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# Classification of hydrogels in skin wound healing applications

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## Abstract

In the past, various methods were used to heal skin wounds, many of which did not have favorable results. Replacing the old methods with dressings based on hydrogel compounds has led to an increase in the quality and speed of wound healing. The role of hydrogels in improving gas exchange and oxygen supply along with absorption of wound secretions and temperature regulation and reduction of infectious agents on the wound is known. In this study, we tried to introduce the most important hydrogel groups that are effective in healing skin wounds. The results of investigations show that a wide range of these compounds include polymer hydrogels with natural bases (cellulose, starch, chitin, chitosan, carrageenan, alginate, dextran, pullulan, etc.), hydrogels produced with physical bases. and chemical (copolymer, homopolymer, etc.), combined hydrogels with natural and synthetic bases (creating complexes with chitosan, collagen, and dextran origin with compounds such as polyvinyl alcohol, etc.) and advanced hydrogels (self-healing , spraying, intelligent, etc.)

**Keywords:** Wounds; Skin; Hydrogel; Natural; Synthetic; Advanced

## 1. Introduction

The skin is the most important organ of the human body and plays an important role in protecting against external threats and also helps to regulate the internal environment of the body [1]. In addition, the skin is used to protect the homeostasis of the internal environment against external threats [2]. The skin also interferes in controlling the humidity and temperature of the body, etc [3]. When the skin is injured, it becomes scarred and its integrity is lost against various threats [4]. The existence of a wound for a long time lowers the tolerance threshold of the skin and against infectious agents, the skin becomes prone to diseases [3]. Research shows that the National Health Service in England spent £10.6 billion on wound management between 2012 and 2017. Of course, this amount is separate from the sales of wound dressings of 16 billion dollars in 2017[2]. For thousands of years, the effects of ulcers have been causing concern and annoyance to patients, and it is known as an epidemic [2].

## 2. Material and methods

Repairing damaged skin is very complicated [5], therefore Before dealing with the management of skin wounds, the structure of the skin and its mechanism of action in protecting the body must first be evaluated. The skin area depends on the height and volume of the human body.

The skin of the body consists of 3 levels, including the epidermis, dermis and the lower surface of the skin. The outer surface of the skin or epidermis, which is responsible for physical protection against external pollutants. The second layer or dermis plays an essential role in maintaining body water and is flexible. This layer is also effective in feeding

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and oxygenating the skin cells. The lower surface of the skin or hypodermis acts as an insulator because it has fatty tissue [2]. Figure 1 shows the layers of the skin of the human body.

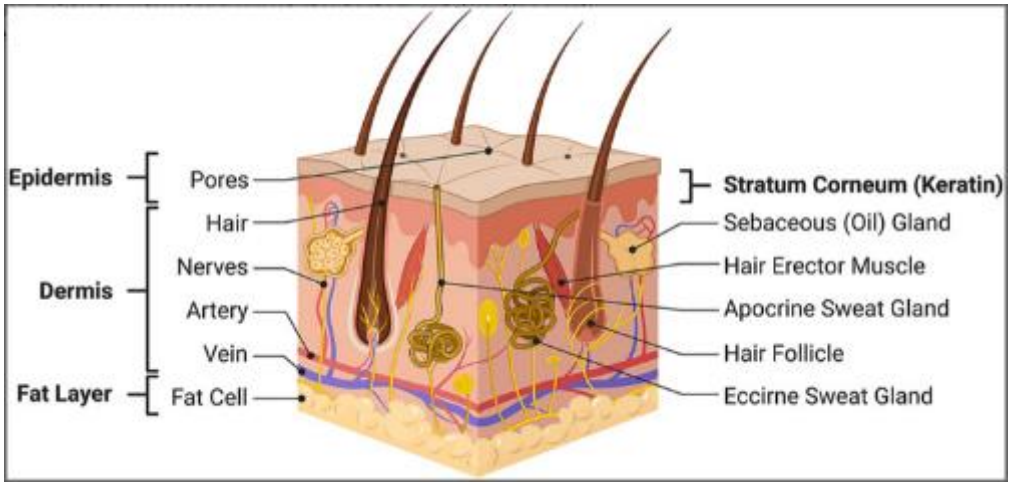


**Figure 1** The cross section of skin [6]

### 2.1. Familiarity with wounds

When a wound is created, a complex process starts automatically in the body, during which several types of body molecules, including platelets, cytokines, inflammatory factors, etc., undertake the repair operation in an integrated manner [5]. Wounds occur when body tissues are damaged by an unconventional agent [7]. If the color of the wound is pink, it means it is still fresh. The main problem of wounds is that they change color to black because it is accompanied by an unpleasant smell and is completely infected. If the wound is kept greasy, the possibility of infection will be low. The presence of secretions caused by the development of infection in the wound is not a good sign and these secretions should be removed by a doctor [7]. Factors affecting the formation of wounds are diverse, so their classification is wide. The origin of wounds can be caused by the small amount of damage, the area of the damaged point, etc[7].

#### *2.1.1. Chronic wounds*

If the wound healing time is more than 3 weeks and lasts up to 4 months, it is defined as a chronic wound. Factors that lead to the development of chronic wounds include age, nutritional status, infection in the body, immunity level, etc [8]. The existence of abnormal chemical reactions can lead to the creation of chronic wounds, such as wounds caused by diabetes. The healing time of this type of wound is long and leads to cell destruction. Subsets of chronic wounds are [10]:

- Venous/vascular ulcers
- Diabetic ulcers
- Pressure ulcers
- Ischemic wounds

Persistence of inflammation and disruption of cell development can be seen in chronic wounds, and for this reason, the recovery and recovery of wound tissue is very long and sometimes irreversible [9].

#### *2.1.2. Acute wounds*

Wounds caused by external factors are known as acute wounds. There is cellular destruction in this wound, but its repair is completely accurate and regular. Subsets of acute wounds are wide, but two general types are defined for them [10]:

- Traumatic wounds
- Surgical wounds

These wounds include open cuts, scrapes, fracture wounds, surgical wounds, and types of skin burns [10]. A conventional acute wound naturally goes through four precise stages, which include hemostasis, development, evolution and return to a state of complete recovery. When blood vessels are ruptured, vascular spasm, platelet spike

formation and then coagulation have been seen in order [11]. Patients usually complain more about acute wounds. Another classification for wounds is based on the degree of damage, which is introduced in 4 classes [12]. Figure 2 shows a Schematic comparison of chronic and acute wound microenvironment**.**

- Class 1- These types of wounds are simple and do not get infected. If there is a need to remove secretions, it is performed in a closed manner. This type of wound does not involve the internal tissues like the wound created on the thyroid gland [12].
- Class 2- These category of wounds are considered clean-contaminated. They are free of unusual contamination. Under controlled conditions, these wounds can enter the respiratory tract, genitals, etc [12].
- Class 3- These wounds are defined as infected wounds. They are usually caused by the non-sterility of the surgical conditions. The presence of acute inflammation can be related to class 3 wounds [12].
- Class 4 - Wounds that are septic and caused by incomplete treatment. This type of wound occurs when tissue cells die [12].

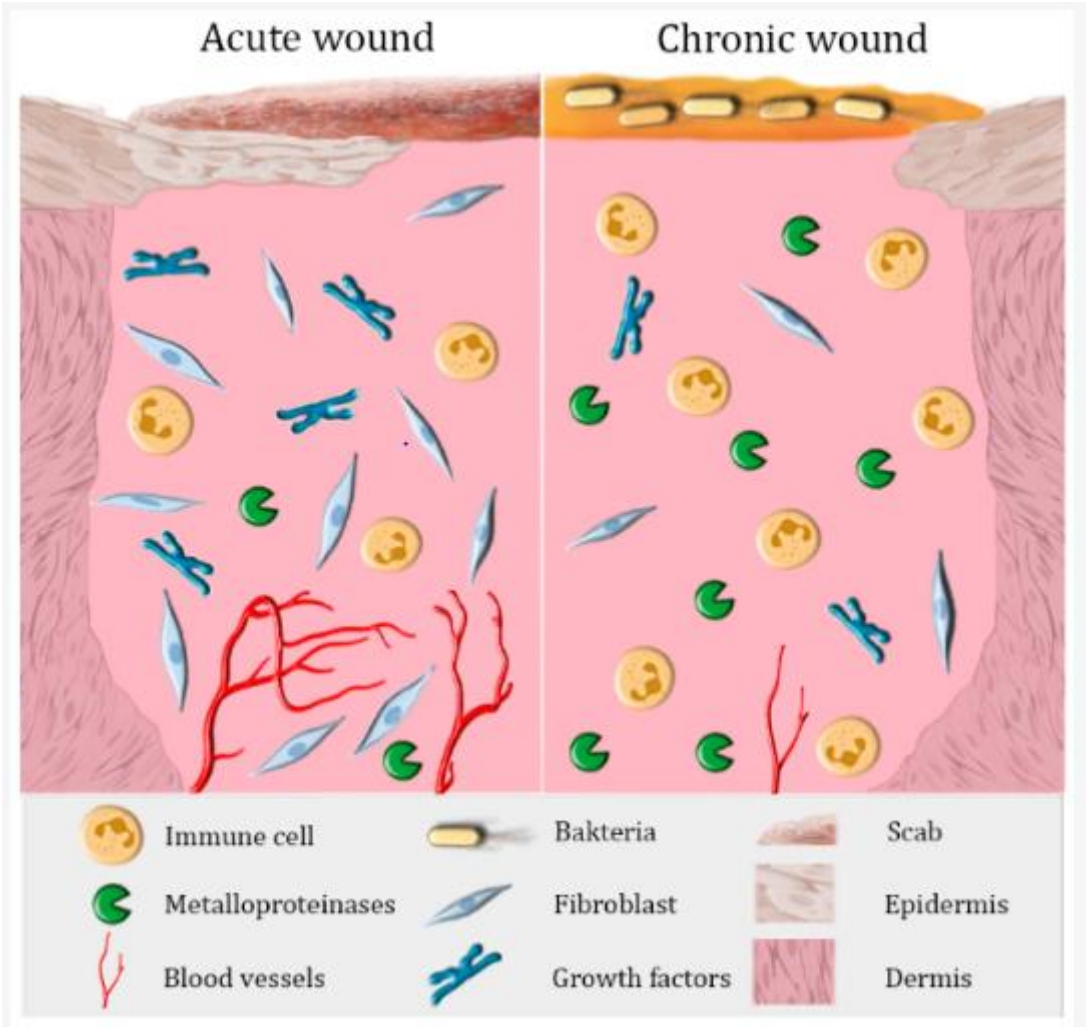


**Figure 2** Schematic comparison of chronic and acute wound microenvironment [35]

*2.1.3. Basic types of wounds*

There is another form of main classification for wounds: 1- Open wounds that are red and without fluid secretion. An open wound is an injury that includes an external or internal break in the body tissue. This type of wound usually involves the skin. Most open wounds are minor and can be treated at home. 2- Closed wounds are usually caused by direct impact after a fall or an accident with vehicles. Although the skin may remain intact, the underlying muscles, internal organs, and bones are likely to be damaged. These wounds may sometimes occur after heavy objects fall on the body[9].

*2.1.4. Closed wounds*

Closed wounds are created under the skin, so they are not visible and can cause serious damage to the human body [14]. Examples of closed wounds include [13]:

- Contusions: Bruising of the skin caused by the rupture of blood vessels under the skin.
- Crushing: under pressure and damage to tissues.
- Closed fracture: the bone breaks under the skin and causes pain and swelling
- Hematomas : Pooling of blood outside the blood vessels under the skin.
- Concussion: Head injury with brain damage and confusion.

*2.1.5. Open wounds*

An open wound is a type of injury on the surface of the skin that exposes the parts under the skin and usually causes external bleeding. This type of wound can quickly become infected and germs can quickly spread to the deeper layers of the skin [14]. Examples of open wounds include:

- Abrasion: when the surface of the skin slides on another rough surface and causes scratches. Although the amount of bleeding is small, wound care must be taken to prevent infection [14].
- Rupture: creating a gap in the skin, which is usually caused by a sharp object or tool. If the dent in the skin is deep, it can lead to severe bleeding [14].
- Peeling: This type of skin damage can be severe. This type of wound occurs as a result of an accident with vehicles or an attack by animals, etc [14].
- Puncture: As a result of sharp object sinking, the lower surface of the skin is damaged and it is usually accompanied by bleeding [14].
- Cutting: This type of injury is caused by the insertion of tools such as a surgical blade or a knife on the surface of the skin. This wound is created as a small longitudinal slit with bleeding and can cause serious damage to some tissues of the body [14].

**2.2. Treatment of skin wounds**

The physiology of the human body and the structure of the skin has the ability to carry out the wound recovery process, but the extent and complexity of the injuries and the depth of the wound delay the stages of skin repair, and the healing of the wound stops and its infection intensifies [5].

The wound healing period starts about 2 to 3 days after its creation. Fibrins are activated and act as a sticky mesh to trap platelets. After this stage, angiogenesis, collagen deposition, granulation tissue formation, epithelialization, and wound contraction occur. In wound contraction, myofibroblasts reduce wound size by grasping the edges of the wound and contracting using a mechanism similar to that of smooth muscle cells. Collagen dressings can provide anti-infective, anti-inflammatory, anti-fibrotic, and analgesic properties, as well as promote angiogenesis, restore the body to its normal state and function, and provide a foundation for wound healing [15]. The optimal dressing for wound healing should have the following characteristics [16] :

- A)Preventing bleeding and reducing pain, protecting against external factors
- B)Absorption of excess secretions and prevention of wound dryness
- C)overlapping with the skin
- D)Creating uniform tissue, preventing infection, proper oxygen supply,
- E)Eco-friendly and skin-friendly

Wound healing studies show that the focus is on the type of dressing that can keep the wound moist. In the past, to heal a wound, it was thought that the surface of the wound should be dry, but new research shows that by keeping the wound moist, the speed of healing increases up to 5 times [16]. Figure 3 shows The phases of the wound healing process.

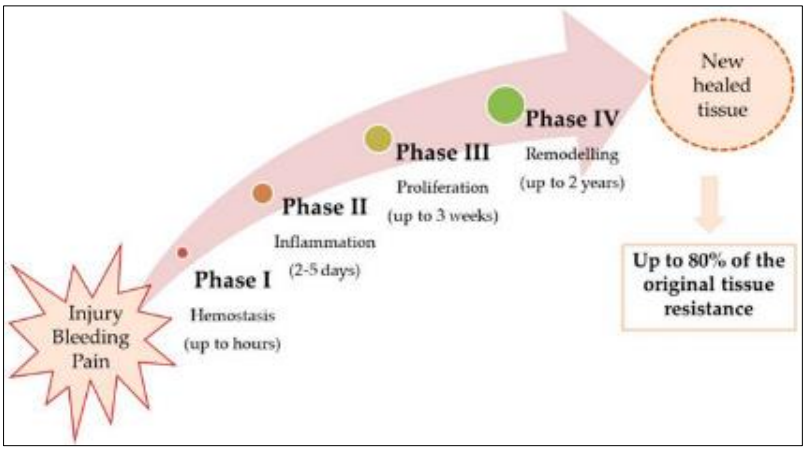


**Figure 3** The phases of the wound healing process [18]

### 2.3. Ancient treatment of skin wounds

Some substances found in nature have healing properties for skin wounds. The effectiveness of these compounds and their mechanism of action in wound healing is known. But their antimicrobial properties and side effects need more studies. In general, traditional medicine is a low-cost method for treating diseases. People in countries that have little income for treatment or do not have access to new drugs, tend to local treatment methods for diseases. New advances in traditional medicine and its combination with new compounds and modern methods have led to the use of Natural substances can be used in the treatment of diseases [5]. The research conducted during the last ten years has led to the identification of 62 families and 109 species of plants for the treatment of skin ulcers. The most important medicinal species used included Euphorbiaceae, Asteraceae and Fabaceae families. The most parts of the plant used for wound healing include leaves, fruits, seeds, roots, flowers, skin, etc [17].

### 2.4. Modern treatment of skin wounds

The new generation of wound healing methods is more than 2000 types, which include creams, gels and ointments, as well as the use of advanced medical devices and 3D printers. Modern multifunctional dressings include foams, films, hydrocolloids, hydrogels, and nanocomposites .New dressings are products that control the damaged tissue and regenerate the skin in optimal conditions of temperature and humidity [18].

#### *2.4.1. Familiarity with hydrogels*

Many different examples of scaffold materials have been used for tissue engineering applications, and hydrogels constitute a group of materials that have wide applications. A gel is defined as a three-dimensional network that is swollen by a solvent, and hydrogels can absorb from 10 to 20 percent and up to hundreds of times more than their dry weight in water. This feature allows cells to adhere to hydrogels, multiply and differentiate [19]. Hydrogels are 3D scaffolds and have the ability to absorb large amounts of biological fluids of the body. The structure of hydrogels is soft and flexible, and for this reason, they are able to absorb proteins in a low amount [20].

#### *2.4.2. Classification of hydrogels*

Hydrogels can be divided from several points of view [4]:

- The main source of hydrogel (natural or synthetic polymer)
- Hydrogel structure (homopolymer network, copolymer network and interpenetrating network)
- Method of transverse connections (physical and chemical)
- Bar hydrogel (anionic and cationic)
- Divided biodegradability (biodegradable, biostable).

Natural Polymer Hydrogels

Natural hydrogels are made from natural polymers. These materials include polynucleotides, polypeptides, and polysaccharides. Natural polymers originate from neutral, anionic, and cationic compounds that are created by covalently bonded monomer units. These compounds are used for medical purposes. Especially, they are used to control

drug delivery and accelerate the healing of wounds. Naturally available polysaccharides, such as cellulose, starch, chitin, chitosan, carrageenan, alginates, dextran, pullulan, and pectin, are studied extensively for industrial, medical, pharmaceutical, and tissue engineering applications [21].

Hybrid hydrogels

Hybrid hydrogels are made from the combination of natural and synthetic hydrogels. In this process, compounds such as chitosan, collagen and dextoran are combined with synthetic polymers such as polyvinyl alcohol and create hybrid hydrogels [21].

Physical hydrogels

When physical hydrogels are placed in the environment, their reaction path may be changed because their formation chain is weak, and for this reason, when they are hot, they easily dissolve in organic solvents [21].

Chemical hydrogels

They are known as permanent hydrogels. They have strong constitutive bonds. They do not have reversible reactions in the external environment [21].

Synthetic hydrogels

This group of hydrogels has a three-dimensional swollen polymer network. These compounds are hydrophilic and formed by ionic covalent bonds, which include poly hydroxyethyl methacrylate, polyethylene glycol hydrogels, and polyacrylic acid [21]. Synthetic hydrogels have desirable mechanical properties and their preparation methods include homopolymers, copolymers, and interpenetrating networks (IPN) [22].

Homopolymeric Hydrogels

They are polymer networks that are composed of single monomer species and cross-linked. Examples of this type of hydrogels include poly(2-hydroxyethyl methacrylate), poly(3-hydroxypropyl methacrylate) and poly(hydroxyalkyl methacrylate) [26].

Copolymeric Hydrogels

This group of hydrogels have covalent and ionic bonds and are insoluble in water. Examples of this category of polymers are: Poly (HEMA-co-AA), poly (NVP-co-HEMA), and poly (NVP-co-HEMA) [25].

Advanced hydrogels

- Self-Healing Hydrogels: These types of hydrogels are suitable for wound healing because they can reduce structural damage. Self-healing hydrogels, which are natural photochemical materials, have antiseptic, anti-inflammatory and antioxidant properties and are effective in healing chronic wounds [23].
- Spraying hydrogels: These hydrogels have a high penetration power due to the drug being thrown by pressure on the wound. It is also spread over the wound and covers a larger area. Using the spraying process makes the drug work more actively [1]. Spraying hydrogels have advantages such as simple application, no need for an expert, patient satisfaction and low production cost. The important point in the production of this hydrogel is its low viscosity, which leads to greater penetration power and uniform and widespread dispersion on the wound site [31].
- Smart hydrogels: The use of smart hydrogels for wound healing in recent years is a very good answer to eliminate and reduce the limitations of its repair in the past. New researches show that smart hydrogels increase the speed of drug delivery due to their proper stability and physico-chemical properties. These types of hydrogels increase the effect of drugs on the wound with the help of external stimuli such as temperature, light, humidity, etc. intensifies Due to the high permeability, the amount of used medicine is reduced. As the dose of medicine decreases, practically less chemical substance enters the body. Another important point is the ease of using smart hydrogel in healing skin wounds. Also, these compounds are environmentally friendly [24].

### 2.5. Applications of hydrogel in medicine

Due to the wide range of diseases and the variety of improvement methods in medical science, the use of hydrogels in the treatment of diseases has been developed. The most important applications of these materials in medical fields include contact lenses, wound dressings, drug delivery, tissue engineering, microneedles, biosensors, etc [26].

*2.5.1. The performance of hydrogels in the treatment of skin wounds*

Hydrogels have properties that help heal skin wounds. These factors include [27]:

- Because hydrogels act as a carrier, they are able to transfer growth factors and proteins and other therapeutic agents in a controlled manner to specific places in the skin tissue and speed up the healing process.
- Hydrogels cause parameters such as hardness, porosity, adaptability, etc. to help the tissue to improve the skin tissue.
- Various ways of using hydrogel, such as injection, implantation, etc., make it possible to accurately locate the site of skin wound repair with maximum penetration.

Due to the chemical, mechanical and electrical properties of the skin, regenerative hydrogels have a positive effect on skin wound healing. These substances are injected or sprayed on the wound site to activate and increase the penetration rate of the drug. They also keep the wound moist [27] . Another important thing that slows down the wound healing process is the increase in ROS factor, which increases the inflammation and infection of the skin wound. This factor indicates the active oxygen species that the use of hydrogel controls ROS [27]. Hydrogel dressings are hydrophilic and have a three-dimensional structure, and by creating granulation, they regenerate the wound tissue. These dressings gain antimicrobial properties by loading cells and based on the severity and size of the skin wound, they have local effects for repairing the damaged point [28].

## 3. Results

Conventional hydrogels are not able to heal the wound immediately, but they can heal the wound gradually [29]. 3D hydrogels have a very good effect on healing skin wounds. It is predicted that in the future, these hydrogels will intensify the healing process of skin wounds with the new approach of injectable/printing hydrogels [30]. Polysaccharides and proteins are scaffolds that can make hydrogels for skin dressings. The subset of these compounds include cellulose, chitosan, alginate, starch, heparin, dextran, etc., which are widely used for dressing skin wounds. Proteins such as collagen, gelatin, etc. are considered excellent options for wound healing. On the other hand, synthetic polymers such as PLGA, PEG and PCL... are the best compounds for making hydrogels. The cross-linking of polymers is effective in the performance quality of hydrogels, and their physical and chemical cross-links make the synthesized hydrogels have different behaviors in wound healing [31].

## 4. Discussion

Hydrogels have been widely used in the drug market, however, their real potential has not yet been fully investigated. The advanced platform of hydrogels in skin wound dressing is being done. The most important research in this direction is to achieve a cheap product and increase its efficiency [32]. Wounds caused by skin burns have many complications that the design of dressings based on adjustable hydrogels should be developed for their repair [33]. Hydrogels act in the process of material engineering to help regenerate the skin as an alternative to skin grafts for the treatment of severe and deep injuries. They easily regenerate vascular tissue and skin appendages. Smart hydrogels dynamically respond to environmental reactions of the wound [34].

## 5. Conclusion

As mentioned, the use of hydrogels in medical services, especially in the healing of skin wounds, has expanded in recent years. The diversity of these compounds and their flexible behavior are promising to help heal wounds. The use of natural and synthetic materials in the production of hydrogels with the aim of improving the healing process of skin wounds shows the various capabilities of these compounds to reduce the time of skin regeneration, which reduces the complaints of patients. According to the above review, it seems that in the future, by conducting laboratory and field research, more capabilities of the use of hydrogels will be identified. Achieving the most important mechanism of action of hydrogels in drug delivery will be the most important research approach for researchers. The important point in this direction is to pay attention to the environmental evaluations of these compounds, which can be seen with the expansion of studies.

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