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Hydrogels: A Novel Drug Delivery System

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ABSTRACT

Hydrogels are water-swollen networks, which are cross-linked structures consisting of hydrophilic polymers. They are made three-dimensional by the creation of the cross-links by joining them through covalent or ionic bonds. Hydrogels have been used in various areas including industry and medicine due to their excellent characteristics such as high swelling capacity, high content of water, compatibility with other biological molecules, controlled chemical and physical properties, high mechanical integrity and biodegradability. They have been the center of attention of researchers from the past 50 years because of their promising applications in industries and other areas. They are used in different fields, in medicine, in the diagnosis of the diseases, in culturing of cells, in injuries as wound healers, in cosmetics, in skin diseases like pruritis, in environmental pollution reduction and other miscellaneous applications such as in diapers for babies and sanitary products. Extensive literature can be found on the subject of hydrogels. The present review discusses the history, description of hydrogels, basic properties, classification, different techniques or methods of hydrogel synthesis and the areas in which hydrogels find applications.

INTRODUCTION

History

The word “hydrogel”, as stated by Lee, Kwon and Park, has been used since 1894 but that material was not a hydrogel but a colloidal gel (of inorganic salts) [1]. These gels are made of polymeric matrices but they do not dissolve instead they swell [2]. Anyhow, the first accurate hydrogel having a cross-linked network was reported by Wichterle and Lim in 1960 for the first time [3]. It was a polyhydroxy ethyl methacrylate hydrogel that was synthesized with the aim of its usage in permanent contacts. Hydrogels are the first to be synthesized for uses inside the patient. After that the researches on the topic of hydrogels and their biomedical applications started to rise [4]. Some influential and important work was performed on hydrogels in the 1980s by Lim and Sun [5].

They have been used in medicine from about fifty years ago. Their history goes way back although the discussion in literature involves more information about their use in medical and pharmaceutical areas. The history of hydrogels has been classified in three different generations. The first generation included cross-linking techniques that involved chemical alterations. These modifications were applied to achieve high swelling and good mechanical characteristics [6]. The second generation contains materials that are sensitive to and respond to specific stimuli, for example, pH, concentration, and temperature. The second-generation hydrogels were made to overcome the problems of mechanical strength. Finally,

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the third generation then focused on investigating and developing stereo complex materials and hydrogels that were cross-linked through physical interactions. This development led to the development of “smart hydrogels” that are polymeric matrices with a broad spectrum of tailorable attributes [7]. These gels maintain their stability in the fluctuating condition such as temperature [8].

WHAT ARE HYDROGELS?

A hydrogel can be described as a three dimensional network formed by hydrophilic polymers which can expand in water. These polymers can hold copious amounts of water without disrupting the structure [9]. Some researchers define it as a swollen polymeric material retaining a significant volume of water in it without itself being dissolved in water [10]. Hydrogels are novel drug deliverers that can aid in the delivery of several kinds of drug molecules either therapeutic or diagnostic nature. They are also suitable carriers for immunological products such as vaccines and other biological products like plasmas and seras and valvular intestinal cells [11].

Hydrogels, owing to their high water load, show flexibility that is similar to natural tissue. They owe this property to the existence of different functional groups in them that are hydrophilic. These groups include:

- -COOH
- -NH₂
- -OH
- -CONH
- -CONH₂
- -SO₃H [12]

A polyampholyte hydrogel consists of negative and positive ions are bound to the backbone [13]. The resistance of hydrogels to dissolution occurs due to the cross-linkage between the chains in the network [14]. This network can include both natural and synthetic materials.

The synthetic hydrogels are gradually taking the place of the natural ones during the last two decades due to the better properties presented by the synthetic hydrogels for instance, high water absorption capacity and incredible strength. They show a well-defined morphology which can also be modified or altered to get desired traits such as strength, functionality and biodegradability [15].

Hydrogels can undergo transitions such as gel-sol transition or transitions in the volume phase as a result of different biochemical stimuli and physical or chemical stimuli [16]. Physical stimuli comprise electric fields, temperature, pressure, light intensity, the composition of the solvent and magnetic field. In contrast, the chemical and biochemical stimuli involve pH, chemical compositions, and various ions. In most cases, these transitions are reversible. A hydrogel's response to stimuli is dependent on the charge

density, nature of monomers, and cross-linkage [17]. The charged hydrogels swell when they are exposed to the electrical field and undergo shape changes [18].

Classification of hydrogels

The main constituents of the hydrogels are biopolymers or polyelectrolytes [19]. Hydrogels can be divided into different types according to the source from which they have been and the ionic charges, appearance, configuration and type of cross-linkages. These are classified based on below fields.

Source:

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

- i. 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.
- ii. Chemical gels: These gels involve covalent bonding for mechanical integrity and resistance to degradation. These gels are also called as permanent gels.
- iii. Biochemical gels: These involve biological agents such as amino acids or enzymes as participants of the gelation process.

Configuration: Hydrogels can be put into different classes depending on their morphology such as:

- i. Amorphous (non-crystalline)
- ii. Semicrystalline
- iii. Crystalline [23]

Physical appearance: Hydrogels can be organized into various classes based on how they appear, these are as follows:

- i. Matrix
- ii. Film
- iii. Microsphere

This appearance usually depends on the polymerization method being used in the preparation process [24].

Type of cross-linking: The cross-link junctions in the hydrogels can have chemical or physical nature.

- i. Chemical cross-linkage has a permanent junction.
- ii. Physical cross-linkages have transient junctions [25].

Polymeric composition: Classification into different types on the method of their preparation is as follows:

Homopolymeric hydrogels: Contain a polymeric network having a single monomer species [26]. These hydrogels can be used as scaffolds for the promotion of cell adhesion and the regeneration of spinal cord cells [27].

Copolymeric hydrogels: Comprise of two or more species of different monomers with a minimum of one lipophobic component. These components are usually arranged in different configurations, such as random or block configuration along the polymer network chain. For example, cellulose and CMC were used in the manufacture of PVP based hydrogels [28].

Semi-Interpenetrating polymeric hydrogels: This network is formed by penetration of one linear chained polymer into another cross-linked network and they have no chemical bonds in between them [29].

Interpenetrating Polymeric Hydrogels (IPN): This class has two synthetic or natural independent and cross-linked polymeric components in a network configuration [30].

Electrical charge:

- i. Nonionic - having no charge [31].
- ii. Ionic - having either a negative or positive charge.
- iii. Amphoteric electrolyte (Ampholytic).
- iv. Zwitterionic [32].

PROPERTIES OF HYDROGELS

Hydrogels are finding many applications in domestic and industrial areas due to its properties.

Hydrogels have:

- Both solid and liquid-like properties
- High biocompatibility [33]
- Maximum absorption capacity
- Preferred particle size and desired porosity
- Shrink on drying
- Responsive to stimuli [34]

Swelling

Hydrogels are polymers with cross-linkages that become

swollen in a liquid medium [35]. They can absorb from a minimum of 10 to 20% to 1000 folds of their dry weight present in water. When a dry hydrogel soaks up the water, the molecules infiltrating the hydrogel matrix moistens the polar hydrophilic groups in it. After the hydration of these oppositely charged groups, the network swells and exposure to the hydrophobic groups occurs [36].

Mechanical properties

These properties of the hydrogels can vary relying on the purpose of use of the substance. A gel with high rigidity can be obtained by increasing the cross-linkages in it. In contrast this rigidity can be reduced by heating these materials. Such as gelatin shows an increase in the Young Modulus through cross-linking [37]. The Young Modulus is the result of the interaction between the gel matrix and solution, i.e., water. The hydrogel cross-linking density can be assessed by employing Flory's theory and Young's Modulus [38].

Porosity and permeation

The factors that affect the hydrogel matrix include the interconnections between the pores, the average size of the pore and the distribution of pore size. All these factors add up to form a significant parameter called tortuosity [39]. The influencing factors for the distribution of pore-size are as follows:

- Chemical cross-link concentrations of the polymer strands.
- Physical entanglements present in the polymer strands.
- Net charge present on the polyelectrolyte hydrogel.

The influencing factors of the porous structure of a hydrogel include:

- Type of the surrounding solution.
- Diffused ionic solutes in solution.
- Dissolved uncharged solutes.

The high porosity enable them to uptake large amounts of water and swell [40]. The porous microstructure of hydrogels can be determined by various methods [41].

Cross linking

The hydrogels are characterized by networks of polymers formed by cross-links. The properties of the hydrogels are altered by the presence of the number of cross-links [42]. The cross-links are of various types and they vary according to the type such as if they are bound physically or chemically [43]. The tailorable characteristics of hydrogels come from the type of cross-linkage and that is how they can be optimized [44].

METHODS OF PREPARATION OF HYDROGELS

They consist of cross-linked water interacting network of polymer that gives it an elastic structure. To produce a hydrogel such techniques are used that can form a cross-linked polymer [45]. A standard method to produce cross-linkage is the free-radical polymerization. Some ways to cross-link water-soluble linear polymers include:

Linking the polymer chains via a chemical reaction

Use of ionizing radiation for the generation of main-chain free radicals that can recombine as cross-link junctions

- 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

Cross-linked homopolymers hydrogels are usually used for contact lens production and one way to prepare it is by selecting poly (2-hydroxyethyl methacrylate) as a monomer, cross-linking agent; polyethylene glycol dimethacrylate and UV-sensitive initiator; benzoin isobutyl ether. The cross-linked film is formed in de-ionized water and then treated with UV radiation ($\lambda = 253.7$ nm) for 20 minutes. The next step is the immersion in water for 24 hrs until fully saturated and non-toxic [46].

Another way to synthesize the poly HEMA hydrogel is the use of low molecular weight cross-linking agent. The use of this agent forms a soft hydrogel containing about 30-40 percent of water and high permeation ability of oxygen. This makes it suitable for contact lenses, soft tissue implants, and carriers for drug delivery [47].

Polyethylene glycol-based hydrogels that are responsive to external stimuli are suitable for efficient and controlled drugs, biomolecules, proteins, and growth factor release. A novel technique of PEG hydrogel formation, introduced by Lin and Anseth, is called as 'Click' chemistry. This method has the advantage of rapid, specific reaction and versatility in bio-conjugation [48].

Polyvinyl alcohol (PVA) hydrogels formation includes interchanging cycles of freezing and thawing. This method of PVA material preparation provides greater mechanical strength as compared to UV radiation. Polyvinyl Pyrrolidone (PVP) hydrogels can be synthesized by radiation technique and used in wound healing [49].

Co-polymeric hydrogels

They comprise of two monomer types from which one is lipophobic (Water-loving). Gong et al. produced the triblock Poly(Ethylene Glycol)-Poly(Ecaprolactone)-Poly(Ethylene Glycol) (PECE) co-polymeric biodegradable hydrogel for drug delivery [50]. The ring-opening copolymerization technique was implied for ϵ -caprolactone. For triblock synthesis the initiator used was mPEG, the catalyst was stannous octoate and the coupling agent was hexamethylene diisocyanate. When applied in-situ, this co-polymeric block forms a hydrogel.

In another study, Kim and his co-workers synthesized copolymers of methacrylic acid (MAA) with PEG-PEGDA by using the technique of free-radical photo-polymerization. They used tetra (ethylene glycol) dimethacrylate as the cross-linking agent and 1-hydroxycyclohexyl phenyl ketone as an initiator. A nitrogen atmosphere was maintained for 30-minutes, and the process was done under UV light. The hydrogel formed was loaded with insulin successfully [51].

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 [52].

An example of IPN is the modification of polyethyleneglycol 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) [53]. 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 methylenebisacrylamide and vinylpyrrolidone. These types of IPN-PU hydrogels find applications in DDS, artificial muscles, wound dressing material, and sensor systems [54].

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 [55], polythene glycol [56], polyacrylic acid [57], polyethylene oxide [58], polymethacrylate [59] and polylactic acid [60] have been cross-linked to form hydrogels. Several methods for the synthesis of hydrogels include physical crosslinking

[25], chemical cross-linking [61], grafting polymerization [62], and radiation cross-linking [63]. These modifications can enhance the viscoelasticity and other properties for applications in the pharmaceutical and biomedical field [64].

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 cross-linking to produce physical gels include:

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 [65]. Hennink and Nostrum reviewed the polyethylene glycol-poly(lactic acid) hydrogels formed by physical cross-linking by simply warming the solutions of polymers [25].

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 [67].

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 [68]. Polyionic complexes form as the proteins are positively charged below their isoelectric points and tend to associate with the negatively charged hydrocolloids [69].

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 [70].

Freeze Thawing: Freeze-thaw cycling is another way of physically cross-linking the polymers to obtain hydrogels. The principle of this technique is the microcrystal formation after freeze-thawing. Giannouli et al. performed cryogelation of the xanthan polymers to form hydrogel [71].

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.

Chemical cross-linkers: Cross-linking agents such as glutaraldehyde [72] and epichlorohydrin [73] were employed to synthesize hydrogels containing both natural and synthetic polymers. This technique includes the addition of new molecules for producing cross-linked chains in the polymeric chains. Literature also shows the

use of 2-acrylamido-2-methylpropanesulfonic acid for cross-linking acrylic acid and κ -carrageenan for producing biodegradable hydrogels [74]. Carrageenan hydrogels also find applications in the industry for the immobilization of enzymes [75]. Epichlorohydrin can be used as a cross-linker for synthesizing hydrogels from cellulose by heating and freezing techniques [76].

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 [77]. Said et al. prepared CMC hydrogel by using electron beam radiation [62].

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 [78].

CHARACTERIZATION OF HYDROGELS

Morphology, elasticity, and the swelling property are various parameters on which the hydrogels can be characterized. The morphology indicates the structure of the hydrogel or its porosity. The swelling property indicated the mechanism by which the drug is released from the polymeric material, and the third parameter elasticity shows the strength and stability of the polymeric network and drug carriers respectively [79]. These three parameters are discussed in detail in the following paragraphs.

Morphological characterization

The morphology of hydrogels includes its shape, form, and structure and it is determined through a stereomicroscope. The texture of the polymers such as starch, can be assessed by the SEM technique [80].

X-ray diffraction

X-ray diffraction is employed to evaluate the molecular organization and nanoscale structure of an organic hydrogel in its hydrated form. It may also be used to the transition of polymers from their crystalline form to another during the processing [81].

In-vitro release study for drugs

The release studies of drugs from the hydrogel carriers are essential to understand the mechanism of release. The duration taken by the hydrogel to release the drug is also of significant importance [82].

FTIR

The IR absorption spectra of the hydrogels changes if there is any alteration in their morphology. These changes in the spectra can be determined by using FTIR. The appearance of bands shows the cross-linking of the polymers [83].

Swelling behavior

The following equation can calculate the swelling percentage (S%) of the hydrogels:

$$S (\%) = (W_s - W_d) / W_d * 100,$$

Wd: Dry hydrogel

Ws: Swollen hydrogel [84].

Rheology

The viscosity of the hydrogels can be evaluated by the Cone plate viscometer at a constant temperature, i.e., 4°C [85].

Measurement of gel content

The gel content can be determined by putting the sample in 200 mesh and washing it three times with distilled water following extraction at 80°C in distilled water for 24 h. The remaining gel was dried.

Gel content can be measured gravimetrically as follows:

$$\text{Gelation (\%)} = W_d / W_o * 100,$$

Wd: Weight after extraction

Wo: Initial weight [86].

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 following fields.

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) [87]. 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 [88]. 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 [89]. Studies have also suggested the use of hydrogels for the long term delivery of drugs by gastro-retentive mechanisms [90].

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 [91]. 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 [92]. To form pH-sensitive hydrogels, both basic and acidic polymers are used, for example:

Acidic Polymers: PAA, Sulfonamide containing polymers [93]

Basic: Ethyl methacrylate, Polyvinyl pyridine [94]

- **Temperature-sensitive hydrogels in DDS:** Temperature-sensitive hydrogels are responsive to changes in the temperature of the body. These can be formed by using thermosensitive polymers, for example, Poly N-isopropylacrylamide and Poly N, N diethyl acrylamide [95]. Methylcellulose has also been seen to be triggered by thermal transitions [96].

Dyes and heavy metal ions removal

The waste-water of many industrial procedures can cause heavy metal pollution, which can be a severe threat to the health of the public and the eco-systems. Thus the removal of these dangerous heavy metal ions is of great scientific interest. Hydrogels find applications in this regard as well. They act as adsorbents to remove heavy metals and toxic compounds. The functional groups such as carboxyl, phosphonic, sulfonic, and nitrogen on the surface of hydrogels can favor the absorption of the metal ions [97]. However, the use of hydrogels for heavy metal ion toxicity on large scales is not economical [98].

Studies have reported that hydrogels are excellent dye adsorbents. They can absorb materials with high amounts of methylene blue dye. Polyelectrolytes have been reported to be significant in heavy metal ions removal as they can bind to the oppositely charged metal ions forming complexes [99].

Other examples of hydrogels that can be used for metal ion removals are starch, chitosan, cellulose derivative, and alginate. Other phenomena like chelation and sorption also aid hydrogels in removing metal ions [100].

Biosensors

A biosensor is a combination of chemical and physical sensors [101]. 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 bioelement which makes analyzing biological information possible. Biosensors find applications in the following areas:

- Point-of-care testing
- Environmental monitoring
- Diagnostics [102]

Bioelement has different structures similar to enzymes, living cells or tissues and antibodies but the critical aspect is its specificity [103]. The biological molecules can be coupled with sensors by various methods such as covalent bonding, entrapment into membranes or matrix and physical adsorption. Hydrogels have also been manipulated to be used in diagnostic purposes or tests such as ECG (Used as medical electrodes).

The hydrogels can be used in biosensors by coating them on the sensing device (Such as an electrode) or by acting as a 3D matrix or supporting bioelements. Hydrogels can protect the sensor parts in a biosensor by preventing undesirable interactions with cells or biological molecules. Various studies have been performed that depict the potential of hydrogels for cell culture. These can be used in endothelial injury, cardiovascular diseases in which the blood vessels may be reformed to treat the disease, the formation of proteins that can accelerate the growth process and bone remodeling [104].

They can give an excellent environment to enzymes or other biomolecules for the preservation of their activity and functional structure. Hydrogels can also immobilize biosensing elements. Some examples for different biosensors in hydrogel matrices include glucose-responsive hydrogels, DNA, antibody-antigen based sensors and oligonucleotides [105].

Living sensors are another group of biosensors, in which hydrogels are combined with living microorganisms or cells forming living cell-polymer composites [106]. The 3D structures, biocompatibility, and the high water content make the hydrogels suitable for the entrapment for cells or bacteria. An example of the living sensor is *Arxula adenivorans* LS3 (A biological recognition element) used to determine the biodegradable pollutants in the waste water [107].

Tissue engineering

Tissue engineering refers to the combination of materials, cells, and engineering for the improvement or replacement of biological organs. This requires the searching and finding proper cell types and a suitable scaffold for culturing them

in appropriate conditions. Tissue engineering offers the potential for regeneration of almost any tissue or organ in a human body [108].

Hydrogels are an excellent option for a scaffold material due to the similarity of their structures to many tissues. They provide the advantage of minimal invasion for delivery and easy processing in mild conditions [109].

The material and scaffold design selection depend upon several variables, such as physical properties, biological properties, and mass transfer properties depending on the environment in which it will be placed and the intended application [110]. For example, the type of scaffold and its structure varies for the production of artificial skin and that for artificial bone.

Hydrogels for this purpose can belong to either synthetic or natural materials. It is easy to control the chemistry as well as the structure of synthetic hydrogels, which in turn can help in altering their properties. The natural polymers forming hydrogels have favorable in vivo interaction, for example, chitosan and alginate [111].

- In tissue engineering applications, the hydrogels have three purposes, which are:
- Agents for filling vacant spaces (Act as bioadhesives, bulking agents, preventing adhesions)
- Carriers for bioactive molecules
- 3D structures for supporting cells
- Hydrogel scaffolds based on polymers such as alginate, collagen, and chitosan are generally used as bulking agents [112]. Synthetic hydrogels such as polyethylene glycol act as anti-adhesive materials in conditions such as in the prevention of post-operative adhesions.

When acting as vehicles for stabilizing and delivering the bioactive molecules to target tissues, the hydrogels allow the drug delivery to only the desired tissues minimizing toxicity to the other tissues. Some of the examples of their carrier hydrogels include ionically cross-linked alginate hydrogels and glutaraldehyde cross-linked collagen sponges [113]. PVA is another hydrophilic polymer that is finding applications in drug delivery [114].

Hydrogels can act as 3D networks for supporting cells and the formation of an ideal tissue because of being able to be highly hydrated. This makes the hydrogels suitable for the goal of tissue development [115].

Blanchard et al. used the keratin-based hydrogels for cell scaffolds in tissue engineering [116]. Chitosan-based hydrogels such as beta-glucan have also been studied as candidates for 2D and 3D scaffolds [117].

Injectable hydrogel for regeneration of the spinal cord

SCI defined as a complex degenerative disorder that is caused by growth inhibition due to trauma to the tissues of the spinal cord [118]. The use of hydrogels can sometimes recover these injuries. The viscoelastic hydrogels are converted from a liquid to a gel after being injected into the site of injury. Small spaces or transected parts are formed in SCI, which are filled by hydrogels [119].

These hydrogels can be loaded with therapeutic agents before injecting them into the site of injury. However, the properties of these hydrogel scaffolds should resemble that of spinal cord tissues [120].

The requirements for the designing parameters include:

- Creating a scaffold for cellular infiltration
- Maintenance of bioactivity
- Provision of sustained delivery of loaded agents
- Tunable and local delivery of therapeutic agents

Design parameters include:

- Designed scaffold's mesh size,
- Mechanical characteristics of the gel material
- Biocompatibility of materials used for injured site
- Conditions of mild solidification
- Suitable porosity
- Rate of degradation
- Bioactivity

Injectable hydrogels can either be natural or synthetic, having their pros and cons. Examples of some injectable hydrogels include glycidyl methacrylate and polyamidoamine macromers (After undergoing gelation process) [121]. Injectable hydrogels are patient-friendly as they are minimally invasive. They provide an easy mixing of cells or bioactive molecules with the polymer solutions which in turn can quickly form the 3D microenvironments in desired shapes [122].

Enzyme mediated injectable hydrogels such as hydrogels containing tyramine conjugated polymers are used in drug delivery systems and as scaffolds due to their high elasticity [123]. Studies have also been done for the role of hydrogels having antigen-antibody interactions in the formation of an injectable 3D network [124].

Contact lenses

Synthetic hydrogels have bio-applications in ophthalmology, especially in contact lenses [125]. The concept of contact lenses was first described in 1508 by

Leonardo da Vinci. Polyhydroxyethyl methacrylate lenses were developed in the late 1960s by Professor Otto Wichterle which then started the era of soft lenses [126].

An acceptable contact lens has a high oxygen permeability because when a contact lens is placed on the cornea that two main problems that occur include the prevention of oxygen exchange and hypoxic stress (disturbance of natural physiological metabolism of the cornea) [127]. A proper choice of contact lens shape and material is necessary for minimizing these problems [128].

Hydrogels are the best solution for this problem because they can cover the following requirements:

- Superior mechanical characteristics
- Oxygen permeability
- Surface wettability
- Good optical properties
- Hydrolysis stability
- Sterilizing
- No toxicity
- Biological tolerance towards living cells [129].

Typical hydrogels used for contact lenses include dihydroxy methacrylates, acrylamides, methacrylic acid and many other monomers [130]. Their right swelling and permeability properties make them suitable and efficient for use in lenses [131].

Colon specific drug delivery

Hydrogels also find applications in the colon-specific drug delivery. For this purpose, polysaccharides are used as polysaccharidase enzymes are present in high concentration in the colon. These hydrogels provide tissue specificity to the drugs in the colon [132]. The controlled delivery of Ibuprofen has been achieved by hydrogel of guar gum with cross-linking agent glutaraldehyde [133]. Dextran based hydrogels are also found to be promising as carriers of therapeutic agents for colon-specific drug delivery [134].

Cosmetology

Hydrogels are also good candidates for cosmetic use as they impart emulsion stability and conditioning [135]. They are useful as carriers for cosmetic agents in delivery and protection purposes as they liquefy at body temperature [136]. They are also used for aesthetic purposes [137].

Topical drug delivery

Hydrogels are also good candidates for the topical delivery of various therapeutic agents [138]. Hydrogels have been made to deliver a synthetic corticosteroid Desonide which is used as an anti-inflammatory. These hydrogels

provide moisturizing properties and prevent scaling and dryness [139]. Antifungal formulations like cotrimazole have also been developed as hydrogel formulations [140]. Hydrogels containing extracts of medicinal plants have been synthesized for the treatment of topical dermatitis [141]. Polyacrylic polymers have been found to have promising results in topical drug delivery due to their bioadhesive properties [142].

Modified dosage forms

Biomacromolecules such as heparin can be manufactured as modified dosage forms [143]. Insulin can be delivered to the absorption site with hydrogels by entrapping in a polymer matrix. Cross linkers such as N, N' – methylene bisacrylamide have been found to provide maximum entrapment efficiency. Thus these hydrogels prevent the unwanted degradation of drugs like insulin [144].

Wound healing

Hydrogels have been developed to treat cartilage defects by using modified polysaccharide occurring in the cartilage [145]. The aldehyde and methacrylate groups functionalizing the polysaccharides react with the proteins in the skin tissue forming a network where chondrocytes are released [146]. Hydrogels containing honey in a matrix are also being used in wound healing [147]. Cell adhesive hydrogels made of PVA and gelatin in addition to blood coagulants have been shown to ensure better effects [148].

Agricultural Uses

Hydrogels not only have biomedical applications but also have been used in the agriculture. They can be used to prevent soil erosion as they can hydrate the soil and improve infiltration in soil. Hydrogels are considered as eco friendly as they can prevent the drying of plants during drought periods. Pesticides have been encapsulated by utilizing hydrogels to improve plant growth and avoid pests. It has also been claimed that hydrogels decrease the leaching of the fertilizers [149].

Food Industry

Hydrogels are being used in the food industry for various purposes as well. A group of hydrogels called as the bio-based hydrogels are used for packaging various food products. Foods such as vegetables or fruits that can become dry because of loss of water may be packed in bio-based hydrogel packing which will then prevent dehydration and keep them fresh. This biodegradable packaging also helps to prevent the food from contamination by various microbial organisms [150].

Miscellaneous

Hydrogels also find applications in various products related to hygiene especially in the diaper industry. Super absorbent hydrogels contain such polymers that can provide excellent retention properties that are utilized making

the diapers for children. A super absorbent cross-linked polymer starch-g-polyacrylate has been used since 1978 for this purpose in Japan [151]. The diapers and other hygiene products made of SAP hydrogels provide the advantage of moisturized skin, no rashes and improved skin health. These hydrogels based diapers also prevent contamination, germ colonization and reduce leakage. The weight of diapers could also be reduced by using these hydrogels other disposable products such as napkins, bed sheets for hospitals and sanitary towels [152].

LIMITATIONS OF HYDROGELS

In addition to all the merits related to hydrogels, there are some demerits or limitations as well. However, the number of advantages of the hydrogels as carriers for drugs relatively high as compared to the demerits. Most of these limitations can be overcome but some substantial challenges remain to exist with the hydrogels. The main drawback of the hydrogels is that they are expensive. The loading of drug in the hydrogels is a complex process and requires skilled labour and mechanical devices for manufacturing. They are very fragile, so they require careful handling. The sterilization of the hydrogels is a complicated process. The concentration of the cross-linkers in the hydrogels is vital as a high concentration may lead to toxicity [153].

CONCLUSION

Hydrogels belong to a class of polymeric materials either natural or synthetic; having the ability to entrap large volume of water in their matrix due to their swelling properties and specific and flexible structures. They can be characterized and evaluated by various tests such as their morphology, appearance, viscosity (rheological properties), microscopic techniques for their crystalline structures, their release characteristics for the drugs entrapped in them, the way they accumulate water in them and swell various times their size, the content of gel or the gelation capacity. They have found a wide variety of applications because of their ability to modify the polymeric structures thus helping them to obtain the desired functionality. The areas of hydrogel applications are rapidly expanding day by day. Hydrogels can also be formulated and designed to respond to specific stimuli. These hydrogels are referred to as stimuli-responsive hydrogels. These stimuli-responsive hydrogels can be employed in biosensors such as for the detection of ulcers or other diseases. They are also being employed in tissue regeneration making them good candidates for the treatment of tissue injuries such as spinal cord injury. They have different applications that involve their use in the reduction of environmental waste, including the heavy metals that are usually present in waste-waters, also they are being used in a sanitary product like towels, napkins, and baby diapers. Among their properties, biodegradability and biocompatibility makes them an excellent candidate for biological and industrial applications; for example, they can act as materials for toxic pollutants removal.

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