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Self-Healing Hydrogels: Mechanisms, Advances and Biomedical Applications

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ABSTRACT

Hydrogels are soft materials that are used for the bioactive agent drug delivery. These hydrogel materials are having tunable structural, mechanical and rheological properties. Networks of water-swollen polymers known as self-healing hydrogels are able to self-repair their structure and functionality following injury by different mechanisms. These self-healing hydrogels are having applications in tissue engineering, personalised medicine, drug delivery systems, wound healing, 3D printing. Despite progress, self-healing hydrogels face challenges like biocompatibility issues, healing mechanisms depending on specific conditions. With their unique ability to mimic biological repair, self-healing hydrogels are poised to enable more durable, adaptable biomedical and engineering applications soon.

Key words: Self-healing hydrogels, smart, Covalent bonds, tissue engineering, regenerative medicine, drug delivery systems.

Introduction

Hydrogels are three-dimensional polymeric networks capable of imbibing and retaining large quantities of water or biological fluids, often exceeding 90% by weight, while preserving their structural integrity by virtue of physical or chemical crosslinks within the polymer matrix(1). Their high water content, tunable mechanical properties, and ability to mimic certain aspects of native extracellular matrices have rendered hydrogels indispensable in fields ranging from tissue engineering and regenerative medicine to personal care products and environmental remediation(2). Nevertheless, conventional hydrogels typically suffer from inherent brittleness and lack of durability: once subjected to mechanical damage such as cracking, cutting, or other forms of structural disruption, their networks fracture irreversibly, leading to compromised mechanical performance and loss of function(3). This drawback has spurred extensive research into so-called “smart” or “functional” hydrogels that can autonomously restore their structure and function after damage(4).

Networks of water-swollen polymers known as self-healing hydrogels are able to self-repair their structure and functionality following injury. In contrast to traditional hydrogels, self-healing varieties use reversible bonds to mend fractures, significantly increasing their longevity and durability(5). Such hydrogels often exploit dynamic covalent or reversible noncovalent interactions to reform crosslinks. For example, reversible covalent bonds (Schiff-base imines, disulfides, Diels–Alder linkages, boronate esters, etc.) and noncovalent forces (hydrogen bonding, metal–ligand coordination, host–guest inclusion, hydrophobic interactions, electrostatic pairing) are widely used (6). There are two main approaches: (1) extrinsic self-healing, in which healing compounds are released into fractures via embedded microcapsules or reservoirs, and (2) intrinsic self-healing, in which the polymer network itself repairs via these dynamic linkages(7). Extrinsic designs (healing monomers in capsules) allow for one-time repair upon capsule rupture, but intrinsic systems allow for repeated healing cycles(8). Modern self-healing hydrogels often combine several of these chemistries to tune performance(9).

The significance of self-healing hydrogels extends beyond academic curiosity. In biomedical contexts, hydrogels that fail mechanically can lead to implant failure, loss of therapeutic payloads, or compromised tissue integration(10). A self-healing scaffold, by contrast, can endure dynamic physiological stresses—such as cyclic loading in cartilage or shear forces in blood vessels—while maintaining functionality over extended periods(11). In soft robotics and wearable electronics, self-healing gels prolong device lifetimes by repairing microcracks that form under bending, twisting, or abrasion, thereby reducing maintenance and replacement costs(12). Moreover, self-healing hydrogels represent a step toward more sustainable materials. By extending service lifetimes and enabling reuse, these materials can lower resource consumption and minimize waste. In environmental applications—such as adsorption of heavy metals or pollutants—a self-healing hydrogel can maintain high adsorption capacity despite mechanical disturbances encountered during deployment and recovery(13).

2. Self-Healing Mechanisms

Hydrogel self-healing, which may be generally classified into intrinsic and extrinsic processes, is a result of the reversible reconstruction of broken crosslinks within the polymer network, allowing for the restoration of structural integrity and functioning following mechanical injury(14). In order to achieve healing efficiencies that frequently surpass 80% in a matter of minutes, intrinsic self-healing depends on dynamic bonds that are incorporated into the polymer matrix and that can dissociate and reassociate under mild conditions without the need for external intervention(15). These dynamic bonds include reversible covalent interactions, such as Schiff-base imine bonds created by condensation of aldehyde and amine groups, which break and reform quickly at physiological pH-acylhydrazone linkages generated via hydrazide–aldehyde condensation that confer pH-tunable healing kinetics, and Diels–Alder cycloaddition adducts (e.g., furan–maleimide pairs) that undergo thermally reversible [4+2] cycloadditions enabling healing upon mild heating and cooling cycles(16-24).

Another healing mechanism is provided by dynamic covalent disulphide bonds exchanged under redox stimuli (such as thiol–disulfide interchange), especially in thiolated polymer networks where bond reshuffling is driven by ambient thiol concentrations(25). Utilised for smart, environment-responsive healing systems in glucose-sensing or diabetic wound patches, boronate ester bonds between boronic acid moieties and vicinal diols also function in a pH-sensitive reversible manner, quickly dissociating in acidic media and reforming in alkaline environments(26-30). Rapid bond exchange kinetics and high bond strength are provided by metal–ligand coordination bonds, such as Zn^{2+} complexing with carboxylate/histidine residues or Fe^{3+} coordinating with catechol-modified polymers, resulting in hydrogels that can self-heal at room temperature and retain strong mechanical properties under load(31-34).

In the meanwhile, different intrinsic healing techniques are supported by reversible noncovalent interactions: When water-soluble segments are recombined at the damaged interface, hydrophobic associations among alkyl side chains in amphiphilic block copolymers or polymeric micelles induce network reformation via the hydrophobic effect; multiple hydrogen bonds (as in urocanic acid-modified polymers or multi-urea motifs) create supramolecular networks that reassemble spontaneously after fracture, albeit with moderate mechanical strength; host–guest inclusion complexes like β-cyclodextrin encapsulating adamantane or azobenzene derivatives facilitate healing through dynamic association/dissociation cycles driven by concentration gradients or light stimuli, π–π stacking interactions between aromatic residues and cation–π interactions also contribute to reversible physical crosslinking in some peptide-based or aromatic polymer hydrogels, and electrostatic pairing of oppositely charged polyelectrolytes (e.g., poly(acrylic acid) with poly(allylamine)) provides ionic crosslinks that dissociate under high ionic strength or extreme pH but rebind upon returning to physiological conditions(35-42).

In many state-of-the-art intrinsic self-healing hydrogels, known as multi-mechanism hydrogels, several of these dynamic interactions are integrated into a single network. Covalent and noncovalent bonds work in concert to combine high mechanical toughness and rapid healing kinetics, avoiding the traditional trade-off between strength and healability(43). For example, combining imine chemistry with hydrogen bonding in chitosan–poly(vinyl alcohol) double networks results in hydrogels that self-repair in a matter of seconds while achieving tensile strengths exceeding 100 kPa and fracture energy exceeding 1,000 J/m(44-45). Extrinsic self-healing, on the other hand, relies on encapsulated healing agents—monomers, crosslinkers, or catalysts—that are contained within microcapsules, microvascular networks, or emulsion droplets embedded in the hydrogel matrix. When these reservoirs are ruptured by mechanical damage, the healing agents are released into the crack plane, where they polymerise or crosslink (often via triggered polymerisation like UV-initiated radical reactions), sealing the damage in a one-time repair that can restore full mechanical strength but is not repeatable and runs the risk of leaching residual monomers if capsules remain unruptured or healing is not complete(46).

Researchers measure the recovery of mechanical properties like tensile strength, fracture strain, and Young's modulus by subjecting hydrogels to controlled damage, typically a complete cut or shear strain in tensile/compression tests, and then allowing them to heal for predetermined periods at predetermined temperatures or pH(47). Healing efficiency is measured as the ratio of recovered property to the original, with high-performance systems routinely achieving >90% recovery in 10–30 minutes under physiological conditions, and some metal–ligand-coordinated gels restoring >80% in less than 5 minutes(48). Rheological oscillatory step-strain tests further elucidate network dynamics: by alternating between high strain (to break bonds, dropping storage modulus G′) and low strain (to permit reformation), the time-dependent recovery of G′ provides insights into bond exchange rates and healing kinetics, with faster recovery indicating more dynamic bond exchange(49). Electrical resistance measurements are integrated into conductive self-healing hydrogels to verify the restoration of ionic or electronic pathways following incision, while optical or confocal microscopy techniques with fluorescent tagging visually confirm crack closure and molecular diffusion across the damaged interface(50).

At the molecular level, self-healing arises from dynamic bond exchange mechanisms: for dynamic covalent systems, bond reformation follows reaction kinetics governed by equilibrium constants (Keq) and activation energies (Ea) of the reversible reaction; lower Ea and higher Keq favor rapid, complete healing, but excessively labile bonds compromise mechanical strength, necessitating a balance achieved through molecular design of bond partners and steric environment(51). Noncovalent networks rely on fast association/dissociation kinetics of physical interactions, where multivalency—multiple weak bonds acting in concert—increases overall network strength and healing resilience while preserving rapid network reassembly. Stimuli-responsive triggers such as slight heating can accelerate bond mobility in some systems (e.g., thermoreversible Diels–Alder) without requiring harsh conditions incompatible with biomaterials. Moreover, the viscoelastic nature of many self-healing hydrogels, exhibiting both fluid-like and solid-like behaviors, contributes to healing: under stress, polymer chains can diffuse across the crack interface before bonds re-form, and the network relaxes stresses that would otherwise impede reattachment; upon cessation of stress, entangled polymer chains and dynamic crosslinks reconstruct a continuous network(52). In biological applications, the healing process must also consider physiological milieu: pH, ionic strength, redox environment (e.g., elevated glutathione concentration in cells), and presence of enzymes can influence dynamic bond behavior—introducing enzyme-cleavable or responsive linkages (e.g., peptide bonds cleavable by matrix metalloproteinases) adds an additional layer of biological control over healing and degradation. Advanced self-healing hydrogels are now tailored to exploit this interplay—such as thiol–disulfide exchange that leverages cellular redox gradients to both heal and degrade on demand, or boronate ester bonds that respond to glucose levels for self-healing diabetic wound dressings that adapt to fluctuating blood sugar(53). Finally, the integration of self-healing with other functionalities—conductivity (via polyaniline or carbon-based fillers), magnetism (via iron oxide nanoparticles), or bioactivity (via growth factor tethering)—often necessitates coupling dynamic bonding chemistries with additional supramolecular interactions or secondary crosslinking strategies, further complicating the healing mechanism but opening the door to multifunctional, long-lived hydrogels for next-generation biomedical and engineering applications. Through the reversible reformation of dynamic bonds—covalent or noncovalent, single or multiple modalities—in an optimized polymer network, self-healing hydrogels achieve autonomous repair, combining the adaptability of biological tissues with the tunability of synthetic materials to address real-world demands in medicine, robotics, electronics, and environmental technology(54-56).

3.Synthesis and Design Strategies

Self-healing hydrogels are typically synthesized by polymerizing functional monomers or crosslinking polymers bearing dynamic groups. Common approaches include:

3.1: Covalent crosslinking with dynamic bonds:

For example, mixing a polymer with pendent aldehyde groups (e.g. oxidized alginate) with an amine-rich polymer (e.g. chitosan) yields a gel crosslinked by dynamic imine bonds. Similarly, dialdehyde-functionalized polymers can form acylhydrazone networks with dihydrazide crosslinkers. Incorporating boronic acid–bearing monomers (e.g. vinyl phenylboronic acid) into an acrylamide gel allows boronate ester crosslinks with diols in polysaccharides(57-59).

3.2: Interpenetrating and composite networks

Toughness and healing can be improved by double-network or hybrid designs. One network (covalently crosslinked) provides strength, while an interpenetrated dynamic network grants healing(60). For instance, a rigid poly(vinyl alcohol) (PVA) network combined with a borate-crosslinked sodium alginate gel yields a strong, self-healing composite(61-63). Nanocomposites with clay or graphene oxide also reinforce hydrogels while the polymer–polymer bonds heal.

3.3 Polymerization techniques:

Standard radical polymerization, click chemistry, and step-growth methods are used, often in situ(64). For example, free-radical polymerization of acrylamide with a dynamic crosslinker (such as poly(ethylene glycol) diacrylate bearing disulfides) yields self-healing PAAM hydrogels. Condensation reactions (Schiff-base formation) are usually done by mixing two prepolymers in mild conditions, causing immediate gelation(65-66).

4. Types of Self-Healing Hydrogels

Self-healing hydrogels can be classified by mechanism type and by polymer composition(67):

Intrinsic vs. Extrinsic: As noted, intrinsic gels heal via internal reversible bonds, while extrinsic gels contain microcapsules or fibers loaded with healing agents. Intrinsic hydrogels are reusable and simplify the matrix, so they are more studied recently(68).

Polymer source: Hydrogels are made from *natural* biopolymers (e.g. chitosan, alginate, hyaluronic acid, gelatin, dextran) or *synthetic* polymers (e.g. polyacrylamide, poly(ethylene glycol), poly(vinyl alcohol), polyacrylates)(69). Natural polymers often impart biocompatibility and biodegradability. For example, chitosan and alginate degrade to harmless products and can be modified with aldehydes for imine linkages. Synthetic polymers offer more control over network architecture and mechanical properties. Many systems use hybrids: e.g., cellulose nanofiber-reinforced chitosan gels(70).

Crosslinking chemistry: Hydrogels may be chemically crosslinked (covalent reversible bonds) or physically crosslinked (dynamic noncovalent interactions, or ionically). Some gels combine both, like ionotropic alginate crosslinked with Ca^2+ plus dynamic boronate bonds(71).

Functional properties: Specialized hydrogels incorporate additional features: *conductive* (by adding ionic salts or conductive fillers), *magnetic* (magnetite nanoparticles), or *photo- or thermo-responsive* (azobenzene or spiropyran groups). These can be combined with self-healing networks(72-73).

5. Characterization Techniques

Characterizing self-healing hydrogels involves both mechanical tests and healing assays.

Mechanical testing: Tensile/compression tests measure strength and stiffness before and after damage. Typical protocol: cut or shear the gel to introduce damage, then allow it to heal (often at ambient or slightly elevated temperature), and retest mechanical properties(74). Healing efficiency is quantified by the percentage of original strength or elongation recovered. As one review notes, hydrogels are tested by “compression and tension experiments including rigidity, tensile, shearing, and compressive strain” before and after healing(75). Good self-healing hydrogels recover a large fraction of their tensile strength (sometimes >80%) within minutes(76).

Rheology: Oscillatory rheology (strain-sweep or continuous step strain) probes network recovery. A sample is subjected to high strain to break bonds (drop in modulus), then returned to low strain; a true self-healing gel will show restoration of its storage modulus over time. These tests give quantitative healing rates(77).

Microscopy/Imaging: Optical microscopy can visually confirm crack closure. Fluorescent dyes or particles are sometimes embedded to image mixing across the healed interface. Confocal imaging may monitor bond reformation (78).

Conductivity/electrical tests: For conductive gels, electrical resistance can be monitored before/after healing. A functioning self-healing conductive gel shows a return of low resistance after damage healing(79).

Swelling and degradation: Self-healing ability is often reported alongside swelling behavior or hydrolytic stability, to ensure the gel remains intact and does not simply dissolve(80).

6. Applications of Self-Healing Hydrogels

Self-healing hydrogels have been explored in many fields due to their durability and functionality. Key applications include:

6.1 Tissue Engineering & Regenerative Medicine:

Because hydrogels mimic the hydrated, porous structure of the extracellular matrix (ECM) self-healing variants serve as scaffolds for cell growth and tissue repair. For example, self-healing alginate–gelatin or hyaluronic acid gels have been used to support cartilage, bone or neural tissue formation. The self-healing feature allows the scaffold to maintain integrity under mechanical stress in vivo. They can also incorporate cells or growth factors: injectable self-healing gels enable minimally-invasive delivery of cell-laden constructs. Overall, self-healing hydrogels facilitate 3D tissue models and regenerative implants by combining biocompatibility with structural resilience(81).

6.2 Wound Healing Dressings:

Hydrogels that can self-seal cracks and provide a moist, protective environment are ideal wound dressings. The best wound-healing hydrogels are adhesive, tough, and can load drugs or antibacterial agents. For instance, a chitosan-based self-healing gel with antibacterial silver released angiogenic factors and significantly accelerated diabetic wound closure in animal studies. Self-healing ensures the dressing remains intact on moving skin and allows reapplication of medication by simply rejoining the gel(82).

6.3: Drug delivery system

Injectable self-healing hydrogels have been developed as sustained-release carriers. These gels can be syringe-delivered and then gel in situ via dynamic bonds, conforming to the tissue cavity. Because they heal fractures autonomously, they avoid premature leakage. For example, an imine-crosslinked hydrogel injected into tissue can slowly release embedded drugs; its self-healing nature reduces burst-release and allows the depot to re-form if disturbed. Low-pH self-healing gels also serve as gastric sealants or oral drug patches in the stomach(83).

6.4. Soft Robotics and Actuators

Bio-inspired soft robots and actuators benefit from hydrogels that combine flexibility with self-repair. Self-healing hydrogels can be used as “muscles” or swellable actuating elements: if damaged, the actuator heals and resumes function. For example, a modular hydrogel robotic swimmer propelled by catalytic decomposition of fuel was constructed using imine-bonded hydrogel modules. Actuator and pump systems made of self-healing gels have been prototyped, exploiting the gels’ ability to transmit mechanical load while healing cracks(84).

7.Challenges and Future Perspectives

Despite progress, self-healing hydrogels face challenges. Healing mechanisms often depend on specific conditions (e.g. a certain pH, temperature or redox environment), limiting robustness. Achieving fast healing under physiological conditions while also having high mechanical strength is nontrivial. Many gels heal slowly (minutes to hours) and can have lower toughness than permanent gels. Biocompatibility of dynamic chemistries (e.g. aldehydes or boronic acids) must also be ensured for biomedical use. Current trends aim to overcome these limitations(85). A major direction is multi-mechanism design: combining several reversible bonds or both intrinsic/extrinsic healing to cover weaknesses of each. For example, adding a second dynamic network can allow healing under a wider range of stimuli. Researchers are also developing stimuli-responsive triggers (light, heat) to activate healing on demand. The use of novel polymers (e.g. synthetic peptoids, zwitter ionic monomers) is expanding the toolbox for safer, stronger gels(86).

On the application side, scaling up manufacturing and ensuring stability in real-world conditions (humidity, microbes, wear) remain obstacles. Regulatory approval for medical uses will require thorough biocompatibility and durability testing. Nevertheless, many self-healing hydrogels already possess valuable traits (adhesion, conductivity, injectability) that make them suitable for next-generation devices(87).

As noted in recent reviews, the future of self-healing hydrogels is promising: "they may be further developed for various applications and specific fields. Integration with 3D printing and nanotechnology, and deeper understanding of multi-scale healing, will likely drive advances(88).

8.Conclusion

Self-healing hydrogels represent a versatile class of smart materials. By harnessing dynamic bonds and clever designs, they overcome the brittleness of conventional hydrogels, offering repeatable self-repair. Extensive research in the past decade has elucidated mechanisms (intrinsic vs extrinsic, covalent vs noncovalent) and developed numerous synthesis strategies (functional polymerization, dual networks). As a result, self-healing hydrogels now find roles in tissue engineering, wound healing, drug delivery, soft robotics, electronics, and beyond continued innovation in chemistry and fabrication will further improve their performance. With their unique ability to mimic biological repair, self-healing hydrogels are poised to enable more durable, adaptable biomedical and engineering applications soon.

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