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Smart microneedle patches for wound healing and management

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The number of patients with non-healing wounds is generally increasing globally, placing a huge social and economic burden on every country. The complexity of the wound-healing process remains a major health challenge despite the numerous studies that have been reported on conventional wound dressings. Therefore, a therapeutic system that combines diagnostic and therapeutic modalities is essential to monitor wound-related biomarkers and facilitate wound healing in real time. Microneedles, as a multifunctional platform, are promising for transdermal diagnostics and drug delivery. Their advantages are mainly reflected in painless transdermal drug delivery, good biocompatibility, and ease of self-administration. In this work, we review recent advances in the use of microneedle patches for wound healing and monitoring. The paper first provides a brief overview of the skin structure and the wound healing process, and then discusses the current state of research and prospects for the development of wound-related biomarkers and their real-time monitoring based on microneedle sensors. It summarizes the current state of research based on the unique design of microneedle patches, including biomimetic, conductive, and environmentally responsive, to achieve wound healing. It further summarizes the prospects for the application of different microneedle-based drug delivery modalities and drug delivery substances for wound healing, due to their superior transdermal drug delivery advantages. It concludes with challenges and expectations for the use of smart microneedle patches for wound healing and management.

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1. Introduction

Skin wounds have a substantial negative impact on healthcare systems and economies worldwide. On the one hand, wound management is a core issue in clinical care due to the constant occurrence of traumatic injuries and the growing prevalence of chronic wounds such as diabetic ulcers and pressure sores.¹

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The increased prevalence also brings huge economic costs. First, diabetic foot ulcers are one of the most chronic wounds, with a lifetime risk of developing foot ulcers of up to 25%.^{2,3} The healthcare costs for diabetic ulcers and amputations in the UK in 2014–2015 were estimated to be between £837 million and £962 million.⁴ On the other hand, low healing rates exacerbate the problem.⁵ In the real world, cure rates for complex patients are reported to be no higher than 40%, which contradicts the reported rates almost close to 100%.⁶

While treatments including oxygen, growth factors, small drug molecules, autologous and stem cells, gene therapy and tissue engineering have been used to promote wound healing, to modulate various physiological processes, recent reports have pointed to an important factor-point delivery.^{7,8} In general, chronic wounds are covered with a layer of hard skin and necrotic tissue, and the various enzymes contained in the wound exudate locally flush out the therapeutic drugs, which greatly reduces their bioavailability.^{7,9} Microneedle patches with micro-nanostructures enable targeted therapeutic drug delivery to living tissues for optimal therapeutic results.¹⁰ The wound healing phase requires care to ensure a better healing state, mainly because the healing process is influenced by a

variety of factors including environment, age, nutrition, and medications.¹¹ Wounds are in an environment where both internal and external environments work together, and these factors affect the healing process.¹² Limited by the subjective experience of traditional visual assessment of wounds, the specific conditions of wounds cannot be accurately reflected.¹³ For early diagnosis, it is necessary to determine wound characteristics including, most importantly, biomarkers, and to examine the wound environment to monitor the healing process.

In recent years, many wearable devices have been applied for wound monitoring to help understand the wound environment in real time by taking wound environment markers as input.¹¹ Therefore, the new type of wound dressing should simultaneously satisfy real-time monitoring, and early diagnosis, and help achieve accurate treatment. In addition to being developed as a drug delivery system, a significant advantage of microneedle devices is their ability to accommodate multiple independent sensors on a single small array to provide timely multiplexed molecular information.¹⁴ Thus, the concept of microneedle patches combining diagnostic and therapeutic modalities in a therapeutic system to achieve real-time monitoring of wound-related biomarkers and promote wound



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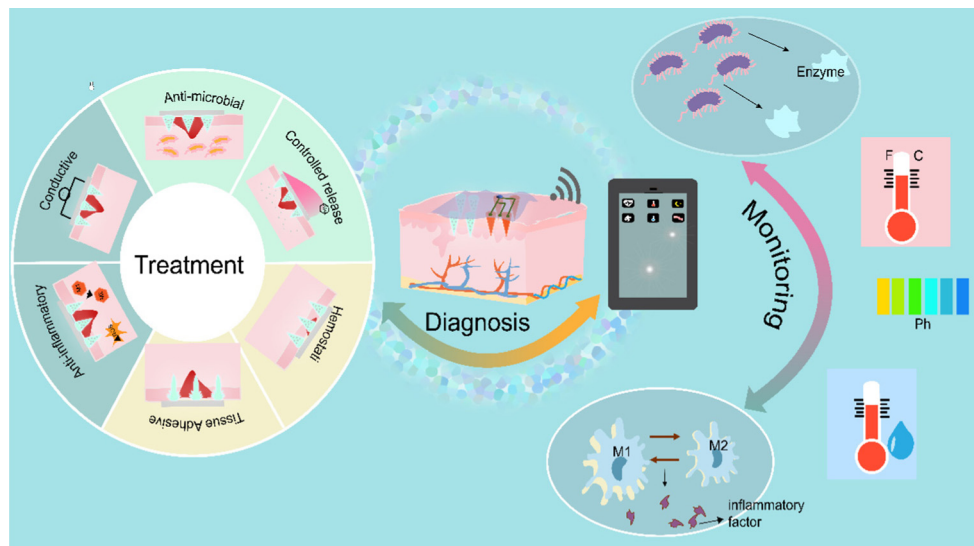


Fig. 1 Schematic diagram of wound intelligent management microneedle patches. Smart microneedle patches combine treatment and monitoring for real-time diagnosis. To summarize, they have five therapeutic modalities: antibacterial, anti-inflammatory, hemostatic, tissue adhesion, and controlled-release drug release. From the monitoring perspective, microneedle patches enable the monitoring of relevant markers such as temperature, humidity, pH, inflammatory factors, and enzymes produced by bacteria.

healing was further elaborated (Fig. 1). Thus, the concept of microneedle patches combining diagnostic and therapeutic modalities in a therapeutic system to achieve real-time monitoring of wound-related biomarkers and promote wound healing is further elaborated. In this review, we describe the skin structure and wound healing process. Then the current research status and development prospects of microneedle sensor-based wound-related biomarkers and their real-time monitoring are discussed. The status of research on microneedle patches based on unique designs, including bionic, conductive, and environmentally responsive, for wound healing is summarized. The prospects of different microneedle-based drug delivery methods and drug delivery substances for wound healing are further summarized. It concludes with challenges and expectations for the use of smart microneedle patches for wound healing and management.

2. Skin structure and the wound healing process

2.1 Skin structure

The human skin is a multilayered structure that primarily consists of the epidermis, dermis, and subcutaneous tissue.¹⁵ The epidermis, mainly composed of cuticles, is the outermost layer of skin. It could resist environmental disturbances such as ultraviolet radiation, pathogenic bacteria, and uncontrollable mechanical damage.¹⁶ It can also prevent dehydration by regulating moisture.¹⁵ The dermis, a thick, collagen-rich connective tissue, is the close-by layer. The extracellular matrix (ECM), living cells, nerve endings, and blood vessels that are abundant in the dermis support the skin's structural integrity, elasticity, and nutrition.^{16,17} The communication between the epidermis and dermis could establish, maintain, and restore

tissue homeostasis.¹⁸ The deepest layer is subcutaneous tissue. It is mainly composed of vascularized loose peri areolar connective tissue and adipose tissue,¹⁹ which provides thermal isolation and mechanical protection to the body.¹⁶ A schematic diagram of the skin structure is shown in Fig. 2A.

2.2 Wound healing process

The normal wound healing process has three stages and is a complex and dynamic process. The first stage is hemostasis and inflammation, which occurs immediately after tissue damage (Fig. 2B). Hemostasis begins with platelet degranulation and the coagulation cascade, culminating in the formation of a hemostatic fibrin clot.²⁰ Fibrin clots then become a scaffold for the infiltration of inflammatory cells such as neutrophils and macrophages, which then migrate to the wound site to remove pathogens (such as bacteria) and cell/tissue debris.²¹ In order to stimulate fibroblasts and epithelial cells to migrate towards the wound site, macrophages also release cytokines such as TGF- α .²²

The proliferative phase starts after the inflammatory phase and occurs after about 4–21 days (Fig. 2C).^{23,24} During this phase, dermal and epidermal cells migrate to and hyperproliferate at the wound site, with the typical events of regenerative epithelialization, collagen deposition, angiogenesis, and formation of granulation tissue.²³ Regenerative epithelialization is the process of establishing an intact epidermis to repair skin damage. This involves the migration and proliferation of keratin-forming cells within the trabecular bed, the differentiation of new epithelial cells into a stratified epidermis, and the restoration of the intact basement membrane zone between the epidermis and dermis.²⁵ Angiogenesis is a process of budding the preexisting blood vessels near the wound, involving endothelial cells migration, proliferation, and branching for the formation of



Fig. 2 Wound healing stage. (A) Skin structure is mainly divided into three layers: epidermis, dermis, and subcutaneous tissue. (B) Hemostatic/inflammatory stage. (C) Proliferative stage. (D) Remodeling stage.

new blood vessels.²⁵ Based on newly formed blood vessels, proliferating fibroblasts invade the clot to form constricted granulation tissue.²⁶

The longest reconstruction phase usually lasts from a few weeks to a few months and is the ultimate stage of wound healing (Fig. 2D).²¹ At this stage, cell proliferation and protein synthesis slow down, and collagen is remodeled into organized fibrils.^{6,21} Type III collagen is gradually being replaced with type I collagen.⁶

Wounds can be divided into acute wounds and chronic wounds according to their stage of healing. Acute wounds undergo the normal wound healing process. In contrast, chronic wounds undergo a disturbed wound repair phase that manifests as a persistent inflammatory phase.²⁷ They may last for weeks, months, or even years and the wounds are highly susceptible to bacterial infections such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and methicillin-resistant *Staphylococcus aureus* (MRSA) that can form biofilms at the wound site.²⁸ Pathological features of chronic wounds include prolonged exposure to pro-inflammatory cytokines, imbalance in the expression of proteases and their inhibitors, altered availability and activity of growth factors, tissue hypoxia and high levels of oxidative stress.²⁹ It is worth noting that chronic wounds are often associated with diseases such as diabetes, obesity, etc. Among the major problems of chronic wounds, diabetes is the most threatening.³⁰ Angiogenesis plays a crucial role in wound healing by providing nutrients and oxygen and by removing metabolic waste products.³¹ In the high glucose environment caused by diabetes, vascular endothelial cells are damaged by oxidative stress, resulting in low cellular activity and reduced proliferation capacity, which delays diabetic wound healing.³² Achieving rapid healing of diabetic wounds is a pressing issue.

3. Microneedle patch for wound monitoring

3.1 Physiological data for monitoring the wound status

It is significant to monitor wound status, which is beneficial to predict the wound trends for real-time treatment.^{33,34} The physiological processes involved in wound healing are intricate. It is also susceptible to environmental factors that can impede or prolong healing, which may contribute to high treatment costs.¹³ Wound dressings that are tailored according to a specific healing situation based on the stage of healing, inflammatory state, moisture levels, and exudation rates are currently used to treat chronic wounds.^{35,36} However, the majority of the time, wound status is assessed through visual inspection, which carries the risk of secondary injury due to frequent replacement and visual errors.^{13,37} Next-generation wound dressings that are capable of real-time monitoring, early diagnosis, and on-demand therapy have received a lot of attention to overcome the wound-healing process's "black box" status.^{38–40} Injured tissue generates exudate, a fluid rich in proteins such as electrolytes, creatinine, fibrinogen, matrix metalloproteinases (MMPs) and c-reactive protein (CRP), and tumor necrosis factor-alpha (TNF- α).^{41,42} Additionally, certain physical wound environment factors, such as temperature, pH, humidity, and exercise, influence wound healing.^{43–48} To achieve early diagnosis of wounds, physiological data related to the wound environment become the main target of monitoring.

During the process of wound healing, pH is an important parameter. Intact skin has a pH of 4.8–6.0.^{49,50} Once stratum corneum is damaged, the underlying tissue is exposed, displaying a normally regulated pH of 7.4. On around day 2, a normally healing wound goes through a brief acidic period with a pH between 4 and 6.5, which helps prevent bacterial growth and

promotes angiogenesis and epithelialization.^{49–51} After a transient decrease in pH, it returns to a neutral pH along with the wound closure.⁵¹ In the meantime, the newly formed skin recovers an acidic milieu. However, the pH tends to remain in a weakly alkaline range at the chronic wound as well as the wound with long-term bacterial colonization.^{51,52} Another crucial parameter in the wound-healing process is temperature. Inflammation or infection may be the cause of a sudden rise in temperature at the site of the wound.⁴⁹ A decrease in temperature at the wound may be caused by ischemia, which tends to hamper wound healing.⁵⁰ It has been demonstrated that a temperature change of approximately 2 °C is the threshold for wound deterioration.⁵⁰ Accordingly, temperature monitoring is generally employed as a potential method of estimating wound status. An inflammatory marker linked to the onset of inflammatory conditions and infection is C-reactive protein (CRP).⁵³ CRP concentrations in the blood suddenly rise from approximately 0.8 mg L⁻¹ to 600–1000 mg L⁻¹ during the acute phase response to inflammation, peaking after approximately 48 h.^{42,54} A biomarker known as urea (UA) has a strong connection to wound healing.⁵⁵ Associated with oxidative stress and bacterial infection in the wound area, uric acid levels rise in unhealed chronic wounds and fall as the wound heals.^{42,56,57} Wound moisture is a key parameter in ensuring optimal healing conditions in wound care.^{47,58} However, moisture-induced infection might increase the exuding of tissue fluid, rendering wounds to be too wet and thus aggravating wound infection.^{47,58} Consequently, moisture monitoring is also important for wounds treated with moist dressings.^{47,58} In addition, studies have reported that glucose,^{59–61} inflammatory factors,⁶² exercise,⁶³ *etc.* can be used as indicators to monitor wound healing.

3.2 Microneedle-based sensors

As the microneedle patches only penetrate the viable stratum corneum and viable epidermis and do not reach the nerve endings or blood vessels, they are minimally invasive procedures and therefore patients do not feel any pain.^{64,65} The microneedle technology is a transdermal drug delivery strategy that overcomes the disadvantages of hypodermic needles, reduces the risk of infection transmission, reduces anxiety, and allows patient compliance.⁶⁶ Microneedle patches have shown high therapeutic advantages in aspects such as immunotherapy,⁶⁵ cancer,⁶⁷ Alzheimer's disease,^{68–71} drug delivery,⁷² and disease diagnosis.^{73,74} By combining electrodes with micronized array substrates, a variety of microneedle-based devices were proposed as sensors and diagnostic systems,⁷⁵ including electrochemical, optical, magnetic, and paper-based biosensors.⁷⁶ Microneedle sensors can be hollow microneedles with sensors on top, electrochemically bonded hollow microneedles, surface-functionalized solid microneedles, or metallized solid microneedles.⁷⁷ Colorimetry, immunoassays, nucleic acid recognition, or electrochemistry can all be used to detect analytes with these microneedle-based biosensors.⁷⁷ Among the existing research reports, electrochemical sensors account for the vast majority. The advantages are small size, speed, low cost, low power consumption, and no sample composition interference.¹⁴ Thanks to the superior biocompatibility and customizable microstructure of microneedle

patches, innovative microneedle-based dressings are likely to be widely used in the future.⁷⁸ Rongyan He and his team placed sensing reagents at the tips of microneedle patches to fabricate a colorimetric skin tattoo biosensor fabricated from a four-region segmented microneedle patch, realizing the detection of four typical biomarkers (pH, glucose, temperature, and uric acid) at the same time. Biosensors change color as markers change, allowing further semi-quantitative analysis by naked eye reading or smart camera capture.⁷⁹ Researchers have recently developed smart colorimetric microneedle patches containing Fe ion-gallate coordination polymer nanodots (FNDs) for on-demand treatment of infected wounds and real-time reporting of these wounds (Fig. 3A).⁸⁰ FNDs have pH-dependent catalase-mimicking activity, and can not only kill bacteria by catalyzing the generation of hydroxyl radicals (OH) from hydrogen peroxide, but also change color depending on pH and hydrogen peroxide. By observing the change in color of the microneedle patch, it is possible to distinguish between normal wounds and bacterially infected wounds.⁸⁰ A colorimetric dermal tattoo biosensor fabricated from microneedle patches was developed for monitoring pH, glucose, uric acid, and temperature. The microneedle biosensor exhibits color changes in response to changes in the concentration of the marker allowing for visual semi-quantitative analysis.⁷⁹

Microneedle patch sensors offer significant advantages in drug delivery and sensing physiological signals. For example, microneedle patches can increase permeability and can facilitate the delivery of various drugs. It has also been demonstrated that the same microneedle-based sensor prevents sweat contamination and signal noise during sensing while also minimizing damage to dermal nerves and blood vessels.⁸¹ For wound healing and sensing, an origami smart silk fibroin-based microneedle dressing (i-SMD) with an inverse opal photonic crystal (IO PC) structure, microfluidic channels, and microcircuits was proposed (Fig. 4A).⁸² By using capillary force, the microfluidic channels can direct the liquid flow to the area of detection, making it possible to detect biomarkers in liquid without the need for an external power supply.⁸² Microelectronic circuits can monitor activity in the trauma area and reduce secondary injuries caused by exercise.



Fig. 3 (A) Schematic diagram of how the ligand polymer nanoparticle enzyme integrated colorimetric microneedle patches are made and how they are used to detect and treat wound infections.⁸⁰ Copyright 2022 Elsevier.

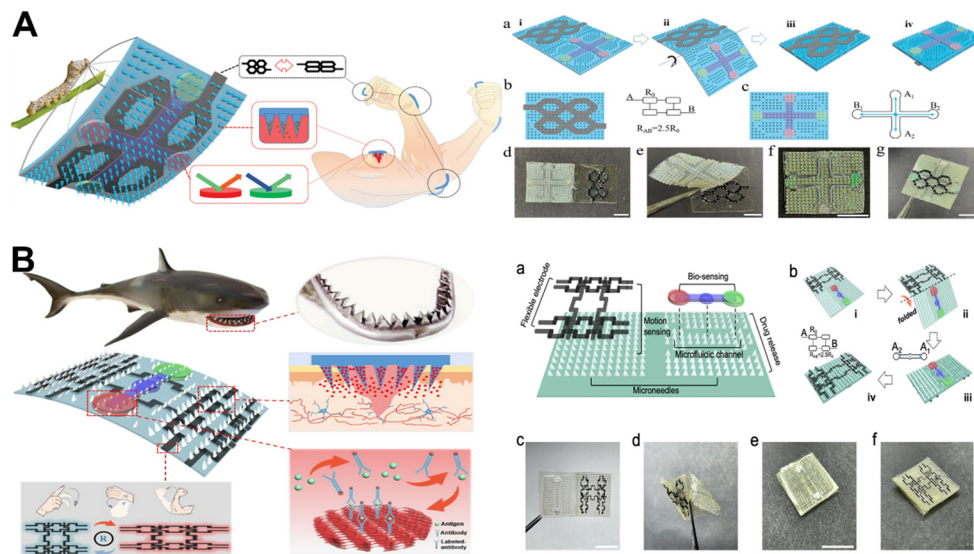


Fig. 4 (A) Diagram of the highly integrated, intelligent, biocompatible, stretchable i-SMD for biochemical sensing, motion monitoring, and wound healing.⁸² Copyright 2020 Wiley-VCH. (B) Diagrammatic representation of a microneedle patches based on shark teeth for intelligent wound management.⁸³ Copyright 2021 American Chemical Society.

Among them, the temperature-responsive *N*-isopropyl acrylamide hydrogel realizes intelligent drug release. On the microneedle patch, a cross-shaped microfluidic channel is made, and the four regions of the channel have IO PC structures.⁸² Capillary force allows the liquid to spontaneously diffuse along the microfluidic channel after the smart patch is applied to the wound, bringing it into complete contact with the IO PC structure in the detection area. The relative levels of biomarkers in wound secretions can be read simply by detecting the fluorescent signal in the detection area. The intelligent microneedle patch integrating motion sensing, intelligent drug release, and wound biochemical analysis can realize intelligent management of wounds and provide a reference for management of other diseases. The article proposes that the microneedle patch can be used to analyze a variety of biochemical indicators at the wound healing stage, but the way to achieve this is to directly use a solution containing a high concentration of target molecules, which still has a certain gap with the actual demand.

The team proposed a microneedle patch for smart wound management inspired by the flat and angled structure of a shark's tooth to further enhance the feasibility of smart wound management (Fig. 4B).⁸³ It was worth noting that the bionic shark teeth enabled the microneedle patches to penetrate the skin with improved grasping force. The microneedle patch was used for the analysis of the effect of IL-6 on inflammatory reaction at the wound site. Interestingly, IL-6 levels increased significantly from day 0 to day 3 and continued to decline from day 3 to day 9 due to treatment, consistent with normal wound healing changes.⁸³

4. Microneedle design for wound healing

4.1 Biomimetic design

Many aspects of wound healing have been studied with microneedle patches. However, as some microneedle patches have

poor adhesion to the skin, they require auxiliary equipment such as medical tape to achieve optimal penetration and fixation.^{84,85} The straight and symmetrical structure of the microneedle patches may be the main reason. Inspired by bionics, the researchers have further improved the structure of microneedle patches in order to improve their adhesion and avoid secondary cracking. For example, a microneedle patch with a claw-like tip, inspired by an eagle's claw, enables stable skin adhesion, and promotes wound healing (Fig. 5A).⁸⁶ In addition, shark teeth-style patches are inspired by a shark's ability to bite and hold on to their prey, with their microneedle patches being designed to resemble the flat, angled structure of shark teeth.⁸⁷ North American porcupines are known for their hair or feathers with tiny, backward-stretching barbs for self-defense, and inspire the new structural design of microneedle patches.⁸⁸ Lamprey teeth-inspired microneedle patches are used for directional traction to shrink the wound area.⁸⁹ Currently, it is still challenging to fabricate microneedle patches with complex microscopic features using traditional fabrication methods. Daehoon Han *et al.* proposed a 4D-printed microneedle patch with biomimetic reverse-curved barbs to enhance tissue adhesion. The results showed that the tissue adhesion of the prepared microneedle patch was 18 times higher than that of the non-barbed microneedle patch.⁹⁰ Microneedle patches based on the bionic concept can be stabilized by 4D printing technology.

A biphasic microneedle patch with shape-variably expanded microneedle tips was developed to mechanically interlock with tissue. The endoparasite *Pomphorhynchus laevis*, which swells its proboscis to attach to the intestinal wall of its host, served as inspiration for the insertion and fixation of microneedle patches.⁹¹ The conical microneedle sheet consists of a poly(styrene) block poly(acrylic) expandable tip and a non-expandable polystyrene core.⁹¹ Eun *et al.*, inspired by the endoparasite



Fig. 5 (A) Schematic illustration of the claw-inspired microneedle patch with liquid metal encapsulation and its wound healing application.⁸⁶ Copyright 2021 Elsevier. (B) Schematic diagram of the working principle of the microneedle patch and the equipment process.⁹¹ Copyright 2017 American Chemical Society. (C) Schematic diagram of the preparation of a hemostatic and bionic pagoda microneedle patch.⁹⁹ Copyright 2021 Elsevier.

Pomphorhynchus laevis, created a structured microneedle patch with a cross-linked biphasic structure.⁹² The microneedle patch comprises an absorbable adhesive external part based on mussel adhesion protein and a rigid internal part based on filament for effective tissue fixation without delamination. The designed novel adhesive microneedle patch achieves mechanical interlocking with tissue and exhibits excellent adhesion on wet and dynamic biological surfaces.⁹² Considering the effect of humid environments on microneedle patches, Chen designed an octopus nanosuction microneedle patch to exhibit strong adhesion in both dry and humid environments (Fig. 5B).⁹³ The biomimetic microneedle patch can provide universal soft tissue adhesion with minimal damage and provide a platform for bioactive therapeutics, reducing the risk of infection and reducing traumatic removal.

The first stage of wound healing is hemostasis. Wound healing depends on hemostatic agents controlling bleeding quickly and effectively. Although currently available hemostatic materials such as cyanoacrylate,⁹⁴ glutaraldehyde cross-linked albumin,⁹⁵ or fibrin-based bandages⁹⁶ can exert high hemostatic efficiency, they have limitations in the treatment of deep bleeding.⁹⁶ In addition, hemostatic materials are often difficult to remove, which also brings a lot of trouble to patients.^{97,98} Therefore, hemostatic materials with high hemostatic efficiency and easy removal have become the focus of researchers to design new hemostatic materials. The layered microstructure of the feet or stings of insects like ladybugs, gadflies, and wasps served as inspiration for Zhang's team. To achieve rapid hemostasis, a novel dodecyl modified chitosan (DCS) coated pagoda shaped microneedle patch was proposed (Fig. 5C).⁹⁹ The multilayered structure allows the

microneedle patch to be firmly anchored to different tissues by physical interlocking, independent of massive blood loss. On the other hand, the DCS coating acts as an anchor on the cell membrane and causes blood cells to coagulate, thus actively promoting hemostasis.⁹⁹

4.2 Environment-responsive design

It has been demonstrated that drug delivery that is intelligently controlled can prevent drug resistance around the wound caused by uncontrolled drug release. Precise regulation of the time, area, and flow rate of drug release can effectively improve the wound environment.¹⁰⁰ Signals that can be responsive include physical and chemical signals, such as light,^{101–104} electricity,¹⁰⁵ magnetism,¹⁰⁶ temperature,^{87,107,108} pH,¹⁰⁹ glucose,¹¹⁰ and ROS.¹¹¹

Near infrared (NIR) light has received attention due to its ease of manipulation, ability to locally focus on a specific site, and its safety, allowing non-invasive propagation in deeper tissues.^{101,112} Light-activated microneedles perform their functions by converting light into heat and raising the ambient temperature.¹¹³ The creation of porous MOF microneedle patches to provide photo-thermally responsive nitric oxide is an example of this (Fig. 6A).¹¹⁴ The use of reactive graphene oxide (GO) encapsulated with an empty copper 1,3,5-tricarboxylate (HKUST-1) MOF enables the controlled release of NO. The photothermal effect of GO leads to a significant increase in the release of NO molecules at high temperatures.¹¹⁴ In the process of wound healing, nitric oxide is primarily responsible for cell proliferation, collagen formation, and wound shrinkage.¹¹⁵ The designed microneedle patch shortens the short half-life of NO. When the microneedle patch is applied to diabetic wounds, the wound

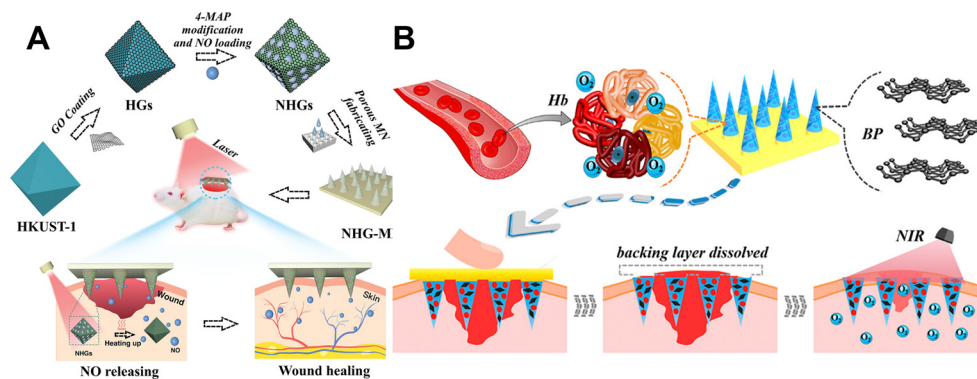


Fig. 6 (A) Schematic diagram of the preparation and application of the porous MOF microneedle patches.¹¹⁴ Copyright 2021 Wiley-VCH. (B) Schematic diagram of using NIR response to rapidly release BP quantum dots and oxygen-carrying hemoglobin to promote wound healing.¹¹⁹ Copyright 2020 American Chemical Society.

closure rate can reach 99% within 13 days.¹¹⁴ In addition, a near-infrared responsive nitric oxide-releasing microneedle was prepared, using nitrosogluthathione (GSNO) as a nitric oxide donor, adding graphene oxide to enhance the photothermal conversion efficiency, and using near-infrared to achieve a controllable release of nitric oxide.¹¹⁶ Adequate oxygenation is important for cell proliferation, bacterial defense, angiogenesis, collagen synthesis, and epithelialization.^{117,118} Therefore, people also put forward higher requirements for oxygen carriers. Under the condition of meeting biocompatibility, finding a carrier with high oxygen-carrying capacity and controlled release that can act deep in the skin is a hot topic of interest. Zhang and his team have recently reported a microneedle patch that uses near-infrared light to achieve controlled oxygen delivery (Fig. 6B).¹¹⁹ Hemoglobin (Hb) utilizes the excellent photothermal efficiency of black-scale quantum dots (BP QDs) for its reversible oxygen binding capability.¹²⁰ The two were encapsulated at the tip of a separable microneedle, and the responsive release of oxygen was achieved by using local heat generated from near-infrared light. The microneedle patch showed ideal wound healing ability in the treatment of diabetic mouse wounds.¹¹⁹ By activating the G protein-coupled adenosine receptor, adenosine, a systemic range of active ingredients, can alter cell behavior.¹²¹ Recently, several studies have shown that adenosine can promote angiogenesis and endothelial cell proliferation,^{122,123} exploit the ability of borates to dynamically covalently bind adenosine, combined with the powerful photothermal conversion of two-dimensional layered MXenes.^{124,125} The controlled release of adenosine is achieved, which promotes wound healing.¹²⁶

The human body's normal physiological temperature is 37 °C. The epidermal temperature in the wound area will rise to 37 °C or higher when there is an infection.¹⁰⁸ The microneedle patch achieves the release of the vascular endothelial growth factor (VEGF) encapsulated by NIPAM hydrogel.¹²⁷ *N*-iso-propyl acrylamide (NIPIM) hydrogel is a temperature-sensitive hydrogel. The NIPAM hydrogel has a volume phase transition temperature of 37 °C. At this point, the NIPAM hydrogel shrinks and then releases the encapsulated

contents.^{108,128} Controllable and intelligent drug release is achieved through the temperature increase caused by the inflammatory response at the wound site. The microneedle patch achieves ideal wound healing by promoting inflammation inhibition, collagen deposition, angiogenesis, and tissue regeneration.¹²⁷ In addition, Wang and his team have achieved controlled drug release from microneedle patches combined with temperature-responsive *n*-isopropylacrylamide (NIPAM) hydrogels.¹²⁹ Inverse opal (IO) photonic crystals (PC) have an ordered three-dimensional porous microstructure. Thanks to the porous structure of IOPCs, the drug-carrying capacity of microneedle patches is greatly enhanced. Furthermore, thanks to the temperature-responsive NIPAM hydrogel, the microneedle patch can control drug release.¹²⁹

The pH of the wound may change in accordance with the type of wound, the stage of the healing process, and other characteristics like infection.¹³⁰ On a microneedle patch, Asad Ullah and colleagues created a porous polymer coating that automatically 'releases' therapeutic drugs according to the pH of the wound (Fig. 7A).¹³¹ The pH-sensitive polymer Eudragit S100 is soluble in tissue fluid with an alkaline pH (pH greater than or equal to 7) but insoluble in an acidic microenvironment.¹³² The test medium contained trace amounts of the microneedle patch released at a pH of 4.5. On the other hand, when the microneedle patch was exposed to wound pH (pH 7.5) conditions, the rate of drug release increased significantly. This study demonstrates the ability of the created microneedle patch to treat contaminated injuries.¹³¹

The dermal microcirculation is affected when the microneedle patches are inserted into the skin.¹¹³ For diabetic wounds, glucose-responsive microneedle patches enable the controlled release of drugs based on glucose concentration. For diabetic wound repair, a hydrogel microneedle patch that responds to glucose and releases insulin was developed (Fig. 7B).¹³³ The glucose-responsive insulin release was achieved using hydrogels with phenylboronic acid (PBA) groups. By promoting angiogenesis, epithelial regeneration, and deposition of the extracellular matrix, insulin can act as a growth-like factor to promote wound



Fig. 7 (A) Wound pH-dependent release system schematic illustration.¹³¹ Copyright 2021 Elsevier. (B) Diagram of glucose responsive microneedle dressing for wound healing in diabetes.¹³³ Copyright 2022 Royal Society of Chemistry.

healing.^{134–136} In conclusion, diabetic wounds may heal more quickly with this hydrogel-based microneedle patches.¹³³

4.3 Electroconductive design

Electrical signals are the primary guiding cues for directed cell migration in wound healing.¹³⁷ Exogenous electrical stimulation is applied to chronic wounds to stimulate electrotaxis (also known as chemotaxis).¹³⁸ A spontaneous potential of 10–60 mV exists between the epidermis and sub-epidermal layer of undamaged skin.¹³⁹ Ion channels and frequent depolarization and repolarization of the cells are the main causes of this phenomenon.¹⁴⁰ When damaged, a short circuit occurs due to the low resistance of the injured part.¹⁴¹ The net movement of ions in the layers between the epidermis and dermis creates endogenous electric fields (EFs). EFs participate in the cell healing process by affecting cell migration. This phenomenon of cell migration under the action of an endogenous electric field is called electrotaxis.¹⁴⁰

To facilitate wound healing, direct cell migration, and encourage cell metabolism, proliferation and differentiation, appropriate electrical stimulation can mimic endogenous wound healing mechanisms.^{142,143} Using the conductive properties of liquid metal, it is combined with microneedle patches to guide cell migration and accelerate wound healing under an electric field of 2 V cm^{-1} generated by a lithium-ion battery that can be recharged.⁸⁶ Recently, a microneedle-based self-powered transcutaneous electrical stimulation system for improving epidermal growth factor pharmacodynamics to promote wound healing has been developed. The system consists of a sliding freestanding frictional electrical nanogenerator and a microneedle patch that enables continuous release of the epidermal growth factor for 24 hours. It is interesting to note that this method converts biomechanical energy generated by finger sliding into biosafe microcurrents.

5. Microneedle-based drug delivery in wound healing

5.1 Delivering antibacterial agents for combating infection

Bacterial infection of wounds is a common and unavoidable challenge in the wound healing process. At the point when a bacterial contamination happens at the injury site, there might

be a persevering provocative reaction at the injury site because of the microscopic organisms, drawing out the injury recuperating time. At present, the treatment of bacterial infection mainly relies on various antibiotics, but the problem of bacterial resistance emerges one after another.¹⁹ Therefore, how to achieve an efficient sterilization strategy is the focus at present.

It has been found that approximately 75% of chronic wounds suffer from a bacterial infection caused by biofilms produced by bacterial colonization at the wound site.¹⁴⁴ Bacterial biofilms are characterized as different bacterial networks joined in total and encompassed by polysaccharides, disciple fimbriae, extracellular DNA, lipids, and proteins; self-blending grids called hydrated extracellular polymers (EPS).^{145,146} Planktonic bacteria are less resistant to antimicrobial compounds than bacterial biofilms.¹⁴⁷ Existing strategies to combat microbial biofilms are limited by the difficulty faced by antimicrobial agents in penetrating their physical barriers.¹⁴⁸ EPS' net negative charge could trap positively charged antimicrobials or repel them. Additionally, some bacteria produce enzymes like beta-lactamases, which accumulate within biofilms and aid in bacterial survival by deactivating specific antibiotic molecules.¹⁴⁹ Microneedle patches appear to be a viable strategy to penetrate these barriers and deliver the loaded cargo to a predetermined depth of the dermis without causing painful, skin damage.¹⁴⁸ We summarize the current status of research on microneedle patch-based delivery of antimicrobial drugs, including delivery drugs, functions, and materials for microneedle preparation as shown in Table 1.

5.1.1 Antibacterial drugs. Antibiotics are still the main strategy for treating clinical wound infection. The researchers encapsulated macrolide (erythromycin and azithromycin) antimicrobial agents in polymeric microneedle patches made of hyaluronic acid (HA) and polyvinylpyrrolidone (PVP). Five days after the treatment, the damage is fully recovered and the hair follicles, dermis, and other skin forms are restored.¹⁵⁶ Researchers have reported the fabrication of water-soluble polymer microneedle patches by encapsulating the antibiotic chloramphenicol in gelatin nanoparticles and a polymer matrix (Fig. 8A).¹⁴⁹ When applied to an infected site, the microneedle patches enter the EPS and genuinely upset the biofilm structure. Following rapid dissolution of the polymeric microneedle patches, the gelatin nanoparticles are

Table 1 Summary of microneedle-based delivery of antibacterial agents to promote wound healing

Delivery substance	Function	Preparation method	Ref.
Vancomycin	Figure skin infections caused by MRSA (methicillin-resistant <i>Staphylococcus aureus</i>)	Polyvinyl alcohol polymethylmethacrylate	150
Tetracycline	Provide an appealing approach to preventing infections in the local area and prevent pathogen growth.	Silk fibroin	151
Bacteriophages	An effective method of treating biofilm infections of the skin.	Polyvinyl alcohols	152
Calcium peroxide	Overcome the bacterial biofilm present in chronic nonhealing wounds and co-deliver oxygen and bactericidal agents	Polyvinylpyrrolidone	153
Carvacrol	At infection sites, achieve a lasting antimicrobial effect.	Poly(ϵ -caprolactone)	154
Antimicrobial Peptide	Treatment of biofilms formed by multidrug-resistant bacteria	Poly(ϵ -caprolactone) polyvinylpyrrolidone	144
Lysozyme	Lyse bacterial infections for dermal applications	Polyvinylpyrrolidone Hyaluronic acid Poly lactic- <i>co</i> -glycolic acid	155
Erythromycin	Enhanced wound healing and anti-bacterial effect	Polyvinylpyrrolidone	156
Azithromycin		Hyaluronic acid	
Chloramphenicol	Improve the delivery of a wide range of antimicrobial agents to biofilm contaminated sites.	Polyvinylpyrrolidone	149
Gelatin nanoparticles	Combating wound infections-associated bacterial biofilms.	Polyvinyl alcohol	157
Levofloxacin poly-dopamine nanoparticles			
Silver nanoparticles	Fast dissolution rates and potent antibacterial activity	Carboxymethylcellulose	158
Silver nanoparticles	Overcome the problem of skin infection associated with bacterial biofilms	Polyvinyl alcohol Polyvinylpyrrolidone	159
Zn-MOF	Dramatically accelerate epithelial regeneration and neovascularization	Methacrylated hyaluronic acid	160
Zn ²⁺	Eradication of bacterial biofilms	Chitosan	161
Mg and panax notoginseng saponins	Achieves antibacterial, neovascularization, and activating a benign immune response	Chitosan polyvinylpyrrolidone	162

dissociated by gelatinase, allowing the release of the encapsulated chloramphenicol into the biofilm matrix. This approach speeds up wound healing and improves targeting compared to direct chloramphenicol usage.¹⁴⁹

Extracellular polysaccharides are one of the important components of EPS. They enhance bacterial adhesion and aggregation, mechanical stability, nutrient and ion adsorption, and nutrient storage and act as a protective barrier for antimicrobial

drugs.¹⁶³ Enzymatic degradation has been reported to disrupt EPS structural integrity.¹⁶⁴ Dissolvable microneedle patches combined with enzymatic and anti-infective agents and photothermal therapy eliminate biofilms from bacterial disease in wounds (Fig. 8B).¹⁵⁷ The microneedle patches have rapid dissolution properties of PVA. The fine tip of the microneedle patch penetrates the biofilm matrix and delivers α -amylase and levofloxacin adsorbed polydopamine nanoparticles into the



Fig. 8 (A) Schematic illustration of the microneedle-mediated biofilm treatment.¹⁴⁹ Copyright 2019 American Chemical Society. (B) Schematic illustration of the mechanism for the treatment using biofilms with dissolvable microneedle patches in infected wounds and biofilm elimination.¹⁵⁷ Copyright 2022 Elsevier.

biofilm. In addition, photothermal response to near infrared light can accelerate the release of therapeutic agents, speeding up the healing process. However, photothermal therapy will inevitably cause damage to surrounding normal cells and tissues, and how to reasonably control the treatment time still needs further research.

Antimicrobial peptides are host defense molecules in multicellular organisms due to their special antibacterial mechanism compared with antibiotics.¹⁶⁵ The antimicrobial peptides have broad-spectrum antibacterial properties and low biotoxicity, which can help solve the problem of drug resistance of traditional antibiotics.¹⁶⁶ Su *et al.* combined electrostatic spinning, microneedle patches and antimicrobial peptides to remove biofilms produced by bacterial infections in wounds, based on a database of antimicrobial peptides.¹⁶⁷

5.1.2 Antibacterial nanoparticles. For potential antimicrobial applications, inorganic metal nanoparticles, such as silver,¹⁶⁸ zinc oxide,¹⁶⁹ copper,¹⁷⁰ and other metal-containing nanoparticles,¹⁷¹ have been extensively investigated. The mechanism of action of nanoparticles on bacteria is mainly manifested in their ability to adsorb on bacterial membranes through electrostatic interactions, destroying the integrity of bacterial membranes.¹⁷² Despite

the safety concerns of nanoparticles, it still does not prevent them from becoming one of the most used antibacterial agents besides antibiotics.

Silver nanoparticles can not only kill bacteria but also inhibit their exopolysaccharide synthesis.^{173,174} For example, silver nanoparticles and carboxymethylcellulose are used to create dissolvable microneedle patches with powerful antibacterial properties.¹⁵⁸ Although silver nanoparticles are reported to be effective, they may be harmful to human cells.¹⁷⁵ As a result, a method for selective drug delivery that prevents silver nanoparticles from being delivered to undesirable locations is required. For instance, Andi utilized silver nanoparticles synthesized with green tea extract due to their potential as antibacterial agents against biofilms of *Staphylococcus aureus* (SA) and *Pseudomonas aeruginosa* (PA) (Fig. 9A).¹⁵⁹ Due to the toxicity of silver nanoparticles, they were incorporated into bacterial reaction particles (MPs) made of chitosan-modified poly(ϵ -caprolactone). In the presence of SA and PA, the MPs showed a 9-fold increase in the *in vitro* release of silver NPs, indicating some selectivity.¹⁵⁹

Metal organic backbones (MOFs) are non-porous materials consisting of metal ions and organic ligands linked to ether by covalent bonds.¹⁷⁶ Metal-organic frameworks (MOFs) are considered

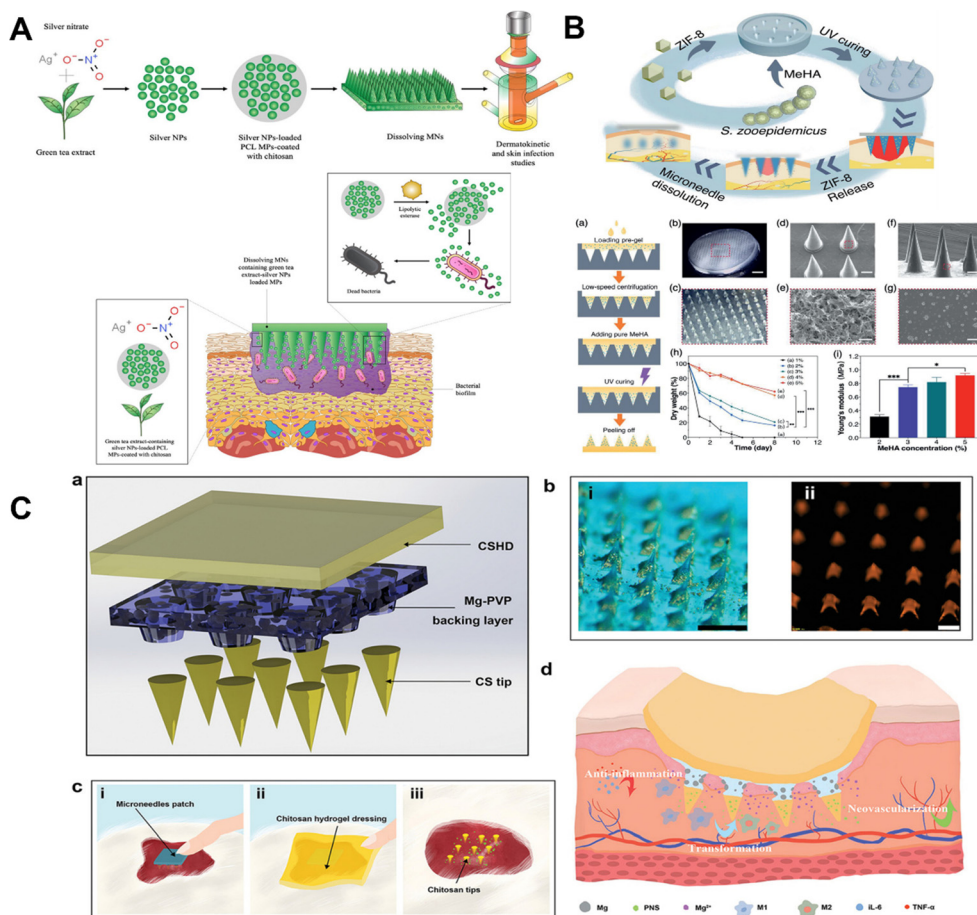


Fig. 9 (A) Schematic illustration of bacteria-responsive microparticles for selective delivery of silver nanoparticles with microneedle patches.¹⁵⁹ Copyright 2020 Elsevier. (B) Schematic diagram of Zn-MOF microneedle patches.¹⁷⁷ Copyright 2021 Wiley-VCH. (C) Schematic diagram of microneedle patches and brief introduction to the process of promoting wound healing.¹⁶² Copyright 2022 Wiley-VCH.

third-generation antimicrobials. They have advantages over conventional bactericidal materials due to their adjustable pore structure, controllable ion release rate, and high specific surface area.¹⁷⁶ The metal ions are gradually released using the metal disassembly of the MOFs to provide long-lasting antimicrobial activity and to achieve the antimicrobial durability of expensive MOFs.¹⁷⁶ For example, Yao *et al.* proposed a novel Zn-MOF-encapsulated microneedle patch with antibacterial activity and degradable properties to promote wound healing, and the Zn²⁺ released from the Zn-MOF can destroy the integrity of the bacterial envelope, catalyzing the production of oxygen free radicals, resulting in bacterial death. Additionally, the rough surface of ZIF-8 nanoparticles has the potential to expand the area of contact between MOFs and bacteria, enhancing antibacterial activity (Fig. 9B).¹⁷⁷

Chitosan (CS) is one of the most encouraging regular polymers known to have antibacterial properties.¹⁷⁸ CS is a natural cationic polysaccharide consisting of (1 → 4)-2-amino-2-deoxy-β-D-glucan, a partially to fully deacetylated form of chitin.^{179,180} CS is biodegradable, non-toxic, biocompatible, antibacterial and hemostatic, and is of great value in biomedical applications.¹²⁷ The electrostatic interaction between the positively charged CS molecules and the negatively charged cell membrane alters the permeability of the cell membrane, leading to lysis, one of the known mechanisms by which CS acts on microorganisms.^{127,181} However, in practical applications, CS and other antibacterial substances are usually used to have a synergistic effect to achieve the antibacterial treatment of wounds. For example, taking advantage of the antibacterial properties of CS and zinc ions (Zn²⁺), composite microneedle patches of CS and zinc nitrate were prepared to eliminate bacterial biofilms.¹⁶¹ Due to the needle-like structure, microneedle patches can pierce EPS and can deliver CS and Zn²⁺ directly into bacterial biofilms. Compared with the patch without needle structure, the needle design increased the area of contact between the drug transporter and the bacterial biofilm by nearly 14–23%, facilitating drug dispersion. More importantly, the synergistic effect of CS and Zn²⁺ enabled the composite microneedle patches to show excellent anti-biofilm properties.¹⁶¹ Furthermore, Ning *et al.* proposed a synergistic detachable microneedle patch with a bilayer structure (Fig. 9C).¹⁶² The bilayer microneedle structure consists of a CS needle tip, CS hydrogel dressing, and a magnesium (Mg)-doped polyvinylpyrrolidone (PVP) backing. It provides a simple method for the programmed treatment of chronic wound management.

5.2 Delivering drugs for regulating inflammation

An excessive or prolonged inflammatory response can cause an undesired polarization of immune cells and lead to wound deterioration.¹⁸² Therefore, the development of dressings with inflammation modulating ability is of great importance to promote wound healing. Macrophages are key players in the wound healing process and serve as important targets for wound healing.¹⁸³ Studies have shown that chronic wounds are closely associated with an impaired phenotypic shift of pro-inflammatory macrophages to an anti-inflammatory phenotype in wounds.¹⁸⁴ Focusing on restoring the normal transformation

of the macrophage phenotype facilitates normal wound healing. Numerous immune cells and non-lymphocytes use reactive oxygen species (ROS) as second messengers, regulate angiogenesis, and are necessary for the normal wound healing response.¹⁸⁵ However, it should be noted that while high ROS production can result in oxidative stress and hinder wound healing, low ROS levels may actually help wound healing.¹⁸⁶ In addition to causing severe inflammation, excessive reactive oxygen species (ROS) in wounds also inhibit the function of endogenous stem cells and macrophages, preventing cell proliferation and wound tissue regeneration.^{187,188} Therefore, to form a normal wound environment with an appropriate amount of reactive oxygen species, it is necessary to remove excess reactive oxygen species around the wound.

The new microneedle patch designed by Ma and his colleagues encapsulates polydopamine nanoparticles (PDA NPs) in a shell of hyaluronic acid methacrylate (HAMA).¹⁸⁹ The structure of polydopamine is rich in reducing functional groups, such as catechol and imines, which allow the polydopamine molecule to exhibit good antioxidant properties.^{19,190} Polydopamine nanoparticles were continuously released to scavenge ROS as HAMA slowly degraded (Fig. 10A).¹⁸⁹ Microneedle patches show antioxidant, anti-inflammatory, and pro-angiogenic properties, and are of some value.

Gallic acid (GA) is a specific plant compound in the phenol group that is also used to promote wound healing.¹⁹¹ GA has many biological activities, including anti-inflammatory, anti-tumor, immunomodulatory, hypoglycemic, and hyperlipidemic.¹⁹² GA has strong antioxidant activity due to its three hydroxyl groups.¹⁹³ A schematic diagram of the multifunctional MOF magnesium microneedle patch prepared with gallic acid and Mg²⁺ is shown in Fig. 10B.¹⁹⁴ The Mg-MOFs in an acidic microenvironment slowly release Mg²⁺ and gallic acid. The gallic acid released acts as an antioxidant, scavenging excessive production of intracellular reactive oxygen species (ROS), thereby reducing ROS-induced inflammation.¹⁹⁴ *In vivo*, therapeutic effects on diabetic wound healing were significantly improved.

Melanin exists widely in nature and has functions such as antioxidation, temperature regulation, and photoprotection.¹⁹⁶ Cuttlefish ink contains many melanin nanoparticles, which can be extracted as well-dispersed spherical melanin nanoparticles.^{197,198} Qi Lei and colleagues presented a hyaluronic acid (HA) microneedle patch functionalized with biomineralized melanin nanoparticles. The microneedle patch enables simultaneous tumor photothermal therapy (PTT) and promotes skin tissue regeneration. Microneedle patches have great potential as adjuvant therapy after skin tumor resection (Fig. 10C).¹⁹⁵ In addition, the researchers designed herbal microneedle patches using two herbs found in nature, *Premna microphylla* and *Centella Asiatica*.¹⁹⁹ The microneedle patch actively shows excellent antioxidant and anti-inflammatory properties of asiaticoside (AS), a natural ingredient is *Centella asiatica*. AS hinders angiogenesis during the remodeling phase in addition to promoting angiogenesis during the inflammatory phase.²⁰⁰ The preparation of Chinese herbal microneedle patches also serves as a booster for the global promotion of Chinese herbal medicine. In addition, Wang's team successfully manufactured a microneedle

Chen and his colleagues fabricated polymer microneedle patches for keratinocyte delivery. The delivery rate can reach 83.2%.²⁰⁹ The design of microneedle patches loaded with mesenchymal stem cells (MSCs) for wound healing was first proposed by Kwangju Lee *et al.* (Fig. 11A).²¹⁰ Benefiting from the outer layer of the polylactic acid–ethanolic acid shell, the MSCs in the GelMA-MSC mixture within the microneedle tip remain viable. Results showed that the vitality and function of MSCs could be maintained up to 24 h, which increased wound closure rates and improved re-epithelialization.²¹⁰

MengYuan and colleagues used a gelatin methacrylate microneedle patch to achieve controlled transdermal release of tazarotene and exosomes. Tazarotene is a retinoid that promotes angiogenesis and hair follicle and collagen regeneration.²¹¹ The MCS-exosome is involved in skin regeneration by promoting macrophage polarization and reducing the release of pro-inflammatory factors.²¹² Microneedle patches are used for the slow release of exosomes and tazarotene deep in the skin to promote cell migration and angiogenesis.²¹³ In addition, the researchers achieved a non-invasive sustained release of the parathyroid hormone in rats through the microneedle patches, which promoted wound healing by accelerating extracellular matrix deposition and improving the structure of the extracellular matrix (Fig. 11B).²¹⁴ Not only this but microneedle patches that deliver collagen to promote wound healing have also been developed.^{215,216} Long *et al.* prepared the first recombinant human-derived collagen (rhCol III) and naproxen (Nap) loaded polylactic acid glycolic acid (PLGA) nanoparticle microneedle patch for the treatment of diabetic chronic wounds.²¹⁷ *In vitro* cell culture results show that microneedles loaded with rhCol III can effectively promote the proliferation and migration of fibroblasts and endothelial cells.²¹⁷

6. Conclusions and prospects

Wound healing is affected by old age, a weakened immune system and malnutrition, which imposes a significant economic burden on society.¹²⁷ Functional dressings for various types of wounds have become increasingly available, but these wound dressings are expected to be able to monitor wound status in real time and provide personalized treatment. A new generation of smart wound dressings with real-time monitoring and on-demand treatment is currently under development to enable real-time tracking of the wound environment. Due to their powerful drug delivery capabilities, customizable microstructure and their superior biocompatibility, microneedle patches have great potential as wound dressings. This article discusses the current application of microneedle patches in promoting wound healing and smart wound management. The microneedle-based sensor enables real-time monitoring of a wide range of biomarkers, enabling early diagnosis of a variety of diseases such as Parkinson's disease and diabetes. However, microneedle-based sensors are still in the preliminary stages of exploration in smart wound management, although microneedle sensors have already realized the monitoring of inflammatory factors at the wound bed and the tracking of motion

sensing. The complex changes in the wound healing environment require them to realize real-time monitoring of more biomarkers and more intelligent wound management. In addition, enabling the monitoring of multiple markers means the interconnection of multiple sensors, and microneedle-based sensors are highly reproducible and stable. Low detection limits are a key requirement for medical problems. Microneedle patches as dressings to facilitate wound healing have undergone tremendous development, from designing individualized microstructures to meeting different adhesion requirements, to enabling the delivery of different functional substances. Based on the bionic, responsive, and conductive properties of microneedle patches, the application of microneedle patches in wound healing is described in three aspects. At the same time, a microneedle patch that promotes wound healing has achieved the delivery of various substances that promote wound healing, including antibacterial agents, living cells, and bioactive factors. However, the adhesion of the microneedle patches to the skin, the delivery efficiency, and the therapeutic effect are the main factors to be investigated. The skin and wounds on the skin are elastic tissues with complicated surface topography and counteracting forces, which can make penetration uneven.¹⁰⁰ Second, skin elasticity and thickness vary according to age, gender, and weight. These complex factors impose higher requirements on the design of microneedle patches. A phase III study of Zosano Pharmaceuticals' microneedle-delivered patch for sumatriptan (migraine) has recently been concluded. However, the FDA requested more data to address differences in the exposure of zolmitriptan and insufficient bridging of the pharmacokinetics of microneedle patches across batches when subjects received different microneedle patches.^{218,219}

The smart microneedle patch combines on-demand drug delivery and real-time monitoring and is a new way forward for intelligent wound management. The therapeutic, diagnostic system should include controllable drug delivery patches, tiny electronic controllers, and high-sensitivity biosensors. The sensors send data to the control *via* bluetooth or WiFi after continuously monitoring different biomarkers in the wound environment. A microneedle patch-based system that personalizes treatment through early analysis and diagnosis. However, as far as the current research is concerned, more biomarkers related to wound healing are worth exploring. At the same time, the coordinated detection of multiple markers can provide more accurate data. As far as the existing research articles are concerned, the smart microneedle wound patch only realizes the monitoring of inflammatory factors and motion sensing. It is necessary to prepare microneedle patches with multiple monitoring properties.

Author contributions

Fangfang Hu: data curation, writing and original draft preparation. Qian Gao, Jinxi Liu, and Wenting Chen: data collection and obtained the permission. Caiyun Zheng Que Bai, Na Sun,

and Wenhui Zhang: supervision. Fangfang Hu, Yanni Zhang, and Tingli Lu: writing, reviewing, and editing. All the authors participated in the conception and design, or analysis and interpretation of the data; drafting of the paper or revising it critically for intellectual content; and the final approval of the version to be published; and all authors agree to be accountable for all aspects of the work.

Conflicts of interest

There are no conflicts to declare.

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