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# HYDROGEL INNOVATION EXPLORING CUTTING-EDGE DEVELOPMENTS

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**ABSTRACT**

Hydrogels are cross-linked polymers with hydrophilic groups which enable them to absorb large amounts of water. Although hydrogels have numerous capability and advantages in drug delivery including biocompatibility, low toxicity and good swelling behavior but depending on chemical moieties of the gel forming polymers and route of administration some limitations would appear in delivery of active pharmaceutical using hydrogel as delivery vehicle. In this review at first classification of the hydrogel with different approaches including chemical moieties, crosslinking agent behaviors and release controller mechanism was performed and limitations arise from each category was described and finally different approaches to overcome each of this limitation was proposed. Hydrogels, types of hydrogels, their properties, advantages of hydrogels and applications in medicine are discussed. Furthermore, hydrogels can be formulated in a variety of physical forms, including slabs, microparticles, nanoparticles, coatings, and films. As a result, hydrogels are commonly used in clinical practice and medicine for a wide range of applications, including Tissue engineering and Regenerative medicine, Diagnostics, Cellular immobilization, separation of biomolecules or cells, and barrier materials to regulate biological adhesions. This biomaterial can hold large number of biological fluids and swell. When swell, they are soft and rubbery and resemble the living tissue exhibiting excellent biocompatibility. The prime objective of this article is to concern the classification of hydrogel on different bases, properties of hydrogel and its method of preparation and physical and chemical characteristics of these products and recent advantages of hydrogels.

**Keywords:** Hydrogels, polymers, biomolecules, crosslinking.

## INTRODUCTION

Polymeric networks known as hydrogels possess the capacity to take in and hold a lot of water. The hydrophilic groups are of the polymeric network dissolve in watery settings to form hydrogel structure. It can alternatively be characterized as a polymeric substance with the capacity to swell and hold a large volume of water within its structure, in addition to dissolving in water. Because of their high-water content, they are relatively flexible, similar to genuine tissue. Crosslinks among network chains give hydrogels their resistance to disintegration, and hydrophilic functional groups connected to the polymeric backbone enable them to absorb water [1].

Natural hydrogels have given way to synthetic hydrogels in the past 20 years due to their extended service lives, high water absorption capabilities, and high gel strengths. A tail can be produced or the utility and degradability of synthetic polymers can be enhanced by changing their clearly defined structure. Hydrogels are classified as "reversible" and "physical" gels if, in addition to the molecular entanglements, secondary forces such ionic, H-bonds, or hydrophobic interactions play a major role in the formation of the network. Polymers known as hydrogels are capable of withstanding weights in water that are many times larger than their own. It is a carboxylic acid polymer. Several negative charges are picked up by the polymer along its length when acidic groups ionize in water [2].

## Introduction

Hydrogels, three-dimensional polymeric networks capable of retaining substantial amounts of water while maintaining their structure, have garnered significant attention in the biomedical field. Their unique properties, including biocompatibility, tunable physical and chemical characteristics, and ability to mimic natural tissue environments, make them particularly suitable for various medical applications. Among these applications, the roles of hydrogels in drug delivery, diagnosis, and treatment have emerged as pivotal areas of research, promising to revolutionize modern medicine.

## Hydrogels in Drug Delivery

Drug delivery systems (DDS) aim to deliver therapeutic agents at controlled rates to targeted sites within the body, minimizing side effects and enhancing therapeutic efficacy. Hydrogels, with their high water content and soft, pliable nature, are excellent candidates for DDS. They can encapsulate a wide range of drugs, from small molecules to large proteins and nucleic acids, and release them in response to specific physiological stimuli such as pH, temperature, and enzyme activity. This ability to respond to environmental changes enables the design of "smart" hydrogels that can release drugs in a controlled and sustained manner, thus improving patient compliance and treatment outcomes.

## Hydrogels in Diagnosis

In the realm of diagnostics, hydrogels have shown great potential due to their ability to incorporate various sensing molecules and bioactive agents. They can be engineered to respond to specific biomarkers or environmental conditions, making them useful for in situ sensing and real-time monitoring of disease states. For instance, hydrogel-based biosensors can detect glucose levels in diabetic patients, measure pH changes indicative of infections, or even identify cancer biomarkers. The versatility of hydrogels in diagnostics stems from their capacity to be tailored for high sensitivity and specificity, which are critical for accurate and early disease detection.

Hydrogels in Treatment

Beyond drug delivery and diagnostics, hydrogels are also being explored as therapeutic agents themselves. In regenerative medicine, they serve as scaffolds that support cell growth and tissue regeneration, aiding in the repair of damaged tissues and organs. Hydrogels can be loaded with growth factors and stem cells, providing a conducive environment for tissue repair and regeneration. Additionally, their injectable nature allows for minimally invasive delivery to damaged sites, promoting healing while reducing recovery times and patient discomfort. In cancer therapy, hydrogels can be used to deliver chemotherapeutic agents directly to tumor sites, maximizing drug concentration at the target while minimizing systemic toxicity

**Advantages of hydrogels:**

- They resemble real tissue in that they are highly flexible due to their high-water content.
- Timing the release of nutrients or medications.
- They can be injected and are biocompatible and biodegradable.
- Hydrogels are also easily modifiable and have good transport characteristics.
- Environmentally sensitive hydrogels have the ability to sense changes in temperature, pH, or metabolite content and release their load accordingly.

**Disadvantages of hydrogels**

- High cost.
- Insufficient mechanical strength.
- Difficult to manage.
- Difficult to fill with nutrition or medications.
- Due to non-adherent nature, they could require a secondary dressing to keep them in place. There's a chance that the maggots' movement will hurt.

## Classification of Hydrogel Products

**Classification based on source**: [3]

- **Natural hydrogels:** Natural hydrogels exhibit strong cell adhesion, biodegradability, and biocompatibility. Proteins like collagen, gelatin, and lysozyme, as well as polysaccharides like hyaluronic acid, alginate, and chitosan, are the two main categories of natural polymers that are utilized to create natural hydrogels.
- **Synthetic hydrogels:** They are more beneficial than natural hydrogels because their mechanical and chemical properties may be created to be far more varied than those of their natural counterparts. Because of their low immunogenicity, compatibility, and non-toxicity, hydrogels based on polyethylene glycol are one type of material that is frequently employed in biomedical applications.
- **Hybrid hydrogels:** They are a blend of artificial and natural hydrogels made of polymers. The benefits of synthetic and natural hydrogels have been combined by combining synthetic polymers like poly (N-isopropylacrylamide) and polyvinyl alcohol with numerous naturally occurring biopolymers like dextran, collagen, and chitosan.

**According to the biodegradability**: [4]

- **Biodegradable hydrogels:** The biodegradability of hydrogels Agar, fibrin, chitosan, and many other naturally occurring polymers are biodegradable. Examples of artificially biodegradable polymers are poly (aldehyde guluronate), polyanhydrides, and poly (N isopropyl acrylamide.
- **Non-biodegradable hydrogels:** Non-biodegradable hydrogels are made using a variety of vinylated monomers and macromers, including acryl amide, 2-hydroxyl propyl methacrylate, methoxyl poly (ethylene glycol), and 2-hydroxyl ethyl methacrylate.

## Hydrogel Preparation Methods

Polymers, whether natural or synthetic, can be used to create hydrogels. The chemical strength and hydrophobicity of synthetic polymers are superior to those of natural polymers. Its durability is aided by its mechanical strength, which also slows the pace of disintegration. A design that strikes a balance between these two diametrically opposing features is the best. Furthermore, natural polymers can be employed to create hydrogels based on such polymers if they have the proper functional groups or have been functionalized with radically polymerizable groups [5].

- Bulk polymerization
- Free radical polymerization

- Solution polymerization
- Grafting to a support
- Polymerization by irradiation
- Complex coacervation

**Types of Hydrogels**

- **Natural Hydrogels:** Hydrogels that originate from natural sources are known as natural hydrogels. Hydrogels can be created using natural polymers, which have benefits including non-toxicity, biocompatibility, and biodegradability. Depending on the intended use of biomaterials, natural polymers may be used in the hydrogel-making process. Hydrogels, for instance, that are utilized to discharge materials under control need to be biocompatible, biodegradable, and non-hazardous. Natural polymers that are extensively used as carriers for the release of chemicals are polysaccharides and their proteins [6].
- **Synthetic Hydrogels:** Polyamides and polyethylene glycol (PEG) are examples of synthetic polymers from which synthetic hydrogels are made. Natural polymers have been replaced by synthetic polymers in hydrogel synthesis more recently because of their superior water-absorbing capacity, long lifespan, and gel strength. Hydrogels made from synthetic polymers have a variety of medical uses. In terms of chemical composition and mechanical structure, synthetic polymers outperform natural polymers as they are hydrophobic.
- **Hybrid hydrogels:** They are a blend of artificial and natural hydrogels made of polymers. The benefits of synthetic and natural hydrogels have been combined by combining synthetic polymers like poly (N-isopropylacrylamide) and polyvinyl alcohol with numerous naturally occurring biopolymers like dextran, collagen, and chitosan.

**Applications**

**Application of Hydrogels in Medicine** [7]

Hydrogels are extensively used for various biomedical applications--tissue engineering, molecular imprinting, wound dressings materials, immune-isolation, drug delivery, etc.

- **Wound Dressing:** Hydrogel-based dressings have the ability to absorb water up to six times their dry weight, which makes them useful for absorbing wound secretions, lowering the temperature at the wound site, and providing moisture. The drawbacks of current wound dressings include their poor mechanical qualities, lack of antibacterial activity, and inadequate oxygen and water permeability. Hassan Namazi and his associates employed a hydrogel nanocomposite that contained antibiotics to get around these issues.

- **Drug Release:** The hydrogel's composition, geometric structure, production technique, drug type, and release period environmental circumstances are all thought to play a role in the drug release process. Of these, pH is considered to be one of the most significant elements [8].
- **Tissue Engineering:** Similar to ECMs, which have garnered significant interest for tissue engineering and regenerative medicine applications, hydrogels comprising highly hydrated polymer networks are also hydrogels. Rebuilding damaged corticocortical joints or articular cartilage tissue has been accomplished thus far using a variety of hydrogels made from natural or artificial polymers[9].

**Applications of hydrogels in drug delivery**

Hydrogels have garnered significant interest as outstanding options for bioadhesive devices, controlled release devices, and therapeutic agent-targetable devices. Hydrogel-based administration systems can be applied subcutaneously, orally, rectal, occularly, or epidermally. There are several locations where hydrogels can be used to deliver drugs [10].

- **Drug delivery in the oral cavity:** The medication is delivered to the oral cavity via hydrogels for the local treatment of oral disorders, including malignancies of the oral cavity, viral infections, fungal diseases, periodontal disease, and stomatitis [11].
- **Drug delivery in the GI tract:** The gastrointestinal tract is the most often used route for medication delivery due to its huge surface area for systemic absorption and ease of administration of pharmaceuticals for compliance therapy.
- **Ocular drug delivery:** The most common application for hydrogels is in drug delivery systems for the eyes. The majority of hydrogel films made of polymers are used to make both hard and soft contact lenses. Due to their ease of dosing as a liquid and their ability to retain their gel form for an extended period of time after dosing, in-situ forming hydrogels are appealing as an ocular drug delivery strategy [12].

**Recent Advantages of Hydrogels**

**Current hydrogel advances in physicochemical and biological response:**

Since hydrogels have different physicochemical, biological, and structural properties, they have been investigated and employed in a wide range of biomedical applications. Various commercial hydrogel products, such as hyaluronic acid-based hydrogel, have been used as fillers in aesthetic medicine, one of the most well-known sectors. Moreover, hydrogels have been extensively used as 3D models of different diseases (e.g., tumour model, tissue fibrosis models, corneal disease model and nerve disease model, An inflammatory bowel disease, etc.) for pathogenesis study or high-throughput drug screening. Due to the in vivo tissue stroma matrix-mimicked property, hydrogels are favourable for cell encapsulation and expansion in vitro and in vivo, enabling high-efficient tissue regeneration and cancer therapy. For instance, various cells (stem cells, islet cells, hepatocytes, endothelial cells (ECs), etc.) that were encapsulated in hydrogels could propagate and concurrently maintain functional characteristics in vitro. Afterwards, they were transferred into the designed disease site and act as protein/factor factory to sustainably promote and induce tissue regeneration and repair. Especially when carrying immune cells (e.g., T cells, natural killer (NK) cells, dendritic cells (DCs), macrophages, etc.), hydrogels can serve as immune niches for cancer immunotherapy [13].

**Recent advances in hydrogels for biomedical applications:**

- **Cancer therapy:** Drugs that significantly lessen the body's load can be extended and targeted via hydrogel microparticles. Superporous hydrogels will be more beneficial than regular hydrogels since they require a bigger and faster swelling. Hydrogels may be immediately injected or transplanted into the tumor for direct administration, such as intratumoral injection. This boosts the anticancer agent's effectiveness. As an alternative to multiple dosage conventional therapy, hydrogel implantation can be employed [14].
- **Gene delivery:** Delivering desired therapeutic genes into cells with the goal of repairing, replacing, and regulating damaged genes to prevent disease is known as gene therapy. Scientists employ polymers such as poly-L-lysine, polyethylene glycol, polyamidoamine dendrimer, polyethylenimine, poly (lactic acid), or (PLA), and poly (di-lactic acids co-glycolic acid) (PLGA) for gene delivery. Researchers have improved wound healing in a diabetic mouse model by delivering the plasmid-beta 1 gene using PEG-PLGA-PEG hydrogel [15]. Transfection is a polymeric carrier-based gene delivery procedure that begins with the complexation of DNA and polymer and ends with the insertion of the DNA/polymer complex into cells for a certain amount of time. The removal of end complexes from the cells is the last step, after which the cells are incubated for a while till the outcomes are noted [16].
- **Ophthalmology:** On average, eye drops or ointments make up the majority of ophthalmic medications. Due to a few limitations, some medications are unable to effectively reach the intraocular tissue. Nonetheless, one of the well-known issues brought up by eye ointments is

corneal tissue irritation. Consequently, investigating other drug delivery methods such as hydrogels, films, particles, and contact lenses aids in overcoming these limitations.

- **Neural therapy:** The central nervous system (CNS) in human physiology has a finite intrinsic capacity for regeneration. Thus, a number of treatments for conditions affecting the central nervous system (CNS), such as those affecting the brain, spinal cord, and retina, are unable to provide a meaningful functional recovery. Since blood-brain barriers prevent these treatments from reaching the central nervous system, one of the problems has always been getting molecules into the brain by conventional oral or intravenous routes. A minimally invasive, targeted, and void-filling platform for medication administration to the central nervous system is thus offered by injectable hydrogels [17].

## Conclusion

This review has highlighted the remarkable advancements and promising uses of hydrogels in a number of fields, such as drug delivery, tissue engineering, biomedicine, and recent developments in the challenges of using hydrogels in clinical or pre-clinical settings, as well as current developments in hydrogels' physicochemical and biological responses. The distinct characteristics of hydrogels, like their biocompatibility, adjustable mechanics, and stimuli reactivity, are spurring innovation and tackling important problems in contemporary science. In the future, more investigation into sophisticated synthesis methods, medicinal uses, and intelligent hydrogel design will surely push the boundaries of this adaptable substance, opening the door to revolutionary medical treatments, useful technologies, and other areas. The advantage of these networks is the lack of use of organic solvents. Release of pharmaceutical agents from hydrogels is mainly done by swelling of the structure. In recent years, attention to stimulus-responsive hydrogels has increased. Hydrogels are considered as an attractive biomaterial for various medical applications due to their water absorption, soft structure, biocompatibility and similarity to ECM.

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