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Microneedle: A Potential Strategy in Transdermal Drug Delivery

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ABSTRACT

Microneedle-based drug delivery systems showed promising approaches to become suitable and alternative for hypodermic injections and can control agent delivery without side effects compared to conventional approaches. Besides, the novel refining fabrication methods, types of materials, and instruments are other issues that need further attention. Microneedle (MNs) can penetrate through SC layer of the skin into viable epidermis, avoiding contact with nerve fibers and blood vessels that resides primarily in the dermal layers. This review summarizes the techniques to insert microneedles into the skin, the types of MNs, fabrications and methods, challenges in the development of MNs. Furthermore, various techniques used in the application of microneedles and mechanism of action , advantages and disadvantages of MNs are described. The safety aspects of the materials used for fabrication have been discussed in detail. Various strategies have been employed by many research groups and pharmaceutical companies worldwide, for the fabrication of MNs. Herein this review tried to summarize recent achievements and evaluation of MN patches in TDDS.

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INTRODUCTION

Microneedle patches or Microarray patches are micron-scaled medical devices used to administer vaccines, drugsand other therapeutic agents. While micro-needles were initially explored for transdermal drug delivery applications their use has beenextended for the intraocular, vaginal, translingual, cardiac, vascular, gastrointestinal and intracochlear delivery of drugs. Microneedles are constructed through various methods usually involving photolithographic processes or micromolding. Microneedles made from a variety ofmaterial ranging from silicon, titanium, stainless steel and polymers. Microneedles usually applied through even single needle or small arrays. The arrays used area collection of microneedles ranging from only a few microneedles to several hundred attached to an applicator sometimes a patch or other solid stamping device[1]. The arrays are applied to the skin of patients and are given time to allow for the effective administration of drugs. In (Figure1.1) Microneedles(MNs) consist of a plurality of micro-projections generally ranging from 25-2000µm in height of different shapes which are attached to a base support.. In addition, MNs could also use for sampling body fluids such as for measuring the blood glucose levels in diabetic therapy. MNs been shown to penetrate the skin across the stratum corneum (SC) and into the viable epidermis (VE) avoiding contact with nerve fibers and blood vessels that reside primarily in the dermal layers. Therefore, the principle benefit of using MNs is the promise of pain-free delivery of both small and large molecular-weight active pharmaceutical ingredients (APIs)[2].

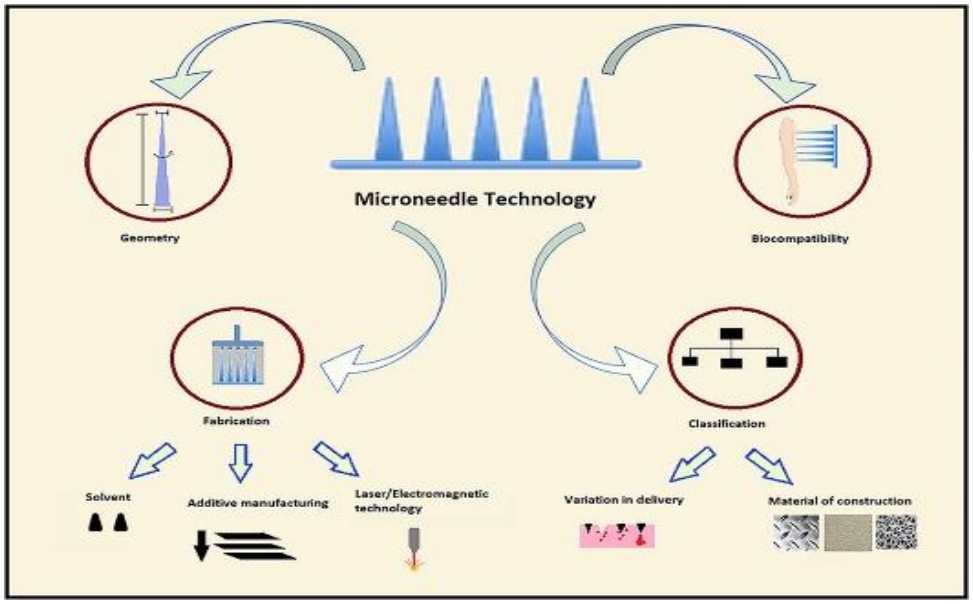

Figure 1.1: View of Microneedle technology

ANATOMY OF SKIN

Human skin has several functions such as photoprotection, thermoregulation, hormonal synthesis sensor, sensory perception and protection function as a barrier for chemical, physical and microbial agents.

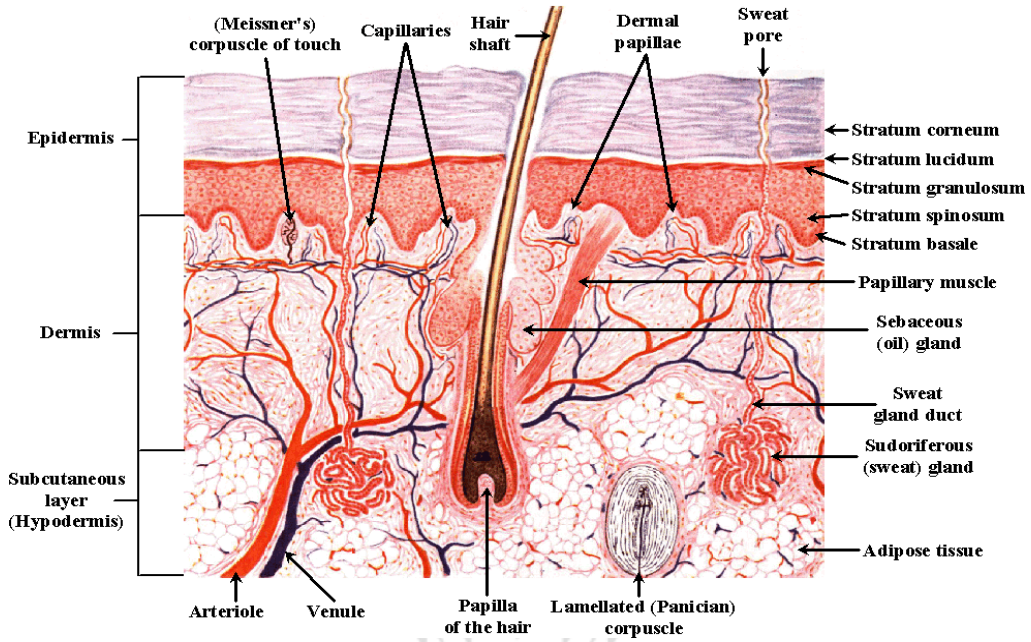

Figure 1.2: Layers of skin penetration routes

Anatomically the layers of the skin may are of three types they are:

- Epidermis
- Dermis
- Hypodermis (Subcutaneous tissue)

The epidermis thickness is around 0.12mm and comprises five layers;the basal or germinating layers, the stratum spinosum, the granular layers, the lucidum layers and the sc. The s.c is the main barrier thesheilds that skin from the entry of foreign substances[3]. The s.c has an average thickness of 20µm this layer is composed of corneocytes (dead anucleated epidermis cells) which are filled with keratin filaments and embedded in a continuous multilamellar lipid matrix (shown in Figure 1.2) .

The lipid composition is complex and includes components like long-chain ceramides, fatty acids and cholesterol compared to most other biological membranes that basically have phospholipids. The lower three sublayer are;

- Stratum Granulosum
- Stratum Spinosum
- Stratum Basale

This constitue the viable part of the epidermis that has cell like melanocytes, Langerhans cells and merkel cells. The dermis has a thickness of 3-5mm. This mtarix is formed of connective tissue which made up of collagen and fibers and elastin.This tissue is vascularized, presenting blood vessels and nerve including apocrine glands, seat gland and pilosebaceous follicles. The dermis is constitued by the subcutaneous fascia and chorions layers[4].

The hypodermis is the innermost layer of the skin where the function of transporting nutrients and migrating cells is observed. It acts as an isolator which helps the body to retain heat. This layer is consistued of adipose tissue. This skin layer is where more irrigation exists because there are many blood vessls in addition to numerous nerve endings. It is important to mention that the skin thickness is different of the skin is a critical factor is transdermal drug delivery[5].

TECHNIQUES TO INSERT MICRONEEDLE INTO THE SKIN

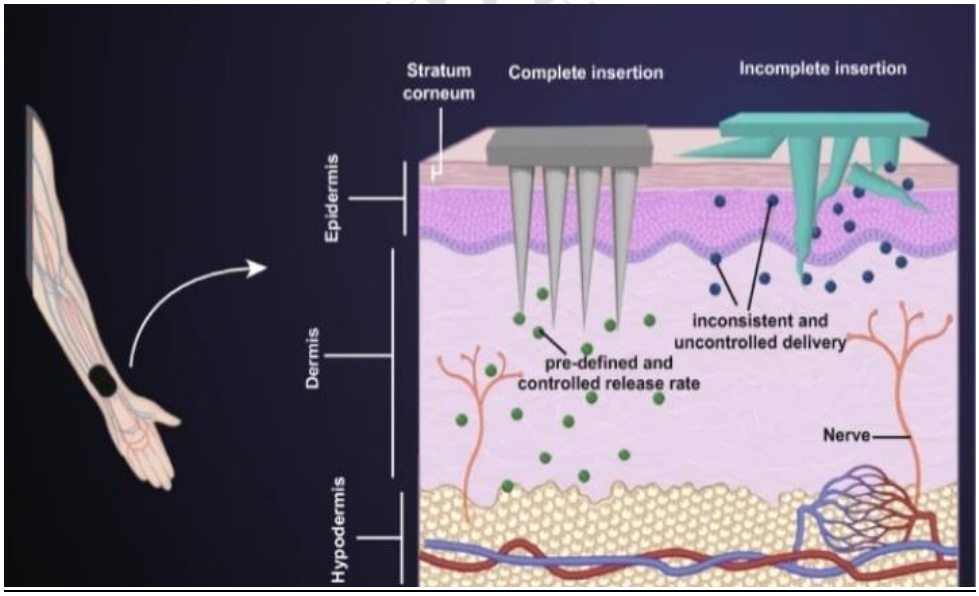

Figure 1.3: Insertion of microneedle into the skin

These are the diverse ways of releasing drugs from microneedles. The first is a novels technique called “poke with patches” where solid silicon or metal microneedles are used to creates micro- channels and then applying a transdermal patch to the surface of the skin shown in Figure 1.3. The transport occurs by drug diffusion. The second is called “coat and

poke" where the needles are first coated with the drug and then inserted into the skin. After that the drug in released a variation of the second method is "dip and scrapes" where the microneedle are first immersed in a solution containing the drug and then the entire surface of the skin is scraped to introduce the drug into the micro-abrasions created by the needles.The third is "Poke and flow" for hollow microneedle delivering a drug like a micro-injection. Finally "poke and release" is for dissolving microneedles fabricated from polymers or polysaccharides realeasing the drug during the dissoluton of microneedles[6].

HISTORY OF MICRONEEDLE

Over the years, microneedle concept have evolved from the use of large needles to the current modern design of the microneedle. Microneedling was used thousand of year ago as part of ancient chinese medicine.In first recorded use of a micro needling procedure was in 1905 by German dermatologist Ernst Kromayer. He used various-sized dental burs(small surgical drill) powered by motor driven flexible cord equipment to treat scars, birthmarks and hyperpigmentation.Perhaphs as we know it was the first used in 1995 by Dr.Desmond Fernandes in Philadelphia, to treat wrinkles and scars with hypodermis needles. The first piece of literature that mentions in microneedle was in 1921 by Chambers where he injection the needle into the egg's nucleus. In the 1960's delivering drugs by injection into stratum corneum began to attract attention..The study describe the use of microfabricated microneedles for the purpose of enhance drug delivery across the skin. Different materials such as glass, ceramic,metal and polymers were introduced to fabricated microneedles[7].Hence microneedling was discovered to be successful in treatinn other skin conditions besides scars. Capitalising on the body's own natural healing processes, a microneedling procedure induces collagen and elastin producion to help soften wrinkles and lines, smooth out the skin, and treat pigment issues and brown spots.

TYPES OF MICRONEEDLE PATCHES

There are sevaral advances have been made in terms of the variety of types of microneedles that can be fabricated. The five main types of microneedles are as follows which shown in Figure 1.4:

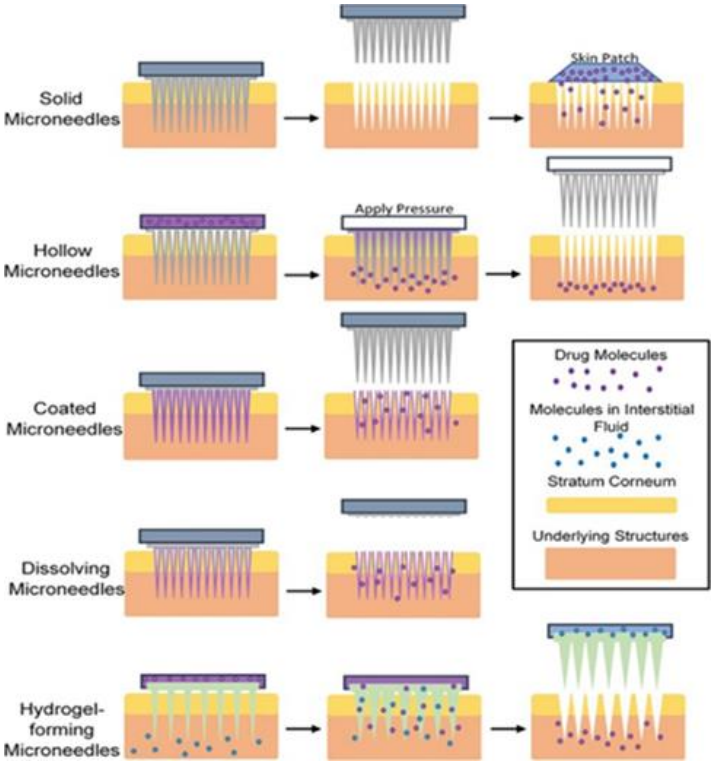

Figure 1.4: Types of Microneedles

- Solid Microneedle
- Hollow Microneedle
- Coated Microneedle
- Dissolvable/Dissolving Microneedle
- Hydrogel-Forming Microneedle

1. Solid Microneedle Patches

A solid microneedle punctures the surface of the skin and applies the drug to the skin layer allowing the drug to slowly diffuse through the holes. The first microneedle array was etching into a silicon wafer and developed for intracellular delivery in vitro.They are generally used as skin pretreatment. After insertion and removal the tips of these MNs generate micron-sized pores on the skin surface. When the formulation is applied over the pores they facilitate the permeation of drugs into the skin either for local or systemic effect. The formulation can be in the form of a topical patch or a semisolid composition like gel, ointment, cream or lotion.

2. Hollow Microneedle Patches

Hollow microneedles have a close resemblance to hypodermic injections with a distinctive feature of micron range size. They comprise a conduit at the center of each protrusion. They are utilized for the infusion of liquid formulations into the skin or diffusion fron a drug reservoir. These have larger drug volumes in a fashion that is similar to conventional hypodermal needles and typically have faster delivery rates by utilizing the active fluid flow into skin.

3. Coated Microneedle Patches

A coated microneedle is a versatile delivery system. The same microneedle patch can be used for the delivery of a broad spectrum of materials ranging from small molecules, to proteins, to DNA, to viruses and even to microparticles. They are solid microneedle coated with suitable drug formulation which serve the purpose of drug delivery supplementary to piercing of the skin. After insertion of microneedles the coated dissolves in the skin following which the microneedles are removed.The results of the delivery of the vaccines using coated MN were similar to vaccines using intradermal and intramuscular routes.

4. Dissolvable/Dissolving Microneedle Patches

The dissolvable MNs are fabricated with biodegradable polymers by encapsulating the drug into the polymer. After inserting the microneedle in the skin dissolution takes places which release the drug. The application involves only a single step as the microneedle is not to be removed out after insertion as in another case. The polymer gets degraded inside the skin and controls the drug release. The Bio accept ability and dissolution of the polymer inside the skin make it one of the best choices for long-term therapy with improved patient compliance these modifications in dissolving microneedles showed the possibilities of the rapid drug delivery with controlled release kinetics.

5. Hydrogel Microneedles

In hydrogel microneedles, the drug is contained in all areas of the microneedle tip base substrate and patch backing and is released at a slow rate while the patches are primarily composed of hydrogel and when they encounter fluids like skin they are hydrated but not dissolved. A high amount of the drug in the hydrogel is delivered to the skin through diffusion. Since the drug can be incorporated in the entire microneedle patch this system is suitable for large dose delivery.

ADVANTAGES

- Microneedles are a minimally invasive techique for transdermal drug delivery.
- Microneedles are very samll.(length of 50 to 900µm).
- Microneedle can penetrate the sc without stimulation of nerves with a constant rate and a prolonged period the drug can be administered allowing the correct dose of drugs.
- There is a reduction of adverse reaction.
- Microneedle are easy and safe to use.
- Microneedle can be produced.
- With high precision accuracy and low cost[8].
- Hollow needle can be used with patches and times pumbs to deliver drugs at precise times.
- Small microneedle could target drugs to each cell.Hollow microneedles offer continuous infusion through the skin.
- They are biologically non-toxic.
- Microneedle have less microbial penetration than convectional needles.
- Microneedle can be removed immediately if adverse reaction is occurs .

DISADVANTAGES

- Microneedle can only ne inserted into the skin if they have the correct shape and adequate physical properties.
- Microneedles used to be applied with the required force to avoid breaking or bending before insertion.
- Microneedles made of metal,stainless steel or silicon have fracture risks.
- They can leave fragments in the skin.
- Microneedles can cause skin irritation and in some cases allergy.
- Microneedles need micro-tools and microelectronics to be produced in bulk.

APPLICATIONS

Microneedles are used in different areas related to health based on the numerous advantages they offer. Microneedles are an attractive candidate to administer several drugs (anti-cancer drugs, oligonucleotide, vaccines, proteins, DNA and even nanoparticle) throughout the skin. Moreover, microneedle have many application in the pharmacy, medicine, and cosmetology fields. The use of microneedles in medicine has grown and allowed to administer drugs through different medicine has grown and allowed to administer drugs through different medical procedures such as the case of treatment for glaucoma other important applications have been in the use of diagnotics such as monitoring of various biomarkers.

1. Therapeutic application

- **Antiglaucoma :**

Microneedle can be used to introduce drugs into the supraciliary space. They show dramactic dose sparing of antiglaucoma agents compared with eyes drops.Targeted delivery in this way increase safety comparaed with eye drops.Targeted deliery in this way increase safety, diminishes side effect and permits a single injection with enough drug for prolonged term sustained delivery.Microneedle have a sfe, simple and efficacious ocular drug delivery. However, the limited drug carryig capacity of devices demonstrated to date may limit the potential for clinical translation.

2. Diagnostics :

It is impossible to make a good therapy without proper diagnosis. This is basic and essential for the success of therapy without a proper diagnosis. This is basis and essential for the success of therapy thus, the use of microneedles has helped in this field. The microneedle with PVP deliver intact protein or peptide to the skin for diagnostic or therapeutic application. On the other hand development of biosnsor that enable continuous real time detection of biomoolecles for monitoring of patient health.

- **Blood glucose measurements:**

There is a huge market in glucose testers due to diabetic patients and hospitals. Kumetrixs is an example of a company that fabricates such a devices. The microneedle is penetrating to the skin and draws a very small volume of blood (less than 100naniliters) into the disposable. Chemical reagents in the disposable react with the glucose in the blood to produced a color.

The blood glucose concentration will be measured either electrochemically or optically and the resultant value displayed on the monitor[9].

3. Vaccine therapy

DNA vaccine was delivered using microneedle. Immune responses seen were much better than that of the normal injection. An attempt to develop a microneedle patch which can be used for administering influenza vaccine was made. Vaccine are biological preparation . It provides active acquired immunityto a particular disease. Its stimulates the immune systems of the body and protects the future micro-organism encounter. Microneedle approach was found to be effective in vaccine therapy.

MATERIALS REQUIRED

Microneedle can be fabricated from a wide diversity of materials for example, metals, polymers, glass, silicon, ceramic, hydrogel and sugar as shown in figure 2.1.

- Silicon; materials has been developed for several decades because this material has relatively high hardness. However, the manufacturing methods of silicon are expensive and need clean room processing. Moreover, silicon is a fragile material thus,silicon microneedles are prone to fracture in transportion and application. Therefore, microneedle made from brittle materials like silicon, ceramice and glass could present problems ath the time of application. In addition, silica glass cause granulomas in the skin. Currently, there is insufficient evidence regarding the biocompatibility of silica glass and silicon for microneedle manufacture.

- Metals: used in the manufacture of microneedles are stainless steel, titanium, nickel, palladium and palladium-cobalt arrays. Metal microneedle toughness, strength and hardness which can protect microneedle against mechanical failure. Metal microneedles can be manufactured at relatively low cost using a variety of methods (electroplating, photochemical etching, micromiling and laser cutting). Titanium is a viable alternative to stainless steel because this material is adequately strong for biomedical appilcations. Titanium has been used mainly for biosenseor and as transdermal delivery systems. Titanium alloys have good biocompatility with silicon in microneedle production. Nevertheless, metal microneedle producesharp bio-hazardous tip waste.

- Polymers: Microneedles made of polymers generally have high toughness to support the polymer to avoid brittle fracture during their insertion into the skin. Some polymers are

biodegradable such as poly glycolic acid (PGA), poly lacticacid (PLA) and chitosan or water-soluble so that drugs can be encapsulated in these dissolvable microneedle. After insertion into the skin drugs will release with the degradation or dissolution of these disslvable microneedle. Biodegrable polymeric microneedles induce almost no harsh side effects thus these microneedle are considered the most promising materials due to their biocompatibility, biodegradability, low toxicity, strength against breaking and low cost. The Main materials used for this kind of microneedle are polymethyl methacrylate (PMM),poly carbonate (PC), poly (vinylpyrrolidone (PVP)), poly (vinyl alcohol (PVA)), poly styrene(PS) and poly methyl vinyl ether-comaleic acid.

- Ceramic:The main type of ceramic is alumina. The main advantage of this material is the resistance and good biocompatibility nevertheless,under tensile stress, ceramic is brittle. Other types of ceramic used to prepare microneedles include calcium sulfatedihydrate and calcium phosphate dihydrate. These materialshave good mechanical and drug loading properties. Ceramic microneedles are produced using micro molding techqiue by casting ceramic slurry into micro molds.

- Glass:Silica glass is physiologically insert allowing the visuslisation of fluid flow. Moreover, microneedles can be produced with different geometries and dimensions. However, glass is a brittle material Borosilicate glass is more elastic because it presents a lower value of elastic module. In general glass microneedle require more time for production because they are created by hand thus, these microneedles are not recommendable for the industry. Glass microneedles can be quickly produced in various geometries for small scale laboratory use. It is physically insert allow easy visuallization of fluid flow and finallly fabricated with dimentions similar to those of microfabricated microneedles.

- Sugar: Maltose is the most common sugar used to prepare microneedles. Carbohydrates (trehalose, sucrose, mannitol, xylitol and galactose) are good alternatives because they are affordable and safe for human health[10].

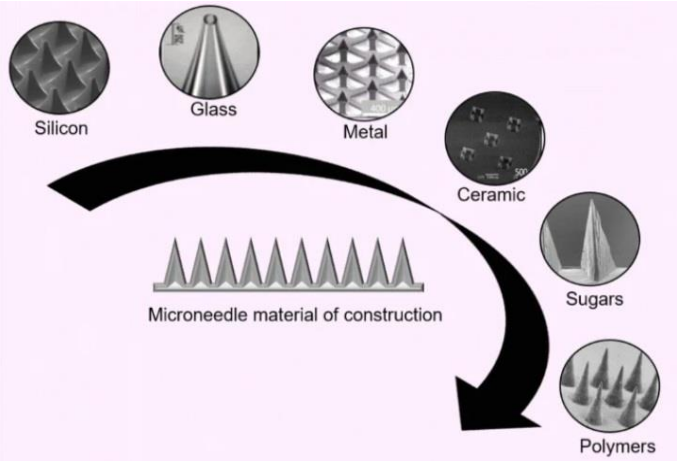

Figure 2.1: Materials for microneedle patches

MICRONEEDLE FABRICATION TECHNIQUES

➢ The fabrication process of microneedle mold which specified in figure 2.2.

1. Clean the glass substrate.
2. Dispense UV resin droplets on substrate.
3. Install the upper and lower glass subrates on the platform.
4. Move the upper glass substrate down to contact the droplets on the lower glass substrates.
5. Separate the upper and lower glass substrate.
6. Control the rising velocity of Z-axis linear translation platform to slowly lift the upper glass substrate and fabricate microneedles. Turn on the UV light.
7. Pour PDMS and bake for 40 min in an oven at 70ºC hours obtain a microneedle mold after demoldind.

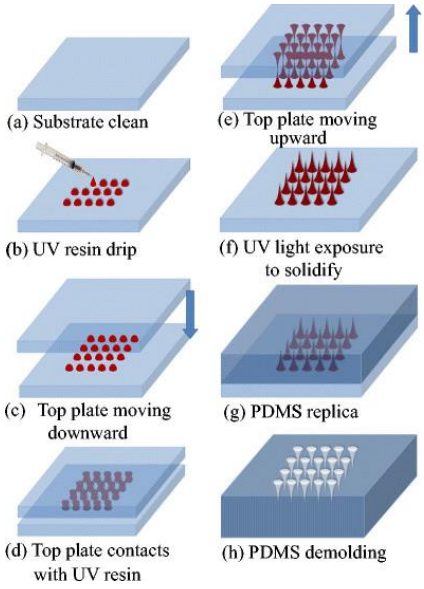

Figure 2.2: Fabrication process in Microneedles

➢ **Methods of fabrication of MNs and the type of needles produced.**

S.NO	METHODS	TYPE OF MICRONEEDLES PRODUCED
1.	Laser cutting	Solid metallic
2.	Laser ablation	Solid metallic
3.	Vapor deposition	Solid silicon
4.	Photolithography	Dissolvable/hydrogel-forming,soild ceramic,hollow type
5.	Deep X-ray lithography	Dissolvable/hydrogel forming,hollow type
6.	Dry etching	Silicon silicon, hollow type
7.	Wet etching	Solid silicon,solid metallic,hollow type
8.	Pulling pipettes	Hollow glass
9.	Metal electroplating	Solid metallic,hollow type
10.	Drawing Lithography	Dissolvable/hydrogel-forming,hollow type
11.	Micromolding and melt casting	Dissolvable/hydrogel forming,solid ceramic
12.	Drawing lithography	Dissolvable/hydrogel forming
13.	Two photon polymerization	Dissolvable/hydrogel-forming,solid ceramic, hollow type
14.	Dipping	Coated type
15.	Spraying	Coated type
16	Microstereolithography	Solid silicon, Solid metallic

MECHANISMS OF ACTION

- Microneedle devices with drug solutions.
- Device inserted into the skin.
- Temporary mechanism disruption of the skin .
- Releasing the drug in the epidermis .
- Transport of the drug to the site of action .

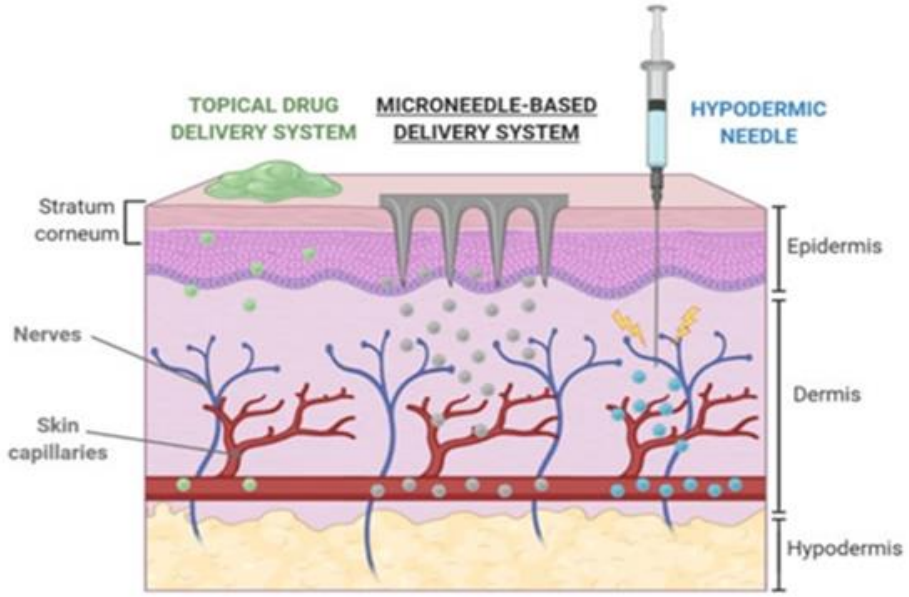

Figure 2.3: Mechanisms of Action of Microneedles

Microneedle array composed of hundreds of microneedles with length less than 1mm long to deliver drug and vaccines into skin. If microneedle array is attached to an adhesive backing to enhance its application to the skin called as microneedle patch.The mechanism for drug delivery is based on the temporary mechanical interruption of skin and deposition of drug and vaccine within the dermis where it can readily reach to its target site which is shows in figure 2.3. Moreover,microneedle form microscale drug delivery channels without impacting blood vessels and nerve endings present in viable epidermis and dermis[11].

MICRONEEDLE FOR DRUG DELIVERY

MN technology is a mode of active transdermal drug delivery and is intended to be used as a replacement to traditional syringe injections. The MN array is used to penetrate the stratum corneum and deliver the drug with a minimally invasion action.These arrays are micro-sized needles with a height ranging fron 25 to 2000µm. MNs have been used for different appications such as drug and vaccine delivery, cosmetic and disease diagnostics. 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 microneedles has been fabricated with a range of sizes, shapes and materials. Hence the drug can diffuse through residual holes in skin from a topical formulation. After the insertion of drug-coated microneedles into the skin, the drug coating dissolves off the microneedles in the aqueous environment of the skin. Microneedle insert into the skin of human subjects were reported as painless. Together, these results suggest that microneedles represent a promising technology to deliver therapeutic compounds into the skin for a range of possible application[12].

Figure 3.1: Current microneedle devices(single needle with applicator, microneedles array patch,microneedles pan,microneedle pump patch,and microneedle roller)

In recent years, the alteration has been drawn to a new type of delivery method where arrays needles are used of miniaturized needles are used to penetrate the skin layer shown figure 3.1. Since the needle are short they do not reach the nerve rich regions of the lower parts of the skin. Microneedle has all favorable properties i.e continous release, ease of use, unobtrusiveness and painlessness[11].

CHALLENGES IN THE DEVELOPMENT OF MICRONEEDLES.

Endorsing the translation of MNs from research laboratories to the relevant industries is an exciting but demanding task for the near future. To translate this innovative technology from the lab bench to feasible products in the relevant markets, some crucial question and challenges should be considered promptly. We hereafter discuss these challenges and active strategies to address these difficulties which could determine the future of the field and its commercial applications. The main issues concerns for the development of a microneedle-based delivery system is summarised[13].Hence which is shown in figure 3.2.

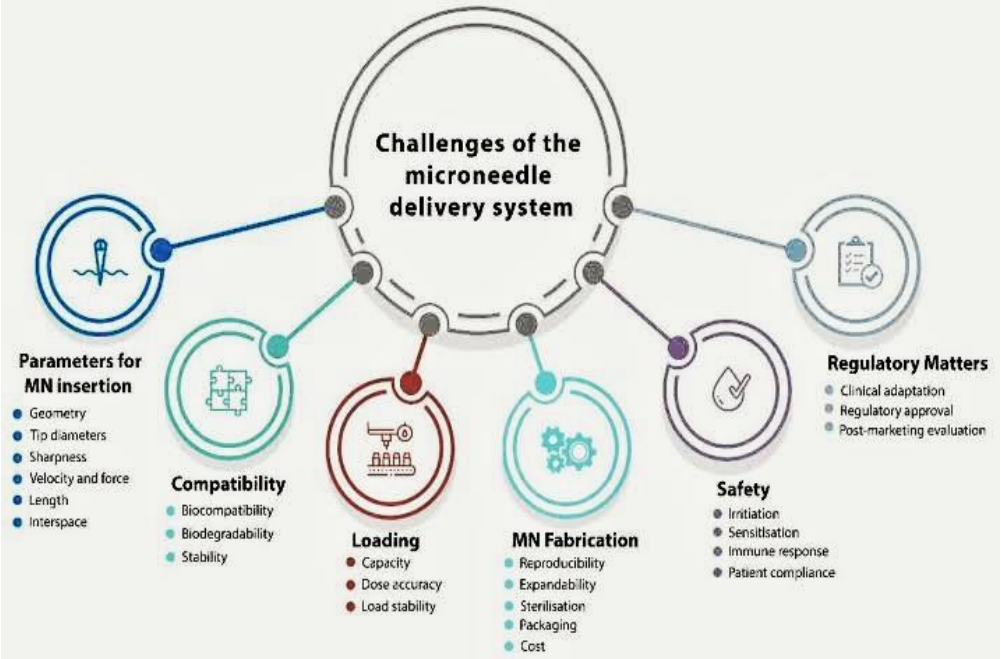

Figure :3.2 challenges of the microneedle delivery system

1. Parameters affecting MN insertion

The capability of MN patches to adequately puncture the skin is a vital requirement. When addressing this matter the skin's characteristics which might vary across the body and vary from person to person should also be taken into account. The insertion and penetration

behaviour of MNs to overcome the skin's elasticty is strongly dependent on several parameters such as geometry,base and tip diameters, length and interspace (centre-to-centre spacing).An approach of "one-size-fits-all"cannot be envisaged in any design and development are stringly related to the geometry of individual MNs and the array. MN materials, MN manangement method and the characteristics of skin tissue.

- **The geometry:**

The geometry of MNs is a parameter that should be taken into consideration early on when developing MNs for clinical appilcations, A recent study indicated that the mechanical strength and penetration characteristics of MNs are affected by the geometric structure of microneedle arrays simulations have shown a linear relationship between the mechanical strength and the number of vertices in the polygon base (eg, triangular,square and hexagonal microneedle bases) showing better insertion depths for the triangular and square built microneedle bases)showing better insertion deptths for the skin was observed for the sharper edges of triangular and square MNs compared to the hexagonal MNs.

- **Tips diameter and sharpness**

Tip diameter is another parameter for MN insertion. Relatively blunt MNs (tip diameters of 60-160µm) require a relatively high insertion force (0.08-3.04N)for controlled appilcations of MNs and are linearly reliant on the tip frontal area.To achieve a well controlled manner to the desired depth, the fabrication of MNs with sharp tip is essential.For the successful delivery of therapeutics, it has been reported that MNs with smaller tip diameter(<15µm)access the skin more smoothly than MNs with a tip diameter of larger magnitude. An increased tip sharpness however, not only reduces the puncture force but also reduces the structural strength of the microneedles, leading to a high risk breakage.

- **Application velocity and force**

In the close relationship with the tip diameters,the application velocity and force are other parameters in the MN delivery system that should be considered in detail. Several studies have reported that the penetration depth of MN arrays varies(from 10%up to 80%)increases with the application velocity and force.A variety of patch configurations have been used with similar outcomes of the penetration force per microneedle obtained.A 25-microneedle array with a tip radius of <100nm requires an insertion force of 10mn per microneedle for effective penetration into the skin.

- **Length**

The thickness of the SC and other skin layer differ across individually, the particle insertion depth may also vary. The transport capability of the skin once a MN patch has been appiled will depend on the perforation depth of the tissue. If a drug is relatively small and has diffusion capacity creating surface pores by microneedle application should be sufficient for therapectic function. However,if rapid delivery to the bloodstream is the goal, it may be referable to create pores that reach the dermis where capillaries are located.This may be one reason for assorted microneedle length that have been reported to date.

- **Intersapce(centre-to-centre spacing)**

The skin is a topographically diverse surface capable of withstanding significant deformations prior to penetration. A significant number of distinct punctures must be generated when there is a high density array of microneedles (eg more than 500/cm²) this takes a lot of energy. Naturally,as the density and number of microneedle grow so does the necessary forcefor skin puncture.This can result in increased feeling for the patient and may require the use of a large/stronger device can result in large, longer and more crowded holes through which a higher amount of medication may diffuse.

2. Biocompatibility, Biodegradability and Stability

One of the safety aspects of MN systems in clinical use is biocompatibility.To ensure that MN products are acceptable for human exposure several tests are required to evaluate their biocompatibility based on contact periods of less than 24h between 24h and 30h.For the former two periods, the corresponding tests are cytotoxicity, sensitisation, irritation and intracutaneous reactivity tests. Genotoxicity systematic toxicity tests are additionally recommended for the latter period of use. The use of biodegradable materials is desirable for microneedles because these materials can be degraded and removed from the body safely.

3. Loading Capacity and Dosage Accuracy

- **Loading capacity**

A coated microneedle devices can only deliver a bolus dose of amoung 1mg of medicine.Although hollow microneedles allow for continuous infusion or “as needed/on-demand of dosing”. Central exists may be obstructed by compressed skin tissue after microneedle insertion. Even though MNs have have the potential to overcome the skin barrier

properties, their success is very much dependent on passive diffusion of the bological formulation into the skin.This can make it difficult to administer large dosages amd much of the dose can be lost on the skin's surface.As aresult the time of appilcation and the inability to monitor dose delivery have caused reluctance to use this technology for certain clinical applications.

- **Dosage accuracy**

The dosage accuracy of MN delivery systems in continouse drug delivery is an issue that requires close attention.Several Methods using separable Microneedles have been proposed for minimising the patch-wearing time and quickly removing the formulation from the MNs. Storing and delivering protein drugs, including insulin, erythropoietin, glucagon, growth hormones and parathyroid hormones are challenging tasks as bio-macromolecules are prone to quick degradation and inactivation. These matters could be best handled by not only the incorporation of stabilisers but also by considerating the whole process of MN manufacturing parameter such as manufacturing and storage temperatures and drying conditions,polymer concentration, sterilization and packageing.

- **Skin Irritation and Recovery**

The immunogenic nature of the skin makes it a highly responsive organ towards the MN delivery of any therapeutic agent.Mild and temporary erythema may develop as aside effect depending on the size,substance and type of the given medication skin irritation, sensitisation and immune response must also be evaluated as part of the safety assessments of MN products during clicical trials.This safety concern must be evaluated using animal testing before any human clinical trials. ON the other hand,great immune responsiveness of the skin may present an opportunity for MN based vaccine delivery if other obstacles have been addressed properly as discussed.

4. Cost of Microneedle fabrication

Current microneedle manufacturing processes needle to be improved to reach large scale production in order to completely transfer microchip-based microneedles into therapeutic applications. Until now,extensive economic evalutions of the technology have not yet been quantified thoroughly, but it is hit difficult to predict that as with every new technology the clinical use ofMNs can be comparatively expensive due to the complex fabrication and storage procedures and the slow and long approval process.

5. Sterilisation of the Microneedle Patches

MN based products are aimed for commercial application. If sterilization is necesssary then the method of choice will be critical because the most widely used methods such as moist heart, gamma or microwave radition and ethylene oxide may deleteriously affect sensitive ingredients including biomolecules, vaccines, peptides or even the microneedles themselves. Although the risk of introducing bioburden into the sterile area of the body (eg, epidermic and dermis)by MNs is significantly smaller than a single puncture by a hypodermic needdle complete sterilisation of MNs based products may be obligatory by the regulatory bodies .

6. Regulation of the Microneedle Patches

The quality of submissions received from combination products employing microneedles has been a source of concern for the US FDA particularly in the areas of stability testing content consistency,risk analysis,sterility validation and manufacturing. As discussed earlier, MNs are a viable option for the delivery of therapeutic agents such as hormone, vaccines, enzymes, mRNA and difficult-to-deliver small molecules via the skin[14].

SAFETY ASPECTS

Even though few studies have investigated the safety of microneedle application, a potential for microbial penetration into the viable epidermis through the micron-sized pathways created by these microneedles was not reported. Therefore microneedle products mustn't contain microbial loads which can cause skin or systemic infections.Additionally, the bioburden of microneedle products should be controlled and minimized to avoid immune cell population present in the viable epidermis and dermis.

In recent studies demonstrated that microorganisms (pseudomonas aeruginosa, Staphylococcus epidermis and candida albicans) can transfer through the micronnedle induced holes in the SC. In order to guarantee patient safety. A possible solution solution may be the production of sterile microneedle products. By employing sterilization methods like termainal sterilization, steam sterilization, dry heat sterilization and ionizing radition sterilization, sterility of microneedles can carried out. However, the injection risk associated with the application of microneedles is minimal when compared to hypodermis needles.

Another vital safety aspect of microneedles is having insertion force and mechanical properties of skin. These microneedles should be able to establish sufficient strenghth to

penetrate into the skin or other biological tissues without breaking or bending before or during insertion.Major factors liable for microneedle performance are needle height, tip-radius, type of material, base diameter,needle thickness, needle density etc can determine the overall insertion insertion and fracture force of the microneedle[15].

Microneedle insertion forces(0.1-3 N) divorced linearly with the interfacial area of the needle tip and fracture force increased with increase in the tip and fracture force increased with increase in the tip radius, wall angle and wall thickness. For all types of microneedles, the fracture force should be significantly greater than the force required for insertion into the patient's skin However, the safety ratio between fracture force and insertion force were high .

Apart from all above microneedles could produce other health issues such as:

- Local inflammation if thr amount of drug is high under the skin,
- Proper knowedge of the clinician is must for the successful application of the microneedle technique.
- A repetitive injection may collapse the veins.
- Compressed dermal tissue can block hollow microneedles.
- The tip of microneedle may break off and remain within the skin on the removal of the patch 15.

EVALUATION

✓ Physical examination patches:All the formulated patches were evaluated visually for apperance in terms of surface smoothness, brittleness, transparency, stickiness, flexibility and homogeneous appearance.

✓ Weight variation: Weight variation was tested by selecting three patches randomly out of each formulation and weight uniformity of dried and cut patches was checked on a digital weight balance. Average weight of three patches of 1.5cm^2 from each formulation provided information regarding weight variation among different formulation.

✓ Folding endurance: The folding endurance of patches was evaluated by folding repeatedly a polymeric film of 1×1cm at the same point until it broke. The 1×1cm of film was taken from the center as well as from edege of the patch. The test was conducted on three randomly selected patches from each formulation.

✓ Percentage moisture content:The percentage moisture content was determined for each formulation. A film of 1×1cm was taken each patch. These films were weighed individually using a digital weight balance. These polymeric films were then placed in labeled petri dishes and stored in a desicator containing silica beads at 25ºC. The films were weighed until constant weight was achieved. The percentage moisture content was calculated using the following formula:

- Percentage moisture content = Initial weight-Final weight ×100.

✓ Percentage moisture uptake:The percentage moisture uptake was determined for each formulation. A transdermal film of 1×1cm was cut from each patch. Films were weight individually by using a digital weighing balance. These film were placed in labeled petri dishes and stored in a humidity chamber at 25ºC with 84% relative humidity(RH). The transdermal films were continously weighed until constant.

- Percentage moisture uptake = final weight-initial weight/initial weight×100.

✓ Scanning electron microscopy: Surface morphology of the microneedle patch was examined by scanning electron microscopy for analysis of array formation and sharpness of the needle.:

✓ Drug content:To determine the drug content microneedle patch was dissolved in phoshate buffer ph7.4 after the appropriate dilution the drug content was determined by UV visible spectrophotometry.

✓ In vitro release kinetics: The results of invitro release profile obtained for all the formulations were plotted in modes of data treatment as follows. Cumulative percent drug release verse time (zero order kinetics model) Log cumulative percent drug remaining verse time (first-order kinetic model) cumulative percent drug release verse square root of time. Log cumulative percent drug released versus log time[15].

- Drug release kinetics-model fitting of the data; Whenever a new soild dosage form is developed or produceses, it is necessary to ensure that drug dissolution occurs appropriately.Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug(Q)is a function of the test time,t or Q=f(t). Some analytical definitions of the Q (t) function are commonly used such as zero order, first order,Higuchi, and Korsmeyers-Peppas models[16].

- Zero order equation

The zero order release kinetics can be obtained by plotting cumulative % drug released(vs) time (hours). It is ideal for the formulation to have release profile of zero order to achieve pharamcological prolonged action.

$$C=k_0 t \ldots\ldots\ldots\ldots\ldots\text{equation 1.}$$

Where,

k_0=Zero order constant in conc./time.

t = Time in hours.

- First order equation

The graph was plotted as log % cumulative drug remining (vs) time in hours.

$$\text{Log C= log } C_0 = kt/2.303\ldots\ldots\ldots\ldots\ldots\text{..equation 2.}$$

Where,

C_0 =Initial drug concentration.

K= First order constant.

t= Time in hours..

- Hixson and Crowell erosion equation

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, t \ldots\ldots\ldots\ldots\text{Equation 3.}$$

Where,

Qt = Amount of drug release at time.

Q_0= Initial amount of drug.

K_{HC} = Rate constant for Hixson Crowell equation 15.

✓ Ex Vivo permeation studies:

Ex vivo permeation study was carried out by using Franz diffusion cell. Full thickness abdominal skin of male.Wistar rat weighing 200 to 250g was used. Hair from the abdominal region was removed carefully by using an electric clipper; the dermal side of the skin was

thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels and equilibrated for an hour in phosphate buffer pH 7.4 before starting the experiment.It was placed on a magnetic stirrer for uniform distribution of the diffusant[17].

FUTURE PROSPECTIVES

- Immunization program.
- Mass vaccination.
- Administration of antidotes in bioterroism incidents.
- Encapsulation of microneedles for oral insulin delivery.
- Removal fluids from the body.
- Microneedles can be used for delivery of nanoparticles.
- Microneedles can be used for vesicular drug like ethosomes.
- Delivery of proteins.
- Delivery of anticancer drugs.

DISCUSSION

Recently microneedle patches in transdermal drug delivey system can be used for delivery of nanoparticles and also it can used for vesicular drug like ethosomes.hereby microneedles are may organized in delivery of proteins,anticancer drugs. hereby MNs shows the encapulation of oral insulin delivery and administrated of antidotes in bioterrorism incidents.Therefore, microneedle patches are includes in mass vaccination and immunization program.

CONCLUSION

Microneedles allow painless insertion with minimum tissue damage better control over the dosage do not generate infectious waste and are more acceptable and comfortable for patients. Consequently, microneedles have been growing in field of drug development,therapeutics and cosmetology[18].It is possible to administer peptides avoiding multiple daily injection like the case of insulin.They are being used in the diagnosis, treatment for glaucoma,alopecia,anti-agingand scars. Microneedle can be fabricated by several different methods to yield a variet needle size, shapes and materials. Solid microneedle have been shown to increase

transdermal by “poke with patch”,coatand poke” and “ dip and scrape” methods and hollow microneedle have been shown to microinjet into skin.

Therapeutic respones have been achieved invivo following delivery of protein,DNA and vaccine. Proper needle design can assure insertion into the skin that prevents needle fracture or patients pain.These studies suggest that microneedle may provide a powerful new approach to transdermal drug delivery. Microneedle application has the potential to overcome the problems associated with delivery of samll hydrophilic molecules, macromolecules and biopharmaceuticals across biological barrier particularly the stratum corneum.[19]

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