Chapter 12

Hydrogels in Regenerative Medicine

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Abstract

Polymer scaffolds have many various applications in the field of tissue engineering, drug delivery, and implantation. They are applied as dispensing devices for bioactive molecules and as three-dimensional (3D) structures that provide stimulants that organize cells and direct desired original tissue formation. Hydrogels are preferred scaffolding material because they are structurally similar to the extracellular matrix of many tissues, often processed under mild conditions, and can be delivered in a minimally invasive manner. Hydrogel materials formed a group of polymeric materials. The hydrophilic structure allows them to hold large amounts of water in their three-dimensional backbone. As a result, hydrogels are used as scaffolding material for drug and growth factor transmission, tissue engineering modifications, and many other applications. In this chapter, we describe the physical and chemical structure of hydrogels, side groups, cross-linkings, swelling properties, types of polymers and fabrication methods, and application fields.

Keywords: hydrogel, polymers, drug delivery, tissue engineering

1. Introduction

Hydrogels are polymer-based substances that contain high levels of water and show the physical characteristic of the extracellular matrix. In regenerative medicine, in terms of the material requirements for tissue scaffold or therapeutic transfer systems, the cell matrix is preferred due to its structural and compound-based similarities. Moreover, hydrogels are preferred as they promote cell attachment and proliferation.

In this chapter, compiling the studies about the preparation of hydrogels and application of hydrogels in regenerative medicine is aimed.

2. Physical and chemical properties of hydrogels

2.1. Crosslinking and general characteristic of hydrogels

Hydrogels are a three-dimensional (3D) polymeric network structure with the ability to absorb water and other biological fluids. The water content of hydrogels determines its specific physicochemical character: mildness, density, and low surface tension of hydrogels [1–4].

Hydrogels can be classified according to their preparation methods, ionic charges, physical structures, and cross-linking conditions. According to physical structures, hydrogels can be divided into some groups that are called amorphous hydrogels, semi-crystalline hydrogels, hydrogen-bonded hydrogels, physical hydrogels, and chemical hydrogels.

Various cross-linking approaches, including chemical and physical, have been used to create polymer networks and to protect 3D structures in aqueous media. Physical interactions between the polymer chains in the physically cross-linked gels prevent hydrogel breakdown, while the covalent bonds between the polymer chains in the chemically cross-linked gel form a constant hydrogel.

Physically cross-linked hydrogels are formed by changes in environmental conditions (pH, temperature, and ionic interactions), hydrogen bonds, and protein interactions. Chemically cross-linked gels are obtained by radical polymerization, chemical reactions, energy irradiation, and enzymatic cross-linking [5].

Hydrogels can also have many physical forms: solid mold forms (such as soft contact lenses), pressed powder matrices (pills or capsules taken orally), microparticles (bio-structured carriers or wound treatments), coatings (in implants or in catheters, in pills or capsules, or in capillary electrophoresis), membranes or disks (such as two-dimensional electrophoresis gels), encapsulated solute (in osmotic pumps), and liquids (gel forms that are heated or cooled) [6].

2.2. Hydrogels side groups

Hydrogels are also called "hydrophilic polymers" because of their water-like properties. Hydrogels have functional groups, such as $-SO_3H$, $-COOH$, $-CONH_2$, $-OH$, and $-NH_2$, which provide hydrophilic character to the polymer chains in their networks. Some of these functional groups ($-SO_3$ and $-COO$ hydrogel nets) are negatively charged in aqueous media and can adsorb metal ions through electrostatic interactions [7].

Depending on their chemical and physical structure, there are three types of hydrogels: neutral hydrogels, ionic hydrogels, and interconnected network structures. Neutral (nonionic) hydrogels are homopolymeric or copolymeric hydrogels which do not have charged groups in their structure. Ionic hydrogels, also known as polyelectrolytes, are prepared from ionically charged monomers. These hydrogels are termed cationic and anionic hydrogels, as their monomeric charge is positive and negative [8]. The presence of charged groups in the main chain of ionic hydrogels enhances their susceptibility to stimuli. The presence of ionizable functional groups such as carboxyl and sulfonic acid or ammonium salt increases the

hydrophilicity of the polymer and thus increases the water absorption capacity. As a result of the electrostatic repulsive forces of these loads, the solubility and swelling ratios in the web structure are increased. In ionic hydrogels containing acid groups, swelling increases in basic medium, while hydrogels containing basic groups increase swelling in acidic media [9, 10].

2.3. Cross-linking methods in hydrogel fabrication

Hydrogels are polymeric webs that absorb and retain water in large quantities. In the polymeric cannula, there are hydrophilic groups or areas that provide a hydrated hydrogel structure in an aqueous environment. As is the case with the term "network," cross-links must be present to prevent the hydrophilic polymer chains from dissolving in aqueous phase.

2.3.1. Physically cross-linked hydrogel

Physical gel called hydrogels is the result of cross-linking of ionic interaction and physical interactions such as hydrogen bonds, coordination bonds, and hydrophobic interactions [11]. These hydrogels alter the temperature, pH, or solvent composition to form a homogeneous solution and re-gel when they return to their initial conditions. Because of these behaviors, physical gel is also known as reversible gel [12]. They are generally unstable and mechanically weak [13].

Generally, ionic interactions are used to produce physically cross-linked hydrogels. For example, alginate hydrogels are formed with calcium ions. The physical cross-links are found between ionic interactions [14], crystallization [14], amphiphilic block and graft copolymers [15], hydrogen bonds [16], and protein interactions [17].

2.3.2. Chemical cross-linked hydrogels

The hydrogels in this group are called as irreversible because they are cross-linked by strong chemical bonds between their chains and are not redissolved by changing temperature, pH, or solvent composition. Chemical cross-linked nets have permanent junctions [18, 19]. Chemical cross-linking involves permanent covalent bonds that result in better mechanical strength and more stable hydrogels than physical cross-linking. Incorporation of chemical cross-linkers, however, can cause toxicity problems. Cross-linking of hydrogel can occur with some other method such as radical polymerization, chemical reaction, and high-energy irradiation.

Chemically cross-linked gels can be obtained by radical polymerization of polymers of low molecular weight drugs in the presence of cross-linking agents; poly(2-hydroxyethyl methacrylate) (pHEMA) is a well-known and frequently studied hydrogel system. This hydrogel was first described by Wichterle and Lim [19] and was obtained by polymerization of HEMA in the presence of a suitable cross-linking agent (e.g., ethylene glycol dimethacrylate). A wide variety of hydrogel systems have been synthesized using similar procedures [20].

The covalent bonds between the polymer chains can be formed by reaction with complementary reactivity of the functional groups, formation of an amine carboxylic acid, or OH/NH_3 reaction such as isocyanate or Schiff base formation. Chemical cross-linking bonds can occur with aldehydes, with additional reactions and condensation reactions. Water-soluble

polymers owe their solubility properties to the presence of functional groups (mainly ─OH, COOH, NH) which can be used for hydrogel formation.

High-energy radiation, especially gamma and electron beams, can be used to polymerize unsaturated compounds. This means that water-soluble polymers derivatized with vinyl groups can be converted into hydrogels by high-energy irradiation [21]. Hydrogels may also be obtained by radiation-induced polymerization of a mixture consisting of a monofunctional acrylate (e.g., acryloyl-L-proline methyl ester) and a suitable cross-linker [22]. Moreover, high-energy irradiation cross-links water-soluble polymers without additional groups. During irradiation of aqueous solutions of polymers (gamma or electron transfer), the radicals are generally present in the polymer chain, e.g., homolytic cleavage of C–H bonds.

2.4. Water content and resources

Hydrogels can generally hold 20–100 times water and their own weight depends on their structures [23]. If hydrogels can hold higher than 100%, they are called superabsorbent hydrogels. According to the water contents, hydrogels can be categorized as low swelling grade hydrogels (20–50%), medium swelling grade hydrogels (50–90%), high swelling grade hydrogels (90–99.5%), and superabsorbent hydrogels (>99.5%) [24, 25].

High water content hydrogels are usually more useful in the medical field because of permeability and biocompatibility [26]. Synthesis of biodegradable hydrogels with both good mechanical properties and high water content is still a major challenge, because as the amount of water increases, the mechanical properties of hydrogel become weak [27].

Because water content of hydrogels is high, these gels resemble natural living tissues more than synthetic biological materials, so the biocompatibility is higher. When the polymer network contacts the aqueous solutions, swelling occurs to achieve thermodynamic stability due to the water concentration gradient [28].

The hydrophilicity of the polymer chain and the cross-link density are parameters effective in hydrogel swelling. Hydrophilic groups of polymer networks in hydrogels are groups that like water. Therefore, they have a high affinity for water. These groups allow hydrogels to swell in water, become soft, and gain elastic properties [29]. Hydrophilic group-containing hydrogels swell at a higher rate than hydrophobic group-containing hydrogels. Because hydrophobic groups do not like water, they prevent water molecules from penetrating into the structure [30].

The structures of the high cross-linked hydrogels are more rigid, and cross-linking inhibits the movement of the polymer chain. When the amount of cross-linking agent increases, the hydrogel becomes less flexible, and the swelling ability of the hydrogel is reduced [31, 32].

2.5. Polymers used in hydrogel fabrication

Polymer materials have many uses such as catheters, heart valves, contact and intraocular lenses, dental prostheses, ophthalmic applications, urology, and gastroenterology applications [33]. In tissue engineering different polymers are used for different tissues. It is possible to classify them in four different groups.

2.5.1. Natural and synthetic polymers

Natural polymers have been used as scaffolds for tissue engineering as natural hydrogels, regarding their biological compatibility, natural biodegradability, and critical biological functions. There are four main types of natural polymers, including:

- proteins such as collagen, silk, gelatin, fibrin, lysozyme, Matrigel™, and genetically engineered proteins [34–36] like calmodulin (a calcium-binding protein), elastin-like polypeptides, and leucine [37] zipper;
- polysaccharides like hyaluronic acid (HA), dextran, agarose, and chitosan [38].
- protein/polysaccharide hybrid polymers like collagen/HA, laminin/chitosan, fibrin/cellulose, and gelatin/alginate [39]; and
- DNA [40].

Compared to natural polymers, synthetic polymers have more reproducible physical and chemical properties that are critical for the construction of scaffolding. At present, synthetic polymers have emerged as an important alternative option in the manufacture of hydrogel tissue-engineered skeletons, since they can be molecularly modified by block structures, molecular weights, mechanical strength, and biodegradability [41–43]. Synthetic polymers used in the preparation of synthetic hydrogels can be classified into three main types: non-biodegradable [44, 45], biodegradable [46], and bioactive polymers [47]. In the following section, the biodegradable synthetic polymers are disclosed because of its widespread use from among these three main types.

2.5.2. Biodegradable synthetic polymers

Biodegradability is one of the most important aspects of scaffolds for tissue engineering. It is highly desirable to ensure that the biodegradation rate coincides with new tissue regeneration at the defect site [48, 49]. Many polymers, proteins, cellulose, starch, and chitin created in the environment are limited to making hydrogel skeletons that are biodegradable but have their own biodegradability and mechanical properties. Most common biodegradable synthetic polymer groups contain poly (lactic acid) (PLA), poly(ε-caprolactone) (PCL), poly(glycolic acid) (PGA) and copolymers [50]. They can be used to modify hydrophilic polymers such as PEG to form acrylate macromers or amphiphilic polymers to produce biodegradable hydrogels by chemical or physical cross-linking [51, 52].

The mechanical stability of the gel is an important feature when a scaffold is designed. The strength of the hydrogels can be increased by incorporating cross-linking agents, comonomers, because the higher cross-linking degree provides more fragility and less elasticity.

Biodegradable synthetic hydrogels include various vinylic monomers such as 2-hydroxyethyl methacrylate (HEMA), N-isopropylacrylamide (NIPAM), 2-hydroxypropyl methacrylate (HPMA), acrylamide (AAm), acrylic acid (AAc) or macromers [53–55] N,N′-methylenebis and methoxyl poly(ethylene glycol) (PEG), monoacrylate (mPEGMA or PEGMA), and diacrylate (PEGDA) with cross-linkers such as ethylene glycol diacrylate (EGDA), and these

nonbiodegradable polymers such as self-assembly of Pluronic® polymers that have poly(ethylene oxide) (PEO)-poly(propylene oxide) (PPO)-PEO structure [53–55] are modified with poly(vinyl alcohol) (PVA) via chemical cross-linking.

Synthetic polymers can be easily synthesized on a large scale and manipulated at the molecular level by polymerization, cross-linking, and functionalization. However, most synthetic hydrogels alone generally function as passive scaffolds only for cells and do not increase active cellular interactions [56]. As already mentioned, natural polymers such as proteins exhibit different tertiary structures and regulate active cellular response, biological identification, and cell-triggered remodeling. Thus, combining the properties of synthetic and natural polymers to form hybrid hydrogels has become a direct approach to creating bioactive hydrogel scaffolds for tissue engineering. These same examples of hybrid hydrogel polymers include:

- PEG-modified natural polymers [57–60], like fibrinogen, heparin, dextran, HA, and albumin;
- PNIPAm-modified natural polymers, like collagen, chitosan, and alginate [61];
- Synthetic peptide-modified proteins or polysaccharides [62]; and
- PVA and other synthetic polymer (e.g., pluronic)-modified natural polymers [63].

The hydrogel is obtained in different forms depending on the application area by selecting the appropriate polymer. It is possible to produce hydrogels which can be heat-adjusted, injectable, or in the form of film, foam, or gel. These can be controlled by different parameters such as cross-linking of structures and synthesis of polymers.

3. Application of hydrogels

The hydrogels with various features are widely used as wound dressing, drug delivery, dental equipment, pharmaceutic industry, injectable polymer systems, implants, and tissue engineering.

3.1. Applications of hydrogels in dentistry

In recent years, injectable hydrogels have emerged as a promising biomaterial for the therapeutic delivery of cells and bioactive molecules for tissue regeneration in dentistry. The controllability of deterioration and release behavior, its adaptability in the clinical setting for minimally invasive surgical procedures, and its ability to remain three-dimensional (3D) after gelling mean that these hydrogels can be used in medical practice [64]. In dental tissue engineering, injectable hydrogels are used to replace countless tissues, especially cartilage, bones, nerves, blood vessels, and soft tissues. Furthermore, it has been demonstrated that the feasibility of introducing dental pulp stem cells with hydrogels has supported the matrix and growth factors [65].

Hydrogel is biologically compatible and absorbed into the body without any side effects. The gel is completely disintegrated so no by-products or new chemicals are formed. For these reasons, they are preferred as dental fillers, as dental equipment, and even as coating for dental implants [66].

Hydrogels are administered as low-viscosity liquids that penetrate the dentin tubules when exposed to capillary action. Treatment with a gel that forms a long-term block is provided when it is swollen and wet; at this point it is also permeable to oxygen and electrolytes [67]. The use of hydrogels in dental equipment offers several advantages over other biomaterials such as (1) long-term grip despite the effects of surface abrasion, (2) its softness removes the pressure (3) brushing and abrasion only cleanse the exposed parts of the gel and leave the remainder in the tubules for a long time (4), the hardened gel is colorless and therefore maintains the normal appearance of the tooth, (5) the gel structure continues to be permeable to oxygen and electrolytes, and (6) there are no hydraulic pressures that can cause pain without fluid flow [68].

Oral hydrogels are drug-free, are completely natural as wound dressings, and are approved by the FDA (Food and Drug Administration) for all oral injuries. They can be used in tooth extractions, grafts, implants, lesions, or for wounds in the mouth [69].

Depending on the hydrostatic pressure, the sharp fluid movements in these micro-channels can cause dentin pain. The microorganisms present in the oral cavity ferment carbohydrates to form lactic acid, which causes the pH to drop. The acidic medium then causes the hydroxyapatite to dissolve in the hard walls of the micro-channels. This increases the permeability of the channels and facilitates the penetration of microorganisms. The spread of bacterial toxins causes an inflammatory reaction in the pulp, which causes symptoms such as hypersensitivity and pain. For this reason, the development of new prophylactic agents and methods to reduce tooth decay and an overly sensitive tooth neck is of great importance [70]. Ionic hydrogels, especially nanogels, have started being used in toothpastes. Micro-channels filled with a fibrous protein and a bio-hydrogel composed of a liquid phase enter the human teeth. The gel network is bound to the organic collagen matrix and the hydroxyapatite crystals on the walls of the dentin tubules [71].

3.2. Applications of hydrogels in drug delivery

Conventional drug administration can result in toxicity and side effects because of requirement of high dosages and repeated administration to stimulate a therapeutic effect, and these can reduce efficacy and patient compliance [72–74]. Researchers have focused on controlled drug delivery systems during the recent years for reducing toxicity and by enhancing efficacy of therapeutics [75]. Drug release is controlled by drug delivery systems in terms of transportation to tissues and cells in time and in space [76, 77].

Hydrogels have been considerably researched as the carrier for drug delivery systems [78]. They have low interfacial tension; thus, they exhibit minimum tendency to adsorb proteins from body fluids [79, 80]. These biomaterials have paid attention due to their peculiar properties such as temperature and pH sensitivity, swelling in aqueous medium, and sensitivity toward other stimuli [78]. Their highly porous structure can be modified through controlling the density of cross-links in the gel matrix and the affinity of the hydrogels for the aqueous environment in which they are swollen. Drug release at a rate dependent on the diffusion coefficient of the small molecule or macromolecule through the gel network and loading of drugs into the gel matrix can be provided due to their porous structure [80, 81].

Hydrogels have also been served as drug protectors particularly for proteins and peptides from in vivo environment. Furthermore, these swollen polymers are beneficial as targetable carriers for bioactive drugs with tissue specificity [78]. In general hydrogels are divided for their morphology, swelling property, and elasticity. The release mechanism of the drug from the swollen polymeric material is determined by swelling, and also elasticity affects both the stability of these drug carriers and the mechanical strength of the network [82].

The body has environmental variables, known as low pH and high temperatures. In this endeavor, it either includes physical, such as temperature, or chemical, such as in pH, ions which can be used for site-specific controlled drug delivery [80, 83]. Due to their ability to "sense" changes in environmental properties, stimuli-sensitive hydrogels, also known as "smart" hydrogels, are very different from inactive hydrogels. Their response will be to increase or decrease their degree of swelling [84, 85]. "Smart" hydrogels have a property of changing the intensity which is particularly useful in the application of drug delivery as drug release can be set off upon environmental changes.

Besides, molecules of different sizes have the ability to go into and out of hydrogels (going in is called drug loading and going out of is called drug release) which makes them permissible for dry or swollen polymeric networks as drug delivery systems for nasal, oral, ocular, buccal, parenteral, epidermal, and subcutaneous routes of administration [86].

3.2.1. Peroral drug delivery

Up to now, pharmaceutical application of hydrogels has been most commonly done orally. Taken orally, hydrogels are able to deliver drugs to four major areas: the mouth, stomach, small intestine, and colon. If their swelling properties or bioadhesive abilities are controlled, hydrogels can be useful in the release of drugs in a controlled manner at these desired areas. Additionally, they can also stick to certain specific regions in the oral pathway, leading to a locally enhanced drug concentration and, thus, promoting the drug absorption at the release site [87].

3.2.2. Drug delivery in the oral cavity

Drug delivery to the oral cavity can have many functions. Hydrogel are used ın the local treatment of diseases pertaining to the mouth (i.e., periodontal, stomatitis, viral and fungal infections) and oral cavity cancers. With this in mind, many types of bioadhesive hydrogel systems have been devised since the early 1980s. To name one, a hydrogel-based ointment can also be used for the topical treatment of certain diseases in the oral cavity. It can be used not only as a drug delivery device but also as a liposome delivery medium [88, 89].

3.2.3. Drug delivery in the gastrointestinal (GI) tract

The GI tract is undoubtedly the most popular route of drug delivery because of the easiness of administration of drugs for a manageable therapy and its large surface area for absorption to the entire body. It is, however, the most complex route, so that changeable approaches are needed to give drugs for effective therapy [90]. Like buccal delivery, hydrogel-based

devices can be designed to administer drugs locally to the specific areas in the GI tract. Several hydrogels are currently being investigated as potential devices for colon-specific drug delivery. These include chemically or physically cross-linked polysaccharides, such as dextran, guar gum, azo cross-linked poly(acrylic acid), amidated pectin, and inulin [91–93]. They are designed to be highly swollen or degraded in the presence of colonic enzymes or microflora, providing colon specificity in drug delivery [94].

3.2.4. Ocular delivery

The eye has shielding mechanisms at work, like tear drainage, the power of blinking, and low permeability of the cornea. These are some of the many physiological constraints preventing a successful drug delivery to the eye [95].

The usual eye drops that contain a drug solution are most likely to be eliminated quickly from the eye; thus, medication administered will have limited absorption. This in turn leads to poor ophthalmic bioavailability (the degree to which a drug or other substances is absorbed at the site of physiological activity after being given) [96].

Researchers have been motivated to come up with a system that delivers the drug for a longer stay time in the eye. Suspension and ointments which are some of the dosage forms can remain in the eye, but they also can be uncomfortable at times due to the unpleasant feeling given to the eye from characteristics of solids and semisolids [97].

Hydrogels have elastic properties, and this is why they can also represent an ocular drainage-resistant device. Additionally, they could give a better feeling to patients, with less gritty sensations. In particular, in situ forming hydrogels are attractive as an ocular drug delivery system because of their facility in dosing as a liquid, and their long-term retention property as a gel after dosage has been given [98].

3.2.5. Transdermal delivery

Drug delivery to the skin has been traditionally conducted for a specific area use of dermatological drugs to treat skin diseases or for disinfection of the skin itself. Longer duration and a constant rate are among the benefits of transdermal drug delivery that drug delivery can be easily canceled on demand by simply removing the devices. Thus, since hydrogels are high in water content, swollen hydrogels can provide a better feeling for the skin when compared to traditional ointments and patches [96].

3.2.6. Subcutaneous delivery

Subcutaneously inserted exogenous materials may more or less evoke potentially undesirable body responses, such as inflammation, carcinogenicity, and immunogenicity. Therefore, biocompatibility is a prerequisite that makes materials implantable.

Due to their high water content, hydrogels are generally considered as biocompatible materials. Hydrogels have been used to improve cellular adhesion [99]. They also provide several promising properties: minimal mechanical irritation upon living organism implantation, due

to their soft, elastic properties; prevention of protein adsorption and cell adhesion arising from the low interfacial tension between water and hydrogels; broad acceptability for individual drugs with different hydrophilicities and molecular sizes; and unique possibilities (cross-linking density and swelling) to manipulate the release of incorporated drugs. Some of these may offer an advantage for the delivery of certain delicate drugs, such as peptides and proteins [73, 80].

3.3. Applications of hydrogels in tissue engineering

Tissue engineering is an interdisciplinary field that uses the principles of engineering and life sciences that aims to improving, maintaining, and renewing the functions of tissues and organs. It was emerged by Y. C. Fung in 1985 as a technical science department by using medical and material engineering [100].

Hydrogels are frequently used in biomedical and bioengineering fields due to their controllable different properties, similarity to tissues, and their ability to form scaffolds for different tissues due to their tunable physical and mechanical properties [101, 102]. Hydrogels used in tissue engineering have low viscosity before injection and require rapid gel formation in the physiological environment of the tissue [99]. It is frequently used in bone tissue, cartilage tissue, vascular tissue, meniscus, tendon, skin, cornea, and soft tissues. Hydrogel film can be used to fabricate or repair tissue in a loss of function. In the tissue engineering studies, synthetic or natural polymers are used for hydrogel production [103–105]. In tissue studies, adhesion of cells to artificial tissues in the course of cell culture, spreading, and population is an important feature.

3.3.1. Bone tissue engineering (BTE)

The bone is a dynamic and vascularized tissue with the ability to heal naturally on injury. However, repair mechanism cannot be sufficient in large bone defects. Current approaches often impose limitations that consider autografts and various allografts. BTE is based on the use of 3D matrices that both promote cellular growth and divergence to promote bone regeneration. The hydrogel matrices may contain biological materials such as cells and growth factors [106]. One of the studies is about that to assess the effect of different natural skeletons on this coculture system, cells were encapsulated in alginate and/or collagen hydrogel scaffolds. A researcher has discovered that in addition to the cell-cell proximity between the two cell types, the natural cell-binding capabilities of hydrogels such as collagen are preferred. Researchers have discovered increased osteogenic and angiogenic potential, as evidenced by increased protein and protein expression of ALP, BMP-2, VEGF, and PECAM [107].

3.3.2. Cartilage tissue engineering

Simply, articular cartilage is a tissue composed of a single cell type (chondrocytes) embedded in an extracellular matrix (ECM). However, the structure is more complex, and, depending on depth, the three ECM contents include three depth-related layers with varying behavior of structure and chondrocyte: superficial zone, middle zone, and deep zone. In the mid-region—the

largest region—the cartilaginous tissue has a low density of round chondrocytes surrounded by an ECM consisting of hard, avascular glycosaminoglycan (GAG) and type II collagen [108, 109]. Hydrogel design to improve cartilage repair has progressed in recent years. Some using hydrogels include the development of improved network cross-linking (e.g., double networks), new techniques for processing hydrogels (e.g., 3D printing), and better incorporation of biological markers (e.g., controlled release).

Hydrogel has emerged as a promising port because of its potential features in a wide range and its ability to trap cells in the material.

3.3.3. Meniscus tissue engineering

The meniscus plays an important role in maintaining homeostasis of the knee joint [110]. Meniscus lesions are tight, have poor healing ability, and can produce tibiofemoral osteoarthritis. Current options for reconstructive treatment focus primarily on the treatment of lesions in the peripheral vascularized area [111]. On the contrary, a small number of approaches can stimulate the repair of damaged, meniscal tissue in the middle, avascular part. Tissue engineering approaches are of great interest to repair or replace damaged meniscus tissue in this area.

Hydrogel-based biomaterials show a special interest for meniscus repair, as their cores contain relatively high rates of proteoglycans responsible for viscoelastic compaction properties and degree of hydration. Hydrogels that exhibit high water content and provide a specific three-dimensional (3D) microenvironment can be designed such that the meniscus tissue can exactly resemble this topographic composition [112].

Different polymers of both natural and synthetic origin have been manipulated to produce hydrogels that host the respective cell populations for meniscus regeneration and to provide platforms for meniscus tissue replacement. To date, these compounds have been used to design controlled delivery systems of bioactive molecules involved in the meniscus repair process or to host genetically modified cells to improve meniscus repair.

3.3.4. Tendon tissue engineering

Significant advances have been made in repair techniques for tendon injuries in recent years, but the treatment of finger flexor tendon injury is still one of the most difficult and important problems in the orthopedic area.

The main problem in tendon repair is adhesion between the tendon and surrounding tissue. We note that polyvinyl alcohol hydrogel (PVA-H) has a high water content with both adhesion-inhibiting function and synovial perfusion function. PVA-H has been extensively studied as a biomaterial [113, 114], and mechanical strength and biocompatibility have been excellent.

It has been reported that high water content PVA-H has selective permeability penetrating into low molecular weight nutrients such as glucose and protein, but not substances with cell-size levels such as fibroblasts and leukocytes [114, 115]. In addition, the gel prevents

adhesion on the surface by preventing cell viability. Successful tendon tissue engineering requires the use of three-dimensional (3D) biomimetic scaffold molds with physical and biochemical properties of native tendon tissue. Here, the development and characterization of a new composite scaffold fabricated by co-electrospinning of poly-ε-caprolactone (PCL) and methacrylated gelatin (mGLT) are reported.

3.3.5. Skin tissue engineering

Various types of tissue engineering scaffolds have been developed and used for epidermic engineering [116]. Ideally, this scaffold should have some biologic properties (i.e., to support keratinocyte adhesion, proliferation, and differentiation) and appropriate mechanical properties [117]. The mechanical properties of the skeletons are defined as a key modulator of keratinocyte behavior with increased cell adhesion and proliferation on hard surfaces [118].

The scaffold should also be strong enough and flexible to support easy handling during surgery and to support the natural movements of the tissues [119]. In addition, these scaffolds should only ideally deteriorate after adequate recovery, and this process can take up to 8 weeks [120]. In addition, for some clinical applications, the scaffold molds need to be cross-linked quickly in place for the contour of the wound [121].

Based on these requirements, natural hydrogels are considered attractive candidates for epidermis engineering due to their unique combination of biological and physical properties, including biocompatibility, as well as on-site cross-linking capacities, mimicking extracellular matrix (ECM), adjustable mechanical, swelling, and degradation properties [122].

3.3.6. Hydrogel wound dressing

An ideal wound dressing should maintain a moist environment at the wound interface, allow gas exchange, create microorganism barrier, and remove extreme exudates. It should also be made from a readily available biomaterial that is nontoxic and nonallergic, unattached, and easily removed without trauma, requires minimal processing, has antimicrobial properties, and accelerates wound healing [123].

Hydrogels are promising materials for wound dressing and for treatment of severe burns. In these applications, the use of hydrogel dressing offers several advantages. These are light materials and contain water in significant quantities. For this reason, hydrogels imitate some of the important qualities of people's skin and texture. Hydrogels can absorb large amounts of water or biological fluid content. They also protect the three-dimensional structure. Its advantages over other wound dressings are its good mechanical properties, oxygen permeability, liquid absorption, hydration of the wound bed, shape stability, softness similar to soft peripheral tissue, and cooling effect on the wound surface. Depending on the hydration state of the tissues, the hydrogel may give or absorb water to the wound periphery [124].

Hydrogel dressings' elastic sheet, film, or gel (amorphous) can be found in form. The hydrogel in leaf form has many of the ideal wound dressing properties. The hydrogels in this form have convenient constructions and can be cut and prepared in a manner suitable for the

wound. In addition, hydrogel dressings, when placed on a dry surface of the wound, provide a moist wound environment that enables the rapid healing of the wound moistening of wounds [125].

Hydrogel wound dressings can easily be shaped and leave no residue. Since the dressing does not stick to the wound surface, it is painless to remove from the wound surface and can be easily cleaned. Compared to semipermeable membranes, they have water vapor permeability. In addition, using hydrogel dressing, the drug can be applied locally to the wound, and the diffusion of the drug into the wound can be controlled by controlling the gel cross-linking grade. Hydrogels are used in dry necrotic wounds, superficial wounds, non-exudate, noninfected wounds [126, 127].

PVA has excellent and easy film-forming properties and can be mixed with synthetic and natural polymers due to its water-soluble, biodegradable, noncarcinogenic, and biocompatible character. The final properties of the mixed material depend on the properties of the materials being assembled, and the PVA properties change after mixing. Sodium alginate is one of the popular natural polymers used in wound dressing applications by combining PVA polymer as the main or additional component due to its high water swelling ability [128].

Gelatin is a protein produced by partial hydrolysis of collagen extracted from the skin (44%, usually cow and pig), bone (27%), and connective tissues or organs (28%) of animals. Gelatin has biological activities due to its natural origin, which is suitable to be used as a wound dressing material, a drug delivery carrier, and a scaffold for tissue engineering. Gelatin has the ability to form strong hydrogels and transparent films that are easily designed as insoluble hydrophilic polymers for strong regeneration and tissue implantation [129].

3.3.7. Cornea tissue engineering

Corneal disease is a leading cause of blindness all over the world [130]. Donor corneal transplantation is preferred in corneal disease. However, they are limited in supply, especially in developing countries.

For this reason, alternative treatment methods are needed to meet the demand for increased corneal replacement. Efforts have focused on the development of tissue engineering structures that use hydrogels and biopolymer materials to replace native corneas [131–135].

An ideal tissue engineering structure should imitate the native cornea closely in order to fulfill its critical functions. Ruberti and Zieske have described three design considerations that must be met for an artificial corneal formation to be functional: (i) protection, (ii) transmission, and (iii) refraction [136].

In order to meet the abovementioned design criteria, the tissue engineering structure must have the following essential characteristics [137]: (i) to stimulate the migration and proliferation of corneal epithelial cells for the formation of a functional corneal epithelium, (ii) to resist the intraocular pressure, and thus to prevent rupture, (iii) simulating the nanoscale fibrillary order of the corneal stroma to show a high degree of transparency (>90°C) and a refractive index comparable to that of the native cornea (3.8 MPa) [138] and the refractive

index, (iv) transparency to support the maintenance of functional keratocytes to preserve and de novo collagen tissue synthesis, and (v) to compensate for and thereby prevent the swelling rate of the native cornea to preserve and distribute the water content [139].

3.3.8. Hydrogel prosthesis

In general, medical bionic implants include innumerable solutions that remove injuries and post-resection losses, as well as various dysfunctions resulting from the operative treatment of tumors or inflammatory processes [140]. Swelling ability of hydrogel is used for various body regions in prostheses. A simple example of this is the design of an endoprosthesis which is not removed from the site for use in the treatment of patients with biliary obstruction. Here, the hydrogel ring located in the grooves around the endoprosthesis is placed on both sides of the occlusion. The swelling of the rings prevents the device from coming out of its place, thus protecting the internal drainage [141].

Carboxymethyl cellulose (CMC) hydrogel is a biodegradable, nontoxic, and non-mutagenic viscoelastic gel. It has been in clinical use since 1984 and has been used as a monobloc breast prosthesis since 1994. In the study by Brunner et al., 122 patients with hydrogel implants were evaluated between February 2000 and February 2005. It has been found that CMC hydrogel implants have higher radiotranslucency than silicone gel and that the integrity of this material is easy to prove by clinical examination. In the event of a rupture, the implant can be replaced immediately. It can be easily attached and placed by means of a small cut due to its high elastic shell. Studies conducted in patients with CMC hydrogel-filled breast prostheses have determined that a negligible complication rate and a high satisfaction rate in patients are seen. Another advantage of the CMC hydrogel-filled implant is that it is a natural feel comparable to that of silicone gel-filled breast implants [142].

Another usage area of hydrogels is contact lenses. The use of contact lenses to treat visual impairment began in the nineteenth century. The materials used in contact lenses for visual impairment must be pure. They must possess the necessary physical and mechanical properties such as malleability, transparency, wettability, mechanical stability, and oxygen permeability. They should be able to be sterilized and must be noncarcinogenic.

Contact lenses are generally classified as “hard” or “soft” depending on their elasticity. Although hard contact lenses are more durable, users do not prefer them, since they require an adaptation period. Hard contact lenses are resistant to hydrophobic substances such as poly(methyl methacrylate) (PMMA) or poly(hexafluoroisopropyl methacrylate) (HFIM). Despite this, soft contact lenses are resistant to hydrogels [143].

FDA-approved hydrogel contact lenses are divided into four groups depending on their water contents and the reactive groups on their polymer surface. These four groups are low water content, high water content, ionize (reactive chemical groups on the polymer surface), non-ionize (those who do not carry reactive chemical group on the polymer surface). Low water content lenses should be compatible with all lens care systems. Contact lenses have some properties which are suitable for implantation. These properties are about protein accumulation, tensile strength, and color changing. Protein accumulation and color changing should be low, and lens strength has to be durable.

Sterilization of high water content lenses is not possible by heat and enzymatic way for a long time. They have high protein accumulation and oxygen permeability, and they easily lose water; thus, their tensile strength durability is low [144].

The materials of soft contact lenses that contain polymers are not natural. They can be split into two main groups. One of these groups is hydrogel materials: hydrogel materials and silicone. The second most important material used in soft contact lenses is silicone. Elastic silicone is soft in the elastomer form. In this form, soft silicone has high oxygen permeability but also has low surface wettability. For this reason, it is coated with hydrophilic materials. The most important development in contact lenses in the recent years has been on the combination of silicone and hydrogel materials. The high oxygen permeability of silicone when added to other materials lowers its disadvantages due to the high water maintenance of hydrogels [145].

Silicone hydrogel lenses contain less water than traditional hydrogel lenses. Transparent silicone hydrogel lenses with high oxygen permeability cause less dryness in the eye and are much more comfortable to use throughout the day. With the development of silicone hydrogel lenses, the contact lens industry has experienced a revolution. With these new "super permeable" transparent contact lenses, much more oxygen can reach the cornea layer. A high oxygen supply is vital for the maintenance of eye health. This development has lead to the production of "long lasting" contact lenses, which can be used 24/7. The silicone hydrogel material is so effective that it is used to make more than 50% of contact lenses that are manufactured. Compared to traditional and hydrogel contact lenses, silicone hydrogel contact lenses have been found to have about 40 times less risk of producing infective keratitis. The fact that silicone hydrogel contact lenses are adapted to the cornea physiology, have high oxygen permeability, and have advanced surface and design features should not overshadow that they too have mechanical and inflammatory effects on the cornea [146].

3.4. Future aspect

Hydrogels have a very important role in the field of biomedicine and nanotechnology. The future success of hydrogels is based on the synthesis of new polymers or on the modification of natural polymers to solve certain biological and medical difficulties. Most scientific research shows that the studies of hydrogels have a bright future. New approaches to hydrogel design are increased in the investigation of these biomaterials. Fast response, self-assembly, high and good mechanical properties, and super-porous hydrogel are just a few examples of biomaterials with an intelligent future.

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