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# The role of microneedles in the healing of chronic wounds

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ABSTRACT

Chronic wounds occur for several reasons, such as trauma, accidents, and diseases. Diabetes has been one of the primary causes of non-healing wounds, and the number of people with diabetes is increasing in most countries. Wounds in diabetic people have a complex and prolonged treatment process, with high treatment costs to both healthcare providers and patients. They often have severe consequences, such as pain, wound infection, tissue necrosis, and even limb amputation. Various methods have been used to treat chronic wounds, but clinical success has been limited due to inefficient delivery to the wound bed. Microneedles (MNs), as new platforms, can offer an effective treatment, easy to use and non-invasive with less tissue damage, capable of delivering a wide range of drugs to accelerate the wound healing process. Different methods and materials can be used for this technique, and there are different geometric parameters such as needle length, tip angle, shape and radius, together with needle array density to optimize for the most effective treatment. This review paper will investigate the role of MNs in healing chronic wounds and discuss the most recent development in MN-based devices in the field and their effectiveness. The manuscript will also discuss the various types of MNs and their potential applications for delivering therapeutic agents. Finally, the challenges associated with using MNs to heal chronic wounds and future directions in this field are discussed.

## 1. Introduction

Wound healing is a biological process with three essential overlapping stages: inflammatory response, cell migration and tissue regrowth (Cañedo-Dorantes and Cañedo-Ayala, 2019). But in the case of particularly severe skin injuries or the presence of diseases such as diabetes, the wound-healing process can be disrupted. Approximately 2 million cases of chronic wounds currently exist in Europe and 6 million in the USA (Harding, 2002; Lindholm and Searle, 2016). Such wounds present major healthcare challenges worldwide, imposing devastating human and financial burdens (Barnum et al., 2020; Yao et al., 2021b). It has been reported that approximately $50 billion are consumed per annum on the care management of chronic wounds (Dian et al., 2020). Their consequences include pain, depression, impaired sleep, reduced mobility, tissue necrosis, infection, invasive surgical debridement, and, in the most severe cases, amputation of all or part of a limb may be necessary. Chronic wounds, specifically diabetic ulcers, are the leading cause of non-traumatic limb amputation (Barnum et al., 2020) in a world where diabetes is increasing. An increase of 16 % is expected due to population ageing alone, and it is estimated that the greatest increase from 2021 to 2045 will occur in middle-income countries (IDF Diabetes Atlas, 2021). Clearly, developing therapeutics and treatment options that enhance healing and close wounds quickly is essential. Different methods like cell transplantation, pharmacologic intervention, and artificial substitutes could be applied to treat wounds. Pharmacologic intervention includes drug delivery using biomaterials in different forms, such as nanoparticles (NPs), microfibers, carbon-based nanostructures, and MNs. These methods reduce drug toxicity and gradually release the dosage over time (Bagheri et al., 2022; Gittard et al., 2011; Sun et al., 2021a).

Patches containing arrays of MNs have received significant interest in recent years for their considerable potential for a range of healthcare applications, including the treatment of wounds and wound management (Guo et al., 2022). They have a high loading capacity, bypass skin

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barriers (Ebrahiminejad et al., 2022a; Khan et al., 2014), and may be used in most tissues and organs such as oral cavities, the gastrointestinal tract, nails, and eyes (Jeon et al., 2019; Rzhevskiy et al., 2017). MNs are miniature projections with a length of ~500 μm. By creating micropores on the stratum corneum layer of the epidermis, MNs could deliver pharmacologic agents such as antigens, cells, anti-inflammatories and other drugs, vaccines, and pro-regenerative molecules into the deeper layers of the skin to accelerate wound healing. There are many advantages of using MNs for drug delivery, including ease of use, rapid administration, and low tissue damage due to their small size (Faraji Rad et al., 2021a; Frydman et al., 2020; Jeon et al., 2019). Researchers have also shown that MNs can induce cell proliferation to heal wounds when used to create tiny electrical signal currents in the skin (Liebl and Kloth, 2013). One study showed that wound-healing capabilities are increased by enhanced collagen content delivered using MNs, leading to raised tissue growth factors from fibroblasts and blood platelets (Sun et al., 2015).

Many researchers have studied different MN designs and materials, but few have examined the role of MN devices in wound healing and other clinical settings (Yao et al., 2022), and the complexities of the wound-healing process demand much more research (Hu et al., 2023). However, it is already clear that MNs might play an important role in wound healing. This paper explicitly focuses on the role of the MNs in drug delivery for this clinical application and discusses the critical mechanical properties for efficient penetration through the skin. In addition, the latest developments in the field of MNs for wound healing are critically discussed. Notwithstanding the many advantages of MNs, some generic problems exist, such as inadequate penetration or the fouling of needle holes with skin tissue. However, using physical and chemical auxiliary methods, such as an inserter to replace manual force, improves drug delivery and speed of application of MNs for wound healing (G. Nava-Arzaluz et al., 2011; Nayak et al., 2016). The current study discusses emerging novel therapeutic methods to overcome the limitations of MN devices.

## 2. Materials and manufacturing methods of MNs

Selecting suitable material and geometry is crucial for efficient MN penetration and drug delivery into the skin. Consideration must be given to the mechanical and geometrical properties of the MNs to facilitate non-invasive penetration into the skin without bending or breaking during insertion (Choi et al., 2012; Nagarkar et al., 2020). A wide range of materials can be used to create MNs: silicon (Ahmad et al., 2021), metal (Zhang et al., 2018), polymers (Lima and Reis, 2021), and natural materials such as traditional Chinese herbs (Chi et al., 2021b) and silk fibroin-based MN dressing (Gao et al., 2020) have also been used.

MN patches are generally classified according to their drug, delivery mechanism, and structure. Common MN types are solid, coated, dissolvable, separable, hollow (Kang et al., 2021), hydrogel-forming, swellable (Al-japairai et al., 2020), and porous structures (Abe et al., 2021). Other less common designs are merged-tip MNs (Lim et al., 2018) or microblade structures (Ebrahiminejad and Faraji Rad, 2022; Faraji Rad et al., 2020). Fig. 1 shows the most common designs of MNs and their drug delivery mechanisms. Table 1 summarizes the benefits and drawbacks of each different type of MN.

MN arrays could be fabricated in several ways based on their geometry, penetration depth requirement, and material. For example, solvent casting is suitable for polymeric MNs, whereas

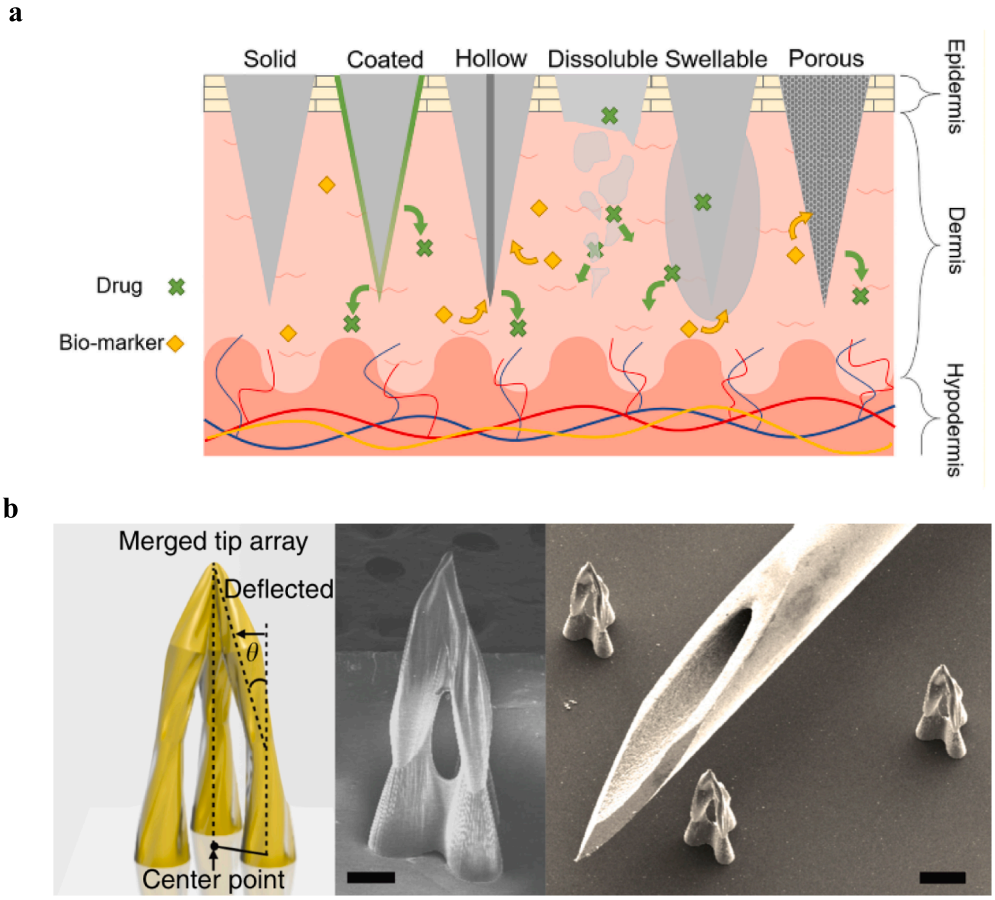


**Fig. 1.** Different types of MNs: (a) solid, coated, hollow, dissoluble, swellable, and porous MNs. Reprinted with permission from (Bao et al., 2022). Reproduced under the terms of the CC-BY 4.0 license. Copyright 2021, Springer Nature. (b) Merged-tip MNs compared with a conventional steel hypodermic needle. Adapted with permission from (Lim et al., 2018). Reproduced under the terms of the CC-BY 4.0 license. Copyright 2018, Springer Nature.

**Table 1**
Different types of typical MN arrays with their advantages and disadvantages (Faraji Rad, 2023; Meng et al., 2020).

| Type of MNs | Properties | Advantageous | Disadvantageous |
|---|---|---|---|
| Solid | Contain no drugs; used to create micropores before application of drugs, sometimes in cream form | Increased permeability of drugs so small doses can be administered; more straightforward fabrication process than other designs; better mechanical properties | Requires two-step procedures for delivery; broken MNs can result in skin irritation; non-biodegradable properties; drugs need to be reformulated for delivery |
| Coated | Drugs can be coated on MN surface | Higher stiffness; simple fabrication process; flexibility in the choice of material | Complicated drug coating procedure; low control on dose delivery |
| Hollow | Incorporates a microchannel to transfer the drugs and therapeutics | Potential combination with microfluidics network in lab-on-a-chip devices; precise dose delivery | Require a precise and expensive manufacturing process; risk of leakage or uncontrolled drug release; risk of blockage in the narrow channels; reduced MN strength |
| Hydrogel/ dissoluble | Integral drug storage; reactive through swelling with interstitial fluid | Safety; no sharp waste; controlled drug release. Biocompatible materials – polysaccharides, etc. | Low mechanical strength and penetration; not suitable for very wet wounds; limited to small drug doses; drug reformulation may be needed |
| Porous | A large variety of pore sizes can be achieved for drug loading; porosity and pore size can be controlled during fabrication | High drug loading capability; functionalization with different moieties; relatively simple fabrication methods | Low strength; pore blockage may occur; limited materials can be used (e.g., porous Si) |

microelectromechanical methods are more appropriate for silicon and metal MNs (Nagarkar et al., 2020). Other fabrication methods are silicon micromachining (Gardeniers et al., 2003), metal electroplating (Miller et al., 2020), polymer patterning and molding (Meng et al., 2020), microelectromechanical systems (Mohammed et al., 2021), photolithography, drilling holes (Kang et al., 2021), spatially discrete thermal drawing (Choi et al., 2012), CNC machining (Malek-Khatabi et al., 2023), 3D printing (Faraji Rad et al., 2021b; Quisling et al., 2021), and microinjection compression molding (Chen et al., 2020). Fig. 2 shows MNs of different materials made using a variety of manufacturing procedures.

Most MNs were initially made from metal and silicon. The idea of making polymer MNs was only developed in the early 2000s. Polymers offer good biocompatibility, are cheap, and some are biodegradable in the body. Polymer MNs do not cause any immune response, and their composition can be adjusted to exhibit different strengths and functions (Liu et al., 2023). They also offer routes to mass production (Faraji Rad et al., 2017).

Different polymers have been used to fabricate MNs, such as hydrogel/swellable, dissolving, and biodegradable (Al-japairai et al., 2020; Azmana et al., 2020; Meng et al., 2020; Saifullah and Faraji Rad, 2023). Azmana et al. classified polymeric MNs, based on formulation, applications, forms, and performance, into six categories: solid polymer MNs, biodegradable polymer MNs, dissolvable polymer MNs, hollow polymer MNs, coated polymer MNs, and bioresponsive polymer MNs (Azmana et al., 2020). Each of the categories is selected based on the type of polymer. For instance, hydrophilic polymers that dissolve quickly in the skin (e.g., polyvinyl alcohol and hyaluronic acid) are classified as dissolving MNs (Kang et al., 2021). Table 2 compares the drug loading capacity, sustained delivery, and molecular range among different types of polymer MNs, showing that dissolvable polymer MNs are perhaps the ideal candidate for drug delivery. Polymer MNs can be manufactured with a variety of techniques, including micromolding, atomized spraying to fill molds, droplet-born air blowing, electromagnetic/micro-system/laser technology, laser cutting, laser ablation, deep x-ray lithography, two-photon polymerization (Faraji Rad et al., 2022), and micro-stereolithography (Nagarkar et al., 2020). Table 3 summarizes the recent findings using MNs in wound healing with different materials, techniques, and drugs.

## 3. Geometry of MNs

The geometry of MNs directly affects their mechanical strength and skin penetration (Kang et al., 2021). The design should minimize bending and prevent fracture during insertion (Chevala et al., 2021). The significant factors that should be considered during the design process are MN length, tip radius, base diameter, shape and angle of the tip, and density which determines the overall insertion and fracture forces of the MNs (Olatunji et al., 2013). In general, the geometry of the MNs is determined by factors such as the required penetration depth (Ro, 2014), the dose of the drug, the place of use, skin thickness (Chevala et al., 2021; Al-qallaf and Das, 2009a), molecular sizes of drugs, the weight of drugs (Al-qallaf and Bhusan, 2009a), the elasticity of human skin (Chen et al., 2020), and age of the patient (Chevala et al., 2021; Kelchen et al., 2016). Considering all these parameters, it may be best to design a MN device according to the individual patient's condition and requirements. The following sections discuss the general indicators of optimal MN geometry (Loizidou et al., 2016).

### 3.1. Length of MNs

One of the most important design considerations of MNs is the length which defines the skin penetration depth and affects permeability. Researchers have shown that the length of MNs directly affects the pain experienced by patients; when the length is increased three times, the pain is increased seven times (Gill et al., 2008). Most MN heights vary between 150 and 1500 μm, but more studies need to be performed to determine the optimal length of MN patches for each application. A recent study showed that when 400 MNs, 150 μm long, were inserted into the human body, it was deemed painless compared to a 2-mm deep insertion of a 26-gauge hypodermic needle (Nagarkar et al., 2020). Romgens et al. (Römgens et al., 2016) showed that by increasing MN length, the number of activated antigen-presenting cells decreased in the epidermis, and more cells were activated in the dermis. Yan et al. (Yan et al., 2010) found that the optimum MN length for increased penetration efficiency of the anti-viral drug acyclovir was 600 μm. Further increase of MNs length above 600 μm did not enhance the penetration efficiency of the loaded drug.

### 3.2. Spacing and number of MNs

Spacing between the MNs is an important design aspect of MN geometry, an increase in average penetration depths as a fraction of MN length has been observed with an increase in needle spacing (Kochhar et al., 2013). Al-Qallaf and Bhusan Das extensively evaluated the pattern and distribution of MNs in the patch and their influence on skin permeability and transdermal drug delivery (TDD). The study demonstrated that the skin permeability of the drug increase by reducing the aspect ratio of MNs and spacing (Al-qallaf and Das, 2009a). In addition, studies have shown TDD by low-density MN arrays is more effective than

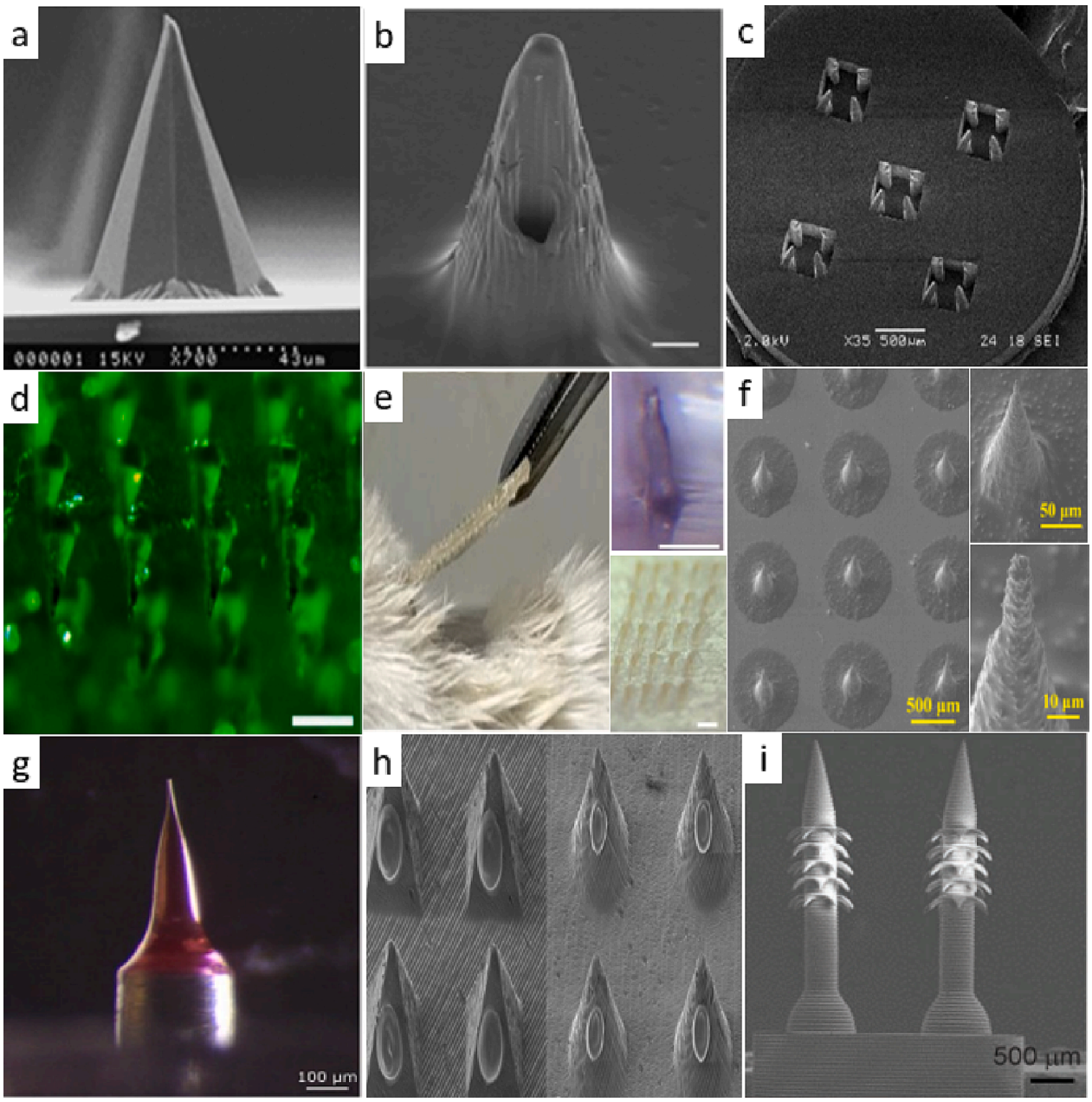


**Fig. 2.** Different materials and methods used to manufacture MNs in biomedical applications. (a) Short solid wet-etched Si MNs for delivering galantamine (GAL) (Galantamine (GAL) is used to treat cognitive decline due to Alzheimer's Disease (Wei-Ze et al., 2010).) using silicon wet etching technology. Reprinted with permission from (Wei-Ze et al., 2010). Copyright 2010, Elsevier. (b) Hollow SU-8 resin MNs. Reprinted with permission from (Jiang and Lillehoj, 2020). Reproduced under the terms of the CC-BY 4.0 license. Copyright 2020, Springer Nature. (c) An alumina-based slurry for ceramic nanoporous MN arrays. Reprinted with permission from (Boks et al., 2015). Copyright 2015, Elsevier. (d) Chinese herb MNs made from a silicone mold. Reprinted with permission from (Chi et al., 2021b). Reproduced under the terms of the CC-BY 4.0 license. Copyright 2021, Elsevier. (e) Shark tooth-inspired MN fabricated by laser engraving and elevated out-of-plane using origami design. Adapted with permission from (Guo et al., 2021). Adapted under the terms of the CC-BY 4.0 license. Copyright 2021, American Chemical Society. (f) Polyethylene terephthalate (PET) cone-shaped MNs fabricated by magnetorheological drawing lithography. Reprinted with permission from (Chen et al., 2019). Reproduced under the terms of the CC-BY 4.0 license. Copyright 2019, American Chemical Society. (g) Polymeric MN using the electro-drawn approach. Reprinted with permission from (Onesto et al., 2020). Reproduced under the terms of the CC-BY 4.0 license. Copyright 2020, Springer Nature. (h) 3D printed based-stereolithography (SLA) MNs. Reprinted with permission from (Pere et al., 2018). (i) 4D printing of bioinspired MNs. Reprinted with permission from (Han et al., 2020).

**Table 2**
Different types of polymeric MNs and associated properties (Chevala et al., 2021).

| Ability | Hollow Polymer MN | Solid Polymer MN | Surface-coated Polymer MN | Dissolvable Polymer MN | Hydrogel forming Polymer MN |
|---|---|---|---|---|---|
| **Drug loading** | high | low | high | high | high |
| **Sustained delivery** | moderate | low | high | high | high |
| **Drug molecular weight range** | high | moderate | moderate | high | moderate |

**Table 3**
Different materials, methods, and drugs used in MNs for wound healing applications.

| Material | Fabrication method | Drug | Ref. |
|---|---|---|---|
| Chitosan[4] | Silicone mold | Vascular endothelial growth factor | (Chi et al., 2020) |
| Poly (vinyl pyrrolidone) (PVP) Water soluble | Solvent – casting method | Chloramphenicol-bearing and gelatinase-sensitive gelatin NPs | (Xu et al., 2019) |
| PVP e.g., on nanospun fibre backing | Polydimethylsiloxane (PDMS) micromold | antimicrobial peptide e.g., for treating MRSA | (Su et al., 2020) |
| Poly (ethylene glycol) diacrylate (PEGDA) and 2-hydroxy-2-methylpropiophenone (HMPP) | Top-down photolithography method and a negative mold | Liquid metal-coated MNs for accelerating incisional wound healing by electric currents | (Zhang et al., 2021) |
| PEGDA | Silicone mold | Premna microphylla and Centella asiatica (herbal extracts) | (Chi et al., 2021a) |
| 3(acrylamido) phenylboronic acid-(PBA-) integrated PEGDA | Silicone mold | Adenosine-MXene | (Sun et al., 2021a) |
| Polyvinyl alcohol (PVA) | Laser and molding techniques | Porphyrin-like metal centers NPs | (Sun et al., 2021b) |
| PVP and PVA | Casting | Carvacrol -poly (caprolactone) NPs | (Mir et al., 2020) |
| Methacrylated hyaluronic acid | Molding | Zn-MOF | (Yao et al., 2021a) |
| Sodium hyaluronate and poly (vinylpyrrolidone) | Casting | Gentamicin (GEN) | (González-vázquez et al., 2017) |
| PVA | Casting | Parathyroid hormone (PTH) | (Yao et al., 2021b) |
| Manuka honey | Molding | Table honey and Manuka honey | (Frydman et al., 2020) |
| PVA backing layer and gelatin methacryloyl (GelMA) hydrogel tips | Casting | Black phosphorus-quantum dots and hemoglobin (Hb) | (Zhang et al., 2020) |

[4] Chitosan is a polysaccharide naturally occurring in the shells of crustaceans such as lobsters and crabs.

by high-density arrays (Chen et al., 2020). High-density arrays can cause the 'bed of nails' effect, whereby the skin will fold around the MNs during the insertion, affecting penetration efficiency (Ebrahiminejad et al., 2022b). Thus, simply increasing the number of MNs in the patch does not improve skin permeability (Al-qallaf and Bhusan, 2009; Nagarkar et al., 2020). The number of MNs has also been shown to affect the level of pain on insertion: a 10-fold increase in the number of MNs increased pain by over 2-fold, whereas MN tip angle, thickness, and width did not significantly affect pain level (Gill et al., 2008).

### 3.3. Radius and tip angle of MNs

Multiple studies have found that more efficient insertion is achieved when the tip radius of MNs is reduced (Al-Qallaf and Das, 2009b; Davidson et al., 2008). For example, a study showed if the tip radius is reduced from 80 to 30 μm: the force required to pierce the stratum corneum is reduced from 3.04 to 0.08 N per needle. This is related to a smaller contact area between the MN and the skin, generating a higher pressure at the tip for improved penetration (Sabri et al., 2019).

Another crucial parameter that affects skin penetration is the tip angle. Bao et al. suggest an optimal tip angle of 30° to pierce the skin easily (Bao et al., 2022). Sabri et al. found that biodegradable MNs possessing low tip angles (15−30°) and thin needle shafts of 120 μm effectively enhanced MN insertion without causing tensile failure (Sabri et al., 2019).

### 3.4. Shape of MNs

Designing a MN that satisfies all the requirements of mechanical strength and small insertion force is difficult (Ma et al., 2015), but still provides major benefits of better functionality and easier penetration. Loizidou et al. found that by increasing the number of vertices in polygon MNs, the mechanical properties were enhanced, but their ability to penetrate the skin was decreased (Loizidou et al., 2016). Hexagonal MNs could tolerate a higher level of critical buckling loads and compressive stress than square and triangular MNs, though, due to their sharper edges, the latter could penetrate the stratum corneum better than hexagonal MNs. In experiments, pyramidal MNs with triangular and square bases exhibited higher penetration depths - up to one-third of their shaft length - than those with hexagonal bases. The square shape is not recommended for shorter MNs because the maximum buckling force is low. However, for MNs longer than 1200 μm, the maximum buckling force is the same for square and circular geometries. In short, buckling force increases from triangular to square and hexagonal. Square pyramidal MNs would combine long penetration depth with mechanical strength (Loizidou et al., 2016).

In addition to simple geometric shapes such as pyramids, cones, cylinders, rounded, triangular, and hexagonal, a wide range of other MN shapes have been studied, including rocket-like, mosquito-fascicle biomimetics, arrow-like, ultra-sharp tip, obelisk, octagonal cone, bullet-shaped (Faraji Rad et al., 2021c; Kang et al., 2021; Nagarkar et al., 2020), tapered-cone, pyramid, and bevelled-tip (Shen, 2021), some of which are shown in Fig. 3. Bediz et al. showed that solid MNs with an obelisk design are more productive in enabling deeper and more reproducible insertion than pyramidal-shaped MNs (Bediz et al., 2014). Sabri et al. found that tapered/pyramidal hollow MNs gave better penetration than obelisk/straight hollow MNs (Sabri et al., 2019).

### 3.5. The pattern and angle of MN patches

The pattern of MNs in a patch and the angle can influence their penetration and functionality, as studied experimentally by Al-Qallaf et al. and mentioned above. The results show that among square, triangular, diamond, and rectangular distributions of MN, the rectangular pattern for both solid and hollow MNs brings the highest value of skin permeability (Al-qallaf and Das, 2009a). Choi et al. created biodegradable polymer MNs on a curved surface to ensure conformal contact with the exterior of blood vessels to deliver drugs to the tunica media (Fig. 4). The *ex vivo* and *in vivo* studies showed that the cuff-shaped MN patches could deliver a drug to vascular tissue (Choi et al., 2012).

### 3.6. Bio-inspired shape for MNs – bio-mimetic

Recently, MNs have been developed based on animal and insect-inspired models, including mosquito-fascicle-inspired MNs. The mosquito can penetrate human skin with a force of just 18 μN, whereas for a single MN, a minimum force of 0.058 N is needed (Park et al., 2005). This difference in force is partly attributable to the low-frequency vibration sawing action of the serrated penetrating fascicle employed by the mosquito (Fig. 5a). Honeybees pierce the skin without vibration but with excellent penetration abilities (Chen et al., 2018). Micro-structured

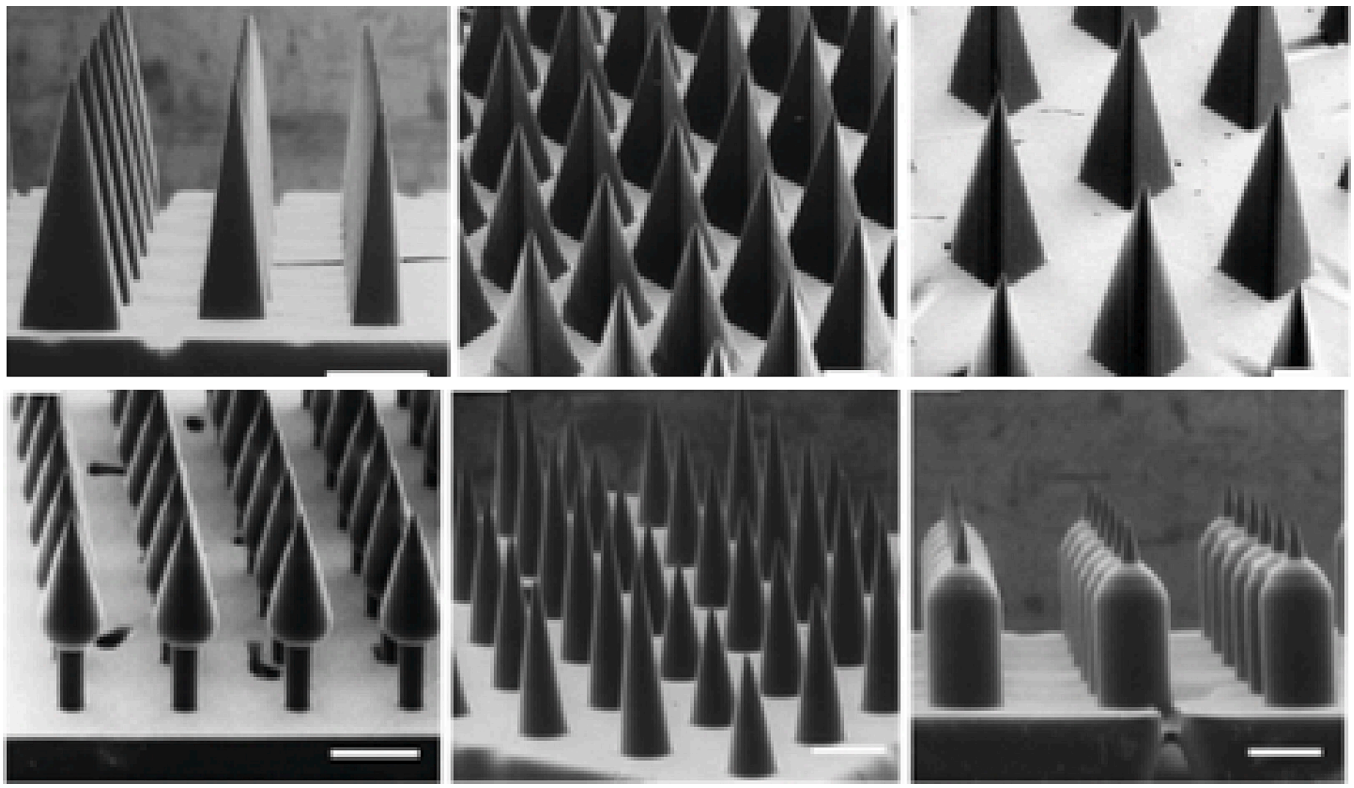

**Fig. 3.** Different geometries of MN tip (cylindrical, rectangular, pyramidal, conical, octagonal and quadrangular). Reprinted with permission from (Nagarkar et al., 2020). Copyright 2020, Elsevier.

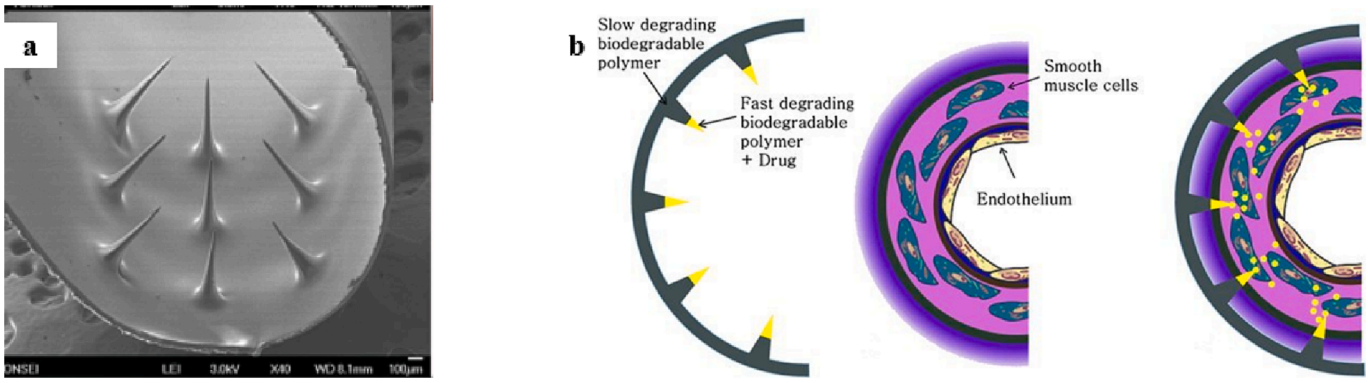


**Fig. 4.** (a) MNs with cuff shape to cover vascular tissues. (b) Schematic diagram of a MN cuff for targeted delivery to the tunica media, used in covering a blood vessel before and after installation. Reprinted with permission from (Choi et al., 2012). Copyright 2012, Wiley-VCH.

barbs on a MN can confer unique properties, like piercing the skin easily due to reducing the friction during insertion and increasing the pull-out force during retraction because of interlocking between the barb and skin tissue. A study showed that the tissue adhesion of backwards-facing barbed MNs was 18 times stronger than the barbless type (Fig. 5b) (Chen et al., 2018). Ma et al. studied bio-MN caterpillar spines (Fig. 5c) that can penetrate mouse skin by application of a force of just 173 μN with suitable mechanical properties (high hardness and elastic modulus near the tip end, therefore not fragile) (Ma et al., 2015). Zhang et al. built a MN patch with a claw-like clamping structure according to Fig. 5d-g (See also Table 3). The benefits of this geometry are fixing and tightening the wounded area to avoid secondary wound dehiscence. Furthermore, the incorporation of a gallium liquid metal alloy connected the tips of each MN part to an external power source, producing an electric field distributed around the wound. Such an electric field can directly affect cell migration, enhance cell proliferation, and thus accelerate active wound healing (Zhang et al., 2021).

The geometric shape of MNs is an important factor for effective wound healing. The amount of MNs penetration in the skin and, consequently, the release of the target drug generally depends on the overall geometry and the penetration depth in the skin. Designing an optimized geometry of MNs that meets all requirements for mechanical properties and full insertion is challenging, but the shape of the MNs is becoming more complex, sometimes inspired by animal and insect models, thus facilitating better penetration with lower applied force. Studies have shown increasing the length of MNs will result in improved penetration, though this might be at the expense of greater pain experienced by patients. A low-density MN patch avoids the 'bed of nails' effect and causes less pain, potentially eliminating it. Another strategy to enhance penetration would be to decrease the tip radius and tip angle of MNs; however, this will add to the manufacturing cost (Ebrahiminejad et al., 2022b).

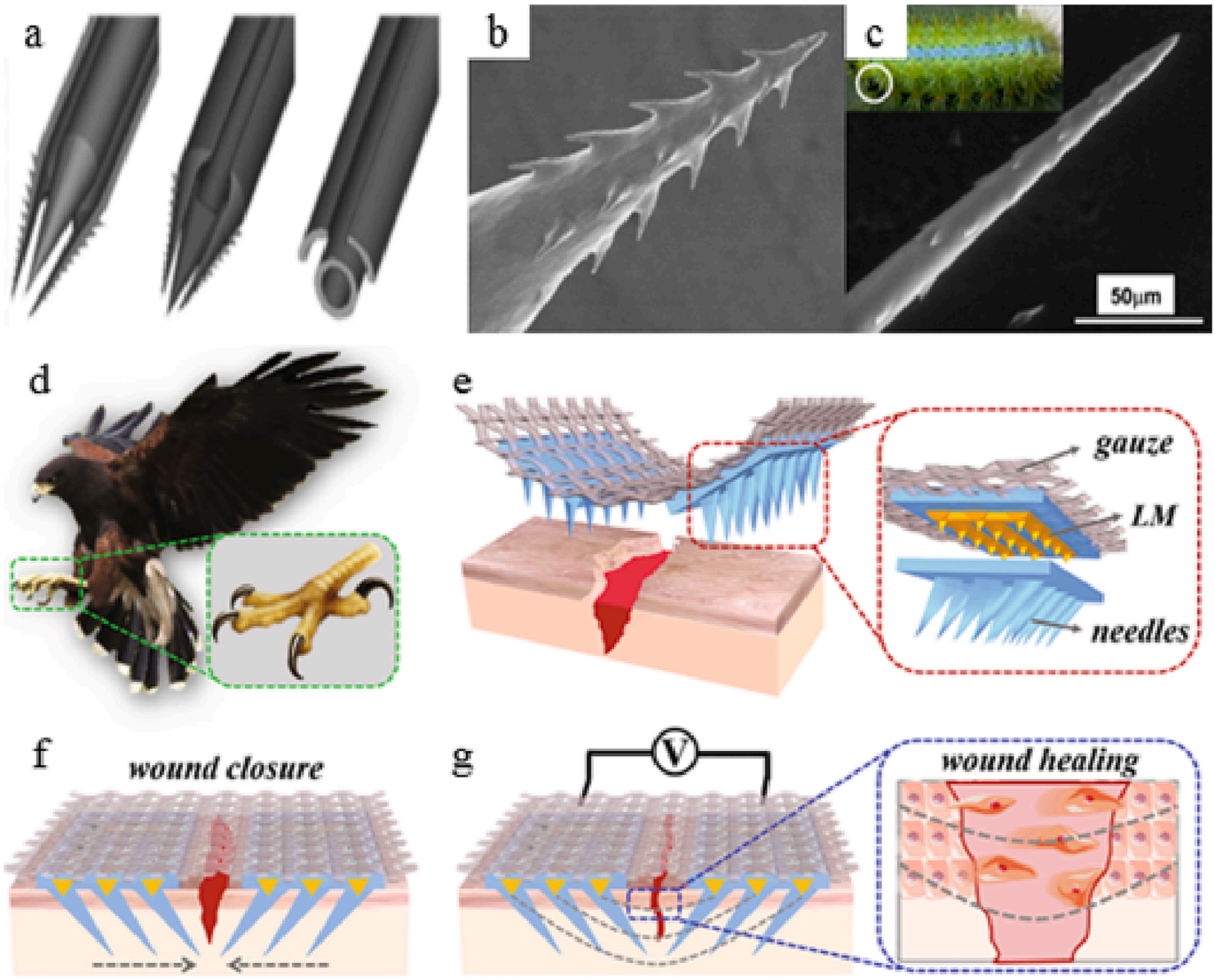


**Fig. 5.** (a) 3D images of mosquito-inspired MNs. Reprinted with permission from (Suzuki et al., 2015). Reproduced under the terms of the CC-BY 4.0 license. Copyright 2015, Fuji Technology Press. (b) SEM image of honeybee-inspired MNs with barbs. Reprinted with permission from (Chen et al., 2018). Copyright 2018, American Chemical Society. (c) SEM images of a Parasa Consocia caterpillar spine. Reprinted with permission from (Ma et al., 2015). Copyright 2011, American Society of Mechanical Engineers. (d) Schematic illustration of the eagle's claw-inspired MN. (e) The composition, structure, and wound healing application of MNs. (f) The MN patches can tighten the wounded area and lead to the closing of the wound. (g) The mechanism of wound healing is by applying the MN patch. (d-g) Adapted with permission from (Zhang et al., 2021). Copyright 2021, Elsevier.

## 4. Role of MNs in drug delivery

TDD has drawn considerable attention owing to the accessibility to the skin, as the largest organ of the human body, with an area of approximately 1.8 $m^2$ (Kahraman et al., 2019). After oral administration and injection drug delivery methods, TDD is the third-largest drug delivery system (Carthew, 2021). The TDD method could overcome many issues associated with oral drug delivery, such as eliminating the first-pass metabolism, thus avoiding harmful metabolites, increasing bioavailability and patient satisfaction (Carthew, 2021), and decreasing gastric irritation. In addition, a stable blood concentration will be provided by selecting a transdermal route for drug delivery (Van Der Maaden et al., 2012). The critical challenge in this method is the first protective layer of the skin, the stratum corneum, which acts as a barrier and has a 15–20 μm thickness. Overcoming the stratum corneum is the first step to increasing the effectiveness of drug release (Carthew, 2021; Van Der Maaden et al., 2012).

As shown in Fig. 6, three generations of TDD exist. The first generation is transdermal patches without MNs; the method is limited in the type of drug that can be delivered, relying entirely on skin permeability. The second generation uses skin permeability enhancement strategies such as chemical additives, iontophoresis, and noncavitational ultrasound to deliver the drug of interest. These techniques aim to preserve deeper tissues from physiological threats and improve the distribution of drug molecules via the skin barrier. The third generation uses chemical enhancers, electroporation, cavitational ultrasound, thermal ablation, and microdermabrasion as methods of TDD. These techniques have been shown to increase the efficacy of TDD in human clinical trials by providing better penetration into dermal layers. Some of these methods, particularly those employing radiofrequency and heat, could damage the skin and have other undesirable side effects.

The presence of high exudate and necrotic tissue in the wound bed can be a barrier to drug delivery. As a result, a considerable amount of drugs may get deactivated without penetrating the desired tissue to play their role in healing (Barnum et al., 2020; Saghazadeh et al., 2018). These challenges could be solved by applying MNs for non-invasive TDD. MNs have been shown to release drugs efficiently without stimulating nerves and using a lower drug dose (Al-japairai et al., 2020). MNs

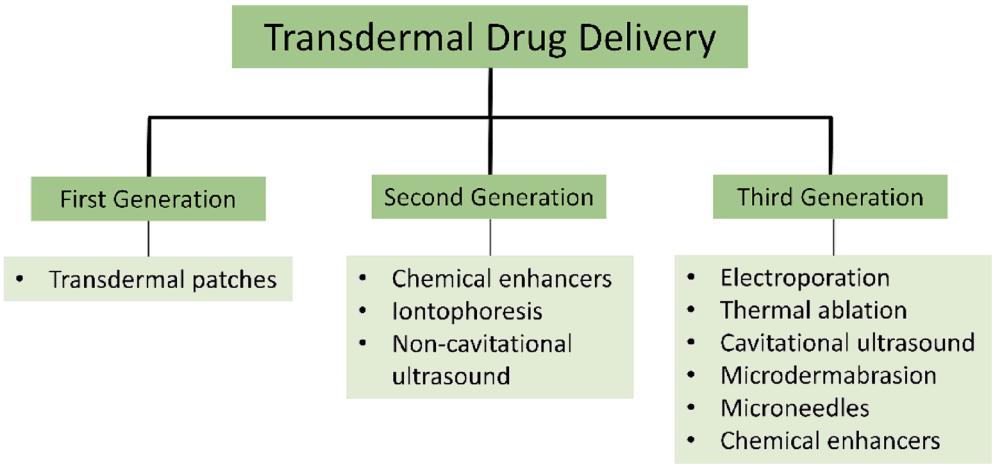


**Fig. 6.** Three generations of TDD systems (Al-japairai et al., 2020).

do not penetrate the dermis layer and cannot reach nerves, so it is a painless drug delivery method (Bariya et al., 2012). In particular, they have demonstrated outstanding results in drug delivery for wound healing; they can enhance local accessibility of the therapeutics in the wound and bypass the physiochemical barriers in a chronic wound environment, enabling drug delivery to be more targeted, thus producing faster healing (Barnum et al., 2020). Loading a wide range of therapeutic agents in MNs, ranging from low to high molecular weight, is another advantage (McAlister et al., 2021). Since MNs can be made from a wide variety of materials and are capable of releasing drugs in a controlled manner, they are very promising for the future of wound healing (Jung and Jin, 2021).

Jamaledin et al. demonstrated that among different drug delivery systems, including hand-applied topical cream, conventional topical patch with no physical skin penetration, MN patch, and hypodermic needle (Fig. 7), a patch with MNs of 100 – 1000 μm length demonstrated better skin penetration by the drug and significantly less interaction with the nerve endings in the dermis (Jamaledin et al., 2020). Waghule et al. showed that the ideal factors for effective MN application in TDD are a needle length of 150–1500 μm, tip diameter of 1–25 μm, and needle width of 50–250 μm (Waghule et al., 2019).

## 5. Role of MNs in wound healing and bacterial biofilms

More than 80 % of wounds form bacterial biofilms, a barrier to wound healing due to widening planktonic bacteria, biofilm fragments, and microcolonies of mature biofilms that lead to invasive infections. Debridement of infected wounds (the process of removing damaged

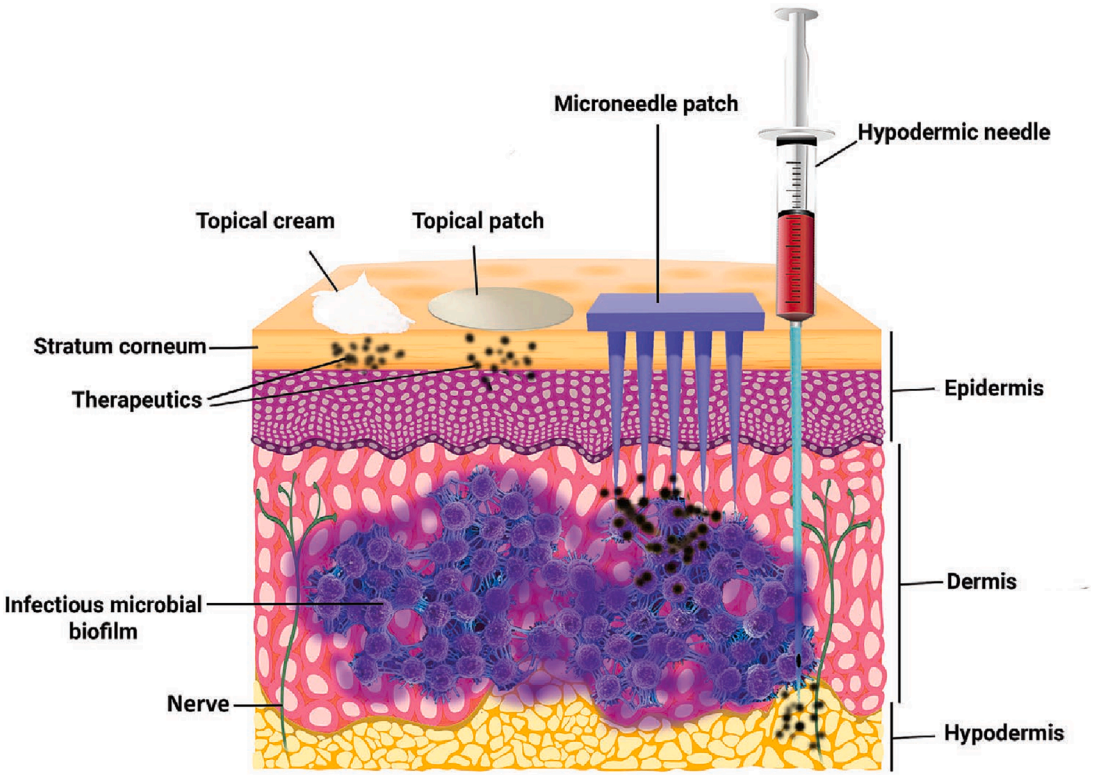


**Fig. 7.** A comparison of the skin penetration depths of different drug delivery systems. Reprinted with permission from (Jamaledin et al., 2020). Copyright 2020, Wiley-VCH.

tissue or foreign objects from a wound) can remove biofilms formed in the wound, but the biofilms reform a few days after removal. To overcome this issue, long-term antibiotic use has been considered. However, limitations like toxicity, the low availability of appropriate antibiotics, and the polymicrobial nature of biofilms, which possess 1000–fold resistance to antimicrobial agents compared to planktonic bacteria cells, constrain this method. Besides, the adhered biofilm in the wound is surrounded by extracellular polymeric substances (EPS), which act as a mechanical obstacle to the penetration and action of antimicrobial agents (Kaiser et al., 2021; Xu et al., 2019).

A MN patch could effectively eliminate bacterial biofilms by permeating them and delivering antibiotics to areas of active growth (Dian et al., 2021; Xu et al., 2019). Fig. 8 shows the life cycle of a biofilm and how MNs could control it. Dian et al. fabricated doxycycline (DOX) dissolving MNs loaded with NPs prepared from poly (lactic-co-glycolic acid) and poly (Ɛ-caprolactone) coupled with chitosan. The NPs significantly enhanced the dermatokinetic profiles of DOX, and the release of DOX was improved in the bacteria-producing biofilm up to 7–fold. Notably, the antibiofilm activity in the *ex vivo* biofilm model indicated that, after 48 hr, the bacteria decreased by up to 99.99% (Dian et al., 2020).

## 6. Combined treatments for wound healing

Factors limiting the use of MNs include local swelling due to the high concentration of subcutaneous drugs. In addition, the thickness of the outer layer of the skin differs in different people requiring different penetration depths, while hollow MNs are prone to blocking with skin tissues. For all types of MN, there is a risk of breaking its tip during insertion. Different strategies have been adopted to increase the penetration of drugs in the skin and obtain a synergetic effect on MNs (Nava-Arzaluz et al., 2011) with the potential to improve wound healing. Recent research studies resulting in combined synergetic treatments of this kind are discussed below.

### 6.1. MNs with nano- and microstructures

Nanosuspension - colloidal dispersions of nanosized drug particles stabilized by surfactants - enhances the solubility of drugs (Agrawal and Patel, 2011). It is a good method to enhance MN skin penetration and

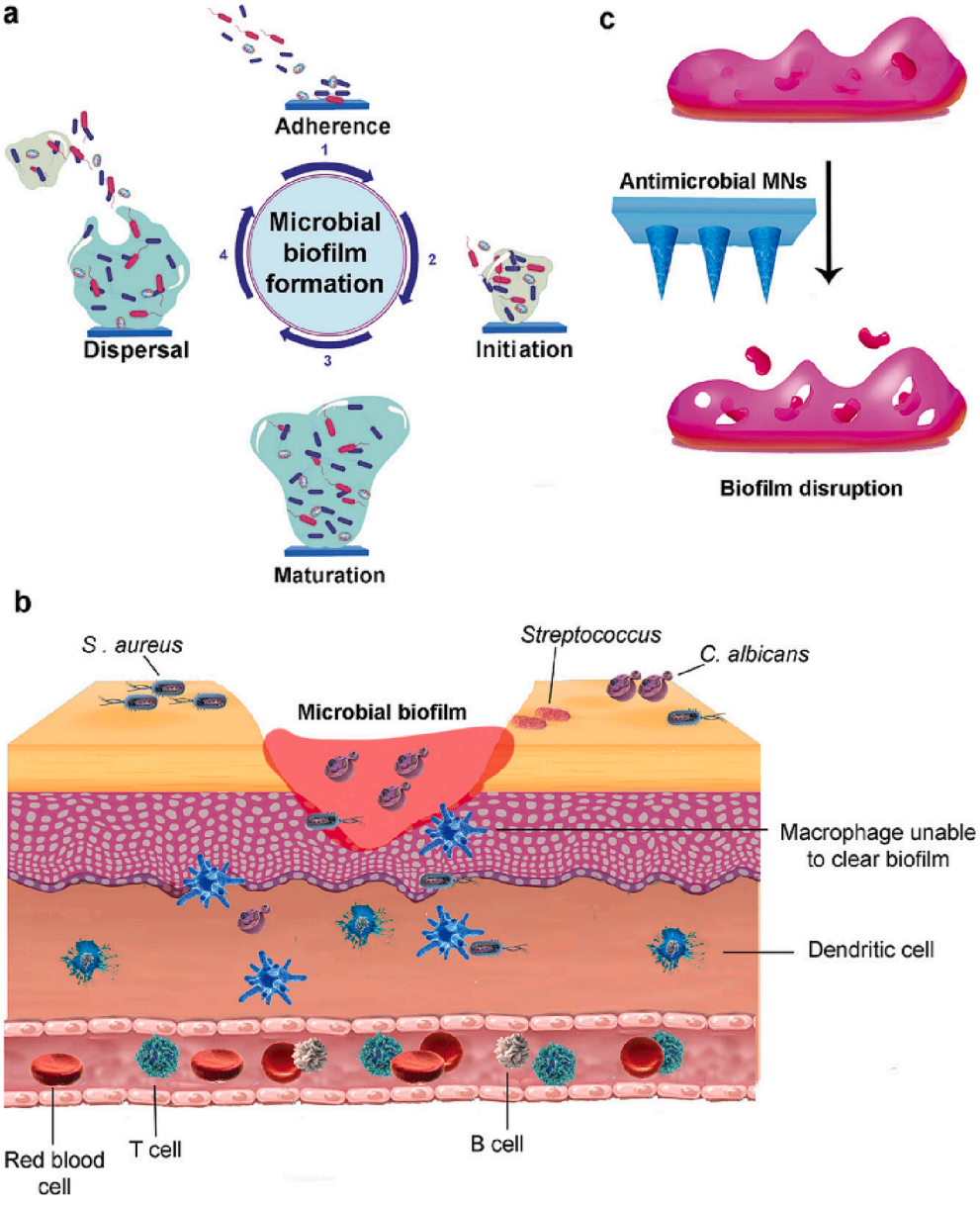


**Fig. 8.** (a) The cycle of biofilm life. 1) Sticking the planktonic (free-floating) bacteria into the surface of the skin leads to exuding extracellular polymeric substances (EPS), which dwell on the surface. 2) The generated EPS creates a three-dimensional structure and biofilm community that mature within hours. 3) Biofilms disperse by separating different sizes of clump cells or by releasing "seeding dispersal" from individual cells. (b) Polymicrobial biofilm preserves the bacteria in breached skin wound and prevents the access of systemic and topical antibiotics. (c) Inserting antimicrobial MNs in the skin pierces the microbial biofilm and releases antimicrobial cargoes. Finally, the microbial biofilm is disrupted. Reprinted with permission from (Jamaledin et al., 2020). Copyright 2020, Wiley-VCH.

reduce skin inflammation by forming nanocrystal depots within skin pores (Pireddu et al., 2020). Abdelghany et al. used PVA-based MNs loaded with curcumin nanosuspension (Abdelghany et al., 2019). The extraordinary properties of curcumin in wound healing have been proven in many studies (Abdelghany et al., 2019; Akbik et al., 2014), but its use in MNs is limited because lipophilic compounds do not dissolve in aqueous media. Hence, nanosuspension is used to ensure uniform drug distribution. This increases the particles' specific surface area and solubility rate. Combining nanosuspension and MNs increases the release of curcumin into the interstitial fluid, producing more effective wound healing. *In vitro* dissolution studies have shown that, by applying a nanosuspension of curcumin rather than its powder form, solubility in the skin increases from 16 % to 34 % after 48 hr, as shown in Fig. 9 (Abdelghany et al., 2019).

In addition to nanosuspensions, microemulsions have been employed to load various drugs onto MNs, including lipophilic compounds on a MN roller, to facilitate wound healing and repair skin barriers (Bakht et al., 2014; Mojeiko et al., 2019). Microparticles and NPs have drawn much attention due to their high specific surface area, fine particle size, and biopharmaceutical properties. NPs are more penetrating than creams and can easily pass through the skin's stratum corneum without disturbing its function. Combining these particles with MNs could produce transient transdermal aqueous channels for NP drug delivery, for example, to provide new methods to overcome antibiotic resistance, an important factor in wound healing (Mir et al., 2019). Mir et al. formulated Carvacrol (CAR), which is an effective drug against multidrug-resistant pathogens, as a NP by using poly (caprolactone) (PCL) (Mir et al., 2019). The CAR NPs were loaded into dissolving MNs. A sustained antimicrobial effect was observed in an infected wound, overcoming the necrotic tissue barrier hindering drug penetration into the wound bed. Encapsulation of CAR in PCL NPs resulted in a 2–4-fold increase in antimicrobial activity due to a significantly higher release of CAR in the presence of bacteria. Dermatokinetic studies revealed that CAR-PCL NPs-MNs were able to enhance skin retention of CAR after 24 hr (83.8 ± 5.15 %) compared to free CAR-MNs without NPs (7.3 ± 2.04 %). The MN-NP combination has overcome the problem of bacterial biofilm, which is the leading cause of the non-healing of wounds and is superior to conventional solutions.

Among other methods to improve the delivery of drugs for healing wounds using MNs, lipid-based nanovectors may overcome the difficulty that macromolecules have in crossing the stratum corneum to promote the intercellular delivery of drugs (Bellefroid et al., 2019). Among microstructures, combining micropumps with MNs could control fluid withdrawal for medical analysis and deliver a controlled drug in response to metabolite levels.

### 6.2. MNs and stem cells

Stem cells have roles in tissue regeneration and wound healing. Many stem cell therapies for healing wounds are currently under development using animal models and human studies. A lack of migration capacity limits local hypodermic injection of mesenchymal stem cells (MSCs). Lee et al. (Lee et al., 2020) report a detachable hybrid MN patch (d-HMND) for this application. A mixture of gelatin methacryloyl (GelMA) and MSCs was loaded in a poly(lactic-co-glycolic) acid shell. Next, the double-sided scotch tape was used to create d-HMND. After application to the target tissue and delivery of the stem cell, these d-HMNDs were separated. This study showed that a minimal dose of cells ($10^7$ cells/mL) was achieved through facilitating localized MSC delivery, producing elevated wound closure rates, improved re-epithelialization, and increased CD31-positive microvasculature compared to controls (as shown in Fig. 10).

Growth factors are anti-aging, biologically active molecules that could enhance wound healing. A 2012 study revealed that a conditioned medium (CM) (i.e., with added growth factors to promote cell survival/proliferation) of secretory factors of endothelial precursor cells (EPC) derived from human embryonic stem cells (hESC) accelerates wound healing and enhances the tensile strength of wounds after topical treatment and subcutaneous injection (Seo et al., 2012). Lee et al. combined MNs with hESC-EPC CM to enhance skin penetration (Lee et al., 2014). Applying these two techniques shows visually improved scars and wrinkles and stimulates collagenation (tissue replacement by collagen). El-Domyati et al. (El-Domyati et al., 2019) also combined amniotic fluid-derived mesenchymal stem cell-conditioned media (AF-MSC-CM) with microneedling to heal post-acne scars. The study applied MN and AF-MSC-CM on the right side of the face and MN alone on the left side. Improved collagen and elastic fiber density were noted, preferentially on the right side, as seen in Fig. 11, showing more effective healing of atrophic post-acne scars.

### 6.3. MNs and vesicles

Several studies have reported on using lipid vesicles for TDD. Extracellular vesicles (EVs) derived from MSCs contain many molecules,

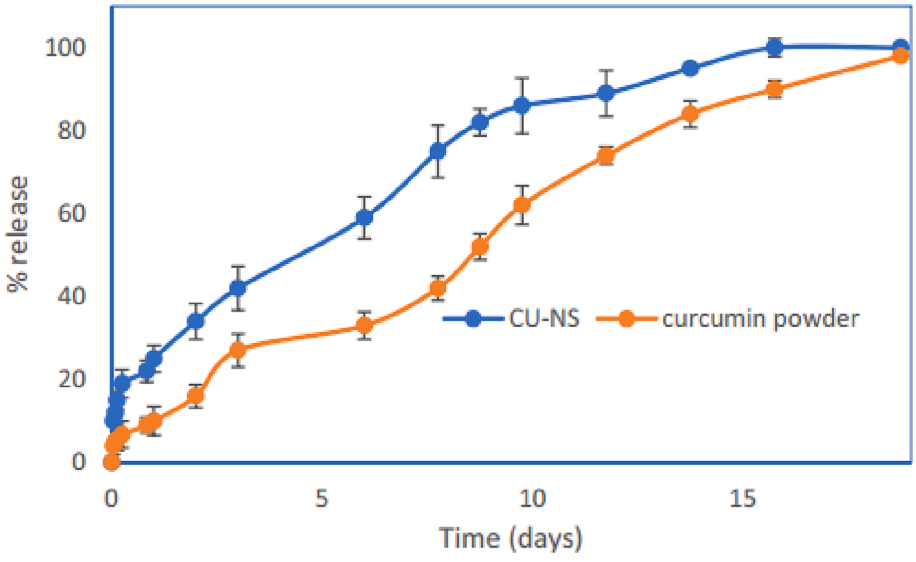


**Fig. 9.** Comparison of in vitro dissolution/release of curcumin powder and curcumin nanosuspension at 37 °C. Reprinted with permission from (Abdelghany et al., 2019). Reproduced under the terms of the CC-BY 4.0 license. Copyright 2019, MDPI.

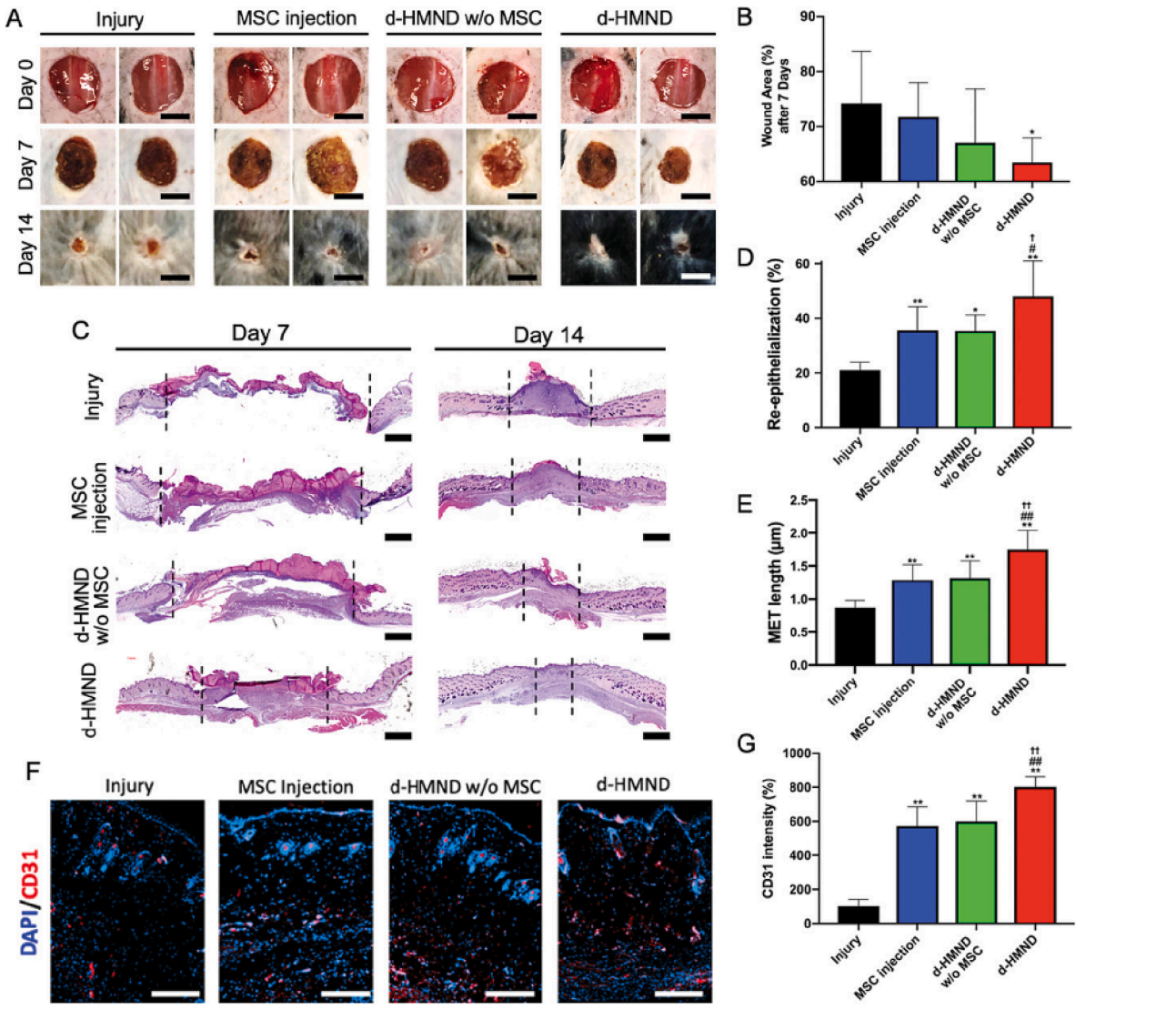


**Fig. 10.** (A) The procedure of wound healing in different groups: untreated (control), injection of MSC, d-HMND patch without MSCs, and d-HMND with MSCs (scale bars = 10 mm). (B) Wound area of each group after 7 days. (C) Histologic images of wound beds cured by mentioned methods after 7 and 14 days (scale bars = 1 mm). (D) Re-epithelialization after 14 days. (E) Migrating epidermal tongue (MET) length after 14 days. (F) immunofluorescence images of the wound edge cured by mentioned methods daily (scale bars = 200 μm). (G) Quantitative analysis of CD 31 positive area. Reprinted with permission from (Lee et al., 2020). Copyright 2020, Wiley-VCH.

such as cytokines, lncRNAs, and microRNAs, that play a role in collagen synthesis and regeneration - vital steps in wound healing (Albaugh et al., 2017). EVs cannot be absorbed directly through the skin and, if injected intravenously or subcutaneously, cause pain and uneven drug distribution. Using a MN roller with topically applied EVs provides an alternative therapy, initiating the wound-healing process and balancing the absorption of EVs. Cao et al. investigated the effect of MNs combined with adipose-derived stem cell-derived EVs (ADSCs-EVs) on skin photoaging. MN + EVs showed the highest post-treatment collagen density (62.0 % ± 9.8 %), which was higher than that of the control (54.8 % ± 12.2 %) and treatment by the MN roller alone (53.4 % ± 11.4 %). Inflammation was also lower in the MN + EV group. CD11b + cells are the earliest responsive inflammatory cells in acute inflammation and the early phase of wound healing. The CD11b + cell infiltration level was lower in the MN + EVs group than in the MN group three days after the treatment. These results indicate that MN treatment alone did not improve the epidermal structure and function of photo-aged skin, but a combination of MNs with ADSCs-EVs accelerates skin restoration after inflammation caused by the MNs and improves collagen content for better wound healing (Cao et al., 2021). Another method of transferring lipid vesicles from the stratum corneum into the skin is by utilizing vesicular systems with chemical penetration enhancers, such as niosomes (vesicles composed of nonionic surfactants), transferosomes (a type of liposomes consisting of phosphatidylcholine), ethosomes (vesicles made mainly of phospholipids, relatively high concentration of ethanol, and water), and invasomes (vesicles formed by phospholipids, ethanol, and terpenes). Combining MNs with vesicular systems can enhance TDD when applied to different skin parts (Nayak et al., 2016).

### 6.4. MNs and chemical peeling

Chemical peeling can efficiently cure scars, producing a controlled partial thickness exfoliation of the epidermis and dermis and accelerating skin restoration. Atrophic acne scarring is an indented scar that forms when the skin cannot regenerate tissue. It is a permanent complication of acne vulgaris and can significantly influence the quality of life. It mainly affects people between the ages of 11 and 30 years and is commonly caused by the destruction of collagen after inflammatory

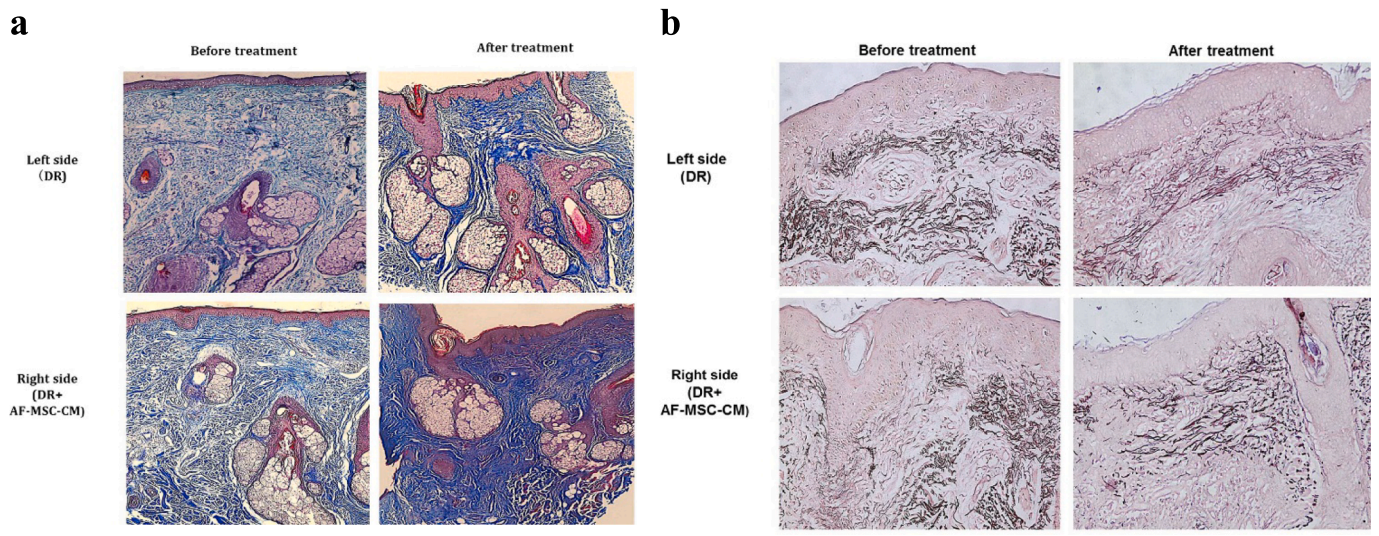


**Fig. 11.** (a) Before treatment, biopsies demonstrated irregular collagen clusters consisting of increased interfibrillary spaces on both sides. After treatment, biopsies showed more dense fine collagen fibers that have organized distribution with a darker stain and reduced interfibrillary spaces, more pronounced on the right side of the face. (b) Elastic fibers in biopsies before treatment showed unusually dense elastic tissue near the epidermis on both sides of the face. After treatment, biopsies showed newly built fine and well-distributed elastic tissue in the dermis, especially on the right side of the face. Reprinted with permission from (El-Domyati et al., 2019). Copyright 2019, Wiley-VCH.

acne, chickenpox, and staphylococcus infection (Gozali et al., 2015). Ali et al. combined the technique of MN and Jessner's solution for peeling (using a mixture of 14 % resorcinol, 14 % salicylic acid, 14 % lactic acid, and ethanol) for curing atrophic acne scars, and the results showed better clinical improvement compared with conventional topical treatments (Ali et al., 2019). Another study found that by combining 35 % glycolic acid peel and microneedling (Dermaroller MF8) the scars were improved compared to microneedling or chemical peel alone with a reduction of superficial acne scars and post-inflammatory pigmentation. The mean improvement in scars increased from 31.33 to 62 % using glycolic acid peel (Sharad, 2011).

### 6.5. MNs and platelet-rich plasma

Autologous platelet-rich plasma (PRP) has a higher-than-normal concentration of platelets, which can enhance wound healing. Applying autologous platelet-rich plasma to surgical wounds has accelerated tissue repair and reduced postoperative pain. A combination of MN with PRP improves the atrophic scars of different etiologies. Combining skin microneedling and platelet-rich plasma is more efficacious and safer, with fewer sessions, in all types of atrophic scars (Mohamed and Mahmoud, 2017). Asif et al. investigated the effect of combining microneedling with PRP on the right half of the face with atrophic acne scars, while the left half of the face was treated with intradermal administration of distilled water (Asif et al., 2016). The right and left halves showed 62.20 % and 45.84 % progress, respectively, showing the benefits of combining microneedling with PRP to manage atrophic acne scars. Other benefits of these combined methods are excellent improvement of the skin lesions striae distensae (stretch marks), formation of denser collagen and elastic fibers, improvement in proliferative activity in the epidermis, and reduced expression of caspase-3 protein, which is involved in the apoptosis of various cell types in the epidermis (Abdel-motaleb et al., 2020; Akasaka et al., 2000).

### 6.6. MNs and photodynamic therapy

Photodynamic therapy (PDT) is highly effective in treating superficial lesions such as thin actinic keratoses (AKs), Bowen's disease, and superficial basal cell carcinomas. In treating chronic wounds, the delivery of photosensitizing agents often has limitations and low efficacy due to the thick hyperkeratotic/necrotic tissue layer and the polymicrobial nature of infected wounds. MNs could penetrate the outer layers of the skin and overcome the layers of dead cells. Delivering photosensitizing drugs using this platform has advantages compared to conventional photodynamic therapy, such as improved delivery efficiency and reduced erythema and pain. Microneedling-assisted PDT is a safe and effective method and can achieve better cosmetic results than traditional methods for improving photodamaged skin, eradicating biofilm forms of the common wound pathogens tested and decreasing healing time (Torezan et al., 2013).

### 6.7. MNs and sonophoresis

Sonophoresis involves the application of ultrasound, which causes disarray of a lipid bilayer, induces a change in the lipid arrangement of the stratum corneum, forms cavitation, and thus enhances the transport of drugs through the skin. Drug permeation can be controlled by controlling the frequency of the ultrasound. Increasing the frequency from 20 kHz to 1 MHz causes a 1000-fold increase in skin disturbance. By combining sonophoresis with MNs, a synergetic effect on the permeation of molecules through the skin can be achieved (Nayak et al., 2016). Yoon et al. found that combining microneedling and sonophoresis gave an approximately 2.3-fold higher glycerol transdermal diffusion rate than the microneedling method alone (Yoon et al., 2010). Petchsangsai et al. showed that by combining electroporation, sonophoresis, and MNs, the transdermal permeation of fluorescein isothiocyanate-dextran (FD-4) dye through in vitro porcine skin increased significantly compared with the individual methods, without any significant skin damage. The permeation amount for FD-4 across porcine skin in MNs, MNs + sonophoresis, MNs + electroporation, and MNs + electroporation + sonophoresis was around 50, 100, 175, and 325 μg/cm$^2$, respectively (Petchsangsai et al., 2014).

Combined MN and sonophoresis tackle disfiguring pathological human keloid scars by enhanced drug penetration. Traditional treatments, such as bolus injection of drugs or surgery, are invasive and require an in-person visit to the clinic. Combining sonophoresis with MNs considerably improves drug permeation in scar tissues compared to that achieved without sonophoresis (Yang et al., 2021b).

### 6.8. MNs and iontophoresis

The transdermal iontophoresis technique generally involves applying a physiologically reasonable low electric current density (<0.5 $mA/cm^2$) to the skin (Pandey et al., 2019). It works based on "like repels like" to advance charged transfer and polar substances through the skin's stratum corneum. The obstacle disruption thus caused by employing iontophoresis in combination with MNs increases the possibility of several drugs, such as macromolecules, that can be administered transdermally and effectively regulated by applying different current intensities for the treatment of wounds (Yang et al., 2021a). Among the few studies reported on the iontophoresis/MN combination, Vemulapalli et al. determined the technique for *in vivo* delivery of salmon calcitonin (SCT). They found that the serum concentration of SCT was higher using MN and iontophoresis combined compared to MNs alone (Vemulapalli et al., 2012). Another study confirmed these results and reported approximately 99 % skin penetration rate, minor cytotoxicity, and good biocompatibility without skin irritation and hypersensitivity (Li et al., 2020).

Ronnander et al. combined iontophoresis and dissolving polymeric MN arrays of sumatriptan (used to treat migraines), polyvinylpyrrolidone, glycerine, and polysorbate (Ronnander et al., 2019). Iontophoresis improved the performance of dissolving MNs and increased the permeation rate of the drug molecules across the skin using a small electrical current ranging from 100 to 500 $\mu A/cm^2$ during a 6-hr period. An optical examination of skin samples treated with a pH indicator dye (nitrazine yellow, 0.01 % w/w) demonstrated that the needles penetrated and entirely dissolved in the skin, as shown by a distinct blue pattern, which was darker and more pronounced in samples treated with iontophoresis, especially at the higher current density (500 $\mu A/cm^2$). Iontophoresis studies with MNs conducted with Gottingen minipig skins (Fig. 12) demonstrated a notable flux increase relative to passive diffusion.

### 6.9. MNs and electroporation

Electroporation is a new and highly efficient method with low cost, versatility, and biochemical and biological non-toxicity to deliver molecules into cells or tissues for clinical applications like wound healing. Electroporation by applying short electrical pulses (generally 50–1000 V/cm) of milliseconds duration leads to the rearrangement of lipid bilayer structures resulting in the formation of aqueous pathways for molecules across the stratum corneum. This process helps deliver large hydrophilic drug species like molecules, proteins, peptides, and oligonucleotides, including biopharmaceuticals with molecular weights up to several kDa. Electroporation assisted by the MN roller showed significant advantages, providing an electrical driving force to enhance drug delivery through the lipid bilayer pathways (Huang et al., 2018).

Hooper et al. used a MN array with electroporation to administer a DNA vaccine (Hooper et al., 2007). The plasmid DNA was dried onto the

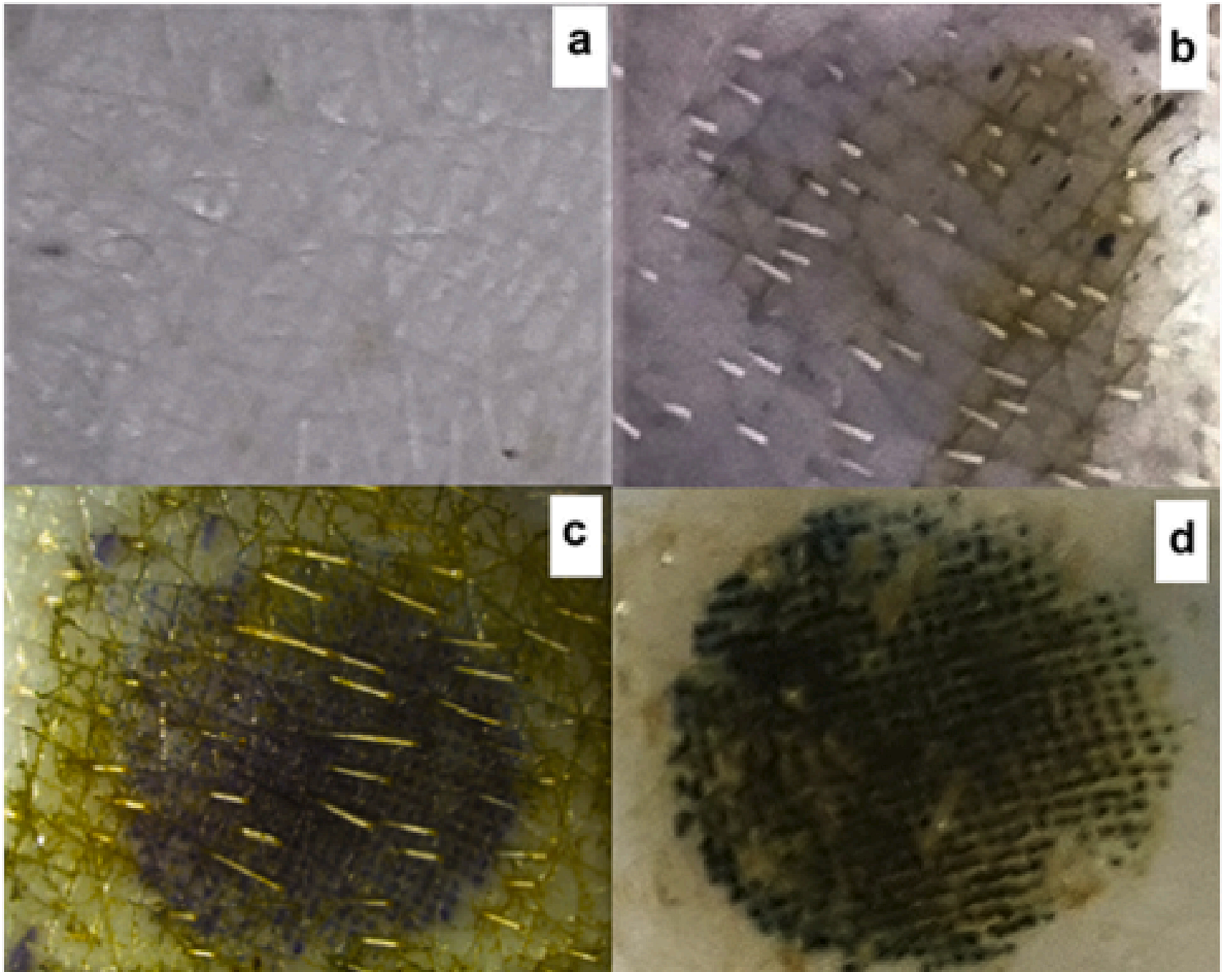


**Fig. 12.** Images of minipig tissue samples stained with nitrazine yellow indicator (blue dye) after diffusion experiments in four groups. (a) A blank minipig tissue sample (no dye). (b) Minipig skin using MN array control sample (inverted). (c) Minipig skin treated with MN array; (d) Minipig skin treated with MN array and iontophoresis. Reprinted with permission from (Ronnander et al., 2019). Copyright 2019, Elsevier. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tips of MNs, and then inserted *in vivo* into the skin of mouse models. The DNA dissolved and was transferred into the cells by applying electroporation. The mice produced higher levels of IgG1 than those vaccinated by scarification, with similar levels of IgG1 and IgG2. These findings indicate that vaccination using dry DNA, which is a preferred stable state, is possible by combining MNs with electroporation. The amount of DNA required per vaccine is lower than conventional injected DNA vaccines, with less pain. Huang et al. found that the electroporation method combined with MNs created a spatially uniform electric field both on the surface and inside the skin using a low voltage (50 V), and successful gene (RFP) expression and siRNA transfection were achieved compared to results without MNs for treatment of skin diseases or vaccination (Huang et al., 2018).

### 6.10. MNs and ultrasound

Large molecules such as vaccines, proteins, and microparticles have low transfer efficiency through the skin. To overcome this drawback, combined MNs and ultrasound have shown great potential. Han et al. improved the rate of penetration of bovine serum albumin in porcine ear skin to 1 μm/s with the combination of a MN patch and ultrasound - about ten times higher penetration than the permeability obtained in passive diffusion (Han and Das, 2013).

### 6.11. MNs and electrospinning

Electrospinning is another technique for improving the functionality of MNs. Su et al. fabricated Janus-type antimicrobial wound dressings for human skin, including diabetic wounds, as shown in Fig. 13a (Su et al., 2020). The dressing consists of F127/W379-PCL core–shell electrospun nanofiber coupled with dissolvable polydimethylsiloxane (PDMS) with PVP and W379 antimicrobial peptide MN arrays, which delivered database-designed antimicrobial peptide effectively to both inside and outside of biofilms. MN and electrospinning created a wound dressing with a two-sided/biphasic structure. Each side achieves different tasks: the immobilized MN arrays affected the penetration of the biofilms delivering peptides to disrupt them from the inside, while, simultaneously, the nanofiber membranes provided sustained release of peptides to attack their outside. The coupled actions of an antibiofilm Janus-type dressing may contribute to the removal of biofilms and finally inhibit the resurgence of bacteria. In addition, electrospun nanofiber membranes could serve as a physical barrier between the wound bed and the surrounding environment. The nanofiber membranes could also serve as a scaffold for promoting wound healing after the eradication of the biofilms (Juster et al., 2019). Another benefit of electrospinning fibers is the easy separation of MN into the skin. Yang et al. built dissolving MNs on an electrospun pillar array. By tensile breakage of an electrospun fibrous backing sheet, the dissolving MNs were separated from the pillar array, leaving them inserted in the skin. (Fig. 13b, c) (Yang et al., 2015). Su et al. combined nanofiber mats and MN arrays to effectively deliver multiple antimicrobial agents for treating bacterial biofilms in wounds. Multiple antimicrobial agents, including $AgNO_3$, Ga $(NO_3)_3$, and vancomycin, were incorporated into nanofiber mats by coaxial electrospinning, which enables sustained delivery of these drugs to biofilms when incorporated in dissolvable MN arrays. The results showed that combining these strategies can eradicate methicillin-resistant staphylococcus aureus (MRSA) and MRSA/pseudomonas aeruginosa blend biofilms in *an ex vivo* human skin wound infection model without necessitating surgical debridement (Su et al., 2021).

Many other enhancing technologies could be combined with MNs to improve wound healing, including retinoid therapy[1] (Hiraishi et al., 2013), light-emitting diodes (LEDs), dermaportation[2] (Namjoshi et al., 2008), vitamins, vibratory actuation (Nayak et al., 2016), and proteins (Yao et al., 2021b). Many might be combined in triple combinations (Nava-Arzaluz et al., 2011). Few studies have been performed employing such strategies, and more work is required to explore their considerable potential for the demanding applications of wound healing.

## 7. Conclusion and future perspectives

Chronic wounds are a growing concern in healthcare worldwide; they can be painful, impose financial burdens, and significantly decrease patients' quality of life. They include different types of damage, like diabetic foot ulcers, venous ulcers, pressure ulcers, and burn injuries. Urgent treatments are needed to tackle this significant health challenge. There are different ways to deliver therapeutic drugs to the wound bed, such as parenteral, inhalation, oral, and transdermal (Aldawood et al., 2021). The delivery of therapeutic drugs through the skin can tackle many problems associated with using other conventional methods, such as gastric irritation, first-pass metabolism, pain, and dose efficacy challenges. Among these methods, TDD using MNs would be a promising alternative (Carthew, 2021).

This review has discussed recent advances in using MNs in wound healing, including various physical and chemical processes and their functions. MNs have good drug loading capacity with the ability to deliver drugs to most tissues and organs, the capacity for loading a wide range of pharmacologic cargoes, extending to growth factors from fibroblasts, proteins, blood platelets, genes, vaccines, drug molecules, and antibodies with minimum pain (Ganeson et al., 2023), plus the capacity for collagen synthesis and the ability to disrupt biofilm; all with low tissue damage. Besides, the ability to use different materials and geometries increases the efficiency of MNs. Moreover, this technology can be personalized according to each patient's skin features and the drug used. It can be a self-administered method where no expertise is needed. The tiny MNs are clearly a potentially valuable future medical tool.

Despite the rapidly emerging and clear benefits of MNs, there are inevitably some limitations, such as the complexity of device design, varying penetration due to different types of human skin, fouling or blocking of hollow MN types, local swelling because of the high concentration of the subcutaneous drugs, skin sensitivity and risk of MN tip breakage during insertion. Nevertheless, using physical and chemical auxiliary methods with MNs could provide new medical technologies with a significant widespread impact on wound healing and scar reduction.

The potential market size of MN drug delivery systems is so large that economies of scale will significantly lower the cost of MNs, provided there is industrialization of processes for producing them. Since the MN field is relatively young, more study is needed to realize optimized properties and therapeutic methods. MNs cannot cure all types of wounds because of the complexity of the wound microenvironment (Mo et al., 2023), the need for skin grafting, and the presence of necrotic tissue or severe infection in the bone. MNs may not have enough drug capacity to overcome the worst infections, but they can be an inexpensive tool in routine wound management, considerably accelerating the healing process. In conclusion, there are clear indications that MNs have the potential to play a vital role in the future of wound healing.

## 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.

[1] Retinoids, derived from vitamin A, are *inter alia* used to regulate the growth of epithelial cells.

[2] Dermaportation uses magnetic field technology to enhance delivery of molecules through the skin (Namjoshi et al., 2008).

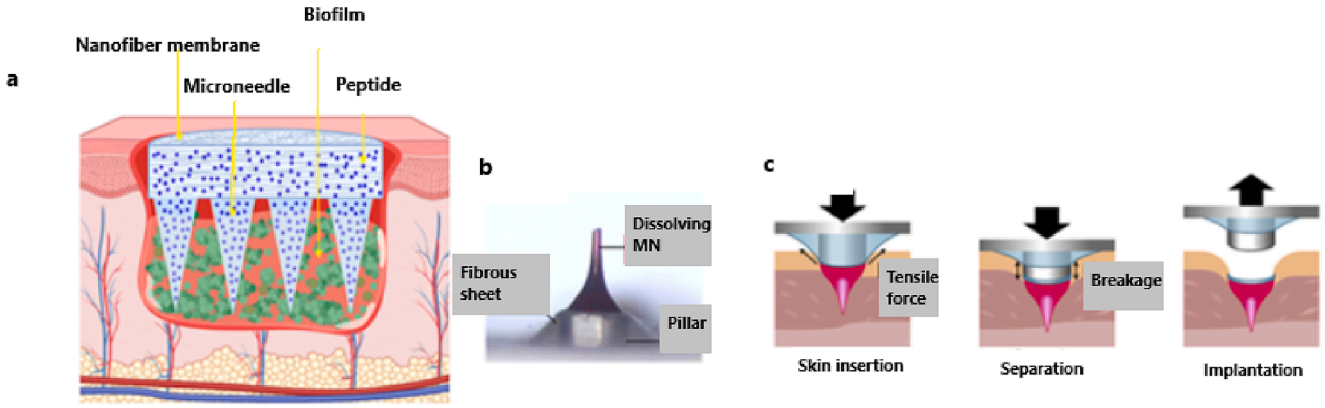


**Fig. 13.** (a) Schematic image of Janus-type wound dressing to treat biofilm in chronic wounds by loading peptide in nanofiber electrospinning membrane and MN patch. Reprinted with permission from (Su et al., 2020). Copyright 2020, American Chemical Society. (b) Schematic image of dissolving MNs on a fibrous sheet electrospun pillar array. (c) Implantation of a dissolving MN on an electrospun pillar array in the skin has three stages; insertion on the skin, separation of the fibrous sheet due to the tensile force, and implantation, where dissolving MNs are released into the skin. Reprinted with permission from (Yang et al., 2015). Copyright 2015, Elsevier.

## Data availability

Data will be made available on request.

## References


Abdelghany, S., Tekko, I.A., Vora, L., Larrañeta, E., Permana, A.D., Donnelly, R.F., 2019. Nanosuspension-based dissolving microneedle arrays for intradermal delivery of curcumin. Pharmaceutics 11. https://doi.org/10.3390/pharmaceutics11070308.

Abdel-motaleb, A.A., Zedan, H., Allah, M., Mostafa, M., Abu-dief, E.E., Gebril, S.M., Hussein, M., 2020. Ac ce pt e d us cr t. J. Dermatol. Treat. 000. https://doi.org/10.1080/09546634.2020.1782323.

Abe, Y., Takizawa, R., Kimura, N., Konno, H., Yoshida, S., Nishizawa, M., 2021. Porous microneedle-based wearable device for monitoring of transepidermal potential. Biomed. Eng. Adv. 1, 100004 https://doi.org/10.1016/j.bea.2021.100004.

Agrawal, Y., Patel, V., 2011. Nanosuspension: an approach to enhance solubility of drugs. J. Adv. Pharm. Technol. Res. 2 https://doi.org/10.4103/2231-4040.82950.

Ahmad, N.N., Nazri, N., Ghazali, N., Wong, Y.H., 2021. Concept design of transdermal microneedles for diagnosis and drug delivery: a review 2100503, 1–22. https://doi.org/10.1002/adem.202100503.

Akasaka, Y., Ishikawa, Y., Ichiro, O., Fujita, K., Masuda, T., Asuwa, N., Inuzuka, K., Kiguchi, H., Ishii, T., 2000. Enhanced expression of caspase-3 in hypertrophic scars and keloid: induction of caspase-3 and apoptosis in keloid fibroblasts in vitro. Lab. Invest. 80 https://doi.org/10.1038/labinvest.3780039.

Akbik, D., Ghadiri, M., Chrzanowski, W., Rohanizadeh, R., 2014. Curcumin as a wound healing agent. Life Sci. https://doi.org/10.1016/j.lfs.2014.08.016.

Albaugh, V.L., Mukherjee, K., Barbul, A., 2017. Proline precursors and collagen synthesis: biochemical challenges of nutrient supplementation and wound healing. https://doi.org/10.3945/jn.117.256404.The.

Aldawood, F.K., Andar, A., Desai, S., 2021. A comprehensive review of microneedles: types, materials, processes, characterizations and applications. Polymers (Basel) 13, 2815. https://doi.org/10.3390/polym13162815.

Ali, B., Elmahdy, N., Elfar, N.N., 2019. Microneedling (Dermapen) and Jessner ' s solution peeling in treatment of atrophic acne scars : a comparative randomized clinical study. J. Cosmet. Laser Ther. 00, 1–7. https://doi.org/10.1080/14764172.2019.1661490.

Al-japairai, K.A.S., Mahmood, S., Almurisi, S.H., Reddy, J., Rebhi, A., Azmana, M., Raman, S., 2020. Current trends in polymer microneedle for transdermal drug delivery. Int. J. Pharm. 587, 119673 https://doi.org/10.1016/j.ijpharm.2020.119673.

Al-qallaf, B., Bhusan, D., 2009. Optimizing microneedle arrays to increase skin permeability for transdermal. Drug Deliv. 94, 83–94. https://doi.org/10.1111/j.1749-6632.2009.04083.x.

Al-qallaf, B., Das, D.B., 2009a. Optimizing microneedle arrays for transdermal drug delivery: extension to non-square distribution of microneedles 17, 108–122. https://doi.org/10.1080/10611860802472370.

Al-Qallaf, B., Das, D.B., 2009b. Optimizing microneedle arrays to increase skin permeability for transdermal drug delivery. Ann. N. Y. Acad. Sci. 1161 https://doi.org/10.1111/j.1749-6632.2009.04083.x.

Asif, M., Kanodia, S., Singh, K., 2016. Combined autologous platelet-rich plasma with microneedling verses microneedling with distilled water in the treatment of atrophic acne scars: a concurrent split-face study. J. Cosmet. Dermatol. 15 https://doi.org/10.1111/jocd.12207.

Azmana, M., Mahmood, S., Hilles, A.R., Mandal, U.K., 2020. Transdermal drug delivery system through polymeric microneedle: a recent update. J. Drug Deliv. Sci. Technol. 101877 https://doi.org/10.1016/j.jddst.2020.101877.

Bagheri, B., Surwase, S.S., Lee, S.S., Park, H., Faraji Rad, Z., Trevaskis, N.L., Kim, Y.-C., 2022. Carbon-based nanostructures for cancer therapy and drug delivery applications. J. Mater. Chem. B. https://doi.org/10.1039/D2TB01741E.

Bakht, M.A., Alajmi, M.F., Alam, P., Alam, A., Alam, P., Aljarba, T.M., 2014. Theoretical and experimental study on lipophilicity and wound healing activity of ginger compounds. Asian Pac. J. Trop. Biomed. 4 https://doi.org/10.12980/APJTB.4.2014C1012.

Bao, L., Park, J., Bonfante, G., Kim, B., 2022. Recent advances in porous microneedles: materials, fabrication, and transdermal applications. Drug Deliv. Transl. Res. 12 https://doi.org/10.1007/s13346-021-01045-x.

Bariya, S.H., Gohel, M.C., Mehta, T.A., Sharma, O.P., 2012. Microneedles: an emerging transdermal drug delivery system. J. Pharm. Pharmacol. 64 https://doi.org/10.1111/j.2042-7158.2011.01369.x.

Barnum, L., Samandari, M., Schmidt, T.A., Tamayol, A., 2020. Microneedle arrays for the treatment of chronic wounds. Expert Opin. Drug Deliv. 17 https://doi.org/10.1080/17425247.2020.1819787.

Bediz, B., Korkmaz, E., Khilwani, R., Donahue, C., Erdos, G., Falo, L.D., Ozdoganlar, O.B., 2014. Dissolvable microneedle arrays for intradermal delivery of biologics: fabrication and application. Pharm Res. 31 https://doi.org/10.1007/s11095-013-1137-x.

Bellefroid, C., Lechanteur, A., Evrard, B., Mottet, D., Piel, G., 2019. In vitro skin penetration enhancement techniques: a combined approach of ethosomes and microneedles. Int. J. Pharm. 118793 https://doi.org/10.1016/j.ijpharm.2019.118793.

Boks, M.A., Unger, W.W.J., Engels, S., Ambrosini, M., van Kooyk, Y., Luttge, R., 2015. Controlled release of a model vaccine by nanoporous ceramic microneedle arrays. Int. J. Pharm. 491 https://doi.org/10.1016/j.ijpharm.2015.06.025.

Cañedo-Dorantes, L., Cañedo-Ayala, M., 2019. Skin acute wound healing: a comprehensive review. Int. J. Inflam. https://doi.org/10.1155/2019/3706315.

Cao, Z., He, Q., Wang, X., 2021. Microneedle based adipose derived stem cells-derived extracellular vesicles therapy ameliorates UV-induced photoaging in SKH-1 mice 1–9. 10.1002/jbm.a.37177.

Carthew, R.W., 2021. Gene regulation and cellular metabolism: an essential partnership. Trends Genet. https://doi.org/10.1016/j.tig.2020.09.018.

Chen, Z., Lin, Y., Lee, W., Ren, L., Liu, B., Liang, L., Wang, Z., Jiang, L., 2018. Additive manufacturing of honeybee-inspired microneedle for easy skin insertion and difficult removal. ACS Appl. Mater. Interfaces 10. https://doi.org/10.1021/acsami.8b09563.

Chen, S., Wu, D., Liu, Y., Huang, Y., Xu, H., Gao, W., Zhang, J., Sun, J., Zhuang, J., 2020. Optimal scaling analysis of polymeric microneedle length and its effect on transdermal insulin delivery. J. Drug Deliv. Sci. Technol. 101547 https://doi.org/10.1016/j.jddst.2020.101547.

Chen, Z., Ye, R., Yang, J., Lin, Y., Lee, W., Li, J., Ren, L., Liu, B., Jiang, L., 2019. Rapidly fabricated microneedle arrays using magnetorheological drawing lithography for transdermal drug delivery. ACS Biomater. Sci. Eng. 5 https://doi.org/10.1021/acsbiomaterials.9b00919.

Chevala, N.T., Jitta, S.R., Marques, S.M., Vaz, V.M., Kumar, L., 2021. Journal of Drug Delivery Science and Technology Polymeric microneedles for transdermal delivery of nanoparticles: frontiers of formulation, sterility and stability aspects. J. Drug Deliv. Sci. Technol. 65, 102711 https://doi.org/10.1016/j.jddst.2021.102711.

Chi, J., Zhang, X., Chen, C., Shao, C., Zhao, Y., Wang, Y., 2020. Bioactive Materials Antibacterial and angiogenic chitosan microneedle array patch for promoting wound healing. Bioact. Mater. 5, 253–259. https://doi.org/10.1016/j.bioactmat.2020.02.004.

Chi, J., Sun, L., Cai, L., Fan, L., Shao, C., Shang, L., 2021a. Chinese herb microneedle patch for wound healing. Bioact. Mater. 6, 3507–3514.

Chi, J., Sun, L., Cai, L., Fan, L., Shao, C., Shang, L., Zhao, Y., 2021b. Chinese herb microneedle patch for wound healing. Bioact. Mater. 6 https://doi.org/10.1016/j.bioactmat.2021.03.023.

Choi, C.K., Kim, J.B., Jang, E.H., Youn, Y., Ryu, W.H., 2012. Curved biodegradable microneedles for vascular drug delivery 1–6. 10.1002/smll.201200441.
Davidson, A., Al-Qallaf, B., Das, D.B., 2008. Transdermal drug delivery by coated microneedles: geometry effects on effective skin thickness and drug permeability. Chem. Eng. Res. Des. 86 https://doi.org/10.1016/j.cherd.2008.06.002.
Dian, A., Mir, M., Utomo, E., Donnelly, R.F., 2020. International Journal of Pharmaceutics: X Bacterially sensitive nanoparticle-based dissolving microneedles of doxycycline for enhanced treatment of bacterial bio fi lm skin infection: a proof of concept study. Int. J. Pharm. X 2, 100047. https://doi.org/10.1016/j.ijpx.2020.100047.
Dian, A., Kurnia, Q., Utomo, E., Volpe-zanutto, F., Paredes, A.J., Mulsiani, Y., Aulia, S., Rezky, M., Nurfadilah, I., Donnelly, R.F., 2021. Materials Science & Engineering C Selective delivery of silver nanoparticles for improved treatment of biofilm skin infection using bacteria-responsive microparticles loaded into dissolving microneedles. Mater. Sci. Eng. C 120, 111786. https://doi.org/10.1016/j.msec.2020.111786.
Ebrahiminejad, V., Faraji Rad, Z., 2022. Design, development, and testing of polymeric microblades: a novel design of microneedles for biomedical applications. Adv. Mater. Interfaces 9, 2201115. https://doi.org/10.1002/admi.202201115.
Ebrahiminejad, V., Faraji Rad, Z., Prewett, P.D., Davies, G.J., 2022a. Fabrication and testing of polymer microneedles for transdermal drug delivery. Beilstein J. Nanotechnol. 13, 629–640. https://doi.org/10.3762/bjnano.13.55.
Ebrahiminejad, V., Prewett, P.D., Davies, G.J., Faraji Rad, Z., 2022b. Microneedle arrays for drug delivery and diagnostics: toward an optimized design, reliable insertion, and penetration. Adv. Mater. Interfaces 9, 2101856. https://doi.org/10.1002/admi.202101856.
El-Domyati, M., Moftah, N.H., Nasif, G.A., Ragaie, M.H., Ibrahim, M.R., Ameen, S.W., 2019. Amniotic fluid-derived mesenchymal stem cell products combined with microneedling for acne scars: a split-face clinical, histological, and histometric study. J. Cosmet. Dermatol. 18 https://doi.org/10.1111/jocd.13039.
Faraji Rad, Z., 2023. Microneedle technologies for food and crop health: recent advances and future perspectives. Adv. Eng. Mater. 25, 2201194. https://doi.org/10.1002/adem.202201194.
Faraji Rad, Z., Nordon, R.E., Davies, G.J., Anthony, C.J., Prewett, P., 2020. Microfluidic devices and fabrication.
Faraji Rad, Z., Nordon, R.E., Anthony, C.J., Bilston, L., Prewett, P.D., Arns, J.-Y., Arns, C. H., Zhang, L., Davies, G.J., 2017. High-fidelity replication of thermoplastic microneedles with open microfluidic channels. Microsyst. Nanoeng. 3, 1–11. https://doi.org/10.1038/micronano.2017.34.
Faraji Rad, Z., Prewett, P.D., Davies, G.J., 2021a. An overview of microneedle applications, materials, and fabrication methods. Beilstein J. Nanotechnol. 12, 1034–1046. https://doi.org/10.3762/bjnano.12.77.
Faraji Rad, Z., Prewett, P.D., Davies, G.J., 2021b. High-resolution two-photon polymerization: the most versatile technique for the fabrication of microneedle arrays. Microsyst. Nanoeng. 7, 71. https://doi.org/10.1038/s41378-021-00298-3.
Faraji Rad, Z., Prewett, P.D., Davies, G.J., 2021c. Rapid prototyping and customizable microneedle design: ultra-sharp microneedle fabrication using two-photon polymerization and low-cost micromolding techniques. Manuf. Lett. 30, 39–43. https://doi.org/10.1016/j.mfglet.2021.10.007.
Faraji Rad, Z., Prewett, P.D., Davies, G.J., 2022. Parametric optimization of two-photon direct laser writing process for manufacturing polymeric microneedles. Addit. Manuf. 56, 102953 https://doi.org/10.1016/j.addma.2022.102953.
Frydman, G.H., Olaleye, D., Annamalai, D., Layne, K., Yang, I., Kaafarani, H.M.A., Fox, J. G., 2020. Manuka honey microneedles for enhanced wound healing and the prevention and/or treatment of Methicillin-resistant *Staphylococcus aureus* (MRSA) surgical site infection. Sci. Rep. 10 https://doi.org/10.1038/s41598-020-70186-9.
Ganeson, K., Alias, A.H., Murugaiyah, V., Amirul, A.-A.-A., Ramakrishna, S., Vigneswari, S., 2023. Microneedles for efficient and precise drug delivery in cancer therapy. Pharmaceutics 15. https://doi.org/10.3390/pharmaceutics15030744.
Gao, B., Guo, M., Lyu, K., Chu, T., He, B., 2020. Intelligent silk fibroin based microneedle dressing 2006839, 1–9. https://doi.org/10.1002/adfm.202006839.
Gardeniers, H.J.G.E., Luttge, R., Berenschot, E.J.W., Boer, M.J.D., Yeshurun, S.Y., Hefetz, M., Oever, R.V., Berg, A.V., Den, 2003. Silicon micromachined hollow microneedles for transdermal liquid. Transport 12, 855–862.
Gill, H.S., Denson, D.D., Burris, B.A., Prausnitz, M.R., 2008. Effect of microneedle design on pain in human volunteers 24, 585–594.
Gittard, S.D., Miller, P.R., Jin, C., Martin, T.N., Boehm, R.D., Chisholm, B.J., Stafslien, S. J., Daniels, J.W., Cilz, N., Monteiro-Riviere, N.A., Nasir, A., Narayan, R.J., 2011. Deposition of antimicrobial coatings on microstereolithography-fabricated microneedles. JOM 63. https://doi.org/10.1007/s11837-011-0093-3.
González-vázquez, P., Larrañeta, E., Maelíosa, T.C., Jarrahian, C., Rein-weston, A., Zehrung, D., Mccarthy, H., Aaron, J., Donnelly, R.F., 2017. Transdermal delivery of gentamicin using dissolving microneedle arrays for potential treatment of neonatal sepsis. J. Control. Release. https://doi.org/10.1016/j.jconrel.2017.07.032.
Gozali, M.V., Zhou, B., Luo, D., 2015. Effective treatments of atrophic acne scars. J. Clin. Aesthetic Dermatol.
Guo, Z., Liu, H., Shi, Z., Lin, L., Li, Y., Wang, M., Pan, G., Lei, Y., Xue, L., 2022. Responsive hydrogel-based microneedle dressing for diabetic wound healing. J. Mater. Chem. B 10, 3501–3511. https://doi.org/10.1039/D2TB00126H.
Guo, M., Wang, Y., Gao, B., He, B., 2021. Shark tooth-inspired microneedle dressing for intelligent wound management. ACS Nano 15. https://doi.org/10.1021/acsnano.1c06279.
Han, T., Das, D.B., 2013. Permeability enhancement for transdermal delivery of large molecule using low-frequency sonophoresis combined with microneedles. J Pharm Sci 102. https://doi.org/10.1002/jps.23662.
Han, D., Morde, R.S., Mariani, S., la Mattina, A.A., Vignali, E., Yang, C., Barillaro, G., Lee, H., 2020. 4D printing of a bioinspired microneedle array with backward-facing barbs for enhanced tissue adhesion. Adv. Funct. Mater. 30 https://doi.org/10.1002/adfm.201909197.
Harding, K.G., 2002. Science, medicine, and the future: healing chronic wounds. BMJ 324. https://doi.org/10.1136/bmj.324.7330.160.
Hiraishi, Y., Hirobe, S., Iioka, H., Quan, Y.S., Kamiyama, F., Asada, H., Okada, N., Nakagawa, S., 2013. Development of a novel therapeutic approach using a retinoic acid-loaded microneedle patch for seborrheic keratosis treatment and safety study in humans. J. Control. Release 171, 93–103. https://doi.org/10.1016/j.jconrel.2013.06.008.
Hooper, J.W., Golden, J.W., Ferro, A.M., King, A.D., 2007. Smallpox DNA vaccine delivered by novel skin electroporation device protects mice against intranasal poxvirus challenge. Vaccine 25. https://doi.org/10.1016/j.vaccine.2006.11.017.
Hu, F., Gao, Q., Liu, J., Chen, W., Zheng, C., Bai, Q., Sun, N., Zhang, W., Zhang, Y., Lu, T., 2023. Smart microneedle patches for wound healing and management. J. Mater. Chem. B. https://doi.org/10.1039/d2tb02596e.
Huang, D., Zhao, D., Wang, X., Li, C., Yang, T., Du, L., Wei, Z., Cheng, Q., Cao, H., Liang, Z., Huang, Y., Li, Z., 2018. Efficient delivery of nucleic acid molecules into skin by combined use of microneedle roller and flexible interdigitated electroporation array. Theranostics 8. https://doi.org/10.7150/thno.23438.
IDF Diabetes Atlas IDF Diabetes Atlas, 2021.
Jamaledin, R., Yiu, C.K.Y., Zare, E.N., Niu, L.N., Vecchione, R., Chen, G., Gu, Z., Tay, F. R., Makvandi, P., 2020. Advances in antimicrobial microneedle patches for combating infections. Adv. Mater. 32 https://doi.org/10.1002/adma.202002129.
Jeon, E.Y., Lee, J., Kim, B.J., Joo, K., il, Kim, K.H., Lim, G., Cha, H.J., 2019. Bio-inspired swellable hydrogel-forming double-layered adhesive microneedle protein patch for regenerative internal/external surgical closure. Biomaterials 222. https://doi.org/10.1016/j.biomaterials.2019.119439.
Jiang, X., Lillehoj, P.B., 2020. Microneedle-based skin patch for blood-free rapid diagnostic testing. Microsyst. Nanoeng. 6 https://doi.org/10.1038/s41378-020-00206-1.
Jung, J.H., Jin, S.G., 2021. Microneedle for transdermal drug delivery: current trends and fabrication. J. Pharm. Investig. 51, 503. https://doi.org/10.1007/s40005-021-00512-4.
Juster, H., van der Aar, B., de Brouwer, H., 2019. A review on microfabrication of thermoplastic polymer-based microneedle arrays. Polym. Eng. Sci. https://doi.org/10.1002/pen.25078.
Kahraman, E., Kaykın, M., Bektay, H.Ş., Güngör, S., 2019. Recent advances on topical application of ceramides to restore barrier function of skin. Cosmetics. https://doi.org/10.3390/COSMETICS6030052.
Kaiser, P., Wächter, J., Windbergs, M., 2021. Therapy of infected wounds: overcoming clinical challenges by advanced drug delivery systems. Drug Deliv. Transl. Res. https://doi.org/10.1007/s13346-021-00932-7.
Kang, N., Kim, S., Lee, J., Kim, K., Choi, Y., Oh, Y., Kim, J., Kim, D., Park, J., 2021. studies SC. Expert Opin. Drug Deliv. https://doi.org/10.1080/17425247.2021.1828860.
Kelchen, M.N., Siefers, K.J., Converse, C.C., Farley, M.J., Holdren, G.O., Brogden, N.K., 2016. Micropore closure kinetics are delayed following microneedle insertion in elderly subjects. J. Control. Release 225, 294–300. https://doi.org/10.1016/j.jconrel.2016.01.051.
Khan, H., Mehta, P., Msallam, H., Armitage, D., Ahmad, Z., 2014. Smart microneedle coatings for controlled delivery and biomedical analysis. J. Drug Target 22. https://doi.org/10.3109/1061186X.2014.921926.
Kochhar, J.S., Quek, T.E.N.C., Soon, W.E.I.J.U.N., Choi, J., Zou, S., Kang, L., 2013. Effect of microneedle geometry and supporting substrate on microneedle array penetration into skin, 4100–4108. 10.1002/jps.23724.
Lee, H.J., Lee, E.G., Kang, S., Sung, J.H., Chung, H.M., Kim, D.H., 2014. Efficacy of microneedling plus human stem cell conditioned medium for skin rejuvenation: a randomized, controlled, blinded split-face study. Ann. Dermatol. 26 https://doi.org/10.5021/ad.2014.26.5.584.
Lee, K., Xue, Y., Lee, J., Kim, H., Liu, Y., Tebon, P., Sarikhani, E., Sun, W., Zhang, S., Haghniaz, R., Çelebi-saltik, B., Zhou, X., Ostrovidov, S., Ahadian, S., Ashammakhi, N., Dokmeci, M.R., Khademhosseini, A., 2020. A patch of detachable hybrid microneedle depot for localized delivery of mesenchymal stem cells in regeneration therapy 2000086, 1–11. https://doi.org/10.1002/adfm.202000086.
Li, Y., Yang, J., Zheng, Y., Ye, R., Liu, B., Huang, Y., Zhou, W., Jiang, L., 2020. Iontophoresis-driven porous microneedle array patch for active transdermal drug delivery. Acta Biomater. https://doi.org/10.1016/j.actbio.2020.12.023.
Liebl, H., Kloth, L.C., 2013. Skin cell proliferation stimulated by microneedles. J. Am. College Clin. Wound Special. 4, 2–6. https://doi.org/10.1016/j.jccw.2012.11.001.
Lim, J., Tahk, D., Yu, J., Min, D.H., Jeon, N.L., 2018. Design rules for a tunable merged-tip microneedle. Microsyst. Nanoeng. 4 https://doi.org/10.1038/s41378-018-0028-z.
Lima, S.A.C., Reis, S., 2021. Marine polymeric microneedles for transdermal drug delivery 266. 10.1016/j.carbpol.2021.118098.
Lindholm, C., Searle, R., 2016. Wound management for the 21st century: combining effectiveness and efficiency. Int. Wound J. 13 https://doi.org/10.1111/iwj.12623.
Liu, L., Xu, X., Zhu, M., Cui, X., Feng, J., Rad, Z.F., Wang, H., Song, P., 2023. Bioinspired strong, tough, and biodegradable poly(vinyl alcohol) and its applications as substrates for humidity sensors. Adv. Mater. Technol. https://doi.org/10.1002/admt.202201414.
Loizidou, E.Z., Inoue, N.T., Ashton-Barnett, J., Barrow, D.A., Allender, C.J., 2016. Evaluation of geometrical effects of microneedles on skin penetration by CT scan and finite element analysis. Eur. J. Pharm. Biopharm. 107 https://doi.org/10.1016/j.ejpb.2016.06.023.

Ma, G.J., Shi, L.T., Wu, C.W., 2015. biomechanical property of a natural microneedle: the caterpillar. Spine 5, 1–6. https://doi.org/10.1115/1.4004651.
Malek-Khatabi, A., Faraji Rad, Z., Rad-Malekshahi, M., Akbarijavar, H., 2023. Development of dissolvable microneedle patches by CNC machining and micromolding for drug delivery. Mater. Lett. 330, 133328 https://doi.org/10.1016/j.matlet.2022.133328.
McAlister, E., Kirkby, M., Domínguez-Robles, J., Paredes, A.J., Anjani, Q.K., Moffatt, K., Vora, L.K., Hutton, A.R.J., McKenna, P.E., Larrañeta, E., Donnelly, R.F., 2021. The role of microneedle arrays in drug delivery and patient monitoring to prevent diabetes induced fibrosis. Adv. Drug Deliv. Rev. https://doi.org/10.1016/j.addr.2021.06.002.
Meng, F., Hasan, A., Mahdi, M., Babadaei, N., Hashemi, P., 2020. Polymeric-based microneedle arrays as potential platforms in the development of drugs delivery systems. J. Adv. Res. https://doi.org/10.1016/j.jare.2020.07.017.
Miller, P.R., Moorman, M., Boehm, R.D., Wolfley, S., Chavez, V., Baca, J.T., Ashley, C., Brener, I., Narayan, R.J., Polsky, R., 2020. Fabrication of hollow metal microneedle arrays using a molding and electroplating method. 10.1557/adv.201.
Mir, M., Permana, A.D., Ahmed, N., Khan, G.M., Rehman, A., Donnelly, R.F., 2019. Enhancement in site-specific delivery of carvacrol for potential treatment of infected wounds using infection responsive nanoparticles loaded into dissolving microneedles: a proof of concept study. Eur. J. Pharm. Biopharm. https://doi.org/10.1016/j.ejpb.2019.12.008.
Mir, M., Dian, A., Ahmed, N., Majid, G., Donnelly, R.F., 2020. European Journal of Pharmaceutics and Biopharmaceutics Enhancement in site-specific delivery of carvacrol for potential treatment of infected wounds using infection responsive nanoparticles loaded into dissolving microneedles: a proof of concept study. Eur. J. Pharm. Biopharm. 147, 57–68. https://doi.org/10.1016/j.ejpb.2019.12.008.
Mo, R., Zhang, H., Xu, Y., Wu, X., Wang, S., Dong, Z., Xia, Y., Zheng, D., Tan, Q., 2023. Transdermal drug delivery via microneedles to mediate wound microenvironment. Adv. Drug Deliv. Rev. https://doi.org/10.1016/j.addr.2023.114753.
Mohamed, K., Mahmoud, I.S., 2017. ce pt e d us cr t. J. Dermatol. Treat. 000. https://doi.org/10.1080/09546634.2017.1365111.
Mohammed, H., Guha, K., Puli, A.K., Einsanwi, A., Kondavitee, G.S., 2021. System microneedle for micropump in drug delivery systems, 484–491. 10.1049/nbt2.12013.
Mojeiko, G., Brito, M.D., Salata, G.C., Lopes, L.B., 2019. Combination of microneedles and microemulsions to increase celecoxib topical delivery for potential application in chemoprevention of breast cancer. Int. J. Pharm. 560, 365–376. https://doi.org/10.1016/j.ijpharm.2019.02.011.
Nagarkar, R., Singh, M., Nguyen, H.X., Jonnalagadda, S., 2020. A review of recent advances in microneedle technology for transdermal drug delivery. J. Drug Deliv. Sci. Technol. https://doi.org/10.1016/j.jddst.2020.101923.
Namjoshi, S., Chen, Y., Edwards, J., Benson, H.A.E., 2008. Enhanced transdermal delivery of a dipeptide by dermaportation, in: Biopolymers - Peptide Science Section. 10.1002/bip.21033.
Nava-Arzaluz, G., M., Calderon-Lojero, I., Quintanar-Guerrero, D., Villalobos-Garcia, R., Ganem-Quintanar, A, 2011. Microneedles as transdermal delivery systems: combination with other enhancing strategies. Curr. Drug Deliv. 9 https://doi.org/10.2174/156720112798376078.
Nayak, S., Suryawanshi, S., Bhaskae, V., 2016. Microneedle technology for transdermal drug delivery: applications and combination with other enhancing techniques. J. Drug Deliv. Therapeut. 6 https://doi.org/10.22270/jddt.v6i5.1285.
Olatunji, O., Das, D.B., Garland, M.J., Belaid, L.U.C., Donnelly, R.F., 2013. Pharmaceutics. Drug delivery and pharmaceutical technology influence of array interspacing on the force required for successful microneedle skin penetration : theoretical and 102, 1209–1221. https://doi.org/10.1002/jps.
Onesto, V., di Natale, C., Profeta, M., Netti, P.A., Vecchione, R., 2020. Engineered PLGA-PVP/VA based formulations to produce electro-drawn fast biodegradable microneedles for labile biomolecule delivery. Prog. Biomater. 9 https://doi.org/10.1007/s40204-020-00143-2.
Pandey, P.C., Shukla, S., Skoog, S.A., Boehm, R.D., Narayan, R.J., 2019. Current advancements in transdermal biosensing and targeted drug delivery. Sensors (Switzerland). https://doi.org/10.3390/s19051028.
Park, J.H., Allen, M.G., Prausnitz, M.R., 2005. Biodegradable polymer microneedles: fabrication, mechanics and transdermal drug delivery. J. Control. Release 104. https://doi.org/10.1016/j.jconrel.2005.02.002.
Pere, C.P.P., Economidou, S.N., Lall, G., Ziraud, C., Boateng, J.S., Alexander, B.D., Lamprou, D.A., Douroumis, D., 2018. 3D printed microneedles for insulin skin delivery. Int J Pharm 544. https://doi.org/10.1016/j.ijpharm.2018.03.031.
Petchsangsai, M., Rojanarata, T., Opanasopit, P., Ngawhirunpat, T., 2014. The combination of microneedles with electroporation and sonophoresis to enhance hydrophilic macromolecule skin penetration. Biol. Pharm. Bull. 37 https://doi.org/10.1248/bpb.b14-00321.
Pireddu, R., Schlich, M., Marceddu, S., Valenti, D., Pini, E., Fadda, A.M., Lai, F., Sinico, C., 2020. Nanosuspensions and microneedles roller as a combined approach to enhance diclofenac topical bioavailability. Pharmaceutics 12. https://doi.org/10.3390/pharmaceutics12121140.
Quisling, S., Vestal, L., Enstrom, A., 2021. Flow visualization of bolus microcapsule delivery through 3D printed microneedles.
Ro, A.M., 2014. Monitoring the penetration process of single microneedles with varying tip diameters. J. Mech. Behav. Biomed. Mater. 40, 397–405. https://doi.org/10.1016/j.jmbbm.2014.09.015.
Römgens, A.M., Bader, D.L., Bouwstra, J.A., Oomens, C.W.J., 2016. Predicting the optimal geometry of microneedles and their array for dermal vaccination using a computational model. Comput. Methods Biomech. Biomed. Eng. 19 https://doi.org/10.1080/10255842.2016.1173684.
Ronnander, J.P., Simon, L., Koch, A., 2019. Transdermal delivery of sumatriptan succinate using iontophoresis and dissolving microneedles. J. Pharm. Sci. 1–8 https://doi.org/10.1016/j.xphs.2019.07.020.
Rzhevskiy, A.S., Raghu, T., Singh, R., Donnelly, R.F., Anissimov, Y.G., 2017. NU, J. Controll. Rel. Elsevier B.V. 10.1016/j.jconrel.2017.11.048.
Sabri, A.H., Kim, Y., Marlow, M., Scurr, D.J., Banga, A.K., Kagan, L., Lee, J.B., 2019. Jo ur l P. Adv. Drug Deliv. Rev. https://doi.org/10.1016/j.addr.2019.10.004.
Saghazadeh, S., Rinoldi, C., Schot, M., Kashaf, S.S., Sharifi, F., Jalilian, E., Nuutila, K., Giatsidis, G., Mostafalu, P., Derakhshandeh, H., Yue, K., Swieszkowski, W., Memic, A., Tamayol, A., Khademhosseini, A., 2018. Drug delivery systems and materials for wound healing applications. Adv. Drug Deliv. Rev. https://doi.org/10.1016/j.addr.2018.04.008.
Saifullah, K.M., Faraji Rad, Z., 2023. Sampling dermal interstitial fluid using microneedles: a review of recent developments in sampling methods and microneedle-based biosensors. Adv. Mater. Interfaces 2201763. https://doi.org/10.1002/admi.202201763.
Seo, K.Y., Yoon, M.S., Kim, D.H., Lee, H.J., 2012. Skin rejuvenation by microneedle fractional radiofrequency treatment in Asian skin; clinical and histological analysis. Lasers Surg. Med. 44 https://doi.org/10.1002/lsm.22071.
Sharad, J., 2011. Combination of microneedling and glycolic acid peels for the treatment of acne scars in dark skin. J. Cosmet. Dermatol. 10 https://doi.org/10.1111/j.1473-2165.2011.00583.x.
Shen, Y., 2021. Optimal design and fabrication of a microneedle arrays patch. https://doi.org/10.1016/j.jmapro.2020.02.024.
Su, Y., Mainardi, V.L., Wang, H., McCarthy, A., Zhang, Y.S., Chen, S., John, J.V., Wong, S. L., Hollins, R.R., Wang, G., Xie, J., 2020. Dissolvable microneedles coupled with nanofiber dressings eradicate biofilms via effectively delivering a database-designed antimicrobial peptide. ACS Nano 14. https://doi.org/10.1021/acsnano.0c04527.
Su, Y., McCarthy, A., Wong, S.L., Hollins, R.R., Wang, G., Xie, J., 2021. Simultaneous delivery of multiple antimicrobial agents by biphasic scaffolds for effective treatment of wound biofilms. Adv. Healthc. Mater. 10 https://doi.org/10.1002/adhm.202100135.
Sun, W., Inayathullah, M., Manoukian, M.A.C., Malkovskiy, A. v., Manickam, S., Marinkovich, M.P., Lane, A.T., Tayebi, L., Seifalian, A.M., Rajadas, J., 2015. Transdermal delivery of functional collagen via polyvinylpyrrolidone microneedles. Ann. Biomed. Eng. 43. 10.1007/s10439-015-1353-0.
Sun, L., Fan, L., Bian, F., Chen, G., Wang, Y., Zhao, Y., 2021. MXene-integrated microneedle patches with innate molecule encapsulation for wound healing. Research 2021. 10.34133/2021/9838490.
Sun, Y., Liu, J., Wang, H., Li, S., Pan, X., Xu, B., Yang, H., Wu, Q., Li, W., Su, X., Huang, Z., Guo, X., Liu, H., 2021b. NIR laser-triggered microneedle-based liquid band-aid for wound care 2100218, 1–10. https://doi.org/10.1002/adfm.202100218.
Suzuki, M., Sawa, T., Takahashi, T., Aoyagi, S., 2015. Fabrication of microneedle mimicking mosquito proboscis sing nanoscale 3D laser lithography system. Int. J. Autom. Technol. 9 https://doi.org/10.20965/ijat.2015.p0655.
Torezan, L., Chaves, Y., Niwa, A., Sanches, J.A., Festa-Neto, C., Szeimies, R.M., 2013. A pilot split-face study comparing conventional methyl aminolevulinate-photodynamic therapy (PDT) with microneedling-assisted PDT on actinically damaged skin. Dermatol. Surg. 39 https://doi.org/10.1111/dsu.12233.
Van Der Maaden, K., Jiskoot, W., Bouwstra, J., 2012. Microneedle technologies for (trans)dermal drug and vaccine delivery. J. Control. Release 161, 645. https://doi.org/10.1016/j.jconrel.2012.01.042.
Vemulapalli, V., Bai, Y., Kalluri, H., Herwadkar, A., Kim, H., Davis, S.P., Friden, P.M., Banga, A.K., 2012. In vivo iontophoretic delivery of salmon calcitonin across microporated skin. J. Pharm. Sci. 101 https://doi.org/10.1002/jps.23222.
Waghule, T., Singhvi, G., Kumar, S., Monohar, M., 2019. Biomedicine & Pharmacotherapy Microneedles: A smart approach and increasing potential for transdermal drug delivery system. Biomed. Pharmacother. 109, 1249–1258. https://doi.org/10.1016/j.biopha.2018.10.078.
Wei-Ze, L., Mei-Rong, H., Jian-Ping, Z., Yong-Qiang, Z., Bao-Hua, H., Ting, L., Yong, Z., 2010. Super-short solid silicon microneedles for transdermal drug delivery applications. Int. J. Pharm. 389 https://doi.org/10.1016/j.ijpharm.2010.01.024.
Xu, J., Danehy, R., Cai, H., Ao, Z., Pu, M., Nusawardhana, A., Rowe-magnus, D., Guo, F., 2019. microneedle patch-mediated treatment of bacterial bio films. ACS Appl. Mater. Interfaces 11, 14640–14646. https://doi.org/10.1021/acsami.9b02578.
Yan, G., Warner, K.S., Zhang, J., Sharma, S., Gale, B.K., 2010. Evaluation needle length and density of microneedle arrays in the pretreatment of skin for transdermal drug delivery. Int. J. Pharm. 391 https://doi.org/10.1016/j.ijpharm.2010.02.007.
Yang, H., Kim, S., Huh, I., Kim, S., Lahiji, S.F., Kim, M., 2015. Biomaterials Rapid implantation of dissolving microneedles on an electrospun pillar array. Biomaterials 64, 70–77. https://doi.org/10.1016/j.biomaterials.2015.06.027.
Yang, J., Li, Y., Ye, R., Zheng, Y., Li, X., Chen, Y., Xie, X., 2021a. Array patch for controlled transdermal delivery. Microsyst. Nanoeng. https://doi.org/10.1038/s41378-020-00224-z.
Yang, Y., Xia, L., Ning, X., Hu, T., Xu, C., Liu, W., 2021b. Enhanced drug permeation into human keloid tissues by sonophoresis-assisted microneedling. SLAS Technol. 26 https://doi.org/10.1177/24726303211024568.
Yao, S., Chi, J., Wang, Y., Zhao, Y., Luo, Y., Wang, Y., 2021a. Zn-MOF Encapsulated antibacterial and degradable microneedles array for promoting wound healing 2100056, 1–10. https://doi.org/10.1002/adhm.202100056.
Yao, S., Luo, Y., Wang, Y., 2022. Engineered microneedles arrays for wound healing. Eng. Regen. https://doi.org/10.1016/j.engreg.2022.05.003.
Yao, Z., Xue, T., Xiong, H., Cai, C., Liu, X., Wu, F., Liu, S., Fan, C., 2021b. Promotion of collagen deposition during skin healing through Smad3/mTOR pathway by

parathyroid hormone-loaded microneedle. Mater. Sci. Eng. C 119. https://doi.org/10.1016/j.msec.2020.111446.

Yoon, J., Park, D., Son, T., Seo, J., Nelson, J.S., Jung, B., 2010. A physical method to enhance transdermal delivery of a tissue optical clearing agent: Combination of microneedling and sonophoresis. Lasers Surg. Med. 42 https://doi.org/10.1002/lsm.20930.

Zhang, X., Chen, G., Sun, L., Ye, F., Shen, X., Zhao, Y., 2021. Claw-inspired microneedle patches with liquid metal encapsulation for accelerating incisional wound healing. Chem. Eng. J. 406, 126741 https://doi.org/10.1016/j.cej.2020.126741.

Zhang, N., Dangol, M., Cearbhaill, E.D.O., 2018. Metallic microneedles with interconnected porosity: a scalable platform for biosensing and drug delivery. Acta Biomater. https://doi.org/10.1016/j.actbio.2018.09.007.

Zhang, X., Chen, G., Liu, Y., Sun, Lingyu, Sun, Lingyun, Zhao, Y., 2020. Carriers for wound healing. 10.1021/acsnano.0c01059.