Drug delivery systems based on microneedles for dermatological diseases and aesthetic enhancement

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ABSTRACT

Background: Microneedle (MN) devices comprise micron-sized structures that circumvent biological barriers in a minimally invasive manner. MN research continues to grow and evolve; the technology was recently identified as one of the top ten overall emerging technologies of 2020. There is a growing interest in using such devices in cosmetology and dermatological conditions, where the MNs mechanically disrupt the outer skin barrier layer, creating transient pathways that allow the passage of materials to underlying skin layers. This review aims to appraise the application of microneedle technologies in skin science, provide information on potential clinical benefits, as well as indicate possible dermatological conditions that can benefit from this technology, including autoimmune-mediated inflammatory skin diseases, skin aging, hyperpigmentation, and skin tumors. A literature review was carried out to select studies that evaluated the use of microneedles to enhance drug delivery for dermatologic purposes. MN patches create temporary pathways that allow the passage of therapeutic material to deeper layers of the skin. Given their demonstrable promise in therapeutic applications it will be essential for healthcare professionals to engage with these new delivery systems as they transition to the clinic.

Keywords: drug delivery, microneedle, diseased skin, aesthetic enhancement.

Introduction

The skin is the largest organ in the human body, reaching up to 16% of body weight, covering an area of 1.8 m^2, and performing multiple functions [1]. It is a metabolically active organ, with a variety of essential functions for the maintenance of homeostasis and body protection. The skin can be considered a safe and effective route of administration of various medications. Topical administration is a preferred route for the therapy of skin diseases having the advantage of the therapeutic acting directly on the target or very close to it, thus requiring a smaller amount of active substance and decreasing the risk of side effects [2]. In addition to topical administration, the skin can also be used for transdermal delivery, as pharmaceutical formulations can be placed on the skin surface to allow a drug to penetrate transepidermally or through the skin adnexa to reach the bloodstream for systemic effect [3,4].

As mentioned, topically applied drugs may have a local action or a systemic action [5], the latter facing the significant challenge of crossing the skin barrier, mainly exerted by the stratum corneum (SC) [6]. The SC is made up of keratinized and flattened dead cells, called corneocytes, and a surrounding lipid matrix; the barrier is often referred to as a "bricks and mortar" structure. The SC is rich in lipids (5-15%) and proteins (75-85%), mainly keratin. Due to these characteristics, the SC represents the primary barrier to skin permeation, resulting in transdermal delivery being restricted to a small number of drugs, with specific physicochemical properties, such as high potency, low molecular weight (<500 Daltons) and moderate lipophilicity [6–9]. Whilst the permeation of drugs through the skin can be influenced by several factors, such as molecule size, lipophilicity, pH of the formulation, drug concentration, skin hydration, temperature and integrity of the SC, the cutaneous bioavailability of most drugs is very low, ranging from 1 to 5% [10–12].

Microneedle (MN) devices are micron-sized structures, generally ranging from 100 to 1000 µm, that cross biological barriers in a minimally invasive manner [13]. MNs have been proposed as an effective approach to mechanically promote the disruption of the SC, creating temporary pathways that allow the passage of molecules to deeper skin layers. The MN device was first conceptualized in 1976 [14]. Since that time MN research has grown considerably and currently represents one of the most promising transdermal drug delivery technologies [15], and one of the top ten overall emerging technologies of 2020 [16]. MN patches have been applied in various health-related fields as diverse as the delivery of new treatments for type I diabetes [17], enhancing the time-to-effect of anesthetics [18], self-administrable vaccines[19], as well as the extraction of biomarkers [20].

Microneedle technology

MN patches employ microscopic projections made from a wide variety of materials including metal, silicon, glass, polymer and carbohydrate [21–25]. The application of an array of MNs results in the disruption of the skin barrier, creating superficial micropores and microchannels into the deeper skin layers. The skin recovers within a few hours after removing the MNs, preventing the penetration of pathogens into the treated site [26]. The depth of insertion of each MN depends on interrelated parameters such as MN

length, MN density (spacing and distribution on the support base), the radius of the tip, the angle of the tip, the radius of the base and the force applied [26–31].

MNs are commonly categorized as solid, hollow, coated, hydrogel-forming, and dissolving/degrading (Fig. 1) [32]. Solid removable MNs: the skin is treated with solid MNs before or after application of a topical drug formulation to allow the drug to pass through the pores into the skin; Coated MNs: the insertion of drug-coated MNs into the skin resulting in the coating dissolving in the skin; Dissolving/degrading MNs: the drug is loaded into the structure of MNs made of materials that dissolve or biodegrade once in the skin; Hollow MNs: a liquid drug formulation is injected into the skin in a similar, yet less invasive, way to conventional hypodermic needles; Hydrogel-forming MNs: on insertion into the skin the MNs swell, passively absorbing the skin's interstitial fluid [26]. Table 1 shows the application of these various types of MN technology (which are expanded upon below) in dermatologic-related fields.

Solid Microneedles

Solid MNs are composed of materials such as stainless steel, silicon, ceramic or titanium, which are capable of piercing the skin, creating microchannels as a drug delivery route [33,34]. Depending on the material, several techniques can be used to produce solid MNs. The solid MN approach is considered the most mechanically robust, which makes penetration into the skin easier compared to other types of MNs [35]. On the other hand, it requires a two-step process (opening the microchannels and then applying the drug) [33,34], and accurate dosing is not possible. Another disadvantage is the difficulty of controlling the released dose of the drug within the skin. Nevertheless, solid MNs are considered simple, and can be self-administered.

In the dermatological area, studies on the application of solid MNs arrays are not abundant. Liang et al. (2021) evaluated the combination of skin pretreatment with solid polylactic acid polymer MNs followed by topical application of calcipotriol (15g/0.75mg) in the treatment of imiquimod-induced psoriasis in mice. It was observed that the combination of calcipotriol and MN provided a superior therapeutic effect when compared to the group without pre-treatment with MNs [36].

In the cosmetic area, using excised human skin, Mohammed et al. (2014) used a 304 stainless steel solid MN patch to enhance the skin permeation of cosmetic and therapeutic peptides with increasing chain length and increasing molecular weight. Penetration studies were conducted in Franz type diffusion cells for 1 and 24 hours. After 1 hour, MNs enhanced melanostatin penetration and distribution in the dermis and epidermis. On the other hand, MNs did not improve the topical application of Rigin and Pal-KTTKS; higher molecular weight peptides [37].

Hollow microneedles

MNs can be used to inject material into the skin in much the same way as a conventional needle and syringe, albeit with less invasiveness, enabling pressure-controlled flow of fluids [24]. This enables more precise dose control when compared to solid MNs, since hollow MNs offer sub-dermal fluid injection, while solid MNs depend on passive diffusion of fluid through holes created in the previous step [24]. This fact may explain the low number of articles applying this technology in cosmetic applications, as opposed

to therapeutic indications, since some cosmetics do not require such a fine precision of delivery into the skin [24].

Recent advances in MN technology also makes it possible to deliver powdered active into the skin, for example in the treatment of autoimmune-mediated inflammatory skin diseases. Cárcamo-Martínez et al. (2021) proposed the intradermal delivery of tofacitinib citrate powder using hollow and dissolving MNs arrays. Hollow MN arrays showed superior deposition of tofacitinib in skin epidermis and dermis when compared to a control cream. Dissolving MN arrays showed superior deposition of tofacitinib in the dermis [38].

Coated microneedles

Typically, a coated MN comprises a sharp core MN structure, on which a solid, soluble film containing the drug and excipients is coated. The water-soluble excipients catalyze the release of the film from the MN surface when inserted into the skin, specifically when the coating meets the interstitial fluid present in the tissue. Contact with this aqueous medium initiates the detachment of the surface coating, which, depending on the aqueous solubility of the coating excipients, can be completed in seconds to minutes. It is important that the coating is detached from the MN surface before the MNs are removed from the skin; however, complete dissolution of the material left behind may occur over a longer time period [39]. Coated MNs can only deliver a relatively small amount of drug [40], thus potent drugs are required [39] and the amount of excipient in the formulation needs to be minimized [41].

Coated MNs are attractive because they allow for drug storage in the solid phase, providing long-term stability, even at room temperature [42]. This characteristic is particularly significant in the case of vaccine-coated MNs, reducing the need for vaccine reconstitution and reducing or even eliminating the need for the cold-chain, conventionally required for transport and storage of vaccines [26]. This is a key issue, as cold-chain distribution increases costs and inherently limits the availability of vaccines in low- to middle-income countries [43].

Coated MNs also can be used to conveniently and rapidly deliver high molecular weight molecules into the skin, as they do not require delivery expertise and can be self-administered by the user [42]. Coated MNs can be used to release the drug not only in the skin, but also in other tissues, such as the eye and the oral cavity [39,44,45].

Several manufacturing processes and techniques can be used to coat MNs, including dip coating, gas jet coating, spray coating, processes based on electro-hydrodynamic atomization and piezoelectric inkjet printing, among others. An important review on this subject is presented by [46]. Selecting an appropriate MN coating process will include consideration on the sterility requirements and the fate of non-therapeutic materials that dissolve and can accumulate in skin, particularly after repeated administrations [47].

pH-responsive MN coatings have attracted interest as “smart” drug delivery systems to overcome deficiencies in conventional drug formulations. These systems can deliver medications in a highly controlled manner, at a specific time and place, which can result in improved therapeutic efficacy. Specifically, sites of inflammation, tumor tissue, skin cancers: basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma have slightly acidic microenvironments, so the application of therapeutic

coatings that release the drug at acidic pH may be desirable [43]. Based on this principle, a biomimetic drug delivery system has been developed using a pH-responsive formulation using MNs coated with porous polymer [43].

Coated MNs have been used for the treatment of skin tumors and skin infections [48–50]. Chong et al. (2013) studied the combination of steel MN devices and synthetic small interfering nucleic acid (siRNA)-based gene silencing technology for the treatment of skin conditions caused by aberrant gene expression [51]. Using transgenic mouse skin, the silencing of functional genes in vivo after MN siRNA delivery was confirmed. Jain et al. (2016) used stainless steel coated MNs to enhance the dermal delivery of 5-aminolevulinic acid (5-ALA), a biological precursor of photosensitizer protoporphyrin IX (PPIX), for skin tumor treatment using photodynamic therapy [52]. The photodynamic therapy effect was evaluated using a mouse skin-tumor model. MN treatment with a lower dose of 1.75 mg 5-ALA suppressed the growth of subcutaneous tumors by 57%, while a topical cream containing 5 mg of 5-ALA did not suppress the tumor volume and led to tumor growth comparable to the untreated control group. Uddin et al. (2020) developed a new 3D-printed biocompatible polymeric MN coated with cisplatin, an antitumor drug, for A-431 epidermoid skin tumor treatment. In vitro assays revealed rapid cisplatin release rates of 80–90% within 1 h [53]. In vivo pre-clinical trials demonstrated sufficient cisplatin permeabilization with high anticancer activity and tumor regression.

Coated MN patches have also been used in the treatment of warts, a skin disease caused by infection of the human papilloma virus infection [54–56]. Ryu et al. (2018) compared the therapeutic effects of a newly developed bleomycin coated MN patch with conventional cryotherapy therapy for the treatment of warts. In a clinical study it was observed that the treatment efficacy of the bleomycin MN patch was comparable to cryotherapy therapy. Bleomycin MN patch treatment was significantly less painful than cryotherapy and more tolerable for patients [55].

Dissolving/Degrading Microneedles

Dissolving/degrading MNs are developed using a soluble and/or biodegradable matrix associated with the active substance that, after insertion into the skin, cause the matrices to dissolve and then release the incorporated drug [35]. Conventionally, micromoulding techniques are used to produce such MNs [57–59]. The substances most commonly used in the production of biodegradable MNs are carbohydrate sugars or synthetic polymers [57,60]. Because such MNs can be prepared from biocompatible and biodegradable materials, side effects can be minimal [61,62] with the dimensions of the MNs limiting the patients' sensation of pain [63]. Such systems are suited to self-administration and ease of disposal, as any sharps material dissolves in the skin and does not remain on the patch. They also offer the potential for controlled release, e.g., using microparticles which deposit quickly in the skin when the surrounding matrix dissolves yet can release their drug-loaded cargo slowly.

Polymeric MNs have numerous advantageous properties in relation to other substances, such as biocompatibility, biodegradability, strength, hardness and optical clarity [64,65]. Furthermore, fabrication of polymeric MNs can be considerably more cost-effective [66–69]. On the other hand, such systems may raise more regulatory questions as it is difficult to control the exact concentration of deposited drug, one

has to account for the fate of the deposited polymer and product manufacture and packaging requirements may be more challenging due to the inherent restricted aqueous and temperature stability of the matrix.

Polymeric materials that have been used in the effective manufacture of MNs include hyaluronic acid (HA), polymethylmethacrylate (PMMA), poly-L-lactic acid (PLA), poly-glycolic acid (PGA) and poly- lactic-co-glycolic (PLGA), cyclic olefin copolymer, polyvinylpyrrolidone and sodium carboxymethyl cellulose [62,64,66–73]. Among the sugars used to produce MNs, galactoses, maltoses, trehalose and dextrins are perhaps most prevalent [23,74–76].

Dissolving MNs have been used to treat a variety of dermatological conditions, including psoriasis [77], atopic dermatitis [78], hyperpigmentations [79–82], hair growth [83], acne [84], keloids [85], skin tumors [86–88], skin infections [89,90], and other diseases of inflammatory skin conditions in general [91]. MN patches comprising hyaluronic acid have shown to reduce the severity of psoriatic plaques resistant to topical calcipotriol-betamethasone therapy (Daivobet; LEO Pharma, Ballerup, Denmark). In addition, the use of hyaluronic acid MN patches has not been associated with any adverse effects commonly seen in pharmacological therapies in patients with psoriasis, such as infection, irritation or worsening of pre-existing psoriasis. The clinical effects of microneedling in psoriasis can be a result of enhanced percutaneous drug penetration into the psoriatic plaques, that are characterized by a thickened SC [92].

Biodegradable MN patches delivering doxorubicin (25, 50, and 100 µg) have been used in patients with mycosis fungoides cutaneous T-cell lymphoma. The therapy, administered once a week for four weeks followed by a week without treatment, was considered safe, with no late and limited toxicities or adverse events. In addition, there was complete resolution of mycosis fungoides lesions and a 31% reduction in the Severity Weighted Assessment Tool (SWAT) [93].

MN technology, particularly dissolving MN patches comprising hyaluronic acid with other additives, has reportedly shown improvement of skin quality, wrinkles, dermal density, elasticity, hydration, and skin barrier restoration [33,37,70,94–98]. The use of such devices is generally well supported in the literature, and several studies with humans have already been performed. The manufacture of MNs using cross-linked hyaluronic acid provides for sustained drug release which can delay skin degradation and reduce swelling of the skin [99].

Hydrogel-forming Microneedles

Created just over a decade ago [100], hydrogel-forming MNs purported to overcome the difficulties faced by existing devices at the time [100]. This approach has the ability to deliver drugs for a longer period with minimal polymer residues in the skin, and can be easily sterilized, thereby reducing the risk of infection [100–103]. Hydrogel-forming MN arrays are removed intact from the skin [102,104] as opposed to the aforementioned dissolvable MNs systems which rely upon polymer deposition in the skin [104].

Prepared from crosslinked polymers, hydrogel-forming MNs are rigid initially, enabling penetration through the SC. After insertion, MNs begin to passively absorb the skin's interstitial fluid, leading to a significant expansion of the polymeric network structure. The drug from the reservoir attached at the base of the MN starts dissolving as the skin's interstitial fluid reaches through the osmotic pathway, leading to drug release into the skin [26,102].

The permeation of α-arbutin (tyrosinase activity inhibitor and skin lightening agent) into the skin has been compared with dissolving MNs made from polyacrylic acid-co-maleic acid (PAMA) and polyvinyl alcohol (PVA) (1:4), and hydrogel-forming MNs made from crosslinking PAMA and PVA (1:4) [103]. Both the hydrogel and the dissolving MNs improved the permeation and delivery of α-arbutin when compared to topical formulations on in vitro and in vivo tests [103]. In another study of tyrosinase activity inhibitors, the properties and drug permeation effects of glabridin-loaded hydrogel-forming MNs produced by different methods were compared [101]. PVA and carbomer were used as the hydrogel system to fabricate arrays by chemical or physical cross-linking. The data indicated the device fabricated by chemical cross-linking had better insertion properties and permeation profile when compared to the physical cross-linking device [101].

Clinical studies using different types of MNs

Table 2 shows a compilation of clinical studies for cosmetic and dermatological applications classified by the different types of MNs used in the studies. It should be noted that only a few of the recent studies present in vivo efficacy assessments and many do not perform a standardized evaluation, making data interpretation and comparisons between different MN types challenging at this stage.

Conclusions and perspectives

MN devices represent an extremely promising drug delivery system that mechanically disrupts the stratum corneum to create temporary pathways that allow the painless passage of material to deeper layers of the skin. Whilst still an emerging technology, these systems have already shown to be highly suitable for the delivery of a wide range of low molecular weight drugs and macromolecules for dermatological and other applications. Given their demonstrable promise in cosmetic and therapeutic applications it will be essential for healthcare professionals to engage with MN technology as products become clinical reality.

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Figures

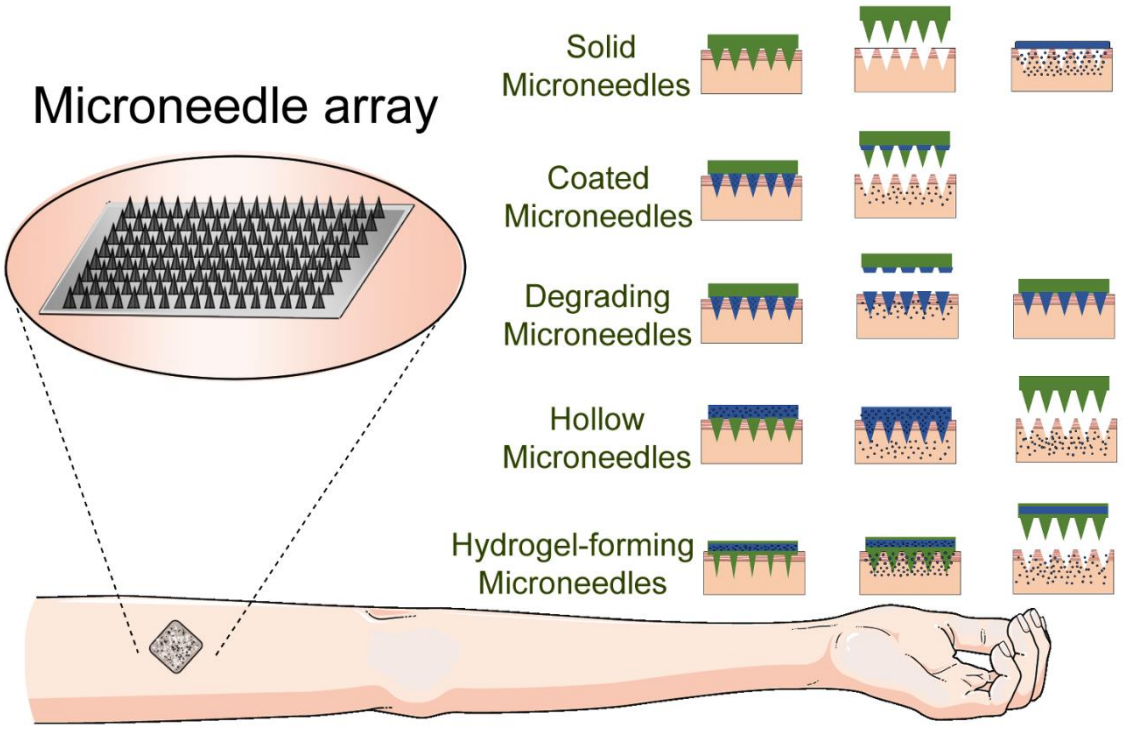

Figure 1. Different formats of MNs for drug delivery. Solid removable MNs: the skin is treated with solid MNs before or after application of a topical drug formulation. The drug passes through the pores into the skin. Coated MNs: the insertion of drug-coated MNs into the skin. The coating dissolves in the skin. Dissolving/degrading MNs: the drug is loaded into MNs made of materials that dissolve or biodegrade once in the skin. Hollow MNs: used to inject liquid drug formulations into the skin in a similar, yet less invasive, way to conventional hypodermic needles. Hydrogel-forming MNs: on insertion into the skin the MNs swell, passively absorbing the skin's interstitial fluid. Adapted from [26].

Tables

Table 1. MN patch technology used in dermatologic studies: main characteristics and applications.

Skin conditions	Type of microneedle	Type of microneedle/Material used/Drug delivered	Specifications
Skin tumors (Actinic keratosis, basal cell carcinoma, squamous cells carcinoma, cutaneous T-cell lymphoma, and melanoma)	Coated MNs [49–53,88]	-Coated MNs with of octaarginine/BRAF siRNA nanocomplexes [50] and dissolving MNs with spatiotemporally controlled pulsatile release nanosystem for synergistic chemo-photothermal therapy [88] for melanoma.	-Two-dimensional MN arrays from stainless steel. Each of 57 MNs have length of 700 μm and base of 200 μm. MNs coated by dipping into the micro-reservoir by different concentrations of aminolevulinic acid [52].
	Dissolving MNs [86,87].	-Coated MNs with therapeutic siRNA for antitumor skin therapy [51].	-MN array prepared with copolymer solution and different concentrations of aminolevulinic acid. MNs length of 350 – 400 μm. Patch mold composed of a dense pyramidal array with 19 x 19 pyramidal holes with arrays ranging about 6.6 × 6.6 mm. Pyramids were 500 μm long and 300 μm wide at the base each, spaced by 50 μm gaps [87].
		-Cisplatin coated MNs patch for antitumor skin therapy [53].	
		-PEGylated gold nanorod coated poly(L-lactide) MN system for antitumor skin therapy [49].	
		-Aminolevulinic acid coated [52] and dissolving [87] for non-melanoma skin tumors.	-Stainless steel MN devices (containing 8×8 needles of length 750 μm) [50].
		-Gold nanocage and doxorubicin-loaded hyaluronic acid dissolving MN arrays for chemo-photothermal combined therapy [86].	-Stainless steel MN devices (containing either 5 or 10 needles of 700 μm length and 200 μm base width) [51].
			-3D printed polymeric MN arrays with 1000 μm in height. Patches of 99 MNs [53].
			-Composed by biodegradable poly(l-lactide) MNs (PLLA MNs), photothermal agent GNR-PEG, and antitumor nanodrug MPEG-PDLLA-DTX micelles. Patch was 1cm×1cm which consisted of 400 (20 × 20) MN tips. MNs with height of 480 μm [49].
			-Pyramid-shaped MNs with a height of 800 μm and tip-to-tip space of 750 μm. MN patch mold was made from brass and consisted of 144 needles [88].

			-MNs 450 µm in height and 200 µm in base width arranged into a 10 × 10 MN array [86].
Skin infections (warts caused by human papillomavirus (HPV) infection, mycosis fungoides, cutaneous candidiasis, bacterial biofilms in wounds)	Coated MNs [48,54,55]. Dissolving MNs [56,89,90,93].	-Poly(ethylene glycol) diacrylate (PEGDA) MN patch with surface coating of a nanosilver encapsulated gelatin/sucrose film [48]. -Bleomycin-Coated MNs patch for warts caused by human papillomavirus (HPV) infection [54,55]. -Imiquimod dissolving MN patch for warts [56]. -Dissolving MN array at doxorubicin dose for mycosis fungoides. [93]. -Two-layered dissolving MNs of itraconazole nanocrystals for cutaneous candidiasis [90]. -Bacterially sensitive nanoparticle-based two-layered dissolving MNs of doxycycline for bacterial biofilms [89].	-MN length of 900 µm with tip diameter of ~10.8 µm [48]. -A patch of 100 MNs with 30.644 mm^2 of surface area [54]. -Pre-coated MNs with pyramidal shape. Array of 100 MNs on an area of 49 mm^2, the MN base diameter was 250 µm, and the length of the MNs was 600 µm. Coated with 518.12 µg of bleomycin on the surface [55]. -Gelatin MNs uniformly shaped in a 10×10 array, around 500 µm needle length, with a total area of 64 mm^2 [56]. -Silicone mould with needle density of 16 × 16, pyramidal needles; 850 µm height [600 µm pyramidal tip, 250 µm base column] and 300 µm width at base and 300 µm interspacing [90]. -Silicone MN mould has 16 × 16, pyramidal needles; 850 µm height (600 µm pyramidal tip, 250 µm base column) and 300 µm width at base and 300 µm interspacing [89]. -Not mentioned [93].
Acne	Dissolving MNs [84].	-Polymeric dissolving MNs loaded with azelaic acid and matrine [84].	-Cylindrical base patch with 0.56 cm^2 of area. 144 conical MNs with diameter and height of 300 um and 500 µm, respectively [84].
Keloids	Dissolving MNs [85].	-Dissolving triamcinolone-embedded hyaluronic acid MN patch [85].	-MNs 600 µm in height arranged in 14x14 arrays. Triamcinolone acetonide embedded into 50% of the MNs from the sharp end [85].
Skin rejuvenation (improvement of skin quality, wrinkles, dermal density, elasticity,	Solid MNs [37].	-Dissolving hyaluronic acid MN application and post-treatment with 0.42% (w/w) adenosine / Topical adenosine-loaded cream [97]. -Dissolving hyaluronic and ferulic acids MN patch [94,95].	-MNs average length of 288.2 ± 3.3 µm with tip diameter of 27.7 ± 1.1µm [97].

hydration, and skin barrier restoration)	Dissolving MNs [33,70,94–99].	-High and low molecular weight hyaluronic acid dissolving MN with adenosine encapsulated (Ad-HMN with 800 kDa and Ad-LMN with 39 kDa) [96].	-Patch contained 650 cone-shaped MNs with 1 mm intervals. MN base diameter of 350 ± 11.2 μm and height of 450 ± 23.5 μm. Total surface area of the MN array on the patch was 660.5 mm^2 [95].
		-Horse oil and adenosine-loaded dissolving MN patch [98].	-Tip diameter of Ad-HMN and Ad-LMN 37.89 ± 0.83 μm and 37.59 ± 0.83 μm, respectively. Both Ad-HMN and Ad-LMN exhibit a streamlined conical shape and weights of 5.80 ± 0.08 mg and 8.03 ± 0.07 mg, respectively [96].
		-Dissolving hyaluronic acid MN patch with additives for wrinkle improvement (adenosine, melatonin, sh-decapeptide-9, and SCM2 [70].	
		-Dissolving Retinyl retinoate- and ascorbic acid-loaded MNs [33].	-25 adenosine dissolving MNs (5×5 array) located in an adhesive patch, the horse oil was spread around the MNs. MN cone shape with a length and tip diameter of ~332.4 μm and ~29.05 μm respectively [98].
		-Dissolving MNs containing cross-linked hyaluronic acid (X-linked HA) particulates [99].	
		-Solid MN patch. Post-treatment with Fluorescein conjugated peptides solution [37].	-Patch contained 100 MNs/cm^2 with 100 μm-intervals, shaped as a pyramidal structure, with a basement area of 200×200 μm and a height of 250 μm. Over 70% of the HA MN patches dissolved within 30 min and the patches dissolved completely after 1 hour when applied to the skin [70].
			-Dissolving MN patches of average length of 220 ± 20 μm; average tip diameter of 30 ± 10 μm; total number of MNs per patch was 153 (17 × 9 array); total area of MN array in the patch was 2 × 1 cm^2 and distance between MNs was 1.3 mm. The retinyl retinoate and ascorbic acid content per patch was 80 ± 8 and 230 ± 20 μg, respectively [33].
			-Patch with a 1 cm circumference containing 280 MNs. X-linked HA MNs 90 μm in diameter at the base, 270 μm long, and less than 10 μm in diameter at the tip [99].
			-MNs with an average height of 703.1 ± 16.1 μm and an average width of 257.8 ± 9.4 μm [37].

Hyperpigmentation (melasma, dark spots, and skin lightening)	Dissolving MNs [79–82]. Hydrogel-forming MNs [101].	-Dissolving hyaluronic acid-based MN patches loaded with anti-melanogenic actives for improvements of skin discoloration (niacinamide, ascorbic acid 2 glucoside, tranexamic acid, resveratrol, 4-n-butyl-resorcinol, and *Halidrys siliquosa* extract) [82]. -Dissolving MNs loading hydrophilic ascorbic acid and hydrophobic vitamin A palmitate [81]. -Alpha-arbutin-loaded dissolving MNs for skin lightening [80]. -Dissolving MNs containing tranexamic acid and licorice extract for melasma treatment [79]. -Glabridin-loaded hydrogel-forming MNs for pigmentation disorders [101].	-Total number of MNs on Luna Microcare-Luminous and Enlighten patches was 120 and 76, respectively, with the length of 350 μm [82]. -MNs prepared in a 10 × 10 array with a center-to-center spacing of 300 μm, and each conical MN with a base radius of 300 μm and a height of 600 μm [81]. -MNs cone shaped with a 520 ± 1.70 μm height, a 294 ± 3.85 μm base width, and a 10 ± 0.15 μm tip width [80]. -MNs comprised 144 (12 × 12) cone-shaped arrays in an area of 0.56 cm^2 and MN height of 500 μm [79]. - Poly(vinyl alcohol) (PVA) and carbomer as hydrogel system to fabricate glabridin-loaded hydrogel-forming MNs by cross-linking. MNs comprised 144 (12 × 12) cone-shaped arrays in an area of 169 cm^2. MN height of 800 μm, 350 μm base width, and 880 μm tip width [101].
Autoimmune-mediated inflammatory skin diseases (Psoriasis, dermatosis, alopecia areata, vitiligo, atopic dermatitis)	Solid MNs [36]. Hollow MNs [38]. Dissolving MNs [38,77,78,91,92].	-Tofacitinib citrate powder-loaded hollow polymeric MN and dissolving MN arrays for autoimmune inflammatory skin diseases [38]. -Solid polylactic acid polymer MNs for psoriasis. Post-treatment with Calcipotriol cream [36]. -Hyaluronic acid MN patch for psoriasis. Pre-treatment with topical agent calcipotriol–betamethasone ointment [92]. -High-dose steroid dissolving MN for atopic dermatitis [78]. -Hyaluronic acid dissolving MN patch loaded with methotrexate for psoriasis [77]. -Candlelit-shaped triamcinolone acetonide-loaded dissolving MNs for recalcitrant lichenified lesions [91].	-Master templates consisted of a square array of 0.35 cm^2 containing 81 pyramidal needles (9 × 9). Needles had a length of 1.2 mm, a base width of 0.460 mm and interspace of 0.210 mm [38]. -Height and interspacing distance between adjacent MNs of 300 and 1000 μm, respectively. Base cross section diameter of single needle of 150 μm [36]. -Patches of 26×26-mm-sized HA-fabricated MN patches (Therapass® RMD-6·5A; Raphas, Cheonan, Korea) containing 76 circular cone-shaped MNs 650 μm in height [92]. -108 array of fabricated TA–DMN distributed in a uniform shape with average length and tip diameter of 604.9 ± 16.5 and 36.9 ± 6.1 μm, respectively, with a slightly rough surface [78].

		-	-MN patch consisted of 100 (10 × 10) needles on a baseplate with a height of 650 ± 19 µm, base width of 220 ± 7 µm, and center space of adjacent needles of 500 ± 12 µm. MNs exhibited a pyramid-like shape with uniform dimension and sharp tips, which was necessary to insert into the skin [77]. -DMNs with a height of 804.3 ± 8.2 µm. An applicator used to apply the Candlelit-DMN into the skin in a uniform manner [91].
Androgenetic alopecia	Dissolving MNs [83].	-Valproic acid-encapsulated carboxymethyl cellulose dissolving MNs [83].	-DMNs with a height of 600 ± 22.32 µm and a tip diameter of 20 ± 8 µm were fabricated over 7 × 7 micro-cavities [83].

Legend - MNs: microneedles; DMNs: Dissolving microneedles.

Table 2 – Clinical trials using MNs for cosmetic and dermatological applications.

Skin conditions	Type of microneedle /Drug delivered	Alleged Benefit	Study design and main results	References
Skin wrinkles	Dissolving MNs/ Adenosine, melatonin, sh-decapeptide-9, and human stem cell conditioned media 2 (SCM2)	Improvement of crow's feet wrinkles.	The study compared the effectiveness of microneedle patches and topical applications in treating crow's feet wrinkles in 34 Korean female subjects with mild to moderate wrinkles. It was used a randomized split-face design, where one side of each subject's face was treated with a HA microneedle patch twice a week for 8 weeks, while the other side was treated with a HA essence application. The efficacy was evaluated at weeks 2, 4, and 8, using various measures such as skin wrinkles, skin elasticity, and global visual wrinkle assessment score. The study was conducted using PRIMOS® equipment, and the changes were evaluated by two independent blinded dermatologists. The subjects also assessed the wrinkles using the subject global assessment score.	[70]
Mycosis fungoides	Dissolving MNs/ Doxorubicin	Therapy for mycosis fungoides cutaneous T-cell lymphoma.	The clinical trial used a single-arm, placebo-controlled, open-label, traditional 3+3 dose escalation approach involving nine participants. The treatment was administered once a week for four weeks, followed by a week without treatment. The study found the treatment was safe, with no late or significant toxicities or adverse events. The treatment also resulted in complete resolution of mycosis fungoides lesions and a 31% reduction in the Severity Weighted Assessment tool (SWAT).	[93]
Keloids	Dissolving MNs/ Triamcinolone	Reduction in keloid volume.	The 8-week clinical trial used a single-blind, intra-individual controlled two-phase approach involving 28 patients in the first phase and 17 patients in the second phase. The treatment involved a once-daily, 2-minute application of microneedles for 4 weeks, followed by no treatment for the next 4 weeks. The primary outcome was the change in keloid volume, which was assessed using a high-resolution 3D scanner with a high-definition optical coherence tomography. The trial found a significant reduction in keloid volume, particularly with high doses of triamcinolone.	[85]
Hyperpigmentation	Dissolving/ anti-melanogenic actives (niacinamide, ascorbic acid 2-glucoside, tranexamic acid, resveratrol, 4-n-butyl-	Treatment of facial skin discolorations.	The 12-week clinical trial used HA-MNs arrays on subjects with hyperpigmented skin. The arrays were applied to the affected areas of the face, and the color properties of the skin were analyzed using spectrophotometry at a single center.	[82]

	resorcinol, and *Halidrys siliquosa* extract)			
Psoriasis	Dissolving/ calcipotriol–betamethasone ointment	Treatment of psoriatic plaques.	The study involves ten patients with psoriatic plaques that were resistant to topical calcipotriol-betamethasone ointment. The study used MN arrays placed over the thickest areas of the plaques after application of the ointment. The arrays were applied once daily at night for one week. The clinical improvement was evaluated using the modified Psoriasis Area and Severity Index (mPASI) at week 0 and week 1, and patient satisfaction was assessed using a four-point scale. The study found no adverse effects, such as infection, irritation, or aggravation of pre-existing psoriasis. The MNs arrays were well-tolerated for the treatment of psoriatic plaques.	[92]
Skin winkles	Dissolving MNs/ ascorbic acid and retinyl retinoate.	Wrinkle improvement.	The study involves 24 Korean women divided into two groups. Group A received retinyl retinoate-loaded dissolving MN arrays, while group B received ascorbic acid-loaded dissolving MN arrays. The arrays were applied twice daily for 12 weeks. Both showed significant differences in all Visiometer® parameters, particularly in R1 (skin roughness) and R5 (arithmetic average roughness).	[33]
Warts	Coated MNs/ Bleomycin.	-Treatment of warts caused by human papilloma virus. -Compare the therapeutic effects of a newly developed bleomycin microneedle patch with cryotherapy in the treatment of warts.	The study involves 42 patients with multiple warts, including *Verruca vulgaris* and *Verruca plantaris*. The treatment efficacy was evaluated using the Physician's Global Assessment (PGA) and the Patient's Global Assessment (PaGA). The pain experienced during the treatment was assessed using a visual analogue scale (VAS) ranging from 0 to 10. The treatment involved a single application at 2-week intervals until the lesions were completely cleared.	[55]

Legend - MNs: microneedles; HA-MNs: hyaluronic acid microneedles.