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Hydrogel: A Review

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ABSTRACT

Hydrogels are three-dimensional, cross-linked polymer networks that have gained significant attention in various fields due to their unique properties, such as high water retention, biocompatibility, and versatility in drug delivery. This review provides an overview of the preparation, characterization, and diverse applications of hydrogels. The methods for hydrogel synthesis, including physical and chemical crosslinking techniques, are discussed in detail. The review also explores the vast array of applications of hydrogels, with a focus on their use in biomedical fields like wound healing, drug delivery (oral, transdermal, ocular, and rectal), gene delivery, and tissue engineering. Moreover, non-biomedical applications, including their use in water purification, plant watering systems, and cosmetics, are also discussed. The potential challenges, including environmental concerns and material stability, are considered, along with the future perspectives of hydrogel technology. With ongoing advancements in hydrogel research, these materials continue to show promise for innovative therapeutic and industrial applications, offering a platform for developing novel, effective, and sustainable solutions.

KEYWORDS: Hydrogel, drug delivery, wound healing

INTRODUCTION

Hydrogels are polymeric networks that can absorb and retain large amounts of water.[1] These networks contain hydrophilic groups that become hydrated when in contact with water, leading to the formation of the hydrogel structure. Another way to define hydrogels is as polymeric materials that can swell and retain a significant amount of water within their structure without dissolving. Due to their high water content, they possess flexibility that resembles natural tissue. Hydrogels' ability to absorb water is due to the hydrophilic functional groups attached to the polymeric backbone, while their resistance to dissolution comes from crosslinks between the polymer chains. Over the years, researchers have defined hydrogels in various ways, but the most common definition describes them as water-swollen, cross-linked polymeric networks formed through the reaction of one or more monomers.

In recent decades, natural hydrogels have been replaced by synthetic ones, which offer advantages such as longer service life, higher water absorption capacity, and greater gel strength. Synthetic polymers are generally well-defined, making them easier to modify for specific properties such as degradability and functionality.[2] Hydrogels are categorized as "reversible" or "physical" gels when molecular entanglements or secondary forces (such as ionic bonds, hydrogen bonding, or hydrophobic interactions) play a significant role in network formation. These hydrogels can retain multiple times their weight in water, and they typically consist of carboxylic acid-based polymers. In water, these acid groups ionize, leaving the polymer with negative charges along its length. This results in two effects: first, the negative charges repel each other, causing the polymer to expand; and second, water molecules are attracted to the negative charges. This swelling increases the viscosity of the mixture as the polymer takes up more space and resists the movement of surrounding solvent molecules.

The polymer remains in equilibrium with the surrounding water, but this equilibrium can be altered in various ways. For instance, increasing the ionic concentration of the solution (by adding salt) can cause positive ions to neutralize the negative charges on the polymer, causing it to collapse. Conversely, adding alkali removes acid ions, pushing the equilibrium to the right and causing the polymer to swell, while adding acid has the opposite effect. Hydrogels expand and contract depending on factors like pH, temperature, and ionic concentration, and by adjusting the mixture of monomers used to create the polymer, these properties can be fine-tuned.[3]

ADVANTAGES

- Hydrogels are more elastic and durable.
- They have excellent transparency and are easy to modify.
- Due to their high water content, hydrogels exhibit a flexibility similar to that of natural tissue.
- Hydrogels are biocompatible, biodegradable, and can be injected.
- They are responsive to changes in pH, temperature, or metabolite concentrations and can release their contents accordingly.
- Hydrogels allow for controlled and timely release of medicines or nutrients.

DISADVANTAGES

- High cost.
- They are non-adherent and may require secondary dressings, and movement of the maggot may cause discomfort.
- Sterilizing hydrogels can be challenging.
- In contact lenses, they may lead to hypoxia, dehydration, and red-eye reactions due to less deposition.

TECHNICAL FEATURES OF HYDROGEL:

An ideal hydrogel material should possess the following functional properties:

- Maximum absorption capacity in saline solutions.
- Adjustable absorption rate according to the specific requirements of the application.
- Minimal soluble content and residual monomers.
- High durability and stability in both swollen conditions and during storage.
- Colorless, odorless, and fully non-toxic.

PROPERTIES OF HYDROGEL

1. **Swelling Properties**: Even small changes in environmental conditions can trigger rapid and reversible changes in hydrogels. Factors such as electric signals, pH, temperature, and the presence of enzymes or other ionic species can lead to alterations in the hydrogel's physical texture.[4]

2. **Mechanical Properties**: The mechanical properties of hydrogels can be adjusted based on their intended use. By increasing the degree of crosslinking, a hydrogel with greater stiffness can be produced, or by heating the material, its stiffness can be reduced. Changes in mechanical properties are influenced by various factors, so different analyses are required depending on the specific material.[5]

Polymers Used in Hydrogels:

- Natural Polymers: Examples include chitosan, gelatin, alginates, and fibrin.[6]
- Synthetic Polymers: Examples include vinyl acetate, acrylic acid, and methacrylate-vinyl pyrrolidine.

3. **Biocompatible Properties**: Biocompatibility refers to a material's ability to interact with a host in a way that elicits an appropriate response for a specific application. [7] It consists of two main aspects:

(a) Bio-functionality: The material's ability to perform the specific function it is designed for.

(b) Bio-safety: Ensuring a suitable host response, both systemically and locally (in the surrounding tissue), which includes the absence of mutagenic effects and cytotoxicity.

CLASSIFICATION OF HYDROGELS [8]

1. CLASSIFICATION BASED ON SOURCE

1. **Natural Hydrogels**: Natural hydrogels are biodegradable, biocompatible, and have good cell adhesion properties. There are two major types of natural polymers which are used to produce natural hydrogels are proteins such as collagen, gelatin and, lysozyme, polysaccharides such as hyaluronic acid, alginate and Chitosan.

2. **Synthetic Hydrogels**: They are more useful as compared to natural hydrogels because they can be engineered to have a much wider range of mechanical and chemical properties than their natural counterparts. Polyethylene glycol based hydrogels are one class of the widely used material in biomedical application due to their non-toxicity there compatibility and low immunogenicity.

3. **Hybrid Hydrogels**: They are a combination of natural and synthetic polymer hydrogels. To combine the advantages of both synthetic and natural hydrogels many naturally occurring biopolymers such as dextran, collagen, and Chitosan, have been combined with synthetic polymers such as poly (N-isopropylacrylamide) and polyvinyl alcohol.

2. CLASSIFICATION ACCORDING TO POLYMERIC COMPOSITION

1. **Homo-Polymeric Hydrogels**: Homo-polymeric hydrogels are referred to as polymer network derived from a single species of a monomer, which is a basic structural unit comprising of any polymer network. Homopolymers may have cross-linked skeletal structure depending on the nature of the monomer and polymerization technique.

2. **Co-Polymeric Hydrogels**: Co-polymeric hydrogels are comprised of two or more different monomer species with at least one hydrophilic component, arranged in a random, block, or alternating configuration along the chain of the polymer network.

3. **Multi-Polymer Interpenetrating Polymeric Hydrogel (IPN)**: An important class of hydrogels, having a network system that is made of two independent cross-linked synthetic or natural in the semi-IPN hydrogel, one component is a cross-linked polymer and the other component is a non-cross-linked polymer.

3. ACCORDING TO THE BIODEGRADABILITY

1. **Biodegradable Hydrogels**: Hydrogels are biodegradable many polymers created by nature are biodegradable, such as Chitosan, fibrin, and agar. Poly (aldehyde guluronate), polyanhydrides and poly (N-isopropyl acrylamide) are examples of synthetic biodegradable polymers.

2. **Non-Biodegradable Hydrogels**: Various vinylated monomers or macromers such as 2- 2-hydroxyl ethyl methacrylate, methoxyl poly (ethylene glycol), 2- hydroxyl propyl methacrylate, and acryl amide are widely applied in the preparation of non-biodegradable hydrogels.

4. CLASSIFICATION BASED ON CONFIGURATION

1. **Amorphous (Non-Crystalline)**

2. **Semi Crystalline**: It is a complex mixture of amorphous and crystalline phases.

3. **Crystalline**

5. CLASSIFICATION BASED ON TYPE OF CROSS-LINKING

1. **Chemically Cross-Linked Network:** They have permanent junctions

2. **Physical Networks**: They have transient junctions that arise from either polymer chain entanglements or physical interactions such as hydrogen bonds, or hydrophobic interactions.

6. CLASSIFICATION ACCORDING TO NETWORK ELECTRICAL CHARGE

1. **Nonionic (Neutral)**

2. **Ionic (Including Anionic or Cationic).**

3. **Amphoteric Electrolyte (Ampholytic) Containing Both Acidic And Basic Groups**

4. **Zwitter Ionic (Polybetaines) Containing Both Anionic And Cationic Group**

PREPARATION METHODS OF HYDROGELS

Hydrogels are composed of polymer chains, and their properties depend significantly on the polymer used. The defining feature of hydrogels is their ability to absorb water, though not all polymers are suitable for hydrogel synthesis in hydrogels, polymer chains are interconnected through cross-links, forming a three-dimensional network. Cross-linking impacts various physical properties, such as elasticity, viscosity, solubility, glass transition temperature, strength, toughness, and melting point. Cross-linking raises the glass transition temperature due to the restricted rotational motion between polymer chains. It also increases the molecular weight of the polymer chains, which limits their translational movement and decreases solubility. These polymers are insoluble yet capable of absorbing significant amounts of solvent, leading to gel formation. The quantity of solvent absorbed by the hydrogel depends on the cross-linking density, which increases as interactions between the polymer chains and solvent molecules decrease.

Hydrogels can be prepared through two primary methods: physical cross-linking and chemical cross-linking. These methods yield hydrogels with different properties due to the nature of the cross-links between the polymer chains. Ionizing radiation, including X-rays, gamma rays, accelerated electrons, ion beams, and high-energy ultraviolet rays, can initiate polymerization and cross-linking processes. These radiations possess sufficient energy to break chemical bonds and trigger polymerization or cross-linking reactions. Ionizing radiation is frequently used in industries such as coatings, adhesives, and 3D printing, where rapid and efficient polymerization is essential. In cross-linking, radiation creates chemical bonds between polymer chains, forming a three-dimensional network. This network improves the mechanical properties, stability, and other beneficial characteristics of the polymer material. The cross-linking process can be controlled by adjusting exposure time, radiation frequency, temperature, and pressure.

Hydrogel Formation Materials: Materials used in hydrogel formation include polyethylene oxide, PVA, poly (acrylic acid) (PAA), poly (propylene fumarate-co-ethylene glycol) (P (PF-co-EG)), and polypeptides. Some materials are naturally derived polymers, such as agarose, alginate, chitosan, collagen, fibrin, gelatin, and hyaluronic acid. Table 1 lists hydrogel preparation methods and doped elements. [9]

1. **Physical Cross-Linking**: In physically cross-linked hydrogels, the interactions between polymer chains are not covalent but based on physical forces like hydrogen bonding, van der Waals forces, hydrophobic interactions, or coordination bonds. Unlike chemical cross-linking, physical cross-linking is reversible under specific conditions, meaning the hydrogel can undergo structural changes without breaking covalent bonds. This property makes physically cross-linked hydrogels highly responsive to external stimuli such as temperature, pH, or ionic strength. These hydrogels may exhibit unique characteristics, such as "self-healing," where the gel re-forms after being broken. Hydrogels prepared by these methods are primarily physical gels with high water sensitivity and thermal reversibility. However, they generally have a short lifespan, ranging from a few days to a month in physiological media. Consequently, they are used in applications requiring short-term drug release. Because the gelation process does not involve toxic covalent cross-linking agents, these hydrogels are considered safe for clinical use. Non-covalent methods like electrostatic interactions, hydrogen bonding, and hydrophobic forces can be used to prepare hydrogels. For instance, chitosan can be used in combination with small anionic molecules, such as sulfates, phosphates, and citrates of Pt, Pd, and Mo, for hydrogel preparation using physical methods. The synthesized hydrogels depend on the charge and size of anions and the deacetylation concentration of chitosan.

2. **Chemical Cross-Linking**: The formation of physical gels through molecular clustering causes free chain loops, leading to inhomogeneities that result in short-lived network imperfections. In contrast, chemical cross-linking offers more precise control over the hydrogel network. This method can modify the physical properties of hydrogels. In chemically cross-linked hydrogels, covalent bonds form between polymer chains, creating a stable three-dimensional network. These cross-links are typically formed via chemical reactions such as polymerization or reactions involving cross-linking agents. The covalent bonds enhance the stability of the hydrogel, making it more resistant to environmental changes like temperature or pH. As a result, chemically cross-linked

hydrogels tend to have higher mechanical strength and long-term stability. Unlike physical hydrogels, the preparation and application of chemically cross-linked hydrogels are not dependent on pH.

3. **Irradiation-Based Cross-Linking**: Irradiation-based cross-linking is an attractive approach for hydrogel synthesis, particularly when rapid gelation and cost efficiency are crucial. By using light-sensitive functional groups and UV irradiation, researchers can quickly form hydrogels, making them suitable for applications in biomedicine, tissue engineering, drug delivery, and more. However, it is important to consider factors such as the compatibility of light-sensitive moieties with the target application and the sensitivity of the hydrogel to environmental factors like light and temperature. This method offers several advantages over traditional chemical cross-linking, such as:

- Speedy preparation: Hydrogel formation is much faster using light-sensitive functional groups and UV irradiation compared to chemical cross-linking methods, which often require longer reaction times.

- Low cost: The use of light-sensitive groups and UV light reduces the need for expensive cross-linking agents or catalysts, making the process more cost-effective.[10]

APPLICATIONS OF HYDROGEL

1. **Wound Healing**: Hydrogels, due to their cross-linked structure, can retain water and drugs, which helps hold wound exudates. Polyvinyl pyrrolidine or polyacrylamide gels, containing 70-95% water, are commonly used.[11]

2. **Colon-Specific Hydrogels**: These hydrogels are designed for drug delivery in the colon, exploiting the high concentration of polysaccharide enzymes in the region. An example is Dextran hydrogel, formulated for colon-specific drug delivery.[12]

3. **Gastrointestinal drug delivery**: Hydrogels are used to deliver drugs to specific sites in the gastrointestinal tract (GIT). Colon-specific hydrogels, in particular, utilize changes in pH or enzymatic activity to trigger drug release at targeted sites.[13]

4. **Rectal Delivery**: Bio-adhesive hydrogels are employed for drug delivery via the rectum, ensuring better retention and controlled release.[14]

5. **Transdermal Delivery**: Hydrogel-based drug delivery systems are developed to facilitate the transdermal route of administration, including Iontophoresis, which enhances the permeation of substances like hormones and nicotine.[15]

6. **Drug Delivery in the Oral Cavity:** Hydrogels are used to deliver drugs for local treatment of oral diseases, such as stomatitis, fungal infections, periodontal disease, viral infections, and oral cancers.[16]

7. **Gene Delivery:** Changes in the composition of hydrogels improve the targeted delivery of nucleic acids to specific cells, offering potential for gene therapy applications.[17]

8. **Tissue Engineering**: Micronized hydrogels are used to deliver macromolecules into antigen-presenting cells, and natural hydrogels like agarose and methylcellulose are utilized in tissue engineering.[18]

9. **Ocular Drug Delivery:** Hydrogels are widely used for ocular drug delivery systems, providing controlled or sustained release to reduce dosing frequency and improve drug effectiveness by localizing the drug at its site of action. [19]

10. **Watering Beads for Plants**: Hydrogels in the form of watering beads or crystals are used to provide long-term water storage for plant growth, though there are environmental concerns regarding the toxicity of some materials used.

11. **Diapers**: Hydrogels, especially sodium polyacrylate, are used in super-absorbent diapers, providing long-lasting dryness and reducing dermatological issues related to wetness.

12. **Perfume Delivery**: Hydrogels are used in controlled-release devices for perfumes, utilizing their swelling properties to release volatile particles slowly when wet.[20]

13. **Cosmetics:** Hydrogels are used in products like beauty masks and cosmetic formulations, such as moisturizers and anti-aging treatments, often incorporating ingredients like hyaluronic acid or collagen.[21]

14. Plastic Surgery: Hydrogels are used in plastic surgery, including injectable forms like Hyaluronic Acid (HA) for body contouring or as a biocompatible alternative to silicone implants.

15. Environmental Applications: Hydrogels can help in water pollution treatment by holding microorganisms for purification or by capturing pollutants within their network.

16. Bacterial Culture: Hydrogels, such as agar, are used for culturing bacteria in biotechnological applications.

17. Electrophoresis and Proteomics: Hydrogels are widely used in gel electrophoresis for protein separation. The structure and functional properties of these hydrogels are optimized for improved resolution and performance in protein analysis.

18. Applications in Electronics: Hydrogels serve as matrixes in electronics, particularly for capacitors with hydrogel dielectrics, providing low-cost and high-performance materials. [22] Organic polymers like poly (ethylene oxide) and poly (vinyl alcohol) are commonly used in these applications.

CONCLUSION

Hydrogels have emerged as versatile materials with immense potential across a wide range of applications, particularly in the biomedical and industrial sectors. Their unique properties, such as high water content, biocompatibility, and tunable physical characteristics, make them ideal for use in drug delivery systems, wound healing, tissue engineering, and gene therapy. Furthermore, hydrogels offer promising solutions in non-biomedical fields, such as water purification, agriculture, and cosmetics. Despite their advantages, challenges related to material stability, environmental impact, and the complexity of synthesis and functionalization remain areas that need further exploration. Advancements in hydrogel technology, including the development of smart and stimuli-responsive hydrogels, are paving the way for more efficient and sustainable applications. Continued research into improving their performance, scalability, and environmental compatibility will enhance their practical use, potentially revolutionizing numerous industries and healthcare treatments. As the field evolves, hydrogels are likely to remain a central focus of innovation, offering new avenues for addressing critical global challenges.

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