frontiers | Frontiers in Biomaterials Science

TYPE Mini Review
PUBLISHED 13 August 2025
DOI 10.3389/fbiom.2025.1641339

OPEN ACCESS

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RECEIVED 04 June 2025
ACCEPTED 23 July 2025
PUBLISHED 13 August 2025

CITATION
Al Mamun A, Shamiya Y, Hasan A and Paul A (2025) Unlocking the potential of stimuli-responsive injectable hydrogels for bone healing applications.
Front. Biomater. Sci. 4:1641339.
doi: 10.3389/fbiom.2025.1641339

Unlocking the potential of stimuli-responsive injectable hydrogels for bone healing applications

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Stimuli-responsive, or "smart", injectable hydrogels respond to real-time stimuli through physical or chemical changes. This allows hydrogels to be dynamic within their environment in the presence of internal or external stimuli. Owing to this, smart injectable hydrogels have gained noticeable implications within the field of biomedicine. Over the past decade, stimuli-responsive injectable hydrogels have been extensively studied for wound healing and cancer therapies but remain largely unexplored for bone healing applications. In this mini-review, we aim to explore the role of smart injectable hydrogels and assess their current and future implications within the field of bone healing. Specifically, we discuss the physicochemical and biological aspects that must be taken into consideration when developing a material in this field, as well as the various strategies for designing such a material. Additionally, we discuss the current role of stimuli-responsive injectable hydrogels for an array of bone healing applications and their potential for successful clinical translation.

KEYWORDS

stimuli-responsive, injectable, hydrogels, bone healing, biomaterials

1 Introduction

Injectable hydrogels represent a transformative class of biomaterials and have gained significant attention in the biomedical field due to their unique properties and remarkable versatility. Injectable hydrogels are 3-dimensional (3D), highly swelling polymeric networks that are stable in physiological conditions (Yu and Ding, 2008). Accordingly, injectable hydrogels can be administered as liquids and subsequently form gels *in situ* or be administered as shear-thinning gels, making them well-suited for non-invasive therapies (Alonso et al., 2021; Shamiya et al., 2024). The significance of injectable hydrogels lies in their capacity to closely mimic the natural extracellular matrix (ECM), which is a 3D network of macromolecules within the body that provides structural and biochemical support to the surrounding cells in tissues. In this manner, injectable hydrogels provide a biomimetic environment that supports critical biological processes (Yang et al., 2014).

However, traditional hydrogels are often limited by their static nature. Their fixed physical and chemical properties can act as limiting factors to their adaptability in real-time

physiological environments (Lavrador et al., 2021). Stimuli-responsive, or "smart", injectable hydrogels have recently been developed to address this limitation. Smart hydrogels are designed to react to external and internal stimuli, such as pH (Ghauri et al., 2021; Shi H. et al., 2024; Li M. et al., 2024), temperature (Liu et al., 2022; Tallapaneni et al., 2023; Liu X. et al., 2024), enzymes (Carlini et al., 2019; Kumar et al., 2023a; Kumar et al., 2023b), or others (Rybak et al., 2024; Liu L. et al., 2024; Shi et al., 2024b; Choi et al., 2022), such that they offer dynamic interactions with their environment. This allows them to have precise spatial and temporal control over their therapeutic actions.

The development of smart injectable hydrogels has been extensively studied for many biological applications, including wound healing (Yang Y. et al., 2023; Rasool et al., 2019; Chen Q. et al., 2024; Shi et al., 2024c; Li S. et al., 2024), myocardial infarctions (Carlini et al., 2019; Matsumura et al., 2019; Zhang F. et al., 2024), and cancer therapies (Zhou et al., 2021; Jia et al., 2020; Augustine et al., 2021). However, the study of these stimuli-responsive materials for bone healing applications has been limited. This is largely due to their limited mechanical properties and lack of inherent osteogenic factors. Bone healing is a complicated process that requires synchronization between various growth factors, cells, and the ECM, and requires that this synchronization occur in a series of stages in response to bone healing (Zhang et al., 2020; Coyle et al., 2025). Recently, stimuli-responsive hydrogels have been studied for bone healing specifically for their minimally invasive properties and their ability to adapt to a changing environment. Smart materials have been developed to respond to external and internal stimuli to induce changes in stiffness and other mechanical properties, as well as to release osteogenic therapies such as growth factors, small molecule drugs, or nanoparticles with osteogenic potential (Choi et al., 2025).

This review explores the various types of stimuli-responsive injectable hydrogels, highlighting their classification based on different stimuli, their mechanisms of action, and their recent advances in a variety of bone healing applications. Further, we evaluate the strengths and limitations of using smart injectable hydrogels and their future clinical potential to repair bone fractures and defects.

2 Physical, chemical, biological considerations for injectable hydrogels

Bone is a structurally complex and mechanically demanding tissue, composed of cortical (compact) and trabecular (spongy) bone, each with distinct mechanical and biological microenvironments. Its ECM is a biphasic system, consisting of approximately one-third organic components, primarily type I collagen fibers and two-thirds inorganic minerals, mainly hydroxyapatites (Hassan et al., 2023). In contrast to hydrogels intended for soft tissue applications, like skin or myocardium, those designed for bone regeneration must emulate the significantly higher stiffness of bone (in cortical bone), along with its viscoelastic properties and mineralized ECM. Designing an effective injectable hydrogel for bone regeneration requires careful consideration of several key factors (Lee and Shin, 2007; Bai et al., 2018). The hydrogel must be inherently biocompatible, noncytotoxic, and nonimmunogenic to prevent adverse immune responses. It should possess osteoinductive, osteoconductive, osteogenic, and osteocompatible properties to actively promote new bone formation. Mimicking the natural ECM is crucial to support cell adhesion, proliferation, and osteogenic differentiation. Additionally, the hydrogel must degrade in harmony with tissue ingrowth, creating space for new bone tissue. It should maintain sufficient structural integrity and mechanical strength to withstand load-bearing conditions. Tunable pore size and interconnected porosity modulated through polymer composition and crosslinking density are essential for enhancing cell interactions, regulating the release of bioactive factors, and ensuring efficient exchange of nutrients.

The performance and functionality of injectable hydrogels are inherently governed by a combination of physical, chemical, and biological factors (Figure 1). Physically, these hydrogels must exhibit suitable viscosity and shear-thinning behavior to allow for facile injection, followed by rapid gelation under physiological conditions (Alonso et al., 2021). This facilitates minimally invasive administration and stable *in situ* formation. Chemically, the constituent materials should be stable, non-toxic, and capable of undergoing crosslinking under mild, physiologically relevant conditions, often triggered by stimuli such as pH, temperature, or enzymatic activity (Bustamante-Torres et al., 2021). Biologically, the hydrogels must be biocompatible and biodegradable, supporting cellular viability and tissue integration while avoiding adverse immune responses (Revete et al., 2022). These hydrogels are fabricated using natural and/or synthetic polymers that offer tunable mechanical properties, degradation, and shape. However, it is important to note that injectable hydrogels are still limited in their mechanical integrity, and they are often restricted to non-load bearing defect sites.

Injectable hydrogels can be broadly classified into *in situ* forming and shear-thinning systems. *In situ* forming hydrogels transition from a liquid to a gel state upon administration, without the use of toxic reagents or heat (Chen et al., 2018). Shear-thinning hydrogels, such as nanocomposite systems incorporating materials like laponite, can flow under applied stress during injection and subsequently retain their gel structure once the stress is removed (Liu et al., 2017). Injectable hydrogels are highly suitable for bone healing due to their minimally invasive delivery, ability to conform to irregular defects, and *in situ* gelation without toxic triggers. Their biocompatibility, biodegradability, tissue adhesiveness, and porosity support cell infiltration and new tissue growth (Liu B. et al., 2020; Park et al., 2022; Zheng J. et al., 2023; Liu C. et al., 2020). Shear-thinning hydrogels, especially those with nanomaterials with osteogenic potential, enhance structural stability post-injection and promote osteogenic activity, making them effective scaffolds for bone regeneration (Zandi et al., 2021).

Crosslinking strategies play a pivotal role in defining the structural and functional properties of injectable hydrogels. Physically crosslinked hydrogels rely on non-covalent interactions, including electrostatic forces, hydrogen bonding, hydrophobic interactions, van der Waals forces, and host–guest chemistry (Rizzo and Kehr, 2021). These networks are reversible and often responsive to environmental stimuli such as temperature, pH, or light. In contrast, chemically crosslinked hydrogels involve covalent bond formation through methods such as click chemistry, Michael-type addition, Schiff base reactions, photopolymerization, or enzymatic catalysis (Li et al., 2021; Basu et al., 2018). These covalent networks are typically irreversible and

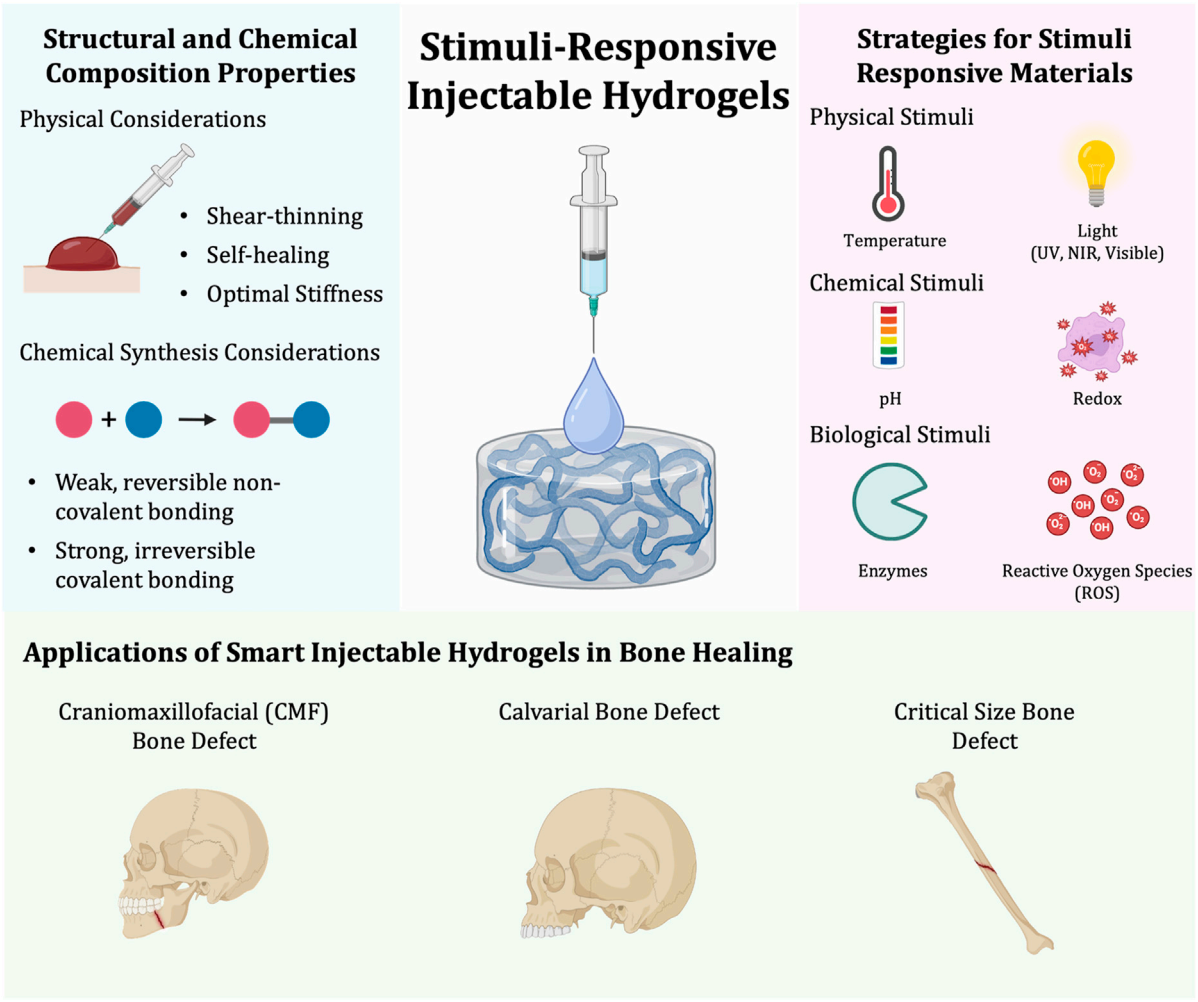

FIGURE 1
Synthesis of stimuli-responsive injectable hydrogels and their applications in bone healing. The structural and chemical composition of stimuli-responsive injectable hydrogels needs to be considered and can be synthesized by taking physical and chemical properties into account (left). Stimuli-responsive hydrogels can be synthesized in a variety of ways. Some strategies for developing a stimuli-responsive material can be classified to be responsive to physical, chemical, and/or biological stimuli (right). Lastly, there are a variety of bone healing applications in which smart injectable hydrogels can be applied to. Some of these include craniomaxillofacial, calvarial, and critical size bone defects (bottom).

offer enhanced mechanical stability, prolonged retention at the target site, and controlled drug release. The robustness of chemically crosslinked hydrogels minimizes premature degradation and drug diffusion, thus enabling precise control over gelation kinetics, degradation profiles, and biofunctionalization. This ensures consistent and predictable *in vivo* and *in vitro* performance, which is critical for therapeutic success. The advantages, disadvantages, and possible applications of various crosslinking strategies for injectable hydrogels are considered in Table 1.

3 Classification of stimuli-responsive injectable hydrogels

There are a variety of strategies to synthesize stimuli-responsive material. These strategies are commonly classified under physical, chemical, and/or biological stimuli and encompass most materials making up stimuli-responsive injectable hydrogels (Figure 1).

3.1 Physical stimulus

3.1.1 Temperature responsive

Temperature-responsive hydrogels alter their volume in response to temperature changes. The variation in temperature affects any hydrophobic interactions and hydrogen bonding between polymer chains, leading to structural and volume changes (Xue et al., 2002; Mah and Ghosh, 2013). This behavior occurs at the hydrogel's lower critical solution temperature (LCST) or upper critical solution temperature (UCST) (Pardeshi et al., 2022). Depending on the ratio of hydrophobic to hydrophilic groups, two outcomes are possible:

TABLE 1 Overview of crosslinking strategies and functional attributes of injectable hydrogels.

Crosslinking strategy	Chemical bond	Application(s)	Advantages	Disadvantages
Physical Crosslinking	Ionic	Wound healing and drug delivery (Yang et al., 2023b; Kuddushi et al., 2022)	• Stimuli responsive • Self-healing • Simple gelation	• Mechanical weakness attributed to non-covalent interactions • Uncontrolled degradation • Highly sensitive to ions
	Hydrogen Bond	Regenerative medicine, targeted therapy and tissue engineering (Yang et al., 2023b)	• Triggered release • Biocompatible • Low risk of inflammatory response	• Short stability • Uncontrolled degradation or swelling
	Hydrophobic interaction	Controlled drug administration, 3D Bioprinting and tissue reconstruction (Karvinen and Kellomäki, 2024; Zhang et al., 2016)	• Dynamic response • Self-Healing • Cell-friendly	• Limited Mechanical Strength • Limited Control Over Network Architecture • Batch Variability
	Host-Guest chemistry	Bioengineered tissues and Biosensor (Lee et al., 2021)	• Stimuli Responsive • Self-Healing Capability • Tunability of Properties	• Dilution Sensitivity • Complex Synthesis • Lack of covalent bonds leads to poor mechanical integrity
Chemical Crosslinking	Click chemistry	Drug delivery and Cell delivery/encapsulation (Wang et al., 2017; Gopinathan and Noh, 2018)	• Quick gelation • Tunable Mechanical and Chemical Properties • Good Stability and Mechanical Strength Due to Covalent Bonding	• Potential Cytotoxicity of Some Catalysts • Multi-Step Synthesis • Does not respond to physical stimuli due to strong covalent bonds
	Schiff base	Wound healing, Osteochondral defect repair and bone tissue engineering (Mo et al., 2021; Cao et al., 2021; Amiryaghoubi et al., 2024)	• Customizable physical and chemical properties • Fast gelation • pH-Responsive	• Loss of mechanical stability in aqueous environment • Aldehydes can cause toxicity
	Michael-type addition	Chronic wound healing, controlled drug delivery (Chen et al., 2024b)	• Efficient reaction with minimal byproducts • Fast gelation	• Slightly basic pH is required for gelation • Not responsive to internal or external stimuli due to covalent bonds • Potential cytotoxicity for some chemicals
	Photopolymerization	Bone tissue engineering, skin regeneration (Wang et al., 2021; Ding et al., 2021)	• Precise control over gelation • Highly Tunable mechanical properties • Instantaneous gelation under light activation • Adaptability to 3D Bioprinting	• Limited light penetration/ exposure can cause uneven gelation • Some photoinitiators can be toxic • Require specialized equipment
	Enzyme	Regenerative medicine, targeted therapy, bone defect filling and healing (Bae et al., 2015; Moreira Teixeira et al., 2012)	• Gelation occurs at physiological conditions • Biocompatible • Controlled gelation	• Enzymes can be expensive • Limited gelation due to uneven enzyme distribution • Changes in physiological conditions can alter the efficacy of enzymes

(1) Number of hydrophilic groups > Number of hydrophobic groups: This is a case of positive thermosensitive hydrogels, where the water solubility of the hydrogel increases with rising temperatures. This means that temperature increases cause the hydrogel to swell, and temperature decreases cause the hydrogel to shrink.
(2) Number of hydrophilic groups < Number of hydrophobic groups: This is a case of negative thermosensitive hydrogels, where the hydrogels shrink above the LCST. This is due to the stronger hydrophobic interactions, which reduce the contact area with water (Huang et al., 2019). Below the LCST, hydrogen bonding between the hydrophilic groups and water dominates and leads to swelling.

Commonly used thermoresponsive hydrogels are prepared from natural polymers, proteins or polypeptides, pluronics, and copolymers based on polycaprolactone, poly(N-isopropylacrylamide), poly(D, L-lactide), polyethylene glycol, and poly(amino ester urethane) (Tanga et al., 2023).

3.1.2 Light responsive

Light-responsive injectable hydrogels are commonly engineered for their easy accessibility and controllable external stimuli.

Clinically, this offers a technology which is easy, non-invasive, and allows for precise spatiotemporal control. In this regard, the properties of light-responsive hydrogels change upon the irradiation of light, including visible light, ultraviolet (UV), and near-infrared radiation (NIR) (Li et al., 2019).

Specifically, there are two primary mechanisms that drive these responses:

(1) Photothermal effects, wherein certain substances that can be integrated into injectable hydrogels have the ability to absorb and emit light radiation, resulting in the production of heat (Anugrah et al., 2019). One such example is indocyanine green, a photothermal agent approved by the U.S Food and Drug Administration, which can generate and transfer heat in response to NIR.
(2) Photodegradation, wherein hydrogel chains are functionalized with photosensitive functional groups (Zhao et al., 2018). Here, photochemical reactions take place to induce phase transitions of the hydrogel. One such example is the use of *o*-methoxy-nitro-benzene family monomers—these functional groups can be grafted onto synthetic polymers before *in situ* gelation, such that they result in the rapid cleavage and degradation of the hydrogel upon exposure to UV light.

3.2 Chemical stimulus

3.2.1 pH responsive

pH-responsive hydrogels undergo volume changes in response to shifts in the external pH, enabling them to swell and degrade. Over recent decades, various pH-sensitive hydrogels have been developed. These hydrogels typically contain ionizable groups, such as acidic (e.g., carboxylic and sulfonic acids) or basic (e.g., ammonium salts) side chains (Jabeen et al., 2017). When the pH of the surrounding environment changes, the ionization of these groups is affected, altering the crosslinking density of the gel network and consequently impacting the hydrogel's swelling behavior. Various pH-responsive self-healing hydrogels, employing borate ester and imine bonds as typical pH-responsive reversible dynamic covalent bonds, hold promise for targeting the acidic tumor microenvironment while concurrently exhibiting self-healing properties, thereby showing broad application prospects in the field of medicine (Gu et al., 2022).

pH-responsive hydrogels are extensively utilized in biomedical applications, particularly in targeted drug delivery systems, where their ability to respond to subtle pH changes enables precise and controlled release of therapeutic agents (Liu et al., 2023; Zheng Z. et al., 2023). They are especially valuable in cancer therapy, as the slightly acidic extracellular environment of tumors (pH 5.4–6.0) can trigger drug release from these hydrogels, minimizing off-target effects and enhancing therapeutic efficacy (Thambi et al., 2023). They are also widely explored for wound healing, as the slightly alkaline pH of infected wounds or chronic wounds (pH 7.2–8.0) can trigger hydrogel degradation or drug release, promoting tissue regeneration and infection control (Bennison et al., 2017). Additionally, these hydrogels are utilized in regenerative medicine for pH-triggered delivery of growth factors or stem cells to injury sites, as well as in oral and gastrointestinal drug delivery, where acidic pH along the digestive tract (pH 1.2) can be leveraged for site-specific release (Thambi et al., 2023). While these materials find applications across various biomedical fields, drug delivery and cancer therapy remain the primary areas of research and development due to their significant potential in improving targeted treatment strategies.

3.2.2 Redox responsive

Injectable hydrogels can be designed to respond to oxidation and reduction cues in the cellular environment. Redox-responsive hydrogels are normally achieved through redox-sensitive chemical linkages (He et al., 2021). This includes disulfide bonds (-S-S-), thioketals, or selenium-containing moieties (Grocke et al., 2021). In an oxidative environment, such as those with high reactive oxygen species (ROS) levels, these linkages undergo a cleavage or transformation, triggering the degradation of the hydrogel and the release of any loaded cargo. In a reducing environment, such as those with high levels of intracellular glutathione, disulfide bonds can be broken, which can lead to gel dissolution or structural remodeling.

Redox-responsive hydrogels can be commonly used for targeted drug delivery *via* site-specific degradation. Here, injectable hydrogels can be designed such that their networks are interconnected through disulfide crosslinking (Altinbasa et al., 2022). This approach allows for the hydrogel network to be stable under normal physiological conditions and degrade only in areas with high ROS or glutathione levels, such as in tumor microenvironments or injury sites.

3.3 Biological stimulus

3.3.1 Enzyme responsive

Injectable hydrogels can be designed with an enzyme-responsive moiety that can undergo specific reactions when exposed to a specific enzyme. These reactions can result in the formation or degradation of a hydrogel network, enabling reversible or irreversible gel-sol transitions (Coulter et al., 2024). These hydrogels can be prepared for enzyme-initiated *in situ* gelation, allowing them to solidify in the presence of the enzyme at the target location. Contrastingly, these hydrogels are often designed with enzyme-triggered degradation in response to enzymatic activity. This allows for smart injectable hydrogels, where the therapeutic agent carried by the hydrogel is released in response to the presence of specific enzymes (Coulter et al., 2024; Vera-González et al., 2024).

Enzyme-responsive injectable hydrogels can be engineered using a variety of strategies:

(1) Peptide sequences can be used to serve as the substrate for enzymes (i.e.,; matrix metalloproteinase (MMP)-sensitive peptides, elastase-sensitive peptides) (Carlini et al., 2019).
(2) Using crosslinkers with enzyme-cleavable bonds (i.e.,; amide, ester, or thiol bonds) (Joshi et al., 2018).
(3) Polymer backbones can be grafted with enzyme-sensitive units (i.e.,; polyethylene glycol, hyaluronic acid, gelatin) (Soeriyadi et al., 2014).
(4) Using self-assembling peptide amphiphiles of block copolymers that degrade upon enzymatic activity (Xiao and Huang, 2024).

TABLE 2 Stimuli-responsive injectable hydrogels for bone healing: applications, crosslinking strategies and outcomes.

Application	Crosslinking strategy	Stimuli	Key findings	Ref.
Irregular Bone Defect	Schiff base and hydrogen bonds	• Ultrasound responsive	• The hydrogel exhibits a ~3-fold increase in bone adhesive strength due to inorganic-organic interactions • Under ultrasound stimulation, the hydrogel generates a controllable electrical output (−41.16–61.82 mV) to enhance osteogenesis • Accelerated bone healing was validated in rat critical size calvarial defect models	Zhou et al. (2024)
Craniomaxillofacial bone defects	Photopolymerization	• Light (NIR) responsive	• The heat generated by photothermal therapy induced a gel-sol transition in gelatin, leading to controlled, on-demand DOX release from the scaffold core • Degradation of gelatin created hollow channels within the scaffold, facilitating bone tissue ingrowth • SC ($SrCuSi_4O_{10}$) nanosheets released bioactive ions (Sr, Cu, Si), which promoted vascularized bone regeneration	Zhang et al. (2023)
Periodontal antibacterial and bone regeneration	Photopolymerization	• Light (NIR) responsive	• Dual therapeutic releasing thermoresponsive injectable hydrogel • The hydrogel demonstrated excellent antibacterial efficacy, bone regeneration, and biocompatibility in both *in vitro* and *in vivo* models • The hydrogel showed sustained release of Bone Morphogenetic Protein 2 (BMP-2)	Wang et al. (2023)
Calvarial bone defects	Ionic interaction	• Thermoresponsive	• *In vivo* bone repair model exhibited complete regeneration of bone within 8 weeks without the need for added cells or growth factors • The hydrogel induced both bone tissue formation and vascularization, demonstrating dual osteogenic and angiogenic capabilities	Wu et al. (2019)
Bone healing	Host-Guest chemistry	• Enzyme (MMP) responsive	• Dual-Release strategy for optimal healing with fast release of platelet-derived growth factor BB (PDGF-BB) followed by sustained release of BMP-2—was engineered, resulting in enhanced bone healing outcomes • The hydrogel enhance low-dose BMP-2 bone regeneration by mobilizing endogenous mesenchymal progenitor cells (MPCs)	Lienemann et al. (2020)
Critical-sized bone defects	Schiff base	• Enzyme (MMP) responsive	• A matrix metalloproteinase (MMP)-responsive injectable hydrogel was developed by integrating an MMP-cleavable peptide into a PEG network, enabling inflammation-triggered drug release • *In vitro* and *in vivo* results showed that the hydrogel effectively promoted macrophage polarization toward the M2 (anti-inflammatory) phenotype and osteogenic differentiation	Zhang et al. (2024b)
Critical-sized bone defects	Hydrogen Bond	• pH responsive	• A pH-responsive hydrogel based on chitosan and *in situ* synthesized hydroxyapatite was developed, using sodium bicarbonate ($NaHCO_3$) as a non-cytotoxic gelling agent • The hydrogel exhibited fast gelation (within 4 min) without generating excess sodium ion • *In vitro* studies show good viability, uniform dispersion, and proliferation of encapsulated cells	Rogina et al. (2017)

These strategies encompass a variety of materials that can act as building blocks for injectable hydrogels, including, but not limited to, peptides, synthetic polymers, fatty acid amphiphiles, and DNA. These hydrogels can be further fine-tuned for their responsiveness to the target enzyme by modifying the structure and concentration of the moieties present in the hydrogel.

3.3.2 ROS responsive

Reactive oxygen species (ROS) are a highly reactive group of oxygen-containing chemicals and exhibit significantly higher reactivity than the ground state oxygen. Their impact is often deemed dual in nature—beneficial under physiological conditions, but harmful under pathological conditions (Yang et al., 2025). While ROS can play essential roles in enhancing and supporting cellular functions, excessive production of ROS can inhibit cellular activity. Beyond the cellular antioxidant capacity, ROS leads to oxidative stress and damaged macromolecules within the cell, leading to cell death and/or carcinogenesis.

Recently, smart injectable hydrogels have been developed to be triggered by an excess of ROS, including hydroxyl radicals, superoxide anions, hydrogen peroxide, and others (Yu et al.,

2022). These hydrogels are engineered with ROS-sensitive linkages or moieties, such as borate ester bonds and thioketals. Here, structural integrity of the hydrogel is maintained under physiological conditions but is degraded in response to elevated ROS levels. This degradation occurs by consuming excess ROS and can also help facilitate controlled and localized drug release.

4 Applications of stimuli responsive injectable hydrogels for bone healing

Smart injectable hydrogels have been extensively studied for many biomedical applications, but remain largely unexplored for bone healing applications. Stem cell therapy, growth factor delivery, and drug-free mineral-based delivery are some strategies that have been thoroughly studied for osteogenesis. Here, we will review some of these strategies that have since been paired with stimuli-responsive materials for optimal cargo delivery and/or inherent bone healing (Figure 1). The articles discussed herein are summarized in Table 2.

4.1 Craniomaxillofacial (CMF) bone defects

Craniomaxillofacial (CMF) bone defects are a major clinical challenge wherein portions of bone are missing from the skull or jaw. Traditionally, CMF bone defects require surgical intervention for repair (Dewey and Harley, 2021). Injectable hydrogels have offered an alternative approach for CMF bone defects due to their ability to conform to complex and irregularly shaped defects. Moreso suitable for CMF bone regeneration, stimuli-responsive injectable hydrogels can interact dynamically with the physiological environment and enable tissue regeneration when needed. Additionally, due to their biocompatibility and potential to induce osteogenesis, some bioceramics and biopolymers are currently approved by the United States Food and Drug Administration (FDA) for craniomaxillofacial utilization. In this regard, bioceramics have been used in conjunction with a gelatin-based hydrogel and loaded with doxorubicin, beta-tricalcium phosphate (B-TCP) and $SrCuSi_4O_{10}$ nanosheets (Zhang et al., 2023). The $SrCuSi_4O_{10}$ nanosheets allowed the hydrogel to absorb NIR light and convert it to heat, triggering a series of events: (i) a gel-sol transition of the hydrogel, which (ii) on-demand releases the loaded doxorubicin and B-TCP, and (iii) breaks down the $SrCuSi_4O_{10}$ nanosheets into their bioactive ions, all of which partake in bone healing. Another approach for CMF bone defects is loading an injectable hydrogel with a photosensitizer and an osteoinductive agent, bone morphogenetic protein 2 (BMP-2), was usable for photothermal and photodynamic therapy in the treatment of periodontitis (Wang et al., 2023). When irradiated with NIR light, the composite hydrogel was able to absorb the light and convert it to heat, raising the local temperature enough to release BMP-2 through hydrogel degradation and kill surrounding pathogens. Further, upon exposure to NIR, the photosensitizer produced ROS, decreasing local inflammation and further enhancing bone healing.

4.2 Calvarial bone defects

Calvarial defects are critical-sized cranial injuries that are defined by a localized absence or deficiency of bone. Calvarial defects do not heal spontaneously and are therefore a commonly used method to assess the efficacy of materials for bone healing applications (Alvarez Echazú et al., 2022). *Wu et al.* have developed a thermo-sensitive *in situ*-forming injectable hydrogel, wherein the system undergoes a sol-gel transition in response to physiological temperature (Wu et al., 2019). Here, the hydrogel system is mainly composed of ionic interactions between chitosan and glycerophosphate, the nature of which are dictated by the environmental temperature. At low temperatures (ie., room temperature), the hydrogel remains in a liquid state; however, as the temperature rises to a physiological temperature (37°C), the number of ionic interactions between the two materials increases, leading to gelation. The adaptability of the hydrogel allowed the authors to apply the hydrogel system to a calvarial bone defect in mice, such that the hydrogel precisely conformed to the defect site before stabilizing into a solid scaffold. Further, the authors incorporated bioactive glass nanoparticles to stimulate osteogenesis through the release of active ions and silk fibroin to add structural integrity. Taken together, this allowed the calvarial bone defect to fully heal within 8 weeks, as opposed to the untreated group, which did not heal at all. In another instance, authors developed a polyethylene glycol-based hydrogel with MMP-sensitive peptide linkers to co-deliver growth factors in a sequential time-controlled manner (Lienemann et al., 2020). First, these hydrogels were able to fast release platelet-derived growth factors that were weakly encapsulated in the hydrogel *via* non-covalent interactions. This was then followed by a sustained and enzyme-triggered release of a low dose of BMP-2, which was encapsulated within the hydrogel and held together by MMP-sensitive peptide crosslinkers. By tailoring the number of MMP-degradable linkages within the hydrogel network, the authors were able to design the hydrogel to degrade and release BMP-2 in a sustained manner and at the site of injury. Taken together, this hydrogel was able to mimic the events of the healing cascade—cell mobilization first, followed by cell differentiation—using a combination of MMP activity (biological stimulus) and engineered timing (material design).

4.3 Critical size bone defects

Critical size bone defects have been a long-standing clinical challenge due to delayed healing, risk of infection, and inadequate vascularization (Alvarez Echazú et al., 2022). Traditional treatment, often involving metallic fixation devices and bone grafts, are invasive and may not fully restore the structural and/or functional integrity of the bone. Smart injectable hydrogels have recently become a strategy to improve upon traditional methods. However, injectable hydrogels are limited in their mechanical strength, and as such, are best suited for non-load-bearing areas or as adjuncts to structural implants. *Zhang et al.* studied the *in vitro* and *in vivo* effects of using a matrix metalloproteinase (MMP)-responsive injectable hydrogel for osteogenic differentiation (Zhang M. et al., 2024). The authors integrated an MMP-cleavable peptide into a polyethylene glycol

network, such that in instances of inflammation and thus elevated levels of MMPs, the hydrogel would degrade and release loaded cargo—in this case, pro-regenerative phosphatidylserine. It was found that the hydrogel was both mechanically and biologically adaptable to the defect site by promoting anti-inflammatory macrophage polarization and osteogenic differentiation in response to MMP-driven degradation. In another approach, *Zhou et al.* developed an injectable nanocomposite hydrogel composed of piezoelectric amino-modified barium titanate nanoparticles embedded within a gelatin-based matrix for the treatment of critical-sized bone defects (Zhou et al., 2024). The embedded nanoparticles are able to respond to external ultrasound stimulus by converting mechanical energy into electrical signals. These electrical signals, localized by the hydrogel, mimic the natural bioelectric environment of bone healing and are simultaneously able to stimulate osteogenic differentiation of surrounding cells.

5 Conclusions and future perspectives

There is an increasing need for effective, safe, and minimally invasive strategies to treat a variety of bone defects. Non-load bearing, craniomaxillofacial, and calvarial bone defects affect millions of patients each year (Aghali, 2021; Gaihre et al., 2017). Current treatments are effective to a certain degree; however, they carry the potential to delay bone healing, introduce pathogens, and can result in repeat surgeries (Masters et al., 2019). As mentioned, stimuli responsive injectable hydrogels can be used as an alternative or as adjuncts to existing strategies to better attend to patient needs.

Over the past decade, smart injectable hydrogels have shown great potential, specifically for (1) their ability to on-demand deliver therapeutic agents, such as cells, and (2) their ability to conform and adapt to defect sites due to their stimuli responsive sol-gel transitions. However, there are design difficulties limiting the ability of these hydrogels to be used for clinical bone healing applications, specifically regarding their mechanical properties, or lack thereof, when applied to load-bearing defects. Some strategies to circumvent these issues include increasing crosslinking density or material stiffness, which can also be useful for osteodifferentiation. However, this creates an unfavorable environment and reduces the efficacy for encapsulated cells to proliferate and migrate.

Recently, hydrogels have been designed to react to spatiotemporal mechanical cues for optimal cell-assisted bone regeneration. Xue et al. have developed a new type of macroporous hydrogel for stem cell-assisted bone healing (Xue et al., 2025). This hydrogel is developed with a rigid shell for sustained mechanical cues in guiding stem cell osteodifferentiation and to withstand mechanical load. Further, the developed hydrogel has a soft matrix with tunable degradation rates capable of synchronizing with new tissue deposition to allow for proliferation and migration of cells. Taken together, this new "smart" spatiotemporal system can facilitate bone regeneration in *vivo* models and address the mechanical limitations of current technologies.

Another alternative to current technologies is using bioprinted 4D hydrogels. 4D bioprinted hydrogels are another form of "smart" technologies—it is a combination of 3D bioprinted technologies that can respond to external or internal stimuli and the fourth dimension, time (Prakash et al., 2024). Unlike injectable hydrogels, these materials can be prefabricated yet still allow for post-printing shape transformations and functional adjustments in the same way injectability can. This up-and-coming technology has the potential for structural flexibility, incorporation of a wide array of bioactive molecules, and the development of neural networks. Smart 4D bioprinted scaffolds have very recently been studied in relation to other biomedical applications (Hann et al., 2023; McLoughlin et al., 2023; Joshi et al., 2023); however, studies for bone healing applications are currently limited. This technology is projected to be most useful for engineering tissues, development of prosthetics, and for surgical implants (Bodaghi et al., 2024).

Despite significant advancements with stimuli-responsive injectable hydrogels, several challenging issues still need to be resolved before these materials can be moved to the clinics. Some of the potential limitations include – (a) toxicity arising from the degradation products of the hydrogels (Stewart et al., 2024), (b) uncontrolled off-target release of cargo molecules (therapeutic or diagnostic agents) (Decuzzi and Cook, 2021; Guo et al., 2025), (c) relatively low mechanical strength and poor physical stability of most stimuli-responsive hydrogels (Guo et al., 2025). Nonetheless, smart injectable hydrogels have made significant preclinical advancements for diverse orthopedic applications. Developing multi-stimuli responsive hydrogels (e.g., hydrogels that respond to light, pH, redox agents, enzymes or metal ions) and hydrogels that are primarily composed of natural polymers (e.g., gelatin, hyaluronic acid, decellularized extracellular matrix) might help overcome some of the above-mentioned obstacles. Use of naturally-derived polymers might help reduce the potential cytotoxic effects arising from degradation products of synthetic hydrogels, as well as assessing *in vitro* cytotoxicity by inducing stimuli-responsive degradation and evaluation cell viability in the presence of these by-products. Further, the use of multi-stimuli triggered hydrogels with programable functions might better facilitate target-specific drug release from hydrogel carriers. Lastly, exploring dynamic covalent bonds to create smart injectable hydrogels, instead of using non-covalent bonds, might be another promising strategy to improve the rigidity and long-term stability for these hydrogels for broader biomedical applications such as in soft robotics, tissue engineering, drug delivery, and as coating materials for medical devices including bone graft substitutes.

Author contributions

AA: Visualization, Conceptualization, Investigation, Writing – original draft, Writing – review and editing. YS: Writing – original draft, Writing – review and editing, Investigation, Project administration, Visualization. AH: Writing – review and editing. AP: Investigation, Writing – original draft, Writing – review and editing, Funding acquisition, Visualization, Conceptualization, Supervision.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. Arghya Paul is

thankful to the following funding agencies for providing support: Early Research Award (ERA) from the Province of Ontario, Canada Research Chairs Program of the Natural Sciences and Engineering Research Council (NSERC) of Canada (CRC-2024-00196), Wolfe-Western Fellowship At-Large for Outstanding Newly Recruited Research Scholar, and Canadian Institutes of Health Research Operating Grant (CIHR – IMHA, Grant no: 185629). Yasmeen Shamiya would like to acknowledge the funding and support from NSERC Canada Graduate Scholarship—Doctoral Program (CGS D). MD Anwarul Hasan and Arghya Paul gratefully acknowledges the support received from the Qatar Research, Development and Innovation (QRDI) Council through the Academic Research Grant (ARG01-0531-230440).

Acknowledgments

The authors would also like to thank BioRender, as some of the images and illustrations were created with BioRender.com.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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