

HYDROGELS IN TARGETED DRUG DELIVERY: EMERGING TRENDS AND APPLICATIONS

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Article Received on
24 July 2025,

Revised on 13 August 2025,
Accepted on 02 Sept. 2025

DOI: 10.20959/wjpr202518-38275



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ABSTRACT

Hydrogels, three-dimensional hydrophilic polymer networks retaining up to 99% water, are versatile platforms for targeted drug delivery. Their tissue-like structure, biocompatibility, and responsiveness to pH, temperature, light, or glucose enable precise, controlled drug release. Prepared via bulk, free-radical, solution, suspension polymerization, or cross-linking, hydrogels are customized for diverse biomedical uses. Drug release occurs through diffusion, swelling, or chemical degradation, ensuring sustained delivery. Classified by source (natural/synthetic), cross-linking (physical/chemical), or responsiveness, they excel in oral, ocular (e.g., Restasis®), transdermal, vaginal, colonic, and injectable applications, supporting wound healing, ophthalmology, biosensing, tissue engineering, and oncology. Advances in nanotechnology, bio-orthogonal cross-linking, and AI-driven design optimize formulations, overcoming biocompatibility challenges, while 3D-printed bio-inks enhance regenerative therapies. As intelligent carriers, hydrogels are poised to

advance personalized medicine and clinical drug delivery, offering tunable, biocompatible solutions for next-generation therapeutic systems. This review highlighted the emerging potential of hydrogels as intelligent, biocompatible carriers, paving the way for next-generation personalized drug delivery systems.

KEYWORDS: Hydrogels, Targeted Drug Delivery, Biocompatibility, Stimuli-responsive hydrogels, Bio-orthogonal Cross-linking.

INTRODUCTION

Hydrogels are three-dimensional cross-linked polymer networks derived from natural or synthetic polymers, capable of absorbing and retaining large amounts of water due to hydrophilic groups such as amino, carboxyl, and hydroxyl.^[1] A substance is considered a hydrogel when water makes up at least 10% of its weight or volume. Because of this high-water content, hydrogels remain soft, flexible, and mimic the properties of natural tissues. They exhibit reversible volume or phase transitions (gel–sol) in response to physical stimuli like temperature, light, electric/magnetic fields, solvent composition, and pressure, or to chemical/biochemical stimuli such as pH, ions, and specific molecules.^[2] The response depends on factors like monomer type, charge density, side chains, and degree of cross-linking. Their hydrophilic nature makes them suitable for biopharmaceuticals such as proteins, peptides, antibodies, and nucleotides, while nanocomposite hydrogels can also carry hydrophobic drugs^[3] with high biocompatibility, softness, and biodegradability, hydrogels have broad applications in medicine, including contact lenses, biosensors, artificial skin, heart linings, and drug delivery devices.^[4]

Additionally, they serve as carriers for vaccines, plasma, serums, and intestinal cells due to their swelling ability and structural stability. Their biodegradability allows complete drug release in vivo without surgical removal. Owing to their tuneable network and controlled diffusion, hydrogels are ideal for targeted drug delivery within the gastrointestinal tract, making them a promising platform for advanced drug release systems.



Figure 1: Hydrogel.

CLASSIFICATION

Hydrogels can be classified in several ways. Based on their source, they may be natural or synthetic. According to polymeric composition, they are grouped as homopolymer, copolymer, or multipolymer hydrogels. Their physical structure can be amorphous, semi-crystalline, or crystalline. Based on the type of cross-linking, hydrogels can be categorized as either physically or chemically cross-linked with respect to electrical charge, hydrogels may be non-ionic, cationic, anionic, amphoteric, or zwitterionic. Finally, by drug release mechanism, they are classified as time-controlled or stimuli-responsive (smart) hydrogels.^[5]

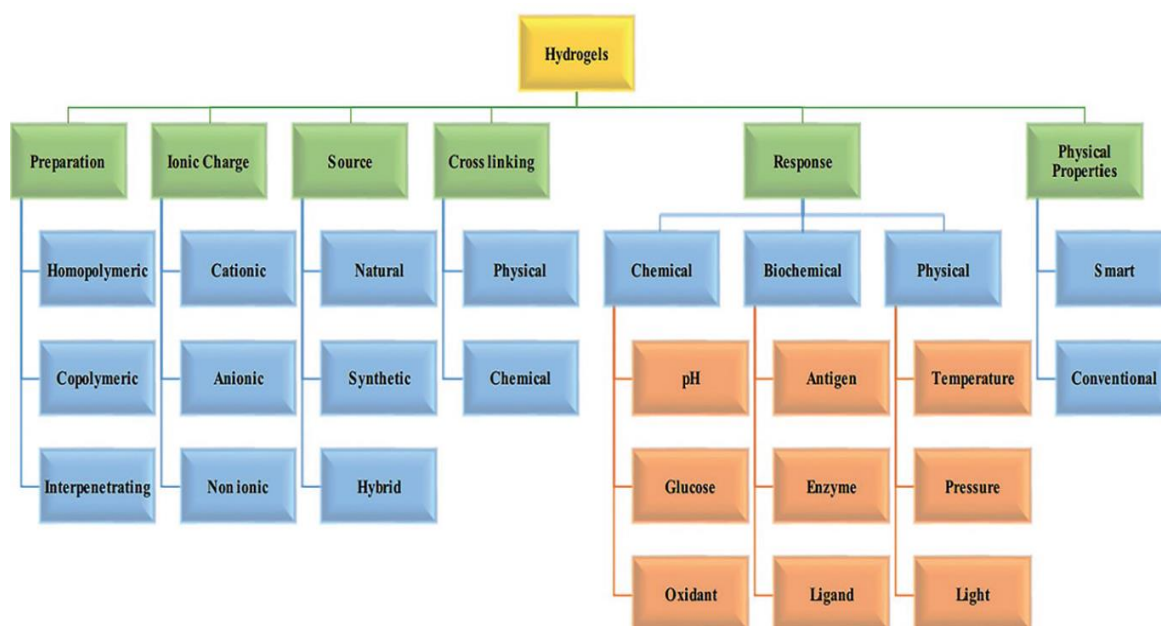


Figure 2: Classification of Hydrogel.

Table 1: Classification of Response Hydrogels.^{[6],[7],[8]}

Type	Key Features	Examples / Mechanism	Applications
pH-Responsive Hydrogels (PRHs)	Undergo swelling or phase transition with pH changes; developed from polyelectrolytes containing weak acidic (-COOH) or basic (-NH ₂) groups	Anionic (acidic groups) and Cationic (basic groups) hydrogels; swelling depends on surrounding pH relative to pKa/pKb	Oral drug delivery, site-specific release in GIT
Temperature-Responsive Hydrogels (TRHs)	Exhibit sol–gel transition in response to physiological temperature; liquid/semi-solid at room temperature, solidify at body temperature	Contain hydrophobic groups (methyl, ethyl, propyl); undergo phase change at ~37°C	Injectable drug delivery, minimally invasive administration

Electrically & Magnetically Responsive Hydrogels (ERHs & MRHs)	Swell or de-swell when exposed to electrical or magnetic stimuli	Synthetic: polyaniline, polypyrrole, sulfonated styrene, polythiophene, PVA; Natural: chitosan, alginate, HA; behavior governed by osmotic pressure balance	Controlled, on-demand drug release, bio-actuators
Light-Responsive Hydrogels (LRHs)	Contain light-sensitive chromophores; respond to UV, visible, or NIR light via de-crosslinking, shrinking, heating, or functional activation	Chromophores in backbone, side chains, crosslinking points, or matrix; NIR hydrogels penetrate deeper (~2 mm in tissue)	Photothermal therapy, targeted drug delivery, tissue engineering
Glucose-Responsive Hydrogels	Sensitive to glucose; regulate insulin release in response to blood sugar levels	Trigger insulin release when glucose concentration rises; maintain sustained release	Diabetes management, glucose sensing, self-regulated insulin delivery

Preparation of Hydrogels

Hydrogels are hydrophilic polymer networks that can be prepared using both hydrophilic and hydrophobic monomers, depending on the desired application. They are commonly synthesized by polymerizing hydrophilic monomers with multifunctional cross-linkers through copolymerization or free-radical polymerization techniques. Several methods are used for hydrogel preparation.

A]. Bulk Polymerization

Hydrogels are synthesized from one or more vinyl-type monomers in the presence of a small quantity of cross-linking agent. Polymerization is initiated by radiation, UV light, or chemical catalysts. The resulting hydrogels can be obtained in forms such as rods, films, membranes, particles, or emulsions.

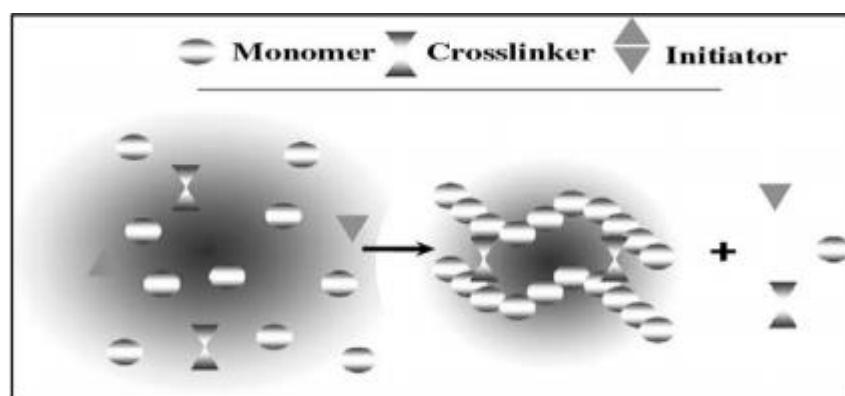


Figure 3: Schematic diagram of hydrogel preparation.

B]. Free Radical Polymerization

Monomers such as acrylates, vinyl lactams, and amides are polymerized through a typical free-radical process involving initiation, propagation, chain transfer, and termination. Radicals are generated by thermal, UV, visible light, or redox initiators, which then activate the monomers for hydrogel formation.

C]. Solution Polymerization / Cross-linking

In this method, ionic or neutral monomers are polymerized with cross-linking agents in the presence of solvents (water, ethanol, water–ethanol mixtures, benzyl alcohol). The solvent acts as a heat sink, making the process safer than bulk polymerization. The final hydrogel is washed to remove impurities such as unreacted monomers or initiators.

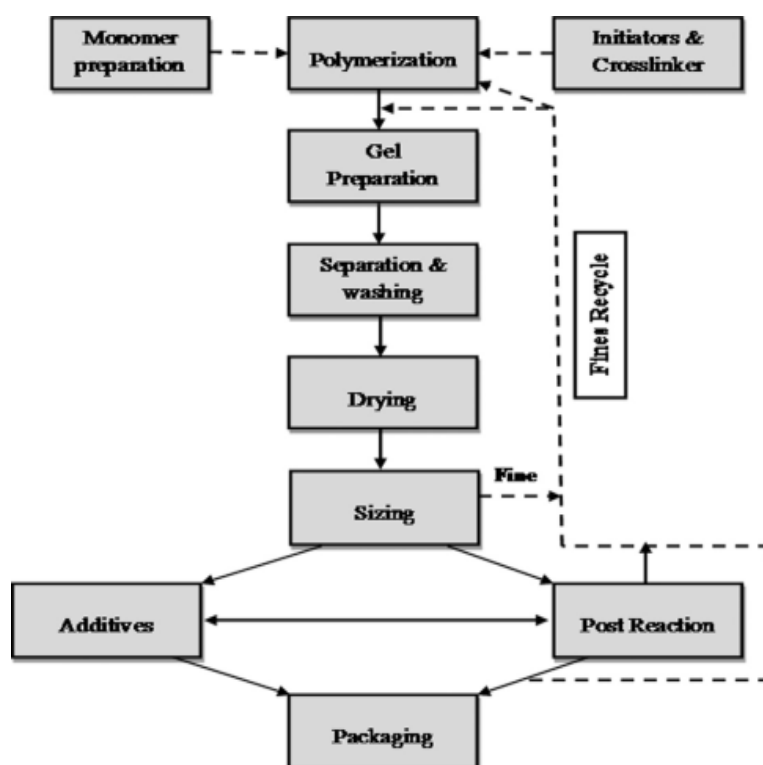


Figure 4: Hydrogel preparation block diagram (solution polymerization/cross-linking procedure).

D]. Suspension (Inverse-Suspension) Polymerization

Hydrogels are obtained as powders or microspheres (beads), eliminating the need for grinding. The process involves dispersing monomers and initiators in a hydrocarbon phase (water-in-oil system). Particle size and shape are controlled by agitation speed, dispersants, and rotor design. A low HLB suspending agent is added to stabilize the dispersion.^[9]

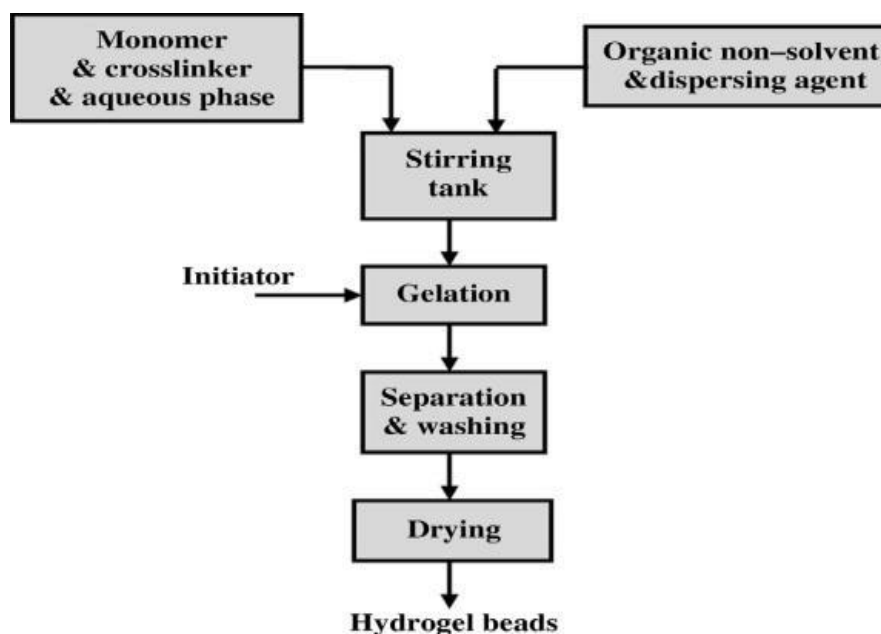


Figure 5: Suspension polymerization.

E]. Grafting to a Support

To improve the weak mechanical strength of bulk hydrogels, monomers can be grafted onto stronger support surfaces (e.g., polymeric supports). Free radicals are generated on the support, enabling covalent bonding of polymer chains, thereby enhancing hydrogel stability.^[10]

F]. Physical Cross-linking

Hydrogels may also be formed through non-covalent physical interactions, including hydrogen bonding, ionic interactions, hydrophobic associations, and polyelectrolyte complexation. Common techniques include:

- Heating/cooling a polymer solution
- Complex coacervation
- Ionic interaction
- Hydrogen bonding

G]. Chemical Cross-linking

In this method, polymer chains are covalently linked using chemical cross-linkers. Functional groups ($-\text{OH}$, $-\text{COOH}$, $-\text{NH}_2$) on natural or synthetic polymers react with agents such as glutaraldehyde or adipic acid dihydrazide. Interpenetrating polymer networks (IPNs) can also be formed by polymerizing a monomer within another polymer matrix.^[9]

Properties of Hydrogels

A]. Surface Properties

The surface features of hydrogels influence their applications and biocompatibility. Smooth surfaces are preferred for drug delivery, while porous surfaces are useful in tissue engineering for cell growth. Due to their crosslinked network, hydrogels have flexible surface chains that change morphology in water. Hydrophilic surfaces reduce protein adsorption, improving biocompatibility, and they also show low friction because of high water content. Surface properties can be further modified (e.g., by surface tethering) for specialized biomedical uses.^[11]

B]. Mechanical Properties

Mechanical strength is vital for applications such as wound dressings, tissue engineering, drug delivery, and cartilage repair. Crosslinking degree controls strength and flexibility—higher crosslinking increases strength but makes the gel brittle. Copolymerization can also enhance mechanical stability via hydrogen bonding. Studies on calcium alginate hydrogels show that mechanical analysis (stress relaxation, Young's modulus) can estimate crosslinking density and mesh size, which are critical for biomedical applications.

C]. Biocompatible Properties

Hydrogels must be non-toxic and biocompatible for safe biomedical use. Biocompatibility involves Bio-safety: no cytotoxicity, mutagenicity, or carcinogenicity Bio-functionality: ability to perform its intended role. This is especially important in tissue engineering, where hydrogels interact with tissues during healing and degradation. However, residual toxic chemicals from synthesis (initiators, solvents, cross-linkers) may affect safety if not removed properly.^[12]

D]. Swelling Properties

Hydrogels act as super macromolecules with crosslinked chains. They can swell or shrink in response to environmental stimuli such as pH, temperature, or ionic strength. pH-sensitive hydrogels (e.g., polyacrylic acid) swell based on ionization of functional groups. Temperature-sensitive hydrogels like PNIPAM undergo phase transitions; copolymerization with hydrophilic or hydrophobic monomers can tune their swelling and thermal response.^[13]

E]. Rheology

Viscosity of hydrogels is typically measured at low temperature ($\approx 4^{\circ}\text{C}$) using a cone-plate viscometer. This enables precise assessment of flow and mechanical behaviour.

F]. X-ray Diffraction (XRD)

XRD is used to study crystalline vs. amorphous nature of hydrogels. The presence of new peaks indicates drug–excipient interactions, while broad halos suggest impurities or disordered structures within the hydrogel.

G]. Light Scattering

Gel permeation chromatography with multi-angle laser light scattering (GPC-MALLS) is widely applied to measure molecular weight distribution and hydrogel parameters. It is useful for studying hydrocolloids (e.g., gum arabic, gelatin, pullulan) and quantifying radiation-induced hydrogel formation.^[14]

H]. Biodegradability

Biodegradable hydrogels break down into small, non-toxic molecules in biological environments. This property is crucial for implants and drug delivery systems. Studies show that hydrogels can degrade safely without causing inflammation, making them highly suitable for medical applications.

I]. High Water Absorption and Retention

Hydrogels can hold up to 99% water due to their crosslinked structure. In wound dressings, they absorb exudates, maintain a moist environment, and prevent tissue adhesion, reducing pain during dressing changes. Their smooth and elastic surface fits wounds closely, lowers bacterial contact, and enhances healing, making them one of the most advanced dressing materials available.^[15]

Drug Release Mechanism

Controlled drug release from hydrogels mainly occurs through three processes: drug diffusion, matrix swelling, and chemical reactions within the polymer. Based on these, hydrogel release systems can be classified as:

A] Diffusion-controlled (matrix and reservoir systems)

B] Swelling-controlled (solvent-activated or osmotically driven systems)

C] Chemically-controlled (biodegradable, erodible, or pendant chain systems).^[16]

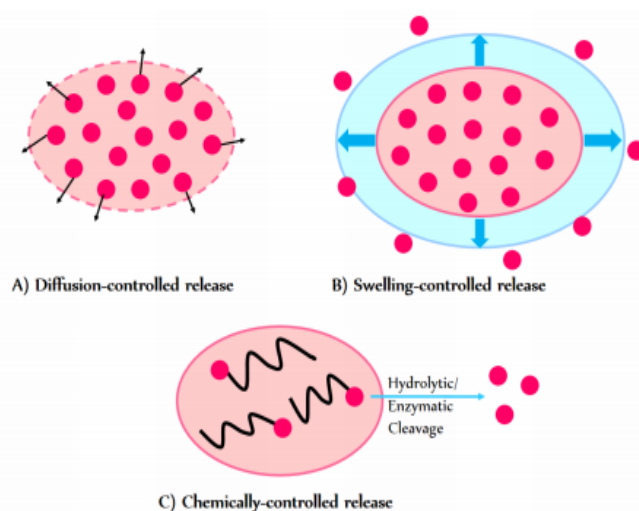


Figure 6: Drug release mechanism.

A]. Diffusion-Controlled Release

This is the most common mechanism for hydrogels. It is generally described by Fick's law of diffusion with constant or variable diffusion coefficients.^[17] Hydrogels are cross-linked polymer networks containing open pores that permit the diffusion of liquids and small solutes. The drug release profile is governed by the relationship between mesh size (R_{mesh}) and drug size (R_{drug}).^[18]

- $R_{\text{mesh}}/R_{\text{drug}} > 1 \rightarrow$ Mesh is larger than the drug \rightarrow Free diffusion, rapid release.
- $R_{\text{mesh}}/R_{\text{drug}} \sim 1 \rightarrow$ Mesh size similar to drug \rightarrow Steric hindrance slows release \rightarrow Extended release.
- $R_{\text{mesh}}/R_{\text{drug}} < 1 \rightarrow$ Mesh too small for drug \rightarrow Drug trapped until swelling or network degradation enlarges the mesh.^[16]

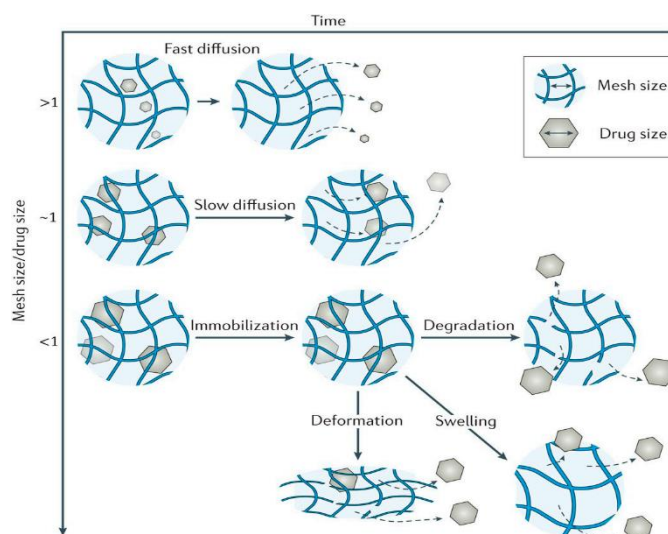


Figure 7: Mesh size mediated drug diffusion.

B]. Swelling-Controlled Release

This mechanism takes place when drug diffusion outpaces hydrogel swelling, with drug molecules being released at the boundary between the swollen (rubbery) and unswollen (glassy) regions of the gel.^[13] The release rate depends on Swelling speed of the hydrogel (faster swelling → faster release), Water absorption capacity, Thickness of the gel matrix.^[16]

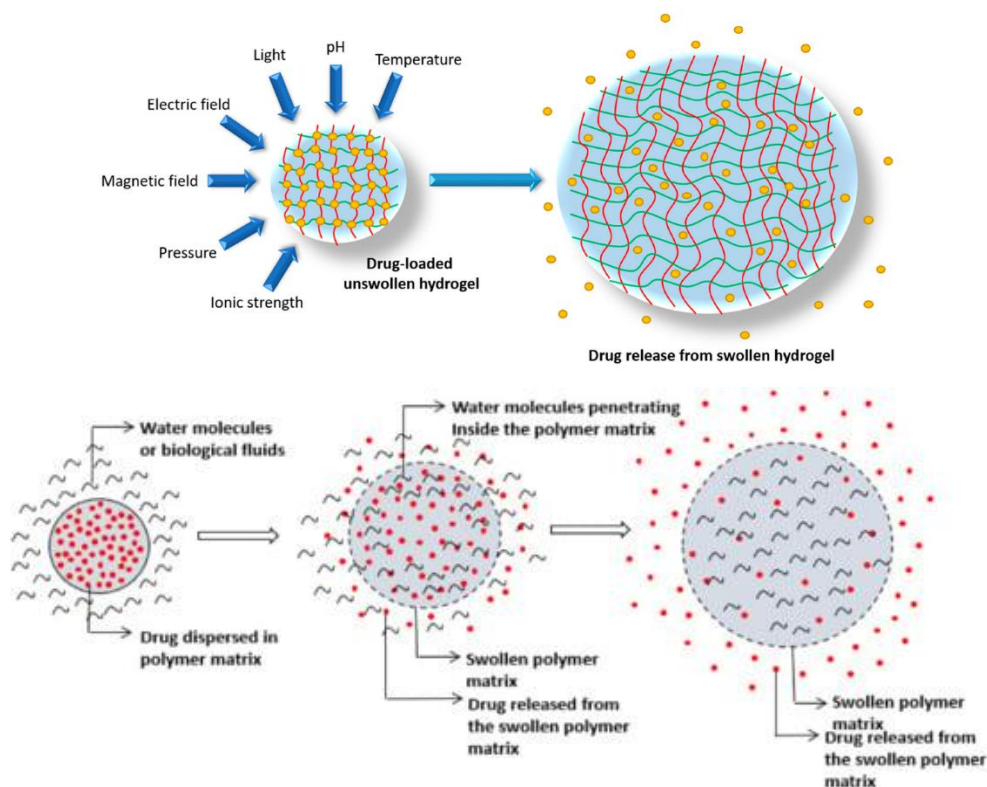


Figure 8: Schematic of mechanism of drug release from the chemically controlled drug delivery systems.

C]. Chemically-Controlled Release

In this mechanism, drug release is governed by chemical reactions in the hydrogel matrix, mainly:

- Polymer degradation via hydrolytic or enzymatic cleavage.
- Surface or bulk erosion controlling release rate.
- Drug-polymer binding (reversible/irreversible) influencing release kinetics.^[17]

Here, the rate-limiting step is the cleavage of polymer chains, which allows entrapped or tethered drugs to be released from the hydrogel.^[16]

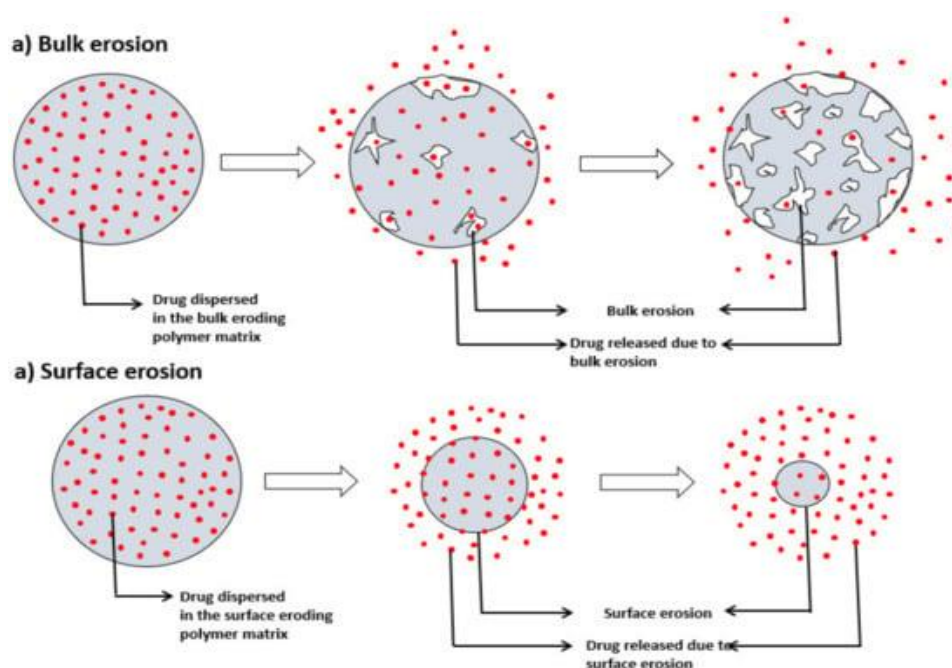


Figure 9: Schematic of mechanism of drug release from the chemically controlled drug delivery systems.

Applications of Hydrogels

Hydrogels are versatile carriers for drug delivery through oral, buccal, rectal, nasal, vaginal, ocular, and transdermal routes. They are applied in treating oral cavity cancers, osteoporosis, gastrointestinal ulcers, ocular diseases, and for subcutaneous protein delivery due to their elasticity, water content, and biocompatibility.^[19]

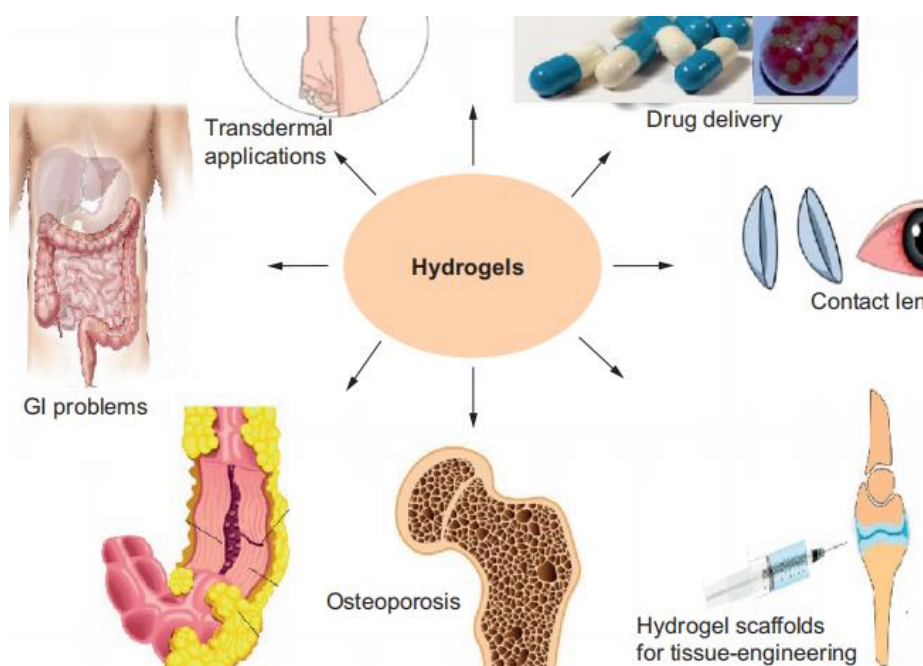


Figure 10: Various applications of Hydrogels.

1. Hydrogels in Transdermal Drug Delivery

Hydrogels made from polymers and polysaccharides are widely explored in biomedical and pharmaceutical delivery systems. Their nontoxicity, biodegradability, sustained release, cost-effectiveness, and large-scale producibility make them ideal candidates. They are particularly useful for skin-related disorders and wound healing, as their high-water content, flexibility, and biocompatibility reduce irritation and enhance healing. Hydrogels are also applied in cosmetology and dermatology, minimizing systemic side effects.^[19]

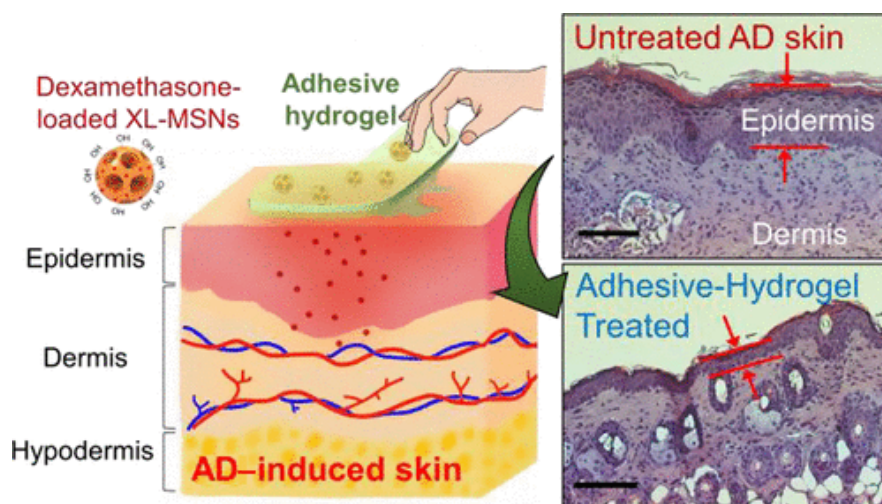


Figure 11: Adhesive composite hydrogel patch for sustained transdermal drug delivery to treat atopic Dermatitis.

2. Hydrogels in Colonic Drug Delivery

Hydrogels can be tailored for colon-targeted therapy to treat colon cancer, ulcerative colitis, and Crohn's disease. Since the colon contains a high level of polysaccharide enzymes, enzyme-sensitive or pH-responsive hydrogels enable localized drug release. For example, ibuprofen-loaded guar gum hydrogels crosslinked with glutaraldehyde allow controlled drug delivery specifically to the colon.^[19]

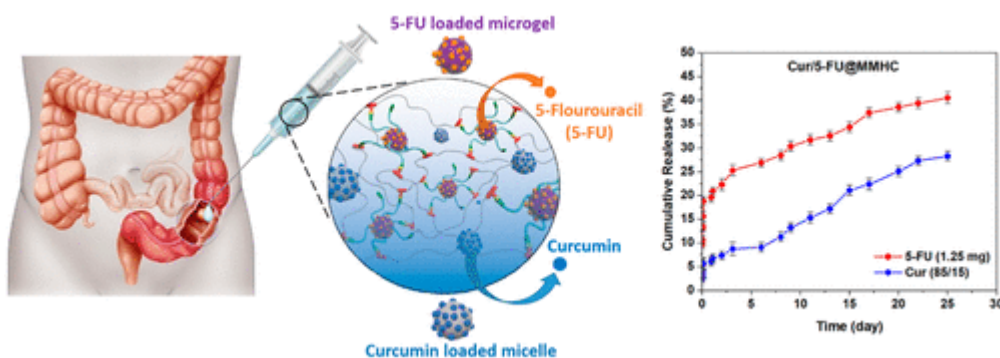


Figure 12: Gelatin based injectable hydrogel therapy of colorectal cancer.

3. Hydrogels in Ocular Drug Delivery

Hydrogels are highly suitable for ophthalmic drug delivery due to their 3D network, viscoelasticity, water retention, and responsiveness to stimuli (pH, heat, light). Applications include soft contact lenses (SCLs) and intraocular lenses (IOLs) as drug carriers. Sustained release of anti-glaucoma drugs such as pilocarpine and timolol using gel-forming polymers (e.g., xyloglucan). Hydrogel eye drops (containing sodium hyaluronate) for long-lasting lubrication in dry eye treatment. Commercial products such as Lacrisert and Vitraser for lubrication and intravitreal delivery against cytomegalovirus retinitis in AIDS patients.^[19]

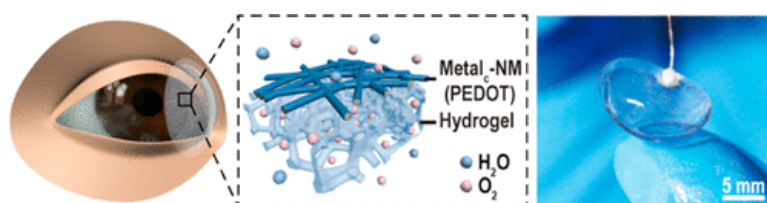


Figure 13: Hydrogel based formulations for drug delivery to the anterior segment of the eye.

4. Hydrogels in Wound Dressings

Hydrogels are effective wound dressings because they: Absorb wound exudates while preventing fluid loss. Deliver oxygen and antimicrobial agents to accelerate healing. Protect wounds from bacterial invasion. They are available as sprays, emulsions, and pastes with embedded drugs for controlled release. Advanced examples include self-assembling peptide hydrogels that accelerate burn healing and silver nanoparticle–PVP–carrageenan hydrogels that control infections and improve tissue regeneration.^[20]

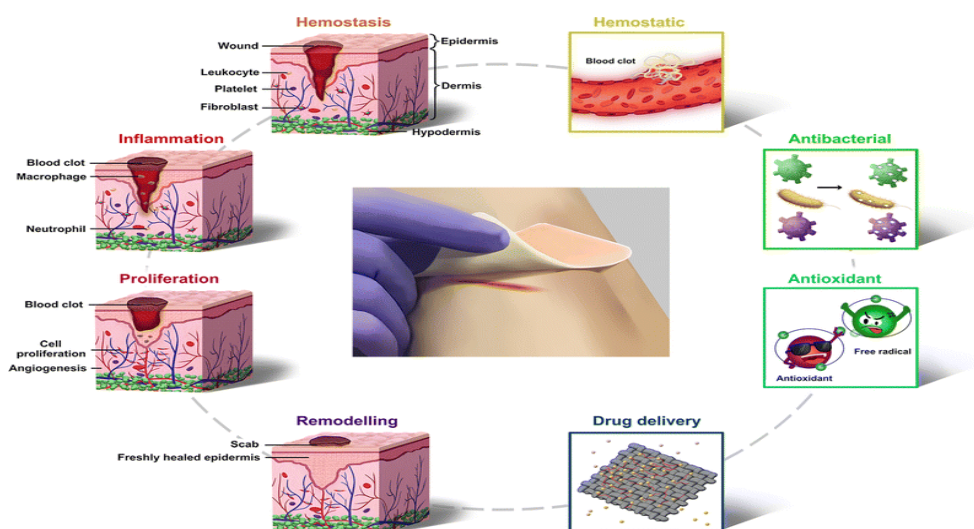


Figure 14: Hydrogel membranes in accelerating enhancing the wound healing.

5. Hydrogels in Biosensors

Hydrogels are also used as functional films in biosensors, linking biomolecules with electronic components. Examples include Chitosan-based hydrogel sensors for rapid detection of hydrogen peroxide (H₂O₂) with high sensitivity (response within 7 seconds). Hydrogel–pH indicator films integrated with CMOS image sensors, capable of detecting a full pH range (1–14) and converting results into digital signals. Such systems are promising for real-time detection of toxins, chemicals, and biological markers.^[20]

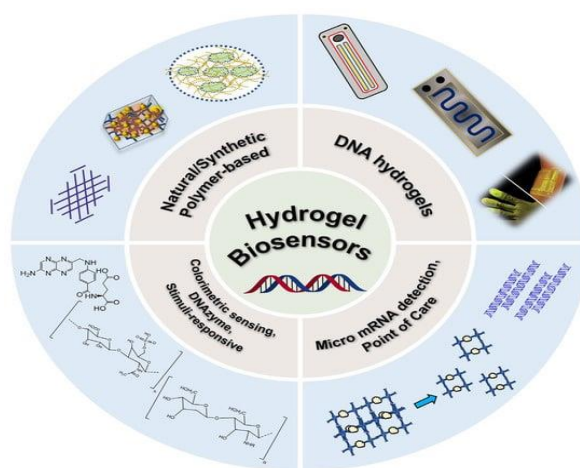


Figure 15: hydrogel biosensors.

6. Hydrogels in Tissue Engineering

Hydrogels serve as 3D scaffolds for tissue engineering, supporting cell growth, proliferation, and extracellular matrix secretion. These scaffolds gradually degrade while new tissues form, enabling regeneration of damaged organs or tissues. This approach, often called regenerative medicine, allows the construction of biological substitutes that mimic the morphology and function of natural tissues.^[20]

Table 2: Marketed products.^{[21],[22]}

Route of Administration	Product (Trade name)	Manufacturer / Marketer	Hydrogel Composition	Therapeutic Indication	Remarks
Buccal	Nicorette®	Johnson & Johnson	Hydroxypropyl methylcellulose	Smoking cessation	Nicotine delivery via gum/spray
Oral	Concerta®	Alza Corporation	Hydroxypropyl methylcellulose & Polyethylene oxide	Attention deficit hyperactivity disorder (ADHD)	OROS® osmotic-controlled release tablet
Vaginal	Cervidil®	Controlled Therapeutics,	Polyethylene oxide & urethane	Cervical ripening at	Contains 10 mg dinoprostone,

		UK; marketed by Forest / Ferring Pharma		term	release ~0.3 mg/h
Transdermal	Lidoderm®	Teikoku Pharma USA	Sodium carboxymethylcellulose	Post-herpetic neuralgia	Lidocaine hydrogel patch
Ocular	Restasis®	Allergan	Carbomer	Dry eye (increase tear production)	Ophthalmic emulsion with immunomodulator

FUTURE PERSPECTIVES

Over five decades, hydrogels have advanced from simple sustained-release systems to sophisticated platforms for controlled, multi-drug delivery with high precision and biocompatibility.^[23] In situ forming hydrogels, using physical/chemical cross-linking, enhance injectability and strength for applications like wound healing and tissue engineering, overcoming early targeting and scalability issues.^{[24],[25]} Nanoparticle-hydrogel hybrids, incorporating antimicrobial metal/metal oxides or polymeric carriers with antibiotics, peptides, or extracts, provide sustained, localized release to combat antibiotic resistance, improving bioavailability and reducing toxicity.^[27] In oncology, nanogels leverage EPR effects for tumour-specific delivery, radio sensitization, and photothermal therapy, minimizing off-target effects and addressing multidrug resistance.^[28] Bio-orthogonal cross-linking ensures safer, selective gelation, supporting rapid responsiveness and regeneration with growth factors.^{[25],[29]} AI and ML revolutionize hydrogel design by predicting properties, optimizing formulations, and enabling high-throughput screening and automated discovery from vast datasets.^{[26],[29]} Future prospects include personalized AI-driven hydrogels for drug delivery, 3D-printed bio-inks, biosensors, and regenerative therapies, addressing challenges like biocompatibility, immune responses, and regulatory hurdles through rigorous clinical trials.

CONCLUSION

Hydrogels have transformed drug delivery with their porous, tissue-like structure, biocompatibility, and tunable viscoelasticity, enabling targeted oral, ocular, dermal, and subcutaneous applications. Their high-water retention and similarity to natural tissues distinguish them from other biomaterials, supporting advanced formulation design for protein and anticancer drug delivery. Biocompatible and biodegradable, hydrogels excel in nanobiotechnology, tissue engineering, wound healing, biosensors, and contact lenses. Future

advancements in polymer chemistry, AI-driven design, and nanoparticle integration promise personalized, stimuli-responsive systems for precise drug release and regenerative therapies. These innovations position hydrogels as intelligent, next-generation carriers, poised to revolutionize drug delivery and clinical applications.

ACKNOWLEDGEMENTS

The authors would like to gratefully acknowledge the Dean Dr. Arul Kumar Sundaresh, M.S. (ENT)., and the Principal, College of Pharmacy, Dr. T. Venkata Rathna Kumar, M. Pharm., Ph. D., Madurai Medical College, Madurai, for providing these necessary facilities for the research work.

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