RSC Advances

REVIEW

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2026, **16**, 25236

The critical role of hydrogels as an advanced polymeric scaffold in biomedicine: recent progress and challenges

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Received 14th February 2026
Accepted 21st April 2026

DOI: 10.1039/d6ra01314g

rsc.li/rsc-advances

Hydrogels have emerged as pivotal materials in biomedical engineering due to their unique properties, including high water content, biocompatibility, and tunable mechanical characteristics. These three-dimensional hydrophilic networks can mimic natural biological tissues, making them suitable for a wide range of applications, including drug delivery systems, tissue engineering scaffolds, and wound healing and regenerative medicine. This review explores the composition, classification, and mechanisms of hydrogels, highlighting recent advancements and innovative trends in the field. The aim of using hydrogels in biomedical engineering is to create materials that closely mimic natural tissue, providing biocompatibility and support for cellular functions. This study explored the application of hydrogels in drug delivery, wound healing, tissue engineering, and diagnostics, offering insights into their clinical relevance. This review also includes a discussion on current trends and future directions, highlighting innovations such as smart hydrogels, 3D printing, and biosensing technologies. It further discussed their applications and challenges faced in clinical translation, providing insights into future directions for research and development in biomedical engineering.

1. Introduction

For constructing a three-dimensional structure capable of retaining water or biological fluids, hydrogels are an ideal choice. This hydrophilic polymer, which is also used in the form of nanogels in biomedical applications, is porous and biocompatible. The hydrophilicity of nanogels enables them to maintain structure and swell when in contact with water.[1] Controlled degradation of hydrogels, preservation of initial shape, and maintenance of mechanical properties in an aqueous environment are essential features to consider in the design of hydrogels.[2] Hydrogels, which possess properties similar to those of biological tissues, such as high-water content, softness, low surface tension when interacting with fluids, and insolubility in various solvents, are promising alternatives to natural tissues.[3] The most important molecular properties of this polymer are the mesh size and molecular weight between cross-links (both covalent and physical).[4] Hydrogels can exhibit pH-sensitive properties, allowing them to respond to changes in the local environment. This responsiveness can influence swelling behavior, drug release rates, and overall mechanical properties. For instance, certain hydrogels swell or shrink based on the pH of their surroundings, making them useful for drug delivery systems that target specific sites within the body. The manipulation of pH-responsive characteristics can lead to improved performance in biomedical applications, enhancing the effectiveness of treatments and the compatibility of materials with biological systems.[5] In general, by creating stimuli such as heat, chemical agents and changes in pH, the properties of hydrogels can be modified.[6]

Stimuli-responsive peptide hydrogels are an exciting area of research in biomedical engineering, offering tailored solutions for drug delivery, tissue engineering, and regenerative medicine. These hydrogels can undergo structural changes in response to various stimuli such as pH, temperature, light, or specific biomolecules. By incorporating drugs or bioactive agents within the hydrogel matrix, these systems can provide controlled release mechanisms, enhance therapeutic efficacy while minimizing side effects.[7] In the context of hydrogels used for drug delivery, hydrogen bonding interactions play a crucial role in determining their properties. These interactions facilitate the formation and stability of the hydrogel network, influencing its swelling behavior, mechanical strength, and drug release profiles. Hydrogen bonds can occur between water molecules and

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functional groups within the hydrogel, as well as between polymer chains, enhancing the material's ability to retain water and drugs. This results in a controlled release mechanism, which is essential for effective drug delivery systems.[8] The relevance of hydrogels, particularly self-healing hydrogels, in biomedical engineering is profound.[9] The relevance of hydrogels in biomedical engineering cannot be overstated. Their unique properties, including biocompatibility, controlled drug release, moisture retention for wound healing, and adaptability in tissue engineering, make them indispensable in modern medicine.[10]

2. Classification of hydrogels

Hydrogels can be classified based on several criteria. Fig. 1 illustrates a summary of the classification of hydrogels along with its subcategories.

2.1. Source

2.1.1. Natural hydrogels. Natural hydrogels derived from natural sources (*e.g.*, alginate, gelatin, chitosan) and features such as biocompatibility, biodegradability, and suitable mechanical properties, making them ideal for tissue engineering applications.[11] These hydrogels support cell adhesion, proliferation, and differentiation. Additionally, these polymeric materials can be designed to resemble the extracellular matrix, providing a conducive environment for tissue regeneration.[12]

2.1.2. Synthetic hydrogels. Synthetic Hydrogels are made from synthetic polymers (*e.g.*, polyacrylamide, polyethylene glycol).[13] Synthetic hydrogels can be engineered to achieve specific mechanical and chemical properties, allowing customization for various applications. Many synthetic hydrogels are designed to be biocompatible, minimizing adverse reactions when used in biological settings. They exhibit high water retention, which is essential for applications like drug delivery and tissue engineering, as it mimics biological tissues. These hydrogels can respond to environmental changes, swelling, or shrinking in response to factors such as temperature and pH.[14] Unlike many natural hydrogels, synthetic variants can be designed to have enhanced mechanical properties, making them suitable for load-bearing applications. The degradation rates of these hydrogels can be precisely controlled, allowing for the predictable release of drugs or gradual scaffold absorption in tissue engineering.[15]

2.1.3. Semi-synthetic hydrogels. Semi-synthetic hydrogels simultaneously possess the advantages of both natural and synthetic polymers and has enhanced mechanical and biological activity.[16] Semi-synthetic hydrogels are derived from natural polymers that undergo chemical modifications to improve their properties for specific applications, particularly in drug delivery systems. These modifications can enhance stability, control swelling behavior, and optimize release kinetics for sensitive drugs.[17]

2.2. Chemical structure

There are different structures for the natural and synthesized hydrogels. For example, homopolymeric hydrogels made from

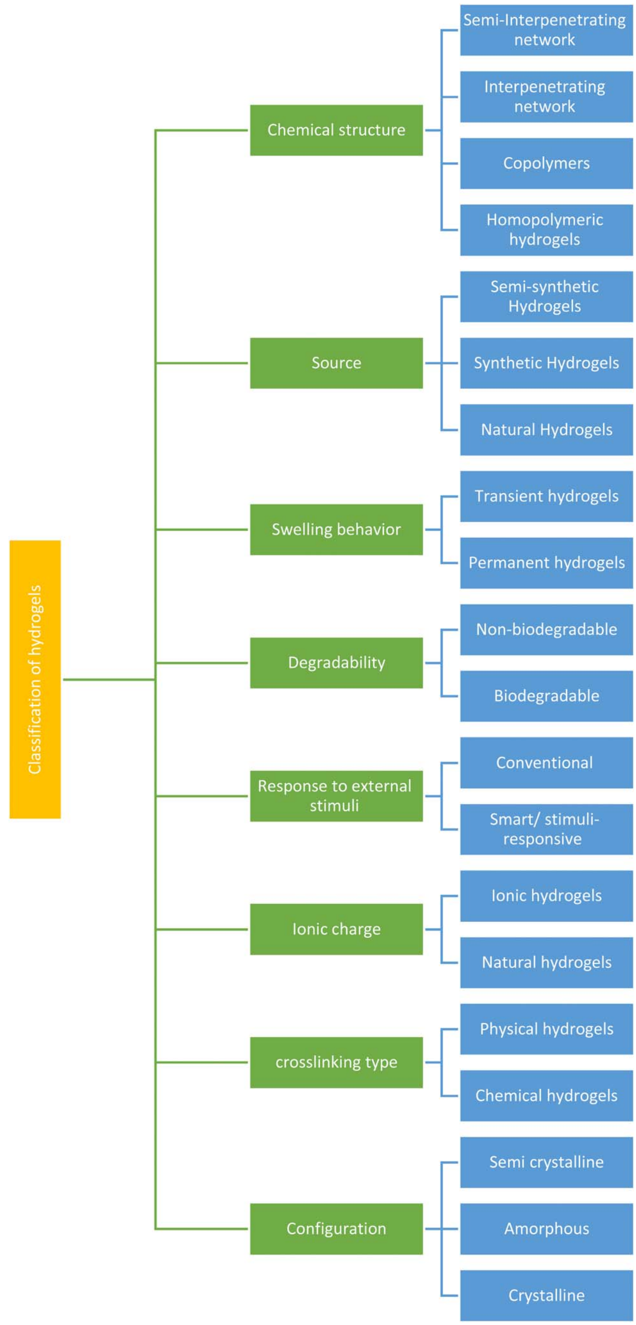

Fig. 1 Summary of hydrogel classification.

a single type of monomer. Homopolymeric hydrogels, such as polyvinyl alcohol (PVA) and polyacrylamide, are designed to be biocompatible, making them suitable for medical uses like drug and tissue scaffolding.[18] Also, copolymers are composed of two or more different monomers. Poly(ether–ether) and poly(ether–ester) block copolymers are known for their versatility in biomedical applications due to their biocompatibility, tunable mechanical properties, and ability to form micelles or hydrogels. This block nature of these copolymers enables them to self-assemble into nanostructures, such as micelles, which can be used for targeted drug delivery.[19] In addition, interpenetrating network the interpenetrating polymer networks consist of two or more polymers that are entangled at the molecular level but not covalently bonded. This unique structure allows for enhanced material properties.[20] Interestingly, semi-interpenetrating network semi-interpenetrating consists of two interpenetrating polymer networks, where one is a cross-linked polymer and the other is linear or lightly cross-linked. This combination enhances the mechanical and functional properties of the hydrogel.[21]

2.3. Swelling behavior

Permanent hydrogels maintain a constant volume after swelling. Unlike traditional hydrogels, which may degrade or lose their properties, permanent hydrogels are designed for long-term stability and functionality.[22] But, transient hydrogels swell and shrink in response to external stimuli. Transient hydrogels refer to hydrogels that undergo temporary, reversible changes in their physical properties, such as swelling or shrinking, in response to environmental stimuli. Unlike permanent hydrogels, which maintain their structure over time, transient hydrogels can respond dynamically to factors like moisture, temperature, or pH changes.[23]

2.4. Configuration

There is different configuration like crystalline, amorphous, semi crystalline for the hydrogels in biomedical science. For example, crystalline refer to the arrangement of polymer chains or nanoparticles in a structured, ordered manner within the hydrogel matrix.[24] Also, amorphous configurations in hydrogels refer to the disordered arrangement of polymer chains within the hydrogel matrix. This structural characteristic plays a significant role in determining the physical and chemical properties of the hydrogel.[25] Importantly, semi-crystalline hydrogels exhibit a combination of amorphous and crystalline regions. This unique structure imparts distinct properties that are beneficial for various applications. These hydrogels can remember their original shape and return to it upon external stimuli (*e.g.*, temperature changes), making them ideal for applications in flexible electronics, soft robotics, and biomedical devices.[26]

2.5. Type of cross-linking

For the cross-linking of hydrogel there are two different method which are categorized as chemical and physical strategy. Chemical cross-linking can enhance the biocompatibility of hydrogels by modifying their surface properties, reducing potential toxicity and promoting cell adhesion and proliferation.[27] Some chemically cross-linked hydrogels exhibit self-healing capabilities, allowing them to recover from damage, which is beneficial for long-term use in biomedical setting.[28] Physically cross-linked hydrogels are formed through non-covalent interactions, such as hydrogen bonds, ionic interactions, or hydrophobic interactions, rather than through chemical bonds.[29]

2.6. Ionic charge

Natural hydrogels are typically uncharged, but many-like alginate-form stable networks through ionic cross-linking with ions such as calcium, however, this process is sensitive to variations in ionic strength, which can influence the hydrogel's mechanical properties and stability.[30]

Ionic hydrogels carry a positive or negative charge, which can influence their interaction with ions and water. Ionic hydrogels are characterized by their ability to conduct electricity due to the presence of mobile ions within their structure.[31]

2.7. Response to external stimuli

Some hydrogels can swell or shrink in response to temperature changes, making them useful for applications where thermal regulation in needed.[32] This is smart/stimuli-responsive hydrogels. Bioresponsive DNA hydrogels are presented as an advanced form of hydrogels that respond to specific biological stimuli, such as nucleic acids, proteins, or other biomolecules. Unlike conventional hydrogels that typically react to physical stimuli, DNA hydrogels leverage the unique properties of DNA, allowing for highly specific and programmable responses.[33]

2.8. Degradability

There are two different types of hydrogels based on their biodegradability. Biodegradable hydrogels can be easily injected into target sites, where they can form gels *in situ*, minimizing the need for invasive surgical procedures.[34] They are engineered to degrade through biological processes, allowing for gradual absorption by the body and eliminating the need for surgical removal.[35] But non-biodegradable is specifically designed to retain their structure and function without being metabolized or absorbed by biological systems.[36]

For complete of our discussion, Table 1 summarized properties, applications, and examples of hydrogels.

Fig. 2 briefly illustrates the properties related to hydrogels such as biocompatibility, hydrophilicity, degradability, porosity, and mechanical properties. In this subsection of review, we focused on the above-mentioned properties of hydrogels which is important for their specific application in biomedical science.

3. Main properties of hydrogels

3.1. Biocompatibility

Hydrogels interact with cells in a way that can support cell adhesion, proliferation and differentiation. This is critical because cells need to attach to the scaffold for tissue formation. Hydrogels can be engineered with specific surface properties, such as the incorporation of bioactive molecules to promote cell attachment and signaling.[37] Smart biocompatibility refers to the ability of conductive hydrogels to not only be compatible with biological tissues but also to respond dynamically to the surrounding biological environment, thus enhancing their functionality and therapeutic potential. Conductive hydrogels are often designed to be smart in that they can respond to environmental stimuli such as changes in pH, temperature or

Table 1 Property and application hydrogel

Material type	Examples	Properties	Applications	Ref.
Natural	Alginate: derived from algae	• Derived from brown algae • Biocompatible and biodegradable • Excellent gelation properties due to interaction with divalent cations like calcium • Forms hydrogels suitable for drug delivery and cell encapsulation	Bone: bone regeneration Soft tissue: cartilage repair Other tissue: wound healing	43
	Gelatin: derived from collagen	• Derived from collagen • Biodegradable and promotes cell adhesion • Hydrophilic, allowing high water absorption • Supports tissue regeneration and wound healing	Bone: bone regeneration Soft tissue: cartilage repair Other tissue: wound healing	44
	Chitosan: derived from chitin	• Derived from chitin (found in crustacean shells) • Antibacterial and antifungal properties • Stimulates hemostasis and wound healing • High biocompatibility and ability to form hydrogels at acidic pH	Bone: bone regeneration Soft tissue: cartilage repair Other tissue: wound healing	45
	Collagen: natural EMC mimic	• Natural extracellular matrix (ECM) protein • Promotes cell adhesion, proliferation, and differentiation • Biodegradable and supports angiogenesis • Mimics native tissue environment	Bone: bone regeneration Soft tissue: cartilage repair Other tissue: wound healing	42
Synthetic	Polyacrylamide	• High water retention capacity • Adjustable mechanical properties through cross-linking • Biocompatible but lacks biodegradability	Bone: fracture repair Soft tissue: tendon healing Other tissue: skin substitutes	19
	Polyethylene glycol	• Hydrophilic, non-immunogenic, and biocompatible • Provides customizable degradation rates by adjusting molecular weight • Often used as a base for drug delivery and injectable hydrogels	Bone: fracture repair Soft tissue: tendon healing Other tissue: skin substitutes	13

Table 1 (*Contd.*)

Material type	Examples	Properties	Applications	Ref.
	Polycaprolactone	• Biodegradable polyester with a slow degradation rate • High mechanical strength and flexibility • Hydrophobic but can be combined with hydrophilic materials for enhanced properties • Suitable for load-bearing applications like bone scaffold	Bone: fracture repair Soft tissue: tendon healing Other tissue: skin substitutes	52
Composite materials	Hydroxyapatite-based scaffolds	• Mimics natural bone mineral composition • Osteoconductive and enhances mechanical strength • Biocompatible but brittle when used alone; often combined with polymers	Bone: hydroxyapatite scaffolds Soft tissue: hybrid cartilage repair Other tissue: multi-tissue scaffolds	50
	Natural-synthetic blends (*e.g.*, Collagen-PEG)	•Balances biocompatibility (natural) and mechanical tunability (synthetic) • Supports cell adhesion and controlled degradation • Suitable for hybrid tissue scaffolds like cartilage or tendon repair	Bone: hydroxyapatite scaffolds Soft tissue: hybrid cartilage repair Other tissue: multi-tissue scaffolds	13
	Nanocomposite hydrogels	• Incorporates nanoparticles like nano clays or hydroxyapatite for enhanced properties • Improved mechanical strength, durability, and bioactivity • Enables applications in multi-tissue engineering and 3D-printed scaffolds	Bone: hydroxyapatite scaffolds Soft tissue: hybrid cartilage repair Other tissue: multi-tissue scaffolds	71

ion concentrations. This responsiveness enables the hydrogel to adapt its properties in real time to optimize the interaction with biological tissue. For instance, the swelling behavior of a hydrogel can be controlled to facilitate the diffusion of nutrients and waste, while the conductivity can be tuned optimal electrical stimulation.[38] One important application of the biocompatibility of hydrogels is that the interaction between calcium ions and phosphate groups, when in contact with physiological solutions, leads to the formation of hydroxyapatite on the surface of the hydrogel, which aids in the growth of new tissue in bone injuries. The presence of phosphate groups in hydrogels increases their chemical affinity in the body, as well as their bioactivity and biocompatibility.[39] The properties of hydrogels make them suitable for applications where flexibility and durability are important. In particular, their biocompatibility ensures that they can be safely used in biological environments, such as wearable sensors or medical devices. The hydrogel's ability to adhere to surfaces without the need for external adhesives, its self-repair capability and resistance to wear and tear over time make it a promising material for advanced flexible electronics applications.[40]

3.2. Hydrophilicity

Hydrogels, particularly those designed for cartilage replacement, exhibit significant water retention properties due to their high hydrophilicity. This ability to retain water is crucial in maintaining the mechanical and biological functions necessary for cartilage like behavior in the body. Cartilage, as a natural tissue, is composed primarily of water, and its unique function depends on maintaining a hydrated, gel-like state to provide shock absorption and facilitate joint movement. The hydrophilic nature of hydrogels ensures they can absorb and retain large amounts of water, mimicking the water content and mechanical properties of natural cartilage.[41] In the synthesis and characterization of chitosan/collagen/PCL hydrogel films for artificial tendon applications, the hydrogel's ability to retain water is fundamental for both the mechanical and biological success of the material. Water retention supports the

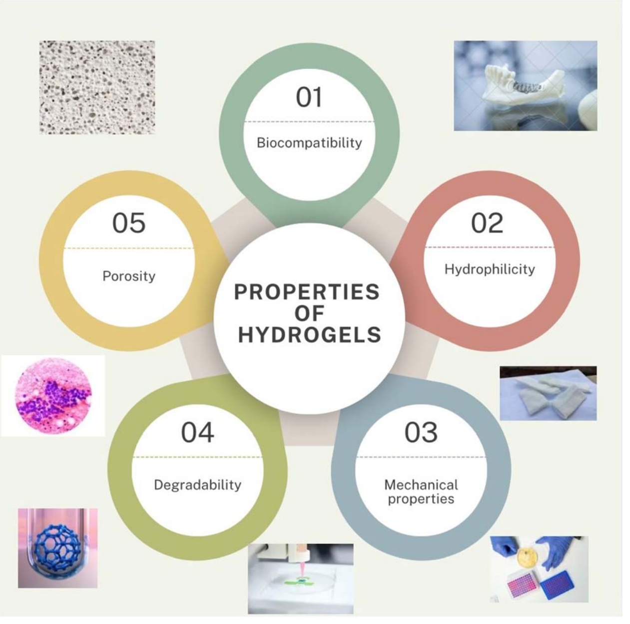

Fig. 2 A summary of the properties of hydrogels.

mechanical flexibility and biocompatibility required for tendon replacement, enhances cellular function and tissue regeneration and helps the hydrogel mimic the natural tendon environment. The careful balance of hydrophilic and hydrophobic components in the hydrogel ensures that it can maintain hydration, integrate well with surrounding tissues and provide a supportive matrix for tendon healing and regeneration.[42]

3.3. Mechanical properties

Hydrogels cross-linked with multivalent cations exhibit high resilience and the ability to recover from strain. The ionic cross-linking between alginate chains provides elasticity, allowing the material to return to its original shape after being stretched or compressed which is critical for applications like wound healing soft tissue repair.[43] The tensile strength of gelatin-based hydrogels is primarily influenced by the degree of cross-linking. Photopolymerization allows for precise control over the cross-linking density, thereby affecting the structural integrity of the hydrogel. A higher cross-linking density results in stronger gels that can better resist mechanical forces, which is important for supporting cells in stress-bearing applications, such as cartilage or bone tissue engineering. The compressive strength of these hydrogels can be modulated by adjusting the exposure to light during photopolymerization. Stronger, more densely cross-linked hydrogels can withstand higher compressive forces without collapsing, which is particularly relevant for applications that require scaffolds to endure physical pressure, such as in soft repair.[44] The ability of the hydrogel to recover its original shape after deformation is important for ensuring its performance during drug release. Elastic recovery can be adjusted by altering the composition of the hydrogel, allowing for optimal delivery characteristics, including the controlled release of drugs over time.[45] Fig. 3 illustrates the mechanical properties of hydrogels, emphasizing the role of multivalent cations in cross-linking alginate chains. The cross-linked structure enhances resilience and elasticity, allowing the hydrogel to recover after deformation.

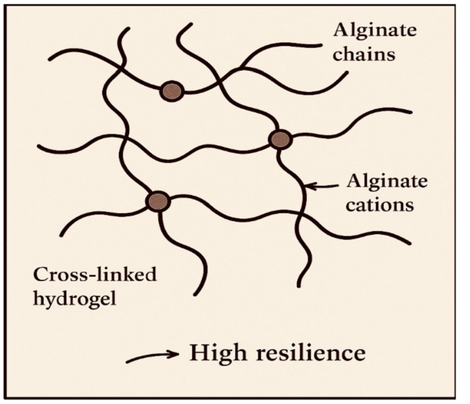

Fig. 3 A schematic of the mechanical properties of hydrogels.

3.4. Degradability

Hydrogels can be synthesized with biodegradable linkages, such as ester or amide bonds, that are susceptible to hydrolysis or enzymatic cleavage. These bonds degrade when exposed to water, enzymes, or changes in pH, leading to a controlled breakdown of the hydrogel matrix over time. Some hydrogels undergo physical degradation *via* changes in temperature, ionic strength, or pH, which destabilize the polymer network. For example, temperature sensitive hydrogels can transition from a gel to a sol phase at higher temperatures, resulting in material degradation.[46] The ionic strength and salt concentration in the surrounding environment can also influence the stability of DNA hydrogels. A high concentration of salts can destabilize the hydrogel network, leading to gradual degradation over time, while lower ionic conditions may maintain the gel's structural integrity.[47]

3.5. Porosity

The size, shape, and distribution of pores within a hydrogel play a key role in determining its biological functionality. Large pores facilitate the migration of cells and the diffusion of nutrients, whereas smaller pores may provide more support for cellular attachment. The ideal pore size for tissue engineering depends on the type of tissue being targeted. For example, scaffolds for bone tissue engineering may require larger pores compared to those used for skin or cartilage regeneration.[48] Various methods are employed to introduce porosity into hydrogels. These include gas foaming, freeze-drying, porogen leaching and template-assisted methods. Porous hydrogels can be used in environmental cleanup, such as removing contaminants from water, due to their high surface area and absorption capabilities.[49] Fig. 4 demonstrates the porosity of hydrogels, showing how larger pores support cell migration and nutrient diffusion, while smaller pores enhance cellular attachment. The diagram highlights the significance of pore size and distribution in tissue engineering applications.

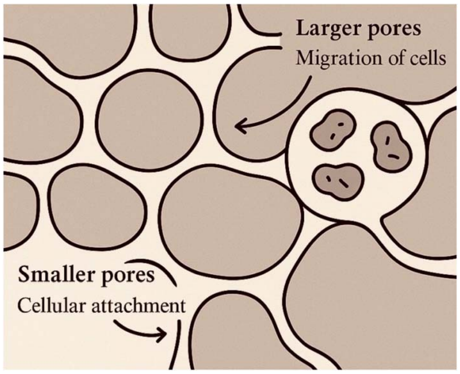

Fig. 4 A schematic of porosity in hydrogels.

4. Biomedical applications of hydrogel

Considering the properties and characteristics discussed in the previous sections, hydrogels are used in various industries and have widespread applications. In the medical and pharmaceutical industries, hydrogels are utilized for producing advanced wound dressings, controlled drug delivery systems, tissue engineering, and contact lenses. In agriculture, these materials help improve water retention in soil, enable the gradual release of fertilizers, and control moisture in arid regions.[50] In the cosmetics and personal care industries, hydrogels play a role in the production of facial masks, moisturizing creams, and hair care products. In the food industry, they are used as thickening agents and in smart packaging to extend the shelf life of food products. Hydrogels are also applied in biotechnology and environmental sciences, where they are used for water purification, pollutant absorption, and the development of biosensors. In the textile industry, these materials are utilized in the production of self-cleaning and moisture-absorbing fabrics. Additionally, in the electronics and battery industries, hydrogels are employed in the development of flexible batteries, biosensors, and soft electronic devices.[51] In the next section, the application of hydrogel in biomedical engineering and medicine will be specifically examined.

4.1. Drug delivery

Utilization of hydrogels and related nanocomposites for drug delivery, highlighting their ability to encapsulate therapeutic agents and release them over time in a controlled manner and at specific rates.[52] Nanoparticles like halloysite nanotubes, can enhance the performance of hydrogels in drug delivery systems by improving drug loading, release control, and therapeutic efficacy. Fig. 5 shows a summary indicating that when nanoparticles and hydrogels are integrated, under controlled environmental conditions, they can be used in various medical fields.[53]

Caprolactone is a lactone monomer commonly used to synthesize polyesters like polycaprolactone (PCL), which is known for its good mechanical properties, slow degradation rate, and biocompatibility. In combination with succinic acid, caprolactone can help create a more flexible and durable hydrogel. Its incorporation can improve the material's ability to support tissue growth and also extend the hydrogel's functional lifespan *in vivo*.[54] Hydrogels can be tailored to release drugs in a specific manner, such as through diffusion, erosion, or a combination of both. In diffusion-controlled systems, the drug diffuses through the hydrogel matrix at a rate that can be controlled by adjusting the network's porosity or cross-linking density. In erosion-controlled systems, the hydrogel slowly degrades over time, releasing the drug as the matrix breaks down.[55] In a study, created a thermoresponsive hydrogel, which could undergo a phase transition in response to temperature changes. This temperature sensitive property allowed the hydrogel to remain in a sol state at lower temperatures, facilitating easy injection or implantation. Upon reaching body temperature, the hydrogel underwent gelation, forming a stable network at the target site, where it could then release the encapsulated doxorubicin in a controlled manner. The mathematical modeling aspect of this study focused on predicting the drug release kinetics from the hydrogel. The researchers used models to understand how parameters such as gelation time, cross-linking density, and drug loading influenced the release rate. Through careful modeling, they were able to optimize the formulation to ensure that doxorubicin was released gradually, maximizing therapeutic efficacy while minimizing toxic side effects.[56] In addition to these points, there are also other challenges and limitations. Precisely controlling the drug release rate is difficult, especially for drugs with varying solubilities. Some hydrogels are brittle and degrade over time, which can lead to the sudden release of the drug. In certain synthetic hydrogels, inflammatory and immune reaction may occur in the body.[57] Not all drugs can dissolve or disperse uniformly within the hydrogel structure, and some hydrophobic drugs require chemical modifications. The production cost of certain advanced hydrogels is high. The swelling rate of hydrogels in biological environments may lead to changes in drug release rates. Microbial growth in hydrogels with high water content can become problematic. In some cases, the drug may be unintentionally released before reaching the target site.[58] Given these challenges, research continues improving hydrogel properties and designing smart hydrogels to minimize these limitations and optimize their application in drug delivery. To enhance drug release control, smart hydrogels and nanocarriers can be utilized. Increasing cross-linking and incorporating reinforcing nanoparticles improve mechanical stability. Using biocompatible polymers helps reduce immune reactions. For better loading of hydrophobic drugs, surface chemical modifications and nanoencapsulation are effective. Production costs can be lowered by using low-cost biopolymers and 3D printing. Hybrid hydrogels and dynamic cross-linking help control swelling and prevent early degradation. Antimicrobial agents prevent bacterial growth. Additionally, targeting biomolecules enables more precise drug delivery.[59] This structure is achieved through the cross linking of polymer chains *via*

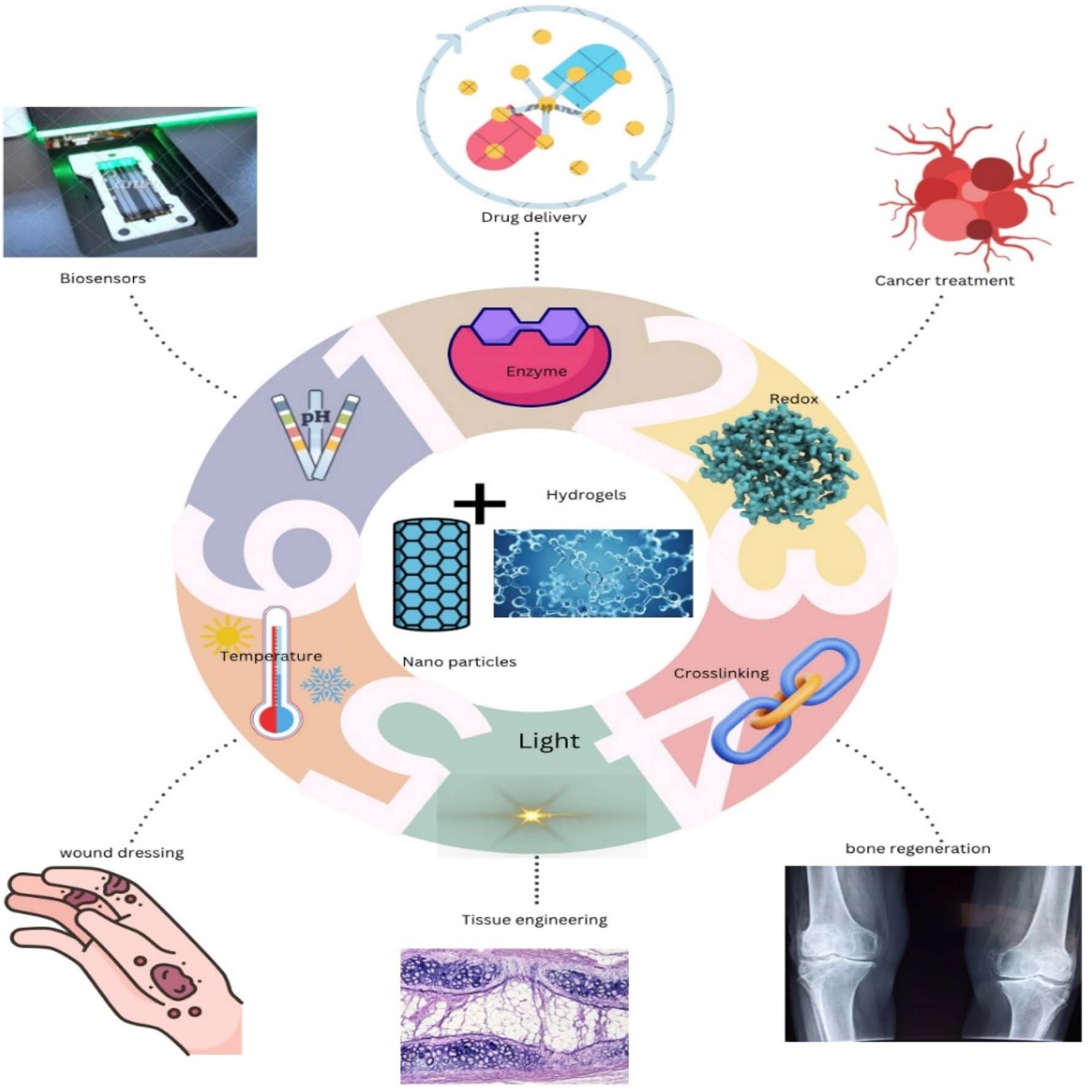

Fig. 5 Different parameters on the applications of hydrogels in biomedical studies.

chemical or physical bonds.[60] The results of various experiments have shown that increasing the solid content of the hydrogel enhances interfacial toughness and shear strength. These findings indicate that hydrogels possess a high tissue adhesion capability and can be beneficial in medical applications such as wound healing or surgery.[61]

4.2. Wound healing

The role of hydrogel rolls in wound care centers around their ability to absorb exudate from the wound while also providing hydration to the tissue, preventing the wound from drying out. A moist environment is beneficial because it accelerates the healing process by promoting cell migration, reducing pain, and minimizing the risk of scab formation, which can impair tissue regeneration. The hydrogel's water content can also aid in the breakdown of necrotic tissue, which further supports the healing process. Hydrogel roll dressings are typically easy to apply and conform to the shape of the wound, providing both physical protection and a moisture-retentive barrier. This barrier helps to prevent infections by keeping contaminants out while maintaining the optimal conditions for cell growth and tissue repair.[62] In the healing process, especially in bone injuries that might involve surgical intervention, the risk of infection is a significant concern. Hydrogels act as a protective barrier, reducing the chances of bacterial contamination while maintaining moisture at the wound site.[63] Hydrogels support the movement of fibroblasts, keratinocytes, and endothelial cells, which are essential for tissue regeneration and wound closure. Hydrogels can incorporate antibacterial compounds like silver nanoparticles, chlorhexidine, or natural antimicrobial agents (*e.g.,* honey or tea tree oil) to prevent bacterial growth, minimizing the risk of infection.[64] Self-healing hydrogels are a cutting-edge advancement that allows the hydrogel to recover its original structure after mechanical damage, such as tearing or puncturing. This is particularly important in the clinical setting because diabetic wounds often require frequent dressing changes, and the risk of disrupting the healing tissue during dressing changes is high.[65] Diabetic patients often experience delayed or impaired wound healing due to factors like poor circulation, chronic hyperglycemia, and immune dysfunction. Some hydrogels are designed to mimic to improve oxygen diffusion to the wound bed, a critical factor for healing in diabetic patients.[66] However, in diabetic wounds, there are additional challenges, as high blood sugar levels and low oxygen availability lead to increased exudate, infection, and persistent inflammation.[67] Zhao and colleagues recently developed a groundbreaking hydrogel, GEL-MOF-rPDA, inspired spiders hunt. This innovative material combines reduced polydopamine nanoparticles (rPDA) with a copper-based MOF, all embedded in a biocompatible matrix created through Schiff base chemistry. What sets it apart is its ability to fight infections by breaking down bacterial membranes and releasing antibacterial agents like copper ions and singlet oxygen, achieving an impressive 99.9% success rate against bacteria. In tests using a rat skin defect model, the hydrogel promoted 92% wound closure in just ten days. By combining multiple benefits—such as stopping bleeding, reducing inflammation, fighting infection, and supporting tissue repair, this hydrogel also encouraged blood vessel growth and new tissue formation, making it a promising tool for real-world wound care.[68] In summary, some of the advantages of hydrogels in wound dressings include the following. Hydrogels have a high-water content, which creates a moist environment for the wound. This moisture speeds up tissue repair and prevents the wound from drying out and forming scabs.[69] Hydrogels provide a cooling sensation when applied to the skin, helping to reduce pain and inflammation. This feature is particularly useful for burns and painful wounds. Some hydrogels contain antibacterial agents that prevent the growth of bacteria, reducing the risk of infection. Hydrogels help soften and naturally remove dead tissue from the wound without damaging healthy tissue. These dressings are effective for various types of wounds, including pressure ulcers, diabetic wounds, surgical wounds, and burns. Hydrogels have high oxygen permeability, which improves cell function and accelerates tissue regeneration.[70] Alongside all the advantages, there are also some disadvantages in these systems, which can be briefly mentioned as follows. Due to their high-water content, hydrogels may dry out quickly, requiring frequent replacement, which can be time-consuming and costly. These dressings are not suitable for highly exuding wounds as they have a low absorption capacity and may need to be combined with more absorbent dressings.[71] If not used correctly or left too moist, hydrogels can create an environment that promotes bacterial growth, increasing the risk of wound infection. These dressings are ideal for dry and necrotic wounds, but they are less effective for deep wounds with heavy exudate.[72]

4.3. Tissue engineering

Smart hydrogels can encapsulate cells within their matrix, providing both physical support and controlled microenvironment for cell growth. This is particularly useful in applications like stem cell therapy or in creating tissue constructs, where cells need to be delivered to the injury site in a viable state.[73] The mechanical properties of hydrogels can be tuned to match the specific requirements of the tissue being regenerated. For example, hydrogels designed for bone tissue engineering might need to have higher stiffness and compression (like skin or cartilage) may need to be more flexible and elastic.[74] Hydrogels have been used in trials for skin regeneration in burn victims, bone repair, and even as injectable solutions for cartilage defects.[75,76] In this approach, hydrogels serve as three dimensional scaffolds that encapsulate the cells and provide the necessary environment for cell growth and proliferation. This combination is especially useful in the regeneration of damaged tissue such as skin, cartilage, or bone, as hydrogels can easily mimic the properties of natural tissue and aid in more effective and faster healing. The use of hydrogels in tissue engineering comes with challenges and limitations. Hydrogels generally have a soft structure and weak resistance to mechanical forces, making them unsuitable for load-bearing tissue such as bone and cartilage.[77] Many hydrogels degrade rapidly or undergo structural changes after implantation in the body, potentially leading to the loss of their intended function. Hydrogels sometimes fail to adequately regulate biological interactions and processes such as cell adhesion, proliferation, and differentiation.[78] In thick tissues, insufficient diffusion of nutrients, oxygen, and growth factors within the hydrogel can result in cell necrosis. Many hydrogels are not well-suited for bioprinting techniques due to difficulties in controlling their viscosity and structural stability. However, several solutions can also be proposed.[79] Combining hydrogels with nanoparticles, reinforcing polymers (such as polycaprolactone or nanocomposites), or using double-network hydrogels can improve mechanical strength.[80] Engineering hydrogels with controlled degradation using smart cross-linking mechanisms (such as enzyme – or pH sensitive polymer bonds) can enhance their longevity and controlled breakdown. Modifying the hydrogel surface with bioactive peptides (such as RGD sequences), incorporating growth factors, or applying bioactive coating can enhance cell adhesion and differentiation. Designing porous structures or integrating microchannels and smart delivery systems within hydrogels can improve nutrient and oxygen flow within the tissue.[81] Employing innovative techniques such as extrusion-based bioprinting, prepolymerized hydrogel printing, or hybrid natural-synthetic polymer combinations can enhance the precision and structural integrity of printed hydrogels.[82] The following subsections discuss other applications of hydrogels in tissue engineering.

4.3.1. Cell culture. Hydrogels play a very important role as three-dimensional scaffolds in cell culture for tissue engineering. Due to their structural similarity to the natural extracellular matrix, they provide an environment in which cells can grow, proliferate, and differentiate.[83] Hydrogels can recreate physical and chemical conditions like the internal environment of tissues, allowing cells to maintain their natural functions.[84] By adjusting stiffness, permeability, and other characteristics of hydrogels, optimal conditions for cell adhesion and growth can be achieved.[85] Hydrogels act as carriers for drugs or growth factors, enabling controlled delivery of these substances to the cells. The use of hydrogels in bioprinting makes it possible to fabricate complex three-dimensional structures that closely mimic the natural architecture of tissues.[86]

4.3.2. Stem cell studies. With their 3-D network structure and tunable mechanical properties-such as elastic modulus and network density-hydrogels can create a microenvironment like that of the native ECM. This feature greatly facilitates the study of cell–matrix interactions and the investigation of mechanosensitive responses in stem cells.[87] Through chemical engineering of the hydrogel surface and the incorporation of bioactive ligands such as the RGD peptide, it is possible to create adhesion sites for cellular adhesions (integrins). This enhances proliferation and directs signaling pathways related to differentiation.[88] Due to their capacity to retain biological molecules, hydrogels serve as effective systems for the controlled release of growth factors (such as BMP) and drugs. This sustained release creates signaling gradients within the three-dimensional environment that precisely guide stem cell differentiation pathways.[89] Fig. 6 demonstrates the impact of bone cells and hydrogels on the bone regeneration process.

4.3.3. Self-healing. Self-healing hydrogels are composed of polymer networks in which the bonds-whether hydrogen bonds, ionic bonds, or reversible covalent bonds are dynamically formed. As a result, if fractures or damage occur, these bonds rapidly reassemble, restoring the overall structure of the material.[90] Thanks to their self-healing ability, these hydrogels can be used as protective coatings for sensitive surfaces or in electronic components. In the event of scratches or cracks, the hydrogel automatically repairs the damages area, preventing the ingress of harmful agents into the system.[91] In flexible sensor systems and wearable devices that are frequently subjected to mechanical deformations like bending and compression, self-healing hydrogels help maintain long-term performance. Their rapid healing enhances the durability and stability of sensor functions.[92]

4.4. Diagnostics (imaging and sensing)

In biomedical imaging, hydrogels are utilized as carriers for imaging agents like fluorescent dyes, quantum dots, or contrast agents for magnetic resonance imaging (MRI) and computed tomography (CT). The high-water content of hydrogels allows for better compatibility with biological tissues, enabling clearer and more accurate imaging. Furthermore, hydrogels can be designed to release imaging agents in a controlled manner, improving the resolution of images over time or in response to specific stimuli.[93] Hydrogels can be designed to detect a wide range of biomarkers, including pathogens, glucose levels, or cancer biomarkers, facilitating real-time monitoring and diagnostics.[94] In some applications, hydrogels combine both biosensing and imaging functions. For example, a hydrogel may both sense a biomarker and release a fluorescent dye for real-time tracking and monitoring.[95] Hydrogels have many applications in biosensors due to their unique properties. One of the main advantages of hydrogels is their flexibility and biocompatibility, which allows them to interact easily with living tissues, making them ideal for use in biological environments.[96] Additionally, hydrogels can absorb and retain a large amount of water, which is beneficial for biosensors that operate in moist or

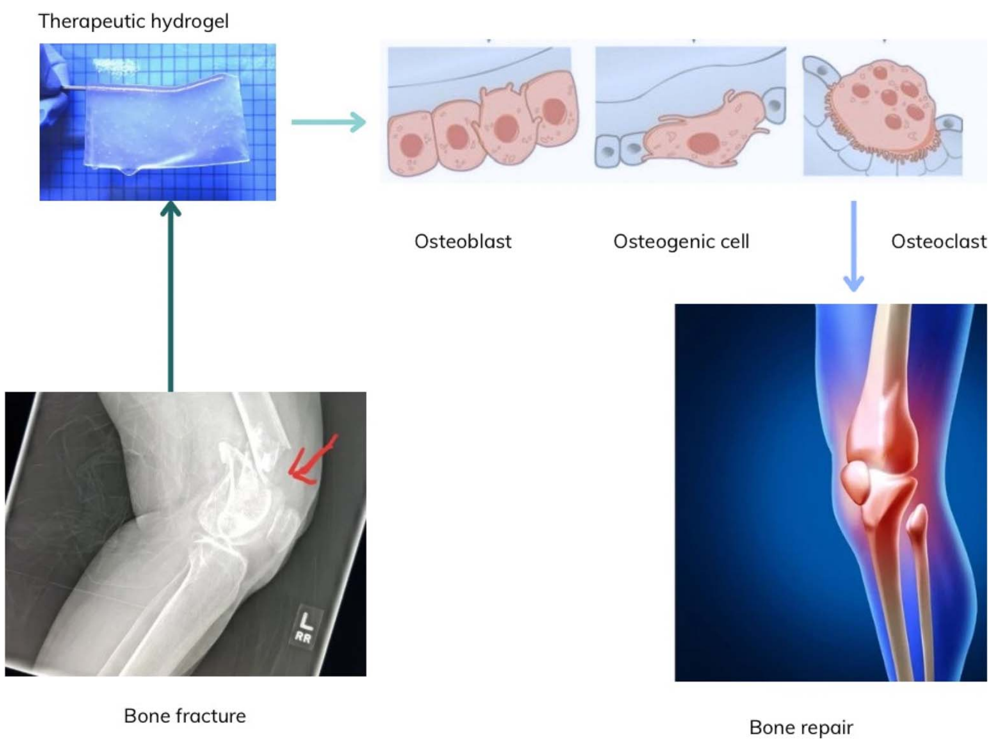

Fig. 6 A schematic illustration showing the involvement of bone cells and hydrogels in bone regeneration.

biological environments. Some hydrogels can also respond to environmental changes such as pH, temperature, or ions, making them suitable for use as active sensors in biosensors.[97] Furthermore, hydrogels can be molded into various shapes, which is advantageous for creating sensors with specific designs. They can also help with signal transmission in biosensors, enhancing sensor performance. However, hydrogels also have some drawbacks. One significant disadvantage is their low stability over time. Hydrogels may undergo structural changes due to environmental changes or the passage of time, which can affect the performance of the biosensor.[98] Additionally, hydrogels generally have weak mechanical properties and may be vulnerable to stretching or pressure, which can be problematic in applications requiring high mechanical strength. Hydrogels are also highly dependent on water, so they may not perform well in dry or low-moisture environments. The production cost of hydrogels may also be higher compared to other materials. To improve the performance of hydrogels in biosensors, several solutions can be considered. One solution is to enhance the mechanical structure of hydrogels.[99] This can be achieved by adding nanoparticles, reinforcing polymers, or fibers to the hydrogels. To improve performance in dry environments, special hydrogels with better water-retaining properties can be used, or they can be combined with other materials. Accurate shaping and molding of the hydrogels can also help improve their properties and the performance of biosensors. Additionally, engineering the surface of hydrogels can help modify their reactivity to different materials, increasing the sensitivity of the sensors.[100] Using smart hydrogels that respond to environmental changes can further improve biosensor performance. In conclusion, despite some drawbacks, hydrogels are considered one of the most promising materials for biosensors due to their numerous advantages. With further optimization, they can achieve better performance in various fields.[101]

5. Conclusion and future perspective

In summary, hydrogels have emerged as a cornerstone material in biomedical engineering, owing to their unique combination of water retention, biocompatibility, and flexibility. These properties make them highly effective for a wide range of applications, from drug delivery systems and wound healing to tissue engineering and prosthetic devices. Recent advances in hydrogel technology, particularly in the development of responsive and functionalized hydrogels, have further expanded their potential in addressing complex medical challenges. The ability of hydrogels to mimic natural biological tissues and respond to environmental stimuli allows for more effective and personalized treatment options, enhancing patient outcomes. Moreover, the integration of hydrogels with advanced techniques such as 3D printing and nanotechnology has opened new frontiers for regenerative medicine and implantable devices. Ultimately, hydrogels are poised to play an even more pivotal role in the future of biomedical engineering. Their versatility and adaptability make them indispensable for developing next-generation therapeutic solutions and medical technologies. As research continues to advance, hydrogels will undoubtedly drive innovations that improve the quality of healthcare and redefine the possibilities of medical treatments.

One of the most significant advancements discussed is the use of microfluidic technology for the controlled preparation of hydrogels. This technology allows for the precise manipulation of fluid flow to create hydrogels with uniform size and shape at a microscale level. Microfluidic devices can precisely control parameters such as polymer concentration, cross-linking conditions, and particle size, leading to more consistent and reproducible hydrogel properties. The microfluidic system enables rapid and scalable production of hydrogels, which is essential for large-scale applications in drug delivery.[102] Another important aspect is hydrogel-based electrochemical biosensors. Hydrogel-based wearable electrochemical biosensors have gained significant attention in recent years due to their potential to revolutionize real-time health monitoring, particularly in the context of wearable devices. These sensors leverage the unique properties of hydrogels, which are water-swollen, biocompatible polymers, to interact with biofluids like sweat, interstitial fluid and saliva. When combined with electrochemical detection mechanisms, they offer a non-invasive, continuous and real-time way to monitor biomarkers associated with various health conditions.[103] Another recent advancement has led to the development of smart hydrogels that can monitor wound conditions in real-time. These hydrogels are integrated with sensors that detect PH, temperature, glucose levels, or infection markers in the wound. For diabetic patients, monitoring glucose levels is crucial, as elevated blood glucose can impend the healing process. Smart hydrogels equipped with sensors can provide continuous data to healthcare providers, enabling more personalized and effective wound management. Additionally, these sensors are often coupled with wireless communication technologies, allowing remote monitoring, which is especially useful for patients with limited mobility or access to healthcare facilities.[104] Recent research has focused on enhancing the bioactivity of hydrogels to promote tissue healing and regeneration. Bioactive hydrogels, such as those incorporating growth factors, bioactive peptides, or small molecules, can stimulate the proliferation and differentiation of dental pulp stem cells (DPSCs). These bioactive components play a key role in guiding cell behavior, promoting angiogenesis, and enhancing pulp tissue regeneration. For instance, hydrogels containing factors like BMP-2 (Bone Morphogenetic Protein 2) and VEGF (Vascular Endothelial Growth Factor) have shown potential in supporting vascularization and dentin-pulp complex regeneration. The development of 3D printing technologies has revolutionized the design of hydrogel scaffolds for tissue engineering. 3D bioprinting allows for the precise fabrication of scaffolds with complex geometries that can more accurately mimic the structure of native pulp tissue. By using hydrogels as the printing bioink, researchers can create scaffolds that promote cellular infiltration, vascularization, and proper tissue organization. This approach enables the creation of highly customized scaffolds tailored to specific patient needs in dental pulp regeneration.[105] Nanocomposite hydrogels can serve as soft actuators and sensors in soft robots. These materials can be used to create flexible and responsive robots capable of performing precise tasks in unstructured environments, such as healthcare, agriculture, or disaster relief. Future research may focus on integrating these hydrogels into bio-inspired robots or prosthetics to achieve more natural movement and better control. Additionally, the development of nanocomposite hydrogels for 3D printing is growing and can be applied in tissue engineering, organ regeneration, and prosthetic development. By combining the biocompatibility of hydrogels with the structural strength of nanoparticles, these materials can be used to create precise and efficient structures for medical applications. Recent advancements in nanocomposite hydrogels indicate that these materials have high potential for applications beyond traditional uses. From medicine and the environment to energy storage, smart textiles, and food packaging, these materials are transforming many industries. However, to fully realize their potential, further research is needed to optimize their properties, scale up production, and understand their interactions in complex systems. The future of nanocomposite hydrogels is promising, offering innovative opportunities across various fields.[106]

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Acknowledgements

We express our sincere appreciation to the Islamic Azad University, Amirkabir University of Technology, and the Pharmaceutical Analysis Research Center at Tabriz University of Medical Sciences, Tabriz, Iran (78783) for their significant support and critical contributions to this research endeavor. Their essential contributions to this work were invaluable.

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