Acta Tecnología - International Scientific Journal about Technologies
Volume: 11 2025 Issue: 2 Pages: 75-79 ISSN 2453-675X

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https://doi.org/10.22306/atec.v11i2.272 Received: 06 Mar. 2025; Revised: 10 May 2025; Accepted: 13 June 2025

Hydrogels as bioactive scaffolds in biomedical engineering

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Keywords: hydrogels, scaffolds, biomedical engineering.
Abstract: Hydrogels have emerged as promising biomaterials in tissue engineering and regenerative medicine due to their high water content, biocompatibility, and structural similarity to the extracellular matrix (ECM). This article reviews the design principles and key physicochemical properties of bioactive hydrogels—such as stiffness, porosity, degradation rate, and biochemical functionalization—and their role in modulating stem cell behavior and guiding tissue regeneration. Special attention is given to the influence of hydrogel mechanics on mechanotransduction, strategies for controlled drug and growth factor delivery, and surface functionalization to enhance cell adhesion and lineage-specific differentiation. Recent advances in dynamic, cell-responsive, and degradable hydrogels are highlighted as crucial developments for creating personalized and clinically relevant scaffolds.

1 Introduction

Tissue engineering and regenerative medicine rely on biomaterials that can support cellular processes and guide tissue regeneration. Hydrogels, due to their high water content, biocompatibility, and ECM-mimetic properties, have been extensively studied as scaffolding materials for stem cell culture, drug delivery, and regenerative therapies (Figure 1). Hydrogels can be tailored to mimic the mechanical, chemical, and biological properties of native tissues, making them highly suitable for applications in bone, cartilage, neural, and cardiovascular repair [1].

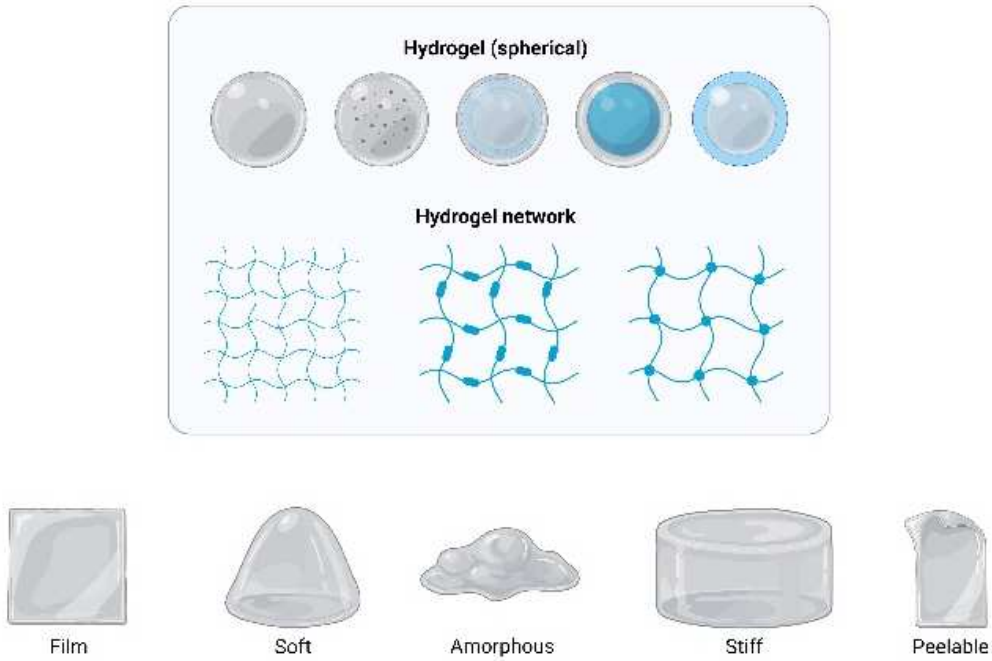

Figure 1 Illustration of various hydrogel forms and structures, showcasing spherical hydrogels, hydrogel networks, and different physical states, including film, soft, amorphous, stiff, and peelable hydrogels (created with Biorender.com)

Stem cells, including mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs), require a biologically active environment that provides essential cues for proliferation, differentiation, and lineage commitment. Hydrogels can be engineered to include bioactive peptides, growth factors, and extracellular matrix (ECM) proteins that interact with cell surface receptors and regulate downstream signaling pathways. Furthermore, the mechanical and topographical properties of hydrogels, such as stiffness, porosity, and degradation rates, influence cell migration, morphogenesis, and tissue remodeling [2,3].
This article explores the design principles of bioactive hydrogels, their influence on stem cell behavior, and their role as scaffolds for regenerative medicine.

2 Physicochemical properties of hydrogels and their role in cell behavior

The success of hydrogel-based scaffolds in tissue engineering and regenerative medicine relies on a precise balance of physicochemical properties that influence mechanical integrity, cellular interactions, biodegradability, and bioactivity. These properties dictate how stem cells adhere, proliferate, and differentiate, ultimately determining the scaffold's effectiveness in tissue repair [4]. The ability to fine-tune hydrogel stiffness, porosity, degradation rate, and biochemical functionalization allows researchers to mimic the extracellular matrix (ECM) and optimize hydrogel performance for specific biomedical applications. The mechanical properties of a hydrogel define how it responds to external forces and cellular traction, playing a crucial role in stem cell mechanotransduction [5]. Hydrogels with higher stiffness can direct stem cells toward osteogenic differentiation, while softer matrices support neuronal and chondrogenic differentiation. The swelling capacity and water retention ability of a hydrogel influence nutrient diffusion and metabolite exchange, affecting stem cell survival and metabolic activity [6]. Additionally, porosity and permeability regulate cell migration, vascularization, and tissue infiltration, which are essential for long-term regenerative success. Degradation kinetics, governed by enzymatic and hydrolytic processes, determine how well a hydrogel integrates with host tissue and whether it degrades at a rate synchronized with new tissue formation [7]. Finally, biochemical modifications, such as growth factor incorporation, ECM protein conjugation, and peptide functionalization, enhance the hydrogel's ability to interact with stem cells and stimulate lineage-specific differentiation [8,9]. Each of these physicochemical properties is interconnected, requiring a multifactorial approach when designing hydrogel scaffolds for biomedical applications [10].

2.1 Hydrogel stiffness and mechanotransduction

The stiffness or elastic modulus (E) of a hydrogel plays a pivotal role in cell fate determination. Stem cells are highly sensitive to the mechanical properties of their microenvironment, a phenomenon known as mechanotransduction, where extracellular mechanical signals are converted into biochemical responses that regulate gene expression.

- Soft hydrogels (0.1–1 kPa) mimic the mechanical properties of brain and neural tissues, promoting neuronal differentiation of stem cells.
- Intermediate stiffness (5–15 kPa) is optimal for muscle and soft tissue engineering, supporting myogenic differentiation.
- Stiff hydrogels (>30 kPa) resemble bone ECM, directing osteogenic differentiation of MSCs.

Mechanotransduction is mediated through integrin clustering, focal adhesion formation, and cytoskeletal tension. Advances in dynamic hydrogels that can alter stiffness in response to external stimuli allow for the sequential differentiation of stem cells into multiple lineages, mimicking native tissue development [11,12].

2.2 Porosity and diffusion properties

Porosity is a defining characteristic of hydrogels that influences cell infiltration, vascularization, and nutrient diffusion. The pore size, distribution, and interconnectivity of a hydrogel impact stem cell migration, tissue integration, and oxygen exchange, which are essential for successful tissue regeneration [13].

Hydrogels with small pores (<5 µm) create a dense matrix that restricts cell penetration, making them suitable for barrier applications such as wound dressings or cartilage protection. In contrast, macroporous hydrogels (50–300 µm) provide a scaffold architecture that supports cell migration, vascular network formation, and tissue remodeling. Highly porous hydrogels allow for rapid diffusion of oxygen, glucose, and bioactive molecules, preventing the formation of hypoxic cores in engineered tissues [4,14].

The ability to tailor hydrogel porosity is crucial for different tissue engineering applications:

- Bone and cartilage scaffolds require interconnected macropores (50–200 µm) to facilitate osteoblast infiltration and extracellular matrix deposition.
- Neural scaffolds benefit from aligned microchannels that guide neuronal extension and synapse formation.
- Cardiovascular applications utilize anisotropic pore networks to mimic the aligned fiber structure of blood vessels, ensuring proper endothelialization and vascular patency [15,16].

Modern fabrication techniques such as cryogelation, porogen leaching, and 3D bioprinting enable precise control over pore size, gradient structuring, and multi-layered hydrogel designs that replicate the hierarchical organization of native tissues [15,17].

2.3 Biodegradability and enzymatic degradation

Biodegradability is an essential feature of hydrogels that allows for progressive tissue replacement as the scaffold degrades. The rate of degradation must be finely tuned to match tissue formation dynamics; premature degradation can compromise scaffold integrity, while excessive persistence may lead to fibrotic encapsulation [18,19].

Natural hydrogels such as collagen, gelatin, hyaluronic acid, and fibrin degrade enzymatically, mimicking native ECM turnover. The incorporation of matrix metalloproteinase (MMP)-sensitive sequences allows for cell-driven degradation, where stem cells secrete enzymes to remodel the hydrogel in a biologically controlled manner. Synthetic hydrogels like polyethylene glycol (PEG), polyvinyl alcohol (PVA), and polyacrylamide degrade via hydrolytic cleavage, which can be engineered to occur over weeks to months, depending on polymer crosslinking density [20].

Cell-responsive degradation is crucial for applications such as:

- Bone tissue engineering, where slow-degrading hydrogels (weeks to months) support prolonged mineral deposition and osteogenesis [21].
- Wound healing applications, where fast-degrading hydrogels (days to weeks) enable rapid epithelialization and matrix remodeling [22].
- Drug delivery systems, where degradation is programmed to release growth factors, cytokines, or small molecules in a time-controlled manner.

Recent innovations in bio-orthogonal click chemistry and self-healing hydrogels have enabled the development of smart degradable materials that respond to cellular enzymatic activity, pH changes, or inflammatory signals, allowing for on-demand scaffold remodeling [23,24].

3 Functionalization strategies for bioactive hydrogels

3.1 Growth factor and drug delivery

Hydrogels act as localized delivery platforms for bioactive molecules, providing sustained release of growth factors, cytokines, and small-molecule drugs. Controlled delivery of vascular endothelial growth factor (VEGF) promotes angiogenesis, while bone morphogenetic proteins (BMP-2, BMP-7) induce osteogenic differentiation in bone regeneration. Encapsulation of anti-inflammatory agents such as dexamethasone or IL-10 can modulate immune responses to implants, improving graft survival [25,26].

Authors Hu et al. developed a hyaluronic acid (HA) and chitosan-based hydrogel (OHA-CMC) with antibacterial and hemostatic properties, created through a Schiff base reaction. They incorporated nanotechnologically-modified curcumin (CNP) and epidermal growth factor (EGF) into the hydrogel. The resulting OHA-CMC/CNP/EGF hydrogel demonstrated significant antioxidant, anti-inflammatory, and migration-promoting effects in vitro. The hydrogel released curcumin in the early phase of wound healing to reduce inflammation and oxidative stress, while EGF was gradually released to support later stages, such as proliferation and extracellular matrix (ECM) remodeling. In a diabetic skin defect model, the hydrogel significantly enhanced wound healing, including re-epithelialization, granulation tissue formation, and skin appendage regeneration, showcasing its potential as a therapeutic dressing for diabetic wounds [27].

3.2 Surface functionalization with ECM proteins

Hydrogel surfaces can be modified with ECM-derived proteins such as fibronectin, laminin, vitronectin, and collagen to enhance cell adhesion and integrin signaling. Peptide motifs such as RGD (Arg-Gly-Asp) improve cell attachment, while IKVAV and YIGSR sequences promote neuronal differentiation [4]. Álvarez-López et al. developed a biofunctionalization strategy using covalent immobilization of extracellular matrix (ECM)-derived oligopeptides on Ti-6Al-4V surfaces via activated vapor silanization (AVS) and EDC/NHS crosslinking chemistry. The immobilization was stable, even under chemical denaturing conditions. The modified surfaces enhanced mesenchymal stem and progenitor cell attachment, spreading, and growth, supporting chondro- and osteo-regeneration. Additionally, the method improved adhesion of a neural cell line with poor anchorage properties, demonstrating its versatility [28].

4 Discussion

The physicochemical properties of hydrogels—including stiffness, porosity, degradation, and biochemical functionalization—serve as the foundation for their biological performance in tissue engineering. The ability to engineer hydrogels with tunable mechanics, precise pore architectures, and controlled degradation profiles allows researchers to create microenvironments that guide stem cell behavior and tissue regeneration. Advances in dynamic and stimuli-responsive hydrogels further enhance the adaptive capabilities of these biomaterials, opening new frontiers in personalized regenerative medicine, bioactive implant coatings, and controlled drug delivery systems. Future research must continue optimizing these parameters to bridge the gap between laboratory-scale hydrogel design and clinical translation, ensuring their successful integration into regenerative therapies [8,27].

5 Conclusion

Hydrogels represent a transformative class of biomaterials in biomedical engineering, offering a versatile platform for tissue regeneration, drug delivery, and stem cell modulation. Their tunable physicochemical properties—such as stiffness, porosity, degradability, and biofunctionalization—allow for precise control over the cellular microenvironment, enabling the engineering of scaffolds that mimic native extracellular matrices. Continued advancements in smart and stimuli-responsive hydrogels, along with biofabrication techniques, hold significant promise for translating these materials from bench to bedside. However, challenges related to mechanical stability, biocompatibility, and large-scale manufacturing must be addressed to fully realize the clinical potential of hydrogel-based therapies. Future research should focus on integrating multidisciplinary approaches to design next-generation hydrogels that can dynamically adapt to biological cues and promote personalized regenerative outcomes.

Acknowledgement
The state grant agency supported this article with projects KEGA 018TUKE-4/2023 and VEGA 1/0403/25.

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Review process
Single-blind peer review process.