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Antibacterial Agents Employed in Microneedles for the Management of Diabetic Ulcers: *Review*

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Abstract: Infected diabetic ulcers are one of the most serious complications of diabetes mellitus. Nearly, half of diabetic ulcers develop infections, and twenty percent of them require lower extremity amputation. Microneedles showed promising results in diagnostic and medical fields including diabetic ulcers. This is due to the painless and minimally intrusive nature of the drug delivery technique, which enhances patient acceptance and adherence to prescribed treatment plans and sustains ideal medication concentration at the wound site for a prolonged amount of time. Additionally, it aims to lessen systemic exposure and the associated negative effects by concentrating medication delivery on the wound site. Microneedles, despite not being clinically tested, have shown promising effects on wound healing in diabetic wounds. They have several beneficial properties, including the structural ability to be loaded with compounds like nanoparticles, stem cells, antibacterial agents, and nucleic acids, the ability to overcome physical barriers, the ability to deliver drugs on demand, mechanical stimulation that triggers collagen deposition and rearrangement, and the ability to overcome bacterial resistance and biofilms. Additionally, microneedles can monitor wound bed conditions like temperature, pH, proteins, and procreative oxygen species. This review addressed 33 pre-clinical studies that successfully loaded antibacterial agents to microneedles and the resulting consequences on animal models. Various antibacterial agents like metallic nanoparticles, antimicrobial peptides, Polymixin B, derivatives of Fluoroquinolones, and Tetracycline are among the agents that are showing promising results for further investigation. The most common types used in these studies are dissolving and hydrogel-forming. Further preclinical investigations and well-designed clinical trials are required to evaluate the efficacy and safety of microneedles as transdermal drug delivery devices for antibacterial agents in diabetic wounds.

Keywords: Antibacterial agents; microneedles; delivery system, nanoparticles; Diabetic wound infection; biofilm; wound healing.

Introduction

Diabetic ulcers are complications characterized by wound formation, especially due to pressure, disruptions in the normal healing process, improper epithelization kinetics, and prolonged inflammation. Many factors contribute to the pathology of diabetic wounds such as hyperglycemia, peripheral vascular disease, neuropathy, nephropathy, decreased blood flow, atherosclerosis, impaired fibroblasts, decreased neuropeptide signaling, accumulation of glycation end products, disrupted nitric oxide levels and immunological changes in the wound microenvironment including.(1–4) Diabetic wounds also have a polymicrobial organization, particularly within the biofilm, and a complex microbiome. Over 50% of wounds develop an infection, and 20% of moderate-to-severe infections result in the amputation of a lower extremity.(5) Patients with diabetes may develop arterial, venous, or mixed ulcers (a combination of both arterial and venous ulcers), as well as furuncles, carbuncles, cellulitis, and diabetic bullae. Diabetic foot ulcers are a chronic, non-healing wound that affects 25% of diabetic patients, the most significant consequence of diabetic foot ulcers is amputation due to gangrene and infection. Compared to persons with diabetes without foot ulcers, the death rate for those with diabetic foot ulcers rises from 182 to 231 fatalities per 1,000 people annually. (1,4,6)

Diabetic ulcers require more time to heal and present a global public health challenge as they raise morbidity and mortality rates in diabetic patients. These wounds financially burden patients and their families. The diabetic foot ulcer market alone is predicted to grow from 7.03 billion USD in 2019 to 11.05 billion USD in 2027 since they are a major factor in lower-extremity amputations among diabetics and account for over 50% of all diabetes-related hospital admission days.[1,3, 5,6]

Therefore, restoring wound hemostasis and the natural healing process is an important process that involves multidisciplinary steps including removal of infectious resistant microorganisms, detrition of biofilm, recovery of complementary signaling pathways between cytokines, chemokines, growth factors, and metabolites in different healing stages of the wound.(7) Strategies for diabetic ulcer management can be divided into two approaches: *Firstly*, the standard of care therapies like wound debridement, offloading, proper glycemic control, and infection management by choosing proper systemic antibacterial therapy. *Secondly*, advanced therapies that involve the application of bioactive compounds that promote wound healing and tissue regeneration like growth factors, stem cells, platelet-rich plasma, cell, and tissue-based products, or techniques that improve oxygenation like hyperbaric oxygen therapy, and negative pressure wound therapy.(2,3)

One of the most prevalent issues found in diabetic wounds is the existence of complex polymicrobial biofilms which hinder wound healing due to extracellular polymeric substances that prevent antibiotic diffusion. Innovative antibacterial delivery is needed to combat biofilms, especially due to multidrug-resistant bacteria(3–5). Generally, systemic antibacterial agents, either enteral or parenteral, control infections in diabetic wounds.

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However, they present disadvantages, namely systemic adverse effects like nephrotoxicity, allergic interactions, and insufficient penetration to the wound bed, which frequently negatively impact therapeutic success.(2–4,7)

Microneedles device represents new technology designed for delivering substances like drugs, enzymes, and proteins to the epidermis and dermis layers through the array of microscale needles (**Figure 1**). Microneedles exhibit diverse structural configurations, shapes, compositions, and production techniques.(8–10)

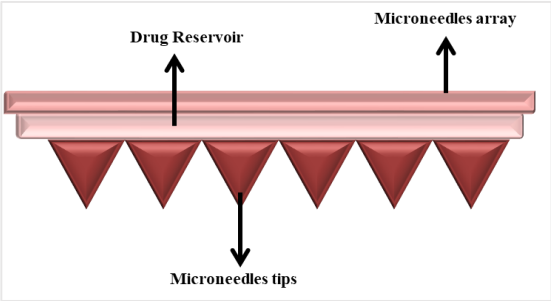

Figure (1): Microneedles device structure featuring key components

This technology has been assessed across various applications as drug delivery, vaccination, cosmetics, and disease diagnosis.(8) Few applications have been clinically tested on humans, for instance, microneedles were used to administer low-dose flu vaccines into the dermis, this method was as effective as traditional intramuscular injection(11). Also, microneedles have been employed in diagnostic examinations like COVID-19 testing, where microneedles were incorporated into the oropharyngeal swab that was used for specimen collection.(12)

Microneedles manufacturing is a growing area in pharmaceutical and material science research, especially diabetic ulcer therapy. Not surprisingly, the microneedle drug delivery systems marketplace has the potential to expand to USD 10.14 billion by 2030, with a CAGR (Compound annual growth rate) of 6.5% compared to the estimated USD 5.71 billion in 2021.(13)This is due to advantageous features of the enhancement of drug penetration through skin layers, targeting and controlling drugs administered to the wound area, decreasing the adverse effects accompanied with systemic exposure, also they are painless and non-invasive approach which consequently enhance patient acceptance and adherence to prescribed treatment regimens, and maintain optimal drug concentration at the wound site for an extended duration(14).

This review focused on 1) The geometry, types, and materials used to deliver antibacterial agents into diabetic ulcers 2) The beneficial effects of microneedle devices on diabetic ulcers 3) The potential risks and complications of microneedle application on diabetic ulcers 4) Antibacterial agents that are successfully loaded and delivered by microneedle technology in diabetic rat ulcer models as no clinical studies have been conducted.

From 2020 to 2024, articles on wound healing with an emphasis on microneedles were retrieved from the Web of Science, the Google Scholar database, and associated websites; such as PubMed, and Medline. Different keywords were used in the search which include; microneedle, antibacterial, diabetic wound, diabetic ulcer, and diabetic foot. The selection standards were based on animal studies that assessed the antimicrobial activity of microneedles incorporated with antimicrobial agents. Thirty-three studies were found and included in this review.

1. The current status of microneedle application in diabetic wound management

1.1 Types of microneedles employed in diabetic ulcers

Microneedles can be classified into different categories including solid coated and non-coated, hollow, dissolving, porous, multilayered, separable, hydrogel-forming biomimetic microneedles. (9,10,14–18)

This paper focused on dissolving and hydrogel-forming microneedles, which are the most common types employed for delivering antibacterial compounds to diabetic wounds.

1.1.1. Dissolving microneedles:

Dissolving microneedles (**Figure 2**) are manufactured to entrap drugs like antibacterial agents and wound-healing promoters within biodegradable soluble polymers or sugars.

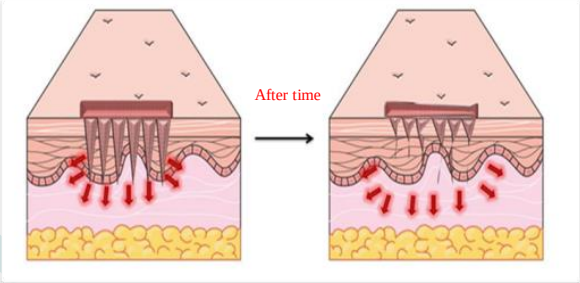

Figure (2): Dissolving Microneedles upon administration (left), and after dissolving and release of embedded drug (right).

After penetrating the stratum corneum, the microneedles dissolve, and the encapsulated drug is released within minutes or hours via (poke and release) approach (9,15,19,20)

Biodegradable polymers like Polylactic Acid (PLA) and PolyLactide-Co-Glycolic Acid (PLGA), Polyvinyl Alcohol (PVA), and Polyvinyl Pyrrolidone (PVP), along with water-soluble sugars such as Trehalose, Raffinose, and Hyaluronan represent the most widely used materials to synthesize dissolving microneedles. The properties of dissolving microneedles, including mechanical strength, dissolution rate, and tissue penetration capabilities, are dependent on the material employed during their fabrication. For example, the use of Polylactic Acid (PLA)& PolyLactide-Co-Glycolic Acid (PLGA) is associated with better mechanical strength and controlled release for the drug.(9,10,14,15,19)

Dissolving microneedles can accommodate up to 33 mg of drug(10). Dissolving microneedles are user-friendly, have no removal step, reduce needle-stick injuries, and eliminate bio-contaminated residue in the skin. Furthermore, the potential for drug loss during administration is decreased as the microneedles are dissolved in the skin.(10,14,19,20)

1.1.2. Degradable (separable) microneedles

Degradable microneedles are a subcategory of dissolving microneedles designed for the controlled release of the payload. They consist of two main parts: dissolving bases, which are composed of rapidly dissolving and degradable bases such as polyvinyl alcohol (PVA) or Hyaluronic acid (HA), and PolyLactide-Co-Glycolic Acid (PLGA) based tips, in which many compounds can be encapsulated and released in a controlled manner over time. Following application, separable microneedles exhibit base detachment at the dermal interface, facilitating a rapid influx of the payload from the base, and slower release from tips, also these microneedles enhance patient compliance due to the absence of post-insertion removal, and potentially stimulate wound oxygenation(9,10,17,19).

1.1.3. Multilayered Dissolving microneedles

Multilayered dissolving microneedles (**Figure 3**) consist of two or more distinct layers, each with specific functionalities with different dissolution rates. They are manufactured by adding layers of material to a mold through repeated stacking or by atomized spraying method, in which the needed formulation is filled in polydimethylsiloxane (PDMS) molds through the production of atomized spray and dried for 2h at ambient temperature. Laminate and horizontally-layered dissolving microneedles are manufactured by this method.(9,14,19)

Figure (3): Laminate layered dissolving microneedles (Left) horizontally-layered dissolving microneedles (Right)

1.1.4. Hydrogel (swelling or softening) Microneedles

Hydrogel microneedles (**Figure 4**) are made from crosslinked hydrogels, which are swelling polymers like polymethyl vinyl ether combined with maleic acid (PMVE/MA). Anti-bacterial agents and other wound-healing promoters are either incorporated into the polymeric structure or loaded into a separate reservoir attached to the microneedle tips. These microneedles absorb interstitial fluid surrounding cells and swell, allowing drug diffusion from the patch through the swollen tips of microneedles. (9,14,21)

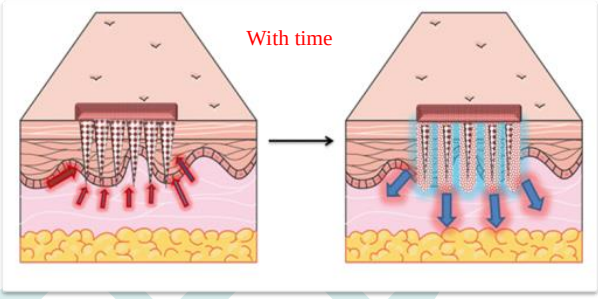

Figure 4: Hydrogel Microneedles poke the skin, uptake interstitial fluids (Left), and induce diffusion of the drug from the patch through the swollen Microneedles (Right)

Hydrogel microneedles are minimally invasive, as they do not penetrate skin deeply to trigger pain receptors. Additionally; they have higher drug loading capacity and a controlled release rate. The drug release rate from these microneedles is easily adjusted by modulating the density of the polymer matrix. They can be easily fabricated in various shapes and sterilized before insertion. Phase transition microneedles release active substances from the matrix, leaving some or no residue after application. However, the matrix may dissolve or degrade in the skin, making it unsuitable for everyday use.

The most promising type of microneedles is one made of hydrogel that does not dissolve or degrade in the skin but has a controlled or continuous release of active substances.(9,14,21) Differences between dissolving and hydrogel microneedles are summarized in **Table 1**.

Table 1: Key differences between hydrogel and dissolving microneedles adapted from (11,21,22)

Feature	Dissolving Microneedle	Hydrogel Microneedle
Material	Biodegradable polymers that dissolve in the skin	Polymeric hydrogels that swell upon absorbing interstitial fluid (ISF)
Mechanism of Action	Dissolve in the skin, releasing the drug payload quickly	Swell and release drugs slowly as they absorb ISF
Drug Dose	Low	High
Drug Release	Immediate release upon dissolution	Controlled, sustained release
Residual Material	No residual material left in the skin	Swollen hydrogel microneedle tip
Fabrication	Relatively simpler, involves embedding the drug in a dissolvable matrix	Complex, involving multiple steps and precise control of hydrogel properties
Applications	Ideal for single-use applications requiring rapid drug release	Suitable for long-term, multiple drug delivery and continuous monitoring
Advantages	Simple fabrication, no sharp waste, quick drug release	High drug loading capacity, controlled release, non-toxic

Challenges	Limited to drugs that can be embedded in the dissolvable matrix, the potential for rapid degradation	Complex fabrication, regulatory hurdles, potential for swelling variability

1.2 Geometry of Microneedles

The geometry of microneedle arrays including (needle shape, needle length, space between needles, needle density needle tip diameter, and base diameter) must be carefully considered to enhance successful painless penetration. [15]

A variety of microneedle shapes is available such as cylinders, pyramids, triangles, hexagons, circles, stars, and cones. The mechanical properties of microneedles for diabetic wounds increase with the number of vertices, but their penetration capability decreases. The star and pyramidal shapes appear to be the most effective due to their ability to ensure optimal penetration, drug delivery, and mechanical stability.(14,17,23)

Microneedles' optimal length ranges from 600 to 1100 micrometers since this is the range where they are most likely to avoid stimulating blood vessels and nerve endings in the skin's deeper layers.(14) The impact of space between microneedles on drug delivery is negligible with short microneedles (<1000 micrometers). However, the density of the microneedle array plays a crucial role in drug permeation. The optimal density of 400-900 needles per square centimeter is generally recommended for achieving optimal drug delivery since wider spacing reduces the "bed-of-nails" effect (skin folding around needles).(14,16,24)

1.3. Microneedle Manufacturing Techniques and Materials

Numerous techniques, including Micro-Electro-Mechanical System (MEMS) based techniques, mold-based techniques, drawing-based techniques, and 3D printing techniques, can be used in manufacturing microneedles.(15) The most common method for fabricating microneedles used in diabetic wound therapy is solution-cast micro-molding. This is a multi-step process as shown in Figure 5.

First, a master mold is created using a durable material like metal or silicon. A negative mold is then produced from this master mold using a polymer such as liquid silicon or PDMS. The negative mold is subsequently filled with a drug loaded polymer solution, which solidifies to form microneedles that replicate the shape and dimensions of the original mold. (15,15,22,24)Micro molding allows for precise control over the shape, size, and drug loading of the microneedles. This technique is also highly efficient and easy to implement, making it a popular choice for microneedle fabrication. (14,25)

Generally, various materials including silicon, metals, ceramics, and polymers are employed in manufacturing microneedles. (8,16) Silicon and polymer materials are commonly used for microneedles designed to treat diabetes, including natural biopolymers like hyaluronic acid (HA), poly γ-glutamic acid (γ-PGA), chitosan, gelatin, silk fibroin, and synthetic polymers like polyvinyl alcohol (PVA) and polyethylene glycol diacrylate (PEGDA), are most commonly used to design microneedles for wound healing.(8,26) Key features of each polymer are illustrated in Table 2 and Table 3.

The choice of material for microneedle fabrication is critical, as it directly impacts the device's performance and safety. Ideal materials should possess properties such as low cost, ease of processing, flexibility, mechanical strength, biocompatibility, and biodegradability. Additionally, the material should be compatible with the active ingredient and facilitate controlled drug release. (16,26)

The selection of the appropriate fabrication method is also crucial. The method should be compatible with the desired microneedle design and ensure precise control over the shape, size, and drug loading. (4,17,24,26)

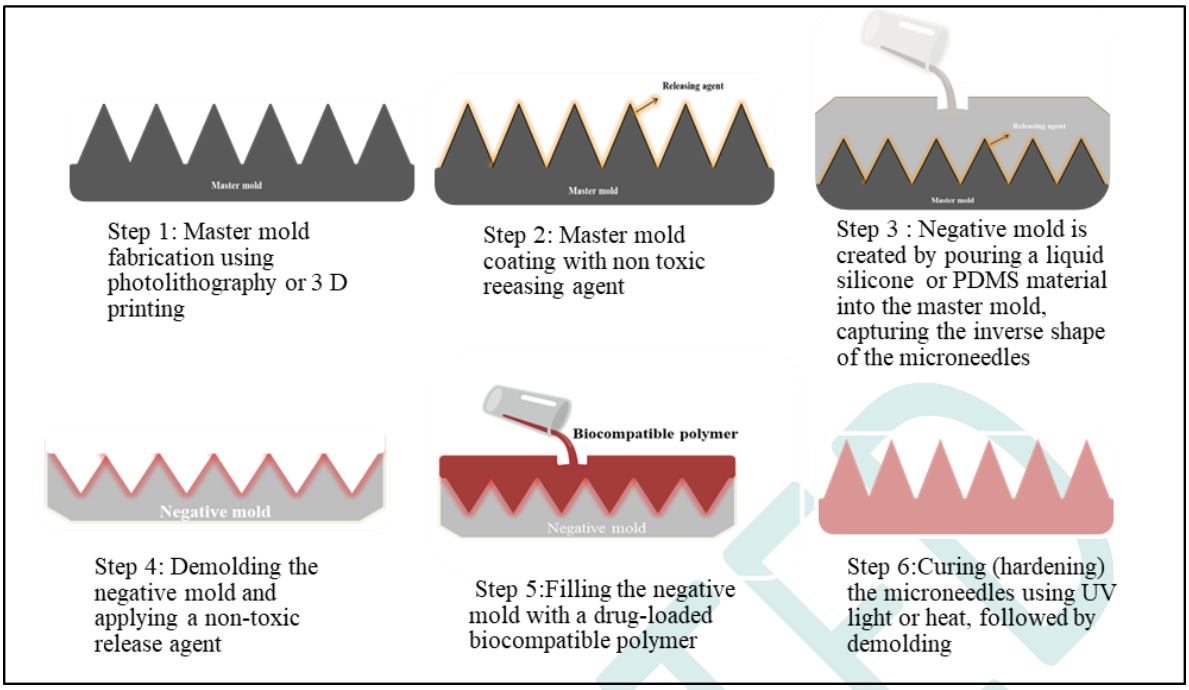

Figure 5:Micromolding process basic steps for microneedles fabrication

Table 2: Characteristics of Common Synthetic Polymers Used in Microneedle Synthesis

Material	Advantage	Disadvantage	Antibacterial Properties	Ref.
Polyvinyl Alcohol (PVA)	Mechanically strong, easy to process	May not be as biocompatible as natural polymers	Good	(27, 28)
Poly ethylene glycol diacrylate (PEGDA)	Mechanically strong, can be crosslinked	May not be as biocompatible as natural polymers, Irritating	Poor antibacterial properties	(29)

Table 3: Characteristics of Common Natural Polymers Used in Microneedle Synthesis

Material	Advantage	Disadvantage	Antibacterial Properties	Ref.
Hyaluronic Acid (HA)	Excellent biocompatibility, Promotes wound healing	Sensitive for pH and temperature	Can be modified to have antibacterial properties	25,26
Poly(γ-glutamic acid) (γ-PGA)	Biodegradable, Excellent biocompatibility, promotes cell proliferation	Low mechanical strength, sensitive to pH and temperature	Natural antibacterial effects due to its negative charge	(30, 31)
Chitosan	Biodegradable, Good biocompatibility, promotes wound healing	May be slightly irritating especially chitosan derived from shellfish	Natural antibacterial effects due to its positive charge	(32–34)
Gelatin	Biodegradable, Excellent biocompatibility, promotes cell migration	Sensitive for humidity and temperature	Can be modified to have antibacterial properties	(35, 36)
Silk Fibroin	Biodegradable, Excellent biocompatibility, promotes cell adhesion	Low mechanical strength, difficult to process	Naturally antibacterial due to its amino acid composition	(37, 38)

1.4. Beneficial effects of Microneedles in diabetic ulcers

Microneedles represent a promising strategy compared to conventional wound dressings as they possess many beneficial properties that support tissue regeneration and wound healing process, including (1) Structural capability to be loaded with a variety of compounds that promote wound healing, like nanoparticles, stem cells, antibacterial agents, nucleic acids and

many others. (2) Overcoming physical barriers at the wound bed such as exudates, clots, and scars. (3) Ability to deliver drugs on demand according to the wound healing phase. Furthermore, demonstrates better sustained release of medicine as compared to standard dressings. (4) Providing mechanical stimulation, which triggers deposition and rearrangement of collagen, which enhances tissue regeneration and wound healing (5) Physically distorted bacterial biofilm which facilitates overcoming bacterial resistance accompanied by biofilms. (6) Monitoring of wound bed conditions including temperature, pH, proteins, and reactive oxygen species (ROS).(14,17,39)

However, there is a pressing need for clinical trials to confirm these findings and assess their safety and efficacy in human patients.(8,14)

1.5. Potential risks and complications of microneedle application on diabetic ulcers

Microneedle patches are designed to enhance skin penetration with minimal invasion. However, additional investigation is warranted to refine their safety and efficacy for use in diabetic wounds, considering the challenges associated with these patients. One major risk is the potential for microbial infections, particularly those involving biofilm formation, to pose a significant risk to wound healing. These infections potentially delay recovery and increase pain and systemic complications. The punctures created by the microneedle tips in the skin can serve as entry points for bacteria and other microorganisms, potentially leading to wound infections. Moreover, microneedles were also reported to blunt trauma, skin avulsion, and increased susceptibility to bacterial biofilms, particularly in fibrous tissues.(15,22,40–42)

An additional risk is the possibility of inflammatory reactions triggered by microneedle materials, which can result in allergies, immune system reactions, and impaired wound healing.(40,42) For instance, using mineral nanoparticles, while offering potential antibacterial benefits, can also pose certain risks. Their toxicity can vary depending on factors such as size, concentration, and exposure time. Some nanoparticles may induce oxidative stress and cellular damage, while others can trigger inflammation, potentially delaying wound healing. Additionally, in some cases, residual nanoparticles may accumulate and form granulomas, localized areas of inflammation due to foreign substances [27–29]

Another potential drawback of microneedle patches is the difficulty of removing them from the skin after application. Additionally, multiple applications may be required for high-dose treatments, as a single patch might not deliver a sufficient amount of medication. Despite the potential of microneedle patches, further study is required to solve issues including removal, decreased toxicity, and administering large dosages without damaging tissue.(26,40,42)

2. Antibacterial compounds loaded to microneedle patches

Delivering antibacterial compounds via microneedles is a current field of research in the management of diabetic wounds, as it offers evident benefits such as targeted delivery of elevated antibacterial concentrations to the site of infection, minimal systemic exposure, and consequently, minimal adverse effects.(43) Furthermore, it addresses obstacles such as impaired blood circulation and the presence of biofilms that diminish the bioavailability of systemic antibacterial substances within the wound site.[8] Various antibacterial compounds incorporated in the microneedle patches and tested on animal models are discussed in the next subsections.

2.1 Inorganic metal nanoparticles

The application of nanotechnology is one of the promising strategies to develop safe and effective antibacterial agents, in addition to decreasing the bacteria resistance rate. Nanoparticles (NPs) of several metals and their oxides, such as silver, zinc, iron, copper, and others are validated to have antimicrobial activity through *in vitro* and *in vivo* studies.[9] Furthermore, the low toxicity of metal nanoparticles makes them ideal options for integration in wound dressings like nanocoating and microneedles. Within this context, this section focuses on the utilization of metal nanoparticles for designing microneedle patches intended for diabetic wounds.

2.1.1 Sliver

The use of silver in wound dressings is well-established due to its antibacterial properties. By disrupting the electron transport chain in bacterial mitochondria and interacting with sulfur-containing proteins in bacterial membranes and phosphorus in DNA, silver ions diminish the burden of bacteria and combat infection. The use of silver, especially in the form of nanoparticles, to create microneedles has been the subject of several research that have examined its beneficial effects.8

Mengli Sun and colleagues designed an oxygen-releasing silk fibroin mathacryloyl (SilMA) hydrogel microneedle patch coated with silver nanoparticles and incorporated with Calcium Oxide (CaO2) and catalase on tips. The patch promotes wound healing in mouse models of Type 1 Diabetes Miletus by continuous oxygen release in deep skin layers and reduction of reactive oxygen species in the wound bed. Silver nanoparticles play a critical role in decreasing bacterial load in the wound.(45)

Other promising outcomes were noted by Jingjing Gan and colleagues in a mice model of Type 1 Diabetes Mellitus after the utilization of a novel hydrogel microneedle patch containing silver nanoparticles and mesenchymal stem cell-derived exosomes (MSC-exos) This microneedle patch exhibited efficacy in combating bacterial contamination, promoting angiogenesis, mitigating inflammatory responses, and expediting wound healing closure. (46)

Xiao Yang and colleagues demonstrated in vivo and in vitro antibacterial activity particularly against methicillin-resistant Staphylococcus aureus after the application of microneedles loaded with silver nitrate (AgNO3), chitosan, tannic acid, and Bletilla striata polysaccharide It is proposed that reduction of silver ions to silver nanoparticles in-situ by the copious polyphenols of tannic acid results in the antibacterial properties. Moreover, the incorporation of Bletilla striata polysaccharide facilitates biofilm penetration capability and accelerates wound healing processes.(47)

Mengting Yin and colleagues devised (MN-MOF-GO-Ag) microneedle, which features a backing layer consisting of γ-PGA hydrogel, graphene oxide-silver (GO-Ag), and magnesium organic frameworks (Mg-MOFs). This infusion of (GO-Ag) shows significant antibacterial effects using a diabetic mouse model with full-thickness cutaneous wounds. Administration of MN-MOF-GO-Ag to mice results in a notable enhancement in their wound healing progression.(48)

2.1.2 Zinc

Zinc oxide nanoparticles (nZnO) are utilized in the fabrication of multifunctional, multicomponent microneedles due to their antimicrobial properties. The antimicrobial properties can be attributed to releasing zinc ions which inhibit respiratory enzymes, amino acid metabolism & active transport across plasma membrane in bacteria. In addition, nZnO produces reactive oxygen species leading to oxidative damage to bacterial DNA, proteins, and lipids. Furthermore, it tends to accumulate near bacterial cells interacting with negatively charged bacteria cells leading to membrane depolarization, deformation, and cell death(49).

For instance, in a study involving mice with streptozotocin-induced (STZ)-induced diabetes, Yang, J.; Chu, and colleagues explored a multicomponent enzyme-responsive hyaluronic acid (HA) microneedle, embedded in a cerium/zinc-based nanomaterial (ZCO). By controlling the release of Zn^{2+} and $Ce^{3+/4+}$, the designed microneedles were able to mitigate oxidative damage, expedite wound healing, and suppress inflammatory response(50). Another multifunctional self-powered microneedle device known as TZ@mMN-TENG, was devised by Li, W. and colleagues which dispenses tannin and zinc ions and administers electrical stimulation (ES) to diabetic individuals via the self-powered triboelectric nanogenerator (TENG). Both *in vivo* and in vitro studies exhibited antibacterial activity against Staphylococcus aureus and Escherichia coli (>99% antibacterial rates) as well as an acceleration of wound healing through enhanced collagen deposition, angiogenesis, and inhibition of inflammatory mediators TNF-α and IL-6 expression(51).

Also, Zinc oxide nanoparticles were used in conjunction with Phoptotheraml hair microparticles (HMP) for creating microneedles. This combination was reported to possess antibacterial properties and to significantly enhance wound healing. For instance, Jiao Zhang and colleagues devised a near-infrared (NIR) responsive microneedle patch consisting of hierarchical microparticles (HMP) loaded with Zinc Oxide nanoparticles, vascular endothelial growth factor, and basic fibroblast growth factor (H-Z-MN-VEGF&bFGF). The antibacterial activity of Zinc ions increased through the photothermal effect of HMPs under NIR irradiation (52). To mention also Cai, Y, and colleagues employed (HMP) and zwitterionic polymer polysulfobetaine methacrylate (PSBMA) besides loading zinc oxide nanoparticles (ZnO NPs) and asiaticoside in the needle tips. These microneedles were tested on diabetic rats with Staphylococcus aureus-infected wounds, demonstrating that the combination of the drug and photothermal multi-treatment hastened tissue regeneration, and collagen deposition, and significantly boosted wound healing(53).

2.1.3 Copper

Copper has long been illustrated as an antibacterial, antiviral &antifungal agent. The antimicrobial activity of copper is primarily attributed to the production of reactive oxygen species (ROS) that cause irreversible damage to bacterial membranes. In addition, copper ions are released from surfaces and lead to the degradation of RNA and the disintegration of enveloped viruses and fungal membranes(54).

Two studies demonstrated the use of copper to create microneedle patches and studied wound healing effects on diabetic wounds. The first patch, CuGA-MOF@OKGM-MNs, is made of oxidized konjac glucomannan (OKGM-MNs), which encloses a Copper-gallate metal-organic framework (CuGA-MOF). Copper ions released from the microneedle in the dermis act as an antibacterial agent and promote angiogenesis, while GA, through its role as a scavenger of reactive oxygen species, displays antioxidant properties. The effectiveness in wound healing was validated in diabetes mouse models with full-thickness skin wounds, showing complete healing within 3 weeks upon treatment(55). The Other was a photodynamic-controllable multifunctional MnO_2/PDA@Cu-HA microneedle patch designed by encapsulating an inorganic nanosheet (MnO_2/PDA@Cu) composed of manganese dioxide (MnO_2), copper (Cu) ions, and polydopamine (PDA) into a soluble methacrylated hyaluronic acid (HA) hydrogel soluble microneedle patch. (MnO_2/PDA@Cu) releases MnO_2 & copper which is believed to play a role as an antibacterial agent, ROS scavenger, and angiogenic and re-epithelization enhancer. Cu ions release is stimulated by PDA's photothermal effect NIR irradiation. The combination of these multiple beneficial factors synergistically contributed to improved healing in infected diabetic rat models with full-thickness dorsal skin wounds. The microneedle treatment resulted in a satisfactory wound closure rate and re-epithelialization and collagen formation, showcasing its potential as an effective treatment for infected wounds.(56)

2.1.4 Gold nanoparticles

Gold nanoparticles showed moderate antibacterial activity against gram-negative and gram-positive bacteria respectively.(44) Single study presents a catalytic microneedle patch that incorporates near-infrared-II responsive and dual-nanozyme active Au-Cu_2MoS_4 nanosheets (Au-CMS NSs) for treating diabetic wound infection. The patch uses nanozyme actions like glucose oxidase and catalase to consume glucose, produce oxygen, and eliminate bacteria. It has shown effective antibacterial effects in laboratory tests and is useful for treating MRSA-infected wounds in diabetic mice.(57)

2.1.5. Iron nanoparticles

Iron oxide nanoparticles (IONPs) exhibit antimicrobial properties with considerable biocompatibility and safety, positioning them as a promising strategy for addressing bacterial infections. (58) Sun C *et al* developed microneedles called Fe^{+2} C/GOx@MNs) with biodegradable tips that promptly discharge Fe^{+2} C nanoparticles (NPs)/glucose oxidase (GOx) in the active regions of the biofilm. the effectiveness in eradicating biofilms and averting reinfection during wound healing was confirmed by using a diabetic mouse model with full-thickness wounds infected by methicillin-resistant Staphylococcus aureus biofilms. (59) In a distinct study, microneedle patches derived from hydrogel nanocomposite of iron/tannic acid (FeIIITA) with the ability to generate nitric oxide (NO) were developed by Wang and colleagues. The composite nanoparticles of iron/tannic acid (FeIIITA) exhibited noteworthy photothermal properties that collaborate with the innate antibacterial properties of polylysine to enhance the antibacterial efficacy of the hydrogels and enable deep NO release. In diabetic wounds. (60)

2.1.6. Calcium oxide nanoparticles (CaO_2)

Calcium oxide (CaO_2) nanoparticles demonstrated inhibitory effects on both gram-positive and gram-negative bacteria as well as biofilms.(61) Zeng G and colleagues loaded CaO_2@polydopamine (CaO_2@PDA) and metformin into polycaprolactone and gelatin (PCL/Gel) electrospun nanofiber films as microneedle back patches to provide oxygen, absorb the excess exudates also inhibiting bacterial growth and

inflammation. the as-fabricated demonstrated a high level of CD31 and a low level of TNF-α, leading to accelerated diabetic skin-wound closure.(62) Another multilayer microneedle patch was created by Liu, T., and loaded with metformin and CaO_2 nanoparticles modified by sodium hyaluronate. Such patches have antibacterial effects and promote wound healing.(63)

2.2. Anti-Microbial Peptides (AMP)

Anti-Microbial Peptides (AMPs) also known as Host Defense Peptides are acknowledged as a new era in antibiotics, suggesting their significance in addressing the complexities of infections with polymicrobial infections. The AMPs exhibit a broad spectrum of activity against gram-positive, gram-negative, fungi, viruses, and persisted cells of both *P. aeruginosa* and *S. aureus*. Furthermore, AMPs have wound-healing anti-inflammatory and angiogenic properties. Despite their usefulness, the delivery of AMPs for wound beds is challenging as they are degradable by bacterial and host proteases. Microneedles appear to be a promising approach to enhance the delivery of AMPs and to increase peptide stability while ensuring a sustained release of these molecules.(64)

Few studies demonstrated the incorporation of AMPs with microneedle patches and tested them on animals. For example, Lei X and associates created the biodegradable AMP-Cypate@GNP microneedle patch, which combines conjugate molecules made of antimicrobial peptide (AMP) and near-infrared fluorescent dye Cypate with gelatin nanoparticles (GNPs). The pathogen *S. aureus* is effectively eradicated by applying this microneedle patch to chronically infected wounds in rat models. It penetrates the layers of the epidermis, stratum corneum, and dermis, dissolves the AMP-Cypate@GNPs, and applies a gelatinase-responsive photothermal therapy under near-infrared (NIR) irradiation.(65)

Another intriguing dissolvable microneedle patch with dual delivery was developed by Su, Y., and colleagues. This innovative patch contains synthetic antimicrobial peptides W379 with anti-PBP2a monoclonal antibodies. It exhibited antibacterial efficacy both in the type II diabetic mouse wound biofilm model and *in vitro*. (66)

Another multifunctional microneedle was designed by incorporation of Type III recombinant collagen and AMP (KKLRLKIAFK) linked to Cy3 with nanogel CGA-NPs formed by chitosan and gum Arabic CGA-NPs. Such microneedles promote gradual and controlled release of collagen III and AMP when applied to the infected skin and Staphylococcus aureus biofilm and enhance wound recovery and staphylococcus eradication. (67)

2.3. Tetracycline and Doxycycline

Tetracycline and Doxycycline are synthetic derivatives of tetracycline, stand as potent broad-spectrum antibiotics, and showcase remarkable efficacy in the face of bacterial resistance. Moreover, their impact transcends mere antibacterial properties, as they boast exceptional abilities in promoting wound healing processes. For instance, Doxycycline expedites wound healing by inhibiting matrix metalloproteinases (MMPs) – namely, MMP-1, MMP-2, and MMP-9 – commonly found in chronic wounds. Consequently, it lessens the breakdown of collagen and extracellular matrix components. The process of wound healing might be hampered by high MMP activity because it can cause an excessive breakdown of extracellular matrix (ECM) components.[41](69)

Tetracycline hydrochloride (TCH) and doxycycline were both incorporated into microneedle patches in separate research studies. Two research studies utilized microneedle patches loaded with tetracycline hydrochloride (TCH), while two others employed microneedles containing doxycycline. Liu et al. designed a multifunctional double-layer microneedle patch (DMN@TH/rh-EGF) composed of hyaluronic acid, carboxymethyl chitosan, and gelatin, and loaded it with recombinant human epidermal growth factor (rh-EGF). This microneedle patch effectively inhibited inflammation and promoted angiogenesis, collagen deposition, and tissue regeneration in a diabetic wound rat model.(70) Gao et al. developed another double-layer microneedle system (DMN@TCH/DFO) composed of hyaluronic acid, chitosan, and silk fibroin. This system, loaded with tetracycline hydrochloride (TCH) and deferoxamine (DFO), effectively reduced inflammation and accelerated diabetic wound healing in animal models. The rapid dissolution of hyaluronic acid at the tip facilitated the timely release of TCH, providing early antibacterial action. (71)

Yang et al. developed a microneedle patch (Dox-DFO@MN Hy) designed specifically for chronic wounds. The patch incorporated doxycycline hydrochloride (Dox) encapsulated in lipase-responsive polycaprolactone (PCL) microspheres, along with Deferoxamine (DFO) to enhance the treatment of chronic wounds infected with biofilms. A hydrogel layer seals the wound and allows for rapid drug release of Dox and DFO from the hydrogel backing, which consequently promotes healing by stimulating angiogenesis, cell migration, and effective disruption of biofilms, The (Dox-DFO@MN Hy) patch accelerated wound healing in animal rat models. (72)

Another Doxycycline microneedle patch (DH/VEGF@Gelma-MNs), created by Tan et al., is made of biocompatible polyvinyl alcohol (PVA) and gelatin methacrylate (Gelma). It is packed with vascular endothelial growth factors (VEGF) and doxycycline hydrochloride (DH). Gelma-MNs have well-aligned conical structures, excellent mechanical and swelling features, also they exhibit good antibacterial activity, inhibiting the development of Staphylococcus aureus and Escherichia coli. As a result, DH/VEGF@Gelma-MN speeds up diabetic wound closure *in vivo* when compared to DH/VEGF@Gelma-plain patch (DH/VEGF@Gelma-PPs) flat patch and DH/VEGF solution injection. (73)

2.4. Polymyxin B

Polymyxin B sulfate, an antibacterial peptide, shows promise for treating chronic refractory wounds. This is due to its effectiveness against a broad spectrum of gram-negative bacteria commonly found in these wounds, including Escherichia coli, Klebsiella, Pseudomonas aeruginosa, and Acinetobacter sphaeroides. Studies suggest that topical application of Polymyxin, following thorough wound debridement, can effectively reduce and control wound infections. This may potentially lead to faster healing with minimal reported side effects.(74)

Recognizing the therapeutic potential of polymyxin B, two research investigations employed microneedle patches loaded with this antibiotic. *Cai et al.* employed a biomimetic mineralization method to synthesize novel nanozyme-supported natural enzymes (CAT-Mn(SH)x). In this approach, catalase (CAT), a naturally occurring enzyme, served as a biological template. Subsequently, polymyxin B was immobilized on the surface of these nanozymes through electrostatic assembly to

produce a novel nanomedicine called (CAT-Mnx@PMB), which delivers hydrogen sulfide(H_2S) gas known to remove reactive oxygen species (ROS). The resulting CAT-x@PMB is then loaded to the microneedle patch. The designed microneedle patch is biocompatible, soluble, and demonstrates both anti-inflammatory and antibacterial activity. It decreases pro-inflammatory cytokines, upregulates M2 macrophages, promotes angiogenesis, and enhances nerve regeneration. Ultimately, combating free radicals and bacterial infection creates a more favorable environment for wound healing. (75)

In another study, Polymyxin B is encapsulated in the base layers of a multifunctional microneedle patch along with silk fibroin methacryloyl. Microneedle tips were loaded with Prussian blue nanozymes and vascular endothelial growth factors. The combined properties of these components enable the multifunctional microneedle patches to exhibit remarkable biocompatibility, sustained drug release, pro-angiogenesis, antioxidant effects, and antibacterial properties (37).

2.5. Fluoroquinolones

Fluoroquinolones (Ciprofloxacin, Levofloxacin, Ofloxacin) are a class of broad-spectrum antibiotics effective against a wide range of infections. This includes some infected ulcers and wounds caused by *S. aureus* (methicillin-susceptible strains), *S. epidermidis*, or *S. pyogenes* (group A β-hemolytic streptococci), *E. coli*, *K. oxytoca*, *K. pneumoniae*, *M. morganii*, *P. mirabilis*, *P. vulgaris*, *P. stuartii*, *Ps. aeruginosa*, *S. marcescens*. Despite the proven power of fluoroquinolones as systemic antibacterial agents, their potential for topical application remains largely unexplored (76–78).

2.5.1 Ofloxacin

Ofloxacin is an antimicrobial agent with excellent activity against both gram-positive and gram-negative bacteria. A study by *Chen, Y. et al.* explored dissolving microneedles with a biphasic release mechanism for wound healing. The microneedles deliver Ofloxacin rapidly to reduce bacterial burden, followed by the sustained release of basic Fibroblast Growth Factor (bFGF) encapsulated in biocompatible and biodegradable poly-lactic-co-glycolic acid (PLGA) microspheres to enhance tissue repair. Animal studies confirmed the microneedle's antibacterial activity and its ability to promote wound healing.(20)

2.5.2 Ciprofloxacin

Zhou et al. designed multifunctional dissolving microneedles (CIP/GOx@ZIF-8 MNs) for diabetic wounds. These microneedles are made from a nanocomposite containing ciprofloxacin hydrochloride (CIP) and glucose oxidase (GOx) embedded within a zeolitic imidazole framework-8 (ZIF-8) structure. The enzyme glucose oxidase catalyzes the decomposition of glucose in the wound bed to gluconic acid and hydrogen peroxide (H2O2) which further release ciprofloxacin and zinc from the nanocomposite (CIP/GOx@ZIF-8). The combination of glucose depletion, and release of CIP, zinc ions, and H2O2 inhibit bacterial growth and reduce bacterial resistance. Furthermore, polyvinylpyrrolidone (PVP) is used in the fabrication of these microneedles, PVP demonstrates good mechanical strength for easy application, efficient puncture performance to deliver the medication, and controlled dissolving behavior. Additionally, they exhibit responsiveness to glucose levels, effective antibacterial action, and biocompatibility, indicating minimal adverse effects on surrounding tissues. (CIP/GOx@ZIF-8 MNs) Microneedles facilitated wound healing in animal models by promoting tissue regeneration, combating infection, and reducing inflammation. They hold promise as a novel treatment approach for diabetic wounds.(79)

2.5.3 Moxifloxacin

Younas et al. developed a microneedle patch (TH + LH + MOXNPs@MN) loaded with moxifloxacin nanoparticles (MOXNPs), lidocaine (LH), and thrombin (TH) embedded in a pullulan base. This patch is biocompatible and biodegradable. It facilitated the quick release of thrombin and lidocaine within 1 hour, promoting blood clotting and pain relief, respectively. Additionally, the patch provided sustained release of moxifloxacin over 24 hours, offering continuous antibiotic action. In vivo studies demonstrated the patch's efficacy in healing skin wounds in mice within 7 days. It promoted collagen deposition, accelerated cell proliferation, granulation tissue formation, and reduced levels of pro-inflammatory cytokines, signifying its potential for wound healing and inflammation control (80).

Conclusions and Future Perspectives

Various animal studies have demonstrated promising results for using microneedles as transdermal drug delivery systems in diabetic wounds for various antibacterial compounds including metallic nanoparticles, antimicrobial peptides (AMPs), Polymyxin B, and Fluoroquinolones and Tetracycline derivatives.

Advanced microneedle patch designs, such as multi-layered, multifunctional, bio-responsive, dissolving, and hydrogel-forming microneedles, offer significant benefits. These cutting-edge approaches minimize pain, reduce invasiveness, and enable controlled drug release, making them highly effective for managing chronic wounds, including those related to diabetes.

However, the success of microneedle patches for diabetic ulcers depends on several factors. Material selection, mechanical and biochemical properties, drug dosage, and the specific characteristics of the wound all play crucial roles in determining the effectiveness of microneedle therapy.

Future studies should focus on optimizing these factors to enhance the safety, effectiveness, and broader acceptance of microneedle technology in diabetic wound management. Several elements need to be taken into account during the design phase, including patient demographics, the stage and bacterial composition of wounds, the healing rate after microneedle treatment, infection risk mitigation, and the overall patient experience. Furthermore, it is essential to gain a thorough understanding of the cytotoxicity and long-term safety of the materials used in microneedles, as well as the medications delivered within the local diabetic wound environment.

Availability of data and materials

This study is a review article based on publicly available resources obtained through literature searches, primarily from PubMed and other scientific databases. No new datasets were generated or analyzed.

The raw data required to reproduce these findings are available within the body and illustrations of this manuscript.

Author's contribution

As this is a sole-authored review article, all aspects of the study were conducted independently by the author.

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Conflicts of interest

The author declares that there is no conflict of interest regarding the publication of this article.

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