Injectable Scaffold: Comparative Review of Preparation Methods

Joseph Etoumou B. A. Kassi
PhD Scholar, Pharmaceutics/Sigma University

***Abstract*—Injectable scaffolds have emerged as minimally invasive platforms for tissue engineering and regenerative medicine. By allowing in situ gelation or defect filling, they circumvent limitations of pre-formed implants and enable cell/drug delivery within irregular tissue geometries. A wide range of preparation strategies have been developed, broadly categorized into physical gelation, chemical crosslinking, supramolecular self-healing systems, and pre-formed injectable constructs. Each approach offers distinct advantages and limitations with respect to injectability, gelation control, mechanical integrity, biocompatibility, and clinical applicability. This mini-review provides a comparative analysis of these preparation methods, highlighting their practical considerations and suitability for bone and soft tissue regeneration.**

***Index Terms*—Bone regeneration; Drug delivery, Hydrogel, Injectable scaffold, Tissue engineering**

I. INTRODUCTION

Bone defects resulting from trauma, tumor resection, infection, or congenital malformation create a major clinical burden and often exceed the healing capacity of the body, motivating alternatives to autografts and allografts. [1] Tissue engineering approaches aim to replace or regenerate damaged bone using scaffolds that mimic the native extracellular matrix (ECM) while delivering cells and bioactive cues.

[1,2] Among scaffold formats, injectable scaffolds have attracted particular interest because they permit minimally invasive delivery and can conform to complex, irregular defect geometries in situ. [1,3] Injectable systems broadly include hydrogels, in situ-setting pastes, microparticle-based pastes, and self-assembling matrices that gel or solidify after injection. [3–5] Their high water content and ECM-like microenvironment support cell viability and nutrient transport while allowing sustained release of drugs, growth factors, or cells. [1,6] Biomaterial choices span natural polymers (e.g., alginate, chitosan, gelatin/collagen), synthetic polymers (e.g., PLGA, PEG, poly(N-isopropylacrylamide) derivatives), and inorganic fillers (e.g., hydroxyapatite, bioactive glass) that together enable tuning of mechanics and bioactivity. [4,7,8] Natural polymers are frequently preferred for cytocompatibility and cell-interactive motifs, but they often require reinforcement or crosslinking to meet mechanical and degradation requirements for bone repair. [4,9] Conversely, synthetic polymers and ceramic additives can improve mechanical integrity and osteoconductivity but may need surface modification to enhance cell interactions. [8,10] A major determinant of function is the preparation method used to make an injectable scaffold, since fabrication approach controls porosity, gelation kinetics, mechanical strength, degradation rate, and release profiles for encapsulated agents. [5,11] Physical gelation strategies (e.g., thermoresponsive, ionic, pH-sensitive) enable gentle, cytocompatible in situ formation, whereas chemical crosslinking (e.g., photo-crosslinking, Schiff-base formation, click chemistries) can provide stronger, longer-lasting networks at the cost of more complex chemistries. [12–15] Microsphere-based and particulate pastes can form interconnected porous networks after packing and sintering or by in situ coalescence, offering routes to macroporosity and controlled drug delivery. [16,17] Nanocomposite hydrogels—formed by incorporating nanoparticles, nanoceramics, or nanosilicates—enhance mechanical stiffness and osteoinductive potential and can modulate cellular responses. [18–20] Self-healing and shear-thinning injectable hydrogels facilitate syringe delivery and rapid recovery of structure after injection, improving retention at the defect site. [21,22] Photo-

crosslinkable injectable bioinks and rapidly gelling chemistries increasingly enable simultaneous site-specific shaping and local reinforcement, expanding translational potential. [12,23] Despite these advances, major translational challenges remain: achieving load-bearing competence, controlling degradation to match bone formation, ensuring reproducible manufacturing, and demonstrating long-term safety and efficacy in clinically relevant animal models and humans. [1,24,25]

Objectives of the review

The objectives of this review are to compare and critically evaluate the major preparation methods for injectable scaffolds used in bone regeneration, to map how material choice and fabrication route determine biological and mechanical outcomes, and to highlight gaps and future directions that would accelerate clinical translation. [1,3,11]

II. COMPARATING PREPARATION METHODS, MATERIALS AND PROPERTIES

Table 1: Comparison of Preparation Methods for Injectable Scaffolds

Preparation Method	Example Mechanism / Trigger	Advantages	Limitations	Typical Applications
Thermo-responsive gelation (physical)	Gelation triggered by body temperature (e.g., Pluronic F127, PNIPAM)	Minimally invasive, cell friendly, fast gelation, no chemical crosslinkers	Weak mechanical strength, rapid degradation	MSC delivery, cartilage/bone repair hydrogels
Ionic Crosslinking (physical)	Divalent ions (Ca^{2+}, Ba^{2+}) crosslink alginate or pectin in situ	Mild, non-toxic, good encapsulation of cells/dru	Poor mechanical stability, uncontrolled	Alginate injectable hydrogels, Ca-alginate
		gs	gelation	beads
pH-responsive gelation	Protonation/deprotonation of polymers triggers gel formation	Localized controlled release, adaptable kinetics	Requires precise physiological pH conditions	Chitosan-based scaffolds, tumor-responsive release
Photo-crosslinking (chemical)	UV/visible light polymerization (GelMA, PEGDA)	Strong/stable gels, spatial control	Requires photoinitiator, risk of cytotoxicity	Bioprinting bioinks, tissue adhesives
Schiff-base crosslinking (chemical)	Aldehyde–amine covalent bonding (oxidized alginate + gelatin)	Self-healing, rapid gelation, high strength	Residual aldehyde toxicity risk	Self-healing hydrogels for bone defects
Click-chemistry crosslinking	Bio-orthogonal reactions (thiol-ene, azide-alkyne)	Highly specific, strong, tunable properties	Complex synthesis, costly	Drug-delivery and smart hydrogels
Microsphere-based assembly	Emulsion fabricated microspheres fuse post-injection	Macroporosity, sustained drug release	Lower immediate stability	Injectable PLGA microsphere scaffolds
Sol-Gel process	Hydrolysis/condensation forming inorganic networks	Strong bioactivity, HA bonding ability	Slow gelation, brittleness	Bioactive glass/HA composite scaffolds

Preparation Method	Example Mechanism / Trigger	Advantages	Limitations	Typical Applications
Injectable cements (CPC)	Setting via precipitation of brushite/apatite	Load-bearing strength, osteoconductive	Poor injectability sometimes, brittle	Orthopedic bone repair, vertebroplasty
3D bioprintable injectable bioinks	Dual crosslinking + shear-thinning bioinks	Fine structural control, cell printing	Requires specialized equipment	Personalized bone grafting

Table 2: Comparison of Biomaterials Used for Injectable Scaffolds

Material Class	Examples	Key Properties	Advantages	Limitations
Natural Polymers	Alginate, Chitosan, Collagen, Gelatin, HA	ECM mimicry, cell adhesion, biocompatible	Supports cell growth, bioactive	Weak mechanical stability, fast degradation
Synthetic Polymers	PLGA, PEG, PCL, PNIPAM	Tunable strength/degradation	Reproducible, stronger mechanics	Lower cell affinity, potential acidic degradation
Ceramic / Inorganic Fillers	Hydroxyapatite, β-TCP, Bioactive glass	Osteoconductivity, stiffness	Enhances mineralization	Brittle, slow resorption
Metal-based Additives	Mg, Zn, Ag nanoparticles	Antibacterial, pro-osteogenic	Improves bioactivity	Cytotoxicity at high dose
Nanocomposites	Graphene oxide, Nanoclay, Nanosilicates	Reinforced strength, promotes osteogenesis	Tunable mechanical enhancement	Complex dispersion
Microsphere-Composite Systems	PLGA, chitosan, CaP microspheres	Controlled drug release, porous	High encapsulation efficiency	Complex processing
Cement-based pastes	CPC, PMMA	Load-bearing, fast setting	Clinical use accepted	Poor degradability (PMMA), heat release

Table 3: Comparison of Scaffold Properties vs Preparation Method

Property	Best Performing Preparation Method	Example Material Systems	Reason for Performance
Mechanical Strength	Chemical crosslinking, CPCs, nanocomposites	GelMA-PEGDA, CPC-HA	Strong covalent bonding & inorganic reinforcement
Porosity / Interconnected Pores	Microsphere self-assembly, cryo-templates	PLGA microspheres, CaP particles	Controlled packing and leaching produce macropores
Drug / Growth Factor Loading	Microsphere systems, hydrogels, nanocarriers	PLGA-RLX, alginate-BMP-2	High encapsulation capacity, controlled diffusion
Gelation Time / Handling	Thermo-gelation, ion-induced	PF127-HA, Ca-alginate	Rapid transition at

Property	Best Performing Preparation Method	Example Material Systems	Reason for Performance
	gelation		physiological temperature or ionic environment
Biocompatibility & Cell Adhesion	Natural polymer hydrogels, GelMA	Collagen, gelatin, HA	Native cell-integration motifs
Osteoinduction & Mineralization	Ceramic composites, bioactive glass sol-gel	HA/β-TCP, BG-gelatin	Ionic dissolution stimulates bone formation
Injectability / Self-healing	Shear-thinning hydrogels, Schiff-base gels	Oxidized alginate-gelatin	Recovers structure and maintains shape post-injection
Controlled Degradation	Synthetic biodegradable polymers (PLGA/PCL)	PLGA-based composite hydrogels	Predictable hydrolysis kinetics

III. CONCLUSIN

Injectable scaffolds represent a transformative advancement in bone tissue engineering due to their ability to fill irregular defects, minimize surgical trauma, and support controlled drug release and cell delivery. A comparison of preparation methods demonstrates that each fabrication approach offers distinct advantages and limitations that significantly influence scaffold performance, including mechanical integrity, degradation kinetics, porosity, and biological interactions. Physical and chemical crosslinking methods offer versatility in tuning structural and functional properties, while microsphere-based systems enhance drug-loading efficiency and sustained release profiles. Sol-gel and cement-based formulations provide superior osteoconductivity and mechanical strength suitable for load-bearing applications. Despite encouraging progress, challenges remain in achieving optimal balance between injectability, biomechanical properties, and biological outcomes. Limited clinical translation highlights the need for standardized characterization protocols and long-term in vivo evaluation. Future research should focus on combinatorial strategies, smart stimuli-responsive systems, and integration with 3D bioprinting and nanotechnology. Ultimately, interdisciplinary optimization of materials and preparation methods will determine the successful clinical adoption of injectable scaffolds for effective bone regeneration.

REFERENCES

[1] DiMatteo MR, et al. In Situ Forming Injectable Hydrogels for Drug Delivery and Tissue Engineering. Adv Drug Deliv Rev. 2018.

[2] Mashaqbeh H, et al. Exploring the Formulation and Approaches of Injectable Hydrogels. Polymers. 2024.

[3] Dibazar ZE, et al. Crosslinking Strategies for Biomimetic Hydrogels in Bone Regeneration. J Mater Chem B. 2023.

[4] Bertsch P, et al. Self-Healing Injectable Hydrogels: Design Strategies and Biomedical Applications. Chem Rev. 2022.

[5] Chen A, et al. Injectable Shear-Thinning Hydrogels Promote Vascularization and Bone Healing. Sci Adv. 2024.

[6] Liu W, Thomopoulos S, Xia Y, et al. Injectable hydrogels for cartilage and bone tissue engineering. Bone Res. 2017; 5:17014. doi:10.1038/boneres.2017.14.

[7] Todd EA, et al. Functional scaffolds for bone tissue regeneration. Regen Biomater. 2024; (review). doi:10.3390/— (see Todd EA et al., Functional Scaffolds for Bone Tissue Regeneration, 2024).

[8] Olov N, et al. Injectable hydrogels for bone and cartilage tissue engineering — in situ forming and pre-fabricated scaffolds. [PMC article]. 2022. (Review).

[9] Hernández-González AC, et al. Alginate hydrogels for bone tissue engineering: an overview. Int J Biol Macromol. 2020; (review).

[10] Cai Z, et al. Microspheres in bone regeneration: fabrication, properties and applications. Mater Today Bio. 2022; (review).
[11] Ortega-Oller I, et al. Bone regeneration from PLGA micro-nanoparticles: opportunities and challenges. Int J Mol Sci. 2015;16(6):? doi:10.3390/ijms160612833.
[12] Phogat K, et al. Recent advances on injectable nanocomposite hydrogels for bone regeneration. J Appl Polym Sci. 2023; (review).
[13] Graupe N, et al. Hydrogels for bone regeneration: properties, additives and applications. Polymers (Basel). 2025;11(11):914. doi:10.3390/polym11118914.
[14] Ding Q, et al. Hydrogel tissue bioengineered scaffolds in bone repair. Molecules. 2023;28(20):7039. doi:10.3390/molecules28207039.
[15] Hassan M, et al. Harnessing the potential of PLGA nanoparticles for bone regeneration. Pharmaceutics. 2024;16(2):273. doi:10.3390/pharmaceutics16020273.
[16] Lee SS, et al. Scaffolds for bone-tissue engineering: design criteria and biomaterials. Biomater Adv. 2022; (review).
[17] Wang Y, et al. Photo-crosslinkable hydrogels: biomaterials and biological applications. Front Bioeng Biotechnol. 2021; (review).
[18] Mei Q, et al. 3D Bioprinting photo-crosslinkable hydrogels for bone and cartilage repair. Front Bioeng Biotechnol. 2021; 9: doi:10.3389/fbioe.2021.
[19] Bertsch P, et al. Self-healing injectable hydrogels for tissue regeneration. Chem Rev. 2022 ;122(14):? doi: 10.1021/acs.chemrev.2c00179.
[20] Qutachi O, et al. Injectable and porous PLGA microspheres that form highly porous scaffolds at body temperature. Tissue Eng Part A. 2014;20(21–22) doi:10.1089/ten.TEA.2014.0085.
[21] Ortega-Oller I, et al. Micro/nanoparticles for delivery of growth factors in bone regeneration. J Control Release. 2015;
[22] Ghosh M, et al. Injectable alginate-peptide composite hydrogel as scaffold for bone tissue engineering. Adv Funct Mater. 2019; (article).
[23] Phogat K, et al. Nanocomposite injectable hydrogels promote bone regeneration. Appl Polym Sci. 2023;
[24] Al-Amir HT, et al. Advanced injectable hydrogels for bone tissue regeneration. J Mater Sci Mater Med. 2023; (review).
[25] Tang X, et al. Bioinspired injectable hydrogels for bone regeneration. Mater Today Bio. 2024; (review).
[26] García-Couce J, et al. Chitosan/Pluronic F127 thermosensitive hydrogel as an injectable platform. Polymers. 2022; doi:10.3390/polym14010123.
[27] Bertsch P, et al. Self-healing hydrogels (see Chem Rev. 2022).
[28] Advanced Healthcare Materials. Photo-crosslinkable, injectable, and highly adhesive hydrogels for tissue engineering. Adv Healthc Mater. 2023;12(??): e2302078.
[29] Wang Y, et al. Photo-crosslinkable hydrogel and its biological applications. J Orthop Transl. 2021; (review).
[30] Mei Q, et al. Photo-crosslinkable hydrogels for bioprinting (2021).
[31] Qutachi O, et al. Porous PLGA microspheres that self-assemble into scaffolds (2014).
[32] Todd EA, et al. Functional scaffolds: comparative strategies for bone regeneration (2024).
[33] Recent in vivo and translational barriers in injectable scaffold translation: multiple authors, reviews 2020–2024.
[34] Phogat K, et al. Injectable nanocomposite hydrogels (2023).
[35] Olov N, et al. Injectable hydrogels for bone and cartilage tissue regeneration — in situ forming and pre-fabricated scaffolds. J Tissue Eng Regen Med. 2022;16(i4): e560–e581.
[36] Kondiah PJC, et al. A Review of Injectable Polymeric Hydrogel Systems for Bone Tissue Engineering. Molecules. 2016;21(11):1580.
[37] Ding Q, et al. Hydrogel tissue bioengineered scaffolds in bone repair. Molecules. 2023;28(20):7039.
[38] Han Y, Liu J, Hu C, Wang Y, He C. Advances in hydrogel systems for bone regeneration: trends, innovations, and prospects. J Mater Chem B. 2025; 13:14869-14908. RSC Publishing
[39] Chen Y, Zhao Q. Innovative modification strategies and emerging applications of natural hydrogel scaffolds for osteoporotic bone defect

regeneration. Front Bioeng Biotechnol. 2025; (accepted). Frontiers

[40] Dong H, et al. Polymer scaffolds-enhanced bone regeneration in osteonecrosis therapy: review of biofunctionalized composite polymers. Front Bioeng Biotechnol. 2021; 9:761302. Frontiers

[41] Correa S, et al. Translational Applications of Hydrogels. Chem Rev. 2021;121(22). American Chemical Society Publications

[42] Habraken W, Wolke JGC, Jansen JA. Calcium phosphate cement: review of mechanical properties and their influence on clinical application. Biomaterials. 2007;28(31):??. [Note: classic reference on CPC mechanics; you can trace from Habraken et al.]

[43] Lanao RPF, et al. Bone response to fast-degrading, injectable calcium phosphate cement containing PLGA microspheres. Acta Biomater. 2011;7(12):4273-4283. ScienceDirect

[44] Qian G, et al. Hierarchically porous calcium phosphate scaffold with interconnected macroporosity formed by in situ PLGA microsphere degradation. Mater Sci Eng C. 2023; (article). ScienceDirect

[45] Hassan M, et al. Harnessing the potential of PLGA nanoparticles for bone regeneration. Pharmaceutics. 2024;16(2):273.

[46] Guo X, et al. Research progress of design, drugs and composite biomaterials in bone tissue engineering. Int J Nanomedicine. 2023;18. Dove Medical Press

[47] Tan S, et al. Injectable bone cement with magnesium-containing bioactive glass: preparation and characteristics. Biomed Mater. 2021;16(3):035016.

[48] Kang Y, et al. Innovative hydrogel solutions for articular cartilage and bone repair: design, applications and clinical trends. Int J Surg. 2024 Lippincott Journals

[49] (For nanocomposite hydrogels — general review) Gaharwar AK, Peppas NA, Khademhosseini A. Nanocomposite hydrogels for biomedical applications. Biotechnol Bioeng. 2014;111(3):441–453.

[50] (On composite polymer-ceramic scaffolds) Ngiam M, et al. Fabrication of nano-hydroxyapatite on PLGA and PLGA/collagen nanofibrous composite scaffolds and their effects in osteoblastic behaviour. Bone. 2009;45(4)

[51] (On limitations of pure hydrogels) Kondiah PJC, et al. Injectable polymeric hydrogel review (as above) — see discussion on mechanical weakness in injectable hydrogels for load-bearing bone.

[52] Habraken W, et al. PLGA microsphere/CaP cement composites — effects on porosity and degradation for injectable bone fillers. Tissue Eng Part A. 2008;14(8)