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Review Article

Revolutionizing diabetic wound healing: The power of microneedles

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ABSTRACT

Diabetic wounds significantly affect patient quality of life. Microneedles are a promising treatment to accelerate wound healing owing to their high drug-loading capacity and efficient drug delivery; however, few studies to date have comprehensively reviewed microneedles for diabetic wound healing. This up-to-date review summarizes the research progress in microneedles for diabetic wound healing, including manufacturing materials and techniques, structures, designs, release mechanisms, delivery substances, and their specific effects. This study showed that most microneedles designed for diabetic wounds are made of synthetic polymers and/or natural materials using polydimethylsiloxane micromolding. The geometric structure and design directly influence penetration ability and drug delivery capacity. Microneedles can deliver antibiotics, hypoglycemic agents, traditional Chinese medicines, metal ions, growth factors, exosomes, stem cells, and microorganisms, thus promoting diabetic wound healing through diverse mechanisms, such as antibacterial, anti-inflammatory, antioxidant, hypoglycemic, and angiogenic activities, at different stages of the healing process. In conclusion, microneedles are promising drug delivery systems for the treatment of diabetic wounds.

1. Introduction

The prevalence of diabetes has significantly increased in the aging population. It is estimated that the number of global diabetic patients will reach 195.2 million by 2030,[1] 15%–25% of whom will develop chronic non-healing wounds such as diabetic ulcers. The number of global patients with diabetic wounds will range from 9.1 to 26.1 million by 2030.[2,3] Diabetic wounds severely impact patient's quality of life and physical and mental health, and impose a significant economic burden on the healthcare system.[4] The estimated medical costs for diabetic wounds will reach $300 billion by 2030, accounting for one-third of the total expenditure of diabetes.[5]

The healing process of diabetic wounds is complicated, involving tissue regeneration and skin restoration.[6] Wound healing consists of four stages: hemostasis, inflammation, proliferation, and remodeling.[7] The hyperglycemic environment in diabetic wounds impacts the normal progression and transition of these stages, leading to chronic inflammation, recurrent infections, tissue necrosis, and subsequent unhealed wounds.[8] Treatment methods for diabetic wounds include surgical debridement, negative pressure wound therapy, vascularized flaps, and different types of local dressings.[9] Commonly used dressings include gauze, metal ion dressings, hydrogel dressings, electrospinning dressings, and platelet-rich plasma dressings.[10] However, traditional dressings have limited drug loading capacity and permeability and cannot deliver active medications to the deep wound bed.[11,12] Therefore, developing an effective and multifunctional transdermal delivery system is essential to promote the healing of diabetic wounds.

Recently, microneedles have become a research focus in wound management due to their high drug load/delivery capabilities, minimal invasiveness, convenience, and strong adhesion, which significantly reduce patient discomfort and improve compliance.[13,14] Microneedles enhance the efficiency and permeability of transdermal drug delivery by penetrating the skin barrier and incorporating drugs,[15] proteins,[16] and nanoparticles[17] and delivering them to the wound bed.[18] Microneedles

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can also achieve long-term drug release, reducing secondary damage caused by dressing changes. Despite the numerous advantages of microneedles, many challenges remain, such as insufficient penetration, fragility, and the potential risk of infection due to micropore formation.

To date, few studies have comprehensively reviewed the research progress on microneedles for diabetic wound healing. This review aimed to (1) summarize the manufacturing materials, techniques, structures, designs, release mechanisms of microneedles, and classifications of delivered substances and their effects on different stages of wound healing; (2) discuss the challenges of microneedle therapy and their solutions and provide an outlook on its research prospects and clinical applications.

2. Materials, manufacturing techniques, and structures of microneedles for diabetic wound healing

2.1. Manufacturing materials

Manufacturing materials are significantly associated with the characteristics and functions of microneedles. Reported materials for the production of microneedles for diabetic wounds include polymer materials, such as polyvinyl alcohol (PVA) and hyaluronic acid (HA),[19] and natural materials, such as gelatin,[20] chitosan,[21] and silk fibroin[22] (Table 1). Inorganic and metallic materials such as silicon, ceramics, glass, and magnesium can also be used for manufacturing microneedles; however, these materials have not yet been used in the production of microneedles for diabetic wounds.

2.2. Production technology

Various techniques are available for the fabrication of microneedles, including microfabrication/micromolding techniques.[22,30] and 3D printing techniques.[27] Micromolding techniques use polydimethylsiloxane (PDMS) or silicone molds to create microneedles by injecting material into the molds, followed by drying and demolding. The micromolding technique is convenient and exhibits high fabrication efficiency. Most microneedles used for the treatment of diabetic wounds are made from hydrogels, thus the major fabrication technique is micromolding with PDMS. Compared to micromolding, 3D printing and photolithography techniques are more precise and complex and are commonly used for the fabrication of microneedles with intricate structures (e.g., biomimetic microneedles,[54] microneedles loaded with exosomes[27] or stem cells[45]). Different manufacturing techniques are employed according to different materials to achieve the required geometric structures for the treatment of diabetic wounds.

2.3. Geometric structure

Microneedles are designed to penetrate the skin and deliver drugs to a deep wound bed. Different geometric structures of microneedles, including length, density, radius, angle, and shape, can influence their mechanical strength, penetration ability, drug loading capacity, and drug delivery efficiency.

2.3.1. Length

The length of the microneedle is the most crucial factor influencing penetration capability because longer needle tips go deeper. The lengths of most reported microneedles range from 150 to 1 500 μm. Skin thickness varies among different areas: for example, 91, 80, 170, and 596 μm for the forearm, abdomen, dorsum of the foot, and sole of the foot, respectively.[55] Therefore, the appropriate length of microneedles can be decided on the application site. Studies have shown that the optimal balance between drug delivery and comfort is achieved when the length of microneedles is between 600 and 1 100 μm. A further increase in length does not guarantee more drug permeation but aggravates pain.[56]

Table 1
Advantages and disadvantages of different materials and their production techniques of microneedles for diabetic wounds.

Materials	Production technology	Advantages	Disadvantages
SF	PDMS micromolding[22]	Good mechanical properties; Biocompatibility; No cytotoxicity;[23,24] No inflammatory stimulation[25]	Long manufacturing time[25]
PVA	3D printing silicone molding[19,26]	Thermal degradation;[27] Biocompatibility; Low cytotoxicity; No skin irritation[28]	Low water solubility; low biodegradability[27]
PEDGA	PDMS micromolding[29]	Rapid dissolution and drug release;[30] Adjustable pore size[31]	Low mechanical strength;[30] Mild cell and tissue toxicity[31]
HA	PDMS micromolding[32,33]	Biocompatibility and non-toxicity; Biodegradability; Non-immunogenicity; Water solubility; High compatibility with drug molecules[25]	Low mechanical strength; Low drug distribution[31]
PLGA	PDMS micromolding[34]	Good mechanical strength; Biocompatibility and non-toxicity;[35] Adjustable porosity[36]	High manufacturing temperatures or organic solvents are required.[25]
Chitosan	PDMS micromolding[37]	Rapid dissolution and drug release; Biodegradability; Biocompatibility and non-toxicity;[38] Antibacterial and hemostatic property[39]	Low mechanical strength; Skin irritation[30]
Gelatin	PDMS micromolding[13,40]	Biocompatibility and non-cytotoxicity;[41] Good mechanical strength; Good solubility; No immunogenicity[42,43]	Unstable degradation[43]
HAMA	PDMS with microfluidics[44] PDMS micromolding[45]	Good mechanical properties; High expansion rate; Good biocompatibility[46,47]	Slow degradation[48]
γ-PGA	PDMS micromolding[49,50]	Good biocompatibility and no cytotoxicity; Biodegradability;[51] No immunogenicity;[52]	High production cost and complex production procedures[53]

SF, silk fibroin; PDMS, polydimethylsiloxane; PVA, polyvinyl alcohol, PEDGA, polyethylene glycol diacrylate; HA, hyaluronic acid; PLGA, poly(lactic-co-glycolic acid); HAMA, hyaluronic acid methacryloyl; γ-PGA, poly(γ-glutamic acid).

2.3.2. Density

The density of the microneedle array also affects drug permeation capability.[57] A high-density array may induce a "bed-of-nails" effect (i.e., skin folds around the microneedles), thereby reducing skin penetration.[58] The optimal drug permeation capability is observed when the density ranges from 400 to 900 needles per square centimeter. A further increase in density results in decreased drug permeation.[57]

2.3.3. Radius

Studies have shown that a smaller radius of a microneedle tip leads to more efficient skin penetration.[59] When the radius of the microneedle tip is decreased from 80 to 30 μm, the contact area between the tip and the skin decreases, resulting in higher intensity of pressure and increased

penetration ability.[60] However, it is worth noting that long and fine needles increase the risk of tip breakage.

2.3.4. Angle

The penetration capability of a microneedle is also influenced by the inclination angle of the needle tip. Research has shown that microneedle tips provide an optimal penetration capability when the inclination angle ranges from 15° to 30°.[61,62]

2.3.5. Shape

The shape of microneedles affects the resistance encountered during skin penetration. Common microneedle shapes include pyramids, cones, triangles, cylinders, circles, and hexagons.[63,64] As the number of vertices increases, the mechanical properties increase, but the penetration capability decreases.[65,66] Most microneedles for diabetic wounds employ pyramidal or conical tips to ensure both mechanical strength and penetration capability.

3. Designs of microneedles for the treatment of diabetic wounds

The reported microneedle designs for diabetic wound management can be categorized into six types: porous, multilayered, dissoluble, separable, softened, and biomimetic (Table 2).

3.1. Porous microneedles

Porous microneedles are fabricated from biocompatible metals, ceramics, or polymers with small, interconnected pores that facilitate large loading and delivery of both solid and liquid substances.[61,68] Most porous microneedles for diabetic wound treatment are designed to deliver drug-loaded nanoparticles.[34] In addition, liquids can circulate through these pores, allowing the humoral collection to monitor the wound environment and healing status.[68] Guo et al. introduced porous microneedles with an inverse opal photonic crystal structure to enhance the drug-loading capacity and control drug release.[54] Although the size and distribution of the pores can be changed, the mechanical strength of porous microneedles is relatively low.[65] Furthermore, the porous structure may be blocked by debris of skin tissue, cells, or secretions.

Table 2
Advantages and disadvantages of common design types of microneedles for diabetic wounds.

Design types	Materials	Advantageous	Disadvantageous	Citation
Porous	PVA; HA	Adjustable porosity and pore size; Large drug load; Both solid and liquid drugs can be delivered	Low mechanical strength; Pores may be blocked	34 61 66
Multilayer	HA; Gelatin	Multiple drugs can be released at different times; High drug delivery efficiency	Complex production	20 69 70
Dissoluble	γ-PGA; Chitosan	Macromolecular drugs load; Biocompatibility; Non-toxicity; Controllable release	Low mechanical strength; Low drug load; Unmatched dissolving time	21 49 67 72
Separable	PVA; Gelatin	Increased comfort; Rapid drug release; Increased oxygenation	Risk of infection; Low adhesion	19 74 75 76
Softening	PVA	Increased comfort; Increased adhesion; Sustainable drug delivery	Low convenience; Softener may cause irritant reaction	27 28
Biomimetic	SF; PDA binding PAM.	Increases adhesion; Increases penetration	Complex production; High cost; Low drug load	70 54

SF, silk fibroin; PVA, polyvinyl alcohol; HA, hyaluronic acid; γ-PGA, poly(γ-glutamic acid); PDA, polydopamine; PAM, polyacrylamide.

3.2. Multilayer microneedles

Multilayered microneedles are manufactured by adding layers of material to a mold through repeated stacking. Multilayered microneedles can incorporate more types and higher volumes of drugs,[20] achieve staged or spatiotemporal drug release,[20] and enhance drug delivery efficiency.[69,70] Liu et al. fabricated dual-layer microneedles, where the outer layer was loaded with tetracycline hydrochloride, and the inner layer was loaded with recombinant human epidermal growth factor. This design enabled the release of different drugs at the corresponding stages of wound healing: antibiotic release to prevent infection during the inflammatory stage and growth factor release to promote re-epithelization during the proliferation stage.[20] Liu et al. created three-layered microneedles loaded with a mixture of CaO_2, hyaluronic acid nanoparticles, metformin, and copper ions. This design allows the sequential delivery of multiple drugs for increased skin adhesion, glycemic control, and infection prevention.[70]

3.3. Dissolving microneedles

Dissolving microneedles are composed of biodegradable materials that release loaded molecules during dissolution in the wound bed. For example, Wang et al. utilized poly(lactic-co-glycolic acid) microneedles loaded with MgH_2 for the treatment of diabetic wounds.[35] Yin et al. constructed microneedles using γ-poly(glutamic acid) hydrogel and loaded them with graphene oxide-silver nanoparticle composite material.[50] Dissolving microneedles employs different soluble materials to achieve staged dissolution and drug release for therapeutic purposes.[20] Although the mechanical strength of dissolving microneedles can be improved by altering the composition of hydrogels and polymers, their mechanical strength is often insufficient, resulting in limited skin penetration.[71,72] The introduction of artificial materials such as graphene and MXene can enhance the mechanical strength of hydrogel-based microneedles. A study combining MXene with γ-PGA hydrogel to create composite hydrogel microneedles found the combination had increased mechanical strength and skin penetration ability.[49]

3.4. Separable microneedles

Separable microneedles detach their base upon entering the skin and separate from the needle tip.[73] The base of separable microneedles is typically composed of rapidly degradable materials such as polyvinyl alcohol (PVA). Separable microneedles have advantages including rapid drug release,[74] increased patient comfort,[75] and improved oxygen penetration to the wound site.[19] Zhao et al. used PVA as the base material and methacrylated gelatin (GelMA) loaded with oxygen-generating microalgae as the needle tip to improve the hypoxic environment in diabetic wounds.[19] Similarly, Zhang et al. utilized PVA as the base material and GelMA loaded with black phosphorus and hemoglobin as the needle tip. The needle tip can generate oxygen under near-infrared irradiation.[76] However, separable microneedles may sacrifice the protective effect of the microneedle patch at the wound site and prolong wound infection.

3.5. Softening microneedles

Most reported softening microneedles for diabetic wounds are made of PVA hydrogels. PVA hydrogels exhibit ion-responsive properties (Hofmeister effect), that is, an increase in mechanical strength with sulfate ions and a decrease in mechanical strength with nitrate ions.[77] These ion-responsive microneedles can modulate their mechanical

strength under different environmental ions and can, for example, soften needle tips for patient comfort and compliance and retain needle tips for continuous drug delivery. Zhang et al. produced needle tips with a PVA hydrogel, loaded them with exosomes derived from mesenchymal stem cells and sodium sulfate, and attached them to a 3 M tape base dressing. Sodium sulfate increased the mechanical strength of the PVA tips before their insertion into the skin. The base of the 3 M tape was detached after skin penetration. Extra ferric nitrate caused the needle tip to soften and remain in the wound for the sustainable release of exosomes.[27] Drawbacks of softening microneedles include less adhesion and convenience, and sulfate/nitrate ions may cause skin irritation.

3.6. Bionic microneedles

Biomimetic microneedles are biologically inspired. Their appearance or structure is similar to organs or structures of animals or insects, such as shark teeth[54] and porcupine quills.[70] Biomimetic microneedles are typically made of polymer materials with good biocompatibility. Fabrication methods for biomimetic microneedles include 3D printing,[54] micromolding,[70] laser engraving,[70] etc. Liu et al. developed three-layered microneedles by mimicking the barb structure of porcupine quill to increase skin adhesion and penetration.[70] Guo et al. produced microneedles that mimic shark teeth to enhance adhesion. The challenges of biomimetic microneedles include complex fabrication processes and high costs.

3.7. Other designs of microneedles

Solid, coated, hollow, and swellable microneedles have also been used to treat chronic wounds. Solid microneedles have a simple manufacturing process, high mechanical strength, and a strong skin penetration ability. However, some of them are non-biodegradable and may cause skin irritation and infection.[78] Coated microneedles are coated with drugs on the surface of solid microneedles and can rapidly release drugs upon insertion into the skin.[61] However, the coating has a small drug loading capacity and lacks controlled sustainable drug release.[72] Hollow microneedles have hollow needle tips that connect to a device that delivers drugs and extracts wound exudate through the lumen.[72] Hollow microneedles can control the volume and rate of drug delivery.[79] However, lumen blockage or drug leakage may occur.[80] Swellable microneedles expand upon insertion into the skin through water absorption or photothermal effects. The pore size is then altered and loaded drugs are released.[61]

4. Release mechanisms of microneedles for diabetic wound healing

Microneedles release drugs to treat diabetic wounds via different mechanisms (Fig. 1), including diffusion, dissolution, and response release. The release mechanism depends on the size of the loaded drug and the microneedle pores.[81]

4.1. Diffusion release

Diffusion release is the major release mechanism when the pore size of the microneedle matrix is larger than that of the loaded molecules, such as in hydrogel, porous, and swellable microneedles.[82] The drug molecules pass through the pores and are released into the wound environment.

4.2. Dissolution release

Dissolution-based release is the primary drug release mechanism employed by microneedles in diabetic wounds. The loaded molecules cannot be released through diffusion because of their larger size compared to that of the matrix pores. Instead, the molecules are released when the materials are dissolved. The duration of dissolution determines the drug release time, which can be adjusted by mediating the polymer degradation to achieve sustained release.[81] This sustained drug release prolongs the therapeutic effect on diabetic wounds, enhances treatment efficacy, and accelerates wound healing.

4.3. Responsive release

Responsive release refers to the release of drugs in response to factors such as pH, temperature, glucose concentration, and near-infrared light. Responsive microneedles intelligently release drugs by sensing changes in the wound environment. Guo et al. used a temperature-responsive N-isopropylacrylamide hydrogel to create microneedles. This hydrogel released the encapsulated drugs when the local temperature elevated due to infection or inflammation in diabetic wounds.[54] Guo et al. synthesized a glucose-responsive hydrogel using gelatin and 4-(2-acrylamidoethylcarbamoyl) 3-fluorophenylboronicacid, which can sense the glucose concentration in the wound environment and trigger insulin release.[13] Shan et al. utilized the photothermal conversion ability of Au–Cu_2MoS_4 nanosheets and NIR-II irradiation to trigger the enhanced enzymatic reaction activity of the enzymes loaded in the microneedles, achieving therapeutic effects on diabetic wounds.[83] Yang et al. used

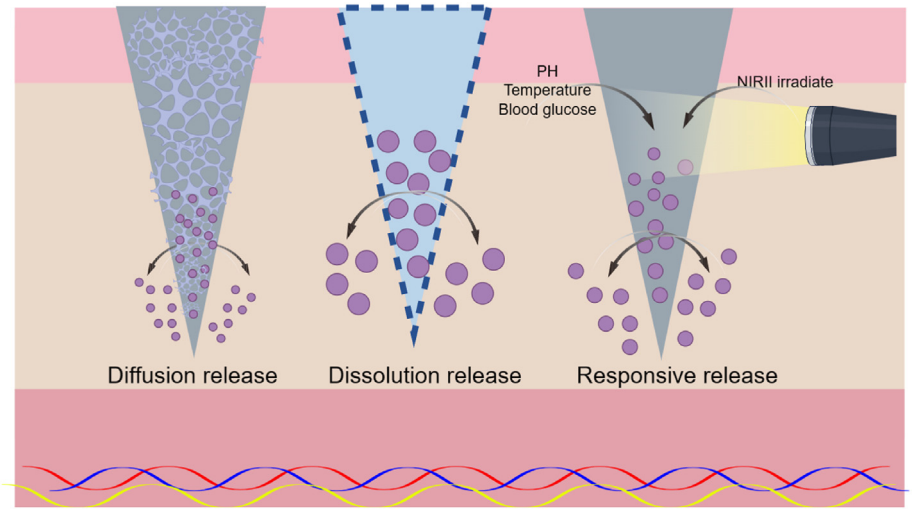

Fig. 1. Release mechanisms of microneedle delivery (By Figdraw.).

HA-loaded cerium/zinc-based (ZCO) nanoparticles to release ZCO nanoparticles by sensing pH changes.[84]

5. Classifications and functions of delivered substances by microneedles

Various substances can be loaded and delivered by microneedles for the treatment of diabetic wounds, including antibiotics, hypoglycemic agents, traditional Chinese medicines, nanoparticles, growth factors, stem cells, exosomes, enzymes, and microorganisms (Table 3). Researchers have also used microneedles to deliver antibodies and nucleic acids (DNA, mRNA, miRNA, and siRNA), although these have not yet been used for diabetic wound healing.[85–87]

5.1. Drugs

Common therapeutic agents loaded with microneedles for diabetic wound healing include antibiotics, hypoglycemic agents, and traditional Chinese medicines. Liu et al. loaded tetracycline hydrochloride and recombinant human epidermal growth factor to increase the ability of anti-infection and reepithelialization.[20] Wang et al. delivered a multifunctional Chinese herb, asiaticoside, using poly-γ-glutamic acid hydrogel microneedles to achieve anti-inflammation, antioxidation, epithelialization, and angiogenesis in diabetic wounds.[49]

5.2. Nanoparticles

Nanoparticles reported for diabetic wound microneedles include CaO_2, Zn, Fe, and Mg. These nanoparticles have antibacterial functions and promote wound healing through the photothermal effect or inherent properties of metal ions. For instance, Zhang et al. generated HA microneedles and loaded them with photothermal ZnO nanoparticles to enhance the antibacterial effect.[88] Similarly, Zeng et al. utilized electrospun nanofiber membranes and loaded with photothermal CaO_2/polydopamine nanoparticles for antioxidation via oxygen production.[41] Wang et al. developed a water-based gel by combining polylysine and

Table 3
Loaded therapeutic substances, their release mechanisms, and effects on diabetic wound healing.

Category	Therapeutic substances	Carrier material	Effect	Release mechanism
Antibiotics	TH	HA	Anti-infection	Diffusion release from the HA base[20] Dissolution release of HA tip[33]
	Polymyxin	SF	Anti-infection	Diffusion release[22]
Metallic ion	Ag	γ-PGA	Antibacterial[95]	Diffusion release[50]
	Mg	γ-PGA	Antibacterial Angiogenesis[96]	Diffusion release[50]
	Cu	PAM/PDA hydrogel	Antibacterial Antioxidation[97,98]	Diffusion release[70]
Chinese herb	Asiaticoside	γ-PGA/MXenes	Epithelialization Angiogenesis[99] Antioxidation, Anti-inflammation[100]	Dissolution release[49]
Hypoglycemic agent	Metformin	Gelatin	Hypoglycemic	Dissolution release[41]
	Insulin	Gelatin/AFPBA hydrogel	Hypoglycemic	Responsive release[13]
Growth factor	VEGF	SF	Angiogenesis	Dissolution release[22]
		HA		Responsive release[88]
	b-FGF	HA	Fibroblast migration Angiogenesis	Responsive release[88]
	rh-EGF	Gelatin	Angiogenesis	Dissolution release[20]
Nanoparticle	ZnO	HA	Antibacterial[86]	Responsive release[88]
	CaO_2/polydopamine	Electrospun nanofiber	Photothermal effect Antibacterial Produce oxygen Antioxidation[41]	Dissolution release[41]
	CaO_2/HA	PAM/PDA hydrogel	Photothermal effect Antibacterial Produce oxygen Antioxidation[41]	Dissolution release[70]
	Iron/tannic acid nanoparticles	Polylysine	Photothermal effect Antibacterial	Diffusion release[89]
	MgH_2 nanoparticles	PLGA	Anti-inflammation Angiogenesis;[96] Antioxidation[35]	Dissolution release[35]
	Cerium/zinc-based nanoparticles	HA	Antibacterial Antioxidation Anti-inflammation	Responsive release[84]
Exosome	M2 macrophages	HAMA	Promote M2 macrophage polarization Anti-inflammatory[101] Angiogenesis[102]	Diffusion release[26]
	HUVECs	PEDGA	Cell proliferation and migration Angiogenesis[30]	Diffusion release[30]
	MSCs	PVA	Promote M2 macrophage polarization Anti-inflammatory Angiogenesis[30]	Diffusion release[27]
Enzyme	Glucose oxidase	PVA/HA	Hypoglycemic Antioxidation[38,83] Scar prevention Anti-inflammation[34]	Diffusion release[34,83] Dissolution release[38]
	Horseradish peroxidase	HA	Scar prevention Anti-inflammation[34]	Diffusion release[34]
	Glutaminase	Polylysine	Angiogenesis Anti-infection[89,103,104]	Diffusion release[89]
Enzyme-like substances	Prussian blue nanoenzyme	SF	Antioxidation Anti-inflammation[105,106]	Dissolution release[22]
	Fe_2C nanoenzymes	PVA	Antioxidation Antibacterial[38]	Dissolution release[38]
Stem cells	ADSC	HAMA	Modulating immune cells Anti-inflammatory Angiogenesis	Diffusion release[45]
Microorganism	chlorella vulgaris	Gelatin	Produce oxygen Antioxidation[107]	Diffusion release[19]

TH, tetracycline hydrochloride; SF, silk fibroin; PVA, polyvinyl alcohol; PEDGA, polyethylene glycol diacrylate; HA, hyaluronic acid; PLGA, poly(lactic-co-glycolic acid); HAMA, hyaluronic acid methacryloyl; γ-PGA, poly(γ-glutamic-acid); PDA, polydopamine; PAM, polyacrylamide; AFPBA, acrylamidoethylcarbamoyl-fluorophenylboronic acid.

gelatin and loaded it with iron/tannic acid nanoparticles to increase the antibacterial function.[89] Wang et al. utilized a polylactic-co-glycolic acid copolymer and loaded it with MgH_2 nanoparticles to achieve anti-inflammation, antioxidation, and angiogenesis.[35] Yang et al. used HA-loaded cerium/zinc-based nanoparticles for enhanced antibacterial and antioxidant effects.[84]

5.3. Stem cells

Microneedles are excellent carriers for stem cells and can directly deliver them to the wound site.[90] Microneedle delivery avoids the high loss rate and uneven local concentration in topical applications, as well as untargeted migration and insufficient homing to the wound site in intravenous injections. Mesenchymal stem cells derived from tissue, including the bone marrow, adipose, umbilical cord, and placenta, are crucial in wound healing owing to their ability of differentiation and paracrine of various growth factors and cytokines.[91] Adipose-derived stem cells are the most commonly delivered stem cells via microneedles for diabetic wounds.[45] For example, Wu et al. utilized a microfluidic chip to aggregate adipose-derived stem cells into microspheres within microneedles and deliver them to diabetic wounds.[45]

5.4. Exosomes

Exosomes are small vesicles (diameters ranging from 50 to 150 nm) released by cells. Exosomes regulate intercellular communication by transferring bioactive substances such as miRNA, mRNA, and extracellular matrix proteins.[92] Exosomes have shown significant pro-healing potential in different stages of wound healing.[93] However, the clinical translation of exosomes is restricted by the short half-life, *in vitro* instability, and poor absorption rate by the skin through topical application.[94] As a promising carrier, microneedles can penetrate through the skin barrier and deliver exosomes to the wound. Previous studies reported that exosomes derived from M2 macrophages,[26] human umbilical vein endothelial cells,[30] and mesenchymal stem cells[27] can be delivered using microneedles to treat diabetic wounds. For example, Zeng et al. delivered exosomes derived from M2 macrophages using methacrylated HA microneedles for enhanced antibacterial, antioxidant, and anti-inflammatory effects.[26] Yuan et al. delivered exosomes derived from human umbilical vein endothelial cells using polyethylene glycol diacrylate microneedles to promote cell proliferation, migration, and angiogenesis.[30] Zhang et al. delivered exosomes derived from mesenchymal stem cells using PVA microneedles to promote M2 macrophage polarization, anti-inflammation, and angiogenesis.[27]

5.5. Enzymes or enzyme-like substances

Enzymes or enzyme-like substances catalyze or participate in biological reactions. Previous studies have reported the delivery of glucose oxidase,[34,38,83] horseradish peroxidase,[34] catalase,[83] glutaminase,[89] Prussian blue nanozymes,[22] and Fe_2C nanozymes[38] using microneedles. Different enzymes and enzyme-like substances exhibit different therapeutic effects during wound healing. For example, when combined with horseradish peroxidase.[34] Glucose oxidase can also synergize with catalase to improve oxygen production.[83] Fe_2C nanozymes possess peroxidase activity but their function is influenced by H_2O_2 and pH.[38]

5.6. Microorganisms

Microorganisms, including prokaryotes (e.g., bacteria), eukaryotes (e.g., fungi, algae), and non-cellular organisms (e.g., viruses) have various effects on the wound healing process.[95] Researchers have utilized microneedles to deliver eukaryotic *Chlorella vulgaris* to the wound bed. Photosynthesis by *C. vulgaris* generates oxygen, improving the hypoxic environment in diabetic wounds and promoting wound healing.[19]

6. Effects of microneedles on different stages of diabetic wound healing

Wound healing is an intricate process that can be divided into four stages: hemostasis, inflammation, proliferation, and remodeling.[108] Dysregulation of any stage can result in delayed wound healing. Many factors can impair diabetic wound healing, including hyperglycemia, prolonged inflammation, an imbalance between the generation and clearance of reactive oxygen species (ROS), bacterial infection, reduced angiogenesis, reduced proliferation, increased apoptosis of regenerative cells, decreased extracellular matrix deposition, and disrupted arrangement. These factors affect different stages of wound healing in multiple ways.

6.1. Hemostatic phase

Immediately after skin injury, damaged blood vessels contract rapidly. Platelets are also activated, and procoagulant factors are secreted to initiate the coagulation cascade, leading to thrombus formation to prevent blood loss and further vascular damage.[109,110] However, in diabetic wounds, the hyperglycemic environment causes an excessive coagulation response and excessive formation of thrombi or blood clots, leading to reduced nutrient supply to the wound and delayed wound healing.[111]

Microneedles can improve the hypercoagulable state through the loading of hypoglycemic agents such as metformin[41] and insulin.[13] Studies have also indicated that microneedles promoted the generation of temporary extracellular matrix protein during the hemostasis phase, which shortened the duration of the inflammatory stage and accelerated wound healing.[112]

6.2. Inflammatory phase

The inflammatory phase involves various immune cells such as macrophages, neutrophils, and mast cells. When activated by the inflammatory response, M1 macrophages phagocytose necrotic tissue, bacteria, pathogens, and other debris.[113] Upon injury, mast cells undergo degranulation and release chemokines or cytokines that recruit neutrophils.[114] Neutrophils eliminate pathogens through phagocytosis and release ROS, leukotrienes, and proteolytic enzymes.[115] Neutrophils can also capture and kill pathogens with DNA-based structures, such as antimicrobial peptides and cytotoxic proteins, in extracellular traps.[116] Therefore, normal inflammatory responses facilitate wound healing. However, diabetes delays M1-to-M2 macrophage polarization,[117] inhibits the function of neutrophil extracellular traps,[118] and induces oxidative stress through excessive ROS generation.[119] These factors contribute to a prolonged inflammatory stage and delay intra-phase transition.

Therapeutic agents delivered via microneedles control infections and mediate inflammation to promote wound healing in diabetes. For example, microneedles can directly exert antimicrobial effects by delivering antibiotics and metal ions[20,50,70] and can indirectly combat bacteria through the photothermal effect of loaded nanoparticles.[41,87,88] Excessive ROS production can lead to sustained inflammation by inducing oxidative stress. Microneedles loaded with *C. vulgaris* can produce oxygen via photosynthesis and eliminate ROS,[19] those loaded with CaO_2 nanoparticles can generate hydrogen peroxide.[41,70] Enzyme and enzyme-like substances loaded onto microneedles generate hydrogen peroxide[38,83] and enhance ROS clearance.[22] Microneedles can also deliver MgH_2 nanoparticles that generate hydrogen ions for enhanced antioxidative and anti-inflammatory effects.[35,70] Furthermore, microneedles regulate important signaling pathways of wound healing by loading stem cells,[45] generate bioelectricity by loading enzymes,[34] and modulate macrophage polarization by loading exosomes derived from macrophages or mesenchymal stem cells.[26] By delivering various substances, microneedles modify the inflammatory stage of wound healing in diabetic wounds.

6.3. Proliferation phase

During the proliferation stage of wound healing, various cells such as keratinocytes, fibroblasts, and endothelial cells proliferate and migrate to coordinate wound closure, matrix deposition, and blood vessel formation.[120] In this stage, keratinocytes exhibit enhanced proliferation, migration, and differentiation, gradually migrating from the wound edge toward the center to restore the integrity of the skin (i.e., re-epithelialization).[121] Fibroblasts secrete proteins such as fibronectin and collagen to generate new, permanent extracellular matrix proteins.[122] Additionally, fibroblasts can secrete matrix metalloproteinases to degrade inflammatory matrix and promote keratinocyte migration. Fibroblasts can also differentiate into myofibroblasts to facilitate wound contraction.[123] The proliferation and migration of endothelial cells increases, leading to accelerated blood vessel formation around the wound, which promotes nutrient supply to the wound and facilitates wound healing. In diabetic wounds, the local hyperglycemic environment and accumulation of advanced glycation end-products impair the normal function of keratinocytes, resulting in delayed re-epithelialization. In addition, the proliferation and migration capacity of fibroblasts decreased, and apoptosis of fibroblasts increased. The secretion of collagen and other extracellular matrix proteins is also reduced, leading to delayed skin repair and wound healing. Furthermore, the proliferation and migration capacity of endothelial cells and VEGF production decrease, leading to impaired blood vessel formation and delayed wound healing due to wound hypoxia.[124,125]

Microneedles can promote re-epithelialization by delivering asiaticoside,[49] enhance fibroblast proliferation and migration by delivering basic fibroblast growth factor and adipose-derived stem cells,[45,88] increase collagen deposition by delivering exosomes derived from M2 macrophages through NIRII irradiation,[26] and promote endothelial cell proliferation and regeneration by delivering exosomes derived from umbilical vein endothelial cells and mesenchymal stem cells.[27,30] Additionally, microneedles can directly deliver VEGF and recombinant human epidermal growth factor to promote endothelial cell proliferation and regeneration while inhibiting apoptosis, thus facilitating diabetic wound healing.[17,22] Furthermore, microneedles can deliver substances such as glutaminase and magnesium ions to promote blood vessel formation and accelerate wound healing during the proliferation stage.

6.4. Remodeling phase

Remodeling is the final phase of wound healing and is characterized by the formation of mature type I collagen by fibroblasts.[126] The unstable neovasculature degenerates and condenses, leaving stable blood vessels.[127,128] Additionally, the immune cells that are predominant in the inflammatory phase become redundant. Most of them migrate out of the wound area, while a small portion undergo apoptosis and diminish.[129] Fibroblasts replace the initial fibrin clots by secreting HA, fibronectin, and proteoglycans.[130] Fibroblasts continue to secrete collagenase and matrix metalloproteinases to organize the arrangement of collagen.[127,128] The temporary ECM (e.g., type III collagen) is replaced by a permanent ECM (e.g., type I collagen), enhancing the tensile strength of the scar tissue.[131] The arrangement of elastic fibers is initially disorganized, while mature organized elastic fibers are observed in scar tissue several months after the injury.[132] In diabetic wounds, collagen deposition is disorganized, and ECM remodeling is compromised. Increased secretion of MMP-9 and decreased secretion of MMP-2 by fibroblasts result in excessive ECM degradation.

Microneedles facilitate wound healing during the remodeling stage by promoting collagen synthesis and deposition and ECM remodeling. For example, microneedles deliver glucose oxidase and horseradish peroxidase to create an enzyme-coupled bio-battery that consumes glucose and generates bioelectricity.[34] Collagen fibers are aligned in the direction of electrical fields to prevent scar formation. Microneedles can also deliver adipose-derived stem cells to modulate gene expression related to ECM production.[45] Moreover, silk fibroin microneedles can stimulate the NF-kB signaling pathway, a significant pathway in ECM synthesis and remodeling.[33]

7. Challenges and solutions

Although research indicates that microneedles are a promising treatment for diabetic wounds, several challenges remain regarding their clinical application. First, the efficacy of microneedles in diabetic wounds with severe infections is compromised. The use of microneedles in severely infected wounds may aggravate the infection. Therefore, thorough and repeated debridement and negative-pressure wound therapy are recommended before microneedle use. Second, the microneedle tip may be lengthened to increase its penetration depth into deep wounds; however, this increases the risk of tip breakage. Third, nonbiodegradable tips, if broken and left in the wound, are difficult to remove and may cause skin irritation as foreign bodies. Therefore, biodegradable and biocompatible polymer materials are recommended for manufacturing microneedles. Fourth, the clinical application of microneedle treatment may cause pain and discomfort. To alleviate pain, the density and radius of the microneedle tips can be adjusted, and topical anesthesia can be administered before microneedling. Finally, the cost of microneedles is higher than that of traditional dressings. Further industrialization and simplification of the microneedle production process can help reduce manufacturing costs and make microneedles more accessible and cost-effective.

8. Prospects

Current research has primarily focused on the materials, structures, and design of microneedles. Few studies have investigated the interaction between microneedles and their delivery agents in diabetic wounds. The therapeutic effects of microneedle therapy mostly rely on the delivered agents. The molecular biological mechanisms of microneedle therapy warrant further investigation. Patient responses to these drugs are distinct owing to their inherent heterogeneity. For example, some patients are sensitive to metformin, while others are not, or become metformin-resistant after a period of medication. Therefore, further research is needed to identify new therapeutic targets by integrating multi-omics data, such as genomic, transcriptomic, proteomic, and clinical data. Personalized treatments can thus be developed by exploring novel therapeutic agents for diabetic wound healing.

Furthermore, intelligent microneedles that can respond to the wound environment may be of future research interest, these include future microneedle patches that can change color by sensing changes in wound temperature, inflammation, and glucose concentration to monitor the wound status. Wound healing is a dynamic process. For example, appropriate inflammation is critical for the initiation of regeneration. A high level of inflammation impairs wound healing, whereas an exceptionally low level of inflammation or chronic inflammation prolongs wound healing because low levels of inflammation cannot recruit fibroblasts. Therefore, microneedles that can intelligently mediate and control the inflammatory level to an optimal range for smooth transition among wound healing stages will be of interest. Other research prospects for microneedles include a combination of microneedle therapy with light, temperature, mechanics, electronics, and magnetism. Nanotechnology can also be used to fabricate nanostructured microneedles that offer enhanced stimulation and precise drug delivery capabilities. No clinical trials have been published or registered on microneedles for diabetic wound healing. Therefore, the application of microneedles must be promoted in clinical trials.

9. Conclusion

This article reviews recent research regarding microneedles for diabetic wound healing. In general, most microneedles designed for diabetic wounds are made of synthetic polymers or natural materials using PDMS

micromolding methods. The geometric structure and design of microneedles directly influence their penetration ability and drug loading/delivery capacity. Microneedles can deliver antibiotics, hypoglycemic agents, traditional Chinese medicines, metal ions, growth factors, exosomes, stem cells, and microorganisms. Through this, microneedles can promote diabetic wound healing through diverse mechanisms, such as antibacterial, anti-inflammatory, antioxidant, hypoglycemic, and angiogenic activities, at different stages of the healing process. In conclusion, microneedles are promising drug delivery systems for the treatment of diabetic wounds.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All the authors have consented for the publication.

Authors' contributions

Liang C: Conceptualization, Writing-Original draft, Data curation, Visualization. Wang R: Methodology, Software, Investigation. He T: Methodology, Software, Investigation. Chen D: Investigation. Zhang G: Investigation. Yin X: Supervision. Wang H: Supervision. Xie J: Investigation. Li Y: Conceptualization, Validation, Writing-Review and editing. Chen Y: Conceptualization, Validation, Writing-Review and editing.

Declaration of competing interests

Chen Y is an Editorial Board Member for *Chinese Journal of Plastic and Reconstructive Surgery* and was not involved in the editorial review or the decision to publish this article. All authors declare that there are no competing interests.

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