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Review article

Microneedles as a potential platform for improving antibiotic delivery to bacterial infections

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ABSTRACT

Bacterial infections are mainly managed by the administration of antibiotics, which are either cytotoxic or cytostatic to microbes. In some cases, it is inconvenient to treat infections caused by bacteria using the traditional oral route for antibiotic administration. This can be due to the limited oral bioavailability of antibiotics, their gastrointestinal tract (GIT) adverse effects, and the increased possibility of the appearance of resistant strains. In addition, the fact that many populations are needle-phobic restricts the switch from the oral to the parenteral route. Furthermore, poor drug permeation throughout the *stratum corneum* of topically applied antibiotics causes low systemic bioavailability. Therefore, microneedles (MNs) have emerged as viable medicinal devices for the delivery of antibiotics, either for local or systemic effects. MNs represent a minimally invasive, painless way of administration that can be self-administered by the patient without the need of medical professionals. This review has specifically focused on MNs as a promising approach for the delivery of antibiotics; it has discussed the different types of MNs, their advantages, and possible limitations for the delivery of antibiotics. Recent studies on the incorporation of antibiotics into various types of MNs, either for topical or transdermal delivery are highlighted, and finally, we present the conclusion and future perspectives.

1. Introduction

Antibiotics are used to eradicate microorganisms that are either cytotoxic or cytostatic. They often function as membrane disruptors that hinder bacteria from making their own cell walls, proteins, DNA, or RNA [1]. Antibiotics can be administered by various routes of administration including oral, inhalation, intravenous (IV), intramuscular (IM) and topical administration as illustrated in Fig. 1 [2].

One of the most important drawbacks associated with antibiotic therapy is antimicrobial resistance (AMR) and gastrointestinal tract (GIT) side effects [3]. AMR arises when bacteria undergo mutations and cease to respond to antibiotics, making it more challenging to treat infections and raising the risk of disease transmission, serious sickness, and mortality [4]. Suboptimal antibiotic doses also aid in the development of AMR. On chromosomal and, progressively, on extrachromosomal elements that are transmissible, resistance genes are located. The resistant clones that resulted (such as methicillin-resistant *Staphylococcus aureus* (MRSA) USA 300, *Escherichia coli* ST131, and *Klebsiella* ST258) spread quickly throughout the world. Its proliferation is fuelled by a number of factors, including gene transfer across species, poor hospital and community hygiene practices, and the rising prevalence of international travel, trade, and disease transmission [3]. Since antibiotics interact with gut flora, oral intake of antibiotics has been demonstrated to

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promote the emergence of antibiotic resistance [5]. Overly subjecting the gut microbiota to antibiotics can lead to a range of concerns, including dysbiosis and increased susceptibility to infection [6]. Compared to oral delivery, injecting antibiotics considerably lowers the development of resistance in gut bacteria, particularly when antibiotics are eliminated largely through the kidneys. However, it is certainly unrealistic to expect a patient to self-inject at home, given that over twenty percent of people are afraid of needles [7].

It was found that the systemic administration of antibiotics has been established as the standard care for treating deep skin infections and chronic wounds caused by multidrug resistant bacteria. Antibiotics with molecular weights greater than 500 Da have difficulty penetrating the *stratum corneum*, limiting the effectiveness of topical treatment. For instance, vancomycin is 1448 Da, and colistin is 1155 Da [8]. In addition, most topically administered drugs are lost through sweating or wiping. Nephrotoxicity and hepatotoxicity are examples of potentially fatal side effects linked to the systemic treatment of broad-spectrum antibiotics. These unfavourable impacts add stress to patients' recovery processes and raise the risk of complications and death [9–11]. Cefazolin (CFZ) for instance, is one of the commercial β-lactam antibiotics [12]; it is a first-generation cephalosporin that kills via inactivation of penicillin-binding proteins in the bacterial cell wall [13]. Due to the high polarity of the CFZ, the oral bioavailability of the drug is low, typically 15% of the administered dose [14]. Therefore, antibiotics with similar properties (high polarity and low oral bioavailability) are commonly administered by intramuscular or intravenous injection. However, the injections are invasive, painful, and may not be suitable for people with needle phobia [15]. To address these issues, a transdermal approach has been proposed as a replacement route for antibiotic delivery to overcome the obstacles associated with the other routes.

Transdermal drug delivery technologies are currently employed for a wide range of medical disorders, from motion sickness and cardiovascular illness to pain treatment and smoking cessation [18]. The possibility of steady-state drug levels, bypassing first-pass hepatic metabolism, increased patient compliance, and the lack of gastrointestinal adverse events are all benefits of transdermal drug delivery [19]. The topical application of drugs for transdermal delivery has several advantages over the more common oral administration. Most significantly, it inhibits unwanted effects from occurring in the gastrointestinal tract and diminishes the possibility of the drug being inactivated by first-pass metabolism before it reaches its target. In contrast to parenteral administration, transdermal drug delivery is non-invasive, self-administered, and allows the opportunity to provide controlled, long-term release of drugs into the body [20,21].

The *stratum corneum* provides a major barrier to skin permeation, thus limiting the therapeutic efficacy of topically applied compounds [22]. To overcome this obstacle, many active methods to boost transdermal drug absorption have been investigated. One of the promising techniques is the application of microneedles (MNs) [23].

MNs which consist of miniature needles, have emerged as an active technique for delivering antimicrobial drugs to the dermis through the *stratum corneum* in a less invasive way [24–26]. These micron-sized projections are typically shorter than 1000 μm, allowing them to breach the *stratum corneum* with minimal interaction with nerve terminals in the dermis [27]. It causes less pain, tissue injury, and skin irritation than conventional needles and may be preferable for chronic disease patients [28]. Additionally, the use of MN array patches reduces the needle phobia involved with the use of hypodermic needles to administer parenteral medications [29]. In comparison to vesicular nanocarriers such as liposomes, transferosomes, microemulsions, and nanoemulsions, MNs represent an active penetration enhancement technique that effectively overcomes the *stratum corneum* barrier by creating microchannels through which a variety of drugs can be delivered at therapeutic doses into/across the skin layers [30]. This efficient transdermal delivery produced by MNs application enables the transport of hydrophilic permeants and macromolecules that are difficult to be transported using other passive enhancement methods [31]. On the other hand, vesicular nanocarriers as a passive strategy may

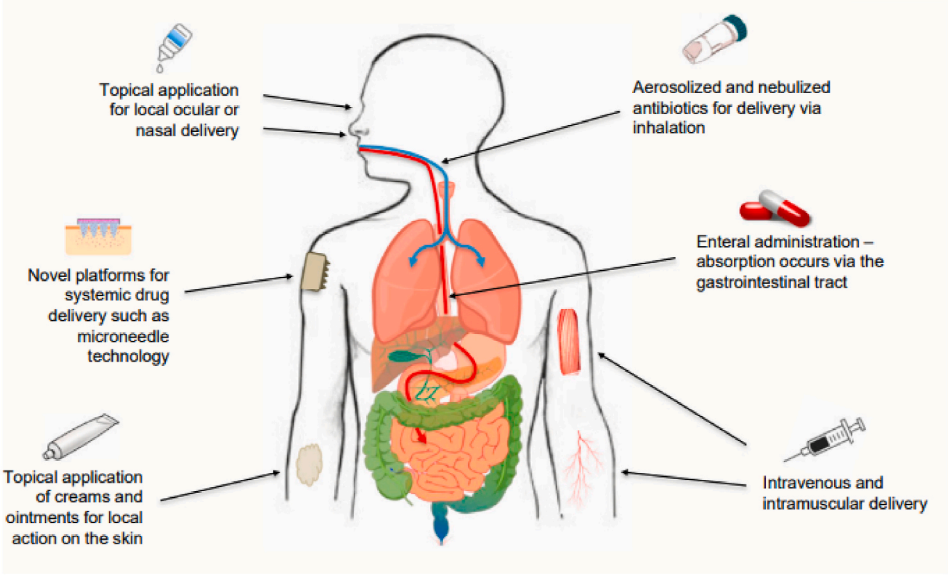

Fig. 1. Administration routes of antibiotics. Reprinted with permission [2].

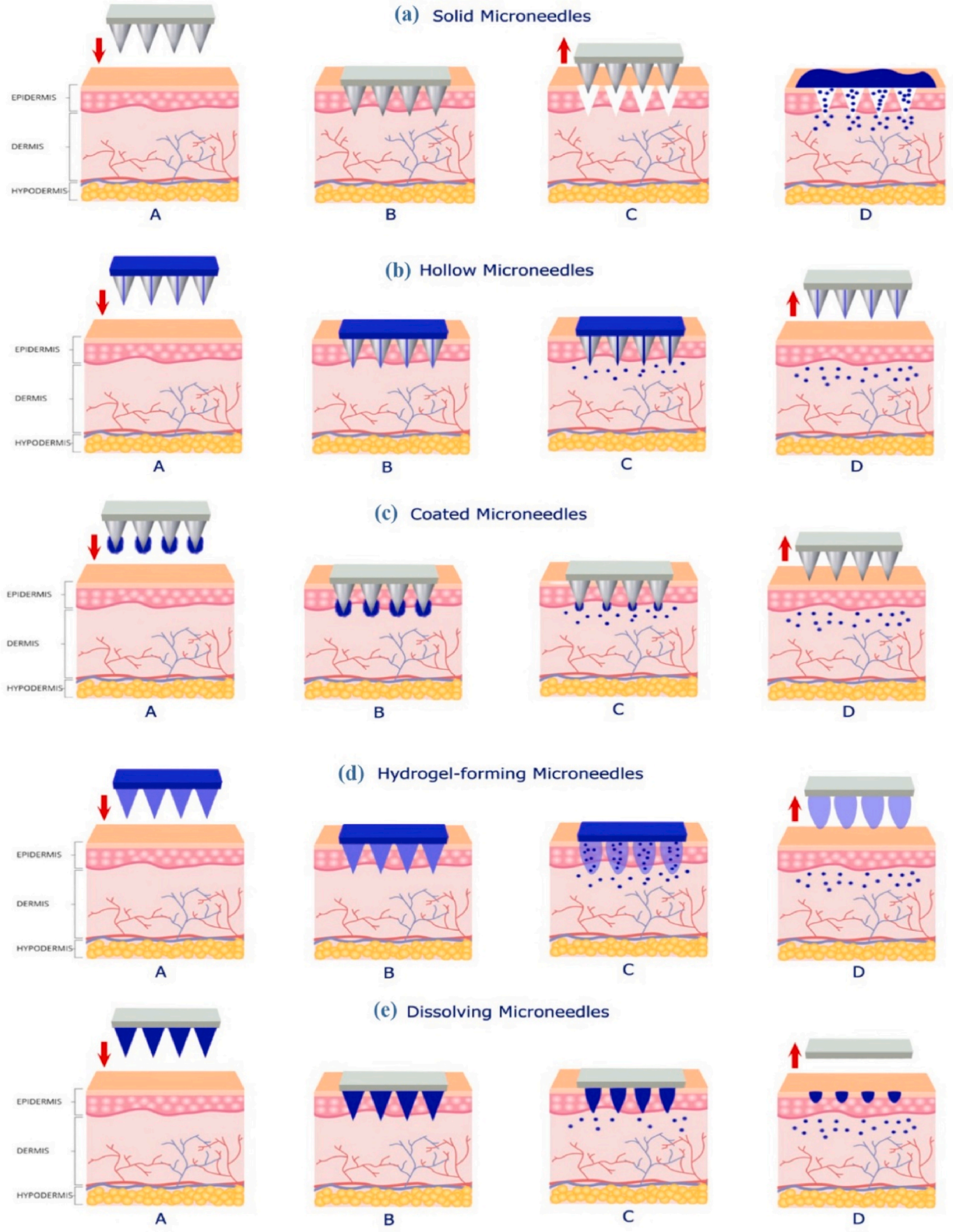

Fig. 2. Types of microneedles and their drug release mechanism, where (a) represents solid MNs, (b) hollow MNs, (c) coated MNs, (d) hydrogel MNs, and (e) dissolving MNs [45].

undergo limited skin penetration to transdermally deliver the required therapeutic doses. In addition, they may show an issue with drug loading capacity and instability due to environmental conditions [32]. However, vesicular nanocarriers can provide a drug-targeting and controlled-release property. Therefore, the combination of both technologies vesicular carriers and MNs can provide a complementary and synergistic effect in transdermal drug delivery [31].

This review aims to highlight the potential role of MNs in enhancing the delivery of antibiotics to treat local or systemic bacterial infections, since other routes such as oral, parenteral, and topical have many limitations that may restrict the efficacy of antibiotics and reduce the patient's compliance. This paper represents the most recent review that specifically focuses on the delivery of antibiotics using various types of MNs to combat bacterial infections, with twelve detailed examples of antibiotics administered. Previous review articles on this topic [16,17] were broader that discussed the delivery of antimicrobials in general, including antibacterials, antivirals, and antifungals using only dissolving MNs with fewer examples of antibiotics.

2. Microneedles (MNs)

Numerous MN designs have garnered substantial attention over the past several decades. Based on the drug delivery method, each MN type is classified as follows: (a) solid, (b) hollow, (c) coated, (d) hydrogel, and (e) dissolving MNs, as shown in Fig. 2. The advantages, disadvantages, and applications of the variant types of MNs are summarised in Table 1.

a- Solid MNs: are made of silicon [33], titanium [34], stainless steel [35], and in certain circumstances polymers [36]. The "poke and patch" method uses solid MNs to create microchannels in the skin, which are then removed (skin pre-treatment) and followed by the application of a formulation containing the active ingredient [37] as illustrated in Fig. 2a.

b- Hollow MNs: containing a void within each needle and a cavity at the apex (Fig. 2b). Using the "poke and flow" technique enables the injection of microvolumes of drug solutions into the epidermis. Ceramics, metal, silicon, and glass are used to manufacture hollow MNs [38]. Overcoming the *stratum corneum* and creating non-collapsing microchannels that could remain in place are both achieved with hollow MNs. Nevertheless, microchannel blockage in hollow MNs is a potential issue that can be mitigated by giving the needles an off-centre hole [39].

c- Coated MNs: developed with the purpose of eliminating the demand for a two-step treatment used in solid MNs. This can be achieved by coating the MNs with a thin layer of the appropriate therapeutic ingredient and then inserting them into the patient's skin (Fig. 2c). Coating is frequently accomplished using dip coating, inkjet printing, and other spray drying techniques [40]. The efficiency and uniformity of coatings on MNs are of particular concern. For instance, the baseplate of the MNs being coated unnecessarily, the coating being peeled off during insertion and left on the skin, and the drug being retained on the MNs after being removed from the skin [41]. The coating layer thickness and the needle sizes determine the maximum drug load.

d- Hydrogel MNs: are manufactured from extensible hydrophilic cross-linked polymers. Due to the polymer's inherent hydrophilicity, the hydrogel MNs swell upon insertion into the skin in the presence of interstitial fluid [42] (Fig. 2d). Hydrogel-forming MNs represent a recent innovation in MN technology. Because of their passive absorption of interstitial fluids and their capacity to work as a drug delivery device into or across the skin, they may also be useful as a diagnostic tool [43,44]. Polymethyl vinyl ether co-maleic acid (PMVE/MA) crosslinked with polyethylene glycol (PEG) is one of the most common polymers utilised in the preparation of hydrogel MNs. Hydrogel MNs are not devoid of complications, as delayed fluid absorption may lead to a delay in swelling and difficulty maintaining the therapeutic levels of drug release after a burst release [45].

e- Dissolving MNs: are manufactured by encapsulating the medication in biodegradable polymers [46,47]. After entering the *stratum corneum*, the polymer that forms the geometry of the needles degrades and releases the drug (Fig. 2e). Dissolving MNs are applied in a single step, as the MNs containing the drug remain in their position after application. As a result of their mechanism of

Table 1
An overview of MN types.

Type of MNs	Advantages	Disadvantages	Application	Materials	Reference
Solid	Strong needles with sharper tips. Easy to manufacture.	Damage to the skin. Two-step application.	Drug delivery Cosmetic	Silicon Metal Polymer	[49,50]
Hollow	Deliver a large amount of drug solution.	Weak needles. Require intensive care in terms of needle design. Might cause leakage and clogging.	Disease diagnosis Drug delivery	Silicon	[51–53]
Coated	Rapid delivery of drugs into the skin. One-step application.	Dose loading limitations. Prone to infection.	Drug delivery Vaccine delivery	Silicon	[24,54]
Hydrogel	High drug loading capacity using drug reservoir. No polymeric residue remains within the skin.	Delay in swelling and consequently in drug release.	Drug delivery Disease diagnosis	Cross-linked polymers	[27,55,56]
Dissolving	Ease of administration with a one-step application. Avoid needle-stick injuries.	Require technical expertise to manufacture. May undergo a delay in dissolution.	Drug delivery Cosmetic Vaccine delivery	Polymer	[57–59]

action “poke and release”, dissolving MNs circumvent several problems associated with solid MNs, since they are a single-step process that improves the patient’s compliance. In addition, they minimise the likelihood of needle-stick injuries following application as they dissolve within the skin [48].

2.1. Benefits and drawbacks of administering antibiotics using microneedles

Microneedle technology is a non-invasive method for increasing the skin’s permeability to antibiotics that have poor absorption and permeability after being administered orally or topically. The benefits include the following [27,29,60]:

- Avoid GIT deterioration and first-pass hepatic metabolism. This can reduce the overall used dose and thus decreasing the systemic adverse effects.
- The application of MN arrays does not require qualified or trained personnel.
- Easy and painless self-administration which improves patient compliance.
- In comparison to parenteral hypodermic injections, MNs eliminate the production of biohazardous sharps and minimise the likelihood of wounds from needle sticks and the transmission of blood-borne infections.

However, there are some limitations with the use of MNs that need to be resolved before commercialisation; these include [61–63]:

Table 2
Summary of the antibacterial MNs used in the treatment of different bacterial infections.

MNs type	MNs design	Material used	Antibiotic used	Indication	Reference
Dissolving MNs	14 × 14 MNs density 200 μm height	PVA/PVP	Ciprofloxacin	Skin bacterial infections	[71]
Dissolving MNs	10 × 10 MNs density 600 μm height	PVA/PVP/PMMA	Vancomycin	MRSA skin infections	[72]
Dissolving MNs	10 × 10 MNs density 600 μm height	Hyaluronic acid/PVP	Clarithromycin	Bacterial biofilm	[73]
Dissolving MNs	16 × 16 MNs density 850 μm height	PVA/PVP	Doxycycline	Bacterial biofilms	[74]
Dissolving MNs	15 × 15 MNs density 500 μm height	PVP	Chloramphenicol	Bacterial biofilms	[75]
Hydrogel MNs	11 × 11 MNs density 600 μm height	reactive oxygen species (ROS)-responsive PVA/methacrylated hyaluronic acid (m-HA)/diatomaceous earth (DE)	Clindamycin	Acne vulgaris	[76]
Dissolving MNs	6 × 6 MNs density 1500 μm height	PVA/PVP	Besifloxacin	Ophthalmic infections	[77]
Dissolving MNs	19 × 19 MNs density 500 μm height	Sodium hyaluronate/PVP	Gentamicin	Neonatal sepsis	[79]
Hydrogel MNs	11 × 11 MNs density 600 μm height	Gantrez/PEG/Carbopol	Cefazolin	Septic arthritis, osteomyelitis, and cellulitis	[80]
Hydrogel MNs	11 × 11 MNs density 600 μm height	PVA/PVP/citric acid	Tetracycline hydrochloride	Systemic bacterial infections	[81]
Hydrogel MNs	11 × 11 MNs density 600 μm height	Gantrez/PVA/PVP	Rifampicin Isoniazid Pyrazinamide and Ethambutol	Tuberculosis	[82]

- The majority of studies were employed for hydrophilic drugs. There are very few reports on the delivery of hydrophobic and water-insoluble drugs.
- The fabrication materials and methods should be compatible with the various types of drugs for the large-scale production of MNs at a low cost. These MNs should have sufficient mechanical strength to pierce the skin and deliver the required drug dose without creating adverse effects such as skin irritation and redness.
- Most antibacterial MNs are in the research and development phase. In addition, the effectiveness of antibacterial MNs is generally tested using *in vitro* agar plate assays and *in vivo* mice and rabbit models with skin features that may differ from the human skin.

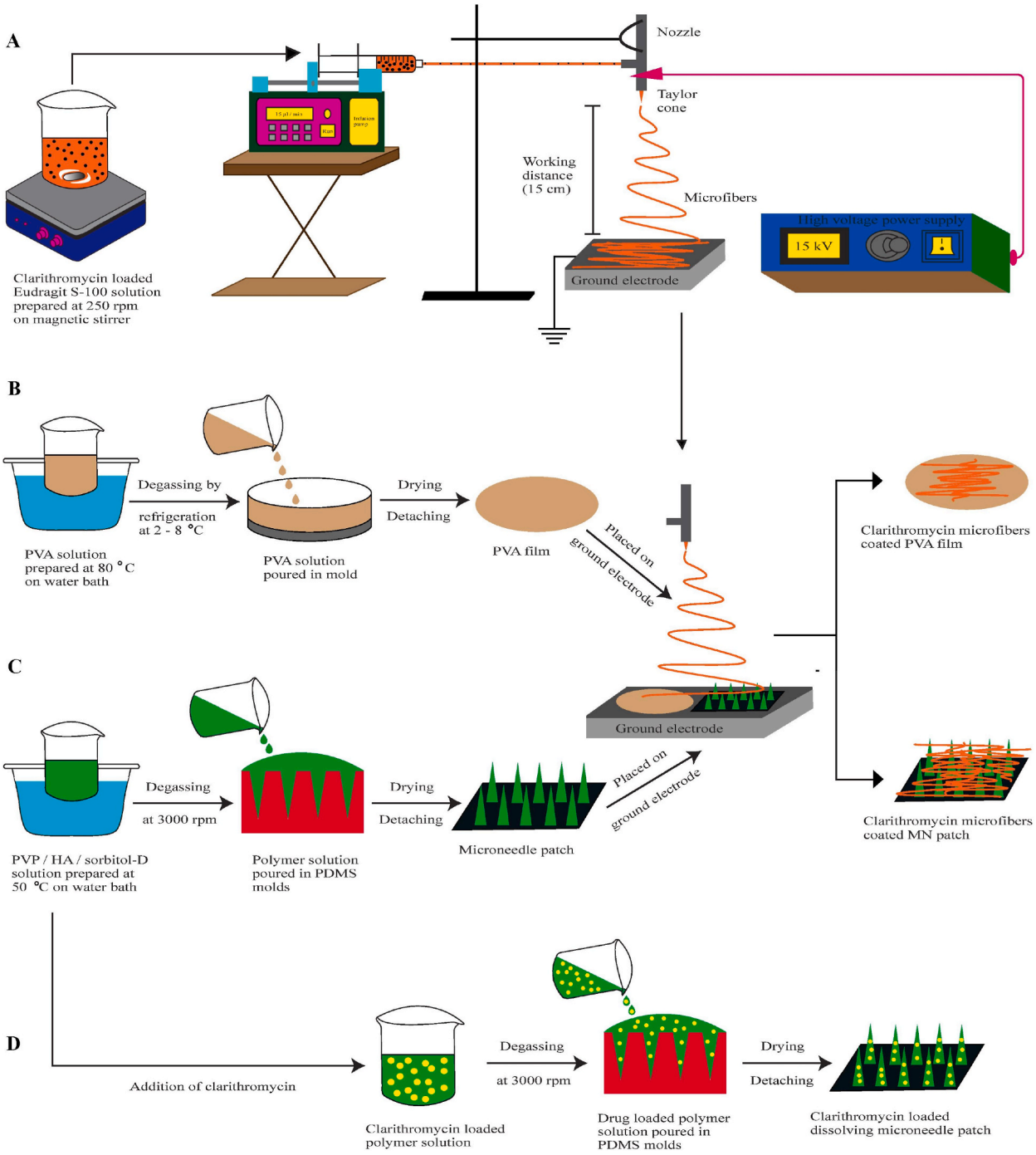

Fig. 3. Preparation of: (A) clarithromycin containing Eudragit S-100 fibers [MF], (B) clarithromycin fibers coated PVA film [MB], (C) clarithromycin fibers coated MN patch [MP], and (D) clarithromycin loaded dissolving MN patch [CP]. Reprinted with permission [73].

3. Delivery of antibiotics using microneedles for the management of bacterial infections

The MNs must easily penetrate the skin with the subsequent delivery of their payload [64]. By carefully selecting the materials and fabrication method, one can regulate MNs properties such as mechanical strength and drug release to optimise their efficacy and safety [65].

The fabricated MNs may vary in terms of their design, composition, needle height, base diameter, tip sharpness, and needle density. The MNs can bypass the *stratum corneum* barrier to reach the viable epidermis, or the upper layer of the dermis, avoiding the nerve fibres located at the lower dermal layer. Thus, the principal benefit of using MNs is the potential for pain-free delivery of both small and large molecular weight drugs [66]. The enhanced permeation of various molecular weight drugs is well recognised. Several *in vitro* and *in vivo* studies support the use of MNs for the delivery of hydrophilic drugs. MNs create aqueous microchannels that facilitate the easy transport of hydrophilic drugs. The dimensions of these microchannels are larger than the molecular ones, allowing for the transport of large hydrophilic molecules [67]. As a result of overcoming the *stratum corneum*, efficient drug delivery will no longer be dependent on the drug's physicochemical properties [68].

Several studies have been performed to fabricate MNs containing antibiotics to treat either local or systemic bacterial infections. Representative examples of the recent development of antibacterial MNs are detailed in the following sections as well as summarised in Table 2.

3.1. Microneedles for topical local antibiotic delivery

Soft tissue and skin infections (STSI) can be caused by a wide variety of microorganisms, including bacteria, viruses, fungi, and parasites. The development of antibacterial MNs has allowed for the treatment of bacterial skin infections [69,70].

In order to treat *Staphylococcus aureus* skin infections, Abdelghany et al. investigated the feasibility of PVA and PVP copolymers as the basis for dissolving MNs loaded with ciprofloxacin. According to their findings, PVA/PVP MNs demonstrated a sustained insertion force and completely penetrated both parafilm and agarose gel. Furthermore, this method of administration was shown to be superior to the administration of free gel in both an *in vitro* skin infection model and on excised human skin. This can be very useful for the non-invasive topical and transdermal delivery of antibiotics, as it can help overcome the skin's natural barriers and lessen the side effects associated with the therapeutic dose of ciprofloxacin when utilising traditional delivery methods, both of which contribute to its current restricted use in the management of STSI caused by *Staphylococcus aureus* [71].

To combat skin infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), Ziesmer et al. created MNs with water-soluble tips and water-insoluble support layer. The water-soluble drug loaded MN tips (polyvinyl alcohol, PVA), and the water-insoluble support layer (polym-ethylmethacrylate, PMMA) are made utilising MN moulds for the controlled delivery of vancomycin into the skin. The designed MNs can pass through the barriers of both fresh human skin and porcine skin. Studies on the permeation of vancomycin through the porcine skin indicated that most of the administered drug remains within the skin. It has been demonstrated that the vancomycin MNs inhibited the growth of MRSA on skin both *in vitro* and *in vivo* as well as prevented the emergence of resistant bacterial strains following systemic exposure via other routes [72].

Disruption of the skin's epithelial layer due to injury creates a window of opportunity for microbial invasion and colonisation of the deeper layers of subcutaneous tissue. The prolonged inflammatory stage caused by pathogen growth in infected wounds is detrimental to the wound healing process because it is caused by the release of pro-inflammatory cytokines from microorganisms. Later, these microbes establish themselves as a mono or polymicrobial biofilm within the site of injury. Zafar et al. fabricated clarithromycin-laden Eudragit S-100-based microfibers (MF). After that, these clarithromycin microfibers were incorporated into three formulations: microfibers coated PVA films (MB), microfibers loaded within polyvinylpyrrolidone, hyaluronic acid, and sorbitol-based dissolving microneedle patches (CP), and microfibers coated microneedle patches (MP) as illustrated in Fig. 3. MF displayed a homogenous surface and network connectivity. The morphological analysis of CP showed microstructures with pointed tips and regular surfaces. Within 2 h, clarithromycin microfiber-based formulations (MF, MB, MP, and CP) exhibited a drug release of approximately 79 %, 78 %, 81, and 82 %, respectively. In Comparison to the MB and CP, the MP displayed a 13 % broader inhibitory zone against *Staphylococcus aureus*. Infected wounds treated with MP showed faster skin regeneration and elimination of *Staphylococcus aureus* than those treated with MB or CP, suggesting its effectiveness in the treatment of microbial biofilms [73].

In wounds, the existence of bacterial biofilms is a major problem during the healing process. Traditional treatments for bacterial biofilms have limitations due to the non-specificity of antibiotics and their difficulty in penetrating the physical barrier of infected skin. For better biofilm penetration and selective delivery of doxycycline (DOX) to the site of infection, Permana et al. described a combination strategy using nanoparticles sensitive to bacteria (NPs) and dissolving microneedles (MNs) containing DOX. The dermatokinetic profiles of DOX were greatly improved by the inclusion of these NPs in dissolving MNs, as shown by increased retention time in comparison to needle-free patches. Notably, 48 h after applying this method, bacterial bioburdens fell by up to 99.99 % in an *ex vivo* biofilm model. This study's findings provide proof of concept for the enhancement of DOX's dermatokinetic profiles and antibiofilm activities by formulating the drug into bacterial-sensitive NPs and delivering them using MNs [74].

A challenge in treating bacterial biofilms is the development of resistance to antibiotics, the difficulty of antibiotics in penetrating the biofilm's physical barrier, and the antibiotics' considerable off-target toxicity. Xu et al. developed patches with self-dissolving MNs and needle tips laden with chloramphenicol (CAM) and gelatinase-sensitive gelatine nanoparticles (CAM@GNPs). When the microneedles inserted and reach their destination, they dissolve and release the CAM@GNPs evenly throughout the surroundings. Disassembled CAM@GNPs release CAM into the biofilm's active areas in response to gelatinase generated by the metabolically active bacterial community. In addition, CAM@GNPs exhibited less off-target toxicity than direct CAM administration, thereby promoting

wound healing. Treatment of *Vibrio vulnificus* biofilms with a MN-mediated approach is more effective than with the drug in free solution, which is an important finding. Many antibiotics may be more effectively delivered to biofilm-infected areas by employing this novel treatment approach [75].

Acne vulgaris, an inflammatory skin illness caused by the *Propionibacterium acnes* microorganism, can have serious psychological and physiological consequences on patients. The majority of anti-acne products are epicutaneous medicines; however, their inadequate dermal penetration makes them ineffective against acne bacteria. Better therapeutic efficacy is seen with oral antibiotics or isotretinoin, despite the fact that these drugs frequently show the possibility of damaging the intestinal microflora and other adverse effects, including teratogenicity. Therefore, Zhang et al. demonstrated a novel method of clindamycin delivery using a reactive oxygen species (ROS)-responsive microneedle (MN) patch for acne treatment. To maximise the antibacterial activity while minimising the negative effects, it is necessary to release the antibiotic in a controlled and prolonged manner in response to the excess ROS produced within acne. Additionally, the patch base, which is composed of hyaluronic acid (HA) and diatomaceous earth (DE) with a high physical adsorption capacity, is advantageous for boosting skin healing by absorbing pus and dead cell debris. *In vivo* studies on a mouse model induced by *Propionibacterium acnes* revealed that this bioresponsive patch with adsorption capacity effectively reduced skin inflammation and inhibited bacterial growth [76]. The mechanism of ROS-responsive microneedles for the treatment of acne vulgaris is shown in Fig. 4.

The treatment of ophthalmic infections presents several difficulties, including the utilisation of home cures and OTC drugs as well as empirical treatment without identifying the causative organisms. This would hinder the achievement of successful treatment. Furthermore, successful treatment requires the hourly application of topical drugs, with a high likelihood of noncompliance. For many patients who develop these infections, both incorrect and inadequate treatment results in not only vision loss but also eye loss. Therefore, there has always been a desire for a drug administration method that boosts compliance and guarantees fast, high corneal drug tissue concentrations. Bhatnagar, Saju et al. described the development of rapidly dissolving polymeric MNs for the efficient delivery of besifloxacin through the cornea. Two polymers, polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP), were used to produce MNs. Mechanically, PVA-PVP MNs are robust enough for corneal implantation, and their depth of penetration is up to 200 μm. In the cornea, the MNs dissolved rapidly, releasing besifloxacin. Application of MN resulted in considerably higher besifloxacin deposition than application of a free drug solution. Compared to topical drops, MNs were more effective in preventing *Staphylococcus aureus* infections in both *in vitro* and *ex vivo* models [77].

3.2. Microneedles for transdermal systemic antibiotic delivery

For the transdermal delivery of drugs, MNs are considered minimally invasive devices aiming to pierce the *stratum corneum* barrier and create microconduits for the transport of drugs at a higher concentration into the dermal layer. The vasculature of the dermis, including blood vessels and lymphatics, plays an important role in carrying the permeated molecules into the systemic circulation at a therapeutic level. MNs combine the patient-friendly benefits of a transdermal patch's simple and convenient application with the

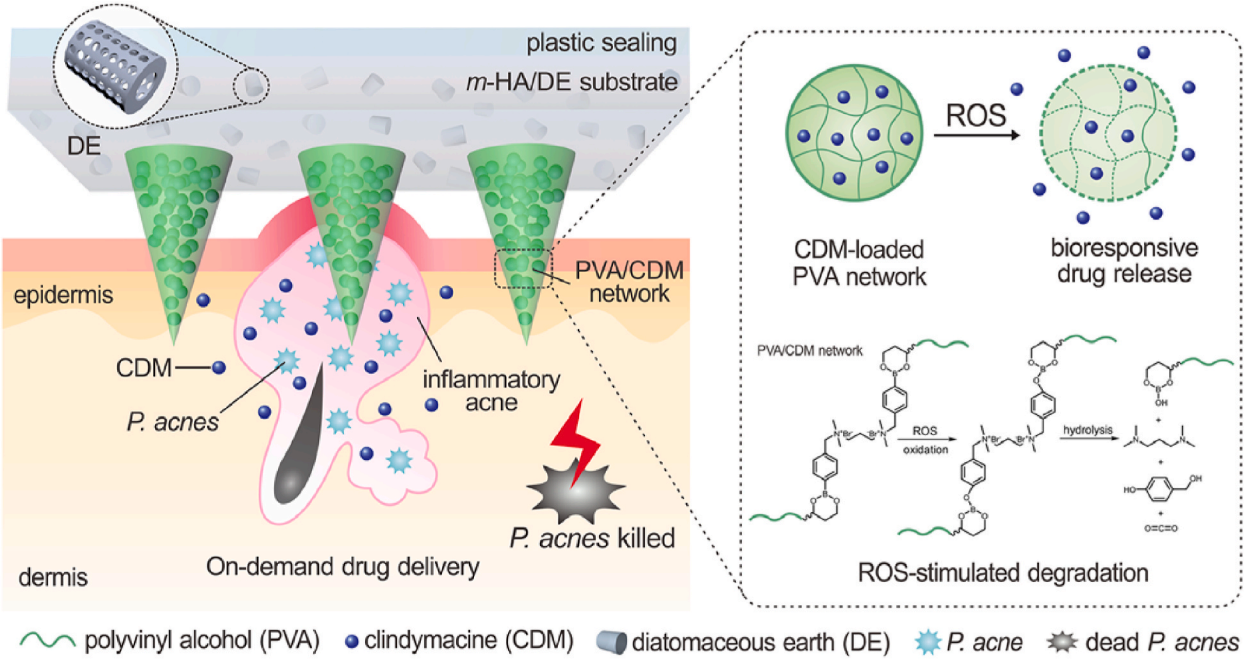

Fig. 4. Schematic representation of the mechanism of ROS-responsive microneedles for the treatment of acne vulgaris. Reprinted with permission [76].

efficiency of delivery accomplished by a conventional hypodermic injection [68,78]. The studies that reported the successful use of MNs for the systemic delivery of antibiotics will be discussed in the following paragraphs.

González-Vázquez et al. designed dissolving polymeric MNs for transdermal delivery of gentamicin (GEN) for the management of neonatal sepsis. MNs were fabricated from aqueous blends comprising 30% (w/w) gentamicin and two polymers, sodium hyaluronate and polyvinylpyrrolidone (PVP). This study documented the optimal formulation and mechanical characterisation of dissolving MNs containing gentamicin. Additionally, in an *in vivo* experiment, rats received doses of the antibiotic that were therapeutically relevant, demonstrating the potential for utilising this delivery method for the administration of GEN. This promising technology may provide an easier way to administer GEN in developing countries, increasing the number of newborns who can receive life-saving outpatient antibiotic treatment [79].

Cefazolin (CFZ) is a widely used cephalosporin antibiotic. Because CFZ is highly polar, its oral bioavailability is low approximately 15%. As a result, IM or IV injections, which are uncomfortable and painful are used to administer the antibiotic. The study conducted by Sabri et al. outlines the synthesis and evaluation of Gantrez S-97-PEG 10,000-Carbopol 974P NF hydrogels as a CFZ delivery system. They detailed how hydrogel-forming MNs were integrated with CFZ dry reservoirs to create a hybrid pharmaceutical system. Hydrogel MNs with a high swelling capacity have been created, and they can penetrate *ex vivo* newborn porcine skin to a depth of 350 μm while producing MN pores with a diameter of 300 μm. Additionally, two distinct CFZ-loaded reservoirs (directly compressed tablet DCT, and lyophilized LYO reservoirs) were prepared and investigated for use with the hydrogel-forming MNs. It was shown that the combined system (DCT with hydrogel-forming MNs) can deliver higher amounts of CFZ into and across the skin at 24 h. They demonstrated the intradermal delivery of CFZ into the epidermis and dermis, as well as the transdermal delivery into the receiver compartment. This could provide patients with a minimally invasive, patient-friendly way to administer CFZ for the treatment of localised and systemic infections such as septic arthritis, osteomyelitis, and cellulitis [80].

One of the most pressing health issues of our day is antibiotic resistance, which is only going to get worse over the next few decades. It has been proposed that antibiotic delivery methods that avoid the human gut may be able to address this issue. Zhao et al. created a novel antibiotic hydrogel-forming microarray patch (HF-MAP) system that showed excellent swelling properties, with more than 600% swelling in PBS after 24 h. It has been demonstrated that the HF-MAP needles can penetrate a skin model with a thickness greater than the *stratum corneum*. The antibiotic drug reservoir (tetracycline hydrochloride) was mechanically robust and dissolved rapidly in aqueous medium. *In vivo* animal tests employing a Sprague Dawley rat model indicated that antibiotic delivery via HF-MAP resulted in a prolonged release profile in comparison to animals receiving oral and IV injection, with a transdermal bioavailability of 19.1% and an oral bioavailability of 33.5%. They concluded that HF-MAP can deliver antibiotics transdermally in a sustained manner [81].

The current tuberculosis (TB) treatment has numerous drawbacks, including the possibility of liver damage and intestinal dysbiosis because of the regular administration of oral antibiotics. *Mycobacterium tuberculosis* treatment could be enhanced by the transdermal administration of antibiotics. As a result, Anjani et al. devised a novel method for transdermally delivering TB drugs, namely rifampicin (RIF), isoniazid (INH), pyrazinamide (PYR), and ethambutol (ETH), which have different physicochemical properties. These drugs were separately manufactured into a drug reservoir of three types: polyethylene glycol tablets, directly compressed tablets, and

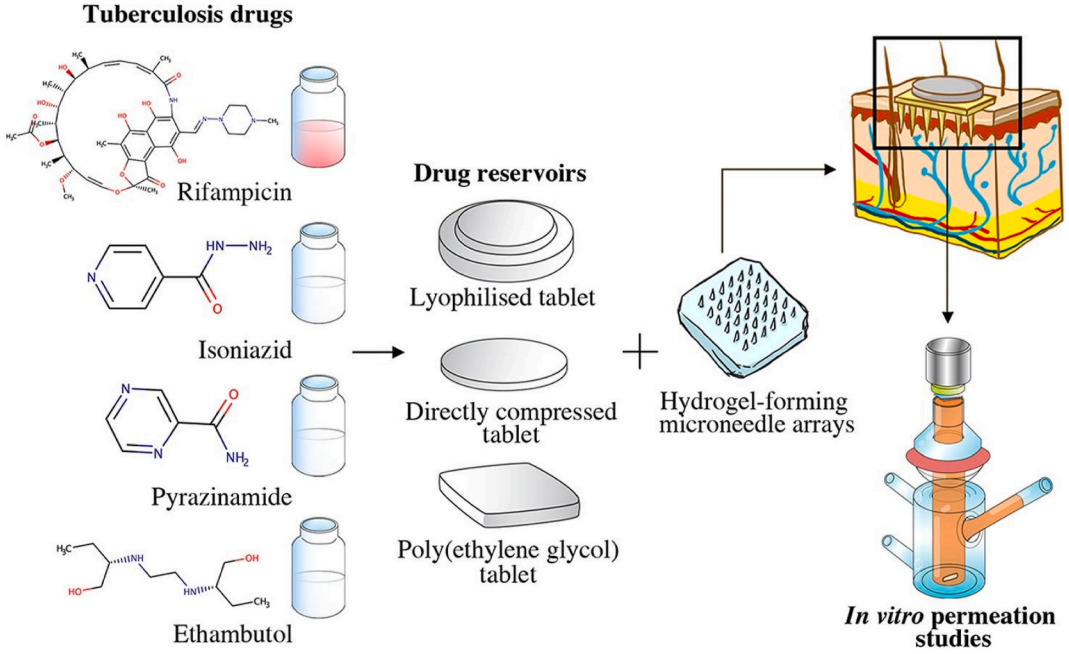

Fig. 5. Schematic illustration of the prepared TB drugs loaded in 3 types of reservoirs which then adhered to hydrogel-forming MN arrays and tested in modified Franz Cell chamber system for *in vitro* permeation across neonatal porcine skin. Reprinted with permission [82].

lyophilized tablets. After that, they were attached to hydrogel-forming MNs as demonstrated in Fig. 5. The hydrogel-forming MNs were assessed for their morphology, physical properties, and swelling behaviour. The results of the *in vitro* permeation experiments showed that these MNs could deliver RIF, INH, PYR, and ETH from their reservoirs through newborn porcine skin. This research provided a template for the design of hydrogel-forming MN arrays for transdermal delivery of a wide variety of high-dose TB drugs [82].

4. Conclusion and future perspectives

The rise in resistant bacteria is a huge threat to public health worldwide. Considering the growing problem of antibiotic-resistant bacteria, research into potential substitutes for the standard practice of using antibiotics to treat infections has become urgently necessary. MNs can provide a new avenue for the topical and transdermal delivery of antibiotics into and through the skin for the treatment of varying infectious diseases with the aim of reducing bacterial resistance. MNs have replaced painful intralesional injections of drugs and bioactive substances by delivering their payloads directly to the skin. However, the research on antimicrobial MNs is still in its infancy, with most studies being conducted at the preclinical level. Several challenges are required to be addressed prior to the transition into clinical practice, such as the sterility, stability, and dose accuracy of the MN array patches. Further collaboration between academia, industry, and clinicians is required to perform more clinical trials to validate the therapeutic value of antimicrobial MNs. There is a lot of potential for future research in this developing field due to the rapid rise of multidrug-resistant bacteria. The synthesis of next-generation MNs may involve altering or functionalizing their polymer matrices or integrating antibacterial nano/micro-formulations into the polymer matrix to create genuine antimicrobial MNs. Synergistic delivery platforms that combine antibiotics with antibacterial nanoparticles, for instance, have been shown to boost antibacterial effects while also preventing drug resistance and lowering acute toxicity. A noteworthy point regarding the development of bacterial resistance is that the fabricated antibacterial MNs should contain a sufficient amount of the desired antibiotic above the minimum bactericidal concentration that can be delivered for the complete eradication of the susceptible microorganisms. Furthermore, antibacterial MNs may be beneficial in a variety of other applications, including wound repair and tissue engineering.

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Zainab Mohammed Abid Al-Wahaab: Writing – original draft, Visualization, Resources. **Mohammed Hussain Al-Mayahy:** Writing – review & editing, Visualization, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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