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Review

Smart Polymer-Derived Injectable Hydrogels: Current Status and Future Perspectives

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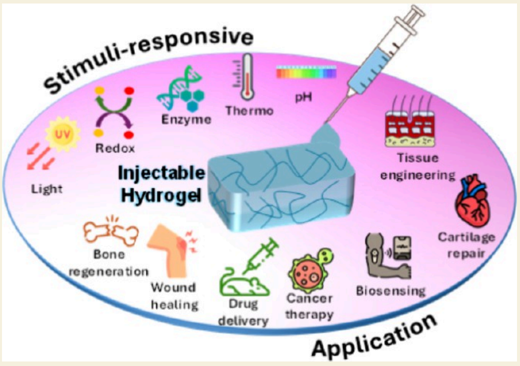

ABSTRACT: Because of their tissue-conforming qualities, *in situ* gelation, and less invasive distribution, injectable hydrogels (IHs) have become a revolutionary class of soft materials with enormous potential in biomedical applications. The ability of stimuli-responsive polymer-derived smart injectable hydrogels (SIHs) to react dynamically to external stimuli like temperature, redox potential, pH, or enzyme activity has drawn more attention than any other. This responsiveness enables precise spatiotemporal control over therapeutic delivery, tissue regeneration, and self-healing capabilities. Recent advances in cross-linking strategies, including reversible covalent and supramolecular interactions, have expanded the design space for SIHs, enhancing their adaptability to dynamic physiological environments. With an emphasis on structure-property connections, rheological behavior, dynamic cross-linking mechanisms, and stimuli-triggered transitions, we provide a thorough summary of the basic ideas guiding the injectability and functioning of SIHs in this review. From biosensing and regenerative medicine to tissue engineering and cancer treatment, we critically analyze the most recent advancements in their biomedical applications. Despite substantial progress, challenges such as mechanical fragility, limited biodegradability, cytotoxicity concerns, and scalability remain significant barriers to clinical translation. This review also highlights emerging strategies such as bioinspired polymer design, modular cross-linking architectures, and scalable fabrication methodologies aimed at overcoming current limitations. By bridging fundamental material design principles with translational objectives, we provide an integrated perspective to guide the development of next-generation smart injectable hydrogels (SIHs) with enhanced functional performance, biocompatibility, and clinical relevance.

KEYWORDS: *smart injectable hydrogels (SIHs), in situ gelation, shear-thinning hydrogel, microgel-based IHs, biomedical application, tissue engineering, drug delivery, natural polymer-based SIHs, biocompatible SIHs, self-healing hydrogel*

1. INTRODUCTION

Three-dimensional, hydrophilic networks of polymers, known as hydrogels, may hold onto more than 98% of their weight in water while still retaining their structural integrity because of chemical or physical cross-linking.[1] They can replicate the extracellular matrix of biological tissues in biomedical settings because of their exceptional water-retention ability, biocompatibility, softness, and permeability.[2] The origin of synthetic hydrogels has its roots in 1960, when they were first introduced for biological applications.[3] Since then, the field has expanded rapidly, with hydrogels being employed in diverse domains such as tissue engineering,[4−7] wound healing,[8,9] drug delivery,[10−12] sensors,[13,14] and soft robotics.[15−19] Their ability to provide a hydrated and mechanically supportive microenvironment has positioned them as a valuable class of materials in biomedical research and clinical practice. Since injectable hydrogels (IHs) can be administered minimally invasively and undergo *in situ* gelation at the target site, they have drawn a lot of interest among other hydrogel systems.[20] Conventional preformed hydrogels frequently have drawbacks, including low mechanical strength and difficult implantation processes, particularly when conformance to varying anatomical features is required. However, IHs are made to be supplied in a liquid or semisolid state via a catheter or syringe, and then they go through a sol—gel transition that is brought on by physiological or environmental stimuli like temperature and pH.[21−25] This feature allows IHs to adapt to tissue morphology while

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reducing surgical invasiveness and procedural complexity. For instance, a hydrogel based on *N*-isopropylacrylamide (NIPAM) remains soluble at 10 °C but rapidly forms a gel at 37 °C, the average human body temperature, within 30 s.[23] Upon injection, the polymer undergoes a hydrophilic-to-hydrophobic transition, promoting physical cross-linking and gel formation at the targeted location. This *in situ* gel formation ability enhances patient comfort and enables more localized and controlled therapeutic effects.

IHs can be broadly classified based on their method of formation. One common strategy is *in situ* gelation, where the hydrogel forms in response to physiological triggers after injection.[26,27] Another widely used method is shear-thinning, wherein the hydrogel behaves as a non-Newtonian fluid that exhibits reduced viscosity under high shear rates (approximately 100 s^{-1}) during injection and rapidly recovers its mechanical strength once the shear is removed.[28−33] Because of its rheological characteristics, the hydrogel can restore its structural integrity at the target site and pass through a small syringe needle with ease and without clogging. Under high shear circumstances, the viscosity of such shear-thinning systems must stay below 1 Pa in order for injection to be successful.[34] To facilitate reversible sol−gel transitions and self-recovery, these hydrogels often incorporate dynamic interactions such as hydrogen bonding,[35−37] hydrophobic associations,[38,39] and dynamic covalent linkages like Schiff base[40,41] and disulfide bonds.[42] These interactions enable the hydrogel network to withstand mechanical stresses and recover postdeformation, thereby extending its utility in dynamic physiological environments.

The development of smart injectable hydrogels (SIHs), which are made of stimuli-responsive polymers that show reversible changes in their chemical or physical state in response to a particular internal or external stimuli, is a significant breakthrough in this field. In the context of SIHs, such responsiveness allows for precisely controlled drug release,[43] tissue-engineering,[44] and self-healing properties.[45] For example, Cimen et al.[46] reported a hybrid pH-responsive IH system that remains stable under physiological pH but undergoes network disassembly in acidic environments, thereby releasing the encapsulated therapeutic agents. The hydrogel also demonstrated self-healing capabilities, a property particularly beneficial for long-term biomedical implants or repeated mechanical stress.

The goal of this review is to thoroughly examine the formation and use of IHs made from smart polymers. We start with a summary of how SIHs are categorized according to their origin and stimulus-responsiveness, then go into great detail about the mechanisms controlling their injectability and the essential design factors. The links between structure and properties, rheological behavior, cross-linking techniques, and stimuli-triggered reactions that control their functional performance are highlighted. We also draw attention to the latest developments in the use of SIHs in a number of biomedical fields, including as biosensing technologies, cancer treatment, tissue engineering, and regenerative medicine. In addition, the review addresses the current challenges in this field, such as limited mechanical strength, incomplete biodegradation, potential cytotoxicity of cross-linkers, and difficulties in large-scale manufacturing. Finally, we propose future directions to overcome these limitations, including the incorporation of novel bioinspired chemistries, optimization of stimulus-response kinetics, and advancement in scalable synthesis techniques. The overall goal of this review is to give readers an extensive understanding of injectable smart hydrogels' potential and advancement. Opportunities for targeted therapies and customized medicine have been made possible by the use of smart polymer chemistry onto injectable platforms. Translating these cutting-edge materials from the lab to clinical and industrial settings, however, will necessitate interdisciplinary cooperation spanning chemistry, materials science, biology, and clinical medicine in order to fully realize their potential. We hope to stimulate creative research that will advance the creation of next-generation hydrogel systems with revolutionary societal impact by synthesizing existing knowledge with future perspectives.

2. CLASSIFICATION OF SMART INJECTABLE HYDROGELS

2.1. Based on Stimuli Responsiveness

An innovative class of biomaterials known as "smart injectable hydrogels" is made to change chemically or physically in response to particular external stimuli. The stimulus-responsive behavior of the hydrogel network is primarily governed by the reversible formation and dissociation of its cross-linking bonds. Gelation, swelling, shrinkage, degradation, or sol−gel transitions are examples of reversible changes in the network architecture that can be brought about by stimuli like pH, temperature, light, redox potential, and enzymes.[47−49] Controlled and intelligent therapeutic interventions are made possible by these dynamic changes, which enable the on-demand, site-specific release of encapsulated therapeutic agents, including as proteins, drugs, cytokines, and cells.

2.1.1. pH-Responsive Injectable Hydrogel. Since pathological environments like tumor tissues and inflammatory sites have mildly acidic pH levels (usually less than 6.8) compared to the physiological pH of 7.4, pH-responsive IHs have drawn a lot of attention among the different stimulus-responsive systems because of their potential for site-specific drug delivery.[50] pH-responsive hydrogels exhibit tunable physical behaviors, such as swelling, disintegration, or reversible sol−gel transitions, arising from the ionization or protonation of pH-sensitive functional groups (e.g., carboxylic acids or amines) incorporated into the polymer backbone.[51] At different pH values, changes in electrostatic interactions or hydrogen bonding within the network modulate the hydrogel's structural integrity, thereby allowing controlled responsiveness to the surrounding environment. The design strategy for such hydrogels generally involves three key approaches: (i) Incorporation of pH-sensitive covalent linkages, such as imine (Schiff base) or acyl hydrazone bonds, which undergo hydrolysis under acidic conditions; (ii) Utilization of polymers with ionizable functional groups, including acidic groups like carboxyl (−COOH) and sulfonic acid (−SO_3H), or basic groups like amino (−NH_2), which alter their ionization state based on pH; (iii) Construction of hydrogels via electrostatic interactions or coordination bonds, which are inherently sensitive to proton concentration.[52] When primary amines condense with aldehydes or ketones, imine linkages are created that are hydrolytically unstable in acidic environments. Because of their acid-labile nature, they are especially well-suited to creating pH-responsive drug delivery systems. For instance, Zhou et al.[53] created an injectable hydrogel using carboxymethyl chitosan (CMCS) and oxidized hydroxypropyl cellulose (OxHPC). The hydrogel network was stabilized via

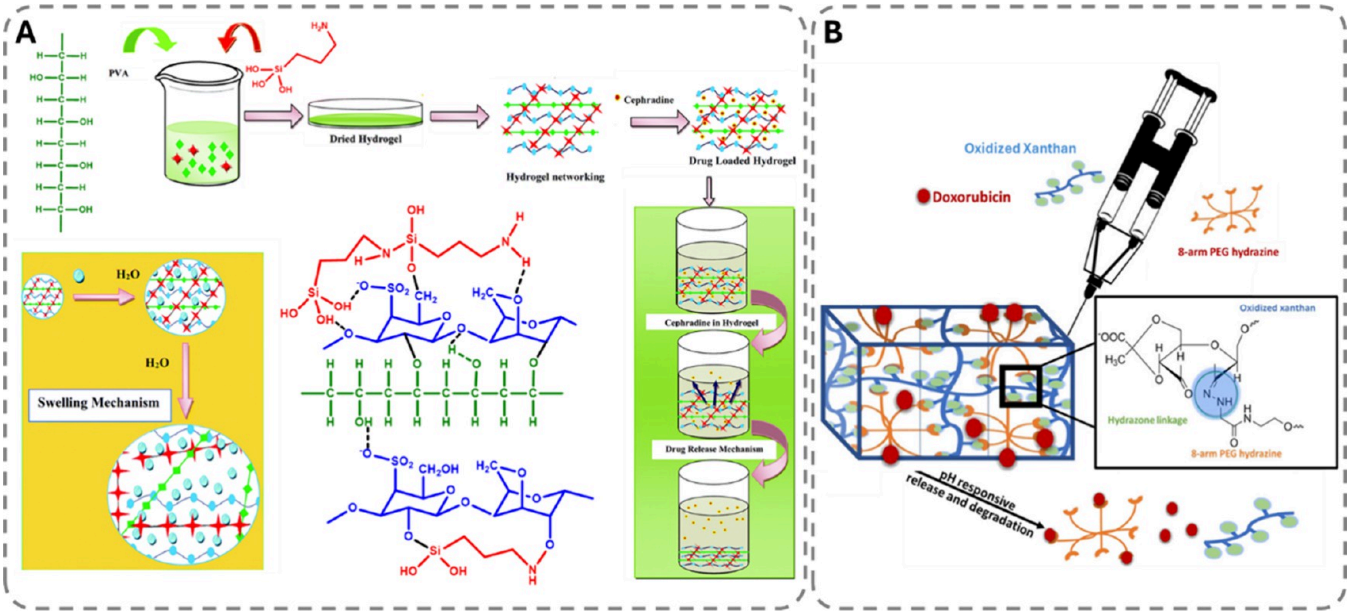

Figure 1. (A) The pH-responsive hydrogel is shown schematically utilizing carrageenan and poly(vinyl alcohol) (PVA), which are cross-linked chemically and physically using (3-aminopropyl)triethoxysilane (APTES). Reproduced with permission of ref 54. Copyright 2019 The Royal Society of Chemistry. (B) Development of pH-responsive and sustained-release hydrogels based on oxidized xanthan and 8-arm PEG hydrazine via hydrazone bonding for doxorubicin delivery. Reproduced with consent of ref 57. Copyright 2018 American Chemical Society.

reversible imine bonds between aldehyde and amino groups, imparting self-healing and shear-thinning characteristics. The imine linkages experienced rapid hydrolysis in acidic circumstances that mimicked the tumor microenvironment. This resulted in network breakdown and improved release of the encapsulated medicinal drug, phenylalanine. Similarly, Rasool et al.[54] created a pH-responsive hydrogel utilizing carrageenan and poly(vinyl alcohol) (PVA), chemically and physically cross-linked with (3-aminopropyl)triethoxysilane (APTES) (Figure 1A). The presence of sulfate (-OSO_3^-) and hydroxyl (−OH) groups in carrageenan contributed to the pH sensitivity. At acidic pH (1.0−3.0), protonation of sulfate groups enhanced intermolecular hydrogen bonding, reducing the swelling ratio. Conversely, at alkaline to neutral pH (~7.0), ionization led to increased electrostatic repulsion and maximum swelling. Bingol et al.[55] created a thermo- and acid-responsive injectable hydrogel using an aza-Michael addition between cystamine and poly(ethylene glycol) diacrylate (PEGDA) or a PEGDA/1,6-hexanediol diacrylate (HDDA) blend. In reaction to physiological temperature, the precursor quickly gelled *in situ* after remaining liquid until injection. The resulting hydrogel showed acid-triggered degradation, making it suitable for site-specific release. Natural polymers like hyaluronic acid (HA), alginate, and chitosan, which contain weakly basic or acidic functional groups, also demonstrate pH responsiveness.[56] For instance, a hydrogel was created for in vitro insulin delivery using N-succinyl chitosan and aldehyde-functionalized HA that was covalently bound to glucose oxidase. A biomimetic approach to regulated drug release in adipose tissue engineering was demonstrated by the hydrogel matrix's degradation in response to pH variations brought on by the enzymatic production of gluconic acid. Many pH-responsive hydrogels have been developed in the field of cancer treatment to administer chemotherapeutics precisely. These techniques take advantage of the tumor microenvironment's acidic pH (~6.5 or lower) to accomplish localized gelation and drug release. Sharma et al.[57] designed an injectable hydrogel using oxidized xanthan gum (OXG) containing aldehyde functionalities and cross-linked it with 8-arm PEG-hydrazine via hydrazone bonds (Figure 1B). The hydrogel displayed injectability, self-healing, slow degradation, and pH-dependent drug release. A doxorubicin (DOX)-loaded variant showed accelerated release at pH 5.5 compared to pH 7.4, validating its potential for tumor-targeted therapy. Wu et al.[34] advanced this approach further by creating nanocomposite IHs using Schiff base reactions involving amine-modified silica nanoparticles and aldehyde-functionalized polymers. These hydrogels gelled rapidly (within 10 s), were injectable, self-healing, and showed excellent stability at neutral pH. Upon exposure to mildly acidic conditions, the imine linkages cleave, triggering gel-to-sol transition and enabling controlled drug release. In conclusion, pH-responsive IHs offer a flexible platform for stimuli-responsive drug delivery, with potential uses in regenerative medicine, cancer treatment, and inflammation-targeted medications. Their ability to respond intelligently to microenvironmental cues and release therapeutic payloads in a site-specific, temporally controlled manner is dependent on the strategic integration of ionizable groups or pH-sensitive chemical motifs.

2.1.2. Temperature Responsive Injectable Hydrogels.

A class of "smart" biomaterials known as temperature-responsive IHs responds to temperature changes by undergoing reversible physical changes, such as gel−sol or sol−gel transitions. The formation and dissociation of cross-linking bonds or thermally induced conformational changes in the polymer chains are the causes of these transitions. Because of this responsiveness, the hydrogel may adjust to physiological conditions, allowing for the accurate *in situ* gelation filling of irregular tissue cavities. After being injected into the body, the sol phase turns into a gel at body temperature, providing injured tissues with mechanical support, promoting cellular adhesion and migration, and permitting the localized and prolonged release of therapeutic substances like medications or cytokines.[58,59] The majority of IHs have a temperature

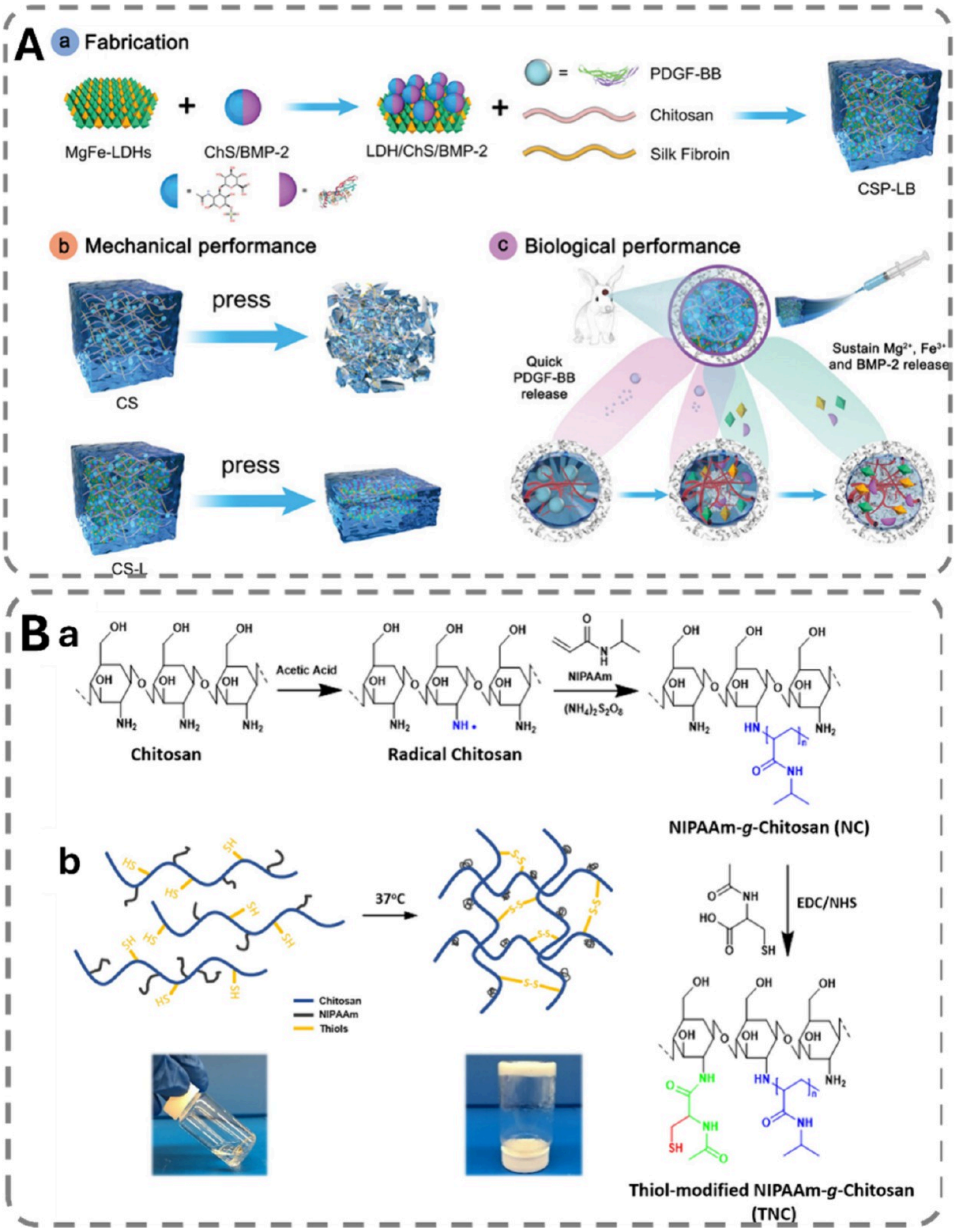

Figure 2. (A) Diagrammatic representation of CSP-LB hydrogel synthesis, highlighting improved mechanical strength and biological performance. Reproduced with permission of ref 66. Copyright 2022 Wiley-VCH GmbH. (B) (a) Illustration of the synthesis process involving free-radical copolymerization of NIPAM with chitosan, followed by thiol modification via carbodiimide-mediated conjugation of NAC to chitosan. (b) Representation of the gelation mechanism, incorporating both physical interactions (helix-to-coil transitions) along with chemical cross-linking through disulfide bond formation. Reproduced with permission of ref 42. Copyright 2018 Elsevier.

sensitivity mechanism that is based on polymers that have a lower critical solution temperature (LCST). The polymer chains are hydrated and soluble below this temperature, and they undergo phase separation and collapse due to entropically driven dehydration above it. Poly(*N*-isopropylacrylamide) (PNIPAM), is a common example,[60,61] with an LCST near 32−37 °C, and poly(ethylene glycol) (PEG),[62,63] which is often used to improve biocompatibility. PNIPAM is particularly attractive due to its phase transition near physiological temperature, making it ideal for biomedical applications. However, PNIPAM also presents certain limitations, such as its potential to induce thrombosis when in contact with blood, necessitating the development of alternative biocompatible polymer systems for safer clinical use.[64,65]

Several research groups have developed novel temperature-responsive hydrogels with improved properties. For instance, Lv and co-workers[66] created a thermosensitive injectable hydrogel system by incorporating MgFe-layered double hydroxide (LDH) into the polymer network. The addition of LDH lowered the gelation temperature from 37.4 to 32.7 °C (Figure 2A), enabling rapid *in situ* gelation at physiological temperatures. This hydrogel acted as an in vivo drug depot, fitting perfectly within tissue defects and supporting angiogenesis and osteogenesis through sustained release of growth factors. Zakerikhoob and colleagues[67] developed a thermoresponsive wound dressing hydrogel by grafting PNIPAM onto sodium alginate chains. In the physiological range (27−42 °C), this hydrogel demonstrated sol−gel transition, making it easy

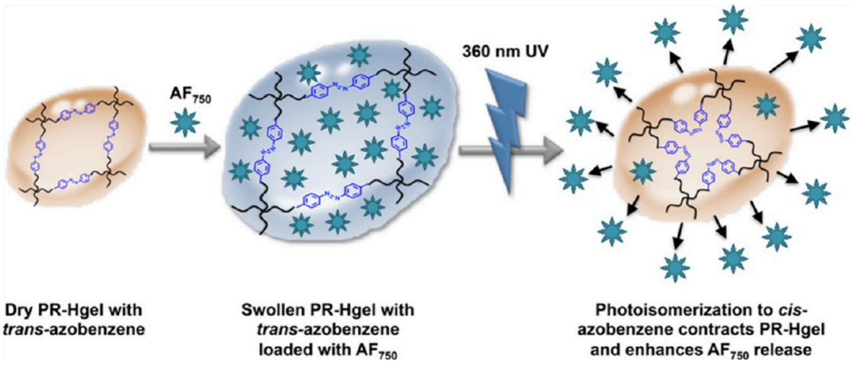

Figure 3. Diagrammatic representation of the host−guest chemistry process used to create a light-responsive injectable hydrogel using four-arm polyethylene glycol (PEG) and bifunctional azobenzene. Reproduced with permission of ref 77. Copyright 2017 American Chemical Society.

to inject into wounds and then gel *in situ* to adapt to the shape of the wound. Similarly, Sim et al.[68] created a biodegradable temperature-responsive hydrogel system using a heparin-bearing triblock copolymer, poly(*ε*-caprolactone-*co*-lactide)-*b*-poly(ethylene glycol)-*b*-poly(*ε*-caprolactone-*co*-lactide) (Hep−PCLA), to use as a cationic proteins carrier. This system demonstrated efficient temperature-induced gelation and biocompatibility. In another study, Pertici et al.[69] developed an IH based on a pentablock copolymer, PNIPAM-*b*-PLA-*b*-PEG-*b*-PLA-*b*-PNIPAM, derived through ring-opening and nitroxide-mediated polymerization techniques. The presence of poly(lactic acid) (PLA) introduced biodegradability, allowing the hydrogel to degrade into low-molecular-weight fragments under physiological conditions. The amphiphilic nature of the copolymer enabled gelation at 30 °C, facilitating its use in biomedical applications. Furthermore, Xu and colleagues[70] fabricated a composite thermosensitive hydrogel by combining heparin-poloxamer with decellularized spinal cord extracellular matrix (dECM) for the localized delivery of fibroblast growth factor-2 (FGF-2). This hydrogel promoted structural recovery and functional regeneration of neurons in a rat model of spinal cord injury. Similarly, Wu et al.[42] developed a thermoresponsive hydrogel by grafting NIPAM onto chitosan using a disulfide cross-linking approach. This strategy improved the hydrogel's biocompatibility and mechanical properties, and the material demonstrated excellent cytocompatibility when tested with osteoblasts (MC3T3-E1), fibroblasts (NIH-3T3), and infrapatellar fat pad-derived mesenchymal stem cells (IFP-MSCs) (Figure 2B).

Temperature changes not only affect polymer−solvent interactions but also modulate the integrity of the hydrogel network by influencing the stability of cross-linking interactions. In physically cross-linked systems, such as PNIPAM or Pluronic-based hydrogels, heating above the LCST promotes hydrophobic collapse and network formation, while cooling reverses these associations, leading to dissociation. In systems involving dynamic covalent bonds (e.g., Schiff base, Diels−Alder linkages), elevated temperatures can accelerate the reversible cleavage of cross-links, enabling controlled gel degradation or sol−gel transitions.[71] Thus, temperature plays a dual role by inducing gelation and facilitating thermal dissociation of reversible bonds, offering precise control over the mechanical and functional behavior of injectable hydrogels.

2.1.3. Light Responsive Injectable Hydrogels. Light-responsive IHs are an emerging class of ″smart″ biomaterials that undergo structural and functional transformations upon exposure to light, including ultraviolet (UV), visible, and near-infrared (NIR) wavelengths.[72] These transformations can lead to sol−gel transitions or reversible cross-linking, enabling on-demand drug release, degradation, or photothermal conversion. The potential to precisely control the behavior of these hydrogels in space and time, along with their inherent biocompatibility and tunability, makes them highly attractive for a wide range of applications in biomedicine, soft robotics, and tissue engineering.[73] The formulation of light-responsive IHs typically involves incorporating photosensitive moieties (such as azobenzene[74] or coumarin[75] derivatives) into biocompatible polymeric matrices. These systems can release encapsulated therapeutic compounds in a regulated manner through photoisomerization, photocleavage, or photothermal activation when exposed to light. In recent years, a number of creative light-responsive hydrogel designs have been published. Yang et al.[76] created an injectable composite hydrogel (HD/Se/ICG) by incorporating indocyanine green (ICG) into a hydrogel network cross-linked via dopamine (DA), sodium selenite (Se), and hyaluronic acid (HA). The selenium-mediated cross-linking prolonged ICG retention within the network and enhanced the photothermal conversion efficiency under NIR light. This method demonstrated notable therapeutic efficacy in inhibiting the growth of breast cancer tumors both in vitro and in animals after intratumoral injection, indicating its promise as a localized breast cancer treatment. Rastogi et al.[77] employed host−guest chemistry to fabricate a light-responsive injectable hydrogel using bifunctional azobenzene and four-arm polyethylene glycol (PEG) (Figure 3). The hydrogel exhibited reversible photoisomerization between cis and trans forms of azobenzene under different light wavelengths (>400 nm and 300−380 nm, respectively). Under UV light irradiation, the transition to the cis form induced a volume contraction in the hydrogel matrix, facilitating the controlled release of a model drug (Alexa Fluor 750).

The photoreactive units embedded within these hydrogel networks act as molecular switches. Upon irradiation, photochromic molecules absorb incident photons and convert optical signals into chemical or thermal signals, triggering a cascade of structural changes such as polymer chain collapse, cross-link cleavage, or heat generation. This mechanistic approach enables the development of highly controllable therapeutic platforms. Li et al.[78] introduced a light-sensitive injectable hydrogel capable of releasing bioactive molecules in the central nervous system upon NIR stimulation. This system was engineered by integrating polypyrrole nanoparticles

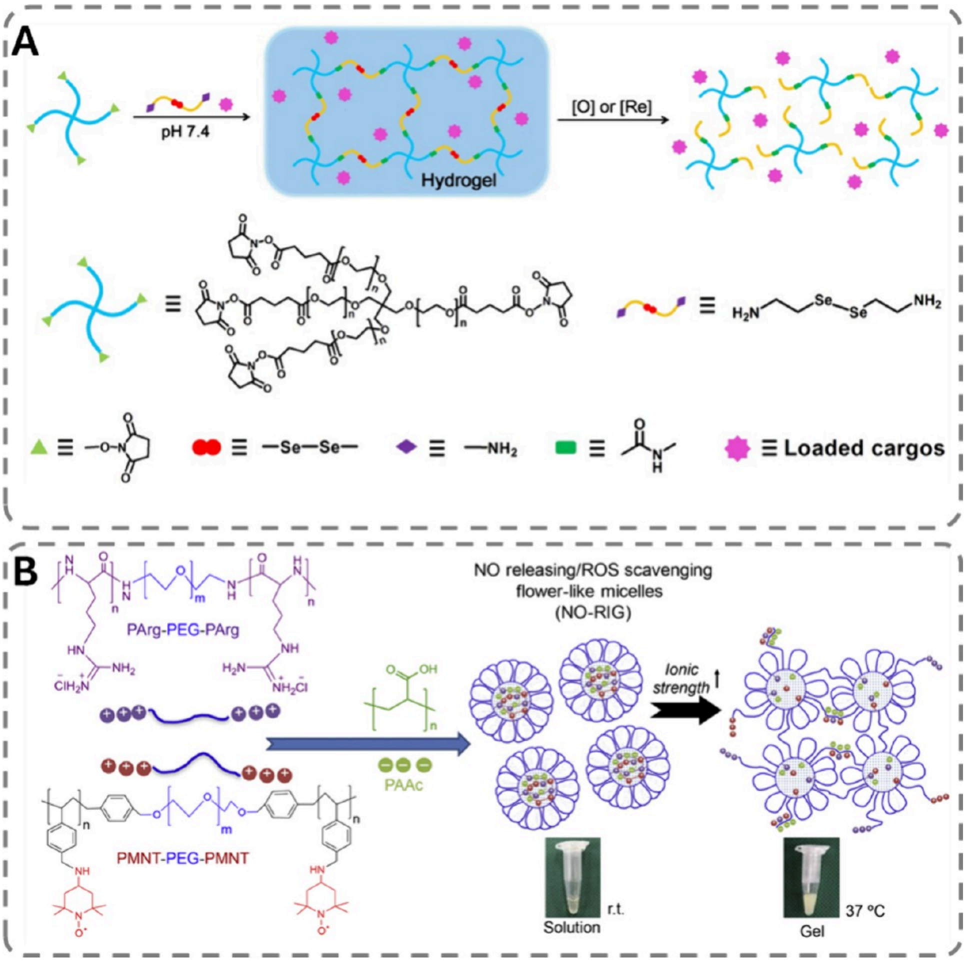

Figure 4. (A) Schematic presentation of the preparation of dual redox-responsive IHs, cargo encapsulation, and controlled release triggered by oxidative or reductive environments, utilizing diselenide-containing PEG networks. Reproduced with permission of ref 83. Copyright 2017 Wiley Periodicals, Inc. (B) Diagrammatic representation and description of the injectable hydrogel that releases NO and scavenges ROS (NO-RIG). With PAAc, flower-type polyion complex (PIC) micelles made of PMNT−PEG−PMNT and PArg−PEG−PArg combine to produce the hydrogel. In this system, PArg−PEG−PArg generates nitric oxide (NO) via macrophage activation, while PMNT−PEG−PMNT scavenges excess reactive oxygen species (ROS) at injury sites. Gelation is induced at 37 °C through partial destabilization of the PIC micelles, resulting in cross-linking and hydrogel formation. Reproduced with permission of ref 84. Copyright 2018 Elsevier.

(photothermal-responsive) with poly(*N*-isopropylacrylamide) (PNIPAM, thermal-responsive), yielding a dual-stimuli-responsive matrix. Both in vitro and in vivo evaluations demonstrated its ability in modulating the release of neurotransmitters such as glutamate, highlighting its therapeutic potential for neurological disorders. Furthermore, a hydrogel-coated upconversion cyanobacterium nanocapsule (UCCy@Gel) was introduced by Liu et al.,[79] wherein the outer methacrylate-based hydrogel provided tissue adherence and stability. The encapsulated upconversion nanoparticles (UCNPs, β-$NaErF_4$@$NaLuF_4$) absorbed deeply penetrating NIR light and emitted higher-energy photons via upconversion luminescence (UCL). This property enabled spatiotemporal control of embedded biological functionalities, suggesting utility in phototherapy, imaging, and remote-controlled drug delivery.

2.1.4. Redox Responsive. Redox-responsive IHs have gained considerable attention due to their ability to undergo reversible chemical and structural transformations in response to redox stimuli.[80,81] These hydrogels are engineered with redox-sensitive functional groups or cross-linkers that undergo reduction or oxidation under physiological conditions, particularly in environments rich in reactive oxygen species (ROS) or reductive agents such as glutathione (GSH) and dithiothreitol (DTT). Numerous intelligent features, like as sol−gel transitions, self-healing, shape memory, and controlled drug release, are made possible by this redox-triggered behavior, which qualifies them for a variety of biological applications.[80,81] Certain functional groups, such as disulfide and diselenide bonds, have redox reversibility, which allows hydrogels to exhibit adaptive mechanical characteristics, control cargo release, and transition between hydrophilic and hydrophobic states.[82,83] One notable example is the development of disulfide-cross-linked hydrogels, which serve as effective platforms for redox-stimuli-responsive drug delivery. Boz et al.[81] developed the synthesis of redox-responsive hydrogels via a thiol−disulfide exchange strategy. Linear telechelic poly(ethylene glycol) (PEG) polymers bearing pyridyl disulfide termini were cross-linked with thiol-functionalized four-arm PEG polymers. This reaction enabled rapid gelation and the formation of microporous hydrogel networks with high water absorption capacity. Crucially, under reductive conditions, as in the presence of DTT or GSH, the hydrogels were able to fully degrade and self-heal thanks to the dynamic disulfide connections. These hydrogels showed promise in regulated drug delivery systems by effectively encapsulating and releasing bovine serum albumin (BSA). Extensively, Gong et al.,[83] fabricated dual redox-responsive IHs with diselenide-containing PEG networks (Figure 4A). Seleno-cystamine was used as the redox-sensitive cross-linker, reacting with *N*-hydroxysuccinimide (NHS)-activated 4-arm PEG through NHS-amine coupling chemistry. This system represents the first report of injectable diselenide-linked PEG hydrogels. The resulting hydrogels were highly sensitive to both oxidative and reductive agents, undergoing degradation at low concentrations of oxidants or reductants. Redox-responsive release profiles were investigated using rhodamine B (RB) as a model drug, proving that this approach can precisely control drug release kinetics in response to redox conditions. Because of these characteristics, diselenide-based hydrogels are intriguing options for redox-responsive drug delivery, especially in cancer treatment applications where the tumor microenvironment is marked by high ROS levels. Additionally, redox-responsive hydrogels are being investigated for targeted treatment of cardiovascular disorders. For example, Vong et al.[84] developed a redox-sensitive formulation composed of PMNT−PEG−PMNT and PArg−PEG−PArg block copolymers blended with poly(acrylic acid) (Figure 4B). When the formulation was injected, temperature variation caused the formation of polyion complex (PIC) micelles that underwent a sol−gel transition. Nitric oxide (NO) release and ROS scavenging capabilities of the resultant hydrogel allowed for targeted treatment at infarcted heart tissue. Through consistent distribution within the heart and reaction to the oxidative milieu, the hydrogel enhanced cardiac function, lowered infarct size, and stimulated angiogenesis after injection.

2.1.5. Enzyme Responsive Injectable Hydrogels.

Enzyme-responsive IHs are a group of smart biomaterials that undergo sol−gel or gel−sol transitions in response to unique enzymatic stimuli, enabling controlled drug release and tissue-specific therapeutic action.[85] These hydrogels consist of cross-linked polymer networks containing enzyme-cleavable moieties that undergo structural changes or degradation when exposed to target enzymes. This responsiveness can be controlled by adjusting the structure, concentration, and type of the enzyme-sensitive linkages to suit specific biological environments. Protease- and glucosidase-sensitive hydrogels are among the most studied systems.[86] Proteases cleave peptide bonds, while glucosidases hydrolyze glycosidic linkages in polysaccharides. Enzyme sensitivity in these hydrogels is often introduced via peptide modifications or DNA self-assembly techniques. Upon enzymatic exposure, the hydrogel either forms or degrades, facilitating localized and time-controlled drug release. Kumar et al.[87] reported an esterase-responsive injectable hydrogel for ulcerative colitis using glycerol monostearate (GMS). Budesonide, dimethyl sulfoxide, and water were mixed with GMS, which upon cooling, self-assembled into a hydrogel due to its amphiphilic nature. This structure effectively encapsulated the hydrophobic drug and provided sustained delivery. Najafi et al.[88] reported enzyme-responsive hydrogels based on micelles formed from HPMA-Cys or HPMA-ETSA, which were cross-linked with pentablock copolymers containing enzyme-cleavable peptide sequences. These hydrogels degraded in response to specific enzymes, allowing controlled drug delivery. Adak et al.[89] developed an MMP-9-responsive hydrogel for neuroprotection, incorporating a hexapeptide (NV) linked via PLGL, a matrix-degradable linker. In the presence of MMP-9, the hydrogel released NV, promoting neural regeneration by mimicking extracellular matrix behavior.

2.2. Based on Polymer Origin

2.2.1. Natural Polymer-Based Injectable Hydrogels.

IHs derived from natural polymers have garnered significant attention in biomedical applications because of their near resemblance to the extracellular matrix (ECM) of biological tissues, intrinsic biocompatibility, and biodegradability.[90] These hydrogels are typically obtained from biological sources like animals, plants, or microorganisms.[91] Since natural polymer-based IHs have a biological origin, they frequently contain biochemical cues that promote cell adhesion, migration, proliferation, and differentiation, all of which are critical for wound healing and tissue regeneration.

One of the most widely studied natural polymers for injectable hydrogel formation is collagen.[92,93] Cells receive biochemical messages and mechanical support from collagen, the most prevalent structural protein in the extracellular matrix. Injectable collagen hydrogels can be formulated to form gels under physiological circumstances, allowing for minimally invasive delivery and localized cell encapsulation. In tissue engineering, collagen hydrogels are ideal for skin, cartilage, and bone regeneration because they encourage cell adhesion and proliferation.[94,95] However, collagen hydrogels often suffer from poor mechanical stability and rapid degradation, which can limit their use in load-bearing tissues unless combined with other reinforcing materials.[93,95]

Hyaluronic acid (HA) is another extensively used natural polymer in IHs.[96] HA is a glycosaminoglycan that is widely present in the vitreous humor of the eye, synovial fluid, and connective tissues.[96] Its unique viscoelastic properties and ability to retain water make HA hydrogels excellent candidates for cartilage repair, ophthalmic applications, and soft tissue augmentation.[97,98] HA-based IHs are often chemically modified to control gelation kinetics, mechanical strength, and degradation rates. The natural presence of HA in the ECM supports cell signaling pathways related to wound healing and tissue remodeling,[99] which is advantageous in regenerative medicine. Nonetheless, native HA hydrogels typically exhibit low mechanical strength, and their fast enzymatic degradation requires stabilization strategies.[100]

Chitosan, a polysaccharide obtained from the deacetylation of chitin found in crustacean shells, presents distinct advantages such as biodegradability, antimicrobial properties, and hemostatic activity.[101,102] Injectable chitosan hydrogels can be prepared through various cross-linking methods, such as ionic gelation and thermal gelation.[103] Chitosan hydrogels have been extensively researched for wound healing, drug delivery, and cartilage regeneration.[102] Their positive charge at physiological pH enables interactions with negatively charged biological molecules and cells, enhancing bioadhesion. However, chitosan's limited solubility at neutral pH and relatively weak mechanical properties often require blending with other polymers or chemical modifications to improve performance.[104]

By ionic cross-linking with divalent cations like calcium ions, alginate, a naturally occurring anionic polysaccharide that is derived from brown seaweed, creates hydrogels.[105] Alginate hydrogels are widely appreciated for their mild gelation conditions, biocompatibility, and ease of injectability. They have been extensively used for drug delivery, cell encapsula-

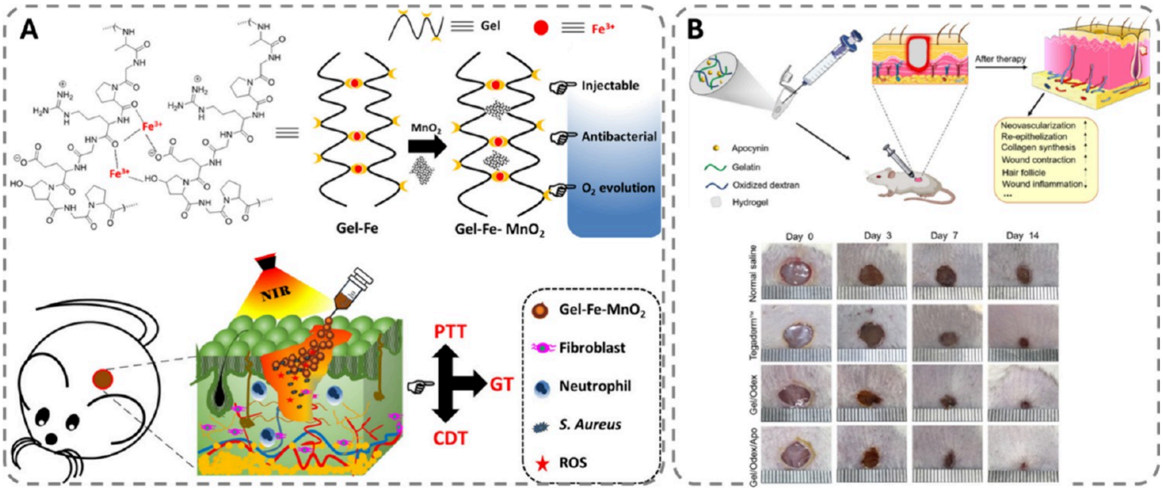

Figure 5. (A) Schematic illustrations depicting the design and multifunctional therapeutic applications of gelatin-based injectable hydrogels with antibacterial, oxygen-generating, and stimuli-responsive properties for advanced wound healing. Reproduced with consent of ref 110. Copyright 2022 American Chemical Society. (B) Schematic illustration and representative images demonstrating the in situ application and therapeutic efficacy of a gelatin-based injectable hydrogel system in a full-thickness wound healing model. Reproduced with consent of ref 108. Copyright 2022 Elsevier.

tion, and tissue engineering.[106] However, unless functionalized with peptides or combined with other bioactive polymers, alginate's lack of particular cell adhesion sites may hinder cell-matrix interactions. The molecular weight and cross-linking density of alginate hydrogels can also have a substantial impact on their mechanical characteristics and degradation behavior.[107]

Gelatin, a denatured form of collagen, inherits many bioactive properties of its precursor, including cell-recognition sites and enzymatic degradability. Thermoresponsive or photo-cross-linkable properties can be included into injectable gelatin hydrogels to allow for *in situ* gelation upon injection. Because of their biocompatibility and biodegradability, gelatin hydrogels have found widespread application in medication administration, wound healing, and cartilage regeneration (Figure 5).[108−110] Despite these benefits, gelatin hydrogels' limited mechanical strength and thermal stability restrict their use as stand-alone materials. To improve their structural integrity, cross-linking with artificial polymers or chemical changes is frequently used.[111]

2.2.2. Synthetic Polymer-Based Injectable Hydrogels.

Synthetic polymeric IHs have become increasingly important in biomedical engineering because of their versatile chemical structures, tunable physical and mechanical behavior, and reproducible synthesis methods. Unlike natural polymers, synthetic polymers can be precisely engineered to achieve desired characteristics such as controlled degradation rates, swelling behavior, mechanical strength, and stimuli responsiveness.[112] These properties make synthetic polymer hydrogels highly adaptable for a broad range of biomedical applications, including drug delivery, tissue engineering, and regenerative medicine. One of the most commonly used synthetic polymers for IHs is poly(ethylene glycol) (PEG).[113] PEG is a hydrophilic, biocompatible, and nonimmunogenic polymer that can be functionalized with reactive groups to enable cross-linking via various mechanisms, including photopolymerization, Michael-type addition, and enzymatic reactions.[113] Because of their limited protein adsorption, regulated breakdown profiles, and adjustable mechanical characteristics, PEG-based IHs are popular for cell encapsulation and controlled drug release. To improve cellular connections, PEG's hydrogels frequently need to incorporate bioactive compounds or peptides because PEG is physiologically inert.[114,115]

PNIPAM is a well-known thermoresponsive polymer widely used for IHs due to its unique lower critical solution temperature (LCST) behavior around 32 °C, close to human body temperature.[116,117] Hydrogels based on PNIPAM can be injected as liquids at room temperature and will form gels *in situ* when exposed to physiological temperature because of their reversible sol−gel transition.[116,117] This property facilitates minimally invasive delivery and localized therapeutic effects. However, PNIPAM hydrogels lack biodegradability, which limits their long-term biomedical use, and efforts are ongoing to develop copolymers or hybrid systems that overcome this limitation.[61,118,119]

Poly(vinyl alcohol) (PVA) is another synthetic polymer generaly used for IHs due to its water solubility, biocompatibility, and film-forming capabilities.[120,121] PVA hydrogels are typically formed by physical cross-linking methods (freeze−thaw cycling) or chemical cross-linking with agents like glutaraldehyde. These hydrogels have been utilized in wound dressings, cartilage repair, and drug delivery.[122] PVA hydrogels exhibit good mechanical strength and flexibility, but their biological inertness requires modification to support cell adhesion and proliferation.

Poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and their copolymer poly(lactic-*co*-glycolic acid) (PLGA) are biodegradable synthetic polymers that are being investigated intensively for IHs with regulated degradation patterns.[123] These polymers degrade into nontoxic metabolites (glycolic acid and lactic acid) that are naturally removed by the body. IHs prepared from PLA, PGA, or PLGA often involve copolymerization with hydrophilic monomers or blending with other polymers to achieve suitable gelation behavior and mechanical properties.[124,125] Such hydrogels are favorable for sustained tissue scaffolding, drug release, and regenerative therapies.[126]

Polyurethane (PU)-based IHs offer excellent elasticity, durability, and tunable mechanical strength.[127,128] It is possible to create PU hydrogels with both hard and soft segments that

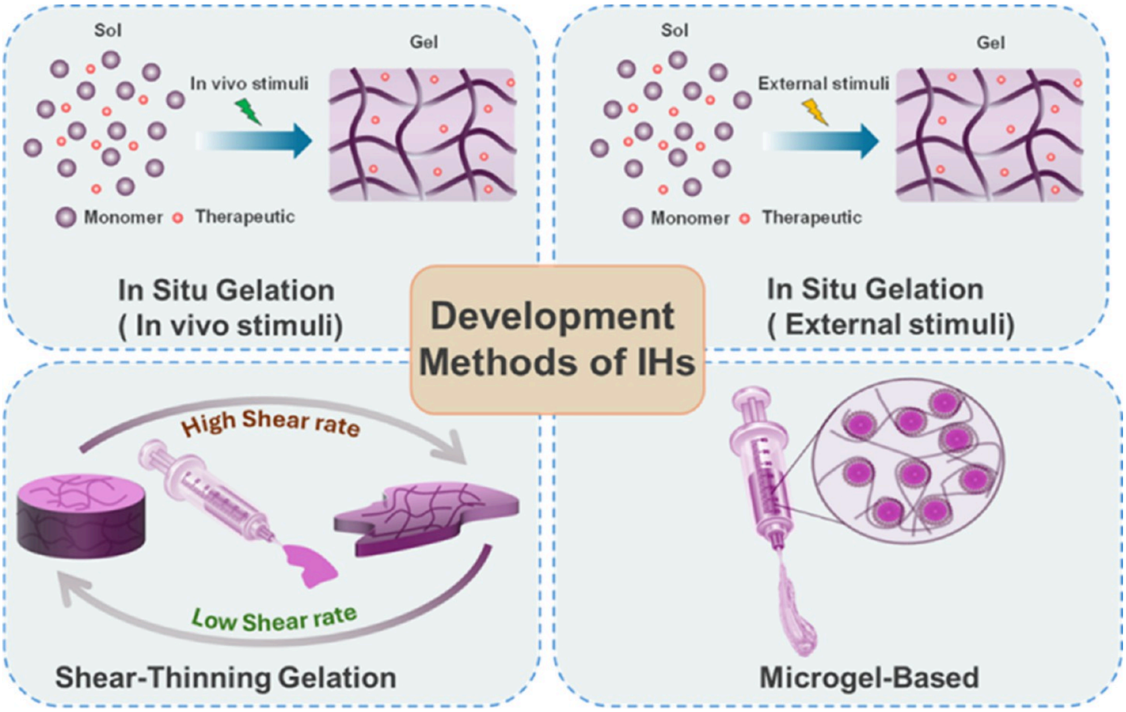

Figure 6. Various techniques employed in the synthesis of IHs.

replicate the mechanical properties of natural tissues. Their chemical versatility allows tailoring of degradation rates, hydrophilicity, and cell interactions. PU hydrogels have been applied in cardiovascular, musculoskeletal, and wound healing applications.[127,129] However, their synthesis often involves complex chemistry and toxic reagents that require careful purification to ensure biocompatibility.

3. MECHANISMS OF INJECTABLE HYDROGEL FORMATION

Due to the extensive utility of IHs, they have garnered significant interest for a broad range of biomedical applications. With respect to conventional hydrogels, IHs offer greater ease of administration owing to their injectability. The formulation strategies for IHs can be categorized into three primary mechanisms: (i) *in situ* gelation, (ii) shear-thinning behavior, and (iii) microgel-based assembly (Figure 6). For in situ gelation systems, liquid precursors undergo sol−gel transitions after injection, triggered by physiological stimuli such as temperature, pH, enzymes, or redox gradients. These systems often utilize thermoresponsive polymers (e.g., PNIPAM), pH-sensitive copolymers, or chemically cross-linkable networks (e.g., via Schiff base or Michael addition), enabling localized gel formation with minimal systemic exposure. Shear-thinning hydrogels exhibit reversible non-Newtonian flow, allowing them to be injected under stress and quickly recover their structure postdelivery. This behavior arises from dynamic interactions such as hydrogen bonding, host−guest inclusion, or reversible covalent bonding (e.g., imine or disulfide linkages), making them ideal for self-healing and conformal applications. Microgel-based assemblies consist of preformed hydrogel microparticles that are injected as a suspension and form cohesive networks via secondary cross-linking or physical interlocking. These systems offer modular design, tunable mechanics, and are well-suited for controlled delivery of drugs and cells. This section aims to provide a comprehensive understanding of these formulation mechanisms, thereby aiding researchers in selecting the most suitable approach for the development of injectable hydrogel systems.

3.1. *In Situ* Gelation

The most extensively explored and widely utilized strategy for designing IHs is *in situ* gelation. In this approach, a pregel solution is administered directly to the target site, where it responds to particular internal or external stimuli by going through a sol−gel transition. Internal stimuli commonly include temperature, pH, enzymes, redox potential, or other bioactive molecules, while external triggers typically involve light or magnetic fields. This method enables the uniform distribution of therapeutic agents within the sol phase and enhances adhesion of the gel to the target tissue postinjection. In contrast, conventional preformed hydrogels often suffer from drawbacks such as excessive leakage and nonuniform drug distribution, making *in situ* gelation a preferred strategy for controlled and localized delivery.

3.1.1. pH-Triggered Gelation. pH-responsive gelation occurs when the pregel formulation undergoes a phase transition upon exposure to specific pH environments. To achieve this, the formulation typically incorporates ionizable functional groups, such as weak bases (amines) or weak acids (carboxylic acids), which respond to environmental pH changes. In acidic conditions, basic functional groups become protonated, generating positively charged species, whereas in basic environments, acidic groups become deprotonated, forming negatively charged species. This ionic behavior facilitates electrostatic interactions or ionic cross-linking, thereby inducing gelation. For instance, Zhang et al.[130] created a pH-responsive IH system for cancer therapy by conjugating methotrexate (a carboxylic acid-containing anticancer agent) and 2,3-dimethylmaleic anhydride (a pH-sensitive linker) to the peptide KKFKFEFEF. Durand et al.[131] introduce a new injectable hydrogel system that responds to osmolarity and pH,

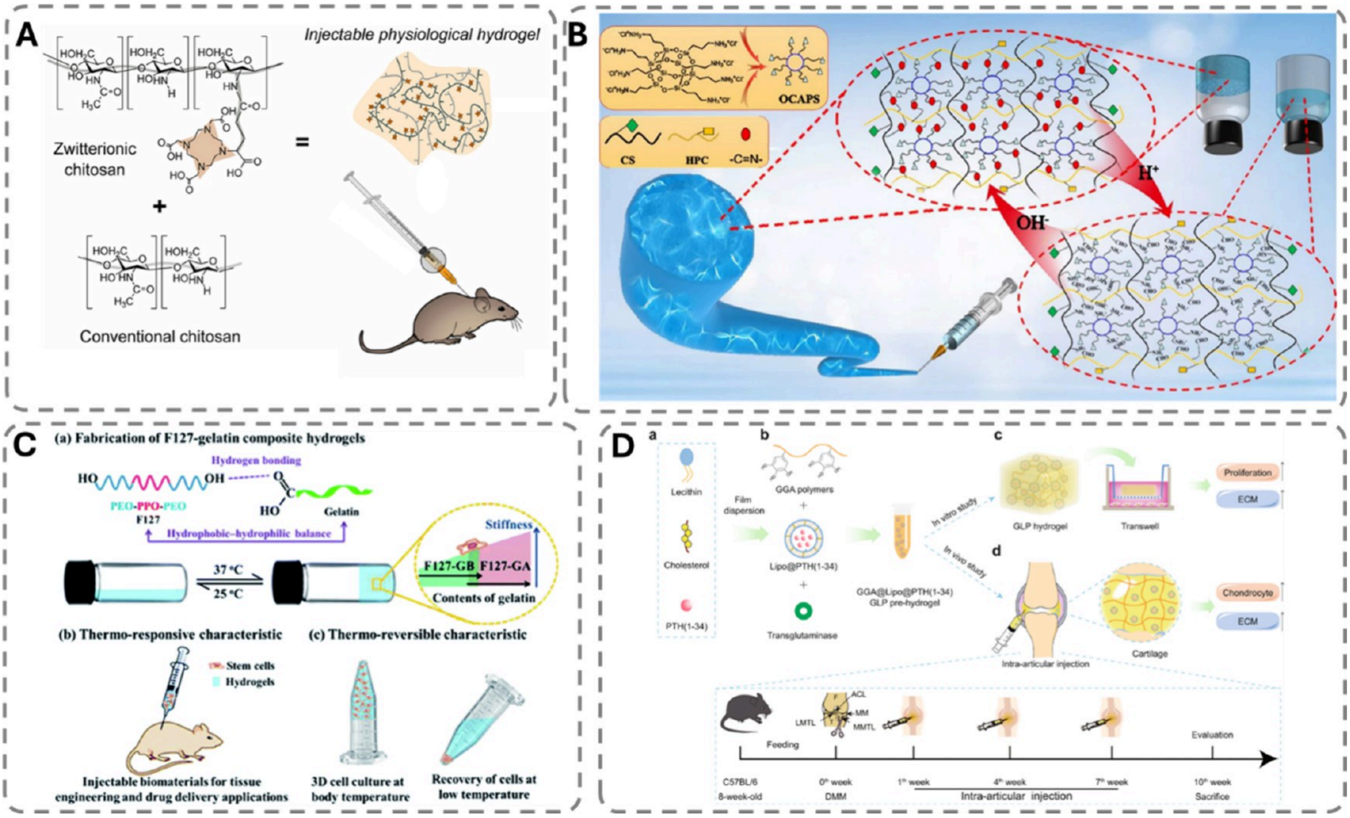

Figure 7. (A) Diagrammatic illustration of the injectable hydrogel system made of zwitterionic and unmodified chitosan that responds to pH and osmolarity. Reproduced from ref 131. Available under a CC-BY 4.0 license. Copyright 2025 Durand et al. (B) Schematic showing the pH-responsive character of the CS/HPC/POSS hydrogel. Reproduced with permission of ref 132. Copyright 2021 Elsevier. (C) Fabrication process of the F127-gelatin composite hydrogel and its potential biomedical applications (PEO: poly(ethylene oxide); PPO: poly(propylene oxide)). Reproduced from ref 133. Available under a CC-BY 3.0 license. Copyright 2017 Yeh et al. (D) Preparation strategy for a liposome-loaded injectable hydrogel system. Reproduced with permission of ref 134. Available under a CC-BY license. Copyright 2023 Li et al.

exhibiting tunable mechanics and quick gelation by zwitterionic chitosan modification. Their thorough structural and in vivo investigations demonstrate its great potential for use in biomedicine (Figure 7A). At physiological pH (7.4), the conjugate remains negatively charged and in a sol state, but upon exposure to a mildly acidic tumor environment (pH ~ 6.5), it transitions to gel state. Additionally, Zhang et al.[132] also synthesized a group of injectable nanocomposite hydrogels via Schiff base reactions between primary amine-functionalized octa(γ-chloroammoniumpropyl) silsesquioxane (OCAPS), chitosan, and aldehyde-functionalized hydroxypropyl cellulose (HPC) (Figure 7B). At mildly basic pH, deprotonation of amine groups initiates cross-linking with aldehydes. When the pH decreases, the system reversibly transitions back to a viscous sol state.

3.1.2. Temperature-Triggered Gelation. Temperature variation across different regions of the human body offers an effective internal stimulus for the *in situ* gelation of IHs. The underlying principle of temperature-responsive gelation lies in the delicate balance between hydrophilic and hydrophobic interactions within the polymeric system.[135] In aqueous environments, such polymers remain soluble at lower temperatures due to dominant hydrophilic interactions. However, upon reaching a critical temperature, a phase transition occurs wherein the polymer becomes more hydrophobic, leading to aggregation and subsequent gelation. This critical temperature is typically defined as either the Upper Critical Solution Temperature (UCST) or Lower Critical Solution Temperature (LCST).[136,137] Polymers exhibiting LCST undergo a sol–gel transition above a specific threshold temperature, while those with UCST exhibit this transition below a defined temperature. For biomedical applications, polymers with an LCST near physiological temperature (~37 °C) are especially useful. These materials maintain a sol state at ambient temperature, making injection simple, and form gel at body temperature, offering mechanical stability and site-specific drug retention. Several naturally occurring polymers, including gelatin, elastin, fibrin, collagen, and agarose,[136] have been widely employed in the fabrication of thermoresponsive IHs due to their inherent biocompatibility and thermogelling behavior. For example, Yeh et al.[133] created a composite hydrogel using gelatin and the amphiphilic block copolymer Pluronic F127 (Figure 7C). This system demonstrated a reversible sol–gel transition within the temperature range of 25–37 °C. Moreover, these F127-gelatin hydrogels demonstrated excellent biocompatibility and supported the viability of human mesenchymal stem cells, making them promising candidates for tissue engineering and regenerative medicine applications. In addition to natural polymers, various synthetic thermoresponsive polymers have been extensively investigated for IHs development. Notable examples include poly(*N*-isopropylacrylamide) (PNIPAM), poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) (PEO–PPO–PEO) triblock copolymers, and poly(ethylene glycol) (PEG)-based block copolymers.[138,139] PNIPAM is particularly suited for biomedical applications since it has an LCST of 37 °C and transitions from hydrophilic

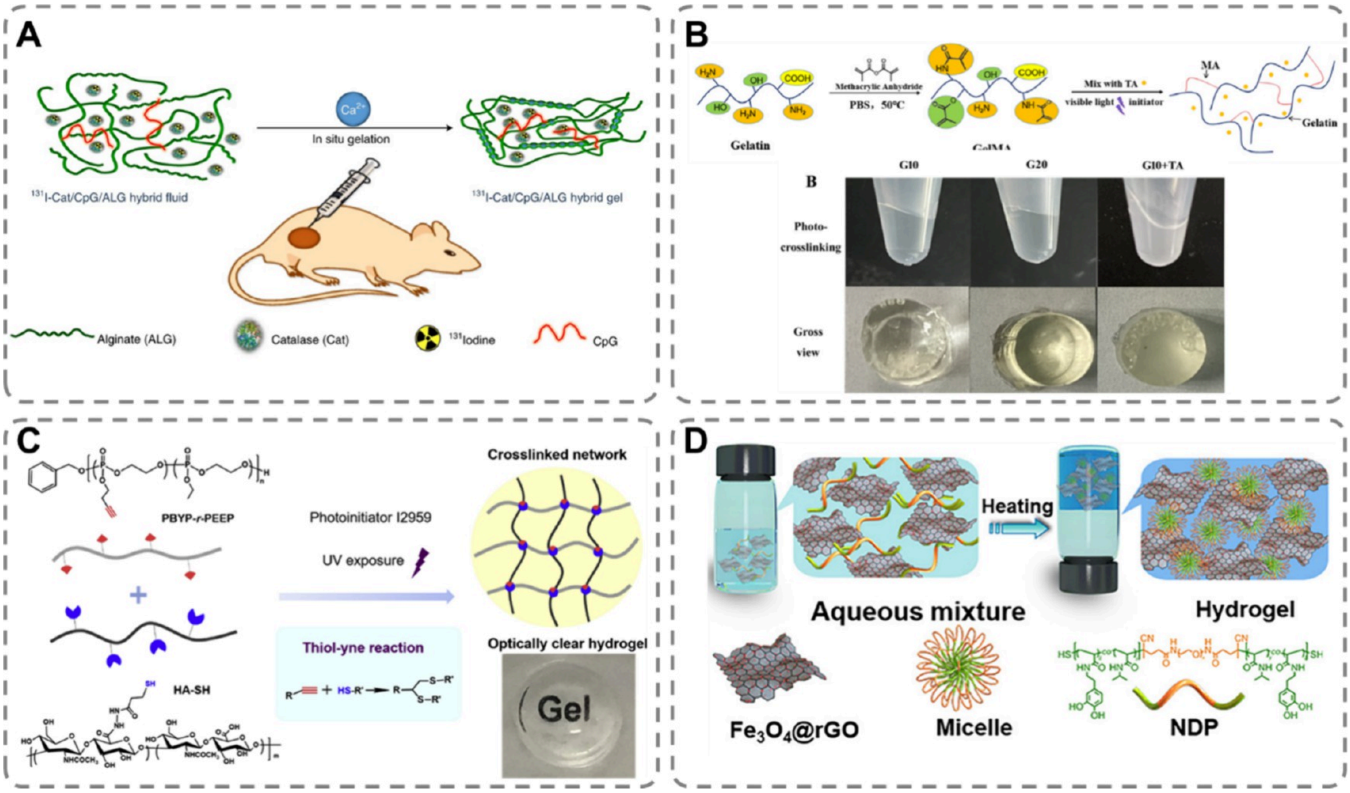

Figure 8. (A) Illustration of *in situ* gelation of the I-Cat/ALG hybrid fluid following direct injection into tumor sites. Reproduced with permission of ref 148. Copyright 2018 Nature Biomedical Engineering. (B) Schematic depicting the synthesis and characterization of gelatin methacrylate. Reproduced from ref 150. Available under a CC-BY license. Copyright 2023 Shen et al. (C) Illustration of the structure and fabrication process of fully biodegradable HA/PPE hydrogels via thiol−ene 'CLICK' photopolymerization. Reproduced with permission of ref 151. Copyright 2019 Elsevier. (D) Schematic representation of the developed biocompatible magnetic-responsive hydrogel using a PNIPAM-based copolymer integrated with iron oxide nanoparticle-decorated reduced graphene oxide. Reproduced with permission of ref 152. Copyright 2022 American Chemical Society.

to hydrophobic above this temperature. For example, Pourjavadi et al.[138] reported a conductive IH system comprising PNIPAM-modified gold nanoparticles (AuNPs), chitosan, and κ-carrageenan. This composite hydrogel exhibited excellent thermoresponsiveness, injectability, and mechanical integrity. Upon administration to the target site, the pregel solution underwent a sol−gel transition driven by the local physiological temperature exceeding PNIPAM's LCST, facilitating localized therapeutic delivery.

3.1.3. Enzyme-Triggered Gelation.

In enzyme-responsive IHs, a sol−gel transition results from cross-linking that is started by the presence of particular enzymes at the targeted spot. This approach offers regio- and stereospecific gelation due to the unique expression and localization of enzymes in various tissues and organs.[140,141] As enzymes function as biological catalysts, the cross-linking reaction is rapid, enabling fast gelation while eliminating the need for additional chemical cross-linkers or external stimuli.[142−146] For effective gelation, the precursor materials must contain functional groups specifically recognized by the active site of the target enzyme. For instance, Li et al.[134] created an innovative enzyme-responsive IH system termed GGA@Lipo@PTH(1−34) (abbreviated as GLP), designed for intra-articular administration to support cartilage regeneration and treat osteoarthritis (Figure 7D). The system utilizes transglutaminase, an enzyme naturally present in joint tissues, to trigger rapid *in situ* gelation within approximately 5 min. In this study, a gelatin-based polymer (GGA) was created by grafting gallic acid onto gelatin by the creation of an amide connection between the carboxyl groups of gallic acid and the amino groups of gelatin. Later, the GLP pregel formulation was created by adding liposomes containing the therapeutic peptide teriparatide [PTH(1−34)] to the GGA solution. Upon intra-articular injection, the TG present in the joint catalyzed the cross-linking of the hydrogel matrix, leading to rapid gel formation. The resulting hybrid hydrogel enabled sustained release of PTH(1−34), promoting the proliferation of ATDC5 chondrocytic cells, enhancing glycosaminoglycan (GAG) synthesis, and reducing degradation of the cartilage extracellular matrix (ECM). This study highlights the potential of enzyme-triggered IHs as minimally invasive platforms for targeted drug delivery and tissue regeneration.

3.1.4. Ions-Triggered Gelation.

Ion-triggered gelation is among the most extensively employed *in situ* gelation strategies due to its controllable and mild gelation conditions, rapid gel formation, and the absence of toxic cross-linking agents.[143] This gelation mechanism is primarily based on the coordination interaction between electron-donating functional groups (e.g., carboxylate anions) present in the pregel matrix and multivalent cations (commonly Ca^{2+}) available at the targeted site. A broad range of ionizable polymers, like poly(acrylic acid), alginate, and pectin, are frequently used as pregel components. These polymers can coordinate with various physiologically relevant cations, including Na^+, K^+, Ca^{2+}, and Ba^{2+}, thereby inducing gel formation via ionic cross-linking.[143,147] For instance, Chao et al.[148] developed IHs utilizing catalase, alginate, and oligonucleotide-based biocompatible components (Figure 8A). Upon administration at the tumor site, the hydroxyl and carboxyl groups in the pregel network interact with endogenous Ca^{2+} ions, leading to rapid coordination-driven sol−gel transition at the molecular level. Similarly, Yan et al.[149] employed calcium carbonate ($CaCO_3$) as a sustained Ca^{2+} source to facilitate *in situ* gelation. In their system, hydroxyapatite, gelatin microspheres, and glucono-δ-lactone were incorporated along with $CaCO_3$. Upon slow release of Ca^{2+}, coordination with donor sites in the pregel formulation promoted gelation and enhanced the mechanical integrity of the hydrogel.

3.1.5. Phototriggered Gelation. Phototriggered gelation refers to the sol−gel transition of a pregel solution upon exposure to light. Among the various external stimuli employed for the formation of IHs, light irradiation is particularly advantageous due to its excellent spatial and temporal control, along with compatibility with physiological conditions such as ambient temperature and pH.[153] This strategy predominantly involves photochemical cross-linking reactions, including radical polymerization (e.g., of acrylates), photoinduced click reactions, and Diels−Alder cycloadditions.[153−156] In this approach, biocompatible polymers functionalized with photoresponsive moieties, such as acrylates, methacrylates, and acrylamides, are employed. Upon light irradiation, a photoinitiator generates free radicals that initiate polymerization or cross-linking by covalently linking the photoactive groups, resulting in gel formation. Commonly used biocompatible macromolecules for photofunctionalization include gelatin and polyethylene glycol (PEG),[153,157] which are often modified with acrylate groups to form pregel precursors suitable for phototriggered gelation. For example, Shan et al.[150] created a gelatin−methacrylate (GelMA)-based pregel formulation for the synthesis of an injectable hydrogel (Figure 8B). Upon exposure to visible light (wavelength = 405 nm) for 60 s, photoinitiator-induced radical polymerization of the methacrylate groups led to rapid *in situ* gelation. The resulting hydrogel exhibited good biocompatibility and was effectively used for the controlled release of triamcinolone acetonide. Another well-established strategy for phototriggered gelation involves thiol−ene and thiol−yne photoclick chemistry.[155] For example, Hao et al.[151] designed a biodegradable hydrogel based on hyaluronic acid. The pregel formulation consisted of a yne-functionalized copolymer, poly(butynyl phospholane)-*random*-poly(ethylethylene phosphate), and thiol-modified hyaluronic acid, along with the photoinitiator Irgacure 2959 (Figure 8C). A thiol−yne click reaction took place after exposure to UV light (λ_{max} = 365 nm), resulting in the creation of a cross-linked hydrogel network.

One of the primary challenges associated with phototriggered in situ gelation is the effective delivery of light to the injected precursor material within biological tissues. This approach is generally well-suited for applications involving superficial or anatomically accessible sites, such as the skin, oral cavity, or ocular surface, where direct light exposure is feasible.[158,159] For applications targeting deeper tissues, controlled illumination can be achieved through intraoperative techniques utilizing optical fibers or endoscopic light delivery systems.[160] Furthermore, recent developments in photochemistry have facilitated the incorporation of NIR light-responsive systems and upconversion nanoparticles[161] (UCNPs), which allow deeper tissue penetration due to the superior transmission of NIR[162] wavelengths compared to ultraviolet (UV) light. These advancements have significantly broadened the clinical scope of photoresponsive hydrogels, enabling their application in both surface-level and minimally invasive biomedical interventions.

3.1.6. Magnetic Field Triggered Gelation. The term "magnetic field-triggered gelation" describes the *in situ* sol−gel transition of a pregel solution when an external magnetic field is present. In this approach, the pregel formulation is supplemented with magnetic nanoparticles, typically paramagnetic or ferromagnetic materials such as Fe_3O_4, Fe_2O_3, or $CoFe_2O_4$,[163] alongside thermoresponsive polymer components. The mechanism depends on the transformation of magnetic energy into heat energy, even if magnetic fields do not directly start chemical cross-linking. Localized heat generation results from the Néel and Brownian relaxation of magnetic nanoparticles in the presence of an alternating magnetic field. This generated heat causes the system's temperature to rise, which in turn causes the sol−gel transition in thermoresponsive polymers with LCST behavior, such as PNIPAM. For example, Yan et al.[152] created a biocompatible magnetic-responsive hydrogel using a PNIPAM-based copolymer integrated with iron oxide nanoparticle-decorated reduced graphene oxide (Figure 8D). Upon exposure to an alternating magnetic field for 10 min, the system's temperature increased from 20 to 49 °C due to the magnetic heating effect. This thermal rise surpassed the LCST of the PNIPAM segment, inducing a rapid sol−gel transition. This indirect yet efficient strategy offers spatial control over gelation and holds promise for remote-controlled, targeted delivery and minimally invasive biomedical applications.

In case of in situ gelation systems, where the sol-to-gel transition occurs directly within the physiological environment, a critical concern is the potential presence of residual unreacted monomers or reactive intermediates, which may pose risks of cytotoxicity or adverse local tissue responses. To ensure complete gelation and reduce the risk of residual unreacted species such as acrylates and amides, in situ-forming injectable hydrogels are typically designed with stoichiometrically balanced functional groups and utilize efficient cross-linking reactions that proceed rapidly under physiological conditions.[165] Reactions such as Schiff base formation, Michael-type additions, and disulfide exchange are particularly favored due to their bio-orthogonality, fast kinetics, and operation under mild, aqueous environments, making them suitable for biomedical applications.[166] Furthermore, physically cross-linked systems, such as temperature- or pH-responsive hydrogels, offer the advantage of avoiding reactive monomeric precursors, thereby reducing the risk of cytotoxicity. To validate safety and ensure that gelation is sufficiently complete, in vitro and in vivo evaluations, including cytotoxicity testing, are routinely employed. These assessments are critical for minimizing local inflammatory responses or tissue toxicity associated with residual reactive groups.

In addition to tunable responsiveness, the structural stability of injectable hydrogels under physiologically relevant and fluctuating conditions is essential for in vivo performance. Most SIHs maintain their integrity within moderate environmental ranges of pH (4.0−8.0), temperature (25−45 °C), and ionic strength (∼150 mM NaCl).[167,168] For instance, thermoresponsive systems such as PNIPAM-based hydrogels undergo reversible sol−gel transitions near physiological temperature and remain functionally stable across multiple heating−cooling cycles. Similarly, pH-responsive hydrogels derived from PMAA, chitosan, or poly(histidine) display reversible behavior in mildly acidic to neutral conditions. However, extreme pH or salt concentrations can lead to hydrolytic degradation or loss of network order. Therefore, approaches such as covalent cross-linking, block copolymer stabilization, and incorporation of buffering or osmotic regulators are employed to enhance robustness and ensure reproducible performance in biologically dynamic settings.

3.2. Gelation by Shear Thinning Process

A flexible and popular type of IHs, shear-thinning hydrogels are distinguished by their capacity to flow under applied tension and quickly regain their gel-like structure after the stress is removed.[169] This behavior arises from the dynamic and reversible nature of the internal cross-linking within the hydrogel network, which allows a transition between gel and sol states. When subjected to high shear or strain, such as during injection through a syringe, the cross-linking interactions within the gel temporarily dissociate, leading to fluid-like behavior. Upon cessation of the external force, the original structure is restored, allowing the hydrogel to regain its mechanical integrity. These systems' reversible nature is controlled by either noncovalent physical interactions or dynamic covalent bonding. Reversible covalent chemistries commonly used in shear-thinning hydrogels include Schiff base reactions,[170−174] disulfide exchange,[175,176] Michael addition,[177,178] and Diels−Alder cycloaddition.[179−181] Among these, Schiff base chemistry is frequently utilized, wherein carbonyl groups (e.g ketones or aldehydes) react with amine functionalities to form dynamic bonds like imines, hydrazones, or oximes.[182] For example, Lei et al.[183] synthesized a shear-thinning hydrogel using hydrazide-modified hyaluronic acid and aldehyde-functionalized hyaluronic acid. The dynamic covalent bonding through hydrazone formation enabled rapid gelation and excellent injectability. According to rheological measurements, the hydrogel could flow through a 0.6 mm needle and rapidly regain its structure after injection. It also showed a drop in viscosity as the shear rate increased. For example, Chen et al.[164] reported a keratin-based hydrogel exhibiting shear-thinning behavior through thiol−disulfide exchange reactions (Figure 9). The hydrogel system was composed of free thiol-containing keratin and disulfide-linked keratin, where disulfide bond reshuffling occurred under basic conditions (pH > 9.5). Rheological analysis demonstrated that this dynamic exchange mechanism supported the reversible sol−gel transition, making the material suitable for injection and delivery applications. Noncovalent interactions like hydrogen bonds, van der Waals forces, hydrophobic contacts, and electrostatic forces can also promote shear-thinning behavior in addition to reversible covalent bonds.[184,185] These physical interactions enable gel formation via spontaneous self-assembly without requiring additional cross-linking agents. Yan et al.[186] developed a β-hairpin peptide-based hydrogel that relied on hydrogen bonding and hydrophobic interactions for gelation. Upon exposure to high shear, the network disassembled into a fluid state and reassembled into a gel after removal of the shear force. Detailed structural analysis using rheology, small-angle X-ray scattering (SAXS), and rheo−small-angle neutron scattering (rheo-SANS) confirmed the dynamic and reversible nature of the system. This hydrogel also demonstrated excellent biocompatibility and was successfully used as a carrier for live cell delivery. Shear-thinning hydrogels are especially appealing for a variety of biomedical applications, such as drug delivery, tissue engineering, and regenerative medicine, because they provide exceptional processability, injectability, and quick structural recovery.

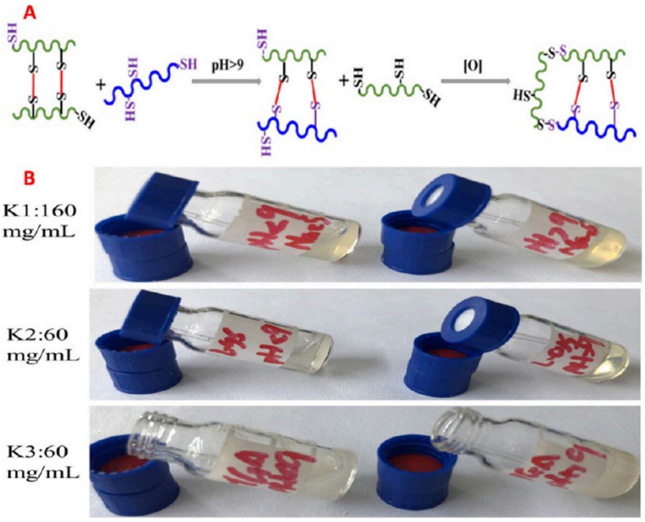

Figure 9. (A) The gelation mechanism of DCC gel is depicted, involving thiol−disulfide bond exchange under alkaline conditions. (B) Keratin hydrogels demonstrate pH-dependent behavior, remaining as a sol at neutral pH (7.4) and undergoing gelation under basic conditions (pH 9.5−10.0). Reproduced with permission of ref 164. Copyright 2021 Elsevier.

3.3. Microgel-Derived Injectable Hydrogel

Microgels offer a highly effective approach for producing IHs by physically downsizing bulk gels to microscopic dimensions, typically under 400 μm, facilitating their smooth delivery through syringe needles. Granular hydrogels and hydrogel microspheres (HMs) are two common types of microgels.[187−190] Four widely adopted fabrication strategies include microfluidics,[191,192] emulsification,[193] extrusion fragmentation, and electrospray techniques for microgel formulation. The microfluidic method employs microchannel devices, commonly made from poly(dimethylsiloxane) (PDMS), to create highly uniform droplets in an oil-based continuous phase, which are then cross-linked to form microspheres.[194] By tuning parameters such as flow rates, channel geometry, and interfacial tension, particle sizes can be adjusted between 5 and 1000 μm.[195] This technique excels in producing monodisperse particles, often achieving coefficient of variation values as low as 1−2%.[195] However, a major drawback is its limited production rate, making large-scale manufacturing challenging.

Emulsification, in contrast, is better suited for mass production. This process involves the vigorous mixing of aqueous hydrogel precursors into an oil phase, leading to the formation of microspheres with a broader size distribution. Key variables such as stirring speed, surfactant levels, and the oil-to-water ratio influence particle characteristics. Although it lacks the precision of microfluidics, this method stands out for its simplicity, rapid processing, and scalability. For example, Yuan et al.[193] utilized this approach to fabricate porous microspheres from gelatin methacryloyl (GelMA), applying gradient cryogelation to introduce internal structural variations influenced by different cooling regimes (Figure 10A).

Extrusion fragmentation takes a mechanical route, where pre-crosslinked bulk hydrogels are pushed through small

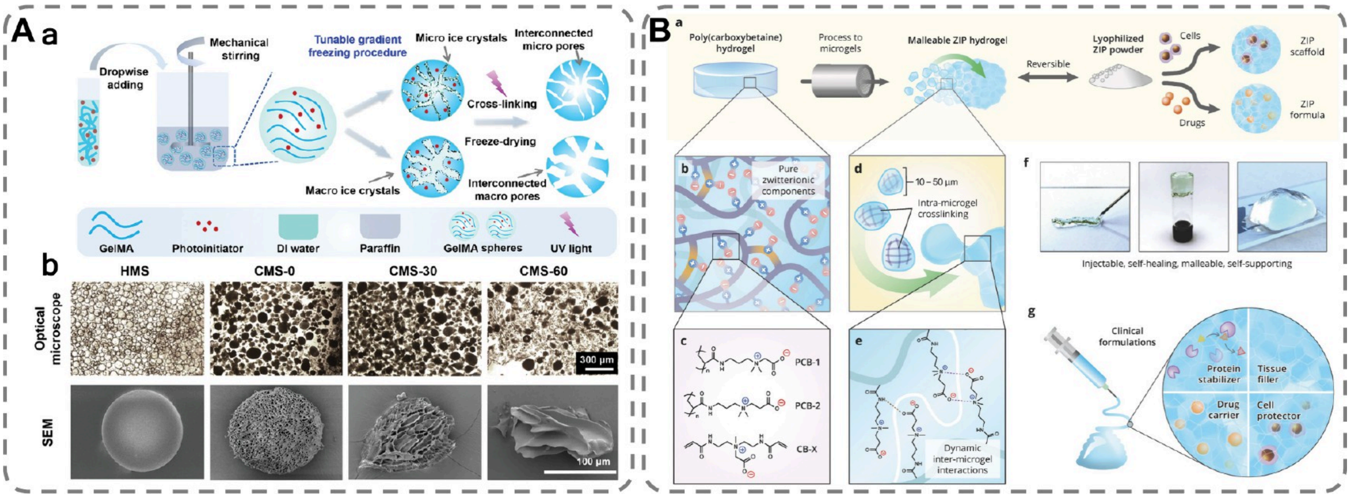

Figure 10. (A) (a) Diagrammatic representation of CMS production via gradient-cooling cryogelation and the emulsion approach. (b) Optical microscopy and SEM images of HMS, CMS-0, CMS-30, and CMS-60. Reproduced with permission of ref 193. Copyright 2021 Wiley-VCH GmbH. (B) Overview of the construction, properties, and applications of ZIP hydrogels. (a) Schematic of ZIP gel fabrication, which involves lyophilization for easy formulation and mixing with therapeutics. (b-c) Hydrogels are composed of zwitterionic polymers (PCB-1 or PCB-2) and cross-linker (CB-X). (d) Covalent cross-links within microgels provide structural support and elasticity. (e) Dynamic interactions enable self-assembly into viscoelastic bulk materials. (f) ZIP gels are injectable, self-healing, and shape-retaining. (g) Applications include soft tissue fillers, therapeutic delivery, and cell scaffolds. Reproduced with permission of ref 196. Copyright 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

apertures or meshes, physically breaking them into microsized particles. This oil- and surfactant-free technique maintains the original biocompatibility and properties of the gel.[197] Resulting microgels are often irregular in shape and show enhanced porosity, reduced average pore sizes, and improved mechanical strength. A notable example is the zwitterionic injectable pellet (ZIP)[196] microgel, which demonstrated superior injectability, self-healing behavior, and mechanical protection, making it perfect for uses such as the delivery of drugs or cells (Figure 10B).

Electrospray, adapted from electrohydrodynamic processes, is a more recent innovation that uses a high-voltage field to generate fine, charged droplets from a hydrogel solution. These droplets rapidly solidify upon reaching a collecting surface. Xie et al.[198] used this technique to create highly uniform GelMA microspheres (∼100 μm) with excellent monodispersity, by adjusting variables such as applied voltage, nozzle size, gas pressure, and different jet modes (like Taylor or oscillating jets). This method allows fine control over particle size and high encapsulation efficiency, though it is technically complex, relies on high-voltage equipment, and presents difficulties in microsphere collection.

4. DESIGN CONSIDERATIONS FOR INJECTABLE HYDROGELS

The design of IHs involves a multidisciplinary approach that balances injectability, biocompatibility, responsiveness to stimuli, and mechanical stability. After being administered by minimally invasive procedures, these systems must form a gel *in situ* while maintaining functionality specific to the application, whether it is drug delivery, tissue engineering, or environmental remediation.

4.1. Polymer Selection and Biocompatibility

The foundation of any injectable hydrogel lies in the careful selection of its polymeric components. Both natural and artificial polymers have been extensively utilized to formulate injectable systems. Natural polymers commonly used for IHs formulation, such as hyaluronic acid,[199] gelatin,[200] alginate,[201] and chitosan,[102] offer intrinsic biocompatibility, biodegradability, and often possess bioactive motifs that promote cell adhesion and proliferation. However, they often lack mechanical robustness and structural consistency.[202] However, synthetic polymers, including PEG,[113] PNIPAM,[203] poly(caprolactone),[204] and PLGA,[63] provide greater control over chemical structure, stimuli responsiveness, and degradation rates for IHs formulation. These synthetic systems are easily tunable to meet specific clinical needs but may require functionalization to improve bioactivity and compatibility with cells or tissues.[205] Importantly, any polymer selected for hydrogel formulation must demonstrate noncytotoxicity, nonimmunogenicity, and suitable degradation kinetics aligned with the intended therapeutic time frame.

4.2. Gelation Mechanism and Injectable Behavior

IHs are designed to sol–gel transition under physiological conditions, typically upon exposure to body temperature, pH, or ionic strength. Thermosensitive systems, based on PNIPAM[138] or Pluronic F127,[206] undergo sol–gel transition near 37 °C, facilitating minimally invasive administration and *in situ* gelation. Similarly, pH-responsive hydrogels take advantage of ionizable functional groups to initiate cross-linking or conformational changes under specific pH conditions. The mechanism of gelation, whether physical (e.g., ionic interactions, hydrogen bonding) or chemical (e.g., covalent cross-linking via Michael addition, click chemistry, Diels–Alder reaction, or enzymatic reactions), must be rapid and predictable to ensure homogeneous gel formation postinjection. Moreover, shear-thinning behavior is highly desirable as it enables ease of injection through narrow-bore needles while recovering mechanical integrity immediately after administration. This characteristic is crucial for guaranteeing the hydrogel's structural integrity in vivo without sacrificing patient comfort or precise administration.

Table 1. A Comparative Analysis of Strategies for Injectable Hydrogel Fabrication with Respect to Scalability, Economic Feasibility, Formulation Complexity, and Industrial Applicability

synthetic strategies	scalability	cost efficiency	formulation complexity	industrial advantages
in situ gelation (e.g., pH-, temperature-, enzyme-, redox-responsive)	moderate to high	high	low to moderate	• simple formulation and injection. • uses physiological conditions. • no external energy input.
in situ photo-induced gelation (e.g., GelMA, PEGDA with UV/visible light)	moderate	moderate to low	high	• precise spatial-temporal control. • on-demand gelation. • suitable for complex tissue architecture.
in situ ion-triggered gelation (e.g., alginate-Ca^{2+} systems)	high	high	low	• simple, rapid, and mild gelation. • widely used in cell encapsulation and 3D printing. • no toxic initiators.
shear-thinning (e.g., dynamic covalent bonds like Schiff base, disulfide, or physical interactions)	high	very high	low	• injectable through narrow needles. • self-healing and fast recovery post-injection. • scalable using standard sterile production methods.
microgel-based hydrogels (e.g., microfluidics, emulsification, electrospray, extrusion)	low to moderate	variable	high	• high drug/cell encapsulation efficiency. • controlled release profiles.

While significant progress has been made in designing injectable hydrogels with advanced functionalities, industrial feasibility remains a key determinant for clinical translation. Among the three primary injectable formulation approaches, shear-thinning hydrogels offer the most favorable profile for large-scale production (Table 1). These systems rely on physical or dynamic covalent interactions, require no external triggers, and are compatible with standard sterile manufacturing environments. In situ gelation approaches, particularly those triggered by physiological temperature, pH, or enzymes, are also scalable, but they require careful control of precursor stability, gelation kinetics, and potential byproduct safety to ensure reproducibility. On the other hand, microgel-based injectable systems, though highly modular and well-suited for payload delivery, involve complex, multistep fabrication processes and currently face limitations in throughput during microfluidic or emulsification-based production.

4.3. Mechanical Properties and Degradation Kinetics

The mechanical integrity of IHs plays a vital role in determining their functional stability, especially in load-bearing or dynamically active biological environments.[165] The cross-linking density, polymer chain length, and architecture significantly influence the stiffness, elasticity, and resilience of the gel. In order to replicate the extracellular matrix (ECM), withstand physiological stresses, and promote cellular infiltration and nutrition diffusion, hydrogels used in tissue engineering must have enough mechanical support.[165] Additionally, the degradation profile of the hydrogel must match the intended therapeutic window.[165] A balance must be maintained between the rate of degradation and the rate of tissue regeneration or drug release. Biodegradation can be tuned via hydrolytically or enzymatically labile linkages within the polymer backbone or cross-links.[207] Importantly, degradation byproducts must be nontoxic and readily removed from the body to prevent long-term accumulation or inflammatory responses.

4.4. Biofunctionality and Therapeutic Payload Delivery

For successful clinical translation, IHs must exhibit high biofunctionality, supporting not only passive functions like filling space or acting as a depot, but also actively participating in therapeutic outcomes. Integration of bioactive ligands such as RGD peptides[208] or growth factors[209] can enhance cellular attachment, migration, and differentiation. Hydrogels designed for controlled drug delivery must ensure stable encapsulation, uniform distribution, and tunable release kinetics of medicinal agents, such as small molecules, proteins, peptides, nucleic acids, or even living cells.[168] The hydrogel network's mesh size, the affinity between the polymer and the payload, and the degradation-mediated diffusion collectively determine the release behavior. In stimuli-responsive systems, release can be externally triggered with the change in temperature, pH, redox environment, or enzymatic activity, enabling spatial and temporal control over therapeutic delivery. Ensuring immunological compatibility is equally important, as the hydrogel must minimize inflammatory responses and foreign body reactions upon administration.[210] Designing such multifunctional hydrogels requires an integrative approach that bridges materials chemistry, molecular biology, and biomedical engineering.

5. CUTTING-EDGE PROGRESS IN SMART INJECTABLE HYDROGEL TECHNOLOGY

Hydrogels are 3D networks contain a large amount of water in it.[211,212] They are cross-linked by different hydrophilic polymers via physical noncovalent connections, chemical covalent bonds, or a mix of the two.[213,214] In 1894, the word ″hydrogel″ was first used in scientific publications.[215] In the 1970s, the introduction of stimuli-responsive features to hydrogels enabled them to react to particular environmental triggers, such as pH[216] and temperature.[217] The characteristics of traditional hydrogels are largely influenced by their cross-linking density and polymer makeup, which considerably restrict their internal architecture and mechanical durability.[218] In addition to enabling numerous new applications (like direct injection followed by *in situ* gelation, producing HMs, injectability depending on shear-thinning property, and participating to 3D printing as bioink), emerging chemistry (dynamic-covalent coupling)[219] and new techniques (microfluidics techniques)[220] have also helped to modify the

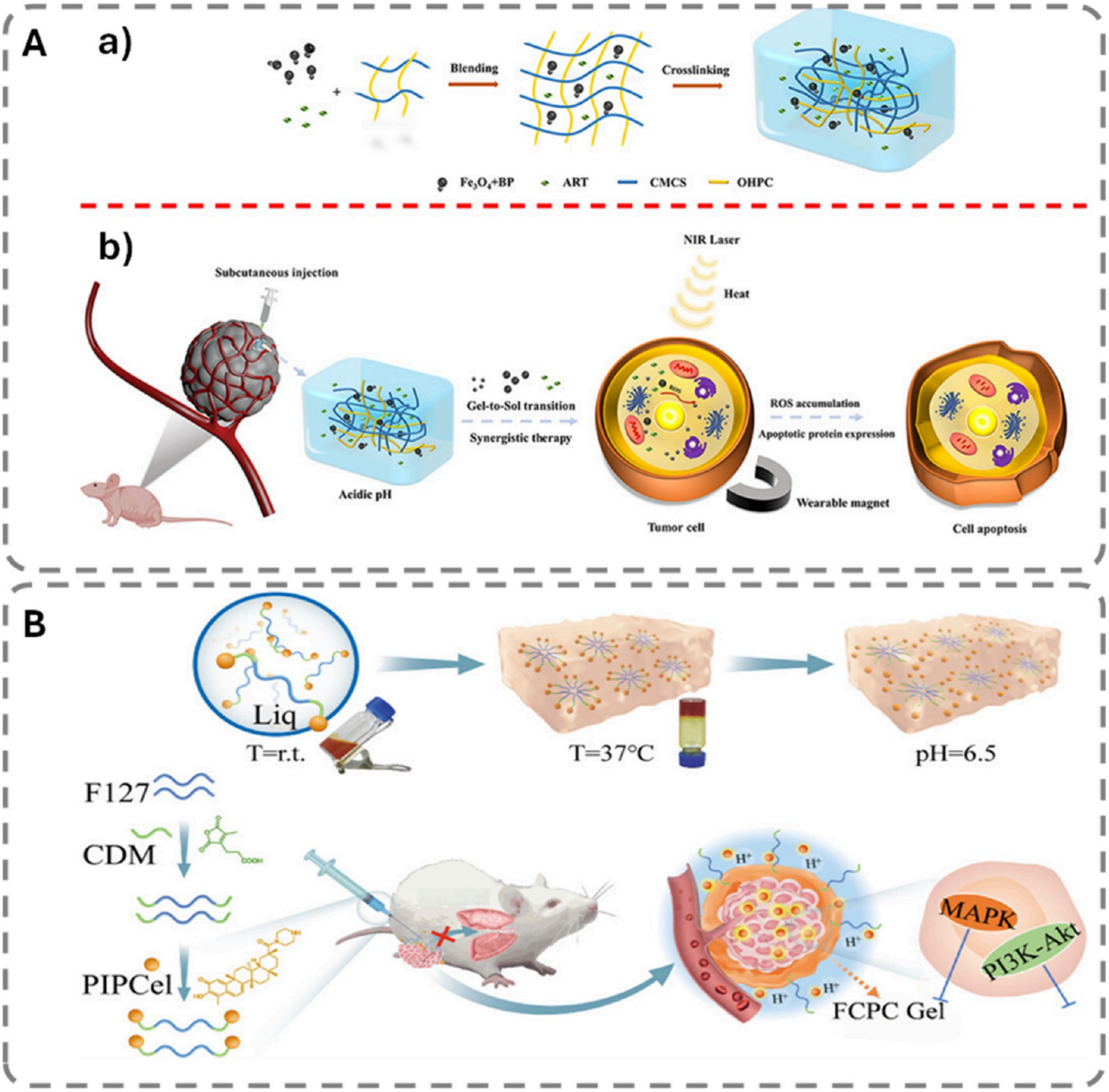

Figure 11. (A) (a) Schematic illustration depicting the formation of a smart injectable composite hydrogel created by cross-linking oxidized hydroxypropyl cellulose with carboxymethyl chitosan, integrated with artesunate (ART), ferroferric oxide (Fe_3O_4) nanoparticles, and black phosphorus (BP) nanosheets. (b) Various functionalities of the drug delivery system (DDS) include magnetic targeting, pH responsiveness, chemodynamic therapy, and photothermal effects. Reproduced with permission of ref 229. Copyright 2023 American Chemical Society. (B) Diagrammatic representation of the FCPC-based thermosensitive drug delivery system. Reproduced with permission of ref 235. Copyright 2025 American Chemical Society.

character of typical hydrogels and resolved many of their remaining drawbacks.[221]

5.1. Biomedical Applications

In biomedicine and tissue engineering, amazing things have been accomplished, like the development of hydrogels.[221] Hydrogels' potential for healthcare and the treatment of human diseases is still being explored, nevertheless, and work is being done to increase the biomaterial's benefits and usefulness in the fight against various pathophysiological processes.[221] The therapeutic effects of many conventional hydrogels were limited because they were manufactured with predetermined shapes before use, making them unable to precisely fill irregular voids after solid tumor removal or massive, intricate bone deformities.[222,223] IHs are more enticing and promising than hydrogels made traditionally since they are simple to inject and can quickly conform to the irregular shape of the targeted tissues or flaws.[224] IHs are able to easily fill deep holes and lesions while also dispersing the therapeutic cargo they contain over a long period of time to the surrounding tissue.[225,226] In addition, IHs, a minimally invasive technology that can be injected locally, can minimize blood loss and trauma caused by surgery, or even prevent invasive surgery. Moreover, they can use a tunable sol−gel transition to get beyond the clinical and surgical restrictions of conventional hydrogel stenting, which has increased patient compliance and therapeutic efficacy.[227]

5.1.1. Drug Delivery. Numerous medications can be contained within the mesh of hydrogels, which are networks of hydrophilic polymers.[228] In this manner, chemotherapeutic medications with acceptable water solubility can be easily incorporated into hydrogels' structures.[229,230] To ensure localized and prolonged drug release at the target region, these hydrogels are made to stay in a sol state during injection and then go through *in situ* gelation in response to internal stimuli like temperature, pH, redox potential,[167] or enzyme activity.[231] They may effectively encapsulate proteins, peptides, small molecules, and even living cells due to their high water content and porous network structure, which also shields them from degradation and systemic clearance.[168] The pH-responsive hydrogels are very helpful in addressing acidic tumor microenvironments, where a pH decrease initiates the release of specific drug.[167] For example, Guo et al.[232] created a polypeptide-based hydrogel that encapsulates doxorubicin (DOX) and releases it in reaction to the acidic environment of tumor tissues, reducing systemic toxicity and increasing therapeutic efficacy. Similarly, redox-sensitive hydrogels are useful for intracellular medication delivery for inflammatory and cancerous conditions because they break down in reaction to increased intracellular glutathione levels.[221] These hydrogels' injectability also reduces invasiveness and enables conformal filling of irregular tissue defects, which is essential for use in postoperative delivery, tumor therapy, and treatment of chronic wounds.[233] Ma et al.[229] developed an intelligent injectable hydrogel drug delivery system (DDS) by cross-linking oxidized hydroxypropyl cellulose with carboxymethyl chitosan, which preloaded with artesunate (ART), ferroferric oxide (Fe_3O_4) nanoparticles, and black phosphorus nanosheets (BPs) to improve the efficacy of tumor therapy (Figure 11A). This DDS has several uses, such as photothermal response, chemodynamic treatment, pH sensitivity, and magnetic targeting. Both in vitro and in vivo experiment showed that this DDS had good biocompatibility and could effectively eradicate the HepG2 tumor. This study gives a novel approach to synergistic photothermal−chemo−chemodynamic treatment and elucidates the potential anticancer mechanism of this ART-loaded nanoparticle-composited hydrogel. Ali et al.[234] attached tetrazine to the terminals of a poly(ethylene glycol) derivative and grafted the norbornene functional group into the carboxymethyl cellulose backbone. These functionalized polymers were combined to create an IH that was built *in situ* using the tetrazine-norbornene cross-linking technique. This hydrogel was subsequently investigated for the administration of doxorubicin. Chen et al.[235] designed an *in situ* injectable sequentially responsive celastrol hydrogel (FCPC) based on the temperature-sensitive poloxamer F127 and tumor-acidity-cleavable maleic acid amide to overcome the poor solubility and systemic toxicity of Celastrol (Cel), a naturally occurring small molecule that effectively inhibits breast cancer. After being injected into tumor tissue (Figure 11B), FCPC quickly stabilizes into a gel state and releases activity molecules continuously for 5 days. The targeted release and medication residence time are enhanced by this injectable thermosensitive drug delivery device. The platform decreases cancer metastasis and harmful side effects while significantly enhancing Cel's anticancer activity both in vitro and in vivo. Dave et al.[236] created a small molecule hydrogel of diglycerol monostearate (DGMS) based on an amphiphile that self-assembles to form hydrogel (DGMSH) for the delivery through an endoscopic catheter. Its fibrous morphology, shear-thinning behavior, simple injectability, scalability, and long shelf life (6 months) are all revealed by the hydrogel's physicochemical characterization. According to *ex vivo* studies on the goat's stomach and intestine, visible submucosal cushion depots with the right height and ease of injectability through the catheters are established. Drugs (such as the hydrophobic Paclitaxel (PTX) or the hydrophilic 6-ACA) or dyes (like Methylene Blue (MB)) can also be contained in the hydrogel. In vivo studies on small animals have demonstrated the hydrogel depot's hemostatic, biocompatible, long-lasting, and nonimmunogenic properties. Thus, next-generation drug delivery systems that combine therapeutic efficacy, biocompatibility, and precision targeting can be built on the solid basis provided by intelligent IHs.

5.1.2. Tissue Engineering and Regeneration. The integrity of tissues can be compromised by a number of reasons, including as inflammation, tumors, trauma, and surgery.[221] These events can also lead to diverse tissue defects with irregular shapes and varying depths and sizes, affecting areas such as bone, cartilage, and skin. The aid of biomaterials is frequently necessary when dealing with these massive and intricate tissue abnormalities because of the human body's limited capacity for regeneration. Hydrogels are widely utilized as soft biomaterials in tissue engineering due to their excellent biocompatibility, resemblance to the extracellular matrix (ECM), and highly tunable properties that can be modified through physical or chemical methods to suit specific applications.[214,237−240] IHs' viscoelastic and diffusive properties allow them to stimulate tissue regeneration in a variety of ways, such as by attracting and/or modifying host cells, delivering controlled-release cells or treatments spatiotemporally, and offering mechanical support.[45] Temperature-responsive injectable hydrogels are widely favored because they allow for uniform distribution of therapeutic agents within the pregel solution in vitro.[221] Temperature-induced *in situ* gelation results in the hydrogel being injected into the defect location, distributing the medicines uniformly throughout the defect.[221] This allows the therapeutics to be released constantly, which aids in tissue regeneration and healing.[221] For example, Lei et al.[241] developed an injectable thermoresponsive poly(ethylene glycol)-*b*-poly(glycolic acid and lactic acid)hydrogel with a core−shell structure embedded in mesoporous silica nanoparticles (MSN). MicroRNA-222 and aspirin (ASP) can be delivered locally and over an extended period of time. Injecting the codelivered MSN hydrogel into a rat mandibular bone defect led to increased bone growth and neurogenesis, suggesting that the current injectable colloidal hydrogel that codelivered ASP and miR222 is a viable material for innervated bone tissue engineering. Chen et al.[242] generated a thermosensitive injectable hydrogel that promotes intervertebral disc regeneration by using sodium alginate microspheres (PNIA-*g*-CS-NaA, HMs) loaded with GDF-5 and poly-*N*-isopropylacrylamide-grafted chondroitin sulfate. The hydrogel's LCST at about 32 °C allowed for *in situ* gelation. Within the lab, GDF-5 decreased inflammatory cytokines and increased NPC growth. In a rat IDD model, HMs-GDF-5 and ADMSCs restored disc height, raised water content, and enhanced COL-II and ACAN expression in vivo, showing great

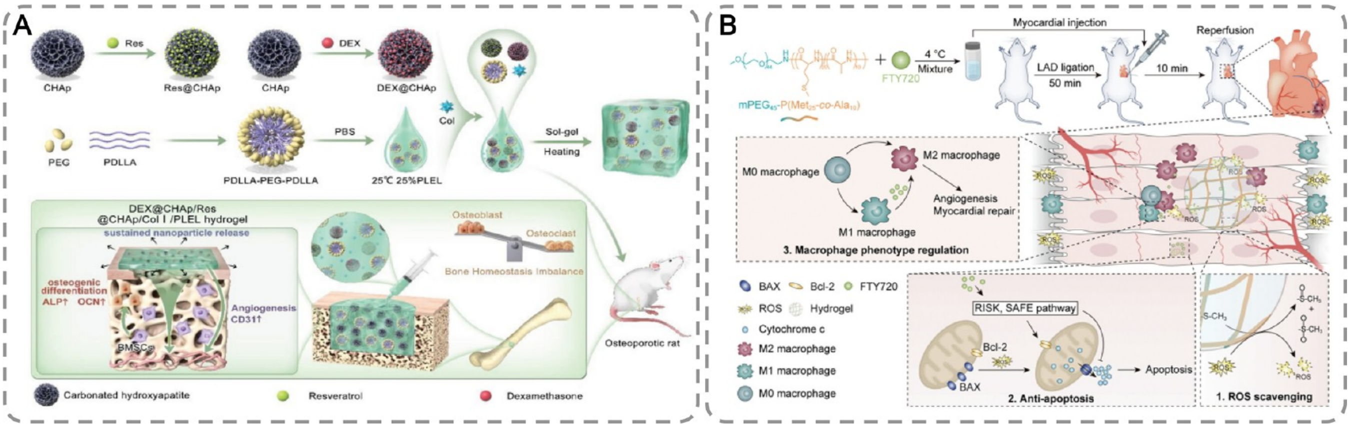

Figure 12. (A) Schematic representation of a temperature-sensitive hydrogel composite system incorporating hydroxycarbonated apatite microspheres, collagen type I (Col I), and PLEL, coloaded with dexamethasone and resveratrol, designed for the treatment of osteoporotic bone defects. Reproduced with permission of ref 243. Copyright 2023 Wiley-VCH GmbH. (B) Illustration of the anti-inflammatory and antiapoptotic mechanisms of a poly(amino acid) hydrogel administered via cardiac injection for ischemia-reperfusion injury (IRI) therapy. Reproduced with permission. Reproduced with permission of ref 244. Copyright 2025 Wiley-VCH GmbH.

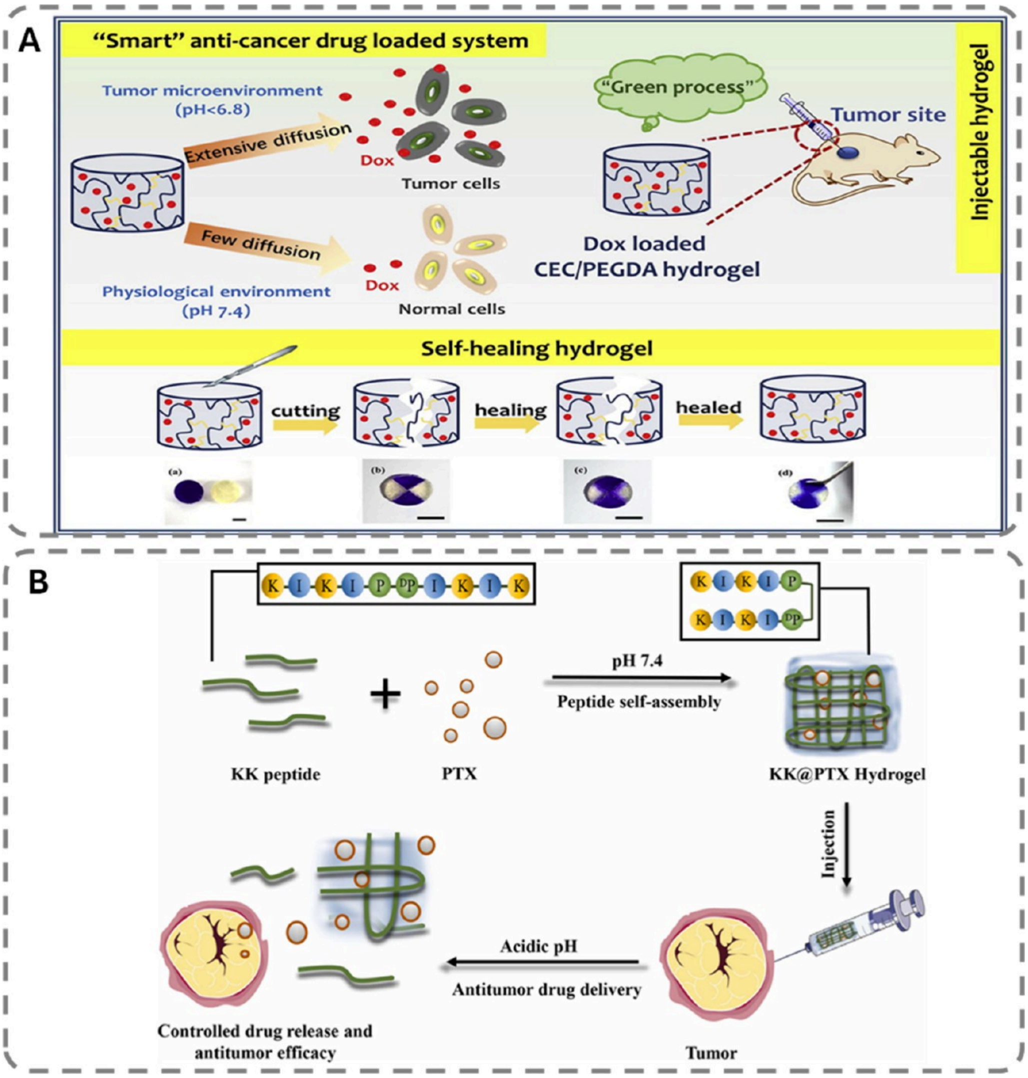

Figure 13. (A) Schematic illustration of an pH-responsive injectable hydrogel composed of aldehyde-terminated PEG and chitosan (CEC) for the targeted delivery of doxorubicin (DOX) for the treatment of hepatocellular carcinoma (HCC). Reproduced with permission of ref 247. Copyright 2017 Elsevier. (B) Formation mechanism of short peptide-based hydrogels and their application in delivering anticancer drugs. Reproduced with permission of ref 248. Copyright 2025 Elsevier.

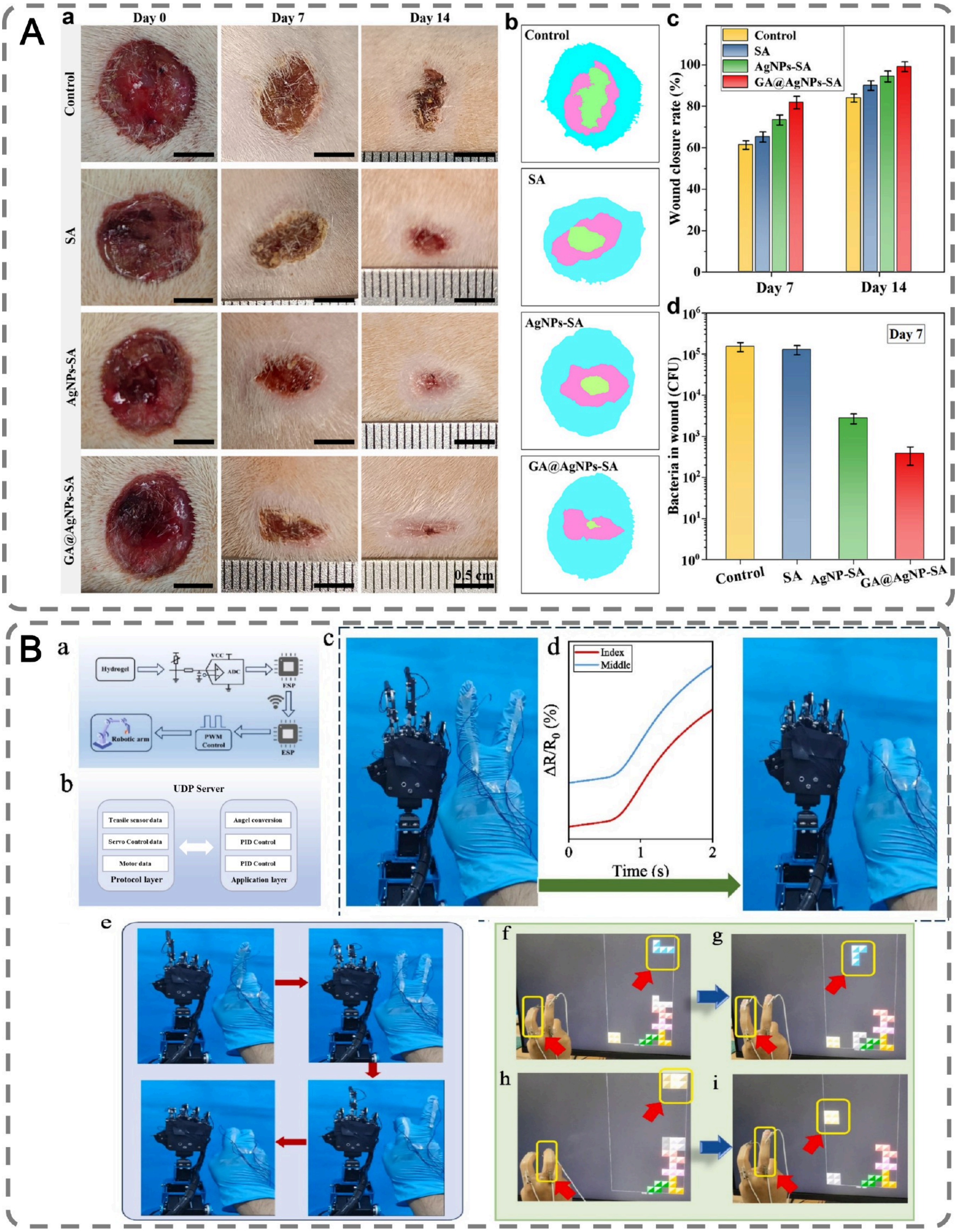

Figure 14. (A) In vivo evaluation of GA@AgNPs-SA hydrogels for wound healing in MRSA-infected models: (a) representative images of wounds treated with various samples; (b) progression of wound healing on days 0, 7, and 14; (c) quantitative analysis of wound closure on days 0, 7, and 14; (d) bacterial load in wound tissues after 7 days of treatment. Reproduced with permission of ref 254. Copyright 2023 Elsevier. (B) Utilization

Figure 14. continued

of PGBL hydrogel-based sensors for human−machine interaction: (a−b) illustration of the hardware framework integrated with PGBL hydrogel sensors for facilitating communication between humans and machines; (c−d) variation in signals and hand gestures during the interaction process; (e) real-time robotic hand movement mimicking finger actions; (f−g) manipulation of shape transformations in a Tetris game through ring finger gestures; (h−i) control over the position of game elements via movements of the middle finger. Reproduced with permission of ref 257. Copyright 2024 Elsevier.

promise for NP tissue regeneration. Lv et al.[66] created an injectable temperature-responsive hydrogel using silk fibroin and chitosan, and then added platelet-derived growth factor-BB (PDGF-BB) and bone morphogenetic protein-2 (BMP-2). Following injection into a critical-sized calvarial defect in New Zealand rabbits, this functionalized hydrogel continuously produced BMP-2, PDGF-BB, Mg^{2+}, and Fe^{2+} at the defect site. About 150 s were needed for the gel to grow in place. The hydrogel exhibited outstanding capabilities in promoting blood vessel formation and bone growth, markedly speeding up the healing of the calvarial defect. Li et al.[243] added resveratrol and dexamethasone to an injectable thermosensitive PLEL hydrogel to promote osteogenesis in osteoporotic bone defects (Figure 12A). The hydrogel quickly underwent *in situ* gelation and filled uneven flaws. It decreased ROS, controlled macrophage polarization, and enhanced MSC osteogenic development in vitro. In vivo, it influenced immunological responses and promoted bone regeneration. This approach improves the local microenvironment and has potential as a dual-purpose medication delivery platform for osteoporotic bone healing. Luo et al.[244] developed a thermosensitive poly(amino acid) hydrogel ($mPEG_{45}$-P($Met_{2}0$-*co*-$Ala_{1}0$), PMA) loaded with FTY720 to treat ischemia-reperfusion injury (IRI) (Figure 12B). *In situ* transition from sol to gel and ROS-induced degradation of the hydrogel allow for on-demand FTY720 release. Together, the PMA/FTY720 system decreased cardiomyocyte apoptosis, changed the polarization of macrophages from pro-inflammatory M1 to anti-inflammatory M2, and encouraged vascular regeneration. Vascular density and left ventricular ejection fraction (LVEF) were markedly enhanced in rat and rabbit IRI models. The combined antiapoptotic and immunomodulatory properties of this hydrogel demonstrate great promise for IRI therapy.

5.1.3. Cancer Therapy. Uncontrolled cell growth and division, which disrupts essential systems, is a characteristic of cancer, making it a difficult and, regrettably, occasionally fatal illness.[245] The traditional methods of cancer treatment, including immunotherapy, radiation, chemotherapy, surgery, and molecularly targeted therapy, have serious disadvantages, including the risk of tumor recurrence and/or metastasis, harm to surrounding healthy tissues, and extremely harmful side effects, even though current treatment options allow for some therapeutic success.[245] Rising incidence and rising mortality rates also indicate for medical attention.[245] IHs have become popular choices in this regard for cancer chemotherapy, immunotherapy, photothermal therapy (PTT), magnetic hyperthermia, photodynamic therapy (PDT), chemodynamic therapy (CDT), radiation, molecularly targeted therapy, and following tumor excision.[245] Accordingly, the lower pH in tumor tissues frequently acts as a powerful catalyst for tumor chemical therapy. Ahmadi et al.[246] established an injectable chitosan-based hydrogel that responds to temperature and pH to improve the anticancer activity of methotrexate (MTX) and curcumin (CUR). Chitosan, a poly(NIPAM-*co*-MA) copolymer, and glycerophosphate (GP) as an ionic cross-linker were combined to create the hydrogel. This resulted in an *in situ* gelling system that gelated quickly (less than a minute) at physiological pH and underwent a sol−gel transition at 38.5 °C. Studies on drug release revealed continuous CUR release and pH-sensitive MTX release, with higher release seen in acidic environments. When compared to single-drug systems, dual-drug-loaded hydrogels demonstrated a considerable increase in cytotoxicity against MCF-7 and MDA-MB-231 breast cancer cells in vitro, indicating the possibility of synergistic cancer therapy. Based on the pH-responsive dynamic covalent bond (Schiff base bonds), Qu et al.[247] developed an injectable hydrogel system that responds to pH changes for delivering doxorubicin (DOX) to treat hepatocellular carcinoma (HCC) (Figure 13A). Specifically, in the physiological pH environment, the hydrogel stayed stable and exhibited minimal DOX release; but, in the acidic tumor, the hydrogel exhibited a pattern of DOX release and pH-dependent breakdown behavior. Yao et al.[248] reported a pH-sensitive short peptide hydrogel with an angular shape that promotes network formation in neutral conditions for efficient paclitaxel (PTX) encapsulation based on a 10-amino acid sequence KIKIDPPIKIK (KK) (Figure 13B). The mildly acidic tumor microenvironment triggered sustained PTX release and injectable delivery by the hydrogel. Circular dichroism and electron microscope characterization verified structural alterations at different pH values, while rheological testing proved injectability. Improved antitumor effectiveness and biocompatibility were shown in both in vitro and in vivo investigations. This small, inexpensive peptide system provides a promising hydrophobic drug delivery platform with significant therapeutic promise.

5.1.4. Wound Healing. The human body's largest organ, the skin is vital for several physiological processes, including protection and secretion.[249] It also acts as a physical barrier to prevent infections and significantly reduce body fluid loss.[250] But injury can cause this barrier to be disrupted, resulting in what are commonly referred to as wounds.[251] Surgical sutures and mechanical fixation are two traditional methods for accelerating wound healing, but they have significant drawbacks, especially for chronic wounds that are susceptible to bacterial colonization and the growth of antibiotic-resistant biofilms.[252] IH effectively promotes wound healing when combined with minimally invasive techniques and flexibility to treat different types of wounds.[253] Hu et al.[254] introduced a unique injectable hydrogel for the treatment of infected injuries. This hydrogel was made by ionic cross-linking gallic acid-functionalized silver nanoparticles (GA@AgNPs-SA) with SA. The findings demonstrated that the regulated release of Ag^{+} ensured long-lasting antibacterial activity, disrupted bacterial cell membranes in in vitro experiments, and inhibited the growth of biofilms. In in vivo experiments, the created hydrogel effectively delayed inflammatory responses, promoted angiogenesis, and sped wound healing. It also showed significant biocompatibility and minimal cytotoxicity (Figure 14A). As a result, this work effectively illustrated the produced

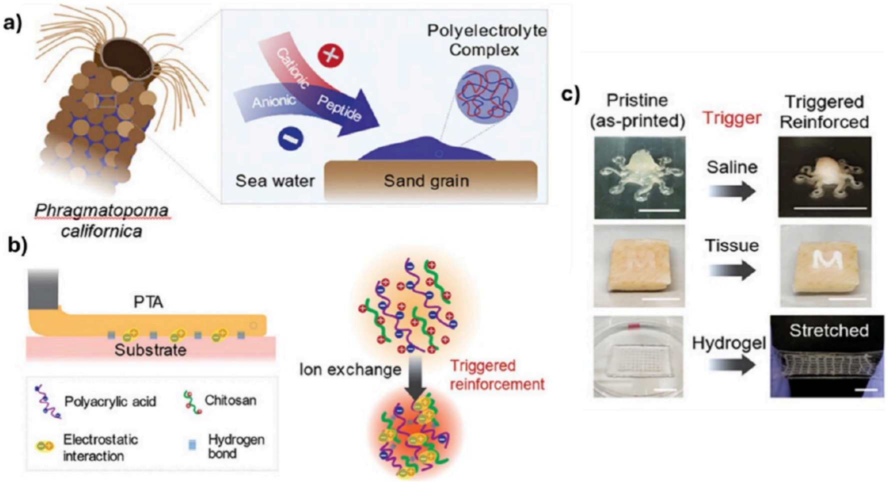

Figure 15. PTA's bioinspired design. a) The sandcastle worm bioinspired the PTA. b) The material design schematic. Injectable and printable, the polyelectrolyte complex of negatively charged poly(acrylic acid) (PAA) and positively charged chitosan (Chit) can undergo a triggered reinforcement (TR) by exchanging ions with its environment. c) A variety of triggers, including hydrogel substrates, biological tissues, and saline solutions, can be used to mechanically improve 3D-printed structures. Reproduced from ref 269. Available under a CC-BY-NC 4.0 license. Copyright 2024 Ma et al.

GA@AgNPs-SA hydrogel's pertinent therapeutic potential as a dependable method of treating infected wounds. Tian et al.[255] created a multipurpose injectable hydrogel (HPCS-C/ODEX/CC) that contains Crinis Carbonisatus (CC) nanoparticles, oxidized dextran (ODEX), and catechol-modified hydroxypropyl chitosan (HPCS-C) for quick wound healing and hemostasis. The hydrogel exhibited strong tissue adhesion through catechol groups, self-healing via dynamic Schiff base bonding, efficient injectability, and effective hemostatic action as a result of CC-induced blood cell aggregation. It dramatically decreased bleeding by up to 94.34% and 92.37% in vivo in models of liver and tail damage, respectively. Together with its antibacterial, antioxidant, and wound-healing-promoting properties, the hydrogel also demonstrated good biocompatibility, making it a viable option for controlling severe bleeding and accelerating wound healing. Qiu et al.[256] created a distinct, unique hydrogel for the treatment of pediatric burn wounds, specifically an HPMC-HAP scaffold hydrogel enhanced with AgNPs. Without the requirement for chemical additives, the hydrogel demonstrated a potent antibacterial effect against *S. aureus* and *Escherichia coli* (*E. coli*) after AgNPs were inserted. In vivo tests demonstrated that the HPMC-HAP/AgNPs hydrogel could accelerate wound healing more quickly than control groups and hydrogels lacking AgNPs, while in vitro investigations showed the gradual release of Ag$^+$ ions. Histological analyses demonstrated that tissue regeneration happened rapidly, and scarring was lessened. Therefore, by utilizing its dual antibacterial and tissue-repairing properties, the HPMC-HA/AgNPs hydrogel showed promise as a burn wound care treatment.

5.1.5. Biosensing and Diagnostics. Recently, hydrogels have become essential components in biosensing. Through certain physical and chemical alterations, a wide range of responsive hydrogels can be produced due to their remarkable biocompatibility and distinctive mechanical properties.[258,259] By interacting with enzymes, antibodies, and other biomolecules, these hydrogels preserve the activity of biomolecules, making it possible to identify and track particular biomarkers.[258]

A nanofiber hydrogel response sensor was created by Ren et al.[260] This sensor's advantage is its high mechanical strength, which is achieved by cross-linking TPU-PVAc@AgNP/MXene nanofibers with formic acid. Its ECM structure gives it high sensitivity and makes it appropriate for detecting a variety of fine movements, especially those that occur underwater. In conclusion, by utilizing the mechanical characteristics of hydrogels, novel hydrogel sensors with increased sensitivity can be created. By combining the high viscoelasticity and exceptional biocompatibility of gelatin with ionic chemicals like LiCl and β-sodium glycerophosphate, Liu et al.[257] created a natural hydrogel sensor. Human respiration and movement could be detected by this hydrogel sensor (Figure 14B). A plasma hydrogel was created by Castellanos et al.[261] utilizing CS, which was produced by noncovalent interactions between CS and diethyl latinate. Because of its great biocompatibility, this CS hydrogel offers research ideas for developing novel biomaterials that respond to biological signals.

5.2. Non-biomedical Applications

5.2.1. Injectable Hydrogels in Agriculture. Because of their exceptional capacity to hold onto water, transfer nutrients, and react to environmental cues, IHs have become a viable tool in agriculture.[262,263] When applied directly to soil or plant tissue, these hydrogels which are made of biocompatible and biodegradable polymers form *in situ* gels that allow for the controlled release of agrochemicals like growth regulators, fertilizers, and insecticides.[264] They are very useful for increasing crop production, decreasing environmental pollution, and improving water usage efficiency because of their high water absorption capacity and adjustable release patterns.[264] Injectable hydrogel technologies provide a flexible and environmental friendly structure for smart agricultural applications as sustainable agriculture gets popularity. Bucak et al.[265] developed an environmental friendly water-retaining material called borax cross-linked, moldable, and self-healing IHs of carboxymethyl cellulose/poly(vinyl alcohol) (CMC/PVA) to enhance soil water conservation for agricultural use. The hydrophilic PVA/CMC hydrogel was found to improve loamy soils' hydroretention capacity by 10%. The moisture absorbs and retains the hydrogel's effectiveness, and its moldability, injectability, and self-healing qualities make it an ideal agricultural additive to improve soil water retention. In particular, the 2.5% PVA/CMC hydrogel-amended soil showed exceptional water-retention properties. With its features of soil water conservation and environmental safety, the novel hydrogel holds significant promise for use in sustainable agriculture to maximize crop water availability. Using a terpolymer of acrylic acid, acrylamide, and 2-acrylamido-2-methylpropanesulfonic acid [P(AA-AM-AMPS)], cross-linked with multifunctional aziridine compounds, Yan et al.[266] created an affordable injectable superabsorbent hydrogel. The hydrogel showed outstanding injectability and controlled underwater gelation by adjusting the cross-linking kinetics. Due to its enhanced wettability, the optimized formulation demonstrated strong underwater adhesion to various surfaces such as wood, polyethylene, and aluminum, while still allowing sufficient time for injection-based application. This hydrogel exhibits significant promise for agricultural uses, such as soil water retention and slope stabilization, due to its high swelling capacity of up to 509 g/g and its ability to penetrate and bind wet sandstone.

5.2.2. Injectable Hydrogels in 3D/4D Printing and Soft Robotics. The variety of injectable electroactive gels has been investigated for 3D extrusion printing as they are linked to conductivity, stretchability, and self-healing properties. IHs were used to create soft neural probes and assess mice's neural response.[267,268] Chen et al.[36] utilized supramolecular pyrimidinone groups as dynamic cross-linking points in a polyaniline/poly(4-styrenesulfonate) network to create a multifunctional injectable conductive polymer hydrogel. This design gave the hydrogel outstanding stretchability (~300%), quick self-healing (within 30 s), high conductivity (13 S/m), and injectability. With a gauge factor of 3.4, the hydrogel demonstrated a dependable strain-sensing performance that allowed for precise human motion detection. Because of its moldability and self-repairing properties, it can be used in wearable biosensors, soft electronics, and 3D printing, showcasing the promise of supramolecular chemistry to advance the design of electroactive hydrogels. Ma et al.[269] presented printable tough adhesives (PTAs), a family of supramolecular hydrogels that can be 3D printed into precise shapes and then strengthened in place with physiologically safe triggers like salt or water (Figure 15). When exposed to such conditions or come into direct touch with biological tissues, these PTAs showed notable gains in stiffness, tensile strength, and toughness. The study investigated how pH and polymer composition affect reinforcement kinetics and mechanical performance. PTAs show promise in applications such as connective tissue engineering, targeted bioadhesion, and 4D soft robotics because of their excellent adhesion to diverse surfaces and outstanding mechanical properties. This makes them a flexible platform for advancements in biomedicine and engineering.

6. CHALLENGES AND LIMITATIONS

6.1. Current Limitations and Strategic Advancements

Despite notable progress, stimuli-responsive IHs still encounter significant barriers in their translational and clinical applications. One primary limitation is the balance between biocompatibility, biodegradability, and mechanical robustness.[168] Traditional thermosensitive hydrogels, such as poly(*N*-isopropylacrylamide) and pluronic-based systems, exhibit sol−gel transitions near physiological temperatures, yet often suffer from inadequate biodegradability and potential cytotoxicity.[167,270] Although poly(ester)-based alternatives present improved profiles, they too demand further optimization for prolonged in vivo performance and stimuli-specific response.[271,272] The formulation of IHs for controlled drug delivery faces additional hurdles, particularly regarding premature burst release, limited encapsulation efficiency, and degradation of bioactive agents like proteins and peptides due to harsh cross-linking conditions or toxic initiators.[273] PEG-based and poly(ester)-based hydrogels, while FDA-approved for implantation, remain suboptimal for oral and nasal routes and for long-term therapeutic release.[274,275] For example, Choi et al.[276] created a dual supramolecular network-based injectable hydrogel with orthogonal host guest cross-links and methyl cellulose to improve mechanical stability, injectability, and stimuli-responsiveness,. More than 90% of the cells in the hydrogel were viable, it self-healed in 1 min, and it released diclofenac when heated, dissolved in chemicals, or stimulated by ultrasound. Its therapeutic efficacy when administered to a rat model of osteoarthritis demonstrated its potential as an intelligent drug delivery system for use in biomedical applications.

6.2. Design and Functional Performance Constraints

Achieving precise control over injectability, mechanical integrity, and gelation kinetics remains a key engineering challenge.[277−279] Hydrogels must exhibit low viscosity during injection yet form mechanically stable networks postgelation.[280] Parameters such as polymer chain length, molecular weight, cross-linking density, and gelation mechanism all influence the viscoelastic behavior of the hydrogel.[281] In particular, shear thinning behavior is essential for ease of injection but must be paired with sufficient *in situ* elasticity to withstand physiological loads and repeated administrations.[282,283] For spinal cord regeneration, Borah et al.[284] created an injectable electroconductive hydrogel by mixing silk fibroin with PEDOT:PSS. The hydrogel showed appropriate mechanical characteristics (10−60 kPa), conductivity (~0.2−1.2 S/m), and better structural recovery with (3-glycidyloxypropyl)trimethoxysilane (GoPS) stabilization. It encouraged axonal development and synaptogenesis by supporting hiPSC-derived neurons and astrocytes to mature and survive at a rate of >80%. This technique has great promise for spinal cord repair and neural cell delivery. Drug release dynamics further complicate hydrogel design.[168] The interaction between therapeutic cargo and hydrogel matrix including mesh size, charge interactions, and physical entrapment significantly influences retention and release kinetics.[285,286] Therefore, hydrogels must be engineered to offer tunable release profiles through smart cross-linking strategies that modulate network density and cargo affinity. Devi et al.[287] developed an injectable hydrogel by cross-linking vinyl sulfone-functionalized β-cyclodextrin with thiolated hyaluronic acid through a thiol−ene reaction. Four formulations were created by adjusting the cross-linking density and polymer molecular weight to maximize medication release and viscoelasticity. Combinatorial, tumor-responsive distribution of carvacrol and doxorubicin was made possible by the hydrogel, which also promoted the growth of mesenchymal stem cells and regulated breakdown. Additionally, it successfully inhibited triple-negative breast cancer cells, demonstrating its promise for individualized, minimally invasive cancer treatment.

6.3. Bioactivity, Immunocompatibility, and Biological Integration

Hydrogel bioactivity is crucial for regenerative and therapeutic applications.[288] Effective integration with biological systems requires the hydrogel to support cellular adhesion, proliferation, and differentiation.[289,290] Natural polymers like hyaluronic acid, gelatin, and fibrin inherently provide cell-binding motifs, while synthetic polymers such as PEG and polyacrylamide necessitate chemical modification with bioactive ligands.[291] Gelatin-based hydrogels have shown promise in clinical trials for promoting tissue repair, such as in kidney and heart injuries; however, challenges persist in regulating their degradation rate and maintaining adequate retention time within tissues.[292,293] Liu et al.[294] presented GMOD, an injectable hydrogel modeled after mussels that is made by Schiff base cross-linking gelatin and oxidized dextrin. Dopamine is integrated to improve mechanical strength and adhesion. In mouse models, this double-network method reduced liver bleeding by 76%, greatly increasing hemostatic efficiency. In addition to boosting cutaneous wound healing and lowering inflammation, the hydrogel maintained sustained VEGF secretion. Because of its high tissue adherence, biocompatibility, and degradability, GMOD is a viable option for surgical and intra-abdominal hemostasis applications. In parallel, minimizing immune responses remains a priority. IHs can trigger local inflammation, hypersensitivity, or fibrosis depending on their chemical composition and degradation products.[295] Such responses may alter the local microenvironment (e.g., pH, enzyme levels) and compromise hydrogel functionality. Recent strategies involving biomimetic cell-derived carriers (e.g., erythrocyte or cancer-cell membrane cloaked systems) aim to evade immune surveillance and extend therapeutic action.[296] For chondrocyte culture, Peng et al.[297] created a series of injectable biomimetic hydrogels based on poly(ethylene glycol)-poly(alanine) (mPEG−PA) diblock copolymers. By altering the length of the poly(alanine) chain, which affected the production of secondary structures, the mechanical characteristics and microstructures of these hydrogels could be controlled. Longer PA chains in hydrogels promoted improved ECM formation, collagen and glycosaminoglycan deposition, and chondrocyte clustering. The promise of mPEG−PA hydrogels for cartilage tissue engineering applications was highlighted by SEM analysis, which revealed a fibrillar microarchitecture advantageous for preserving the chondrocyte phenotype.

6.4. Translational Barriers and Regulatory Considerations

From a translational standpoint, significant technological and regulatory barriers impede the clinical adoption of IHs.[298] The transition from lab-scale synthesis to large-scale production demands adherence to current Good Manufacturing Practices (cGMP), reproducibility across batches, and consistent safety and efficacy profiles.[299] The high water content and sensitive nature of hydrogel networks further complicate fabrication, sterilization, storage, and transportation.[300,301] A mussel-inspired injectable nanocomposite hydrogel (PDA NPs@OHA-I-CEC) was created by Han et al.[302] using polydopamine nanoparticles (PDA), carboxymethyl chitosan (CEC), and oxidized hyaluronic acid (OHA). This dynamic hydrogel allows for sequential protein delivery and has injectability, self-healing, and biodegradability. It provides VEGF and BSA with a prolonged release that is regulated by diffusion and cross-linking density. This technology has potential applications in tissue engineering and regenerative medicine for multistage, synergistic protein drug delivery. Moreover, regulatory approval remains a prolonged and complex process. The diversity of hydrogel chemistries, cross-linking mechanisms, and therapeutic uses complicates their classification and standardization.[303]

7. CONCLUSION AND FUTURE PERSPECTIVES

Smart polymer-derived IHs have demonstrated remarkable potential as next-generation biomaterials owing to their potential to undergo sol−gel transitions under physiological conditions. The progress in the rational design of polymer networks, ranging from thermoresponsive and pH-sensitive systems to redox- and enzyme-responsive constructions, has facilitated the engineering of hydrogels with precisely tunable physicochemical and biological properties. These systems are increasingly recognized as integral components in the evolving landscape of regenerative medicine, drug delivery, tissue engineering, and immunotherapeutics. Both natural and synthetic macromolecular systems are presently employed in the field, each presenting distinct strengths and limitations. Natural polymers, like polysaccharides and proteins, provide inherent bioactivity, biodegradability, and compatibility with biological systems; however, they often lack sufficient mechanical stability and exhibit variability in reproducibility. Whereas, synthetic polymers including PEG, PNIPAM, and PCL offer mechanical tunability, processability, and batch-to-batch consistency but are frequently limited by suboptimal biofunctionality and potential for foreign body responses. To address these dichotomies, the development of composite or hybrid hydrogel systems has emerged as a promising strategy, allowing for the integration of mechanical strength, bioactivity, and controlled degradation into a single injectable platform.

Advancements in cross-linking strategies, including dynamic covalent bonding, supramolecular assembly, and photoinitiated polymerization, have enabled the fabrication of hydrogels with enhanced adaptability, self-healing capabilities, and stimuli-triggered therapeutic release. These hydrogels are capable of selectively reacting to pathological microenvironments, like the acidic pH in tumor sites or increased glutathione concentrations in inflamed tissues, thus enhancing therapeutic accuracy while minimizing off-target effects. The porous architecture of these networks further facilitates the diffusion of several components, including oxygen, nutrients, and signaling molecules, which is essential for promoting cellular infiltration, tissue integration, and vascularization. Recent research has extended the functional landscape of IHs beyond their role as passive matrices or localized drug depots. They are now being explored as bioinstructive and multifunctional therapeutic units capable of modulating immune responses, delivering gene-editing components, supporting stem cell fate decisions, and enabling dynamic tissue regeneration *in situ*. Nonetheless, significant challenges remain, such as achieving precise regulation of degradation rates, avoiding immune detection, ensuring long-term safety, and maintaining consistent performance under clinically relevant conditions. Furthermore, the design of hydrogels that maintain integrity under physiological load while simultaneously facilitating matrix remodeling remains a formidable task.

In the future, combining smart hydrogels with cutting-edge technologies like bioelectronics, soft robotics, and high-precision bioprinting is expected to revolutionize therapeutic approaches. The convergence of material science with data-driven approaches, including machine learning and computational modeling, may enable the predictive design of hydrogel systems with optimized performance profiles for specific pathophysiological conditions. Additionally, the development of IHs with intrinsic biosensing capabilities could lead to closed-loop systems that autonomously modulate drug release in response to real-time biological feedback. In summary, smart polymer-derived IHs represent a highly dynamic and evolving class of biomedical materials with substantial translational potential. The continued advancement of this field will depend on a deeper mechanistic understanding of hydrogel-tissue interactions, rigorous in vivo validation, and the establishment of scalable, reproducible manufacturing processes. These efforts are essential to fully harness the therapeutic versatility of IHs and to realize their integration into future precision medicine paradigms.

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Notes

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