Microneedles as a novel transdermal drug delivery

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ABSTRACT

Microneedles have been used to successfully deliver substances across biological membranes which include the skin, mucosal tissue and sclera. In addition, microneedles have been successfully used to deliver large molecules such as peptides, proteins, oligonucleotides, insulin, vaccines and other compounds through the skin employing a number of different strategies to deliver these compounds in a non-invasive manner. These microneedles only penetrate the outermost skin layers, superficial enough not to reach the nerve receptors of the lower skin. These microneedles 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 upto 4 orders of magnitude.

Excellent impervious nature of skin is the greatest challenge that has to be overcome for successfully delivering drug molecules to the systemic circulation by this route. Arrays of microneedles that are 100–1000 µm in length poke through the top layers of skin and allow micron-scale drugs to pass into the body. The needles are too small to stimulate nerve endings; patients wouldn’t feel any pain when a microneedle injection is performed. This review gives an overview of microneedles for drug delivery applications.

Keywords: Microneedle, Characterisation, Evaluation, Application.
1. INTRODUCTION

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 unconventional routes have been developed such as Transdermal-through skin, nasal through nose, ocular through eye, Pulmonary by lungs. In short, many novel drug delivery systems have been developed from last few years for the purpose of the administration of drug to the body to make drug more effective.[1]

Transdermal drug delivery means that a pharmaceutical compound is moved across the skin- the dermis-for subsequent systemic distribution. Hence, strictly semantically this does not only include the more commonly understood “patch” but also traditional subcutaneous administration by means of a hypodermic needle and a syringe as well as novel techniques such as microneedles.[2] 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. Following conventional terminology, a microneedle is a needle with representative parts (e.g. diameter) on the micrometer length scale. However, this definition is rather bold as it includes most of the standard hypodermic needles used in medical practice. Although there are many examples of “microneedles” with lengths of a few millimeters described in the literature, a common understanding of microneedles is that the length of the needle is shorter than 1 mm.

Microneedles were first proposed in the 1970s but it found its application in the 1990s. It was first mentioned by Vander voot and Ludwig. Since then, it has been a potential replacement for hypodermic needles. This has led to an increase in the interest of scientists in this field and a lot of work has been done in the area of fabrication and its use in drug delivery. The first patent of microneedles as a drug delivery device in the United States was filed by inventors, Gerstel and Place in 1971. They used the term ‘puncturing projections’ to describe this invention.[3] In addition, microneedles seldom cause infection during administration of drugs or nanoparticles. Further, it has been tested to increase the rate of permeation of compounds through the skin. Hence, microneedle array technology is an evolving technique that combines the ease of use of transdermal patch and the effectiveness of syringes through the use of multiple projections from a backing plate that enhance penetration and provides a unique form of delivery.[4] Till date, microneedles have been used to successfully deliver substances across biological membranes which include the skin, mucosal tissue and sclera. In addition, microneedles have been successfully used to deliver large molecules such as peptides, proteins, oligonucleotides, insulin, vaccines and other compounds through the skin employing a number of different strategies to deliver these compounds in a non-invasive manner.[5]

Microneedles were made using microfabrication technology, which is the same technology used to make integrated circuit. An advantage of this approach is that microfabrication readily makes structures of micron dimensions in a way that is easily scaled up for cheap and reproducible mass production. In addition to extensive work using microfabrication for non-biological purposes, this technology has been used for biological applications to fabricate
two dimensional arrays of electrodes used to excite neurons and record their activity and three-dimensional arrays of pyramid like structures to facilitate transfection of microorganisms. To adapt this technology for transdermal drug delivery, we created three-dimensional arrays of sharp-tipped microneedles of approximately 150µm in length.\[6\]

1.1 Microneedles

Microneedles are one of the recently developed systems for drug delivery which is similar to traditional needles but the difference is these are fabricated on the micron scale and the size ranges from 1100 microns in length and 1 micron in diameter. These are defined as micro scale needles, arranged on a transdermal patch. These are the microstructure system composed of micro sized array projection coated with a drug or vaccine. These are considered as a combination of hypodermic needles as well as transdermal patches and effective enough to overcome the limitations being possessed by these two systems. Micro needles have been formulated as a novel drug delivery carrier for effective transdermal delivery, as these have been developed by fabrication, done by involving the tools of micro electronics so that the penetration up to hundred microns deep into the skin can be achieved in a painless manner.

Stratum corneum is the limiting barriers for the transport of several drugs and it will be bypassed by the use of microneedles. These are tiny and sleek devices manufactured by silicon etching technology and micro-mechanical system manufacturing (MEMS) technique. Microneedles are just like conventional needles fabricated only in micro scales. These are mainly arranged in the form of arrays. Micro needle arrays have been developed based on etching method used by microelectronics industry to world of research field of transdermal deliver for enhanced bioavailability. Use of microneedles is a recently developed novel approach for transdermal drug delivery and it was shown to dramatically enhance the transdermal delivery of macromolecules.\[7\]

1.2 The Skin

The skin is the largest organ of the human body and has several functions. It is a physical barrier towards the environment, it regulates body temperature and fluid loss, it conveys sensory information to the nervous system, and it processes immunologic information to the immune system. The skin can be divided into three main layers: the superficial epidermis, dermis and hypodermis, The epidermis is approximately 50–150 m² thick and consists largely of constantly renewing, outward moving cells called keratinocytes. Apart for these cells, most of the antigen-presenting Langerhans’ cells are located in the epidermis. The outermost layer of the epidermis is the stratum corneum, a 10– 20 m² thick layer of 15–30 stacked, dead, cornified cells. These so-called corneocytes are flat, hexagon-shaped and partly overlapping cells with a diameter of approximately 30 m². The cells are mechanically coupled to each other through special protein rivets and together with stacked layers of lipids they form an interlinked mechanical scaffold. The stratum corneum forms the major constituent of the water barrier in the skin. The dermis represents the bulk of the skin and the predominant components are collagen fibers and a smaller amount of elastin. This fibrous network gives tensile strength and elasticity to the skin and also provides support for nerve and vascular networks.
In the upper, papillary, region of the dermis the collagen fibers are small and loosely distributed. The deep, reticular region contains densely packed, bundled, collagen fibers mainly running parallel to the skin surface and along certain directions, called Langer’s lines.\textsuperscript{5,6}

The dermis rests on the hypodermis (subcutis) which is composed of loose fatty connective tissue. Its thickness varies considerably over the surface of the body as well as between individuals.

2. TYPES OF MICRONEEDLES

2.1 Coated microneedles (CMNs)

Coated microneedles (CMNs) are usually microneedles which has drug-containing dispersions coated with it. As a result of this, the desired amount of drug can be delivered upon insertion of the MN into the skin. Advantage of this method is the one-step application of its usage compared to the limitation of this approach is that a particular dose of the drug can only be coated onto the tip and shaft of the MN (usually less than 1mg for small MN array). This may restrict the use of coated MN to deliver potent molecules. Also, the loss of drug coating from the MN surface prior to use must be prevented (e.g. during handling) one approach of coating MN is through the use of electrohydrodynamic atomization (EHDA). In this method, stainless steel microneedles with a height between 600–900 \( \mu \text{m} \) in height were coupled with a ground electrode with a varying system of ethanol: methanol ratio of 50:50. Generally, this technique was reportedly used in the making of nano and micrometer- scaled coatings of pharmaceutical products. The remaining component that made up the coating formulation was fluorescein dye and polyvinyl pyrrolidone (PVP, polymer matrix system). Further, Ma and Gill prepared a coated solid microneedle from polyethylene glycol matrix containing the drug lidocaine. Also, the team performed an in vitro study of coated microneedles with PEG-lidocaine dispersion. Another approach is known as the layer-by-layer coating technique. An instance is the coating of the DNA or protein molecules onto metal and polymer MN by alternately dipping them into two solutions of oppositely charged solutions. Hence, a polyelectrolyte multilayer of negatively charged DNA and positively charged polymer is formed.
In one approach, the surface of the individual MN can be coated with an angled gas jet by spraying from a reservoir made from the substrate of the MN array. In addition, spray coating can be applied with the use of an atomizer. Also, coating can be done by dipping either once or repeatedly in coating solution or micro-wells of coating solution for each individual microneedle. Two most important parameters in the dip coating process are surface tension and the viscosity of the formulation. A lowered surface tension facilitates good wetting and slows down the rate of film formation on the MN surface. CMs have been widely used in the delivery of substances such as drugs, vaccines, DNA, micron-scale particles, such as BaSO4 particles (1μm) and latex particles (10μm) and bio molecules. The coating of therapeutics on MNs depends on factors like physical and chemical interaction between the microneedle and the coating compound, the type of coating solution used etc. [3]

![Coated microneedles](Fig. No. 2: Coated microneedles)

### 2.2 Solid microneedles

Solid micro needles are defined as the arrays of projections that are employed for creating holes in stratum corneum and are applied before the application of a drug and then removed afterwards. These can essentially create micron scale holes in the skin, through which drug molecules can easily enters. These can be used by inserting the needles into the skin for specified time period. The micro channels developed by the insertion of micro needles promote the drug transport in to the viable epidermis. Solid micro needles can be prepare by coating with the drug and then inserted into the skin. After removal of the micro needle containing device, drug will remain deposited within the skin membranes. Erodible microneedles when inserted into the skin, dissolves and the drug can easily be loaded into the soluble needles.

These microneedles can pierce through the superficial skin layers then followed by the delivery of drugs. It also suffers from some limitations such as in solid microneedle arrays, the drug delivered cannot easily flow via the holes present in the skin because it remains plugged by the microneedles. An application of a thick layer of drug formulation was not found to be the desirable because it reduces the sharpness of the microneedles and therefore made insertion more difficult and painful. [3]
2.3 Dissolving microneedles

In contrast to polymeric MN, dissolving MNs from the name are basically designed to break into the skin, dissolve and create channels for drugs and other compounds to pass into the skin an interstitial fluid out of the skin. It can also be typically molded into the desired shape before insertion. One major advantage of the use of this MN type is the biodegradable property of the material upon contact with the skin’s interstitial fluid. This process allows the drug to be released from its matrix and subsequently introduced for either local or systemic delivery. Dissolving MNs have been made from sugars such as galactose, maltose and dextrin. Maltose was first reported for use and it has generally been recognized as a safe substance appropriate for its utilization in the fabrication of MN. Upon contact with the skin, it dissolved within three hours and its shape is retained for at least three months at 40% humidity. In a study carried out on maltose MN, research proved that it sufficiently pierces the stratum corneum of hairless rats, creating a micro conduit for the transport of compounds. Therefore, it can serve as a means of transporting protein macromolecules such as human IgG which passively pass through the skin. In addition, another study showed the improved transdermal delivery of nicardipine hydrochloride with the use of maltose MN in the treatment of hypertension. There is however a disadvantage to the use of maltose MN; the fact that the sugar maltose is a disaccharide, it absorbs water under high humidity and this therefore leads to the MN bending in the skin, thereby making insertion difficult. Moreover, a high temperature is needed for the production of maltose MN, under this condition the loss of protein/peptide drugs occurs because the drugs at this temperature becomes easily degradable. A way to overcome this challenge that has been proposed by researchers is the development of new, self-dissolving MNs made of dextrin that can be used for administration. Interestingly, the combination of ion to phoresis and dissolving MNs performed both in vivo and in vitro lead to 25 fold enhancement delivery when compared to the use of either method alone.\cite{3}
2.4 Hollow microneedles

Hollow microneedles contain a hollow bore in the centre of the needle. When inserted into the skin, the hollow bore present bypasses the stratum corneum layer of the skin and produces a direct channel into the other lower layers of the epidermis. These microneedles are mainly employed to inject the drug solutions directly into the skin.\cite{10} These are very expensive to prepare and require expensive micro fabrication techniques.\cite{11} These micro needles contains hollow bore which offers possibility of transporting drugs through the interior of well defined needles by diffusion or for more rapid rates of delivery by pressure driven flow.

![Hollow microneedles](image)

Fig. No. 5: Hollow microneedles

2.5 Hydrogel forming microneedles

Hydrogel MN array has been manufacture from aqueous blends of polymeric materials (poly (methyl ether / maleic acid) and poly (ethylene glycol) with a micro molding process which involves laser-based technology. Hydrogel MNs can be defined as an integrated system which consists of cross-linked needles projecting from a solid base plate to which an adhesive drug reservoir is attached. The method of use of the MN array is such that when it is applied to the skin, diffusion of the drug from the patch occurs through the swollen micro projections. Hydrogel MN are typically suitable for the delivery of small hydrophilic drugs such as caffeine, methylene blue and high molecular weight compounds (i.e. insulin and bovine serum albumin)\cite{5}.

A study by the Donnelly group showed that the hydrogel system of delivery showed a sustained method of transporting drugs in vitro in neonatal porcine skin where the peptides and protein were delivered over a 24h period. Further, complementary studies by the same research group showed the crosslink density of the hydrogel matrix can be modulated to control the transdermal delivery of drug.

This indicates that the drug delivery method can be personalized on a case by case basis to meet the requirement demanded by the drug of interest. This further confirms the versatility of the hydrogel-MN device. Additional advantages of using hydrogel MN in contrast to dissolving MN is that it remains intact when withdrawn from the tissue leaving no residues behind. In addition, the potential toxic effects have not been elucidated following repeated use of dissolving MN and the overall health impact of the accumulation of residues in the body is unknown. Further, hydrogel MN offers better control of the delivery of compounds in the required amount of dose and they are not blocked by the dermal tissue in contrast to that experienced in the use of hollow MNs.\cite{5}
3. MECHANICS OF MICRONEEDLE INSERTION INTO SKIN

Most studies of microneedles have addressed methods of fabrication and assessed drug delivery capability. The mechanics of microneedle insertion have received only limited attention, but are critically important to practical applications. Only microneedles with the correct geometry and physical properties are able to insert into skin. Some needle designs require only μinsertion by hand, whereas others benefit from high velocity insertion, as mentioned above. When the force required for insertion is too large, needles can break or bend before insertion occurs.

These issues have been explicitly addressed by Davis, who measured the force required for fracture, the force required for insertion, and their ratio (termed the margin of safety) as a function of needle geometry and physical properties. In this study, individual hollow metal microneedles were used with tip radii of 30–80µm, wall thicknesses of 5µm to solid tips (equivalent to 58 µm wall thickness) and constant length of 500 µm.

To determine the effect of microneedle geometry on the force of insertion, individual microneedles were inserted into the skin of human subjects while recording the force and displacement of the needle, as well as monitoring skin resistance (which was used to indicate needle insertion into the skin). Forces of insertion varied from 0.1 to 3.0 N (i.e. 10–300 g) and showed an approximately linear dependence on the area of the needle tip. Insertion force was found to be independent of wall thickness; thin-wall hollow needles and solid needles with the same outer tip radii required the same force of insertion. This indicated that skin was insufficiently flexible to dimple into the needle bore.

To determine the effect of microneedle geometry on the force of fracture, individual microneedles were pressed against a rigid surface until they fractured. Over the range considered, measured fracture forces were between 0.5 and 6N. Fracture force increased strongly with increasing wall thickness and increased weakly with increasing wall angle, but was independent of tip radius. These results agreed with analytical and finite element modeling.

The ratio of the fracture force to the insertion force can be considered the margin of safety; values greater than one identify needles that will insert into skin without breaking. Almost all needles tested had margins of safety greater than one and some were greater than ten. The largest margin of safety was achieved using needles with small tip radius (to facilitate insertion) and large wall thickness (to provide strength).[4]

3.1 Mechanism of transdermal permeation

Transdermal delivery of the systemically acting drugs to the targeted tissues showed that the drugs must possess some physicochemical properties which act by facilitating the systemic absorption of drug across the skin and also enhance the drug uptake via capillary network into the dermal papillary layer. The rate of permeation as depicted by dQ/dt, across the skin layers can be expressed as

\[
dQ/dt = P_S(C_d-C_r)
\]

Where

\[C_d\] & \[C_r\] = concentration of skin penetrate in donor and receptor phase respectively.
**P**$_S$ = Overall permeability coefficient of the skin.

**P**$_S$ = $K_S D_{SS}/h_S$

Where

$K_S$ = Partition Coefficient of the penetrant.

$D_{SS}$ = Apparent diffusivity of penetrant.

$h_S$ = Thickness of skin.$^{[12]}$

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4 CHARACTERISTICS OF MICRONEEDLES

The characteristics of micro needles include

**Ruggedness:**-

Micro needles developed must be capable of insertion deep into the skin without breaking. They should be manufactured by taking optimum size and if they are too long, upper portion of micro needles may not have enough rigidity and could undergo breakage before penetration. They must be able to withstand the insertion force without delamination, or fracture.

**Controlled drug release:**-

The micro needles should deliver the controlled amount of drug at a definite and predetermined rate.

**Penetration:**-

The micro needles should be able to penetrate the drug to the required depth in the tissues of the body. Painless insertions of micro needles into the skin can be accomplished by gentle pushing, using approximately 10 Newton forces.

**Dimensions of microneedles:**-

The dimensions of micro needles can vary depending on the types of micro needles. Typical microneedle geometries may ranges from 150-1500 microns in length, 50-250 microns in base width, and 1-25 microns in tip diameter. The tips of microneedles are of different shapes like triangular, rounded or arrow shaped. The hollow microneedle arrays are fabricated with lumen diameter of 30 micro meters and height 250 micro meters. Centre to centre hollow micro needle array 150µm and the axis of lumen is fabricated with the distance of 10 micro meters to the axis of outside column.

**Materials used for construction:**-

The materials required for constructing micro needles include glass, silicone (of brittle nature), metals such as stainless steel, solid or coat of gold over nickel, palladium, cobalt and platinum and bio- degradable polymers.

**Effect of the Length of microneedle on pain:**-
The designing of microneedles can be such so as to minimize the pain. Various studies revealed that specific micro needles of about a couple hundred microns length were reported to be painless. It was reported by various authors that 13-times increment in needle length (i.e., 500-1500 microns) increases the pain by 7 times (i.e., 5-35% caused by hypodermic needle). If the length remains constant, an increase in number of microneedles (i.e., 620 micron long) 10 fold from 5-50 also increases the pain by 3 folds.

5. ADVANTAGES AND DISADVANTAGES OF MICRONEEDLES

5.1 Advantages of microneedles
The commonest advantage to all physical methods, microneedles inclusive (excluding methods using particle carriers), is that the transport mechanism does not depend on the uptake functions of the cell; therefore, physical methods can be applied equally well to all cell types and at all stages of the cell cycle. The process is, by itself, biologically nontoxic and minimally invasive.

The other advantages of microneedles include the following:

1) Solid microneedles could eventually be used with drug patches to increase diffusion rates; methods to increase permeability include poking holes in skin and rubbing drug over area, or coating needles with drug.
2) Microneedles have been fabricated with metals, silicon, silicon dioxide, polymers, glass, and other materials. They can be mass-produced from a range of materials in a consistent and cost effective manner.
3) Microneedles are fabricated on the micro scale (generally 1µm in diameter, ranging from 1 to 100µm in length).
4) Absence of pain or bleeding makes microneedles more clinically appropriate (particularly in pediatric vaccination and for needle-phobic patients).
5) The mechanism for delivery is not based on diffusion as it is in other transdermal drug delivery products. Placement of the drug or vaccine within the epidermis, where it can more readily reach its site of action.
6) Using microneedles avoids first-pass effect. Microneedles allow rapid penetration of drugs into the systemic circulation.
7) Microneedles can be fabricated to be long enough to penetrate the Stratum Corneum but short enough not to puncture nerve endings.
8) Microneedles can provide direct controlled delivery of small molecules, macromolecules, vaccines, or nucleic acids into the viable epidermis.
9) Using microneedles reduces the chances of pain, infection, and injury.
10) Hollow needles could eventually be used with drug patches and timed pumps to deliver drugs at specific times.
11) Very small microneedles could provide highly targeted drug administration to individual cells.
Administration of drugs via microneedles bypasses the gastrointestinal tract.

Single use needles are easily disposable and potentially biodegradable.

A relatively large surface area can be treated.

Drug can be administered at constant rate for a longer period.

5.2 Disadvantages of microneedles

In as much as there are lots of advantages of the use of microneedles in transdermal drug delivery however there are a few inherent demerits in its application. They include the following:

1) Microneedles can be difficult to apply on the skin; the clinician must learn proper application technique.
2) Local inflammation may result if the amount of drug is high under the skin. Skin irritation may result because of allergy or sensitive skin.
3) 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.
4) Advances in the Applications of microneedles in Transdermal Drug Delivery.[13]

6: EVALUATION PARAMETERS

6.1 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 paradimethysiloxane (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.

6.2 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.\[14]
7: APPLICATIONS

1) Microneedles have been used in many different applications, ranging from neurostimulation to gene delivery into individual cells.

2) A common goal is to create a pathway to an object by physically circumventing some kind of barrier. In most applications this barrier is the skin.

3) The rationale of using microneedles, as opposed to macroscale devices, is motivated either by the size of the target or the benefit of piercing in a minimally invasive manner.

4) These extremely slender needles were used as electrical electrodes and designed to stimulate the visual cortex of the brain in order to regain sight.

5) Related to this application, in plane, microneedle probes have been used for activity recording and cellular chemostimuli of brain tissue.

6) Microneedles can be used to deliver bioactive agents systematically as well as locally.

7) Microneedle probes have also been used for diagnostic purposes, where the needles were used for impedance measurements of skin lesion in order to detect skin cancer.

8) Another application for microneedles is sampling of body fluids. Resembling the proboscis of a mosquito, Oka et al. fabricated a millimeter-long, jagged, hollow in-plane microneedle for blood collection.

9) Sampling of interstitial fluid through capillary action has been demonstrated with arrays of 350 μm long, hollow, out-of-plane microneedles. Microneedles have also been fabricated for microdialysis, where a hollow in-plane needle equipped with a semi-permeable membrane filters the sampled liquid.

10) Skin is suitable for gene and oligonucleotide delivery because it is well characterized at the cellular as well as the molecular level.

11) The microneedle delivery system can be used for treatment various genetic disease-related to skin, various type of malignancies and infectious diseases, and for immunisation.

12) A dense array of very sharp pyramidal microneedles were used to delivery gene into cell.[15]

8: CONCLUSION

A review of the literature shows that microneedles can be fabricated by a number of different methods to yield a variety of needle sizes, shapes and materials. Solid microneedles have been shown to increase transdermal delivery and hollow microneedles have been shown to microinject into skin. Therapeutic responses have been achieved in vivo following delivery of proteins, DNA and vaccines. Proper needle design can assure insertion into the skin that prevents needle fracture or patient pain. These studies suggest that microneedles may provide a powerful new approach to transdermal drug delivery.
9. REFERENCES


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