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Review Paper

Polymer-Based Hydrogel Nanoparticles as Advanced Drug Delivery Systems

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ABSTRACT

Hydrogel nanoparticles have emerged as highly promising drug delivery systems due to their ability to merge the beneficial features of hydrogels—such as high-water content and hydrophilicity—with the nanoscale size of particles. In recent years, a wide range of polymer-based hydrogel nanoparticles has been developed and studied, utilizing both natural and synthetic polymers, each offering unique advantages and limitations. Among natural polymers, chitosan and alginate have been particularly well explored for nanoparticle formation. On the synthetic side, materials like poly (vinyl alcohol), poly(ethylene oxide), poly(ethyleneimine), poly (vinyl pyrrolidone), and poly-N-isopropylacrylamide have been used to create hydrogel nanoparticles with diverse properties suited for drug delivery applications. Regardless of the polymer source, the drug release from these systems is typically governed by a complex interplay of factors, including drug diffusion, matrix swelling, and chemical interactions between the drug and the hydrogel network. Various crosslinking techniques have been employed to construct these hydrogel matrices, broadly categorized into two main types: chemical crosslinking and physical crosslinking

INTRODUCTION

The term “Hydrogel,” as noted by Lee, Kwon, and Park, has been in use since 1894, although the substance referenced was not truly a hydrogel but rather a colloidal gel made of inorganic salts. These gels consist of polymeric matrices that do not dissolve; instead, they absorb water and swell. Nonetheless, the first genuine hydrogel with a cross-linked structure was described by Wicht Erle and Lim in 1960. This was a hydrogel made from polyhydroxy ethyl methacrylate, developed with the intention of using it for permanent contact lenses. (1) Hydrogels are three-dimensional polymeric networks that can absorb and retain large quantities of water. These hydrophilic gels, commonly referred to as hydrogels, may also exist as colloidal systems where water acts as the dispersing medium [2]. Their capacity to absorb

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water stems from the presence of hydrophilic functional groups along the polymer backbone. Meanwhile, their insolubility in water is maintained through cross-linking between polymer chains, which stabilizes the network structure. Both natural and synthetic polymers can form hydrogels. Hydrogels can be produced using fully synthetic components and are known for their thermal stability, even under sharp or extreme temperature variations [3]. A defining characteristic of hydrogels is their minimum water content, which must be at least 10% by weight. The high-water content contributes to their swelling capacity, softness, and flexibility, while the chemical or physical cross-links provide the necessary structural integrity [4,5]. The hydrophilic nature of these materials is attributed to functional groups such as amino ($–NH_2$), carboxylic (–COOH), hydroxyl (–OH), amide ($–CONH_2$), imide (–CONH), and sulfonic acid ($–SO_3H$). Due to their soft, tissue-like consistency, hydrogels are well-suited for biomedical applications as they integrate effectively with biological tissues without eliciting adverse reactions [5]. A landmark innovation in this field was the development of soft contact lenses in 1960 by Wichterle and Lim, using natural hydrogel materials [6–8]. Over the past two decades, synthetic hydrogels have increasingly replaced natural ones due to several advantages, including greater durability, higher water absorption capacity, and superior mechanical strength While research on the classification, synthesis, and application of hydrogel systems—whether natural, synthetic, or hybrid—is extensive [6,13,14,17–19], there is relatively limited data on their swelling dynamics and water absorption kinetics [22]. This review seeks to fill that gap by comparing the swelling and gelation behaviour of structurally related natural polymers, such as starch, cellulose, and chitosan, with the goal of enhancing understanding of their structure–sorption property relationships. It further aims to stimulate deeper investigation into biopolymer-based hydrogel systems. Moreover, the review explores the role of water in hydrogel formation and stability, particularly in systems based on natural polymers and hybrid materials. It also highlights various stimuli-responsive hydrogel types and discusses design strategies employed in their development. The use of natural biopolymers like alginate, collagen, starch, cellulose, and chitosan has significantly propelled advancements in the field of functional hydrogel materials.

Types of Hydrogels

Conductive Hydrogels

Conductive hydrogels distinguish themselves from conventional hydrogels through their ability to conduct electricity. First introduced by Gilmore et al., these hydrogels are primarily categorized into two types:

(i) Those incorporating conducting polymers,

(ii) Those integrating metallic nanoparticles.

They are generally formed by combining cross-linked soft hydrogels with electrically conductive materials. Although conducting polymers are non-metallic, they exhibit remarkable electrical conductivity, significantly enhancing both the structural and electrical properties of the resulting hydrogels. Common examples include polyacetylene, polythiophene, and poly(phenylene vinylene).

Injectable Hydrogels

Injectable hydrogels are characterized by their fluid-like nature, enabling administration via injection. These hydrogels undergo a sol–gel phase transition, expanding their potential in biomedical applications and improving patient compliance. They are typically divided into two main categories:

- **Light-activated hydrogels**, which form permanent covalent bonds when exposed to visible or UV light, and
- **Self-assembling hydrogels**, which form either spontaneously or in response to specific stimuli.

  Examples include poly(vinyl alcohol) and poly(ethylene glycol).

3. **Double Network (DN) Hydrogels**

Double network hydrogels consist of two interpenetrating polymer networks: one being a rigid, highly cross-linked network, and the other a soft, loosely cross-linked network. These two networks interact physically rather than chemically. This unique structure imparts a viscoelastic flow behavior, enabling the hydrogel to effectively dissipate fracture energy through network deformation and slippage of polymer chains. As a result, DN hydrogels exhibit superior mechanical strength compared to single-network hydrogels. A typical example includes poly(N,N′dimethylacrylamide)-based hydrogels.

Natural polymer	Chemical structures	Preparation
Cellulose	Composed of β (1-4)-glycosidic-linked glucose units	1. Lignocelluloses purification by chemical treatment. 2.Biological method depending on microbial enzymes. 3.Bacterial cellulose produced by certain types of bacteria
Chitosan	Poly-(β-1-4)N-acetyl-D-glucosamine	Derived from chitin by partial deacetylation though chemical or enzymatic hydrolysis.
Collagen	A helical fibrous protein formed by three peptide chains	1. Extracted and purified from various animal sources by chemical and enzyme treatment. 2. Recombinant collagen produced by recombinant technology and biosynthesi
Alginate	Consisting of α-L glucuronate and β-D mannuronate repeating unit	1. Extraction from brown algae (Phaeophyceae) by treatment with aqueous alkali solutions. 2. Bacterial biosynthesis from Azotobacter and Pseudomonas
Hyaluronic acid	Consisting of N-acetyl-glucosamine and D-glucuronic acid residues	1. Extraction from animal tissues. 2. Microbial fermentation using pathogenic bacteria and nonpathogenic bacteria. 3. Enzymatic polymerization of UDP-sugar monomers
Starch	Composed of α-D-(1-4) and α-D-(1-6)-glycosidic-linked glucose units	Extracted from seeds, roots, tubers, stems, fruits, and all leaves
Guar gum	Composed of (1-4)-β-D-mannopyranosyl units and (1-6)-α-D-galactopyranosyl units	Isolated from the embryos of the leguminous plant *Cyamopsis tetragonoloba*.
Agarose	Consisting of alternating 1,3-linked β-Dgalactose and 1,4- linked 3,6-anhydro- α-Lgalatose units	Extracted from seaweed.
Dextran	Composed of α-1, 6 glycosidic linkages between glucose	2. Produced from several Gram-positive, *Leuconostoc Lesenteroides;*facultative anaerobic

	monomers, with branches from α-1, 2, α-1, 3, and α-1, 4 linkages	bacteria, such as *Leuconostoc and Streptococcus* strains; 3. Synthesized by cationic ring-opening polymerization of levoglucosan

3. **Stimuli-Responsive (Smart) Hydrogels**

Responsive hydrogels adapt their structure and properties in reaction to external stimuli such as pH, temperature, light, electric fields, and salinity. These materials find broad application in tissue engineering, controlled drug delivery, biosensors, and artificial muscles. Changes in environmental conditions induce swelling or shrinkage through non-covalent interactions like hydrogen bonding, ionic interactions, and electrostatic forces. The concept of smart hydrogels was pioneered by Katchalsky in 1949, using methacrylic acid copolymerized with a small amount of divinylbenzene to create pH-responsive swelling behaviour.

3. **Nanocomposite (Hybrid) Hydrogels**

Nanocomposite or hybrid hydrogels are formed by dispersing nano-sized materials (1–1000 nm) uniformly within a polymer matrix. These materials consist of branched or cross-linked polymers and often contain inorganic or metallic nanoparticles (e.g., carbon-based, polymeric, metal/metal oxides). The inclusion of these nanoscale components greatly enhances the mechanical strength and functional properties of the hydrogel. The cross-linking in such systems can be physical or chemical in nature.

4. **Sliding Hydrogels**

Sliding hydrogels feature topologically interlocked, non-covalent cross-links that can move along the polymer backbone. A novel example is a pseudopolyrotaxane formed by threading monothiolated β-cyclodextrin onto a block copolymer of poly(allyl glycidyl ether)–poly(ethylene glycol). This system is prepared via sonication in water and then photo-crosslinked using UV light. The resulting hydrogel displays high stretchability, tunable degradation under acidic conditions, and improved mechanical stability, outperforming many traditional hydrogels.

5. **Other Novel Hydrogel**

Beyond the conventional categories, recent advancements have led to the development of specialized hydrogels such as:

- **DNA-based hydrogels**, synthesized through the reaction between dibenzocyclooctyne-functionalized multi-arm PEG and azide-functionalized single-stranded DNA in aqueous media.
- **Magnetic hyaluronate hydrogels**, which respond to magnetic fields and offer potential in targeted drug delivery and smart medical devices. {15,16,17,18]

1. Hydrogels from Natural Polymers

Natural polymers like polysaccharides and proteins, sourced from nature, exhibit excellent biocompatibility and biodegradability. These properties make them highly suitable for hydrogel fabrication [19].

1.1 Cellulose-Based Hydrogels

Cellulose has a complex supramolecular structure stabilized by hydrogen bonds. During dissolution, these bonds are disrupted, increasing hydroxyl activity and allowing cellulose to recombine with other polymers via new hydrogen bonds [20,21].

1.2 Chitosan-Based Hydrogels

Chitosan is a hydrophilic, naturally occurring polycation composed of D-glucosamine and N-

acetyl-D-glucosamine units [22]. It is derived from chitin—second only to cellulose in abundance—which is found in fungal cell walls and the exoskeletons of crustaceans and insects [23]. Chitosan typically contains at least 60% D-glucosamine for effective use.

1.3 Collagen/Gelatin-Based Hydrogels

Collagen, like cellulose and chitosan, is a widely available natural polymer with extensive biomedical applications [24,25]. Its biocompatibility, biodegradability, hydrophilicity, and mechanical strength make it an essential material in medical research and applications.

1.4 Alginate-Based Hydrogels

Alginate is valued for its biocompatibility, non-immunogenicity, biodegradability, and chelating properties [26]. It absorbs fluids effectively and can be purified to eliminate contaminants like heavy metals and endotoxins, making it suitable for pharmaceutical use, including drug delivery and implants [27–29].

1.5 Hyaluronic Acid-Based Hydrogels

Hyaluronic acid, found in the extracellular matrix (ECM), is a polysaccharide composed of N-acetyl-glucosamine and D-glucuronic acid [30]. It plays vital roles in hydration, lubrication, and cell signaling. Its nontoxicity, biodegradability, and compatibility make it widely used in tissue engineering, wound healing, and drug delivery [31–35].

1.6 Starch-Based Hydrogels

Starch is a biodegradable polysaccharide made of α-D-(1-4) and α-D-(1-6)-linked glucose units [36,37]. Found naturally in granules, it also contains small amounts of proteins, fats, and minerals [38]. Its affordability and renewable nature support its use in biomedical and industrial applications.

1.7 Guar Gum-Based Hydrogels

Derived from the seeds of *Cyamopsis tetragonoloba*, guar gum is a nonionic polysaccharide with high hydrophilicity and biodegradability. Its structure features β-D-mannopyranosyl main chains and α-D-galactopyranosyl side chains [39]. It can be chemically modified for various biomedical purposes.

1.8 Agarose-Based Hydrogels

Agarose, extracted from seaweed, consists of β-D-galactose and 3,6-anhydro-α-L-galactose [40]. It's highly hydrophilic, biodegradable, and compatible with cells, making it valuable in biomedical and bioengineering contexts.

1.9 Dextran-Based Hydrogels

Dextran is a branched polysaccharide mainly linked through α-1,6-glycosidic bonds, with some branches at α-1,2, α-1,3, and α-1,4 positions [41]. It is biocompatible, soluble, and nonimmunogenic, and breaks down safely in the body, making it ideal for drug delivery and biomedical applications [42].

2. Hydrogel Preparation Techniques

Hydrogels can be prepared through physical, chemical, or radiation-induced crosslinking depending on how the polymer network is formed [43–45].

2.1 Physical Crosslinking

Physically crosslinked hydrogels are created through self-assembly using non-covalent interactions (e.g., hydrogen bonds, van der Waals forces, ionic, or hydrophobic interactions) [46,47].

2.1.1 Ionic Interactions

Polyelectrolytes with charged groups can form hydrogels in the presence of counter-ions, categorized as polycations, polyanions, or polyampholytes [47–49].

2.1.2 Crystallization

Crystalline crosslinking provides a safer and more biocompatible alternative to chemical methods, especially in biomedical contexts [50,51].

2.1.3 Hydrogen Bonding

Hydrogen bonding stabilizes hydrogel networks via interactions between hydrogen atoms and electronegative atoms. Although this enhances strength, hydrogels formed this way often lack long-term durability for load-bearing uses [52,53].

2.2 Chemical Crosslinking

This involves forming covalent bonds using chemical crosslinkers, improving the hydrogel's mechanical and thermal stability [54].

2.2.1 Acid-Induced Sol–Gel Transition

Combining polyelectrolytes with opposing charges in acidic environments helps form stable, uniform hydrogels. For instance, chitosan and sodium alginate form hydrogels upon exposure to acetic acid [55].

2.2.2 Double Network (DN) Hydrogels

DN hydrogels combine a rigid, highly crosslinked network with a flexible one to enhance strength and toughness, making them ideal for mechanical applications [56].

2.2.3 Schiff Base Reactions

Hydrogels formed via imine bond formation between amines and aldehydes show reversible and self-healing properties, making them responsive and biocompatible [57–59].

2.3 Radiation Crosslinking

This technique uses gamma rays, X-rays, or electron beams to crosslink polymer chains without chemical agents. It generates free radicals that form covalent bonds, resulting in sterile, highly tunable hydrogels ideal for medical use [60–64].

3. Applications of Natural Polymer-Based Hydrogels

3.1 Biomedical Applications

3.1.1 Drug Delivery

Chitosan-based hydrogels retain chitosan's biocompatibility and can be engineered for adhesive drug delivery systems that remain stable during physical activity, like hand movement [65].

3.1.2 Wound Healing

Carrageenan-based hydrogels are effective in wound care, maintaining a moist environment, absorbing fluids, and allowing oxygen exchange. They can also be enhanced with bioactive agents like thyme oil for faster healing and infection prevention [66].

3.1.3 Cancer Treatment

A porous chitosan-cellulose nanocomposite hydrogel showed enhanced drug delivery for naringenin at acidic pH, significantly improving its anticancer efficacy against skin cancer cells [67].

3.1.4 Gene Therapy

Hydrogels' water-rich, three-dimensional structure allows for safe encapsulation and sustained release of nucleic acids or gene editing

tools, making them promising for gene therapy [68].

3.1.5 Tissue Engineering

Thanks to their ECM-mimicking properties and cell compatibility, hydrogels are ideal scaffolds for tissue regeneration. Chitosan-lignin hydrogels, for instance, support cell attachment and growth [69].

3.2 Other Applications

3.2.1 Environmental and Agricultural Uses

Natural polymer-based hydrogels are utilized in water purification and sustainable agriculture. Superabsorbent hydrogels enhance soil moisture retention in arid regions. While synthetic SAPs pose environmental concerns, natural polymers provide biodegradable, eco-friendly alternatives for improving crop yield and water use efficiency [70,71].

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