ejpmr, 2025, 12(7), 55-59

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN (O): 2394-3211

ISSN (P): 3051-2573

EMERGING ROLE OF HYDROGELS AS DRUG DELIVERY SYSTEMS FOR TISSUE REGENERATION

Aparajita Raina[1]*, Ila Taku[1] and Sapna Raina[1]

[1]Prabha Harjilal College of Pharmacy and Paraclinical Sciences, Chak Bhalwal, Jammu 181122, India.

***Corresponding Author: Aparajita Raina**

Prabha Harjilal College of Pharmacy and Paraclinical Sciences, Chak Bhalwal, Jammu 181122, India.

Article Received on 07/05/2025 **Article Revised on 28/05/2025** **Article Accepted on 17/06/2025**

ABSTRACT

Hydrogels have emerged as versatile and promising platforms for drug delivery, particularly in the field of tissue regeneration. These three-dimensional, hydrophilic polymer networks can absorb large amounts of biological fluids and provide a moist environment that supports cell proliferation and tissue repair. Due to their tuneable physicochemical properties, biocompatibility, and ability to encapsulate and release therapeutic agents in a controlled manner, hydrogels are increasingly being employed to deliver growth factors, peptides, stem cells, and small-molecule drugs directly to damaged tissues. Recent advances in smart hydrogels, which respond to stimuli such as pH, temperature, or enzymes, have further enhanced their precision and efficacy in targeted delivery. Additionally, biodegradable hydrogels reduce the need for surgical removal, promoting seamless integration with host tissue. This review highlights the current trends, design strategies, and applications of hydrogels in drug delivery systems for tissue regeneration, underscoring their potential to revolutionize regenerative medicine and tissue engineering.

KEYWORDS: Drug delivery, hydrophilic polymer, Stimuli-Sensitive Hydrogels, natural extracellular matrix.

INTRODUCTION

Tissue regeneration is a complex biological process that involves the restoration of structure and function to damaged or diseased tissues. Conventional therapies often fall short in achieving effective regeneration due to limited drug retention at the target site, rapid degradation of therapeutic agents, and systemic side effects (Rasekh *et al.*, 2025). In this context, hydrogels have gained significant attention as advanced drug delivery systems capable of overcoming these limitations. Hydrogels are three-dimensional, hydrophilic polymeric networks capable of retaining substantial amounts of water or biological fluids, mimicking the natural extracellular matrix (ECM). Their unique physicochemical properties, such as high porosity, biocompatibility, and biodegradability, make them ideal candidates for localized and sustained delivery of bioactive agents (Ho *et al.*, 2022; Zhao *et al.*, 2023).

Recent advancements in material science have led to the development of smart and stimuli-responsive hydrogels**,** which can release therapeutic agents in a controlled and responsive manner based on environmental cues like pH, temperature, or enzyme activity. These features allow for precise spatiotemporal control over drug release, enhancing therapeutic efficacy while minimizing systemic toxicity. Furthermore, hydrogels can serve as scaffolds for cell encapsulation and delivery of growth factors, supporting tissue regeneration in a wide range of applications including skin repair, cartilage regeneration, and wound healing (El-Sherbiny *et al.*, 2013).

This introduction sets the stage for exploring the design, functionality, and application of hydrogels as drug delivery vehicles, emphasizing their transformative role in regenerative medicine and tissue engineering**.**

Role in Drug Delivery

Hydrogels can encapsulate and deliver therapeutic agents—including small molecules, proteins, peptides, nucleic acids, and stem cells in a localized, sustained, and controlled manner. Their porous structure allows diffusion-based or stimuli-responsive drug release, enhancing the regeneration of damaged tissues (Kaur *et al.*, 2024).

Types of Hydrogels

Hydrogels are classified into two major categories based on the type of polymer used in their formulation:

1. Natural Hydrogels
2. Synthetic Hydrogels

These classifications are essential in determining the biocompatibility**,** biodegradability, and mechanical properties of the hydrogels, especially for biomedical applications such as drug delivery, wound healing, and tissue engineering (Anshika *et al.*, 2024).

1. Natural Hydrogels

Natural hydrogels are derived from biopolymers that occur in nature. Common sources include: Alginate, Chitosan, Gelatin, Collagen, Hyaluronic acid. It showed salient features like excellent biocompatibility and biodegradability, often mimic the natural extracellular matrix, suitable for applications involving direct contact with tissues or blood, etc.

However, they may have lower mechanical strength and limited stability compared to synthetic counterparts.

2. Synthetic Hydrogels

Synthetic hydrogels are produced using man-made polymers such as: Polyethylene glycol (PEG), Polyvinyl alcohol (PVA), Polyacrylamide (PAAm), Polylactic acid (PLA), Poly(N-isopropylacrylamide) (PNIPAm).

Stimuli-Sensitive Hydrogels

Stimuli-Sensitive Hydrogels also known as "smart hydrogels" or "responsive hydrogels". These are a class of intelligent polymeric materials that undergo reversible physical or chemical changes such as swelling, shrinking, or drug release in response to specific environmental stimuli. These changes make them highly suitable for applications in targeted drug delivery, biosensing, tissue engineering, and diagnostics (Jacob *et al.*, 2021).

Types of Stimuli

1. Physical Stimuli

Temperature-sensitive hydrogels

Temperature-sensitive hydrogels are smart polymeric materials that undergo reversible phase transitions (swelling or shrinking) in response to temperature changes. These transitions are often based on the Lower Critical Solution Temperature (LCST) or Upper Critical Solution Temperature (UCST) of the polymer used. A well-known example is poly(N-isopropylacrylamide) (PNIPAM), which has an LCST around 32°C—close to body temperature. Below the LCST, PNIPAM-based hydrogels are swollen and hydrated; above it, they become hydrophobic and shrink, causing the expulsion of water and any loaded drug.

Applications

- **Injectable drug delivery systems:** Form a gel in situ at body temperature, enabling minimally invasive administration**.**
- **Controlled release formulations:** Trigger temperature-dependent drug release**, particularly useful for** hyperthermia-induced cancer therapy**.**
- **Tissue engineering scaffolds:** Support cell encapsulation and release, responsive to physiological temperature.
- **Biosensors and actuators:** Used in devices where thermal sensitivity is essential (Ansari *et al.*, 2022).

Light-sensitive hydrogels

Light-sensitive hydrogels are advanced smart materials that undergo physical or chemical changes upon exposure to light, such as swelling, degradation, or sol–gel transitions. These hydrogels are engineered using light-responsive moieties, such as azobenzene, spiropyran, or photocleavable crosslinkers that respond to specific wavelengths of light (typically UV, visible, or near-infrared).

This responsiveness enables precise spatial and temporal control over drug release, making them ideal for non-invasive, remote-controlled biomedical applications (Xing *et al.*, 2022).

Applications

- **On-demand drug delivery systems:** Trigger localized drug release at specific sites and times by light exposure.
- **Photodynamic therapy (PDT):** Light activation of photosensitizers within the hydrogel to generate reactive oxygen species (ROS) for targeted cancer cell destruction.
- **Wound healing and antibacterial therapies:** Light-triggered release of antimicrobial agents at infected sites.
- **Tissue engineering:** Spatial control over cell behaviour or scaffold degradation via patterned light exposure.

Electric field-sensitive hydrogels

Electric field-sensitive hydrogels are a type of smart hydrogel that change their shape, volume, or permeability in response to an applied electric field. These hydrogels typically contain ionic or conductive components that allow them to interact with electric stimuli, leading to electro-induced swelling, shrinking, or drug release.

The mechanism is often based on ion migration, electro-osmotic effects, or changes in the polymer network charge distribution, which alter the hydrogel's structure or porosity.

Applications

- **On-demand drug delivery systems:** Enable precise, externally controlled release of therapeutic agents.
- **Soft actuators and artificial muscles:** Used in bio-robotics and smart devices due to their fast, reversible deformation.
- **Biosensors and diagnostics:** Electric field-sensitive hydrogels can transduce biochemical signals into electrical responses.
- **Neural and cardiac interfaces:** Potential use in responsive biomaterials for bioelectronic applications (Shang et al.**,** 2007).

Magnetic-sensitive hydrogels

Magnetic-sensitive hydrogels are composite materials that contain magnetic nanoparticles (e.g., Fe_3O_4, iron oxide) embedded within a hydrogel matrix. These hydrogels respond to external magnetic fields, enabling non-invasive and remote control over their physical properties such as swelling, drug release, or movement.

The magnetic component allows the hydrogel to generate localized heat (magnetic hyperthermia) or to be directed to specific target sites using magnetic guidance.

Applications

- **Targeted drug delivery:** Magnetic fields are used to direct the hydrogel to specific tissues (e.g., tumors), improving drug localization and minimizing side effects.
- **Magnetic hyperthermia therapy:** Generation of localized heat under an alternating magnetic field to kill cancer cells or enhance drug release.
- **Tissue engineering:** Alignment and remote positioning of scaffolds or cells using magnetic control.
- **MRI contrast agents:** Dual-functional hydrogels for both treatment and imaging (Kumar *et al.*, 2011).

2. Chemical/Biochemical Stimuli

pH-sensitive hydrogels

pH-sensitive hydrogels are a type of smart hydrogel that can swell or shrink in response to changes in the surrounding pH. This behavior is due to the presence of ionizable functional groups (e.g., –COOH, $–NH_2$) in the polymer network, which gain or lose protons depending on the pH.

In acidic environments (like tumor microenvironments or inflamed tissues), or in different regions of the gastrointestinal (GI) tract, these hydrogels undergo volume phase transitions that can trigger the controlled release of drugs.

Applications

- **Targeted cancer therapy:** Exploits the acidic pH (~6.5) of tumor tissue for localized drug release.
- **Oral drug delivery:** Utilizes pH differences between the stomach (acidic) and intestines (neutral to basic) to protect drugs until they reach the desired site.
- **Wound healing:** pH-sensitive release of antibiotics or growth factors in infected (acidic) wounds (Rizwan *et al.,* 2017).

Glucose-sensitive hydrogels

These hydrogels respond to glucose concentrations, typically through the incorporation of glucose oxidase enzymes. When glucose is present, the enzyme catalyzes its oxidation, producing gluconic acid and hydrogen peroxide. This biochemical reaction leads to changes in the hydrogel’s swelling behavior, pore size, or drug release profile.

Application

Primarily used in self-regulated insulin delivery systems for diabetic patients. The hydrogel can swell or shrink in response to fluctuating glucose levels, enabling controlled, on-demand insulin release (Kang *et al*., 2003).

Enzyme-sensitive hydrogels

Enzyme-responsive hydrogels (ERHs) have gained significant attention in recent years due to their broad potential in biomedical applications**,** particularly in controlled release systems, targeted drug delivery, and tissue engineering. These hydrogels represent a novel class of stimuli-sensitive hydrogels (SHRs) that can respond selectively to enzymatic activity, even under mild physiological conditions such as neutral pH and body temperature.

What sets ERHs apart is their ability to undergo reversible or irreversible changes in their chemical structure or physical properties such as swelling, degradation, or sol–gel transition in direct response to specific enzymatic triggers. These changes are typically induced by enzymes that are overexpressed in pathological conditions (e.g., matrix metalloproteinases in cancer or inflammation), allowing for highly targeted and disease-specific activation.

The enzyme-responsive behavior is usually engineered by incorporating enzyme-cleavable linkers or substrates into the hydrogel network. Upon exposure to the target enzyme, the hydrogel's network structure is altered, enabling the controlled release of encapsulated therapeutic agents or the modulation of mechanical properties to suit dynamic biological environments.

Due to their specificity, biocompatibility, and responsiveness, ERHs hold great promise for next-generation smart biomaterials in personalized medicine, where precise spatial and temporal control over therapeutic functions is critical (Sobczak *et al.*, 2022)

The challenges of Stimuli-Sensitive Hydrogels include Complex synthesis and higher production cost, Potential biocompatibility and degradation issues, Limited mechanical strength in some formulations, Regulatory barriers for clinical use, etc.

Adverse Effects of Hydrogels

1. Biocompatibility Issues

Although many hydrogels are designed to be biocompatible, some synthetic or chemically modified hydrogels may trigger immune responses, inflammation, or foreign body reactions, especially if residual crosslinkers or unreacted monomers are present.

2. Toxicity of Degradation Products

Biodegradable hydrogels may release toxic or acidic degradation products, which can cause local irritation, tissue damage, or interfere with the healing process.

3. Incomplete or Uncontrolled Drug Release
Some hydrogels may not release drugs uniformly or may experience burst release, leading to ineffective treatment or local overdose. Inconsistent degradation rates can affect drug release kinetics, compromising therapeutic efficacy.

4. Mechanical Weakness
Many hydrogels lack mechanical strength and are unsuitable for load-bearing tissues like bone or cartilage unless reinforced. Mechanical instability can lead to premature breakdown or inadequate tissue support.

5. Poor Integration with Host Tissue
Some hydrogels may fail to integrate well with native tissue, leading to encapsulation, implant rejection, or poor cell adhesion and proliferation.

6. Infection Risk
If sterility is not maintained during preparation or implantation, hydrogels may become prone to microbial contamination, leading to infections at the site of application.

7. Storage and Stability Issues
Hydrogels with high water content are often prone to dehydration or microbial growth during storage, limiting their shelf life and practical usability.

8. Regulatory and Scale-Up Challenges
Complex formulation and variable responses in different tissues make standardization and regulatory approval difficult, slowing clinical translation (Ghasemiyeh *et al.*, 2019).

CONCLUSION

Hydrogels represent a transformative approach in the field of drug delivery for tissue regeneration, offering a unique combination of biocompatibility, structural similarity to natural tissues, and the ability to deliver therapeutic agents in a controlled and sustained manner. Their tunable mechanical properties, responsiveness to physiological stimuli, and capacity to encapsulate bioactive molecules and cells make them ideal candidates for promoting efficient tissue repair and regeneration. The integration of smart, biodegradable, and injectable hydrogels into regenerative medicine holds immense potential to overcome the limitations of conventional therapies, enabling localized treatment with minimal invasiveness and enhanced therapeutic outcomes. Despite significant progress, challenges remain in terms of long-term stability, scalability, and regulatory approval. Continued research and interdisciplinary collaboration are essential to optimize hydrogel systems and translate them into clinically viable solutions.

Overall, hydrogels are poised to play a central role in the next generation of advanced biomedical therapies**,** paving the way for innovative and personalized approaches to tissue regeneration.

REFERENCES

1. Ansari MJ, Rajendran RR, Mohanto S, Agarwal U, Panda K, Dhotre K, Manne R, Deepak A, Zafar A, Yasir M, Pramanik S. Poly(N-isopropylacrylamide)-Based Hydrogels for Biomedical Applications: A Review of the State-of-the-Art. Gels, 2022; 8(7): 454.
2. Anshika, Verma S, Thakur V. A Review on Hydrogels. European Journal Of Pharmaceutical And Medical Research, 2024; 11(2): 550-553.
3. El-Sherbiny IM, Yacoub MH. Hydrogel scaffolds for tissue engineering: Progress and challenges. Glob Cardiol Sci Pract, 2013; 2013(3): 316-42.
4. Ghasemiyeh P, Mohammadi-Samani S. Hydrogels as Drug Delivery Systems; Pros and Cons (Review Article). Trends in Pharmaceutical Sciences, 2019; 5(1): 7-24.
5. Ho TC, Chang CC, Chan HP, Chung TW, Shu CW, Chuang KP, Duh TH, Yang MH, Tyan YC. Hydrogels: Properties and Applications in Biomedicine. Molecules, 2022; 27(9): 2902.
6. Jacob S, Nair AB, Shah J, Sreeharsha N, Gupta S, Shinu P. Emerging Role of Hydrogels in Drug Delivery Systems, Tissue Engineering and Wound Management. Pharmaceutics, Mar. 8, 2021; 13(3): 357.
7. Kang SI, Bae YH. A sulfonamide based glucose-responsive hydrogel with covalently immobilized glucose oxidase and catalase, Journal of Controlled Release, 2003; 86(1): 115-121.
8. Kaur H, Gogoi B, Sharma I, Das DK, Azad MA, Pramanik DD, Pramanik A. Hydrogels as a Potential Biomaterial for Multimodal Therapeutic Applications. Mol Pharm., 2024; 21(10): 4827-4848.
9. Kumar CS, Mohammad F. Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery. Adv Drug Deliv Rev., Aug. 14, 2011; 63(9): 789-808.
10. Rasekh M, Arshad MS, Ahmad Z. Advances in Drug Delivery Integrated with Regenerative Medicine: Innovations, Challenges, and Future Frontiers. Pharmaceutics, Apr. 1, 2025; 17(4): 456.
11. Rizwan M, Yahya R, Hassan A, Yar M, Azzahari AD, Selvanathan V, Sonsudin F, Abouloula CN. pH Sensitive Hydrogels in Drug Delivery: Brief History, Properties, Swelling, and Release Mechanism, Material Selection and Applications. Polymers (Basel), Apr. 12, 2017; 9(4): 137.
12. Shang J., Chen X, Shao Z. The electric-field-sensitive hydrogels, Progress in Chemistry –Beijing, 2007; 19(9): 1393-1399.
13. Sobczak M. Enzyme-Responsive Hydrogels as Potential Drug Delivery Systems-State of Knowledge and Future Prospects. Int J Mol Sci., Apr. 16, 2022; 23(8): 4421.

14. Xing Y, Zeng B, Yang W. Light responsive hydrogels for controlled drug delivery. Front Bioeng Biotechnol, Dec. 16, 2022; 10: 1075670.
15. Zhao L, Zhou Y, Zhang J, Liang H, Chen X, Tan H. Natural Polymer-Based Hydrogels: From Polymer to Biomedical Applications. Pharmaceutics, Oct. 23, 2023; 15(10): 2514.