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FORMULATION, EVALUATION AND APPLICATIONS OF HYDROGELS: A REVIEW

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I. ABSTRACT

Hydrogels are a special type of 3-D cross-linked polymer networks which can incorporate a small fraction of aqueous solvents and biological fluids into their structures as a result they swell. They have great biocompatibility when swollen, becoming rubbery and soft and resembling living tissue. Hydrogels are the class of synthetic biomaterials that most nearly resemble genuine living tissue b high porosity, high water content, and soft consistency. Because of this advantage of hydrogels, these are widely applied in many fields. The primary goal of this article is to conduct a literature review on formulation, evaluation, and applications of hydrogels in various ways. The classification of hydrogels on a different basis is also given in this article.

KEYWORDS: Hydrogels, biocompatibility, porosity, evaluation, formulation.

I. INTRODUCTION

Hydrogels have attracted a lot of attention in the pharmaceutical field. The word hydrogel refers to a 3-D polymeric network. This network consists of a group of polymeric materials, the hydrophilic nature that is responsible to hold large amounts of water. The polymeric network can react to variations in environmental factors like ionic strength, temperature, pH, the presence of an enzyme, and electric fields by expanding (swell) or contracting (shrink) accordingly. They have great biocompatibility and are soft and rubbery when enlarged, simulating live tissue.[1]

Researchers have defined hydrogels by a number of methods, the most prevalent is "hydrogel is a water-swollen and cross-linked polymeric network produced by combining one or more monomers".

(or)

"Hydrogel is a polymeric material which exhibits the ability to swell and will not dissolve in water but will remain a significant amount of water within its structure". Hydrogels can be made of diverse substances, both synthetic and natural.

In current times hydrogels were defined as "biphasic systems consisting of three-dimensional polymeric network and space between the macromolecules is filled with water". In the past 2 decades, synthetic hydrogels having a long-life service, higher gel strength & water absorption capacity have gradually replaced natural hydrogels. Synthetic polymers with defined structures might be altered to yield functionality and degradability.

By using medical research, novel therapeutic moieties with specialized carriers are found for the transport of medications into specific regions of the body. Hydrogels can transport genetically modified pharmaceuticals, such as proteins and peptides, via conventional means, which increases the therapeutic efficacy of medications. Hydrogels were employed as a medication carrier extensively because of their ease of manufacture as well as self-application.[2]

Classification of Hydrogels

Hydrogels are classified based on different ways. They are;

1. Depending on Nature of cross-linked junctions

Hydrogels were categorized into 2 classes on the basis of whether the cross-link junctions are physical or chemical.

a. Permanent/chemical hydrogels- These are called permanent hydrogels because these are formed by covalent bonds which are stronger and more stable by replacing weaker hydrogen bonds. They reach a condition of equilibrium swelling that is dependent on crosslink density and polymer-water interaction parameters.

b. Reversible / Physical hydrogels- when the networks are kept together using "secondary forces like hydrophobic, ionic interactions, or hydrogen bonding", as well as molecular entanglements then it is called reversible hydrogels. In this form of gel, dissolution is inhibited by the physical interactions within the distinct polymer chains. Each of these relationships is subject to disruption by stress or environmental changes i.e., reversible.[3]

2. Depending on source

a. Natural hydrogels- These are biocompatible, biodegradable, and have better cell adhesion characteristics.

For example, proteins like gelatin, collagen, lysozyme (LYZ), polysaccharides like chitosan, and hyaluronic acid (HA) are used as natural polymers that are used to form natural hydrogels.[4]

b. Synthetic hydrogels:- They can be manufactured to have far greater variability of chemical and mechanical characteristics compared to their natural counterparts, enhancing their utility over natural hydrogels.

Examples include acrylic acid hydroxyethyl methacrylate, methacrylic acid, polyethylene glycol, etc., which are the synthetic polymers used for manufacturing synthetic hydrogels.[4]

3. Depending on Polymeric composition

a. Homopolymeric hydrogels- These are defined as the hydrogels that are formed by single monomeric species which form the basic structural unit comprising any polymer network. Based on monomer's characteristics and the method of polymerization, homopolymers can possess interconnected skeletal systems. Homopolymeric hydrogels are used extensively in bone marrow, contact lenses, and scaffolds for spinal cord cell regeneration that encourage cell adhesion and are used to make synthetic cartilage.

Example: Polyethylene glycol-based hydrogels are extensively utilized in drug delivery systems.

b. Co-polymeric hydrogels- 2 or more diverse monomer species having at least one hydrophilic substance is combined to form co-polymeric hydrogels, which are then organized in block, random, or alternating pattern along the polymer network chain. This particular hydrogel type is characterized for usage in drug delivery applications and is temperature- and pH-sensitive.

c. Multipolymer interpenetrating polymeric hydrogel (IPN)- It belongs to a significant group of hydrogels where the network system is composed of 2 separate, cross-linked natural and/or synthetic polymer components. A cross-linked and non-cross-linked polymer together makes up the semi-IPN hydrogel. The advantage of these hydrogels is limited phase separation can be found and it overcomes thermodynamic incompatibility which arises as a result of network segments' permanent interlocking. In contrast to other hydrogels, it provides effective drug loading.

4. Depending on type of response

a. Physical responsive hydrogels- This type of hydrogels are described by their capability to shrink and swell when physical factors like temperature, pressure, light, and variations in the surrounding fluid. For instance, when the temperature decreases then it will shrink, and if the temperature increases the hydrogels will swell.

b. Chemical-responsive hydrogels- This type of hydrogel undergoes changes when chemical factors like ionic strength, and pH change. Hydrogels have ionic groups which absorb or release protons as a result of a change in the surrounding pH. In a pH-responsive hydrogel, the level of ionization, or pKa or pKb, is significantly changed at a specific pH. Due to the quick change in the ionized group's net charge, which results in electrostatic repulsive forces between them and a significant osmotic swelling force, there is an abrupt volume transition.[10]

Example: Chitosan-coated “alginate-N, O-carboxymethyl chitosan (NOCC) gel beads” are used to deliver drugs specifically to the colon. Their research showed that these hydrogels are pH sensitive since the swelling level at pH 7.4 was significantly greater than at pH 1.2.

c. Biochemical responsive hydrogels- It includes the response of hydrogels to biochemical agents like antigens, enzymes, and ligands. To transport biomolecules to a specific targeted region, “antigen-responsive hydrogels are developed by grafting antigens onto hydrophilic polymeric backbones”. These hydrogels may be combined with crosslinked hydrophilic polymeric backbones with antibody grafts.

The hydrogel shrinks in absence of free antigen while expanding in existence of free antigen because of “intra-chain antigen-antibody binding in polymer network”.[5]

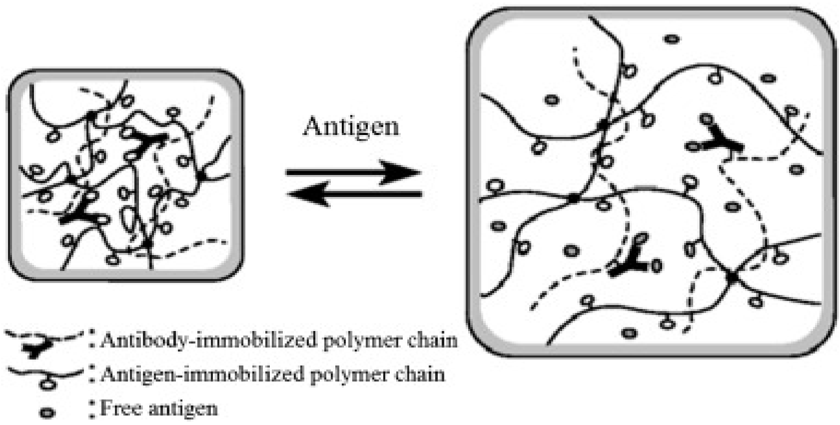

Fig 1: Swelling of hydrogel in response to presence of free antigens.

FORMULATION OF HYDROGELS

The hydrogels preparation consists of 3 necessary elements:

- Initiator,
- Monomer, and
- Cross-linker.

By adding diluents like water or another aqueous solution, it is possible to regulate the polymerization temperature and resulting hydrogels' characteristics.

Preparation Methods

For preparation of monomers both hydrophilic and hydrophobic monomers are used. Typically, polar monomers are utilized to create hydrogels. To create hydrogels, multifunctional cross-linkers, and hydrophilic monomers can be combined through copolymerization or cross-linking free-radical polymerization. To create hydrogels, multifunctional cross-linkers, and hydrophilic monomers can be combined through cross-linking free-radical polymerization or copolymerization. Hydrogels are prepared by using different ways such as

i) Generating main-chain free radicals by ionizing radiation so that they may join to form cross-link junctions.

ii) Use of chemical reactions to join polymer chains.

iii) Physical interactions like electrostatics, entanglements, and crystalline formation are used.

METHODS OF HYDROGEL PREPARATION	
Physical Methods	**Chemical Methods**
- Heating or cooling of polymer solution	- Bulk polymerization
- Hydrogen bonding	- Cross-linking
- Complex coacervation	- Grafting
- Ionic interaction	- Radiation cross-linking

► Bulk Polymerization

It is the simplest method of preparation of hydrogels. It only includes monomers and initiators that are monomer-soluble. Vinyl monomers are the most common type of monomer used to produce bulk hydrogels. In the majority of hydrogel formulations, a trace amount of crosslinking agent is present. The polymerization reaction is initiated using chemical or ultraviolet catalysts, radiation, or both. The choice of initiator is determined by the monomers as well as solvents utilized. The polymerized hydrogels can be made in many diverse forms, like rods, films, emulsions, particles, and membranes. To get rid of any impurities left over from preparation process, the hydrogel mass is required to be washed after it has formed. These impurities consist of initiators, cross-linkers, unintended byproducts of side reactions, unreacted monomers, and others.[8]

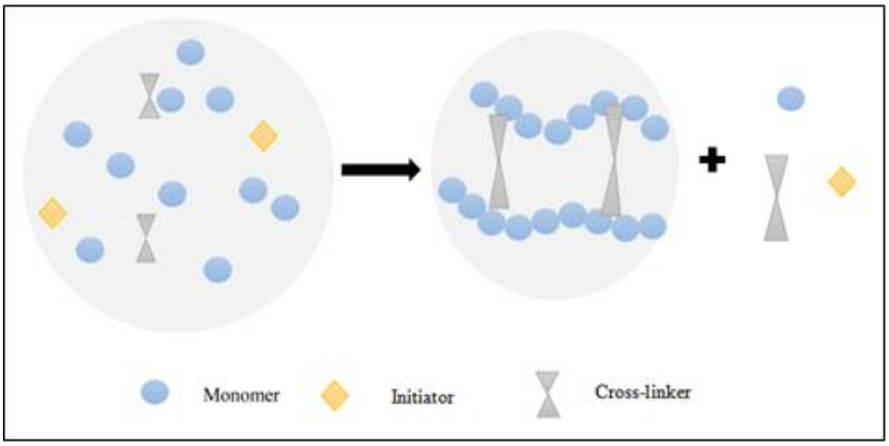

Fig 2: Schematic figure showing the preparation of hydrogels.

► Cross-linking/ Solution polymerization

In this method, the multipurpose cross-linking agent is combined with the ionic or neutral monomers. The polymerization is thermally triggered by redox initiator method or UV radiation. The main benefit of solution polymerization over bulk is solvent presence acting as heat sink. In solution polymerization, phase transfer takes place and When the water content during polymerization exceeds the water content at equilibrium swelling, heterogeneous hydrogel is formed. To get free of monomers, initiators, crosslinking agents, oligomers, extractable and soluble polymers, and other contaminants, the produced hydrogels have to be washed using distilled water.[9]

"Ethanol, water, water-ethanol combinations, and benzyl alcohol are typical solvents used for hydrogel solution polymerization".

► Grafting

It involves polymerizing a monomer onto the backbone of preformed polymer. The inherent structural weakness of bulk-polymerized hydrogels may overcome by grafting the hydrogel onto a surface coated with a more robust support. The surface of the support is first activated by generation of free radicals and monomers are added directly onto it. Consequently, the support is covalently attached to a chain of monomers. Many polymers are used as support material.[6]

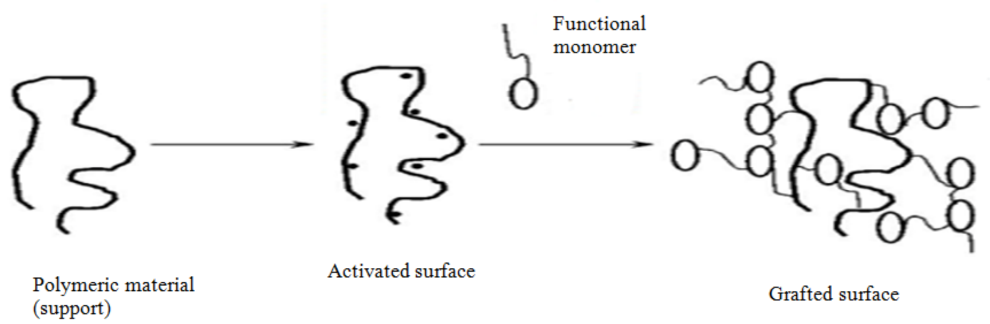

Fig 3: Grafting of monomer onto a polymeric backbone (support) that has been performed, resulting in cross-linking and unlimited branching.

► Cross-linking by irradiation

Radiation cross-linking is a commonly used method which preserves the biopolymer biocompatibility since it does not require chemical additives. Hydrogels of unsaturated compounds have been prepared by using electron beams and gamma rays (High energy radiations) as initiators. Radiation of an aqueous polymer solution results in development of radicals on polymer chains, leading to formation of macro-radicals.

Recombination of macro-radicals on diverse chains leads to the formation of covalent bonds, resulting in cross-linked structure formation. Polyvinyl alcohol, acrylic acid, and polyethylene glycol are examples of irradiation-crosslinked polymers. Principal advantage of radiation initiation over chemical initiation is the formation of hydrogels that are relatively initiator-free and pure.[11]

► Heating or cooling of polymer solution

By cooling hot solutions of carrageenan or gelatin to develop physically cross-linked gels, hydrogels are created with this method. Gel is created through the development of helices, their association, and the formation of junction zones. These helices undergo further aggregation to form stable hydrogels. Examples include “polyethylene oxide-polypropylene oxide and polyethylene glycol-polylactic acid hydrogel”.

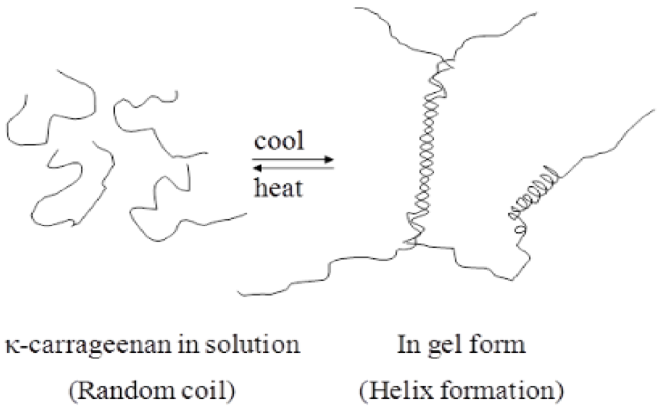

Fig 4: Formation of gel results from helix accumulation after cooling hot carrageenan solution.

► Hydrogen Bonding

A hydrogen atom with a low electron density and functional group with a high electron density combine to form hydrogen bond. This type of hydrogel is produced by decreasing the pH of aqueous solution containing polymers containing carboxyl group.

Eg: Hydrogen-bound CMC (Carboxymethyl Cellulose). To create hydrogen bonds, sodium in CMC is substituted with hydrogen in an acidic solution that results in formation of elastic hydrogel.

► Complex Coacervation

The generation of complex coacervate gel results from the combination of polycationic and polyanionic polymers. The concept behind this approach is that polymers with oppositely charged will accumulate together to produce complexes which are very dependent on the pH and solution concentration.[7]

Example: “Polyanionic xanthan with polycationic chitosan”.

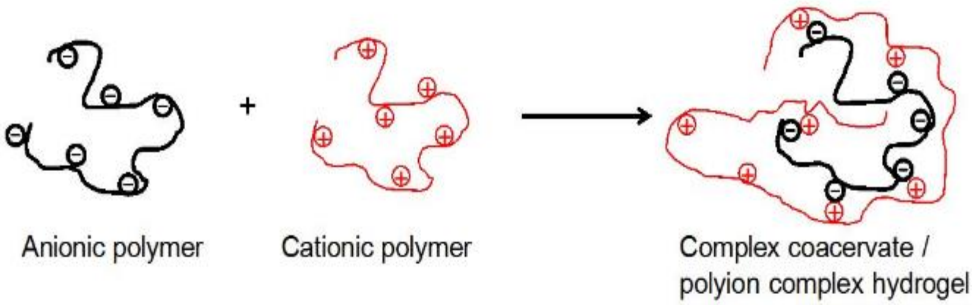

Fig 5: Complex coacervation between polycation and polyanion.

► Ionic Interactions

The addition of tri- or divalent counter ions to an ionic polymer causes cross-linking within the polymers. This method is dependent on idea of gelling a "polyelectrolyte solution", like Na+alginate-, with opposite charges multivalent ion, like Ca_2^++ $2cl^-$. Other examples of ionic hydrogels include chitosan-dextran hydrogel, chitosan-polylysine and chitosan-glycerol phosphate salt hydrogel.

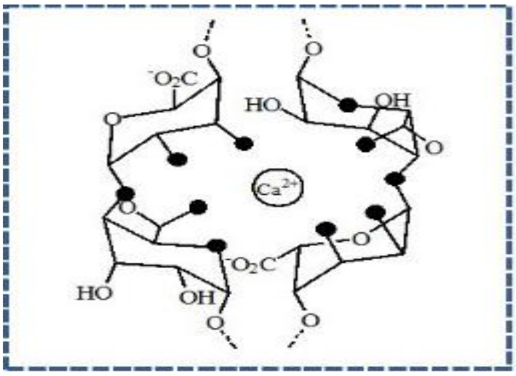

Fig. 6: Anionic groups on alginate (COO-) interact with divalent metal ions (Ca2+) to form ionotropic gels.[5]

EVALUATION

Generally, hydrogels are evaluated for their physical properties and rheological properties. The following are crucial characteristics for hydrogel evaluation:

• Homogeneity

Visual inspection was used to evaluate the gels' physical characteristics, such as color, clarity, and phase separation. They undergo testing to see if there are any aggregates.[12]

• Solubility

Solubility of hydrogels is evaluated by using two different methods;

Method A

The solubility of hydrogel is assessed by determining the amount of its insoluble component in a dried sample after 16 hours of absorption in deionized water or 48 hours at room temp. To confirm that hydrogel substance is completely dispersed in water, the sample must be prepared with low strength (usually less than 1%). Then the insoluble fraction is measured by using formula;

$$Gel\ Fraction(hydrogel\ \%) = \frac{Wd}{Wi} \text{ x } 100$$

Here, W_i = Dried sample's starting weight and

W_d = weight of dried, insoluble portion of sample following water extraction.

Method B

Method B, which involves determining the weight retained following vacuum filtration, provides a more precise estimation of solubility. The filtration is performed by using 70mm glass fiber paper then it is dried for 1 hr at 105^{o}C in an oven and cooled in desiccator. The insoluble content is determined using a formula;

$$\%\ \text{Hydrogel} = \frac{W2 - W1}{S} X\ 100$$

Here, W1 indicates weight of filter paper

W2 indicates weight of the hydrogel after filtration

S indicates weight of sample.

• pH

The pH values of gel compositions were measured using a digital pH meter.1 g of gel was combined with 100ml of distilled water and maintained for 2 hrs. The pH of every formulation is measured in triplicate & average values are determined.[13]

• Swelling measurement

For measuring hydrogel swelling, the "Japanese Industrial Standard K8150 technique" was employed. By this procedure, the dried hydrogel is placed on a roller mixer and submerged in deionized water at room temperature for 48 hrs. After swelling, the hydrogel is passed via 30 mesh (681 m) stainless steel net. The hydrogel swelling is determined using formula;

$$Swelling = \frac{Ws - Wd}{Wd}$$

Here, Wd and Ws indicate weight of hydrogel in dry state and swollen state resp.

• Viscosity

Hydrogel viscosity is determined at a constant 4°C temperature using cone plate-type viscometers. The examination of viscosity performed with this viscometer is with great precision.

• Spredability

A glass plate was attached to concentric circles that were drawn on graph paper with varying radii. Five grams of gel were positioned in the middle of the lower plate. After 1 minute of each addition, a 100±5 gm glass plate was gently placed on the gel, and the spread diameter was measured.[11]

• Drug content

100ml of phosphate buffer having pH 5.8 was used to dissolve 1 g of gel. Appropriate dilutions were made with the help of phosphate buffer pH 5.8. With a UV spectrophotometer, absorbance was measured at 253nm.[15]

• Scanning Electron Microscopy

It is used to evaluate the "sample's composition, surface topography, and other parameters like electrical conductivity". SEM allows for the control of magnification across a range of up to six orders of magnitude, from roughly 10 - 500,000 times.

• Studies on in vitro drug release

Franz diffusion cells were used in in-vitro drug release experiments. On a cellophane membrane used as a donor compartment, 0.5 g of gel was placed. Phosphate buffer with pH 5.8 was utilized as the dissolving media and was placed inside the receptor compartment. The thermostat was set at 37 degrees Celsius, and the entire apparatus was mounted on a magnetic stirrer. Samples were taken regularly, and sink conditions were preserved by replacing the old buffer solution with fresh one. Utilizing a UV spectrophotometer, collected materials are examined at 282 nm.[14]

• X-Ray Diffraction

X-ray diffraction is used to determine whether polymers keep their crystalline structure during the pressurization process or whether they undergo deformation.

APPLICATIONS

Hydrogels are widely used in foods, medications, and water purification systems as well as in separating materials for electrophoresis and chromatography. They are also helpful for the controlled release of medications and the concentration of diluted macromolecule solution. Wide applications of hydrogels include.

Pharmaceutical applications

- DNA can be condensed by nano vector made of "peptide-based nanofibrous hydrogel to trigger strong immune responses against HIV".
- Due to their extra-cellular matrix-like properties, hydrogels have good application contact with human body. This made the use of hydrogels in reconstructing plastic for plastic surgery.
- Acrylamide agarose copolymer hydrogel was projected in 2-D electrophoresis as potential system for separation matrices, due to better resolution of both low and high molecular mass proteins.
- Hydrogels drug delivery is used for ocular, oral, and subcutaneous applications.
- It has been demonstrated that alginate hydrogel is a helpful tool for growing bone and cartilage tissues.[16]

Biosensors

- An important role of hydrogels in bio-sensors is coating and shielding of sensor components to avoid unintended interaction with biological cells or molecules.
- In addition to providing favorable environments for enzymes and other biomolecules to maintain their functional and active structure, hydrogels can also serve as immobilization matrices for biosensing components.
- A promising development involves the development of glucose-responsive hydrogels, which, in response to elevated blood glucose levels, can act as permanent insulin depots and release insulin doses at the appropriate time. By eliminating the need for frequent injections, these hydrogels could offer a more practical treatment option which can increase treatment effectiveness and quality of life for hundreds to millions of individuals.[17]

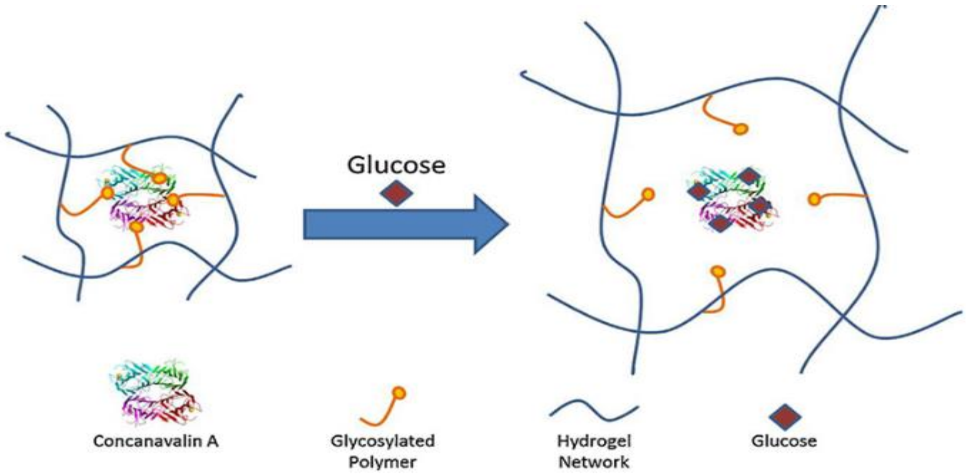

Fig. 7: Mechanism of "Concanavalin A-based glucose-responsive hydrogel".[17]

Tissue Engineering

An interesting scaffolding material is hydrogels. This hydrogel tissue scaffold is used to produce artificial skin and artificial bone. Three uses of hydrogels that are found in tissue engineering are;

- They can be utilized as fillers for empty spaces,
- Distribution systems for bioactive substances, and
- 3-D structures that support cells and help in ideal tissue development.

The scaffold hydrogel's usage as vehicle to enclose secretory cells and transfer bioactive chemicals to the target tissues is another very distinctive application of these materials.[18]

Cardiac Repair

The number of donors and rejection reactions have an impact on the utilization of direct heart transplantation for cardiac repair treatment, and the success rate is low. A three-dimensional polymer network with a high-water content can be constructed to form a hydrogel using a range of naturally occurring or synthetically generated polymers. Because of these features, hydrogels can serve as a vehicle for cell transplantation and replicate the extracellular matrix environment, encouraging cell survival, proliferation, differentiation, and migration while aiding in tissue regeneration.[19]

In Agriculture

The regulated nutrients released from fertilizer-loaded hydrogels into crops is an appealing strategy that has recently been researched. Hydrogels were developed using diverse polysaccharides, comprising chitosan, pectin, and carboxymethyl cellulose, as a release of fertilizer technique to help the soil.[20]

Other Applications

- Hydrogels are excellent materials for construction of micro-optical arrays using dynamically adjustable focal lengths that could be made in a scalable and low-cost manner.
- The development of effective biopolymer packaging materials with desirable qualities may benefit from the use of hydrogels.
- Hydrogels are used in wound dressing and implantable devices.

CONCLUSION

Hydrogel-based delivery systems may be utilized for ocular and epidermal applications, as well as tissue engineering and biosensing, etc. Due to their close resemblance to the living tissues. Numerous hydrogel-based systems were recently created and modified to suit the requirements of various uses. The current review explains how hydrogels are categorized on many criteria, including their chemical and physical properties, technical viability, method of preparation, and uses.

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