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To cite this article: Hye-Rin Jeong, Han-Sol Lee, In-Jeong Choi & Jung-Hwan Park (2016): Considerations in the use of microneedles: pain, convenience, anxiety and safety, Journal of Drug Targeting, DOI: 10.1080/1061186X.2016.1200589

To link to this article: http://dx.doi.org/10.1080/1061186X.2016.1200589

Accepted author version posted online: 09 Jun 2016.
Published online: 30 Jun 2016.

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Considerations in the use of microneedles: pain, convenience, anxiety and safety

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ABSTRACT

Transdermal delivery using microneedles is gaining increasing attention from pharmaceutical and cosmetic companies as one of the promising drug delivery methods. Microneedle products have recently become available on the market, and some of them are under evaluation for efficacy and safety. To be available in the market for cosmetic and therapeutic use, several factors should be considered, including pain, anxiety, convenience and safety. These factors are summarized and reviewed in this article according to type of microneedle. Various kinds of materials have been used for manufacturing microneedles and developing drug formulations for microneedles. Safety information about materials used for microneedles is summarized in terms of type of microneedles. In addition to their biocompatibility, mechanical safety is also discussed. This review can provide guidelines for designing microneedle products for proper use.

Introduction

A transdermal delivery system has been developed to facilitate ease of application and removal of drugs using microneedles, thus increasing patient compliance [1]. However, the size of the active drug ingredient needs to be smaller than 500 Da of molecular weight in order to penetrate the outer skin, the stratum corneum, which is 10–15 μm thick [2]. A microneedle system was introduced about 20 years ago to overcome this skin barrier [3]. Conventional needles can pass through the skin, but they cannot provide targeted drug delivery. Initially, microneedles were fabricated to pierce the stratum corneum with a sharp microstructure, and various active ingredients, including antigen and peptide, can be delivered by the transdermal method regardless of the molecular weight and hydrophobicity of the drug [3,4]. Microneedles were fabricated to be long enough to penetrate the stratum corneum, but short enough to cause minimal pain. As a result, they not only reduce pain but they also can ameliorate anxiety and infection. Since the introduction of solid 80-μm microneedles, various other types of microneedles have been developed [3–5]. Currently, hundreds of journal articles about microneedles are published every year, and the potential of the microneedle system has been demonstrated by various applications [5,6].

The primary applications of microneedles are in cosmetics and medicine [5,7]. Microneedle systems have been utilized for both local and systemic delivery [4,8]. Examples of local delivery are introducing antigen into the skin for cutaneous immunization [9–12] and targeted delivery of drugs into tissue [13–16]. An example of systemic delivery is injecting insulin and exendin-4 into the skin in order to produce quick adsorption through blood capillaries [17,18].

Since the microneedle system was introduced in 1997, companies have been developing microneedle products for cosmetic and medical applications [7]. Some of the products are on the market, and others are under review to gain approval by the U.S. Food and Drug Administration [7,19]. Microneedle products available on the market today are related to cosmetics, and human studies of the microneedle system for medical applications have been conducted [20–24]. In the case of daily administration such as cosmetic applications, pain is a critical issue [25,26], and anxiety is a primary concern in the pediatric application of microneedles [27–29]. To develop a marketable microneedle system, it is necessary to investigate the safety of microneedles to ensure that they are used properly and marketed appropriately. In this article, four factors (pain, anxiety, convenience and safety) will be reviewed and discussed. After a brief description of the types of microneedles that are fabricated, the issues of pain, anxiety and patient convenience will be discussed. Then the safety of the material used to fabricate microneedles will be reviewed. In addition to chemical and biological safety, mechanical safety is included in this review. Our goal here is to provide guidelines for the proper design of marketable microneedles.

Types of microneedles

Microneedles can be categorized as solid, coated, dissolving and hollow as shown in Table 1. Drug delivery methods are different depending on the type of microneedle used, and safety issues vary as well. For example, solid microneedles create holes in the stratum corneum through which the drug is diffused into the skin. The Derma-roller is a kind of solid microneedle that has been used for treatment of acne scars and the delivery of the active ingredient into the skin layer through generated holes [30]. This type of microneedle has the advantages of easy preparation and economical production [5,31–33]. Coated microneedles are prepared by applying the drug to the surface of solid microneedles. Small drug doses can be delivered efficiently using coated microneedles without a complicated preparation procedure [34–39]. Dissolving microneedles encapsulate the drug, which is adsorbed by water when the microneedles dissolve after being inserted into the skin.
Dissolving microneedles do not leave sharp tips after use [11, 40–44]. Hollow microneedles work like a tiny syringe 1–2 mm in length. Their narrow diameter and short length minimize pain. Hollow microneedles have been used to inject a liquid drug formulation [45–47].

The fabrication method and material are also different depending on the type of microneedle. Type of microneedle also determines the method of drug application and disposability. Thus, pain, anxiety, convenience and safety will be discussed based on the type of microneedle.

### Microneedle pain

#### Pain

One of drawbacks of hypodermic needles is pain [56, 57]. Microneedles were developed to overcome patients’ fear of needles (sometimes called needle-phobia). The amount of pain caused by the method of drug administration is an important consideration related to patient acceptance and compliance. Sensory nerves are located in the epidermis and the dermis of the skin layer [3]. Studies indicate that microneedle length has the greatest effect on pain. One study examined clinical administration using 180-µm-long microneedles, 280-µm-long microneedles and conventional 25-gauge needles. When 180-µm microneedles were inserted, participants said it felt as if someone was pressing down hard on the skin. When 280-µm microneedles were inserted, participants described it as someone holding onto your arm. In contrast, almost all participants described the 25-gauge hypodermic needle as immediately painful and uncomfortable [58]. Moreover, 500- to 750-µm-long microneedles were 10–20 times less painful compared to conventional hypodermic needles [59]. All microneedles with lengths ranging from a few hundred microns to 1.5 mm produced less pain than the hypodermic needle, with pain scores 5%–40% lower than those reported with the use of a hypodermic needle [60]. The pain was calculated quantitatively using a visual analog scale (VAS). VAS was defined as the length in millimeters from 0 to the vertical mark made by the rater (scores could range from 0 to 10 cm) [61]. VAS values are summarized regarding microneedle length from several studies in Table 2, and the change in VAS value is shown in terms of length in Figure 1. In addition to the difference in length of microneedles analyzed, studies have

### Table 1. Type of microneedles and their properties.

<table>
<thead>
<tr>
<th>Type</th>
<th>Location of drug</th>
<th>Targeting</th>
<th>Place of drug</th>
<th>Disposability of microneedle</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid</td>
<td>Hole generation</td>
<td>Microneedle pretreatment and use separate</td>
<td>Microneedle remaining</td>
<td>[31–33]</td>
<td></td>
</tr>
<tr>
<td>Coated</td>
<td>Intradermal and systemic delivery</td>
<td>Located on the surface of microneedle</td>
<td>Microneedle remaining</td>
<td>[34, 36–38, 48–50]</td>
<td></td>
</tr>
<tr>
<td>Dissolving</td>
<td>Intradermal and systemic delivery,</td>
<td>Encapsulated in microneedle</td>
<td>Microneedle remaining</td>
<td>[40, 42, 44, 51–53]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>extraction of body fluid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hollow</td>
<td>Intradermal and systemic delivery,</td>
<td>Stored in reservoir</td>
<td>Microneedle remaining</td>
<td>[14, 46, 47, 54, 55]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>extraction of body fluid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Value of visual analogue scale (VAS, scale of 0–10 cm) regarding microneedle length.

<table>
<thead>
<tr>
<th>Length of microneedle (µm)</th>
<th>Visual analogue scale (VAS, cm)</th>
<th>Type/insertion site</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>0.6 ± 0.2</td>
<td>Solid/forearms</td>
<td>[58]</td>
</tr>
<tr>
<td>280</td>
<td>0.2 ± 0.2</td>
<td>Solid/forearms</td>
<td>[58]</td>
</tr>
<tr>
<td>500</td>
<td>0.6 ± 0.7</td>
<td>Hollow/forearms</td>
<td>[62]</td>
</tr>
<tr>
<td>700</td>
<td>0.5 ± 0.2</td>
<td>Solid/forearms</td>
<td>[60]</td>
</tr>
<tr>
<td>750</td>
<td>0.4 ± 0.3</td>
<td>Hollow/forearms</td>
<td>[62]</td>
</tr>
<tr>
<td>1000</td>
<td>0.5 ± 0.2</td>
<td>Hollow/forearms</td>
<td>[62]</td>
</tr>
<tr>
<td>1450</td>
<td>1.5 ± 1.5</td>
<td>Solid/forearms</td>
<td>[60]</td>
</tr>
<tr>
<td>4000</td>
<td>1.5 ± 0.8</td>
<td>Hollow/forearms</td>
<td>[62]</td>
</tr>
<tr>
<td>26-G needle, (5 mm length)</td>
<td>3.8 ± 1.3</td>
<td>Conventional syringe/forearms</td>
<td>[60]</td>
</tr>
</tbody>
</table>

Figure 1. Change of visual analog scale (VAS) according to the increase of microneedle length.
examined difference in injection sites and type of microneedles used. However, there was no significant change in VAS when microneedles were between 180 and 1000 \( \mu \)m in length, as indicated in Figure 1. VAS value did increase when microneedles were longer than 1000 \( \mu \)m. We conclude that microneedles less than 1000 \( \mu \)m in length can be recommended as a way to reduce pain caused by microneedles.

Other factors affecting the level of pain were number of microneedles [63], microneedle tip angle [60], thickness [64] and width. The effectiveness of thin and sharp needle for easy insertion was confirmed [65]. However, these factors did not affect pain significantly compared to microneedle length. Previous studies have shown that the number of microneedles has a minor effect on pain compared to the length of the microneedles. A 10-fold increase in the number of microneedles (from 5 to 50) produced only a two-fold increase in pain. In addition, microneedles with a tip angle ranging from 20° to 90° were tested, and there was no significant relation between pain and tip angle. Thickness and width also did not show a significant relationship to pain [60].

For hollow microneedles, pain is determined not only by the length of the microneedles but also by the infusion of the drug solution itself. The dermis is a dense matrix composed of continuous phase (e.g., water, electrolytes) and coarse fixed elements (e.g., collagen fibrils, elastin) [66]. The dermal structure creates resistance to fluid flow [56,62,67]. Skin can stretch with little pain to accommodate a volume of a few hundred microliters of fluid. Larger volumes of fluid cause pain, however, because of excessive stretching of the skin and increased fluid pressure. Volumes up to 1 ml produce much higher pressure and can cause serious tissue deformation and damage [62]. One study found that pain was not significantly affected by skin stretched less than 1 mm and sample volume of 0.8 ml. The low flow rate reduced infusion pressure, resulting in less pain [62].

In addition to the microneedles, the applicator also can affect the level of pain. An applicator has been developed for the enhancement of microneedle insertion into skin [19]. Vibration was also used to reduce the insertion force of the microneedles. A 40% reduction of insertion force was reported when microneedle insertion was supported by actuator-induced vibratory motions [68]. The applicator, which has an insertion depth close to the length of the microneedles, has improved the insertion of microneedles. The formation of holes by short microneedle arrays was improved in vitro by using an impact insertion system of 3 m/s velocity [69]. Such an assist device could reduce insertion force and increase insertion depth, but pain caused by the device should be evaluated. However, VAS pain scores for 280-\( \mu \)m microneedles using the applicator were not very different from scores for 500-\( \mu \)m microneedles inserted without the applicator. Thus, the increase of pain was insignificant by the use of applicator. The rubber and foam mounting of the applicator could reduce pain, but it hindered efficient penetration of the microneedles due to the cushioning effect [58]. Pain-related factors are summarized in Table 3.

### Table 3. Pain-related factors of microneedles.

<table>
<thead>
<tr>
<th>Microneedle type</th>
<th>Factor</th>
<th>Specification</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid/dissolving/coating/hollow</td>
<td>Geometry</td>
<td>Length</td>
<td>Major effect on pain</td>
</tr>
<tr>
<td></td>
<td>Density</td>
<td></td>
<td>VAS dependence (summarized in Figure 1)</td>
</tr>
<tr>
<td></td>
<td>Tip angle</td>
<td></td>
<td>Minor effect on pain</td>
</tr>
<tr>
<td></td>
<td>Thickness</td>
<td></td>
<td>10-fold increase in the number of microneedles increased 2-fold on pain.</td>
</tr>
<tr>
<td>Hollow</td>
<td>Fluid</td>
<td>Volume</td>
<td>No significant relationship to pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flow rate</td>
<td></td>
</tr>
</tbody>
</table>

### Anxiety

In addition to pain, conventional needles caused enough anxiety that some patients lapsed into unconsciousness. Sixty-eight percent of the pediatric patients and 52% of the adult patients were overtly needle phobic, with children demonstrating significantly more aversion and stress [70,71]. Most of the pediatricians (83.7%) agreed that needle phobia is a significant problem in the clinical setting and that needle use with children can have an adverse impact on their future engagement with health care professionals (90.5%) [72]. When a drug must be administered frequently, moderate or low anxiety is desirable to enhance patient compliance. The pain and unacceptable appearance associated with traditional blood sampling lead to fear and disapproval. In contrast, a microneedle-mediated monitoring approach was appealing to all those involved, despite differences in their age, gender, medical background or school [73]. Because of their small size, microneedles offer not only minimal pain but also an inconspicuous profile. A number of approaches have been used to alleviate fear of microneedles [70]. Diverse companies developed tiny needles (smaller than 31 gauge) such as Fine Plus® needles and 33-gauge NanoPass™ needles for anxiety reduction [59]. One study showed that microneedles had greater visual acceptability and caused less fear in 86 children [73]. From the possible advantages of microneedle use suggested, the greatest agreement was associated with reduced pain (92%) and ease of use with needle-phobic children (91%). [74]. Critically, the microneedle approach assuages many of the safety concerns associated with needles and avoids issues of patient phobia, especially when considering the administration of children [75]. Vaccination is one of the most common causes of iatrogenic pain in the pediatric population [76]. Thus, needle phobia can inhibit patients from receiving vaccinations [77–79]. This fear can lead to pre-procedural anxiety, needle phobia in later life, and health care avoidance, including non-adherence to vaccination schedules [80]. The ability of microneedles to reduce anxiety related to injections is a highly desirable feature [45].

### Convenience

Microneedle has been suggested as a way to increase convenience in comparison with the conventional needle system. For pediatric vaccinations, the microneedle system has been reported to provide high acceptability and suitability [45]. Microneedles are easy to use. Short microneedles do not require application by an expert. However, long microneedles require administration by a trained professional. Commercial use of microneedles will depend on public acceptance of microneedle technology [45]. Thus, convenience...
resulting from pain reduction, anxiety reduction and easy to uses, is a big advantage of microneedles.

With regard to convenience, another consideration is microneedle attachment time. Attachment time is related to user convenience, and it requires from a few minutes to a few hours to deliver a predetermined amount of drug [24,36,51]. Dissolving microneedles encapsulating an influenza vaccine were administered to humans for an efficacy test. In this study, microneedles were applied to the skin of the left upper arm for 6 h using a handheld applicator [24]. This attachment time for the human study was longer than that for in vitro tests and animal studies. For the cosmetic application of dissolving microneedles, 6 h of attachment time was required for several weeks [25]. Such a long attachment time can cause inconvenience to patients and resistance to successful use of microneedles.

As mentioned in pain, an Impact-Insertion applicator could improve the efficiency and reproducibility of high-density microneedle penetration [60], and vibration of microneedles could reduce the insertion force of microneedles [81]. Insertion is affected by the method used, so microneedles were integrated with the applicator to control insertion force, mode [82] and speed [83]. However, use of the applicator can reduce the convenience of microneedle insertion. Thus, a simple and low-cost molded part was attached to the back of microneedles to enhance the insertion procedure [84].

**Safety of microneedles**

The safety of microneedles depends on the type of microneedle because material and additive are different according to microneedle type. Safety, including biocompatibility and mechanical compatibility, will be reviewed based on type of microneedle.

**Safety of solid microneedles**

There are two main considerations in regard to the safety of microneedles: mechanical safety and biological safety. Mechanical safety means the successful insertion of microneedles into the skin without mechanical failure that is breaking of the needles. Mechanical failure can not only damage the skin but also prevent delivery of the right drug dose. Mechanical safety is determined by the strength of the microneedle material, the geometry of the tips, the aspect ratio of height to base diameter and needle sharpness [85,86]. As shown in Figure 2, various microneedle shapes can be fabricated and prepared out of various materials using a microfabrication method. As shown in Figure 3, microneedles with a high aspect ratio can fail by buckling [86]. When the microneedles are short and have an aspect ratio lower than 3, they are prone to compression failure [86,87].

If microneedles do not have sufficient mechanical strength, their failure can threaten biological safety, including causing inflammation due to parts of microneedles remaining in the skin [88,89]. The FDA has recognized microneedles as medical devices but has concerns about micro-injuries [90]. As a result, the FDA has prepared a regulation that length of microneedles determines whether they can be used for medical purposes. Usually only microneedles shorter than 300 μm can be used for cosmetic applications.

Some studies have quantitatively measured skin irritation by evaluating the redness of skin after treatment [26,92].

![Figure 2](image1.png)

**Figure 2.** Various shapes of dissolving microneedles: pyramid microneedles, (a) straight, (b) obelisk microneedles and (c) beveled obelisk microneedles fabricated from different dissolvable materials [85].

![Figure 3](image2.png)

**Figure 3.** Image of biodegradable polymeric microneedle failure as a result of axial force [31] and failed dissolving microneedle [91].
Figure 4 shows the change in redness by the polymeric microneedles regarding the application time. Redness was usually remained until 30 min and decreased between 30 min and 2 h quickly [26]. Disruption of the skin barrier was evaluated by measuring transepidermal water loss (TEWL). After treatment with 400-μm solid microneedle arrays, TEWL and redness values were significantly increased compared values after treatment with 200-μm microneedles. However, irritation was minimal even with 400-μm microneedles, lasting less than 2 h [92]. Another study showed that redness is also a function of microneedle length. With up to 400-μm microneedles, redness dropped to normal within 90 min. Microneedles longer than 550 μm made blood spots in the skin [92], and the skin took approximately 60 min to recover from bleeding after insertion and removal of the microneedles. When microneedles were shorter than 100 μm, no redness was found [93]. Thus, we conclude that recovery from redness took more time with an increase in insertion duration [26].

When microneedles with a length of 700 μm were applied to human facial skin, the skin reaction score (SRS) was 1 for all skin types and age groups at the 5 min skin evaluation. The microneedle device appears to be safe for both sexes and various skin types and ages. Application of the microneedles to facial skin causes mild and rapidly resolving erythema [94]. In a previous study using an in vitro quantitative test, the application of microneedles in an appropriate manner was reported to allow much lower microbial penetration than when hypodermic needles were used [95]. Holes produced by needles can be a path of contamination as well as a path for the drug. According to one study, holes caused by microneedles were resealed within 15 min when the skin was dry, whereas holes remained in the skin for more than 48 h when the skin was wet. Skin sites treated with solid microneedles recovered barrier properties within 2 h, while treated sites with dissolving microneedles resealed slowly. Resealing time ranged quite broadly, from 3 to 40 h, depending on microneedle geometry [63]. Another study found that *E. coli* could not pass through holes in the skin caused by microneedles because the holes resealed quickly [13]. Cross-contamination by microneedles should be considered as well. One study tried to remove this risk factor by using rapidly dissolving microneedles [45].

**Safety of coated microneedles**

Coated microneedles are prepared by applying the drug solution to the surface of solid microneedles as shown in Figure 5. Considerations regarding safety are the same as those for solid microneedles. In addition, ingredients on the needle surface are left in the skin and can cause irritation. Microneedles are physically or chemically treated to increase their sharpness and hydrophilicity [9,96]. Most coated microneedles are prepared from electropolished metal microneedles, and the polishing solution contains phosphoric acid and glycerine [36]. Unnecessary chemicals can remain on the surface of the needles, and they can cause irritation. The coating solution was formulated to obtain a uniform thick coating. Hydrophilic polymers such as cellulose, alginate and sucrose are used for the thickening agent. Surfactants such as Lutrol F-68 are added to enable uniform spreading of the coating solution. Surfactants and thickening agents have proved to be safe, but they can cause minor irritation. The toxicity of additives used in coating solutions is summarized in Table 4.

In addition to the additive, other active ingredients introduced into the skin should also be considered. Lidocaine was delivered using coated microneedles and was cleared in the skin in 30 min. The maximum concentration of lidocaine was below 150 ng/mg, which is far below the maximum recommended dose [97]. Coated microneedles can deliver active ingredients into a defined area of skin quickly compared to other types of microneedles. The safety risk of coated microneedles is less to patients than other types of microneedles because they are removed together after the drug is delivered. However, there is a chance of cross-contamination with coated microneedles.
### Table 4. Toxicity of additives in coating microneedles.

<table>
<thead>
<tr>
<th>Name</th>
<th>Purpose</th>
<th>Toxicology</th>
<th>LD50 Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxy-methyl-cellulose</td>
<td>Thickening agent, uniform coating</td>
<td>Low oral, dermal and inhalation toxicity, nonirritating to eye and skin.</td>
<td>LD50 (rabbit, skin) &gt; 2 g/kg [98]</td>
</tr>
<tr>
<td>Sucrose</td>
<td>Thickening agent, uniform coating</td>
<td>Low toxicity. Used in cosmetics and in topical, parenteral and ophthalmic pharmaceutical formulations. Nontoxic and nonirritant material.</td>
<td>LD50 (mouse, IP): 14 g/kg [99]</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>Thickening agent, uniform coating</td>
<td>Nontoxic and nonirritant material. Subcutaneous implants of particulate PVP showed carcinogenicity in rats, mice and rabbits.</td>
<td>LD50 (cat, IP): 0.25 g/kg [100]</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>Thickening agent, uniform coating</td>
<td>No eye or skin irritation has been observed in rabbits and no skin allergy has been observed in guinea pigs following skin exposure.</td>
<td>LD50 (mouse, IP): &gt; 50 mg/kg [101,102]</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>Thickening agent, uniform coating</td>
<td>Nontoxic and nonirritant material.</td>
<td>LD50 (mouse, IP): 12 g/kg [101,105]</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone (PVP)</td>
<td>Thickening agent, uniform coating</td>
<td>Poloxamers are not metabolized.</td>
<td>LD50 (mouse, SC): 5.5 g/kg [106]</td>
</tr>
<tr>
<td>Pluronic F grade (poloxamer)</td>
<td>Surfactant</td>
<td>Nontoxic and nonirritant materials.</td>
<td>LD50 (mouse, SC): 5.5 g/kg [106]</td>
</tr>
<tr>
<td>Tween 80</td>
<td>Surfactant</td>
<td>Biocompatible nonionic surfactant that is widely used as a solubilizer in pharmaceutical industry.</td>
<td>LD50 (mouse, rat, IP): 7.5, 6.3 ml/kg [107,108]</td>
</tr>
<tr>
<td>Lutrol F grade (poloxamer)</td>
<td>Surfactant</td>
<td>Nonirritating and nonsensitizing when applied in 5% w/v and 10% w/v concentration to the eyes, gums and skin.</td>
<td>LD50 (mouse, SC): 5.5 g/kg [106]</td>
</tr>
<tr>
<td>Trehalose</td>
<td>Stabilizer</td>
<td>Relatively nontoxic and nonirritant material.</td>
<td>LD50 (mouse, IV): &gt; 1 g/kg [109]</td>
</tr>
</tbody>
</table>

### Table 5. The safety of dissolving microneedle material.

<table>
<thead>
<tr>
<th>Needle material</th>
<th>Biocompatibility</th>
<th>LD50 Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxy-methyl-cellulose</td>
<td>Nontoxic and nonirritant material. However, in animal studies, subcutaneous administration of carboxy-methyl-cellulose sodium has been found to cause inflammation, and in some cases of repeated injection, fibrosarcomas have been found at the site of injection.</td>
<td>LD50 (rabbit, skin) &gt; 2 g/kg [98,123]</td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
<td>Biocompatible material. The toxicity of dextran sulfate is dependent not only on the dose and molecular weight of the substance but also on the route of administration.</td>
<td>LD50 (rat, SC): 3.7 g/kg [124]</td>
</tr>
<tr>
<td>Dextran</td>
<td>The toxicity of dextran sulfate is dependent not only on the dose and molecular weight of the substance but also on the route of administration.</td>
<td>LD50 (mouse, parenteral administration): 2.1 g/kg [125]</td>
</tr>
<tr>
<td>Dextrin</td>
<td>Biocompatibility and biodegradability. Soluble in water, and, when processed into scaffolds, results in a biomaterial with excellent mechanical properties, slow biodegradation and well-established biocompatibility.</td>
<td>LD50 (mouse, IV): 0.35 g/kg [126]</td>
</tr>
<tr>
<td>Fibroin</td>
<td>Soluble in water, and, when processed into scaffolds, results in a biomaterial with excellent mechanical properties, slow biodegradation and well-established biocompatibility.</td>
<td>LD50: is not available [127]</td>
</tr>
<tr>
<td>Galactose</td>
<td>Readily dissolved in the skin and it is supposed to accomplish rapid drug delivery.</td>
<td>LD50: is not available [128]</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>Good biocompatible material and not cytotoxic, neurotoxicity, immunogenic, reproductive or developmental toxicant and genotoxic. However, it had a paradoxical effect on carcinogenicity. Overexpression of hyaluronic acid synthases increases the HA level, which leads to the acceleration of tumor growth and metastasis. On the other hand, exogenous oligomeric HA inhibits tumor progression, most likely by competing with endogenous polymeric HA. Hyaluronic acid likely does not play a causal role in cancer metastasis; rather, increased expression of hyaluronic acid genes may be a consequence of metastatic growth. Native non-cross-linked HA and chemically cross-linked HA demonstrate quite modest proliferative effect, but too high degree of cross-linked hyaluronic acid could potentially affect the biocompatibility of the HA hydrogel.</td>
<td>LD50: is not available [128]</td>
</tr>
<tr>
<td>Maltose</td>
<td>Regarded as a generally nontoxic and nonirritant material.</td>
<td>LD50 (mouse, IV): 26.8 g/kg [134]</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials. The greatest toxicity is with glycols of low molecular weight. However, the toxicity of glycols is relatively low.</td>
<td>LD50 (mouse, SC): 38.6 g/kg [135]</td>
</tr>
<tr>
<td>LD50 (rats, intra-abdominal): 9708 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LD50 (rats, IV): 7312 mg/kg</td>
<td>[135]</td>
<td></td>
</tr>
</tbody>
</table>


Safety of dissolving microneedles

Dissolving microneedles encapsulate the drug, and the needle material dissolves and remains in the skin. Dissolving microneedles have the same safety concerns as those of solid microneedles. Another consideration with dissolving microneedles is the micro-needle material that is dissolved in the skin. Materials shown in Table 5 have been used as needle material. Various kinds of water soluble polymers have been used as materials of dissolving microneedles. When dissolving microneedles were first developed, they were made from carboxy-methyl-cellulose (CMC) and polyvinylpyrrolidone (PVP) [42,51]. More recently, hydrophilic materials, especially hyaluronic acid, have been used as microneedle material because of concerns for biological safety [18,52,17]. Dissolving microneedles do not leave sharp tips behind, and there is less chance of contamination from debris and cross-contamination. However, microneedle material is left in the skin for a time and can thus cause safety issues. Nevertheless, material used with dissolving microneedles is generally safe, even with frequent applications [110]. Even though dissolving polymer is used for dissolving microneedles, non-biodegradable polymer segments are cleared mainly by renal excretion, which is controlled primarily by the hydrodynamic volume of the polymer chains when dissolving polymer are not cleared by enzymatic reaction and hydrolysis. Polymer segments with molecular weight below 40 kDa can be cleared from the body by renal excretion [111,112]. Thus, when dissolvable and non-biodegradable polymer was used as microneedle material, the molecular size of polymer segment should be considered.

In addition to dissolving polymer, swellable microneedles were used as a drug pathway from the reservoir [113,114], as well as for increased mechanical strength [115], drug delivery [116], sustained release [117] and sample collecting [118,119]. Swellable microneedles are based on dissolvable microneedles from the preoperative point of view. They are made of hydrolyzed poly(methylvinylether-co-maelic anhydride) (11.1%) and poly(ethyleneglycol) [118,119] and cross-linked hyaluronic acid (HA) [115–117]. Matrix material has biocompatibility and HA can be degraded by enzymatic degradation. However, the safety of the additive for crosslinking should be considered.

In one study, dissolving microneedles loaded with the drug alendronate and encapsulating HA were inserted and irritation was evaluated using the Draize method [120]. Erythema and edema were not found at 24 h after application of a dissolving microneedle array without alendronate; however, light erythema was observed when alendronate-loaded microneedles were administered. Irritation resolved by day 15 for drug-loaded HA microneedles. Thus, HA microneedles without the drug were very safe. Another study examined various lengths of HA microneedles. The 800-μm HA microneedles induced slight or moderate erythema that gradually disappeared within a few days. The 200- and 300-μm HA microneedles induced slight erythema that disappeared within a few hours [121]. CMC and CMC/trehalose microneedle patches showed mild erythema. The erythema produced by CMC microneedles decreased with time and returned to zero within 48 h after patch removal. CMC microneedle patches initially caused more erythema than the CMC/trehalose patches [43]. TEWL by low-molecular weight HA microneedles gradually decreased back to that of intact skin within 10–12 h of removal of the microneedles [122]. Polylactic acid-based microneedles loaded with methotrexate were implanted in a normal rabbit eye, and the toxicology of the microneedles was observed [83]. There was no acute ocular inflammation or infection around the implantation site. Biodegradable...
microneedles provided sustained drug release without toxicity. The safety of dissolving microneedle material is summarized in Table 5.

Dissolving microneedles were made of hydrogel and loaded with the model drugs ovalbumin and ibuprofen sodium. Then they were sterilized using techniques that included gamma irradiation (25 kGy). The microneedles were unaffected by the irradiation in terms of their physical properties. However, ovalbumin content in the microneedles was reduced by the irradiation, and the penetration of the skin by the ibuprofen sodium was less than that provided by non-irradiated microneedles [136]. Dissolving microneedles products are controlled by regulatory authorities such as the FDA, but lower gamma radiation is recommended to avoid the denaturation of the active ingredients in microneedles.

Safety of hollow microneedles

Hollow microneedles have a shell structure and thus have the mechanical weakness of buckling. The amount of force required to fracture hollow microneedles increases with increasing wall thickness. Mechanical failure has been estimated using the thin-shell assumption [82]. Microfluidic flow can also be a problem. The diameter and length of hollow microneedles is a few hundred microns, and the restricted flow caused by condensed tissue can result in unwanted flow properties of hollow microneedles. One study found that insertion followed by partial removal of hollow microneedles reduced the pressure caused by compressed tissue and increased the flow of the drug solution [137].

Another consideration regarding hollow microneedles is leaking on the surface of the skin. To deliver a predetermined dose of drug solution into skin layer effectively, the hollow microneedle system should be understood fully. Single hollow microneedles have been able to infuse a drug solution into the skin at flow rates ranging from 15 to 96 μl/h. Partial retraction of microneedles increased the flow rate up to 11.6-fold. The infusion flow rate was also increased by greater insertion depth, larger infusion pressure and use of a beveled microneedle tip [66,137]. Flow through tapered microneedles is determined by the diameter and angle at the microneedle tip. Flow through tapered microneedles is a function of the axial pressure gradient, viscosity of the solution, length of needle and flow rate [138]. With hollow microneedles, microfluidic properties should be considered in addition to material safety and mechanical safety.

Hollow microneedles are made of various materials, including glass [46], nickel [139], stainless steel [14], and polymers such as SU-8 and poly-glycolic acid [55,140–144], as shown in Figure 6(a) and (b). Safety of materials used for hollow microneedles are summarized in Table 6.

Conclusion

Microneedles are an economical and efficient transdermal drug delivery method. This method is as efficient as intramuscular injection and has the convenience of the transdermal method. Unlike the syringe needle system, the microneedle system reduces pain and anxiety in patients. Thus, the microneedle system is ideal for children. However, microneedles still need improvement for the convenience of patients due to the long application time. On the other hand, the microneedle system has safety issues related to transdermal delivery and intramuscular administration. Because of the small size of microneedles, sufficient mechanical strength is required in order to insert the needles successfully without breakage. Unlike the conventional transdermal delivery method, however, after microneedles are inserted into the skin and deliver the drug, there is no way to remove other material delivered with the drug. Thus, the design of microneedle systems has to be considered based on the biocompatibility of the material and the safety level of the microneedle material, which must be the same as that of the intramuscular delivery system. Safety variables are different, depending on the type of microneedle and microneedle material. Mechanical, chemical and biological safety should be considered together to achieve successful and safe administration of drugs using microneedles.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding information

This work was supported by the GRRC program of Gyeonggi province [GRRC Gachon 2016-B01, Development of drug delivery nanomaterials and system for dental application].

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