International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.4, No.1, pp 181-189, Jan-Mar 2012

Microneedle Technology for Advanced Drug Delivery: A Review

Desale Rohan S[1]*, Wagh Kalpesh S[1], Akarte Anup M[1], Baviskar Dheeraj T[1], Jain Dinesh K[2]

[1]KVPS's Institute of Pharmaceutical Education, Department of Pharmaceutics, Boradi. Tal- Shirpur. Dist- Dhule. 425428 (MH),India.
[2]College of Pharmacy, I.P.S. Academy, Rajendra Nagar, Indore, 452012 (M.P.),India.

***Corres author: desalerohan@gmail.com**
Phone No. +919561901104, +917588518650

Abstract: The objective of this review article is to summarize recent data, description results and basic functionality of silicon microneedles array through biodegradable instructions. In order to avoid the main troubles related to drug degradation by gastrointestinal track and their elimination through the liver, an easy solution can be fabrication of microneedles array with biodegradable instructions. Transdermal drug delivery can avoid drug degradation, and it has a low diffusion coefficient so it is complicated to transport hydrophilic and high molecular weight drug (>500Da) using passive patches. While, there is about 20 species of drug that relevant to former patches. Micro-needle can convey hydrophilic and molecular weight, because it have valuable source of intellectual property. There are many studies in transdermal drug delivery, blood extraction, skin care fields with a micro-needle. Existing micro-needle through using silicon, metal, and polymer materials. To make 3-D shape micro-needle mold, inclined UV lithography is used, but this process is complicated to control process condition and its process output ratio is so low. This review suggests the novel process using dicing progression with an inclined sharp edge to make the sharp shape of microneedle information. And the optical assessment module is made for evaluating the drug delivering ratio according to the needle length and insertion times. This estimation module has a water chamber and membrane to copy the drug delivery mechanism. We can discover that the drug delivering ratio can enlarge when use a longer needle as the surface area with drug sticking can be augmented.

Keywords: Microneedles, stratum corneum, hypodermic needles, micro-electromechanical pump.

INTRODUCTION

Nowadays, the transdermal route has become one of the most successful and innovative focus for research in drug delivery, with around 40% of the drug candidate being under clinical evaluation related to transdermal or dermal systems. The technology has a proven record of FDA approval since the first transdermal patch was approved in 1981. The market for transdermal products has been in a significant upward trend and this is likely to continue for the foreseeable future. An increasing, numbers of TDD products continue to deliver real therapeutic benefit to patients around the world[1].The drug delivery method using the micro-needle can deliver, nevertheless, hydrophilic and molecular weight, since it makes micro scale holes in the skin. *In-vitro* test shows that drug permeability of the skin is 10,000 times better [2] than passive diffusion and there is little skin damage than sand paper or tape[3].

Micro-needle has an advantage that patient compliance, convenience, avoidance of the liver's first-pass metabolism and degradation in the gastrointestinal tract. It needs in a medicine and biology field. Particularly, transdermal drug delivery, blood extraction, skin care fields are much required[4] Drug delivery system has been developed many kinds of ways that are oral delivery, transdermal delivery, parenteral delivery, Implant delivery, etc. The most widely used method is oral delivery. The advantage of oral delivery is the convenience of use. Nevertheless, this method has a big problem due to the drug degradation by gastrointestinal track and their elimination through the liver[5].This delivery system can deliver a drug into the body, so drug absorbed at once then drug concentration in plasma increased rapidly and reaching the apex. The concentration of the drug is slowly reduced by metabolism. This drug concentration profile shows it is harmful to human when drug concentration is higher than adequate concentration[6].

Recently, there are many micro-needle fabrication process methods using MEMS process due to the necessity of the micro-needle. These micro-needles are divided by solid and hollow type needle Hollow type needle has a drug pathway inside the needle while the solid type needle looks like acupuncture. Meanwhile, dissolved type micro-needle, classified another solid type micro-needle.

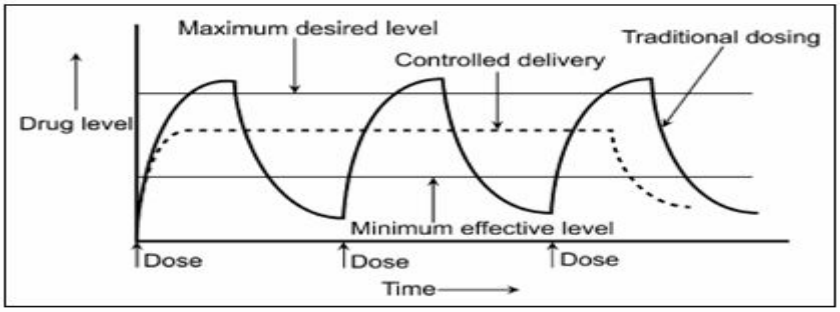


Figure.1Drug concentration in blood during drug delivery

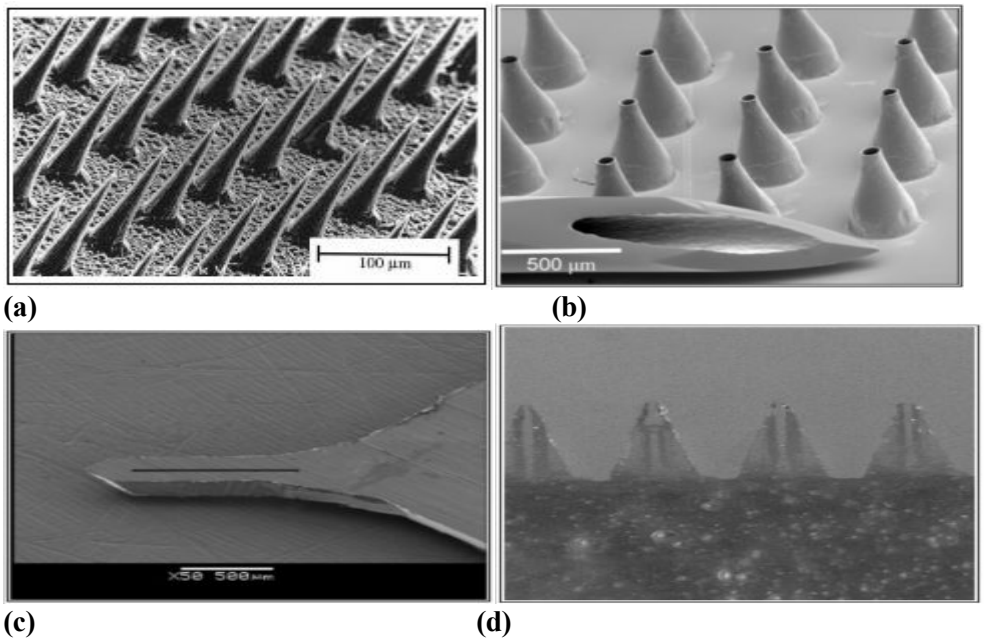
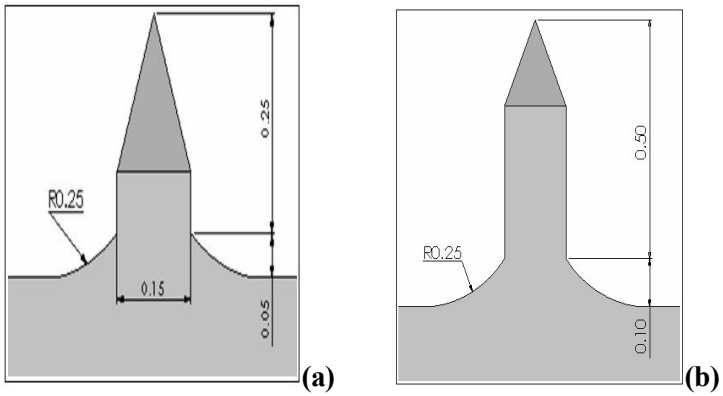


Figure.2 Kinds of Micro-needle:(a) Solid (b) Hollow (c) Semi Hollow (d) Dissolved.

To fabricate solid type micro-needle that can be used practically, we make 3-D sharp needle tip to facilitate needle insertion and round of a corner to increase mechanical strength. First, the in-plane micro-needles were fabricated using UV lithography and were made long enough to ensure sufficient penetration depth. In this step, it was easy to control the length, needle width, and round of a corner.

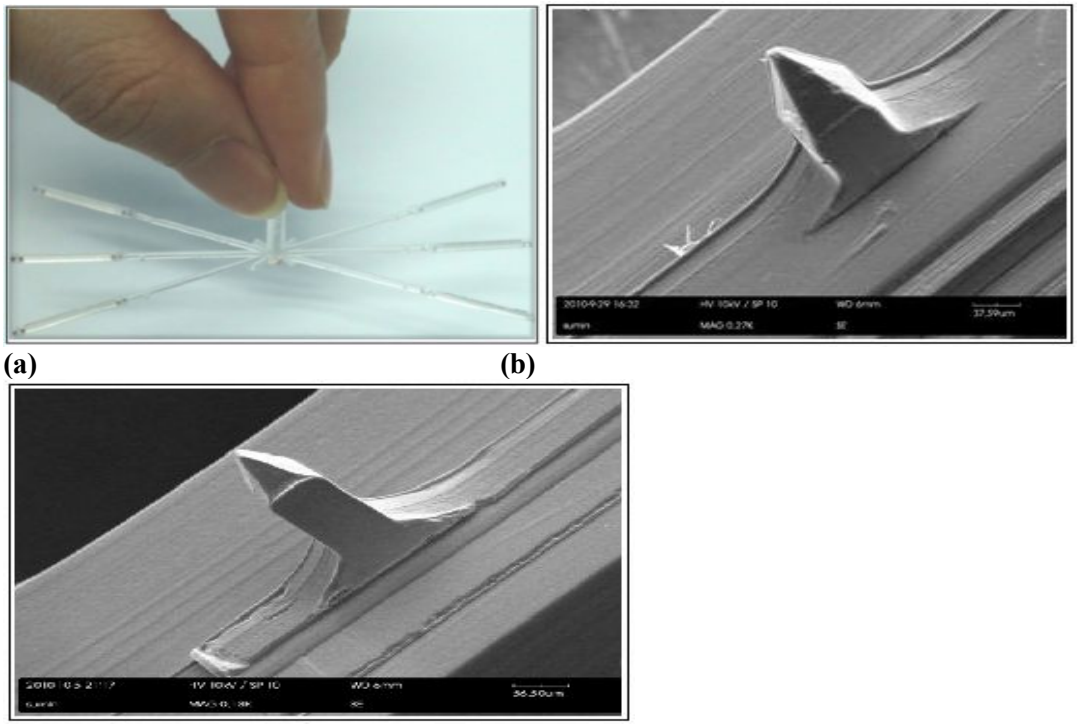
The most common material used for microfabrication of needles is silicon. These microneedles have extremely sharp tips(radius of curvature, <1μm) that facilitate easy piercing of the skin. Individual silicon needles measuring approximately 150 μm in length and with 80 μm base diameter are fabricated onto arrays of approximately 400 microneedles (approx. 3 X 3 mm). Needles with hollow centers have also been produced, each containing a bore of 5-70 μm (depending on the required design) through which drug can be administered. A broad range of compounds such as calcein (623 Da), insulin (6000Da), BSA (66000Da) and polymeric nanoparticles are delivered at significant rates through skin permeabilized by microfabricated microneedles[7, 8].

Micro-needle array can be made by an injection molding process using polycarbonate material as shown in Fig. 4. In this research, the microneedle array is made in two types have needle length areabout 250um and 500um.



(a) **(b)**

Figure.3 Design data of micro-needle: (a) 250um (b) 500um.



(a) **(b)**

(c)

Figure.4 Fabricated out of plane type micro-needle array: (a) Micro-needle array (b) 250um (c) 500um

Micro-needle can make a microscale hole in the skin.Insertion of a micro-needle into the skin was capable ofdramatically increasing permeability. When micro-needleswere inserted and left embedded in the skin, permeabilitywas increased by more than 100-fold. To find the difference of a drug delivery ratio accordingto the micro-needle length, we perform a diffusion test usingthe solid type micro-needle that has a needle length about250 and 500um and drug delivery evaluation test system.

Recently, the use of micron-scale needles inincreasing skin permeability has been proposed and shown to dramatically increase transdermaldelivery, especially for macromolecules.Mostdrugdelivery studies have emphasized solid microneedles, which have been shown to increase skinpermeability to a broad range of molecules and nanoparticles *in-vitro*.*In-vivo* studies havedemonstrated delivery of oligonucleotides, reduction of blood glucose level by insulin, andinduction of immune responses from protein and DNA vaccines. For these studies, needle arrayshave been used to pierce holes into skin to increase transport by diffusion or iontophoresis or as drug carriers that release drug into the skin from a microneedle surface coating. Hollow microneedles have also been developed and shown to microinject insulin to diabetic rats. Microneedles find widespread use; researchers must perfect the techniques for optimally inserting them intothe skin, and complete the integration of microneedles into a full diagnostic, monitoring or drug delivery system [9-12]. Microneedles are expected to be less painful than conventionalhypodermic needles because they are too small to significantly stimulate nerve endings.

The microneedles are fabricated by siliconwith MEMS technologies

Microneedle technology has been developed as an advancedtechnique for penetration of large molecular weight and/orhydrophilic compounds. Micron scale needles assembled ona transdermal patch have been proposed as a hybrid betweenhypodermic needles and transdermal patches to overcomethe individual limitations of both the injections as well as patches[13, 14]. Microneedle technique has been successfullyused to deliver a variety of compounds includingmacromolecules and hydrophilic drugs into the skin. As microneedle system bypasses the stratum corneum barrier of the skin, permeability enhancement of two to four ordersof magnitude has been observed for small molecules like calcein and also for the relatively larger compounds likeand nanoparticles[15].

(a) Hollow microneedles with applied formulation
(b) Solid Microneedles

In the beginning, these minute arrays of solid and hollow microneedles were created using silicon etching technique. The arrays were comprised of needles 150 μm long and tapering from a base of 80 μm to as narrow as 1 μm tip. However, due to the brittle nature of silicon, about 5% of microneedles were observed to break and remain in theskin, leading to loss of drug as well as a risk of toxicity orinfection [16]. To overcome these problems, small gauge metaland plastic micro devices that could be made into veryshort, sharp needles for penetration into upper skin layerare being developed for microneedle systems. Maltose has been tried for formation of biodegradable microneedles [17, 18].

Microneedles manufactured by the silicon etching technologyand micro-mechanical system manufacturing (MEMS)technique are tiny and very thin (even thinner than humanhair), which do not penetrate deep enough into the skin toreach up to the nerve endings and therefore there is noperception of pain during the microneedles insertion into the skin. A number of delivery strategies have been employed to use the microneedles for transdermal drug delivery.

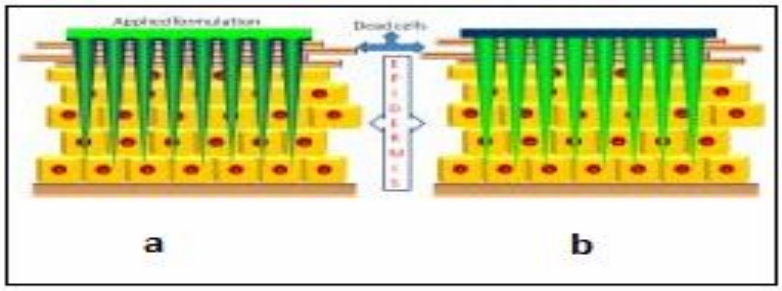


Figure.5Delivery site for microneedle technology

A NUMBER OF STRATEGIES HAVE EMPLOYED TO USE THE MICRONEEDLES

1) **Poke with patch approach.**
2) **Coat and poke approach.**
3) **Biodegradable microneedles.**
4) **Hollow microneedles.**

1. Poke with patch approach

It involves piercing an array of solid microneedles into the skin followed by application of the drug patch at the treatsite. Transport of drug diagonally skin can occur by diffusion or maybe by iontophoresis if an electric field is applied.

2. Coat and poke approach

In this approach needles are first coated with the drug andthen inserted into the skin for drug free by dissolution.The entire drug to be delivered is coated on the needleitself. Dip and rub approach is a variation of this approach, where microneedles are first dipped into a drug solution andthen worn across the skin surface to leave behind the drug within the microabrasions twisted by the needles.

3. Biodegradable microneedles

It involves encapsulating the drug within the biodegradable, polymeric microneedles, followed by the insertion into theskin for a controlled drug release [19].

4. Hollow microneedles

It involves injecting the drug during the needle with ahollow bore. This advance is more evocative of an injectionthan a patch.

DIFFERENT TYPES OF MICRONEEDLES

Hollow Metal Microneedles for Insulin Delivery to Diabetic Rats:The goal of this study was to intend, produce, and test arrays of hollow microneedles for minimally enveloping and continuous delivery of insulin *in vivo*.

1. Electrically conductive micro needle roller

An electrically conductive micro needle roller includes stacked discs, each of which includes aplurality of radial grooves, a plurality of micro needles that are received in the radial grooves ofthe disc, an electrically conductive bracket that supports the stacked discs, and a handle thatsupports the bracket. Electric current flows to the skin via the micro needles and provides electricstimulation. The discs are assembled using UV bond thereby reducing the assembly time. Theroller has enhanced service life since the micro needles do not fall off from the roller since radialgrooves holding the micro needles have tapered shape.

2.Collagen induction therapy with the micro needle derma roller

The Micro needle Derma roller is a small plastic roller studded with about 200 really fine needles of medical mark stainless steel. The skin reacts to these pricks like it reacts to any other injury with the formation of the various growth factors. This process of stimulating collagen tissue production is a normal physiological reaction and is known as Collagen Induction Therapy.

DESIGN AND MECHANISM OF WORKING

The needle can be used to draw blood, insert drugs, and as a glucose-level check fordiabetics. A female mosquito sucks blood by flexing and comforting certain muscles in itsproboscis. This creates suction that draws blood into its mouthparts.In order to penetrate the skin barrier of stratum corneum without reaching the nerves in the dermis layer, the microneedles should be at least 50 μm in length, but not more than 150 μm. The new biocompatible microneedle, designed by Suman Chakraborty of the Indian Institute of Technology in Kharagpur and Kazuyoshi Tsuchiya of Tokai University in Kanagawa is based onthe same principle. In this case, the sucking action is provide by a microelectro-automatic pump, which mechanism using a piezoelectric actuator attached to the needle[20, 21].

A SELECTION OF MICRO NEEDLE RESOURCES

1. Micro needle therapy system: The Micro needle Therapy System (MTS) is acrackthrough device, simple in concept but soft magnificent results for the human skin. TheMTS consists of a run of devices, which have both cosmetic and medical applications. Theirsystem of action is through the painless piercing of the stratum.

2. The derma roller: The Derma roller is the most effective device for deep transdermal Deliveryof active substances through the epidermal barrier.

3. Skin care review: Skin care and renovation information and reviews based on available research and other autonomous sources.

4.The derma roller: The Collagen-Induction-Therapy with the CITDERMAROLLER is a perfect choice to get the same goal: a new collagen-layer on the dermis. The Leaf and Rusher Derma Roller is a exclusive rolling device that considerably enhances the action of the Leaf andRusher Treatment System.

5. MTS micro needle derma roller: Micro channel formation enhances product penetration and stimulates collagen production for renewal and treatments of acne scars and stretch marks.The Collagen-Induction-

Therapy (CIT) with the needling device called DERMAROLLER%u2122 is a rather new procedure for the motivation of new collagen fibers.

CURRENT RESEARCH IN MICRONEEDLES TECHNOLOGY

The first microneedle arrays report in the literature was etched into a silicon wafer and developed for intracellular delivery *in vitro* by Hashmi et al. These needles were inserted into cells and nematodes to raise molecular uptake and gene transfection. Henry et al. conduct the first study to decide if microneedles could be used to increase transdermal drug delivery. An array of solid Microneedles was fixed in cadaver skin, which caused skin permeability to a small model compound. In a transcribe study, McAllister et al. studied permeability of cadaver skin to a range of different compounds and originate that insulin, bovine serum albumin, and latex nanoparticles as large as 100 nm in diameter could cross the skin after action with microneedles. Mathematical modeling of the data indicates that transport of these compounds was by simple diffusion. Extending in vitro findings to the in vivo environment, Linetal. used microneedles either only or in combination with iontophoresis to deliver 20-merphosphorothioatedoligodeoxynucleotidescrosswise the skin of hairless guinea pigs [22-28]. A related study further confirmed microneedle better delivery of desmopressin and human growth hormone using a similar advance.

Several new and exciting microneedle concepts have been recently proposed which may find great helpfulness in the future. For example, biodegradable polymer microneedles have recently been made-up and characterized. The advantage of polymer needles is that they may be produced much more inexpensively and they should not create a problem if they break-in the skin since they are biodegradable [29-32].

A novel micron-scale dip-coating process and a GRAS coating formulation were intended to consistently produce uniform coatings on both individual and arrays of microneedles. This processwas used to coat compounds with calcein, vitamin B, bovine serum albumin and plasmidDNA. Modified vaccinia virus and microparticles of 1 to 20 μm diameter were also coated.

NEW MICRONEEDLE INSPIRED BY MOSQUITO

Joint collaboration between the Indian Institute of Technology Kharagpur and Tokai University of Japan has resulted in a new hypodermic microneedle, which does not come with an iota ofpain. This is due to the fact that it was designed after a mosquito's unique micro-electromechanicalbased suction system. This new design has a diameter of 60 microns, which is waysmaller than a conventional needle that currently stands at 900 microns, and is hoped to bedeveloped further for use in glucose monitoring, blood draws, insulin pumps and other drug deliverydevices [33-35].

SALIENT FEATURES OF MICRONEEDLE DRUG DELIVERY TECHNOLOGY

- Rapid onset of action.
- Painless drug delivery system.
- Possible self-administration.
- Efficacy and safety comparable to approved Injectable products.
- Improved patient compliance.
- Good stability.
- Cost effective.
- Valuable source of intellectual property.

Applications of microneedle technology In a follow up study, Mc-Allister et al found a change in the permeability ofcadaver skin to insulin, latex nanoparticles and bovine serumalbumin after treatment with microneedles, Microneedle technology has been developed as a platformtechnology for delivery of high molecular weight andhydrophilic compounds through the skin. The firstever study of transdermal drug delivery by microarraytechnology was conducted by Henry et alwhodemonstratedan increase in the permeability of skin to a model compound calcein using microarray technology. In a follow up study, Mc-Allister et al found a change in the permeability ofcadaver skin to insulin, latex nanoparticles and bovine serum albumin after treatment with microneedles, and unleashed the mechanism of transport as simple diffusion.

APPLICATIONS OF MICRONEEDLE TECHNOLOGY

1. Oligonucleotide delivery

Lin and coworkers [36] extended the *in-vitro* findings ofmicroarray drug delivery to *in vivo* environment. An oligonucleotide, 20-merphosphorothioated oligodeoxynucleotide was delivered across the skin of hairless guineapig either alone or in combination with iontophoresis. Linand coworkers used solid microneedles etched from stainless steel or titanium sheet prepared with the poke with patchapproach. This delivery system increased the absorption ofthe molecules relative to the intact skin DNA vaccine delivery Mikszta et al [37]reported the delivery of a DNA vaccine using microneedle

technology prepared with the dip and scrapeapproach. The arrays were dipped into a solution of DNAand scrapped multiple times across the skin of mice *in vivo*.Expression of luciferase reporter gene was increased by2800 fold using microenhancer arrays. In addition, microneedle delivery induced immune responses werestronger and less variable compared to that induced by thehypodermic injections. Similar results were obtained byresearchers at Beckett-Dickinson™ in an animal study for antibody response to HepB naked plasmid DNA vaccine.This approach has a potential to lower the doses and thenumber of boosters needed for immunization.

2. Desmopressin delivery

M. Cormier et al (Alza Corporation, USA) examined the use of microneedles to deliver desmopressin, a potent peptidehormone used in the treatment of nocturnal enuresis inyoung children, as well as for the treatment of diabetes insipidus and haemophilia A. Microneedles were coated by an aqueous film coating of desmopressin acetate on titanium microneedles of length 200 µm, a maximal width of 170 µm and a thickness of 35 µm. Microneedle patch was inserted into the skin with the help of an impact applicator [38].

3. Insulin delivery

Insulin is one of the most challenging drugs of all times forthe drug delivery technologists. Martano et al, used microarrays for the delivery of insulin to diabetic hairless rats. Solid microneedles of stainless steel having 1mm lengthand tip width of 75 µm were inserted into the rat skin anddelivered insulin using poke with patch approach.

COMMERCIAL MICRONEEDLE TECHNOLOGIES

A decade after the first microneedles were reported, many commercial technologies have come into the market including the Macroflux technology, h-patch, Micro-Trans.

Macroflux transdermal technology: Macroflux technology (Macroflux® Corporation Inc.) expands the scope of microarray technology to a broader group of drugs, from synthetic drugs to therapeutic proteins as well as vaccines. The technology can be drug coated for direct administration or can be used in combination with iontophoresis. The technique employs a thin titanium screen with microprojections of precise dimensions. Thesemicroarrays can be dip or dry coated, wherein the drycoating may be utilized for bolus/continuous drug delivery [39].

ADVANTAGES OF MICRONEEDLES

The major advantage of microneedles above traditional needles is, when it is inserted into the skin it does not pass the stratum corneum, which is the outer 10-15 µm of the skin. This lead to high precision, good reproducibility, and a sensible fabrication cost [40].Hollow like hypodermic needle, solid increase permeability by poking holes in skin,rub drug over area or coat needles with drug. Arrays of hollow needles could be used to always carry drugs into the body using simple diffusion or a pump system.Very small micro-needles could give highly targeted drugs administration to individual cells. Inoculation programs in developing countries, or mass vaccination or administration of antidotes in bioterrorism incidents, could be applied with minimal medical training.

CONCLUSION

In this review, we suggest the novel process using dicing process with an inclined sharp edge to make the sharp shape of the micro-needle tips. And the optical inspection module is made for evaluating the drug delivering ratio according to the needle length and insertion times. This evaluation module has a water chamber and membrane to copy the drug delivery mechanism. We can find that the drug delivering ratio can increase when use the longer needle because the surface area with drug sticking can be increased.

REFERENCES

1. Langer R., Transdermal drug delivery: past, progress, current status, and future prospects, Advanced Drug Delivery Reviews, 2004, 56,557-558.
2. Gardeniers Han J.G.E., Regina Luttge, Berenschot Erwin J.W., de Boer Meint J., YeshurunShuki Y., Hefetz Meir, van'tOever Ronny and van den Berg Albert, Silicon Micro machined Hollow Microneedles for Transdermal Liquid Transport, Journal of Micro electromechanical System, 2003, 12, 6, 855-862.
3. Jung Hyu, Kim, Improvement of the clinical experiment which uses the Micro-needle and Galvanic Current Machine of skin condition, Master's Thesis, Sookmyung Women's University, 2008.
4. MartantoWijaya, Davis Shawn P., Holiday Nicholas R., Wang Jenny, Grill Harvinder S. and Prausnitz Mark R., Transdermal Delivery of

Insulin Using Microneedles in Vivo, Pharmaceutical Research, 2004, 21, 6, 947-952.

5. Han Manhee, Hyun Dong-Hun, Park Hyoun-Hyang, Lee Seung S., Kim Chang-Hyeon and ChangGyou Kim, A novel fabrication process for out-of-plane microneedle sheets of biocompatible polymer, J. MicromechMicroeng., 2007,17, 1184-1191.
6. Teo Ai Ling, Shearwood Christopher, Ng KianChye, Lu Jia, MoochhalaShabbir, Transdermal microneedles for drug delivery applications, Materials Science and Engineering B., 2006, 132, 151-154.
7. ALZA website, http://www.alza.com/, Retrieved.
8. McAllister D.V., Wang P.M., Davis S.P., Park J.H., Canatella P.J., Allen M.G., Prausnitz M.R., Microfabricated needles for transdermal delivery of macromolecules and nanoparticles fabrication methods and transport studies, Proceedings of the National Academy of Sciences of the United States of America, 2003, 100, 13755-60.
9. Chien Y.W., Transdermal controlled systemic medication, Marcel Dekker, New York, 1987.
10. Shaw J.E., Chandrasekaran S.K., Campbell P., Percutaneous absorption, Controlled drug delivery for topical or systemic therapy, J Invest Dermatol, 1976, 67, 677–678.
11. Bhattacharya A., Transdermal Drug Delivery Technologies, Pharmray, 1999, 10, 4-10.
12. Monkhouse D.C., Hug A.S., Transdermal drug delivery, Problems and promises Drug Dev.,Ind.Pharm., 1988, 145, 2-3,183-209.
13. Prausnitz M.R., Microneedles for transdermal drug delivery, Adv. Drug Deliv. Rev., 2004, 56, 581-587.
14. Gill H.S., Prausnitz M.R., Coated microneedles for transdermal delivery, J. Cont. Release, 2007, 117, 227-237.
15. Henry S., McAllister D.V., Allen M.G. et al., Microfabricatedmicroneedles, a novel approach to transdermal drug delivery, J Pharm Sci., 1998, 87(8), 922-925.
16. Rhodes WE http://www.drugdeliverytech. com/cgi-bin/articles.cgi
17. Kolli C.S. et al., Pharm Res., Article in press, 2007.
18. Micropiles.http://www.texmac.com/.../7-12-2004_Press_Release.html.
19. Park J.H., Allen M.G., Prausnitz M.R., Biodegradable polymer microneedles Fabrication, mechanics and transdermal drug delivery, Journal of Controlled Release, 2005, 104, 1, 51–66.
20. Stanleyand W., Jacob M.D., Structure and Function in Man, 2nd, Saunders, Philadelphia, 1970.
21. GuyR.H.,HadgraftJ.,BucksD.A.W., Xenobiotica, 1987, 17, 325-343.
22. Flynn G.L.,Bronaough R.L. &Mailback, In Percutaneous absorption,HI eds., Marcel Dekker Inc., New York, 1985.
23. Woodbourne R.T., Essentials of Human Anatomy, Oxford University Press, New York, 1965.
24. Lehninger A.L., Biochemistry, Worth Publisher, New York, 1977.
25. Jain Nilu, Talegonkar S., Jain N.K., The Pharm Rev., Sept-oct2004, 41-60.
26. Chien Y.W., Novel Drug Delivery System, Fundamentals development concepts & biomedical assessment, Marcel Dekker Inc., New York, Chapter-9, 1982.
27. Chien Y.W., Transdermal Drug Delivery and delivery System in Novel drug delivery Systems, Marcel Dekker, Inc., New York, 1993.
28. Higuchi T., Mechanism of sustained action medication.Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, J.Pharm. Sci., 1963, 52, 1145-1149.
29. Chien Y.W. and Lambert H.J., U.S. Patent No.3, March 23, 1976, 946.
30. Chien Y.W., Andeson J. and Kim S., Recent Advances in Drug Delivery System, Eds. Plenum Press, New York and London, 1984.
31. Barry B.W., Dermatological Formulations Percutaneous Absorption, Marcel Dekker, New York, 1983.
32. Mortazawi S.A., Reza A., Iranian J. Pharm Res., 2003, 135-140.
33. Barry B.W., Novel mechanisms and devices to enable successful transdermal drug delivery, EurJ. Pharm Sci. 2001, 14, 101-114.
34. Chappelow W.J., Yang J., Weimann J., Utrasound L., Med Biol., 1988, 24, 705- 710.
35. Schram J., Mitragotri S., Pharm Res., 2002, 19, 11, 1673-79.
36. Lin W. et al.,Transermal delivery of antisense oligonucleotides with microprojection patch (Macroflux) technology. Pharm. Res., 2001, 18, 1789-1793.

37. Mikszta J.A. et al., Nat Med., 2002, 8, 415-419.
38. Cormier M. et al., J Control Release, 2004, 97, 503-511.
39. Macroflux technology http://www.macroflux. com/b1.htm
40. Harpin V.A., Rutter N., Barrier Properties of Newborn Skin, J. Pediat., 1983, 102,419 -425.

*****