

Hydrogel for the Treatment of Osteoarthritis

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Abstract. Worldwide, the prevalence of osteoarthritis has grown significantly in recent years, and the rate of growth is accelerating. In recent years, the number of people with osteoarthritis has increased rapidly worldwide, and the rate of increase is on the rise. The development of osteoarthritis at an advanced stage can cause significant physical and psychological damage to patients. This article will introduce the application of natural and synthetic hydrogels in the field of osteoarthritis treatment. Natural hydrogels such as gelatin, alginate and polysaccharide have good biocompatibility and biodegradability and can be used for intra-articular drug delivery after modification. Synthetic hydrogels such as polyvinyl alcohol, polyethylene glycol and poly (lactic acid-hydroxyacetic acid) copolymer have good mechanical properties and can be used for intra-articular drug delivery and joint lubricants. In this article describes the application of hydrogels to carry a range of drugs and cell growth factors for the treatment of osteoarthritis, to act as scaffolds for cell growth, to lubricate joint cavities, and to reduce loads on joints, as well as several hydrogel modification methods to give them better biological or mechanical properties.

Keywords: Osteoarthritis; natural hydrogel; synthetic hydrogel.

1. Introduction

As the global population ages and obesity increases, the number of people suffering from osteoarthritis (OA) has exceeded 250 million and the rate of increase is on the rise. Osteoarthritis is a total joint disease, and its pathogenesis is thought to be a vicious cycle of cartilage degradation, release of cytokines that promote degradation, and more cartilage degradation due to a combination of inflammation and obesity [1]. One of the most common causes of disability, OA not only leaves patients in excruciating physical and psychological agony but also significantly drains the nation's health care budget. The more commonplace treatments for OA include medication, surgery, and other procedures. However, there is no full cure for the condition. Highly cross-linked three-dimensional structures of biocompatible and hydrophilic materials called hydrogels can be used as effective biomaterials for drug delivery systems because they expand when water is ingested. OA is one of the leading causes of disability, which not only causes great psychological and physical pain to patients, but also greatly consumes national health care funds. There is no complete cure for OA, and the more mainstream treatments include medication, surgery and other treatments. Hydrogels are highly cross-linked three-dimensional networks of biocompatible and hydrophilic polymers that swell when water is absorbed and can be used as good biomaterials for drug delivery systems. Because of its close resemblance to extracellular matrix and its 3D network structure, it is able to encapsulate drugs and cells well, which makes it a great potential for application in the field of biomedical scaffold materials. In the field of bone and joint therapy, hydrogel can be used for intra-articular drug delivery due to its drug encapsulation ability, provide an environment for chondrocyte growth due to its three-dimensional structure, and can be used as a lubricant to replace joint weight bearing and relieve friction at the joint due to its high water content and viscoelasticity. According to the source, there are two types of hydrogels: natural hydrogels and synthetic hydrogels. Each type has advantages and disadvantages of its own, and both can be improved through a variety of synthetic design techniques and cross-linking modification to enhance their properties and make them more useful in practice. This essay will go into detail about how these two kinds of hydrogels are used to treat OA.

2. Natural Hydrogels

Natural hydrogels include collagen, silk proteins, hyaluronic acid, chitosan, and alginate and decellularized tissue-derived hydrogels. Natural hydrogels have good biocompatibility, less rejection and inflammatory reactions *in vivo*, and are more biodegradable. However, due to their weak mechanical properties, they need to be cross-linked and modified to optimize their properties.

2.1. Gelatin

Gelatin hydrogels have been shown to have a good biosafety profile in human studies and are modifiable, allowing topical administration. Rapamycin slows the progression of OA through autophagy, Tokio Matsuzaki et al. prepared Ellets of rapamycin-micelle conjugated gelatin hydrogels by using a ring-opening polymerization method. Gelatin hydrogels resulted in a slow release of rapamycin, with approximately 50% of rapamycin released within 24 hours. In experimental mice, OA progression was delayed with and prolonged growth of autophagic markers in mice. However, they did not achieve optimal initial release rates and the hydrogels were not tested in humans [2]. In addition to carrying drugs, gelatin hydrogel scaffolds (GelMA-AG) can be chemically altered with alanyl glutamine (AG), and the resulting GelMA-AG can be catalyzed by proteases *in vivo* to break down glutamine, which promotes chondrocyte metabolism. It was shown that GelMA-AG can fill cartilage irregularities adaptively and has good biocompatibility, and can promote cartilage repair in rabbits [3]. Mesenchymal stem cells (MSCs) have the capacity to control inflammatory reactions, and nanovesicles (NVs), which are similar in composition and size to exosomes, can load twice as much RNA and protein compared to exosomes and promote cartilage formation. GelMA- NVs have a homogeneous porous mesh structure that facilitates the release of drugs. It can extend the drug release time up to 30 d and release close to 100%. Also, it has good biocompatibility, which can increase the cell survival rate to more than 80% and has a slow degradation rate, with only 10%-15% showing degradation in 30d *in vitro*. Compared with gelatin hydrogels, GelMA- NVs has stronger mechanical properties, and the compressive strength of GelMA- NVs rises to 16.779 kPa under 25% cyclic compression, and it has some stability for cyclic compression [4].

2.2. Alginate

A substance called alginate is extracted from brown algae. A linear block copolymer of l-galuronic acid (G) and d-mannuronic acid is called alginate, and the amount of both affects the physical properties of alginate. It has with good biocompatibility, mechanical properties and antibacterial properties. Kleuskens M W A et al. inserted chondrocytes from osteoarthritic (OA) and non-degenerative (ND) human chondrocytes into cartilage organs containing type II collagen and proteoglycan, which were then coated with viscoelastic alginate hydrogels. The alginate solution and the cross-linking agent were reacted at room temperature and a 4.9 ± 0.6 -fold, 32.6 ± 11.5 -fold, and 12.0 ± 4.0 -fold increase in relative stiffness was observed after 28 days for the three groups of hydrogels, respectively. *In vivo* experiments showed that this method promoted the expansion of chondrocytes while preserving their cartilage phenotype [5]. To further enhance the adhesion of hydrogels to cartilage, Zhang F X et al. cross-linked alginate with other substances. Due to the existence of an abundance of hydrogen bonds in the system, the hydrogels prepared by the cross-linked network of chondroitin sulfate, alginate-dopamine and regenerated filamentin (AD/CS/RSF) demonstrated strong adhesion to moist cartilage surfaces, and the AD/CS/RSF hydrogel bond strength reached 121.7 ± 12.3 kPa at 26°C 50% humidity, with a relatively stable storage modulus in the frequency range of 0.1-100 rad/ s frequency range with a more stable storage modulus. Besides its degradation rate was controlled. In the *in vitro* test, the AD/CS/RSF hydrogel still had only a 40% decrease in mass after 20 days [6].

2.3. Polysaccharide

Polysaccharides are formed by the dehydration condensation of monosaccharides and are widely found in nature, such as in the cell walls of plants and animals, heparin in humans, and in the skeletons of plants and animals. Hyaluronic acid is a natural polyanionic mucopolysaccharide that is widely found in dermal tissue and synovial fluid and has good biocompatibility and anti-inflammatory properties. To improve the disadvantages of hyaluronic acid, which is easily degraded in the joint cavity, Monteiro do Nascimento M H M et al. blended it with poloxamers (PL) to change the supramolecular structure of the hydrogel, and the mechanical properties, bioadhesion and water permeability of the resulting gel were improved. In in vivo experiments, the release efficiency of the hydrogel drug was between 76% ~ 92%, and it could avoid the pain caused by repeated injections and delay the static exhibition of OA [7]. Chondroitin sulfate is an acidic mucopolysaccharide widely found in cartilage tissues such as the laryngeal bone, nasal mid-bone, and trachea. Chondroitin sulfate hydrogel consists of good bioactivity, biocompatibility and biodegradability. He Y et al. covalently modified Chondroitin sulfate with photocrosslinkable methacryloyl groups (ChsMA) to give the hydrogel a dual antioxidant function. To avoid the risk of infection associated with repeated injections, the hydrogel was made into microspheres that could be stored in the joint cavity for a longer period of time using electrospraying. The microspheres were uniform in size and contained enough micropores to accommodate liposomes [8].

3. Synthetic Hydrogels

Natural hydrogels have the disadvantage of being mechanically weak and easily degradable in vivo when used. Therefore, synthetic hydrogels, which have stronger mechanical properties and are less likely to be broken down by proteases, can be tried as a drug-carrying platform for the treatment of OA. Synthetic hydrogels can be more easily reactive modified than natural hydrogels to obtain target properties.

3.1. Polyethylene Glycol (PEG)

During joint movements, the joints are repeatedly stressed, which will accelerate the progression of OA. The four-arm maleimide-functionalized polyethylene glycol (PEG-4MAL) hydrogel has good mechanical properties and can withstand repetitive loading to cushion the loads placed on the joint. After 10,000 cycles of experiments at a frequency of 1 Hz, Holyoak D T et al. found that all PEG-4MAL weight percentages were able to perform without depletion of shear storage and loss of modulus. Although the value of load that the hydrogel can withstand increases as the weight percentage of PEG-4MAL increases, the degree of swelling also increases accordingly, so a suitable compromise value needs to be found. In natural hydrogels, the drug can be encapsulated in the hydrogel by chemical bonding with the hydrogel phase. In PEG-4MAL hydrogels, on the other hand, physical interaction is required to encapsulate the drug. Therefore, it releases the drug under the combined action of load and protease depending on the concentration of protease [9]. To give it the ability to carry small molecules of drugs, Mancipe Castro L M et al. functionalized it with peptides. Nanocomposite PEG-4MAL microgels containing poly(lactic-co-glycolic acid) (PLGA) NPs were prepared using microfluidic polymerization, and the average particle size of the gel particles could be controlled between 50.4 and 51.4 μm with a coefficient of variation of less than 6.5%. It is possible to transfer the task of controlling the release rate of small molecules such as rhodamine B from the hydrogel itself to the PLGA NPs inside the gel. Therefore, its mechanical properties and drug transport properties can be considered separately when designing the hydrogel. The hydrogel can be maintained in the body for more than three weeks with continuous drug delivery [10]. Hydrogels containing polyethylene glycol have excellent mechanical properties and can rely on functionalization reactions to enhance their specific binding and sustained drug delivery.

3.2. Polyvinyl Alcohol (PVA)

As one of the oldest hydrogels, polyvinyl alcohol hydrogels can be produced by ammonolysis, hydrolysis and alcoholysis of polyvinyl acetate. Due to its advantages of good stability, low toxicity, high water absorption capacity and easy processing and modification, it has been widely used in biomedical applications such as wound dressings, drug delivery and artificial organs. Although PVA hydrogel has good transparency and high water content, its intermolecular chain interaction is weak, the mechanical properties are weak and difficult to use in practice. Therefore, different physical or chemical cross-linking methods can be used to improve its mechanical properties. Ye Z et al. added the cross-linking agent polyethylene glycol and plasticizer glycerol to the PVA hydrogel by mixing physical cross-linking method to synthesize PVA/PEG-glycerol composite hydrogel. Because polyethylene glycol and glycerol were flexible and rich in hydrogen bonding, the composite hydrogel had good hydrophilic and moisturizing properties, preventing water evaporation and lubricating the joint cavity. Besides the interaction of intra-molecular hydrogen bonding made it have certain self-healing ability. In terms of mechanical properties, experiments showed that when glycerol was added at 20 wt%, the elongation at break of the gel can be increased by 270% and the tensile strength can be increased to 26.6 MPa, which had a mechanical strength comparable to that of natural cartilage. Therefore, PVA/PEG-glycerol composite hydrogel can be used as a substitute for natural cartilage to slow down the process of OA [11]. In addition to cross-linking with glycerol and PEG, Chen Q et al. physically blended polyvinyl alcohol hydrogels with hyaluronic acid grafted-poly-2-acrylamido-2-methylpropanesulfonic acid sodium salt (HA/PA) and hyaluronic acid grafted-poly-2-methacryloyloxyethyl phosphorylcholine (HA/PM). Due to the hydrogen-rich bonds within HA/PA and HA/PM (HPX), the composite hydrogel contained high hydrophilicity and could maintain a low swelling rate and long water retention time at water contents up to 80.0% - 84.2%. After adding HA/PA and HA/PM, the surface roughness of the hydrogel did not change. However, due to the coexistence of boundary lubrication and liquid film lubrication and the ability to form a stable hydrated lubrication layer, the coefficient of friction μ of A5M1 hydrogel was reduced by 32% relative to that of unblended PVA hydrogel during the mechanical property test. Meanwhile, after adding HA/PA and HA/PM, the compressive modulus of hydrogel could reach 300-800 kpa, which was comparable with that of natural cartilage, but its creep deformation and transient deformation would decrease with the increase of HA/PA and HA/PM concentration, and it will deviate from the creep deformation and transient deformation performance of natural cartilage [12]. HPX/PV A hydrogels with good frictional properties and biocompatibility are promising for replacing damaged cartilage. PVA hydrogels have been used in several clinical trials and have shown some potential in the treatment of OA.

3.3. Poly (Lactic-co-Glycolic Acid) (PLGA)

PLGA is created when lactic acid and hydroxyacetic acid are randomly copolymerized, which has excellent properties of degradability, low toxicity and capsule formation, and has been widely used in the field of medical engineering materials. Silymarin (SM) has excellent antioxidant properties, but its bioavailability is low due to its instability in vivo, easy metabolism and poor water solubility. Rezaee-Tazangi F et al. created SM-loaded PLGA nanoparticles with an average dimension of 81.4 nm using solution evaporation to improve their therapeutic impact. The delayed release of SM encapsulated by PLGA hydrogel was enhanced and the delayed release time could last for more than 24 h. The SM-loaded PLGA nanoparticles could effectively delay the oxidative stress response in the joint cavity and slow down the disease progression [13]. To prevent healthy chondrocytes from apoptosis, hyperactivated platelet lysate (sPL) encourages autophagy in injured chondrocytes and boosts the production of anti-inflammatory markers, but it is readily inactivated. Li J et al. found PLGA/chitosan/gelatin hydrogel microspheres encapsulated sPL well, allowing for rapid release for the first 72 hours to reduce patient pain and slow sustained release after 72 hours to promote cartilage repair. The liquid-phase-separated, sPL-loaded PLGA/chitosan/gelatin microspheres had a uniform dimension and shape. Which, in addition to releasing the drug in a controlled manner, also acted as a

film-forming lubricant to reduce friction on the damaged cartilage surface. In in vivo experiments, postoperative scores were improved in the experimental group injected with sPL-loaded PLGA/chitosan/gelatin microspheres compared to the control group, and a decrease in cartilage loss and superficial delamination and an increase in filling of deep cartilage were observed [14]. The sPL-loaded PLGA/chitosan/gelatin microspheres have great potential in the treatment of OA. IL-36 α , IL-36 β and IL-36 γ are pro-inflammatory agonists that exert pro-inflammatory effects in vivo by triggering IL-36R signaling and attaching to the receptor IL-36 (IL-36R). Inflammation can be managed by using IL-36 receptor blocker (IL-36Ra), but IL-36Ra is rapidly metabolized in vivo, so its release rate needs to be controlled using hydrogels. PLGA hydrogels are hydrophobic with low polar group content, Yi Y et al. enhanced hydrophilic properties by forming PLGA-PEG-PLGA triblock copolymers by copolymerization with PEG, which was highly hydrophilic. Compared with PLGA hydrogel, it had stronger compounding properties, water absorption and degradability, and had certain thermal sensitivity, which can be injected into the body in liquid form and cured into gel to reduce the trauma. IL-36Ra@Gel had a large number of laminar pores, and the pores can be tubular or microporous, which can encapsulate a large amount of drug. The enclosed amount of medication was independent of the release rate and the hydrogel performed best at a dosage level of 1 mg/ml. The IL-36Ra@Gel system released about 25 wt% of the drug centrally in the first 12 h, and the rest of the drug was released continuously over a week's time, with only 20 wt% of the drug remaining after ten days. The adhesion rate of IL-36Ra@Gel was also not affected by the drug concentration, and the X collagen and aggrecan expression was also higher than that of the blank control [15]. Thermal hydrogel loaded with IL-36Ra slows the development of OA by slowing the rate of cartilage matrix interpretation.

4. Conclusion

This article describes two types of hydrogels used in the treatment of OA: natural hydrogels and synthetic hydrogels. The sources, modifications and applications of natural hydrogels such as gelatin hydrogels, alginate hydrogels and polysaccharide hydrogels with good biocompatibility are described in detail. Synthetic hydrogels such as PVA, PEG and PLGA are also introduced in terms of their synthesis, mechanical properties and applications. In the future, natural hydrogels will be modified to have better mechanical properties to adapt to the loads applied in the joint cavity, and synthetic hydrogels will be blended to enhance biocompatibility and reduce inflammatory and rejection reactions after implantation.

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