Review Article

Advances in Hydrogel Formulations for Oral and Transdermal Therapeutic Delivery

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Received: 06-10-2025; **Revised:** 18-12-2025; **Accepted:** 25-12-2025; **Published online:** 20-01-2026.

ABSTRACT

Hydrogels are three-dimensional polymeric network structures capable of absorbing and retaining large amounts of water within their porous framework. They can be prepared from natural or synthetic polymers and are widely used in biomedical applications due to their biocompatibility, flexibility, permeability, and ability to mimic biological tissues. Their tunable swelling behavior, elasticity, and controlled biodegradability further enhance their suitability for therapeutic use. This review highlights key functionalization strategies developed to improve the performance of conventional hydrogels by enhancing their mechanical strength, stability, responsiveness, and drug-loading capacity. Special attention is given to advanced systems such as DNA-based and hybrid hydrogels, which offer superior programmability and improved therapeutic potential. Various cross-linking methods, materials, preparation techniques, advantages, and limitations are presented in tabular form for better understanding. Applications of hydrogels in oral and transdermal drug delivery are discussed, focusing on controlled and targeted release. The role of hybrid hydrogels in modern wound care, along with the unique benefits of hydrogel nanoparticles for targeted and intracellular drug delivery, is emphasized. Additionally, hydrogel-based systems used in tissue engineering and contact lenses are reviewed. Commercially available hydrogel products in oral, ocular, and wound-care areas are also summarized. Overall, hydrogels hold strong promises for future advancements in drug delivery and biomedical science.

Keywords: Hydrogels, Drug Delivery, Cross-linking Techniques, Biomedical Applications, Hybrid Hydrogels.

INTRODUCTION

Hydrogels are water-loving (hydrophilic) polymers that form three-dimensional networks capable of absorbing and holding large amounts of water—often many times their dry weight. These networks can be formed through physical interactions or chemical cross-linking, which help maintain the hydrogel's structure and strength[1]. Their usefulness as biomaterials comes from their unique properties: they hold a high amount of water, are soft and elastic like natural tissues, and have low stickiness when in contact with water or body fluids[2]. Drug delivery is a prominent area of focus in pharmaceutical research, as numerous potential therapeutics could become more effective and broadly applicable when paired with an appropriate delivery mechanism. The development of drug delivery systems (DDS) relies on various factors, including the drug's physicochemical characteristics and its intended site of action[3].

Drug delivery system:

1. Transdermal Drug Delivery

Hydrogels used in transdermal drug delivery systems should have key properties such as excellent biocompatibility, biodegradability, elasticity, non-allergenicity, ease of application, soft texture, and high-water content. Their ability to hydrate the skin helps enhance drug transport across the skin, making hydrogels valuable for improving transdermal delivery[4-5]. Transdermal drug delivery is a valuable method for administering drugs through the skin to achieve local or systemic effects. However, its progress has been limited because many drugs, such as proteins and peptides, cannot pass through the skin at effective rates. To overcome this, both chemical and physical methods are used to enhance drug permeation through the skin[4-6].

Microneedle arrays made from cross-linked hydrogel polymers can, upon insertion into the skin, absorb interstitial fluid to create continuous pathways connecting to the dermal circulation. In the initial reported study, an aqueous blend comprising poly (methylvinylether/maleic acid) and PEG 10,000 was utilized to fabricate microneedles using silicone micromole templates. It was shown that hydrogel-based microneedles enabled extended transdermal drug delivery, with the drug release rate primarily determined by the cross-linking density of the hydrogel matrix. Additionally, pulsatile or bolus drug release can be modulated electrically, and this approach involves only minimally invasive patient supervision[8]. The potential of using hydrogels to create microneedle patches for the sustained delivery of high-dose metformin has been explored[9]. After applying the hydrogel microneedle patch, a steady plasma drug concentration of 3.2 µg/mL was maintained for up to 24 hours in a rat model, showing an overall bioavailability increase of about 30%. This suggests that hydrogel microneedle technology holds promise for sustained drug delivery. Additionally, the iontophoretic delivery of methotrexate using hydrogels was found to be more effective than passive delivery, highlighting the potential of hydrogel-based iontophoresis[10]. The difference

in permeation rates from various vehicles may be due to the repulsion between positively charged buprenorphine and cationic chitosan[11]. A new portable and disposable iontophoretic reverse electrodialysis (RED) device has been developed, which is connected to an electroconductive hydrogel made of polypyrrole-embedded PVA[12]. It was concluded that charge-inducing agents in RED-driven iontophoretic systems can effectively enhance the transdermal delivery of both acidic and basic drugs.

Hydrogels, due to their high-water content, offer easier application and greater patient comfort compared to traditional transdermal patches. In our laboratory, a gel formulation containing nebivolol, gellan gum, Carbopol, and PEG 400 was optimized for transdermal delivery and tested in albino rats. The optimized gel showed a significant increase in transdermal flux (30.86 ± 4.08 µg/cm²/h) compared to a nebivolol suspension[13]. Stable hydrogels made from a combination of gellan gum and Carbopol 940 have shown potential for the transdermal delivery of Biopharmaceutics Classification System (BCS) Class II drugs.

Additionally, a paintable oligopeptide-based hydrogel loaded with paclitaxel-encapsulated, cell-penetrating peptide-modified transferosomes was developed for treating melanoma topically. When applied as a patch over the tumour, this paclitaxel-loaded hydrogel offered prolonged drug retention at the site and significantly enhanced tumour suppression, especially when combined with systemic Taxol chemotherapy[14]. Several studies have examined how hydrogels can enhance dermal drug delivery when used with nanoparticle carriers[15].

The potential of three types of nanocarriers—polymeric micelles, solid lipid nanoparticles, and self-nanoemulsifying drug delivery systems (SNEDDS)—was compared for delivering lidocaine through the skin using an artificial skin membrane[16]. SNEDDS showed the highest lidocaine loading compared to polymeric micelles and solid lipid nanoparticles. After 6 hours, both polymeric micelles and SNEDDS delivered significantly more lidocaine than solid lipid nanoparticles.

In another study, a novel composite of micelles and hydrogel demonstrated effective dermal delivery of hydrocortisone. The permeation rate and total amount of hydrocortisone delivered were many times higher than those achieved with a conventional hydrocortisone cream[17]. Incorporating drug-loaded particulate carriers into a hydrogel matrix is a promising and effective approach for transdermal therapy.

In one study, pH-sensitive Eudragit S100 nanoparticles loaded with piroxicam were developed for transdermal delivery using a Carbopol 934 hydrogel. The nanoparticles, sized between 25-40 nm, were prepared using a simple nanoprecipitation method and then dispersed in the hydrogel. The results showed a significant increase in piroxicam delivery through mice skin using this nanocarrier-hydrogel system[18].

2. Oral Delivery:

Hydrogels used in oral drug delivery systems should have key properties such as biocompatibility, the ability to carry a wide range of drugs, adjustable physical and chemical characteristics, targeted delivery, and controlled release of both synthetic drugs and biologics for local and systemic treatments.

One of the main challenges in oral drug delivery is the effective administration of hydrophilic macromolecules like insulin or heparin. Hydrogels are especially suitable for these drugs, as their polymer networks can protect the drugs from the acidic environment of the stomach. To achieve this protection and enable targeted release, natural polymers with anionic side groups are often modified with acrylic acid derivatives, resulting in hydrogels that respond to specific stimuli. Various strategies have been developed to design smart hydrogels with fast responsiveness and improved mechanical strength for a wide range of biomedical applications, as discussed in earlier studies[20].

Several studies have demonstrated the effectiveness of pH-sensitive hydrogels in oral formulations of drugs such as chemotherapeutic agents, insulin, calcitonin, and interferon-β[19-21]. The particle size of hydrogels can be adjusted to deliver drugs to specific targets, such as the small intestine (1–1000 µm), intracellular vesicles like endosomes (50–200 µm), or lymphatic vessels (less than 30 µm). Studies have shown that orally delivered chemotherapeutic drugs can be more effective and cause fewer side effects compared to those given by injection[22].

Superporous hydrogel (SAH) formulations have strong mechanical properties and swell rapidly, making them suitable for oral drug delivery and other biomedical applicationS[23]. Anionic hydrogels are commonly used to protect drugs from stomach acid and ensure their release in the intestine, as they become ionized, swell, and develop larger pores at pH levels above the polymer's pKa[24]. Cationic hydrogels can be used for drug delivery in the stomach and inside cells, as they ionize at pH levels lower than the polymer's pKa. A new type of amphiphilic polymer carrier, made of anionic P(MAA-g-EG) combined with PMMA nanoparticles, has been developed for oral delivery of low-molecular-weight proteins or hydrophobic drugs like doxorubicin, specifically targeting the colon[25]. Studies have shown that increasing the number of embedded nanoparticles results in higher drug entrapment and prolonged release in the colon. Similarly, spray-dried gelatin nanospheres exhibited improved mucoadhesion after oral administration[26].

A new hydrogel, made by grafting polycaprolactone onto a methacrylic acid copolymer, was developed for oral delivery of amifostine. Its radio-protective effect was confirmed by blood tests and a 30-day survival study in mice, showing strong protection. This hydrogel can shield the drug from stomach acid and enzymes, ensuring its delivery to the intestine[27]. Based on the high encapsulation efficiency (94.2 ± 2.6%), drug-loading capacity

(13.5 ± 0.4%), and prolonged in vivo hypoglycaemic effect (up to 24 hours), the study concluded that insulin loaded into lectin-functionalized carboxymethylated kappa-carrageenan microparticles shows strong potential for development as an oral insulin delivery system[28].

Polyelectrolyte complexes formed by combining natural anionic alginate with chitosan can help control drug release and prevent the rapid breakdown of alginate in alkaline conditions. Interpenetrating networks of these complexes have shown potential for delivering proteins and vaccines. Additionally, new biocompatible hyaluronic acid derivatives have been studied for protein and peptide delivery, using α-chymotrypsin under simulated acidic conditions to evaluate their effectiveness[29].

Hydrogel carriers have been used for intracellular delivery of chemotherapy drugs through acid-sensitive oxime linkages or acetals. Temperature- and pH-responsive, acid-degradable carbohydrate-based nanogels have also been explored for delivering DNA and enzymes into endosomes[30]. Novel pH- and temperature-responsive hydrogels made from N-acryloyl-L-phenylalanine and guar gum using free radical polymerization have been proposed for the controlled release of the anticancer drug imatinib mesylate[31]. Hydrogels offer advantages such as stimuli responsiveness, biocompatibility, and high drug loading capacity. However, their main limitation is that their swelling depends entirely on water diffusion. Common hydrogel polymers used for oral delivery of proteins and peptides include PMMA, alginate-based, and chitosan-based hydrogels[32].

Conventional oral hydrogel formulations are usually designed as matrix or reservoir systems (Figure 1).

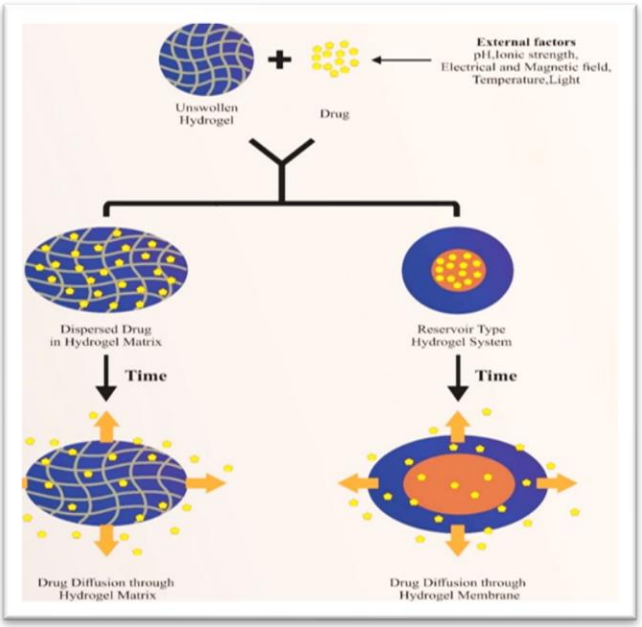

Figure 1: Conventional hydrogel oral preparation methods and drug release behaviour.

In matrix systems, the drug is dispersed throughout the hydrogel and is released as the matrix dissolves in an aqueous environment. In reservoir systems, drug release is mainly controlled by the drug and polymer properties, as well as the thickness of the polymer shell. Overall, drug release from hydrogels depends on both the dosage form and polymer characteristics. Additionally, incorporating nanosuspensions into hydrogels for oral use has shown a significant improvement in bioavailability[33]. Selected examples of commercial dosage form for oral delivery are summarized in table 1.

Table 1: Selected examples of hydrogel-based commercial dosage forms for oral delivery.

Commercial product	Polymers	Active Constituent	Dosage Form	Application	Manufacturer
Buccastem® M	Povidone K30, Xanthan gum	Prochlorperazine maleate	Tablet	Nausea & vomiting in migrane	Alliance
Biotene	Carbomer & hydroxyethyl cellulose	Nil	Gel	Oral moisturizing agent in dry mouth	GlaxoSmithKline
Hydrogel 15%	Carbomer in ozonized sunflower oil	Ozone	Gel	Oral health	Honest 03
Gengigel®	Hyaluronan	Nil	Gel	Mouth & gum care-oral ulcers	Oral science
Lubrajel™ BA	Glyceryl acrylate & glyceryl polyacrylate	Nil	Gel	Oral moisturizing agent	Prospector
Nicotinell®	Xanthan gum & gelatin	Nicotine	Chewing gum	Smoking cessation	GlaxoSmithKline
Zilactin-B Gel®	Hydroxypropyl cellulose	Benzocaine	Gel	Local anaesthetic in minor oral problems	Blairex laboratories Inc.

CONCLUSION

Hydrogels have emerged as highly versatile and adaptive materials with significant potential in modern drug delivery, particularly for oral and transdermal routes. Their tunable physicochemical properties—such as swelling behavior, mechanical strength, biodegradability, and responsiveness to physiological stimuli—enable precise control over drug release and improved therapeutic outcomes. Advances in hydrogel engineering, including smart, pH-responsive, nanoparticle-integrated, and hybrid hydrogel systems, have further enhanced their ability to deliver a wide range of therapeutic agents, from small molecules to peptides and proteins. Transdermal applications, including microneedle-integrated hydrogels and electroconductive systems, demonstrate remarkable improvements in skin permeation and patient compliance, while oral hydrogels offer targeted, protected, and sustained delivery within the gastrointestinal tract.

Despite challenges such as limited stability, drug loading constraints, and the need for improved scalability, continuous innovations in polymer science and nanotechnology are rapidly overcoming these limitations. Overall, hydrogels represent a promising class of biomaterials with the potential to revolutionize future drug delivery platforms, offering safer, more effective, and patient-friendly therapeutic solutions.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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