The Research Progress of Self-healing Polymer Hydrogels in Biomedicine

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Abstract: Self-healing hydrogels are widely used in medical fields because of their excellent properties such as self-repairing properties of damage and fatigue, and good biocompatibility. In this review, the repair mechanism of self-repairing hydrogels is introduced from two aspects: dynamic reversible covalent bonds and non-covalent interactions, at the same time, the research progress of self-repairing natural polymer hydrogels with collagen, cellulose, chitosan and hyaluronic acid, as well as self-repairing hydrogels with temperature, pH and photosensitive self-healing hydrogels are introduced.

1. Introduction

Hydrogel is a semi-solid artificial gel-like material that is composed of hydrophilic polymer chains and can absorb a large amount of water. Self-healing hydrogel is a new hydrogel that can automatically restore its integrity and function after damage. So far, researchers have synthesized a variety of self-healing hydrogels through physical or dynamic chemical bonding. This paper introduces the self-healing natural polymer hydrogels, including cellulose self-healing hydrogels, chitosan self-healing hydrogels, and hyaluronic acid self-healing hydrogels. In addition, stimulus-responsive self-healing hydrogel is also mentioned in this paper. The properties of temperature-sensitive self-healing hydrogels, Ph-sensitive self-healing hydrogels, and photosensitive self-healing hydrogels are analyzed.

2. The Mechanism of Hydrogel Self-healing

2.1 Dynamic Convertible Covalent Bonds

Dynamic covalent bonds possess excellent stability properties of traditional covalent bonds but also have the feature of autonomy to join after breakage, which plays an important role in the self-healing of hydrogels. Schiff bases, borate ester bonds, disulfide bonds, and DA reaction covalent bonds are typical dynamic covalent bonds, and self-healing hydrogels based on these bonds have been well developed, which greatly prolong the service life of hydrogel-based flexible materials. [1] However, the stability of dynamic covalent bonds also has the disadvantage of requiring a high self-healing environment.

2.1.1 Acylhydrazone bond reaction type

Amine bond is a type of bond formed by the reversible condensation reaction between primary amine and reactive carbonyl group, commonly known as Schiff base bond, which is a type of bond that can be dynamically reversibly broken and reorganized. The self-healing behavior is achieved by the dynamic Schiff base bond (-CH =N-) formed between the amino group of polyethyleneimine (PEI) and the aldehyde group of dibenzyl aldehyde-functionalized polyethylene glycol (PEG). In the dynamic reaction with N-carboxyethyl chitosan (CEC), acid dihydrazide (ADH), and oxidized sodium alginate (OSA), dynamic imine and acyl hydrazone bonds exist [2]. Then it needs to be analyzed for pH responsiveness because the change in pH leads to a change in the rate of the forward and reverse reactions, resulting in the breakage and formation of acylhydrazone bonds. At $pH > 4$, the hydrogel will start to self-repair.

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2.1.2 Boronic acid ester reactive type

Borate ester bonds are also widely used in the preparation of self-healing hydrogels as dynamic reversible covalent bonds that can respond to a variety of stimuli. Usually, borate ester bonds are formed by complexing polyvinyl alcohol (PVA) or catechol polymers containing diols with polymers containing phenylboronic acids based on diol-boronic acid esters or catechol-boronic acid esters. The hydroxyl group on the PVA chain in the hydrogel forms a dynamically reconstituted borate ester bond with the phenylboronic acid group of the modified sodium alginate, which allows the hydrogel to self-heal rapidly within seconds; the glycerol adds cold resistance; and NaCl and other inorganic salts have good electrical conductivity, which gives the hydrogel good skin-like properties.[3]

2.1.3 Disulfide bonding reaction type

Disulfide bonds are dynamically reversible covalent bonds that are commonly found in living organisms and play an important role in maintaining the tertiary structure of proteins and intracellular redox potential. Disulfide bonds are widely used in the preparation of self-healing hydrogels because of their rapid transition to thiols, which can be influenced by the external environment such as pH value and redox agents. In an alkaline environment at room temperature, the hydrogel achieves self-healing by disulfide-thiol transition reaction without external stimulation. Alternatively, disulfide-bonded hydrogels can be bonded separately by PEG molecules containing disulfide bonds to two polyamino acid cores using amide bonds. The hydrogel self-heals by reversibly activating or terminating the "sulfhydryl-disulfide bond" exchange reaction under physiological pH conditions [4].

2.1.4 Diels-Alder (DA) reaction type

The Diels-Alder (DA) reaction is used to prepare self-healing hydrogels from dextran modified by enriched alkene and polyvinyl alcohol modified by dichloroacetic acid. It prepares self-healing hydrogels by temperature regulation to achieve dynamic regulation, which has the advantages of high selectivity and no side reactions and is considered to be the most ideal covalent bonding in cross-linked hydrogels.[5]

2.2 Physical Non-covalent Bonds

2.2.1 Ionic bonding type

The ionic bonding type mainly uses the interaction of ionic bonds of metal ions to form cross-linked points, which then expand to facets and finally form multiple cross-linked structures for self-healing. The ion-to-ion interactions are usually coordination interactions caused by transition metal ions with empty orbitals and groups containing lone pairs of electrons. Because the ionic bonding type has a wide selection range, fast response, and can be tuned, it will be applied to the synthesis of many self-healing hydrogels.

2.2.2 Hydrogen bonding type of interaction

Hydrogen bonds are formed when hydrogen atoms interact directly with highly electronegative atoms. It can change reversibly with changes in environment, temperature, and pH. The hydrogel effect causes the temperature to rise and the molecules to move violently, breaking the hydrogen bond; when the temperature decreases, the hydrogen bond is formed, and the hydrogen bonding force pulls the separated molecules back and achieves self-healing.[6]

2.2.3 Hydrophobic interaction type

Hydrophobic interaction is the aggregation of hydrophobic polymer chain segments with each other in aqueous solution to form dynamic cross-linking sites [7]. It is the reversible decomposition of the hydrophobic association micro-region that gives the hydrogel the ability to heal itself. The mechanism of self-healing of hydrophobic associative hydrogels lies in the reconfiguration of hydrophobic microregions. The adjustment of the chemical structure, the location, or the content of the hydrophobic monomers can adjust the strength of the hydrophobic interactions, which will change the properties of the hydrogel.[8]

3. The Self-healing Natural Polymer Hydrogels

3.1 Cellulose Self-healing Hydrogels

Cellulose is a large polysaccharide composed of glucose, the main component of plant cell walls, colorless and odorless, insoluble in water, and most organic solvents. Cellulose is the most abundant natural polymer in the earth's reserves and has the properties of biodegradability, regeneration, and recycling. Cellulose contains a large number of hydroxyl groups, and after a series of chemical or physical modifications, cellulose can be given special properties to make functional polymer materials. The self-healing gel can recover its structure and function after being damaged by external forces. Preparation methods of cellulose hydrogel have physical cross-linking, chemical cross-linking, and interpenetrating polymer network method (IPN).[9]

3.2 Chitosan Self-healing Hydrogels

Chitosan is a natural polymer compound that is non-toxic, and biocompatible, with good film-forming, gelling, and antibacterial properties. Chitosan is the only alkaline polysaccharide in nature. It contains a large number of amino groups in its molecular chain, which can be easily condensed with aldehydes and form amine bond cross-linking sites rapidly to facilitate the construction of chitosan hydrogels. Based on the dynamic equilibrium of imine bonding, chitosan hydrogels cross-linked by several aldehydes exhibit good self-healing properties.[10]

3.3 Hyaluronic Acid Self-Healing Hydrogels

Hyaluronic acid gel, a straight-chain polymeric polysaccharide composed of disaccharide units, is a naturally occurring substance in tissues. Hyaluronic acid gel is a polysaccharide composed of disaccharides, etoglucids, and glucuronic acid, with an average molecular weight between 105 and 107 Dalton. The hyaluronic acid gel can be considered as the skin's moisturizing factor, with the ability to absorb 500-1000 times its volume, compared to collagen molecules that can only carry 30 times the water, making it the most powerful moisturizing substance in the literature today. In addition to its ability to expand in volume after moisturization, its biostability, non-transferability, and non-water resistance make hyaluronic acid gel an excellent choice as a tissue filler. The hyaluronic acid gel in nature is metabolized rapidly, so to be used as an inter-tissue filler, it must be made into a polymer, and the bonding between the molecules in this way not only provides biological durability but also reinforces the viscosity and non-water resistance of hyaluronic acid gel. [11]

There are three methods of hyaluronic acid gel extraction: animal tissue (the main raw materials are cockle and bull's eye vitreous, etc.), microbial fermentation (Glucose was used as the carbon source for the fermentation broth.), and chemical synthesis (Using a natural enzyme polymerization reaction).

4. Stimulus-responsive Self-healing Hydrogel

4.1 Temperaturesensitive Self-healing Hydrogels

Temperature-sensitive hydrogels differ from other hydrogels in that they can undergo reversible sol-gel transition following temperature changes. When the temperature decreases, it becomes a sol-gel state, and when the temperature is higher, it becomes a hydrogel. This property facilitates cell manipulation in experimental operations, such as the easy addition of medium to a cold temperature-sensitive hydrogel, and the ability to collect cells by centrifugation by cooling the culture flask. In the gel state, its high lipophilicity provides a very effective growth environment for cell proliferation, cell signaling, gas mass exchange, and cell and tissue defense against shear forces. Temperature-sensitive hydrogels are a class of hydrogels that have a sudden change in water absorption at a certain temperature, and the temperature at which the sudden change in the swelling ratio occurs is the sensitive temperature. Because of its large temperature sensitivity, large swelling ratio, and sensitive temperature close to people, this makes it has a wide range of applications in material separation, immobilized enzymes, immunoassay, drug release, and other aspects[12].

4.2 Ph Sensitive Self-healing Hydrogels

Since human organs and tissues naturally have different pH values, the preparation of pH-sensitive hydrogels has been a hot topic of research. pH-responsive hydrogels are a class of polymer gels formed by changes in the volume of hydrogels under the effect of changes in pH and ionic strength. When the pH of the external environment changes, the acid and base groups within the gel will dissociate to a certain extent, causing the ion concentration inside and outside to change, breaking the hydrogen bonds within the gel and the cross-linking points of the gel network, which in turn causes changes in the gel network structure and solubility. This is the fundamental nature of pH-sensitive hydrogels to regulate the diffusion and release rate of drugs within the gel.[13]

4.3 Photosensitive Self-healing Hydrogels

Types of light reactions include cleavage, addition, exchange, and isomerization. The interaction of light with photosensitive hydrogels can lead to different responses, gelation or degradation of the hydrogel, contraction or expansion of the network, all of which can directly affect the properties of the material. The photo responsiveness of hydrogels is usually due to the functional groups introduced in the system, and the correct selection of the type and position of the photosensitive groups is required to achieve the desired response. Among several types of known photo-responsive molecules, many have been used for the synthesis of photo-responsive hydrogels. Reversible and irreversible photo-responsive processes can be distinguished according to the molecular mechanism, and the swelling rate of photosensitive hydrogels depends mainly on the hydrophilicity of the network and the crosslink density, both of which can be controlled by light. A similar effect can be achieved by light-induced cleavage of the polymer backbone or crosslinking sites. Most cleavage-type reactions are irreversible, but cycloaddition reactions, reversibly and repeatedly, modulate the crosslink density in the network. Functional groups are critical to the chemical, physical, and biological properties of hydrogels. Light provides the most precise spatial and temporal control of the expression of functional groups in photosensitive hydrogel networks. This can be achieved through the introduction of functional groups by photochemical addition reactions, the release of photocages, and the activation of functional groups by photoisomerization processes. Conversely, photochemical cleavage reactions or photoaddition reactions deactivate the functional groups functionally.[14]

5. Conclusion

Hydrogel plays an indispensable role in our lives and brings great convenience to our production life with its various excellent properties. Self-healing hydrogels can be widely used in particular professional fields such as bio-medical and the preparation of flexible skin materials [15]. Due to its good hydrophilicity, responsiveness to various environmental stimuli, high strength, high tensile strength, high toughness, excellent self-healing, and recycling properties. Hydrogel has unique advantages in biological tissue engineering, electronic skin, etc. It has improved work efficiency, reduced risks for various industries, and has gradually entered people's daily lives. However, the preparation technology of hydrogel is still imperfect, and the high water content makes its mechanical properties poor. There is still much room for development in improving mechanical properties, and for the high R&D cost and professional technology requirements, it has yet to be widely put into the market. Therefore, the future research direction of self-healing hydrogel materials is mainly in reducing the production cost, finding the optimal solution and configuration method, concentrating the respective advantages of various mechanisms of hydrogel in the same material, and developing its use, developing the solution of hydrogel disadvantages and improving the mechanical properties of hydrogel; continuing to develop self-healing materials without restorative agents and contributing to the development of a friendly environment.

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