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Review Article

A Comprehensive Review on Hydrogel

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Abstract

A hydrogel is a three-dimensional network of polymers that is insoluble in water and can absorb bodily fluids in a biological setting. Such a polymer network is created via physical crosslinking, which includes ionic crosslinking, temperature and pH-dependent processes, and enzyme reactions, as well as chemical crosslinking mechanisms like optical polymerization. Chemical hydrogels are created by covalent forces, whereas physical hydrogels are formed by weak secondary forces. Hydrogels are made from a variety of synthetic and natural polymers. The most significant characteristics of hydrogels are swelling, mechanical characteristics, and biological characteristics, all of which have an impact on the hydrogel's morphology and structure. Hydrogen finds value in wound dressings, tissue engineering, contact lenses, and therapeutic drug release, among other medical applications, because of its water absorbing properties and structural resemblance to the extracellular matrix (ECM). We talk about hydrogels, types of hydrogels, their characteristics, and medical applications.

Keywords: Polymer; Hydrogel; Tissue Engineering

Introduction

A great deal of scientific study has been conducted in the area of biomaterials that affect human health [1]. One of the primary subjects of biomaterials research is hydrogels, which we examine in this article. Hydrogels are three-dimensional networks of insoluble polymers that, because of the hydrophilic groups in their structure, can absorb a lot of water or biological fluid from the body [2]. The hydrophilic functional groups included in the primary hydrogel polymer chain include amine (NH2), sulphate (SO3H-), carboxyl (COOH-), and hydroxyl groups (OH-) [3]. Physical crosslinking, chemical crosslinking, or a mix of the two can create polymeric hydrogels [4].

Mechanical strength and intracellular and extracellular transport are among the characteristics of the hydrogel that are influenced by its chemical structure, shape, and equilibrium swelling [5]. Hydrogels have a specific attraction for a variety of medical applications, including tissue engineering and the release of therapeutic agents (proteins, medicines, or genes). These properties include water absorption, soft structure, biocompatibility, low protein adsorption due to low surface tension and similarity to ECM structure. Wound dressings and contact lenses [6]. There are various ways to create hydrogels, such as using natural or synthetic polymers as the primary source, homopolymer networks, copolymer networks, and permeable networks [7]. The study of hydrogels that react to biological circumstances has garnered increased attention recently [5]. By using this kind of hydrogel, also known as injectable hydrogen, the patient is able to eliminate discomfort and inflammation that are associated with implantation surgery. Hydrogels are made in accordance with biological circumstances at the target site within the body [8].

Hydrogels has the ability to take in large amounts of water and expand without breaking down. For a specific or Novel Drug De-

livery System (NDDS), the hydrogel is an innovative transporter [9]. An active pharmaceutical ingredient is added to a polymeric system structure to achieve a regulated rate of medicine release. Medication carriers have been made from a variety of natural and synthetic polymer kinds. The collagen derived from animals may contain residual development and infections of animal tissues, which can have harmful effects on humans. Synthetic polymers are man-made polymers that contain a few connected synthetic chemical moieties or different cross-connecting agents. Hydrogel commonly uses characteristic polymers because they are naturally occurring, pure and easily accessible, safe, and biodegradable [10].

Different types of monomers, such as acrylamide, methacrylamide, and N-isopropyl acrylamide, are added into sodium alginate-based layout hydrogels to provide controlled drug release. The production of hydrogel-like polymers, polyethylene glycol, polyamides, and poly (acrylic acid) also involves the use of synthetic polymers. Advances in hydrogel technology are used in sterile products, packaging, innovative drug delivery systems, tissue engineering for biomedical purposes, regenerative medicine, diagnostics, proteins and peptides, and medicine delivery in cancer or targeted therapy. Hydrogels have a variety of uses in the pharmacological and therapeutic fields [11]. Unlike other types of synthetic biomaterials, hydrogels resemble normal living tissue. This is similar to common tissue because of its higher water content and ease of formation [7]. To prevent an active therapeutic molecule from degrading too soon, increase treatment efficacy, and lessen side effects are the main goals of developing medicine delivery systems. By restricting dosage and frequency of delivery, as well as maintaining the medicine concentration within the therapeutic window throughout time, controlled discharge frameworks can satisfy the requirements [12].

Since stimuli-responsive hydrogel frameworks adapt to changes in the environment, they have essentially been investigated for therapeutic delivery applications. The range of materials and specific physiochemical and natural properties show a multitude of possible uses in medicine [13]. In order to improve the stability of delicate macromolecules such as proteins, the hydrogel system is loaded with antibodies or nucleic acids. Most "smart" hydrogels change their shape in reversible ways in response to external stimuli such as light, heat, or electricity [14].

Due to their intriguing potential uses in soft robotics, biomedicine, and artificial muscles, two of the most well-known "smart" hydrogels, hydrogel actuators (HAs) and shape memory hydrogels (SMHs), are currently gaining popularity. Hydrogel-based actuators are supported by several methods for producing intelligent hydrogels with non-uniform formation and fabrication technologies [15].

In order to achieve multi-step actuation that mimics natural life, chemical structures that are sensitive to multiple stimuli must be combined in a hydrogel matrix. However, there is still a long way to go before making complex deformations from 2D to 3D, much like in general and collaborative multi step actuation in natural life. Further research is needed to better understand the inner motivation behind sophisticated and unique chemical techniques. By creating inhomogeneous hydrogels through the development of improved fabrication processes, future developments in "smart" hydrogels aim to create multi-stimulative hydrogels with intricate but planned self-folding, twisting, and bending capabilities [16].

The process of hydrogel formation

Polymers are carbohydrate materials that are readily available, have functional groups that can be changed, are biocompatible, and have been utilised extensively in the production of chemical and physical hydrogels [18]. By choosing a particular type of monomer or polymer and hydrogel formation reactions, hydrogels can be tailored to a particular use. There are two ways to create hydrogels: chemical crosslinking and physical crosslinking [19].

Chemical crosslinking

Hydrogels that can be chemically cross-linked are those that can undergo covalent bonding to go from a liquid to a solid state. In situ hydrogel systems also employ this technique. This technique uses a variety of processes, including click, enzymatic, and optical polymerization, to create hydrogels. This section will cover the procedures indicated above for creating these hydrogels [4]. Chemically crosslinked hydrogels have gained attention because to their high mechanical strength [20].

Optical polymerization

One technique for creating hydrogen by chemical cross-linking is optical polymerization, which has the benefits of minimal energy consumption and no solvent requirement for the reaction. Light-sensitive molecules with hydrophilic polymers are used in this

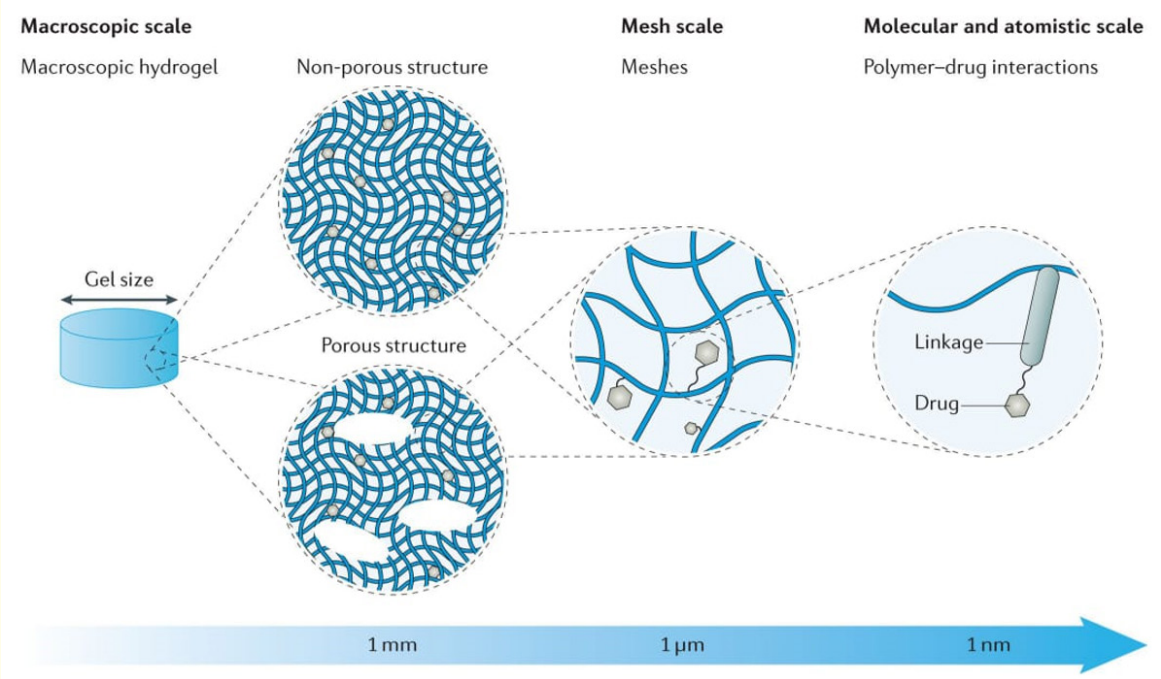

Figure 1: Multiscale properties of hydrogels [17].

technique. The polymerization process occurs when the polymer solution is subjected to UV or visible light, forming free radicals and the optical decomposition initiator [21]. In most cases, light polymerizes the acrylate and methacrylate groups found in polymers that cross-link in this manner. By controlling the gelling rate, therapeutic substances like proteins and medications can be released via this hydrogen [22]. This is one of the best techniques for using an optical initiator to change a monomer into a polymer [23].

Clinical applications use optical polymerization, which fortifies the hydrogel and permits the cells to fade during gel formation. Additionally, this process gives the hydrogel a porous lattice structure [24]. Both inside and outside the body, optical polymerization is simple to carry out at physiological temperature and pH. When using hydrogels in the medical industry, it is recommended to utilise a non-toxic optical primer that emits light at the right wavelength from a light source. One such mechanism is optical crosslinking, which occurs when vinyl groups in contact with UV radiation fail [25].

Chemical reactions involving enzymes

When enzymes are present in the biological environment, enzymatic processes occur. Consequently, there has been a lot of interest in this technique for cellular applications. To crosslink through enzymatic processes, ideal conditions like natural pH, a biological habitat, and the ideal temperature are needed [26]. This method of hydrogel creation has a significant advantage in that the unique enzyme substrate can stop harmful compounds from entering the system as a result of adverse interactions [27]. Hydrogel systems utilised in tissue engineering are prepared using a variety of chemicals as enzymatic catalysts, including tyrosinases, horseradish peroxidase (HPR), and modified glutamines. One of the enzymes, HPR, is utilised in this process to make hydrogels because of its great mechanical stability and simplicity of purification. As a result, it is used in many medical applications, including tissue engineering, drug release, and reconstruction and repair. In order to create natural hydrogels, such as those made of chitosan, hyaluronic acid, dextran, and gelatin, the HPR-H2O2 enzyme water system is frequently utilised.

It was created by enzymatic processes and utilised to release

therapeutic proteins in a study by Kurosawa., *et al.* [2]. This study used amino fluorescein, a fluorescent marker, to label hyaluronic acid after functionalizing it with tyramine. As a result of the shorter subcutaneous gelling time, enzymatic processes are a good way for hydrogel creation since they may be used to establish crosslinking and are also compatible with cells [28].

Click reaction

According to Sharples., *et al*. click chemistry refers to specific kinds of reactions that occur in the presence of a catalyst and are characterised by high biological characteristics, favourable reaction conditions, and high speed and efficiency [2]. Click chemistry is a useful and adaptable technique for functionalizing molecules and is important to the synthesis and activation of polymers. Click chemistry has many advantages, which is why hydrogels, nanogels, and microgels are made with this technique [29].

Moreover, it has been employed as a substrate for medication administration and tissue engineering. One new substrate for polysaccharide-based hydraulic chemical crosslinking is called click chemistry. Click reactions encompass a broad range of reactions, such as cop-per (I) reactions, which are catalysed by sequestered alkyne azide, catalytic reactions involving a free pair of alkyne azides, and silicosterone reactions with disaccharide (DA), including the intergroup reaction. Because of their benefits, which include great selectivity and high efficiency in physiological settings of the body, alkynes and azides are the most evident examples of click chemistry [30]. The reaction occurs without a catalyst or primer and preserves the material's biocompatibility if there are no thermally reversible byproducts that enable the degree of reaction to be controlled. For use in biomedical and tissue engineering applications, starch-based hydrogels were created by a click reaction between the allyl and thiol groups of starch. Good swelling behaviour and biodegradability were displayed by the resultant hydrogel [31].

Physical crosslinking

It is possible to create hydrogels through physical bonding by adjusting intramolecular forces including electrostatic ionic force, hydrophobic interaction, and hydrogen bonding. This method allows for the safe and easy preparation of hydrogel while preventing the potential rise in crosslinker toxicity associated with the chemical procedure. There are three types of physical cross-linking techniques: ionic, temperature-dependent, and pH-dependent [32].

Crosslinking of ions

Among the physical crosslinking techniques, the ion crosslinking agent is utilised to generate the gel and the crosslinking reaction is released without a covalent bond forming between the polymer chains [33]. This process gives hydrogels a high level of resilience. Natural polysaccharide alginate can form gels with its polymer solution against divalent cations like Ca2+. These ions cause ionic bonds to form within the polymer chain and gluronic acid groups in the alginate chain to bind. One popular ECM is hydrogen alginate [34]. Recently, efforts have been directed on enhancing biological interactions, mechanical characteristics, and gelling time optimisation. They can be produced ready for use in injectable biomaterials and cultivated in vitro by adjusting factors including molecular weight, alginate and calcium concentration, and the makeup of alginate in the hydrogel [35]. Chitosan is another naturally occurring polymer that may crosslink ionically; it has been applied to medication release, among other things [36].

Temperature dependent techniques

When hydrogen is formed by physical cross-linking, temperature is a crucial factor. Low temperatures cause temperature-sensitive hydrogels to become liquid, whereas body temperature causes them to gel [37]. The ability of water-soluble polymers to gel at different temperatures has led to the development of hydrogels that are employed in tissue engineering applications. Chemical stimulants are not required for the formation of these hydrogels. They can be injected into a liquid and solidified inside the body because their gel point can be altered to a temperature that is comparable to that of the human body. This approach uses both synthetic and natural polymers [38].

Synthetic polymers include plux-amer, poly-iso-propyl acrylamide (PNIPAAM) and its copolymers, and natural polymers including cellulose, chitosan, and gelatin derivatives. Ploxamers have also been investigated for lung tissue engineering. Current research on the usage of PNIPAAM copolymers in tissue engineering applications has focused on the release of chondrocytes and growth factors. Ploxamer has been physically gelled with a chemical crosslinking agent to enhance its mechanical characteristics

for cell trapping. Researchers have also looked into injectable, temperature-sensitive hyaluronic acid hydrogel because of its high biocompatibility and strong sensitivity to body temperature [39].

pH-dependent techniques

Since each position on the human body corresponds to a particular pH, it should be used as a hydrogel stimulant [40]. pH-sensitive hydrogels are among the stimulus-responsive hydrogels that have been employed extensively in investigations and studies. The average pH of their environment can cause pH-sensitive hydrogels to expand and shrink dynamically. The presence of side acidic groups that can ionise at a particular pH is a common characteristic of hydrogels that are sensitive to pH changes [41]. Due to its capacity to stimulate and react to changes in the environment, pH-sensitive hydrogels have found extensive usage in medical applications, including controlled medication delivery systems and heart valves. Certain applications, particularly those involving drug release, expose hydrogels to varying body temperatures. It is necessary to alter the temperature in order to comprehend how pH-sensitive hydrogels form.@ Hu., *et al.*'s research study used carboxymethyl chitosan in conjunction with an unstable acid crosslinking agent under ideal circumstances to create pH-sensitive hydrogels. Chloromethyl chitosan is a naturally occurring, non-toxic material that degrades naturally. It works well and is frequently used in medical and medical fields [42].

Types of hydrogels

Hydrogels are classified as either natural or synthetic based on the kind of polymer they include. Natural or artificial polymers that have undergone hydrogenation are regarded as raw materials for medical purposes. Hydrogels are made of natural and synthetic polymers that are biocompatible, biodegradable, and, in certain cases, blood compatible when the hydrogel comes into contact with blood [7].

Natural hydrogels

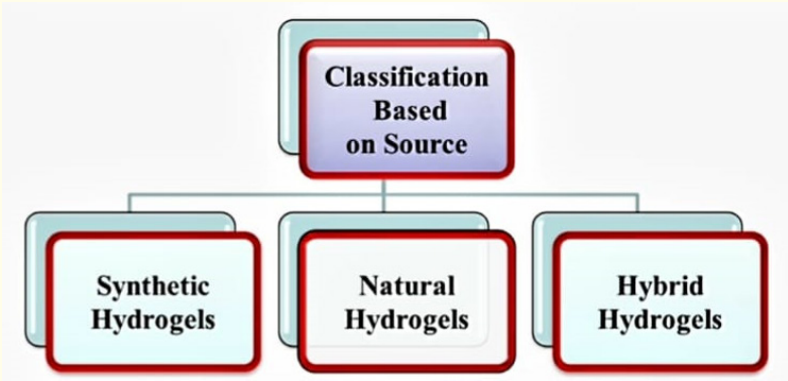

Figure 2: Hydrogel classification according to source.

Gels using polymers derived from natural sources are known as natural hydrogels. Hydrogels made from natural polymers have the benefits of being non-toxic, biocompatible, and biodegradable. The goal of using biomaterials determines whether or not natural polymers are used in the production of hydrogels. For instance, hydrogels utilised for materials with controlled release need to be biocompatible, biodegradable, and non-hazardous [43]. Polysaccharides and associated proteins are examples of natural polymers that are frequently employed as carriers for the release of chemicals. These polymers' biocompatibility was demonstrated by in-body testing; of these, polysaccharides are better because of their biocompatibility, enzymatic breakdown, high durability, and lack of toxicity [44].

Clinical applications involve the utilisation of natural hydrogels such as alginate, collagen, gela-tin, and fibrin. For instance, following a heart attack, alginate has been utilised to restore normal left ventricular function. Vascular bundle replacements have also been tried with collagen. Artificial structures can be made using gelatin, and tissue engineering can use fibrin. Adhesives and anticoagulants can be used during surgery [45].

Synthetic hydrogel

Three-dimensional swelling networks of covalently or ionically cross-linked hydrophilic homopolymers, or copolymers hydrogels, are known as polymeric synthetic hydrogels. Synthetic hydrogels, such as poly (hydroxyethyl methacrylate) or PHEMA, polyethylene glycol (PEG) hydrogels, and polyacrylic acid (PAA), are produced by polymerization of different synthetic monomers [46].

Polyamides and polyethylene glycol (PEG) are examples of synthetic polymers from which synthetic hydrogels are made. In hydrogel manufacturing, synthetic polymers have replaced natural polymers more recently because of their superior water-absorbing capacity, long lifespan, and gel strength. Medical applications for hydrogels made of synthetic polymers are numerous. In terms of chemical composition and mechanical structure, synthetic polymers outperform natural polymers and are hydrophobic [47].

These polymers include PEG, polyvinyl alcohol, and polyacrylamide and its derivatives. PEG is one of the most widely utilised polymers for synthetic hydrogenation in a variety of medical applications, including wound dressings, medication release, tissue engineering, and prosthetic limbs [48]. Because of its characteristics, including its resistance to protein adsorption, biocompatibility, and lack of immunological stimulation, this polymer finds usage in a wide range of medical applications. PEG has the capacity to create insoluble network structures by itself. On the other hand, factor groups enhance the crosslinking within the hydrogen network's structure [49].

Hybrid hydrogels

Natural and manmade polymer hydrogels are combined to create hybrid hydrogels. Synthetic polymers like poly (N-isopropyl acrylamide) and polyvinyl alcohol have been mixed with natural biopolymers like collagen, chitosan, and dextran. Alginate/PEG hydrogels and CTN/PVA hydrogels are examples of hybrid hydrogels [50].

Properties of hydrogel

Network polymers known as hydrogels have the capacity to both absorb and hold water, which results in the hydrogel swelling [11].

Swelling properties

Hydrogels are materials that, when submerged in water, expand and retain a significant volume of water inside their structure without dissolving. The distinctive feature of hydrogels is swelling, which is contingent upon many environmental conditions, including temperature, pH, and ionic strength [12]. Polymers that have undergone various cross-linking processes are combined to form hydrogels. They are all viewed as single molecules as a result. Rapid and reversible changes in hydrogel can be induced by minor environmental changes [44].

The synthesis process, ionic surroundings, cross-linking ratio, and chemical makeup of the polymers are only a few of the variables that might affect the kinetics of swelling and equilibrium. Hydrogels' swelling properties are measured using the swelling ratio, which is the weight-swelling ratio of swelled gel to dry gel. Cross-linking influences a hydrogel's swelling ratio; materials with strong cross-linking have a lower swelling ratio, and vice versa [42]. Hydrogels' swelling behaviour is influenced by their chemical structure since it contains both hydrophobic and hydrophilic groups. In comparison to hydrogels with hydrophobic groups, those with more hydrophilic groups swell more. The expansion of hydrogels is also influenced by pH and temperature. The ionisation of hydrophilic groups, which fluctuate in response to pH changes, causes pH-sensitive hydrogels to expand [15].

The polymer chain experiences electrostatic repulsion, which causes the secondary bonding to break. Water diffusion into the hydrogel network is the first step in the expansion of hydrogels; the unwinding of polymer chains is the next step; and the development of the hydrogel network is the third stage of hydrogel swelling characteristics. The hydrogel is a rubbery substance while it is extended, but it is smooth when it is dried. The glossy state of the hydrogel framework transforms into an expanding, rubbery state when sufficient water reaches it. The diffusion interaction is in charge of the water's entry and departure from the hydrogel matrix [17].

Mechanical properties

Compared to physical hydrogels, injectable chemical hydrogels have superior mechanical properties and longer stability. Howev-

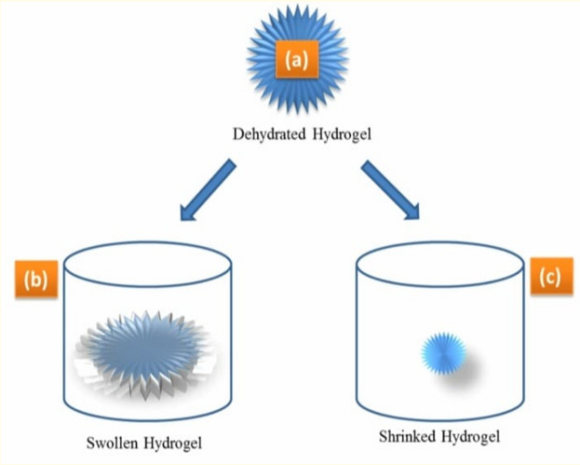

Figure 3: Small variations in external stimuli, such as pH, temperature, and analyte concentration, that affect the hydrogel hydrophilicity result in dehydrated (a), swelled (b), and shrinking (c) hydrogels.

er, the preparation of chemical hydrogels using toxic crosslinking agents may have an adverse effect on biocompatibility; in hydrogels, physical-chemical interactions are established and such toxic initiators are avoided [21]. When designing hydrogels for medical purposes, one of the most crucial factors to take into account is their mechanical qualities. The mechanical characteristics of scaffolds, both at the macroscopic and microscopic dimensions, are crucial in controlling cell behaviour in the field of tissue engineering [26]. Cell shape is directly influenced by biomechanical signals and interactions between cells and extracellular matrix (ECM). For example, adult human skin fibroblasts are impacted by ECM rigidity. Additionally, cells that are exposed to more robust substrates arrange their cytoskeleton and plasma membrane to have a higher elastic modulus [23].

Furthermore, compared to softer substrates, cells grown on tougher substrates proliferate and migrate more quickly. Hydrogel biomaterials' mechanical properties are mainly determined by analysing the hydrogel's structure and calculating the effective crosslinking ratio through the use of time-independent and time-dependent viscoelastic theories [35]. Because of their extreme weakness, PNIPAAM hydrogel made by the free radical polymerization process cannot be identified mechanically using conventional methods. The initial monomer concentration, the quantity of crosslinking agent, the temperature of polymerization, the degree of swelling at the time of measurement, and the measurement technique are some of the parameters influencing the mechanical properties of hydrogels. Because of this, it is highly challenging to compare any mechanical characteristic with accuracy. Graphene oxide was employed by Reza Abdollahi and associates to improve the mechanical characteristics of amylose-bonded PAA. They think that because of its wide aspect ratio and unique mechanical strength, graphene oxide has a good strengthening impact for tensile properties [2].

The way hydrogels behave under stress is one of its mechanical characteristics.

Tensile strength, toughness, Young modulus, and percent elongation to break are among the mechanical characteristics of hydrogels. One can achieve the required mechanical properties of the hydrogel by adjusting the degree of cross-linking. By strengthening the degree of cross-linking, a stronger hydrogel might be produced. The hydrogels' percentage of elongation decreases with increasing cross-linking strength, giving rise to a more brittle hydrogel structure. Consequently, the ideal level of cross-linking exists to produce a hydrogel that is elastic and reasonably strong [19]. In biological and pharmaceutical applications, hydrogels' mechanical properties are essential. In many biological applications, including drug delivery matrix, ligament, tendon healing, and cartilage replacement material, mechanical property assessment is essential. The mechanical properties of hydrogels should allow them to deliver

therapeutic moieties for a predetermined amount of time while maintaining their physical texture, tissue engineering, and wound dressing material [29]. Compression and tension analysis can be performed by frequency-based testing using rheometry or by limited or unconfined local indentation using a probe. Hydrogels can be mechanically analysed in two different methods. Frequency-based sinusoidal testing frequently makes use of a rheometer. Grassi., *et al*. assessed the mechanical properties of calcium alginate hydrogel [36].

The linear viscoelastic range of the hydrogel was determined by the relaxation experiments (at steady deformation, typical stress relaxation), and the Youngs modulus and relaxation spectra were described using the extended Maxwell model. The Youngs modulus and Flory's theory can be used to compute the density of hydrogel cross-linking. The average polymeric mesh size was then determined using the comparable network theory and this figure. Because hydrogels have different mechanical properties from other standard manufactured materials, it is quite challenging to investigate and characterise the mechanical properties of hydrogels. Because of their wide range of mechanical properties, hydrogels are attractive for use in biological applications. The special quality of hydrogels is called poroelasticity. It is a deformation that occurs in relation to time and is not affected by fluid movement. In addition, the two primary mechanical characteristics of hydrogels are rubber elasticity and viscoelasticity. The viscosity of hydrogels is determined by the water mobility in the network cage, which is akin to the aqueous phase. The elasticity of hydrogels originates from the polymer matrix. The viscoelastic properties are largely influenced by applied mechanical force. It is possible to state that the applied stress affects the viscoelastic characteristics of hydrogels. In elastic materials, the stress is directly proportional to the strain; in viscous materials, however, the stress is directly proportional to the strain rate. The Maxwell model is a mathematical model designed for linear viscoelastic characteristics [25].

Biological properties

Biocompatibility and non-toxicity, adequate mechanical qualities, acceptable viscosity, stability, biodegradability, etc. are essential characteristics of injectable hydrogels for a range of medical applications. The mechanical and biological properties of the hydrogel must match those of the tissue it substitutes and be appropriate [16]. By combining cross-linking and electrospinning techniques, Zhao., *et al*. have attempted to attain the best mechanical and biological qualities in a number of investigations. UV light was used to crosslink gelatin methacrylate fibres that had been electrospun. The outcomes demonstrated that varying the exposure duration could alter the electrospun hydrogel's biological and physical characteristics [17].

The development of a hydroxyapatite/carbon nanotube/HA CNT composite with superior mechanical and biological properties is crucial for the usage of bone replacements in order to resemble true bone tissue [28]. In addition to facilitating the flow of bodily fluids, the composite's unique top has an uneven, wet surface that is ideal for cell adhesion, development, and proliferation. Thus, the highly active tissue scaffold preparation and bone replacement applications can greatly benefit from the usage of HA/CNT composite, which has good biological and mechanical capabilities. An essential phase for the fundamental biological characteristics of osteoblasts is cell expansion in biological material [39]. When developing an injectable hydrogel, it is important to assess its biocompatibility because the hydrogel should promote cell proliferation and differentiation without endangering the host or inciting immunological responses. Natural hydrogels have more biocompatibility than artificial hydrogels because most of their components are similar to extracellular matrix (ECM). Additionally, the hydrogel's structure needs to be compatible with body fluids, tissues, and cells. It also needs to be non-toxic, non-cancerous, and not cause long-term physiological or inflammatory reactions after it is destroyed [30].

Utilising hydrogels in medical application

Tissue engineering

Similar to extracellular matrix (ECM) hydrogels, which have garnered significant interest for applications in tissue engineering and regenerative medicine. Until now, damaged osteocortical joints or articular cartilage tissue have been repaired using a variety of hydrogels made of synthetic or natural polymers. A naturally occurring polymer of polysaccharides, alginate is typically derived from brown seaweed and a variety of bacteria. Alginate is special because it can physically cross-link at room temperature with divalent cations like Ca2+. This property makes it valuable for a variety of biotechnical processes like moulding, spraying, and 3D printing

[11].

Physical hydrogels

The items are reasonably priced, biocompatible, and have low toxicity. Alginate hydrogel is appropriate for sustaining the chondrogenic phenotype and facilitating the growth and multiplication of encapsulated chondrocytes. Type II collagen and the advanced cartilage gene are generated 21–28 days after chondrocytes are injected. Alginate is also utilised in the provision of primary bone cells for bone repair, such as chemical stem cells (MSCS).

The collagen extracellular matrix (ECM) that encapsulated MSCS can generate combines with the host tissue [22]. A natural biopolymer derived from renewable sources like oyster shells, insects, fungi, and marine trash, it is the second most abundant type. Because of its excellent biocompatibility and biodegradability, chitosan is a desirable material for tissue engineering applications. Enzymatic grafting yields chitosan, which can promote the growth of stem cells and chondrocytes [33]. Preserve chondrogenic shape and phenotype while increasing ECM deposition in vitro [ECM]. Long acknowledged as the only scaffold that cells rest on, 36 is a support material made by cells. Neutral materials are more biocompatible than other materials and can be employed for a variety of purposes, such as tissue engineering and the replacement of artificial hip joints, because of their ineffectual characteristics [44]. Through the copolymerization of PEG and PNIPAAM, Alexander., *et al*. were able to generate temperature-sensitive injectable hydrogels for tissue engineering applications. They contend that the mechanical and compressive moduli of hydrogels based on PNIPAAM are low. This material is a good candidate for the development of an injectable biological material for use in the regeneration or replacement of soft tissue because of the temperature sensitivity of PNIPAAM polymer [35].

Natural material hydrogels have been a popular choice for tissue engineering scaffolds because of their ability to mimic the extracellular matrix (ECM) structure of biological tissues and to deliver biochemical cues that encourage cell proliferation and differentiation. The creation of polymer scaffolds for tissue engineering has given optical crosslinking a lot of consideration. The reason for this is that these hydrogels may create intricately shaped scanfolds because of their quick cure under biological settings at physiological temperatures and unique control over gel dynamics. It is essential that the mechanical characteristics of hydrogels employed in biomedical and tissue engineering applications resemble those of real tissue [26].

Wound dressing

It was possible for Min Hee Kim and his associates to create MC methylcellulose hydrogels with silver oxide particles for use as wound dressings. In this experiment, field hairs that were four weeks old and Sprague were used. Fieldwork was done in environments with regulated light, humidity, and temperature [7]. According to their histological analysis, the area of the wound that had MC hydrogel treatment and contained silver oxide nanoparticles fared better than the untreated area. It has been observed that using MC hydrogel greatly accelerates the healing of burn wounds [8]. In order to look at untreated tissue, researchers also looked at the burn wound care protocol. Biological dyes were used to assess the particles on days 1, 3, 7, 14, and 21. The findings demonstrated that although hydrogels containing silver nanoparticles did not result in tissue necrosis or inflammation, MC hydrogels lacking silver nanoparticles did [9]. Hydrogel-based dressings are useful for absorbing wound fluids, lowering the temperature at the wound site, and fostering a moist environment since they can absorb water up to six times their dry weight. The drawbacks of current wound dressings include their poor mechanical qualities, lack of antibacterial activity, and inadequate oxygen and water permeability [8].

Hassan Namazi and his associates employed a nanocomposite hydrogel containing antibiotics to get around these issues has been created by combining carboxymethylcellulose and mesoporous silica as a nanoparticle carrier [8]. When administered into the body as antibacterial medications, tetracycline and methylene blue displayed distinct release patterns [2]. Tetracycline is a broad-spectrum antibiotic used to treat wounds, soft tissues, acne, and skin infections. When used topically, tetracycline had very good efficacy against bacterial skin infections [3]. Methylene blue is a cationic dye with antiseptic qualities that is used to treat cyanide, methemoglobin, kidney stones, and poisoning in humans. Furthermore, it is commonly employed as a light-sensitive material in photodynamic therapy, a developing strategy for combating microorganisms resistant to antibiotics [4].

Drug release

Abdullahi., *et al*. were able to create a hydrogel containing fluoroexamine with ultrasonic technology, demonstrating the medication's controlled release in a bodily simulation. They contend that

a number of variables, including the hydrogel's composition, geometric structure, preparation technique, kind of drug, and environmental conditions at the time of release, affect the mechanism of drug release from the hydrogel, with pH being one of the most crucial ones [2]. In a different study, Ganji., *et al*. were able to use injectable hydrogel—which is temperature-sensitive for chitosan—to release pyridostigmine bromide gradually. They think that the darker solution seen in comparison to the unsalted chitosan solution was caused by the addition of glycerol phosphate salt. For solutions containing 8% by weight/volume of salt, turbidity variations of chitosan and chitosan/glycerol phosphate solutions have been observed over time. At 37° C, the turbidity of the chitosan solution did not change noticeably over time. Thus, it can be said that at 37° C, chitosan solution without glycerol phosphate salt is not sensitive to temperature changes and keeps its consistency for an extended period of time [5].

The point of gel formation is when there is a noticeable abrupt increase in opacity. This experiment demonstrated how adding glycerol phosphate salt to the chitosan solution decreased its stability at 37° C and quickly transitioned the phase from the solution state to the gel state [5]. Baghdadit-vancomycin nanostructured scaffold with drug release capability, antibacterial activity, and biocompatibility was successfully constructed by Bakhshashi., *et al*. The drug release was assessed on a net basis. Vancomycin was noted as a drug model in the Baghdad scaffold for drug release behaviour in their investigation [6]. Following immersion in phosphate-buffered saline solution (PBS), the process of drug release from the scaffold was shown both explosively and in a controlled manner. In particular, a stable release was seen after a period of time and during the first six hours of explosive release; yet, for all drug compounds, 45 to 75% of the drug was extracted from the scaffold after 36 hours. S. aureus was destroyed by vancomycin discharge, which also stopped them from proliferating on the scaffold. It can be claimed that Baghdadit/vancomycin scaffolds can suppress bacterial infection in the early stages of bone infection because they reported that 35% of the antibiotic stayed in the scaffold and was not eliminated [7].

Conclusion

The several forms of hydrogels, their characteristics, their creation process, and their medicinal applications were covered in the current review paper. Regarding the hydrogel production mechanism, there exist various techniques for crosslinking the structure. Physically networked hydrogels have been employed as a tissue engineering substrate for a range of medicinal uses, such as the confinement of cells and the release of bioactive chemicals. These networks have the benefit of not requiring the usage of organic solvents.

The primary mechanism via which pharmacological compounds are released from hydrogels is structural swelling. The field of stimulus-responsive hydrogels has seen a rise in interest in recent years. The pH and temperature of medications affect how the pharmacological substances are released from the hydrogel network in a controlled manner. Hydrogels are regarded as an appealing biomaterial for a range of medicinal applications because of its soft structure, biocompatibility, water absorption, and ECM

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