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Hydrogels in Tissue Engineering and Drug Delivery: A Comprehensive Review

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Abstract

Hydrogels are highly hydrated three-dimensional polymeric networks that have emerged as versatile biomaterials for tissue engineering and drug delivery due to their excellent biocompatibility, tunable mechanical and physicochemical properties, and close resemblance to the native Extracellular Matrix (ECM). In tissue engineering, hydrogels act as bioactive scaffolds that support cell adhesion, proliferation, differentiation, and vascularization. Their adjustable stiffness, porosity, and controlled biodegradability facilitate the regeneration of various tissues, including skin, cartilage, bone, and neural tissue. In drug delivery, hydrogels function as intelligent reservoirs capable of sustained, localized, and stimuli-responsive (e.g., pH, temperature, redox, enzymatic, or light) release of therapeutic agents, enhancing treatment efficacy while minimizing off-target effects. Recent advances in self healing, injectable, nanocomposite, and 3D/4D bioprinted hydrogels along with the integration of bioactive molecules and cell-laden constructs have further expanded their potential for clinical translation. This review summarizes key design principles, emerging material innovations, and major translational challenges, highlighting the growing impact of hydrogels in regenerative medicine and precision therapeutics.

Keywords: Hydrogels, Tissue engineering, Drug delivery, Stimuli-responsive, Biomaterials, Regenerative medicine.

1 | Introduction

Hydrogels are a unique class of three-dimensional, hydrophilic polymeric networks that can retain substantial amounts of water or biological fluids while maintaining their structural integrity. Their high water content and tunable physicochemical properties allow them to closely mimic the native Extracellular Matrix (ECM), making them ideal candidates for a wide range of biomedical applications, particularly in tissue engineering and regenerative medicine. By providing a hydrated microenvironment, hydrogels facilitate essential cellular functions such as adhesion, proliferation, differentiation, and migration, which are critical for the restoration of damaged or diseased tissues.

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The versatility of hydrogels arises from the diversity of polymeric materials used in their fabrication, including natural polymers such as collagen, gelatin, hyaluronic acid, and alginate, as well as synthetic polymers like Polyethylene Glycol (PEG), Polyvinyl Alcohol (PVA), and Poly(N-isopropylacrylamide) (PNIPAM). These polymers can be chemically or physically crosslinked to form networks with precisely tunable mechanical strength, porosity, degradation rate, and bioactivity. Additionally, recent innovations have led to the development of "smart" hydrogels capable of responding to various physiological and environmental stimuli, including pH, temperature, ionic strength, enzymatic activity, and external triggers such as light, magnetic fields, or electric currents. Such responsiveness allows for controlled and site-specific delivery of therapeutic agents, enhancing treatment efficacy and reducing systemic side effects.

In tissue engineering, hydrogels serve as bioactive scaffolds that support the regeneration of various tissues, including skin, cartilage, bone, and neural structures. Their modular properties enable customization of the scaffold microenvironment to match the specific requirements of each tissue type. For example, the stiffness and porosity of hydrogels can be adjusted to guide stem cell differentiation, while the incorporation of growth factors, peptides, or other bioactive molecules can further enhance tissue-specific responses. Moreover, advances in fabrication techniques, such as 3D and 4D bioprinting, injectable hydrogels, and nanocomposite hydrogels, have expanded the possibilities for creating complex, patient specific tissue constructs.

Beyond tissue engineering, hydrogels have gained considerable attention in drug delivery applications. Their ability to encapsulate sensitive biomolecules including proteins, peptides, nucleic acids, and small molecule drugs protects them from degradation and enables sustained, controlled, and localized release. Stimuli-responsive hydrogels further allow on-demand drug delivery, which is particularly valuable for precision medicine and personalized therapeutic strategies. Consequently, the intersection of tissue engineering and drug delivery represents a rapidly evolving frontier in biomedical research, with hydrogels occupying a central role due to their unique combination of biocompatibility, tunable properties, and functional versatility.

This review provides a comprehensive examination of hydrogel types, their key physicochemical and biological characteristics, recent advances in tissue engineering and drug delivery applications, current translational challenges, and future perspectives. By highlighting the design principles and clinical potential of hydrogels, this work aims to underscore their growing significance as multifunctional biomaterials in regenerative medicine and precision therapeutics.

2 | Types of Hydrogels

2.1 | Natural Hydrogels

Natural hydrogels are derived from biological polymers, including alginate, chitosan, collagen, gelatin, hyaluronic acid, and fibrin (*Fig. 1*). These materials inherently mimic the ECM, providing a bioactive microenvironment that promotes essential cellular processes such as adhesion, proliferation, migration, and differentiation. Their biocompatibility and bioactivity make them particularly attractive for regenerative medicine and tissue engineering. For example, collagen based hydrogels support fibroblast attachment and vascularization, while alginate and chitosan can form hydrogels suitable for wound healing and cartilage repair. Despite these advantages, natural hydrogels often exhibit weak mechanical properties, rapid degradation, and limited tunability, which can restrict their use in load-bearing or mechanically demanding applications. Researchers have addressed some of these limitations by chemical modification, crosslinking, or blending with other polymers to improve stability and mechanical performance [1].

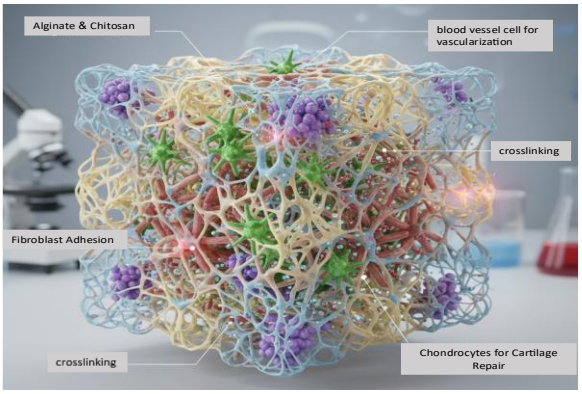

Fig. 1. Natural hydrogels derived from biological polymers (e.g., collagen, gelatin, hyaluronic acid, alginate, chitosan).

2.2 | Synthetic Hydrogels

Synthetic hydrogels are produced from engineered polymers, such as PEG, PVA, and Polyacrylamide (PAM) (*Fig. 2*). These materials offer predictable physicochemical properties, tunable mechanical strength, and controlled degradation, making them highly versatile for biomedical applications. Unlike natural polymers, synthetic hydrogels usually lack inherent bioactivity, but surface functionalization or incorporation of bioactive molecules such as peptides, growth factors, or ECM fragments can significantly enhance cellular interactions. Synthetic hydrogels are widely used in applications requiring precise control over mechanical properties or degradation kinetics, including bone tissue scaffolds, drug delivery matrices, and 3D bioprinting constructs [2].

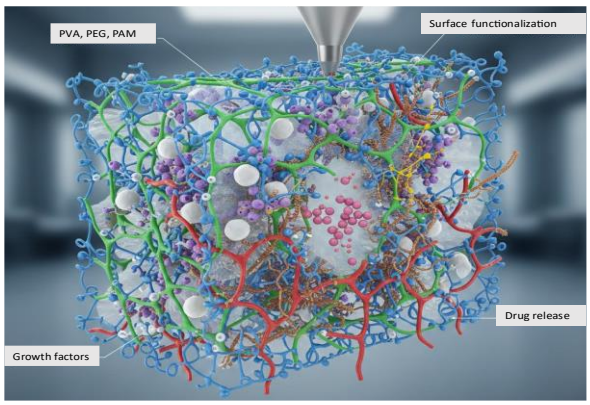

Fig. 2. Synthetic hydrogels based on engineered polymers (e.g., polyethylene glycol, polyvinyl alcohol, PNIPAAm, polyacrylamide).

2.3 | Semi-Synthetic Hydrogels

Semi-synthetic hydrogels integrate the biocompatibility and biological cues of natural polymers with the tunable mechanical and chemical properties of synthetic polymers (*Fig. 3*). Materials such as methacrylated gelatin (GelMA), modified hyaluronic acid, and dextran methacrylate combine these advantages, resulting in hydrogels with improved stiffness, structural stability, and controlled degradation, while maintaining favorable cellular responses. Semi-synthetic hydrogels have been particularly useful in stem cell research, where their tunable microenvironment can guide cell differentiation and tissue-specific responses. Moreover, these hydrogels can be functionalized to release bioactive molecules in a controlled manner, which is essential for regenerative therapies.

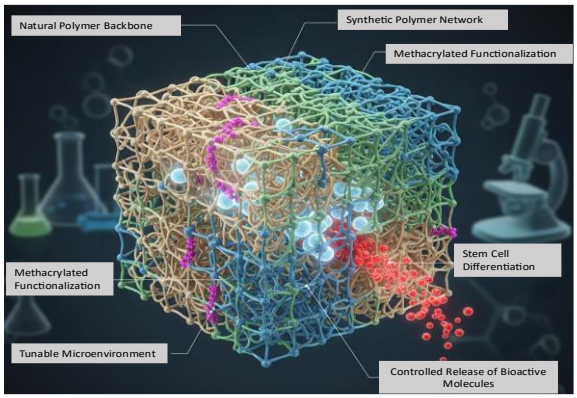

Fig. 3. Semi-synthetic hydrogels combining natural bioactivity with synthetic tunability (e.g., GelMA, HAMA).

2.4 | Stimuli-Responsive (Smart) Hydrogels

Stimuli-responsive hydrogels, or smart hydrogels, can undergo dynamic changes in response to environmental cues such as pH, temperature, ionic strength, enzymatic activity, or external stimuli like light, magnetic fields, or electric current (*Fig. 4*). These changes can manifest as swelling, contraction, degradation, or controlled release of encapsulated molecules. Stimuli-responsive hydrogels are widely employed for controlled drug delivery, tissue engineering, and biosensing applications. For instance, pH-sensitive hydrogels can release chemotherapeutics specifically in tumor environments, while thermoresponsive hydrogels allow injectable delivery that solidifies at body temperature. The design of these hydrogels often involves combining polymers with complementary responsive behaviors to achieve multifunctional performance [3].

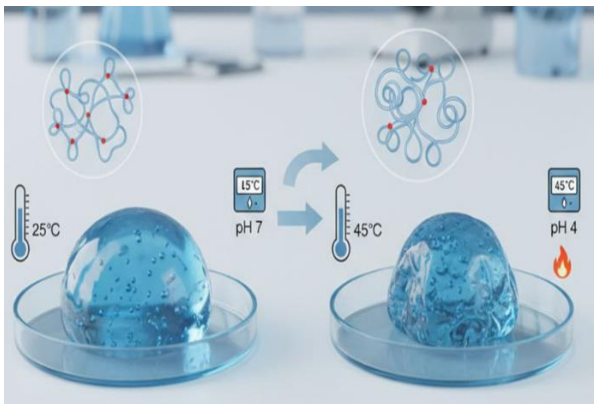

Fig.4. Stimuli-responsiven (smart) hydrogels sensitive to pH, temperature, light, enzyme, or redox triggers.

2.5 | Nanocomposite Hydrogels

Nanocomposite hydrogels incorporate nanomaterials such as nanoclay, carbon nanotubes, graphene oxide, metallic nanoparticles, or silica nanoparticles into the hydrogel network (*Fig. 5*). The inclusion of these nanostructures enhances mechanical strength, electrical conductivity, thermal stability, and stimuli-responsiveness. For example, carbon based nanomaterials can improve the conductivity of hydrogels for neural tissue engineering, while metallic nanoparticles can confer antimicrobial properties. Nanocomposite hydrogels are increasingly utilized in advanced biomedical applications, including regenerative scaffolds, bioelectronic devices, and controlled drug delivery systems. By combining the inherent properties of the hydrogel matrix with the functional advantages of nanomaterials, these systems offer a versatile platform for

next generation therapies [2]. To provide a clear overview of the different classes of hydrogels discussed, *Table 1* summarizes their sources, key advantages, limitations, and primary biomedical applications.

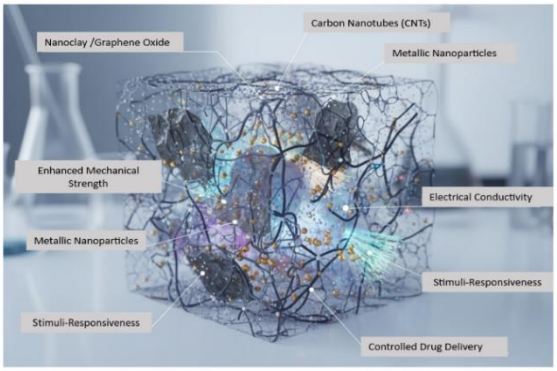

Fig. 5. Nanocomposite hydrogels incorporating nanomaterials (CNTs, graphene oxide, nanoclays, metallic nanoparticles) for enhanced properties.

Table 1. Comparative overview of major classes of hydrogels used in tissue engineering and drug delivery applications.

Hydrogel Class	Representative Materials	Key Advantages	Major Limitations	Primary Biomedical Applications
Natural	Collagen, Gelatin, Hyaluronic acid, Alginate, Chitosan, Fibrin, Silk fibroin, Cellulose	Inherent bioactivity, excellent biocompatibility, excellent cell adhesion and ECM mimicry, low immunogenicity	Poor mechanical strength, fast and uncontrolled degradation, batch-to-batch variability	Wound healing, skin regeneration, cartilage repair, ocular and corneal applications
Synthetic	PEG/PEO, PVA, PNIPAAm, Pluronics, Polyacrylamide, Poly(HPMA), Polyphosphazenes	Highly reproducible, tunable mechanical properties and degradation rate, easy functionalization	Lack of intrinsic bioactivity, may require additional modification for cell adhesion	Drug/growth factor delivery, 3D bioprinting inks, non-fouling coatings, bone scaffolds
Semi-synthetic	GelMA, HAMA, Methacrylated dextran, Thiolated hyaluronic acid, PEG-fibrinogen	Combines bioactivity of natural polymers with mechanical tunability and photopolymerizability of synthetic ones	More complex and costly synthesis, potential residual photoinitiator toxicity	Cardiac patches, neural tissue engineering, stem cell encapsulation, vascular grafts, 3D/4D bioprinting
Stimuli-responsive (Smart)	pH-sensitive (PAA, PDEAEMA), Thermoresponsive (PNIPAAm, Pluronics), Light-sensitive, Enzyme-sensitive, Redox-sensitive, Multi-responsive	On-demand and spatio-temporal control of drug release or shape change, injectable in situ-forming systems	Complex design, sometimes limited reversibility or stability, potential cytotoxicity of monomers	Cancer therapy, diabetes (glucose-responsive), pulsatile insulin delivery, minimally invasive injectables

Table 1. Continued.

Hydrogel Class	Representative Materials	Key Advantages	Major Limitations	Primary Biomedical Applications
Nanocomposite	Hydrogels containing carbon nanotubes, graphene oxide, nanoclays (Laponite), gold/silver nanoparticles, silica NPs, bioactive glass NPs, MXenes	Dramatically improved mechanical toughness, electrical conductivity, thermal stability, antimicrobial activity, enhanced stimuli-responsiveness	Potential nanotoxicity, difficulties in homogeneous dispersion, regulatory hurdles	Neural and cardiac tissue engineering, bioelectronics, conductive scaffolds, antimicrobial wound dressings, bone regeneration

3 | Applications of Hydrogels in Tissue Engineering

Hydrogels have emerged as indispensable scaffolds in tissue engineering due to their remarkable structural and functional similarity to the native ECM. Their hydrophilic, three-dimensional polymer networks facilitate efficient transport of nutrients and oxygen, creating a favorable microenvironment for cell adhesion, proliferation, and differentiation. Furthermore, their tunable mechanical and biochemical properties allow customization for specific tissue requirements [2]–[4]. In skin tissue engineering, hydrogels function as moisture-retentive dressings that accelerate wound healing by providing a supportive ECM. Collagen and alginate based hydrogels are widely employed in the treatment of chronic wounds and burn injuries. These hydrogels can be enriched with bioactive molecules such as Vascular Endothelial Growth Factor (VEGF) or Epidermal Growth Factor (EGF), which promote re-epithelialization and angiogenesis. Clinical and preclinical studies have demonstrated that such hydrogels reduce inflammation and facilitate higher-quality tissue regeneration compared to conventional treatments [5]. Cartilage regeneration poses significant challenges due to its avascular nature and low cellularity. Hydrogels provide a three-dimensional scaffold supporting chondrocyte viability and ECM production. Natural polymers, including hyaluronic acid and collagen, are commonly employed to replicate the biochemical environment of native cartilage. Incorporation of bioactive nanoparticles, such as nano hydroxyapatite or silica, has been shown to enhance mechanical strength and biofunctionality. Injectable hydrogel systems offer additional advantages by enabling minimally invasive administration and conforming to irregular defect geometries, thus improving clinical outcomes [6], [7]. Although hydrogels alone lack the mechanical strength required for load bearing bone tissue, composite scaffolds combining hydrogels with inorganic minerals, such as hydroxyapatite or calcium phosphate, demonstrate improved osteoconductivity and osteoinductivity. These composites support mesenchymal stem cell differentiation into osteoblasts and facilitate new bone formation. Furthermore, hydrogels can be engineered for controlled delivery of osteogenic growth factors, including Bone Morphogenetic Protein-2 (BMP-2), optimizing bone repair processes [8], [9]. For soft tissues including muscle, cardiac, and neural tissues, hydrogels provide a biomimetic and mechanically adaptable matrix conducive to cellular growth and function. Conductive hydrogels incorporating polypyrrole, graphene, or carbon nanotubes have been developed to mimic native electrical conductivity, enhancing cell signaling and tissue integration. These systems also promote neuronal growth and guide peripheral nerve regeneration in preclinical models.

Overall, hydrogels offer excellent biocompatibility, tunable mechanical properties, and the ability to deliver bioactive agents in a controlled manner. Their injectable nature facilitates minimally invasive therapeutic approaches. Nevertheless, challenges such as insufficient mechanical strength for certain tissues, mismatched degradation rates with tissue regeneration, and potential immune responses remain. Current research focuses on developing stimuli-responsive smart hydrogels capable of spatially and temporally controlled therapeutic delivery in response to environmental cues such as pH, temperature, or enzymatic activity [10], [11].

4 | Applications of Hydrogels in Drug Delivery

Hydrogels have attracted considerable attention as versatile platforms for drug delivery due to their high water content, intrinsic biocompatibility, and tunable network structures. These properties enable hydrogels to encapsulate a broad spectrum of therapeutic agents, including small molecules, proteins, peptides, and nucleic acids, and release them in a controlled, sustained, and site-specific manner [11]. A key advantage of hydrogel based drug delivery systems is their ability to respond to physiological stimuli such as pH, temperature, or enzymatic activity. This stimulus responsiveness allows targeted and on demand drug release, thereby minimizing systemic side effects while maximizing therapeutic efficacy. For instance, thermoresponsive hydrogels exhibit sol-gel transitions at physiological temperature, enabling minimally invasive injection of liquid precursors that rapidly gel in situ [12]. pH-sensitive hydrogels have been extensively explored for region specific drug delivery, particularly in areas where pH gradients exist, such as the gastrointestinal tract or tumor microenvironments. These systems undergo swelling or degradation in response to pH variations, facilitating localized drug release. Similarly, enzyme-responsive hydrogels enhance specificity by degrading selectively in the presence of target enzymes that are overexpressed in pathological tissues [13], [14].

Hydrogels also provide a protective environment for labile therapeutics, such as proteins and nucleic acids, shielding them from enzymatic or chemical degradation and enhancing stability during delivery. Advanced hydrogel systems have been engineered to co-deliver multiple therapeutic agents with distinct release kinetics, enabling combination therapies that synergistically enhance treatment outcomes [2]. Injectable hydrogels offer additional advantages for localized drug administration, reducing the need for repeated systemic dosing. These materials can be designed to degrade over predefined timeframes, matching the therapeutic window of encapsulated drugs. Such strategies have been applied in cancer therapy, wound healing, and regenerative medicine [3], [15]. Despite these advantages, several challenges remain. These include controlling mechanical properties to ensure proper tissue integration, preventing burst release, achieving precise degradation kinetics, and minimizing potential immunogenic responses. Current research is focused on the development of multifunctional and stimuli-responsive hydrogel platforms capable of overcoming these limitations, thereby facilitating the clinical translation of hydrogel based drug delivery systems [16], [10].

5 | Recent Advances and Emerging Research in Hydrogels

5.1 | Advances in Hydrogel Design

The field of hydrogels has experienced remarkable progress due to innovations in polymer chemistry, nanotechnology, and biotechnology. These advances have enabled the development of hydrogels with enhanced physicochemical, mechanical, and biological functionalities tailored for specific biomedical applications.

5.2 | Multifunctional and Self-Healing Hydrogels

Multifunctional hydrogels integrating stimuli-responsiveness, self-healing, and shape-memory capabilities have emerged as a major trend. These hydrogels can dynamically adapt to environmental changes, improving performance in tissue engineering and drug delivery. For instance, self-healing hydrogels can autonomously repair mechanical damage, prolonging their functional lifespan in vivo [17], [18].

5.3 | Nanocomposite Hydrogels for Electrically Active Tissues

Nanocomposite hydrogels incorporating nanoparticles such as graphene oxide, carbon nanotubes, and metal-organic frameworks exhibit enhanced mechanical strength, electrical conductivity, and bioactivity. These properties are particularly advantageous for engineering electrically active tissues like cardiac and neural tissues, as well as for advanced drug delivery applications.

5.4 | Advanced Biofabrication Techniques

Technologies such as 3D bioprinting and microfluidics have revolutionized hydrogel-based tissue engineering. They allow precise spatial control over hydrogel architecture and cell distribution, enabling the fabrication of complex tissue constructs that closely mimic native tissue microenvironments [19].

5.5 | Smart Stimuli-Responsive Hydrogels

Hydrogels responsive to multiple stimuli pH, temperature, light, or enzymes offer precise spatial and temporal regulation of drug release and tissue integration. Such smart hydrogels enable personalized and more effective therapeutic strategies [14], [15].

5.6 | Integration with Biological Components

Emerging research focuses on combining hydrogels with biological components such as extracellular vesicles, growth factors, and gene editing tools. For example, hydrogels delivering CRISPR-Cas9 systems in situ represent a novel frontier with significant therapeutic potential [20].

5.7 | Translation to Clinical Applications

Despite the significant advancements, translating hydrogel technologies from laboratory to clinical application remains challenging due to regulatory, scalability, and long term safety concerns. Interdisciplinary research continues to address these limitations, facilitating the development of clinically translatable hydrogel-based therapies [4], [21].

6 | Challenges and Future Perspectives of Hydrogels in Tissue Engineering and Drug Delivery

Despite remarkable progress in hydrogel research and expanding biomedical applications, several challenges hinder their widespread clinical translation. Addressing these limitations is essential to fully harness the potential of hydrogels in tissue engineering and drug delivery [4], [21].

6.1 | Mechanical Integrity and Biocompatibility

Achieving an optimal balance between mechanical strength and biocompatibility remains a major challenge. Natural polymer based hydrogels often exhibit insufficient mechanical integrity, limiting their application in load bearing tissues. Conversely, synthetic hydrogels offer enhanced mechanical properties but may lack adequate biocompatibility or induce adverse immune responses [4], [21].

6.2 | Controlled Degradation

Precise control over hydrogel degradation to match tissue regeneration is critical. Premature scaffold degradation can compromise tissue support, whereas overly slow degradation may hinder tissue integration. Designing hydrogels with tunable degradation profiles continues to be a focus of current research [3], [16].

6.3 | Reproducibility and Scalability

Ensuring consistent hydrogel properties across production batches presents significant manufacturing challenges. Variability in polymer sources, crosslinking techniques, and environmental conditions can affect mechanical and chemical properties, complicating regulatory approval and commercialization [10].

6.4 | Immunogenicity and Inflammatory Responses

Immune reactions induced by hydrogel components or degradation products remain a concern for clinical applications. Development of fully biocompatible and non-immunogenic hydrogels requires careful polymer selection, surface modification, and crosslinker optimization [11].

6.5 | Future Directions and Emerging Technologies

Integrating multifunctionality into hydrogel systems represents a promising avenue. Smart hydrogels responsive to multiple physiological stimuli can enable targeted therapeutic delivery, improved tissue integration, and real time monitoring. Emerging fabrication approaches, such as 4D bioprinting and nanoengineering, offer the potential to create dynamic and complex hydrogel scaffolds that more closely replicate native tissue architectures [14], [15], [19].

6.6 | Integration with Advanced Biological Components

Combining hydrogels with bioactive components, including stem cells, exosomes, and gene editing tools, paves the way for personalized regenerative therapies. For instance, hydrogels delivering CRISPR-Cas9 in situ represent a cutting-edge strategy with substantial clinical potential.

7 | Conclusion

Overcoming these challenges through interdisciplinary research and technological innovation is essential to translate hydrogel-based therapies from bench to bedside, ultimately enabling safer, more effective, and patient-specific treatments [22], [23]. Hydrogels have established themselves as highly versatile and promising biomaterials in tissue engineering and drug delivery due to their unique physicochemical properties, tunable architectures, and excellent biocompatibility. Over recent years, substantial advancements including the development of stimuli-responsive, self-healing, and multifunctional composite hydrogels, as well as innovations in nanocomposite formulations and advanced biofabrication techniques (3D/4D bioprinting) have significantly expanded their biomedical applications. These technologies allow precise spatial and temporal control over drug release, enhanced scaffold functionality, and improved regeneration of complex tissues, including cartilage, bone, neural, and cardiovascular systems. Despite these advances, significant challenges remain. Optimizing mechanical strength, controlling degradation kinetics, ensuring reproducibility and scalability, and minimizing immunogenicity are critical for successful clinical translation. Addressing these limitations requires ongoing interdisciplinary collaboration among material scientists, bioengineers, and clinicians, coupled with continued innovation in manufacturing and regulatory strategies. Looking ahead, the integration of smart, multifunctional hydrogels with biologically active agents, such as stem cells, exosomes, and gene editing tools, promises to enable personalized regenerative therapies. Emerging fabrication techniques and multifunctional designs offer the potential for dynamic, patient specific scaffolds that can adapt to local tissue environments, provide targeted therapeutic delivery, and monitor tissue responses in real time. Overall, hydrogel based platforms are poised to play a transformative role in modern medicine. By bridging material science, bioengineering, and clinical practice, these systems have the potential to revolutionize regenerative therapies, enhance drug delivery precision, improve patient outcomes, and ultimately elevate quality of life across a wide range of diseases.

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