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Review

Recent advances in hydrogels applications for tissue engineering and clinical trials

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ABSTRACT

Hydrogels are biomolecules made of artificial and natural polymers. Their quasi-three-dimensional structure has created unique features. They are very hydrophilic, and in addition to the high inflation rate, they also have excellent water maintenance capacity, biodegradability, biocompatibility, and strong mechanical properties. These properties are used in many tissue engineering applications. All these features have made these scaffolds widely used as attractive structures in the world of tissue engineering and regeneration medicine. In addition to research, scaffolds entered the field of medicine and are expected to play a significant role in the repair of many tissues in the future. This study aims to review the various polymers involved in hydrogel fabrication and their application in the repair of diverse tissues and clinical trials.

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1. Introduction

Three-dimensional scaffolds are growing every year to expand the use of tissue engineering. These scaffolds are made by tissue decellularization methods [1,2] or by biomaterials [3]. The primary applications of hydrogel are related to the Wichterle and Lim studies and the use of hydrophilic networks of crosslinked poly (2-hydroxyethyl methacrylate) as soft contact lens materials [1]. During the last few decades and since 1995, studies related to the investigation of materials based on hydrogels have been developed. Peppas gave the most famous definition of hydrogels [2].

This description states that hydrogels are networked and water-swelling structures that play a vital role in cell culture techniques, tissue engineering, and regenerative medicine development [4,5]. Diseases and accidents cause millions of people to face the problem of organ failure or disability every year and require multiple surgical procedures with a total cost of more than 400 billion dollars per year [6]. Polymers, which are applied to produce scaffolds, have several applications such as space-filling agents, drug delivery, creating three-dimensional structures to stimuli cells for differentiation, and leading cells to form desired tissue [1].

There are various criteria for classifying hydrogels, such as the following: Source (including natural, synthetic, and hybrid hydrogels), ionic charge (including cationic, anionic, and non-ionic hydrogels), Crosslink method (including physical and chemical crosslinked hydrogels), physical properties (including smart and conventional hydrogels), Responsiveness (including chemically, biochemically, and physically responsive hydrogels), and preparation methods (including copolymer, homopolymer, and interpenetrating hydrogels). The nature of swelling, degradability, and crystal structure are other criteria for the classification of hydrogels [7–9].

The purpose of this study is to present a comprehensive review of the structure and application of natural and synthetic polymer-based hydrogels in regenerative medicine and tissue engineering. We described hydrogel properties and applied strategies to create the best environment for tissue engineering of hydrogels in bones, skin, and liver cartilage tissues and reviewed biochemical structure and method of using these materials in tissue engineering.

2. Synthetic-based polymers

2.1. Poly ethylene oxide (PEO)

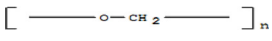
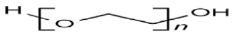
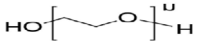
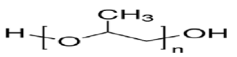
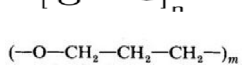
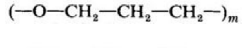
PEO ((c-C_2H_4O)) is a kind of polyether with water solubility property at room temperature. It has a wide range of polymerization degrees; for instance, polymerization degrees can range from 2 to 7 million molecular weight [10]. PEO is an abbreviation for this material, indicating oligomers and polymers of ethylene oxide [11]. Some short polymers have large factors at the end of the chemical structure. This end structure is the cause of solubility or insolubility; for example, both poly (ethylene glycols) and Methyls are water-soluble. Some water-soluble or insoluble Polyethers are listed in Table 1. The interaction of polymers with water and the amount of water in the hydrogel structure is effective on its structural integrity, degradability, and material release. Water can establish a weak/strong bond with the polymer or be present freely in the structure, which type of interaction determines the permeation, absorption, diffusion, and structural properties of the hydrogel. Environmental conditions such as pH, temperature, solvent nature, and ionic strength also affect the mode of this interaction [12,13]. PEO is a small cyclic species and poly acetaldehyde (CH_3CHO) is a non-cyclic species, both of which have a potential role in the amino acids formation [14]. Polyethylene oxide has high ionic conductivity, high salt solubility, crystallinity above 60%, and low mechanical stability. When dissolving polyethylene oxide in water, hydrophilic hydrogen bonds are formed between water molecules and oxygen atoms of polyethylene oxide, and water molecules create a sheath around this polymer, making it an ideal option for creating various hydrogels [15,16]. Poly acetaldehyde, as a polymer with low (or medium) crystallinity, has high and unlimited miscibility in water and can help to create an efficient hydrogel by forming hydrogen bonds with water molecules [17]. In general, if the length of the carbon chain in these polymers increases, it will decrease their solubility in water.

Oligomers are soluble in water, with specific hydrogen bonding between the oxygen of PEO and water. This looks like normal aquatic systems, and it is one of the suitable water structures for tissue engineering and plays a significant role in the specification of solution systems. At higher temperatures, PEO-water junctions separate from each other. Most normal aqueous systems have solubility gaps or separation phases [18].

Ethylene oxide is one of the most promising products that can be used in cells, proteins, and other biological environments. If a hydrophobic non-crystalline substance such as colloids acts with aqueous solutions containing PEO, the polymer automatically attracts a colloid-solution interface [19]. The addition of proteins to the surfaces of polymers may be a problem for colloid durability according to polymer and protein surfaces that play roles as hydrophobic colloids. It is not surprising that hydrophobic polymers that are adsorbed or chemically bound by PEO are resistant to the adsorption of proteins [20].

The combination of copolymers, which are synthesized by anionic polymerization, has been described in detail in other studies. Polycaprolactone-b-poly (ethylene oxide) copolymers are applied with poly (ethylene oxide), but different polycaprolactones

Table 1
Soluble and insoluble Polymers in water.

Polymer	Solubility (room temperature)		Formula
Poly methylene oxide	soluble	Decrease solubility at higher temperature	
Poly acetaldehyde	soluble	Decrease solubility at higher temperature	
Polyethylene oxide	soluble		
Polypropyleneoxide	insoluble		
Poly trimethylene oxide	insoluble		
Poly tetrahydrofuran	insoluble		

are blocked. These polymers are defined as pcl14-b-peo44 and pcl20-b-peo44. Polycaprolactone kernel is suitable for combining a variety of neutral and lipophilic pharmaceutical substances [21].

2.2. Polyvinyl alcohol (PVA)

PVA is the most critical hydrogel which is frequently used in pharmaceutical and biomedical applications [22]. PVA, as a synthetic polymer, was proposed in the 1930s and is the most vital hydrogel in many pharmaceutical and biomedical applications, including surgical sutures and food contact uses [23]. PVA has a simple structure with hydroxyl groups that can be cross-linked by physical methods (such as the freeze-thaw process) or chemical methods [24]. The preparation method of PVA from hydrolysis (complete or partial) of polyvinyl acetate affects its physical properties [25,26].

Different molecular weights of PVA (20,000–400,000), which are caused by the initial length of the vinyl acetate polymer and its alkaline or acid hydrolysis rate, are related to its flexibility, solubility, adhesion, melting point, viscosity, and tensile strength [27]. These materials increased interest in bio-nanoparticles to offer a suitable tool for delivering drugs, proteins, or genes by localized and targeted delivery to tissue. Bio-nanoparticles are biodegradable and colloidal polymers with typical diameters of 10–1000 nm, where a therapeutic agent is entrapped inside the polymer matrix [23].

Another application that results from crosslinked hydrogels in tissues and cells is PVA photo-activity. The cross-linkable groups, photoinitiators, and UV light can help create hydroxyl chains in PVA hydrogels at appropriate pH and temperature [28,29]. This rapid polymerization allows cells to be spread homogeneously inside hydrogels. In addition, the polymerization process of PVA hydrogels and hydroxyl groups can lead to materials with favorable mechanical and the creation of suitable sites for the biological molecules (such as peptides) attachment, and cellular attachment, differentiation, migration, or proliferation [29].

2.3. Polylactic acid (PLA)

For decades, PLA copolymers have been considerably believed in pharmaceutical, biomedical, environmental usages, and petroleum-based polymers [30]. Poly(lactic acid) has three isomeric forms: 1- photoactive and crystallizable poly(L-lactide), 2- photoactive and crystallizable poly(D-lactide), 3- photo inactive and non-crystallizable poly(DL-lactide).

PLA is a bio-degradable aliphatic and thermoplastic polyester that is reinforced in polymeric biodegradable materials and can be obtained from renewable sources like starch substances and has various applications such as food packaging, sanitary products, diapers, and automotive factories and is extensively studied in many degradable and renewable nanocomposite materials [31]. In the production of a polymer, the melt-blending process is an environment-friendly feature for producing PLA polymers as the use of solvent has been limited. Biological polymers are of interest due to their environment-friendly features because PLA is obtained from sugar fermentation, such as corn. It is considered due to its biocompatibility, biodegradability, and non-toxicity [32].

3. Natural-based polymers

3.1. Agarose

Based on its division pattern, agarose includes beta agarose and alpha agarose. The main agar structure is a complex unit-building sequence consisting of β-D-lactose and 3,6-anhydro-alpha-L-galactose [33]. Alpha-Agaroses break into alpha-1,3 bonds to produce agar-oligosaccharides of the agarose-related series, while β-agaroses break into β-1,4 bonds to make neo-agar-oligosaccharides of the agarose-related series [34,35]. Agaroses are extracted from various sources, such as ocean bacteria, marine sediments, etc., and have various applications. Hydrolyzed agars produce oligosaccharides, which have important biological and physiological properties in human health. According to scientists, agar is formed from agaropectin and agarose [36].

Agaropectin has basic disaccharide units, agarose, 3,6-anhydro-alpha-L-galactose hydroxyl groups, and sulfoxide or methoxy and pyruvate units [34]. Agarose has about 100,000 Da with a high molecular section with about 0.15% sulfate content. Agaropectin, with nearly 5%–8% sulfate, has a lower molecular weight (less than 20,000 Da) [36].

The Gracilaria agaropectin concentration is higher than that of Porphyra and Gelidium. Lugol's iodine is used to evaluate agarose activity, investigate agarose production by microorganisms, and estimate the protein band of agarose activity. This stain converts the agar polysaccharide into a dark brown color, but the color of the degraded agar oligosaccharides cannot change. Therefore, a bright zone can be seen around the colony of microorganisms that produce agarose, while other areas are dark brown [33]. Table 2 summarizes more information about Marine Bacteria Agarose specification.

3.2. Alginate

Alginate is a biomaterial with many applications in regeneration medicine and biomedical science because of its desirable properties, including biocompatibility and easy gelatin formation [37].

Table 2
Marine Bacteria Agarose specification [33].

Source	Category (α/β agarase)	Mr (kDa)	Specific activity (U/mg)	Optimal T (◦c)	Stable up to T (◦c)	Optimal PH	Product
Vibrio sp jT010	β	107	6.3	30	40	8	NA2,NA4
Alteromonas sp. C-1	β	52	234	30	30	6.5	NA4
Cytophaga sp.	β	–	–	40	–	7.2	–
Alteromonasagaralyticus	α	180	–	–	45	702	A4
Vibrosp.po -303	β	87.5	7.54	38–55	–	6.5–7.5	NA4,6,2
Thalassomonassp JAMBA33	α	85	40.7	45	40	8.5	A2,A4,A6
Agarivoranssp HZ105	β	58-54	76.8–57.45	–	25	6-9	–
Alteromonassp SY37-12	β	39.5	83.5	0.3	50	7	NA4,6,8
Pseudoalteromonasaltanctica N-1	β	33	292	–	30	7	NA4,NA6
Pseudomonas altantica	β	32	–	–	30	7	NA2
Vibrio AP-2	β	20	–	–	45	5.5	NA2

Alginate hydrogels are now widely used in drug delivery, wound healing, tissue engineering, and cell transplantation. They also have structures similar to extracellular tissue matrices and have a vital role in tissue formation [38].

Alginate, as an anionic polymer, has attracted much attention due to its low cost, biocompatibility, low toxicity, cross-linking ability, and flexibility. Scientists also used it for bioprinting, such as laser-assisted and 3D bio-printing [35], because it has a proper viscosity and gelling speed for accurate printing [37]. Alginate combines [1–4]-linked b-D-mannuronic acid and a-L-guluronic acid monomers. Alginate molecule is a copolymer composed of M units (M-blocks) and G units (G-blocks). $Ca2^{+}$ in Gblocks alginate chains creates ionic inter-chain bridges, which cause solubility, But this ionic capacity has created a weak mechanical property that requires some manipulation in the laboratory [39].

In some cases, alginate has a varied ability with some peptides like RGD peptides to create a homogeneous material for changing some specifications [37]. Numerous studies indicate that the power of adhesion ligands, which are stuck to alginate, was very helpful in tissue engineering because the modified form of alginate was like ECM molecules. Seeded cells create a good connection with this environment, and thus, alginate can support a range of cellular responses. Therefore, an alginate system was taken into account by many studies for its interactions and protein adsorption of anionic polysaccharides [37].

The alginate extracted from Laminariahyperborea, Laminaria japonica, and Macrocystispyrifera are now available in markets. It can be converted into alginic acid by filtering this extract, adding sodium or calcium chloride, and adding HCL. Water-soluble alginate can be produced after purification and transformation [37]. Fischer found that l-guluronate and d-mannuronate are major components of alginate. Alginate is known as a complex of copolymers containing [1,4]-linked- d-mannuronate (M) and -l-guluronate (G) and (G) blocks with about 60% of the whole material [38].

Although alginate is biocompatible, there are discussions about the effectiveness of alginate mixtures. Most scientists think that different levels of alginate purity have various problems. For example, alginate with high M content has been reported to be more immunostimulant than alginate with high G content, but other studies reported that the immune response could be due to alginate impurities (since alginate cannot be extracted in pure form). In some methods, it is obtained from natural sources, and impurities such as heavy metals, proteins, and other substances remain [37].

Alginate Scaffolds are often used with growth factors, and they are beneficial for cell-based therapy. Depending on where we want to do the implantation, the PH of the environment affects biodegradable alginate scaffolds' degradation, mechanical properties, and swelling behavior. Alginates have a critical role in the long period of stability. Other cases of biodegradability include the molecular weight (MW) of alginate, which influences degradation and mechanical features in alginate-based biomaterials [40]. A need for alginate-based biomaterials in critical and non-ignorable cases. In particular, alginate plays a remarkable role in regenerative medicine [41].

3.3. Hyaluronic acid (HA)

HA is a famous glycosaminoglycan composed of N-acetyl-D-glucosamine and D-glucuronic acid units [42]. In animals' extracellular matrix (ECM), N-acetyl-D-glucosamine is a disaccharide unit and the only non-sulfate glycosaminoglycan. This polymer is so polyanionic (molecular weight: 1000 and 10,000,000 kDa) with unique physicochemical characteristics and specific biological functions. By water absorption, HA provides a homeostasis feature for tissues, and it is suitable for the regulation of permeability and has a lubricant role in joints [43].

HA also binds with proteins that are in the ECM, on the surface, and in the cytosol of cells. Some substances and actions have near contact with this material, such as cell motility, growth factors, morphogenesis, embryonic expansion, and inflammation [44]. HA also has a building block role as a polymer in tissue engineering, drug delivery, and visco-supplementation for biocompatible and biodegradable applications. HA derived from biomaterials is not so fortified for stressful applications. We should bring other materials or methods together to overcome this disadvantage [35,45]. HA provides good mechanical features. Alkaline cross-linkers can form networks in hyaluronic acid and raise temperatures to the point where they do not damage the cells inside the hydrogel and the heat-sensitive molecules. Besides, we need considerable purification in production time to apply these materials in physiological systems [46].

3.4. Collagen and gelatin

They are biocompatible, biodegradable, low antigenic polymers for pharmaceutical, food, and medical industries [47]. Fish collagen and gelatin are the most favorable materials, which have been often ignored for some reasons, such as safety and religious concerns contrary to mammalians [48]. Collagen is the most abundant protein (30%) of the total body [49]. Their products are now being used as bioinks in the pharmaceutical, tissue engineering, and nutritional industries [50].

Collagen is categorized into three categories according to its solvent: salt-, pepsin-, and acid-soluble. Salt-soluble category refers to non-cross-linked collagen that is extracted from the salt solution. This extraction system is not sufficiently pure and results in low-grade collagen [51].

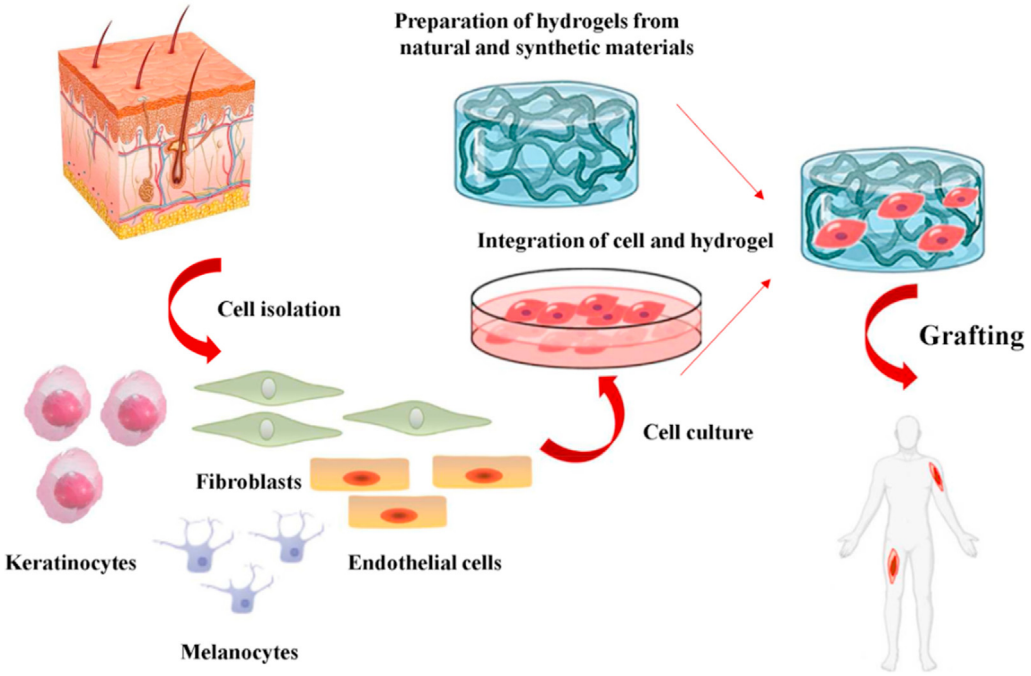


Fig. 1. Cell isolation for made bio scaffold in skin tissue engineering.

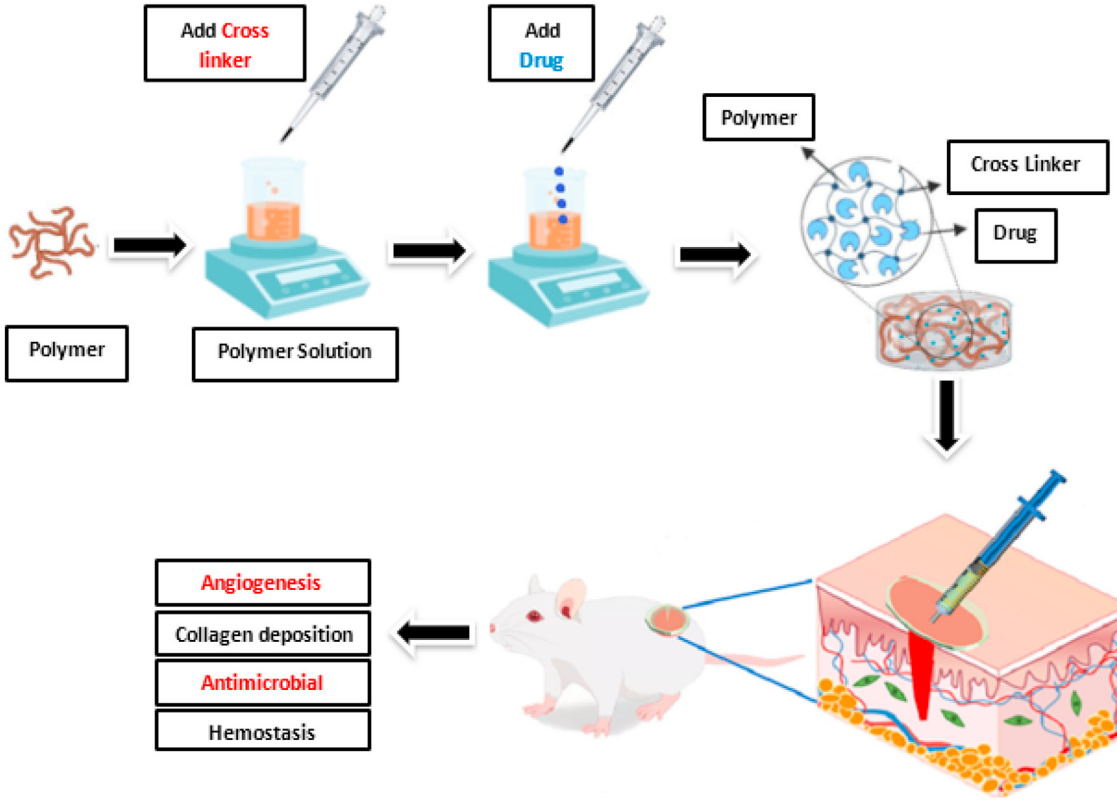


Fig. 2. Preparation of hydrogel for wound healing application.

An organic acid solution not only solves crosslinked collagens, but it could also make the inter-chain crosslink of collagens such as the aldimine crosslinks, causing more collagens solubilization in the extraction period. Moreover, proteolysis systems are limited since the extracted collagens are from different organs of animals, and all tissues have different structures with lots of different molecules that interact with internal collagens. In a study, natural nanocomposite hydrogel (such as collagen and gelatin) are

Table 3
Clinical trials evaluating hydrogel used for Skin Diseases [59–65].

Trial ID	Hydrogel	Phase	Locations	Conditions
NCT03816618	PURLOIN GEL	Early Phase 1	Saudi Arabia	Diabetic Foot
NCT03754465	Hydrogel sheet without Allogenic Mesenchymal Stem Cells	Phase 2	United States	Diabetic Foot
NCT03700580	Hydrogel dressing containing water, carboxymethyl cellulose and sodium alginate (Gel Comfeel ®)	Phase 2	Brazil	Diabetic Foot Foot Ulcer Neuropathy, Diabetic
NCT02910011	doxycycline monohydrate hydrogel (Nanodox 1%)	Phase 2	United States	Dermatitis, Atopic
NCT02718625	SoloSite®	Phase 4	United States	Pressure Ulcer
NCT02631512	Woulgan®	Phase 4	United Kingdom	Diabetic Foot Ulcers
NCT02361931	erythropoietin in a carbopol-based hydrogel	Phase 1 Phase 2	Israel	Diabetic Foot Ulcer
NCT02241811	3% Sodium pentaborate pentahydrate hydrogel	Phase 1	Turkey	Wound healing
NCT01785784	Recombinant Human Granulocyte/Macrophage Colony-stimulating Factor Hydrogel (rhGM-CSF Gel)	Phase 4	Location not provided	Deep Partial Thickness Burn
NCT01446770	Hydrogel scaffold (MF-4181)	Phase 2	Bahamas	Keloid
NCT01427569	IZN-6D4 Gel	Phase 2	Israel	Diabetic Foot Ulcer
NCT01247818	PH-10 (an aqueous hydrogel formulation of rose bengal disodium)	Phase 2	United States	Psoriasis
NCT01143727	Tegaderm Hydrogel	Phase 4	United States	Diabetic Foot Ulcers
NCT00971048	3 M Tegaderm Hydrogel ConvaTec DuoDERM Hydroactive Gel	Not Applicable	United States	Diabetic Foot Ulcers Pressure Ulcers
NCT00764361	NanoDOX™ Hydrogel (1.0% Doxycycline Monohydrate)	Phase 2	United States	Diabetic Foot Ulcer
NCT00690833	topical desonide hydrogel 0.05%	Phase 4	United States	Atopic Dermatitis
NCT03816618	purloin gel	Early Phase 1	Saudi Arabia	Diabetic Foot
NCT00941278	PH-10 (an aqueous hydrogel formulation of rose bengal disodium)	Phase 2	United States	Psoriasis
NCT00690807	PH-10 (an aqueous hydrogel formulation of rose bengal disodium)	Phase 2	United States	Atopic Dermatitis

Table 4
Clinical trials evaluating hydrogel used for Knee Osteoarthritis [74–78].

Trial ID	Hydrogel	Phase	Locations	Condition
NCT04179552	Polyacrylamide	Not Applicable	Denmark	Osteoarthritis, Knee
NCT04045431	Polyacrylamide	Not Applicable	Denmark	Osteoarthritis, Knee
NCT04061733	Hydroxyethyl Cellulose	Not Applicable	Argentina	Osteoarthritis, Knee Pain
NCT03897686	Polyacrylamide Hydrogel With Silver Ions	Not Applicable	Russian Federation	grade II-III knee osteoarthritis
NCT03067090	2.5% polyacrylamide and 97.5% water that is not pyrogenic	Not Applicable	Denmark	Osteoarthritis, Knee
NCT01372475	Hyaluronic Acid	Phase 3	United States	Knee Osteoarthritis
NCT01895959	Hyaluronic Acid	Phase 4	United States	Knee Osteoarthritis

biocompatible and biodegradable materials used to engineer myocardial tissue. It was found that collagen and gelatin nanofibers are compatible with cellular natural productions and allow the formation of some structures, such as the veins if they are used with some Compounds like growth factors and nano bio glasses [52].

The lack of effect of collagens with trivalent bonds and cross-linking on the super triple helix structure has suggested the need for enzymes such as pepsin to easily dissolve collagens [47]. Gelatin, a heterogeneous mixture of peptides, is obtained from the incomplete hydrolysis of collagen. Nowadays, many researchers have been attracted to the natural-source polymers in the medical, pharmaceutical, and food industries because natural products seem to be “safer,” and they are thus more acceptable than synthetic products. Furthermore, studies indicate that many natural compounds have excellent bioactive properties [48].

4. Hydrogel application in wound healing

The main skin structure is composed of the epidermis (the upper layer) and dermis (the lower layer). The upper thinner and protective barrier layer consists of keratinocyte-laden cells [53]. The lower thicker layer consists of fibroblast cells and a collagen network and has an essential role in the flexibility and strength of the skin. The skin tissue engineering biomaterials should copy skin structure at the bilayer. Various compositions, such as collagen sponge, silicone-chitosan film, chitosan-gelatin, gelatin/chondroitin–sulfate, and HA are used as a bilayer structure of skin tissue engineering utilization [54]. Chitosan and gelatin are known as the most favorable polymers for skin tissue engineering and rebuilding injured organs (because of biological qualities and degradability in in-vivo systems). Chitosan/gelatin combinations for skin tissue showed promising in vitro characteristics, but their in-vivo applications could not indicate any suitable ability. According to research, the presence of a membrane at the upper layer was useful to overcome the stress of applied hydrogel in scaffolds for in vivo experiments [53].

For these applications, hydrogels are made by casting method and are then lyophilized. They make some crosslinks with glutaraldehyde (GA), which is crosslinked to amine groups, for instance, between Chitosan and Gelatin used to improve mechanical strength. Chitosan/gelatin can use water molecules in its holes as a sub-layer to maintain moisture [55]. Most of the polymers mentioned above are non-immunogenic and increase cell migration, proliferation, and differentiation. However, hydrogels are widely used for their water solubility, and there is not enough strength for supporting new tissue growth. Fortunately, hydrogels have the potential to be crosslinked with other materials, including Chitosan, Sodium alginate, and PVA, so that their mechanical properties can be improved [56].

A study demonstrated that wounds coated with chitosan agarose hydrogel were sufficiently moisturized and hydrated, preventing water loss from the injury and high cell proliferation in the wound field. The exchange of some materials like nutrients, oxygen, and waste materials could be swapped easily in this environment, and their antibacterial properties were approved by no infection sign in the injured tissue [57]. In a study on hydrogel

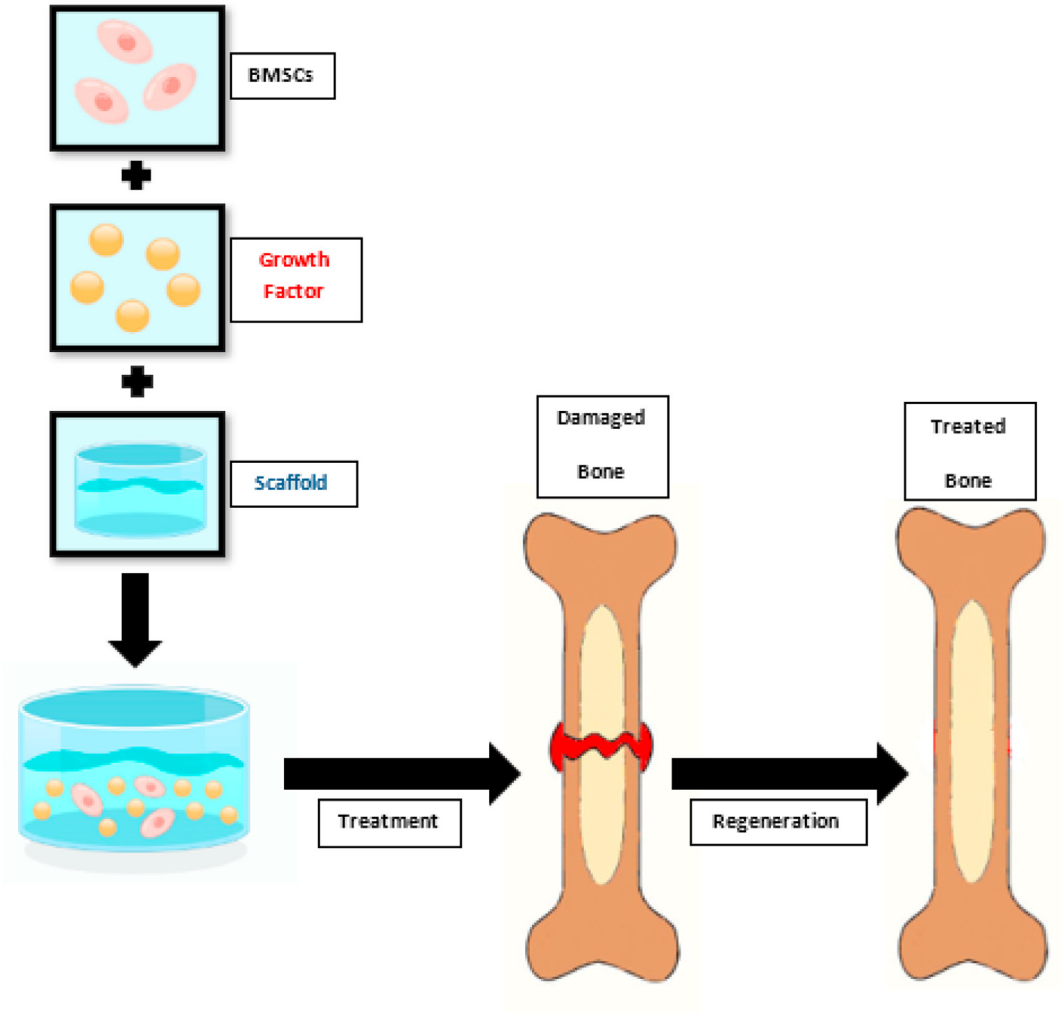


Fig. 3. Application of hydrogel for bone regeneration.

compounds with PVA, it was found that these composites can be used to improve the function of wound dressings because of their water absorption and material (nutrient, oxygen, and west) capacity which keeps the wound site adequately moisturized. The Geliperm membrane is a strong and clear combination, with more than 96% formed from water. The remaining 4% contains agar and polyacrylamide, forming a strong molecular network. The Geliperm membrane has been used for skin lesions such as acute and chronic ulcers and burns until today (Figs. 1 and 2) [58]. Table 3 lists clinical studies in this area.

5. Hydrogel application in bones regeneration

Bone is a very complicated structure that is composed of materials with collagen fibers as a matrix and nanocrystals of apatite. This structure forgives the bone's unique mechanical and biological properties [66,67]. Studies on synthetic bone materials have been conducted for decades, but autografting is a gold standard in clinical applications. Patients need surgery on healthy bone components for autografting to harvest and then transplant into body lesions. For example, the iliac crest is beneficial for transferring to the application site [68].

Other options occur when allografts (from another human) or xenografts (from animals) bones used, they are accompanied by infections transmittance, immunogenic response, pain, and disease transmittance. They are costly and need multiple surgeries. There is an immediate need for new synthetic materials for a good replacement in bone disorders [69].

Various available materials are used for bone replacement, such as metals, polymers, and ceramics. The poor degradability of metals and ceramics has led studies to use degradable polymers with controllable chemical composition and monomer units during construction. So far, most polymeric bone replacements have been prefabricated and implanted by invasive surgical methods. Still, we clinically need materials inserted inside the body by not-invasive methods like injection. In these types of methods, the material should have adequate low viscosity to be injectable and hardened after injection and also should be mixed with drugs, cells, and growth factors before administration [68] also up to now, there are lots of clinical trials for hydrogels (Table 4). Hydrogels are a class of highly hydrated polymers that meet all the above requirements and can be classified according to the preparation methods (copolymer, homopolymer, and interpenetrating hydrogels) or ionic charges (neutral, anionic, and ampholytic) or physical structure (Amorphous, semi-crystalline, and crystalline) [69].

The capacity of a bone-substituting compound can be classified according to the rate of induced bioactivity, nucleation of minerals following proliferation, and sediment of calcium phosphate crystals. Generally, most of the materials which are used as polymers do not have this capacity. Still, the addition of a ceramic phase can

produce composite bioactivity with nucleation sites to increase hydroxyapatite precipitation [68]. Biocompatibility, biodegradability, and commercial availability are among the benefits of natural hydrogels [49]. Acceleration in osteogenesis and osteoconductive properties are indicated by the combination of hydrogels and bioactive phases. Several polymers, such as collagen, chitin, gelatin, fibrin, and chitosan are attractive for tissue engineering. The basic polymer of the bone is type I collagen, which is biocompatible and can be processed in forms such as sponge, fiber, tube, and sheet. According to Zou et al., collagen is composed of the mineral calcium phosphate. The collagen fibers are networked by glutaraldehyde; Ceramic b-TCP particles are homogeneously diffused inside the collagen matrix and bond between particles of ceramic and hydrogel (Fig. 3) [69,70].

In other studies, hydrogels are based on PEG as a matrix for adding mineral HA particles described by Sarvestani et al. [71]. However, tissue engineering for the skeletal system requires the specification of a suitable osteoconductive matrix for designing the release of osteoinductive and osteoprogenitor factors, and thus, cells are differentiated from osteo-like cells. In recent studies, the osteoconductive matrix is produced by a 3D scaffold combined with degradable polymers or ceramics, but nowadays, a situ-forming scaffold may provide advantages [72]. Hydrogels mimic the body's natural texture and are specially designed to have an attribute that is critical to the recovery process and can be used as composites to increase the strength of bone tissue engineering and other tissues [73].

6. Hydrogel application in joint therapy

Articular cartilage friction and wear are too high in the synovial joints. Due to the growing amount of osteoarthritis in recent years, 90% of the cartilages of people over the age of 70 have been affected worldwide. Many artificial joints have been fabricated, and the surgery required to replace them has many complications, intense contact in the joint can cause these complications and wear to worsen [79]. Hydrogels, such as methyl methacrylate, polymethacrylate, and PVA are very helpful in these cases [80].

PVA hydrogel is also applied as a rubber-like gel and has a 3D network structure with extensive biocompatibility. PVA hydrogel has microstructure and mechanical behavior and great effects on artificial cartilage [81]. The natural cartilage is biphasic and composed of a solid matrix and an interstitial fluid part responsible for the lubrication of the joint [82].

Hydrogels have this property like the natural joint lubricant, and that is the best advantage of these materials to substitute cartilage disorders [83]. There are now a lot of studies on PVA properties and applications that investigate articular cartilage exclusively for tissue engineering. Bray and Merrill constructed synthetic cartilage; the materials were based on PVA to replace the synovial joint. There are numerous studies on the morphological and mechanical properties of PVA scaffolds for cartilage disorders. Polyvinylpyrrolidone/PVA-mixture hydrogels are studied to evaluate sliding speed, contact load, and lubrication fluid. It is found that this material increased the lubricant durability of the prosthesis and decreased erosion [82]. Studies indicated that the application of hydrogels is beneficial for erosion characteristics of these materials as artificial cartilage. The application of hydrogels for mimicking the in vivo conditions is essential for synthetic articular cartilage [83]. One of the new treatments (GelStix Hydrogel implant), considered as cartilage and bone, is the replacement of the hydrogel implant in the center of the disc. The advantage of this hydrogel is fast water absorbance, As much as three times its initial structure. The resulting mixture is highly

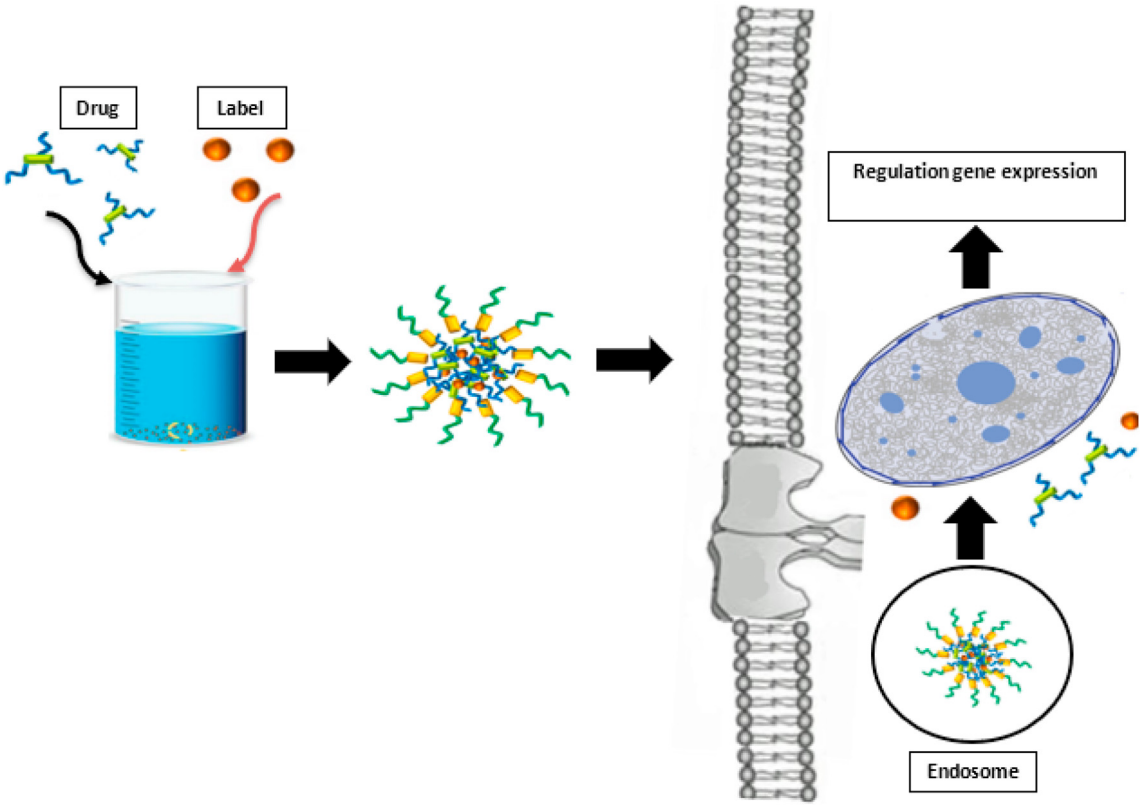


Fig. 4. Application of hydrogel in drug delivery.

resistant, minimizing the trauma loading and acting as normal disc loading. On the other hand, the hydrogel reduces the acidity of the disk and metabolically doesn't hurt the present cells; it is currently in Phase III clinical trials (NCT02763956) [84].

7. Hydrogel application in liver

Hepatocytes for liver tissue engineering are important as implantable structures. It can be used as an artificial liver for patients with liver disorders for in vitro models of drug metabolism and the manufacture of bioartificial liver (BAL) devices. In addition, hepatocyte-based therapies have great potential to restore hepatic functions to create an alternative to transplantation [85]. Micro-organoids of hydrogel microfibers that are so close and similar in in-vivo construction of cords of the liver are among these approaches. Unfortunately, because the liver cells are anchorage-dependent, preserving them under in vitro conditions is difficult. Various techniques such as spheroid culture, patterned co-culture, cell sheet stacking, multilayer cell deposition, and collagen layer sandwich culture have been suggested to maintain hepatic functions outside the body and cultivate hepatocytes. However, this method is applied to biodegradable and biocompatible forms like hydrogels, as described above [86].

8. Hydrogel application in drug delivery

Drug delivery is an important debate in tissue engineering since this system provides different sources like growth factors and drugs for cells in the growth period. When a drug is systemically used, the availability of the drug in the target portion will be very low, and the drug concentration quickly drops in blood plasma leading to a need for re-administration of the specified period. The application of drug delivery systems decreases patient complaints and also decreases the volume of consumable drugs, especially toxic ones [87]. Numerous synthetic and natural polymers are studied as drug carriers [88]. Researchers worked on the modification of these material properties for drug delivery systems (DDS)), particularly their permeability, surface function, environmental response, and biodegradability to produce “intelligent” DDS. Hydrogels are often used as DDS, with some specifications for intelligent drug delivery. These polymer networks trap lots of water without dissolving. There are lots of reviews of synthetic hydrophilic polymers such as hydrogel, which is utilized as DDS, but lots of them are not biodegradable, like poly-isopropyl acrylamide poly2-hydroxyethyl methacrylate [89,90].

Hydrogels have a lot of characteristics as drug delivery devices. Most applied polymers in hydrogel DDS include PAA, PHEMA, PEG, and PVA, which have muco-adhesive and bio-adhesive characteristics that increase permeability to tissue and drug residence time models. The main component of a hydrogel has several parameters containing 1) the water absorbed amount of hydrogel and 2) method of polymer chain binding within the gel network. Amounts of water absorption in hydrophilic polymers are different and depend on the density of inside hydrophilic groups. PEG, PVA, PHEMA, PAA, and PMA are widely used polymers [91].

The amount of inflammation in hydrogel determines molecular weight, charges on the polymer, and the density of crosslinking [91]. Localized release of treatment by DDS is possible because drugs can be systemically delivered to the desired location. Locating a DDS to diseased tissue-releasing drugs leads to the high performance of the drug in the site of action with low complications in other parts of the body [89,92]. The porous hydrogel networks let drugs load inside the DDS to be rapidly disembogued from hydrogels. For control drug release, the drug covalently bonds to the hydrogel matrix so that drug release is controllable by a chemical and enzymatic decomposition method (Fig. 4) [93].

9. Conclusion

Hydrogels have several applications in tissue engineering and new cell-based therapies. Nowadays, hydrogels are widely used in new techniques such as bio-printing. It is critical to be well familiar with these materials—lots of studies used and reported hydrogels. Scientists can design numerous disease models, such as cancer and brain disease. Hydrogels have significant applications in drug delivery. Future studies will further apply these materials in cell-based medicine.

Author contribution

Leila Rezakhani: Investigation, Writing-original draft, Maliheh Gharibshahian: Investigation, Writing-original draft, Majid Salehi: Investigation, Methodology, Sephr Zamani: Writing-original draft, Zahra Abpeikar: Investigation, Methodology, Omid Ghaderzadeh: Conceptualization, Writing-review & editing, Alireza Masoudi: Conceptualization, Validation, Morteza Alizadeh: Conceptualization, Supervision, Project administration.

Declaration of competing interest

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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