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Micro needles: A Novel Trend for Transdermal Delivery technology

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ABSTRACT

The transdermal route of drug delivery overcomes many of the limitations associated with the more common oral and parenteral routes. Micro needles are micronized needles made from biodegradable polymer, ranging from 25 to 2000 µm in height, made up of variety of the material and shape. Advantages associated with micro needles are ease of use, controlled drug delivery, avoidance of first pass metabolism and lack of pain. However, transdermal drug delivery is limited due to the barrier provided by our skin known as stratum corneum which is the outermost non-viable layer of the epidermis. Microneedles were developed with the advantage that these can deliver the drug in a non- invasive painless manner and along with this overcome stratum corneum. The upper layer of the skin is penetrated by the microneedles without reaching the nerve, there by delivering drug transdermally in a painless manner. The present poster discusses the various fabrication techniques of micro needles using microelectromechanical system the design, material consideration and the application of micro needles in transdermal drug delivery system.

Keywords: Controlled drug delivery, Microelectomechanical system, Micro needles, Transdermal drug delivery system.

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INTRODUCTION

The more common oral and parenteral routes are associated with many disadvantages which can be overcome by using transdermal routes of drug delivery. It offers many advantages like lack of pain, ease of use, controlled drug delivery, avoidance of first pass metabolism and gastrointestinal tract, rapid onset of action etc. However, this route of drug administration is limited by the presence of the outer nonviable layer of epidermis, stratum corneum. Stratum corneum is the dead layer of tissue which has ability to protect the body by preventing the permeation of foreign substances. Moreover it is also affected by the molecule weight, dose of administration, octanol: water partition coefficient, melting point of drug, both water and lipid solubility etc. To overcome this problem, several approaches have been proposed like chemical modification, ultrasound, iontophoresis, sonophoresis, permeation enhancers and electroporation. However, these methods have limited degree of success, especially in delivery of hydrophilic or large-molecule-weight active substances.[1] A novel approach was suggested in which the drug delivery across the skin was enhanced with the help of microfabricated microneedles. The length of the microneedles is such that it can cross stratum corneum and create pores for passage of drug, but it does not stimulate the nerve because of it's small size, so it does not cause the pain. Although, this idea was patented by the Alza Corporation in the 1970s (Gerstel and Place, 1976), there was no demonstration to support this concept until microfabrication tools for making small needles became available (Prausnitz, 2004). Today this technology uses for number of drug molecules and also for delivery of vaccines.[1]

Skin structure

Skin is the outer most structure of body which protects the internal organ of the body from the surrounding environment. There are main three layer in the skin: epidermis, dermis and hypodermis (Figure 1).[1,2]

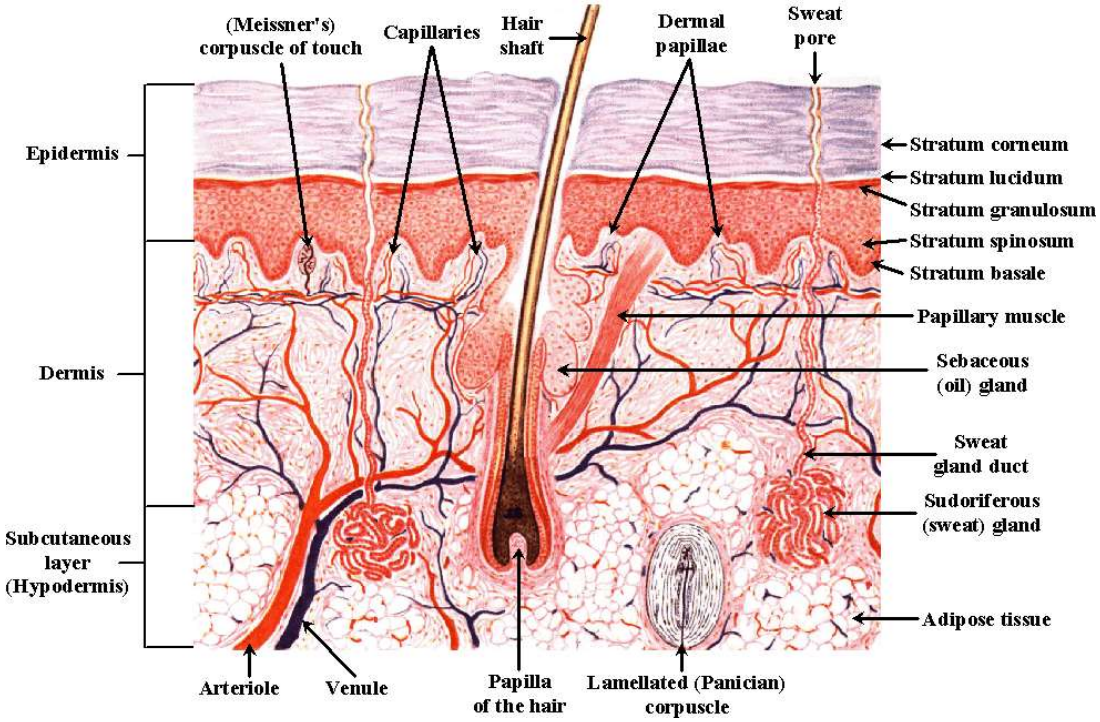

Figure 1: Schematic diagram of skin structure [3]

Epidermis:

It is the outermost layer of the skin. It forms the protective barrier over the body surface and prevent the water loss and pathogen entering in the body. It composed of mainly Keratinocytes, Merkel cells, Melanocytes and Langerhans cells. It is further divided into the four layer: stratum corneum, stratum granulosum, stratum spinosum, and stratum basale. The last three layer have a thickness of around 20-100 µm and they are referred as the viable epidermis. Stratum corneum is mostly concerned with the transdermal drug delivery because it prevents the entering of the foreign substances through the skin from environment including the drug. [1,2]

Dermis:

It is the layer of skin beneath the epidermis. It is the more flexible elastic layer and have thickness of 1.5-3 mm depending upon the anatomical sites. It is tightly connected to the epidermis through basement membrane. It contains blood capillaries, sweat glands, hair follicles, and nerves. To become painless microneedles must avoid to penetrate this layer. [1,2]

Hypodermis:

Hypodermis is not considering as the part of the skin and it lies below the dermis. It is also known as sabcutaneous tissue and it is the deepest layer of the skin. It mainly composes of blood vessels, loose connective tissue and elastin. It also contains various cells like fibroblasts, macrophages and adipocytes. This layer acts as an insulator which helps the body to retain heat. [1,2]

Advantages of microneedles

- They are painless, require no medical expertise, have little risk of infection at the injection site and lower dose requirement.
- Microneedles are non-invasive and painless and overcome the barrier of stratum corneum.
- Presence of antigen-producing cells such as the Langerhans cells and the dendritic cells in the skin make microneedles an alternative method for vaccine delivery and better immune response compared to intramuscular or subcutaneous injection
- In solid-coated microneedles, drugs stored as dried coating which could improve shelf-life of drug even at room temperature.
- It avoids first pass metabolism of drug and allow rapid penetration of drug into systemic circulation.
- Hollow microneedles could be used for removing fluid from body for diagnostic purpose such as blood glucose measurement.[4]

Limitation of microneedles

- It is small size, which limits the therapeutics delivery rates required in relatively low doses such as of proteins and vaccines.
- There can be intersubject variation due in the thickness of the skin due to the difference in sex, race, anatomical origin, etc.
- According to some studies, insertion of microneedles might prove rather difficult in vivo due to the nature of the skin.
- The underlying fat and muscles act as cushion, giving the skin a viscoelastic property that makes insertion difficult.[4]

Microneedele geometry:

Microneedles have been produced in different size and shape like triangular, rounded, arrow shaped etc., with or without bore, for different application. They have length of 150-1500 µm, 50-250 µm in base width and 1-25 µm in tip diameter and capacities to create microchannels in the skin for passage of drug trough skin. Microneedles have been fabricated in-plane or out-of-plane.[5]

Fabrication of microneedles:

The best and the most reliable method for fabricating microneedles is microelectromechanical systems (MEMS). It allows more accurate replication of microneedles to produce more precise devices. A researcher known Hashmi was the first one to use this technique to fabricate microneedles. Afterwards, this technique was used to etch arrays of micron-size needles into

silicon to demonstrate the therapeutic application of microneedles. Since then, so many other materials have been used to produce microneedles like silicon, ceramics, glass, polydimethylsiloxane (PDMS), various polymers, dextrin, as well as metal such as stainless steel, titanium, etc. Among these silicon is most widely used material for preparing microneedles. [4,6,7] There is no common procedure available for different types of MEMS process, but it is generally carried out in three steps: thin film deposition, lithography, and etching.

Thin film deposition:

This step involves processing the surface substrate (typically silicon wafers). Here material is added to the substrate by various method in thin film layer, which can be either structural layer or act as the spacer, which is later removed. Two types of MEMS deposition techniques are used depending on whether the process is chemical or physical. In the first technique, film is deposited because of chemical reaction between the host substrate and inert gases in the chamber at low or atmospheric pressure, while in other technique, the raw materials are released and physically moved to the substrate surface. Chemical deposition is further classified into spin coating, chemical vapor deposition (CVD), plating and atomic layer deposition. The choice of deposition technique depends on operating temperature, substrate structure, rate of deposition and source. [4,6,7]

Lithography:

It is the process by which the master pattern is transferred onto the solid materials usually a silicon wafer. Various types of lithographic techniques are: photolithography, X-ray lithography, charged particle beam lithography, holographic lithography, proximal probe lithography, stereolithography, and lithography on nonplanar substrate, among which most commonly used technique is photolithography. [4,6,7] Photolithography is based on the fact that some materials are opaque to ultraviolet (UV) light while others are transparent. In photolithography first of all the substrate material is covered with a thin film of some materials such as silicon dioxide (SiO_2), on which a whole pattern forms. After this a thin layer of photoresist is deposited on the oxide layer which is usually an organic material. Then, a photomask consisting of a transparent glass is coated with chromium and then it is placed in contact with photoresist-coated surface. After that the wafer is exposed to the illumination by using UV radiation and it transfer the pattern on the mask to the photoresist based on the chemical reaction occur in the photoresist which is either positive or negative. In next step it is developed, which is involves the removal of the exposed or the unexposed area of photoresist by rinsing solution which may be wet (solvent) or dry (vapor phase or plasma) and leaving the pattern and photoresist-coated oxides on the wafer surface. [4,7,8] This whole process is summarized in the figure 2.

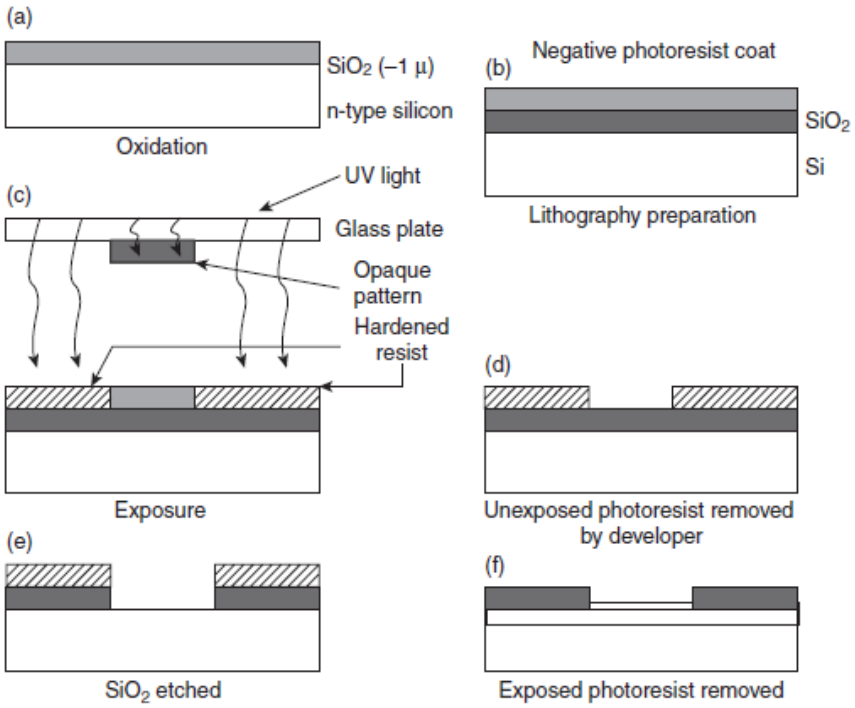

Figure 2: sequential processes in the transfer of a pattern to the substrate surface.[7]

Etching:

Next step in manufacturing the microneedles is selective removal or addition of materials to or from a material chemically or physically. The most important removal process is etching. There are two types of etching process: wet etching (chemical etching) and dry etching (physical etching). Selection of etching process is largely depending on the material of construction and type of microneedles. [8] Wet etching involves the immersion of a material in a liquid bath of a chemical etchant, which are classified into isotropic and anisotropic. Isotropic etchants attack the material at the constant rate in different direction while as anisotropic etchants at different rate in different direction. Most commonly used anisotropic etchants are potassium hydroxide and tetramethyl ammonium hydroxide. Crystal orientation of the substrate or wafer mainly decide the type of the structure from in the substrate. The dry etching technology is classified into reactive ion etching (RIE), sputter etching, high density plasma etching and vapor phase etching. [4,7]

TYPES OF MICRONEEDLES:

Solid microneedles:

One of the earliest and most commonly method to fabricate solid microneedles is LIGA technique. LIGA come from the German Lithographie means lithography, Galvanik means electroplating and Abformung means molding (Khumpuang et al., 2006). This technique was first used by a researcher known as Hashmi to fabricate microneedles. Application to this device was given by a

researcher known as Henry and his coworkers to enhance the penetration across the skin. Polymethylmethacrylate (PMMA) microneedles were fabricated by a Moon and Lee (2003) by using an X-ray lithographic process. [10] Stainless steel microneedles are not only biocompatible but also inexpensive and it were fabricated by using an infrared laser cutting technique.[11]

Hollow microneedles:

The hollow microneedle was invented in 1844 and it has been used for intravenous administration of drug since. [12] It is the reduced form of the hypodermic needle. Pain and tissue trauma related to hypodermic needles is greatly reduced or removed by using these hollow microneedles. Use of hollow microneedles is promoted due to their ease of manufacturing and their ability to provide visualization of fluid flow. Hollow glass microneedle is fabricated from borosilicate glass pipettes by using micropipette puller. Hollow microneedle is generally used for constant infusion of drug solution. But this fluid flow is greatly resisted by dermal tissue compression. This problem is overcome by partially retracting the glass hollow microneedle after insertion into the skin. [1,13] Hollow microneedles for continuous delivery of insulin have been designed and tested by a scientist Davis and his co-workers and they used modified LIGA process for fabricating these microneedles.

Biodegradable microneedles:

Generally, most widely used microneedles are silicon microneedles, but they have fragile nature and nonbiocompatibility, because of this biodegradable microneedle has been designed and introduced. Polyglycolic acid, polylactic acid and their copolymers, poly(lactic-co-glycolic acid) were reported for fabricating this microneedle by Park et al. Microneedle master structures have been created by using wet silicon etching, UV lithography and reactive ion etching with a novel lens based technique. Then, this master structure is used to prepare polydimethylsiloxane (PDMS) molds. The pellets of biocompatible material were placed in the mold after removing the master structures from the molds and then they heated slightly above the melting point of the polymer under the vacuum to fabricate biodegradable microneedles figure (3). e.g. this mold based technique has been used to prepare maltose-based microneedles. [1,14]

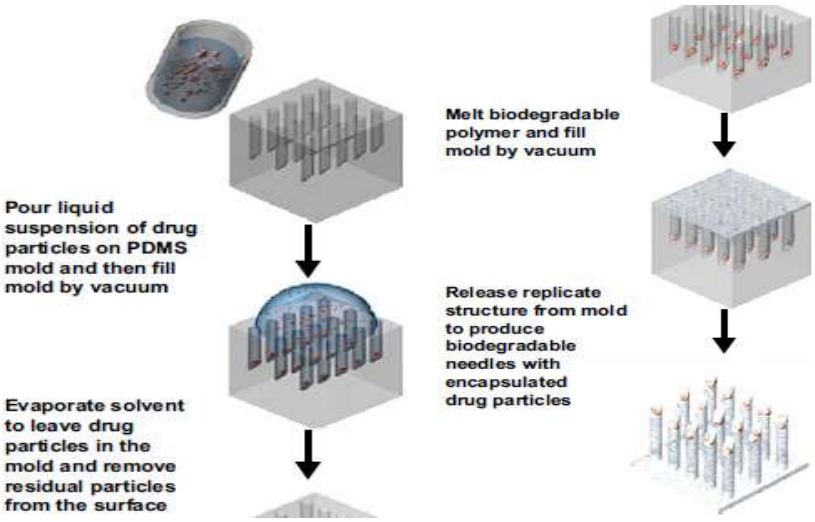

Figure 3: steps of procedure to prepare biodegradable microneedles [1]

CHARACTERISTICS OF MICRONEEDELS

Common characteristics of microneedles are given bellow:

Ruggedness:

Microneedles must be capable of insertion deep into the skin without braking. Microneedles must have optimum size also and if this is not possible then upper portion of microneedles may not have enough rigidity and undergo breakage before penetration. So, they must be able to withstand the insertion force without delaminating or breaking.[15]

Controlled drug release:

They should deliver the controlled amount of drug at a definite and predetermined rate.[15]

Penetration:

Microneedles must be able to penetrate the skin to the desired depth in the tissues of the body without causing pain. This painless insertion of microneedles into the skin can be accomplished by gentle pushing, using approximately 10 Newton forces.[15]

TYPES OF APPROACH

Many different types of approaches have been designed and investigated to deliver the drug by using microneedles, some of which are given below:[16]

Coat and poke technique:

Coated microneedles are used to provide rapid drug delivery, in some cases within one minute. This technique involves coating the microneedles with drug and then inserting them into the skin for administration (Figure 5b). Most commonly used method to prepare these microneedles is dip coating (Figure 4).[17] The coating solution contains drug, surfactant, viscosity enhancer and solvent. The factors which are maintained during coating of microneedles are drying time, withdrawal

speed and temperature.[18] This technique is reserved for potent drug such as vaccines because of limited delivery of drug due to its small dimension at the microneedle shaft and tip, which reduces the surface area of the microneedle array. Both hydrophilic and hydrophobic drugs, along with microparticles, proteins, DNA and RNA have been delivered in this manner.[1]

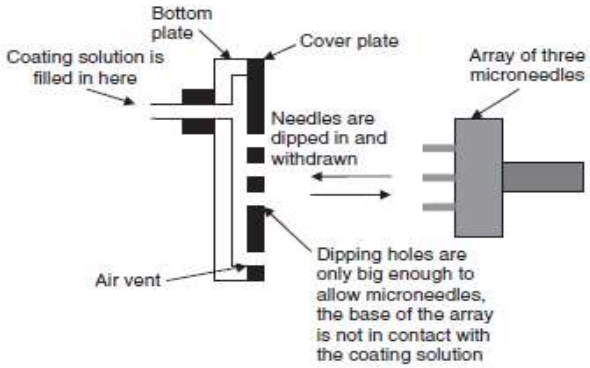

Figure 4: Schematic diagram of the technique of dip coating device. [17,18]

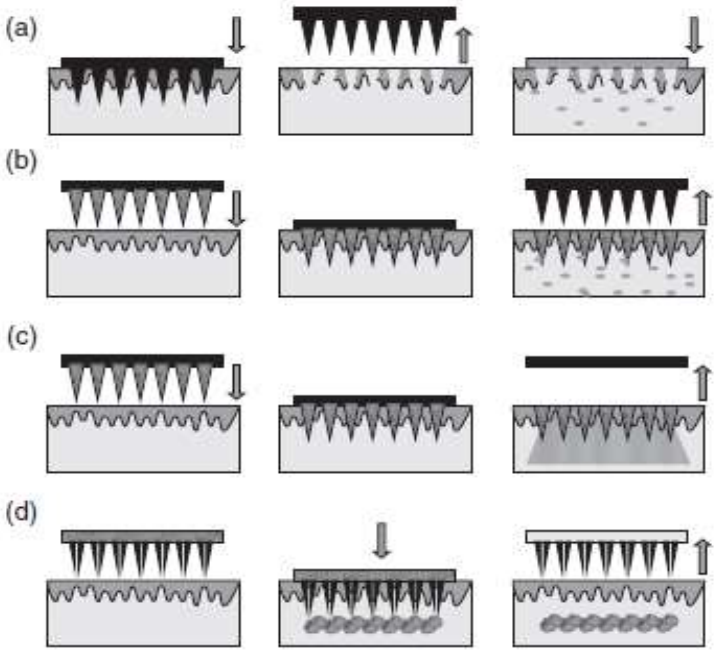

Figure 5: (a) poke with patch technique (b) coat and poke technique (c) poke and release technique and (c) poke and flow[7]

Poke with patch technique:

This technique utilizes an array of microneedles to penetrate the stratum corneum. Once the channel was formed in the stratum corneum by using microneedles, a reservoir of drug is placed on the skin and allowed to pass through channels (Figure 5a). Various types of studies have been done for microneedle insertion time and it is proved that shorter microneedle insertion time results in a

greater pharmacological effects.[19] Nordquist et al. (2007) developed the microneedle patch for active insulin delivery by using poke with patch technique. [20]

Poke & release technique:

Microneedles use in this technique can dissolve/swell or contain pores, through which drug will diffuse into systemic circulation (Figure 5c). The materials use in the preparation of microneedles holds the drug until the release is trigger by dissolution or swelling. Both sugars such as maltose, galactose etc. and polymers such as polylactic acid, carboxymethyl cellulose, amylopectin etc. are used as matrix forming agent in which drug is encapsulated.[21,22,23] These novel microneedles are used for sustained delivery of different molecular weights molecules, such as Bovine serum albumin (67000 Da), theophylline (180 Da), insulin (6000 Da), caffeine (194 Da), etc.[8]

Poke and flow:

Here, hollow microneedles are used for continuous delivery of drug solution. It involves insertion of microneedles into tissue and then drug solution can be transported through the bore of microneedles (Figure 5d).[24] These microneedles were developed because other conformation of microneedles could only administer limited amount of drug. Passive diffusion of the drug solution may occur through the microneedles, but active release may enhance the flow of drug solution. Active delivery of drug solution through the microneedles requires some kind of driving force, which may be produced by using several techniques that have been detained in the literature. Generally, a syringe is used to force the solution through the microneedles into the tissue, but pump or pressurized gas is also used for this purpose. A single hollow microneedle to deliver local anesthesia, lidocaine is prepared and tested for its activity by Gupta et al. [1,25]

MICRONEEDLES DESIGN PARAMETERS AND STRUCTURE:

In the design and fabrication of microneedles, the shape and geometry of microneedles is vital. Microneedles have a suitable length, width and shape to avoid contact with nerve and it must be capable of inserting into skin without breaking. To avoid breaking of needles, it should be prepared from strong metals. Various polymers are also used for preparation of microneedles, but they must have sufficient mechanical strength. [26,27,28]

Microneedles are classified as in-plane microneedle, out-plane microneedle or combination of both based on the fabrication process (Figure 6). In former design of microneedles, silicon wafers(figure 6a) remains in a parallel position to the machined surface and this class gives the advantage of accurately controlled and convenient production of microneedles. On the contrary, if we see out-plane microneedles the fabrication surface of silicon wafer is perpendicular to the microneedles and they are easily produced in arrays than in-plane. [7,8] According to the structure of microneedles,

they can also be classified into solid, coated, dissolving, and hollow. On the basis of overall shape and tip, microneedles are classified into rectangular, cylindrical, pyramidal, octagonal, conical, quadrangular (Figure 7). The tip of microneedle is very important because it decide the penetration capacity of microneedles. Thus, microneedles having sharper tip have a higher potential for penetration of skin.

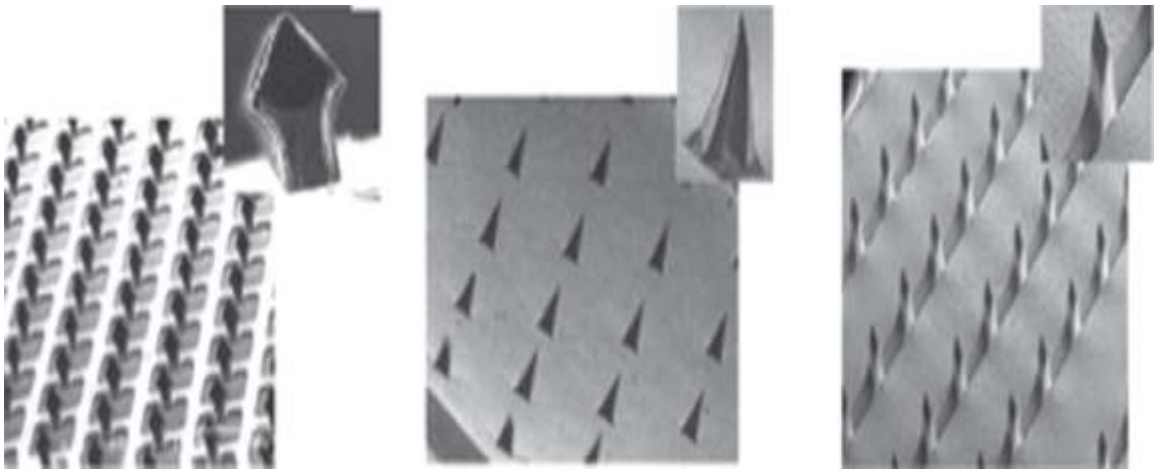

Figure 6: Scanning electron microscope (SEM) images of (a) in-plane microneedles,[29] (b) out-of-plane microneedles,[30] and (c) combined in-plane and out-of-plane microneedles[31].

FACTORS AFFECTING THE TRANSDERMAL PERMEATION

Depth of permeation:

The depth of microneedles that penetrate the skin is a most important factor because it ensures optimum delivery of drug solution through microneedles. Thakur and Michniak (2007) performed the *in vitro* microscopic studies to know the depth of microneedles that permeate the skin membrane and gave the results that microneedles of length 300 and 600 µm penetrate the skin up to depth of 97 and 262 µm respectively. This happened because when short length microneedles are pressed on the skin surface with certain degree of force, a portion of microneedle length and effort is involved in skin tissue compression and thus leave a little microneedle length for skin penetration, which does not happen in case of long microneedles because it leaves a significant length of microneedles for skin penetrating after skin compression. This study is further corroborated by Verbaan et al. (2007), and gave result that microneedle of length less than 300 µm could not penetrate the skin because skin has a thickness of 330-440 µm. Thus, they did not have the critical length to overcome the bulk elastic tissue compression. [1,11]

Coating strategies:

Microneedles have been coated with variety of substances and used for transdermal delivery of various large molecule, including peptides and proteins. [32] In coating technique, microneedles are

coated with drug formulation and then they are inserted into the skin for dissolution of drug within the skin. For reliable and reproducible permeation of the active substance using coated microneedles, it is necessary to optimize the quality and quantity of the coating to get uniform coating.[1,32]

Uniform coating on microneedles can be achieved by controlling the surface tension and viscosity of coating formulation. Gill and Prausnitz (2007b) shown that when microneedles made of stainless steel having surface tension of 39.6 mJ/m^2 are dipped in aqueous solution of Sulforhodamine having surface tension of 72 mJ/m^2, showed no drug coating due to the large contact angle of 47.5 ± 3.0º formed between the stainless steel and coating solution. The contact angle that was formed because of large difference in surface tension of two substrates. This difference was reduced by adding the suitable surfactant, thus when Lutrol® was added to the aqueous solution of Sulforhodamine, a thin coating was obtained on the microneedles. In the same study, when 1 % w/v aqueous solution of carboxymethylcellulose (CMC), viscosity enhancer was added into the Sulforhodamine solution, it increased the drug loading by thickening the drug solution. Choice of excipient for formulating the drug solution also affect the coating of microneedles.[1,18] The effect of mainly four factor on the quantity of the drug coated on microneedle was given by the Gill and Prausnitz namely:[1,18]

a) The effect of drug concertation in the coating formulation
b) The number of coating solution dips
c) The number of microneedles in the array
d) Drug concentration during selective coating of microneedle pockets [1,18]

Microneedle geometry and force of penetration:

Transdermal penetration of microneedles is significantly affected by its geometry and force of penetration. The flow rate of sulforhodamine through hollow microneedles inserted to a depth of 720-1080 µm on human cadaver skin were investigated by Martanto et al 2006a, b, as a function of microneedle tip geometry, microneedle insertion and retraction distance, presence of hyaluronidase, infusion pressure and time. In this study, it was shown that decreasing the net insertion depth resulted in higher flow rate as shown in Fig.8. [1,33] During performing pressure study, it was shown that infusion pressure is directly proportional to the flow rate, but at an infusion pressure of 172 kPa, a disproportionate increase in flow rate was noticed with increase in pressure due to the deformation of dermal tissue high pressure, which gave major resistance to the flow rate.[1,33] The comparison of blunt tip microneedles in which hole is at the tap and bevel tip microneedles in which hole is off to the side was done by the Martanto et al. and they observed

that flow rate of sulforhodamine form the former is less than from the latter as the bevel tip microneedles reduces the resistance by infusing the active substance to the side of the dense tissue formed.[1,33] Martanto et al. also reported that addition of hyaluronidase enzyme increased the flow rate of drug solution through microneedles by 7 fold due to breakdown of hyaluronan within skin collagen fibers. Because of this breakdown resistance to flow rate is decreased.[13,33]

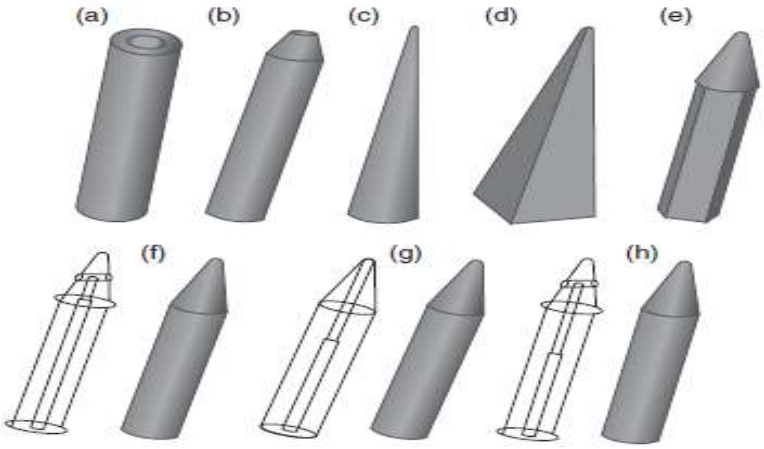

Figure 7: Shapes of MN (a) Cylindrical; (b) Tapered tip; (c) Canonical; (d) Square base; (e) Pentagonal-base canonical tip; (f) Side-open single lumen; (g) Double lumen; (h) Side-open double lumen. (*Source*: Adapted from Ashraf *et al*., 2011.)

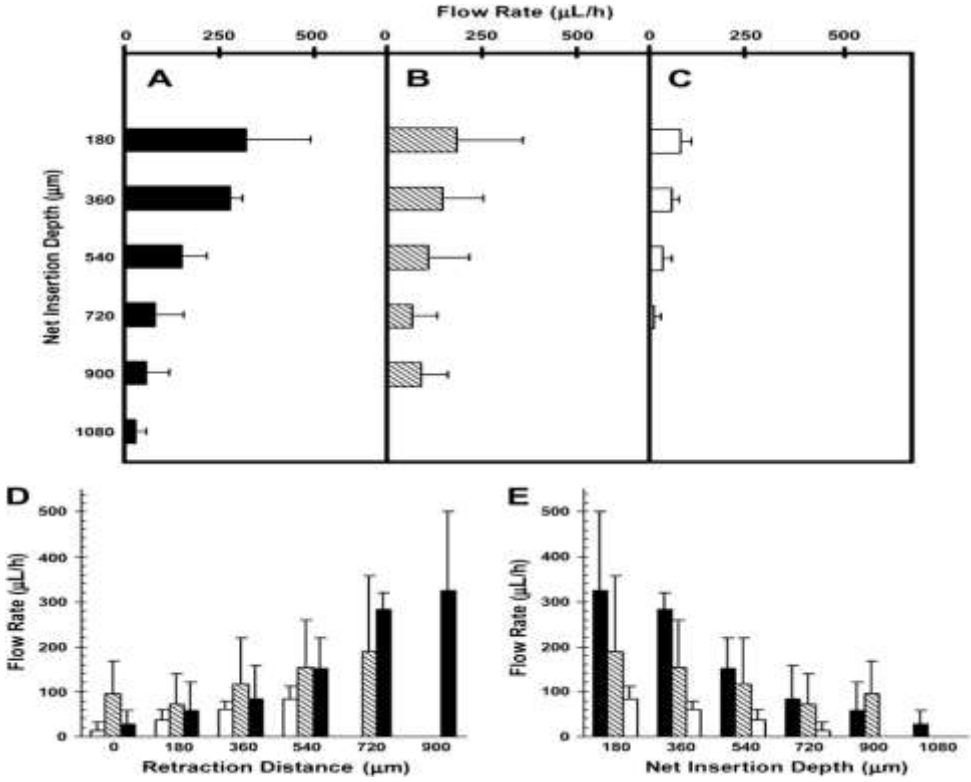

Figure 8: Effect of insertion depth and retraction distance on flow rate into human cadaver skin in vitro. Microneedles were initially inserted to a maximum insertion depth of 1080 mm

(A), 900 mm (B), or 720 mm (C), and then retracted various distances back toward the skin surface to a final, net insertion depth. Pooling the data from parts A, B, and C, flow rate is shown as a function of retraction distance (D) and net insertion depth (E) for maximum insertion depths of 720 mm (white bars), 900 mm (striped bars), and 1080 mm (black bars). [13]

EVALUATION PARAMETER:

In-Vitro study of microneedles

In-vitro evaluation of microneedles is done by using numerous medium like agarose gel and methanol to insert the microneedles. The objective of *in-vitro* tests is optimization of microneedles, finding out the penetration force and bending force, determination of dissolution rate of coating material, evaluation of strength of microneedles and estimation of the efficiency of drug delivery.[15] various methods used for performing *in-vitro* studies are given below:

Method 1:

In-vitro test is performed to find out the delivery efficacy of the microneedles. In this test, the microneedles are incorporated with Paradimethylsiloxane (PDMS) biochip and black ink injected by the microneedles into the petridish, which contain methanol.[15,34]

Method 2:

This method is employed to find out the delivery efficacy and dissolution rate of the coated material. In this test microneedles are inserted into the porcine cadaver skin and pig cadaver skin for 10-20 sec. and 5 min. respectively.[15,34]

Method 3:

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 in this method.[15,34]

In-vivo study of microneedles

Generally, mice, rabbits, mouse, guinea pigs, monkey, dog, etc. are used for conducting the *in-vivo* study of microneedles. The key objectives of *in-vivo* testing of microneedles are determination of penetration force in different individuals, mechanical stability, bending and breakage force, to perform skin toxicity, non-clinical safety study and pharmacological study, determination of various parameter like immunogenicity, acute and chronic dermal toxicity, carcinogenicity, genotoxicity, skin sensitization etc.[15] Various methods used for performing *in-vivo* studies are given below:

Method 1:

In this method, microneedles are pricked into vein of the tail of hairless mice. It is used for determining the penetration force of microneedles.[15,34]

Method 2:

This method is used for the evaluation of vaccine delivery via microneedles. In this method, Ovalbumin is used as a model protein antigen and administered into the hairless guinea pig by solid metal microneedles at the rate of 20 µg Ovalbumin in 5 sec. up to 80 µg.[15]

Method 3:

This method is also used for evaluation of vaccine, but here rabbits are used instead of guinea pig in above method. Here, the anthrax vaccine containing recombinant protective antigen (rPA) of Bacillus anthracis is administered in the rabbit using solid and hollow microneedles.[15,34]

Method 4:

This method is used for determination of penetration force and bending and breaking force. In this method, Rhodamine B is injected into tail laboratory mouse.[15,34]

APPLICATION OF MICRONEEDLES

Microneedles are used for various biomedical application, which include skin rejuvenation, immunization, delivery of DNA to cells, for cancer treatment and drug delivery to skin, eye and neurons. [4] Here, transdermal drug delivery, neural drug delivery and intravascular drug delivery is discussed:

Transdermal drug delivery:

Microneedles are able to penetrate through the stratum corneum and deliver drugs into the body in a minimally invasive manner. It makes them a better candidate for delivering the drug compared to ordinary transdermal patches which effectiveness is limited by the presence of stratum corneum or hypodermic needles which are painful and carry hazards such as transition of infection because of accidental or intentional needle reuse. Various studies have been performed to deliver the drugs such as insulin, naltrexone, and antirestenosis drugs by using microneedles. Henry et al. found that microneedles helped to enhance permeability of calcein across the skin by up to 3 times when compared to diffusion of calcein through intact skin. [4]

Neural drug delivery:

There are so much complex biochemical reactions which occurs in the neurons and important for function of neurons. Ability to deliver drugs to the neurons enhances chances of curing the disease related to neurons such as restoring vision to the blind hearing to the deaf, restoring the control of bodily functions such as those of the limbs and urinary system etc. [4] Microprobs have been designed to deliver very small amounts of drug to very specific sites on the neural tissues in

precise amounts. Chen and Wise fabricated silicon microneedles which they then inserted into guinea pig brain to deliver neural stimulant and depressant kainic acid and γ-aminobutyric acid, respectively, with minimal tissue disruption (Figure 9).[4]

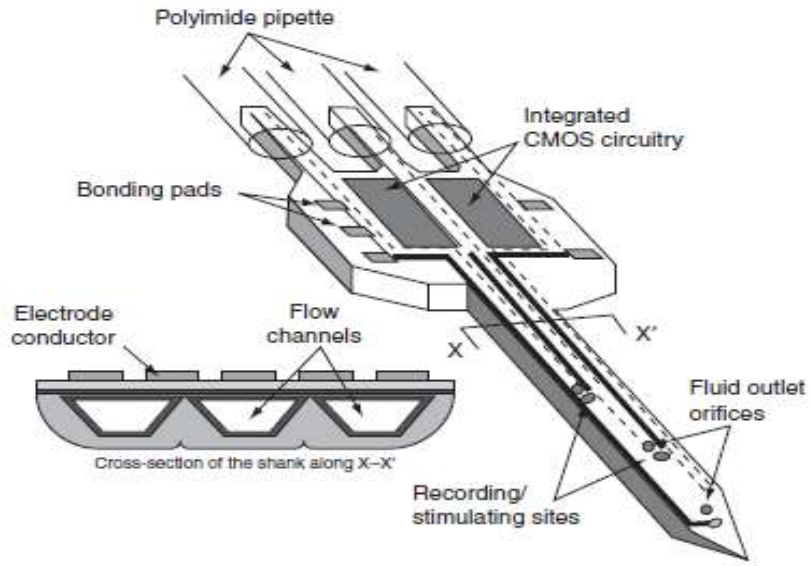

Figure 9: A schematic diagram of the microprobe for chemical delivery to neurons[4]

Intravascular drug delivery:

Restenosis is the blockage of a recently cleared area due to the initiation of a healing process in the treated site. Several attempts have been made to cure this and to deliver therapeutic agent to the area, but most of the methods are proven ineffective due to the need for the antirestenosis drug to diffuse the arterial plaque. This led to the development of a stent studded with microprobes coated with drugs (Figure 10). Probes 140 mm in length successfully penetrate the atherosclerotic vessels with an applied pressure of 500 mmHg.[4]

Figure 10: A metal stent studded with microneedles for gene or drug delivery to the vessel wall.[4]

Ocular drug delivery:

Drugs which are applied topically to the eyes have very low bioavailability; so, it is difficult for these drugs to reach the back of the eye and this limits their effectiveness. Systemic delivery of these drugs have several side effects and intraocular injection is painful and inconvenient to the

patient. Thus, a minimally invasive method to deliver drugs to localized area in the eye is desired. Experiments on human cadaveric sclera and rabbit cornea *in vivo* showed that microneedles are suitable for ocular drug delivery in a minimally invasive manner.[4]

FUTURE TRENDS

There is increase in number and size of microneedle-focused academic research groups and also get an increased attention in industry since 2005. There are currently a number of industries, which are work for commercialization of microneedle technologies, like Zosano Pharma, 3M, Nanopass, Alza, Corium, Valeritas etc. Zosano Pharma are currently preparing to enter a pivotal Phase III clinical trial using the Macroflux® technology developed by Alza. Here, a solid coated microneedle patch system will be used for delivering the parathyroid hormone in the treatment of severe post-menopausal osteoporosis. Importantly, Zosano Pharma have incorporated an applicator system as an essential component of this delivery system. NanoPass technologies Ltd have conducted a number of clinical trials demonstrating effective, safe and painless intradermal delivery of insulin, local anesthetics and influenza vaccine via their MicroJet® technology. Similarly, 3M's microstructured transdermal system, using either solid or hollow microneedles, has shown promising results in several pre-clinical studies for delivering proteins, peptides and vaccines.

The Donnelly's Group is working on the microneedles arrays prepared from hydrogel-forming polymeric system (Donnelly et al., 2012). These arrays are hard in the dry state but, upon insertion into skin, take up interstitial fluid and undergo a transition to form *in situ* hydrogel bulbs. These microneedles do not contain drug, but instead they are connected to a conventional matrix-type transdermal patch, so that drug can diffuse through the swollen microneedles. Benefit of this technology is that, drug delivery is no longer limited by how much drug can be loaded into the microneedles themselves, so delivery of larger dose is now possible. In an alternative application, the microneedles can also be used to extract skin interstitial fluid for diagnostic or therapeutic monitoring purposes.

Table 1: Few Examples of Drug Delivery System Containing Protiens/Peptides to and Across The Skin

Sr. No.	Protein/Peptide	Delivery Method	Main outcome
1	Bovine serum albumin	Polymeric microneedles, ultrasound	Permeability of 1 µm/s is achieved with a 1.5 mm height microneedles and 15 W ultrasound output
2	Botulinum toxin A	Stainless steel microneedles	Efficient diffusion through the dermis
3	Insulin	Insulin loaded dissolvable	Dissolve in 5 min. in rats to relative

		made of starch and gelatin	pharmacological availability and relative bioavailability of 92%
4	Influenza vaccine	Microneedles delivery	Application to intramuscular injection in guinea pigs. Hemagglutinin concentration as high as 20 mg/ml

(source: adapted form Cheung K et al. 2014)

CONCLUSION:

In this article, we have been able to explain advantages of drug delivery using microneedles as an improved method over the delivery using hypodermic injections, oral and parenteral drug delivery system. Three types of microneedles i.e. Hollow, solid and biodegradable along with their fabrication and application are taken in account in this article. Various approaches for delivery of drug is also discussed here. Experimental studies have proven the drug delivery to eye, neurons and vessel and through the skin is more convenient and efficient by using microneedles. Despite some limitations, microneedles have promising prospect in the advancement of transdermal drug delivery.

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