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Application of polymer adhesive hydrogel in wound healing

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Abstract:

As the global adhesive industry continues to grow, researchers are discovering that polymer adhesives are playing an increasing role in the medical field, polymer adhesives have attracted more and more attention from the medical industry due to their unique advantages, such as hydrogels, have gradually appeared, which can effectively help wound healing. Most of the hydrogels have good biocompatibility and water absorption, and have the advantages of controllable structure, adjustable performance and easy degradation. Compared with traditional wound healing methods, hydrogels effectively reduce additional trauma and leakage and allow for greater tissue integration. This paper reviews the types of polymeric adhesive hydrogels and examples of some of them being artificially modified to be applied to the field of wound healing. Analyzes their mechanism of action and the advantages and shortcomings of their clinical applications, and finally looks into the potential functions and clinical efficacy of hydrogels in the future.

Keywords: Hydrogel; wound healing; adhesive.

1. Introduction

A large number of patients currently suffer different kinds of tissue trauma every year due to physical trauma (e.g., car accidents) and various chronic traumas (e.g., chronic or nonhealing wounds in diabetic patients) [1]. Suturing a wound is to keep its skin stable after trauma. The wound healing process is contains tissue regeneration and is complex, and without medical intervention, many conditions can lead to inadequate wound healing. Wound healing may be affected by diabetes or peripheral vascular disease leading to impaired function. Conventional wound healing medications (e.g., gauze, synthetic fiber cloths, etc.) are generally dry so as a result, the wound will heal in a relatively dry environment, which is not conducive to the rapid recovery of the wound, and they are generally not very antimicrobial. Hydrogel is a type of biomedical adhesive. It possesses a unique three-dimensional crosslinked polymer network structure. In the swollen state, it is a material that absorbs water very well and maintaining water binding in its pores while maintaining the integrity of its network structure. The wound will heal quickly in this water-rich condition. Hydrogels show the ability to alleviate inflammatory conditions in the wound area, and their mechanism of action is to exert an antioxidant effect by reducing the amount of reactive oxygen species (ROS). In addition, hydrogels exhibit the potential to promote the growth of fibroblasts and keratinocytes in the wound [2].

2. Classification and characteristics of hydrogel

Hydrogels are categorized as shown in Figure 1. The classification of hydrogels can be divided into two categories according to the differences in their composition: one is natural polymer hydrogels, and the other is synthetic polymer hydrogels (As shown in Table 1) [3]. Natural polymer hydrogels (e.g., those from polysaccharides and proteins) have non-toxic properties and are relatively inexpensive, and are mostly used in biomedical applications. Synthetic hydrogels contain synthetic polymers that make the hydrogels more mechanically flexible with highly controllable physical and chemical properties, but they do not possess any biological activity [3]. The good biocompatibility and degradability of natural polymer hydrogels make them more advantageous for clinical applications. They can also be categorized into physical and chemical hydrogels and hybrid hydrogels depending on the crosslinking method. Based on ionic charge they can be classified as cationic, anionic, and neutral hydrogels [3].

In addition, another way of categorization is based on the era; the first-generation of hydrogels, including simple network hydrogels was invented in 1960. The second-generation of hydrogels with stimulus-responsive properties was applied in 1970. The third-generation hydrogels are composed of stereocomplexes and physically crosslinked hydrogels, and the fourth-generation hydrogels contain dual network structures and synthetic hybridized polymer networks, etc.

Fig. 1 Classification of hydrogels [3]

Table 1: Different kinds of hydrogels and their respective characteristics [3]

Category	Substance	Advantages	
Natural Polymer Hydrogel	Alginate	Low immunogenicity Soft mechanical properties	
	Chitosan	Biocompatible, Biodegradable Non-toxic	
	Cellulose	Good chemical stability Mechanical properties	
	Hyaluronic acid	Biocompatible, Biodegradable Non-toxic	
Synthetic polymer hydrogels	Polyethylene glycol	Highly hydrophilic, Biosafety	
	Polyvinyl alcohol	Biocompatible Excellent adhesion	
	Polyvinylpyrrolidone	Good solubility, Low toxicity	

3. Mechanisms of wound healing

The process of recovery of skin wounds can be categorized into two forms, repair or regeneration, and these two modes of healing are significantly different. During wound repair, new tissue is formed that is not comparable in character and properties to the original tissue. Instead, the goal of wound regeneration is to rebuild the damaged area by generating tissue that is identical to the damaged tissue, aiming to restore its original structure and function.

People's wounds generally go through four stages before they heal and they overlap each other (as shown in Table 2), these four phases are regulated by both cytokines and growth factors [4]. It is worth noting that the duration of each phase varies from person to person, and the data in this table represent only a subset of individuals. When the skin suffers an injury, platelets are stimulated and aggregate in the area of injury while producing a fibrin clot, a process that helps to stop bleeding and attract a variety of cells to the wound. Growth factors, cytokines, and coagulation factors required for the coagulation chain reaction are also secreted during the early stages of wound healing. The coagulation process and degranulation of platelets trigger the inflammatory response phase. This phase is characterized by the release of pentraxin, histamine, and bioactive factors, which leads to increased capillary permeability, which encourages the migration of inflammatory cells into the wound area, including neutrophils, leukocytes, and macrophages. At the same time, the inflammatory cells penetrate the wound surface, causing fluid accumulation and localized swelling [4]. Neutrophils reach their highest concentration at the wound site within 1 to 2 days after injury, and with the assistance of macrophages, they play a key role in the defense against bacterial infection and are also responsible for the activation of keratinocytes, fibroblasts, and immune cells. During the proliferative phase, tissue granulation tissue is formed, wound edges contract and neovascularization occurs [4]. During the remodeling phase fibroblasts and macrophages are replaced by new cells through programmed cell death, allowing for the gradual strengthening of the skin fiber network [4].

Table 2. Stages of wound healing

Phase	Time
Hemostasis	0day-3days
Inflammatory	0day-7days
Proliferative	3days-50days
Remodeling	7days-365days

4. Applications of hydrogels in wound healing

4.1 Photoresponsive hydrogel for promoting wound healing in diabetic gangrene

The main reason for the difficulty in healing gangrenous wounds in diabetic patients is due to the chronically high blood glucose levels of the patients. This hyperglycemic condition promotes the exacerbation of wound infections, causes an inflammatory response lasting longer than expected, destroys the regenerative capacity of the tissues, and creates a lack of localized blood circulation at the wound site. In addition, hyperglycemia reduces the function of antioxidant enzymes and triggers free radical damage, and all these factors work together to make wound recovery exceptionally difficult [4]. There are currently two main therapies for diabetic gangrenous wounds: photodynamic therapy and photothermal therapy.

4.1.1 Photodynamic therapy

Photodynamic therapy is a therapeutic modality that utilizes photosensitizers to absorb light at specific wavelengths and transfer its energy to neighboring molecules, which in turn generates reactive oxygen species (ROS) [4]. These ROS subsequently trigger oxidative stress in cancer cells or bacteria, leading to therapeutic effects. Rojas et al. [5] formed a porphyrin/silk protein hydrogel complex by using silk protein hydrogel as a base material, which was doped with a photosensitizing compound. The complex was able to generate reactive oxygen species (ROS) more efficiently under red light irradiation, which helped to promote the death of peri-wound bacteria and thus enhance the efficiency of wound healing. Mao et al. [6] successfully assembled the Ag/Ag@AgCl nanostructures through a chemical reduction process initiated by UV light using a convenient two-stage procedure, and then introduced the zinc oxide nanostructures using sodium hydroxide precipitation. Finally, a composite hydrogel material was obtained. This hydrogel not only promotes rapid wound healing but also greatly reduces the number of common bacteria.

4.1.2 Photothermal therapy

Photothermal therapy is a method of helping chronic wounds heal by using localized physical heat to disrupt the structure of biofilms.

Chronic wound formation is the result of a combination of factors, including not only internal factors such as age and genetic predisposition, but also external factors such as pressure, friction and humidity. The duration of wound healing is influenced by a variety of factors, while chronic wounds result from a failure to follow the normal healing sequence and timeline, or to return to a normal anatomical and functional state.

Wang et al. [7] used mesoporous polydopamine (MPDA) nanoparticles with lysozyme (LZM). The release of lysozyme into the biofilm and their destruction under the conditions of photothermal therapy is realized, which accelerates the healing process of chronic wounds (e.g., Figure 3). This method can effectively enhance the photothermal treatment effect and enable rapid wound repair. When the temperature increases, this hydrogel can liquefy rapidly, which leads to a large release of nanoparticles and a significant antimicrobial effect. Guo et al. [8] created a range of reduced graphene oxide (rGO) and HA-graft-DA-based hydrogels that were applied as wound dressings. This hydrogel material exhibits excellent photothermal properties and antimicrobial properties under near-infrared light.

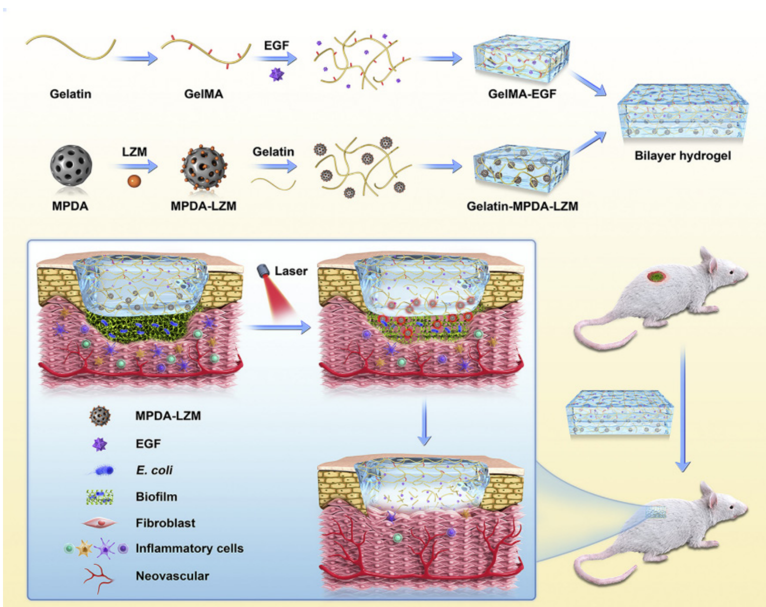

Fig. 2 Bilayer structure hydrogel dressings for the treatment of chronic wounds [7].

4.2 Antioxidant hydrogels for chronic wound healing

The skin plays a huge role in helping the body defend itself against external aggressors. One of the key factors affecting the rate of wound recovery is oxidative damage. Oxidative stress is closely related to the mechanism of chronic wounding, which in turn affects the normal wound healing process by destroying the cellular structure, causing the wound to become inflamed for a period, and impeding the formation of neovascularization [9].

Wang et al. [10] successfully prepared a multi-component hydrogel membrane composed of sericin protein (SF) and polyvinyl alcohol (PVA). Curcumin is a hydrophobic antioxidant that can reduce the amount of ROS and thus bring the wound to redox equilibrium. The membrane was used as a carrier for curcumin nanoparticles (Cur NPs) designed to promote skin wound healing. In vitro, antimicrobial experiments showed that the composite hydrogel membrane doped with Cur NPs could effectively inhibit bacterial growth. In an in vivo skin injury model, the study demonstrated that this curcumin-loaded SF/PVA composite hydrogel membrane promoted wound healing. In addition, the hydrogel film was able to avoid exposing the wound to dry conditions and could be adapted to different shapes of wounds, showing promising applications as a potential cutaneous wound dressing, especially with significant potential in promoting chronic wound healing.

Inflammation is an integral stage in the wound recovery process. However, if a large amount of reactive oxygen species accumulate in the wound area, it may lead to the persistence or recurrence of inflammation, which may delay wound healing. Therefore, hydrogels with the ability to scavenge reactive oxygen species are more beneficial in promoting wound healing.

Tsai et al. [11] selected ferulic acid, a natural polyphenol, as an antioxidant and utilized heat-sensitive chitosan hydrogel as a drug carrier to successfully prepare an antioxidant hydrogel system for corneal alkali burn wound treatment. The experimental results confirmed that the hydrogel could effectively remove free radicals and inhibit the expression of inflammation-related cytokines like IL-1. TNF-α and TGF-β, demonstrating significant anti-inflammatory effects and significantly reducing the rate of apoptosis.

4.3 Conductive hydrogels for wound healing at expandable sites

Injuries to extensible areas of the body often result in persistent pain, and the healing process is more complex than for wounds in fixed areas and can be difficult in the following ways. Firstly, expandable areas such as joints, elbows, knees, etc., are frequently moved in daily life, resulting in constant mechanical stress on the wound. Second, telescopic sites require more frequent splitting and reattachment, increasing the difficulty of tissue repair. Finally, wounds at the expansion site may develop into chronic wounds that are more difficult to heal. Despite this, these types of wounds have received relatively little attention and research compared to other chronic injury types [12].

Conductive dressings have been shown in several studies to be effective in promoting wound healing and tissue regeneration. With the aid of conductive dressings, endogenous electrical currents at the wound edges can effectively diffuse toward the wound center, a process that significantly promotes cell migration toward the wound center [13].

Conductive hydrogels are flexible functional materials consisting of cross-linked hydrophilic polymers and conductive fillers or ions. This material, by combining conductive components with various hydrophilic polymer matrices, endows the conductive hydrogel with a wide range of physical and chemical property modulation capabilities, which include properties such as excellent mechanical strength, cold resistance, self-healing ability, and good biocompatibility [14].

4.4 Bio-glue

Hemostasis and incision management are critical in the wound healing process. Tissue adhesives have developed into an attractive technique in the field of wound management. In a departure from traditional methods of closing wounds, the mechanism by which tissue adhesives are used in the management of open wounds is by bonding the damaged tissue. In order to accomplish this process, the adhesive needs to be able to adhere to the surface of the tissue and have the ability to prevent the wound from re-opening [15]. Bond strength is a key factor in determining the binding efficacy of tissue adhesives. In past studies, researchers have proposed various strategies to prepare bio-glue with stronger bond strength, which mainly include in situ covalent bond formation, ligand cross-linking, physical cross-linking, and light-induced cross-linking reactions [16]. These special hydrogels outperformed conventional protein gels in terms of tissue sealing ability and demonstrated excellent hemostatic effects. Therefore, they possess a promising long-term application as clinical tissue sealants or surgical hemostatic agents. Zhao et al. [17] successfully developed an injectable chitosan-g-polyaniline (QCSP)/benzaldehyde-functionalized poly(ethylene glycol)-polyglycerol trisubstituted ester (PEGS-FA) hydrogel binder by using the Schiff base reaction. They found that this hydrogel binder possessed several compelling properties. The main ones include good tissue adhesion, free radical scavenging ability, self-healing, antimicrobial properties, and biocompatibility. It was demonstrated through modeling that it significantly accelerated the wound healing process in vivo, proving that it is an excellent material for helping wound healing.

5. Conclusion

This paper mainly introduce the classification of polymer hydrogels, the healing mechanism of wounds, and the special roles of different hydrogels in the field of wound healing. As an emerging wound dressing, polymer hydrogel has many advantages in clinical application that cannot be matched by traditional wound dressing methods. Some valuable properties such as non-toxic, biodegradable, etc., make it a material that helps in the healing of chronic wounds caused by diabetes and other diseases that are difficult to heal. In addition, in addition to using hydrogel directly as a dressing, it can also be combined with some antioxidants, antibacterial drugs, etc., to form new composite materials, so that the process of wound contraction and healing is faster. However, some hydrogels still have shortcomings such as poor air permeability, weak mechanical properties, and low adhesion degree. In the future, polymer hydrogel materials can be appropriately improved from scar repair, anti-itching and pain relief, and reducing the risk of infection.

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