REVIEW PAPER

Injectable Hydrogels for Tissue Engineering: From Injectable Biomimetic Matrices to Organoid and In Situ Regeneration

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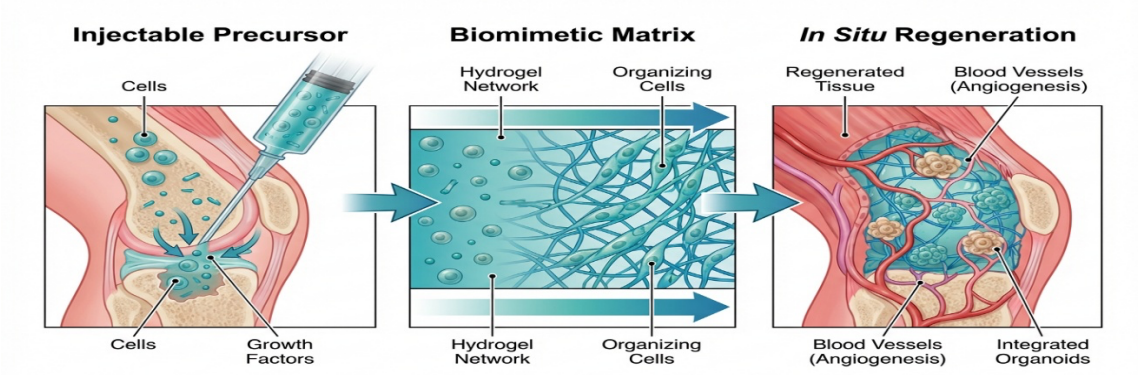
ABSTRACT
Hydrogel injectables mark a revolutionizing step forward for the field of regenerative medicine, as these biomaterials offer a minimally invasive alternative for the repair and reconstruction of tissues and organs. By mimicking the 3D microenvironment of the body, these biomaterials have successfully eliminated the need for surgical intervention, thus reducing the overall cost of healthcare and the rate of patient morbidity. The recent literature on the subject, as reported for the period of 2024-2026, has been focused on the development of hydrogels with enhanced biological and physiochemical properties that mimic the natural extracellular matrix (ECM) of the body. The current review article will discuss the current state of the art for the field of injectable hydrogels, with a special emphasis on the recent advances made with the development of novel and sophisticated hydrogel biomaterials. The different cross-linking mechanisms for the development of these biomaterials will be discussed, including the recent advances made with the development of novel cross-linking mechanisms for the gelation of these biomaterials under physiological conditions. The recent advances made with the encapsulation and co-delivery of cells will also be discussed, including the impact of these biomaterials on the proliferation and differentiation of stem cells. The recent literature on the subject will be analysed for the different applications of these biomaterials for the repair and reconstruction of various tissues and organs, including the recent advances made with the development of injectable in situ organoids and mini-tissues. The recent limitations and future scope for the field of injectable hydrogels will also be discussed.

Graphical Abstract



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INTRODUCTION

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Tissue engineering has been working towards creating scaffolds that can easily integrate with the host tissue and create a favourable environment for cell regeneration. Among all the scaffolds created for tissue engineering, injectable hydrogels have been at the forefront of creating scaffolds that can easily integrate with host tissue, thanks to their unique property of becoming fluid before application and turning solid after application. This property of hydrogels allows them to easily adapt to the irregular shapes of tissue defects and come into contact with the host environment [1-3].

From 2024 to 2026, the research in the field has shifted decidedly towards "smart" and biomimetic hydrogel materials. These are no longer just passive platforms but rather active participants in the process of healing. By mimicking the topology and "feel" of the native extracellular matrix, current injectable hydrogels can now direct the actions of cells [1, 2]. This report synthesizes the latest research in the field, showing the progress we have made from simple injectable platforms towards complex platforms that can support organoids and in situ tissue regeneration.

3D BIOMIMETIC SCAFFOLDS MADE OF INJECTABLE HYDROGELS

1.1. Extracellular Matrix Mimicking Architectures

The human natural extracellular matrix is a complex and layered mixture of proteins, glycosaminoglycans, and signalling signals. Not only does it keep our bodies together, but it is also responsible for guiding cells according to its instructions. One of the major concerns of research carried out today is creating complexity in injectable forms. As stated by Nishiguchi (2024), new injectable hydrogels are being designed with biological roles and physical and chemical properties that are tailored for cell delivery and retention. [1]

One of the most commonly applied techniques is known as Interpenetrating Networks (IPNs). IPNs are materials consisting of two or more separate polymer networks that are intertwined on a molecular scale without necessarily bonding chemically between them. Colleagues developed a hybrid IPN material consisting of silk fibroin and sulfate carboxymethyl cellulose and tyraminated carboxymethyl cellulose. This type of material mimics a dynamic environment similar to that of the ECM and stiffens gradually, similar to natural developmental processes such as those found in cartilage tissue formation [2]. The s-CMC component also assists in storing growth factors, thus providing a biochemical reservoir similar to that of the ECM [2].

A further notable breakthrough can be observed in the design of Microporous Annealable Protein (MAP) scaffolds and granular microgel structures. According to Segura (2024), in this design, microgels that have been injected into the body can be cross-linked in place to form a stable scaffold [4]. The most notable feature of MAP scaffolds is that they can be designed to have porosity that is not coupled to the rate of degradation. In this design, the space between the closely packed microgels forms a porosity that can be used for rapid cell infiltration from the start [4]. Additionally, scientists are exploring anisotropic structures with the potential to direct tissue healing in naturally anisotropic tissues, such as nerves, muscles, and tendons. The development of a magnetically responsive injectable hydrogel, where magnetic collagen bundles (MCollB) are incorporated. By applying a low-intensity magnetic field during gelation, the MCollB can be directed in a biomimetic, aligned way, facilitating fibroblast growth and pro-regenerative macrophages [5].

1.2. Gelation Under Physiological Conditions

The change from a liquid state to a hydrogel state must occur in a body-friendly environment. This means that the hydrogel should form in physiological conditions of 37°C, pH 7, and without harmful initiators or by-products.

This method is highly appreciated because of its high accuracy and biocompatibility. The most widely used method involves the utilization of Horseradish Peroxidase (HRP) and hydrogen peroxide (H2O2) to cross-link tyramine-containing polymers. In 2024, Dixit et al. successfully cross-linked silk fibroin/CMC hydrogels using this exact method, demonstrating its ability to achieve cross-linking kinetics that are appropriate for in situ applications [2]. Photo-crosslinking is still one of the first choices, and indeed one of the best ones, especially when using gelatin methacryloyl (GelMA). In 2024, Pan and co-workers presented a scaffold based on GelMA and filled with carbon dots and FTY720, which is cured under UV light in 30 seconds [6]. Although there are concerns regarding DNA damage when using UV light, progress in visible light initiators and less damaging UV sources, such as 365 nm and 6 mW/cm² setup, have minimized these risks [7]. Dynamic covalent chemistry is also utilized in the form of Schiff base chemistry between amino groups such as in chitosan and aldehyde groups such as in PEG-dialdehyde. This facilitates rapid in situ gelation without requiring additional stimuli. Lin *et al*. (2024) utilized this type of chemistry to create a biodegradable chitosan-PEG/PEG-dialdehyde hydrogel that simply requires mixing of two precursors for gelation. However, aside from facilitating hydrogel formation, this type of chemistry also provides hydrogels with self-healing properties, which is important because hydrogels are expected to be in continuous motion. Other cutting-edge techniques include gels that respond to redox conditions and pH changes. For example, Zheng et al. have developed a thiolated hyaluronan-thiolated chitosan hydrogel that forms in place and responds to redox states, which can be used for the delivery of stem cells for endometrium repair [8]. Similarly, Heng et al. (2026) have developed a bi-layer hydrogel system (HES) that is sensitive to both pH and near-infrared (NIR) laser light for the spatiotemporal control of the delivery of bioactive ions and nanoparticles [9].

2.1. Natural Polymers

Because of their innate biocompatibility, biodegradability, and cell-adhesive motifs, natural polymers are highly valued in tissue engineering.

Hyaluronic Acid (HA): Hyaluronic acid is one of the notable components of the extracellular matrix, and it is often designed for crosslinking. For example, there is hyaluronic acid methacryloyl (HAMA), and it is employed for photopolymerized microgels for cartilage repair [10]. For bone tissue engineering, there is the use of hydrogels based on hyaluronic acid, where dynamic and covalently dual-crosslinked hydrogels are created, employing Schiff base crosslinking and photopolymerization for controlling mechanical properties [11].

Chitosan: A derivative of chitin, chitosan is often blended with other polymers like PEG or hyaluronan. Chitosan has functional amine groups that make it particularly suitable for Schiff base gelation [8, 12]. Chitosan microgels have been studied as a means to assist in the formation of cell microaggregates in osteochondral tissue [14].

Collagen and Gelatin: It provides structural integrity and RGD domains for cell adhesion. Type I collagen for magnetic bundles that assist in alignment [5]. Gelatin is denatured collagen and is often methacrylated for GelMA, a photoinitiating material that maintains bioactivity [6].

Silk Fibroin: Silk fibroin is being utilized in "smart living hydrogels" for cartilage regeneration and organoid manufacturing due to its remarkable mechanical strength and gradual degradation [7,15].

Alginate: Alginate is favored because of its mild gel-forming ability in the presence of divalent cations, e.g., Ca^{2+}. It is also used in combination with other materials, e.g., nerve extracellular matrix/carboxymethyl chitosan/oxidized alginate hydrogel, which is used for spinal cord repair [16].

2.2. Synthetic and Hybrid Systems

However, even though they may not bear any biological signals, they can give more control over mechanical properties and degradation rates. The aim behind using hybrid materials is to obtain "the best of both worlds." Poly (ethylene glycol) (PEG): This is often used to improve injectability and control crosslinking in natural polymers (e.g., PEG-dialdehyde, chitosan-PEG). [12] PVA, or Polyvinyl Alcohol, is often used in hybrid networks. A photo-crosslinkable tyraminated PVA-gelatin hydrogel for growth factor delivery in orthopedic applications was described by Longoni et al. (2026). [17] Jeencham et al. (2024) described the use of silk fibroin and GMA-modified PVA for a biphasic meniscus scaffold. [7] Polypeptides and Synthetic Polypeptide Hydrogels: Though not discussed in as much detail in the main 2024 sources, these are a class of synthetic materials designed to resemble protein structures in figure 1.

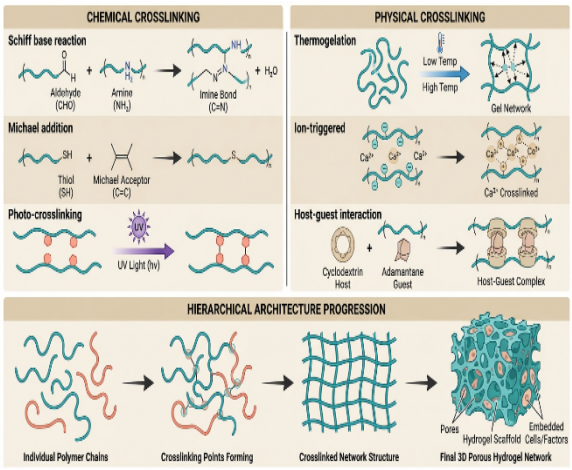

Figure 1: Examples of physical (such as ionic and hydrogen bonding) and chemical (such as covalent and photo-crosslinking) crosslinking processes in injectable hydrogels.

2.3. Comparison of Material Platforms

The benefits and drawbacks of natural vs synthetic platforms are compiled in the following table, which is based on research from 2024 to 2026 in table 1.

Table 1: Comparison of Natural vs Synthetic Material Platforms

Platform	Examples	Advantages	Disadvantages
Natural	HA, Alginate, Chitosan, Collagen, Silk Fibroin	High biocompatibility, intrinsic cell-adhesive motifs, enzymatic degradability, biomimetic.	Potential for immunogenicity, batch-to-batch variability, often weaker mechanical properties.
Synthetic	PEG, PVA, PLGA, PNIPAM	Highly tunable mechanics, predictable degradation, high reproducibility, low immunogenicity.	Lack of biological signaling, potential toxicity of some degradation products, often requires modification with cell-adhesive peptides (e.g., RGD).

Hybrid	GelMA, Chitosan-PEG, PVA-Gelatin, Silk-CMC	Combines biological cues with mechanical tunability; allows for sophisticated crosslinking (IPNs).	Increased complexity in synthesis and characterization; regulatory pathways can be more complicated.

3.1. Viability, Proliferation, and Differentiation of Stem Cells

A large number of injectable hydrogels are mostly used to support and educate stem cells. However, the major problem associated with injectable hydrogels is the maintenance of high viability throughout the process of injection and the subsequent gelation process. For instance, the chitosan-PEG/PEG-dialdehyde hydrogel developed by Lin et al. (2024) showed the ability to support the viability of hADSCs for at least 10 days in vitro. The encapsulated hADSCs also differentiated into 3D spheroids within the hydrogel, which resulted in the upregulated expression of genes and proteins associated with chondrogenic differentiation compared to 2D cultures [12]. The encapsulated OE-MSCs within the nerve ECM/CMC/OA hydrogel also enhanced the process of axonal regeneration and remyelination following spinal cord injuries [18]. In tissue engineering of neural tissue, Pan et al. (2024) showed that a GelMA hydrogel incorporating CDs and FTY720 could facilitate the proliferation and differentiation of NSCs. CDs were employed for scavenging ROS, reducing oxidative stress for NSCs, and FTY720 is an immunomodulatory agent. These effects were reflected by decreased astrocyte differentiation and improved motor function recovery of a rat model of spinal cord injury [6].

3.2. Co-delivery of Cells and Growth Factors

The co-delivery of cells and GFs is a potent approach to direct regenerative processes. However, the rapid diffusion of GFs in hydrogel systems can hinder their regenerative potential. Recent research has employed sequestration and spatiotemporal release as approaches to this problem. Dixit et al. (2024) employed sulfated polysaccharides (s-CMC), which were used in their IPN hydrogel to capture TGF-β. This led to the prolonged presentation of the growth factor, resulting in chondrogenesis, which is comparable to cells supplemented frequently with TGF-β in the media [2]. Recently, Deng et al. (2024) have developed dECM-based hyaluronic microgels (HE microgels) that are able to offer a "spatiotemporal release" of cartilage-specific molecules. These microgels are able to release growth factors such as IGF-1, TGF-β, and BMP-2, followed by a slow release of macromolecules of the ECM such as GAGs and collagen, thus enhancing the function of osteoarthritic chondrocytes and recovery of cartilage matrix in a rat model of osteoarthritis [13]. With respect to soft tissue and neural repair, Segura (2024) has mentioned the application of MAP scaffolds in the delivery of different bioactive factors, such as IL-33, VEGF, and nitric oxide. These factors are released from different "species" of microgels in a heterogeneous MAP scaffold, thus providing precise control over the signaling environment [4].

4.1. Cartilage and Osteoarthritis Therapy

Given the tissue's low potential for self-healing and the less invasive nature of intra-articular injections, cartilage regeneration is arguably the most active topic for injectable hydrogel research. IPNs and Stiffening Matrices: Dixit et al. (2024) employed silk/CMC IPNs to create a chondro-inductive microenvironment that stiffens over time, which is similar to natural development [2]. Chitosan Microgels: Salehi (2025) discussed the application of chitosan microgels to create engineered microaggregates, which can be effective in cartilage development even without the support of growth factors [19].

dECM Microgels: Deng et al. (2024) showed that dECM-based HA microgels could reduce OA severity in rodent models significantly by restoring chondrocyte function and promoting matrix formation [13]. Stem Cell Spheroids: Lin et al. (2024) showed that hADSC spheroids embedded in chitosan PEG hydrogels are highly effective for upregulating chondrogenic markers [12].

4.2. Skin and Soft Tissue Regeneration

Injectable hydrogels in skin regeneration are primarily aimed at rapid wound closure and reduction of fibrosis. MAP Scaffolds: Segura (2024) explained that MAP scaffolds enable rapid cell infiltration and angiogenesis, which ultimately leads to the formation of structures in wound healing in the skin [4]. Antioxidant and Adhesive Hydrogels: Tian et al. (2025) designed a biomimetic nanofiber composite hydrogel with tissue adhesion and antibacterial properties, termed PGF@ALG/PLGA, to be used in infected wound healing [19]. Magnetic Alignment: used magnetically aligned hydrogels to aid in guiding fibroblasts, which is important in the healing of aligned soft tissues, such as tendons [5].

4.3. Neural and Cardiac Tissue Repair

The most difficult repairs are those of the neural and cardiac systems because of their complex structures and harsh post-injury environments.

Spinal Cord Injury (SCI): Pan et al. reported significant motor function recovery in rats using GelMA/CD/FTY720 hydrogels with NSCs [10]. Seidkhani et al. also found improved remyelination and axonal regeneration in rats using nerve ECM/CMC/OA hydrogels with OE-MSCs [16]. Brain Injury and Stroke: The application of MAP scaffolds improved the engraftment of neural progenitor cells and enhanced locomotion in traumatic brain injury and stroke [4]. Cardiac Tissue: Moradi et al. discussed hydrogels as potential materials for cardiac tissue engineering and highlighted growth factor delivery and biomimetic ECM hydrogels as potential applications of hydrogels in cardiac tissue engineering [18]. Parvin et al.

also discussed hydrogels as potential materials for cardiac tissue engineering and mentioned stem cells and organoids as potential applications of hydrogels in cardiac tissue engineering [3].

4.4. Summary of Tissue-Specific Repair: The tactics and results for various tissue types are listed in the following table 2.

Table 2: Summary of Injectable Hydrogels in Tissue-Specific Repair

Target Tissue	Materials	Key Outcomes
Cartilage	Silk-CMC IPN, Chitosan-PEG, dECM-HA Microgels	Chondrogenic differentiation, matrix deposition, reduced OA severity.
Skin	MAP scaffolds, Gelatin-Alginate nanofibers	Faster wound closure, increased angiogenesis, M2 macrophage polarization.
Neuronal (SCI)	GelMA-CDs-FTY720, Nerve ECM-CMC-OA	Enhanced NSC proliferation, axonal regeneration, motor function recovery (BBB score).
Bone	Hyaluronate-based dual-crosslinked gels	Enhanced BMSC proliferation, M2 macrophage recruitment, expedited bone regeneration.
Endometrium	Thiolated Hyaluronan-Chitosan	Increased endometrial thickness, reduced fibrosis, improved pregnancy rates.

4.5 Injectable Hydrogels in Oral and Craniofacial Tissue Engineering

Oral and craniofacial tissues constitute one of the most challenging environments for regenerative medicine due to the structural complexity, the continuous exposure to microbial challenges, the dynamic mechanical loading and the highly specialized functional demands. Unlike many other tissues, regeneration in the oral cavity is complex because it requires the coordinated replacement of hard tissues (enamel, dentin, cementum, alveolar bone) and soft tissues (dental pulp, periodontal ligament, gingiva, oral mucosa, and salivary glands) as well as sufficient vascularization, innervation, and immune regulation. Classical therapies such as guided tissue regeneration, bone grafting, regenerative endodontics and periodontal surgery have brought about significant improvements in clinical outcomes. Nevertheless, these techniques tend to induce repair rather than true biological regeneration. Thus, regenerative dentistry is gradually moving towards biomaterial-based strategies that are capable of mimicking the native extracellular matrix (ECM) microenvironment and simultaneously delivering cells, bioactive molecules and therapeutic agents directly to the defect site. [21, 24].

Of the many biomaterial platforms currently being studied, injectable hydrogels are especially appealing because they can be administered in a minimally invasive manner, have excellent biocompatibility, contain large amounts of water, have physicochemical properties that can be adjusted, and can undergo gelation in situ after injection. The three-dimensional porous architectures resemble the native extracellular matrix to facilitate cellular adhesion, migration, proliferation, nutrient diffusion and tissue remodeling. Injectable hydrogels can be prepared from naturally derived polymers such as collagen, gelatin methacryloyl (GelMA), hyaluronic acid, chitosan, alginate, fibrin or from synthetic polymers such as polyethylene glycol (PEG) allowing to finely tune degradation kinetics, mechanical strength and biological activity according to specific clinical needs [21].

Recent advances have transformed injectable hydrogels from passive scaffold materials to multifunctional therapeutic systems that can actively modulate tissue regeneration. Current hydrogel formulations contain antimicrobial peptides, growth factors, extracellular vesicles, stem cells, immunomodulatory agents, nanoparticles and bioactive ceramics, which collectively induce angiogenesis, osteogenesis, odontogenesis and immunomodulation. These multifunctional biomaterials also allow for sustained and localized delivery of therapeutic molecules, thus overcoming the limitations associated with rapid diffusion and systemic administration while minimizing adverse effects. Injectable hydrogels are increasingly envisioned as dynamic regenerative platforms rather than merely passive structural matrices [21, 23].

In the last few years, injectable hydrogels have been increasingly used in dentistry, including regenerative endodontics, periodontal regeneration, alveolar bone reconstruction, craniofacial bone engineering, oral mucosal repair, temporomandibular joint regeneration, and salivary gland tissue engineering. Importantly, many of these applications take advantage of the unique capacity of hydrogels to encapsulate mesenchymal stem cells, including dental pulp stem cells (DPSCs), stem cells from the apical papilla (SCAPs), periodontal ligament stem cells (PDLSCs), and bone marrow-derived mesenchymal stem cells (BMMSCs), while maintaining cell viability and directing lineage-specific differentiation. These features make injectable hydrogels one of the most promising translational technologies currently being investigated for next-generation regenerative dental therapies [21, 25].

4.5.1 Injectable Hydrogels for Dental Pulp Regeneration

Endodontic regeneration is one of the areas which is developing at an unprecedented rate within restorative dentistry, being focused on preserving the vitality of the pulp and regeneration of the dentin–pulp complex instead of the traditional replacement of diseased tissues by filling root canals. The regenerative process is based on decontamination of microbes and formation of re-vascularization, re-innervation, differentiation of odontoblasts, and physiological dentin. Injectable

hydrogels are considered as perfect scaffolds for endodontic regeneration since they may be injected to the complicated structure of root canals, where they will polymerize and form biomimetic three-dimensional environment. [22, 23].
Among many stem cell populations used in dental regeneration studies, dental pulp stem cells (DPSCs) have been studied the most because of their high proliferative potential, multilineage differentiation capacity, angiogenic activity, and capacity to produce dentin-like structures. Injectable hydrogels are used as a protective extracellular matrix in order to prevent mechanical stress associated with injection, as well as support cell survival, adhesion, migration, proliferation, and differentiation after implantation. In addition, hydrogels are useful in providing a sustained release of various bioactive factors such as vascular endothelial growth factor (VEGF), bone morphogenetic proteins (BMP-2, BMP-7), transforming growth factor-β (TGF-β), fibroblast growth factor (FGF), and dentin extracellular matrix proteins that promote angiogenesis, neurogenesis, odontoblast differentiation, and dentin mineralization [21, 23].
Another significant benefit of the hydrogel delivery system lies in its ability to combine an antimicrobial effect along with an immunomodulatory effect within a scaffold for regeneration. One of the main reasons why regenerative endodontic treatment fails is constant bacterial infection. Thus, the most recent hydrogel delivery systems are designed to include antimicrobial peptides, silver nanoparticles, calcium silicate bioactive particles, quaternary ammonium compounds, extracellular vesicles, and antioxidant molecules that are able not only to prevent bacterial colonization but to stimulate tissue regeneration at the same time. Such multi-functional biomaterials are able to modulate macrophages into anti-inflammatory (M2) state (21, 23).
A synthesis of recent evidence drawn from systematic reviews proves that hydrogel scaffolds always provide better results in terms of pulp-like tissue generation, dentin bridge formation, vascularization, and biological regeneration as opposed to traditional pulp capping materials. While promising preclinical results have been observed, most existing evidence is based on laboratory experiments and animal trials. This is why randomized controlled clinical trials are needed before these injectable hydrogels can be used for clinical purposes [22, 23].

5.1. Injectable In Situ Organoids and Mini Tissues

The term "in situ organoids" utilizes injectable hydrogels as a supportive niche for cells to self-organize and form complex structures.
Mushtaq et al. (2024) identified "Silk Fibroin-Derived Smart Living Hydrogels" as organoid engineering platforms. These were utilized for the formation of cartilage organoids in vitro using MSCs and glucosamine. These platforms were identified as having potential for clinical applications for regenerative medicine [15].
Furthermore, according to Segura (2024), MAP scaffolds and soft microgels have been identified as platforms for hosting cell spheroids and for guiding endogenous cells for self-organization. MAP scaffolds have been identified as having potential for generating mini-tissues in situ due to 3D printing capabilities and for promoting rapid progenitor cell infiltration [4].
Furthermore, cell-free platforms have been identified as having potential for organoid formation. dECM-enhanced microgels, as identified by Deng et al. (2024), have been identified as having potential for acting as regenerative microtissue platforms for tissue repair in situ through a coordinated cascade of biochemical cues that "instruct" host tissue chondrocytes to behave as if they were in a regenerative environment [8].

5.2. Combinatorial Biomaterial–Cell–Biologics Platforms

The most sophisticated systems described in 2024-2026 are combinatorial in nature, with various therapeutic modalities being combined in a single injectable format. These platforms have been shown to combine:
1. Material Cues: Dynamic mechanics (IPNs based on Silk), porosity (MAP Scaffolds), and anisotropy (Magnetically Aligned Bundles).
2. Cellular Components: MSCs, NSCs, or recruitment of endogenous progenitor cells.
3. Biologics: Growth factors (TGF-β, VEGF), small molecules (FTY720), and nanoparticles (Carbon Dots, MNPs) [2,6]

The experimental readouts of these platforms indicate a shift towards functional validation, with gene expression analysis of lineage markers, histologic confirmation of matrix deposition, and functional/behavioural readouts (locomotion and pregnancy rates in animal models) [6-8].

6.1. Long Term Stability and Host Integration

Although preclinical studies have shown promising results, there are still several hurdles to overcome. Perhaps the greatest concern for MAP scaffolds in tissue engineering is their long-term stability. Although several published studies in 2024-2026 report promising results in acute to sub-chronic studies (weeks to months) in rodents, there is insufficient evidence in the provided corpus for long-term (mult-year) stability in large animal studies or human subjects.
Another important consideration for host immune integration. Studies on MAP scaffolds have demonstrated that the immune response plays a central role in the regenerative outcome. Scaffolds for tissue engineering with MAPs have been designed to modulate the immune response to a pro-regenerative, non-fibrotic state [4]. However, there are considerable variations in the immune modulatory requirements for different tissues and conditions.

6.2. Regulatory and Scale Up Challenges

The clinical translation of injectable hydrogels can be hindered by their complexity. In some cases, authors have clearly indicated that their materials can be "clinically translatable" (e.g., silk fibroin living hydrogels [5]), although regulatory pathway analysis for clinical translation has not been discussed in the literature.

Scalability and manufacturing complexity can be another challenge for the clinical translation of microgels. Although microfluidics-based microgel production with consistent microgel sizes can be clearly demonstrated in the laboratory setting, evidence for scaled Good Manufacturing Practice (GMP)-based production with reliable sterilization processes and lot-to-lot consistency remains absent in the literature.

Finally, the complexity of the microgel-based platforms for drug discovery and development will require a higher burden for characterization and reproducibility. The complexity of the materials used in microgels, as well as the complex release kinetics of multiple cargos, will require addressing several engineering and regulatory hurdles that will need to be overcome for the clinical translation of these advanced platforms [1,9,18].

DISCUSSION

The progress in injectable hydrogels from 2024 to 2026 shows a shift away from simple scaffolds and toward more advanced, "intelligent" materials. The discovery of IPNs, which replicate developmental mechanics, and microgels, which separate porosity from degradation, are major breakthroughs in the field of biomaterials. These tools enable a much greater degree of control over the cellular environment than has been possible in the past.

One major trend is the use of multi-modal and multi-functional approaches. The use of nanoparticles, such as those for scavenging ROS (e.g., Carbon Dots), or even magnetic particles, provides a new layer of physical control in conjunction with biochemical signals. Another trend is the emphasis on "in situ organoids," which indicates a paradigm shift in thinking. Instead of trying to build a tissue in a bioreactor, we are now providing the instructions to the body to build the tissue itself.

The "valley of death" between preclinical and clinical success is still very wide. The absence of long-term data and the complexity of these multi-component materials are the major barriers to progress. Future research should focus on large animal models, long-term functional monitoring, and simplification of the manufacturing process

FUTURE PERSPECTIVES

The future development of injectable hydrogels in oral and craniofacial tissue engineering rests on the interconnection of biomaterial science, stem cell biology, nanotechnology, immunoengineering, and digital medicine. Even though the present applications of hydrogels in oral and craniofacial tissue engineering have been shown to be promising in animal studies, the future generation of injectable biomaterials will shift from simple structural matrices to intelligent biomaterials that can sense and respond to the surrounding microenvironment [21, 26].

Multi-functional and stimulus responsive systems: New generation hydrogels will have double or triple responsiveness such as pH, redox, enzyme, NIR which will allow on-demand drug release, stiffness change or degradation induced by pathophysiological conditions like inflammation in arthritis or oxidative stress in spinal cord injury.

Integration of Organoids and 3D bioprinting: Injectable systems will be capable of supporting culture of organoids and in situ bioprinting, creating dynamic microenvironment mimicking ECM where no need for external growth factors to guide fate of stem cells is required. Granular hydrogels and MAPs will allow precise tuning of porosity and independent regulation of degradation and architecture which will be important in case of vascularization of organoids.

Individualized, patient derived ECM hydrogels: dECM hydrogels adjusted for each tissue type (cartilage, nerve tissue, endometrial tissue) will increase bioactivity but decrease immune reaction. In combination with AI-based designing these systems will optimize both mechanical and biochemical environment.

Fibrosis prevention and immunomodulation: Future hydrogels will include immunomodulating substances like FTY720, IL-33 and ROS scavenging materials such as carbon dots which will allow polarization of macrophages into pro-regenerative (M2) state and prevention of scar formation.

Clinical Translation and Regulatory Pathways: Hybrid materials (e.g. GelMA, silk-CMC IPNs) encounter numerous regulatory challenges. Rapid characterization, good manufacturing practices (GMP) fabrication, and standardized in vivo testing in a clinical model system (e.g. large animal osteoarthritis or spinal cord injury) will hasten translation. In situ monitoring using implanted sensors (e.g. NIR-sensor) could lead to closed loop therapy. Ultimately, the field is shifting toward adaptive, biomimetic injectables that not only fill defects but actively reprogram the healing microenvironment—ushering in an era of “living” scaffolds for precision regenerative medicine.

One of the areas of research that holds great promise for future applications is the design of stimuli-responsive (“smart”) injectable hydrogels able to adapt to the physiological changes in injured tissues. Stimuli-responsiveness can be induced by pH changes, temperature changes, enzymatic activity, presence of reactive oxygen species (ROS), inflammatory cytokines, or other stimuli such as magnetic fields and near-infrared light. Stimuli-responsiveness ensures spatiotemporally controlled release of growth factors, antibacterial drugs, anti-inflammatory compounds, and extracellular vesicles from stem cells [21, 27].

An additional promising research field encompasses the development of cell-free regenerative therapy in combination with injectable hydrogels. While mesenchymal stem cells have already proved to be very efficient in regenerative therapy, problems connected with their immune compatibility, ability to survive, production difficulties, and regulatory issues prevent their widespread use in clinics. That is why scientists have focused on the study of extracellular vehicles (EVs), exosomes, secretomes, and bioactive peptides, which are able to provide regeneration similar to that achieved through live-cell therapy but with much lower risks. Injected hydrogels, which can slowly release these substances, may become one of the directions of future regenerative dentistry [21, 23].

Another important technological development for oral tissue engineering is the combination of 3D bioprinting and personalized biomaterials development. Hydrogels created specifically for each individual patient, based on digital images and utilizing additive manufacturing techniques, may be used to create custom scaffolds that will precisely replicate the morphology of the patient's craniofacial defects. These personalized regenerative constructs may dramatically increase functional integration and aesthetic results of the therapy in maxillofacial, periodontal, and implant-associated bone regeneration therapies [26, 28].

The future research will focus on immunomodulatory biomaterials that will help in regulating the host's immune system during the process of tissue repair and regeneration. While earlier efforts were concentrated on the replacement of damaged tissues, the newer versions of injectable hydrogels have started focusing on guiding macrophages polarization to pro-regenerative phenotype, anti-inflammatory activity, angiogenesis, and coordinated tissue remodelling. Immunomodulation combined with the antibacterial property may be beneficial in the oral cavity due to presence of persistent microbial biofilm and chronic inflammation [27].

Despite all these developments, however, a number of obstacles need to be addressed for the translation into clinical practice to become successful. Long-term biocompatibility, controlled biodegradability, sterilization techniques, industrial production, regulatory approval, and cost efficiency still need to be thoroughly researched *via* multicentre clinical trials. Standardization of production processes and evaluation criteria is also going to be necessary in order to increase the reproducibility of results and make the process more acceptable to regulators. Collaboration between biomaterials researchers, clinicians, engineers, and regulatory agencies is therefore very important [21, 29].

In addition to the biological outcomes of treatment, future clinical research on injectable hydrogel therapy must include patient-reported outcomes such as postoperative pain, quality of life of the mouth, satisfaction with the treatment, functional recovery, and mental well-being. With minimally invasive injectables continuing to displace more invasive surgery procedures, patient-reported outcomes will play an important role in evaluating the actual effectiveness of regenerative treatment. Combining biological outcomes and patient-reported outcomes will contribute to more holistic evaluation of regenerative treatments and their use in practice.

Future clinical studies should not only cover radiologic and histological outcomes but also validate outcomes related to the quality of life of the mouth, anxiety reduction, functional recovery, and patient satisfaction. These multidimensional outcomes will reflect the current trends of patient-centred medicine.

Conclusively, injectable hydrogels are anticipated to be the building block of future regenerative dentistry. It is the exceptional feature of injectable hydrogels to incorporate biological materials that can mimic the native matrix, control drug release, modulate immune system, stimulate stem cells, and apply a patient-specific strategy that provides an unprecedented chance for restoration of structure and functions of oral and craniofacial tissues.

CONCLUSION

Injectable hydrogels have now matured to sophisticated biomimetic materials that can support intricate tissue regeneration processes. By utilizing sophisticated natural and synthetic materials and novel cross-linking chemistry, injectable hydrogel systems have emerged as a minimally invasive tool to accurately administer cells and biologics. Starting with cartilage repair using dynamically stiffening IPNs to neural regeneration with immunomodulatory microgel systems, the current literature in 2024 to 2026 suggests that the near future may see "smart" injectable hydrogel systems transform the landscape of tissue and organ failures. Though challenges remain in terms of host integration and approval, the emergence of combinatorial and organoid-supporting hydrogel systems is a major step toward the development of in situ tissue engineering

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Authors' Contribution

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

Availability of Data and Materials

All data generated or analyzed during this study are included in this article and its supplementary information files. Further, the data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

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Ethical Approval

This study does not involve experiments on animals or human subjects**.**

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