RECENT ADVANCES IN HYDROGEL TECHNOLOGY: FROM SYNTHESIS TO CLINICAL APPLICATIONS

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Abstract

Hydrogels are three-dimensional hydrophilic polymeric networks known for their high water absorption capacity, biocompatibility, biodegradability, and resemblance to the natural extracellular matrix, making them highly valuable in pharmaceutical and biomedical applications. Recent advances in polymer science, nanotechnology, and bioengineering have led to the development of smart, injectable, self-healing, and nanocomposite hydrogels with improved mechanical strength and stimuli-responsive behavior. These advanced hydrogel systems have shown significant potential in controlled drug delivery, wound healing, tissue engineering, regenerative medicine, cancer therapy, and ophthalmic applications. Emerging fabrication technologies such as 3D/4D bioprinting, microfluidics, and electrospinning have further enhanced the design and functionality of hydrogel-based systems. Despite promising progress, challenges related to scalability, long-term stability, sterilization, and clinical translation still remain. This review highlights recent advances in hydrogel synthesis, characterization, biomedical applications, clinical developments, and future perspectives, emphasizing the growing importance of hydrogels as next-generation biomaterials in modern healthcare.

Keywords: *Hydrogels, Smart hydrogels, Stimuli-responsive hydrogels, Biomaterials, Nanocomposite hydrogels,*

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1. INTRODUCTION

Hydrogels are three-dimensional hydrophilic polymeric networks capable of absorbing and retaining substantial amounts of water or biological fluids while maintaining their structural integrity. Since their initial development, hydrogels have attracted considerable attention in pharmaceutical, biomedical, and tissue engineering fields because of their unique physicochemical properties, including high water content, flexibility, biocompatibility, biodegradability, and structural resemblance to natural extracellular matrix (ECM). These characteristics make hydrogels highly suitable for a wide range of applications such as controlled drug delivery, wound healing, regenerative medicine, biosensing, and tissue engineering (Ahmed, 2015).

The advancement of polymer science and biomaterials engineering has significantly transformed conventional hydrogels into multifunctional and stimuli-responsive systems with enhanced therapeutic performance. Modern hydrogel technologies incorporate smart responsiveness to environmental stimuli such as pH, temperature, enzymes, light, and magnetic fields, enabling site-specific and controlled therapeutic delivery. In addition, recent developments in nanotechnology, 3D/4D bioprinting, microfabrication, and bioactive material integration have further expanded the biomedical potential of hydrogel systems. These innovations have led to the emergence of injectable, self-healing, nanocomposite, and supramolecular hydrogels capable of mimicking native tissue microenvironments and supporting complex biological functions (Koetting et al., 2015).

Hydrogels have demonstrated remarkable clinical significance in several medical fields. In drug delivery, they enable sustained and targeted release of therapeutic agents while minimizing systemic toxicity and improving patient compliance. In regenerative medicine and tissue engineering, hydrogel scaffolds provide supportive matrices for cell growth, stem cell delivery, and tissue regeneration. Furthermore, hydrogel-based systems are increasingly explored in cancer therapy, ophthalmology, cardiovascular repair, antimicrobial applications, and biosensing technologies. The integration of bioactive molecules, nanoparticles, and growth factors within hydrogel matrices has further enhanced their therapeutic efficacy and functional versatility (Li & Mooney, 2016).

Despite substantial progress, several challenges continue to limit the widespread clinical translation of hydrogel technologies. Issues related to mechanical weakness, long-term stability, sterilization, reproducibility, scalability, and regulatory approval remain major concerns. Additionally, achieving an optimal balance between biodegradability, biocompatibility, and responsiveness remains a significant challenge for researchers and clinicians. Continuous efforts are therefore being directed toward the development of advanced hydrogel systems with improved mechanical performance, multifunctionality, and clinical adaptability (Caló & Khutoryanskiy, 2015).

This review aims to provide a comprehensive overview of recent advances in hydrogel technology, focusing on synthesis approaches, classification, characterization, and emerging biomedical applications. The review also highlights current innovations in smart and stimuli-responsive hydrogels, hydrogel-based regenerative medicine, clinical translation, and future perspectives, thereby emphasizing the growing importance of hydrogels as next-generation biomaterials in modern healthcare and pharmaceutical sciences.

2. Fundamentals of Hydrogels

Hydrogels are three-dimensional hydrophilic polymeric networks capable of absorbing and retaining large amounts of water or biological fluids without dissolving due to the presence of physical or chemical crosslinks within their structure. Their unique properties arise from hydrophilic functional groups such as hydroxyl (-OH), carboxyl (-COOH), amine ($-NH_2$), and sulfonic ($-SO_3H$) groups that strongly interact with water molecules, resulting in high swelling capacity and soft, elastic, tissue-like consistency (Hoffman, 2012; Peppas et al., 2000). Structurally, hydrogels consist of interconnected polymer chains forming a porous and hydrated network, where the mesh size and crosslink density regulate water uptake, diffusion of bioactive molecules, mechanical strength, degradation behavior, and drug release kinetics. Owing to their high water content and structural similarity to the natural extracellular matrix (ECM), hydrogels exhibit excellent biocompatibility and have become highly promising materials for biomedical applications including drug delivery, tissue engineering, wound healing, and regenerative medicine (Caló & Khutoryanskiy, 2015; Drury & Mooney, 2003).

Classification of Hydrogels

Hydrogels can be classified based on their source, crosslinking mechanism, and responsiveness. Based on source, they are categorized into natural, synthetic, and hybrid hydrogels. Natural hydrogels such as alginate, chitosan, and gelatin exhibit excellent biocompatibility and biodegradability, whereas synthetic hydrogels like PEG, PVA, and PAAm provide better mechanical strength and reproducibility. Hybrid hydrogels combine both natural and synthetic polymers to achieve improved biofunctionality and stability (Li & Mooney, 2016; Hoffman, 2012). Based on crosslinking, hydrogels are classified as physically or chemically crosslinked systems. Physical hydrogels are formed through reversible non-covalent interactions, while chemical hydrogels involve covalent bonding that provides greater structural stability (Ahmed, 2015; Peppas et al., 2000). Additionally, hydrogels may be conventional or stimuli-responsive (smart) systems that respond to environmental triggers such as pH, temperature, light, or enzymes, enabling controlled drug release and targeted therapeutic applications (Hoffman, 2012; Li & Mooney, 2016).

Key Physicochemical Properties of Hydrogels

Swelling Behavior

Swelling is the most important characteristic of hydrogels and is governed by the diffusion of water into the polymer network followed by relaxation of polymer chains. Swelling depends on crosslink density, polymer hydrophilicity, pH, ionic strength, and temperature. Highly crosslinked hydrogels exhibit lower swelling due to restricted chain mobility, whereas loosely crosslinked systems show higher water uptake. Swelling behavior directly influences drug loading and release profiles (Peppas et al., 2000; Caló & Khutoryanskiy, 2015).

Porosity

Hydrogel porosity refers to the presence of interconnected void spaces within the polymer network. It plays a crucial role in regulating the diffusion of drugs, nutrients, and metabolites. Higher porosity enhances mass transfer and cellular infiltration, making hydrogels suitable for tissue engineering and regenerative medicine applications (Drury & Mooney, 2003).

Mechanical Strength

Mechanical properties of hydrogels determine their ability to withstand deformation without structural failure. These properties depend on polymer composition, crosslink density, and network architecture. While natural hydrogels often exhibit weak mechanical strength, synthetic and nanocomposite hydrogels can be engineered to achieve higher stiffness and elasticity suitable for load-bearing applications such as cartilage and bone regeneration (Li & Mooney, 2016).

Biocompatibility

Biocompatibility is a critical requirement for biomedical applications. Hydrogels are generally considered biocompatible due to their high water content and soft tissue-like nature, which minimizes protein adsorption and immune response. However, biocompatibility depends on polymer purity, degradation products, and crosslinking chemistry. Natural polymer-based hydrogels often exhibit superior biocompatibility compared to synthetic systems (Hoffman, 2012; Ahmed, 2015).

Table 1. Classification of Hydrogels Based on Source, Crosslinking, and Responsiveness

Classification Basis	Type of Hydrogel	Key Characteristics	Major Applications

Based on Source	Natural Hydrogels	Biocompatible, biodegradable	Wound healing, tissue engineering
	Synthetic Hydrogels	High mechanical strength, tunable properties	Drug delivery, implants
	Hybrid Hydrogels	Combination of natural and synthetic polymers	Regenerative medicine
Based on Crosslinking	Physical Hydrogels	Reversible interactions, no toxic agents	Injectable systems
	Chemical Hydrogels	Covalent bonding, stable structure	Controlled drug release
Based on Responsiveness	pH-responsive	Swelling changes with pH	Oral drug delivery
	Temperature-responsive	Sol-gel transition with temperature	Injectable hydrogels
	Enzyme-responsive	Degrades in presence of enzymes	Cancer therapy
	Light-responsive	Triggered by UV/NIR light	Ophthalmology, phototherapy

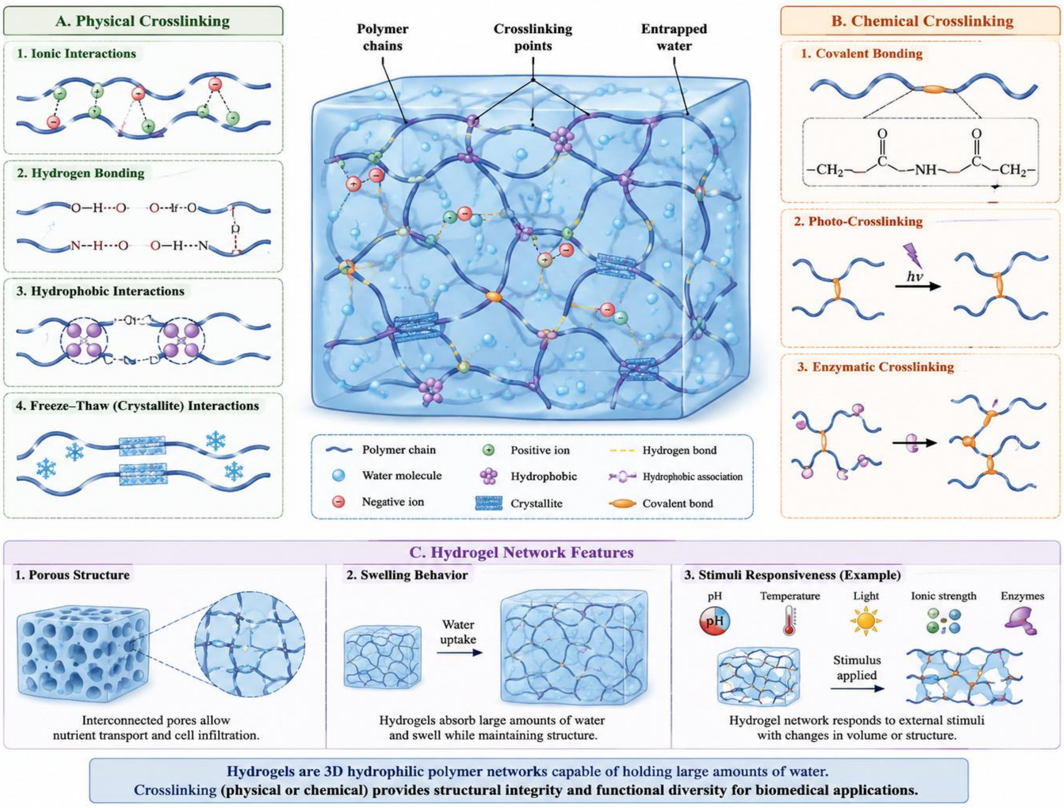

Figure 1. Schematic Representation of Hydrogel Structure and Crosslinking Mechanisms

3. Hydrogel Synthesis Approaches

The synthesis of hydrogels involves the formation of a three-dimensional polymeric network through physical or chemical crosslinking of hydrophilic polymers. The choice of synthesis method significantly influences the structural integrity, mechanical strength, swelling behavior, degradation rate, and overall biomedical performance of hydrogels. Broadly, hydrogel fabrication techniques are classified into physical crosslinking methods, chemical crosslinking methods, and advanced fabrication approaches based on modern engineering technologies (Ahmed, 2015; Hoffman, 2012).

3.1 Physical Crosslinking Methods

Physical crosslinking involves non-covalent interactions between polymer chains, resulting in reversible and often stimuli-responsive hydrogel networks. These methods are widely preferred for biomedical applications due to their simplicity and absence of toxic crosslinking agents.

Ionic Interactions

Ionic crosslinking occurs when oppositely charged polymers interact to form a gel network. A classic example is the gelation of sodium alginate in the presence of divalent cations such as Ca^{2+}, which create an "egg-box" structure. These hydrogels are widely used in drug delivery and wound healing due to their mild preparation conditions and biocompatibility (Lee & Mooney, 2012).

Hydrogen Bonding

Hydrogen-bonded hydrogels are formed through interactions between polar functional groups such as -OH, -COOH, and $-NH_2$. These interactions are weak but reversible, enabling self-healing and stimuli-responsive behavior. Polyvinyl alcohol (PVA)-based hydrogels often rely on hydrogen bonding for network formation (Peppas et al., 2000).

Hydrophobic Interactions

Hydrophobic association occurs when hydrophobic segments of amphiphilic polymers aggregate in aqueous media, forming physical crosslinks. These interactions contribute to the formation of thermoreversible gels and injectable hydrogel systems (Caló & Khutoryanskiy, 2015).

Freeze-Thaw Technique

The freeze-thaw method involves repeated freezing and thawing cycles of polymer solutions such as PVA, leading to crystallite formation that acts as physical crosslinking points. This method eliminates the need for chemical crosslinkers and produces mechanically stable hydrogels suitable for biomedical applications (Hoffman, 2012).

3.2 Chemical Crosslinking Methods

Chemical crosslinking involves the formation of covalent bonds between polymer chains, resulting in stable, durable, and mechanically robust hydrogel networks. These methods are widely used in controlled drug delivery and tissue engineering applications.

Free Radical Polymerization

Free radical polymerization is one of the most widely used techniques for hydrogel synthesis. Monomers such as acrylamide or acrylic acid are polymerized in the presence of initiators (ammonium persulfate) and crosslinkers (N,N'-methylenebisacrylamide). This method allows precise control over network density and mechanical properties (Peppas et al., 2000).

Covalent Crosslinking Agents

Chemical crosslinkers such as glutaraldehyde, carbodiimide, and genipin are used to form stable covalent bonds between polymer chains. These hydrogels exhibit enhanced mechanical strength and reduced solubility, making them suitable for long-term biomedical applications (Ahmed, 2015).

Graft Polymerization

Graft polymerization involves the attachment of polymer chains onto a backbone polymer, resulting in hybrid structures with improved functionality. This technique is widely used to modify natural polymers such as chitosan and cellulose for enhanced performance (Li & Mooney, 2016).

Click Chemistry Approaches

Click chemistry involves highly efficient and selective reactions such as azide-alkyne cycloaddition. These reactions allow the formation of well-defined hydrogel networks under mild conditions, making them highly suitable for biomedical and injectable hydrogel systems (Fairbanks et al., 2009).

3.3 Advanced Fabrication Techniques

Recent advances in material science and bioengineering have enabled the development of highly precise and multifunctional hydrogel systems using advanced fabrication technologies.

3D/4D Bioprinting

3D bioprinting enables layer-by-layer fabrication of hydrogel scaffolds with precise control over architecture, porosity, and cell distribution. 4D bioprinting introduces time-dependent shape transformation in response to stimuli, enhancing applications in tissue engineering and regenerative medicine (Murphy & Atala, 2014).

Microfluidic Synthesis

Microfluidic techniques allow controlled fabrication of hydrogel microstructures with uniform size and shape. This approach is particularly useful for drug encapsulation, cell encapsulation, and production of microspheres with high reproducibility (Whitesides, 2006).

Electrospinning-Based Hydrogels

Electrospinning produces nanofibrous hydrogel scaffolds that mimic the extracellular matrix. These nanostructures enhance cell adhesion, proliferation, and nutrient transport, making them ideal for wound healing and tissue engineering (Li et al., 2013).

Photopolymerization Techniques

Photopolymerization uses UV or visible light to initiate polymer crosslinking in the presence of photoinitiators. This method allows spatial and temporal control over hydrogel formation and is widely used in minimally invasive biomedical applications such as in situ gel formation (Fairbanks et al., 2009).

4. Types of Advanced Hydrogels

Advanced hydrogels are engineered polymeric networks designed to exhibit multifunctional behavior such as environmental responsiveness, self-repair, injectability, and enhanced mechanical performance. These systems go beyond conventional hydrogels by integrating smart molecular design, nanotechnology, and dynamic bonding strategies, making them highly suitable for modern biomedical and pharmaceutical applications (Appel et al., 2015; Li et al., 2018).

Stimuli-Responsive Hydrogels

Stimuli-responsive hydrogels (smart hydrogels) are materials that undergo reversible changes in swelling, structure, or sol-gel transition in response to external or internal stimuli. These include pH, temperature, light, and enzymatic triggers, enabling precise spatiotemporal control of drug release and biological interactions.

pH-Sensitive Hydrogels

pH-sensitive hydrogels contain weak acidic or basic functional groups that ionize depending on environmental pH. This ionization alters electrostatic repulsion within the polymer network, leading to swelling or deswelling behavior. Such systems are widely explored for oral drug delivery and tumor-targeted therapy due to pH variations in the gastrointestinal tract and tumor microenvironment (Qiu & Park, 2012).

Temperature-Sensitive Hydrogels

Temperature-responsive hydrogels exhibit phase transition behavior at a specific critical solution temperature. Polymers such as poly(N-vinylcaprolactam) (PVCL) and poloxamers undergo sol-gel transitions near physiological temperature, making them highly suitable for injectable and in situ gelling drug delivery systems (Buwalda et al., 2014).

Light-Responsive Hydrogels

Light-sensitive hydrogels utilize photo-cleavable or photo-crosslinkable groups that respond to UV or visible light irradiation. These systems allow remote and precise control of gelation and drug release, making them useful in phototherapy, tissue engineering, and minimally invasive treatments (Kloxin et al., 2010).

Enzyme-Responsive Hydrogels

Enzyme-responsive hydrogels are designed to degrade or swell in the presence of specific enzymes such as matrix metalloproteinases (MMPs). These enzymes are often overexpressed in pathological conditions like cancer and inflammation, enabling highly selective drug release (Wang et al., 2017).

Nanocomposite Hydrogels

Nanocomposite hydrogels incorporate inorganic or organic nanomaterials such as silica nanoparticles, carbon nanotubes, nanoclay, or metallic nanoparticles into polymeric matrices. These nanofillers significantly enhance mechanical strength, thermal stability, and biological functionality while also improving drug loading capacity and controlled release behavior. Additionally, they can introduce multifunctional properties such as antibacterial or imaging capabilities (Haraguchi & Takehisa, 2002; Gaharwar et al., 2014).

Interpenetrating Polymer Network (IPN) Hydrogels

IPN hydrogels consist of two or more independent polymer networks physically interlaced without covalent bonding between them. This architecture significantly improves toughness, elasticity, and resistance to deformation. IPNs are particularly useful in drug delivery systems requiring prolonged release and mechanical stability under physiological stress conditions (Sperling, 2005).

Supramolecular Hydrogels

Supramolecular hydrogels are formed through reversible non-covalent interactions such as host-guest interactions, π-π stacking, hydrogen bonding, and metal-ligand coordination. These dynamic interactions provide self-assembly and stimuli-responsiveness, enabling adaptive and reversible material behavior suitable for regenerative medicine and drug delivery applications (Webber et al., 2016).

Self-Healing Hydrogels

Self-healing hydrogels possess the ability to autonomously repair structural damage through reversible covalent bonds or dynamic physical interactions. Mechanisms include Schiff base formation, disulfide exchange, hydrogen bonding, and ionic interactions. These systems are particularly valuable in wound healing, soft robotics, and implantable biomaterials where long-term durability is essential (Hager et al., 2010).

Injectable Hydrogels

Injectable hydrogels are liquid formulations that undergo in situ gelation after administration through minimally invasive injection. Gelation may be triggered by temperature, pH, ionic strength, or enzymatic reactions. These systems are widely used for localized drug delivery, cell encapsulation, and tissue regeneration due to their ease of administration and reduced surgical intervention (Lee et al., 2015).

5. Characterization of Hydrogels

The characterization of hydrogels is essential to understand their structural integrity, physicochemical behavior, and suitability for biomedical and pharmaceutical applications. Since hydrogels are highly hydrated polymeric networks, their performance is governed by swelling behavior, mechanical properties, microstructure, and chemical composition. A combination of analytical, mechanical, and thermal techniques is therefore employed to evaluate their functional characteristics (Peppas et al., 2000; Hoffman, 2012).

Swelling Ratio and Equilibrium Swelling Studies

Swelling behavior is one of the most critical parameters of hydrogels, reflecting their ability to absorb and retain water or biological fluids. The swelling ratio is typically determined by immersing a dry hydrogel in a swelling medium and measuring weight gain over time until equilibrium is reached. At equilibrium, the rate of solvent diffusion into the polymer network equals the rate of polymer relaxation. Swelling is influenced by crosslink density, polymer hydrophilicity, pH, temperature, and ionic strength. Highly crosslinked networks exhibit lower swelling due to restricted chain mobility, while loosely crosslinked hydrogels show higher fluid uptake (Li & Mooney, 2016; Peppas et al., 2000).

Rheological Analysis

Rheological characterization evaluates the flow and deformation behavior of hydrogels under applied stress. Parameters such as viscosity, storage modulus (G'), and loss modulus (G'') are determined using a rheometer. These measurements provide insight into gel strength, viscoelastic behavior, and injectability. A predominance of storage modulus over loss modulus indicates a solid-like elastic structure, which is important for maintaining integrity under physiological conditions (Rao, 2014).

Mechanical Testing (Tensile/Compressive Strength)

Mechanical testing assesses the ability of hydrogels to withstand external forces without structural failure. Tensile strength measures resistance to stretching, while compressive strength evaluates resistance to deformation under pressure. These properties are crucial for load-bearing applications such as cartilage and bone tissue engineering. Mechanical performance depends on polymer composition, crosslink density, and the presence of reinforcing agents such as nanofillers (Annabi et al., 2014).

Morphological Analysis (SEM, TEM)

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are widely used to study hydrogel microstructure. SEM provides surface morphology and pore structure analysis, while TEM offers detailed internal network visualization at the nanoscale. These techniques help determine pore size distribution, connectivity, and network homogeneity, which directly influence drug diffusion and cell infiltration (Drury & Mooney, 2003).

Thermal Analysis (DSC, TGA)

Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) are used to evaluate thermal stability and phase transitions of hydrogels. DSC provides information on glass transition temperature (Tg), melting behavior, and polymer-drug interactions, while TGA measures weight loss as a function of temperature, indicating thermal degradation patterns. These analyses are critical for assessing stability during processing and storage (Ahmed, 2015).

Chemical Characterization (FTIR, NMR)

Fourier Transform Infrared Spectroscopy (FTIR) is used to identify functional groups and confirm chemical interactions between polymer chains and incorporated drugs. Shifts in characteristic peaks may indicate hydrogen bonding or covalent crosslink formation. Nuclear Magnetic Resonance (NMR) spectroscopy provides detailed structural information at the molecular level, confirming polymer backbone integrity and crosslinking chemistry (Hennink & van Nostrum, 2012).

Porosity and Degradation Studies

Porosity analysis evaluates the void fraction within hydrogel networks, which influences nutrient diffusion, cell migration, and drug release behavior. Methods such as liquid displacement and mercury intrusion porosimetry are commonly used. Degradation studies assess hydrogel stability over time under physiological conditions, typically involving enzymatic or hydrolytic breakdown. Controlled degradation is essential for temporary scaffolds in tissue engineering and drug delivery systems (Li & Mooney, 2016; Drury & Mooney, 2003).

6. Drug Delivery Applications of Hydrogels

Hydrogels have emerged as highly versatile drug delivery platforms due to their tunable physicochemical properties, high water content, biocompatibility, and ability to encapsulate a wide range of therapeutic agents. Their three-dimensional polymeric networks enable controlled diffusion of drugs, protection of labile biomolecules, and targeted delivery to specific tissues. Recent advancements in polymer chemistry and nanotechnology have further expanded their applications in controlled, site-specific, and stimuli-responsive drug delivery systems (Langer & Peppas, 2003; Hoffman, 2012).

Controlled and Sustained Drug Release Systems

Hydrogels are widely used to achieve controlled and sustained release of drugs by regulating diffusion through their polymeric network. Drug release is influenced by swelling behavior, crosslink density, and polymer degradation. These systems reduce dosing frequency, improve therapeutic efficacy, and minimize systemic side effects. Both diffusion-controlled and erosion-controlled mechanisms are commonly exploited in hydrogel-based delivery platforms (Peppas et al., 2000; Siepmann & Siepmann, 2008).

Site-Specific Drug Delivery

Site-specific delivery systems utilize environmental triggers such as pH, enzymes, or temperature to release drugs at targeted locations. For example, pH-sensitive hydrogels release drugs in the acidic tumor microenvironment or alkaline intestinal tract. Enzyme-responsive systems enhance targeting in inflamed or cancerous tissues where specific enzymes are overexpressed. This improves drug concentration at the desired site while reducing systemic toxicity (Qiu & Park, 2012; Li & Mooney, 2016).

Protein and Peptide Delivery

Hydrogels are particularly suitable for the delivery of proteins and peptides due to their mild fabrication conditions and ability to maintain biological activity. They protect biomolecules from enzymatic degradation and denaturation while enabling sustained release. Injectable hydrogel systems are often used for growth factors, insulin, and vaccine delivery, improving pharmacokinetic profiles and therapeutic outcomes (Lee & Mooney, 2012; Van Tomme & Hennink, 2007).

Gene Delivery Systems

Hydrogels provide a protective and localized environment for gene delivery, enabling controlled release of DNA, RNA, or plasmid vectors. Cationic hydrogels can electrostatically interact with negatively charged nucleic acids, enhancing cellular uptake and transfection efficiency. These systems are being explored in gene therapy for cancer, genetic disorders, and regenerative medicine applications (Pack et al., 2005; Kim & Langer, 2008).

Transdermal Drug Delivery

Hydrogels are extensively used in transdermal systems due to their excellent skin compatibility, high hydration capacity, and ability to enhance drug permeation. They maintain skin moisture, improve drug solubility, and provide a reservoir for sustained release. Incorporation of permeation enhancers or nanoparticles further improves drug penetration through the stratum corneum (Brown et al., 2006).

Ophthalmic Drug Delivery

Hydrogel-based formulations are highly suitable for ocular drug delivery due to their mucoadhesive properties and ability to increase precorneal residence time. In situ gelling hydrogels transform from liquid to gel upon contact with tear fluid, enhancing drug bioavailability and reducing dosing frequency. They are widely explored for the treatment of glaucoma, conjunctivitis, and dry eye syndrome (Liu et al., 2010).

Oral and Buccal Hydrogel Systems

Hydrogels are increasingly used in oral and buccal drug delivery systems due to their ability to adhere to mucosal surfaces and provide controlled release in the gastrointestinal tract. Mucoadhesive hydrogels prolong residence time, improve drug absorption, and bypass first-pass metabolism. These systems are particularly useful for peptides, antihypertensives, and anti-inflammatory drugs (Peppas et al., 2000; Andrews et al., 2009).

7. Biomedical and Clinical Applications

Hydrogels have gained substantial importance in biomedical and clinical fields due to their high water content, tunable mechanical properties, biocompatibility, and structural resemblance to the extracellular matrix (ECM). Their ability to encapsulate cells, biomolecules, and therapeutic agents while providing controlled release and localized delivery has enabled broad applications in tissue engineering, regenerative medicine, oncology, wound management, and ophthalmology. Recent advances in smart and bioactive hydrogel systems have further accelerated their translation into clinical and commercial applications (Slaughter et al., 2009; Seliktar, 2012).

Wound Healing and Tissue Regeneration

Hydrogels are extensively used in wound healing applications because they maintain a moist environment, facilitate oxygen permeability, absorb wound exudates, and promote tissue regeneration. Their soft and elastic structure minimizes tissue irritation and supports cellular migration and proliferation. Advanced hydrogel dressings can also incorporate antimicrobial agents, growth factors, or nanoparticles to accelerate healing and prevent infection. Injectable and self-healing hydrogels have shown particular promise in chronic wound management and burn treatment (Boateng et al., 2008; Dhivya et al., 2015).

Hydrogels also play a critical role in tissue regeneration by serving as temporary scaffolds that mimic the ECM and support cell adhesion, proliferation, and differentiation. Biodegradable hydrogels gradually degrade as new tissue forms, making them highly suitable for regenerative therapies (O'Brien, 2011).

Cartilage and Bone Tissue Engineering

Cartilage and bone tissues possess limited self-repair capability, creating a significant need for biomaterial-based regenerative approaches. Hydrogels provide a three-dimensional environment that supports chondrocyte and osteoblast growth while enabling nutrient and oxygen diffusion. In cartilage engineering, hydrogels such as gelatin methacrylate (GelMA) and hyaluronic acid-based systems are widely investigated due to their ability to mimic native cartilage ECM (Huey et al., 2012).

For bone tissue engineering, hydrogels are often combined with bioactive ceramics such as hydroxyapatite or bioactive glass to improve osteoconductivity and mechanical strength. These composite scaffolds support bone mineralization and enhance stem cell differentiation toward osteogenic lineages (Gaharwar et al., 2014).

Cardiac Tissue Repair

Cardiovascular diseases remain a leading cause of mortality worldwide, and hydrogels have emerged as promising materials for cardiac tissue repair following myocardial infarction. Injectable hydrogels can be delivered directly into damaged myocardium to provide mechanical support, reduce ventricular remodeling, and improve cell retention. Additionally, conductive hydrogels containing graphene or gold nanoparticles facilitate electrical signal transmission, enhancing synchronization of cardiac cells (Zhu et al., 2016).

Hydrogels are also being explored as carriers for stem cells, growth factors, and angiogenic molecules to stimulate neovascularization and myocardial regeneration (Tous et al., 2011).

Cancer Therapy and Tumor Targeting

Hydrogel-based systems have attracted significant attention in cancer therapy due to their ability to provide localized and sustained delivery of chemotherapeutic agents. Injectable hydrogels can be administered directly into tumor sites, minimizing systemic toxicity and improving drug concentration at the target location. Stimuli-responsive hydrogels further enhance targeting efficiency by releasing drugs in response to pH, temperature, or enzymatic conditions specific to the tumor microenvironment (Bae & Park, 2011).

In addition to chemotherapy, hydrogels are increasingly utilized in immunotherapy and combination therapies involving nanoparticles, photothermal agents, and gene delivery systems to improve therapeutic outcomes (Hoare & Kohane, 2008).

Ophthalmology Applications

Hydrogels have become highly important in ophthalmic applications because of their transparency, flexibility, oxygen permeability, and biocompatibility. Hydrogel-based contact lenses and ocular inserts are widely used for sustained delivery of antibiotics, anti-inflammatory drugs, and glaucoma medications. In situ gelling hydrogels improve precorneal retention time and enhance ocular bioavailability compared to conventional eye drops (Wichterle & Lim, 1960).

Hydrogels are also being explored for corneal regeneration and retinal tissue engineering due to their ability to mimic the hydrated structure of ocular tissues (Ludwig, 2005).

Anti-Infective Applications

Hydrogels containing antimicrobial agents, metallic nanoparticles, peptides, or antibiotics have demonstrated significant potential in preventing and treating microbial infections. These systems provide prolonged local release of antimicrobial compounds, reducing the need for systemic therapy and minimizing drug resistance. Silver nanoparticle-loaded hydrogels, for example, exhibit strong antibacterial activity against both Gram-positive and Gram-negative bacteria (Franci et al., 2015).

Anti-infective hydrogels are widely investigated for wound dressings, implant coatings, and post-surgical infection prevention due to their combined barrier and therapeutic functions.

Regenerative Medicine Applications

Hydrogels are considered one of the most promising biomaterials in regenerative medicine because they can closely replicate the native ECM environment. They support stem cell encapsulation, differentiation, and tissue-specific regeneration while enabling controlled delivery of growth factors and signaling molecules. Advanced hydrogels with bioactive ligands and dynamic mechanical properties are being developed for regeneration of skin, neural tissue, liver, and vascular systems (Place et al., 2009).

The integration of stem cell technology, bioprinting, and smart hydrogels is expected to revolutionize future regenerative therapies and personalized medicine approaches.

Table 2. Biomedical and Clinical Applications of Hydrogels

Application	Hydrogel Type	Therapeutic Role	Example

Area			
Drug Delivery	Stimuli-responsive hydrogels	Controlled and targeted release	pH-sensitive oral systems
Wound Healing	Hydrogel dressings	Moist environment and tissue repair	Alginate hydrogel
Tissue Engineering	Injectable hydrogels	Scaffold for cell growth	Collagen hydrogel
Cancer Therapy	Nanocomposite hydrogels	Localized chemotherapy	Thermosensitive injectable gels
Ophthalmology	In situ gelling hydrogels	Sustained ocular delivery	HEMA hydrogels
Regenerative Medicine	ECM-mimicking hydrogels	Stem cell support and regeneration	Gelatin-based scaffolds
Bone/Cartilage Repair	Self-healing hydrogels	Structural and mechanical support	Chitosan composite gels
Antimicrobial Therapy	Silver nanoparticle hydrogels	Infection control	AgNP-loaded hydrogels

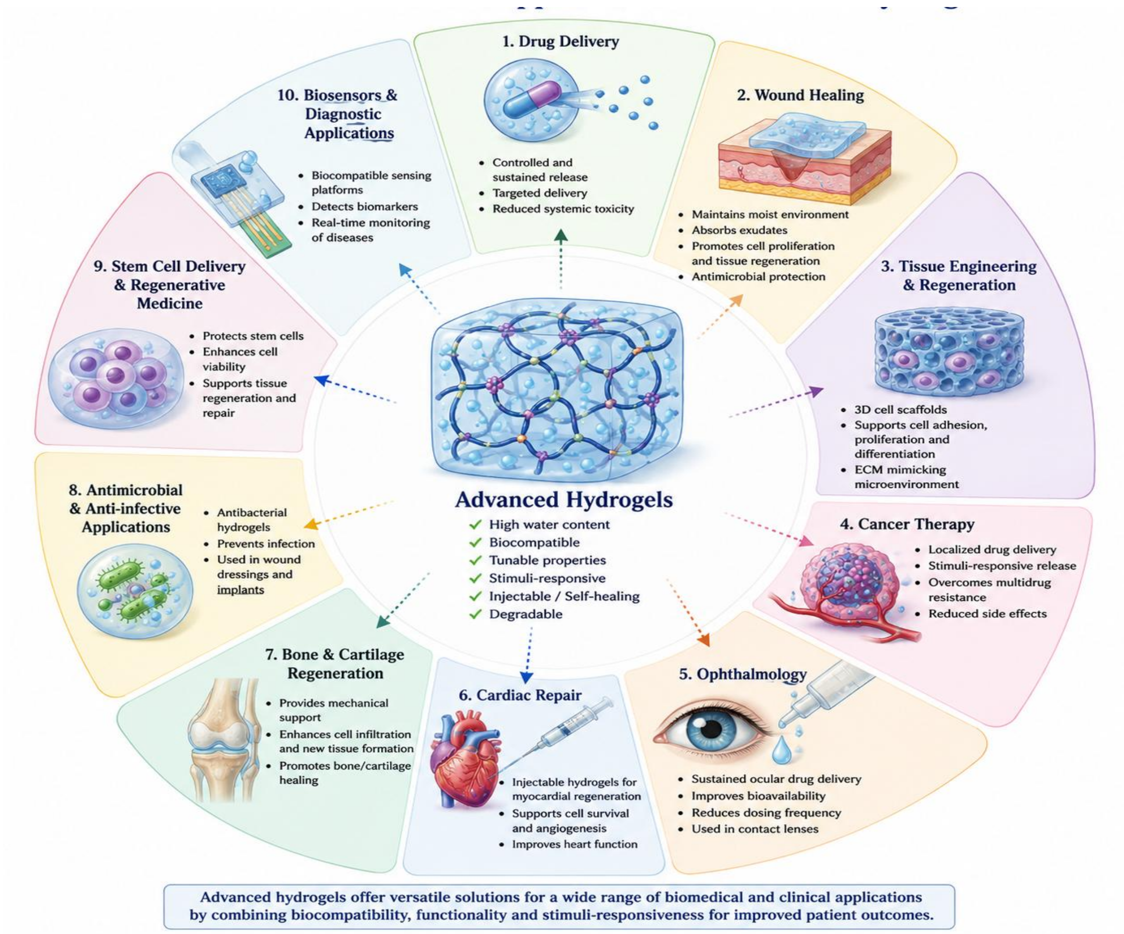

Figure 2. Biomedical and Clinical Applications of Advanced Hydrogels

8. Hydrogel-Based Biomaterials in Regenerative Medicine

Hydrogel-based biomaterials have emerged as one of the most promising platforms in regenerative medicine due to their high water content, biocompatibility, biodegradability, and structural similarity to the native extracellular matrix (ECM). These materials provide a supportive three-dimensional microenvironment for cell adhesion, proliferation, migration, and differentiation, thereby facilitating tissue repair and regeneration. Advances in polymer engineering, stem cell biology, and biofabrication technologies have significantly expanded the therapeutic potential of hydrogels in regenerative medicine applications (Lutolf & Hubbell, 2005; Griffith & Naughton, 2002).

Stem Cell Delivery Systems

Stem cell-based therapies require biomaterials capable of protecting cells from mechanical stress while maintaining cell viability and functionality after transplantation. Hydrogels serve as ideal carriers for stem cell encapsulation and delivery because they provide a hydrated and biomimetic microenvironment that supports cellular survival and differentiation. Injectable hydrogels are particularly advantageous as they allow minimally invasive administration and conform to irregular tissue defects (Tibbitt & Anseth, 2009).

Hydrogel systems have been extensively investigated for delivery of mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and neural stem cells in applications such as cartilage repair, myocardial regeneration, and neural tissue engineering. Incorporation of growth factors and bioactive peptides within hydrogel matrices further enhances stem cell proliferation and lineage-specific differentiation (Khetan & Burdick, 2010).

Scaffold Design for Tissue Engineering

Hydrogels are widely utilized as scaffold materials in tissue engineering due to their ability to mimic the physical and biochemical characteristics of natural tissues. An ideal hydrogel scaffold should possess suitable porosity, mechanical strength, biodegradability, and biocompatibility to facilitate nutrient transport, cell infiltration, and tissue remodeling. Scaffold architecture significantly influences cellular behavior and tissue regeneration outcomes (O'Brien, 2011).

Recent advances in fabrication technologies such as 3D bioprinting and microfabrication have enabled precise control over hydrogel scaffold geometry and internal structure. Composite hydrogels containing ceramics, nanofibers, or nanoparticles are also being developed to improve mechanical stability and bioactivity, particularly for bone and cartilage engineering applications (Murphy & Atala, 2014).

Bioactive Hydrogel Systems

Bioactive hydrogels are engineered to actively interact with surrounding biological tissues rather than serving solely as passive support materials. These systems are functionalized with signaling molecules, peptides, proteins, or growth factors that regulate cellular responses such as adhesion, migration, proliferation, and differentiation. Controlled release of bioactive agents from hydrogels enhances tissue regeneration and accelerates healing processes (Censi et al., 2012).

Growth factor-loaded hydrogels have shown considerable promise in angiogenesis, wound healing, and neural regeneration. Additionally, incorporation of antimicrobial agents and anti-inflammatory compounds can further improve therapeutic outcomes by reducing infection and inflammation at the implantation site (Silva et al., 2014).

ECM-Mimicking Hydrogels

The extracellular matrix plays a crucial role in regulating cell behavior through biochemical and mechanical signaling. ECM-mimicking hydrogels are specifically designed to replicate the composition, structure, and functionality of native ECM, thereby creating a biomimetic environment for tissue regeneration. These hydrogels often contain natural polymers such as collagen, gelatin, fibrin, hyaluronic acid, and decellularized ECM components (Frantz et al., 2010).

ECM-inspired hydrogels can also be engineered with tunable stiffness, degradability, and ligand presentation to direct stem cell fate and tissue-specific differentiation. Such systems are increasingly explored for regeneration of complex tissues including skin, nerve, cardiac muscle, and liver tissue (Gjorevski et al., 2016).

9. Smart and Stimuli-Responsive Hydrogels in Clinical Use

Smart or stimuli-responsive hydrogels are advanced polymeric systems capable of undergoing reversible physical or chemical changes in response to environmental stimuli such as pH, temperature, light, enzymes, electric fields, and magnetic fields. These hydrogels have gained considerable attention in biomedical applications because they enable controlled and site-specific drug delivery, improved therapeutic efficacy, and reduced systemic toxicity (Koetting et al., 2015). Among them, pH-responsive hydrogels are widely explored for oral drug delivery and cancer therapy due to their ability to release drugs selectively in acidic tumor tissues or intestinal environments (Buwalda et al., 2017). Temperature-sensitive hydrogels, including poloxamers and poly(N-isopropylacrylamide) (PNIPAM), undergo sol-gel transition near physiological temperature, making them suitable for injectable and minimally invasive therapies (Klouda & Mikos, 2008). Enzyme-responsive hydrogels can selectively release therapeutics in diseased tissues where specific enzymes are overexpressed, enhancing treatment precision (Torchilin, 2014). Similarly, light-responsive hydrogels provide external control over drug release and have shown promising applications in ophthalmology and photodynamic therapy (Kabanov & Vinogradov, 2009). In regenerative medicine, smart hydrogels act as dynamic scaffolds that support tissue regeneration and stem cell differentiation by mimicking extracellular matrix behavior (Rosales & Anseth, 2016). Despite significant progress, challenges such as large-scale manufacturing, stability, reproducibility, and regulatory approval still limit widespread clinical translation. Nevertheless, ongoing advances in polymer science and nanotechnology are expected to accelerate the development of next-generation smart hydrogel systems for biomedical applications (Wei et al., 2020).

10. Clinical Translation of Hydrogel Systems

The clinical translation of hydrogel systems has advanced considerably due to continuous progress in biomaterials science, polymer engineering, and regenerative medicine. Hydrogels possess favorable properties such as biocompatibility, biodegradability, tunable mechanical strength, and the ability to encapsulate drugs, proteins, and living cells, making them highly suitable for biomedical and pharmaceutical applications (Ratner & Zhang, 2020). One of the major successes in clinical translation is the commercialization of hydrogel-based wound dressings and tissue sealants, which are widely used in burn injuries, diabetic ulcers, and chronic wounds because they maintain a moist environment and promote tissue regeneration (Jones et al., 2006). In ophthalmology, hydrogel-based contact lenses and ocular drug delivery systems have significantly improved drug bioavailability and patient comfort (Peppas et al., 2006). Injectable hydrogels are also being explored for tissue engineering and regenerative medicine applications such as cartilage repair, myocardial regeneration, and bone tissue engineering due to their ability to support cell delivery and tissue remodeling (Lee & Mooney, 2001). In cancer therapy, localized hydrogel-based drug delivery systems have shown promise in reducing systemic toxicity and improving therapeutic efficacy through controlled and stimuli-responsive drug release (Bae et al., 2013). Despite these advances, challenges including large-scale manufacturing, sterilization, reproducibility, long-term biocompatibility, and regulatory approval continue to hinder widespread clinical application (Narayanaswamy & Torchilin, 2019). Nevertheless, recent developments in nanotechnology, 3D bioprinting, artificial intelligence, and personalized medicine are expected to further accelerate the clinical adoption of advanced hydrogel systems in the future (Guvendiren et al., 2016).

11. Recent Innovations and Emerging Trends

Recent years have witnessed significant advancements in hydrogel technology driven by innovations in biomaterials science, nanotechnology, bioengineering, and artificial intelligence. These developments have transformed conventional hydrogels into multifunctional and intelligent systems capable of controlled drug delivery, tissue regeneration, and stimuli-responsive therapeutic action (Catoira et al., 2019). One of the most notable innovations is the development of 3D and 4D bioprinted hydrogels, which enable fabrication of highly organized and dynamic scaffolds for tissue engineering and regenerative medicine applications (Miao et al., 2017). Nanotechnology-integrated hydrogels containing nanoparticles, nanofibers, and graphene derivatives have also gained attention due to their enhanced mechanical strength, electrical conductivity, antimicrobial activity, and controlled drug release behavior, making them highly suitable for wound healing, cancer therapy, and neural tissue engineering (Shin et al., 2016). Additionally, self-healing and injectable hydrogels capable of restoring structural integrity and undergoing in situ gelation are increasingly explored for localized drug delivery and tissue repair (Wei et al., 2015). Bioinspired and biomimetic hydrogels that closely mimic the extracellular matrix are also emerging as promising platforms for stem cell differentiation and tissue regeneration (Liang et al., 2021). Furthermore, the integration of artificial intelligence and computational modeling is accelerating hydrogel design and formulation optimization, while personalized hydrogel systems fabricated through 3D printing are expected to improve precision medicine approaches (Nguyen et al., 2023; Mandrycky et al., 2016). Advances in multifunctional theranostic hydrogels combining diagnostic and therapeutic capabilities have further expanded their biomedical potential, particularly in oncology and targeted therapy (Hu et al., 2020). Despite these innovations, challenges related to large-scale manufacturing, reproducibility, long-term biocompatibility, and regulatory approval continue to limit widespread clinical translation.

12. Future Perspectives

Hydrogel technology is expected to play a major role in the future of biomedical science, regenerative medicine, and advanced drug delivery systems due to rapid advancements in polymer chemistry, nanotechnology, biotechnology, and biofabrication techniques. Future hydrogels are anticipated to become more intelligent, multifunctional, and personalized, enabling precise and patient-specific therapeutic applications. Smart hydrogels capable of responding to multiple stimuli such as pH, temperature, enzymes, and light may significantly improve targeted drug delivery and regenerative therapies (Caló & Khutoryanskiy, 2015; Koetting et al., 2015). The integration of artificial intelligence and machine learning is also expected to accelerate hydrogel design, optimize formulation development, and predict material behavior more efficiently (Nguyen et al., 2023). In addition, personalized hydrogel systems developed using 3D bioprinting and biomimetic approaches may enhance tissue engineering and regenerative medicine applications by closely mimicking native extracellular matrix (Murphy & Atala, 2014; Place et al., 2009). Despite these advances, challenges including large-scale manufacturing, reproducibility, sterilization, long-term stability, and regulatory approval still limit widespread clinical translation (Hoare & Kohane, 2008). Nevertheless, continued interdisciplinary research is expected to transform hydrogels into highly advanced therapeutic platforms for future healthcare applications.

13. Conclusion

Hydrogels have emerged as highly versatile and advanced biomaterials with significant applications in drug delivery, tissue engineering, regenerative medicine, wound healing, cancer therapy, and ophthalmology due to their unique physicochemical properties, biocompatibility, biodegradability, and extracellular matrix-like structure. Recent advancements in hydrogel synthesis, smart stimuli-responsive systems, nanocomposite formulations, injectable and self-healing hydrogels, and biofabrication technologies such as 3D/4D bioprinting have greatly enhanced their therapeutic potential and clinical relevance. These systems provide controlled and site-specific drug delivery, improved cellular interactions, and enhanced tissue regeneration while minimizing systemic toxicity and improving patient compliance. Despite remarkable progress, challenges including large-scale manufacturing, sterilization, long-term stability, reproducibility, mechanical limitations, and regulatory approval still hinder widespread clinical translation. Nevertheless, ongoing developments in nanotechnology, artificial intelligence, biomimetic engineering, and personalized medicine are expected to accelerate the evolution of next-generation hydrogel systems. Overall, hydrogels represent a promising and rapidly evolving platform that is likely to play a crucial role in future biomedical and pharmaceutical innovations, contributing significantly to advanced therapeutic strategies and improved patient healthcare outcomes.

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15. Conflict of Interest

The authors declare that there are no conflicts of interest.

16. References

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