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Advances of Microneedle Patch in Diabetic Wound Healing

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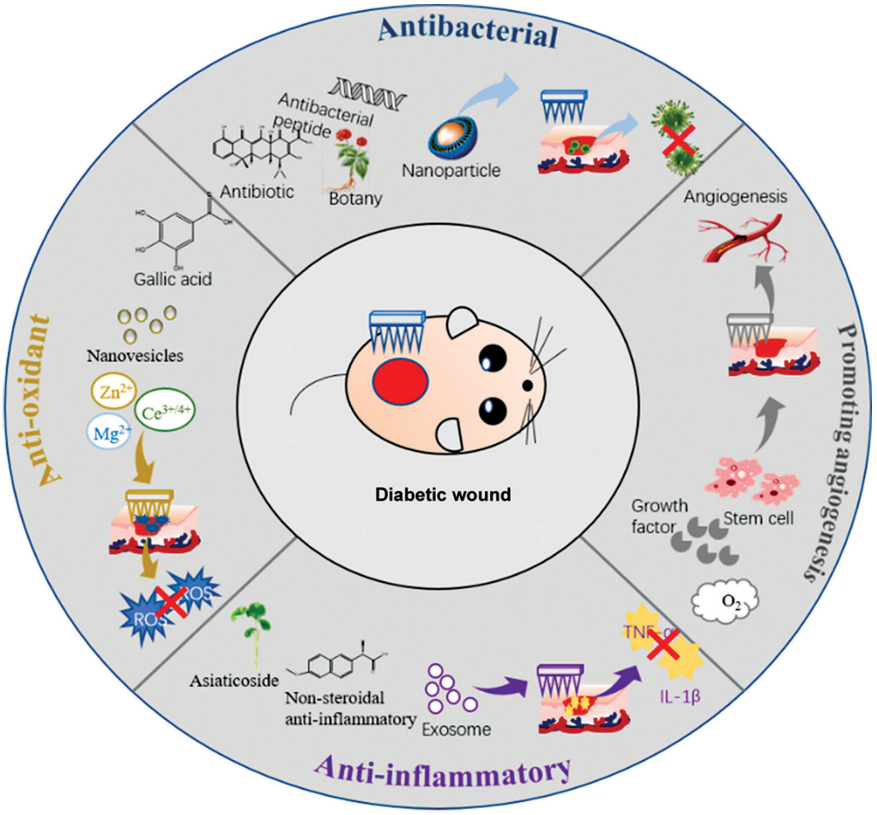

Abstract

Wound healing is an intricate and orderly process of events that occur in response to external trauma, resulting in tissue repair and reconstruction. This process typically involves three phases, including inflammation, angiogenesis, and extracellular matrix remodeling, and any disruption to this process may delay the healing of the wound. Chronic wounds associated with diabetes, in particular, are notorious because they are difficult to handle in a timely and orderly manner. During the treatment of the disease,

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drugs usually accumulate in the stratum corneum due to the skin barrier, leading to a reduction of the drug's bioavailability. Encouragingly, among the treatment strategies, microneedles (MNs) represent a novel and painless drug delivery method that promotes wound healing in diabetic patients by enabling the drug to reach the dermal layer efficiently. In this review, recent advances of MNs in the treatment of diabetic wound healing are summarized by categorizing the designs and strategies. We finally provide an outlook on the prospects and challenges of MN-based therapies for diabetic wound healing in the future.

Introduction

Diabetes is a metabolic disorder primarily identified by hyperglycemia. Hyperglycemia is a condition where the blood glucose levels are higher than normal, resulting from defects in insulin secretion, impaired action of insulin, or both.[1] Chronic wounds, with a high prevalence and severity, threaten the quality of life for both patients and their families, they enhance household medical costs, and have become a pressing issue for those affected.[2] Prolonged hyperglycemia is strongly correlated with various complications, including diabetic wounds. In comparison to typical wounds, diabetic chronic wounds exhibit distinct features, including persistent bleeding, uncontrolled inflammation, impeded cellular growth, and disrupted tissue restructuring, accompanied by the symptoms of stubbornness in healing, ulceration, and peripheral skin infections that bring extreme agony and discomfort to patients.[3,4] Hyperglycemia causes a rapid loss of intracellular and extracellular fluids in the body, due to its osmotic effect, further affecting the healing process of the wound.[5] Hyperglycemia also weakens the motility and function of white blood cells.[6,7] White blood cells are immune cells in the body that defend against pathogens. If they are impaired, the bacteria become active and regenerate, leading to infection and ulceration of the wound, further impeding the healing process. Moreover, prolonged hyperglycemia may result in microvascular stenosis, constriction of large blood vessels, deceleration of blood flow rates, reduction in nutrient delivery, and the subsequent dwindling ability of blood vessels to repair and regenerate.[8]

Conventional care for diabetic wounds primarily includes glycemic control, local debridement, wound dressings, oral antibiotics, etc.[9] Nevertheless, glucose control might be destabilized by a dietary habit, resulting in inadequate glucose regulation and tardy recuperation of wounds.[10] Conventional care brings troubles for patients, for example, a high infection risk induced by the management of recurrent lesions during frequent debridement and dressing replacement,[11] and inappropriate usage of antibiotics that may inadequately control the infection and worsen the condition.[12] Therefore, novel approaches and materials are required. Currently, hydrogels are popular in the treatment of diabetic ulcers because of their advantages of drug incorporation, physical characteristics regulation, exceptional biocompatibility, and multi-functional nature.[13–15] Despite these advantages, they also have limitations of not being able to absorb excessive exudates and not being effective for deep-tissue treatments.[16,17] Microneedles (MNs), as a novel drug delivery system, combine the features of subcutaneous injection and transdermal patch.[18] MNs have needle-like shapes and dimensions at the micrometer level and have good biocompatibility, degradability, and drug-loading performance.[19,20] MNs also have good mechanical strength that allows them to effectively puncture the epidermal layer of the skin and deliver drugs to the dermal layer for deep-tissue treatment.[21] Similarly, MNs also have the ability to puncture diabetic wounds that are affected by bacteria and obstructed by the barrier of biofilms, and improve drug delivery efficiency.[22,23] Additionally, with the use of MNs, dressing replacement in traditional care can be eliminated, avoiding the possible secondary injury caused by the procedure. Furthermore, a dry nature of MNs makes them ideal for highly exuding wounds.

MNs can be loaded with active drugs including antibacterial agents, hemostatic agents, anti-inflammatory agents, vascular growth factors, etc., thereby possessing the abilities of antimicrobial, hemostatic, anti-inflammatory, or tissue regeneration that favors wound healing. Additionally, the combination of MNs and environment-responsive materials allows for targeted therapy of diabetic wounds based on their microenvironments.[24–26] In this review, the design progress of MN patches is summarized for diabetic wound healing. Future perspectives on MN patches are also discussed.

Designs of MN Patches for Diabetic Wound Treatment

Wound healing in diabetics can be prevented by factors including microbial infections,[27] excessive oxidative stress,[28] impaired inflammatory levels,[29] and compromised blood vessel formation.[30] ►**Table 1** lists the design diversity of MN patches that possess antibacterial, antioxidant, anti-inflammatory, angiogenic properties, etc.

MNs with Antibacterial Property

The loss of skin protection and the hyperglycemic environment of patients with diabetes make them more likely to wound infection, which facilitates pathogen invasion and rapid colonization into the wound. Currently, wound infection is a leading cause of amputation and even death in

Table 1 Properties of microneedles for promoting diabetic wound healing

Designs of MN patches	Drug	Materials	Structure	MN length and shape	Drug release patterns	Ref.
MNs with antibacterial property	Engineered peptide W379	PVP	Soluble	500–1000 μm, conical	Responsive release	40
	TCH	HA	Double-layer	600 μm, pyramidal	Rapid release	24
	TCH	HA	Soluble	1000 μm, pyramidal	Rapid release	36
Antioxidant MNs	$Ce^{3+/4+}$	HA	Soluble	600 μm, pyramidal	Responsive release	46
	MOF-GO-Ag	γ-PGA	Soluble	500 μm, pyramidal	Long-termed release	37
	Polydopamine (PDA) NPs	Methacrylated hyaluronic acid and HA	Core-shell	700 μm, pyramidal	Sustained release	29
Anti-inflammatory MNs	MSC-exosomes	Methacrylate gelatin	Biodegradable	800–1,000 μm, conical	Sustained release	48
	Naproxen	HA	Soluble	600 μm, pyramidal	Rapid release	49
Promoting angiogenesis MNs	Adipose-derived stem cells	HAMA	Biodegradable	600 μm, conical	Sustained release	58
	NO	GelMA	Biodegradable	600 μm, pyramidal	Sustained release	60
	NO	Poly(ethylene glycol) diacrylate	Degradation	800–1,000 μm, conical	Responsive release	65
The design of MNs with combined strategies	H_2 and Mg^{2+}	PLGA	Soluble	500 μm, pyramidal	Sustained release	66
	Insulin	GelMA	Soluble	600 μm, conical	Responsive release	67
	Vascular endothelial growth factor	Silk fibroin methacryloyl	Double-layer	700 μm, conical	Sustained release	39
Other designs of MNs	O_2	Polyacrylamide (PAM)	Soluble	750 μm, barb-like structure	Sustained release	68
	Recombinant human epidermal growth factor	HA and polylactic acid (PLA)	Soluble	600 μm, shark tooth-like, flat, and incline	Controllable drug release	69

Abbreviations: HA, hyaluronic acid; MNs, microneedles; MSC, mesenchymal stem cell; NPs, nanoparticles; PLGA, poly(lactic-co-glycolic acid); PVP, poly(vinylpyrrolidone).

patients with diabetes.[31,32] The primary pathogens of the infections are *Staphylococcus aureus* and *Pseudomonas aeruginosa*,[33,34] which form biofilms at the wound site. However, traditional treatment mainly relies on oral or topical antibiotics to control the infections, yet will increase the bodily burden and bacterial resistance risk. To address this, a variety of MN patches loaded with antibacterial drugs such as antibiotics, metal ions, antibacterial peptides, active ingredients of traditional Chinese medicine (TCM), or photothermal antibacterial have been developed to combat infections in diabetic wounds.[35]

Gao et al loaded tetracycline into the soluble MN tips fabricated from hyaluronic acid (HA), which could penetrate the biofilm and quickly release the drug to eliminate pathogens in the wound.[36] Interestingly, Liu and colleagues constructed a double-layer MN consisting of HA, in which tetracycline was loaded to eliminate pathogenic bacteria. Upon application of the MNs to the affected area, interstitial fluid is rapidly absorbed by the antimicrobial basal segment, which, in turn, facilitates the release of tetracycline after the dissolution of HA and then clears pathogenic bacteria in the wound site. Additionally, growth factors located at the needle tips are released as significant amounts of collagenase-degraded collagen within the wound (►**Fig. 1**).[24] Inorganic nanoparticles (NPs) also possess good antimicrobial properties. Yin and colleagues used an oxygenated graphene–silver NP composite (GO-Ag) as the backing layer of MN patches.[37] GO-Ag has excellent antibacterial properties and releases Ag^{+} to inhibit the accumulation of foreign bodies and accelerate the healing process, and has a synergistic effect on wound treatment with the MNs that possess antioxidant activity. Ning et al proposed a dual-layer structure of cooperatively detachable MNs, which continuously released Mg^{2+} to clear pathogens.[38] Antimicrobial peptides (AMPs), as effective antibacterial agents, are also included. For example, Guan et al loaded polymyxin onto silk MN backings to suppress bacterial growth in diabetic wounds.[39] Su et al developed a dissolvable poly(vinylpyrrolidone) (PVP) MN patch that delivers engineered AMP W379 into the biofilm to disrupt it based on the AMP database.[40] In addition, Lei et al loaded AMP-cypate into an enzyme-responsive MN patch,[41] which is released in response to gelatinase to clear pathogens.

Vegetable drugs are an important part of natural medicine, and many of them have certain antibacterial properties and can be used for MN loading. For example, Chi and colleagues combined the traditional Chinese herbs *Premna*

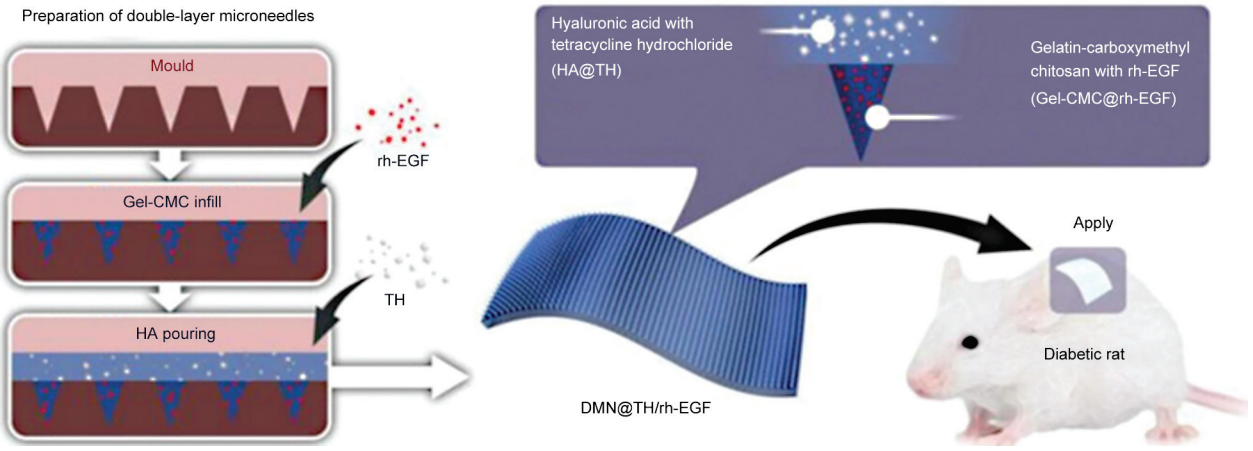

Fig. 1 Schematic representation of DMN@TH/rh-EGF in diabetic wound healing.[24] Copyright 2023 Wiley-VCH. DMN, double-layer microneedle; rh-EGF, recombinant human epidermal growth factor; TH, tetracycline hydrochloride.

microphylla and *Centella asiatica* to develop a pure TCM antimicrobial MN patch,[42] which has a clearance rate of up to 100% for bacteria and promoted wound healing significantly. Near-infrared light-induced photothermal therapy kills bacteria effectively and accelerates wound healing. Based on this, Zeng et al added CaO_2@polydopamine (PDA@-CaO_2) NPs to the MN backing.[43] The MN patch adopts the excellent photothermal effect of PDA and could not only improve the hypoxic microenvironment of diabetic wounds but also clear wound pathogens effectively. Hair has an excellent photothermal effect, and Zhang et al explored hair-derived MN patches for diabetic ulcers.[44] The MN patch exhibits superior photothermal antibacterial performance when exposed to near-infrared light, and effectively eradicates bacteria in the surrounding area of the wound, thus, reducing the risk of infection and inflammation that play a role in promoting diabetic wound healing. However, it is important to note that their ability to accelerate cell proliferation and collagen accumulation may be limited in the later stages of wound healing.

MNs with Antioxidant Property

A reactive oxygen species (ROS) is a high-signaling molecule that plays an important role in wound healing. It is generated as the damage of normal skin and can assist the immune system in clearing pathogens.[45] For diabetic patients, hyperglycemia will destroy the balance between oxidative stress and the antioxidant system, leading to a continuous increase of oxidative stress products that damage the DNA or proteins of cells around the wound, thereby delaying the healing process of diabetic wounds. Interestingly, Ma et al reported a novel core-shell anti-inflammatory MN patch that accelerates the healing of diabetes wounds.[29] The MN patch consists of a shell loaded with PDA NPs and a core of iron-mesenchymal stem cell (MSC)-derived nanovesicles. The surface of PDA NPs contains rich reducible functional groups, which eliminate excess ROS in the wound and promote the healing of diabetes wounds. Yang et al reported an enzyme-responsive MN-based drug delivery system (ZCO-HA MNs) loaded with cerium/zinc NPs.[46] ZCO-HA MNs slowly release Zn^{2+} and $Ce^{3+/4+}$ to eliminate ROS under hyaluronidase conditions, thereby alleviating oxidative stress in the wound bed and accelerating wound healing. Malic acid is a common antioxidant. Taking advantage of this, Yin et al prepared magnesium organic frameworks (MOF-GO-Ag) by combining malic acid and magnesium metal, and mixed MOF-GO-Ag with γ-polyglutamic acid (γ-PGA) hydrogel to prepare MN tips.[37] Mg^{2+} and malic acid were slowly released in the wound site (►**Fig. 2**), and the oxidative stress could be reduced significantly due to the excellent antioxidant properties of malic acid. Fortunately, antioxidant MNs diminish inflammation, reduce the secretion of proinflammatory cytokines, enhance the proliferation of M2 macrophages, initiate peri-wound neovascularization and collagen synthesis, and expedite the mending of wounds. However, their efficacy in controlling infection may be limited in the early phase of wound healing. Therefore, it is imperative to concurrently explore additional methodologies to hinder infection when administering antioxidant MNs as a therapeutic modality for wounds.

MNs with Anti-inflammatory Properties

In diabetic wounds, the high glucose microenvironment stimulates macrophages to secrete proinflammatory cytokines and other factors, favoring polarization disorder of M1 macrophage and inducing the persistence of chronic inflammation.[47] Continuous inflammation and poor tissue remodeling severely affect the healing of diabetic wounds. Gan et al prepared a new type of adhesive MN patch composed of MSC exosomes (MSC-exos) and silver NPs (AgNPs).[48] The MN tips were made from biodegradable methacrylic acid gelatin, which could continuously deliver anti-inflammatory MSC-exos to the wound tissue to accelerate wound healing. As a nonsteroidal anti-inflammatory drug, naproxen (Nap) possesses the properties of clearing heat, relieving pain, and reducing inflammation. Long et al loaded Nap-loaded poly(lactic-co-glycolic acid) NPs and recombinant human type III collagen onto HA MNs.[49] The MN patches could accelerate wound healing by reducing the inflammatory response of the wound bed (►**Fig. 3**). In

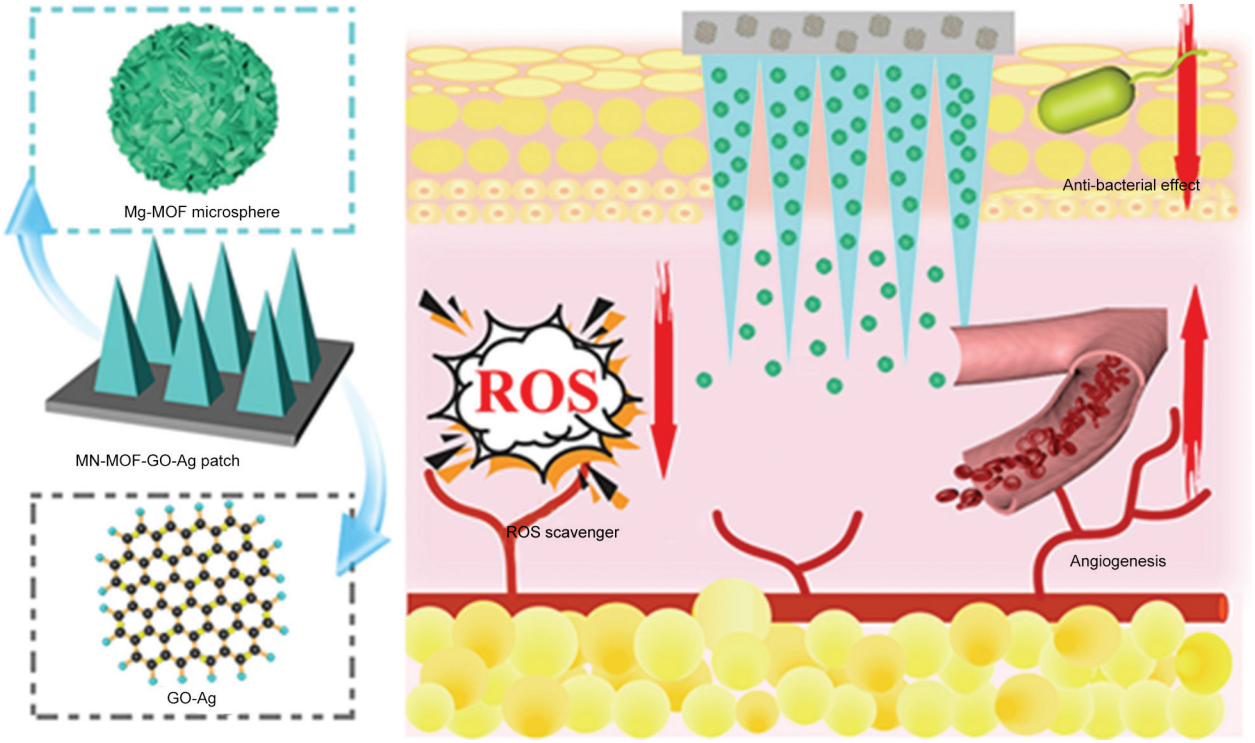

Fig. 2 Schematic illustration of MN-MOF-GO-Ag for accelerating diabetic wound healing.[37] Copyright 2021 American Chemical Society. MN-MOF-GO-Ag, a magnesium organic framework-based microneedle patch.

addition, asiaticoside (AS), a herbal component from *C. Asiatica*, also exhibited excellent anti-inflammatory effects.[50] Wang et al loaded AS into MNs (MN-MXenes-AS) to reduce inflammation reactions in wounds.[51] Anti-inflammatory MNs suppress inflammatory mediator production, inhibit the activation and chemotaxis of inflammatory cells including neutrophils, promote the proliferation of M2 macrophages, block the activation of inflammatory signaling pathways, and reduce the inflammation at the wound site, thereby minimizing swelling and pain around the wound and facilitating wound healing. Despite this, anti-inflammatory MNs have limited effects on cell proliferation and remodeling in the later stages of wound healing.

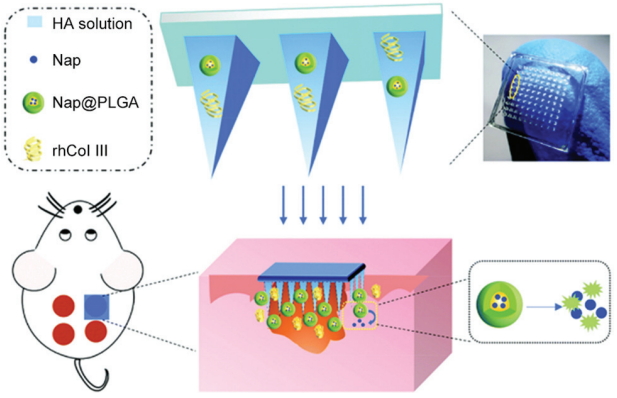

Fig. 3 The fabrication process of rhCol III and Nap@PLGA NP-loaded MN with its application in promoting chronic wound healing.[49] Copyright 2022 Royal Society of Chemistry. MN, microneedles; Nap, naproxen; NPs, nanoparticles; PLGA, poly(lactic-co-glycolic acid).

MNs with the Ability to Promote Angiogenesis

Angiogenesis at the wound site is extremely important, as newly formed capillaries not only deliver nutrients to the newly formed tissue but also assist in the remodeling and reshaping of the wound tissue. In diabetic wounds, the production of multiple angiogenesis-related cell factors, for example, vascular endothelial growth factor (VEGF) may be inhibited by various factors including hyperglycemia, oxidative stress injury, imbalanced inflammatory responses, etc., thus delaying wound healing.

Angiogenesis may be accelerated by sufficient oxygen.[52–54] Zhang et al explored an oxygen-responsive hemoglobin (Hb)-separated MN patch that could release oxygen responsively, thereby accelerating angiogenesis when it was applied to a diabetic wound (►**Fig. 4A**).[55] In addition, Zhao et al suggested a detachable MN system loaded with active *Chlorella vulgaris*, which is designed to regulate oxygen delivery to facilitate wound healing.[51] Growth factors such as platelet-derived growth factor (PDGF), VEGF, and recombinant human epidermal growth factor (rh-EGF) are essential for angiogenesis.[52,56] Inspired, Xu et al reported a gelatin MN patch loaded with PDGF to promote VEGF expression and accelerate angiogenesis at the wound site.[57] Chi et al introduced a VEGF-loaded responsive CS-pNIPAM MN patch that responds to localized high temperature in diabetic wounds, releasing VEGF and enhancing angiogenesis (►**Fig. 4B**).[58] Liu et al loaded rh-EGF into the needle tip to respond to release rh-EGF and promote angiogenesis.[24]

Stem cells have also gained attention in diabetic wound therapy. Ma et al developed a novel core-shell HA MN that encapsulated iron-MSC-derived human artificial nanovesicles

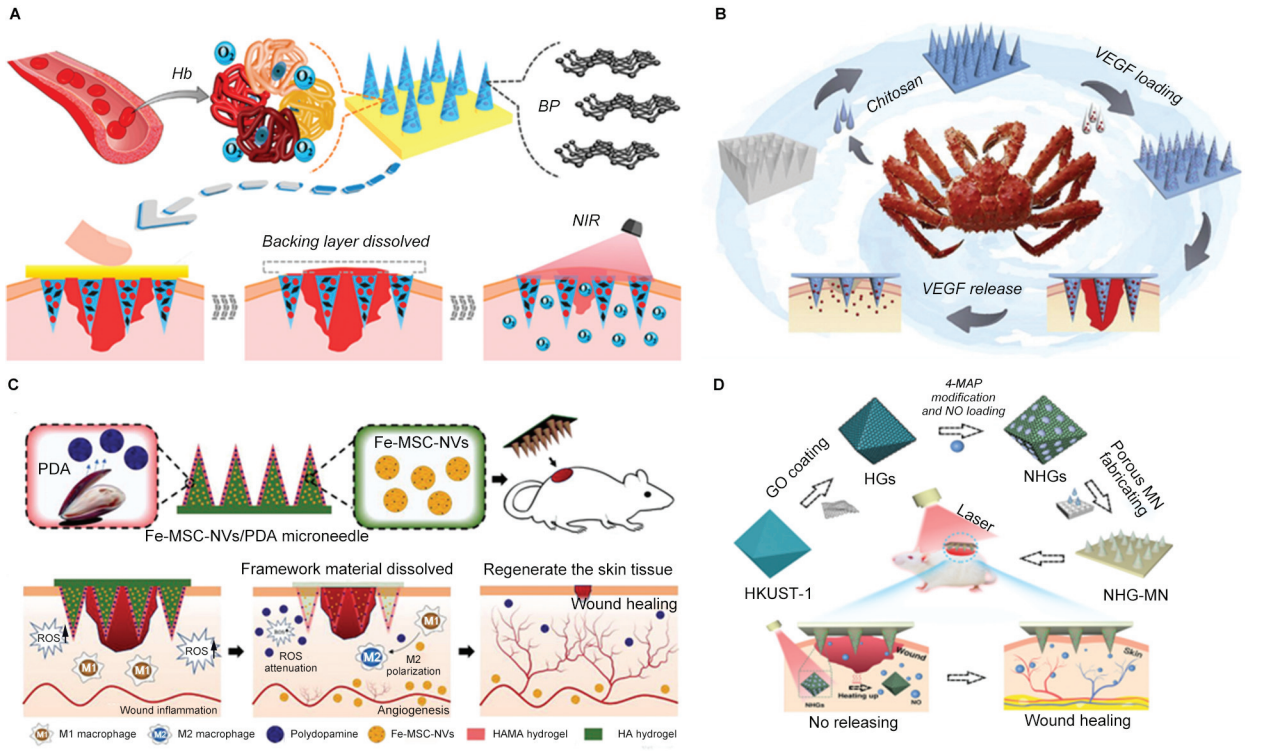

Fig. 4 (**A**) Schematic illustrations of wound healing using NIR-responsive separable MNs which encapsulate BP QDs and oxygen-carrying Hb.[55] Copyright 2022 American Chemical Society. (**B**) Scheme of the fabrication and controllable drug release application of the biomass microneedle patch.[58] Copyright 2020 Elsevier. (**C**) Schematic illustrations of the Fe-MSC-NVs/PDA MN patch for diabetic wound healing.[29] Copyright 2022 Wiley-VCH. (**D**) Schematic illustration of accelerating wound healing by releasing NO in NIR.[64] Copyright 2022 Wiley-VCH. BP QDs, black phosphorus quantum dots; Fe-MSC-NVs, iron-mesenchymal stem cell-derived human artificial nanovesicles; Hb, hemoglobin; MNs, microneedles; NIR, near-infrared; PDA, polydopamine.

(Fe-MSC-NVs) and PDA NPs within the needle tip.[29] Fe-MSC-NVs induce VEGF expression and accelerate angiogenesis (►**Fig. 4C**). Wu et al design a novel MN patch for loading stem cell spheroids that allows for *in situ* generation of uniformly sized stem cell aggregates through precise fluid manipulation using microfluidic template technology. The generated stem cell spheroids effectively induced angiogenesis, collagen deposition, and tissue regeneration by promoting cell proliferation and migration.[59] In addition, magnesium (Mg), as a trace element in the body, has the function of promoting angiogenesis and osteogenesis.[60,61] Yin et al loaded multifunctional Mg-MOF into MNs, and the degradation of Mg-MOF released Mg^{2+} to accelerate angiogenesis.[37] Nitric oxide (NO) plays a role in regulating inflammation and angiogenesis, thereby accelerating diabetic wound healing.[62,63] Yao et al reported a near-infrared responsive MN patch loaded with a NO-doped porous metal-organic framework (NO@HKUST-1), which enabled precise delivery of NO to the deep wounds under near-infrared light, facilitating angiogenesis in wound healing (►**Fig. 4D**).[64] MNs with pro-angiogenic ability accelerate the establishment of intricate blood vessel networks and promote the generation of vital granulation tissue, thus speeding up the intricate process of wound healing. However, it is crucial to acknowledge that the efficacy of such MNs within the inflammatory phase of wound healing remains somewhat constrained. Therefore, integrating complementary strategies, such as the combination of anti-inflammatory agents and implementing a staged wound treatment strategy, would enhance the therapeutic potential of the MNs.

The Design of MNs with Combined Strategies

Since diabetic wound healing is a complex process, composite MN patches that can simultaneously address multiple issues are playing an increasingly important role in diabetic wound treatment. For example, Ning et al designed a dual-layer MN patch with chitosan (CS) needle tip loaded with panax notoginseng saponins (PNS) and a PVP backing loaded with Mg.[38] Mg has antibacterial properties and regulates the immune response of M2 macrophages. PNS regulates inflammation and inhibits hypertrophic scarring. Thus, the combination of PNS and Mg will achieve multi-therapeutic effects of antibacterial, neovascularization, and activation of benign immune responses. Similarly, Liu et al designed a double-layered MN patch that combined infection-control and angiogenesis-promoting effects.[24] rh-EGF is loaded into the needle tip to promote cell migration and angiogenesis, while tetracycline hydrochloride was encapsulated in the backing to achieve rapid sterilization and enhance resistance to external bacterial infections. In addition, Wang et al designed an MN patch loaded with magnesium hydride (MgH_2) that could slowly release hydrogen (H_2) and magnesium ions (Mg^{2+}).[65] The releasing H_2 will reduce ROS production and transform the pathological microenvironment induced by diabetes mellitus. Mg^{2+} promotes the polarization of M2

macrophage, and coordinates with H_2 to promote cell proliferation and migration, vascularization, and tissue regeneration. Guan et al encapsulated Prussian blue nanoenzymes (PBNs) and VEGF at the tip of the MN patch and loaded the antibacterial agent of polymyxin in the backing.[39] PBNs possess antioxidant capacity and VEGF is endowed with proangiogenic ability. Due to the special design, such MN patches exhibit excellent proangiogenic, antioxidant, and antibacterial properties. The integration of MN technology collectively offers renewed optimism for the treatment of diabetic wounds because it can concurrently manifest antibacterial, anti-inflammatory, and angiogenesis-enhancing properties. This dual action accelerates the healing process, mitigates the likelihood of infection, and enhances the overall well-being of patients.

Other Designs of MNs

Currently, in combination with other characteristics of the disease, various types of MNs have been developed that differ from traditional methods. Hyperglycemia is one of the most important reasons for the difficulty of diabetic wound healing. Guo et al formulated a hydrogel MN system (Gel-AFPBA-ins) that released insulin in response to hyperglycemia to facilitate diabetic wound healing (►**Fig. 5A**).[66] Liu et al loaded an antidiabetic drug (metformin) into a hedgehog-inspired multi-layer MN patch to reduce local blood sugar concentrations to accelerate wound healing.[67] Providing directional mechanical force to promote wound contraction is also beneficial for wound healing. Inspired, researchers developed MN patches of shark tooth-like (►**Fig. 5B**) or eagle claw-structure,[68,69] which provide directional traction force from the wound edge to the center, to promote wound contraction to accelerate wound healing.[70] Considering the roles of stimulating and amplifying endogenous bioelectricity in the field of tissue repair, Zhang et al developed a self-powered enzyme-linked MN patch that consumes blood glucose through enzymatic cascade reactions, producing stable and lasting electrical currents that not only reduce glucose concentration around the wound, but also accelerate wound healing and prevent the formation of scar.[71]

Conclusion and Prospects

Wound healing is a complex, orderly, and dynamic process, and it is also a process of skin repair and rebuilding after injury. At present, there are many kinds of functional dressings for the treatment of diabetic wounds, which may be associated with drawbacks including poor breathability, easy detachment, frequent replacement, and low drug bioavailability. Among them, MN emerges as one of the most promising means, as it is minimally invasive, painless, and penetrates the skin or bacterial biofilms, thereby improving drug bioavailability and increasing patient compliance. This review provides an overview of the designs of MNs, including antibacterial MNs, anti-oxidant MNs, anti-inflammatory MNs, angiogenesis-promoting MNs, and other MNs, based on the unique characteristics of the microenvironment in diabetes wounds, such as bacterial infection, high blood glucose level, hypoxia, and abnormally increased ROS.

Despite the rapid progress of MNs, the current research mainly focuses on the materials, structure, and application rather than a thorough exploration of their biosafety. Thus, further research is recommended to assess the impact of MNs on the body and to address any potential concerns related to their safety. This can be done by studying the degradation cycle of materials used in MN manufacturing and assessing their impact on the body of a large number of animals. Some essential aspects of MNs must be taken into account in further human treatment, including drug-loading amount, patient acceptance, the variability in therapeutic effect between individuals, transportation and storage costs of MNs, etc. It has been reported that drug dosage in the MN patch can be increased by enhancing MN length or enlarging the patch area.[72] MN increases patient acceptance,[72] making

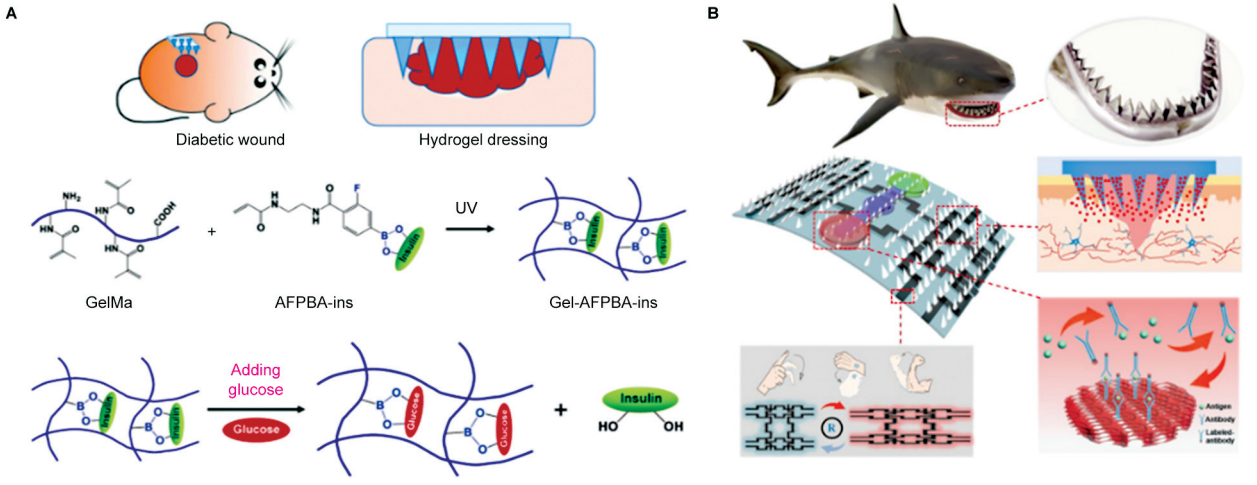

Fig. 5 (**A**) Schematic diagram of responsive microneedle release of insulin for diabetic wound healing.[66] Copyright 2022 Royal Society of Chemistry. (**B**) Schematic diagram of shark tooth-inspired microneedle dressing for wound management.[68] Copyright 2021 American Chemical Society.

it suitable for improving patient compliance during its application in wound healing. Including some special feedback mechanisms (e.g., color change) and improving the stability of MN patches might be helpful in the future design to ensure the successful use of MNs in patients and reduce costs during transportation and storage. Furthermore, the adhesion and drug delivery efficiency of the MNs is suggested to be optimized to ensure perfect performance during the treatment. The development of multifunctional systems with combined capabilities of real-time monitoring and on-demand treatment provides a solid basis for the design of multifunctional MNs for wound healing.[73,74] The integration of such intelligent devices provides insight into the wound environment and helps accelerate the healing process of diabetic wounds.

Conflict of Interest
None declared.

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