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Review Article

ADVANCEMENT IN TRANSDERMAL DRUG DELIVERY SYSTEM : MICRONEEDLES

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ABSTRACT

One of the thrust areas in drug delivery research is transdermal drug delivery systems (TDDS) due to their characteristic advantages over oral and parenteral drug delivery systems. Researchers have focused their attention on the use of microneedles to overcome the barrier of the stratum corneum. Microneedles deliver the drug into the epidermis without disruption of nerve endings. Recently, the use of micron-scale needles in increasing skin permeability has been proposed and shown to dramatically increase transdermal delivery, especially for macromolecules. Using the tools of the microelectronics industry, microneedles have been fabricated with a range of sizes, shapes and materials. The objective of present review is to focus on the recent advancement in transdermal drug delivery which can serve as a platform for the newer research and development of pharmaceuticals drug dosage form for efficient transdermal drug delivery. This review describes various facets of microneedles a transdermal drug delivery in relation to its type, advantage, disadvantages, mechanism of drug action, methodology of drug release, fabrication, characterization, evaluation, pharmaceutical applications and future perspective in drug delivery.

Key words: *Microneedle, Transdermal Drug Delivery System, fabricated .*

INTRODUCTION

Rationale for giving a drug transdermally has to be driven by an unmet medical need that can be met by this route, thus adding value to a drug therapy. For example, stable plasma level time profiles over extended time periods may reduce not only the dosing frequency, but possibly also side effects of the medication and daily doses that have to be administered by other routes. As transdermal drug administration is an easy, painless, and convenient mode of application, patient compliance for this route is in general high, especially in elderly and young people and patients groups who have difficulties swallowing or who are suffering from nausea or emesis.

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But the stratum corneum (SC), the main diffusion barrier of the skin, Antigen presenting cells of viable epidermis reporting to the immune system like Langerhans cells and also cells filtering UV radiation or forming a barrier against chemicals, Immune and inflammatory cells of the dermis which react on any mechanically or chemically induced irritation, like the mast cells. If the outermost skin layer has to be interrupted by microneedles or laser beams, location of nerve endings in the dermis has to be considered as well. Drug candidate must have high lipophilicity (ideal log PO/W ≈ 2), Low molecular weight (ideally below 500 Dalton), Low melting point (ideally below 150 °C), Sufficient solubility in water at pH 6 to 7.4 (e.g., ≈ 0.05 to 1mg/ml if target delivery rate is in the mg range per day), Suitable pKa (determines solubility of the un-ionized form at physiological pH) and appropriate solubility parameter (measure of cohesion energy of the unionized form) (ideally about 18-22MPa$^{0.5}$). All ingredients of the device have to be well tolerated by the skin, systems has to promote drug partitioning into and transport across the skin layers, to maintain drug

activity gradient across the skin nearly constant over the intended application time and to assure a high drug depletion rate from system[1].

So, to enhance the penetration across the skin, various methodologies were developed. These are use of various physical and chemical enhancers, development of new physical techniques such as electroporation, sonophoresis, iontophoresis, microneedles etc. The relative importance of these alternatives depends on many factors that include the time-scale of permeation (steady-state vs. transient diffusion), the physicochemical properties of the penetrant (its pKa, molecular size, stability and binding affinity, and its solubility and partition coefficient), integrity and thickness of the stratum corneum, density of sweat glands and follicles, skin hydration, metabolism, and vehicle effects. Stratum corneum forms highly lipophilic membrane and provides the greatest resistance to penetration of drugs. Thus, the major aim behind the development of transdermal systems is to cross the stratum corneum. The related innovations in the field of research of drug delivery systems have not only resulted in the successful implementation of the novel pharmaceuticals, but also leads to the development of new medical devices with the existing drugs. The designing of transdermal delivery system is one of the most innovative approaches in this aspect, with numerous advantages associated with this. Transdermal drug delivery has made an important contribution to the medical practice, but still more developments are needed to achieve the target of this system as an alternative to oral drug delivery as well the use of hypodermic injections. First generation Transdermal system has gained increment in delivering the low dose of lipophilic drugs for clinical use, whereas second generation delivery systems which used chemical enhancers, non-cavitational ultrasound and iontophoresis have also used in some clinical implications. The third generation delivery systems focussed on targeting the stratum corneum by using microneedles, thermal ablation, electroporation, microderma abrasion etc. Microneedles are one of the recent approaches which are currently designing through clinical trials, in the delivery of macromolecules and vaccines like insulin, parathyroid hormone, and influenza vaccine. The present review currently focuses on the use and development of microneedles as an enhancement strategy for transdermal drug delivery which significantly enhance the impact of drug delivery via transdermal route. From the past ten years, microneedles were proposed as a mechanical carrier which pierces through the stratum corneum to create pores for the drug delivery without stimulating the pain nerves. Since then, this system has been emerged as potential carriers for transdermal applications [2,3,4,5,6,7]

MICRONEEDLES

Microneedle, a microstructured transdermal system, consists of an array of microstructured projections coated with a drug or vaccine that is applied to the skin to provide intradermal delivery of active agents, which otherwise would not cross the stratum corneum(8). Microneedles are somewhat like traditional needles, but are fabricated on the micro scale. They are generally one micron in diameter and range from 1-100 microns in length. Microneedles have been fabricated with various materials such as: metals, silicon, silicon dioxide, polymers, glass and other materials. It is smaller then hypodermic needle, the less it hurts when it pierces skin and offer several advantages when compared to conventional needle technologies. The major advantage of microneedles over 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. 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 to penetrate the stratum corneum, but short enough not to puncture nerve endings. Thus reduces the chances of pain, infection, or injury(9). Various types of needles have been fabricated as well, for example: solid (straight, bent, filtered), and hollow. Solid microneedles could eventually be used with drug patches to increase diffusion rates; solid-increase permeability by poking holes in skin, rub drug over area, or coat needles with drug. Hollow needles could eventually be used with drug patches and timed pumps to deliver drugs at specific times. Arrays of hollow needles could be used to continuously carry drugs into the body using simple diffusion or a pump system. Hollow needle can withdraw body fluid for analysis – such as blood glucose measurements – and to then supply microliter volumes of insulin or other drug as required. The hollow needle designs include tapered and beveled tips, and could eventually be used to deliver microliter quantities of drugs to very specific locations. The researchers demonstrated that an array of 400 microneedles can be used to pierce human skin delivering drug macromolecules. Very small microneedles could provide highly targeted drug administration to individual cells. These are capable of very accurate dosing, complex release patterns, local

delivery and biological drug stability enhancement by storing in a micro volume that can be precisely controlled[10,11]

Types of microneedles

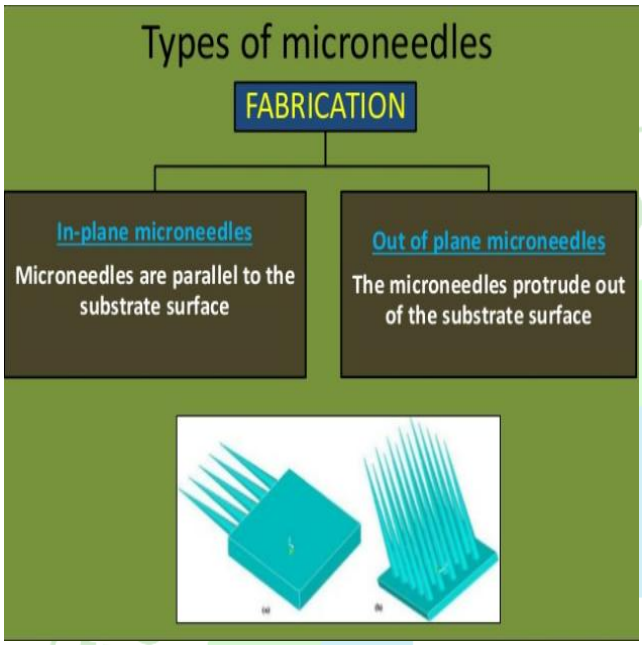

Figure 1: Classification on the basis of fabrication.

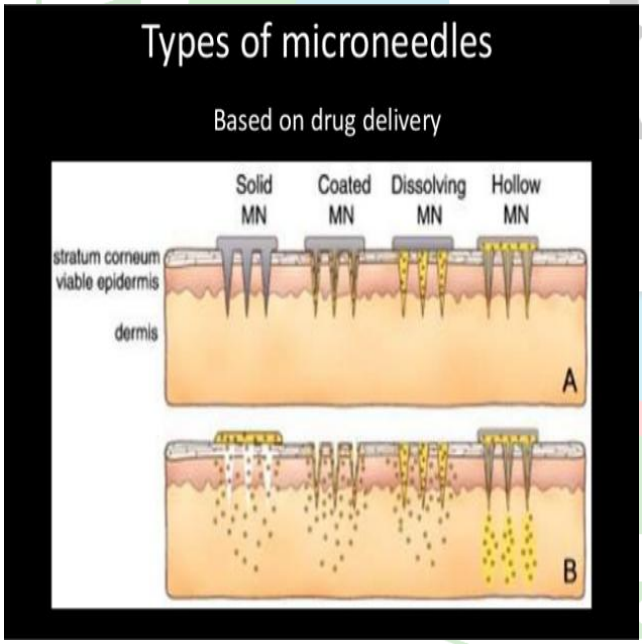

Figure 2: Classification on the basis of drug delivery.

Microneedles are classified on the basis of fabrication (Fig.1) and on the basis of drug delivery (Fig.2)[12]. But are broadly classified into two types mainly these are Solid micro needles and Hollow micro needles.

Solid Microneedles –

Solid micro needles are defined as the arrays of projections that are employed for creating holes in stratum corneum and are applied before the application of a drug and then removed afterwards. These can essentially create micron scale holes in the skin, through which drug molecules can easily enters. These can be used by inserting the needles into the skin for specified time period. The micro channels developed by the insertion of micro needles promote the drug transport in to the viable epidermis. Solid micro needles can be prepare by coating with the drug and then inserted into the skin. After removal of the micro needle containing device, drug will remain deposited within the skin membranes. Erodible micro needles when inserted into the skin, dissolves and the drug can easily be loaded into the soluble needles. These microneedles can pierce through the superficial skin layers then followed by the delivery of drugs. It also suffers from some limitations such as in solid microneedle arrays, the drug delivered cannot easily flow via the holes present in the skin because it remains plugged by the microneedles. An application of a thick layer of drug formulation was not found to be the desirable because it reduces the sharpness of the microneedles and therefore made insertion more difficult and painful.

Hollow Microneedles –

Hollow microneedles contain a hollow bore in the centre of the needle. When inserted into the skin, the hollow bore present bypasses the stratum corneum layer of the skin and produces a direct channel into the other lower layers of the epidermis. These microneedles are mainly employed to inject the drug solutions directly into the skin These are very expensive to prepare and require expensive micro fabrication techniques. These micro needles contains hollow bore which offers possibility of transporting drugs through the interior of well defined needles by diffusion or for more rapid rates of delivery by pressure driven flow[7].

Advantages of Microneedles

The advantages of microneedles are: (1) large molecules can be administered, (2) painless administration of the active pharmaceutical ingredient, (3) first-pass metabolism is avoided, (4) faster healing at injection site than with a hypodermic needle,(13,14,15) (5) no fear of needle, (6) ease of administration, (7) decreased microbial penetration as compared with a hypodermic needle, the microneedle punctures only the epidermis, (8) specific skin area can be targeted for desired drug delivery, (9) enhanced drug efficacy may

result in dose reduction, (10) good tolerability without long-term oedema or erythema, (11) rapid drug delivery can be achieved by coupling the microneedles with an electrically controlled micropump, and (12) the rate of drug delivery can be controlled more effectively by this system as compared with drug delivery via the stratum corneum.

Disadvantages of Microneedles

The disadvantages of microneedles are: (1) dosage accuracy may be less than with hypodermic needles, (2) careful use of the device may be needed to avoid particles 'bouncing off' the skin surface; if the device is not held vertically, the dose may escape or can penetrate the skin to differing degrees, (3) the thickness of the stratum corneum and other skin layers varies between individuals and so penetration depth of particles could vary too, (4) the external environment, like hydration of the skin, could affect delivery, (5) repetitive injection may collapse the veins, (6) the tip of the microneedle may break off and remain within the skin on removal of the patch, (7) a small amount of drug (less than 1 mg) can be given by bolus, and (8) compressed dermal tissue can block hollow microneedles.

Mechanism of Action

The mechanism for delivery is not based on diffusion as it is in other trandsermal drug delivery products. Instead, it is based on the temporary mechanical disruption of 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, in the form of biomolecules, is encapsulated within the microneedles, which are then inserted into the skin in the same way a drug like nitroglycerine is 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 substance is left behind 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 μm of the skin), thus allowing the drug to bypass this important barrier. The tiny needles are constructed in arrays to deliver sufficient amount of drug to the patient for the desired therapeutic response[16,11].

Methodology of Drug Delivery

A number of delivery strategies have been employed to use the microneedles for transdermal drug delivery. These include

Poke with patch approach

Transport of drug across skin can occur by diffusion or possibly by iontophoresis if an electric field is applied.

Coat and poke approach

In this approach needles are first coated with the drug and then inserted into the skin for drug release by dissolution. The entire drug to be delivered is coated on the needle itself.

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.

Dip and scrape

Dip and scrape approach, where microneedles are first dipped into a drug solution and then scraped across the skin surface to leave behind the drug within the microabrasions 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 microabrasions. Unlike microneedles used previously, this study used blunt-tipped microneedles measuring 50– 200 μm in length over a 1 cm2 area[17,11].

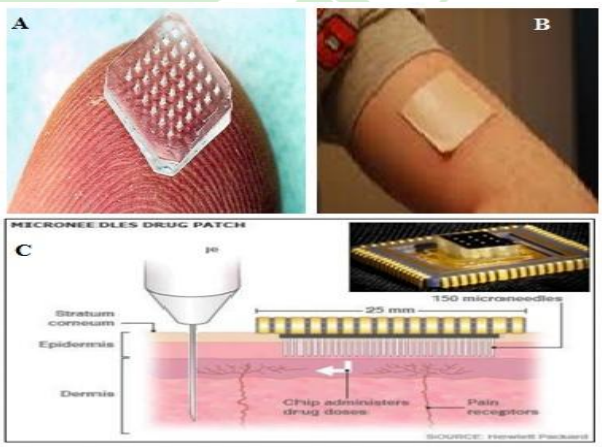

Fig 3: (a) Microneedles (b) Patches (c) Penetration through skin by syringe and patches

Fabrication of Microneedle

Microneedles can be fabricated employing microelectro mechanical systems (MEMS). The basic process can be divided in to three parts: deposition, patterning and etching. Microneedles have become a new type of the bio-medicine injector, it can throw the cuticle and not excite the nerve, and the patient will feel nothing.

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 into a photosensitive material by selective exposure to a radiation source such as light. This process can be 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, 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

Dissolving microneedles are fabricated on the basis of the "poke and release" principle. They are made from polysaccharides or other polymers. These microneedles release encapsulated drug into the skin following application and dissolution. Micromoulding is the preferred fabrication method for making dissolving microneedles. Certain drugs and vaccines are thermolabile so moulds are often filled with solutions of drugs and excipients and then dried under mild conditions. The fabrication process involves pouring the polymer solution into female molds, filling the microcavities of the mould under vacuum or pressure, drying under ambient conditions, centrifugation or pressure. These include the one-step application process which is convenient for patients. Example of this procedure is microneedles were fabricated by a photolithographic method. Briefly, PEGDA containing 0.5% v/v of 2-hydroxy-2-methyl propiophenone, hereinafter referred to as "prepolymer" solution, was exposed to a high intensity (20.9 W/cm^2) ultraviolet light source (Exfo Omnicure, Quebec, Canada) to form the backing layer. In a similar step, the prepolymer solution was pipetted onto this backing layer and exposed to ultraviolet light through a specifically patterned photomask. The microstructures thus formed, due to preferential exposure of the prepolymer solution in transparent regions of the photomask, represented micron-sized rods, defined as "microneedles". Excess unpolymerized prepolymer solution was washed away using purified water and the microneedles left to dry in air. The geometric characteristics of the microneedles (length, base, and tip diameter) were studied using an SMZ-1500 stereomicroscope (Nikon, Tokyo, Japan). [18, 20 & 21].

Coated microneedles refer to microneedles which are process to form uniform coating and limit deposition onto microneedle, avoid high temperature, high coated with the drug-containing dispersion. It is an approach using electrohydrodynamic atomization (EHDA) principles in the preparation of smart microneedle coatings. Essential characters of coating - drug loading, good adhesion of coating solution, aqueous coating solution, rapid or controlled dissolution kinetics.

Characteristics of microneedles

- Ruggedness: Must be able to withstand the insertion force without being fractured
- Penetration: Must penetrate the drug to required depth in the tissues.
- Dimensions: Length 100-900 microns
  Base width 50-30 microns
  Tip Diameter 1-50 microns
- Margin of Safety: It is defined the margin of safety as the ratio between the force required for piercing the Stratum corneum and the force at which microneedles broke.
  If the ratio is <1 then microneedle array can be used in biomedical application.
- Effect of the length of microneedle on pain: The designing of microneedles can be such so as to minimize the pain. Increment in needle length (i.e. 500-1500 microns) increases the pain. An increase in number of microneedles from 5-50 also increase the pain.
- Transepidermal Water loss : It is determined using diffusion cell, intact animal skin and probes that measure TEWL before and after application of microneedles.
- Biological Safety test: Extract chemical from microneedles by immersing them in

physiological saline and apply on intact human skin[12].

- Shape:

Figure 4: Different shape of Mironeedles

Evaluation of Microneedles

- In vitro evaluation – The in vitro evaluation is carried out to determine optimization of microneedles, penetration force, strength of microneedles, delivery efficacy etc.
- In vivo evaluation – The in vivo preclinical evaluation of microneedle was performed on animals like mice and guinea pig in order to determine the delivery efficacy, penetration force, bonding force, and to evaluate the skin toxicity tests using vaccine delivery[19].

Applications of Microneedles

- Cellular delivery
- Insulin delivery
- DNA vaccine delivery
- Desmopressin delivery
- Protein vaccine delivery
- Transdermal drug delivery
- Local tissue delivery
- Systemic delivery
- Microneedle skin therapy

Future perspectives

- Encapsulation of microneedle for oral insulin delivery
- Immunization programs
- Mass vaccination
- Administration of antidote in bioterrorism incidents
- Removal fluids from body[20]

CONCLUSION

Transdermal drug delivery system is an emerging area for systemic as well as local delivery of macromolecules. The biggest drawback of TDDS is poor permeability through stratum corneum and it can be overcome by using microneeddles. Researchers focused their attention on development of different types of microneedles for delivery of proteins, peptides, immunobiological, drugs, cosmetics as well as biofluidic analysis. Microneedles provides devices that are smaller , cheaper, pain-free and convenient method of delivering therapeutics.

REFERENCE

1. *Wolff H. M., Future of Transdermal Drug Delivery Systems (TDDS), American Pharmaceutical Review, 2014* .
2. *Baheti S.R., Wdher K.J., Umekar M.J., A recent approach towards transdermal drug delivery by physical and chemical techniques, Int Pharm Sci 2011; 1:1: 42-53.*
3. *Sivamani R. K., Liepmann D., Maibach H.I. Microneedles and transdermal applications. Exp Opin Drug Del 2007; 4:1: 19-25.*
4. *Chandel A.M., Patil V., Goyal R., Dhamija H., Parashar B., Ethosomes: a novel approach towards transdermal drug delivery, Int J Pharm Chem Sci 2012; 1:2: 563-569.*
5. *Prausnitz M.R., Microneedles for transderml drug delivery, Adv Drug Del Rev 2004; 56: 581-587.*
6. *Prausnitz M.R., Langer R., Transdermal Drug delivery, Nature Biotechnol 2008; 26: 1261-1268.*
7. *Akhtar N., Microneedles: An Innovative Approach To Transdermal Delivery- A Review, International Journal Of Pharmacy And Pharmaceutical Sciences 2014; 6:4.*
8. *Henry S., McAllister D., Allen M.G., Prausnitz M.R., Microfabricated microneedles, J. Pharm. Sci. 1998; 87: 922–925.*
9. *Hashmi S., Ling P., Hashmi G., Reed M., Gaugler R., Trimmer W., Genetic transformation of nematodes using arrays of micromechanical piercing structures, BioTechniques 1995;19: 766–770.*
10. *S.Kaushik, A.H.Hord, S.Smitra, M.R. Prausnitz, Lack of pain associated with microfabricated microneedles. Anesth. Analg 2001; 92: 502–504.*
11. *Jaydeep D., Yadav, Kumar A., Vaidya, Priyanka R., Kulkarni, Rajvaibhav A., Raut. Microneedles: Promising Technique For Transdermal Drug Delivery, International Journal of Pharma and Bio Sciences 2011; 2: 1.*
12. *https://www.slideshare.net/samikshasawant146/microneedles-in-transdermal-drug-delivery 2004*; *56*: *581– 587(2 Sept.*2017).
13. *Gupta J.* et al. *Kinetics of skin resealing after insertion of microneedles in human subjects, J Control Release 2011*; *154*: *148–155.*
14. *Haq M.I.* et al. *Clinical administration of microneedles: skin puncture, pain and sensation, Biomed Microdevices 2009*; *11*: *35–47.*

15. *Burton S.A.* et al. *Rapid intradermal delivery of liquid formulations using a hollow microstructured array, Pharm Res 2011*; *28*: *31–40*.
16. *Harvinder S. Gill., Mark R., Prausnitz, Coated microneedles for transdermal delivery, Journal of Contrrol Release 2007; 117:2: 227-237.*
17. *Mark R. Prausnitz, Microneedles for transdermal drug delivery, Advanced Drug Delivery Review 2004; 56:5: 581-587.*
18. *https://www.slideshare.net/mitu9009/review-on-microneedles*
19. *https://d2cax41o7ahm5l.cloudfront.net/cs/speaker-ppts/33976-Speaker-ppt.pptx (2 Sept. 2017).*
20. *https://www.slideshare.net/AmyMehaboob1/microneedles (2 Sept. 2017)*
21. *Kochhar J. S., Zou S., Chan S. Y., Kang L., Protein encapsulation in polymeric microneedles by photolithography, Int J Nanomedicine. 2012; 7: 3143–3154.*