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"Pharmaceutical Application Of Hydrogel"

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ABSTRACT: Hydrogels are versatile, three-dimensional polymeric networks capable of absorbing significant amounts of water while maintaining structural integrity. First introduced by Wichterle and Lim in 1960, these materials possess biocompatibility, flexibility, and responsiveness to environmental stimuli such as temperature, pH, and ionic strength. Hydrogels are classified based on their origin (natural, synthetic, or hybrid), polymer composition, biodegradability, cross-linking type, and other characteristics. They are synthesized through chemical or physical cross-linking, offering a range of properties such as high swelling capacity, mechanical strength, and adaptability to biomedical applications.Applications of hydrogels span drug delivery systems, tissue engineering, and regenerative medicine. They serve as carriers for controlled drug release via oral, transdermal, ocular, and injectable routes. In tissue engineering, hydrogels mimic extracellular matrices, promote cell proliferation, and enable sustained release of growth factors. Additionally, hydrogels are employed in cancer treatment, contraceptive formulations, wound dressings, and ocular therapies. Innovations like stimuli-responsive hydrogels and nanotechnology integration have expanded their use in personalized medicine and soft robotics. Future prospects include hydrogen-based hydrogels for antioxidative therapies and advanced drug delivery mechanisms.

KEYWORDS: Hydrogel, biocompatibility, drug delivery, stimuli-responsive, tissue engineering.

1. INTRODUCTION

A hydrogel is a 3D network of hydrophilic polymers that can absorb and retain large amounts of water while maintaining structural integrity due to chemical or physical cross-linking. First reported by Wichterle and Lim in 1960, hydrogels are flexible, resembling natural tissues due to their high-water content. Their hydrophilicity arises from groups like -NH2, -COOH, -OH, and -SO3H.

Hydrogels respond to physical (e.g., temperature, light, pressure) and chemical (e.g., pH, ions) stimuli, undergoing reversible phase transitions. These responses depend on factors such as monomer type, charge density, and cross-linking degree, with the reaction magnitude proportional to the stimulus intensity [1].

2. HISTORY OF HYDROGEL

1. 1930s: Polyacrylamide gels were first synthesized, marking the origin of hydrogels.
2. 1960s: Otto Wichterle developed the first soft contact lenses using hydrophilic polymers.
3. 1970s: Recognized for biocompatibility, hydrogels were applied in drug delivery and tissue engineering.
4. 1980s: Natural hydrogels, like alginate and gelatin, were explored for enhanced medical compatibility.
5. 1990s: "Smart" hydrogels emerged, responsive to stimuli like pH and temperature.
6. 2000s: Hydrogels became key in regenerative medicine as scaffolds for tissue repair.
7. 2010s: Integration with nanotechnology enabled advances in drug delivery, biosensing, and wound healing [2,3]

3. STRUCTURE OF HYDROGEL

Hydrogels are three-dimensional, cross-linked polymeric system able to retaining and holding expansive sums of water or biological fluids. Their structure interacts with body fluids through capillary, hydration, and osmotic forces, causing the polymer chains to expand. These forces influence hydrogel properties, including transport, diffusion, and mechanical characteristics. The presence of hydrophilic functional groups, such as amide, hydroxyl, sulfonic acid, and acetamide groups, enables their high-water absorption capacity [4].

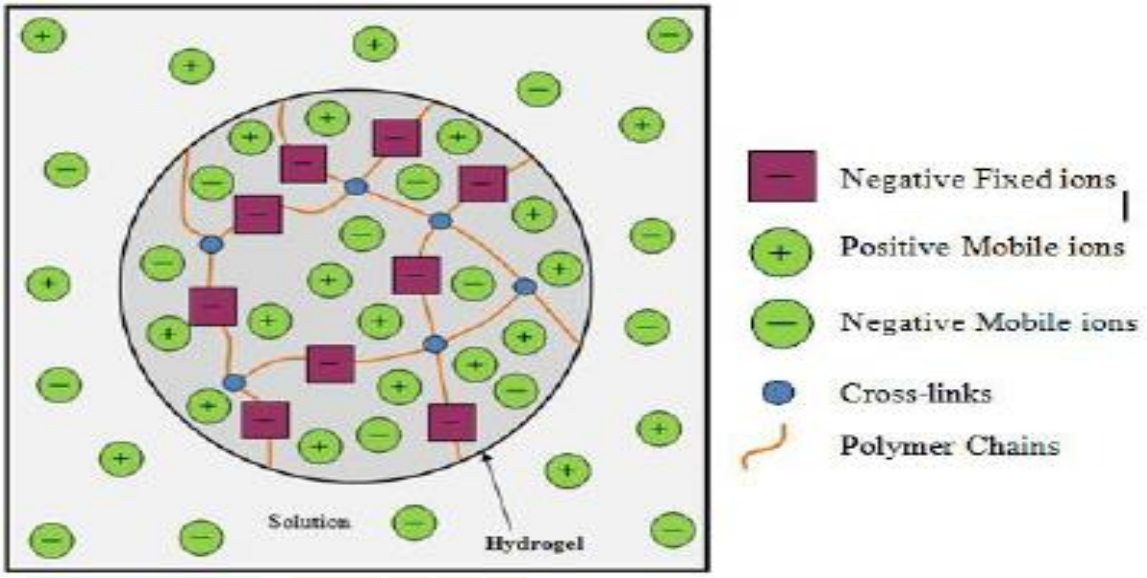

Figure 1. Structure of Hydrogel

1. **Homo-polymeric Network**: Formed from a single type of monomer, these networks can have cross-linked structures depending on the monomers and polymerization technique [5].
2. **Co-polymeric Network**: Composed of two or more monomers, these hydrogels require hydrophilic components to enable swelling [6].
3. **Multi-polymeric Network**: Consist of two independent cross-linked polymers, offering superior properties. Interpenetrating hydrogels combine two polymers, with at least one being cross-linked [6].

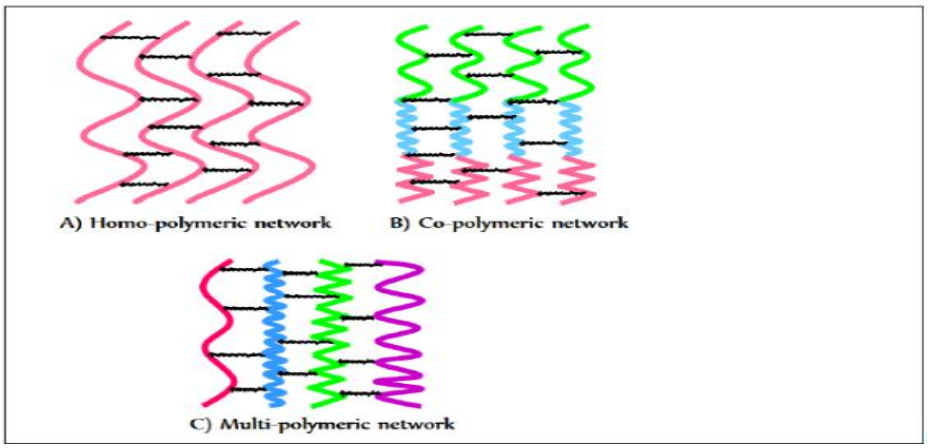

Figure 2. Schematic view of hydrogels A) Homo polymeric network B) Co polymeric network C) Multi polymeric network

4. STRUCTURE AND WATER CONTENT IN HYDROGEL

The water content in hydrogels significantly influences the permeation of active ingredients. Water in hydrogels can be categorized as:

(i) Bound water (primary and secondary)
(ii) Semi-bound water
(iii) Free or bulk water
(iv) Interstitial water

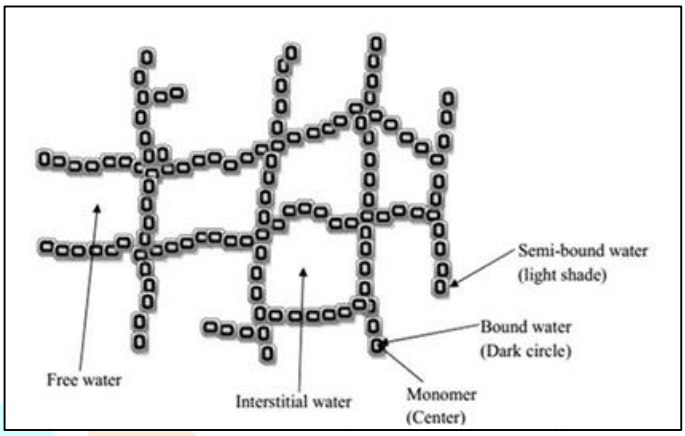

Figure 3. Molecular structure of hydrogel network with different types of water

When a dry hydrogel contacts water, it absorbs water into its matrix. Initially, water binds to hydrophilic groups as primary bound water, causing the polymer network to swell and expose hydrophobic groups. These interact with water, forming secondary bound water. Together, these forms bound water, integral to the hydrogel structure and removable only under extreme conditions. Once hydrophilic and hydrophobic groups are saturated, additional water absorbed by osmotic forces is free or bulk water. Between bound and free water lies semi-bound water, while interstitial water is physically trapped within the polymer network but not chemically attached [7].

5. FEATURES OF HYDROGEL:

- High rewetting capacity and absorbency under load.
- Minimal residual matter and soluble content.
- Stable and durable in swelling environments during storage.
- Colourless, odourless, non-toxic, with high photostability.
- pH neutral and biodegradable in swelling media.
- Suitable for drugs with hydrophilicity, molecular weight <500 Da, and pH 5–9.
- Unsuitable for highly acidic or alkaline drugs in topical delivery systems [8].

6. TYPES OF HYDROGELS

Hydrogels are categorized into natural and synthetic types based on their polymer source. Both types are used in medical applications and must be biocompatible, biodegradable, and sometimes blood-compatible [9].

Natural Hydrogels:
Derived from natural polymers like polysaccharides and proteins, they are biocompatible, biodegradable, and non-toxic. Examples include alginate (used for restoring heart function post-heart attack), collagen (vascular grafts), gelatin (artificial structures), and fibrin (tissue engineering, adhesives, anticoagulants).

Synthetic Hydrogels :
Made from synthetic polymers like polyacrylamide, polyvinyl alcohol, and polyethylene glycol (PEG), they offer durability, gel strength, and high-water absorption. PEG is widely used in drug delivery, tissue engineering, bone prostheses, and wound dressings due to its biocompatibility and resistance to immune reactions [10].

7. MECHANISM OF HYDROGEL FORMATION

Hydrogels, created using polymers with modifiable functional groups and biocompatibility, can be tailored for specific applications via chemical or physical crosslinking methods [11].

1. Chemical Crosslinking

This process involves converting a liquid to a solid hydrogel through covalent bonding, offering strong mechanical properties. Common methods include:

1.1 Optical Polymerization

Uses light-sensitive hydrophilic polymers, which form free radicals under UV/visible light to initiate polymerization. Polymers like acrylates/methacrylate create a porous lattice for drug delivery or clinical applications at physiological conditions. Enzymes catalyse crosslinking under natural conditions (pH, temperature), ensuring biocompatibility. For example, horseradish peroxidase (HPR) facilitates hydrogel formation in applications like tissue engineering and drug release [12].

2. Physical Crosslinking

This safer, simpler method involves non-covalent interactions, including:

2.1 Ionic Crosslinking

Divalent cations (e.g., Ca^{2+}) bond with polymers like alginate, forming gels with high toughness. Parameters like alginate composition are optimized for injectable biomaterials [13].

2.2 Temperature-Dependent Methods

Temperature-sensitive hydrogels transition from liquid at low temperatures to gels at body temperature. Polymers like cellulose, chitosan, and synthetic copolymers are used in tissue engineering [14].

2.3 pH-Dependent Methods

These hydrogels swell or contract in response to pH changes, suitable for controlled drug delivery. For example, carboxymethyl chitosan is used in pH-sensitive hydrogels for medical applications [15].

8. CLASSIFICATION OF HYDROGELS

Hydrogels can be categorized according to a number of factors:

I. Based on Source

1. Natural Hydrogels: Derived from natural polymers like collagen, gelatin, hyaluronic acid, and chitosan.
2. Synthetic Hydrogels: Man-made polymers such as polyethylene glycol, engineered for better mechanical and chemical properties.
3. Hybrid Hydrogels: A combination of natural and synthetic polymers, like dextran with poly(N-isopropylacrylamide) [16].

II. Based on Polymeric Composition

1. Homo-polymeric: Made from a single monomer species.
2. Co-polymeric: Composed of two or more monomers, with at least one hydrophilic component.
3. Interpenetrating Polymer Networks (IPN): Contain two independent polymer networks, one of which may be non-cross-linked [17].

III. Based on Biodegradability

1. Biodegradable: Polymers like chitosan, fibrin, and poly (N-isopropyl acrylamide).
2. Non-biodegradable: Polymers like methacrylate and poly (ethylene glycol) [17].

IV. Based on Configuration

1. Amorphous: Non-crystalline.
2. Semi-Crystalline: Mix of crystalline and amorphous phases.
3. Crystalline: Fully crystalline [18].

V. Based on Cross-linking Type

1. Chemical Cross-linking: Permanent junctions.
2. Physical Cross-linking: Transient junctions (e.g., hydrogen bonds, hydrophobic interactions) [19].

VI. Based on Physical Appearance

Hydrogels can appear as matrices, films, or microspheres, depending on the preparation technique [19].

VII. Based on Electrical Charge

1. Non-Ionic (neutral)
2. Ionic: Anionic or cationic.
3. Amphoteric: Both acidic and basic groups.
4. Zwitterionic: Both anionic and cationic groups [18].

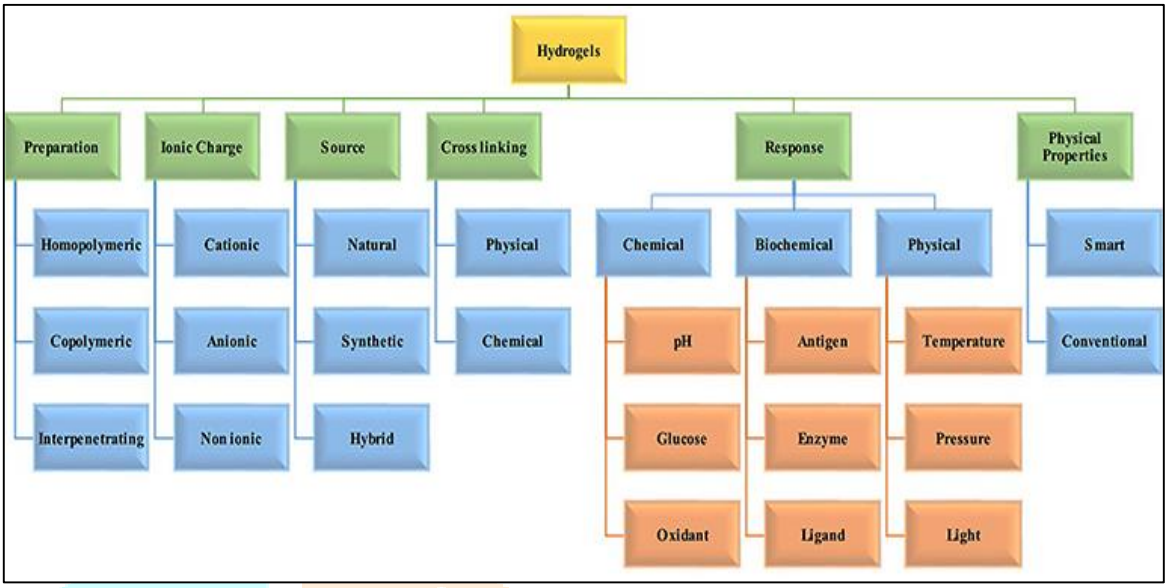

Figure 4. Classification of hydrogels

9. Properties of Hydrogels

1.Swelling of Hydrogels

The swelling ratio of hydrogels is calculated using the formula:
Swelling ratio = (Wt – Wd) / Wd
Where, Wt is the swollen hydrogel weight, and Wd is the dried weight. Hydrogels swell or contract to release drugs, with swelling influenced by the polymer's structure, molecular weight, and crosslinking. pH-sensitive polymers can control drug release by responding to environmental changes like temperature and ion concentration. Crosslinking stabilizes the hydrogel's structure, while PEG can enhance swelling ability [20].

2. Mechanical Properties

Hydrogel mechanical properties are crucial for medical applications like tissue engineering, affecting cell behaviour, proliferation, and migration. The stiffness of hydrogels can influence the cytoskeleton and cell function. Crosslinking and polymerization conditions impact hydrogel strength, with physical hydrogels generally avoiding toxic agents. Enhanced mechanical properties can be achieved using additives like graphene oxide [21].

3. Biological Properties

Injectable hydrogels must be biocompatible, non-toxic, stable, and biodegradable, mimicking the properties of natural tissues. Research has shown that combining cross-linking and electrospinning can improve mechanical and biological properties. Hydrogels for bone substitutes, like HA/CNT composites, promote cell adhesion and proliferation. Natural hydrogels generally offer better biocompatibility compared to synthetic ones [22].

10. APPLICATIONS OF HYDROGEL

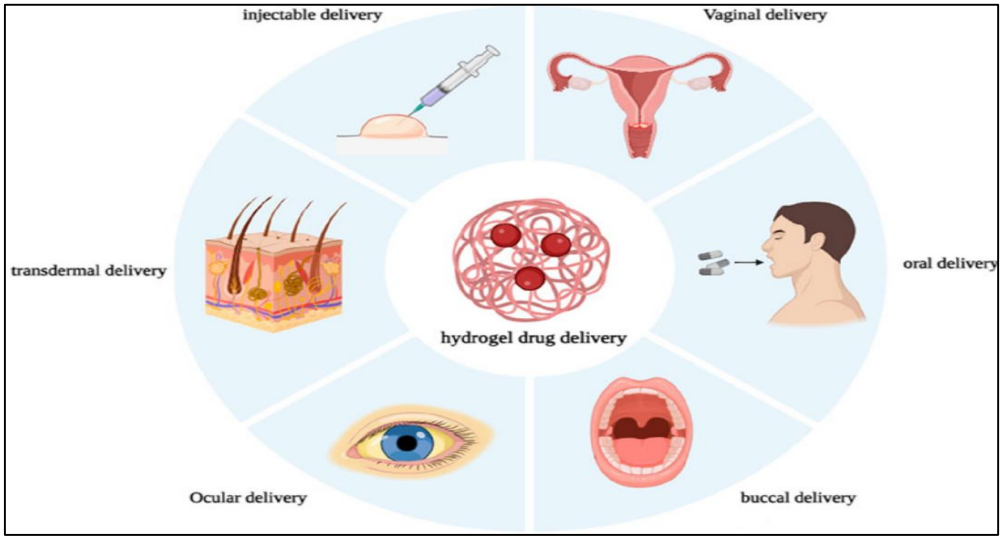

Figure 5. Application of hydrogel in drug delivery system

1. Hydrogel based system via oral route

Hydrogel-based systems are emerging as an effective solution for oral drug delivery, especially for challenging small molecular drugs like peptides and proteins. These drugs often face issues such as enzymatic breakdown, instability, and poor absorption in the gastrointestinal tract (GIT). Hydrogels protect these drugs, improving their stability and facilitating site-specific distribution. The small intestine is a key site for optimal absorption due to its large surface area and specialized cells [23].

2. Rectal and vaginal medication administration using hydrogel

Hydrogels are emerging as a solution to the challenges of traditional vaginal and rectal medication forms, such as suppositories, which can be messy and have a short residence time. By using mucoadhesive polymers like chitosan and Carbopol, hydrogels enhance drug retention and release, improving therapeutic effectiveness. These hydrogels are particularly useful for local diseases affecting the rectum and vagina, offering targeted treatment with fewer metabolic side effects. Studies have shown that hydrogel formulations, such as those loaded with artesunate, can significantly improve drug delivery and retention, overcoming the limitations of conventional dosage forms [24].

3. Injectable hydrogels for drug delivery,

first developed by Elisseeff et al. in 1999, have revolutionized medicine administration. These hydrogels, like the polyethylene-based system they created, can respond to UV and visible light, allowing for controlled drug release. By managing the breakdown and expansion of the hydrogel, side effects in chemotherapy treatments have been reduced. Compared to traditional hydrogels, injectable ones provide better drug delivery, including proteins and other therapeutics. They are used in regenerative medicine, tissue repair, and immune system enhancement. Thermo-responsive polypeptide hydrogels have been developed for cancer treatments, such as delivering doxorubicin and combretastatin effectively to tumours [24].

4. Topical medication delivery based on hydrogel

Topical drug delivery devices, such as hydrogel-based systems, enhance the penetration of active substances through the skin, making them ideal for conditions like skin malignancies. Various formulations, including creams, sprays, and powders, have been developed for this purpose. For example, a hydrogel combining xanthan gum and carbomer has been used to treat cellulite, while a self-adhesive patch with sodium polyacrylate and carboxymethylcellulose efficiently delivers triclosan for acne. Hydrogels, often used in soothing masks, are also effective for skincare. Additionally, microcapsule-integrated hydrogel patches, activated by ultrasound, improve skin penetration and are useful for treating wounds and injuries [25].

5. The ocular channel for medication administration using hydrogel

Ocular drug delivery is challenging due to barriers like poor corneal permeability, tear drainage, and eye blinking, leading to low bioavailability of eye drops. Poloxamers, often combined with polymers like methylcellulose, hydroxypropyl methylcellulose, and chitosan, create hydrogel systems that improve

medication retention. The hydrogel's viscosity prevents washout, while chitosan's mucoadhesive properties extend residence time. These systems are effective for treating conditions like macular edema and uveitis, offering benefits like less irritation, sterilization, and increased residence time. Biocompatible, biodegradable polymers in hydrogels enhance ocular drug delivery [26].

6. Hydrogels in Transdermal Patches

Hydrogels, especially liquid polyacrylates, are used in transdermal patches for extended drug delivery. Traditional patches can cause skin blockage due to their occlusive nature, but non-occlusive water-based hydrogel matrices solve this issue by allowing moisture exchange with the skin. The mechanical properties of these hydrogels are crucial for ensuring proper skin adhesion and withstanding mechanical forces from patient movements during use [27].

11. FUTURE PROSPECTIVE

Hydrogel holds significant potential for future pharmaceutical applications due to its antioxidant, anti-inflammatory, and therapeutic properties. Inhalation of medical hydrogen gas and hydrogen-rich water are being explored as treatments for oxidative stress-related conditions, including neurodegenerative diseases, cardiovascular issues, and diabetes. Hydrogen nanocarriers also show promise in enhancing drug delivery by improving stability, solubility, and targeted action, which could reduce side effects and increase efficacy. Additionally, hydrogen's ability to mitigate oxidative stress positions it as a candidate for regenerative medicine, aiding in wound healing and tissue repair. In cancer treatment, hydrogen therapy is being investigated as an adjuvant to reduce the side effects of chemotherapy and radiotherapy, improving patient outcomes. Furthermore, its antioxidant properties could be utilized in anti-aging and preventive medicine, offering new solutions for managing cellular aging and age-related diseases. While the potential is vast, challenges such as developing standardized delivery systems, regulatory approval, and scalability must be addressed to realize its widespread application in pharmaceuticals.

12. CONCLUSION

Hydrogel-based delivery systems are versatile platforms suitable for oral, ocular, epidermal, and subcutaneous applications. Their high-water content and soft consistency make them resemble natural living tissue more closely than other synthetic biomaterials, enhancing their compatibility in biomedical contexts. Recent advancements have focused on designing and customizing hydrogel networks to meet diverse application requirements. When hydrogels are exposed to aqueous environments, they demonstrate the capacity to swell, a characteristic that contributes to their functionality in controlled drug delivery and tissue engineering. This review explores the classification of hydrogels based on their physical and chemical properties, the technical feasibility of their applications, preparation methods, and their broad range of uses. Several preparation techniques are also highlighted to demonstrate the adaptability of hydrogels for specific purposes.

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