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Human studies with microneedles for evaluation of their efficacy and safety

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Abstract

Introduction: During the past two decades, many studies have documented the development of microneedles (MNs) as a feasible technique for the effective administration of drugs. More and more human studies have been done with MNs to bridge the gap between research and market applications that provide efficacious techniques for clinical implementation.

Areas covered: The aim of this review is provide a brief description of the status of human study with MNs and to demonstrate progress for the right use of microneedle arrays in clinical settings. It also describes the considerations for clinical application with each type of MNs.

Expert opinion: Microneedle systems were introduced to overcome the limitations of conventional methods of drug administration. Lots of microneedle systems have undergone clinical evaluation to
determine their efficacy and safety, and many studies have demonstrated positive results. The successful clinical use of the microneedle in vaccine therapy is remarkable and supports the importance of conducting further tests in a wide range of medical applications. Self-administered MNs appeared to be an attractive alternative method that needs further research to become a reality in the near future.

**Article highlights box**

- MNs have become an attractive alternative drug delivery system through the skin because they provide several benefits, including painlessness, convenience, self-administration, and noninvasive application.

- There are five types of MNs that facilitate improved permeability of molecules and macromolecules: hollow MNs, solid MNs, dissolving MNs, coated MNs, and hydrogel-forming MNs.

- Human studies and clinical trials of MNs have demonstrated their features, safety, and efficacy in human beings.

- The applied protocol is suggested as a critical element for successful application and satisfactory delivery of pharmaceutical agents.

- Human studies of MN applications were performed to provide the evidence for patient compliance, acceptability, tolerance, and usability of this unique system.

**Keywords:** microneedle, human study, efficacy, safety, applied protocol, clinical trials
1. Introduction

Description of MNs

Microneedles are, as the term *microneedle* (MN) indicates, extremely small, micron-size needles. The term can refer to a single needle or to an array of needles. Various materials, including metal [1], polymer [2], silicon [3], and glass [4], are used to make MNs, which are constructed to penetrate the outer layer of skin in order to introduce an active drug ingredient into the body [5]. The length of these devices usually ranges from 25 μm to 2000 μm, with a variety of shapes, which can be mounted on a base for support [6]. They are long enough just to break the stratum corneum barrier but too short to reach the nerve cells in the dermis, thus they do not stimulate a pain reaction. MNs are catalogued into five types (Fig. 1): hollow, solid, dissolving, coated, and hydrogel forming.

![Figure 1](image-url)

**Figure 1.** A schematic of five different microneedle types to apply in the skin: (a) a hollow microneedle is used to pierce the skin and enable release of the drug solution through the holes inside the needles; (b) a solid microneedle provides the micro-holes through which the drug can be released into the skin; (c) a dissolving microneedle provides rapid or controlled release of the drug incorporated in the needles; (d) a coated microneedle provides rapid diffusion of the active drug through the coated layer into the deeper skin; (e) a hydrogel-forming microneedle swells and lets the drug diffuse from the patch through its swollen micro-projections.
Hollow MNs deliver a drug into the skin through holes [7], in a way that is similar to the usage of a hypodermic needle. Solid MNs are usually used in pretreatment situations; this therapy enhances the permeability of the skin, which facilitates the application of drugs through the micro-channels [8]. Dissolving MNs are often made from polymer or polysaccharides with therapeutic molecules dispersed inside the needles. As soon as the needles are inserted into the skin, the biodegradable materials dissolve or degrade so that the encapsulated drug is released. This application prevents cross-contamination by accidental or intentional reuse with other patients. Coated MNs typically have a drug formulation applied to the outside surface of the needles [9]. After these MNs pierce the stratum corneum, the drug is released from the coated layer and diffused into the skin. The amount of the drug is usually limited to less than 1 mg, reflecting the load capacity of the coated layer [10]. The newest application of MNs is the hydrogel-forming type, in which the needles are made of an expanding material and the drug reservoir is attached to the baseplate [11], [12]. The active agent is released from the reservoir into the skin through the micro-channels, and the rate of diffusion is controlled by manipulating the number of crosslinks within the hydrogel framework.

**Human studies**

In 2001, the first research on microneedle use in humans was carried out by Kaushik et al. [13]. Since then, there has been a great deal of work examining microneedle use in human subjects throughout the world, based on a wide range of participant ages and diseases. To translate the research on microneedles from the laboratory to the market, the most important criteria are evidence of safety and the efficacy of microneedle-based applications and demonstrated in clinical trials [14]. The first clinical study was done by Wermeling et al. in 2008 [15]. Figure 2 shows the number of human studies that have been conducted each year.
Currently, a total of 58 trials related to microneedle application have been found using “microneedle” as a keyword search term on clinicaltrial.gov. Figure 2 provides a snapshot of the percentage of trials involving each microneedle system, with hollow MNs being the most commonly selected type for study because of easier regulation compared to other types of microneedles. Table 1 offers an overall view for researchers of the wide range of participants’ ages and phases of clinical study that have been examined with MNs. In this review, solid, coated, dissolving and hydrogel-forming MN will be mainly discussed.

**Figure 2**: Summary of human studies of MNs conducted each year.
Figure 3. Pie chart of current trials of microneedle use in humans on clinical.gov based on type of microneedles: Hollow MN 48%, Solid MN 34 %, Coated MN 9%, Dissolving MN 7% and Hydrogel-forming MN 2%

<table>
<thead>
<tr>
<th>Processing condition</th>
<th>Targeted treatment</th>
<th>Phase</th>
<th>Number of patients</th>
<th>Age (years)</th>
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<tr>
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<td>18-49</td>
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<tr>
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<tr>
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<td>Repigmenting in vitiligo skin</td>
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<td>10</td>
<td>&gt;18</td>
</tr>
</tbody>
</table>

Table 1. Summary of clinical studies using microneedles from clinicaltrial.gov.
2. Microneedle features with human subjects

2.1. Penetration

Pretreatment with solid MNs can improve the permeability of some hydrophilic agents; for example, naltrexone successfully delivered through skin showed a rapid rise or burst of absorption within the first several hours of application [16]. Several factors affect skin permeability; for example, an increase in the tip radius of the MNs caused lower penetration, whereas an increase in MN length resulted in more drug penetration [17]. Different MN shapes cause different insertion depth. The maximum depth of diffusion was found with cone-shaped 200 μm long MNs (170 ± 13 μm), whereas the depth of diffusion of 300 μm long needles with sharp tips and an angle of 15° was 120 ± 10 μm [17]. Another finding showed that micro-channels created by MNs were markedly smaller than the dimensions of the MNs [18]. Velocity of insertion also affects the permeability of the drug; the increase of applicator speed increased the proportion of penetration [19]. Injection in different skin areas may affect the depth of holes; for example, inserting a 280 μm solid MN in the volar arm resulted in average depth of 179 ± 14 μm, whereas inserting the same MN in the fingertip gave an average depth of 146 ± 19 μm [20].

2.2 Skin resealing

One of the most significant concerns about solid MN application is the reversible property of the skin’s natural repair mechanisms. As soon as the stratum corneum is disrupted, the lamellar body secretory responses create a synthesis of the lipid to restore and maintain the stratum corneum structure [21]. This natural process reduces the delivery of drugs, blunting the clinical utility of this unique technique. One study noted that the insertion points can close as quickly as 15 minutes [22], although other studies report closing within 2 hours [23], 8-24 hours [24], and 24 hours [25] after solid MN application when the injection sites are exposed to the air. A study showed that the insertion points reduced from a depth of 158 ± 20 μm to a depth of 76 ± 13 μm in a time frame of 85 minutes [20]. The explanation for variation in time frames between the studies could be the difference in insertion methods and the variable MN geometries. For example, with the impedance
technique, the authors noted that actual micropore closure time frames may be less drastic than their calculations due to difficulty in distinguishing between healing curves, relatively large error bars, and differences in initial impedance drops [23]. A new application of the impedance test is the gel direct condition, which was demonstrated to produce less variation between the young and elderly groups [26]. To prolong the skin’s resealing time, it was treated with occlusion following the solid MN injection; as a result, the time frame was extended to 40 hours in one study [23] and 48-72 hours in two other studies [16], [27]. With occlusion, skin repair also depends on microneedle length; a twofold increase in length resulted in six fold longer closing time, and a fivefold increase in the number of needles corresponded to a tenfold increase in barrier resealing time [23]. An alternative hypothesis is the existence of subclinical local inflammation at the microscopic level; in support of this idea, one study demonstrated that micropore closing time was extended by using topical anti-inflammatory agents such as diclofenac [28].

2.3 Insertion force

Various geometries of MNs need different applied forces. Research has shown that the dependence between the force necessary for injection and the interfacial area of the needle tip is linear and might be described by the balance between the energy applied to the skin and the energy required to create a tear in the skin. Hydration status has been known to alter the mechanical properties of the skin. With skin in a normal condition, approximately 10 mN of force was needed to insert a novel ultra-sharp tip and a side opening silicon hollow MN array [29].

In term of solid MNs, the conically shaped 300 μm long MN needs an applied force ranging from 0.1 N to 3 N. At that force, the fracture discontinuities were rarely apparent; even with forces was as high as 25 N. Most notably, repeated insertion and wear tests failed to result in damage to solid MN arrays [30].

3. Safety of MNs with human subjects

3.1. Safety with solid MN injection
One of the most commonly used measurements of pain intensity in clinical trials is the Visual Analog Scale (VAS). The VAS score for using 150 μm long solid MNs was significantly less than that for using 26 G hypodermic needles (1.7 mm vs 59.8 mm, respectively) [13]. Numerous experiments with solid MN applications have reported that the participants did not experience pain [17], [22], [16] or discomfort [10], or that the use of 750 μm MNs caused much less pain in the ID group compared to the IM group (VAS scores were 1.5 mm vs 15 mm, respectively) [31]. MN length was demonstrated to have the strongest effect on pain sensation, as a threefold increase in length (480 μm to 1450 μm) increased the VAS score by sevenfold (2 ± 2 mm vs 15 ± 7 mm) whereas a tenfold increase in the number of needles (5 to 50 needles) increased pain only about twofold [32]. In contrast, another study reported that injection using a 180 μm long microneedle was more painful than the use of a 280 μm long microneedle; the explanation for this difference was that more force was applied to achieve a certain penetration depth when the 180 μm MN was used [24].

In terms of skin reactions, the increase in the velocity of solid MN application (from 4.3 m/s to 8.5 m/s) resulted in the small spots of bleeding; the slower speed did not significantly increase skin redness. As the tip radius (from 10 μm to 20 μm) and length of needles increase (from 100 μm to 300 μm), there is a trend toward greater skin redness [19]. Another study using solid polymer 500 μm long MNs found little difference in skin redness after injection for various times (2 min to 240 min) and rapid recovery between 30 min and 2 hours; additionally, the greater initial redness was measured at 2 min after MN application [33]. Erythema was observed in some studies as the most common skin reaction at the injection site [28], [27]. Concern about skin irritation at treated sites has also been assessed in several other studies that report no clinically significant skin irritation with solid MN administration [13], [16], [24].

3.2. Safety with dissolving MN injection

Participants in various studies using dissolving MNs have reported little or no pain. In a study
that used maltose dissolving 500 μm long MNs, the participants did not complain of any pain when the needles were inserted [34]. Another study of dissolving MNs of different lengths (300 μm, 500 μm, and 800 μm) assessed pain, and the results indicated that VAS scores gradually increased from the 10 mm to less than 20 mm, consistent with the increased length of the MNs [35]. 600 μm long MN patches were self-administered, and participants who provided feedback said the application was pain free [36]. No pain was reported by volunteer participants when they applied a 650 μm long MN patch to the forearm region [37], and 96% of participants reported no pain when an 800 μm long dissolving MN application was used to treat influenza [38].

Insignificant erythema was found in human subjects after administration of dissolving MN made of maltose. [34]. An 800 μm long dissolving microneedle known MicroHyala® was loaded with all-trans retinoic acid (ATRA) for treating seborrheic keratosis. Immediately after the patch was removed, a weak positive reaction indicating erythema was observed in all subjects; this reaction disappeared 7 days after injection and participants’ skin returned to normal 30 days after injection [39]. This MN system also was used in a clinical trial for treating seborrheic keratosis and senile lentigo for 4 weeks. In another study, faint erythema was observed as the application number increased; this reaction was temporary and the participants recovered completely after 3 months [40]. A similar observation was also recorded in another study using different lengths of MicroHyala® MNs (300 μm, 500 μm, 800 μm) without active agents being loading [35]. In influenza-loaded MicroHyala® MNs, erythema was seen in all 40 subjects, and purpura and pigmentation were observed in half of the volunteers [41].

Most notably, there are a few studies of the self-applied method. Results were erythema at the injection site, which dissipated after 15 min and was not noticeable after one hour when the large MN patch application was used [36]; or mild erythema that resolved fully after several days [37]. In a study of influenza treatment using dissolving MNs by self-injection, more local reaction events were reported in the ID group than in the IM group, such as pruritus (82% vs 16%) and erythema (40% vs 0%). However, the local events were mild and self-limited, lasting 2–3 days on average [38]. Taken together, the results of the safety tests of dissolving MNs were acceptable, with no observed severe
local and systemic adverse events.

### 3.3. Safety with coated MN injection

A phase II clinical trial of parathyroid hormone–coated microneedles was integrated into the ZP applicator system (formerly Macroflux®, ALZA Corp.) to treat advanced osteoporosis in men and postmenopausal women. Over the 6-month outpatient daily application experience, there was no evidence of patch site skin infection or skin sensitization caused by injection using 190 μm long coated MNs [42].

### 3.4. Safety with hydrogel-forming MN injection

The average VAS score resulting from the use of 600 μm long hydrogel-forming MNs with a density of 361 needles per 0.5 cm² was greater than an array with a density of 121 needles per 0.5 cm². Additionally, VAS scores increased for both MN designs during the 24-hour treatment protocol [43]. Minor erythema also was observed in all volunteers in another study using the same MN system; erythema occurred no matter how long the MNs were inserted, indicating that initial insertion may be the reason for the erythema. There were no local skin reactions or infections when participants were followed up at weekly intervals for 4 weeks. Pain scores in this study were measured at two time point: at insertion the VAS score (6.5 ± 5.8 mm) was higher than when the participants were wearing the patch (2.8 ± 3.1 mm) [44].

### 4. Efficacy of MNs with human subjects

#### 4.1. Efficacy with solid MNs

In general, studies of pretreatment with solid MNs have focused on the accepted strategy with topical pharmaceutical form, as in anesthetics therapy. Pretreatment of the skin using solid 70 μm MNs reduced the time required for topical anesthetics to take effect threefold, and pain reduction in the ID group was higher (39% versus 19% for no pretreatment) [45]. In another study, incubation time
was reduced from 60 min to 30 min in a lidocaine application [46].

4.2. Efficacy with dissolving MNs

Recently, dissolving MNs have been improving as an attractive means for medication therapy, especially in the vaccination field. The MicroHyala® system used an array of 800 μm long dissolving MNs to deliver 15 μg TIV influenza vaccine and produced equivalent immunogenicity compared to SC administration [41]. A 15 μg TIV influenza vaccine was delivered with another dissolving MN patch system and had a similar immune response compared to 15 μg IM injection. Most notably, a study found no difference between a self-administration group and a physical workers injection group in the successful delivery of identical drug doses when the influenza strain was injected into the skin [38]. In a study that explored an alternative hypothesis that a large MN patch can be successfully self-applied by participants, 16 single MN patches (10 cm × 12 cm) offered no significant difference in disruption of the skin barrier compared to a single patch application (0.5 cm² per array, 600 μm long). This study supports the possibility of expanding the size of the patch for the MN application as well as for transdermal drug delivery [36].

4.3. Efficacy with coated MNs

Zosano Pharma has developed a device using a novel transdermal MN drug delivery system known as Macroflux®-ZP, which is an array of titanium MNs integrated into a patch and a handheld reusable applicator. Clinical trials evaluated the pharmacokinetics and pharmacodynamics of PTH(1-34) (parathyroid hormone) attached in this unique system. In the phase I test, this drug offered a threefold $T_{\text{max}}$ and half $T_{1/2}$ time, compared to a controlled conventional SC injection drug. In the phase II results, different doses (20, 30, 40 μg) indicated a proportional increase in plasma and provided an enormous rise in spine bone mineral density [42]. These findings indicate that ZP-PTH provides an effective treatment therapy for post-menopausal women with osteoporosis. Zolmitriptan MN patch for acute migraine was developed by Zosano Pharma and phase III study of zolmitriptan
MNs is currently underway. In another example of coated microneedle, Nanopatch™ is a high density array of short silicon microneedles with 230 μm height to deliver vaccine into the skin including influenza vaccine and human papilloma virus-like particle vaccine [47, 48]. Nanopatch™ is also ongoing the clinical study of polio vaccination.

4.4. Hydrogel-forming MNs

The reaction of skin to gamma-sterilized hydrogel-forming MNs 600 μm long was documented, and the deformation of the needles after injection prevented re-insertion. Thus, there was a safety issue with the current design [11]. The capacity of hydrogel-forming MNs to swell and retain morphology has produced a great interest in this type of MN as a device for withdrawing the fluid from the skin and thus serving as a means for diagnosis. A study demonstrated that fluid uptake from skin using hydrogel-forming MN arrays could be quantified and that the amount of fluid withdrawn was about 0.9-2.7 μl after 1 hour. In addition, the mass of the MNs increased approximately 30% after 6 hours in the skin [44]. Hydrogel-forming MNs were used to collect and detect the concentration of the interstitial fluid of participants who received oral caffeine or glucose [49].

4.5. Efficacy of nanoparticulate vaccination using MN in vivo

A nanoparticulate system was delivered into dermal layer to stimulate antigen presenting cell in skin [50, 51]. Administration of the nanoparticle formulation with the antigen offered a higher antibody response compared to the administration of the antigen alone [52]. Dissolving MN containing poly-lactide-co-glycolide (PLGA) nanoparticles with ovalbumin demonstrated the capability of providing highly protective immunity against viral challenge [53]. Recently, the administration of a nanoparticle vaccine formulation using hollow microneedles showed clinical feasibility. Vaccination with tetanus toxoid-loaded chitosan nanoparticles using hollow MN showed that microneedle injection offers an antibody titer level comparable to that of a commercial tetanus toxoid vaccine [54]. PLGA nanoparticles and liposomes with ovalbumin induced higher IgG2a by
sustained release of the antigen [55, 56].

5. Applied protocol

Currently there are no standard worldwide protocols for administration of MNs because of the numerous novel applications involving great differences in specific MN shapes, types, and treatment purposes. Several critical elements on applied protocol in studies have been summarized in Table 2. For example, injection time is different for dissolving MNs and hydrogel-forming MNs due to the time necessary for swelling or scattering into the deeper layer of skin to provide the therapeutic effect. As another example, the site of the injection is very important for the successful delivery of the drug and depends on the target disease: abdominal skin is injected for treatment of diabetes, the deltoid region is injected for vaccination, and the forearm is used as the site for overall studies.

<table>
<thead>
<tr>
<th>Injection site</th>
<th>Applicator/Hand (application duration)</th>
<th>Self-applied</th>
<th>Purpose</th>
<th>References</th>
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<td>Volar forearm</td>
<td>Hand (a few seconds)</td>
<td></td>
<td>Penetration</td>
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<td>Volar arm and dorsal aspect of the fingertip</td>
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**Dissolving MNs**

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<td>X Penetration</td>
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<tr>
<td>Forearm</td>
<td>Hand (20 min)</td>
<td>X Tolerability</td>
<td>[37]</td>
</tr>
<tr>
<td>Wrist</td>
<td></td>
<td>X Influenza</td>
<td>[38]</td>
</tr>
</tbody>
</table>

**Coated MNs**

<table>
<thead>
<tr>
<th>Area</th>
<th>Application Duration/Device/Method</th>
<th>Endpoint</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forearm</td>
<td>Hand (30s)</td>
<td>Trehalose delivery</td>
<td>[58]</td>
</tr>
<tr>
<td>Lateral abdomen, upper forearm, thigh and worn</td>
<td>ZP patch Applicator (30 min)</td>
<td>Parathyroid hormone</td>
<td>[42]</td>
</tr>
</tbody>
</table>

**Hydrogel-forming MNs**

<table>
<thead>
<tr>
<th>Area</th>
<th>Application Duration/Device/Method</th>
<th>Endpoint</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventral forearm</td>
<td>Spring loaded applicator (0, 2, 24h)</td>
<td>Tolerability</td>
<td>[43]</td>
</tr>
<tr>
<td>Forearm</td>
<td>Hand (2, 4, 6h)</td>
<td>Safety</td>
<td>[44]</td>
</tr>
<tr>
<td>Ventral forearm</td>
<td>Hand (30 min)</td>
<td>X Efficacy</td>
<td>[59]</td>
</tr>
<tr>
<td></td>
<td>Hand (1h)</td>
<td>Drug monitoring</td>
<td>[49]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X Insertion</td>
<td>[60]</td>
</tr>
</tbody>
</table>
Table 2. Summary of the protocols for using microneedles in human subjects.

The applicator is one of key elements in the effective application of MNs. Several applicator systems have been developed. In the field of single MN administration, the BD™ Micro Injection System is a prefilled syringe combined with a 1.5 mm long microneedle extending from the proximal end of the glass syringe. The syringe tip has a specifically designed needle penetration depth limiter to ensure correct needle placement into the dermis [61], [62]. This system also has been known as the BD Soluvia™, which has been used in many clinical trials of the influenza vaccine [63]. Another system developed for prefilled vaccine single hollow MN therapy is VAX-ID™; this device allows one-time use to deposit the active drug agent into the dermal layer of the skin; with this method the needle auto-retracts after application [64]. A holder applicator has been introduced for MN delivery of insulin through the abdominal skin; this device comprises four main parts positioned concentrically within each other to allow the glass microneedle to pass through. It consists of components that (a) hold the device on the skin’s surface, (b) control the depth of injection, (c) keep the needle firmly positioned within the system, and (d) minimize skin deflection during microneedle insertion. A non-tip end of the needle extends beyond the device and is connected to tubing. During the process, MN length can be precisely controlled within ± 10 μm, although the insertion depth into the skin is less accurate because of the variable deformation of the skin during MN usage [65]. A system for supporting ID MN infusion of insulin is called an investigational ID microneedle catheter set; it consists of 1.5 mm MNs, a fluid tubing line, skin adhesive, and a luer connector for joining the tubing line to the insulin infusion pump [66].

For the application of the MN array, a manual applicator has been designed in which 30 G hypodermic needles various lengths (550 μm, 700 μm, and 900 μm are assembled onto a polymer base to create a 4 × 4 MN array. Many of these features need to be assessed further because the design of this applicator is intended to increases the speed of MN insertion into the skin as well as provide successful treatment [67]. An applicator is ideal for controlling application speed because the activity
of mainspring and the change in loading distance use the metal rings as spacers to adjust injection velocity. The return ring allows the MN array to rebind when it contacts the skin; thus, the piercing period is < 1 ms [19].

**Figure 4.** (a) the microneedle patch is manually administered to the wrist, enabling self-administration by study participants. Reused with permission from [38]; (b) images showing the application of thumb pressure by the subject to the microneedle patch on the ventral forearm (left) and the resulting color change of in the pressure sensor (right). Reused with permission from [60]

Another aspect of applied protocol that has increasingly been considered is self-injection. Typically, MNs have been injected by experienced staff members; researches have been conducted on self-administration, and the results are promising as an easy-to-use alternative technique. In an experiment with the BD Micro System, the group that had not trained or practiced had a higher percentage of successful injection than the well-trained group [61]. In a study of BD Soluvia™ prefilled syringe MN, volunteers injected themselves and demonstrated a high success rate for self-administration, resulting in the suggestion that self-injection is a viable option for health care workers. [68]. An array with 50 solid MNs 750 μm long was attached with a snap-based device to facilitate insertion using polypropylene screw caps; there was a snapping sound when the force of approximately 37 N was reached. This amount of force is necessary for successful application. The median percentage of insertion sites observed on the first attempt was 96 % (without the snap-based
device this number was 90%), and the variability between subjects was lower than before (5% compared to 13%–15%) [31]. In regard to dissolving MNs, there have been three studies in 2017 that apply the MN array by volunteers that have demonstrated successful delivery. To facilitate satisfactory outcomes, several signals have been integrated into MN arrays to enable recognition of the right application, including a colored change pressure sensor when enough force was applied, a click sound for correct administration, or audible and tactile feedback when sufficient force was used [36], [37], [38]. Equally important, the procedure for applying MN patches has been provided as one of the first attempts to standardize the usage of dissolving MN patches. There are three main stages of application: (a) removing the protective cap, (b) pushing the patch by thumb until a clicking sound is heard. and (c) removing the patch 20 min after injection [37] (Fig. 6a).

Figure 5. Procedure to apply a microneedle patch to the skin: (a) protocol for dissolving MN patch applied by the volunteer without the support of an applicator. Reused with permission from [37]; (b) protocol for coated MN applied by the subjects with the support of an applicator. Reused with permission from [42]

There is one study of coated MNs applied by patients to treat post-menopausal women with osteoporosis with the help of self-applicator. Patch application is a simple press and apply with the ZP-PTH patch in a ring attached to a handheld, reusable applicator; the patient presses against the
skin to release the patch. It is a simple method that participants completely achieved and that provided successful drug delivery [42].

In regard to hydrogel-forming MNs, there was an insignificant difference in disruption of the skin barrier between two groups, one of well-trained researchers and the other of untrained volunteers, using 400 μm long MN arrays [59]. The authors also provided a protocol for self-injection. A leaflet inside the patch package has pictures illustrating the stages of application. In addition, the volunteer’s awareness and detailed instruction are important for successful usage. Recently, the change in color of the pressure sensor has facilitated an easy-to-use process for self-application because in certain situations it is useful to use this sensor to confirm MN insertion [60].

6. Perception of patients and health care workers

Patient compliance and perception is important for proper use of drugs in the clinic. Four studies have sought to assess the point of view of participants following an ID influenza vaccination using BD Soluvia™. In one study, 96% and 97% of 1,679 adults and 2,262 elderly people, respectively, reported their acceptance of revaccination, and 80% and 90% in the two groups, respectively, indicated that they would probably or definitely want to be vaccinated again. More than 96% of the volunteers vaccinated intradermally in both groups were “satisfied” or “very satisfied” with the injection system [69]. A similar finding with a satisfactory endpoint was cited in 1,402 vaccines and 30 prescribers in Australia and 264 vaccinees and 16 prescribers in Argentina after MN application because the injection was considered minimally painful and was quickly administrated. A total of 95% of the vaccinees reported that they would prefer to receive this vaccine next time [70]. After this research, the opinions of 1,261 vaccinees in the Czech Republic and Turkey were recorded, with 96.1% and 95.3% in the two countries reporting satisfaction. Of this number, 43 prescribers were very satisfied with drug delivery, and 93.9% of volunteers were willing to receive the same vaccination next year [71]. These results suggest that MN-based vaccination would be the most effective approach for increasing the proportion of patients receiving vaccinations throughout countries. Recently another
study has found contrasting results to previous studies; in the Netherlands, 41.7% of health care workers preferred the ID injection for the immediate 9 µg ID vaccination; after they were intramuscularly injected with a 15 µg vaccine and two weeks following, by a twofold increase, participants considered the ID less pleasant than the IM route [72]. There was a study to determine the opinion of public and healthcare professionals on the use of MN, 100% of public participants and 74% of professional participants reported the wide advantages of MN technology [73]. In several human studies, patient acceptance was also evaluated; for example, 97% of subjects who received an injection ID using the prefilled syringe MN system were willing to have another vaccination by this method [74]. In a self-vaccination trial, 70% of volunteers either strongly (51%) or somewhat (19%) preferred the ID injection, 26% had no preference, and 4% either somewhat or strongly (1%) preferred IM injection [68]. In the study with the VAX-ID™ MN system, the vaccinators confirmed the next to the highest degree of usability for non-medical personnel and by any subject through self-administration (88.9%) [64].

In the insulin MN delivery field, after three days wearing either the ID infusion system or the SC system, patients reported that both routes of insertion had high rate of acceptability (100% and 96%, respectively); however, assessment of infusion set overall favored SC administration, with 96% reporting it as very acceptable versus 83% for the ID route. Additionally, when asked about their willingness to receive the next injection, 61% favored ID and 80% preferred SC [66]. In a subject preference survey of 14 patients after the MicronJet™450 device was used for ID insulin administration, five patients preferred ID injection in the future, eight patients were neutral, and one preferred the SC route [75]. Obviously, MN insulin delivery has not yet been shown to be the most preferred method among participants in studies; thus, further investigation is needed to demonstrate the advantages of the microneedle system in term of patient acceptance.

7. Conclusion

A microneedle system was introduced to overcome the limitations of conventional drug delivery
methods. Many human studies have been conducted with MNs to bridge the gap between research and commercialization. Various microneedle systems have undergone clinical evaluation to determine their efficacy and safety, and many studies have reported positive results. In this review, the status of human studies with MNs was summarized. Many microneedle systems are undergoing clinical evaluations, and the successful results of clinical tests of MNs used in vaccines, immune therapy, diabetic treatment, and migraine treatment are notable. Self-administered MNs appear to be an attractive method compared to other administration methods. Self-administration studies have demonstrated the advantages of MN systems. The protocol for using MNs is an important factor that determines patient compliance and successful treatment.

8. Expert opinion

This is the first time that studies of MN usage in human beings have been summarized in terms of feature, safety, and efficacy in order to provide a comprehensive, complete picture of MN application as a drug-based delivery system. In the field of vaccine therapy, the numerous research conducted has demonstrated the sufficiency of ID hollow MN delivery compared to the current administration route [76, 77]. Especially, the newest study of dissolving MNs for influenza vaccination provided an insignificant difference in immune response between ID and IM injection; this has led to other options in MN vaccine delivery. Undoubtedly, in near future, MN studies will be conducted with different types of vaccines, opening a novel era for vaccine therapy. In term of MN for insulin therapy, MNs has provided safety and efficacy in patients [65, 78]. Taken together, MN-based drug delivery methods are facilitating examination of the key issues, which are the limitation of macromolecules in treatment because of poor bioavailability in oral methods or pain with current methods of needle injection. Over two decades, the idea was just to reduce the dimensions of conventional hypodermic needles from mili-size to micro-size. However, the expansion of MNs to other types (solid MNs, dissolving MNs, coated MNs, and hydrogel-forming MNs) has facilitated widespread knowledge and application of MNs; for examples, MNs for minimally invasive
intraocular drug delivery [79]. Most notably, several human studies of MNs and injections have examined self-application by participants; these studies have shown that participant self-injections resulted in equal efficacy and safety compared to injections by health care workers. This unique technique offers more opportunities for patients to inject by themselves and might make them more responsible and interested in treatment.

During the early period of research, MNs were used only with adults; little research was conducted with children for insulin delivery and vaccination [80], [81]. However, more recent research has begun to document the safety and efficacy of MN application in pediatric populations. Additionally, the perception of patients reported in several studies has demonstrated the usability, tolerability, and acceptability of this innovative technique. These studies also will contribute to successful practice with future products and MNs used in the clinic.

Overall, until now, studies of MNs in human beings have been well done to provide proof of safe and efficient application in different populations, including as children, the elderly, and patients who are have experienced renal transplants. However, from the viewpoint of clinicians, MNs should offer advancement in clinical practice compared to current methods of drug delivery. MN applications should incorporate notable enhancements in stability, bioavailability, and potency as well as a decrease in adverse reactions. Other considerations include safety, lower infection risk, reduced chances of wrong administration, and administration of the proper therapeutic dose for the desired outcome. An equally important factor is the shape and dimension of the MNs, which can gain the acceptance of patients because they can apply this drug delivery system without the help of well-trained practitioners. Comprehensive additional clinical research is essential to demonstrate that insertion of these needles into the skin is not risky, especially for a long duration of treatment. To prevent undesired effects on patients, it is incontrovertible that further studies of MNs used in humans are essential before they are approved for use in the market. The other consideration is that there have not yet been established international regulatory guidelines regarding the standard for evaluation of safety and efficacy because of the novelty of MNs. There should be parallel development of MN applications and accepted regulatory standards in order to orient scientists in studies that reflect reality,
in order to serve the human beings.

To sum up, the results of MN-based drug delivery in human subjects has seen very promising outcomes and is one of the expected contributions to the development of pharmaceutics in particular and human health in general.

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**Declaration of interest**

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Papers of special note have been highlighted as:

* of interest

** of considerable interest


(*) These studies investigate the feature of MN in human subjects


(*) Safety and efficacy of dissolving MN injection


(*) Safety and efficacy of hydrogel forming MN injection


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(••) These references are about the efficacy of MN in delivery nanoparticle system


(••) Applied protocol for MN administration


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