

How Effective are Nano-Based Dressings in Diabetic Wound Healing? A Comprehensive Review of Literature

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Abstract: Chronic wound caused by diabetes is an important cause of disability and seriously affects the quality of life of patients. Therefore, it is of great clinical significance to develop a wound dressing that can accelerate the healing of diabetic wounds. Nanoparticles have great advantages in promoting diabetic wound healing due to their antibacterial properties, low cytotoxicity, good biocompatibility and drug delivery ability. Adding nanoparticles to the dressing matrix and using nanoparticles to deliver drugs and cytokines to promote wound healing has proven to be effective. This review will focus on the effects of diabetes on wound healing, introduce the properties, preparation methods and action mechanism of nanoparticles in wound healing, and describe the effects and application status of various nanoparticle-loaded dressings in diabetes-related chronic wound healing.

Keywords: diabetic wound healing, nanoparticles, antibacterial, low cytotoxicity, good biocompatibility, drug delivery

Introduction

As a chronic disease characterized by hyperglycemia, diabetes affects 10% adults worldwide.¹ About 15% of patients with diabetes experience diabetic limb ulcers, which are the leading cause of hospitalization and amputation.² The treatment of diabetic ulcer is a complex process, which requires de-trauma, drainage and anti-inflammatory treatment on the basis of blood glucose control. Among them, the treatment of the wound surface plays a very important role in the process of wound healing. Normal wound healing process is a continuous dynamic process, in this process, a variety of cells orderly migrate to the wound site under the change of wound local microenvironment and growth factors to play their functions, successively multiply and secrete synthetic materials such as collagen protein and polysaccharide required for wound healing, and finally complete the wound healing.^{3,4} Diabetes is based on the changes of blood glucose, and the main pathological changes are microvascular changes, which then lead to nutrient supply disorders, abnormal inflammatory responses and other changes, and ultimately lead to delayed healing or even delayed healing of wounds.⁵ In addition to strictly controlling blood glucose level, it is also very important to improve wound local microenvironment and provide favorable conditions for wound healing.⁶

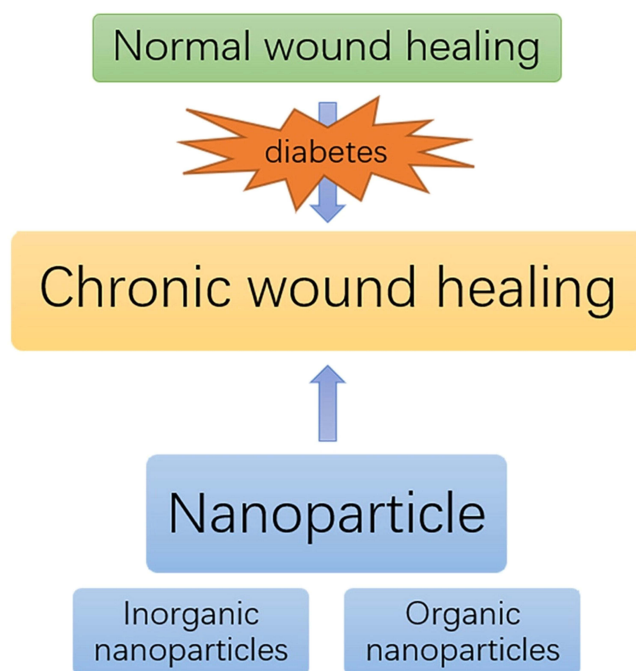
Wound dressing can provide protection to the wound. For a wound dressing, the ideal wound dressing should have good biocompatibility, good water absorption and water retention.⁷ In addition, the wound dressing should have good air permeability and antibacterial properties to ensure gas exchange in the wound while avoiding infection.⁷ Besides, the economy of dressings is one of the factors to be considered. In order to meet the needs of wound dressings, hydrogel, electrospinning, biofilm and other forms and types of wound dressings have been developed.⁸ At the same time, antibiotics, growth factors, cells and other substances are added to wound dressings, and compound wound dressings are constructed to meet the requirements as much as possible.⁹

Nanoparticle is a kind of material which has been widely used in recent years. Its small diameter endows nanoparticle with more characteristics. Different kinds of nanoparticles have different properties. The antibacterial properties, drug loading capacity, sensitization effect, good biocompatibility and low toxicity of nanoparticles make them very suitable for the preparation and modification of wound dressings.¹⁰ Adding nanoparticles to the dressing matrix and using nanoparticles to deliver drugs and cytokines to promote wound healing has proven to be effective.¹¹ This review will introduce the effect of diabetes on wound healing and the properties of ideal dressing from the characteristics of wound healing (Scheme 1). On this basis, the preparation, properties and action mechanism of nanoparticles are introduced. Finally, the effects and applications of nanoparticles in promoting wound healing are described in detail, and some problems and application prospects of nanoparticles in chronic wound healing are discussed.

Characteristics of Skin Wound Healing

Pathophysiological Changes in Normal Skin Wound Healing

Skin is the largest organ of the human body. It isolates the internal environment of the body from the outside world and prevents harmful factors in the external environment from directly entering the body and causing internal environmental disorders. Skin is an important inherent immune barrier of the human body. At the same time, the skin can also perform functions such as excretion, temperature regulation and external stimulation through the abundant hair follicles and nerve endings on its surface.^{12,13} A tight, intact skin structure is essential for proper skin function. Normal skin tissue consists of the outer epidermis and the inner dermis. The epidermis is divided into five layers, the innermost of which are the basal cells, which are capable of self-proliferation and differentiation. Basal cells complement the number of spinous cells by proliferating and differentiating into spinous cells, and maintain the stability of the number of epidermal cells, thus playing a role of self-renewal.^{14,15} Dermis is the dense connective tissue located below the epidermis, which is divided into the papillary layer rich in capillaries and the reticular layer mainly composed of collagen fibers.¹⁶ The papillary layer provides various nutrients for the epidermis through abundant capillary structure, and a large number of collagen fibers in the reticulated layer interweave into a network structure, providing the skin with toughness and elasticity.¹⁷ In the physiological state, the basal cells in the basal layer of the epidermis get nutrients from the capillaries



Scheme 1 Schematic diagram of this review.

in the dermis, and partly differentiate into spinous cells while proliferating to supplement the number of spinous cells. The outer layers of epidermal cells change over time into more outer layers until the outermost keratinocytes are shed.¹⁸

The normal continuous dense structure of skin can protect the body from external harmful stimulation and harmful substances, which plays an important role in the innate immunity of human body.¹⁹ However, the protective effect of skin has a certain limit. When external injury factors exceed a certain range, the normal structure of skin will be destroyed, the continuity of skin will be interrupted, and the protective effect on the body will be weakened or disappear.²⁰ Or the normal structure of the skin changes under the influence of diseases and drugs, so that the skin's resistance to external stimulation and damage is weakened.²¹ At this time, even if the slight stimulation or damage that can be resisted under normal conditions can lead to the destruction of the skin structure, causing the skin to fail to play its function normally.²² Skin healing is a continuous and complex dynamic process. The healing process can be roughly divided into hemostatic/inflammatory stage, proliferative stage and remodeling stage according to the main changes at different stages.²³ After injury, the exposed intravascular subcutaneous matrix attracts platelets from the blood to bind to basement membrane collagen, allowing platelets to adhere and activate. Besides, activated platelets activate endogenous and exogenous clotting cascades by releasing ADP and TXA₂, which in turn encourage platelets to aggregate on vascular walls and form platelet thrombus.²⁴ Platelet α particles contain a large number of cytokines and growth factors. When platelet thrombus is degraded, cytokines and growth factors such as IL-1 β , TNF- α , FGF and PDGF in platelets are released, attracting neutrophils and macrophages in blood to gather in the damaged area.²⁵ In the early stage of injury, neutrophils first accumulate in the wound area, while phagocytosis and release of ROS, antimicrobial peptides, proteolytic enzymes and other substances to remove necrotic tissue and pathogens. Mast cells and macrophages then arrive at the damaged area to remove remaining cell debris and neutrophils.²⁶

Under normal conditions, the hemostatic/inflammatory stage of the wound lasts about 72–96 hours, the cell debridement is basically completed, and the wound healing begins to enter the proliferative stage.²⁷ During the proliferation stage, the tissue metabolism of the wound changes from catabolism to anabolism. Fibroblasts and keratinocytes proliferate continuously under the stimulation of PFGF, FGF and EGF, and at the same time synthesize large amounts of type III collagen, proteoglycan and fibronectin, providing the skeleton structure for cell migration, proliferation and growth to the damaged area.²⁸ At the same time, endothelial cells migrate to the wound site under the action of VEGF and form a new capillary network to provide nutrients for other cells in the injured area and remove metabolic waste.²⁹ The main changes during wound remodeling were the remodeling and recombination of collagen. Type III collagen is mainly formed during the proliferation stage of injury repair, while type I collagen is the main component in normal skin tissue.³⁰ During the remodeling phase, fibroblasts continuously synthesize type I collagen to reduce the proportion of type III collagen in the wound area.³¹ In the meanwhile, through the rearrangement of collagen fibers, the parallel collagen structure in the early stage of the wound is transformed into a lattice network structure, improving the strength and toughness of the skin tissue in the injured area, and finally reaching a level close to or consistent with normal skin^{32,33} (Figure 1).

Causes and Pathophysiological Changes of Delayed Skin Wound Healing

Wound healing is a dynamic and continuous complex process, from the emergence of the wound to the complete healing process requires a variety of cells, the joint action of cytokines and growth factors, but also the local wound to maintain a good environment conducive to growth³⁴(Figure 2). Therefore, any factors that can affect the normal function of cells, interfere with the normal synthesis and secretion of growth factors and affect the local microenvironment of wound will cause wound healing disorders, resulting in delayed wound healing or non-healing. These influencing factors can be roughly divided into local factors and systemic factors according to the scope of influence (Figure 2). Local factors directly affect the wound site and affect the normal healing process of the wound. Common local factors include abnormal local pressure, impaired vascular perfusion, direct stimulation of physical and chemical factors, and local nerve defects in wound. Local infection caused by bacteria or fungi is an important factor affecting wound healing.³⁵ A large number of bacteria will release endotoxin in the process of removal, causing necrosis and inflammation of local tissues.³⁶ Due to the increase of pro-inflammatory cytokines, the number of growth factors released decreased, which inhibited the growth of cells in the proliferation stage, resulting in delayed wound healing or unhealed (Figure 2).

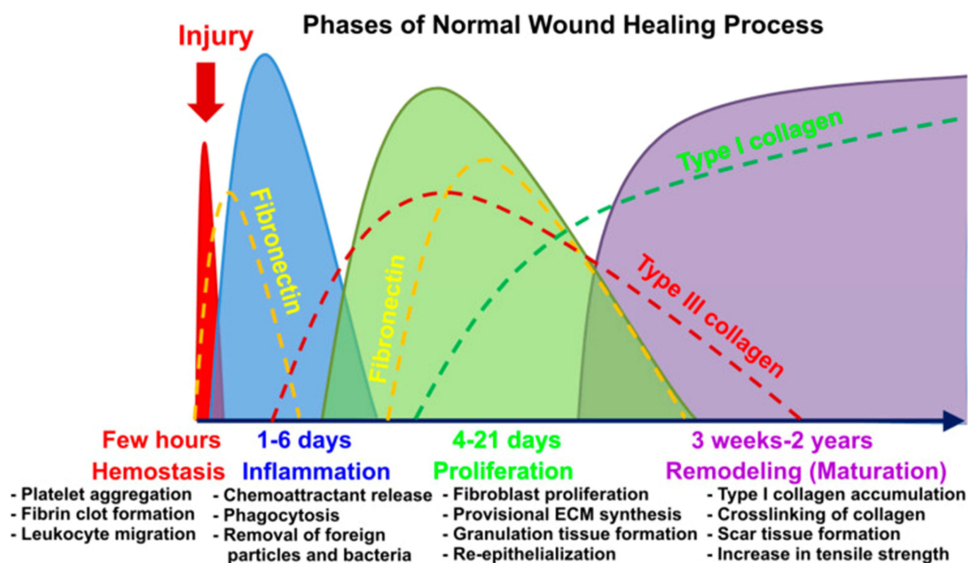


Figure 1 Stages of wound healing and pathophysiological changes in different stages.³³

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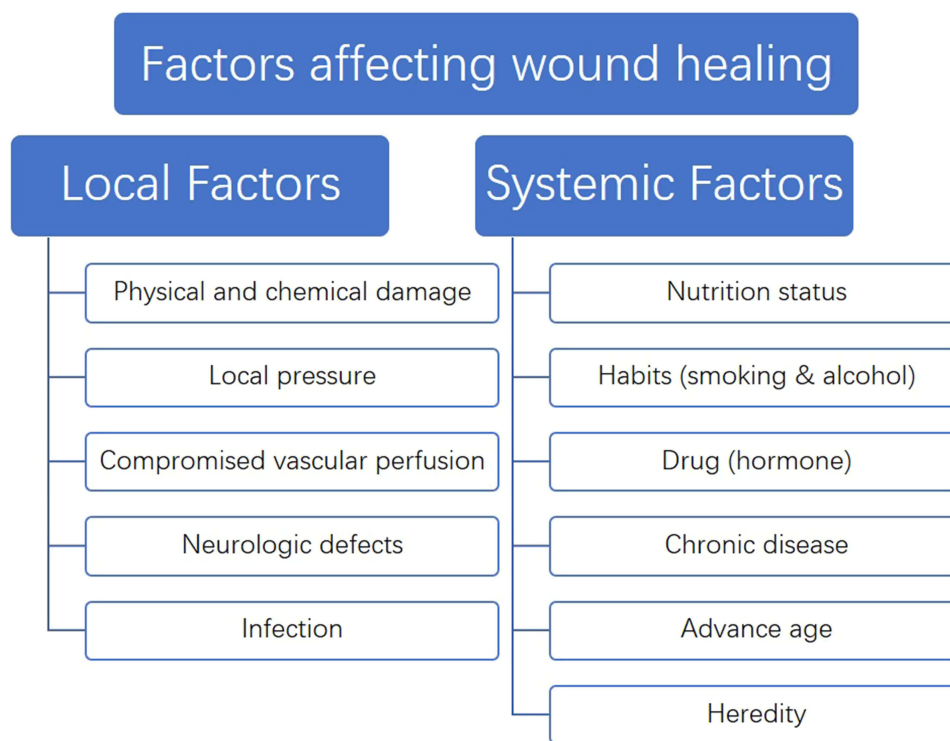


Figure 2 Factors affecting wound healing.

In addition to local factors, systemic factors also play an important role in wound healing. Individual basic conditions such as age, nutritional status, genetic susceptibility and other factors have a certain impact on the wound healing process³⁷ (Figure 2). Personal habits such as smoking, alcohol consumption and hormone drug use also delay the healing process to varying degrees.³⁸ Finally, the health status of the body has an important influence on the healing process of the wound. Some chronic diseases such as diabetes and uremia will seriously affect the normal healing of wounds.³⁹

When the wound cannot heal within the normal healing time range under the influence of various adverse factors, and the wound still does not heal or has no tendency to heal after more than a month, this kind of wound is called chronic wound.⁴⁰ The normal wound healing process begins at the hemostatic/inflammatory stage and is completed by the proliferative and remodeling stages³³(Figure 1). Chronic wounds are in a continuous inflammatory stage under the action of local and systemic destructive factors⁴¹ (Figure 2). The large release of pro-inflammatory cytokines leads to excessive synthetic release of metalloproteinases and inhibits the production of protease inhibitors.⁴² This inhibits the formation of new matrix and basal cell-mediated epithelialization, while the matrix hydrolyzes massively under the action of protease and cell death. The cell debris further stimulates the accumulation of inflammatory cells in the wound area, creating a vicious cycle.⁴³

Effects of Diabetes on Wound Healing

Common causes of chronic wounds include diabetes, venous ulcers of the lower extremities, and pressure ulcers. Diabetic foot ulcers occur in about 15% of people with diabetes and account for 80% of all lower limb amputations.² Diabetes can affect wound healing in many ways and stages (Figure 3). The hyperglycemia associated with diabetes can lead to microvascular disease, a narrowing or even occlusion of the capillaries that carry nutrients to the wound.⁴⁴ At the same time, hemoglobin glycosylation and changes in the structure of erythrocyte membrane led to insufficient oxygen and nutrient supply in the injured area, which affects wound healing.⁴⁵ Bone marrow cells represented by macrophages and neutrophils play an important role in the inflammatory stage during wound healing, while oxidative stress and hyperglycemia caused by local hypoxia change the expression of related genes that lead to macrophage polarization and its regulatory changes, leading to macrophage polarization disorder.⁴⁶ Overactivation of macrophages leads to over release of pro-inflammatory cytokines, and the continued inflammatory phase leads to abnormal apoptosis of fibroblasts and keratinocytes, interrupted the normal transition from the inflammatory phase to the proliferative phase of the wound⁴⁷ (Figure 3).

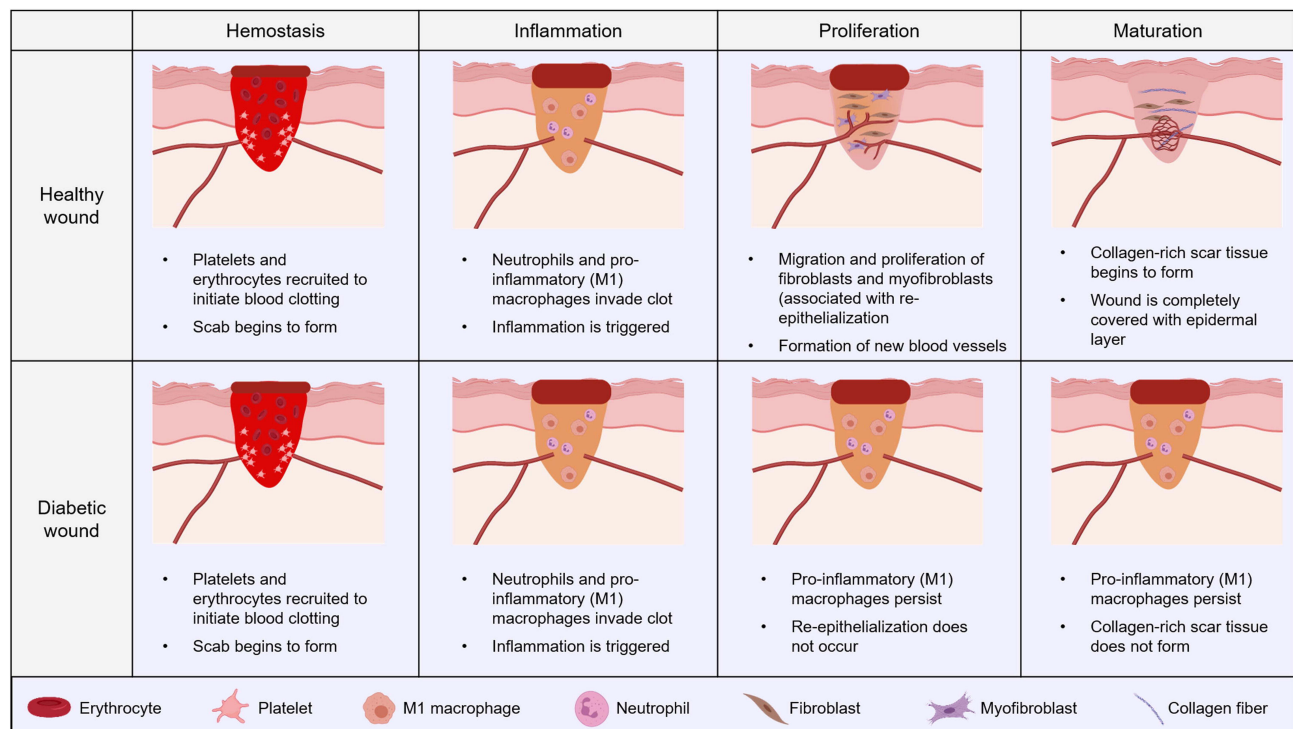


Figure 3 Differences of wound healing between diabetic and non-diabetic patients.

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Oxidative stress caused by free radicals and reactive oxygen species has adverse effects on wound healing in diabetic patients. ROS is a regulator in the process of wound healing. Low levels of ROS can promote the aggregation of inflammatory cells in the inflammatory stage and inhibit the colonization and growth of bacteria on the wound surface.⁴⁸ However, in diabetic patients, activated polyol pathway, hexosamine pathway, activated AGE pathway, PKC pathway and other pathways stimulate the excessive production of reactive oxygen species in mitochondria.^{49–51} A large number of ROS triggers a severe local oxidative stress response, resulting in excessive accumulation of inflammatory cells and prolonged inflammatory period.⁵² At the same time, excessive ROS affects the normal synthesis and reepithelialization of collagen in fibroblasts and keratinocytes, leading to the failure of the wound to enter the normal proliferation and remodeling stages^{53,54} (Figure 3).

Growth factors also play an important role in wound healing. IGF-1 is involved in cell granulation and epithelial regeneration, and stimulates chemotaxis of endothelial cells and proliferation of keratinocytes and fibroblasts. TGF- β can recruit fibroblasts and keratinocytes in the wound area, stimulate the synthesis and release of growth factors, and accelerate the formation of damaged local blood vessels and ECM formation.⁵⁵ PDGF can promote the synthesis of glycosaminoglycan, proteoglycan and collagen in fibroblasts, and play an important role in the migration and proliferation of fibroblasts and the formation of ECM.⁵⁶ The decreased expression levels of IGF-1, TGF- β and PDGF in wound tissue of diabetic patients slowed down the proliferation and differentiation of fibroblasts and the formation of ECM, and prolonged wound healing time.⁵⁷ VEGF is the main growth factor promoting angiogenesis and angiogenesis. The decreased VEGF mRNA expression level and increased VEGFR-1 level in diabetic patients lead to delayed angiogenesis and are not conducive to wound healing.⁵⁸ Under the combined action of the above-mentioned factors, the diabetic wound healing disorder is easily developed into chronic wound prolonged without healing.

Deficiencies of Existing Materials and Properties of Ideal Wound Excipients Available Wound Dressings and Characteristics

After the wound was formed, various wound dressings covering the wound were noticed and soon used in treatments to promote wound healing (Figure 4). With the passage of time, the development of science and technology and the deepening of people's understanding of the mechanism of wound healing, the functions of wound dressings are constantly changing and updating. The traditional wound dressing is mainly made of gauze, cotton and polyester fiber.

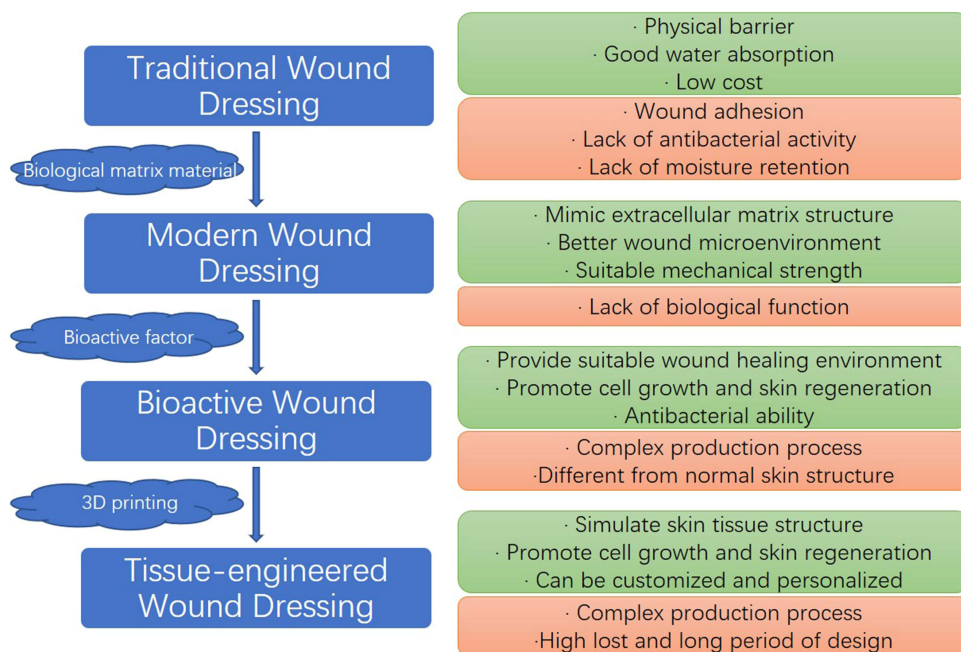


Figure 4 Development of wound dressings and characteristics. The advantages and disadvantages of different dressings are shown in green and red squares, respectively.

These wound dressing materials are easy to obtain, easy to prepare, and can fully absorb the local exudation of the wound to help the wound drainage.^{59,60} However, the deficiency of traditional wound dressing limits its protection and healing effect. Traditional wound dressings lack moisture, and excessive water absorption makes the wound exude and absorb quickly. After drying, wound dressings stick to the wound, which can easily cause secondary injury when dressing is replaced.⁸ Traditional excipients can only provide a physical barrier to the wound surface, but their large pore structure cannot isolate the direct contact between bacteria in the environment and the wound surface.⁶¹ At the same time, these traditional dressings also lack antibacterial and anti-inflammatory ability, which cannot effectively create an appropriate aseptic environment for wound healing.⁶² Because of the disadvantages mentioned above, traditional excipients are gradually being replaced by more advantageous modern wound dressings.

Modern wound dressings are constructed using substrate materials with superior properties (Figure 4). These constructed wound dressings can mimic the structure of extracellular matrix to some extent and promote wound healing by inducing cell growth.^{63,64} At the same time, all kinds of matrix materials themselves have a certain promoting effect on wound healing. Alginate, for example, has properties such as stopping bleeding, moisturizing and allowing gas exchange.⁶⁵ In addition, by preparing wound dressings with different forms of matrix materials, different properties and functions can be given to the dressings, thus providing a better microenvironment for wound healing.⁶⁶ On this basis, various bioactive substances were added to the matrix material to improve the properties and functions of wound dressings, endowing them with anti-inflammatory, antibacterial, proliferation and differentiation biological functions. These wound dressings are called bioactive dressings, which promote the growth and healing of wound surface cells by loading them with bioactive substances⁷ (Figure 4). Bioactive dressings with biological functions can obviously promote skin wound healing, but the final healing effect is still not as good as that of autologous skin grafting. In order to better simulate the structure and state of autologous skin grafting, tissue engineering dressings begin to receive attention (Figure 4). Tissue-engineered dressings use different kinds of polymers or 3D printing technology to simulate dermal tissue structure consistent with normal skin tissue, thereby promoting cell migration, adhesion and proliferation and speeding up the repair process.⁸

Properties of Ideal Wound Excipients

At present, all existing wound dressings can promote wound healing and repair to a certain extent, but due to the limitations of material properties and technology, there is no perfect wound dressing product that can be applied in clinical treatment. From the original gauze, bandage and cotton to the latest tissue-engineered dressings and smart dressings, the level and properties of dressings continues to advance. The original traditional dressing can only play a certain physical barrier and drainage and absorption function to the wound, and it is easy to stick to the wound and cause secondary injury due to its lack of anti-inflammatory and antibacterial ability.^{8,61} On this basis, a variety of modern dressings based on natural materials such as chitosan and sodium alginate and synthetic materials such as polyurethane and PNIPAAm have been developed.⁶⁷⁻⁶⁹ By preparing these matrix materials into hydrogel, hydrocolloid and other forms, the moisturizing and water absorption of the dressing can be significantly improved, which can maintain appropriate fitting with the wound and provide certain humidity for the wound, which is conducive to wound healing.⁷ However, the properties of a single biological matrix material are relatively limited, unable to meet the needs of wound anti-inflammatory, antibacterial, hemostatic and growth promotion. On this basis, the dressing was further modified by adding bioactive substances into functional matrix materials such as chitosan and hyaluronic acid to enrich the function of the dressing.^{70,71} Adding silver ions to the matrix, for example, can improve the antibacterial ability of the dressing, improve the immune response, and speed wound healing.⁷² The addition of NGF to matrix stimulates the release of nerve cells, immune cells and other cytokines, and promotes the migration and growth of fibroblasts.⁷³ Although bioactive materials can provide a more suitable microenvironment for wound healing, their structure is still different from that of normal skin. Therefore, 3D printing or a variety of materials have been used to construct tissue-engineered dressings that more closely resemble normal skin tissue structure, providing a better skeletal structure for cell growth and skin remodeling. However, its relatively high cost limits the application of this dressing.⁷⁴

In summary, the ideal skin wound dressing should have the following properties.⁷⁵ (1) good moisturizing effect, (2) good water absorption ability, (3) good air permeability, (4) appropriate mechanical strength, (5) good attachment to

wound, but not sticky with the wound, (6) antimicrobial properties, (7) good biocompatibility, (8) relieve wound pain, (9) low economic cost, (10) simulate skin tissue structure, promote cell growth and skin regeneration. For diabetic wounds, more factors are needed. For example, the pathological changes at different stages in diabetic chronic wounds, the emergence of multiple drug-resistant bacteria, and the effects of some other treatments and drugs on wound healing.^{76,77}

Characteristics and Preparation of Nanoparticles

The Types of Nanoparticles

Nanoparticles, also known as ultra-microparticles, range in size from 1 to 1000nm, with diameters in the transitional region between the cluster of atoms and the macroscopic object.⁷⁸ The small particle diameter of nanoparticles gives them very high specific surface area, quantum size effect and macroscopic tunneling effect.⁷⁹ These characteristics make the material in the state of nano particles have significant improvement in photoelectric, thermodynamic and magnetic physical properties. At the same time, the high specific surface area of nanoparticles makes them have a good application prospect in the fields of reaction catalysis, drug delivery and biotherapy.⁸⁰ Nanoparticles can be roughly divided into inorganic nanoparticles and organic nanoparticles according to their raw materials. Inorganic nanoparticles can be further divided into metal nanoparticles and non-metal nanoparticles.

Preparation Method of Nanoparticles

Inorganic Nanoparticles

Different kinds of nanoparticles have different preparation methods. According to the size of the starting material, inorganic nanoparticles can be roughly divided into bottom-up and top-down methods.⁸¹ The basic principle of top-down is to reduce the size of the starting material by mechanical means or laser ablation to achieve the purpose of preparing nanoparticles. The specific methods mainly include mechanical milling, laser ablation and ion sputtering.^{82–84} Mechanical milling is the use of ball mill, bulk raw materials and grinding ball together in the container, by adjusting grinding parameters and to the reaction system to add different kinds of proportion of raw materials to achieve the particle size reduction of raw materials, and the use of chemical reaction between different raw materials to achieve the purpose of modification.⁸² This preparation method can produce high purity nanoparticles on a large scale and is simple. However, the grinding process requires a long time and a high energy supply, and the materials of the grinding sphere may also be mixed into nanoparticles during the grinding process to reduce the purity of the product.⁸⁵ Laser ablation method uses high energy laser beam to irradiate the target material, causing the fragmentation of raw materials in the form of nanoparticles.⁸⁶ The nanoparticles generated after fragmentation form colloid with the solution of soaking raw materials. This method can prepare nanoparticles in suspension state. Nanoparticles with different parameters can be obtained by adjusting the duration and wavelength of laser pulse.⁸⁷ However, due to the product forming colloid and dispersing in the solution, the contact between laser and raw material is hindered, which limits the overall yield.⁸⁸ Another preparation method is ion sputtering, in which the solid surface is vaporized by an inert gas ion beam to produce nano-diameter particles.⁸⁹ This method is especially suitable for the preparation of refractory metals and intermetallic compounds, but its application is limited by complex preparation conditions.⁹⁰

The bottom-up approach starts with smaller molecules that contain raw materials and eventually forms nanoparticles through physical or chemical reactions. According to the state of matter in the preparation process of nanoparticles can be roughly divided into solid method, liquid method and gas phase method.^{91–93} The solid-state method excites or breaks the raw materials into nanoparticles by means of pulse laser and thermoactive chemical vapor deposition, and then redeposits them as films or particles on the surface of the collection plate.⁹¹ Liquid synthesis methods mainly include sol-gel method, chemical reduction method and solvothermal method.⁹² Different kinds of nanoparticles are prepared by redox reaction and gel formation. The gas phase method is to spray the precursor solution into the reactor to form atomized steam, which forms nanoparticles under the action of photothermal and is finally collected in the collection system. According to the different reaction chamber can be divided into spray pyrolysis, laser pyrolysis and flame pyrolysis.^{94,95} In addition to the above methods, the green synthesis method using microorganisms or plants has been increasingly widely used in recent years. The desired nanoparticles are obtained by applying different microorganisms and enzymes,

isolates and extracts of plant products.⁹⁶ This preparation method does not involve the use of high temperature and high pressure and toxic chemicals, and is an economical, efficient and environmentally friendly preparation method. After solving the safety risk of microorganism and the purity of plant extraction, it will have excellent application prospect.⁹⁷

Organic Nanoparticles

The preparation methods of organic nanoparticles are different from those of inorganic nanoparticles. Due to the limitations of organic compounds, most of the preparation methods are completed in liquid phase.⁹⁸ It can be divided into monomer polymerization and polymer dispersion according to top-down and bottom-up synthesis methods. The classical methods to obtain polymer nanoparticles by polymerization of monomers are emulsion polymerization and solution-like polymerization.^{99,100} By limiting the polymer monomer and initiator system to a small space, the size of the product is controlled by controlling the micellar size, so that the diameter of the product is controlled at the nanometer level. Common methods include conventional emulsion polymerization, soap-free emulsion polymerization, fine emulsion polymerization and microemulsion polymerization.^{101–104} Monomer polymerization technology is mature and suitable for the preparation of large-scale nanoparticles. However, the products prepared by this method often have residues of unreacted monomers and initiators, which affect the purity of the products to a certain extent.¹⁰⁵ At the same time, various adjuvants and surfactants in the reaction system may have certain toxicity, which limits the application of the product in the biological field.¹⁰⁴

The top-down method is to prepare small-sized polymer nanoparticles by dispersing and emulsifying large-sized polymer materials. The specific methods include emulsification-solvent evaporation method, emulsification-solvent diffusion method, solvent substitution method, supercritical fluid technology and nano precipitation method.^{106–110} Compared with monomer synthesis, these methods are easier to operate and require milder conditions than monomer polymerization, so they are more suitable for the preparation of biological related nanomaterials.¹¹¹ In the dispersion process, drugs or other substances can also be mixed to prepare drug-carrying nanoparticles or modified nanoparticles, which enriches the function and effect of nanoparticles.¹¹² Although this preparation method solves the problem of monomer and toxic substance residues, but the control effect of product size is not good, and further research is needed.

The Mechanism of Nanoparticles

Wound healing is a continuous and dynamic process, in addition to the body's own internal healing process, a good external environment and various beneficial interventions for wound healing can accelerate the healing process. In this process, nanoparticles play a role in promoting wound healing by virtue of their two characteristics. The first kind of nanoparticles are used in wound dressings by virtue of their biological functions. For example, the metal nanoparticles represented by silver nanoparticles can attach to the bacterial cell membrane to promote the destruction of cell membrane structure and inhibit the activity of bacterial enzymes, thus producing good antibacterial effect.¹¹³ The other kind of nanoparticles are mainly used in the construction of wound dressings by virtue of their physical and chemical properties. These nanoparticles become carriers of some drugs or growth factors through the adsorption capacity of their high specific surface area or the ability of their surface chemical structure to bind to drugs. For example, when PLGA nanoparticles are loaded with VEGF, the exogenous local delivery of VEGF can be realized, which can promote the formation of neovascularization and reepithelialization of wound tissue, and accelerate the formation of granulation tissue.¹¹⁴

Effects of Nanoparticles on Wound Healing

The biological function and physical characteristics of high specific surface area of nanoparticles make them have a very good application prospect in promoting wound healing. According to the different types of nanoparticles, we will introduce the representative inorganic and organic nanoparticles in the field of wound healing.

Inorganic Metal Nanoparticles

AgNPs

The antibacterial ability of Ag in nature has long been noted, so AgNPs is one of the earliest nanoparticles used in skin healing. Solid silver has no antibacterial properties and only has its biological effects when it is in its soluble form.¹¹⁵

Silver can interfere with the cytochrome in the bacterial respiratory chain, blocking the microbial respiratory chain.¹¹⁶ At the same time, silver can also change the membrane potential, damage the membrane function of microorganisms.¹¹⁷ In addition, silver can also bind to the genetic material of microorganisms, inhibiting the normal replication, transcription and translation in microbial cells.¹¹⁸ Silver also promotes wound healing by regulating the levels of cytokines in the wound to reduce inflammation, reduce lymphocyte infiltration, and enhance epithelial reformation.¹¹⁹ In addition to its own antibacterial effect, AgNPs can also enhance the antibacterial ability of silver itself by combining with other materials or achieve antibacterial effect through other ways. Zhou et al found that the constructed Ag/AgCl/rGO nanomaterials could achieve bactericidal effect by promoting the generation of oxygen free radicals or oxidation free radicals.¹²⁰

While silver has proven antibacterial, antifungal, and antiviral properties, its direct application to the wound site alone poses a number of problems. Silver alone has a certain biological toxicity, and silver alone in the wound site cannot maintain a stable concentration of silver, easy to lead to local aggregation and adverse reactions, and the wound required a moist and breathable growth environment which is not AgNPs can provide.¹¹⁸ Therefore, it is of great significance to modify AgNPs and equip them with other biological materials to prepare hydrogel, fiber membrane or scaffold and apply them in wound healing (Table 1). The existing modification applications are mainly developed from two aspects. One is to directly combine AgNPs with matrix materials with good biocompatibility or certain biological activity. Matrix materials play the role of carrier, and AgNPs plays a major role in dressing. For example, Chen et al prepared AgNPs using green deoxidizing agent egg white, and then added konjac glucomannan (KGM) powder to AgNPs solution to prepare KGM/AgNPs composite sponge.¹²¹ The results showed that this wound dressing had good antibacterial activity, and could promote the growth of fibroblasts, accelerate wound epithelialization and wound healing. Another approach is to modify AgNPs, which is combined with other biologically active drugs, proteins or factors, and then loaded with the complex in the matrix material for promoting wound healing. In this combination, AgNPs and its bound drugs, proteins or factors often play a synergistic role, which enhances the biological effects of each other while retaining their own characteristics, so as to achieve better therapeutic effects. For example, the combined application of chitosan and AgNPs can enhance their own antibacterial effect and further improve the overall antibacterial effect.¹²² Liu et al modified AgNPs with aloe vera, which not only improved the antibacterial ability of AgNPs, but also endowed the combined ability to promote proliferation and migration.¹²³ They applied the aloe vera in the hydrogel based on silk fibroin protein to treat full-layer skin wounds, and the results showed obvious healing effect.

AuNPs

Gold nanoparticles have the same biocompatibility as silver and are currently used in drug delivery, photothermal therapy and tissue regeneration. When gold nanoparticles come into contact with bacteria, they form void structures in the cell walls of the bacteria, causing the loss of bacterial contents.¹⁰ AuNPs can also cause bacterial metabolic dysfunction by interfering with ATP synthesis. In addition, AuNPs, like AgNPs, can interfere with the transcription and replication of genetic material and inhibit bacterial proliferation until death.¹³⁵ AuNPs also has significant antioxidant activity, which can reduce DPPH, OH and other reactive oxygen components by neutralizing free radicals.¹³⁶ The antibacterial and antioxidant effects of AuNPs can inhibit the accumulation of reactive oxygen species, reduce the accumulation of inflammatory cells, and maintain a sterile environment in the wound, thus promoting wound healing.² AuNPs also has sensitization effect. When AuNPs is combined with other antibacterial drugs or substances, the antibacterial effect can be significantly improved.¹³⁷ This feature also makes AuNPs have a wide prospect of combined application in the field of wound healing (Table 2).

Chen et al constructed a wound dressing based on dextran/sericin, and carried AuNPs into the material to construct a wound dressing with significant antibacterial activity. Animal experimental results showed that wound healing was significantly accelerated and scar formation was significantly reduced.¹³⁸ Although AuNPs can inhibit bacterial growth and promote wound healing, more often AuNPs is used in combination with other antibacterial substances or particles. Li et al constructed a chitosan wound dressing embedded with Au-Ag nanoparticles, and compared with CS-Ag without Au, the antibacterial effect of CS-Au-Ag was significantly enhanced. In the presence of AuNPs, lower concentrations of silver nanoparticles can achieve the same antibacterial effect as CS-Ag. AuNPs also have similar effects to drugs with

Table I Different Kinds of Material Combinations of AgNPs and Their Therapeutic Effect

Material	Dressing Form	Results	Ref.
KGM	Sponge	Excellent antibacterial activity No obvious cytotoxicity Promote wound healing	[121]
Hyaluronic acid, alginate	Membrane	Antibacterial activity to planktonic bacteria Stimulate wound healing	[124]
γ -glutaminate	Hydrogel	Continuous release of antibacterial factors Promote collagen deposition	[125]
Sericin, chitosan	Hydrogel	Significantly increase antibacterial activity Promote fibroblast growth	[122]
Hydroxyapatite, polyurethane	Foam	Accelerate epithelial reformation Antibacterial effect of four kinds of bacteria Promote collagen deposition Promote scar-free wound healing	[126]
Chitosan, PVP	Membrane	Wound healing can be observed directly Enhanced antibacterial activity	[127]
Polyvinyl alcohol, cellulose	Hydrogel	Significant antibacterial effect Promotes angiogenesis Accelerate wound healing	[128]
Chitosan, PEG	Hydrogel	Antibacterial and antioxidant activities Promote chronic wound healing	[129]
AGAR, fumaric acid	Hydrogel	Synergistic antibacterial action Promote wound collagen deposition Accelerate angiogenesis	[130]
Aloe, silk fibroin	Hydrogel	Significantly enhance antibacterial properties Promote cell proliferation and migration Accelerate chronic wound healing	[123]
rhEGF, polyurethane	Foam	Promote cell growth Accelerate diabetic wound healing Good absorption and antibacterial ability	[131]
bFGF, chitosan	Hydrogel	Obvious bacteriostatic effect Promote granulation Promote regeneration of infected wounds	[132]
EGF, chitosan	Hydrogel	Good sustained release capability Significantly enhanced antibacterial activity Accelerate diabetic wound healing	[133]
Bamboo cellulose nanocrystals	Hydrogel	Promote growth factor release Increases blood vessel formation Accelerate collagen deposition	[134]

antibacterial properties.¹³⁹ Zou et al constructed a KGM/Gelatin@AuNPs/GS sponge by combining gentamicin sulfate (GS) with AuNPs. The results showed that the combined application of GS and AuNPs had significantly better antibacterial effect than AuNPs or AuNPs alone, which could effectively remove superbacteria, inhibit bacterial growth and promote wound healing.¹⁴⁰

CuNPs

In addition to AgNPs and AuNPs, two of the most widely used nanoparticles in wound healing, other metal nanoparticles have also been used in the design of wound healing dressings. CuNPs can release Cu²⁺, which changes the enzyme's function by solidifying the protein structure, thus achieving its killing effect on bacteria.¹⁴⁷ Studies have found that copper has significant inhibitory effect on a variety of fungi and drug-resistant bacteria, which is very beneficial for

Table 2 Different Kinds of Material Combinations of AuNPs and Their Therapeutic Effect

Material	Dressing Form	Results	Ref.
Dextran, sericin	Cotton Fabric	Accelerate wound healing Reduce scar formation	[138]
Pig diaphragm	Scaffold	Enhanced cell proliferation Lower ROS levels Promote wound healing	[141]
Collagen	Scaffold	Reduce inflammation Promote granulation tissue formation	[142]
Gentamicin, KGM, gelatin	Sponge	Enhance antibacterial effect Good water retention Deadly to super bacteria	[140]
Dextran, polyvinyl alcohol	Cotton Fabric	Good biocompatibility Accelerate wound healing	[143]
Ag, chitosan	Sponge	Significantly enhance antibacterial effect Low cytotoxicity Significantly promote wound healing	[139]
Poloxamer 407, PEG, PAH	Hydrogel	Obvious antibacterial and antifungal ability Good biocompatibility Enhanced reepithelialization Promote collagen deposition	[144]
KGF, gelatin	Hydrogel	Promotes keratinocyte proliferation Good biocompatibility Promote wound reepithelialization	[145]
Chitosan, arginine	Membrane	Accelerate wound healing Promote collagen deposition	[146]

chronic wounds of diabetes.^{148,149} As a cofactor of superoxide dismutase and cytochrome oxidase, copper can promote the formation of the enzymes.¹⁵⁰ Copper also boosts immunity by stimulating the production of interleukin 2. Copper also induces the expression of VEGF, which stimulates angiogenesis in the wound.¹⁵¹ However, the antimicrobial effect of copper is dose-dependent, and high concentration of copper has certain toxicity to cells, which should be considered in dressing design.¹⁵²

CuNPs is also used in both direct and modified applications. Klinkajon et al constructed a copper alginate hydrogel using alginate, and the results showed that the effluent gel showed significant antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis* and *Streptococcus*, which was proportional to the Concentration of Cu²⁺ ions.¹⁶⁰ Modified CuNPs can be used in wound dressings to obtain better therapeutic effect (Table 3). Xu et al constructed a composite hydrogel composed of PDA and Cu-Cs doped calcium silicate ceramic, and found that the hydrogel has a rapid and long-term inhibitory effect on methicillin-resistant *Staphylococcus aureus* and *Escherichia coli*, and can promote blood vessel formation and accelerate wound healing.¹⁵³

Other Metal Nanoparticles

Metal nanoparticles can also play a role in promoting wound healing in the form of compounds in addition to acting as simple substances. ZnO can kill bacteria and fungi by accumulating ROS directly on the surface of bacteria and inducing ROS production.¹⁶¹ As the main component of metalloproteinase, Zn can participate in the formation of ECM and promote wound healing.¹⁶² Li et al constructed a ZnO/Ag/PVP/PCL nanofiber to enhance tissue regeneration and wound healing, and found that this composite structure had better anti-inflammatory, antibacterial, skin regeneration and wound healing effects than traditional drugs or single metal nanofibers.¹⁶³ In addition to ZnO, TiO₂, CeO₂, Fe₂O₃ and other emerging nanoparticles also play a certain role in skin wound healing. TiO₂ has good biocompatibility and bioactivity,

Table 3 Different Kinds of Material Combinations of CuNPs and Their Therapeutic Effect

Material	Dressing Form	Results	Ref.
PDA, calcium silicate	Hydrogel	Inhibit drug-resistant bacteria growth Promote angiogenesis	[153]
Chitosan, polyvinyl alcohol	Membrane	Inhibit Gram-positive bacteria growth Promote wound healing	[154]
Chitosan, gallic acid	Membrane	Significant antibacterial properties Promote healing of infected wounds	[155]
GelMA, BACA	Hydrogel	Promote angiogenesis Reduce the level of inflammation Significant antibacterial properties	[156]
Chitosan, CDs, GO	Hydrogel	Inhibit bacterial growth Promote wound healing	[157]
GO, chitosan, hyaluronic acid	Sponge	Good biocompatibility Reduce inflammation Speed up the healing process	[158]
PDA, hydroxyapatite	Hydrogel	Promote angiogenesis Promote collagen deposition Good antibacterial properties	[159]
Alginate	Hydrogel	Promote blood clotting in the wound Significant antibacterial properties	[160]

and also has good water retention effect, which can promote the healing of burn wounds.^{164,165} Iron oxide nanoparticles are easy to synthesize, have good degradation and low toxicity, and also have certain antibacterial effect.^{166,167} Cerium oxide nanoparticles have strong free radical scavenging ability, which can significantly improve the free radical aggregation of chronic diabetic wounds.^{168,169} Meanwhile, cerium oxide also has good biocompatibility,¹⁷⁰ which makes it have a good application prospect in the field of diabetic wound healing.

Inorganic Non-Metallic Nanoparticles

SiO₂ Nanoparticles

Silicon dioxide, one of the non-metallic materials, has attracted much attention because of its good biological properties. Silica has good biocompatibility and does not cause additional immune responses in organisms, especially in wounds.^{171,172} The raw materials of silica are easy to obtain, and the processing and preparation methods are mature.^{171,172} Silica can be prepared into mesoporous nanoparticles, non-porous nanoparticles, silica gel and other structural forms.¹⁷³ These structures give silica good physical and chemical adsorption capacity and can be used as an ideal carrier for carrying a variety of drugs and proteins. Mirzahosseini et al constructed curcumin-silica nanoparticles by loading curcumin onto the surface of silica nanoparticles, taking advantage of silica's good drug loading capability.¹⁷⁴ The composite nanoparticles showed photodynamic inactivation against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Ferenc et al constructed a SiO₂-PVP composite gel that demonstrated significant ability to promote wound contraction and epithelialization, with the regenerated epidermis showing better differentiation and multilayer structure.¹⁷⁵ Jin et al constructed a mesoporous Silicon nanoparticles loaded with Ag/AgBr, which has a very strong killing effect on bacteria under the photocatalytic action¹⁷⁶ (Figure 5). Alvarez et al constructed a silica-collagen I nanocomposite hydrogel loaded with gentamicin and rifamycin. This hydrogel showed good continuous drug release ability and antibacterial activity, which is beneficial to the infection prevention of chronic diabetic wounds and promote wound healing.¹⁷⁷

Carbon Nanoparticles

Carbon nanoparticles can be roughly divided into carbon dots, carbon nanotubes and graphene/GO according to the different combinations of carbon elements. The structure of carbon nanoparticles is beneficial to the growth of cells and

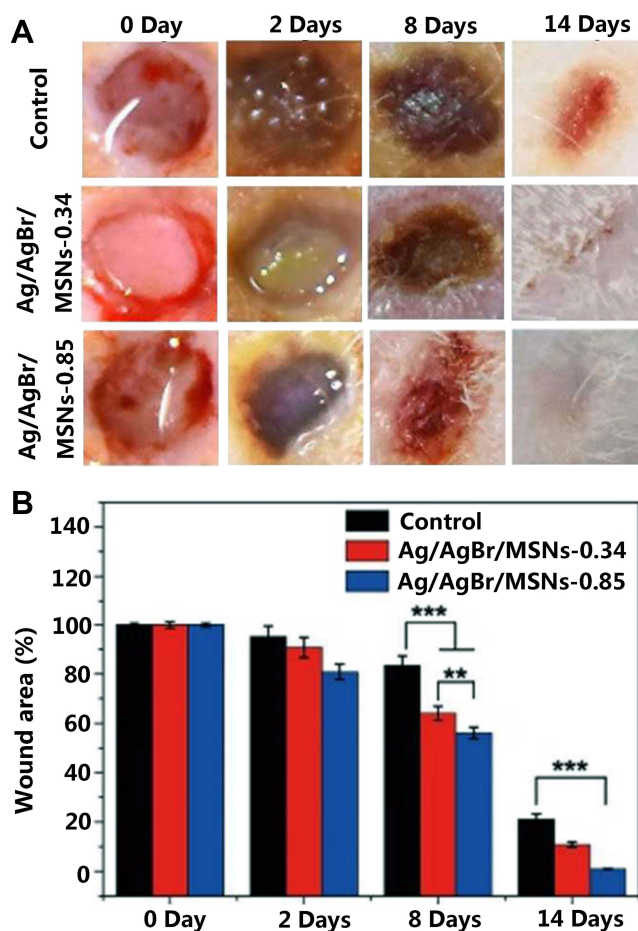


Figure 5 The corresponding wound photographs (A) and the recovery progress of the wounds (B) of control group and different concentration Ag/AgBr/MSNs (** $p < 0.01$; *** $p < 0.001$).

Notes: Republished with permission of Royal Society of Chemistry from Jin C, Liu XM, Tan L et al. Ag/AgBr-loaded mesoporous silica for rapid sterilization and promotion of wound healing. *Biomaterials Science* 2018, 6 (7), 1735–1744, permission conveyed through Copyright Clearance Center, Inc.¹⁷⁶

tissues. Carbon nanotubes have a similar structure to collagen fibers and can affect cell adhesion, proliferation and differentiation.¹¹ Graphene's unique base plane structure and shape allow it to be used for surface functionalization of drugs, biomolecules and other nanomaterials.¹⁷⁸ At the same time, the high surface area and adsorption capacity of graphene nanosheets make it conducive to cell adhesion and growth.¹⁷⁹ Carbon nanoparticles also have certain antibacterial activity and can enhance the antibacterial effect of other antibacterial substances. It was found that carbon dots, carbon nanotubes and graphene can kill bacteria in many ways, such as changing the surface charge environment of bacteria, mechanically destroying the cell wall of bacteria, and promoting ROS release.^{180,181} Cui et al constructed a carbon point release hydrogel with antibacterial activity, high biocompatibility and fluorescence properties. The results showed that carbon hydrogel has a long-term and broad-spectrum antibacterial ability¹⁸² (Figure 6). Aslan et al constructed an antibacterial biofilm of carbon nanotubes assembled layer by layer with polypeptides, and the result shows a significant and rapid bactericidal effect.¹⁸³ Fan et al constructed a hydrogel based on silver and graphene polymers, which showed good bactericidal efficacy and accelerated wound healing.¹⁸⁴

Organic Nanoparticles

Synthetic Polymer Nanoparticles

Biodegradable polymer materials with good biocompatibility are widely used in tissue bioengineering. Common synthetic polymers include but are not limited to PLGA, PCL, PU and polyethylene glycol. Nanoparticles prepared by synthetic polymer matrix have the following characteristics: There are various construction methods. Monomers or raw

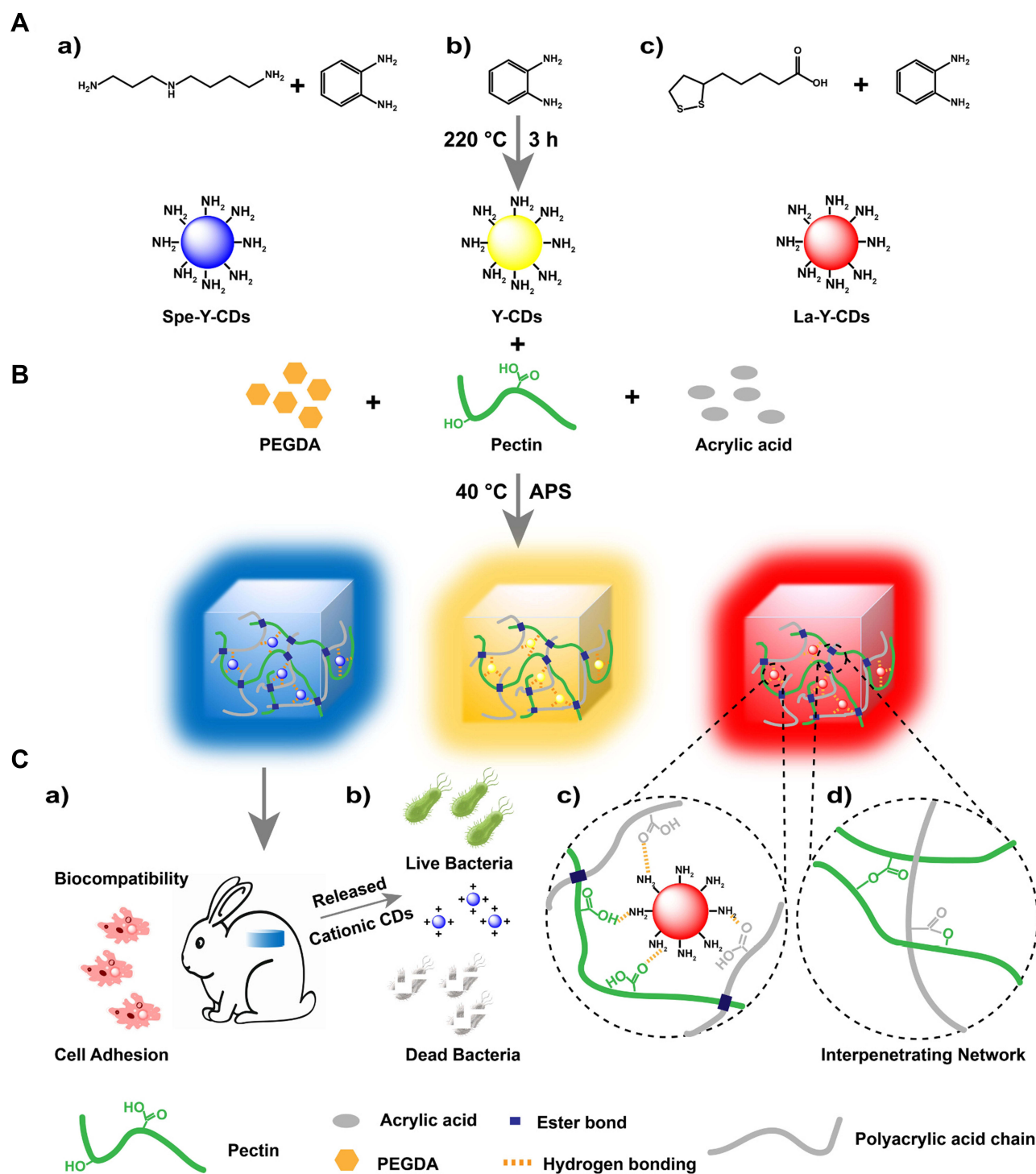


Figure 6 Design strategy of the SCDs-AP hydrogel. (A) Synthesis of cationic antibacterial CDs starting from (B) assembly of the fluorescent antibacterial CDs hydrogel through pectin, acrylic acid, CDs, APS, and PEGDA. (C) Scheme of molecular structure and applications of fluorescent antibacterial hydrogel.

Notes: Reprinted from Cui FC, Sun JD, Ji J et al. Carbon dots-releasing hydrogels with antibacterial activity, high biocompatibility, and fluorescence performance as candidate materials for wound healing. *Journal of Hazardous Materials* 2021, 406. Copyright 2021, with permission from Elsevier.¹⁸²

materials with different functional groups can be selected according to requirements to prepare nanoparticles that meet requirements. Rich functional groups can combine with a variety of drugs, growth factors or proteins to achieve the purpose of local drug delivery.¹⁸⁵ By adjusting the degradation rate and degradation environment of degradable polymer nanoparticles, the targeted drug or factor can be released at a fixed point or sustained release, so as to achieve better

effect with a smaller dose.² Agel et al constructed a nanoparticle with PLGA, polyvinyl alcohol and chitosan as the matrix materials, and prepared a nanoparticle with good photodynamic effect and antibacterial performance on the surface loaded on the surface.¹⁸⁶ Hasan et al constructed a poly (lactic-co-glycolic acid)-polyethylenimine (PLGA-PEI) nanoparticles loaded with clindamycin, which can achieve continuous release of clindamycin and has a significant killing effect on MRSA.¹⁸⁷

Natural Polymer Nanoparticles

In addition to synthetic polymer nanoparticles, nanoparticles prepared from natural polymers also have a wide application prospect in wound healing (Table 4). Collagen, chitosan, hyaluronic acid, alginate and other natural polymers can be prepared into nanoparticles either alone or mixed with other drugs or particles in various ways. Compared with synthetic polymer, the structure of natural polymer is more similar to normal tissue, which is conducive to the formation of wound extracellular matrix.¹⁸⁸ At the same time, most natural polymers are polysaccharides or peptides, which have better hydrophilicity and adhesion, and are more suitable for cell adhesion growth on its surface.⁹ In addition, some natural polymers have their own wound-healing properties. Chitosan itself has a certain inhibitory effect on the growth of bacteria, which can reduce the chance of wound infection.¹⁸⁹ Alginate can promote platelet aggregation and accelerate the early process of wound hemostasis.¹⁹⁰ Collagen itself as a protein, its degradation products can also be reused to promote wound cell growth and ECM formation.¹⁹¹

Although natural polymers are more often involved in the construction of wound dressings as matrix materials, their preparation as nanoparticles can give them more properties. Natural polymers also have some disadvantages. Some natural polymers may induce an immune response, and the rapid degradation rate of natural polymers is also an issue to be considered in wound dressing construction.^{190,199} Wang et al constructed a calcium alginate hydrogel supported by bioactive chitosan nanoparticles. This hydrogel shows significant antibacterial activity and promotes il-6 synthesis and secretion by regulating ROS production. Animal experiments showed that the gel could promote angiogenesis and accelerate wound healing.¹⁹² Choudhary et al used silver nanoparticles as antibacterial agents, calcium alginate nanoparticles as hemostatic agents, serum to provide nutrients and growth factors, and chitosan as a matrix of composite hydrogels. The results showed that the combination had antibacterial effect, promoting proliferation, promoting angiogenesis and accelerating wound healing.¹⁹⁷

Table 4 Different Kinds of Combinations of Natural Polymer and Their Therapeutic Effect

Material	Supplementary Materials	Results	Ref.
Chitosan	Alginate	Significant antibacterial activity Regulate ROS formation Promote angiogenesis	[192]
Chitosan	Alginate	Promote granulation tissue formation Reduce inflammation	[193]
Chitosan	Rosmarinic acid	Good biocompatibility Promote wound healing	[194]
Chitosan	Curcumin, collagen, alginate	Reduce inflammatory cell infiltration Promote granulation tissue formation Accelerate wound healing	[195]
Alginate	Polymyxin, lidocaine, chitosan	Accelerate wound contraction Inhibit bacterial growth	[196]
Alginate	Ag, chitosan, fresh blood	Broad-spectrum antibacterial properties Promotes cell proliferation Promote neovascularization Accelerate diabetic wound healing	[197]
Hyaluronic acid	Vitamin E, lecithin	Keep releasing vitamin E Reduce water loss from the wound	[198]

Future Perspectives

Compared with normal wound healing, chronic wound healing caused by diabetes has more complex healing process and more unfavorable self-condition environment. Long-term exposure to the external environment greatly increases the chance of infection. Meanwhile, the persistent inflammatory environment in chronic stage and the vascular barrier caused by hyperglycemia greatly delays the rate of tissue regeneration. On the basis of the antibacterial properties and good biocompatibility of the raw materials of nanoparticles, the high surface area, dispersion and adsorption brought by the nano-diameter particles give nanoparticles better delivery ability and binding performance.

Different kinds of nanoparticles have different advantages and disadvantages in the application of wound dressing. Metal nanoparticles are relatively easy to prepare and have better stability. At the same time, the ions brought by metal nanoparticles give it better antibacterial performance. However, the metabolism and accumulation of metal nanoparticles in vivo are also worthy of attention. The rich functional groups of organic nanoparticles can be combined with other drugs and growth factors to achieve better local delivery and sustained release effects. Some natural polymer-derived nanoparticles have better biocompatibility and are more suitable for cell adhesion. But the construction of organic nanoparticles is relatively more complex, so how to efficiently construct organic nanoparticles with uniform diameter also needs further exploration.

Using nanoparticles loaded with drugs and growth factors or using nanoparticles to modify traditional wound dressings to promote chronic wound healing has very definite therapeutic effects and advantages. But nanoparticles in application and diabetes chronic wound healing process there are still some problems need to consider: wound inflammatory environment in different stages of chronic wound healing has the opposite effect, how to make the nanoparticles on the inflammatory reaction in different stages of different degree of regulation is one of the problems that need to be solved in the future. The antibacterial properties of some nanoparticles showed obvious concentration dependence, but high concentration nanoparticles had certain cytotoxicity. How to balance antibacterial performance and biosafety is also an issue to be considered. The combination of multiple nanoparticles or nanoparticles with other drug factors may be a possible way to achieve a comprehensive therapeutic effect. Finally, it is also worth exploring how to improve the preparation process of nanoparticles and reduce the cost while ensuring purity and functionality, so that nanoparticles can be commercialized and applied in clinical practice. It is foreseeable that when these problems are solved, nanoparticles have unimaginable application prospects in chronic wound healing.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial/non-financial relationships that could be construed as a potential conflict of interest.

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