The transdermal drug delivery biology essay

Science, Biology

Abstract

Transdermal drug delivery has made important contribution to the field of medicine, however its success has been limited; and until now has been unable to achieve its full potential as a substitute to conventional drug delivery systems such as oral delivery and hypodermic injections. The progress of transdermal drug delivery has been constrained by the inability of most drugs to enter the skin at rates that are therapeutically useful. Use of microneedles is currently advancing through clinical trials being performed on the delivery of macro molecules, drugs and vaccines, such as parathyroid hormone, insulin and influenza vaccine. Technology from the microelectronic manufacturing is applied to fabricate microneedles of a wide range of sizes, shapes and materials. Studies on drug delivery have emphasized the use of solid microneedles, which have demonstrated an increase in skin permeability to a broad range of molecules and drugs like insulin to reduce blood glucose levels, delivery of oligonucleotides, and elicitation of immune responses from protein and DNA vaccines. To carry out these studies microneedles have been used to pierce holes into the skin to increase permeability of skin to drugs. Hollow microneedles have also been developed and in vivo clinical trials have been conducted. The practical applications of microneedles was addressed and their mechanism of drug delivery was understood, it was concluded that for penetration by least force the radius of tip of needle had to be small. All these results in combination indicated that microneedles constitute a assuring future to delivery of drugs and vaccines into the skin for a wide range of applications.

Introduction

Transdermal drug delivery is the technique of administering a therapeutically effective amount of drug across a patient’s skin. The comprehensive biophysical, morphological and physiochemical properties of the skin are to be taken into consideration during the delivery of drugs across the skin. Transdermal drug delivery not only allows for controlled, constant administration of drug; but also allows for the uninterrupted input of drugs with short half lives and negates sporadic entry of drugs into the system which causes unwanted side effects. Transdermal drug delivery can provide solutions to the problems being faced by the conventional methods of drug delivery like oral and hypodermic drug delivery systems. The world wide transdermal market is currently worth US $2 billion and constitutes the most flourishing non oral systemic drug delivery systems. This market however constitutes only eight FDA approved active agents: nitroglycerine, scopolamine, clonidine, oestradiol, nicotine, fentanyl, norethisterone and testosterone.[2] the first drug to be successfully delivered by this method was Scopolamine for anti- motion sickness drug in 1979, it was followed by the introduction of the nicotine patch which raised the visibility of the drug in both among the scientific community and the consumers. Presently 19 different drug delivery systems are available in the market which have the capability to release a wide range of drugs into the body.[3]

The need/ advantages

Although oral and hypodermic delivery of drugs have been used for a long period of time transdermal drug delivery system seeks to provide solutions to long standing problems faced by the conventional systems. The

advantages of transdermal drug delivery over the conventional drug delivery systems are as follows: Firstly first pass metabolism of drugs is avoided; the first pass effect or metabolism is a physical process of drug metamorphosis where the concentration of a drug is greatly reduced before the drug enters the circulation system. The liver metabolizes the drugs such that only a small concentration of the drug is available for circulation as it comes out of the liver greatly reducing its bioavailability. Secondly reduced plasma concentration of drugs therefore low incidence of side effects caused by fluctuations in concentration, plasma concentration is the amount of drug present in the blood stream. High plasma concentration of drug can cause adverse side effects. Thirdly reduced fluctuations in plasma levels of drugs, utilization of drugs with short half life and low therapeutic index, therapeutic index is the ratio of concentration of drug that causes therapeutic effect to the concentration of drug that causes death. Fourthly due to the low concentration of drug, it can easily be eliminated from the system in case of toxicity of the drug. Fifthly The dosage frequency is greatly reduced because the drug is more effective and hence the patient compliance is greatly improved. Sixthly Transdermal medications deliver a non-fluctuating infusion of a drug over and lengthy period of time. Untoward consequences or therapeutic failure often associated with sporadic dosing can also be averted. Seventhly transdermal delivery can enhance the therapeutic value of many drugs via avoiding problems particular to that drug. Eighthly an equivalent therapeutic effect can be evoked via transdermal drug input with a dose lower than that is necessary, compared to a drug that is given orally.

Lastly The simplified systemic plan for treatment leads to improved patient conformity and reduced inter and intra-patient variance.

Limitation of TDDS

Transdermal drug delivery has many advantages over conventional drug delivery systems however it has certain limitations: Firstly The drug must possess suitable physicochemical properties for incursion through stratum corneum. Secondly the transdermal delivery is not suitable for drugs whose dosage required for effective therapeutic value is more than 10 mg/day. Thirdly Localized skin irritation or contact dermatitis is caused due to localized drug delivery or due to the drug. Fourthly the clinical need for the drug has to be examined carefully before the decision to develop a transdermal product is made. Lastly The barrier function of the skin changes from one site to another on the same person, from person to person and with age hence there is no standard way of drug delivery and varies according to the function and design of the system.

Limitations for a drug substance to be incorporated into a transdermal delivery system are: -

Drugs molecules with sizes greater than 500 Da usually find it difficult to penetrate the stratum cornea. Drugs with partition coefficient in the extreme range fail to reach blood circulation system.

Transdermal methods in each generation

1st GENERATION TRANSDERMAL PATCHES

The first generation transdermal patches were pioneers in transdermal drug delivery and were capable of containing and releaseing low molecular-

weight, lipophilic drugs at therapeutic doses. These systems very preferred due to their low oral bioavailability and the want of less frequent dosings. The first-generation approach to transdermal delivery is constrained chiefly by the barrier posed by the stratum corneum, which is about 20 μm thick. Histological structure of mammalian skin. (a) Skin structure (b) Stratum corneum structureUnder this is the epidermis and even beneath that the dermis which is rich in capillaries. Drug transport occurs through intercellular lipid pathways in the stratum corneum. Examples of first generation are testosterone gels, a transdermal spray for estradiol delivery.

Cross section of human skin

2nd GENERATION TRANSDERMAL PATCHES

The second generation incorporated methods to enhance skin permeability to expand the scope of transdermal drug delivery. This generation of delivery systems has encouraged clinical practice mainly by improving the delivery of small molecule for localized, cosmetic, dermatological and other systemic applications, but little developments have been made in the area of delivery of macromolecules.[4][5]The enhancers that were primarily used wereIontophoresis: This increases skin permeability by the application of a constant, low voltage current. It also acts as an electrical driving force for drug transport and is applicable to small ions and some charged macromolecules. It is currently being used to administer rapid doses of lidocaine for anaesthesia.[6] Chemical enhancers: The role of these chemicals is to release amphiphilic molecules e. g. Azone, which disrupt the organisation of the lipid bilayers of the stratum corneum. Non-cavitational ultrasound: the lipid structure of the stratum corneum is disrupted by

Ultrasound waves, hence increasing permeability. This is applicable to small, lipophilic molecules.

3rd GENERATION TRANSDERMAL PATCHES.

The third generation is more effective than the earlier two generations because it directly targets the stratum corneum. Such a targeting makes it possible for more potent disruption of the stratum corneum barrier, and promotes efficient transdermal delivery, whilst protecting underlying tissues. This principle has been applied to more novel chemical enhancers, cavitational ultrasound, electroporation, microneedles, microdermabrasion and thermal ablation have demonstrated the ability to deliver macromolecules, including therapeutic proteins and vaccines, across human skin in clinical trials. These improvements were made possible mainly due to the growth of technologies to localize effects to the stratum corneum combined with identification of the fact that the safety afforded by localization should make these approaches competitive and acceptable medically. The third generation techniques target the stratum corneum directly using a whole array of methodologies [7]: Cavitational ultrasound: Ultrasound waves instigate the formation, oscillation and collapse of cavities/bubbles. Bubbles that oscillate and collapse at the stratum corneum, disrupt its structure; increasing permeability. Electroporation: This delivers a short, high voltage pulse which disrupts the lipid bilayers in the stratum corneum. The electric field lasts for milliseconds, but the remaining driving force for the diffusion of drugs remains for hours.

MICRONEEDLES

Microneedles may be defined as needles that are between 10-2000 microns in height and 10-50 microns in width. They may be solid or hollow depending on the function or the tissue targeted and may be integrated with a syringe, pump and patch.[8] They are built on the main principle that involves creating transdermal pathways of micron dimensions using arrays of microscopic needles. These pathways are of the order of microns and hence allow for the free transport of macro molecules. The microneedle development has been largely limited due to lack of proper fabrication methods; it was only in the 1990s that the manufacturing technology of microelectronics was applied. The driving force behind the development of microneedles is that they can provide a way of minimally incursive method of transporting molecules into the skin. A large majority of work focused on making of microscopic pathways into the skin to disperse drug molecules into the skin, transport can occur by diffusion. There are number of delivery approaches that have been employed to use the microneedles for TDDS. These includes [9]-Poke with patch approach- Involves piercing into the skin followed by application of the drug patch at the site of treatment. Coat and poke approach- Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution. Biodegradable microneedles- Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin. Hollow microneedles- Involves injecting the drug through the needle with a hollow bore.

(a) Solid microneedles etched from a silicon wafer (b) Solid microneedles (1000 µm tall) laser-cut from a stainless steel sheet (c) Solid microneedles (‘‘ microprojection array’’, 330 µm tall) acid-etched from a titanium sheet (d) Solid microneedles (‘‘ microenhancer array’’, 200 µm tall) chemically etched from a silicon wafer were dipped in plasmid DNA solution (e) Hollow microneedles (500 µm tall) formed by electrodeposition of metal onto a polymer mold

Studies on transdermal drug delivery using microneedles

Henry et al. [10] conducted the first study to determine if microneedles could be used to increase transdermal drug delivery. Cadaver skin was was embedded with an array of solid microneedles causing skin permeability to a small model compound, calcein, to increase three fold. There was an increased transport through leakages between skin and needles. The skin permeability further increased after removing the needles by a large factor. A follow study by McAllister et al. [11] studied permeability of cadaver skin to a range of different compounds and determined that insulin, bovine serum albumin, and latex nanoparticles as large as 100 nm in diameter could cross the skin after being punctured by microneedles. The microneedles in these studies were made from a silicon wafer using lithography and reactive ion etching, the needles were a 20-by-20 array, with each needle measuring 80µm at the base and tapered to a height of 150 µm with a radius of curvature at the tip close to 1 µm. The implication of these studies is that they exhibited increased transdermal transport using microneedles and as a result demonstrated that the permeability of the skin can be increased many fold.

Microneedle device components

The microneedle device includes the following components:

Substrate:

The substrate includes the base to which the microneedles are attached. The substrate in certain applications is made from a thin, rigid material that is stiff enough so that the microneedle can be forced through the biological barrier in regions where deformation is resisted by the biological barrier. In certain other applications the substrate is made flexible so that the device can fit through the countours of the biological barriers. The substrate can be made up of various materials like metals, ceramics, semiconductors, organics, polymers and composites.

Microneedle:

The microneedle devices are usually constructed from a large range of materials like metals, ceramics, semiconductors, composites, organics and polymers. The microneedles need to posses the mechanical strength to withstand the impact of insertion into the skin and being removed after insertion. Even in case of bio degradable needles the need to withstand the force of insertion. The preferred materials include pharmaceutical grade steel, titanium, nickel, gold, iron, tin, chromium; biodegradable materials include polymers of hydroxyl acid and copolymers with PEG, poly anhydrides, poly esters, polyurethanes and non biodegradable polymers include polycarbonate, polymethylacrylic acid, ethylenevinyl acetate and polyesters.

Reservoir:

The microneedle may include a reservoir attached to the substrate for the storage of drug. The reservoir may be either hollow or porous matrix or having the drug in a solid form. The preferred materials for the construction of the reservoir include synthetic polymers, metals, semiconductors, ceramics, composites and organics. The reservoir could have multiple chambers and have holes connecting the reservoir to the hollow or porous microneedles.

TYPES OF MICRONEEDLES

Microneedles can be made from a variety of materials, including metals, silicone, polymers, ceramics and glass, and are manufactured using micro fabrication techniques similar to the processes used in nanotechnology and the production of microchips. Microneedles are broadly classified into three categories Solid, Hollow and Special types of microneedles.

SOLID MICRONEEDLES

Solid microneedles can be used with drug patches to provide increase diffusion rates due to increased permeability. They are used pierce microscopic holes into the skin. Solid microneedles are usually coated with model compounds that dissolve once entered into the skin. They are of two types depending on the type of material used, silicon and metal microneedles. However, 1. 5 mm solid microneedles have been reported to leave a small droplet of blood after the insertion of the microneedle. A joint study by researchers from Emory University and the Georgia Institute of Technology found that the delivery of inactivated influenza virus through the

skin using metal microneedle arrays induced strong humoral and cellular immune responses capable of conferring protection against virus challenge as efficiently as intramuscular immunization, which is the standard vaccination route and microneedle vaccination to vaccinate mice against influenza virus was just as effective as deep tissue injection in the short term, but that it was significantly more effective when the mice were exposed to the disease three months after vaccination.

HOLLOW MICRONEEDLE

Hollow microneedles contain a fine bore at the tip of the needle for the flow of drugs through the needle. The length of the microneedle should be short enough to not reach the pain receptors and the bore size should be small enough to provide rapid rate of drug delivery. They are harder to use and are inherently weaker than solid microneedles. The bore opening at the needle tip makes insertion harder by diminishing the sharpness. Drug flow through the bore of the microneedle is also difficult to achieve due to the resistance provided by the thick dermal tissue and blockage due to possible tissue coring within needle bore. There are silicon, metal and glass hollow microneedles depending on type of material used. Intradermal influenza vaccines based on 1. 5 mm stainless steel microneedle in a glass prefilled syringe with a self-deploying safety shield after delivery has been reported in several studies.

SPECIAL TYPE MICRONEEDLES

DISSOLVABLE MICRONEEDLES

In dissolvable microneedles, the needle tip dissolves upon insertion into the skin. Disposal of conventional needles produces bio hazardous sharp waste, these microneedles are environmentally friendly. They are fabricated using micro molding approach that reproduces microneedle structures in an economical manner suitable for mass production. Polysaccharides are generally used to make dissolving needles such as carboxymethylcellulose and amylopectin. Polysaccharides are used for the following reasons: They are biocompatible. They are mechanically strong- high young's modulus. They are highly water-soluble. Dissolving microneedles for bolus delivery into skin. (a) CMC pyramidal microneedles encapsulating sulforhodamine B within the microneedle shafts, but not in the backing layer. (b) Skin surface showing sulforhodamine delivered into the skin by insertion. (c) Cross-sectional histological image of skin at the penetration site. (d) Cross-sectional histological image of skin pierced by an array of sulforhodamine-containing microneedles. A team of Japanese researchers developed a dissolving microneedle delivery system. When a chip containing 225-300 insulin-loaded microneedles was pressed into the skin, it delivered insulin transdermally. In a preclinical study, it successfully reduced blood glucose in rats, with the amount dependent on how far the microneedles were pressed into the skin, and how long they remained in place.

SILK MICRONEEDLES

The harsh conditons essential for the production of some of the existing microneedles can destroy the sensitive biochemical that they are alleged to

deliver. In order to fine-tune the rate at which microneedles deliver their medication and prevent infections that can occur where they enter the skin, silk microneedles were developed and were found to address these problems. They are biocompatible and have the ability to be shipped and stored easily without refrigeration. By addition of tetracycline to the needle, the growth of Staphylococcus aureus bacteria at the application site on the skin could be inhibited. Arrays of microneedles contained in aluminum molding masters each needle measuring 500 micrometers in height, with tips less than 10 micrometers in diameter were cast over by an elastomer to create a negative mold, then a drug-laden silk protein was cast over that mold. Investigators at Tufts University (Medford MA, USA) described the use of silk fibroin for the production of microneedles and found that silk microneedles could deliver simultaneously a large-molecule, enzymatic model drug (horseradish peroxidase), and the antibiotic tetracycline at controlled rates while maintaining bioactivity.

COATED MICRONEEDLES

Coated microneedles are also used to deliver protiens and DNA into skin. Coating methods and their applications are still in the nascent stage of research. Methods such as micron scale dip coating are used to produce this type of microneedles. The uniform coating process provides reproducibility and dosage control. They do not require high temperatures to maintain drug integrity. They help in achieving high drug loading per needle. Good adhesion of the coating provides no residue on skin surface. ADAVANTAGES of microneedlesLocal or systemic delivery for both large and difficult to deliver molecules, including proteins, peptides and vaccinesImproves

delivery efficiency and absorption time of some drugs and vaccinesPotential for dose sparing – important for high-value biologicsCapability to enhance stability for some drugsAvailable in a solid or hollow design to meet the needs of your program

Applications

TYPE 1 DIABETES

Microneedles can work with the interstitial fluid, which is the fluid that surrounds the cells, just below the skin in the layer of skin above the blood vessels and nerves. According to research, this fluid correlates well with blood glucose serving as an excellent location for insulin delivery. With the help on an enzyme-based flow-through glucose sensor an extremely compact device that monitors glucose and delivers insulin as needed can be manufactured and used. Studies have indicated that microneedles inserted at the shallowest depth of 1mm within the skin led to rapid insulin absorption and reduction in glucose levels and bolus insulin delivery followed by intake of a standardized meal revealed that microneedles were efficient in reducing postprandial glucose levels. There is no pain associated with microneedle treatments and no adverse events. It can be applied to the body once a day or twice and not really feel pain unlike hypodermic needles. Children suffering from diabetes particularly omit insulin injections and glucose monitoring often due to the pain and apprehension associated with needles, in such cases, microneedles may provide a better interface to deliver insulin because of painless administration, due to rapid insulin pharmacokinetics and reduce the need for glucose monitoring by enabling automatic closed-loop insulin therapy based on subcutaneous glucose sensing and

subcutaneous insulin delivery. Increased compliance leads to better-maintained type 1 diabetes with fewer future complications. The faster onset of insulin and decrease in the average time to peak insulin level could also lead to tighter glucose control. It’s a huge healthcare expenditure and it keeps growing.

MASS VACCINATION

Despite remarkable progress in the control of infectious diseases through vaccination, better delivery systems have been poorly explored and hence there is an interest in the discovery of novel vaccines. Transdermal delivery using microneedles could revolutionize the way prophylactic interventions for infectious diseases are carried out in the future. Some of the recent developments in the field of non-invasive cutaneous delivery of vaccines for infectious diseases involve the use of microneedles. Dissolving microneedle patches for influenza vaccination using a simple patch-based system that targets delivery to skin’s antigen-presenting cells proved to be a major development in this field. Microneedles fabricated using a biocompatible polymer compressing inactivated virus can be inserted into the skin and it dissolves into the skin within minutes. Many countries often have inadequate infrastructure to keep vaccines as cold as required, Scientists from King’s College London have found that it is possible to contain a dried live vaccine in a microneedle array that does not require refrigeration. Microneedles help with mass vaccinations by: Simplifying logistics. Increasing ease and speed of delivery. Offering improved safety and compliance. Decreasing costs. Reducing pain associated with vaccinations. Enhanced cellular recall responses after challenge. Hence dissolving microneedle patches can

provide a new technology for simpler and safer vaccination with improved immunogenicity that could facilitate increased vaccination coverage.

DNA DRUG DELIVERY

Microneedles improve protective immunity compared to conventional intramuscular injections. They are found to generate significantly stronger humoral responses. They help with post challenge protection, as measured by survival, recall antibody-secreting cell responses in spleen and bone marrow, and interferon. Micron-scaled needles coated with DNA were tested as a simple and inexpensive means for transdermal delivery. Vaccinations with a plasmid encoding hepatitis C virus nonstructural 3/4A protein using microneedles effectively primed specific cytotoxic T lymphocytes (CTLs)The minimally invasive microneedles were as efficient in priming CTLs as more complicated or invasive delivery techniques, such as gene gun and hypodermic needles. Thus, microneedles may offer a promising technology for DNA vaccination.

Mechanism

The skin’s barrier function is accomplished completely by the few outermost microns of the skin, the stratum corneum (SC), a intergratively and morphologically unique biomembrane. The stratum corneum is extremely thin and is the least permeable of all the skin layers. The lipids of the stratum corneum are unique in many respects, it is the only continuous phase from the skin surface to the base of the SC; the composition of the stratum corneum is quiet unique among biomembranes and particularly remarkable is the fact that the phospholipids are absent; despite this

shortfall of polar bilayer-forming lipids, the stratum corneum lipids exist as multilamellar sheets; and the saturated, long-chain hydrocarbon tails make way for a highly ordered configuration and the formation of gel-phase membrane domains in opposition to the liquid crystalline membrane systems. The mechanics of microneedle insertion are of critical importance in practical application. Microneedles need to have the right geometry and physical properties to be able to effectively be inserted into the skin. Depending on the design they can be inserted by hand or by high velocity insertion. Needles can break or bend if not properly designed due to high force of insertion. Davis et al [14] measured force required for fracture; the force required for insertion and defined a new term margin of safety which is the ratio of force of insertion and force of fracture as the function of needle geometry and physical properties. Hollow microneedles with radius between 30-80 µm and wall thickness 5 µm and length of 500 µm were used. The effect of microneedle geometry on the force of insertion was determined by using individual microneedles that were inserted into human skin as the force and displacement of the needle was being recorded. Skin resistance was monitored and it was observed that the forces of insertion varied from 0. 1 to 3. 0 N showing a linear dependence on the area of the needle tip. Force of insertion was determined to be independent of the wall thickness. From this it can be inferred that thin-walled hollow needles and solid needles with the same outer tip radii required the same force of insertion. This was an indication that skin was not flexible enough to dimple into the needle bore. The effect of microneedle geometry on the force of fracture was determined by pressing the individual microneedles against a rigid surface until they

fractured. The measured fracture forces were between 0. 5 and 6 N. The force of fracture increased strongly with increasing wall thickness and increased weakly with increasing wall angle, but was independent of the radius of the tip. Margin of safety values greater than one imply needles that will insert into skin without breaking. In the experiment carried out all margins of safety were greater than one and were dependent on the tip radius.

Manufacturing:

The microneedle device is made by microfabrication process for creating smaller mechanical structures in silicon, metals, polymers and other materials. These microfabrication processes are based on conventional methods used to make integrated circuits electronic packages and other microelectronic devices, these processes are improved upon by developments in the field of micromachining. The dimensions of these Microneedle devices can be as small as a few nanometers and generally can be mass produced to achieving economies of scale thus reducing the cost per unit. The various methods of processing micro needles are discussed. Manufacturing process by structurea. solid microneedle

Electrochemical etching

Electrochemical etching of silicon is used to create extremely fine silicon networks on the order of 0. 01 µm which can be used as piercing structures. The process involves an electrolytic anodization of silicon in aqueous hydrofluoric acid potentially in combination with light to etch channels into silicon. By varying the concentration of hydrofluoric acid added to the

silicon wafer to be etched; the electrolytic potential during etching; incident light intensity and the electrolytic concentration control over the pore structure can be achieved. The unetched material forms the micro needle structure, this method has been used to produce irregular needle like structures measuring tens of nanometers in width.

Plasma etching

Plasma etching process uses the plasma etching of silicon to create micro needles with diameters on the order of 0. 1μm. Photolithography is used to pattern needles rather than controlling the voltage therefore we have greater control over the final microneedle geometry. An appropriate masking material such as a metal like chromium is deposited on the silicon wafer substrate and arranged in to dots having the diameter equal to that of the desired microneedle. These wafers are then loaded into an ion etcher and subjected to highly controlled plasma to carefully etch deep trenches into Silicon. The regions masked by the metals remain and form needles.

Electroplating:

A metal layer is first evaporated onto a planar substrate, a layer of photoresist is deposited on the metal to form a pattern mold leaving an area of metal that is exposed in the shape of needles. Electroplating is done on the exposed region; the mold and the photoresist are removed finally to leave behind an array of microneedles. The diameters of microneedles produced by this method is about 1μm or larger.

b. Hollow or Porous Microneedles

i. Porous Microneedles

Instead of having a single, well-defined hole down the cross section of the needle, a network of channels or pores which allow passage of drug or fluid through the shaft of the needle. Porous needles can be formed electrochemical oxidation of silicon, pores with high aspect ratios and various pore sizes can be synthesizedThese can be classified as (1) microporous regime with average pore dimensions less than 2 nm, (2) mesoporous regime with average pore sizes of between 2 nm and 50 nm, and (3) macroporous regime with pores greater than 50 nm. either (a) the silicon wafer is first made porous and then etched as described above to form needles or (b) solid microneedles are etched and then rendered porous, for example, by means of electrochemical oxidation, such as by anodization of a silicon substrate in a hydrofluoric acid electrolyte. Porous microneedles can be formed, by micromolding a polymer containing a volatilizable or leachable material, such as a volatile salt, dispersed in the polymer or metal, and then volatilizing or leaching the dispersed material, leaving a porous polymer matrix in the shape of the microneedle.

ii. Hollow Needles

Three-dimensional arrays of hollow microneedles can be fabricated by using combinations of dry etching processes [14] micromold creation in lithographically-defined and/or laser ablated polymers and selective sidewall electroplating; or direct micromolding techniques using epoxy mold transfers. Distinct and continuous pathways are created through the interior of microneedles. Ideally a microneedle has a single continuous pathway that

can be achieved by initially chemically or physically etching the holes in the material and then etching away microneedles around the hole. Alternatively, the microneedles and their holes can be made simultaneously or holes can be etched into existing microneedles. As another option, a microneedle form or mold can be made, then coated, and then etched away, leaving only the outer coating to form a hollow microneedle. Coatings can be formed either by deposition of a film or by oxidation of the silicon microneedles to a specific thickness, followed by removal of the interior silicon.

Conclusion

Transdermal Delivery System using Microneedles based on micro channel principle is an innovative and new method of drug delivery. It is a comfortable, pain free, and less intrusive substitute to hypodermic injection and can be used as an effective way for dispensing large molecules like proteins, peptides, antibiotics, vaccines at a low cost. In comparison to oral drug delivery, microneedles avoid first pass effect and due to low concentrations have lesser or no side effects due to lower plasma concentrationsThe future looks bright for microneedles that can be used for delivery of large molecule drugs with the right set of properties, especially those drugs that are currently administered orally and by injection. These methods have special promise, because they appear broadly capable of delivering not only small molecules, but macromolecules and vaccines as well. Unpublished clinical trials appear to yield promising results, and published data suggest that these methods can be safe and effective. A microneedle product for vaccine delivery has been submitted in Europe for regulatory approval and other microneedle and thermal ablation products

are proceeding through advanced clinical trials. A limitation of diffusing large compounds through micron-scale disruptions is that diffusivity is a strong inverse function of molecular size. Thus, even though, for example, an inactivated virus particle vaccine can easily fit though a micron-sized hole, it may take a long time to diffuse through. When rapid delivery is desirable, it may be preferable to use microneedles that actively drive macromolecules and drugs into the skin or to combine micron-scale disruption with an added driving force, such as iontophoresis. Skin can also be disrupted on the micron scale by using microneedles. Overall, transdermal drug delivery offers compelling opportunities to address the low bioavailability of many oral drugs; the pain and inconvenience of injections; and the limited controlled release options of both. Drug delivery by microneedles could enable transdermal delivery of macromolecules and vaccines. These scientific and technological advances that enable targeted disruption of stratum corneum while protecting deeper tissues have brought the field to a new level of capabilities that position transdermal drug delivery for increasingly widespread impact on medicine.