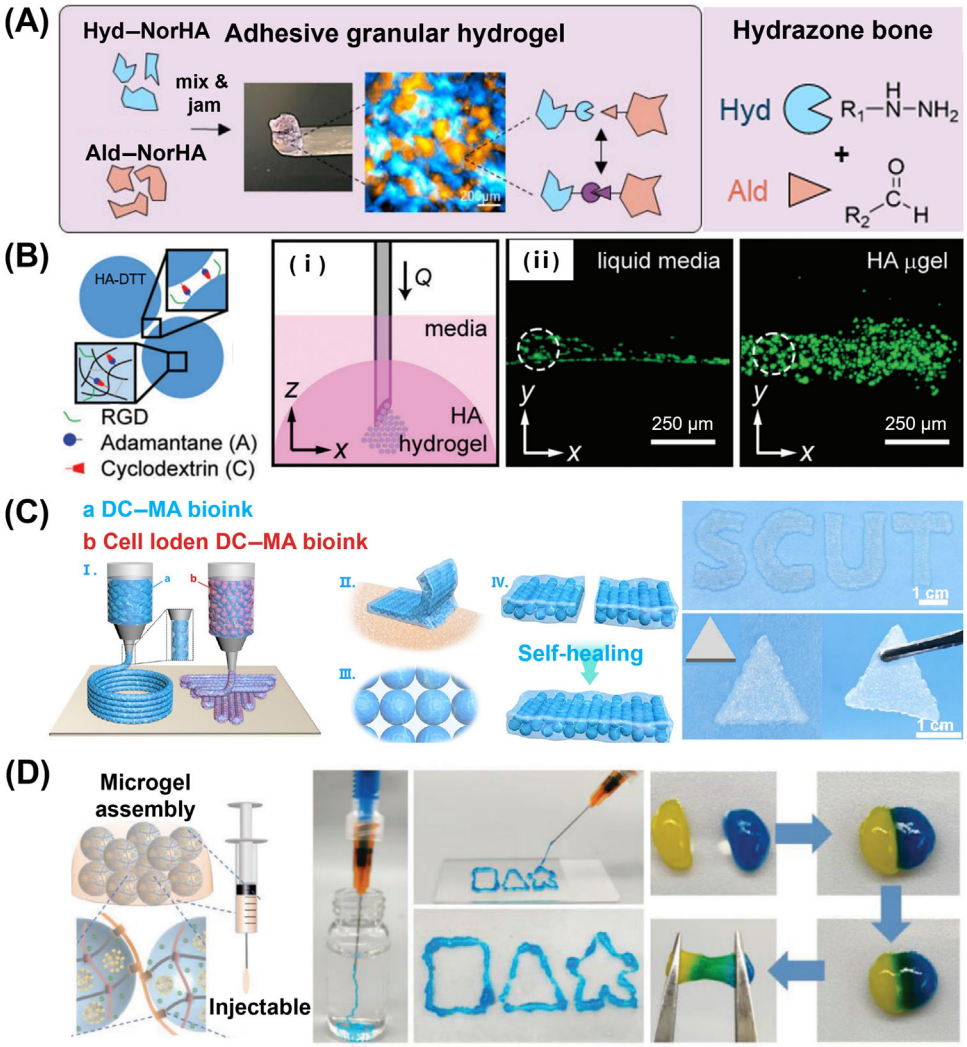


FIGURE 4 | Extrusion bioprinting based on dynamic crosslinking microgels. (A) The use of dynamic covalent inter-particle crosslinking to enhance injectable granular hydrogels [96]. Copyright 2022, Wiley-VCH. (B) Microgel ink has a higher volume retention after extrusion than the liquid hydrogel mode [99]. (i) Injection into hydrogels to measure the volume retention capacity of granular materials; (ii) comparison of the extrusion effects of liquid hydrogel ink and microgel ink loaded with cells. Copyright 2023, Wiley-VCH. (C) A strategy of formulating a dynamic crosslinked microgel assembly (DC-MA) bioink, which can achieve high printability and shape fidelity [22]. Copyright 2022, American Chemical Society. (D) Injectable and self-healing behaviors of microgel assemblies. The dynamic borate ester bond between the microgel and hydrogel gives the microgel injectable and self-healing properties [97]. Copyright 2023, American Chemical Society.

dynamic crosslinked assembly bioink allows high-fidelity printing of diverse 3D structures, with encapsulated cells maintaining high viability during extrusion (Figure 4C) [22]. This design also enhances tissue adhesion and self-healing.

Dynamic covalent bonds can respond to external stimuli and dissociate when damaged, allowing the material to have good mobility, and can be rebonded after the external stimulus is removed, restoring its mechanical properties (Figure 4D) [100]. Mechanisms such as entanglement of polymer chains, responsive material properties, enzymatic reactions, and host–guest chemistry can all contribute to the self-repair of microgels upon damage [101, 102]. In addition, the microrheological processes during extrusion further enhance the interactions between particles and also contributes to the stability of the printing structure [82, 103]. For example, Sayed et al. [104] introduced supramolecular bonding in poly(N-isopropylacrylamide) microgels, with un-crosslinked microgel inks demonstrating rheological characteristics typical of particulate materials, including yield stress, shear-thinning, and rapid recovery. Supramolecular bonds form between adjacent microgels after curing, enabling the printed structures to remain stable for 2 months.

Although microgel-laden bioinks utilizing dynamic crosslinking mechanisms can enhance extrudability by modulating rheological properties, their propensity for shear-induced stress accumulation during printing induces substantial cell viability impairment. To overcome this issue, microgels are mixed into hydrogel solutions to form biphasic bioinks, which can further balance the cell viability and printing performance during the extrusion process (Figure 5A,B) [105, 106]. Fang et al. [105] encapsulated HepG2 and human umbilical vein endothelial cells (HUVECs) into GelMA hydrogel and microgels, respectively, creating cell-laden microgel-based biphasic (MB) bioinks. This

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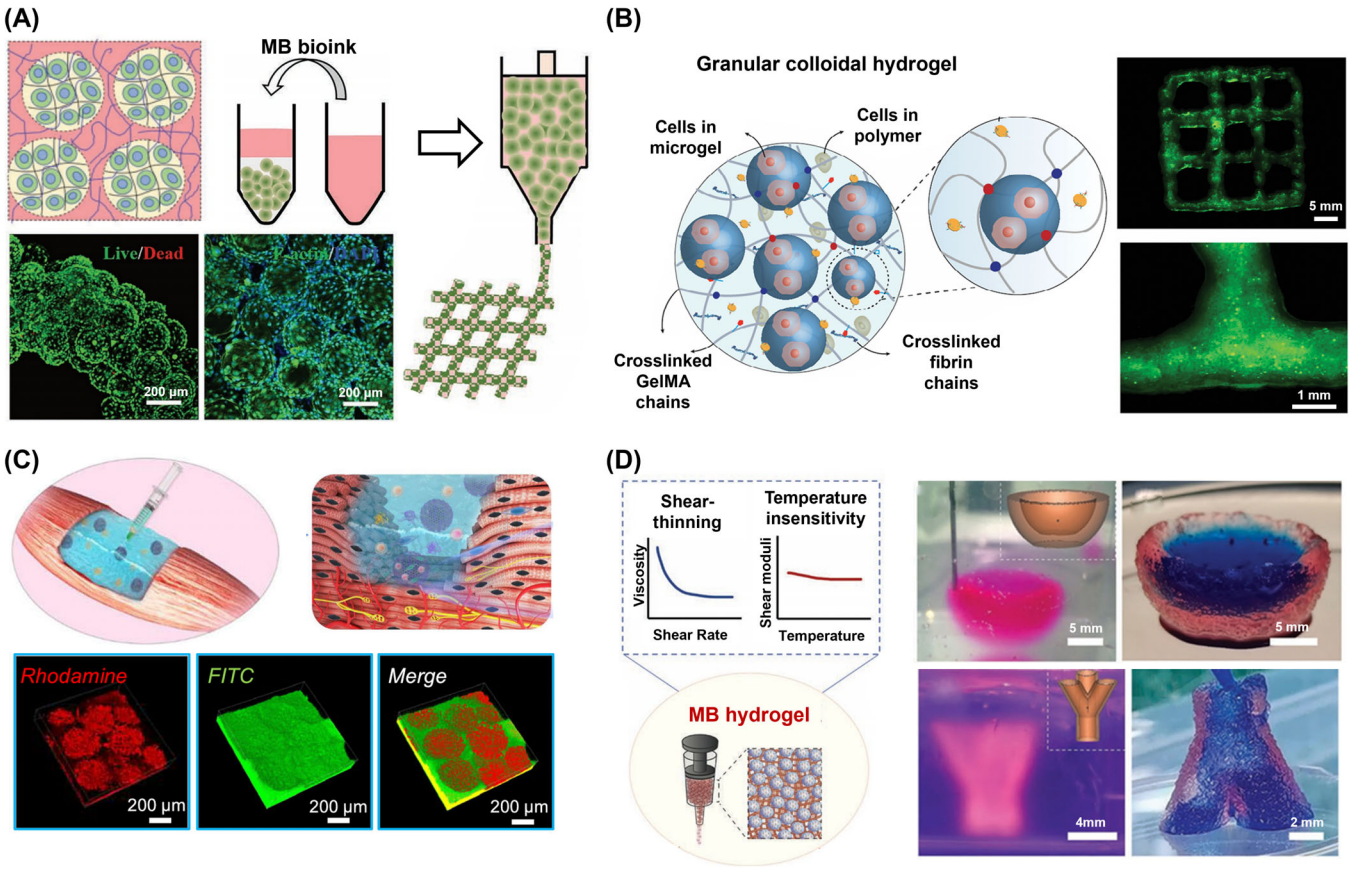


FIGURE 5 | Granular biphasic colloidal hydrogels for biofabrication. (A) A dual-phase ink composed of hydrogel precursor solution and microgel can achieve extrusion bioprinting with high cell viability [105]. Copyright 2023, Wiley-VCH. (B) An extracellular matrix hydrogel and porous microbead composite biological ink for injection therapy. This composite bioink has good printability [106]. Copyright 2024, Wiley-VCH. (C) An extracellular matrix hydrogel and porous microbead composite biological ink for injection therapy to achieve muscle tissue regeneration [107]. Copyright 2024, Springer Nature. (D) Embedded 3D printing of MB bioink for complex tissue models [108]. Copyright 2023, Wiley-VCH.

approach demonstrated that spatially patterned, locally enhanced cellular density accelerated cellular reorganization and induced vascularization within the printed liver tissue by establishing a heterogeneous microenvironment. Similarly, Deo et al. [106] also loaded β-islet cells and HUVECs into the two phases, which similarly promoted vascularization. These results fully demonstrate the potential application of this biphasic ink strategy in complex tissue engineering with multicellular and heterogeneous microenvironments. In this biphasic system, the densely packed microgels provide the necessary rheology for extrusion, while the hydrogel precursor solution forms a secondary network. This network mitigates particle over-accumulation, enhances structural stability, and synergistically creates a microscale heterogeneous microenvironment conducive to complex tissue formation (Figure 5C) [107].

A key challenge in biomanufacturing functional tissue structures on demand in vitro is the fabrication of multichamber geometries integrated with vascular networks. Fang et al. [108] utilized MB bioink and successfully printed a ventricle model with a perfusable vascular network by integrating the sequential printing in a reversible ink template strategy (Figure 5D). The printed ventricle demonstrated initial maturation, providing valuable practical insights for the fabrication of complex organs. This granular biphasic colloidal hydrogel system might serve as a general strategy for extrusion-based printing biomanufacturing.

In summary, microgel-based bioinks exhibit significantly superior particulate rheological properties compared with traditional bioinks, enhancing the adaptability of extrusion bioprinting. However, these systems often require secondary crosslinking or blending with hydrogel components to achieve adequate structural stability. Furthermore, while dynamic covalent interparticle crosslinking imparts shear-thinning and self-healing capabilities to microgel bioinks, it also faces challenges such as bond instability [109].

3.2 | Microgels-Based Support Bath in 3D Biofabrication

In 3D bioprinting, the application of soft hydrogel-based bioinks has been limited by the lack of structural integrity and mechanical stability after printing. To address this, embedded suspension printing within a support bath has been developed for extrusion-based systems [110]. The support bath provides buoyancy and spatial confinement, counteracting gravitational and surface tension effects on the extruded material, thereby preventing collapse of soft hydrogels and enabling high-fidelity printing

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of low-viscosity materials [111]. This approach also expands the material choices for extrusion bioprinting and is increasingly used for constructing complex free-form structures [25, 110, 112].

Successful embedded printing critically depends on the support bath material. Currently, the range of suitable microgel support baths is relatively limited, restricting adaptability. Commonly used including agarose [113], gelatin [114], alginates [115], κ-carrageenan [116], and Carbopol [117]. Carbopol was one of the first successful support bath materials, enabling the fabrication of cell-laden structures with resolutions of 100–200 μm and is one of the first materials that have been successfully utilized as support baths [108, 118]. Agarose and gelatin are both thermosensitive materials that can be removed through temperature control or enzymatic methods. Notably, the adjustment of the viscosity of shear-thinning gels is associated with improvements in *XY* directional resolution, although it adversely affects the *Z* direction, resulting in lower printing resolution in the *Z* dimension [2].

Before support bath removal, cell-containing printed structures are susceptible to reduced cell viability, primarily due to insufficient dissolved oxygen levels within the support bath and limited nutrient diffusion [119]. Microgel support baths address this limitation through their porous structure, which enhances mass transfer. Crosslinked microgels provide structural support while enabling resolution control through size modulation. Generally, smaller particles typically yield superior accuracy, whereas larger sizes compromise precision. This principle is demonstrated in vascular bioprinting using micron-sized starch particles as a support bath [120]. The vascular networks printed by starch particles with sizes less than 5 μm showed the lowest indicated roughness, which is very approach to that of the native blood vessels morphology (Figure 6A). Moreover, the microgel-based support bath can also be printed for constructing complex structures. For instance, Fang et al. [108] printed sacrificial gelatin solutions in a microgel-based suspension bath, solidifying the suspension bath through photo-crosslinking to remove the printed filaments and successfully obtained a perfusable network of channels (Figure 6B).

The microgel-based suspension support bath has special flow characteristics [120]. Cheng et al. [121] presented a versatile microgel-directed suspended printing technique, wherein the viscosity of the support gel was meticulously adjusted by varying the concentration of Carbopol within the microgel and modulating the nozzle velocity. The support bath can provide a very fast and short response after printing (Figure 6C). During suspension printing, the microgel is densely packed and relatively moves, exhibiting stable flow behavior [122]. Specifically, during printing, microgels exhibit localized shear-thinning fluidization near the nozzle without disturbing adjacent areas, reverting instantly to a viscoelastic solid postextrusion to lock structures in place [116]. Following printing, the microgel medium can be simply removed, leaving the desired printed structure intact [115].

By optimizing the composition and properties of the microgel, researchers can provide a more suitable growth environment for cells, thereby improving the cell survival rate during the printing process and promoting the functionalization of the printed structure [123, 124]. Many studies have demonstrated the feasibility of high-precision printing of complex models, such as heart, kidney, lung, and blood vessel structures within microgel-supported baths (Figure 6D,E) [24, 108, 116, 124, 125]. For example, Fang et al. [126] fabricated vascularized hepatic tissues using granular biphasic bioink, achieving high cell density with concomitant enhancement of metabolic functions. In response to the limitations of material types, controllability of the cell microenvironment, and precise control of oxygen levels and vascular-like channels during printing, Kajtez et al. [124] developed a novel microgel suspension bath called self-healing annealable particle–extracellular matrix (ECM) composites, successfully embedding functionally mature human neural structures into 3D prints with precise patterning (Figure 6F).

Furthermore, the freeform reversible embedding of suspended hydrogels (FRESH) technique represents an innovative approach. This method enables 3D bioprinting with micrometer-level resolution by extruding bioink within a thermoreversible microgel suspension, eliminating support structures [115, 122, 127, 128]. FRESH v1.0, reliably prints collagen fibers approximately 250 μm, while FRESH v2.0 achieves a tenfold resolution improvement (20–200 μm) [24]. Using unmodified collagen bioink, FRESH v2.0 promotes collagen self-assembly via rapid pH shifts, enhancing mechanical properties and enabling complex architectures. It accommodates diverse bioinks (collagen, alginate, fibrinogen, methacrylated hyaluronic acid) through orthogonal gelation triggered by $CaCl_2$, thrombin, or UV irradiation [122]. It is also possible to achieve fast and efficient printing of ventricular models with fusible blood vessel networks, which is not possible with current 3D printing strategies [108]. Multimaterial support baths create tailored microenvironments, while extended temperature ranges enable gentle object retrieval [129]. This approach is expected to provide the optimal growth environment for the printed cells and enhance the interaction between cells and the production of ECM.

In summary, microgel support baths advance bioprinting fidelity through tunable rheology and size-dependent resolution control, serving as a versatile platform for biomimetic tissue fabrication. This has important implications for studying areas such as tissue development, disease models and drug testing.

3.3 | Microgels-Based Sacrificing Porous Scaffold

In tissue engineering, hydrogels should meet the fundamental requirements of mimicking the ECM by providing a three-dimensional environment, effective mass transport, biocompatibility, and biodegradability [130]. While traditional hydrogels often restrict cellular activities due to dense networks, porous hydrogels enhance cell attachment, migration, and mass transport, which are essential for biofabrication.

Current methods for fabricating porous hydrogels include freeze-drying [131], sacrificial templating [132], porogen leaching [133], phase separation [134], and electrospraying [135]. In these approaches, cells are typically seeded onto scaffolds after pore formation, which can limit their uniform distribution and growth throughout the scaffold. Furthermore, achieving precise control over pore size, shape, and distribution to meet the specific requirements of various cell and tissue types remains a significant

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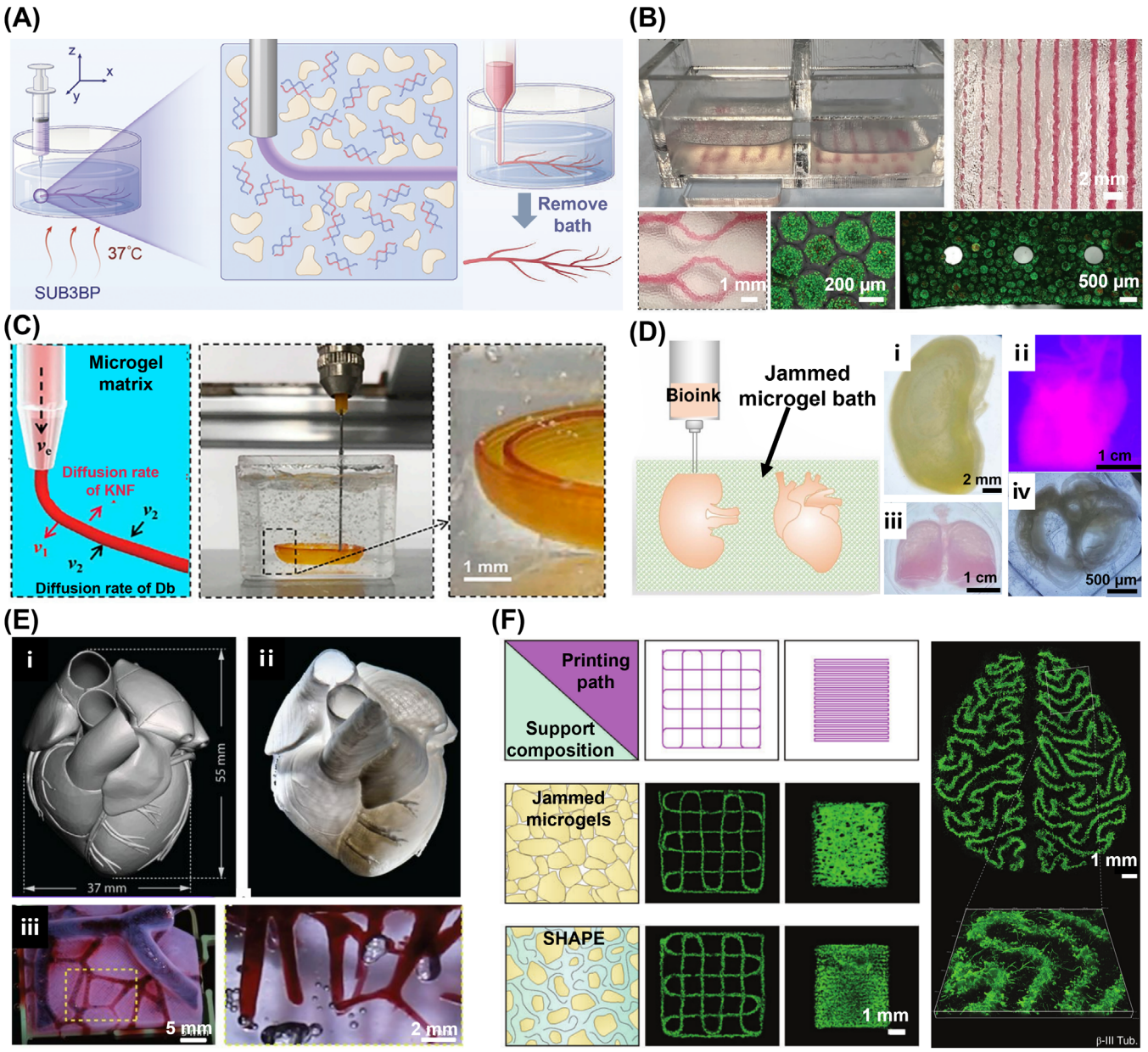


FIGURE 6 | Microgel serves as a suspension medium for embedded 3D printing. (A) Suspension support baths composed of starch-based microgels allow for the printing of vascular network structures [120]. Copyright 2024, Wiley-VCH. (B) Freeform vascular printing using MB bioink as a suspension medium [108]. Copyright 2023, Wiley-VCH. (C) Microgel-directed suspended printing strategy for printing aerogels [111]. Copyright 2023, Elsevier. (D) Cation-crosslinked κ-carrageenan sub-microgel medium for high-quality embedded bioprinting [116]. (i) A kidney model printed with the GelMA/SA ink; (ii) embedded 3D bioprinting of human heart; (iii) a photograph of a 3D printed lung featuring trachea; (iv) a cross section of the 3D printed heart. Copyright 2024, IOP Publishing. (E) Freeform reversible embedding of suspended hydrogels (FRESH) composed of gelatin particles for printing heart [24]. (i) MRI-derived 3D human heart scaled to neonatal size. (ii) FRESH-printed collagen heart. (iii) Perfusion of the vascular network with glycerol (red) through the coronary artery, showing interconnectivity. Copyright 2019 American, Association for the Advancement of Science. (F) Self-healing annealable particle-extracellular (SHAPE) composite material is used as a support bath to support the precise embedding printing of human neural stem cell ink, which can provide long-term structural and functional support for cells [124]. Copyright 2022, Wiley-VCH.

challenge. Microgels offer an innovative solution for fabricating porous scaffolds through microscale precision manipulation.

GelMA-based microgels have emerged as a promising approach due to their biocompatibility, tunable mechanical properties, and ease of fabrication into complex structures through 3D printing [136]. As structural units, Huang et al. [137], a reversed-engineered human alveolar lung-on-a-chip model was developed, showcasing the potential of using a porous hydrogel made of GelMA with an inverse opal structure (Figure 7A). This three-dimensional porous architecture significantly enhances primary alveolar epithelial cell function compared with planar models by recapitulating ECM microenvironments. As sacrificial templates, gelatin-based microcavitary gel (G-MCG) could serve as sacrificial microspheres and be mixed with the hydrogel precursor solution to fabricate porous scaffolds

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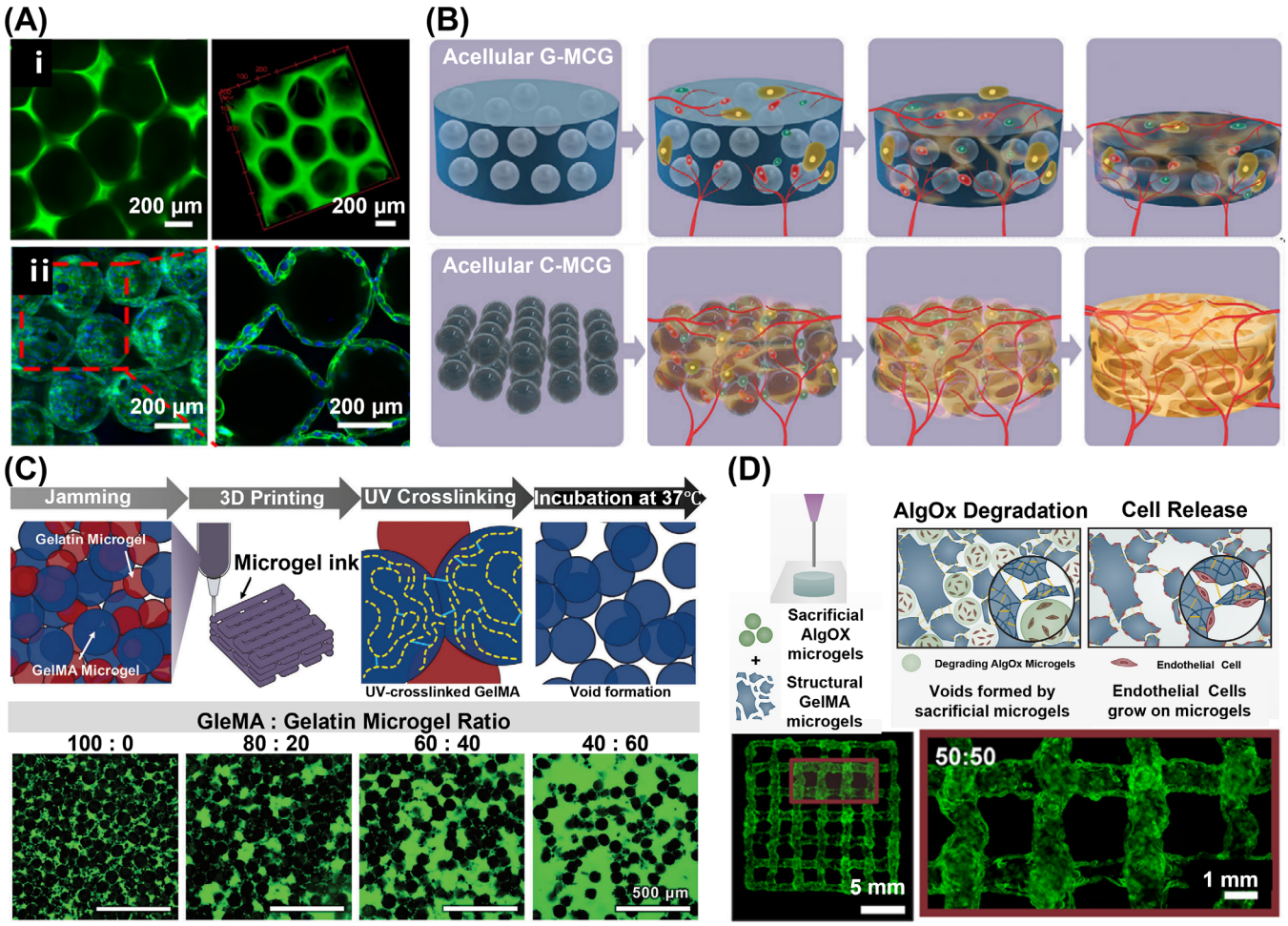


FIGURE 7 | Porous hydrogel scaffolds were prepared based on microgel strategy. (A) Fabrication of the alveoli-like 3D GelMA inverse opal structure and formation of the alveolar lung model [137]. (i) Fluorescence confocal images illustrating the GelMA inverse opal hydrogel structure, where GelMA was chemically labeled with FITC. (ii) Confocal reconstruction view (left) and sectional view (right) of the hAECs after culturing for 14 days in the GelMA inverse opal hydrogel structure, in which the fully confluent alveolar epithelium was formed. Green, f-actin; blue, nuclei. Copyright 2021, National Academy of Sciences. (B) Schematic representation of C-GMSs and G-MCG and their applications in bone defect repair, endogenous bone-forming cells (orange), vascular forming cells (red), and immunocyte (green) [138]. Copyright 2022, Wiley-VCH. (C) A porous microgel-based scaffold with adjustable pore size was designed using microgel ink [85]. Microgels are shown in black, and voids (which are filled with 2000 kDa FITC-dextran) are shown in green. Copyright 2021, Wiley-VCH. (D) Biofabrication of cell-ladened porous scaffold by integration of photo-crosslinking and sacrificial microgels. Sacrificial AlgOx microgels rapidly degrade to reveal internal voids, sufficient space was provided for cell growth, which was conducive to cell growth [95]. Copyright 2023, Royal Society of Chemistry.

[138]. Similarly, chemical-crosslinked gelatin microspheres (C-GMSs) could be directly piled up and crosslinked to obtain porous scaffolds (Figure 7B). These overcome diffusion barriers of dense hydrogels, enabling cell migration, vascularized bone regeneration, and in vivo defect repair.

Conventional hydrogels possess limited pore sizes that restrict deep cellular infiltration. To address this, sacrificial microgels enable the engineering of scaffolds with tunable porosity through active incorporation of macroporous structures within printed constructs (Figure 7C) [85]. Nevertheless, enhanced porosity alone fails to resolve postseeding cellular heterogeneity. Consequently, researchers developed composite bioinks featuring cell-preloaded sacrificial microgels. This design achieves simultaneous pore generation and controlled cell release postprinting, effectively overcoming the slow migration and uneven distribution inherent to traditional approaches (Figure 7D) [95]. Unlike freeze-drying, salt-leaching, or postseeding techniques, this microgel-centric strategy decouples structural support from biological functionality. It integrates shear-thinning behavior and self-healing capacity for printability with custom porosity and uniform cell distribution to enhance biological performance. Collectively, this establishes a scalable, functionalizable platform for vascularized tissues, organ-on-chip systems, and regenerative medicine applications.

The biphasic aqueous system, represents a prevalent category within liquid–liquid phase separation systems. This biphasic aqueous system serves as a cell-friendly method for fabricating porous hydrogels [38, 139, 140]. It operates by forming emulsions through the interaction of two immiscible aqueous solutions, followed by the solidification of one phase using techniques such as photopolymerization. In contrast, the other phase is subsequently, resulting in a porous structure. This method provides a

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gentler and more controlled approach, as they do not necessitate the use of toxic organic reagents or high-temperature treatments. Moreover, it facilitates the construction of soft materials with multiscale heterogeneous structures by exploiting the phase separation of two polymers in an aqueous solution [141, 142]. This process creates two distinct phases with varying physicochemical properties, allowing for incorporation regions within the hydrogel that exhibit tailored mechanical properties, molecular affinity, and spatial selectivity [143, 144].

Compared with traditional methods, we have summarized the advantages of microgels in the preparation of porous scaffolds. First, it allows for creating highly uniform and controlled pore sizes by controlling the size of microgels to meet specific requirements [85, 95]. Second, The integration of 3D printing technology allows for precise control over the macroscopic architecture of hydrogels. This combination mimics the complexity of natural tissues that can serve as scaffolds for tissue engineering with specific mechanical characteristics and biological functionalities [144]. In general, the sacrificial microgel approach provides a versatile platform for incorporating various bioactive molecules and cellular components, enhancing the functionality and bioactivity of the engineered tissues [145, 146].

To sum up, microgel systems advance 3D biomanufacturing through three synergistic modalities. As bioinks, their unique rheological properties enable superior printability and heterogeneity engineering; as suspension support baths, they provide stable platforms for fabricating soft constructs and complex free-form architectures; and as porous scaffold templates, they innovate precision fabrication of regulated macroporous biomimetic scaffolds. These compatible modalities can be integrated for complex tissue fabrication, with design strategies tailored to tissue-specific requirements encompassing structural complexity, functional demands (e.g., vascularization), and manufacturing feasibility.

4 | Application of Microgels

These microscale gelatinous matrices, composed of either natural or synthetic polymers, demonstrate excellent biocompatibility and biodegradability, making them an ideal platform for tissue regeneration. The modular nature of microgels allows for the formulation of multifunctional materials by mixing distinct microgel populations, each with different compositions and sizes. Their high water content, diverse properties, and similarity to the native ECM enhance their suitability for a wide range of biomedical applications, including cell culture, tissue engineering scaffolds, and drug delivery systems [147–151]. In tissue engineering, microgels combined with additive manufacturing technologies can mimic the multiscale behavior of natural tissues, providing a multifunctional and tunable platform for biomedical research.

4.1 | Drug Delivery System

Conventional drug delivery strategies are plagued by problems such as systemic toxicity and repeated administration. Hydrogels are favored for their high-water content, good biocompatibility, and controlled physicochemical properties [152]. These properties not only protect the integrity of the drug for successful delivery to a site, but also reduce the side effects associated with direct delivery [31]. Second, by controlling the degradation rate of the hydrogel the release time of the drug can be shortened or lengthened [153]. Additionally, some hydrogel materials of natural origin, such as hyaluronic acid, bind to cell surface-specific receptors and can be used for direct targeted delivery without additional chemical modifications [154, 155]. This section delineates three distinct structural categories of microgels central to advanced material design: porous versus homogeneous (nonporous) microgels, Janus-type microgels exhibiting binary spatial asymmetry, and compartmentalized multicompartment architectures.

4.1.1 | Porous and Nonporous Microgels

The three-dimensional polymeric network of microgels can encapsulate a diverse array of therapeutic agents, including small molecules, proteins, extracellular vesicles and nucleic acids, positioning them as a universal platform for drug delivery [156–160]. However, most materials do not allow direct observation of tissue repair after drug delivery. Yao et al. [161] encapsulated the small molecule drug and fluorescein together in GelMA microgels, which promoted cartilage regeneration while allowing monitoring of the repair process of the cartilage layer (Figure 8A). In addition, the microgel injected into the articular cavity was able to act as a cushioning lubricant for the joint cavity and reduce the friction between articular cartilage.

High drug load delivery systems can reduce the use of excipients, thereby enhance therapeutic efficacy while minimize side effects [162]. Microgels have higher drug loading capacity compared with nanocapsules, micelles, and liposomes. By means of the sequentially cured microgel strategy, the researchers prepared high-dose methylprednisolone for injection into the spinal cord injury site. Compared with free drugs and conventional doses, the high-dose microspheres demonstrated higher efficacy and fewer side effects [162]. Based on the nonporous structure of microgels, drug release is mainly dependent on diffusion and polymer degradation mechanisms, and there may be a certain stagnation period for drug release [147]. Porous microgels have a higher specific surface area, which is theoretically capable of adsorbing more drug. Second, the presence of porous structure facilitates the immersion of body fluids and cells and drug release. Compared with nonporous structures, the release of the drug has no significant lag period and a continuous and stable release of the drug can be achieved. In order to deliver hypoxic exosomes efficiently in vivo, the researchers adsorbed exosomes onto polydopamine coating porous microgels, which not only improved the loading efficiency of exosomes, but also optimized their release kinetics, and was able to induce vascularized bone regeneration at the cranial defects of the rats effectively (Figure 8B) [163].

Targeted drug delivery is pivotal for effective disease treatment. Microgels can be custom-designed to respond to specific stimuli, such as changes in pH, temperature, or enzymatic activity, thus enabling the triggered release of drugs in response to specific biological signals [164–166]. One of the key advantages

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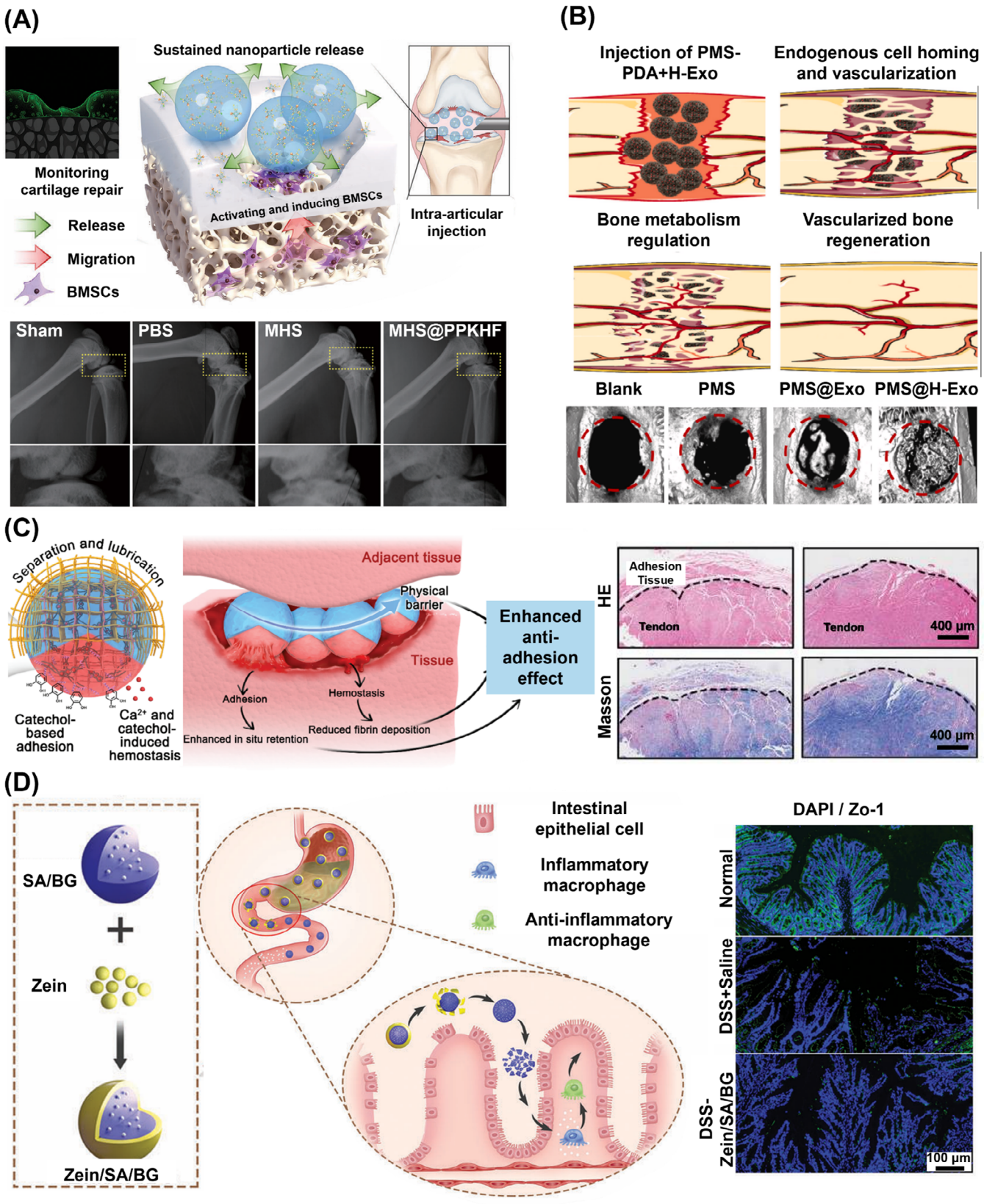


FIGURE 8 | Injectable microgels for drugs delivery. (A) POSS-based micro–nano hydrogel microsphere enables cartilage regeneration monitoring via fluorescence imaging, and has the ability to lubricate and promote cartilage repair [161]. Copyright 2023, Wiley-VCH. (B) Injectable PMS-PDA porous microspheres delivered exosomes induced vascularized bone regeneration in rat skull defects [163]. Copyright 2022, Elsevier. (C) Janus-structured microgel barrier with tissue adhesive and hemostatic characteristics for efficient prevention of postoperative adhesion [170]. Copyright 2024, Wiley-VCH. (D) Oral zein/SA/BG core–shell hydrogel microspheres can significantly reduce intestinal inflammation and promote epithelial tissue regeneration [172]. Copyright 2023, Wiley-VCH.

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of microgels is their ability to protect encapsulated drugs from premature degradation while allowing for controlled release at the target site. For instance, Murthy et al. [167] designed a PH-dependent microgel for releasing proteins, which can selectively deliver drugs to diseased tissues.

4.1.2 | Janus Microgels

Janus microgels are a class of multicomponent, multifunctional composite materials distinguished by their asymmetric architecture, which endows them with unique physicochemical properties [168]. This structural asymmetry facilitates the encapsulation of distinct drugs or biomolecules in separate regions, enabling the combinatorial delivery of multiple therapeutics [169]. However, due to the particulate nature of microgels, they do not stay well in place after injection into a site. In order to enhance their degree of adhesion to the target tissue, one side of the Janus microgels can be designed as an adhesion surface. For instance, Ding et al. [170] cited the adhesion agent catechol to make one side of the Janus microgels tissue adhesive, while the other side retains an antiadhesive surface (Figure 8C). In postoperative adhesion treatment, the adhesive side can help the microgels to be fixed at the injury site, while the antiadhesive side can reduce the nonspecific adhesion with the surrounding tissues, which not only reduces the complications of postoperative adhesions, but also has a hemostatic effect and improves the prognosis.

4.1.3 | Multicompartmental Microgels

Multicompartmental microgels have can coload multiple drugs, enabling synergistic drug administration. Such a design enhances therapeutic efficacy and mitigates side effects by allowing the codelivery of various pharmaceuticals. microgels can encapsulate cells and a variety of therapeutic agents either individually or in combination, and respond to specific biological signals to target particular cells or tissues. However, some drugs are usually subject to premature degradation or failure by body fluids when they reach the target site. Oral administration is one of the most acceptable methods of drug delivery for most patients. However, gastric fluids are highly acidic, and oral administration is extremely detrimental to acid-unstable drugs. Hence, for similar drugs it is often necessary to provide a layer of protection for them to reach the therapeutic site smoothly. For example, bioactive glass (BG) has been shown to modulate the inflammatory response, but it dissolves prematurely in gastric acid [171]. Therefore, Zhu et al. [172] designed a core–shell microgel in which the BG is encapsulated in a sodium alginate microgel, and the zein shell serves as a protective layer that protects the drug from gastric acid, and when it reaches the site of intestinal inflammation it can be degraded by pancreatic enzymes thereby releasing the drug, which can significantly reduce intestinal inflammation and promote epithelial tissue regeneration (Figure 8D). Besides, multicompartmental microgels can be engineered to respond to specific environmental cues, such as pH levels, temperature, or the presence of enzymes, thereby achieving targeted drug release. For instance, Qu and colleagues [173] developed an enzymatic cascade reaction-based alginate/chitosan multi-compartment microcapsule. Two enzymes were immobilized within the microcapsule's two separate compartments, with the shell's chitosan component responding to pH signals to control enzyme release. Mihalko et al. [174] encapsulated two drugs within a core–shell structured microgel, allowing for the initial release of plasminogen activator to reduce fibrin deposition, followed by a sustained release of cell contraction inhibitors to prevent fibrosis progression. This dual-release mechanism simultaneously restored blood flow and addressed fibrosis in myocardial infarction, offering a novel therapeutic possibility for this condition.

Hydrogels hold great potential in precise drug delivery and regenerative medicine. However, critical challenges including biocompatibility assurance, controllable degradation kinetics, and residual material risks postdegradation require resolution. Current research remains predominantly at the preclinical stage, with the clinical translation potential of hydrogel-based systems yet to be comprehensively validated. In the future, efforts can be focused on material innovation, simplification of preparation processes, and theoretical modeling, to accelerate the transition from laboratory research to routine clinical implementation.

4.2 | Cell Culture Scaffolds

Individual microgels serve as versatile vehicles for drug and bioactive substance delivery. Microgel aggregates assembled through diverse strategies constitute a robust platform for tissue engineering research, expanding biomanufacturing potential. These assembly strategies can be categorized into five primary types: (1) physical interactions, (2) chemical interactions, (3) intercellular communication, (4) external stimuli-driven assembly, and (5) hydrogel-embedded microgel systems. Table 1 summarizes the specific methodologies corresponding to each assembly approach.

It is well established that the environment provided by plastic or glass culture plates in 2D systems differs significantly in both physical properties and functionality from the three-dimensional growth environments found in vivo [175]. This discrepancy imposes limitations on our ability to thoroughly investigate cellular behavior and function. Researchers have compared transcriptome and proteome sequencing of human adipose-derived stem cells cultured in both 2D and 3D systems [176]. The results indicated that the transcriptome and proteome profiles of human adipose-derived stem cells in a 3D culture environment, constructed using microgels, exhibited greater similarity to the in vivo transcriptome profiles of adipose-derived progenitor cells. Furthermore, two-dimensional culture can also cause changes in cell phenotype and functional loss.

The synergy between materials and biology has not only transformed our understanding of cellular processes but has also endowed us with the ability to design organ models in vitro for diverse applications. The nanoporous network channels of traditional bulk hydrogels limit the migration of large molecular substances and the infiltration of host cells [177]. Compared with porous scaffolds, cells located deep within the hydrogel are prone to necrosis (Figure 9A) [178]. Microgels assembly scaffolds can achieve pores ranging from nanometers to micrometers

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TABLE 1 | Assembling strategies for microgel assembly.

Types	Driving forces	Merits	Limitations	References
Physical reaction	Host–guest interaction Electrostatic interaction Hydrogen bonding Biotin–streptavidin conjugation	Reversible and spontaneous Injectability No toxic crosslinker	Weaker mechanical strength	[99, 192, 227, 228]
Chemical reaction	Enzymatic catalysis Photo-induced radical polymerization Click chemistry Nonenzymatic amidation reaction	High stability and mechanical strength Fast and efficient	Potential cytotoxicity Complicated synthesis steps for functional group modification	[49, 82, 229, 230]
Cell–cell interaction	Cell–cell junction	No cytotoxicity No additional chemicals or external stimuli	Low assembly efficiency Weaker mechanical strength	[231]
External driving force	Fluidic force Surface tension Magnetic and acoustic force	No complicated design for microgel materials Simple	Unstable Secondary crosslinking Assembly complexity challenges	[232–234]
Hydrogel-embedded microgel systems	Microgels mixed into a continuous hydrogel matrix	Stronger mechanical properties Injectability	Interface fusion defect Restricted cell behavior	[105, 107]

and even centimeters, significantly promoting the infiltration of effective substances and cells, thereby creating a more favorable microenvironment for cell growth (Figure 9B) [179]. Due to the small size of microgels, their regular or irregular surfaces possess a higher specific surface area, which not only provides more sites for cell adhesion but also supports the creation of bioscaffolds with spatially defined characteristics and anisotropy, guiding the paths of cell migration and proliferation (Figure 9C) [180, 181].

The chemical composition or structure of microgels can also affect cell adhesion behavior. For instance, gelatin and its derivative GelMA, which are rich in cell binding and matrix metalloproteinase-responsive peptide motifs, facilitate cell adhesion in three-dimensional cell culture without the need for additional design [182]. Consequently, achieving specific cellular objectives (e.g., chondrogenesis) requires biomaterial selection tailored to cell type-specific requirements to deliver appropriate mechanical support and bioactive signaling [183–185].

What is more, the strategy of cell loading into microgels significantly impacts cell growth and differentiation [87]. The previous discussions have largely focused on three-dimensional scaffolds where cells are seeded on the surface of microgels. When cells are encapsulated within the microgels, microgels can protect cells from the stresses of transplantation, thereby improving cell viability and engraftment [186]. This is particularly crucial for stem cells and other cell types used in transplantation, as these cells often encounter challenges related to low viability and functional loss during in vitro culture and delivery processes. Encapsulation within microgels allows for the creation of compartmentalized 3D scaffolds that can control cellular microenvironments, promoting cell survival, and guiding cell fate decisions [187]. Coculture systems can also be designed using microgels, allowing for the encapsulation of multiple cell types within the same microgel to improve paracrine signaling between cell types, which is crucial for recreating functional biomimetic tissue in vitro. Additionally, when serving as a drug screening platform, heterogeneous and homogeneous 3D cell scaffolds exhibit significant differences (Figure 9D) [188], which also suggests that the microenvironment of hydrogel scaffolds has a non-negligible impact on the state of cells. In general, microgel based scaffolds can be mixed with microgels of different sizes, types, and shapes, providing more relevant and instructive results for the cultivation of multicellular systems and the study of cell behavior.

Collectively, microgels function as versatile platforms for both single-cell cultures and multicellular cocultures, while serving as modular units for constructing assembled microporous scaffolds that recapitulate tissue heterogeneity. However, batch-to-batch variability in microgel fabrication compromises experimental reproducibility and impedes translation into standardized products. Relative to conventional biological scaffolds, microgel production and assembly entail greater complexity and cost, limiting scalability and clinical adoption.

4.3 | Tissue Engineering and Regenerative Medicine

The functionality of human tissues relies on the interplay between various cell populations and their interactions to exert their roles. 3D printing enables precise spatial deposition of multicellular systems and biomaterials to construct functional tissues and scaffolds in vitro, representing an indispensable technological platform for tissue engineering and regenerative medicine [189, 190]. Previous studies have demonstrated that microgels

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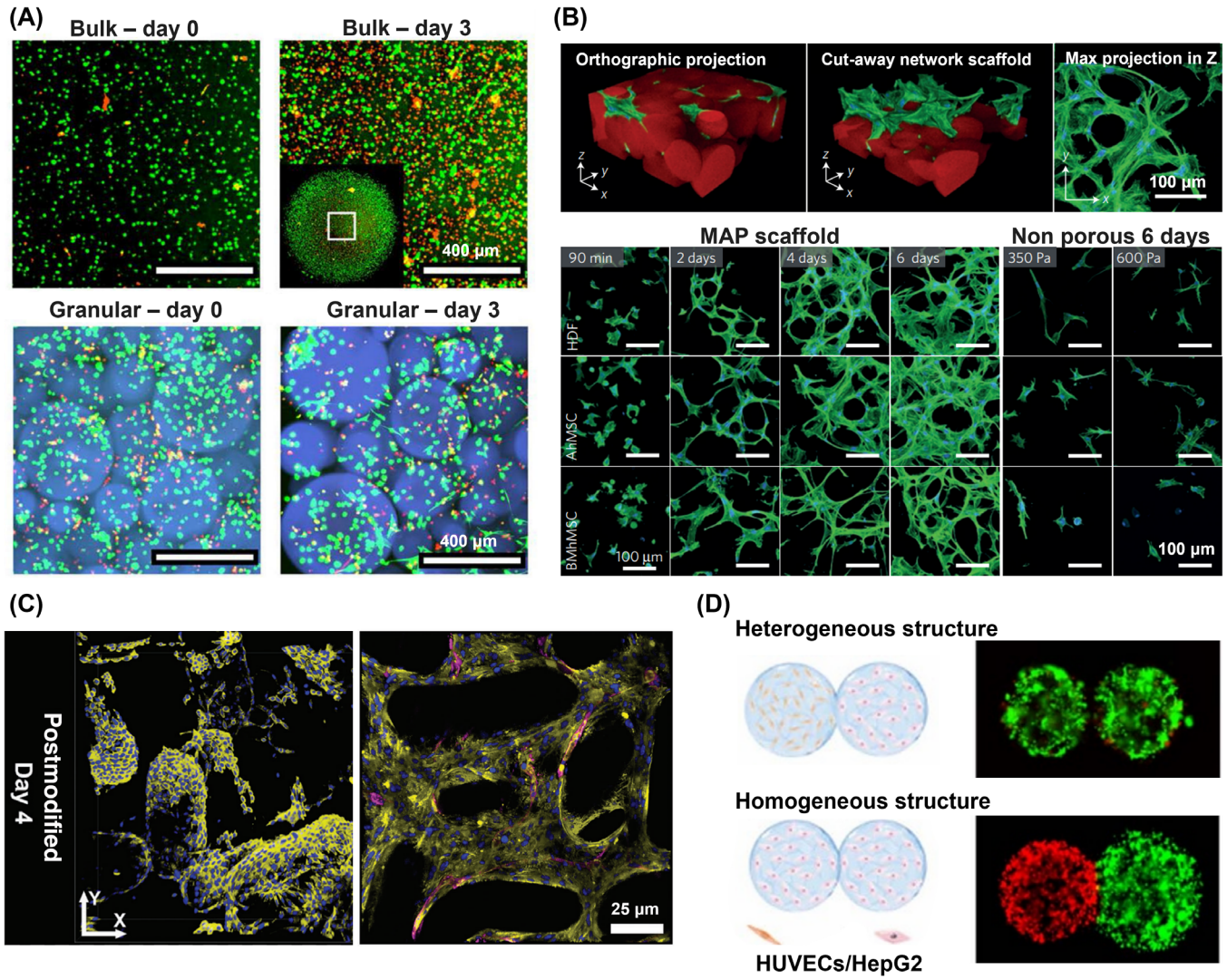


FIGURE 9 | Hydrogel microgel assemblies as 3D cell culture scaffolds. (A) Bulk hydrogel versus microgel annealed porous scaffold encapsulation of cells. In contrast to bulk hydrogels, cells viability in granular scaffolds significantly improved over 3 days [178]. Copyright 2022, Wiley-VCH. (B) MAP scaffolds facilitate 3D cellular network formation and proliferation in vitro. Cells were stained with DAPI (nuclei, blue) and phalloidin (actin, green) [179]. Copyright 2017, Wiley-VCH. (C) 3D fibroblast growth inside interlinked microporous microgel scaffolds [180]. Copyright 2022, Wiley-VCH. (D) Cells encapsulated in microgels can be assembled into homogeneous and heterogeneous structures, which can be used as 3D drug screening models [188]. Copyright 2023, IOP Publishing.

and hydrogel precursors within MB bioink can encapsulate various cell types, leveraging the heterogeneity of composite inks to print heterogeneous tissues and create microenvironments at the microscale [105]. Compared with traditional hydrogel inks, utilizing MB ink to load hepatocytes and endothelial cells for liver tissue printing resulted in enhanced cell proliferation, induced cell reorganization, and promoted vascularization, thereby improving liver function.

The application of microgels in tissue engineering requires precise adaptation to the physiological characteristics and functional demands of the target tissue. This adaptation hinges critically on matching the tissue's mechanical environment, structural features, and regenerative dynamics. For instance, in cartilage repair, microgels engineered with high crosslinking density are imperative to deliver the essential compressive stiffness; this mechanical support is strategically integrated with surface mineralization and the sustained release of osteogenic factors, thereby achieving the dual objectives of structural integrity and osteoinduction [191]. Similarly, addressing the needs of highly metabolically active tissues such as the liver, or vascularized tissues like skin and muscle, demands the utilization of highly porous, granular microgels. These architectures fulfill critical demands for efficient nutrient/waste exchange and facilitate robust cellular infiltration and vascular network formation [179]. Furthermore, within neural tissue engineering, microgels possessing intrinsic directional alignment capabilities are synergistically combined with conductive materials. This integration generates essential anisotropic topographical cues and establishes functional pathways for electrical signal conduction. Supplementing this construct with controlled gradients of neurotrophic factors further orchestrates a conducive microenvironment for guiding targeted axonal elongation [192]. Thus, through the tailored design of microgel systems across these diverse tissue contexts,

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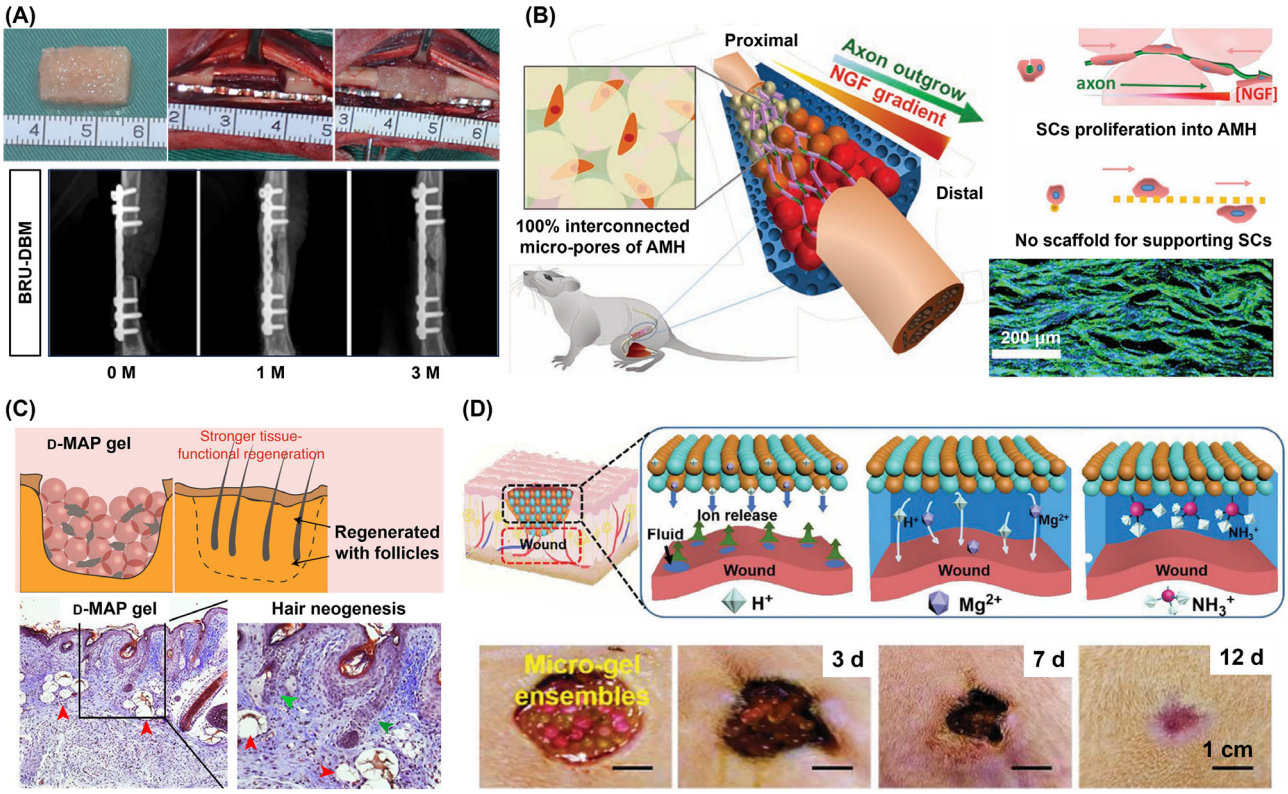


FIGURE 10 | Application of microgel assembly scaffolds in tissue engineering. (A) Repair of large-sized bone defects based on BRU-loaded DBM framework [191]. Copyright 2022, Elsevier. (B) Porous microgel scaffolds with gradient concentrations of load-bearing growth factors can recruit and guide SCs cells to migrate, promote synaptic nerve growth, and the scaffolds can provide structural support for regenerated nerve synapses in the early stage [192]. Copyright 2019, Wiley-VCH. (C) D-MAP hydrogel induces neogenesis of hair follicles in full-thickness skin wounds in B6 mice [86]. Masson's trichrome staining of healed 4 mm full-thickness splinted skin wound on day 18, regenerate de novo hair follicles (green arrowheads), the D-MAP hydrogel remnants are marked with red arrowheads. Copyright 2020, Springer Nature. (D) Microgel assembly can precisely tune the pH value of wound surface and accelerate wound healing [205]. Copyright 2022, Wiley-VCH.

the overarching goals of biomimetic structure and functional regeneration can be advanced.

Researchers are attempting to transition from research-focused bioprinting to clinical bioprinting, but challenges abound. One such challenge is the selection of appropriate bioinks that maintain high cell viability before and after printing, as well as scaffolds that provide a conducive environment for the continuous growth and maturation of cells. Transplantable biomaterials of natural origin, such as decellularized matrix and decalcified bone matrix, can serve as ideal regenerative scaffold materials [193–196]. However, low cell implantation efficiency and poor tissue-induced microenvironment limit their application in large-size tissue regeneration. Microgel assembly porous scaffolds can control the number and size of micropores by adjusting the packing density of the microgels, catering to diverse research and application requirements. When used as acellular scaffolds in vivo, these micropores can enhance the infiltration of recruited endogenous cells and facilitate the inward growth of vasculature, thereby promoting tissue regeneration [85, 197, 198]. In bone regeneration, regenerative treatment of large bone defects is challenging due to the lack of suitable bone regeneration grafts. The demineralized calcium matrix in the form of microgels can be assembled into transplantable modules of arbitrary size by a postassembly strategy (Figure 10A) [191]. This effectively repair bone regeneration in rabbit tibial defects, which provides a new therapeutic strategy for large-area bone regeneration.

Bone tissue is a highly vascularized and dynamic organization, and its structural and functional reconstruction requires precise control over cellular spatial distribution, vascular network formation, and the microenvironment of the ECM. Traditional methods, such as scaffold-based tissue engineering technologies, often fail to precisely control internal structures and cell distribution, limiting their application in constructing complex vascularized bone tissues with precise biomimetic characteristics. The pores between the microgels not only provide sufficient space for cell and blood vessel regeneration, but also provide scaffold support. In one study, researchers used GMSs as a scaffold structure with interconnected macropores that recruit endogenous cells (such as osteogenic and angiogenic cells), utilizing the surrounding microenvironment as a natural bioreactor to promote vascularized bone regeneration and integration with host bone [186]. Spherical microgels are the most extensively studied type of microgel. Recently, microgels of various shapes, including rod-shaped, microfibers, and square microgels, have been developed. For instance, Conrad et al. [199] developed a gelatin-based microribbon that can mimic the shock-absorbing mechanics of cartilage and accelerate the formation of new cartilage. Nonspherical microgels can better guide cell alignment

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in anisotropic tissues [83]. However, the fabrication techniques for nonspherical microgels are relatively limited.

Microporous scaffolds are predominantly fabricated in vitro and subsequently transplanted to a designated site, rendering them unsuitable for injection. Injectable hydrogels have a unique application advantage in complex tissue defects with the ability to adaptively fill the defect site [200, 201]. However, achieving gradient release of active substances in injectable hydrogels is difficult. Microporous annealed particle scaffolds are injectable, in situ crosslinked microporous scaffolds based on microgels [202]. In one study, investigators developed an injectable microgel ink containing graded concentrations of growth factors that accelerated and directed peripheral nerve regeneration. This scaffold was also able to provide scaffolding support for bridging of nerves, with potential translational applications to the clinic (Figure 10B) [192].

Premature degradation of porous scaffolds compromises structural integrity and tissue infiltration, diminishing mechanical support capacity [203]. Conversely, slow degradation impedes tissue regeneration and may promote fibrosis. Achieving equilibrium between material degradation kinetics and tissue remodeling is therefore critical for functional repair outcomes. To modulate degradation rates, crosslinked peptides with engineered chirality have been incorporated into hydrogels. This approach alters material residence time while concomitantly modulating immune responses and follicular regeneration during wound healing (Figure 10C) [86]. Skin wound healing is one of the most complex physiological processes in the human body, and the change of the pH value in the wound environment significantly affects the rate of wound healing [204]. To some extent, the materials themselves can play a role in specific therapies. For instance, researchers have utilized a microgel composite made from two materials to precisely regulate the pH at the surface of chronic wounds to accelerate healing (Figure 10D) [205]. This composite responds to changes in the wound microenvironment at different stages of the healing process, releasing and absorbing H^+ to achieve dynamic pH regulation of the wound.

In vivo, cells are located near blood vessels, which provide nutrients and oxygen to tissues and metabolize waste and carbon dioxide. It is essential for cellular proliferation, structural integrity, and functional homeostasis [206]. Vascular network formation within bioprinted constructs is therefore critical for large-tissue survival [207]. Therefore, developing effective strategies to promote neovascularization and integration is imperative. However, the availability of biomaterials for bioprinting microvascular systems is relatively limited, and significant challenges remain in developing new materials [208]. Recent advances include hollow-fiber printing via aqueous biphasic systems and microfluidics, creating perfusable conduits with 98% postencapsulation cell viability [209]. Based on this research, it can be envisioned that if microgels are used as extrusion inks for microvascular printing, the pores between microgels will be more conducive to cell infiltration and vascular formation. Alternatively, biphasic systems combine sacrificial microgels (porogen) with crosslinked hydrogels (structural support) for integrated vascularization.

The clinical translation of microgel-based biomanufacturing confronts significant hurdles. First, replicating native tissue complexity demands precise orchestration of 3D hierarchical architectures and dynamic biochemical gradients—a capability beyond current microgel assembly techniques. Second, translational progress is hampered by insufficient long-term animal data, scarce clinical validation, and undefined protocols for product storage and distribution. Third, scaling production faces challenges: stability control during manufacturing and efficient scaffold assembly remain poorly understood. Finally, standardized characterization methods for critical properties like pore connectivity and degradation kinetics are notably absent. Overcoming these barriers will require coordinated efforts across materials science, engineering, and clinical disciplines.

5 | Challenge and Outlook

As an advanced hydrogel derivative, microgel systems provide unprecedented functionality through modular design, spatiotemporal controllability, and programmable assembly. These characteristics enable their dual roles as cell/drug delivery vector. In 3D bioprinting, where conventional bioinks struggle to balance printability with biofunctionality, microgel-based bioinks present a promising solution.

While microgel-based bioinks demonstrate moderate printability in extrusion-based bioprinting systems, challenges such as nozzle clogging, printing instability, and compromised long-term cell compatibility persist. These issues arise from the inherent conflict between the discrete nature of microgels and the continuous requirements of biological processes. In extrusion bioprinting, nozzle clogging results from the entrapment or interlocking of large microgel particles and their adhesion to the inner nozzle walls [93]. Furthermore, extruded microgel inks exhibit inferior adaptability to adjacent structures compared with continuous hydrogel inks, leading to inadequate interlayer bonding and reduced structural stability. The overall structural integrity, relying on physical or chemical crosslinking between microgels, remains insufficient, hindering their application in mechanically demanding biological contexts like bone repair [210]. Batch-to-batch variations in microgel quality can induce heterogeneous degradation rates among individual microgels, potentially triggering localized structural failure within the scaffold. What is more, the bioinertness of material surfaces and residual cytotoxic molecules further undermine cell viability [211]. Addressing these challenges requires a multidisciplinary strategy, spanning from the development of sustainable microgel fabrication to novel paradigms in bioprinting. For instance, tuning rheological properties—such as through xanthan gum incorporation—could optimize print fidelity by balancing shear-thinning behavior. Alternatively, advanced techniques like in situ volumetric bioprinting (VBP) may enable high-resolution fabrication of complex architectures, as detailed in later sections. In Figure 11, we have presented an outlook on microgels and their future development prospects in biomanufacturing.

5.1 | Emerging 3D Bioprinting Platforms Enabling Next-Generation Microgel Production

3D printing technology enables precise spatial control of cell-laden bioactive materials, facilitating fabrication of complex

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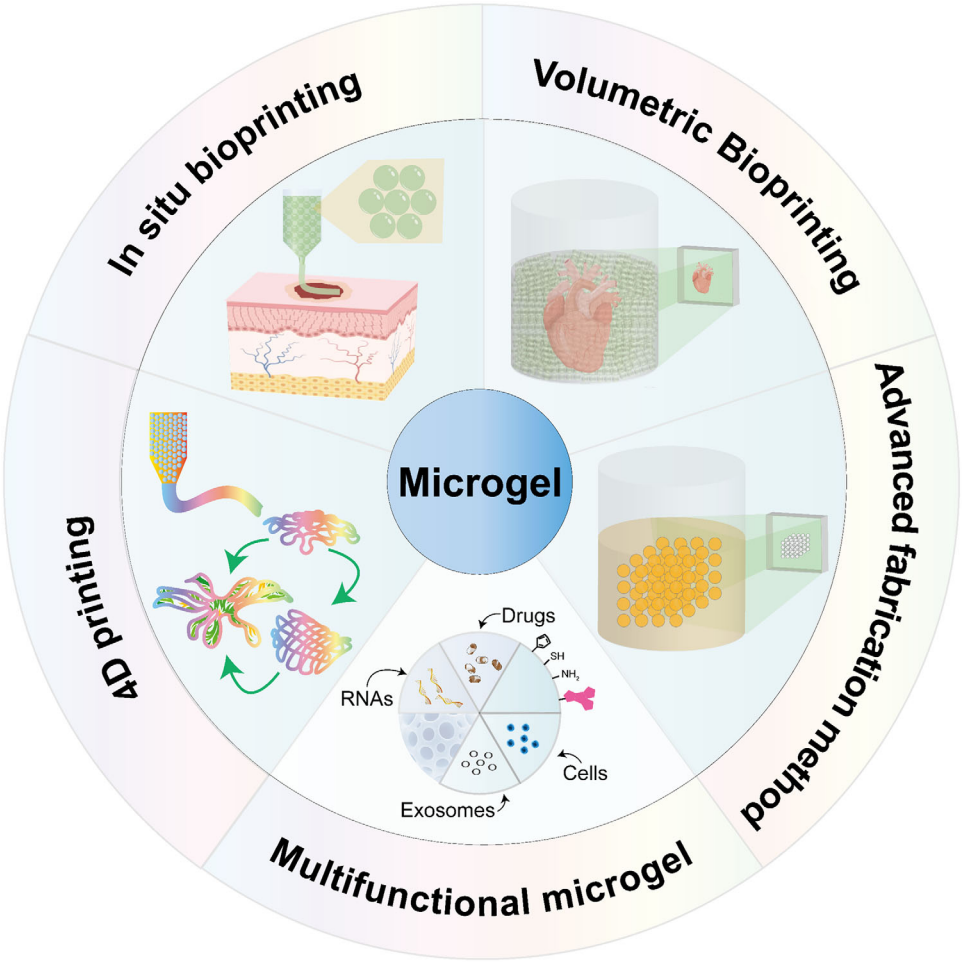


FIGURE 11 | Outlook of microgels.

architectures. Recent advancements in DLP and VBP have achieved micrometer-scale resolution, establishing a theoretical foundation for 3D-printed microgel fabrication. For instance, researchers have successfully utilized the DLP printing technology to successfully print stem cell-carrying microgels [77]. Typically, printing rate is inversely proportional to printing resolution. Continuous liquid interface production is a printing technology based on single-digit micron resolution [212]. By introducing an oxygen-permeable window to achieve a continuous liquid interface, its printing speed is increased by 25–100 times compared with traditional additive manufacturing [213]. It has broad application prospects for efficient and precise biofabrication and promoting personalized medicine [214, 215].

Volumetric printing, also termed volumetric additive manufacturing, is an emerging printing technique. Its principle involves projecting multiangled 2D light patterns into a rotating ink reservoir containing cell-laden hydrogel, enabling rapid in situ formation of complex 3D structures [216, 217]. However, the technique is limited by light scattering and cumulative dose inaccuracies. High cell density within the bioink significantly compromises printing precision due to exacerbated light scattering. In 2020, Regehly et al. [218] introduced xolography technology. This method utilizes a two-color light intersection to achieve localized dose control, only polymerizing the material at the intersection of the light sheet and projection pattern. This innovation substantially improves printing resolution (up to approximately 25 μm) [219]. This technique avoids ink disturbance, layer-by-layer deposition, and the use of nozzles, thereby removing mechanical stresses that could be harmful to cells. This makes it particularly suitable for cell-laden printing, such as organoid printing [125]. Furthermore, from the perspective of printing microgel aggregates, traditional microgel-based printing methods require excessive consideration of the ink's rheological properties to meet printing demands. In contrast, volumetric printing technology, leveraging its in situ printing advantage, minimizes the requirements for the ink's physicochemical properties, thereby offering greater flexibility in ink composition. As a result, VBP is poised to become one of the preferred technologies for printing microgel aggregates.

5.2 | Multimaterial Multicellular Biomanufacturing

The construction of multimaterial and multiscale architectures represents a pivotal strategy for achieving complex biological structures and functionalities in biomanufacturing. Multimaterial multicellular biomanufacturing enables simulation of native tissue heterogeneity across hierarchical scales. However, different types of cells have specific environmental requirements, including the biocompatibility of scaffold materials, mechanical

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strength, and degradation rates [220]. Designing materials that can accommodate various cell types remains a major challenge in tissue engineering. Microgels, as precrosslinked microunits, can be functionally modified through various postmodification strategies to meet specific needs (such as tissue adhesion or antiadhesion effects, targeting, etc.). Microgel-based systems, leveraging their multifunctionality and combinatorial bioink formulations, permit ordered assembly into complex structures with well-defined physicochemical properties. This capability shows promise for replicating the biological gradient architectures inherent to native tissues.

Conventional hydrogel scaffolds face inherent limitations as their nanoporous architectures impede functional tissue formation. In contrast, macroporous hydrogel scaffolds enhance mass transport efficiency, demonstrating significant potential for biomedical applications [221]. Microgel-assembled scaffolds emerge as a novel strategy for macroporous scaffold fabrication, exhibiting marked advantages in promoting damaged tissue regeneration [179, 221].

5.3 | Integrating Multifunctional Microgels with Advanced Bioprinting Methods

Given the multifunctionality and adaptability of microgels, their integration with other biomanufacturing technologies to construct complex functional structures may potentially reduce the disparity between engineered and natural tissues. In situ bioprinting enables the precise deposition of bioink directly onto pathological sites. Combining with customizable microgel-based bioinks offers transformative potential for fabricating functional porous scaffolds at lesion sites. Furthermore, if the microgel is designed as a porous microgel and combined with the microgel porous scaffold to form a multilevel porous structure, it will be very attractive for applications that require the construction of microvascular networks [4, 222]. Such multiscale porous systems simultaneously permit microvascular ingrowth while providing mechanical support for neovascularization, though this requires further investigation.

4D printing combines "smart materials" with 3D bioprinting technology, enabling the printed structure to undergo structural changes over time [223–226]. The constructs are able to realize changes in shape, function, and so on over time in response to external stimuli. Microgels are also an excellent bioink that can be mixed on demand into multiresponsive composites, and the combination of the two opens up new possibilities for the design of complex engineered tissues as well as personalized engineered tissues.

However, the interaction between cells and scaffolds, dynamic regulation of the microenvironment, balance of mechanical properties, demand for biological functionalization, as well as the manufacturing precision and reproducibility of 3D printing, all add to the difficulty of biofabrication. Overcoming these challenges to achieve true tissue engineering and regenerative medicine is still a long way off. The integration of multifunctional microgels with multimaterials and biomanufacturing technology will undoubtedly further advance the development of tissue engineering and regenerative medicine, enabling the printing of more complex tissues and organs.

Microgels still encounter multifaceted challenges on their path to clinical application and industrialization. For instance, large-scale production is hampered by batch-to-batch quality variations and the fabrication efficiency of microgel biomanufacturing. Bottlenecks exist in achieving optimal vascularization and mechanical property matching, and internationally standardized quality evaluation systems are lacking. Overall, commercializing microgel biomanufacturing requires surmounting the triple hurdles of regulatory complexity, the risk of clinical failure, and ensuring manufacturing consistency.

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Conflicts of Interest

All authors declare no conflicts of interest.

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