Hydrogels Based Drug Delivery System – A REVIEW

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Abstract- Hydrogels are polymers that have been cross-linked and contain hydrophilic groups, which allow them to absorb a lot of water. Hydrogels are a great tool for drug delivery because of their many benefits, such as their biocompatibility, low toxicity, and good swelling behaviour. However, there are certain limitations when it comes to the delivery of active pharmaceuticals through hydrogels, depending on the chemical properties of the gel-forming polymers and the administration route. In this review, the hydrogel was first classified using various techniques, such as chemical moieties, crosslinking agent behaviours, and release controller mechanism. The limitations resulting from each category were then described, and lastly, various methods to get around each of these limitations were suggested.

Keywords: Hydrogels, Homopolymers, Grafting, Biosensors, Cross-linking.

INTRODUCTION

History

According to Lee, Kwon, and Park, the term "hydrogel" has been in use since 1894; however, the substance in question was a colloidal gel made of inorganic salts [1]. These gels, which are composed of polymeric matrix, swell rather than dissolve [2]. In any case, Wichterle and Lim reported the first accurate hydrogel with a cross-linked network for the first time in 1960 [3]. It was a hydrogel made of polyhydroxy ethyl methacrylate that was created with the intention of using it in long-term interactions. The first materials to be created specifically for use inside patients are hydrogels. Following that, there was an increase in study on hydrogels and their potential uses in biomedicine [4]. Lim and Sun conducted some significant and impactful hydrogel research in the 1980s [5]. Since roughly fifty years ago, they have been utilised in medicine. Although the literature discusses them mainly in relation to their application in pharmaceutical and medical fields, their history is far longer. Three distinct generations have been identified in the history of hydrogels. Crosslinking methods involving chemical changes were part of the first generation. High swelling and good mechanical properties were the goals of these improvements [6]. Materials from the second generation react and are sensitive to particular stimuli, such as temperature, pH, and concentration. The mechanical strength issues were addressed with the development of the second generation of hydrogels. The third generation then concentrated on studying and creating hydrogels and stereo complex materials that were physically cross-linked. The creation of "smart hydrogels," which are polymeric matrices with a wide range of customizable properties, was facilitated by this advancement [7]. These gels remain stable in conditions that change, like temperature [8].

What are Hydrogels?

A three-dimensional network made of hydrophilic polymers that expand in water is known as a hydrogel. Large volumes of water can be held in these polymers without the structure being compromised [9]. According to some experts, it is a bloated polymeric substance that holds a sizable amount of water inside of it without dissolving in water [10]. Hydrogels represent innovative drug delivery agents that can facilitate the administration of various drug compounds, whether of a therapeutic or diagnostic nature. Additionally, they serve as appropriate carriers for biological products including plasma, sera, and valvular intestinal cells, as well as immunological items like vaccinations [11]. Because of their high water content, hydrogels exhibit tissue-like elasticity.In [12] They owe this characteristic to the various hydrophilic functional groups that they contain. Positive and negative ions are bonded to the backbone of a polyampholyte hydrogel [13]. The cross-linking between the chains

in the network is what gives hydrogels their resistance to dissolution [14]. Both manmade and natural materials may be a part of this network. Over the past 20 years, synthetic hydrogels have steadily replaced natural ones because of their superior qualities, which include remarkable strength and a great capacity for absorbing water.They have a distinct morphology that can be changed or adapted to acquire desirable qualities such biodegradability, usefulness, and strength [15]. Hydrogels can experience changes due to various biological stimuli, as well as physical or chemical stimuli, such as gel-sol transitions or volume phase transitions [16]. Electric fields, temperature, pressure, light intensity, solvent composition, and magnetic fields are examples of physical stimuli. On the other hand, pH, chemical compositions, and different ions are the chemical and biological stimuli. These changes are usually reversible. The type of the monomers, cross-linkage, and charge density all affect how a hydrogel reacts to stimuli [17]. The charged hydrogels swell when they are exposed to the electrical field and undergo shape changes[18].

CLASSIFICATION OF HYDROGELS

Biopolymers or polyelectrolytes are the primary components of hydrogels [19]. Hydrogels can be classified into many categories based on their origin, ionic charges, appearance, configuration, and type of cross-linkages. These are classified based on:

Source

Natural Origin: These hydrogels contain natural polymers, for instance, proteins (gelatin and collagen) and other polysaccharides (starch, agarose, and alginate) [20].

Synthetic Origin: These are constituted from synthetic polymers that are synthesized by chemical polymerization methods [21]. Nature of Hydrogel Hydrogels can be of different types in nature [22].

Physical Gels: These transitions from liquid to gel in turn of environmental changes (pH, temperature or pressure) or mixing. Physical gels are also called as reversible gels.

Chemical Gels: These gels involve covalent bonding for mechanical integrity and resistance to degradation. These gels are also called as permanent gels.

Biochemical Gels: These involve biological agents such as amino acids or enzymes as participants of the gelation process.

Methods of Preparation of Hydrogels

They are made of an elastic network of cross-linked polymer that interacts with water. These cross-linked polymer-forming processes are employed to create hydrogels [23]. One common technique for creating cross-links is through free-radical polymerization. Some ways to cross-link water-soluble linear polymers include:

a) Linking the polymer chains via a chemical reaction

b) Ionising radiation is used to produce main-chain free radicals, which can then recombine to form cross-link junctions.

c) Physical interactions, i.e.,electrostatics [24]

As stated in the above classification, they are divided into three classes based on the technique used in their preparation. These are as follows:

Homopolymers

In order to manufacture cross-linked homopolymers hydrogels, which are typically employed in the production of contact lenses, one method is to choose poly (2-hydroxyethyl methacrylate) as the monomer, polyethylene glycol dimethacrylate as the cross-linking agent, and benzoin isobutyl ether as the UV-sensitive initiator. After being created in de-ionized water, the cross-linked film is exposed to UV radiation (λ = 253.7 nm) for a duration of 20 minutes. Submersion in water for a full day, or until completely saturated and non-toxic, is the following stage [25]. Using a low molecular weight crosslinking agent is a further method of creating the poly HEMA hydrogel. When this agent is used, a soft hydrogel with a high oxygen permeability and roughly 30–40% water content is created. This qualifies it for use in soft tissue implants, contact lenses, and drug delivery carriers [26]. Hydrogels based on polyethylene glycol and sensitive to external stimuli are appropriate for the controlled and efficient release of growth factors, biomolecules, pharmaceuticals, and proteins. "Click" chemistry refers to a unique method of PEG hydrogel synthesis that was first presented by Lin and Anseth. The expeditious, targeted reaction and adaptability of this bioconjugation technique are its advantages [27]. The process of forming polyvinyl alcohol (PVA) hydrogels involves repeated cycles of freezing and thawing. When compared to UV radiation, this method of PVA material preparation offers higher mechanical strength. Radiation therapy can be used to create polyvinyl pyrrolidone (PVP)

hydrogels, which are then applied to the healing of wounds. [28].

CO-POLYMERIC HYDROGEL

They are made up of two types of monomers, one of which is lipophobic (loving water). Triblock poly(ethylene glycol)-poly(εcaprolactone)-poly(ethylene glycol) (PECE) co-polymeric biodegradable hydrogel was created by Gong et al. [29] for the purpose of drug distribution. For εcaprolactone, the ring-opening copolymerization method was suggested. Hexamethylene diisocyanate was the coupling agent, stannous octoate was the catalyst, and mPEG was the initiator employed in the triblock synthesis. This copolymeric block generates a hydrogel when applied in-situ. In a different study, Kim and his colleagues used the free-radical photopolymerization approach to create copolymers of Methacrylic Acid (MAA) with PEG-PEGDA. Tetra (ethylene glycol) dimethacrylate was employed as the initiator and 1-hydroxycyclohexyl phenyl ketone as the cross-linking agent. Under UV light, a nitrogen environment was maintained for thirty minutes during the operation. Successfully, insulin was put into the hydrogel that was created.

INTER PENETRATING NETWORK (IPN)

IPNs are formed by combining two polymers intimately when one polymer is synthesized in the presence of the other polymer. This is done by immersion of a pre-polymerized hydrogel in a solution of monomers and an initiator. The main advantages of IPNs are resilient mechanical properties, more efficient drug loading, and controllable physical properties. An example of IPN is the modification of polyethylene glycol diacrylate hydrogel with β-chitosan. This modification resulted in improved biocompatibility. This was done by using a 2 percent chitosan solution for mixing a 10 percent aqueous PEGDA solution. UV radiations were used for the formation of cross-links leading to the formation of IPN hydrogel. Kim et al. attempted to extend the applications of another classic biomaterial; Polyurethane (PU), by making its IPN with polyacrylamide (PAA). The result was an IPN hydrogel that could control water absorption. For this purpose, both PAA and PU were mixed and exposed to UV radiation. The cross-linking agents used for this process were methylene bisacrylamide and vinyl pyrrolidone. These types of IPN-PU hydrogels find applications in DDS, artificial muscles, wound dressing material, and sensor systems [30].

METHODS OF CROSS-LINKING

Cross-linked networks of natural biopolymers such as alginate, carboxymethylcellulose, and chitosan have been seen. Synthesis polymers such as polyvinyl pyrrolidone [31]. polythene glycol polyacrylic acid, polyethylene oxide , polymethacrylate and polylactic acid [32]. have been cross-linked to form hydrogels. Several methods for the synthesis of hydrogels include physical crosslinking chemical cross-linking grafting polymerization , and radiation cross-linking [33]. These modifications can enhance the viscoelasticity and other properties for applications in the pharmaceutical and biomedical field [34].

1.PHYSICAL CROSS-LINKING

Physical or reversible gels have been a topic of interest because they do not need cross-linking agents for their production and they are relatively easy to produce. Various methods used for crosslinking to produce physical gels

Heating or cooling a polymer solution:
The hot solutions of carrageenan or gelatin are cooled to form cross-linked gels. The gels formation occurs because of the helix formation and association between the helices [35]. Hennink and Nostrum reviewed the polyethylene glycol-polylactic acid hydrogels formed by physical cross-linking by simply warming the solutions of polymers [36].

Ionic Interactions:
This method includes the addition of divalent and trivalent counter ions to cross-link the polymers. Some examples of hydrogels formed by ionic interaction include chitosan-glycerol phosphate salt [66] and chitosan-polylysine [37]

Complex Coacervation:
Literature has also shown another method that involves the sticking of oppositely charged polymers and forming complexes that depend on the pH and concentration of the solutions. Esteban et al. formed a polyionic hydrogel by coacervating xanthan and chitosan. Polyionic complexes form as

the proteins are positively charged below their isoelectric points and tend to associate with the negatively charged hydrocolloids [38].

Hydrogen Bonding:
Hydrogels formed by hydrogen bonding involve reducing the pH of polymer solutions that have carboxyl groups. Takigami et al. reported the formation of CMC hydrogel by hydrogen bonding after dispersing CMC in a solution of HCL 0.1M [39].

Freeze Thawing:
Freeze-thaw cycling is another way of physically cross-linking the polymers to obtain hydrogels. [40].The principle of this technique is the microcrystal formation after freeze-thawing. Giannouli [41]. performed cryogelation of the xanthan polymers to form hydrogel [42].

2.CHEMICAL CROSS-LINKING
It can be done by various techniques that involve the grafting process or linkage of two polymer chains by a cross-linking agent[43].
Chemical Cross-Linkers:
Cross-linking agents such as glutaraldehyde and epichlorohydrin were employed to synthesize hydrogels containing both natural and synthetic polymers[44]. This technique includes the addition of new molecules for producing cross-linked chains in the polymeric chains[45]. Literature also shows the use of 2- acrylamido-2-methylpropanesulfonic acid for cross-linking acrylic acid and κ-carrageenan for producing biodegradable hydrogels[46]. Carrageenan hydrogels also find applications in the industry for the immobilization of enzymes . Epichlorohydrin can be used as a cross-linker for synthesizing hydrogels from cellulose by heating and freezing techniques. [47].

Grafting:
Grafting is done by the polymerization of a monomer on a preformed polymer backbone. Grafting can be divided into two types: chemical grafting of radiation grafting. Chemical grafting involves the activation of polymer chains by chemical reagents for example the use of N-vinyl-2-pyrrolidone to graft starch with acrylic acid. Said et al. prepared CMC hydrogel by using electron beam radiation. Radiation Cross-linking Another technique for the preparation of these systems is by cross-linking the polymers. This method involves the use of free radical production in the polymer followed by its exposure to a high energy source[48].It is a useful method as it does not require any chemical additives. It is also a cost-effective process for the modification of biopolymers to be used for biomedical applications[49].

3. RADIATION CROSS-LINKING
Another technique for the preparation of these systems is by cross-linking the polymers. This method involves the use of free radical production in the polymer followed by its exposure to a high energy source. It is a useful method as it does not require any chemical additives. It is also a cost-effective process for the modification of biopolymers to be used for biomedical applications. [50].

APPLICATIONS OF HYDROGELS

Hydrogel applications are widespread in various fields, due to their compatibility with different usage conditions and their specific structures. The flexibility of hydrogels makes them easy to be availed in various areas that range from biological to industrial areas. Due to their non- toxic nature and chemical compatibility with biological environments their use extends to medical sciences. Some primary uses of the hydrogels in industry and medicine are as follows:

Drug Delivery:
The astounding characteristics of hydrogels make them a significant candidate for controlled drug delivery systems (systems that deliver the drug at a predetermined rate and time) [51].This can help to overcome various problems that may occur while handling some formulations. The hydrogels are suitable for the loading and proper release of many drugs because of their high porosity (due to cross-linking and swelling) that, in turn, give them the property of high permeability [52]. The main advantage is that they can be used for sustained release of drugs with a high concentration to a specific area in the body [53]. Studies have also suggested the use of hydrogels for the long term delivery of drugs by gastro-retentive mechanisms [54]. To enhance the binding of a drug to the matrix of hydrogel (to extend the drug release time), both chemical and physical strategies can be used [55]. The drug can be released from hydrogels according to different local changes (stimuli) such as

temperature, pH, physical stimuli, or some specific enzymes. The examples of such hydrogels are as follows-

PH-Sensitive Hydrogels:
PH is one of the most crucial parameters for DDS, as pH changes occur at many body sites such as the stomach or other specific tissues.To form pH-sensitive hydrogels, both basic and acidic polymers are used, for example:
Acidic Polymers: PAA, Sulfonamide containing polymers [56].
Basic: Ethyl methacrylate, Poly vinyl pyridine.

Temperature-sensitive hydrogels in DDS:
Temperature sensitive hydrogels are responsive to changes in the temperature of the body [57]. These can be formed by using thermosensitive polymers, for example, Poly N-isopropylacrylamide and Poly N, N diethyl acrylamide. Methylcellulose has also been seen to be triggered by thermal transitions [58].

Dyes and Heavy Metal Ions Removal:
Many industrial processes generate waste water that can lead to heavy metal pollution, which poses a serious risk to the general public's health as well as the environment. Therefore, there is a tremendous deal of scientific interest in removing these hazardous heavy metal ions. Hydrogels are also useful in this context. They eliminate hazardous substances and heavy metals by acting as adsorbents. Functional groups on the surface of hydrogels, such as carboxyl, phosphonic, sulfonic, and nitrogen, can promote the absorption of metal ions [59]. On the other hand, hydrogels are not cost-effective when used extensively to treat heavy metal ion toxicity. According to studies, hydrogels work incredibly well as dye adsorbents. Materials containing a lot of methylene blue dye can be absorbed by them. Because polyelectrolytes can bind to oppositely charged metal ions and form complexes, they have been claimed to be important in the elimination of heavy metal ions [60]. Additional hydrogels that are suitable for removing metal ions include alginate, chitosan, starch, and cellulose derivatives. Hydrogels help remove metal ions in addition to other phenomena like chelation and sorption.

Biosensors:
A biosensor is a combination of chemical and physical sensors. It is a device used to sense and report a biophysical property of any system. A biosensor has a biological recognition part known as a bio element which makes analyzing biological information possible [61].

Biosensors find applications in the following areas:
a) Point-of-care testing
b) Environmental monitoring
c) Diagnostics
Although the structure of a bio element can resemble that of enzymes, live cells or tissues, or antibodies, its selectivity is what matters most. Numerous techniques, including covalent bonding, trapping in membranes or matrices, and physical adsorption, can link biological molecules with sensors. Hydrogels have also been modified for use as medical electrodes in electrocardiograms and other diagnostic testing. Hydrogels can serve as a 3D matrix, support bio components, or be coated on the sensing device (such an electrode) in biosensors. Hydrogels can shield biosensor components from unwanted interactions with biological substances or cells. Numerous investigations have demonstrated the potential of hydrogels in cell culture. These have applications in endothelial damage, cardiovascular disorders where the disease may be treated by reshaping the blood vessels, protein synthesis that quickens the process of growth, and bone remodelling [62].

Injectable Hydrogel for Regeneration of the Spinal Cord:
Spinal cord injury (SCI) is a complex degenerative disorder resulting from development inhibition brought on by damage to the spinal cord's components. These injuries can occasionally be healed with the use of hydrogels. Once the viscoelastic hydrogels are injected into the injury site, they solidify from a liquid to a gel. Hydrogels fill the small voids or transected portions that occur in SCI. Therapeutic chemicals can be added to these hydrogels before being injected into the injured area. Nonetheless, these hydrogel scaffolds ought to have characteristics similar to those of spinal cord tissues.

The requirements for the designing parameters include:
a) Creating a scaffold for cellular infiltration
b) Maintenance of bioactivity
c) Provision of sustained delivery of loaded agents
d) Tunable and local delivery of therapeutic agents

Design parameters include:
a) Designed scaffold's mesh size,
b) Mechanical characteristics of the gel material
c) Biocompatibility of materials used for injured site
d) Conditions of mild solidification
e) Suitable porosity
f) Rate of degradation
g) Bioactivity

Each type of injectable hydrogel—natural or synthetic—has advantages and disadvantages. Glycidyl methacrylate and polyamidoamine macromers (after going through the gelation process) are two examples of injectable hydrogels. Because injectable hydrogels are minimally invasive, they are patient-friendly. They provide the simple blending of bioactive compounds or cells with polymer solutions, enabling the rapid formation of 3D microenvironments in the appropriate forms.Because of their great elasticity, enzyme-mediated injectable hydrogels, such those made of tyramine conjugated polymers, are employed as scaffolds and in drug delivery systems. Studies on the function of hydrogels with antigen-antibody interactions in the development of an injectable three-dimensional network have also been conducted [63].

LIMITATIONS OF HYDROGELS

Hydrogels have many benefits, but they also have certain drawbacks or restrictions. Nonetheless, the benefits of using hydrogels as drug carriers outweigh the drawbacks by a wide margin. The majority of these restrictions are surmountable, but there are still some significant difficulties with the hydrogels. The primary disadvantage of hydrogels is their high cost. The complicated procedure of putting drugs into hydrogels calls sophisticated mechanical equipment and trained labour during production. Handle them carefully as they are quite fragile. The procedure of terilizing the hydrogels is intricate. Cross-linker concentration in the hydrogels is crucial since too much of them can be harmful [64].

CONCLUSION AND FUTURE PERSPECTIVE

The spectrum of medicines and kinetics that can be delivered via a hydrogel-based delivery vehicle has been expanded, and significant progress has been made in enhancing the characteristics of hydrogels utilised for drug delivery. To increase the therapeutic usefulness of hydrogels for drug delivery, a number of obstacles still need to be overcome. Improving clinical usage ease is one set of significant issues. The possibility of early gelation inside the needle during injection could be decreased by designing physical gelators that gel at lower polymer concentrations and at more precise gelation temperatures. Comparably, for covalently cross-linked hydrogels, more research should be done to develop methods for the cross-linker to be released inside the body in response to stimuli. This will reduce the likelihood of syringe clogging, enhance the localization of cross-linker release to reduce in vivo toxicity, and allow the chemically reactive gel precursors to be mixed in a single syringe, doing away with the need for double-barreled syringes. Better applicator systems for the hydrogels could be developed in order to further improve this domain. To enhance the potential of injectable hydrogels for drug delivery and tissue engineering applications, novel physicochemical strategies or combinations of current cross-linking techniques could be utilised to regulate not only the gelation process but also the interactions between the gel and native tissues. Extending the range of kinetic release profiles that hydrogels can produce is another ongoing problem. Hydrogels may replace hydrophobic systems for long-term release applications if the release period was extended. This would be beneficial in a variety of applications. Because hydrogels have a higher level of biocompatibility, this would be advantageous. Applications that need to administer different dosages of a drug over time, like the delivery of insulin or analgesics, may profit from the development of hydrogel-based systems that allow the rate of drug delivery to be readily modified one off over time. These kinetic problems might be resolved with the use of hydrogels with various degradation profiles and/or environmentally responsive segments. Delivery of more sensitive molecules, such as proteins, antibodies, or nucleic acids, which are easily deactivated or unfolded by interactions with the hydrogel delivery vehicle, also needs to be improved further in addition to hydrophobic molecules. This is a specific problem with in situ cross-linking hydrogels, where the biological activity of the entrapped biomolecule can be greatly impacted by the hydrophobic domains generated in thermally gelling polymers or the functional group chemistry employed to form

covalently gelling hydrogels. This problem might be solved by pre-encapsulating or complexing biomolecules before in situ hydrogel production. The potential of hydrogel-based drug delivery to effectively deliver the upcoming generation of tailored medications at the appropriate rate and location in the body would be considerably expanded by advancements on any or all of these difficulties. Furthermore, there is still a lot of space for advancement in the several wide and pecialized applications that this assessment does not address. Much as in many other areas of drug delivery, "convergence" [65], or the coming together of once unrelated scientific disciplines, is probably going to influence how drug-eluting hydrogel design develops in the future.

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