



## Review Article

# Microneedles -A Potential Transdermal Drug Delivery

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Transdermal drug delivery presents various advantages including enhanced patient compliance, sustained release, circumvent gastric irritation, as well as elimination of pre-systemic first-pass effect. However, only few medications can be delivered through the transdermal route in therapeutic amounts. Microneedles can be used to augment transdermal drug delivery. In this review, microneedles are described and their methods of fabrication highlighted. Microneedles can be fabricated in different forms such as hollow, solid, and dissolving. There are also hydrogel-forming microneedles. A special attention is paid to hydrogel-forming microneedles. These are innovative microneedles which do not contain drugs but imbibe interstitial fluid to form continuous conduits between dermal microcirculation and an attached patch-type reservoir. Several microneedles approved by regulatory authorities for clinical use are also examined.

**Key words:** Transdermal Drug Delivery, Microneedles, Dissolving Microneedles, hydrogel-forming microneedles

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## 1. INTRODUCTION

The skin is the largest organ in the body. It is about 1.5 m<sup>2</sup> in adults and provides protection for internal organs<sup>1</sup>. It also protects the human body against ingress of toxic chemicals and egress of water and other essential endogenous substances. Despite the large surface area of the skin, it is challenging for compounds including drugs and vaccines to cross the skin in therapeutically relevant amounts. The major barrier in the skin is provided by the stratum corneum (SC), which is the outermost layer of the skin<sup>2</sup>. Below the stratum corneum is the viable epidermis (VE), which is a cellular, avascular tissue measuring 50–100 μm thick<sup>3</sup>. Cells in the basal layer of the epidermis form the most important

structural and functional connection to the dermis below<sup>4</sup>. The stratum corneum and viable epidermis together form the full epidermis. There is a basement membrane at the base of the epidermis and the existence of tight junctions in the viable epidermis has been recently documented. Base membrane and tight junctions may both offer resistance to the transport of molecules across the epidermis<sup>5</sup>. The dermis is the thickest component of the skin, up to 4 mm in depth. Its upper layer, the 100–200 µm thick papillary dermis, consists of thin collagen bundles, elastin fibers, and fibrocytes. Below this layer is the reticular dermis, made up of thick collagen bundles and coarse elastic fibers<sup>6</sup>. Although the stratum corneum (SC) is the major contributor to the barrier properties of the skin, the role of the full epidermis should be taken into consideration<sup>5, 7</sup>. Only compounds which are able to get into the SC diffuse through living epidermis and pass through the upper part of the papillary dermis has the potential to reach circulation and exhibit systemic effects<sup>7</sup>. The dermis contains blood vessels, lymphatics and nerves, as well as the various skin appendages. Below the reticular dermis lies the hypodermis (subcutaneous fat tissue), which may have a thickness of up to several millimeters. Comprising fat microlobules and fibrous collagen, it also contains blood vessels, lymphatics and nerves<sup>6</sup>.

Hypodermic needles are used in clinical practice to deliver medications across the skin into the bloodstream. Injections with hypodermic needles are important from a clinical standpoint, but painful. They may also induce hypersensitivity, bruising, discomfort and bleeding at the site of administration and in some cases are associated with risks of contamination. There are other concerns linked to their use including accidental needle injury and the necessity to train personnel regarding the proper use of needles. The difficulty in crossing the skin is caused by its anatomical peculiarities. Microneedles (MN) are currently being utilized to enhance transdermal delivery of small and large molecules. With the emergence of microfabrication manufacturing technology over the past several decades, MN has been developed by academic laboratories and pharmaceutical companies<sup>8–13</sup>. Transdermal MNs create micron sized pores in the skin to enhance delivery of the drug across the skin<sup>11, 13</sup>. MN is ideal for patient adherence as they do not stimulate nerves that are associated with pain. MN improves patient compliance as patient with needle phobia will be more likely to apply the patch because of its painlessness<sup>13</sup>. Additionally, patients can administer the drug by themselves<sup>13</sup>. When MN is fabricated in arrays on a backing that can be applied to the skin like a bandage, the device is called a MN patch<sup>8</sup>. MN can be divided into four categories- hollow, solid, coated and polymer<sup>6</sup>.

## 2. NECESSITY FOR THE USE OF MICRONEEDLES

When oral administration of drugs is not feasible due to poor drug absorption or enzymatic degradation in the

gastrointestinal tract or liver, injection using a painful hypodermic needle is the most common alternative. An approach that is more appealing to patients, and offers the possibility of controlled release over time, is drug delivery across the skin using a patch. However, transdermal delivery is severely limited by the inability of the large majority of drugs to cross skin at therapeutic rates due to the great barrier imposed by skin's outer stratum corneum layer.<sup>14</sup> To increase skin permeability, a number of different approaches have been studied, ranging from chemical/lipid enhancers to electric fields employing iontophoresis and electroporation to pressure waves generated by ultrasound or photoacoustic effects.<sup>15</sup> Although the mechanisms are all different, these methods share the common goal to disrupt stratum corneum structure in order to create “holes” big enough for molecules to pass through. The size of disruptions generated by each of these methods is believed to be of nanometer dimensions, which is large enough to permit transport of small drugs and, in some cases, macromolecules, but probably small enough to prevent causing damage of clinical significance.<sup>16</sup>

An alternative approach involves creating larger transport pathways of microns dimensions using arrays of microscopic needles. These pathways are orders of magnitude bigger than molecular dimensions and, therefore, should readily permit transport of macromolecules, as well as possibly supramolecular complexes and microparticles. Despite their very large size relative to drug dimensions, on a clinical length scale they remain small. Although safety studies need to be performed, it is proposed that micron scale holes in the skin are likely to be safe, given that they are smaller than holes made by hypodermic needles or minor skin abrasions encountered in daily life.<sup>17</sup>

Transdermal drug delivery is a noninvasive, user-friendly delivery method for therapeutics. However, its clinical use has found limited application due to the remarkable barrier properties of the outermost layer of skin, the stratum corneum (SC). Physical and chemical methods have been developed to overcome this barrier and enhance the transdermal delivery of drugs. One of such techniques was the use of microneedles to temporarily compromise the skin barrier layer. This method combines the advantages of conventional injection needles and transdermal patches while minimizing their disadvantages. As compared to hypodermic needle injection, microneedles can provide a minimally invasive means of painless delivery of therapeutic molecules through the skin barrier with precision and convenience. The microneedles seldom cause infection while they can allow drugs or nanoparticles to permeate through the skin. Increased microneedle + assisted transdermal delivery has been demonstrated for a variety of compounds. For instance, the flux of small compounds like calcein, diclofenac methyl nicotinate was increased by microneedle arrays. In addition, microneedles also have been tested to increase the flux of permeation for large

compounds like fluorescein isothiocyanate-labeled Dextran, bovine serum albumin, insulin and plasmid DNA and Nano spheres.

Microneedles may create micro conduits sufficiently large to deliver drug-loaded liposomes into the skin. The combination of elastic liposomes and microneedles may provide higher and more stable transdermal delivery rates of drugs without the constraints of traditional diffusion-based transdermal devices, such as molecular size and solubility. Though it could offer benefits mentioned above, the combined use of elastic liposomes and microneedle pretreatment has received little attention<sup>18</sup>

### 3. TYPES OF MICRONEEDLES

The different types of microneedles are etched by different materials: The first type of the microneedle is single-tip microneedles that have a sharp tip. These types of microneedles are in straight shape, 200µm in length. It contains sharp tip with different angles of 15 degree, 30 degree, 45 degree and 75 degree. The second type of Quadruplet microneedles and the third type of microneedle is hollow microneedles. The quadruplet and hollow microneedles are good in strength and not very expensive respectively. A classification for microneedles usually used in literature is based on the fabrication process:

#### *In-plane or Out-of-plane microneedles.*

**In-plane microneedles** are fabricated with the shaft being parallel to substrate surface. The advantage of this arrangement is that the length of the needle can be very accurately controlled. A disadvantage is that it is difficult to fabricate two-dimensional arrays.

**Out-of-plane microneedles** on the other hand, protrude from the substrate and are straightforward to fabricate in arrays. Instead, the length and high aspect-ratios become significant challenges in the fabrication of these kinds of needles.<sup>19</sup>

- **Hollow microneedles**

Skin permeability can be dramatically increased by the holes created from solid microneedles insertions. However, it is still necessary to have more controlled and reproducible transport pathways to delivery drugs into the tissue. The fabrication of hollow microneedles that allow transport through the hollow shaft of the needle was based on this need. The inclusion of a hollow lumen in a microneedle structure expands its capabilities dramatically and can offer the following advantages: the ability to deliver larger molecules and particles; deliver material in a convective transport fashion (for example, pressure-driven flow) instead of passive diffusion; and minimize the cross-contamination of the deliverables and its surrounding. A variety of hollow microneedles has been fabricated and has demonstrated success in transdermal drug delivery.

#### **a. Metal hollow microneedles**

#### **b. Silicon hollow microneedles**

#### **c. Glass hollow microneedles**

- **Other types of microneedles**

Besides solid and hollow microneedles, various other types of microneedles were fabricated using different materials such as biodegradable polymers, polysilicon and sugar with additional functionalities. Because of their biocompatible nature with the tissue, biodegradable polymer microneedles were developed. These needles were fabricated by initially making master structures using lithography-based methods, creating inverse structures from the master molds, and finally producing replicate microneedles by melting biodegradable polymer formulations (i.e. Poly-lactic acid, PLA, or poly-lactic-co-glycolic acid, PLGA) into the molds. The resulting microneedles can be loaded with molecules, drugs, DNA or proteins. Unlike solid and hollow microneedles, polymer microneedles themselves serve as the drug implants after insertion into the tissue. Park et al. (2006) inserted the microneedles loaded with calcein or bovine serum albumin (BSA) into full thickness human cadaver skin.<sup>20</sup>

#### **Dimension of Microneedles.**

The solid tip microneedles and hollow microneedles have different dimension. Solid microneedles are fabricated in 750-1000 µm in length, 15°-20° tapered tips angle and 190-300 µm bases area. The masks of microneedles are designed to 400-600 µm triangles length, 70-100 µm conduits diameter, and 25-60EA/5 mm<sup>2</sup> arrays density. The hollow microneedles arrays are fabricated with lumen diameter of 30 µm and height of 250 µm. The center-to-center the distance of the hollow microneedles array is 150 µm. The axis of lumen is fabricated with the distance of 10 µm to the axis of outside column.<sup>21</sup>

### 4. MECHANISM OF ACTION

The mechanism for delivery is not based on diffusion as it is in other transdermal drug delivery products. Instead, it is based on the temporary mechanical disruption of the skin and the placement of the drug or vaccine within the epidermis, where it can more readily reach its site of action. The drug, in the form of biomolecules, is encapsulated within the microneedles, which are then inserted into the skin in the same way a drug like nitroglycerine is released into the bloodstream from a patch. The needles dissolve within minutes, releasing the trapped cargo at the intended delivery site. They do not need to be removed and no dangerous or biohazardous substance is left behind on the skin, as the needles are made of a biodegradable substance.

In microneedle devices, a small area (the size of a traditional transdermal patch) is covered by hundreds of microneedles that pierce only the stratum corneum (the uppermost 50 /m of the skin), thus allowing the drug to bypass this important barrier. The tiny needles are constructed in arrays to deliver

sufficient amount of drug to the patient for the desired therapeutic response.<sup>22</sup>

## 5. MERITS

- The major advantage of microneedles over traditional needles is, when it is inserted into the skin it does bypass the stratum corneum, which is the outer 10-15  $\mu$ m of the skin. Conventional needles which do pass this layer of skin may effectively transmit the drug but may lead to infection and pain. As for microneedles they can be fabricated to be long enough to penetrate the stratum corneum, but short enough not to puncture nerve endings. Thus reduces the chances of pain, infection, or injury.
- By fabricating these needles on a silicon substrate because of their small size, thousands of needles can be fabricated on single wafer. This leads to high accuracy, good reproducibility, and a moderate fabrication cost.
- Hollow like hypodermic needle; solid-increase permeability by poking holes in skin, rub drug over area, or coat needles with drug.
- Arrays of hollow needles could be used to continuously carry drugs into the body using simple diffusion or a pump system.
- Hollow microneedles could be used to remove fluid from the body for analysis- such as blood glucose measurements – and to then supply microliter volumes of insulin or other drug as required.
- Immunization programs in developing countries, or mass vaccination or administration of antidotes in bioterrorism incidents, could be applied with minimal medical training.
- Very small microneedles could provide highly targeted drug administration to individual cells.
- These are capable of very accurate dosing, complex release patterns, local delivery and biological drug stability enhancement by storing in a micro volume that can be precisely controlled.<sup>23</sup>

## 6. DEMERITS

- The needles are very small and much thinner than the diameter of hair, so the microneedle tips can be broken off and left under the skin.
- Microneedles can be difficult to apply on the skin; the clinician must learn proper application technique.
- Skin irritation may result because of allergy or sensitive skin.
- Local inflammation may result if the amount of drug is high under the skin<sup>24</sup>

## 7. MATERIALS USED FOR FABRICATION

The materials used for fabrications are-

- Silicon
- Metal
- Polymers
- Glass

**SILICON-** First the microneedles were fabricated using silicon to have sharp and hard microneedle because of greater mechanical strength. Fabrication by microneedle is costly because it requires clean room microfabrication for processing. Silicon is brittle and may break in the skin.

**METAL-** Metal is used for fabrication as they have good mechanical strength, cost is low, metal used are stainless steel, titanium, nickel, iron.

**POLYMERS-** Biodegradable polymer used are Polylactic acid and Polyglycolic acid because they are cost effective. This biodegradable polymer is used owing to the chance of microneedle breaking off in the skin.

**GLASS:** Fabrication is also done by glass. They are physically capable of insertion into the tissue and they have high drug loading capacity and one can see how much amount of drug is delivered after use<sup>25</sup>

## 8. FABRICATION OF MICRONEEDLES

Microneedles can be fabricated employing microelectro mechanical systems (MEMS). The basic process can be divided into three parts: deposition, patterning and etching. Microneedles have become a new type of the bio-medicine injector, it can throw the cuticle and not excite the nerve, and the patient will feel nothing. Moreover, it can be made by different kind of materials, like as SU-8, PMMA, PDMS, COC, silicon etc.

**Deposition:** Refers to the formation of thin films with a thickness anywhere between a few nanometers to about 100 micrometers.

**Patterning:** Is the transfer of a pattern onto the film.

**Lithography:** Is used to transfer a pattern into a photosensitive material by selective exposure to a radiation source such as light. This process can involve photolithography, electron beam lithography, ion beam lithography or X-ray lithography. Diamond patterning is also an option for lithography.

**Etching:** Is a process of using strong acid or mordant to cut into the unprotected parts of a material's surface to create a design in it and can be divided into two categories: wet etching or dry etching. The selection of any of the above mentioned methods largely depends on the material of construction and the type of microneedle.

**Polymer Microneedle:**

The SU-8 2050 as the material of the microneedles. SU-8 is a high contrast, epoxy based photoresist designed for micromachining and other microelectronic

applications. The UV-light absorptivity of SU-8 is lower than others and therefore can get the high-aspect ratio structures. As the turning model technique to fabricate is the microneedles, V-groove on the silicon wafer should be considered. At first, the V-groove is built with the depth of 320  $\mu\text{m}$  on silicon wafer, and then coated with the SU-8 on the silicon wafer with the depth of 450  $\mu\text{m}$  and use the scraper to put the SU-8 uniformly. Silicon wafer covered the SU-8 will be set in the oven to break away the bubbles and to smooth the surface by heating and vacuum. Finally, the SU-8 developer is used to form the microneedles.<sup>26</sup>

## 9. METHODOLOGY FOR DRUG DELIVERY

A number of delivery strategies have been employed to use the microneedles for transdermal drug delivery. These include

- Poke with patch approach
- Coat and poke approach
- Biodegradable microneedles
- Hollow microneedles
- Dip and scrape

### **Poke with Patch Approach:**

It involves piercing an array of solid microneedles into the skin followed by application of the drug patch at the treated site. Transport of drug across skin can occur by diffusion or possibly by iontophoresis if an electric field is applied. E.g.: Insulin Delivery.

### **Coat and Poke Approach:**

In this approach needles are first coated with the drug and then inserted into the skin for drug release by dissolution. The entire drug to be delivered is coated on the needle itself. E.g.: Protein vaccine delivery.

### **Biodegradable microneedles:**

It involves encapsulating the drug within the biodegradable, polymeric microneedles, followed by the insertion into the skin for a controlled drug release.

### **Hollow microneedles:**

It involves injecting the drug through the needle with a hollow bore. This approach is more reminiscent (suggestive of) of an injection than a patch. E.g.: Insulin Delivery.

### **Dip and Scrape Approach**

Dip and scrape approach, where microneedles are first dipped into a drug solution and then scraped across the skin surface to leave behind the drug within the micro abrasions created by the needles. The arrays were dipped into a solution of drug and scraped multiple times across the skin of mice *in vivo* to create micro abrasions. Unlike microneedles used previously, this study used blunt-tipped microneedles measuring 50–200 $\mu\text{m}$  in length over a 1  $\text{cm}^2$  area. E.g.: DNA Vaccine Delivery.<sup>27</sup>

## 10. EVALUATION

### **In-Vitro study of Microneedles**

In-vitro evaluation microneedles are accomplished by using various mediums like agarose gel and methanol to insert the microneedles. In vitro tests are used to determine the characteristics of new test device or compound. The main key objectives of the in vitro testing of microneedles involves optimization of the microneedles, finding out the penetration force and bending force, evaluation of strength of microneedle, determination of the dissolution rate of coating material and the estimation of the efficiency of drug delivery. Various methods employed for conducting in vitro studies are as follows.

#### **Method 1**

In vitro methods tested the delivery efficacy of the microneedles. In this test, the microneedles are integrated with Paradimethylsiloxane (PDMS) biochip and black ink is injected by the microneedles into the petridish, which contains methanol. The right triangular microneedles with 8.5 and 15 tip taper angles and isosceles triangular microneedles with 9.5 and 30 tip taper angles have been used for this purpose.

#### **Method 2**

In this method, the diluted form of Rhodamine B dye is injected through the microneedles into the 1% agarose gel to evaluate the penetration and flow of the solution after penetrating into the 1% agarose gel.

#### **Method 3**

Inserting microneedles into the porcine cadaver skin and pig cadaver skin for 10s to 20s and 5 minutes respectively are evaluated by this method. This method is used to test the delivery efficacy, dissolution rate of the coated material, which is coated on the microneedle tip, coated with vitamin B, calcein or sulforhodamine

### **In Vivo Testing of microneedles**

To conduct the in vivo preclinical study, generally mice, rabbits, guinea pigs, mouse and monkey etc. are used. The main motive of the in vivo testing is the determination of safety as well toxicity of the tested compound. The key objectives behind in vivo testing of the microneedles includes to perform skin toxicity test, determination of penetration force in different skin, mechanical stability, bending breakage force, to perform various non-clinical safety study and pharmacological study, determination of various parameters like immunogenicity, genotoxicity, skin sensitization and allerginisation, study, developmental toxicity, acute and chronic dermal toxicity, carcinogenicity.

#### **Method 1**

This in vivo method involves testing of microneedles by pricking the microneedles into vein of the tail of hairless mice. It is used for the determination of the penetration force of the microneedle into the skin.

#### **Method 2**

This method of in vivo testing of the microneedles, Rhodamine B is injected into tail of laboratory mouse-tail



and anaesthetized for the determination of penetration force and bending breakage force.

### Method 3

This method has been performed for the evaluation of vaccine delivery via microneedles. Ovalbumin is used in this method, as a model protein antigen and administered into hairless guinea pig by using solid metal microneedles at the rate of 20 µg ovalbumin in 5s up to 80 µg.

### Method 4

In this method rabbits have been used to evaluate the vaccine delivery. The anthrax vaccine containing recombinant protective antigen (rPA) of *Bacillus anthracis* has been administered in the rabbits via solid and hollow microneedles.<sup>28</sup>

## 11. APPLICATIONS OF MICRONEEDLES

Microneedle technology has been developed as a platform technology for delivery of high molecular weight and hydrophilic compounds through the skin. The first ever study of transdermal drug delivery by microarray technology was conducted by Henry et al who demonstrated an increase in the permeability of skin to a model compound calcein using microarray technology. It is applied in the following-

- Oligonucleotide delivery
- DNA vaccine delivery
- Desmopressin delivery
- Insulin delivery
- Porphyrin Precursor 5-Aminolevulinic Acid (ALA) Delivery<sup>29</sup>

## 12. FUTURE ASPECTS

Integration of solid microneedles with transdermal patch provides a minimal invasive method to increase the skin permeability of drugs, including the macromolecules such as proteins. Till date, microneedles made up of silicon, metal, glass and plastics have been utilized for transdermal delivery. However, with rapid advancement in technology, microneedles composed of biodegradable and biocompatible materials have been explored. For instance, fabrication of dissolving microneedles using polysaccharide biomaterials have been utilized for controlled drug delivery. Microneedle approach of drug delivery is currently being evaluated for a number of drugs, but extensive studies would be required to foster the application of these delivery modes in the clinical set up. Results from several groups suggest that microneedles are a promising, possibly powerful technology for the administration of therapeutics (e.g. Vaccines or drugs) into the skin. However, a few issues will have to be studied in greater depth before microneedles can be widely used clinically.

As the variety of microneedles increases, a comprehensive series of tests that can be applied to test all needles should be proposed. These tests should include pre-

clinical tests (in vivo tests in animal models), clinical tests (to test pain, inflammation, etc.), mechanical tests (to evaluate parameters such as margin of safety) as well as fluidic flow tests (e.g. Fluid pressure needed for particular flow rate, etc.). This will help not only in objectively comparing the microneedles but aid in the selection of the most appropriate microneedle for each application.<sup>30</sup>

## 13. CONCLUSION

Microchannel based Transdermal Delivery System by using Microneedles is a Novel Approach for Drug delivery system. It is a convenient, painless, and less invasive alternative to injection and it can be used a common method for administering large proteins and peptides, antibiotics, vaccines in low manufacturing cost. In contrast to oral delivery, microneedles avoid first pass effect and offer the benefit of immediate cessation of drug administration in case of an adverse effect or overdose. In contrast to passive delivery, this allow for the delivery of water-soluble drugs. In contrast to Iontophoresis, this is use for long time. There is also no molecular size limitation, no molecular electrical charge requirement, and no specific formulation pH constraint. In contrast to conventional TDDS, this is used for potent & less potent drug, the more extended release delivery system.

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