ISSN: 0975-766X
Review Article

Available Online through
www.ijptonline.com

MICRO NEEDLE PATCHES IN DRUG DELIVERY – A REVIEW

Dr. Prathima Srinivas*, Chede.Laxmi Shanthi, Dr.M.Sadanandam
Department of pharmaceutics, Sri Venkateshwara College of Pharmacy, Affiliated to Osmania University Madhapur, Hitech City, Hyderabad-500081, Andhra Pradesh, India.
Email: *drpssvcp@gmail.com*

Received on 19-08-2010 ***Accepted on 31-08-2010***

ABSTRACT:

Drugs are administered by using different drug delivery systems. A number of drug delivery systems have evolved over the years. In the last 20 years TDDS (Transdermal drug delivery system) has been growing at a rapid pace. Now the micro needles are being developed as a novel drug delivery system. The micro needle skin patch system is also a drug delivery system, which will be used transdermally.

The success of TDD has severely limited by the inability of most drugs to enter the skin at therapeutical useful rates. Thus, the use of micro-needle patches in increasing skin permeability has been proposed and shown to dramatically increase in transdermal delivery, especially for macromolecules. Using the tools of the microelectronics industry, microneedles have been fabricated with a range of sizes, shapes and materials. Most drug delivery studies have emphasized microneedles, which have been shown to increase the skin permeability to a broad range of molecules and nanoparticles *invitro*. This review briefly deals with types, mode of drug delivery, coating and applications of microneedle patches. Overall the microneedle skin patches are prone to be a very versatile drug delivery technology, allowing easy and reproducible delivery to skin.

Keywords: TDD (Transdermal drug delivery), Microneedles, Coated microneedle array, fabrication of microneedles**.**

INTRODUCTION:

Oral drug delivery of pills is the most common and convenient method, but is not always appropriate because drugs must survive the harsh environment of gastro intestinal tract and first pass metabolism of liver. More sensitive drugs including proteins are usually administered by hypodermic injection ,which avoids firstpass metabolism but causes pain and requires medical expertise .In addition, bolus delivery from conventional injections reduces the effectiveness of drugs that would benefit from controlled release overtime Therefore effectively transporting drugs into the body is a significant challenge [1].

An approach that is more appealing to patients and offers the possibility of controlled release overtime is drug delivery across the skin using a patch. Transdermal drug delivery system (TDDS) made great progress in this angle and several drugs like estrogen, nicotine and nitro glycerin are clinically applied as patch preparations [2]. However the skin has a strong function for permeation of other drugs, especially macro molecular drugs. To increase the skin permeability different methods like chemical enhancers, electric fields, ultra sound and thermal methods have been approached .However the application of these has been limited because of strong barrier function of the skin. Micro needle patches could be promising solution to tackle such problems [3,4,5].

Introduction to microneedles:

Micro needles are one of the recent advances in drug delivery which are similar to traditional needles, but are fabricated on the micron scale, the sizes range from 1- 100 microns in length and 1 micron in diameter. It is defined as micro-scale needles and are assembled on a transdermal patch .They are a combination between hypodermic needles and transdermal patches and are suitable to overcome the individual limitations of both injections and patches [6]**.** Micro needles have been proposed as a novel drug delivery system , these have been fabricated by adapting the tools of micro electronics industry to penetrate typically hundreds of microns into the skin in a painless manner. Relative to hypodermic needles micro needles have been to be painless in human subjects [7,8].

LACK OF PAIN CAUSED BY MICRONEEDLES:

A formidable barrier to transdermal drug delivery is the stratum corneum, the superficial layer of the skin .Micro needles were proposed as a mechanical tool to pierce through the stratum corneum , in order to create drug delivery channels without stimulating underlying pain nerves , and the other basic reason is stratum corneum do not have pain nerves. Conventional needles which pass this layer of skin effectively transmit the drug but may lead to infection and pain. On the other hand, micro needles can be fabricated such that they are long enough to penetrate the stratum corneum, but short enough not to puncture the nerve endings, thus reducing the chances of pain, injection or injury. Kaushik *et al* carried out a small trial to determine if microneedles are perceived as painless by human subjects [9].

REASON FOR EFFECTIVE RESPONSE THROUGH SKIN:

Skin is very sensitive organ of the body, and it represents the first immunological defense barrier to outside injury and has evolved into a major immune competent organ [10,11]. Foreign agents and antigens that penetrate the outer most stratum corneum encounter a defense network of potent antigen-presenting cells, the epidermal langherhans cells, and the dermal dendritic cells [12]. This will enable the drugs to produce a pharmacological response or effect on administration which is faster when compared to traditional methods of drug delivery These langherhan cells readily take up foreign antigens, and initiate antigen specific immune responses, The skin is therefore is an attractive target site for vaccine delivery, allowing the most effective immunization with the least amount of antigen [13-15].

A robust, practical cost effective convenient and efficient intracutaneous antigen delivery technology will have broad application in the field, especially if the delivery can be achieved by minimally invasive and pain less technique.

TYPES OF MICRONEEDLES:

Micro needles generally fall into one of the two design categories

1] Solid micro needles

2] Hollow micro needles

1] Solid micro needles:

Solid micro needles are essentially arrays of projections that are used to make holes in the stratum corneum and are sequentially removed before a drug is applied to the skin. They can be used to create micron scale holes in the skin through which molecules can easily transport [16].

Disadvantages over hollow microneedles:

- In case of solid microneedle arrays, the drug cannot readily flow through the holes in the skin because it remains plugged by the microneedles. This problem can be overcome by the deposition of a drug directly on the surface of these solid micro needles. However the deposition process is unreliable and the thin layer of drug formulation could be easily chipped off from the micro needle during storage, transport or administration of the micro needles
- Application of a thicker stronger layer of drug formulation was found to be the undesirable because it reduced the sharpness of the microneedles and therefore made insertion more difficult and painful.

2] Hollow micro needles:

Conventional hollow micro needles with a central bore are expensive to make and require exotic and expensive micro fabrication method .In particular it is difficult to make sharp tips on hollow micro needles

Advantages over solid microneedles:

- In contrast to solid micro needles discussed above microneedles containing hollow bore offer possibility of transporting drugs through the interior of well defined needles by diffusion or for more rapid rates of delivery by pressure driven flow.

According McAllister et al studies showed that single glass micro needles inserted into the skin of diabetic hairless rates in *vivo* to deliver insulin during a 30 minute infusion .This study demonstrated up to a 70 % drop in blood glucose level over 5 hour period after insulin was administered [17] .Smart and Subramanian used single microneedles to extract nanolitre quantities of blood from the skin to measure glucose levels [18]

DESIGN PARAMETERS:

In general terms the design parameters to be considered are:

- Microneedles should be capable of inserting into skin without breaking
- Polymers should be selected to have sufficient mechanical strength
- Biocompatibility
- They should not produce any pain
- Micro needle geometry is also important, where sharpness of tip strongly effects the microneedle insertion into skin [19,20]

PROPERTIES OF MICRONEEDLES:

1. **Ruggedness**: Microneedles must be capable of inserting into the skin without breaking .They are to be manufactured in optimal size parameters. If they are too long, upper portion of microneedles may not have enough flexural rigidity and could break off before penetration they must be able to withstand insertion force without buckling, delamination, or fracture.

2. **Controlled release**: The microneedles should be capable to deliver controlled amount of drug at specific rate

3. **Penetration**: The microneedles should be able to deliver the drug to the required depth in the tissues of the body

Painless insertions of micro needles into the skin can be accomplished by gentle pushing, using approximately 10 N forces. Microneedle geometry is also important, where sharpness of tip strongly affects the force required for the insertion into skin. Other parameters including microneedle length, width and shape also influence the force required for microneedle fracture [19, 20]

DIMENSIONS OF MICRONEEDLES:

The dimensions of micro needles can be different depending on their types .Typical microneedle geometries vary from 150-1500 microns length, 50-250 microns in base width, 1-25 microns in tip diameter. The tips of microneedles are in various shapes like triangles, rounded or arrow shaped [21]. The hollow microneedle arrays

are fabricated with lumen diameter of 30 micro meters. Height 250 micro meters. Centre to centre hollow micro needle array 150µm, The axis of lumen is fabricated with the distance of 10 micro meters to the axis of outside column.

MATERIALS FOR CONSTRUCTION:

1. Glass

2. Silicone (brittle nature)

3. Metals- Stainless steel, solid or coat of Gold over Nickel, Palladium Cobalt and Platinum

5. Bio- degradable polymers: if a tip snaps of while inserted, it will easily bio degradable

EFFECT OF MICRONEEDLE LENGTH ON PAIN:

Micro needles can also be designed to minimize pain. Initial studies showed that specific microneedles of a couple hundred microns length were reported painless [7,8]. Gill et al (2008) in the study carried out on the influence of length of microneedles on pain showed that a 3-fold increase in needle length (i.e., 500-1500 microns) increases pain by 7 fold (i.e., 5-35% caused by hypodermic needle. [22]**.** Keeping the length constant increase in number of microneedles (i.e., 620 micron long) 10 fold from 5- 50 also increased pain by a factor of 3 .Other geometrical parameters did not influence pain significantly [22].

Four different modes of microneedles based drug delivery is currently accepted according to the t modes are [23]

1. Piercing an array of solid micro needles into the skin followed by the application of a drug patch at a treated site [17,24].

2. Coating drug into micro needles and inserting them into the skin for subsequent dissolution of the coated drug within the skin [25].

3. Encapsulating drug within biodegradable polymer microneedles followed by insertion into skin for controlled drug release [26].

4. Injecting drug through hollow micro needles [27]

Among these approaches coated microneedles are attractive for a rapid bolus delivery of high molecular weight molecules into the skin and can be implemented as a simple band- aid like system for self administration. Further storing drugs in a solid phase as coating on micro needles may enhance their long term stability even at room temperature [28]. Among various coating processes such as dip coating, roll coating and spray coating dip coating is particularly appealing for coating micro needles because of its simplicity and ability to coat complex shapes. Dip coating has been developed to coat macroscopic objects mostly by submerging them completely within the coating solution because surface tension becomes dominant on the micron scale [29]

MICRO DIP COATING:

Micro needles were coated with different molecules like proteins, peptides and DNA using a novel micron scale dip coating process and a specially formulated coating solution [30] . For the coating of microneedles different drug molecules are used like proteins, DNA, peptides using the novel micron scale, dip coating process specially formulated solution that made for the coating

The Coating solution contains 1% (w/v) car boxy methyl cellulose sodium salt and 0.5% w/v – lutrol F- 68 NF and model drug like 0.01% suforhodamine, 0.01% calcein, 3% vitamin,*0.05%* luciferase ,10% barium sulphate particles,12% 10 µm diameter. DNA and virus were made fluorescent by incubating with YOYO- 1 (molecular probes) at a dye: base pair /virus in the ratio of 1:5 for 1 hr at room temperature in the dark [28]

Single microneedles were dip- coated by horizontally dipping the micro needle into 20 – 30 µliters of coating solution held as a droplet on the tip of a 200 micro liter large orifice pipette tip. Whereas for coating rows of micro needles they were dip coated using an in house designed. The coating device consisted of two parts 1.coating solution reservoir 2. Micro positioning dip coater [28]

MICRONEEDLE ARRAY PATCH:

To facilitate their insertion and retention into the skin, arrays of microneedles were integrated into adhesive patches comprised of a low-density Polyethylene backing with a Poly isobutylene adhesive. These patches were designed to have a uniform pressure- sensitive adhesive layer on one complete side of the patch intended to

contact the skin. The adhesive layer was periodically disrupted via small holes or slits to allow the microneedles to stick out for penetration. The adhesive served to hold the microneedles firmly against the skin by compensating for the mechanical mismatch between the flexible skin tissue and the rigid microneedle substrate ,especially in case of out of plane microneedles (i.e., which are bent at 90^0) .The final system for Desmopressin delivery coated onto microneedles had a patch area of 5.3 cm^2 , including the 2cm^2 microneedle array. The patch was loaded onto a disposable retainer ring [31].

APPLICATIONS:

1. **Blood glucose measurements**:

Hollow micro needles are used to withdraw blood samples about (very small volume less than 100 nl) into the disposable that immediately flows into the needle into a tiny reservoir and reacts with chemicals to produce read out of blood glucose level [32]

2. Human clinical trials by Zozano pharmaceuticals (Free mont , CA, USA) has completed phase II clinical trials for delivery of parathyroid hormone from coated micro needles [33].

3. Microneedle patches have been used to penetrate vessel walls, of normal and atherosclerotic rabbit arteries *in vitro* demonstrating potential use for targeted delivery of anti restenosis drugs [34]

4. Insulin delivery “poke with patch” technique has been tried for transdermal drug delivery which has reduced glucose levels to about 80% within 4 hours [35].

5. Desmopressin is a synthetic peptide hormone chiefly used for treatment of eneuresis in young children. It is available in the form of injectable, intra nasal and oral formulation. Administration by injection is not advisable for a routine use in children. Intra nasal and Oral administration results in low and variable bio availability of desmopressin. If administered transdermally by using micro needle patch 0f 2cm× 2cm array the bioavailability was found to be 85% and peak levels in serum reached after 60 min.Only 10 % of the drug was found on the skin surface after application [31].

6. Immunization and vaccination:

Immunization programs in developing countries or mass vaccination or administration of antidotes in bioterrorism incidents, could be applied with minimal medical training. Immunization to the model antigen ovalbumin was investigated using a novel intra cutaneous delivery system consisting of antigen coated microneedle arrays .Vaccination delivery of influenza vaccine via microneedle patches elicited immune responses comparable to or better than intramuscular injection in mouse model [36].

Immunization to the model antigen ovalbumin was investigated using a novel intra cutaneous delivery system consisting of antigen coated microneedle array patch system[37]

7. Molecular and cell biology:

Micro needles have been applied for the delivery of membrane impermeable molecules into cells for application in molecular cell biology, methods for the delivery of peptides , proteins , olio nucleotides , DNA and other probes that alter or assay cell function is desired . Arrays of micro needles were fabricated and utilized to deliver DN into plant and mammalian cells ,as a method for transforming cells

8. Micro needle skin therapy:

Micro needle skin therapy is the most recent application to rejuvenate skin without damaging the epidermis. It is similar to laser treatment and with minimal surgical intervention. Micro needles can penetrate the epidermis .The old collagen strands are destroyed and new collagen is recreated under the epidermis due to the new collagen the ageing symptoms are clearly masked and skin looks young .

9. Acne Treatment:

Dissolvable microneedle patches have been successfully demonstrated in the treatment of acne and has shown promising results in the first 24 hrs of use. There is rapid intradermal drug delivery by the micro needle patch. (The versatile theraject MAT, dissolvable micro needle path contains API in an inert GRAS matrix .The system can deliver hundreds of µg of API rapidly through the stratum corneum into epidermal tissue . Thus microneedle patch technology can be applied effectively for various cosmetic applications [38].

EVALUATION:

In-Vitro Testing of Microneedles

In vitro tests for microneedles are performed by using various mediums like agarose gel and methanol to insert microneedles. The porcine cadaver skin and skin of various animals are also used for the *in vivo* testing of the microneedle by using Rhodamine B solution, black ink as a test solution, insulin and bovine serum albumin. The In vitro tests are used to determine various properties of new test device or compound.

The main key objectives of the In vitro testing of microneedles are as follows.

Key objectives

1. Optimization of the microneedles
2. To find out penetration force and bending force of microneedles
3. To evaluate strength of microneedle
4. To determine the dissolution rate of coating material
5. Estimate the efficiency of drug delivery.

Method 1

The delivery efficacy of the microneedles has been tested by in-vitro methods. In this test the microneedles are integrated with Paradimethylsiloxane (PDMS) biochip and black ink is injected by the microneedles into the petridish, which contains methanol. The right triangle microneedles with 8.5 and 15 tip taper angles and isosceles triangle microneedles with 9.5 and 30 tip taper angles have been used for this purpose [39].

Method 2

In this In vitro method, the diluted Rhodamine B dye is injected into the 1% of agarose gel through the microneedles to determine the penetration and flow of the solution after penetrating into the 1% agarose gel. Even in this method, the right triangle microneedles with 8.5 and 15 taper angles and isosceles triangle microneedles with 9.5 and 30 tip taper angles have been used for this purpose [40].

Method 3

Inserting microneedles into the porcine cadaver skin and pig cadaver skin for 10s to 20 s and 5 minutes respectively performs this method. This method is used to determine the delivery efficacy, dissolution rate of the coated material, which is coated on the microneedle tip. The microneedles are coated with vitamin B, calcein or sulforhodamine for this method [39]

In-Vivo Testing of Microneedles

For the in-vivo preclinical evaluation, generally used like mice, rabbits, guinea pigs, mouse and monkey are used. The main purpose of the In vivo tests is the assessment of safety as well toxicity of the test compound or device. There are at least two species of animals used *in vivo* preclinical study for determination of different kind of toxicity concerning with microneedles.

The key objectives of the In vivo testing of the microneedles are as follows.

Key Objectives

1. To perform skin toxicity test.

2. To determine penetration force in different skin.

3. To determine mechanical stability of microneedle.

4. To determine bending breakage force.

5. To perform various non-clinical safety study and pharmacological study.

6. To determine various parameters like immunogenicity, genotoxicity, skin sensitization and allerginisation study, developmental toxicity, acute and chronic dermal toxicity, carcinogenicity.

Method 1

In this *In vivo* method employs testing microneedles, by pricking microneedles into tail vein of the mice in laboratory hairless mice. This method is used for the determination of the penetration force of the microneedle into the skin [39].

Method 2

In this method for the *In vivo* testing of the microneedles, the Rhodamine B is given into laboratory mouse-tail and anaesthetized rabbit ear for the determination of penetration, penetration force and bending breakage force [40]

Method 3

This method has been performed for a vaccine delivery by using microneedles. In this method ovalbumin as a model protein antigen was administered into hairless guinea pig by using solid metal microneedles at the rate of 20µg ovalbumin in 5s up to 80 µg [41].

Method 4

This method was used for a vaccine delivery through microneedles. In this method rabbits have been were used. The anthrax vaccine that contains recombinant protective antigen (rPA) of Bacillus anthracis has been administered (lethal aerosol dose of anthrax spores) in the rabbits by using solid and hollow microneedles [40].

CONCLUSION:

Micro needle patches are novel delivery systems with varied applications in the delivery of drugs through skin. Given the delivery in their use, these patches are currently a promising delivery system for various types of drugs. These painless systems are slowly gaining importance and would qualify to be one of the important devices for controlled drug release in future.

REFERENCES:

1. Langer,R., Drug delivery and targeting nature 392, 5-10 lin, L.,Pisano, AP., Silicone processed micro needles. IEEE Journal of micro mechanical system 8, 1999,78-84.
2. Asmussen, B., Transdermal therapeutic system actual state and future developments. Methods Find EXP clinical pharmacol 8, 1991, 343-351.
3. cormier, M.,Johnson, B.,Ameri, M.,Nyam, etal .Transdermal delivery of desmopressin using a coated microneedle arraypatch system.J. contol. Release.,97,2004,503-511

4. Davis, S.P., Martanto, w.,allen, M.G.,prausnitz,M.R., Hollow metal microneedles for insulin delivery to diabetic rats.IEEE Tans.Biomed Eng.52,2005,900-950.

5. Park,J,H.,Allen, N.G.,Prausnitz.,M.R.Polymer microneedles for controlled release drug delivery .Pharm.Res 23,2006,1008-1019.

6. M.Prausnitz , J.Mikszta ,J.Reader –Dvens , in E.smith, H.Maibach(eds) ,Percutaneous penetration enhancers, CRC,press Boca Ralon Fl, 2005 , PP 239- 255.

7. S.Kaushik, A.H.Hord, D.D.Denson , D.v.Mc allister , S.Smitra M.G.Allen, M.R.Prausnitz, lack of pain assosciated with micro fabricated microneedles, Anesth, Analg 92 (2)(2001)502-504.

8. J.A.Miktszta , J.B. Alarcon, J.B.Alarcon , J.B. Brittingham , D.E.sutter, R.J.Pettis , N.G.Harvey, improved genetic immunisation via micromechanical disruption of skin-barrier function and targeted epidermal delivery , Nat Med 8(4)(2002)415-419.

9. S.Kaushik, A.H. Hord, D.D. Denson, D.V. Mc Allister ,S.Smitra, M.G.Allen, M.R.Prausnitz ,Lack of pain associated with microfabricated microneedles, Anesth. Analg.92,2001,502-504.

10. Boss JD.Skin immune system (SIS) cutaneous immunology and clinical immune dermatology.New York : CRC press 1981.

11. Fichtelius KE, groth O, Leiden S.The skin , a first level lymphoid organ ? int arch allergy appl immunol 1970; 37: 607-620.

12. YURC,Abrams Dc, Alaibac M, chu AC. Morphological and quantitative analysis of normal epidermal Langherhans cells using confocal scanning laser microscopy ,Br J. Dermatol 1994 ; 131:843-8.

13. Mark R.Prausnitz, microneedles for transdermal drug delivery advanced drug delivery reviews 56(2004) 581-587.

14. D.V. Mc Allister , P.m. Wang , s.p. Davis , J.H.Park , M.G. Allen ,M.R.Prausnitz, Micro fabricated needles for transdermal of macromolecules and nano particles:novel fabrication methods and transport studies, submitted for publication.

15. W.H.Smart, K.Subramanian, The use of silicon microfabrication technology in painless blood glucose monitoring technology.ther2(2000)549-559.

16. S.Hashmi , P.Ling ,G.Hashmi ,M.Reed ,R.Gaugler,w.Trummer ,Genetic transformation of nematodes using arrays of micro mechanical piercing structures , BioTechniques 19 (1995) 766-770.

17. Harvinder S.Gill, Mark R. Prausnitz , coated microneedles for transdermal delivery , Journal of contolled release 117(2007)227-237.

18. D.J.Bebe ,G.A. Mensing, G.M. Walker , Physics and applications of microfluids in biology , Annu Rev Biomed Eng 4(1) (2002) 261-286.

19. Davis, S.P., Landis, B.J., etal ., Insertion of microneedles into skin : Measurement and prediction of insertion force and needle fracture force .J.Biomech. 37, 2004, 1155-1163.

20. Park,J.H., Allen, M.G.,et al., Biodegradable Polymer microneedles : fabrication, Mechanics and transdermal drug delivery .J. Control Release 104, 2005, 51-66.

21. Moon, Sang-Jun and Lee S.S; Fabrication of microneedles array using inclined LIGA process ; June 2003,1546-1549.

22. Gill,H.S., Prausnitz ,M.R., Effect of microneedle design on pain in human subjects.clin.J.Pain 24,2008,585-594.

23. M.Prausnitz, J.Mikszta, J.Reader-Devens, in; E.Smith, H.Maibach (EDS) Percutaneous penetration enhancers Boca Raton,FL, 2005, 239-255.

24. W.Martano, S.P.Davis, N.R.Holiday et al., Transdermal delivery of insulin using microneedles invivo, Pharm Res .21(6)2004,947-952.

25. M.Cormier, B.Johnson, M.Ameri K.Nyam et al Transdermal delivery of Desmopressin using a coated microneedle array patch system,J.Control Release 97(3)2004,503-511.

26. J.H.Park, M.G.Allen , Prausnitz, Polymer microneedles for controlled release drug delivery ,Pharm res.23(5)2006,1008-1019.

27. J.D.Zahn, N.H.Talbot , D.Liepmann, A.P.Pisano, Micro fabricated polysilicone microneedles for minimally invasive biomedical for minimally invasive biomedical devices, Biomedical devices, Biomed, Microdevices 2(2000) 295-303.

28. Harvinder S.Gill, Mark R. Prausnitz, coated microneedles for transdermal delivery, Journal of controlled release 117(2007)227-237.

29. D.J.Bebe ,G.A. Mensing, G.M. Walker , Physics and applications of microfluids in biology , Annu Rev Biomed Eng 4(1) (2002) 261-286.

30. G.P.Bierwagen, film coating technologies and adhesion, electrochim Acta 3s7(9) (1992)1471-1478.

31. Michel cormier, Bonny Johnson, Mohmoud Ameri ,Kofi Nyam , Transdermal delivery of desmopressin using a coated micro needle array patch system 97(2004)503-511.

32. Weber A, Medical device makers push new frontiers, assembly magazine, Jan 2004,1-8.

33. Anubhav Arora , Mark R.Prausnitz , samir Mitragotri , micro-scale devices for transdermal drug delivery, International Journal of pharmaceutics 364(2008)227-236.

34. Mc.Allister DV, Allen MG and Prasnitz MR.Microfabricated microneedles for gene and drug delivery Ann .Rev. Biomed.Engg.2, 2000, 289-313.

35. W.Martano, S.Davis, N.Holiday, J.Wang, H.Gill, M.Prausnitz, Transdermal delivery of insulin using microneedles in vivo, Proceedings of International Symposium on controlled Release Material, No 666,2003.

36. George Widera , Juanita Johnson, Lomikim , kofinyam effect of delivery parameters on immunization to ovalbumin following intracutaneous administration by a coated microneedle array patch system vaccine 249(2006) 1653-1664.

37. Alarcon, J.B.Hartley, A.W., et al ., Preclinical evaluation of microneedle technology for intradermal delivery of influenza vaccines. Clinc. Vacc.Immunol.14, 2007, 375-381.

38. A.Kasprowicz, L.Krowczynski; R. Jachowicz and A.Bialeeka, Erythromycin and Penetrating agents containing ointment in acne vulgaris therapy, pol J.Pharmacol pharm 40(5),1988,465-469.

39. Paik SJ, Lim JM, Jung I,Park Y ,Byun S, Chung S et al " A novel microneedle array integrated with a PDMS biochip for micro fluid system" TRANSDUCERS Solid-State Sensors, Actuators and Microsystems ,2,2003,1446-1449.

40. Paik SJ, Byuna S, Lima JM,Park Y,Lee et al., single-crystal-silicone microneedles for minimally invasive microfluid systems" sensors and Actuators A 114,2004,276-284.

41. Smith E.W, Maibach H.I; The textbook of Percutaneous Penetration Enhancers; 2nd edition,2006, 252-253.

Corresponding author
Dr. Prathima Srinivas*,
Email : *drpssvcp@gmail.com*