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A Comprehensive Review on Hydrogel as a Novel Drug Delivery System

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Abstract: *Hydrogel products represent a class of polymeric materials characterized by their hydrophilic networks, which enable them to absorb and retain substantial amounts of water within their three-dimensional structures. Owing to their high-water content, porosity, and soft, elastic consistency, hydrogels closely mimic the physical properties of natural living tissues, surpassing other synthetic biomaterials in this regard. These materials can be engineered into various physical forms, including slabs, microparticles, nanoparticles, coatings, and films, thereby broadening their applicability in biomedical and clinical contexts.Hydrogels are widely utilized in areas such as tissue engineering and regenerative medicine, diagnostics, cellular immobilization, biomolecule or cell separation, and as barrier materials for modulating biological adhesion. Their ability to absorb biological fluids and swell results in a soft, rubber-like texture that enhances their biocompatibility and suitability for interaction with biological systems. This article aims to provide a comprehensive overview of hydrogel classification based on different criteria, along with an examination of their properties, preparation methods, and the physical and chemical characteristics that define these versatile biomaterials.*

Keywords: Applications, current Research on Hydrogels, types, Methods, Characterization, Properties

I. INTRODUCTION

Hydrogels are three-dimensional, crosslinked polymeric networks that have the ability to absorb and retain large amounts of water or biological fluids while maintaining their structural integrity. These materials can be composed of natural, synthetic, or hybrid polymers and exhibit properties such as high biocompatibility, flexibility, and tunable mechanical strength. Hydrogels are three-dimensional, crosslinked polymeric networks capable of retaining large amounts of water while maintaining their structural integrity[1]. Due to their unique physicochemical properties, such as high biocompatibility, tuneable mechanical strength, and responsiveness to environmental stimuli, hydrogels have gained significant attention across various scientific and industrial domains. Initially developed for biomedical applications, their usage has expanded to diverse fields, including drug delivery, wound healing, tissue engineering, agriculture, and environmental remediation[2].

The development of hydrogels has evolved from simple water-absorbing materials to sophisticated smart hydrogels that respond to pH, temperature, light, or biological molecules. With recent advances in material science, researchers are focusing on enhancing the functionality, durability, and degradability of hydrogels to meet the specific needs of various applications. This review aims to provide an in-depth analysis of the latest advancements in hydrogel technology, their structural characteristics, evaluation methods, and emerging applications[3].

Advantages

1. Biocompatibility: Hydrogels are biocompatible and can be used in biomedical applications.
2. High water absorption: Hydrogels can absorb large amounts of water, making them useful for applications such as wound dressings and diapers.
3. Mechanical strength: Hydrogels can be designed to have mechanical strength, making them suitable for applications such as tissue engineering and biomedical devices.

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4. Controlled release: Hydrogels can be designed to release substances in a controlled manner, making them useful for applications such as drug delivery and agricultural applications.
5. Flexibility: Hydrogels can be designed to be flexible, making them suitable for applications such as biomedical devices and sensors[4].

Disadvantages

1. Limited mechanical strength: Hydrogels can have limited mechanical strength, which can limit their use in certain applications.
2. Swelling: Hydrogels can swell significantly in aqueous solutions, which can affect their mechanical properties and stability.
3. Degradation: Hydrogels can degrade over time, which can affect their performance and stability.
4. Toxicity: Some hydrogels can be toxic, which can limit their use in biomedical applications[4].

II. CLASSIFICATION OF HYDROGELS

Based on Polymeric Composition:

The structural properties of hydrogels are largely determined by their polymeric composition, which influences their mechanical strength, swelling behaviour, and functionality. Based on their polymeric makeup, hydrogels can be categorized into three major types:

- Homopolymeric hydrogels.
- Copolymeric hydrogels.
- Interpenetrating polymeric networks (IPNs).

1. Homopolymer Hydrogels

Homopolymeric hydrogels are composed of a single type of monomer, forming a polymer network with repeating structural units. The nature of the monomer and the polymerization technique dictate whether the hydrogel has a cross-linked skeletal structure. These hydrogels are widely employed in biomedical applications, such as contact lenses, wound dressings, and drug delivery, due to their high-water retention capacity and biocompatibility[5].

2. Co-polymeric Hydrogels

Copolymeric hydrogels consist of two or more distinct monomers, with at least one being hydrophilic. These monomers can be arranged in different configurations, including:

- **Random copolymers** – Monomers are distributed randomly along the polymer backbone.
- **Block copolymers** – Monomers are grouped into distinct segments, forming "blocks" along the chain.
- **Alternating copolymers** – Monomers are arranged in a strictly alternating sequence.

The ability to manipulate monomer arrangement provides flexibility in tailoring the physical, chemical, and mechanical properties of the hydrogel. As a result, copolymeric hydrogels are extensively explored for controlled drug release, biosensors, and tissue engineering applications[6].

3. Interpenetrating Polymeric Networks (IPN)

Interpenetrating polymeric networks (IPNs) represent a unique class of hydrogels in which two or more polymer networks coexist while maintaining independent cross-linking. IPNs can be classified into:

- **Full IPN Hydrogels** – Both polymer components are cross-linked, leading to enhanced mechanical strength, swelling control, and stability.
- **Semi-IPN Hydrogels** – One polymer component is cross-linked, while the other remains non-cross-linked, providing a balance between flexibility and durability[7].

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Based on Source:

Hydrogels can be classified into three main categories based on their source: **natural, synthetic, and hybrid hydrogels**. Each type offers distinct properties that make them suitable for various applications.

Natural Hydrogels – Derived from biopolymers, these hydrogels are biodegradable, biocompatible, and support cell adhesion. They are mainly composed of:

Proteins (e.g., collagen, gelatin, lysozyme)

Polysaccharides (e.g., hyaluronic acid, alginate, chitosan)

Due to their biological origin, they are widely used in **wound healing, drug delivery, and tissue engineering**.

Synthetic Hydrogels – Engineered to offer greater mechanical strength, chemical stability, and controlled properties compared to natural hydrogels. A widely used example is **polyethylene glycol (PEG)-based hydrogels**, known for their non-toxicity, biocompatibility, and low immunogenicity, making them ideal for biomedical applications.

Hybrid Hydrogels – A combination of **natural and synthetic polymers**, these hydrogels integrate the biocompatibility of natural materials with the durabilityandtunability of synthetic polymers. Examples include dextran, collagen, and chitosan blended with synthetic polymers like poly(N-isopropylacrylamide) (PNIPAAm) and polyvinyl alcohol (PVA). Hybrid hydrogels are extensively used in tissue scaffolding, regenerative medicine, and drug delivery[8].

CELLULOSE- BASED HYDROGEL

Cellulose is a polysaccharide that consists of a linear chain of $\beta\,(1 \rightarrow 4)$ linked D-glucose unit It has properties of tasteless, odourless, and insoluble in water and most organic solvents. It is a hydrophilic material with high inter and intramolecular hydrogen bonds and van der Waals forces that make it difficult for the dissolution.

Cellulose needs to undergo dissolution to widen the applications. Several solvent systems for cellulose dissolution have been studied, such as ionic liquids, LiOH/urea, NaOH/urea, and NaOH/thiourea. The mixture of alkali/urea in cellulose dissolution is more effective than alkali only, and the different solvent systems give a different level of homogeneity of cellulose. Thus, cellulose dissolution using different solvent systems is essential to ensure that the cellulose is homogenous throughout the solution preparation[9].

Cellulose is the most abundant natural material as it can be found in the biomaterials such as trees, plants, fruits, vegetables, and bio-waste. Nowadays, the green and renewable concept is an important aspect of every research to develop and apply environmentally friendly products from natural raw materials. Bio-based materials are the materials from agricultural commodities and a waste of food products. Thus, bio-based materials become new materials in various applications for renewable resources and tackle environmental issues[10].

DERIVATIVES OF CELLULOSE:

Cellulose derivatives are chemically modified forms of **cellulose**, a natural polysaccharide found in plant cell walls. These derivatives enhance **solubility, mechanicalproperties, andfunctionality**, making them widely useful in **biomedical, pharmaceutical, food, andindustrialapplications.**

1. Methylcellulose (MC)

Modified by introducing methyl groups ($-CH_3$) into the cellulose backbone.

Water-soluble and forms gels upon heating.

Used in pharmaceuticals (tablet binders, controlled drug release), food thickeners, and construction materials.

2. Hydroxypropyl Methylcellulose (HPMC)

Contains hydroxypropyl ($-CH_2CHOHCH_3$) and methyl ($-CH_3$) groups.

Biocompatible, non-toxic, and widely used in oral drug delivery.

Found in ophthalmic solutions, capsules, and food coatings.

3. Carboxymethyl Cellulose (CMC)

Water-soluble anionic cellulose derivative, modified with carboxymethyl ($-CH_2COOH$) groups.

Highly absorbent, used in wound dressings, drug delivery, and food stabilizers.

Improves viscosity in cosmetics and industrial applications.

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4. Hydroxyethyl Cellulose (HEC)

Modified with hydroxyethyl (-CH_2CH_2OH) groups, enhancing water solubility.

Used as a thickener in pharmaceuticals, personal care products (shampoos, lotions), and paints.

5. Ethyl Cellulose (EC)

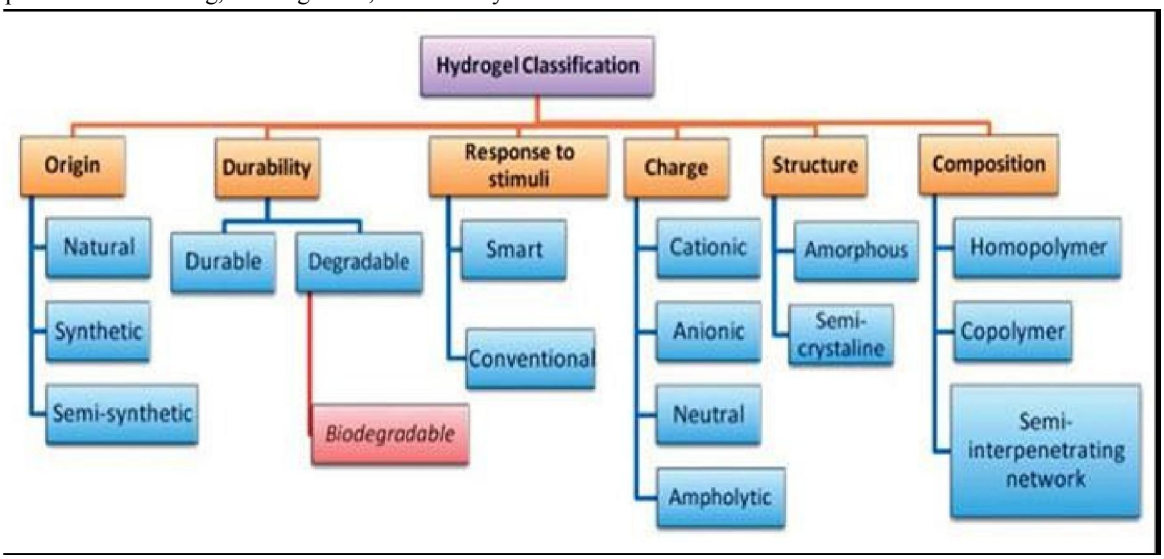
Contains ethyl (-C_2H_5) groups, making it water-insoluble but organic solvent-soluble.

Common in sustained-release drug formulations and protective coatings.

6. Microcrystalline Cellulose (MCC)

A purified, partially depolymerized cellulose used as an excipient in pharmaceuticals.

Improves tablet binding, disintegration, and stability[10].



III. MATERIALS USED IN THE PREPARATION OF HYDROGELS

Hydrogels are composed of natural or synthetic materials, each offering unique properties suited for specific applications.

Natural Materials for Hydrogels:

Sodium Alginate (SA) – A linear anionic polysaccharide with high pH sensitivity and gel-forming ability under mild conditions. Its biocompatibility makes it ideal for **wound care products**, mimicking the extracellular matrix (ECM).

Collagen (COL) – The main component of ECM, offering biocompatibility,biodegradability, and low antigenicity. It promotes **ce**ll growth, coagulation, and reduces scar formation, making it widely used in wound dressings.

Starch – A biodegradable, biocompatible, and renewable polymer. Due to its low mechanical strength and hydrophilicity, it is often modified (e.g., oxidized starch) for enhanced **stability, viscosity,** and film formation, particularly in pharmaceutical applications[11].

Synthetic Materials for Hydrogels:

Acrylamide (AM) – Known for biocompatibility, non-toxicity, and mechanical tunability. AM-based hydrogels exhibit self-healing, pH sensitivity, fatigueresistance, and thermal stability, making them promising for smart biomedical applications.

Polyvinyl Alcohol (PVA)– A biocompatible and mechanically strong polymer. However, pure PVA hydrogels lack hemostatic and antibacterial properties. Recent research focuses on combining PVA with functional additives to enhance wound healing efficiency.

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Polyethylene Glycol (PEG) – A biodegradable, biocompatible, and non-toxic polymer with a wide molecular weight range. It is widely used in wound dressings but requires careful selection of cross-linking agents to ensure cytocompatibility[11].

Methods of Preparation:

HYDROGEL PREPARATION METHODS:

Hydrogels are polymer network like structure having hydrophilic structure. These are prepared based on hydrophilic monomers and rarely prepared hydrophobic polymers also used during the preparation. Generally natural and synthetic polymers are also used in the preparation of hydrogels. Their mechanical strength shows slow degradation rate, and also provide the durability also. These two properties are managed by optimal design. These are also prepared by using natural polymers have suitable functional groups or functionalized with radically polymerizable groups. These techniques are described below:

Bulk polymerization:

Bulk hydrogels can be formed with one or more types of monomers mainly include vinyl monomers for the productions of hydrogels. Usually, a small amount of cross-linking agent is added in any hydrogel formulation. Radiation, ultraviolet, or chemical catalysts is used for the initiation of the polymerization reaction. The initiator is chosen which depends upon the type of monomers and solvents being used. The polymerized hydrogel may be produced in a wide variety of forms including rods, particles, films and membranes, and emulsions. [12]

Free radical polymerization

The main monomers which are used in this method for the preparation of hydrogels are such as acrylates, vinyl lactams and amides. These polymers have suitable functional groups or have been functionalized with radically polymerizable groups. This method involves the chemistry of typical free-radical polymerizations, which includes propagation, chain transfer, initiation, and termination steps. For the radical generation in the initiation step a wide variety of thermal, ultraviolet, visible, and redox initiators can be utilized, the radicals react with the monomers which convert them into active forms.[13]

Solution polymerization

In these ionic or neutral monomers are mixed with the multifunctional crosslinking agent. The polymerization is initiated thermally by UV-irradiation or by a redox initiator system. The major advantage of the solution polymerization over the bulk polymerization is the presence of solvent serving as a heat sink. The prepared hydrogels is washed with distilled water to remove the initiator, the soluble monomers, oligomers, cross-linking agent, and extractable polymer, and other impurities. Solvents used water–ethanol mixtures, water, ethanol, and benzyl alcohol. [14]

Suspension polymerization

This method is employed to prepare spherical hydrogel micropartical with size range of 1µm to 1mm. in this method the monomer solution is dispersed in non-solvent forming fine droplet, which is stabilized by stabilizer. The polymerization initiated by thermal decomposition of free radical. The prepared microparticle washed to remove un-reacted monomers cross-linking reagent and initiator. [15]

Polymerization by irradiation

For the preparation of hydrogels of unsaturated compounds, the initiators such as the ionizing high energy radiation, like gamma rays and electron beams, has been used. The irradiation of aqueous polymer solution results in the formation of radicals on the polymer chains. Recombination of the macro-radicals on different chains results in the formation of covalent bonds, so finally, a crosslinked structure is formed.[16]

Physical cross-linking

It is the most common and easy routes for hydrogel formation by cross linking of polymers through physical interactions. This physical cross linking includes interaction of ions such as hydrogen bonding, polyelectrolyte complexation and hydrophobic association.

Complex coacervation

Formation of complex coacervate gels by mixing of polyanions with a polycations. The underlying principle of this method is that polymers with opposite charges stick together and form soluble and insoluble complexes depending on

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the concentration and pH of the respective solutions. One such example is coacervating polyanionic xanthan with polycationic chitosan. Proteins below its isoelectric point are positively charged and likely to associate with anionic hydrocolloids and form polyion complex hydrogel. [17]

IV. DRUG RELEASE MECHANISM[18]

Diffusion controlled:

Most common drug release mechanism for hydrogel is Diffusion controlled. Fick's law of diffusion with either constant or variable diffusion coefficients is commonly used in modellingdiffusion-controlled release. Drug diffusivities are generally determined empirically or estimated a prior using free volume, hydrodynamic, or obstruction-based theories.

Chemically controlled:

Chemically-controlled release is used to describe molecule release determined by reactions occurring within a delivery matrix. The most common reactions that occur within hydrogel delivery systems are cleavage of polymer chains via hydrolytic or enzymatic degradation or reversible or irreversible reactions occurring between the polymer network and releasable drug. Under certain conditions the surface or bulk erosion of hydrogels will control the rate of drug release. Alternatively, if drug-binding moieties are incorporated in the hydrogels, the binding equilibrium may determine the drug release rate.

Swelling controlled:

Swelling-controlled release occurs when diffusion of drug is faster than hydrogel swelling. The modelling of this mechanism usually involves moving boundary conditions where molecules are released at the interface of rubbery and glassy phases of swollen most common drug release mechanism of hydrogel is diffusion controlled.

V. EVALUATION METHODS[19,20]:

1. Physical Appearance

The homogeneity, clarity, and texture of hydrogels are visually inspected. Any irregularities, such as phase separation or grittiness, indicate formulation inconsistencies.

2. Spreadability Test

The hydrogel is spread on a flat surface to observe its smoothness and uniformity. Proper spreadability ensures ease of application, especially for topical formulations.

3. pH Determination

A pH meter is used to measure the pH of a 1% hydrogel solution in deionized water. Maintaining an appropriate pH is crucial to ensure biocompatibility and prevent skin irritation in biomedical applications.

4. Drug Content Analysis (For Drug-Loaded Hydrogels)

To determine drug concentration, 1 g of hydrogel is dissolved in 20 mL of phosphate buffer (pH 7.4), filtered, and analysed using a UV-VIS spectrophotometer at specified wavelength. This ensures uniform drug distribution in the hydrogel matrix.

5. Viscosity Measurement

The Brookfield viscometer measures the hydrogel's viscosity at 25°C and 100 rpm. An optimal viscosity ensures ease of application, stability, and controlled drug release.

6. Scanning Electron Microscopy (SEM)

SEM can be used to provide information about the sample's composition, surface topography, and other properties such as electrical conductivity.

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7. Fourier Transform Infrared Spectroscopy:

FTIR studies were carried out for hydrogel with and without drug. Hydrogen bonding has a significant influence on the peak shape and intensities, generally causing peak broadening and shifts in absorption to lower frequencies. On analysing the graphs of hydrogel with and without drug, we determine the backbone structure of hydrogel with drug.

8. Swelling measurement:

Method A

According to this method the dry hydrogel is immersed in deionized water for 48 hours at room temperature on a roller mixer. After swelling, the hydrogel is filtered by a stainless-steel net of 30 meshes (681 μm). The swelling is calculated as follows.

Swelling = W_s W_d / W_d

Where, W_s is the weight of hydrogel in swollen state and $W_d$is the weight of hydrogel in dry state.

Method B

Alternatively, to measure the swelling of hydrogel, in a volumetric vial the dry hydrogel (0.050.1g) is dispersed into sufficiently high quantity of water (25-30 ml) for 48 hrs at room temperature. The mixture is then centrifuged to obtain the layers of water bound material and free unabsorbed water. The free water is removed and the swelling can be measured according to Method A.

Method C

According to this method, the dry gel is immersed in deionized water for 16 h at room temperature. After swelling, the hydrogel is filtered using a stainless-steel net of 100-mesh. Swelling is calculated as follows.

Swelling =C/B*100

Where, C is the weight of hydrogel obtained after drying and B is the weight of the insoluble portion after extraction with water.[24]

V. CONCLUSION & FUTURE PROSPECTUS

hydrogel-based networks have shown great promise in various applications due to their unique properties. The development of new hydrogel materials, such as super-porous hydrogels, has further expanded their potential uses. To optimize the production of these materials, batch or semi-batch reactors can be employed, and variables such as temperature, pressure, and batch cycle time can be controlled. Additionally, the use of effective impellers, such as ribbon mixers with screws or baffles, can enhance the mixing and blending of high-viscosity materials. By understanding the properties and production technologies of hydrogels, researchers and manufacturers can develop new and innovative materials for various applications.Future research should focus on exploring new applications of hydrogel-based networks, such as in biomedical and pharmaceutical fields. Additionally, the development of more efficient and cost-effective production technologies, such as continuous flow reactors, could further enhance the commercial viability of these materials.

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