IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
September 2018 Vol.:13, Issue:2

Microneedles - A Potential Transdermal Drug Delivery

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Mohammed Abdul Rahman*

B.Pharm, Deccan School of Pharmacy, Hyderabad, T.S. India.

Submission: 20 August 2018
Accepted: 27 August 2018
Published: 30 September 2018

www.ijppr.humanjournals.com

Keywords: Transdermal Drug Delivery, Microneedles, Dissolving Microneedles, hydrogel-forming microneedles

ABSTRACT

Transdermal drug delivery presents various advantages including enhanced patient compliance, sustained release; circumvent gastric irritation, as well as an elimination of pre-systemic first-pass effect. However, only a few medications can be delivered through the transdermal route in therapeutic amounts. Microneedles can be used to augment transdermal drug delivery. In this review, microneedles are described and their methods of fabrication highlighted. Microneedles can be fabricated in different forms such as hollow, solid, and dissolving. There are also hydrogel-forming microneedles. A special attention is paid to hydrogel-forming microneedles. These are innovative microneedles which do not contain drugs but imbibe interstitial fluid to form continuous conduits between dermal microcirculation and an attached patch-type reservoir. Several microneedles approved by regulatory authorities for clinical use are also examined.

INTRODUCTION:

The skin is the largest organ in the body. It is about 1.5 m^2 in adults and provides protection for internal organs [1]. It also protects the human body against ingress of toxic chemicals and egress of water and other essential endogenous substances. Despite the large surface area of the skin, it is challenging for compounds including drugs and vaccines to cross the skin in therapeutically relevant amounts. The major barrier in the skin is provided by the stratum corneum (SC), which is the outermost layer of the skin [2]. Below the stratum corneum is the viable epidermis (VE), which is a cellular, avascular tissue measuring 50–100 μm thick [3]. Cells in the basal layer of the epidermis form the most important structural and functional connection to the dermis below [4]. The stratum corneum and viable epidermis together form the full epidermis. There is a basement membrane at the base of the epidermis and the existence of tight junctions in the viable epidermis has been recently documented. Base membrane and tight junctions may both offer resistance to the transport of molecules across the epidermis [5]. The dermis is the thickest component of the skin, up to 4 mm in depth. Its upper layer, the 100–200 μm thick papillary dermis, consists of thin collagen bundles, elastin fibers, and fibrocytes. Below this layer is the reticular dermis, made up of thick collagen bundles and coarse elastic fibers [6]. Although the stratum corneum (SC) is the major contributor to the barrier properties of the skin, the role of the full epidermis should be taken into consideration [5, 7]. Only compounds which are able to get into the SC diffuse through the living epidermis and pass through the upper part of the papillary dermis has the potential to reach circulation and exhibit systemic effects [7]. The dermis contains blood vessels, lymphatics, and nerves, as well as the various skin appendages. Below the reticular dermis lies the hypodermis (subcutaneous fat tissue), which may have a thickness of up to several millimeters. Comprising fat microtubules and fibrous collagen, it also contains blood vessels, lymphatics, and nerves [6].

Hypodermic needles are used in clinical practice to deliver medications across the skin into the bloodstream. Injections with hypodermic needles are important from a clinical standpoint but painful. They may also induce hypersensitivity, bruising, discomfort and bleeding at the site of administration and in some cases are associated with risks of contamination. There are other concerns linked to their use including accidental needle injury and the necessity to train personnel regarding the proper use of needles. The difficulty in crossing the skin is caused by its anatomical peculiarities. Microneedles (MN) is currently being utilized to enhance

transdermal delivery of small and large molecules. With the emergence of microfabrication manufacturing technology over the past several decades, MN has been developed by academic laboratories and pharmaceutical companies [8–13]. Transdermal MNs create micron-sized pores in the skin to enhance delivery of the drug across the skin [11, 13]. MN is ideal for patient adherence as they do not stimulate nerves that are associated with pain. MN improves patient compliance as a patient with needle phobia will be more likely to apply the patch because of its painlessness [13]. Additionally, patients can administer the drug by themselves [13]. When MN is fabricated in arrays on a backing that can be applied to the skin like a bandage, the device is called a MN patch [8]. MN can be divided into four categories- hollow, solid, coated and polymer [6].

II. NECESSITY FOR USE OF MICRONEEDLES

When the oral administration of drugs is not feasible due to poor drug absorption or enzymatic degradation in the gastrointestinal tract or liver, injection using a painful hypodermic needle is the most common alternative. An approach that is more appealing to patients, and offers the possibility of controlled release over time, using a patch. However, transdermal delivery is the majority of rates due to the great barrier imposed by the skin's outer stratum corneum layer.[14] To increase skin permeability, a number of different approaches have been studied, ranging from chemical/lipid enhancers to electric fields employing iontophoresis and electroporation to pressure waves generated by ultrasound or photoacoustic effects.[15] Although the mechanisms are all different, these methods share the common goal to disrupt stratum corneum structure in order to create "holes" big enough for molecules to pass through. The size of disruptions these methods are believed to be of nanometer dimensions, which of small drugs and, in some cases, macromolecules, but probably small enough to prevent causing damage of clinical significance. [16].

An alternative approach involves creating larger transport pathways dimensions using arrays of microscopic needles. These pathways are orders of magnitude bigger than molecular dimensions and, therefore, should readily permit transport of macromolecules, as well as possibly supramolecular complexes and microparticles. Despite their very large size relative to drug dimensions, on a clinical length scale, they remain small. Although safety studies need to be performed, it is proposed that micron-scale holes in the skin are likely to be safe, given that they are smaller than holes made by hypodermic needles or minor skin abrasions encountered in daily life. [17]

Transdermal drug delivery is a noninvasive, user-friendly delivery method for therapeutics. However, its clinical use has found limited application due to the remarkable outermost layer of skin, the stratum corneum (SC). Physical and chemical methods have been developed to overcome this barrier and enhance the transdermal delivery of drugs. One of such techniques was the use of microneedles to temporarily compromise the skin barrier layer. This method combines the advantages of conventional injection needles and transdermal patches while minimizing their disadvantages. As compared to hypodermic needle injection, microneedles can provide a minimally invasive means of painless delivery of therapeutic molecules through the skin barrier with precision and convenience. The microneedles seldom cause infection while they can allow drugs or nanoparticles to permeate through the skin. Increased microneedle+ assisted transdermal delivery has been demonstrated for a variety of compounds. For instance, the flux of small compounds like calcein, diclofenac methyl nicotinate was increased by microneedle arrays. In addition, microneedles also have been tested to increase the flux of permeation for large compounds like fluorescein isothiocyanate-labeled Dextran, bovine serum albumin, insulin and plasmid DNA and Nanospheres.

Microneedles may create micro-conduits to deliver drug-loaded liposomes into the skin. The combination of elastic liposomes and microneedles may provide higher and rates of drugs in traditional diffusion-based, such as molecular size and solubility. Though it could offer benefits mentioned above, the liposomes and microneedle pretreatment have received little attention.[18]

III. TYPES OF MICRONEEDLES

The different types of microneedles are etched by different materials: The first type of the microneedle is single-tip microneedles that have a sharp tip. These types of microneedles are in straight shape, 200μm in length. It contains sharp tip with different angles of 15 degrees, 30 degrees, 45, and 75 degrees. The second type of Quadruplet microneedles and the third type of microneedle is hollow microneedles. The quadruplet and hollow microneedles are good in strength and not very expensive respectively. A classification for microneedles usually used in literature is based on the fabrication process:

In-plane or Out-of-plane microneedles.

In-plane microneedles are fabricated with the shaft being parallel to the substrate surface. The advantage of this arrangement is that the length of the needle can be very accurately controlled. A disadvantage is that it is difficult to fabricate two-dimensional arrays.

Out-of-plane microneedles, another hand, straightforward to fabricate in arrays. Instead, the length and high aspect-ratios become significant challenges in the fabrication of these kinds of needles. [19]

- **Hollow microneedles**

Skin permeability can be dramatically increased by the holes created from solid microneedles insertions. However, transport pathways to deliver drugs into the tissue. The fabrication of hollow microneedles that allow transport through the hollow shaft of the needle was based on this need. The inclusion of a hollow lumen in a microneedle structure expands its capabilities dramatically and can offer the following advantages: the ability to deliver larger molecules and particles; convective transport fashion (for example, pressure-driven flow) passive diffusion; the cross-contamination of the deliverables and its surrounding. A variety of hollow microneedles has been fabricated and has demonstrated success in transdermal drug delivery.

a. Metal hollow microneedles

b. Silicon hollow microneedles

c. Glass hollow microneedles

- **Other types of microneedles**

Besides solid and, various other types were fabricated using different materials such as biodegradable polymers, polysilicon, and sugar with additional functionalities. Because of there with the tissue, microneedles were developed. These needles were fabricated by initially making master structures using lithography-based methods, creating inverse structures from the master molds, and finally producing replicate microneedles by melting biodegradable polymer formulations (i.e. Poly-lactic acid, PLA, or poly-lactic-co-glycolic acid, PLGA) into the molds. with molecules, drugs, DNA or proteins. and hollow microneedles, as the drug

implants after insertion into the tissue. Park et al. (2006) inserted the microneedles loaded with calcein or bovine serum albumin (BSA) into full thickness human cadaver skin. [20]

Dimension of Microneedles.

The solid tip microneedles and hollow microneedles have the different dimension. Solid microneedles are fabricated in 750-1000 µm in length, 15º-20º tapered tips angle and 190-300 µm bases area. The masks of microneedles are designed to 400-600 µm triangles length, 70-100 µm conduits diameter, and 25-60EA/5 mm2 arrays density. The hollow microneedles arrays are fabricated with a lumen diameter of 30 µm and height of 250 µm. The center-to-center the distance of the hollow microneedles array is 150 µm. The axis of the lumen is fabricated with the distance of 10 µm to the axis of outside column. [21]

IV. MECHANISM OF ACTION

The mechanism for delivery is not based on diffusion as it is in other transdermal drug delivery products. Instead, based on the skin and the placement of the drug or vaccine within the epidermis, where it can more readily reach its site of action. The drug, form of biomolecules, is the microneedles, which are then inserted into the skin in the same way a released into the bloodstream from a patch. The needles dissolve within minutes, releasing the trapped cargo at the intended delivery site. They do not need to be removed and no dangerous or biohazardous on the skin, as the needles are made of a biodegradable substance.

In microneedle devices, a small area (the size of a traditional transdermal patch) is covered by hundreds of microneedles that pierce only the stratum corneum (the uppermost 50 /m of the skin), thus allowing the drug to bypass this important barrier. The tiny needles are constructed in arrays to deliver a sufficient amount of drug to the patient for the desired therapeutic response. [22]

V. MERITS

- The major advantage of microneedles over traditional needles is when it is inserted the stratum corneum, the outer 10-15 /m of the skin. Conventional needles which do pass this layer of skin may effectively transmit the drug but may lead to infection and pain. As for microneedles they can be fabricated to be long enough the stratum corneum, but short enough not to puncture nerve endings. Thus reduces the chances of pain, infection, or injury.

- on a silicon small size, thousands of needles can be fabricated on single water. This leads to high accuracy, good reproducibility, and a moderate fabrication cost.

- Hollow like a hypodermic needle; solid-increase permeability by poking holes in the skin, rub drug over the area, or coat needles with the drug.

- Arrays of hollow needles could be used to continuously carry drugs into the body using simple diffusion or a pump system.

- used to a body for analysis- such as blood glucose measurements – and to then supply microliter volumes of insulin or another drug as required.

- Immunization programs in developing countries, or mass vaccination or administration of antidotes in bioterrorism incidents, could be applied with minimal medical training.

- Very small microneedles could provide highly targeted drug administration to individual cells.

- capable of very accurate dosing, complex release patterns, local delivery, and stability enhancement by storing in a can be precisely controlled. [23]

VI. DEMERITS

- 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.

- Microneedles can be difficult to apply on the skin; the clinician must learn proper application technique.

- allergy or sensitive skin.

- Local inflammation may result if the amount of drug is high under the skin.[24]

VII. MATERIALS USED FOR FABRICATION

The materials used for fabrications are-

- Silicon

- Metal
- Polymers
- Glass

SILICON: First the microneedles were fabricated using silicon to have sharp and hard microneedle because of greater mechanical strength. Fabrication by microneedle is costly because it requires microfabrication for processing. Silicon is brittle and may break in the skin.

METAL: Metal is used for fabrication as they have good mechanical strength, the cost is low, the metal used are stainless steel, titanium, nickel, iron.

POLYMERS: Polylactic acid and are cost-effective. This biodegradable polymer is used owing to the chance of microneedle breaking off in the skin.

GLASS: also done by the glass. They are physically capable of insertion into the tissue and they have and one can see how much amount of drug is delivered after use.[25]

VIII. FABRICATION OF MICRONEEDLES

Microneedles can be fabricated employing microelectromechanical systems (MEMS). The basic process can be divided into three parts: deposition, patterning, and etching. Microneedles have become a new type of the bio-medicine injector, not excite the nerve, and the patient will feel nothing. Moreover, it can be made a kind of materials, like as SU-8, PMMA, PDMS, COC, silicon etc.

Deposition: Refers to the formation of thin films with a thickness anywhere between a few nanometers to about 100 micrometers.

Patterning: Is the transfer of a pattern onto the film.

Lithography: Is used to transfer a pattern onto a photosensitive material by selective exposure to a radiation as light. can involve photolithography, electron beam lithography, ion beam lithography or X-ray lithography. Diamond patterning is also an option for lithography.

Etching: Is a process of using strong acid or mordant to cut into the unprotected parts of a material's surface to create a design in it and can be divided into two categories: wet etching or dry etching. The selection of any of the above-mentioned methods largely depends on the material of construction and the type of microneedle.

Polymer Microneedle:

The SU-8 2050 as the material of the microneedles. SU-8 is a high contrast, photoresist designed for other microelectronic applications. The UV-light absorptivity of SU-8 is lower than others and therefore can get the high-aspect-ratio structures. As the turning model technique to fabricate is the microneedles, V-groove on the silicon wafer should be considered. At first, then the depth of 320 μm on a silicon wafer, coated with the SU-8 on the silicon wafer with the depth of 450 μm and use the scraper to put the SU-8 uniformly. Silicon wafer SU-8 will be set in away the bubbles smooth the surface by heating and vacuum. Finally, the SU-8 developer is used to form the microneedles. [26]

IX. METHODOLOGY FOR DRUG DELIVERY:

A number of delivery strategies have been employed to use drug delivery. These include

- Poke with patch approach
- Coat and poke approach
- Biodegradable microneedles
- Hollow microneedles
- Dip and scrape

Poke with Patch Approach:

It involves piercing an array of solid microneedles into the skin followed by application of the drug patch at the treated site. Transport of drug across the skin can occur by diffusion or possibly by iontophoresis if an electric field is applied. E.g.: Insulin Delivery.

Coat and Poke Approach:

In this approach, needles are first coated with the drug and by dissolution. is coated on the needle itself. E.g.: Protein vaccine delivery.

Biodegradable microneedles:

It involves encapsulating the drug within the biodegradable, polymeric microneedles, followed by the insertion into the skin for a controlled drug release.

Hollow microneedles:

It involves injecting the drug through the needle with a hollow bore. This approach is more reminiscent (suggestive of) of an injection than a patch. E.g.: Insulin Delivery.

Dip and Scrape Approach

Scrape approach is first dipped into a drug solution and then scraped across the skin within the micro-abrasions created by the needles. The arrays were dipped into a solution of drug and scraped multiple times across the skin of mice in vivo to create micro abrasions. Unlike microneedles used previously, this study used blunt-tipped microneedles measuring 50–200μm in length over a 1 cm^2 area. E.g.: DNA Vaccine Delivery. [27]

X. EVALUATION

***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 a 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 the strength of microneedle, coating material, and the estimation 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 Paradimethylsiloxane (PDMS) biochip and black ink is

injected by the microneedles into the Petri dish, 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, the dissolution rate of the coated material, which is coated on the microneedle tip, coated with vitamin B, calcein or sulforhodamine

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 as the 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 the vein of the tail of hairless mice. It is used for the into the skin.

Method 2

This method of *in-vivo* testing of the microneedles, Rhodamine B is injected into the tail of laboratory mouse-tail and anesthetized 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 a 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. [28]

XI. APPLICATIONS OF MICRONEEDLES:

Microneedle technology has been developed with high and hydrophilic compounds through the skin. The first-ever study of transdermal drug delivery technology was Henry et al who demonstrated an increase in the permeability of skin to a odel compound calcein using microarray technology. It is applied in the following-

- Oligonucleotide delivery
- DNA vaccine delivery
- Desmopressin delivery
- Insulin delivery
- Porphyrin Precursor 5-Aminolevulinic Acid (ALA) Delivery [29]

XII. FUTURE ASPECTS:

Integration of solid microneedles with transdermal patch provides a minimally invasive method to increase the skin permeability of drugs, including the macromolecules such as proteins. Till date, microneedles made up of silicon, metal, glass, and plastics have been utilized for transdermal delivery. However, with rapid advancement in technology, microneedles composed of biodegradable and biocompatible materials have been explored. For instance, fabrication of dissolving microneedles using polysaccharide biomaterials have

been utilized for controlled drug delivery. Microneedle approach of drug delivery is currently being evaluated for a number of drugs, but extensive studies would be required to foster the application of these delivery modes in the clinical setup. Results from several groups suggest that microneedles are a promising, possibly powerful technology for the administration of therapeutics (e.g. Vaccines or drugs) into the skin. However, a few issues will have studied in greater depth before microneedles widely used clinically.

As the variety of microneedles increases, a that can be being proposed. pre-clinical tests (*in-vivo* tests in animal models), clinical tests (to test pain, inflammation, etc.), mechanical tests (to the margin of safety) as fluidic flow tests (e.g. Fluid pressure needed for particular flow rate, etc.). This will help not only in objectively comparing the of the microneedle for each application. [30]

CONCLUSION:

Microchannel based Transdermal Delivery System by using Microneedles is a Novel Approach for Drug delivery system. It is a convenient, painless, and less invasive alternative to injection and it can be used as a common method for administering large proteins and peptides, antibiotics, vaccines in low manufacturing cost. In contrast to oral delivery, microneedles avoid first pass effect and offer the benefit of immediate cessation of drug administration in case of an adverse effect or overdose. In contrast to passive delivery, this allows for the delivery of water-soluble drugs. In contrast to Iontophoresis, this is used for a long time. There is also no molecular size limitation, no molecular electrical charge requirement, and no specific formulation pH constraint. In contrast to conventional TDDS, this is used for potent & less potent drug, the more extended release delivery system.

ACKNOWLEDGMENT:

Most importantly, we are thankful to the Almighty, who is the creator and director of all that initial and final modes to destiny. It is a genuine pleasure to express the deep sense of gratitude to Mrs. Shrisha Mittapally, Assistant Professor, Department of Pharmaceutics, Deccan School of Pharmacy, who constantly encouraged us during this work.

REFERENCES:

1. Lhernould, M.S.; Deleers, M.; Delchambre, A. Hollow polymer microneedles array resistance and insertion tests. Int. J. Pharm. 2015, 480, 152–157.
2. Kim, K.S.; Ita, K.; Simon, L. Modelling of dissolving microneedles for transdermal drug delivery: theoretical and experimental aspects. Eur. J. Pharm. Sci. 2015, 68, 137–143.
3. Danso, M.O.; Berkers, T.; Mieremet, A.; Hausil, F.; Bouwstra, J.A. An ex vivo human skin model for studying skin barrier repair. Exp. Dermatol. 2015, 24, 48–54.
4. Danso, M.O.; van Drongelen, V.; Mulder, A.; Gooris, G.; van Smeden, J.; El Ghalbzouri, A.; Bouwstra, J.A. Exploring the potentials of nurture: 2nd and 3rd generation explant human skin equivalents. J. Dermatol. Sci. 2015, 77, 102–109.
5. Andrews, S.N.; Jeong, E.; Prausnitz, M.R. Transdermal delivery of molecules is limited by full epidermis, not just stratum corneum. Pharm. Res. 2013, 30, 1099–1109.
6. Jepps, O.G.; Dancik, Y.; Anissimov, Y.G.; Roberts, M.S. Modeling the human skin barrier-Towards a better understanding of dermal absorption. Adv. Drug Deliv. Rev. 2013, 65, 152–168.
7. Flaten, G.E.; Palac, Z.; England, A.; Filipović-Grčić, J.; Vanić, Ž.; Škalko-Basnet, N. In vitro skin models as a tool in optimization of drug formulation. Eur. J. Pharm. Sci. 2015, 75, 10 24.
8. Jacoby, E.; Jarrahian, C.; Hull, H.F.; Zehrung, D. Opportunities, and challenges in delivering influenza vaccine by microneedle patch. Vaccine 2015, doi: 10.1016/j.vaccine.2015.03.062.
9. Chu, L.Y.; Choi, S.O.; Prausnitz, M.R. Fabrication of dissolving polymer microneedles for controlled drug encapsulation and delivery: Bubble and pedestal microneedle designs. J. Pharm. Sci. 2010, 99, 4228–4238.
10. Donnelly, R.F.; Moffatt, K.; Alkilani, A.Z.; Vicente-Pérez, E.M.; Barry, J.; McCrudden, M.T.; Woolfson, A.D. Hydrogel-forming microneedle arrays can be effectively inserted in the skin by self-application: A pilot study centered on pharmacist intervention and a patient information leaflet. Pharm. Res. 2014, 31, 1989–1999.
11. Olatunji, O.; Das, D.B.; Garland, M.J.; Belaid, L.; Donnelly, R.F. Influence of array interspacing on the force required for successful microneedle skin penetration: Theoretical and practical approaches. J. Pharm. Sci. 2013, 102, 1209–1221.
12. Cheung, K.; Han, T.; Das, D.B. Effect of Force of Microneedle Insertion on the Permeability of Insulin in Skin. J. Diabetes Sci. Technol. 2014, 8, 444–452.
13. Kaur, M.; Ita, K.B.; Popova, I.E.; Parikh, S.J.; Bair, D.A. Microneedle-assisted delivery of verapamil hydrochloride and amlodipine besylate. Eur. J. Pharm. Biopharm. 2014, 86, 284–291.
14. Kim, Y.C.; Park, J.H.; Prausnitz, M.R. Microneedles for drug and vaccine delivery. Adv. Drug Deliv. Rev. 2012, 64, 1547–1568.
15. Verbaan, F.J.; Bal, S.M.; van den Berg, D.J.; Dijksman, J.A.; van Hecke, M.; Verpoorten, H.; van den Berg, A.; Luttge, R.; Bouwstra, J.A. Improved piercing of microneedle arrays in dermatomed human skin by an impact insertion method. J. Control. Release 2008, 128, 80–88.
16. Cheung, K.; Das, D.B. Microneedles for drug delivery: Trends and progress. Drug Deliv. 2014, doi:10.3109/10717544.2014.986309.
17. Yuzhakov, V.V. The AdminPen™ microneedle device for painless & convenient drug delivery. Drug Deliv. Technol. 2010, 10, 32–36.
18. Lyon, B.J.; Aria, A.I.; Gharib, M. Fabrication of carbon nanotube-polyimide composite hollow microneedles for transdermal drug delivery. Biomed. Microdevices 2014, 16, 879–886.
19. van der Maaden, K.; Jiskoot, W.; Bouwstra, J. Microneedle technologies for (trans) dermal drug and vaccine delivery. J. Control. Release 2012, 161, 645–655.
20. Gardeniers, H.J.G.E.; Luttge, R.; Berenschot, E.J.W.; de Boer, M.J.; Yeshurun, S.Y.; Hefetz, M.; van't Oever, R.; van den Berg, A. Silicon micromachined hollow microneedles for transdermal liquid transport. Microelectromech. Syst. 2003, 12, 855–862.
21. Perennes, F.; Marmiroli, B.; Matteucci, M.; Tormen, M.; Vaccari, L.; Di Fabrizio, E. Sharp beveled tip hollow microneedle arrays fabricated by LIGA and 3D soft lithography with polyvinyl alcohol. J. Micromech. Microeng. 2006, 16, 473–479.

22. Vinayakumar, K.B.; Hegde, G.M.; Nayak, M.M.; Dinesh, N.S.; Rajanna, K. Fabrication and characterization of gold coated hollow silicon microneedle array for drug delivery. Microelectron. Eng. 2014, 128, 12–18.
23. Henry, S.; McAllister, D.V.; Allen, M.G.; Prausnitz, M.R. Microfabricated microneedles: A novel approach to transdermal drug delivery. J. Pharm. Sci. 1998, 87, 922–925.
24. Gill, H.S.; Prausnitz, M.R. Coated microneedles for transdermal delivery. J. Control. Release 2007, 117, 227–237.
25. Wang, Q.; Yao, G.; Dong, P.; Gong, Z.; Li, G.; Zhang, K.; Wu, C. Investigation on fabrication process of dissolving microneedle arrays to improve effective needle drug distribution. Eur. J. Pharm. Sci. 2015, 66, 148–156.
26. Ita, K. Transdermal delivery of drugs with microneedles: Strategies and outcomes. J. Drug Deliv. Sci. Technol. 2015, 29, 16–23.
27. HenryS, McAllister DV, Allen MG, and Prausnitz MR, Microfabricated Microneedles: A Novel Approach to Transdermal Drug Delivery, Journal of Pharmaceutical Sciences, 1998; 87: 922-925.
28. Mark R, Prausnitz MR, transdermal drug delivery Advanced Drug Delivery Reviews, 2004;56(5): 581-587.
29. E.L. Giudice, J.D. Campbell, Needle-free vaccine delivery, Adv. Drug Deliv. Rev. 58(2006) 68–89.
30. Sharma N, Bharat PS, Mahajan U. Blooming pharma industry with transdermal drug delivery system. Indo Global J Pharm Sci 2012; 2(3): 262-278.