

MICRONEEDLES: AN EFFECTIVE TECHNIQUE FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT

Optimization of drug delivery through human skin is important in modern therapy. With limitations of oral drug delivery, pain and needle phobias associated with traditional injections drug delivery research has focused on transdermal delivery route. A new approach to transdermal delivery that acts as a bridge between the user friendless of patches and the broad effectiveness of hypodermic needles has recently received attention. by using needles of micron dimensions, termed microneedles, skin can be pierced to effectively deliver the drugs. The mechanism of action is based on temporary mechanical disruption of skin. The drug, in the form of biomolecules, is encapsulated within the micro needles, 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. The present review focus on various studies related to micro needles for transdermal drug delivery and technology applications in various fields.

KEY WORDS: Micro needles, Trans dermal drug delivery.

1. INTRODUCTION

More recently, considerable interest has arisen regarding Microporation technologies that create micronized micro channels or micro pores in the skin by using technologies such as laser ablation, thermal or radiofrequency ablation, or mechanical microneedles.^[1] Researchers have described these minimally invasive technologies as third-generation technologies that will have a significant impact on medicine.^[2] Microneedles, a microstructure transdermal system, consists of an array of micro structured projections coated with a drug

or vaccine that is applied to the skin to provide intradermal delivery of active agents, which otherwise would not cross the stratum corneum.^[3] They are generally one micron in diameter and range from 1-100 microns in length. These have been fabricated with various materials such as: metals, silicon, silicon dioxide, polymers, glass and other materials. 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. 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. [4] Various types of needles have been fabricated as well, for example: solid (straight, bent, filtered), and hollow. Solid microneedles 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. Hollow microneedles could also 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. The hollow needle designs include tapered and beveled tips, and could eventually be used to deliver microliter quantities of drug to very specific locations. 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. [5]

2. 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 [6]. 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. In terms of processing there are also many advantages. 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.

3. PROCESSING OF MICRONEEDLES

As stated previously, there are many types of materials, shapes and methods of processing of microneedles. Silicon microneedles are fabricated by using a wet etch method using a KOH solution, which requires a four step process [7]. The first step is to deposit a pad oxide (350 \AA) and a nitride double layer (1000 \AA) through LPCVD (low pressure chemical vapor deposition) on a (100) silicon wafer. By using photolithography, masking and plasma etching small micron sized circles are patterned on the silicon. The wafer is then submerged in a 29% KOH solution with the temperature at 79°C. The solution etches away faster on the (100) planes, which creates eight high index planes that create the needle shape and sharp needle tip. Another method of creating the solid microneedles is done by using a reactive ion etching process. The same circular dots are fabricated onto the silicon and the portion not covered is etched away using SF_6/O_2 plasma etch. This type of fabricated needle can be used as a product or can also be used as a mold for polymer or metallic microneedles which are the same or hollow shaped. This process is called micromoulding. Hollow microneedles are

fabricated with the solid micro needle array shown above and forming a mold made of thick photoresist. The whole mold covers the array except for the tips which are removed by plasma etch. The mold can then be electroplated or sputtered depending on the desired material ^[6]. The sacrificial photoresist layer is then removed to release the electroplated/sputtered array, which is shown below in figure 1.

4. NEED FOR USING 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. ^[8] To increase skin permeability, a number of different approaches have been studied, ranging from chemical/lipid enhancers ^[9] 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 ^[10]. An alternative approach involves creating larger transport pathways of micron 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 micro particles. 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. ^[11] 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 micro needle-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 micro needle 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 nanospheres. 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 microneedles pretreatment has received little attention.

5. 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 (Figure 1). The tiny needles are constructed in

arrays to deliver sufficient amount of drug to the patient for the desired therapeutic response.^[12]

6. METHODOLOGY OF DRUG DELIVERY^[13]

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 micro needles
- Hollow microneedles
- Dip and scrape

Poke with patch approach: It involves piercing an array of solid micro needles 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 micro needles: 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.

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 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 μm in length over a 1 cm^2 area.

7. PREPARATION OF MICRONEEDLES^[14]

Molding: Micro molds were fabricated using photolithography and molding processes. In brief, a female micro needle master-mold was structured in SU-8 photoresist by UV exposure to create conical (circular cross section) or pyramidal (square cross section) microneedle tapering from a base measuring 300 μm to a tip measuring 25 μm in width over a micro needle length of 600–800 μm . A male microneedle master-structure made of polydimethylsiloxane was created using this mold. The PDMS master-structure was sputter coated with 100 nm of gold to prevent adhesion with a second PDMS layer cured onto the male master-structure to create a female PDMS replicate-mold. Excess PDMS on the female replicate-mold was trimmed so that the mold fit within the 27-mm inner diameter of a 50 ml conical tube. This metal coated male master-structure was repeatedly used to make replicate-molds that were repeatedly used to make microneedle devices.

Preparation of microneedle matrix

To serve as microneedle matrix materials, ultra-low viscosity carboxymethylcellulose (CMC), amylopectin and bovine serum albumin (BSA) were dissolved in deionized water. Water was then evaporated off until the concentration of solute (e.g., CMC) was approximately 27 wt.%, which resulted in a viscous

hydrogel. CMC was concentrated by heating at 60–70 °C at ambient pressure or vacuuming at –50 kPa at room temperature. Amylopectin and BSA were concentrated only by the heating method at 60–70 °C or 37 °C, respectively. Solute concentration was determined by measuring solution mass before and after evaporation. Viscosity of concentrated hydrogels was measured using a Couette viscometer. In some cases, a model drug was added by hand mixing to solubilize or suspend the compound in the concentrated hydrogel. Three model drugs were added at final concentrations of 0.15–30 wt. % sulforhodamine B (Molecular Probes), 20 wt. % BSA (Sigma), or 5 wt. % lysozyme (Sigma). The term “model drug” is used to indicate that these compounds have physicochemical and transport properties representative of certain classes of drugs, but not to suggest that these compounds have pharmacological activity representative of drugs.

Casting: To mold microneedles from concentrated hydrogels, 100–300 mg of hydrogel was placed on a female PDMS mold in a conical centrifuge tube (Corning) and centrifuged in a 45° angled rotor at 3000 $\times g$ and 37 °C for up to 2 h to fill the microneedle mold cavities and dry the hydrogel. To prepare microneedles with model drug encapsulated only within the microneedles and not in the backing layer, 8–10 mg of hydrogel mixed with model drug was filled just into the microneedle cavities in the mold and then dried under centrifugation for up to 30 min. Residual hydrogel on the surface of the mold was removed with dry tissue paper and 100–200 mg pure hydrogel without drug was then applied and dried onto the mold to form the backing layer. To prepare microneedles with model drug encapsulated only in the backing layer and not within the microneedles, the

same 2-step process was followed, except pure hydrogel was filled into the microneedle mold cavities and a hydrogel mixed with model drug was used to form the backing layer.

Other methods^[12]

Laser cutting: Microneedles were cut from stainless steel sheets using an infrared laser. The desired microneedle shape and dimensions were first drafted in AutoCAD software. Using this design, the infrared laser was operated at 1000 Hz, 20 J/cm² energy density and 40% attenuation of laser energy to cut the microneedles. A total of three passes were required to completely cut through the stainless steel sheet. A cutting speed of 2 mm/s and air purge at a constant pressure of 140 kPa was used. Microneedles were either prepared as individual rows of needles ('in-plane' needles) or as two-dimensional arrays of needles cut into the plane of the stainless steel sheet and subsequently bent at 90° out of the plane ('out of-plane' needles).

Cleaning and bending microneedles:

Laser-cut stainless steel microneedle arrays were manually cleaned with detergent to de-grease the surface and remove slag and oxides deposited during laser cutting, which was followed by thorough rinsing in running water. To prepare 'out-of-plane' microneedles, microneedles cut into stainless steel sheets were first manually pushed out of the sheet using either forceps or a hypodermic needle (26 gage, 1/2 inch long) while viewing under a stereo microscope, and then bent at 90° angle with the aid of a #9 single-edged razor blade.

Electro polishing: To clean microneedle edges and to make the tips sharp, microneedles were electro polished in a

solution containing glycerin, orthophosphoric acid (85%) and water in a ratio of 6:3:1 by volume. Electro polishing was performed in a 300 ml glass beaker at 70 °C and a stirring rate of 150 rpm. A copper plate was used as the cathode, while microneedles acted as the anode. The anode was vibrated at a frequency of 10 Hz throughout the electro polishing process using a custom-built vibrating device to help remove gas bubbles generated at the anodic surface during electro polishing. A current density of 1.8 mA/mm² was applied for 15 min to electro polish the microneedles. After electro polishing, microneedles were cleaned by dipping alternately three times in de-ionized water and 25% nitric acid for 30 s each. This was followed by another washing step in hot running water and a final wash in running deionized water. Due to the electro polishing process, the thickness of the microneedles was reduced to 50 µm. Microneedles were dried using compressed air before storing in air-tight containers until later use.

Micro-dip-coating: Microneedles were coated with different molecules using a novel micron-scale, dip-coating process and a specially formulated coating solution.

a. Coating solution: The coating solution was composed of 1% (w/v) carboxymethylcellulose sodium salt (low viscosity, USP grade), 0.5% (w/v) Lutrol F-68 NF and a model drug/biopharmaceutical. The model drugs tested included 0.01% suforhodamine, 0.01% calcein, 3% vitamin B, 1% bovine serum albumin conjugated to Texas Red (Molecular Probes), 0.05% gWizTM luciferase plasmid DNA, 2 × 10⁹ plaque forming units per ml of modified vaccinia virus-Ankara, 10% barium sulfate particles (1 µm diameter), 1.2% 10-µm diameter latex beads and 8.2% 20-µm diameter

latex beads, all w/v. DNA and virus were made fluorescent by incubating with YOYO-1 (Molecular Probes) at a dye: basepair/virus ratio of 1:5 for 1 h at room temperature in the dark.

b. Coating single microneedles: Single microneedles were dip-coated by horizontally dipping the microneedle into 20–30 μ l of coating solution held as a droplet on the tip of a 200- μ l large orifice pipette tip. The large-orifice pipette tip was mounted horizontally in a clamp and the microneedle was mounted opposite to it on a manual linear micro positioner. Immersion/withdrawal of the microneedle into the liquid droplet was performed manually by moving the microneedle while viewing under a stereo microscope.

c. Coating rows of microneedles: In-plane rows of microneedles were dip-coated using an in-house designed coating device. The coating device consisted of two parts:

- The coating-solution reservoir
- The micropositioning dip coater.

(1) Coating-solution reservoir: The coating-solution reservoir was designed to restrict access of the coating liquid only to the microneedle shaft to prevent contamination of the base. The coating-solution reservoir consisted of two laminated parts: the ‘bottom plate’ and the ‘cover plate’, both of which were made of polymethylmethacrylate (Fig. 4A). The bottom plate had a central feeding channel (1 mm deep \times 0.5 mm wide) machined into one of its faces, with a through-hole drilled across to the other face. This hole acted as the inlet port to fill the channel with the coating solution. The cover plate had five holes (400 μ m diameter) drilled into it at the same interval as the microneedles in the in-plane row to be coated. These ‘dip-holes’ acted as individual dipping reservoirs to coat each of the microneedles in the row. The two plates (bottom and cover plates) were

aligned and adhered to each other using solvent bonding with methylene chloride (Fisher Scientific) as the solvent.

(2) Micro positioning dip coater: To enable three-dimensional alignment and dipping of microneedle rows into the dip-holes, three linear micropositioners were assembled on a 6.35-mm thick, flat, acrylic plate (Fig. 4B). The first micropositioner was used to control the position of the in-plane microneedle row. The other two micropositioners were assembled one on top of the other on the acrylic plate to create a composite Y–Z motion micropositioner that was used to control the position of the coating-solution reservoir. The three micropositioners together allowed the alignment of the in-plane microneedle row to the dip-holes. The X-micropositioner was used to horizontally dip the microneedles into and out of the dip-holes. The coating was performed manually while viewing under a stereo microscope. Control over the length of the microneedle shaft to be coated was exercised manually using the X micropositioner. Tolerance for misalignment was included by designing the dip-hole diameter to be twice the width of the microneedles.

8. FABRICATION OF MICRONEEDLES

A variety of technologies have been developed for fabrication of microneedles, which are typically used for drug and gene delivery. Many of the fabricated solid needles in the reference articles are applied for transdermal drug delivery with increasing skin permeability through creation of pathways in the skin. Certain drugs such as drugs in anti-restenosis and anti-tumor therapies cannot be absorbed efficiently in transdermal delivery. Microneedles with lumen and reservoir

were further developed for local delivery with precise dose in controlled release to overcome the over dosage problem and decrease side-effects in drugs.

The fabricated microneedles for local delivery can generally be categorized into in-plane and out-of plane microneedles.

Out-of-Plane Microneedles: In the literature, microneedle devices can be categorized as either out-of-plane (where the fluid flow channel is normal to the substrate) or in-plane (where the fluid flow channel is parallel to the substrate) [15]. For out-of-plane devices, bulk micromachining and/or micromolding fabrication techniques are utilized. Therefore, microneedle shape is typically dictated by some sort of removal process, which can be costly in terms of machine time, controllability, and maximum depth producible (100 to 500 μm). Furthermore, fluid access to the microneedle lumens is typically through the backside of the substrate which can also complicate the fabrication process. Due to their nature, out-of-plane microneedles are micro machined in two-dimensional arrays, making them ideal for patch-like transdermal drug delivery applications. However, this geometry may also make it difficult to integrate planar microfluidic components on-chip. Material selection is also limited by the fabrication techniques used to manufacture out-of-plane microneedles. For example, traditional bulk micromachining has produced several different microneedle designs in single crystal silicon [16]. Using micromolding, out-of-plane devices have been fabricated in both polymers [17] and electrodeposited metals [18]. However, silicon is brittle, polymers lack the required stiffness to penetrate into viable epidermis strata, and electroplated metals such as nickel are not considered to be

biocompatible (nickel is a well-known skin irritant and carcinogen) [19]. Figure 4.2 shows several existing out-of-plane microneedle technologies.

Figure 2. Scanning electron micrographs of several existing out-of-plane microneedle technologies fabricated using: (a) micro molded polymers (b) dry etched single crystal silicon; and (c) electrodeposited nickel [13].

In-Plane Microneedles: In-plane microneedle devices, where the lumen is parallel to the substrate, have several advantages over out-of-plane designs. First, microneedle length and shape can be defined lithographically. Also, in-plane microfluidic components can be easily integrated. But traditionally, in-plane microneedles have relied heavily on surface micromachining techniques which limit deposited film thicknesses and therefore overall device strength. Also, in-plane microneedle arrays are typically limited to one-dimension, which can limit fluid throughput considerably. Existing technologies have utilized a number of different materials (see Fig.3), including polysilicon [20], electrodeposited metals [21], and single crystal silicon [22]

However, similar to those commonly used for out-of-plane microneedles, these micromechanical materials impose limitations on device performance which ultimately constrains their utility and efficacy. For example, the low fracture toughness of silicon and polysilicon can detrimentally affect device reliability and damage tolerance. And the materials associated with electrode position (e.g. nickel) may not be well-suited for microneedle applications. Consequently, there is a distinct need for the development of micromechanical

materials to address these shortcomings. Titanium represents one such material.

Figure 3. Scanning electron micrographs of several existing in-plane microneedle technologies fabricated using: (a) polysilicon (b) electrodeposited nickel and (c) single crystal silicon^[23]

9. APPLICATIONS OF MICRONEEDLE TECHNOLOGY

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. In a follow up study, McAllister et al found a change in the permeability of cadaver skin to insulin, latex nanoparticles and bovine serum albumin after treatment with microneedles, and unleashed the mechanism of transport as simple diffusion.

Oligonucleotide delivery: Lin and coworkers extended the in vitro findings of microarray drug delivery to in vivo environment. An oligonucleotide, 20-mer phosphorothioated oligodeoxynucleotide was delivered across the skin of hairless guinea pig either alone or in combination with iontophoresis. Lin and coworkers used solid microneedles etched from stainless steel or titanium sheet prepared with the poke with patch approach. This delivery system increased the absorption of the molecules relative to the intact skin. Iontophoresis combined with

microneedles was able to increase the transdermal flux by 100 fold compared to the iontophoresis alone.

DNA vaccine delivery^[13]: The cells of Langerhans present in the skin serve as the first level of immune defense of the body to the pathogens invading from the environment. These cells locate the antigens from the pathogens and present them to T lymphocytes, which in turn stimulate the production of antibodies. Mikszta et al reported the delivery of a DNA vaccine using microneedle technology prepared with the dip and scrape approach. The arrays were dipped into a solution of DNA and scrapped multiple times across the skin of mice in vivo. Expression of luciferase reporter gene was increased by 2800 fold using micro enhancer arrays. In addition, microneedle delivery induced immune responses were stronger and less variable compared to that induced by the hypodermic injections. Similar results were obtained by researchers at Beckett-Dickinson™ in an animal study for antibody response to HepB naked plasmid DNA vaccine. This approach has a potential to lower the doses and the number of boosters needed for immunization.

Desmopressin delivery: M. Cormier et al (Alza Corporation, USA) examined the use of microneedles to deliver desmopressin, a potent peptide hormone used in the treatment of nocturnal enuresis in young children, as well as for the treatment of diabetes insipidus and haemophilia A. Microneedles were coated by an aqueous film coating of desmopressin acetate on titanium microneedles of length 200 µm, a maximal width of 170 µm and a thickness of 35 µm. Microneedle patch was inserted into the skin with the help of an impact applicator. A target dose of 20 µg of

desmopressin was delivered to hairless guinea pig from 2 cm² microneedle array within 15 minutes.

Insulin delivery: Insulin is one of the most challenging drug of all times for the drug delivery technologists. Martano et al [10], used microarrays for the delivery of insulin to diabetic hairless rats. Solid microneedles of stainless steel having 1 mm length and tip width of 75 µm were inserted into the rat skin and delivered insulin using poke with patch approach. Over a period of 4 hours, blood glucose level steadily decreased by as much as 80% with the decrease in glucose level being dependent on the insulin concentration.

Porphyrin Precursor 5-Aminolevulinic Acid (ALA) Delivery: Photodynamic therapy of deep or nodular skin tumours is currently limited by the poor tissue penetration of the porphyrin precursor 5-aminolevulinic acid (ALA). Ryan F. Donnelly and co-workers have shown that, in vivo experiments using nude mice showed that microneedle puncture could reduce application time and ALA dose required to induce high levels of the photosensitizer protoporphyrin IX in skin. This clearly has implications for clinical practice, as shorter application times would mean improved patient and clinician convenience and also that more patients could be treated in the same session.

In vitro transdermal delivery of monoclonal antibody: In all the previously mentioned studies, purified human IgG was used as a model drug for large proteins in transdermal delivery, and later the feasibility of microneedle-mediated transdermal delivery was further investigated using a human monoclonal antibody IgG to demonstrate the applicability of this technique for delivery of macromolecules.

10. COMMERCIAL MICRONEEDLE TECHNOLOGIES

A decade after the first microneedles were reported, many commercial technologies have come into the market including the Macroflux technology, h-patch, Micro-Trans and many more are given in table 1.

11. FUTURE TRENDS

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. [23] 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. Firstly, other methods of improving microneedle penetration (e.g. various ways of limiting the viscoelasticity of the skin, coating the needles, further improving needle/array design) should be explored. While high-speed injectors are currently being used, another method may be more feasible especially if the microneedles are integrated into a drug delivery device. Also, microneedles have been touted as being particularly suited for administration of drugs requiring slow release. Hence, another issue that will need to be looked into is whether the microneedles will remain in the skin (after insertion) and how to keep needles in the skin during normal daily activities. 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. Yet other groups are working on needles which are made of materials that incorporate drugs which are released when the needles dissolve (personal communication). 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.

12. FUTURE PROSPECTS

Early microneedles were made of single crystal silicon^[24] The device wafer was sacrificed or dissolved away in silicon etchant leaving the microneedle behind. The fluid channels of these microneedles only occupy a small fraction of the interior volume of the needle resulting in a small fluid carrying capacity. These microneedles are useful for delivering fluid at low (50.1 ml/sec) flow rates but cannot deliver sufficient fluid for many therapeutic injections such as insulin. Micromolded needles leave the majority of the interior volume free, and allow larger fluid flow rates for the same size needle outer diameter. Other approaches to microneedles have been investigated. One approach uses SF₆/O₂ plasma to create high aspect ratio barbs for piercing the skin to allow therapeutics to diffuse across the skin^[3] However, these needles are not sufficient for injecting large amounts of fluids or clinically relevant dosages of much therapeutics. Another approach uses electroplated palladium as the needle structural material and thick photoresist to define the needle channel^[25]. However, because these needles are electroplated, they have very blunt tips. Future work needs to be performed to determine the biological response to needles. The first response to tissue distress from needle insertion is an inflammatory

response at the insertion site ^[26]. During this time there may be tissue edema, which may affect delivery from the needles, and the migration of leukocytes to the injury site. Protein adsorption to the surface of the silicon will promote adhesion of leukocytes to the needles. Surface modifications of silicon surfaces to reduce protein adsorption are an active area of research. Some surface modifiers include: silicon carbide ^[27], polyethylene glycol (PEG) ^[28], or plasma enhanced chemical vapor deposition (PECVD) of a Teflon-like fluoropolymer. Any of these coatings could be incorporated into needle fabrication to improve biocompatibility. Since microneedles are designed for short term intradermal drug delivery, fibrous encapsulation is not expected because the needle is not inserted long enough for encapsulation to occur. Thrombosis is also not expected since the needle will not be in contact with the blood stream. Due to the small size of microneedles, strength and robustness are the major factors in determining the range of their applications. Needles must be able to tolerate forces associated with insertion, intact removal and normal human movements if they are to be integrated into portable biomedical devices.

13. CONCLUSION

Micro channel 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 & it can be used as 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 allows for the delivery of water-soluble drugs. In contrast to iontophoresis, this is useful 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 useful for potent & less potent drugs, then more extended release the delivery system.

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Table no 1:Commercially available microneedle technologies

S.No	Marketed micro needle technologies
1	Macroflux Alza None PTH patch, Vaccines, Proteins
2	h-patch Valeritas Bolus insulin delivery
3	Microinfusor BD None Vaccines, Macromolecules
4	Micro-Trans Valeritas None Fluid sensing of glucose, hormones, blood gases, Vaccines, Proteins
5	Micro structured transdermal system 3M None Hydrophilic molecules, Macromolecules
6	Micro piles Texmac- Nanodes 10% Lidocaine and Indomethacin
7	Micro-Trans Valeritas None Fluid sensing of glucose, hormones, blood gases, Vaccines, Proteins
8	Microstructured transdermal system 3M None Hydrophilic molecules, Macromolecules
9	Micro Needle Therapy System Clinical resolution lab Microneedle Dermaroller

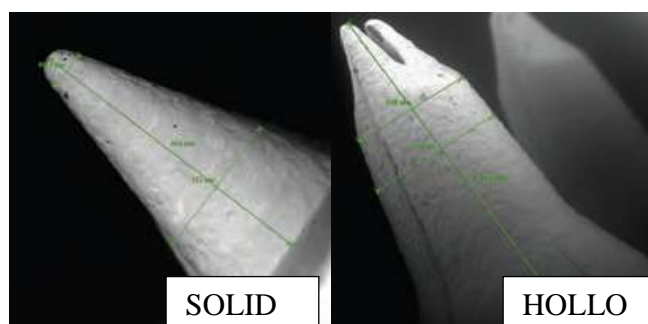


Figure 1: Solid and hollow metal microneedles ^[1]

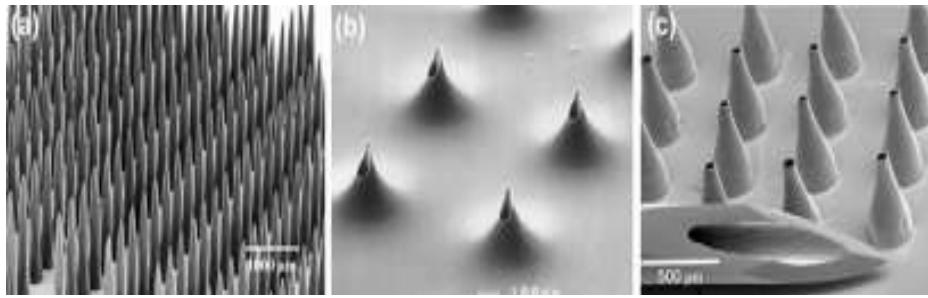


Figure 2. Scanning electron micrographs of several existing out-of-plane microneedle technologies fabricated using: (a) micro molded polymers (b) dry etched single crystal silicon; and (c) electrodeposited nickel ^[13].

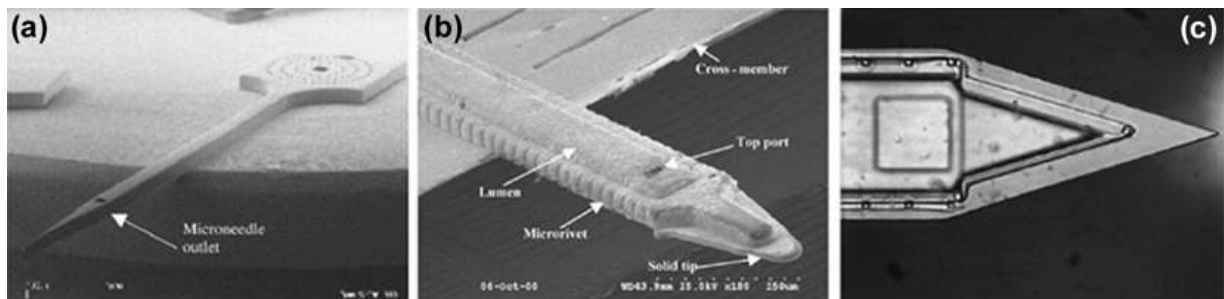


Figure3. Scanning electron micrographs of several existing in-plane microneedle technologies fabricated using: (a) polysilicon (b) electrodeposited nickel and (c) single crystal silicon ^[23]