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REVIEW

The Design, Fabrication and Miniaturization of Polymeric Hydrogels for Therapeutic Actions

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ABSTRACT: Polymeric hydrogels are three-dimensional hydrophilic macromolecular networks capable of retaining varying amounts of water, similar to the extracellular matrix (ECM). To effectively translate these materials into therapeutic actions, it is of importance to control their molecular design, structural architecture, and physical dimensions, ensuring that these factors are strictly optimized to meet the demands of therapeutic applications. Existing reviews mainly focus on specific hydrogel aspects, but there is a gap in translating hydrogel miniaturization into therapeutic potential. This review highlights developments in hydrogel miniaturization, focusing on microfluidic strategies for precise microgel control. Miniaturized hydrogels improve cell-material interactions, making them ideal for targeted drug delivery and regenerative medicine. By connecting these multiscale design and fabrication strategies with therapeutic performance, this review provides a more comprehensive framework for understanding how polymeric hydrogels can be engineered for biomedical applications. It also discusses challenges in the clinical translation of functionalized hydrogel systems and their future potential.

KEYWORDS: Polymeric hydrogels; biomaterials; fabrication methods; miniaturization; therapeutic actions; microgels; microfluidics; drug delivery systems

1 Introduction

The development of clinically relevant biomaterials has been primarily driven by the needs of tissue engineering, regenerative medicine, and drug delivery [1]. Polymeric hydrogels are three-dimensional hydrophilic macromolecular networks capable of retaining substantial amounts of water [2]. They have gained increasing attention in clinically relevant biomaterials research for a broad range of biomedical applications [3]. The structural and functional properties of natural ECM can be emulated in hydrogels by tailoring their composition and architecture through material science and bioengineering [4]. Additionally, the semipermeable nature of hydrogels allows bidirectional transport of nutrients and metabolites [5]. This bidirectional exchange is essential for sustaining cell viability and enabling long-term biochemical communication within hydrogel constructs [6].

Despite these advantages, limited flexibility of traditional hydrogels constrains their application in complex therapeutic environments and dynamic release-based therapeutic strategies. This review addresses this limitation by focusing on recent innovations in hydrogel miniaturization and fabrication techniques.

As shown in Fig. 1, the number of hydrogel-related publications has increased exponentially in recent years, highlighting the growing research interest and promising future of this field. However, current fabrication and modification methods have advanced to promote the development of polymeric hydrogels [7]. For instance, various responsive hydrogels have been developed to react to specific physiology and pathological stimuli to meet the complex requirements of specific diseases and clinical demands [8]. By tailoring their chemical components, crosslinking strategies, and physical structures, developed hydrogels are equipped with versatile properties that allow them to directly regulate cellular behaviors, elicit specific cell phenotypes, and achieve controlled release and disease-specific targeting [4]. With the rapid development of biomedical engineering, driven by cell therapy, immunotherapy, and regenerative medicine, the application of hydrogels could be further expanded [9].

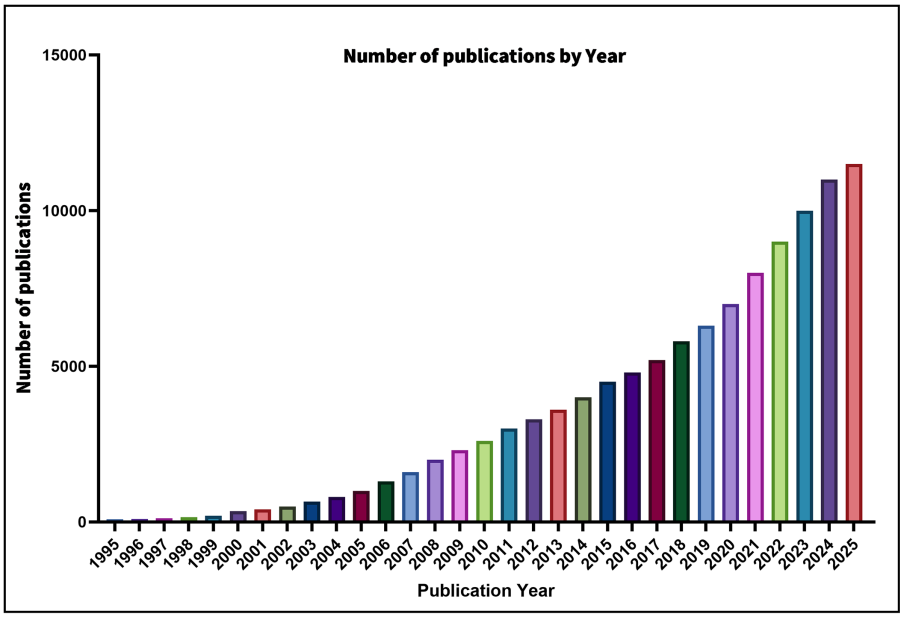

Figure 1: Trends and distribution of hydrogel-related publications from 1995 to 2025 [10].

With these considerations in mind, this review summarizes the major classification of hydrogels and their crosslinking mechanisms, and then highlights chemical and physical modification strategies that tune mechanical properties and bioactivity. We provide a novel perspective on advanced fabrication and miniaturization approaches, focusing on microfluidic strategies for microscale architecture control [11]. These strategies allow for the precise generation of uniform microgels with well-defined sizes and morphologies. As microscale hydrogel platforms, microgels improve control over interactions between cells and materials and are compatible with minimally invasive delivery [12]. Furthermore, this review highlights how functionalized and tailored hydrogel systems can be translated into effective therapeutic actions. We highlight the advantages of hydrogels over traditional materials, particularly their enhanced ability to control cellular interactions and support targeted therapeutic approaches. Finally, we conclude by outlining emerging developments that utilize advanced biofabrication technologies with hydrogels to highlight their prospective research directions and challenges, aiming to provide a comprehensive roadmap for polymeric hydrogels for therapeutic applications.

2 Design of Hydrogels

This chapter summarizes key design considerations for hydrogels, including classification, fabrication, and post-fabrication modification. Common classification criteria is introduced, and how crosslinking strategies and subsequent modifications modulate mechanical behavior, mass transport, and bioactivity, thereby shaping the performance of hydrogel-based human organ models is discussed (Fig. 2).

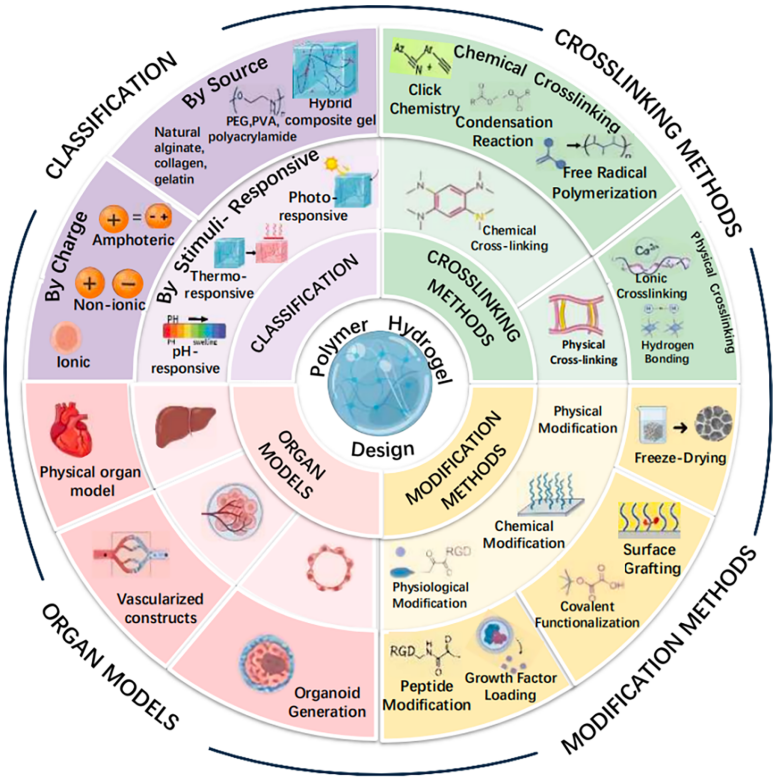

Figure 2: Schematic summary of hydrogel classification, crosslinking methods, modification strategies, and representative organ model applications.

2.1 Types of Hydrogels

Hydrogels are three-dimensional networks of crosslinked hydrophilic polymers. They typically exhibit high water retention and favorable biocompatibility [4]. Owing to their tunable composition and network architecture, hydrogels can display a wide range of physical and chemical properties. Accordingly, they can be classified using criteria such as precursor origin, electric charge, stimulus responsiveness, and network structure [13].

2.1.1 Source of the Precursor

Based on precursor origin, hydrogels are commonly categorized as natural, synthetic, or hybrid systems [14]. Natural hydrogels are derived from biopolymers, including polysaccharides and plant gums such as guar gum and xanthan gum [15–19]. Synthetic hydrogels are prepared from well-defined polymers such as polyethylene glycol (PEG) [20] and poly(vinyl alcohol) (PVA) [21]. Synthetic hydrogels can also incorporate biodegradable segments such as poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) [22,23]. Hybrid systems combine natural and synthetic components to balance bioactivity with mechanical tunability [24]. Additionally, functional additives like nanoparticles can be incorporated to

introduce therapeutic behaviors [25]. Precursor selection governs the balance between bio-instructive capacity and mechanical stability. This balance allows hybrid hydrogels to effectively sustain long-term tissue viability.

2.1.2 Electric Charge

Hydrogels are categorized as ionic, nonionic, or ampholytic based on charge distribution in crosslinked networks [2]. Charge strongly influences swelling behavior, protein adsorption, and interactions with cells and biomolecules. Ionic hydrogels are further divided into cationic and anionic types depending on their charged moieties [26]. Cationic hydrogels are often pH-responsive and bind anionic molecules through electrostatic interactions [27]. This feature can facilitate Small interfering RNA (siRNA) encapsulation and controlled release for non-viral gene therapy and cancer targeting [28,29]. Anionic and ampholytic systems exhibit distinct binding behaviors toward proteins and growth factors. Conversely, nonionic hydrogels are selected to minimize nonspecific binding due to their neutral nature [30,31]. Beyond basic classification, manipulating network charge is a powerful tool for controlling molecular diffusion and cell-matrix interactions. This facilitates the targeted retention of therapeutic agents and regulation of local osmotic pressures.

2.1.3 Stimulus Responsiveness

Stimuli-responsive hydrogels are categorized by triggers such as temperature, pH, light, electric fields, or biomolecules [32]. These materials are also grouped into single-stimulus or multi-stimuli-responsive systems [33]. Single-stimulus hydrogels react to one specific environmental trigger through predictable physical or chemical changes [34]. Thermoresponsive hydrogels undergo phase transitions due to temperature-induced solubility changes. For Lower Critical Solution Temperature (LCST) polymers, rising temperatures promote polymer-polymer associations and gel formation [35]. pH-sensitive hydrogels swell or deswell based on the ionization of acidic or basic functional groups. Anionic networks expand at high pH, while cationic hydrogels swell under acidic conditions. Photo-responsive hydrogels utilize chromophores to transform light signals into chemical responses [36]. Light-induced isomerization or bond cleavage modulates the functional properties of the network [37]. Electro-responsive hydrogels undergo precise expansion or contraction under external electric fields. These materials are primarily engineered for biomimetic artificial muscles and soft actuation [38]. Magneto-responsive hydrogels contain magnetic nanoparticles that align or heat under magnetic fields [39,40]. These stimuli trigger reversible deformation, enabling applications in targeted delivery [41]. While single-stimulus hydrogels offer precision, complex biological environments often require more sophisticated control [42]. Multi-stimuli hydrogels integrate two or more inputs to achieve synergistic and programmable responses [43]. Multi-stimuli hydrogels respond to multiple external factors like pH, temperature, and magnetic fields simultaneously or sequentially. These systems offer enhanced versatility and higher specificity compared to single-stimulus hydrogels. Precise control over swelling and drug release reduces unintended responses in complex environments [32]. Synergistic effects enable advanced behaviors like directional motion and chemo-magnetic hyperthermia therapy. Their adaptability makes them invaluable for soft robotics, tissue engineering, and smart sensors [44]. Such systems offer high specificity and stability in complex biomedical environments [45]. These advanced properties facilitate sophisticated applications in controlled release and localized actuation [32]. Integrating stimuli-responsiveness transforms hydrogel networks from static supports into dynamic, smart platforms. Such adaptive systems provide high specificity for targeted drug delivery and localized mechanical actuation.

2.1.4 Polymer Architecture and Assembly

Hydrogels are categorized by their polymer system design, including blends, block copolymers, and polyelectrolyte complexes [2]. Polymer blends combine different macromolecules to enhance mechanical performance and cell encapsulation [46]. For instance, collagen-hyaluronic acid blends provide a biomimetic environment for cartilage repair [47]. Block copolymer hydrogels have covalently linked segments and can self-assemble for drug delivery or antimicrobial use [48,49]. Polyelectrolyte complex hydrogels form by electrostatic attraction and often show self-healing, such as hyaluronic acid-chitosan systems [50,51]. Precise control over polymer assembly facilitates the creation of multiscale hydrogel structures. Such architectures exhibit self-healing and durability in bio-manufacturing applications.

2.2 Crosslinking Methods

Crosslinking scheme governs gelation rate, network stability, mechanical strength, and mass transport properties, and is therefore central to biomedical hydrogel design [52]. This section compares physical and chemical crosslinking in terms of mechanism, controllability, and typical applications.

2.2.1 Chemical Crosslinking

Chemical crosslinking forms hydrogel networks through covalent bonds, providing high stability and tunable mechanical properties [53]. Common chemical crosslinking approaches include free-radical polymerization and coupling reactions such as click chemistry. Representative reactions include Diels-Alder cycloaddition and Michael-type addition [54]. Other routes include radiation crosslinking, graft polymerization, and condensation reactions such as Schiff-base formation [55]. Enzyme-mediated strategies, including transglutaminase and peroxidase-catalyzed gelation, enable mild and cell-friendly *in situ* crosslinking. Photo-initiated reactions and click chemistry can further provide precise spatiotemporal control for biofabrication [54]. Notably, crosslinking efficiency must be balanced against biocompatibility, because residual initiators or reaction byproducts may induce cytotoxicity [56].

2.2.2 Physical Crosslinking

Physical hydrogels rely on reversible non-covalent junctions instead of covalent bonds [57]. These networks exhibit dynamic rearrangement, injectability, and rapid self-recovery [58]. Physical junctions include ionic and electrostatic interactions [54,55,59], hydrogen bonding [54,55], and hydrophobic interactions [60,61]. Host-guest binding and crystallization can also form networks [54,60]. Protein-based gels rely on multivalent protein interactions and affinity domains [62]. Physical gels form under mild conditions with tunable viscoelasticity. However, pH, temperature, ionic strength, and solutes can reduce stability [63]. However, physical crosslinking methods often suffer from limited mechanical strength and stability due to the reversible nature of the intermolecular interactions, making them less robust compared to chemically crosslinked hydrogels [54]. Chemical crosslinking is often introduced to enhance long-term integrity [64].

2.3 Hydrogel Modification Strategies

Post-fabrication modifications enable tuning of mechanics, bioactivity, and compatibility without changing the initial gelation process. This section classifies these strategies into physical, chemical, and biological approaches.

2.3.1 Chemical Modification

Chemical modification introduces new functionalities to hydrogels through surface functionalization or bulk modification [65]. Surface functionalization typically employs grafting techniques to control interfaces. Common methods include graft-to, photo-immobilization, and graft-from approaches. Representative techniques include silanization [66], Michael addition, and thiol-ene photopolymerization [67]. Vapor-based polymerization and atom transfer radical polymerization (ATRP) facilitate precise polymer layer growth [68]. Interface engineering can also incorporate responsive coatings via interfacial polymerization [69]. Bulk modification incorporates reactive groups through click reactions or quaternization [70]. Other methods include epoxy ring-opening [71], or silylation [72] for subsequent functionalization steps.

2.3.2 Physical Modification

Physical modification employs non-covalent methods to adjust microstructure and surface properties without introducing new covalent bonds [73]. This approach modifies porosity and hydration while preserving the primary chemical backbone. Freeze drying creates interconnected pores through ice templating and sublimation. These porous architectures significantly alter molecular diffusion pathways [74]. Air plasma treatment increases surface energy and introduces polar groups to improve hydrophilicity. This technique controls protein adsorption without altering bulk mechanical properties [75]. Physical encapsulation preserves and releases therapeutic cargos under mild conditions. Such methods protect sensitive cells or proteins while enabling specific biological functions [76].

2.3.3 Biological Modification

Biological modification introduces bioinstruction to regulate inflammation and support tissue repair [77]. Immunomodulatory designs mitigate oxidative stress through reactive oxygen species (ROS)-scavenging nanoparticles or ROS-labile linkers. These linkers also facilitate matrix remodeling and trigger controlled drug release in oxidative microenvironments [78]. Wound healing applications rely on surface biofunctionalization to enhance antimicrobial activity and re-epithelialization [79]. Neural repair utilizes peptide-based ECM mimics to present neuroactive cues. Such scaffolds can be formed via self-assembly or entrapment to guide neural regrowth [80]. These biological cues are typically incorporated via the chemical modification techniques described earlier. The timing and mode of cue presentation strongly influence therapeutic outcomes and physiological mimicry.

2.4 Hydrogel-Based Human Organ Models

This chapter explores hydrogels as core materials for constructing complex human organ models. These systems either replicate vascularized tissue functions or mimic the physical characteristics of human organs. Furthermore, hydrogels provide specialized microenvironments for organoid generation, supporting cell differentiation and self-organization. By tuning biochemical and mechanical cues, these scaffolds facilitate the development of functional organ-level models. Such biomimetic platforms bridge the gap between simplified 2D cultures and complex *in vivo* physiology. To organize these applications, we classify hydrogel-based models into three levels. The first level is physical organ models that reproduce form and mechanics. The second level is vascularized tissue constructs that enable mass transport and physiological function. The third level is organoid-supportive matrices that guide development and self-organization.

2.4.1 Physical Organ Models

At the physical-mimicry level, advanced hydrogels enable 3D printing of organ phantoms. These models closely mimic the external anatomy of human organs. These biomimetic structures replicate the mechanical properties of organs such as the brain, heart, and lungs [81]. The tunable mechanical and tactile properties of hydrogels, such as stiffness and elasticity, are crucial for surgical training and anatomical studies [82]. These platforms also help understand drug diffusion and mechanical strain in hollow organs, such as the stomach [83].

2.4.2 Vascularized Tissue Engineering

Changing from physical form to physiological function, vascularization is a key challenge. Hydrogels serve as more than just a support, they bridge the gap between simplified *in vitro* models and the physiological complexity of living organs [84]. Hydrogels act as ECM-mimetic matrices that integrate structure and bioactive cues. Key variables include channel permeability and degradability. As a tunable biomaterial platform, hydrogels facilitate the fabrication of biomimetic constructs that recapitulate hepatic units and integrated multi-organ systems [85]. For example, 3D liver organoids and vascularized pancreatic transplant models provide stable platforms for investigating organ failure and disease progression [86]. Beyond traditional laboratory models, advanced manufacturing enables the generation of functional tissues such as vascularized kidney constructs and gastric cancer models [87,88]. These high-fidelity models are crucial for studying tumor growth and response to new treatments under physiologically relevant conditions.

2.4.3 Hydrogels for Organoid Generation and Culture

As *in vitro* models that mimic the structure and function of human tissues, organoids are highly dependent on the biological interaction environment provided by hydrogels for their generation and culture [89]. Hydrogels not only provide physical support for stem cells, but also deeply regulate the self-organizing behavior of stem cells by precisely simulating the biophysical and chemical induction signals of the native ECM [90]. In regulating stem cell properties, the mechanical properties of hydrogels such as stiffness and viscoelasticity determine the differentiation fate of stem cells through mechanotransduction pathways such as the Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) signaling pathway. For example, Cruz-Acuña et al. used a synthetic four-armed poly(ethylene glycol) macromer that has maleimide groups at each terminus (PEG-4MAL) hydrogel to optimize matrix stiffness by adjusting the crosslinking density, thereby inducing efficient differentiation of pluripotent stem cells and their self-assembly into intestinal organoids without animal-derived components. The advantage of this synthetic platform is that it can independently regulate the density and mechanical strength of biochemical ligands such as RGD peptides, thereby precisely guiding cell adhesion and polarization [91]. Furthermore, recent studies have shown that matrix stiffness can also dominate cellular gene expression by regulating the subcellular localization of histone deacetylase 3 (HDAC3). Increased basal stiffness enhances cell contractility and triggers anucleoplasmic redistribution of key epigenetic regulators such as HDAC3. This repositioning effectively relieves the inhibition of histone acetylation, leading to increased-levels of histone acetylation in the nucleus, thereby regulating chromatin state and promoting thetranscription of related genes [92]. In the regulation and optimization of intercellular communication, material design directly affects the efficiency of molecular transport within niches and the physical contact between cells. Vallmajo-Martin et al. developed a transglutaminase (TG)-PEG/hyaluronic acid (HA) hybrid system for *in vivo* bone marrow organoid generation. This hydrogel not only optimizes mechanical strength but also significantly improves the diffusion characteristics of nutrients, growth factors, and cell-secreted proteins, thereby enhancing paracrine signal exchange between hematopoietic stem cells and stromal cells. Furthermore, by

introducing matrix metalloproteinase (MMP)-sensitive sites, the hydrogel can be actively degraded and remodeled by cells, enabling cells to establish direct physical connections through pseudopodia extension such us cadherin-mediated cell contact, which is crucial for maintaining homeostasis and synchronous differentiation within organoids [93].

3 Fabrication Methods of Macroscopic Hydrogels

This section summarizes the fabrication of polymeric hydrogels from prepolymer solutions into functional constructs with defined geometries and hierarchical architectures (Fig. 3). Fabrication methods are categorized into electrospinning, template-assisted molding, porogen-based pore formation, and additive manufacturing. Advanced manufacturing, including extrusion, inkjet, and lithography-based 3D printing, enables the construction of complex three-dimensional geometries. These routes provide the fabrication precision required for biomimetic organ modeling and functional tissue engineering.

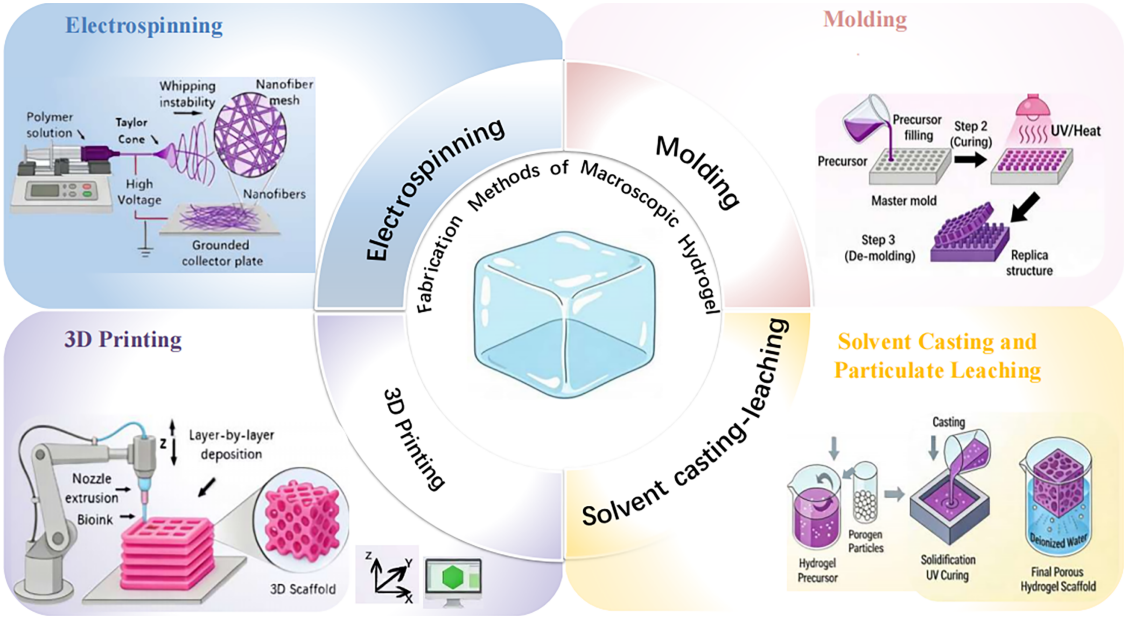

Figure 3: Overview of macroscopic hydrogel fabrication from prepolymer solutions. Highlighting electrospinning, template-assisted molding, porogen-based pore formation by solvent casting-particulate leaching, and manufacturing by 3D printing.

3.1 Electrospinning

Electrospinning is a versatile technique for fabricating fibers with tunable secondary structures [94]. Under a high-voltage electric field, polymer solutions or melts are stretched into nanometer- to micrometer-scale fibers, which are then deposited as nonwoven mats [95]. By adjusting solution properties and processing parameters, electrospun architectures can be precisely controlled across multiple length scales, from one-dimensional fibers to two-dimensional membranes and three-dimensional scaffolds. Electrospinning has been widely explored for biomedical and engineering applications, including tissue engineering, sensors, drug delivery, and wound dressings [96].

3.2 Molding

The molding method for fabricating hydrogels of specific shapes involves the following key steps. First, a solution containing hydrogel precursors is poured into a mold, which can be made of materials such as glass, polydimethylsiloxane (PDMS), polytetrafluoroethylene (PTFE), plastic, or wax [97]. The solution is then kept stationary or centrifuged to remove entrapped air bubbles, preventing structural defects in the final hydrogel. After crosslinking, the molded hydrogel is carefully demolded, resulting in a hydrogel with the desired geometry. This approach has been applied in biomedical therapy. For example, Chen et al. engineered a biocompatible microneedle patch using gelatin methacryloyl and loaded with a transforming growth factor-beta (TGF-β)-specific inhibitor to treat excessive cardiac fibrosis after myocardial infarction [98].

3.3 Solvent Casting-Leaching and Gas Foaming-Leaching

The solvent casting-leaching method uses particulate salt, which is soluble in water but insoluble in organic solvents, with specific dimensions. With the evaporation of the solvent, these salt particles are trapped in the hydrogels. After the dissolution of the salt paticles in an aqueous media, hydrogels with controlled pore dimensions are obtained [99]. Solvent casting-leaching has the advantages of simple equipment, easy control of pore size and porosity, and good repeatability [100]. However, residual organic solvents may be toxic to cells and make it difficult to fabricate thick-walled three-dimensional scaffolds [101]. In the gas foaming-leaching technique, the salt used decomposes to produce gases, whereby a porous matrix is created. Gas foaming-leaching avoids the use of organic solvents and is more suitable for the introduction of bioactive molecules. However, it is more difficult to control the uniformity of foaming [102]. Their main application fields are tissue engineering scaffolds [103], controlled drug delivery carriers, and filtration membranes.

3.4 3D Printing

3D printing, also known as additive manufacturing, is a layer-by-layer fabrication used to create three-dimensional objects. The unique rheological properties of hydrogels enable precise extrusion or solidification into shapes, while their excellent biocompatibility, tunable mechanical properties, and functional features make the printed structures highly suitable for applications in fields such as biomedicine [104]. However, due to the sensitivity of hydrogels to harsh conditions, not all 3D printing methods are suitable. Common methods for 3D printing of hydrogels include extrusion-based printing, lithography-based printing, and inkjet-based printing [99].

Direct ink writing (DIW) is one of the most common extrusion-based printing techniques, which is driven by air pressure, pistons, and screws. Hydrogel precursor solutions with specific rheological properties are extruded through a micro-nozzle to form continuous filaments, which are deposited layer by layer and then solidified through immediate or subsequent crosslinking reactions, ultimately forming a 3D hydrogel structure [105]. DIW has advantages such as simple equipment and low cost, but the maximum printing resolution is only 100 μm, and the printing speed is slow due to the requirement for layer-by-layer deposition [106]. In addition to direct ink writing, extrusion-based printing methods also include fused deposition modeling (FDM), electrohydrodynamic (EHD) printing, and binder printing [107].

The principle of inkjet printing involves using miniaturized nozzles to deposit a hydrogel precursor solution in controlled droplets onto designated locations, thereby constructing three-dimensional hydrogel structures with complex geometries and specific functions layer by layer [108]. According to the droplet generation mechanism, inkjet-based printing can be classified into thermal bubble inkjet printing, piezoelectric inkjet printing, pneumatic microvalve jetting, and acoustic jet printing [109]. Thermal bubble-based methods are primarily used in non-biological applications, where biological activity is not required, such

as flexible electronics and patterned templates. In contrast, piezoelectric, pneumatic, and acoustic inkjet printing methods are all applied in the biomanufacturing field, focusing respectively on high-precision cell printing, high-density tissue construction, and the deposition of advanced sensitive materials [110].

Lithography-based 3D printing including stereolithography, two-photon polymerization, digital light processing (DLP) and volumetric additive manufacturing (VAM) have become promising techniques that rely on the spatial crosslinking of photosensitive hydrogels. Stereolithography and two-photon polymerization use continuous or pulsed laser scanning to crosslink hydrogel precursor solution into 3D object [111]. Although stereolithography and two-photon polymerization offer extremely high resolutions of up to 100 nm [112], they have printing speeds measured in hours and are limited by the working distance of the objective lens, making it difficult to print large-scale structures [113]. Digital light processing technology projects two-dimensional light patterns using digital micromirror devices to solidify hydrogel precursor solutions layer by layer. DLP has micron-level resolution and minute-level printing speed. One limitation of digital light processing is the staircase effect: visible step-like patterns appear on the surface of printed objects [111]. Continuous liquid interface production (CLIP) is an improved digital light processing technology designed to address the staircase effect [114]. CLIP projects light patterns while the build platform rises, relying on oxygen inhibition to create a "dead zone", forming a thin layer of uncrosslinked hydrogel on the surface of the print, enabling continuous printing. Although CLIP allows manufacturing speeds exceeding 50 cm per hour, the requirement for dead zones limits this method to hydrogels that are sensitive to oxygen [111]. Volumetric additive manufacturing accumulates light dose in the hydrogel precursor solution through multi-angle light projection, achieving simultaneous solidification of the entire object [115]. VAM allows for an extremely fast printing speed of up to seconds, but the resolution is relatively low, with a maximum of only 200 μm.

4D printing, an evolution of 3D printing, introduces the dimension of time to the fabrication process [116], wherein printed objects can undergo transformations in shape, properties, or functionality in response to external stimuli such as temperature, moisture, or light. This transformative capability is enabled by incorporating smart materials, such as shape memory polymers and hydrogels, that can change their state or configuration post-fabrication [106]. The integration of 4D printing with bioprinting offers significant potential for developing adaptive, responsive biological systems that can react to physiological changes within the body. For instance, bioresponsive hydrogels could be designed to release therapeutic agents in response to specific biological signals, providing a more controlled and effective treatment strategy [117].

4 Miniaturization of Polymeric Hydrogels

This section reviews strategies to convert bulk hydrogels into microgels (1–1000 μm) to enhance mass transport and cell-matrix interactions for regenerative medicine (Fig. 4). Based on the reviewed work, miniaturization methods include emulsification-based miniaturization, microfluidic techniques for microgel generation, lithography-based microgel patterning, and electrospraying. Other approaches include centrifugation-based miniaturization, gas-shearing methods, 3D bioprinting-enabled microgel fabrication, and mechanical fragmentation.

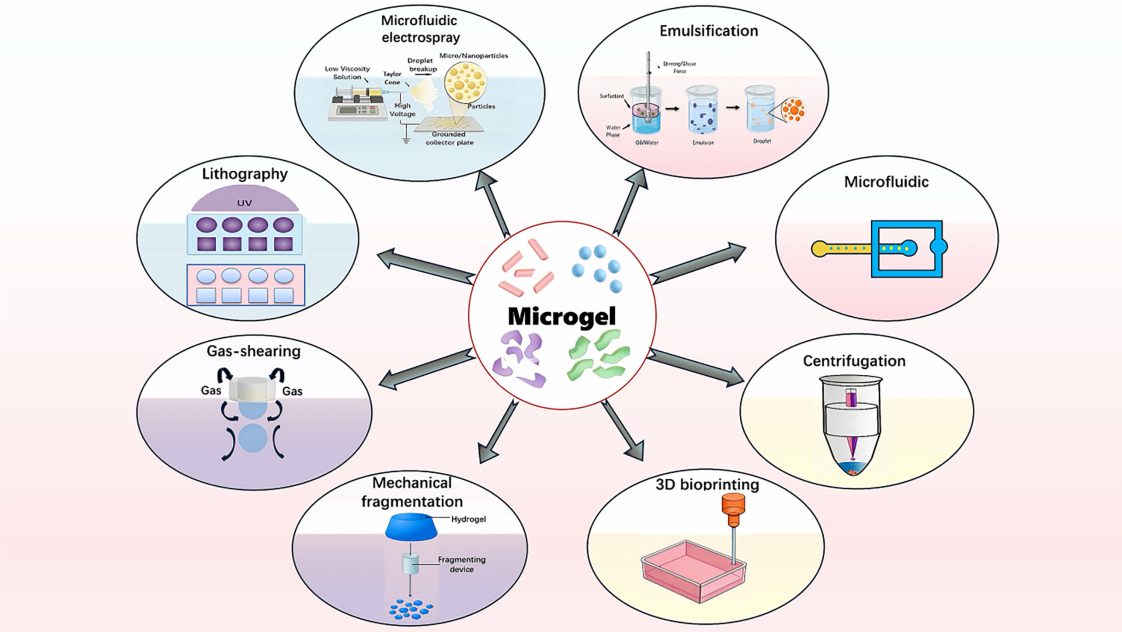

Figure 4: Overview of representative strategies to miniaturize macroscopic hydrogels into microgels. Including emulsification, microfluidic droplet generation, lithography, electrospraying, centrifugation, gas-shearing, 3D bioprinting, and mechanical fragmentation.

4.1 Emulsification-Based Miniaturization

Emulsification-based methods use emulsion droplets as templates to form hydrogel microspheres with tunable sizes. This droplet-templated approach replaces bulk molding with micrometer-scale droplet formation, serving as a practical route for microsphere fabrication [118]. Conventional approaches, such as mechanical stirring and ultrasonication, rely on bulk shear to break liquids into droplets. Although simple to implement, they provide limited control over droplet size and often yield poor monodispersity [119]. This limitation restricts applications that require high uniformity, including controlled drug release and cell encapsulation. Therefore, more precise droplet-generation strategies are needed to obtain monodisperse microgels. In the following sections, microfluidic droplet generation is discussed as a high-control platform.

4.2 Microfluidic Techniques

Microfluidics generates microgels by forming uniform droplets in microscale channels and then crosslinking the droplets. Common geometries include T-junction, flow-focusing, and co-flow designs [120]. Droplet breakup is governed by interfacial tension and viscous shear. Microgel size is primarily tuned by the flow-rate ratio of the two phases and channel dimensions [121]. This platform offers tighter control over size, shape, and monodispersity compared to bulk emulsification [122]. This precise control capability also applies to the synthesis of nanogels. When the size of hydrogels is further reduced to the submicron range (<1000 nm), they are defined as nanogels. By utilizing lab-on-a-chip technology on microfluidic chips, precise manipulation of fluids at the nanoscale can be achieved, thereby preparing nanocarriers with high surface area, excellent drug loading efficiency, and high environmental responsiveness [123]. For example, microfluidic technology can be used to prepare highly uniform microgels with diameters of only 10–50 μm [124]. Furthermore, at the nanoscale, by controlling crosslinking strategies such as photoinitiated free radical polymerization, gel particles ranging in size from several nanometers to hundreds of nanometers

can be further precisely manipulated [125]. Beyond size control, microfluidics enables precise structural control, allowing the fabrication of complex architectures like core-shell, Janus, and multicompartment microgels [126]. High monodispersity improves mass transport and can reduce variation in cell behavior within encapsulated microenvironments [127]. All-aqueous microfluidics further avoids organic oils and conventional surfactants, utilizing immiscible aqueous phases to enhance the cytocompatibility of cell-laden microgels [128]. Finally, device parallelization increases throughput without loss of precision, helping scale microgel fabrication beyond the laboratory [129].

4.3 Lithography-Based Microgel Patterning

Lithography-based microgel patterning is a high-precision and shape-controllable approach for preparing microgels. There are three classes of lithography technologies: flow lithography, imprint lithography and photolithography [130]. It involves the following key steps. First, the photopolymerizable hydrogel precursor solution, such as polyethylene glycol diacrylate, polylactic acid (PLA)-PEG-PLA diacrylate, or composite systems containing magnetic nanoparticles, is prepared by adding photoinitiators and functional additives as needed [131]. Then, the precursor solution is introduced into a microfluidic channel or a closed microchip, and the flow is stopped to stabilize the precursor in the target region. Next, UV light is projected through a pre-designed photomask to initiate localized photopolymerization, forming microgel structures matching the mask pattern [132]. Finally, the flow is restarted to flush out the unpolymerized precursor, and the patterned microgels are collected, with optional post-processing such as purification or surface modification to enhance performance [133]. This method has been widely applied in the fields of biomedicine and functional materials. Researchers synthesized non-spherical superparamagnetic microgels via stop-flow lithography combined with *in-situ* coprecipitation of magnetic nanoparticles, achieving precise control of particle shape and magnetic responsiveness for targeted delivery applications [134].

4.4 Electrospraying

Electrospraying is an electrohydrodynamic technique closely related to electrospinning. Under a high-voltage electric field, hydrogel precursor solutions can be dispersed into fine droplets with sizes spanning the micro- to nanoscale range, and the droplets can be crosslinked to form hydrogel particles [135]. Particle size and shape can be tuned by voltage, distance, flow rate, concentration, solvent, and solution viscosity [136]. Electrospraying can also produce hydrogel particles with complex microstructures. Examples include core-shell microspheres, porous microcarriers, hollow microspheres, nanocups, and Janus particles [96].

4.5 Centrifugation-Based Miniaturization

Centrifugation-based miniaturization utilizes centrifugal force to drive polymer solutions through micro-sized orifices or needles [137]. As the device rotates, the liquid is ejected into an immiscible continuous phase to form discrete droplets, which are then crosslinked to produce microgels [138]. The droplet size is primarily determined by the rotational speed and the nozzle diameter. This technique eliminates the need for complex pumping systems, offering a portable and simplified fabrication platform [139]. Centrifugal force can promote consistent droplet detachment, often yielding microgels with high monodispersity and uniformity [139]. This approach provides higher throughput than single-channel microfluidic devices by using parallelized radial nozzles. It is particularly suitable for the rapid encapsulation of cells and heat-sensitive biological reagents. However, stable droplet formation and size consistency require precise control over the rheological properties of the hydrogel precursors [137]. Overall, centrifugation remains an efficient and scalable strategy for the batch production of functional microgels.

4.6 Gas-Shearing Methods

Gas shearing is an oil-free and scalable approach for preparing microgels, which involves the following key steps: First, the hydrogel precursor solution such as sodium alginate, hyaluronic acid, or sodium alginate-polyvinyl alcohol composite [140], is loaded into a syringe. The syringe is connected to a homemade coaxial needle system (spray ejector device, SED), which is composed of liquid-flow needles and an outer shell [141]. Then, gas is introduced through the gap between the needle and the shell to generate shear force, which fragments the precursor solution into uniform microdroplets [142]. Droplet size can be tuned by adjusting gas flow rate, liquid flow rate, needle diameter, or polymer concentration. Finally, the formed microdroplets are collected in a receiving bath for crosslinking and subsequent purification, to obtain microgels with controllable particle size, narrow size distributions, and high biocompatibility [143]. This method has been widely applied in the field of precision medicine and tissue engineering. For example, researchers used gas shearing to produce single-bacterium microgels for probiotic delivery in inflammatory bowel disease (IBD), avoiding oil and surfactants and improving bacterial survival in the gut [144].

4.7 3D Bioprinting-Enabled Microgel Fabrication

3D bioprinting increasingly facilitates the fabrication of microgels for cell delivery and engineered microenvironments [145]. Inkjet bioprinting ejects picoliter-sized droplets that can be rapidly crosslinked *in situ* to form microgels with precise spatial placement [146]. Extrusion-based printing utilizes pneumatic or mechanical pressure to create microgel-based inks for building larger constructs with defined architectures. These approaches can mimic key features of spatial organization and hierarchical organization, spatial distribution and heterogeneity of native biological tissues [147]. Advanced bioprinting strategies enable the simultaneous integration of multiple cell types and bioactive growth factors [148]. Despite these advantages, high shear stress can reduce cell viability during printing. Therefore, printing parameters and bioink rheology should be optimized to balance fidelity and cell survival.

4.8 Mechanical Fragmentation

Mechanical fragmentation follows a "top-down" strategy to break bulk hydrogels into microscale fragments [149]. Methods such as high-shear homogenization, grinding, or sieving are commonly employed for this purpose [150]. The resulting fragments are irregular and can assemble into granular hydrogels with interconnected pores for cell infiltration. This process is highly scalable and cost-effective, requiring no specialized microfabrication equipment. Granular scaffolds can improve nutrient transport and host tissue integration compared to bulk hydrogel systems [151]. Polydispersity and limited shape control remain challenges, especially for applications requiring high precision.

5 Biomedical Applications of Polymeric Hydrogels

Polymer hydrogels, with their unique three-dimensional hydrophilic network structure, high water content, excellent biocompatibility and adjustable physicochemical properties, have become a key bridge connecting materials science and modern life medicine. Their structure is highly similar to the natural extracellular matrix, not only capable of simulating the microenvironment of biological tissues, but also achieving multiple intelligent functions such as drug loading, response to stimuli, and guiding cell behavior through molecular design (Table 1). These characteristics have transformed hydrogels from a basic material into an advanced tool for addressing a series of clinical challenges. This chapter will systematically elaborate on the core applications of polymer hydrogels in biomedicine, with the main contents as follows (Fig. 5).

Table 1: Recent polymer-based hydrogels for tissue engineering applications.

Types of Hydrogels	Polymers Used	Crosslinking Methods	Application	References
Natural hydrogels	Methacrylated silk fibroin	Chemical crosslinking	Combined photosensitizers for improving cancer therapy and promoting wound healing	[152]
Natural hydrogels	Alginate, Fibrin	Physical crosslinking	Used for bone regeneration, especially for dental, craniofacial, and orthopedic defects	[153]
Natural hydrogels	Alginate, Chitosan	Physical crosslinking and chemical crosslinking	Delivering active substances to promote the repair of skin damage	[154]
Synthetic hydrogels	N-carboxyethyl chitosan, PEGDA	Chemical crosslinking	Delivery of drugs for treating hepatocellular carcinoma	[155]
Synthetic hydrogels	Modified hyaluronic acid	Chemical crosslinking	Used as a long-lasting ocular surface lubricant for the treatment of dry eye syndrome	[156]
Synthetic hydrogels	imidazole-poly (organophosphazenes)	Physical crosslinking	Used to treat spinal cord injury in rats	[157]
Synthetic hydrogels	Hyaluronic acid modified with cyanuric acid	Physical crosslinking	Used for delivering medications to treat rheumatoid arthritis	[158]
Synthetic hydrogels	Poly carboxybetaine acrylamide	Chemical crosslinking	Used to treat burns and other severe skin injuries	[159]

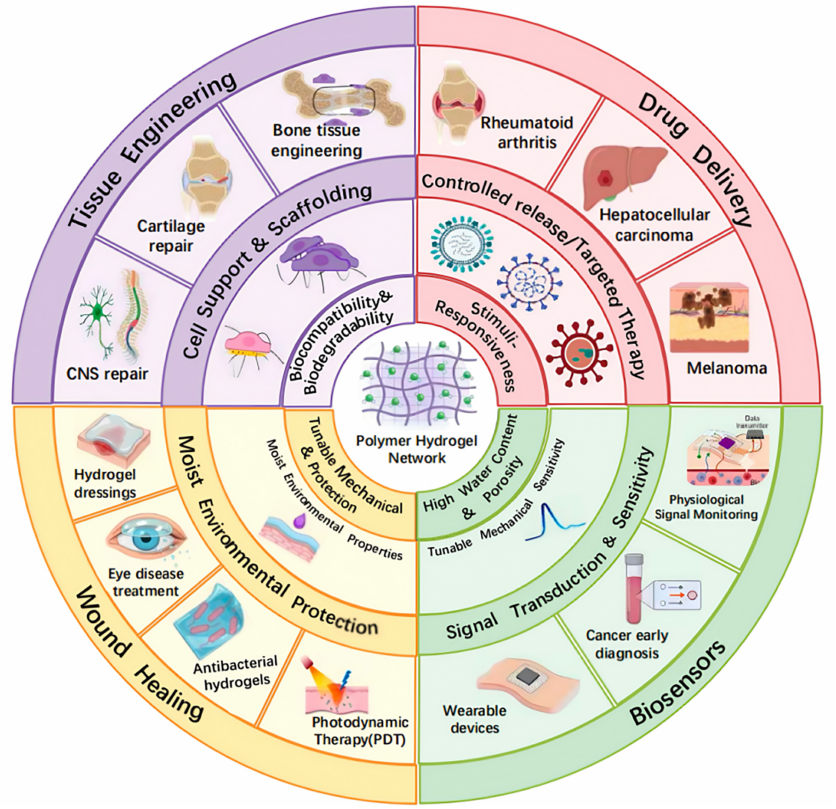

Figure 5: Biomedical applications of polymeric hydrogels, highlighting key functional features and representative uses in drug delivery, tissue engineering, wound healing, and biosensing. The mechanism of action of hydrogels in the field of drug delivery is to limit the outflow rate of drugs through pore size and to automatically disintegrate in response to environmental signals such as pH or enzymes, thereby achieving precise, timed, and quantitative release of drugs at the lesion site. The mechanism of action of hydrogels in the field of tissue engineering is to provide physical support and guide cells to eventually reconstruct into functional biological tissues through the synergistic effects of mechanical, chemical and biological signals. The mechanism of action of hydrogels in wound healing is to maintain moisture balance, provide a physical barrier, and precisely release biochemical signals, thereby creating an ideal microenvironment for accelerated tissue regeneration in the wound. The mechanism by which hydrogels function in the field of biosensors is to precisely convert minute biomolecular information into readable physical or electrical signals by loading biorecognition elements at high density and utilizing their own volume deformation or changes in conductivity.

5.1 Drug Delivery

As a three-dimensional polymer network, hydrogels have demonstrated great application potential in drug delivery due to their excellent biocompatibility, high drug loading capacity and tunable physicochemical properties.

In the field of cancer treatment, hydrogels are widely used to deliver chemotherapy drugs such as doxorubicin (DOX) for targeted release and to reduce systemic toxicity. Besides improving pharmacokinetic properties, hydrogels play a key role in reversing drug resistance by modulating the tumor microenvironment (TME). Studies have shown that hydrogels can overcome DOX-mediated drug resistance by precisely regulating the level of oxidative stress within the TME. Specifically, they can increase the generation of reactive oxygen species (ROS) to damage cellular lipids, proteins, and DNA, thereby bypassing traditional drug efflux pathways [160]. Additionally, hydrogels provide a multifunctional platform for the combined

delivery of DOX with epigenetic modifiers or genes such as siRNA or microRNA (miRNA), which can trigger epigenetic remodeling within the TME [161–163]. For instance, such systems can promote the degradation of mutant proteins such as mutant p53 or inhibit the epithelial-mesenchymal transition (EMT) pathway, effectively resensitizing drug-resistant cancer cells to chemotherapy [164]. For instance, pH-responsive self-healing injectable hydrogels based on N-carboxyethyl chitosan (CEC) can target drug release by taking advantage of the acidic characteristics of the tumor microenvironment. Meanwhile, their self-healing properties and shear-thinning performance enable direct injection into lesion sites such as hepatocellular carcinoma, avoiding drug diffusion into normal tissues [155]. Additionally, silk fibroin *in situ* hydrogels can combine photodynamic therapy (PDT) and immune-enhancing functions, inhibiting melanoma recurrence while promoting wound healing and tissue regeneration in infected areas [152].

In the treatment of chronic inflammatory diseases such as rheumatoid arthritis (RA), hydrogels also perform well [165]. To address the issues of low solubility and difficulty in sustained administration of first-line drugs such as methotrexate (MTX), researchers have developed a supramolecular hydrogel based on structural tautomerism. This hydrogel can respond to the pathological pH value within the joint, enabling the co-delivery of MTX and magnesium ions, thereby achieving dual therapeutic effects of anti-inflammation and bone remodeling [158].

Furthermore, hydrogels have demonstrated remarkable therapeutic potential in the field of cardiovascular diseases, particularly for the treatment of acute myocardial infarction (MI) and subsequent heart failure (HF). As a minimally invasive tissue engineering strategy, injectable hydrogels can be delivered directly to the infarcted myocardium to provide essential mechanical support, which effectively reduces ventricular wall stress and attenuates pathological cardiac remodeling [166,167]. Beyond structural reinforcement, functionalized hydrogels serve as versatile platforms for the sustained and localized delivery of biotherapeutic agents. For instance, an injectable hydrogel system based on gelatin methacrylate (GelMA) and thiolated hyaluronic acid (HASH) has been developed to co-deliver deferoxamine (DFO) and carvedilol. This system can effectively modulate the post-MI microenvironment by scavenging ROS, inhibiting cardiomyocyte apoptosis, and promoting angiogenesis [168]. Recent studies have shown that redox-responsive hydrogels can alleviate local oxidative stress and reprogram downstream signaling pathways involved in cell survival and tissue repair [169].

In summary, modern hydrogel delivery systems are moving towards intelligence and multifunctionality. By introducing pH-responsive, redox-responsive or thermosensitive and other stimulus response mechanisms, as well as physical properties such as self-healing and *in situ* gelation, they provide an ideal platform for achieving precise medical treatment and tissue repair.

5.2 Tissue Engineering

Hydrogels have shown great application potential in the field of tissue engineering due to their ability to simulate the physical and biological properties of the natural ECM. They not only support cell proliferation, migration and differentiation, but also effectively ensure the transport of oxygen and nutrients, providing an ideal microenvironment for the regeneration of soft and hard tissues.

At the specific application level, the bio-functionalization design of hydrogels is their core advantage. For example, in bone tissue engineering, the combination of cell-loaded hydrogel microfibers with injectable calcium phosphate cement (CPC) scaffolds can significantly enhance bone regeneration and achieve minimally invasive implantation [153]. In the repair of cartilage and osteochondral interfaces, hydrogels are often used as artificial ECM to promote the growth of chondrocytes and osteogenic differentiation [170]. In the field of tumor tissue engineering, the application of hydrogels has shifted from basic support to the construction of highly biomimetic pathological models. Through 3D bioprinting technology, by precisely proportioning

components such as GelMA, chondroitin, and hyaluronic acid, hydrogels can reconstruct a complex prostate cancer microenvironment containing stromal cells, effectively inducing epithelial-mesenchymal transition (EMT) and simulating the biochemical signals of tumors [171]. Additionally, the combination of hydrogels and mineralized scaffolds can successfully simulate the microenvironment of prostate cancer bone metastasis, not only supporting the long-term colonization of prostate cancer cells in the scaffold but also being used to observe adaptive evolutionary behaviors such as neuroendocrine transdifferentiation of cancer cells under androgen deprivation therapy. This functional design provides a key *in vitro* platform for revealing tumor drug resistance mechanisms and high-throughput drug screening [172,173].

Injectability and self-healing ability are another major trend in modern hydrogel design. Injectable hydrogels allow for local targeted drug delivery through syringes, avoiding the risks of invasive surgery and self-adjusting according to the shape of the patient's damaged area. Self-healing hydrogels can temporarily fluidize under shear force and quickly restore mechanical strength after injection, which is crucial for maintaining the structural integrity of the scaffold [174]. In the repair of the central nervous system (CNS), specific types of injectable hydrogels such as imidazole-polyorganophosphazene have been proven to promote extracellular matrix remodeling, eliminate cystic cavities after spinal cord injury, and significantly improve coordinated motor function [157].

Finally, the performance of hydrogels largely depends on the choice of polymers. Natural polymers such as alginate and chitosan have excellent biocompatibility, while synthetic polymers such as PEG are easier to precisely control mechanical strength and degradation rate [175]. By combining advanced manufacturing techniques such as 3D bioprinting, researchers can develop tissue constructs with complex gradient structures, thereby more accurately simulating the complex microenvironment of natural tissues [170,176].

5.3 Wound Healing

As the largest organ of the human body, the skin serves as a crucial barrier against external pathogens. The repair process following skin damage involves four complex and consecutive stages: hemostasis, inflammation, proliferation, and remodeling. Among various biomedical dressings, hydrogels are regarded as the most competitive candidate materials for promoting wound healing due to their three-dimensional porous structure similar to the ECM, excellent biocompatibility, and high water content. Compared with traditional dressings, modern functionalized hydrogels not only maintain a moist environment for the wound and absorb exudate but also integrate multiple advanced functions to address complex clinical challenges.

Current research emphasizes the development of multifunctional hydrogels tailored to specific pathological disorders. For instance, in response to the clinical challenge of drug-resistant bacterial infections, researchers have developed hydrogels loaded with antibiotics such as ciprofloxacin and gentamicin, metal nanoparticles [177], or antimicrobial peptides, which can effectively inhibit pathogens like *Staphylococcus aureus* and prevent chronic infections. Specifically, composite hydrogels based on polylysine (PLL) utilize their surface positive charges to induce bacterial membrane rupture, demonstrating broad-spectrum antibacterial activity [178]. In burn care, considering the characteristics of extensive exudation and susceptibility to infection, dressings containing natural polymers such as chitosan and hyaluronic acid can synergistically reduce inflammation. For example, chitosan liposome hydrogels integrated with xylitol can achieve sustained release of drugs such as mupirocin, significantly accelerating wound closure in a porcine model of infected burns; while hyaluronic acid dressings combined with adipose-derived stem cells (ASCs) effectively promote granulation tissue formation by regulating the levels of Interleukin-1β (IL-1β) and TGF-β1 [179]. Additionally, for chronic wounds such as diabetic foot ulcers (DFU), pH or temperature-responsive smart hydrogels enable precise drug delivery. Studies have shown that conductive hydrogels loaded with growth factors such as basic fibroblast growth factor (bFGF) can release the factors on demand based on the

concentration of matrix metalloproteinases, thereby improving the high oxidative stress microenvironment and inducing nerve migration [180]. Recent studies have also demonstrated multifunctional dressings integrated with sensors, which can achieve remote digital diagnosis of early infections by monitoring changes in wound temperature or pH [181].

Beyond skin applications, the multifunctionality of hydrogel systems extends to special tissues such as ocular surface repair. These systems enhance bioavailability through *in situ* gelation and stimulus-responsive mechanisms. For instance, a bio-inspired synthetic hyaluronic acid soft hydrogel remains elastic under low shear stress but exhibits viscosity under high stress, serving as a long-lasting ocular surface lubricant that significantly improved symptoms in over 65% of dogs with dry eye in clinical trials [156]. Moreover, supramolecular hydrogels or hydrogel microneedles constructed with cyclodextrin/polyethylene glycol (PEG) can protect the activity of protein-based biologics and extend their half-life in the vitreous [182]. In summary, biomedical hydrogel dressings are evolving from simple physical barriers to intelligent systems with active therapeutic and real-time monitoring capabilities, offering broad prospects for tissue engineering and skin repair.

5.4 Biosensors

The tissue-like flexibility of hydrogels and their ability to mimic the ECM provide an ideal 3D immobilization matrix for biomolecular recognition elements such as enzymes, antibodies, aptamers, and whole cells [183,184]. Compared with traditional two-dimensional sensing surfaces, 3D network structure of hydrogels ensures the activity of biomolecules through interconnected pores, optimizes the loading and diffusion of analytes, and significantly enhances the sensing sensitivity [185].

The advanced nature of hydrogels in biosensing largely stems from their stimulus-responsive properties. Through the introduction of specific functional groups, hydrogels become capable of sensing subtle environmental changes. These include pH fluctuations, temperature variations, ROS levels, or specific chemical gradients. In response, the hydrogels generate measurable physical signals, such as volume phase transitions, refractive index changes, or sol-gel transitions [7,186]. In the field of *in vitro* diagnostics (IVD), hydrogel-based sensing platforms have demonstrated exceptional accuracy in detecting biochemical small molecules, protein biomarkers, and disease-specific gene sequences [183]. Particularly in the early monitoring of cancer, functionalized hydrogels can capture extremely low concentrations of circulating tumor cells (CTCs) or exosomes through signal amplification mechanisms, providing crucial evidence for precision medicine [187]. In recent years, research on hydrogel biosensors has shifted towards wearable devices and real-time monitoring. With the help of advanced manufacturing techniques such as 3D printing, microfluidic chips, and electrochemical deposition, researchers have developed flexible hydrogel electrodes with high mechanical strength, fatigue resistance, and self-healing capabilities. These devices can non-invasively collect and analyze biological fluids such as sweat, saliva, tears, and interstitial fluid (ISF), enabling continuous dynamic monitoring of the body's metabolic state. For instance, electrochemical hydrogel sensors integrated into patches can monitor electrolyte balance and metabolic stress in real time during exercise [188].

Despite these advancements, the transition of hydrogel-based biosensors from laboratory prototypes to commercial clinical tools faces several hurdles. Key challenges include ensuring long-term stability in complex physiological media, enhancing the signal-to-noise ratio in multi-interference environments, and achieving cost-effective large-scale fabrication [188,189]. Future research is expected to focus on the development of multifunctional, self-healing, and biocompatible hydrogel interfaces that can seamlessly integrate with wireless data transmission systems for next-generation point-of-care testing (POCT).

6 Perspectives

Polymeric hydrogels offer versatile platforms for drug delivery and regenerative medicine, yet clinical translation remains limited by performance gaps and incomplete biological integration. Despite increasing clinical approvals, hydrogel translation remains limited by challenges in large-scale manufacturing and current good manufacturing practice (cGMP) compatibility. Long-term biocompatibility and immune responses remain critical concerns affecting clinical safety and performance. Future research should balance biocompatibility, biodegradability, and mechanical stability to meet therapeutic needs. Advances in microfluidic and 3D bioprinting technologies allow precise fabrication of microgels with specific shapes and better cell interactions. These innovations open up new possibilities for drug delivery, tissue engineering, and biosensors. However, challenges like maintaining hydrogel stability under physiological conditions and improving scalability remain. Clinical reports show that approved hydrogel sealants can still cause spinal cord compression from *in vivo* swelling, underscoring the need to control expansion in confined spaces [190]. In conclusion, the continued development of hydrogel materials and fabrication methods will enable new treatments and the creation of effective biomaterials for regenerative medicine. The future looks promising for hydrogel-based therapies in personalized medicine.

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