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Injectable Hydrogels for Articular Cartilage Regeneration: Design and Network Formation Strategies

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Abstract. Articular cartilage degeneration and focal defects contribute to chronic pain and functional limitation, yet durable regeneration remains challenging because cartilage is avascular and has low cellularity. Injectable hydrogels adaptively fill defects, which can provide an extracellular matrix microenvironment and deliver therapeutic signals. This review surveys recent injectable hydrogel technologies for articular cartilage regeneration, emphasizing how network formation mechanisms govern retention and early function at the joint. Three representative strategies are discussed, including in situ gelling systems where precursor is injected and solidified on demand, shear thinning and self-healing hydrogels that flow under shear via reversible interactions and recover after injection, and injectable hydrogel microparticles where building blocks assemble into porous scaffolds. The results reveal that successful injectable hydrogels are a balance among operability, spatiotemporal control of network formation, early structural integrity, and tissue interaction.

Keywords: injectable hydrogels, articular cartilage regeneration, in situ gelation, network formation

1. Introduction

Cartilage degeneration and focal cartilage injuries affect a large proportion of the population and are common causes of chronic pain and functional limitation. Osteoarthritis (OA), a cartilage-related joint disease, was estimated to affect 595 million people in 2020, which is 7.6% of the global population [1]. This prevalence translates into substantial clinical and economic burden worldwide, emphasizing the need for more durable repair strategies. However, articular cartilage has a limited intrinsic capacity for self-repair. Its low cellularity and lacking in blood vessels and nerves, together restrict the delivery of biological cues after injury [2]. These constraints partly explain why current interventions rarely deliver durable cartilage regeneration and long-term function.

Hydrogels are attractive biomaterials for cartilage regeneration due to their hydrated polymer networks which can provide a microenvironment very similar to extracellular matrix (ECM) and their tunable chemistry, transport, and mechanics. Hydrogels can be formulated as injectable systems to enable minimally invasive delivery to the injured joint. In addition, in situ gelation after injection can improve defect conformability and retention at the target site [3]. Moreover, injectable hydrogels can locally deliver cells and bioactive cargos, enabling spatially confined regeneration.

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This review summarizes injectable hydrogel technologies for articular cartilage regeneration focused on how network formation mechanisms govern performance. For clarity, representative approaches are divided into three design strategies: in situ gelling systems that crosslink at the target site, shear thinning and self-healing hydrogels that flow under shear and recover after injection, and injectable hydrogel microparticles that assemble from pre-formed building blocks [4]. It aims to guide the rational design of next-generation hydrogels with improved clinical translational potential.

2. Fabrication and network formation of injectable hydrogels

In injectable hydrogels, fabrication primarily refers to how the polymer network forms after delivery. Gelation chemistry and kinetics determine injectability, defect filling, and early stability at the joint.

2.1. In situ gelling hydrogels

Thermo-responsive injectable hydrogels undergo a sol-gel transition near physiological temperature, forming a network in situ. This allows delivery as a low-viscosity precursor followed by rapid solidification to improve defect conformability and in situ retention. A common limitation of Poly(N-isopropylacrylamide) (PNIPAM)-based thermogels is hydrophobic collapse around the lower critical solution temperature (LCST). This reduces hydration and causes volume shrinkage. Such shrinkage is undesirable for cartilage repair as it weakens the stability of shape and defect filling. To address this problem, Chen et al. grafted PNIPAM onto hyaluronic acid (HA) to introduce a cartilage-relevant, hydrophilic backbone while preserving thermogelation [5]. They reported a hyaluronic acid–g–poly(N-isopropylacrylamide) (HPN) thermogel with a transition temperature of 32–33 °C and gelation completed within 300 s at 37 °C. For the data, the hydration increased from 2.6 ± 0.3 to 6.7 ± 0.9 g water/g polymer, with an increase in the viscoelastic strength peak G* from 35 to 100 Pa. Functionally, chondrocytes encapsulated in the HA–PNIPAM network showed enhanced matrix deposition. By day 28, collagen and glycosaminoglycans (GAG) production reached 17-fold and 21-fold relative to monolayer control. Overall, thermo-responsive HA-based hydrogel networks are simple to handle and solidify rapidly, but controlling dehydration shrinkage remains essential for defect filling and shape retention.

Photo-crosslinkable injectable hydrogels are designed for specific demand. The precursor solution is injected and positioned at the defect site, then rapidly cured through a light-initiated free radical reaction. This workflow offers strong temporal and even spatial controllability. In a representative study, Catori et al. engineered hybrid hydrogels based on methacrylated hyaluronic acid (HAGMA) and thiolated gelatin (GELSH), introducing parallel radical crosslinking and thiol–ene bonding to accelerate gelation [6]. This design is to maintain fundamental biological functions of the biopolymers. As for the mechanism, the thiol–ene reaction is relatively faster and less sensitive to oxygen inhibition, allowing shorter in situ irradiation time. Rheological data showed that adding GELSH accelerated gelation by 4.6 times faster. This research also demonstrates that free S-nitrosothiols (RSNOs) such as S-nitrosoglutathione (GSNO) eliminate free radicals and inhibit photopolymerization. In their system, the thiol–ene accelerated network formation overcomes this inhibition. Overall, photo crosslinking offers rapid, user-triggered solidification with spatiotemporal control. However, it depends on light or initiator systems and requires attention to how the load may interfere with the radical process.

Visible-light triggered systems enhance intraoperative control by combining injectable delivery with on-demand rapid fixation. Nie et al. built a silk–elastin-like protein (SELP) hydrogel

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engineered by de novo method [7]. At the gene sequence level, they encoded tyrosine and lysine motifs into the protein backbone to enable visible light–triggered covalent bonding. Arginine–Glycine–Aspartic (RGD) motifs were also introduced to improve cell adhesion. This system uses a Ru/SPS light-initiated system to form dityrosine bonds under 450 nm blue light, achieving ultra-fast gelation in less than 2 seconds and obtaining a high wet adhesion strength of approximately 90.8 ± 1.8 kPa. At the same time, they further increased network density and mechanical support by increasing the number of repeating units. In their rabbit partial-thickness cartilage defect model, the material could rapidly solidify at the defect site and maintain tight interface integration, promoting the regeneration of a matrix closer to hyaline cartilage. Therefore, this bottom-up design achieves ultrafast gelation and high adhesive strength. However, the complexity of the molecular design grows, making practical production and clinical adaption more challenging.

Overall, in situ gelation routes such as thermo-sensitive, photo-crosslinking, and visible light-triggered methods each involve different trade-offs between ease of operation, spatiotemporal control, and gelation speed.

2.2. Shear thinning and self-healing hydrogels

Shear thinning and self-healing injectable hydrogels rely on reversible network interactions. This means that the material's viscosity decreases when sheared inside the needle, enabling it to flow. After the injection is completed and the shear is removed, it can quickly rebuild its network and return to a gel state. Its molecular mechanisms usually stem from dynamic covalent bond exchange (such as Schiff-base, boronate ester formation) and/or reversible non-covalent interactions (e.g. hydrogen bonding, electrostatic, etc.). In intra-articular applications, this from flowable to recoverable transition determines whether the material can conform to defects, remain stable in a flushing fluid environment, and maintain early structural stability under mechanical load [8].

A classic implementation of this concept uses dynamic Schiff-based chemistry, where aldehyde- and amine-bearing polymers form reversible imine-type linkages under mild conditions. Huang et al. developed an injectable hydrogel by crosslinking carboxymethyl chitosan (CMC) with aldehyde-modified cellulose nanocrystals (DACNCs) and further combined the matrix with mesenchymal stem cells (MSCs) and kartogenin (KGN) to enhance chondrogenesis [9]. In this system, the formulation space of CMC/DACNC is used to regulate engineering parameters such as mechanical support and swelling. In their rabbit femoral trochlear cartilage defect model, the incorporating KGN and MSCs within the injectable construct improved repair outcomes in vivo. This study demonstrates how dynamic covalent exchange can link injectable and recoverable with biological function into a closed loop.

Apart from rheological testing, the self-healing system also faces more critical transformation issues. It is unknown whether the materials can remain stable and maintain a continuous network like avoiding disruption from irrigation, in an arthroscopy environment that is damp and constantly irrigated. Yang et al. reported an injectable adhesive hydrogel featuring dynamic Schiff-base bonds and hydrogen bonding, loaded with bone marrow–derived mesenchymal stem/stromal cells (BMSCs)-derived exosomes for therapeutic signaling [10]. In a pig model under arthroscopic irrigation conditions, the material could be smoothly injected into the defect and gel in situ. It's direct evidence of injectable and self-healing under real operational constraints. They linked the sustained release of exosomes to immunomodulatory effects (for example, through macrophage polarization/NF-κB-related pathways), providing a more complete logic. A mechanically stable material platform is more likely to achieve effective bioactive delivery and repair.

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Dynamic covalent chemistry can also be used to construct transient HA networks that more closely resemble the viscoelastic behavior of synovial fluid, while maintaining injectability. Said et al. designed a self-healing HA hydrogel formed by mixing complementary HA precursors bearing phenylboronic acid and fructose-derived diols, yielding dynamic boronate ester crosslinks that enable rapid network reconstruction after shear [11]. The author anchored an iodine-containing contrast agent to the polymer to make a clear image for hydrogel. This step allowed verification of the outcome of the joint cavity injection and tracked its retention in the mouse knee joint for several weeks. Then they combined this delivery evidence with the disease endpoints of the OA model, finding that OA progress was slower compared to the control group. For shear thinning and self-healing systems, this work suggests a direction of combining reversible mechanical networks with quantifiable, traceable intra-articular retention to serve more precise joint cavity treatment strategies.

In general, these studies make it clear that injectability is more of a dynamic property. Balancing exchange kinetics, noncovalent dissipation, and wet-joint retention is the more practical design strategy.

2.3. Injectable hydrogel microparticles

Injectable microgel systems redefine injectability by replacing in situ bulk gelation with in situ particle assembly. The method is to prepare and crosslink the microgel particles, then jam them into a flowable paste-like system. This system can inject through a needle and establish a solid-like scaffold rapidly. A key advantage is intrinsic macroporosity supporting transport, infiltration, and ECM deposition without waiting for bulk degradation.

A practical question then follows: chondrogenesis depends more on microgel stiffness, or on packing-defined porosity or connectivity. To answer this question, Asadikorayem et al. designed a zwitterionic granular hydrogel platform [12]. Critically, intra-particle and inter-particle crosslinking were independently controlled. Therefore, they could decouple microgel stiffness from porosity. The researchers first obtained zwitterionic hydrogels through photo crosslink and mechanically crushed them into microgel particles. Then in the presence of cells, a secondary crosslinking is mediated by horseradish peroxidase (HRP) to form cell-laden particle scaffolds. By adjusting intra-microgel crosslink density, they produced microgels with stiffness of 1–3 kPa. Even if the weight fraction is the same, differences in the swelling degree of microgels can still change the packing density, thereby varying the porosity to about 5–40%. When porosity was held constant, stiffness had a diminished effect on chondrogenic phenotype, indicating that porosity can dominate biological outcomes in granular networks.

Nikolas et al. proposed a granular composite of mesenchymal stem/stromal cell spheroids (MSC spheroids) and norbornene-modified hyaluronic acid microgels (NorHA microgels) [13]. The idea is that the cell spheroids maintain contact between cells, while microgels provide structural support after injection. After shaping, constructions were stabilized by visible-light interparticle crosslinking for 3 min, which was a fast fixation. The composites supported robust chondrogenesis: expression of SRY-box transcription factor 9 (SOX9), aggrecan (ACAN), and collagen type II alpha 1 chain (COL2A1) increased by hundreds to thousands-fold versus undifferentiated MSCs, while fibrocartilage and hypertrophic markers increased only minimally. Besides, they advanced the evaluation from the cartilage phenotype at the molecular level to tissue integration at the interface level. This step is crucial as the stability of the interface often determines whether the material can function long-term within the joint. Following experiments showed that the strength of this composite system was better than that of the microgels alone but still did not reach the level of native cartilage. Therefore, interface integration remains a weakness of the particle strategy.

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Beyond serving as structural scaffolds, microgels can function as injectable depots that extend intra-articular residence of fragile biologics. Shang et al. encapsulated engineered exosomes in injectable methacrylated hyaluronic acid (HAMA) microgels to achieve sustained release and prolonged residence [14]. They linked efficacy to chondrocyte pathway modulation and reported improved repair with the microgels. This work highlights a design distinct from purely mechanical scaffold. That is microgels can be optimized as delivery vehicles while maintaining injectability.

Together these studies position injectable microgels as a third design route. The most transferable insight is that microgel systems are architected materials: porosity and interparticle annealing often dominate biological outcomes.

3. Challenges

The development of hydrogels has reached a satisfying stage, but there are still many challenges remaining to be solved. Apart from the research mentioned before, the current clinical used hydrogels are mostly simple in the structures. This is because hydrogels with complex structures are facing translation barriers, requiring more specialized equipment with more time and cost. Even for the current hydrogels, most of them are still produced on a small scale. And natural biopolymers can show batch-to-batch variability, requiring standardized production and making regulatory approval much harder [15]. For the mechanism, the individual temperature differences at the joint and the external temperature change can lead to unstable gelation and drug release. For enzyme-responsive hydrogels, pathogenic enzyme types or activity in OA are complex and not fully understood, limiting the specialized design and affecting release efficiency and timeliness [16]. There is still an urgent need for many high-quality trials to advance the reliability and safety of clinical applications of hydrogels.

4. Conclusion

Articular cartilage has limited ability in self-repair, so it's still difficult to achieve long-term and stable functional recovery under current treatment conditions. This review focuses on the topic of injectable hydrogels for articular cartilage regeneration, mainly addressing the network formation after injection and maintenance within the joint. Three design routes are highlighted and discussed. In situ gelling systems can inject first and solidify at the target site, but clinical reliability depends on the compatibility of gelation kinetics and triggering conditions in constrained situations. Shear thinning and self-healing systems rely on reversible interactions to enable injectable flow and recover a solid-like state after injection, but the retention and structural stability remain unclear after washing and loading. The injectable hydrogel microparticles make the assemble process in the body instead of gelation in the body, which is highly related to porosity, particle connectivity, and interface integration. Besides, microgels can prolong the intra-articular residence of fragile biological agents. The central conclusion is that a good design of injectable hydrogels requires striking a balance between tissue interaction, operability, spatiotemporal control of network formation, early structural integrity, and .spatiotemporal control of network growth.

Since this article is a brief review, its limitations are also quite clear. This review uses representative studies rather than exhaustive coverage, and the lack of unified standards for evaluation endpoints in different studies limit horizontal comparisons. Future research should establish a unified standard that is built on clinical practice. As for the material itself, manufacturability should be given greater attention. Combining the efficient design strategies with

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the clinical practice is a better way to make the regeneration of articular cartilage real for patients in the world.

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