MICRONEEDLE AS A NOVEL DRUG DELIVERY SYSTEM: A REVIEW

Memon Shakeel*, Pathan Dilnawaz N, Ziyaurrrahman A.R, Bagwan Akber, Sayed Bushra
M.C.E.Society’s Allana College of Pharmacy, Azam campus, Camp, Pune, India.411001

*Memon Shakeel, M.C.E.Society’s, Allana College of Pharmacy, Azam campus, Camp, Pune. India.
411001. Email: memon.shakeel@gmail.com
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ABSTRACT
Patch-based transdermal drug delivery offers a convenient way to administer drugs without the drawbacks of standard hypodermic injections relating to issues such as patient acceptability and injection safety. However, conventional transdermal drug delivery is limited to therapeutics where the drug can diffuse across the skin barrier. By using miniaturized needles, a pathway into the human body can be established which allow transport of macromolecular drugs such as insulin or vaccines. These microneedles only penetrate the outermost skin layers, superficial enough not to reach the nerve receptors of the lower skin. Thus, microneedle insertions are perceived as painless. These microneedle arrays could be easily inserted into skin without breaking and were shown to increase permeability of human skin in vitro to a model drug, calcein, by up to 4 orders of magnitude. Limited tests on human subjects indicated those microneedles were reported as painless.

KEY WORDS: Microneedle, Transdermal, standard hypodermic injections.

INTRODUCTION
Microneedles are micron-scale needles assembled on a transdermal patch have been proposed as a hybrid between hypodermic needles and transdermal patches to overcome the individual limitations of both injections and patches. Every drug needs a drug delivery system. Drug delivery is defined as the administration of the drug into the body through different routes. There are different types of drug delivery systems developed to administer the drug to the body. Previously, the drug delivery systems were developed for the traditional routes of administration like oral or parenteral route but in the last few years many nonconventional routes have been developed such as Transdermal- through skin, nasal, ocular- through eye, pulmonary- by lungs. In short, many novel drug delivery systems there have been developed from last few years for the purpose of the administration of drug to the body to make drug more effective and easy to administer. The mechanism for delivery, however, 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. Microneedle are somewhat like traditional needles, but are fabricated on the micro scale. They are generally one micron in diameter and range from 1-100 microns in length. Microneedles have been fabricated with various materials such as: metals, silicon, silicon dioxide, polymers, glass and other materials. It is smaller the hypodermic needle, the less it hurts when it pierces skin and offer several advantages when compared to conventional needle technologies. Various types of needles have been fabricated as well, for example: solid (straight, bent, filtered), and hollow. Solid microneedle could eventually be used with drug patches to increase diffusion rates; solid-increase permeability by poking holes in skin, rub drug over area, or coat needles with drug. Hollow needles could eventually be used with drug patches and timed pumps to deliver drugs at specific times. Arrays of hollow needles could be used to continuously carry drugs into the body using simple diffusion or a pump system. Microneedles are a relatively new medical technology and are the subject of extensive research.
The size of a microneedle is measured in microns. One micron is one thousandth of a millimeter, and a microneedle is usually no more than 1 micron in diameter, and 1-100 microns long. Patches coated with microneedles are described as feeling similar to sandpaper when touched. These needles are so small that they have been used to deliver drugs into individual cells. Microneedles are designed to be painless whilst overcoming the natural barrier function of the skin. Microneedle arrays can be deployed using an applicator device that moves microneedle arrays into contact with a target location, such as a location on a patient's skin.

NEED FOR USING MICRONEEDLES
To increase skin permeability, a number of different approaches has been studied, ranging from chemical/lipid enhancers to electric fields employing iontophoresis and electroporation to pressure waves generated by ultrasound or photoacoustic effects. 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. 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.

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 µm 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.

METHODOLOGY OF 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.

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.
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) an injection than a patch.

Dip and scrape
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 microabrasions 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 microabrasions. Unlike microneedles used previously, this study used blunt-tipped microneedles measuring 50–200 µm in length over a 1 cm² area.

ADVANTAGES OF MICRONEEDLES

✓ The major advantage of microneedles over traditional needles is, when it is inserted into the skin it does not pass the stratum corneum, which is the outer 10–15 µm of the skin.²
✓ By fabricating these needles on a silicon substrate because of their small size, thousands of needles can be fabricated on a single wafer. This leads to high accuracy, good reproducibility, and a moderate fabrication cost.⁸
✓ These are capable of very accurate dosing, complex release patterns, local delivery and biological drug stability enhancement by storing in a microvolume that can be precisely controlled.⁹
✓ Microneedles with a length of a few hundred micrometers, only penetrates the superficial layers of the skin where the density of nerve receptors is low. As a consequence, insertion of microneedles into skin is perceived as painless.¹⁰
✓ Like an ordinary transdermal patch, an envisioned system can be applied by the patient himself virtually without any training. However, to achieve this, special insertion tools and procedures are highly unwanted.¹⁰
✓ when inserted into skin it doesn’t pass sc so no pain, where as conventional needles which do pass this layer may effectively transmit the drug but may lead to infection and pain By fabricating these needles on a silicone substrate because of their small size, thousands of needles can be fabricated on a single wafer.- leads to high accuracy, reproducibility, and moderate fabrication cost Arrays continuously carry drugs into skin.¹

DISADVANTAGES OF MICRONEEDLES
This system carries some disadvantages too. The needle made of silicon and if the silicon left under the skin after removing the patch, it may create problems. 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 therefore problems may be developed. Skin irritation or allergy may create in case of sensitive skin. The designs of microneedles are difficult to apply on the skin therefore proper application is needed and self-administration is not easy.

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 degree²,⁸
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

**1. 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**

**2. 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 calcine or bovine serum albumin (BSA) into full thickness human cadaver skin.

**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 mm2 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.

**CURRENT RESEARCH IN MICRONEEDLES TECHNOLOGY**

The first microneedle arrays reported in the literature were etched into a silicon wafer and developed for intracellular delivery in vitro by Hashmi et al. These needles were inserted into cells and nematodes to increase molecular uptake and gene transfection. Henry et al. conducted the first study to determine if microneedles could be used to increase transdermal drug delivery. An array of solid Microneedles was embedded in cadaver skin, which caused skin permeability to a small model compound.

Extending in vitro findings to the in vivo environment, Lin et al. used microneedles either alone or in combination with iontophoresis to deliver 20-mer phosphorothioated oligodeoxynucleotides across the skin of hairless guinea pigs. A related study further demonstrated microneedle-enhanced delivery of desmopressin and human growth hormone using a similar approach.

Using solid microneedles of a different design, Martanto et al, delivered insulin to diabetic hairless rats in vivo. Microneedle arrays were inserted into the skin using a high-velocity injector and shown by microscopy to embed fully within the skin. Matriano et al. examined the use of Microneedles to deliver ovalbumin as a model protein antigen coated onto the needle surface. Microneedles were prepared with a dry-film coating of antigen and then inserted into the skin of hairless guinea pigs in vivo using a high-
velocity injector. Mikszta et al.\textsuperscript{12} studied delivery of naked plasmid DNA into skin using microneedles. The arrays were dipped into a solution of DNA and scraped multiple times across the skin of mice in vivo to create microabrasions.\textsuperscript{14}

Kaushik et al, carried out a small trial to determine if microneedles are perceived as painless by human subjects. Microneedle arrays were inserted into the skin of 12 subjects and compared to pressing a flat surface against the skin (negative control) and inserting a 26-gauge hypodermic needle into the skin surface (positive control). Subjects were unable to distinguish between the painless sensation of the flat surface and that caused by microneedles. All subjects found the sensation caused by the hypodermic needle to be much more painful. Other studies have also reported that microneedles were applied to human subjects in a painless manner.\textsuperscript{15}

Several new and interesting microneedle concepts have been recently proposed which may find great utility in the future. For example, biodegradable polymer microneedles have recently been fabricated and characterized. The advantage of polymer needles is that they may be produced much more inexpensively (compared to silicon) and they should not pose a problem if they break in the skin since they are biodegradable. This study addresses microneedles made of biocompatible and biodegradable polymers, which are expected to improve safety and manufacturability. To make biodegradable polymer microneedles with sharp tips, micro-electromechanical masking and etching were adapted to produce beveled- and chisel-tip microneedles and a new fabrication method was developed to produce tapered-cone microneedles using an in situ lens-based lithographic approach.\textsuperscript{16}

Gill et al (2007) have been studied on coating of Microneedle. A novel micron-scale dip-coating process and a GRAS coating formulation were designed to reliably produce uniform coatings on both individual and arrays of microneedles. This process was used to coat compounds including calcein, vitamin B, bovine serum albumin and plasmid DNA. Modified vaccinia virus and microparticles of 1 to 20 μm diameter were also coated. In conclusion, this study presents a simple, versatile, and controllable method to coat microneedles with proteins, DNA, viruses and microparticles for rapid delivery into the skin.\textsuperscript{17}

Recently Lee et al (2008) has studied on dissolving microneedles for transdermal drug delivery. This study presents a design that encapsulates molecules within microneedles that dissolve within the skin for bolus or sustained delivery and leave behind no biohazardous sharp medical waste.\textsuperscript{18}

REFERENCES