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The Future of Painless Injection: Exploring the Materials Used, Manufacturing Materials and Its Applications in Transdermal Drug Delivery System

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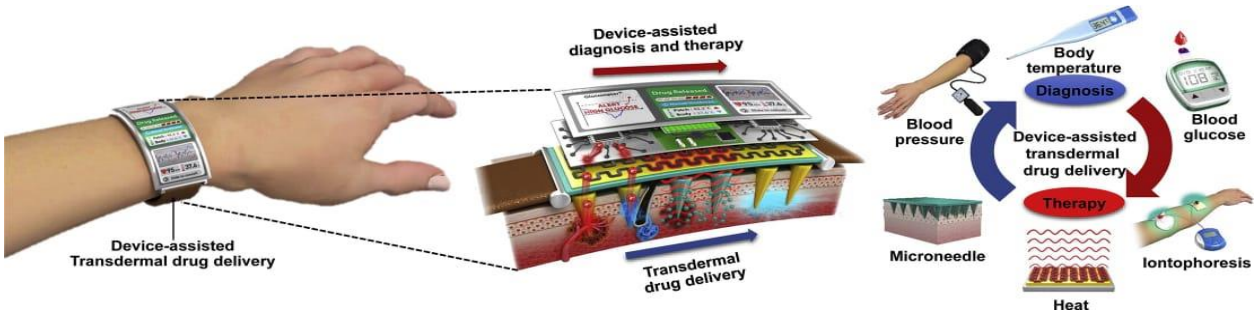
ABSTRACT:
This article review's about the high barrier qualities of biological membranes, such as the stratum corneum (SC) of the skin or the sclera/cornea of the eye, among others, many therapeutic medicines that have the potential to be very effective are constrained by their inability to reach the systemic circulation. The SC, the skin's outermost layer, serves as the main deterrent to drugs given topically. Thus, the intact SC acts as the body's primary defense against foreign chemicals, such as pharmaceuticals. The only medications that can be successfully supplied transdermally are those with very particular physicochemical characteristics (molecular weight 500 Da, sufficient lipophilicity, and low melting point). It is difficult to administer hydrophilic medications and macromolecular targets including peptides, DNA, and small interfering RNA transdermally. Therefore, bypass or reversible disruption may be used to facilitate medication penetration through the SC. When used to penetrate skin, microneedles (MNs) will bypass the SC, form temporary micron-sized aqueous transport channels, and increase transdermal permeability. Since these micro pores are several orders of magnitude larger than molecular dimensions, hydrophilic macromolecules should easily be able to go through them. Many research teams and pharmaceutical businesses around the world have used different methods to create MNs. This review describes different MN types and fabrication processes.

KEYWORDS: TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS), MATERIALS, MICRONEEDLES, TYPES, APPLICATIONS, DEVICES USED AS MICRONEEDLES.

INTRODUCTION:

Transdermal drug delivery system is a painless method of delivering drugs systemically by applying a drug formulation onto healthy skin. The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer.1

A novel drug delivery system was developed; in this transdermal delivery system medicated adhesive patches are prepared that deliver therapeutically effective amount of drug across the skin when it is placed on skin. Medicated adhesive patches or transdermal patches are of different sizes, having more than one ingredient. Once they apply on unbroken skin they will deliver active ingredients into systemic circulation passing via skin barriers.2



The approaching year, the transdermal market is predicted to be profitable with growth opportunities because of the use of technology and innovations in transdermal, such as micro needle arrays and mechanical arrays. The innovations involve alterations in penetration enhancers, transdermal patch designs, and internalization of pressure sensitive adhesives, which increases the capacity of the reservoir to hold a large quantity of drugs and improved drug diffusion. Furthermore, advancement contains highly developed transdermal patches, advanced reservoir type, and miniaturization that distribute accurate medication dosage.3

Fig. 2 Transdermal Patch

Advantages of transdermal drug delivery system

1. First pass metabolisms of drug get avoided.
2. Gastrointestinal incompatibilities get avoided.
3. Self-medication is possible.
4. Duration of action gets extended & predictable.
5. Unwanted side effects get minimized.
6. Drug plasma concentration gets maintained.
7. Number of doses get reduces which improve patient compliance.
8. Therapeutic value of many drugs get increased by avoiding problems associated with drug like-lower absorption, GI irritation, decomposition due to hepatic first pass metabolism.

Disadvantages of Transdermal drug delivery System

1. Chances of allergic reactions at the site of application like-itching, rashes, local edema etc.
2. Larger molecular size of drug (above 1000) creates difficulty in absorption.
3. Barrier function of skin varies from site to site on the same or different person.
4. Drug with hydrophilic character is less suitable as compare to drug with lipophilic character because of their low permeability.4

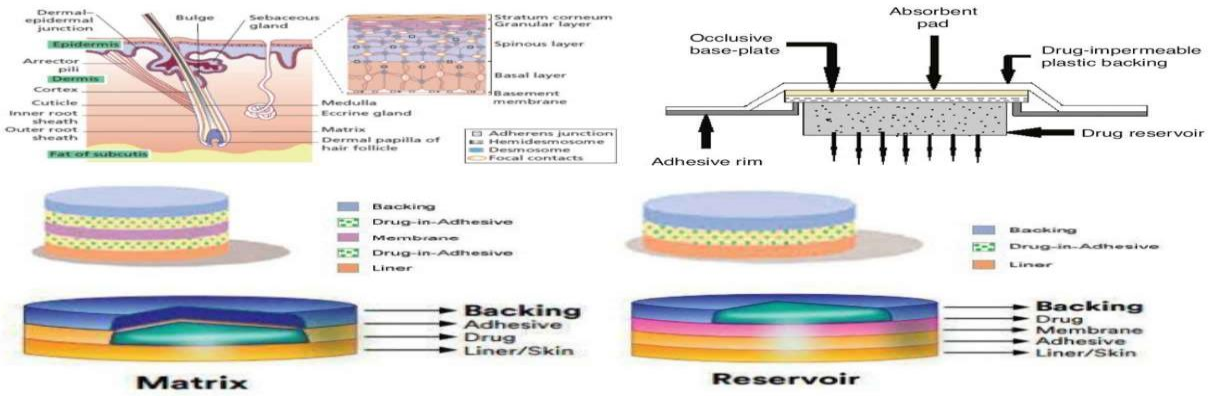


Fig. 3 Mechanism of TDDS

MICRONEEDLE TYPE OF TRANSDERMAL DRUG DELIVERY SYSTEM

When oral administration of drugs is not feasible due to poor drug absorption or enzymatic degradation in the gastrointestinal tract or liver, injection using a painful hypodermic needle is the most common alternative. An approach that is more appealing to patients, and offers the possibility of controlled release over time, is drug delivery across the skin using a patch.5

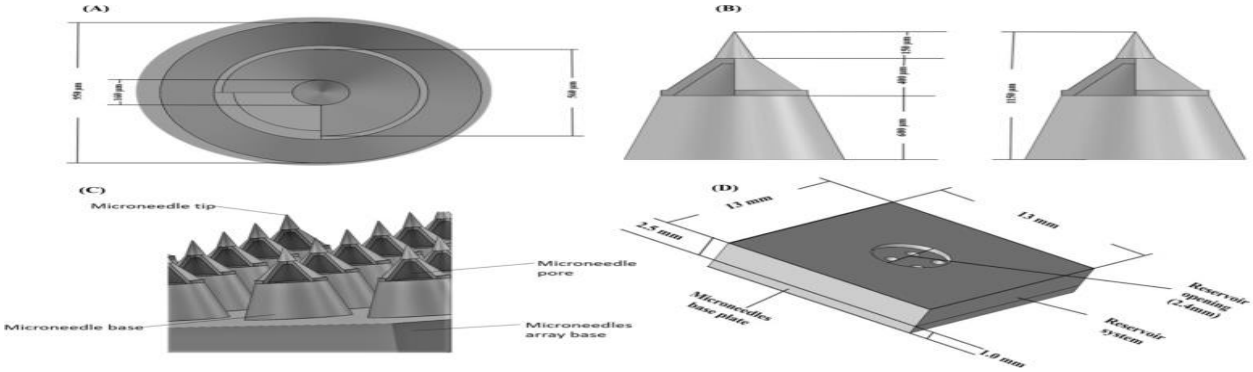


Fig.4: Different types of Microneedles in TDDS

Transdermal drug delivery using microneedles

The overarching motivation for microneedles is that they can provide a minimally invasive means to transport molecules into the skin. Guided by this goal, a number of specific strategies have been employed to use microneedles for transdermal delivery. Most work has focused on making microscopic holes in the skin by inserting solid microneedles made of silicon or metal. The “poke with patch” approach uses microneedles to make holes and then apply a transdermal patch.

Mechanics of microneedle insertion into skin

Most studies of microneedles have addressed methods of fabrication and assessed drug delivery capabilities. The mechanics of microneedle insertion have received only limited attention, but are critically important to practical applications. Only microneedles with the correct geometry and physical properties are able to insert into skin. Some needle designs require only insertion by hand, whereas others benefit from high-velocity insertion.6

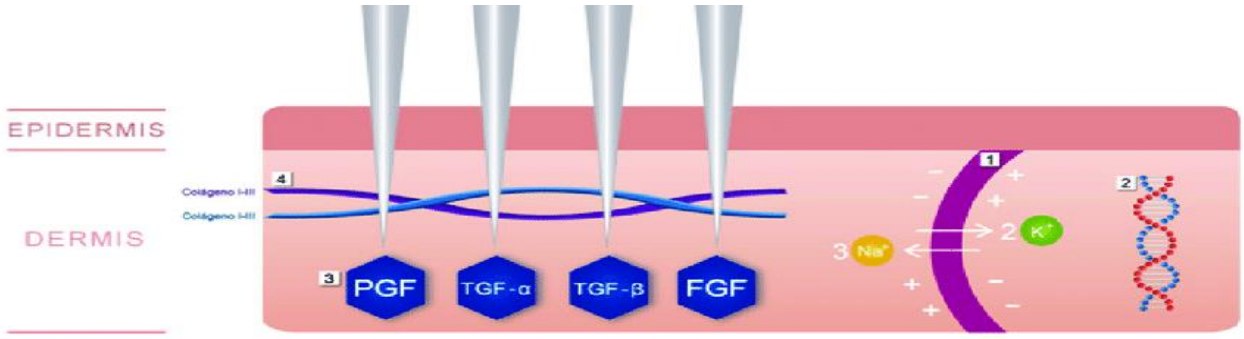
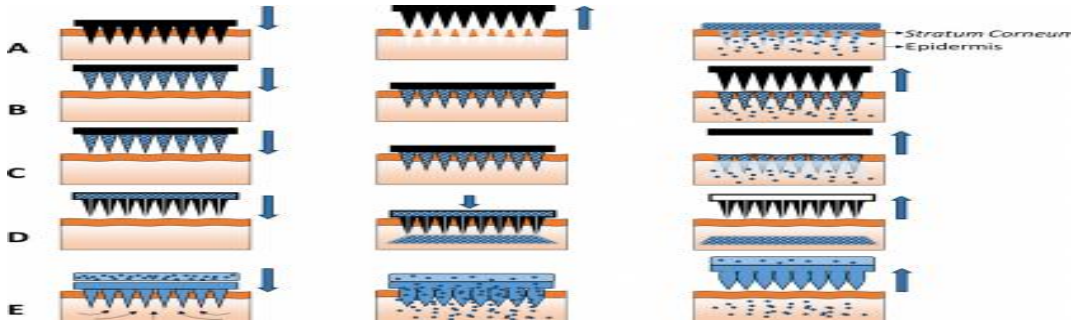


Fig. 5: Mechanism of MNs

Mechanism of action of Microneedles

Types of Microneedles in Transdermal drug delivery system

Different types of microneedles fabricated and investigated for their application in drug delivery are solid, coated, dissolving, hollow, and hydrogel microneedles. Different types of microneedles with their unique properties are displayed in below diagram. Each type of microneedle has its own way of delivering the drug into the epidermis. Some are used just to create pores in stratum corneum, some are precoated with the drug solution on their surface, some are dissolvable and some are prefilled with the drug solution .



1. Solid Microneedles

Solid microneedles are mostly used for pre-treating the skin by forming pores. Pointed tips of the needles penetrate into the skin, create channels of micron size, through which the drug directly enters the skin layers on the application of a drug patch, thus increasing the permeation. The drug is taken up by the capillaries to show a systemic effect. It can be used for a local effect also . Solid microneedles deliver the drug with passive diffusion to skin layers. The microneedles having 800 µm depth and density of 256 MNs per cm2 was found to enhance the drug permeation . Stainless steel microneedles are also studied by various researchers. Enhanced delivery of captopril and metoprolol tartrate was studied after application of stainless steel MN arrays

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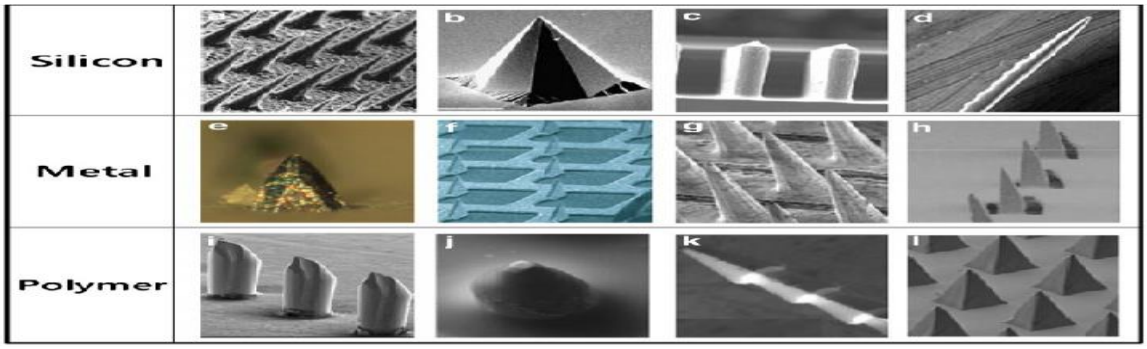

Fig. 7 Solid type of microneedle

2. Coated Microneedles

The microneedles are surrounded with the drug solution or drug dispersion layer [1]. Subsequent dissolution of drug from the layer takes place and the drug is delivered quickly. The amount of drug that can be loaded depends on the thickness of the coating layer and the size of the needle which is usually very less [29]. Baek et. al loaded lidocaine on poly L-lactide (PLLA) microneedle arrays.

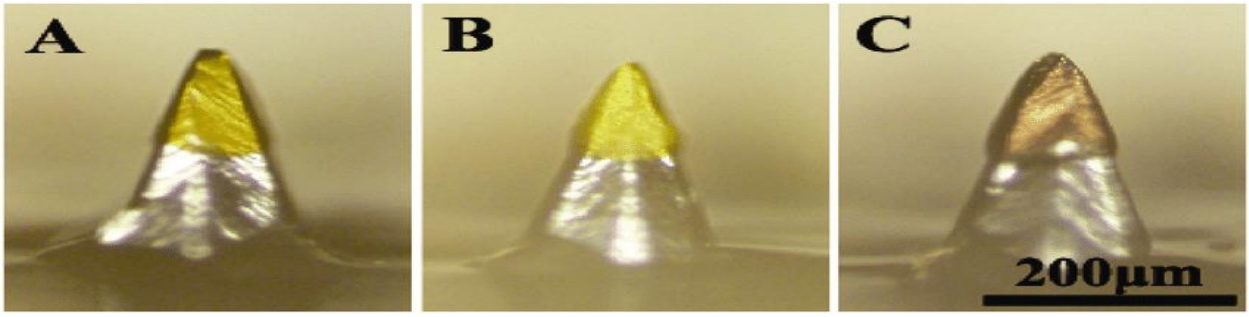

Fig.8: Coated type of microneedle

3. Dissolving Microneedles

Dissolving microneedles are fabricated with biodegradable polymers by encapsulating the drug into the polymer. After inserting microneedle in the skin, dissolution takes place which releases the drug. The application involves only a single step as the microneedle is not to be removed out after insertion as in other cases. The polymer gets degraded inside the skin and controls the drug release. The bio-acceptability and dissolution of the polymer inside the skin make it one of the best choices for long-term therapy with improved patient compliance.

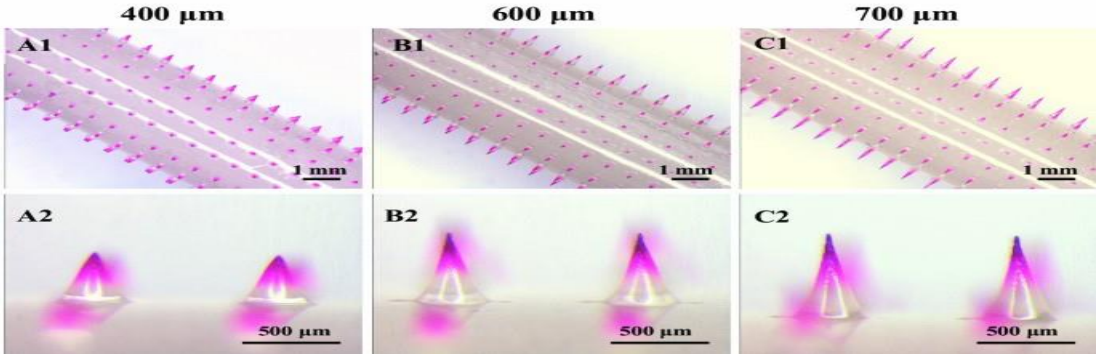

Fig. 9: Dissolving type of microneedle

4. Hollow Microneedles

Hollow microneedles have an empty space inside which is filled with the drug dispersion or solution. They have holes at the tips. On inserting into the skin, the drug is directly deposited into the epidermis or the upper dermis layer. Mostly it is used for high molecular weight compounds such as proteins, vaccines, and oligonucleotides [1]. The drug flow rate and release pressure can be adjusted if the drug is to be given by a rapid bolus injection. These microneedles are capable of administering a large dose of the drug as more amount of drug can be accommodated into the empty space inside the needle. Maintaining a constant flow rate is essential here.

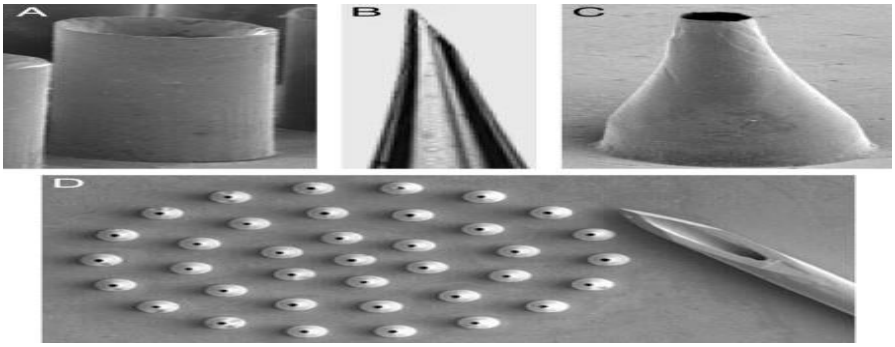

Fig. 10: Hollow type of microneedle

5. Hydrogel Microneedles

This type of microneedle is recently developed. Super-swelling polymers are used to make microneedles. The polymers constitute the hydrophilic structure which makes it capable of taking up a large amount of water into their three-dimensional polymeric network. These polymers swell when inserted into the skin due to the presence of the interstitial fluid. This leads to the formation of channels between the capillary circulation and the drug patch. Before needling, these microneedles are just used to disrupt the skin barrier. On swelling, they behave as a rate controlling membrane. They have flexibility in size and shape. Easy sterilization and intact removal from the skin are the unique properties of such microneedles7.

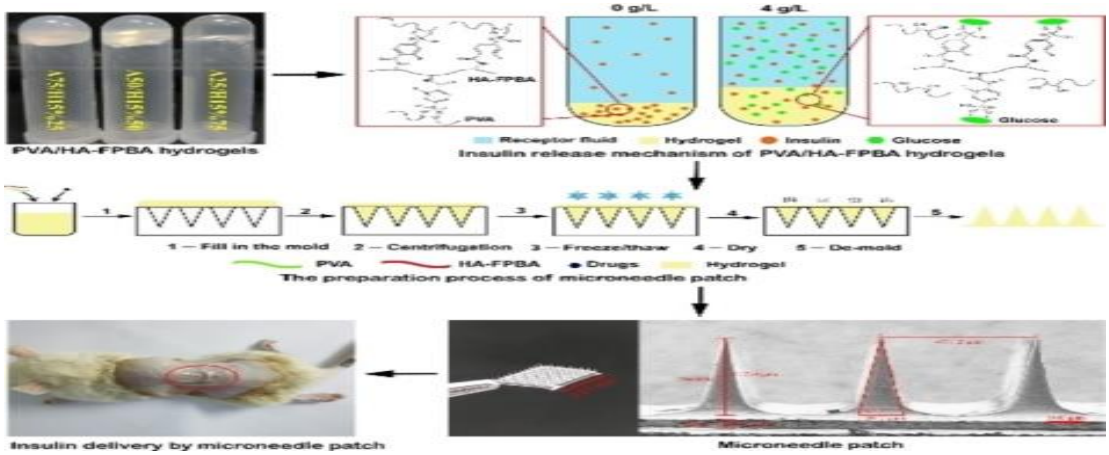

Fig.11: Hydrogel type of microneedle

General manufacturing method for microneedles

Manufacturing technologies in order to produce MN devices, investigators have used a plethora of manufacturing methods, including chemical isotropic etching, injection moulding, reactive ion-etching,

surface/bulk micromachining, polysilicon micromolding, lithography-electroforming-replication, laser-drilling and two-photon polymerisation. Furthermore, MNs have been produced in a wide range of designs .

The two basic designs are in-plane and out-of plane MNs. Some designs combine in-plane and out-of-plane MN. For in-plane designs, the MNs are parallel to the fabrication surface, while for out-of-plane designs the MNs are perpendicular to the fabrication surface.

1. Laser Cutting

Laser cutting is primarily used for manufacturing a metal or polymer microneedle; the most used material is stainless steelThe 2D shape of a microneedle is generated through cutting on a fat metallic sheet using a laser. The size and orientation of the microneedle array is designed through a computer-aided design (CAD) software. The microneedle drawn in 2D is bent by 90 degrees to create a 3D microneedle. Needle tips or rough surfaces can be cleaned using electropolishing8.

2. Laser Ablation

Laser ablation incorporates the use of a focused optical light beam in eliminating material from a substrate to create MN arrays. Lasers have been used to process different materials ranging from micro- and nano-scale for several applicationsVarious laser types have been studied for the manufacture of MN arrays. These include CO2 UV excimer, and femtosecond laser machine. The laser ablation method is considered an effective and fast method for MNs fabrication. Polymers 2021, 13, 2815 14 of 34 The laser beam takes 10 to 100 nanoseconds to approach the burn point in the material sheet .Laser could also be used to shape any metal. This method is associated with thermal effects at the cutting surface that result in the alteration of MN structure and mechanical properties. This might lead to undesirable effects in MNs such as cracking, or fatigue resistance. The laser ablation method is a non-contact process and subjects low heat loads to the substrate. However, the cost of the laser is higher compared to other types of equipment. The laser ablation method is not suited for large scale manufacturing.

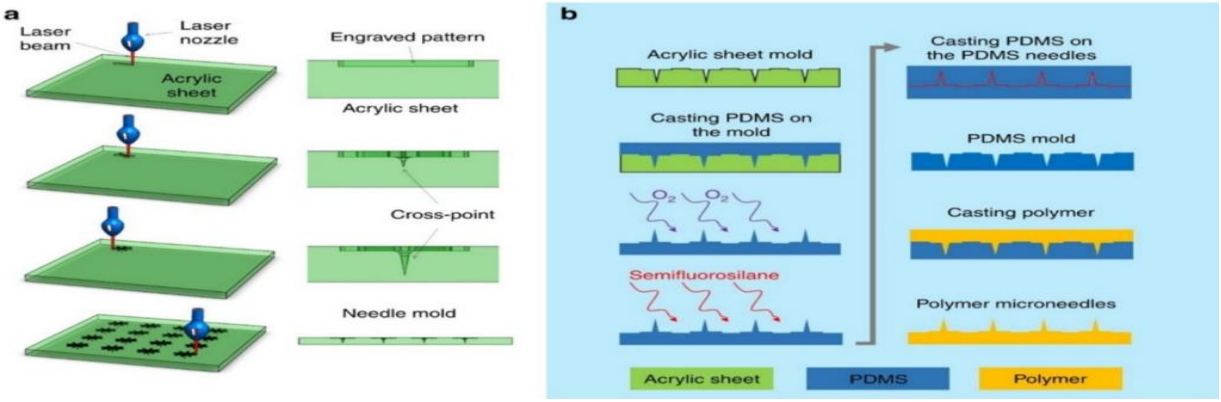

Fig.12: Manufacturing of methods of microneedles

3.Micro-Molding

The micro-molding process consists of making replicates of the master mold. The mold is casted with a solution containing a polymer and active pharmaceutical substances. Micro-molding is considered a cost-effective method and is used for mass production. Micro-molding is commonly used with polymer material for MN fabrication. The PDMS has several advantages in micro-molding techniques such as low cost, ease of use, low surface energy, and thermal stability. The limitations associated with this

technique are difficulties associated with controlling the depth of penetration, drug load capacity, and mechanical behavior of the polymer.

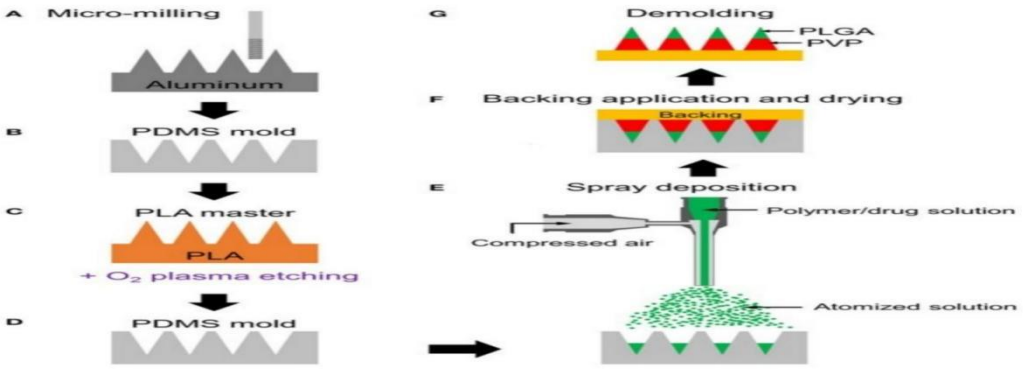

Fig. 13: Micro molding method

4. Injection Molding

Injection molding is another MN fabrication method. The process of fabricating MNs using injection molding and the hot embossing technique is shown in. Lhernould et al. used poly carbonate (PC) material to fabricate a 4 × 4 hollow polymer MN array. The MNs were shown to withstand high force and were used for multiple insertions without blunting the needle. Another study used a micro-injection molding process to fabricate a solid MN. These needles could deliver hydrophilic-high molecular weight molecules. Sammoura et al. fabricated a polymeric MN by molding plastic material. The needles were used to successfully penetrate a fresh chicken leg and beef liver and ~0.04 µL of liquid was drawn from these tissues. The proposed method allows the mass production of MNs at low cost9.

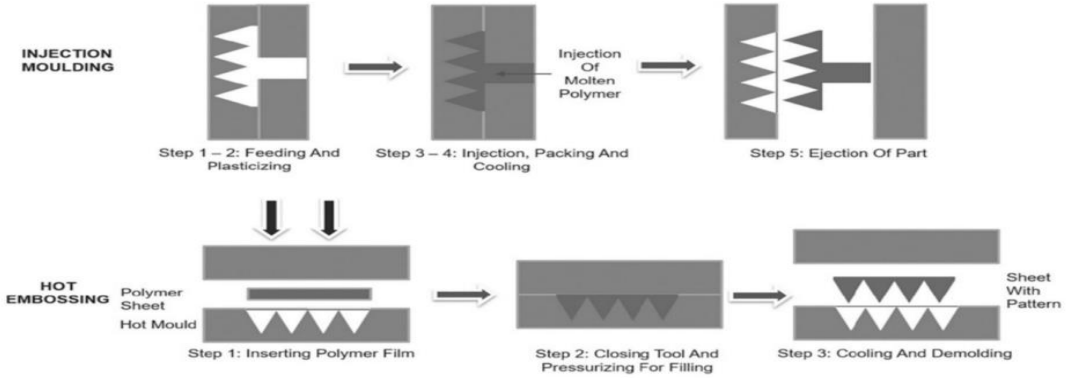

Fig.14: Injection molding method

5. Lithography

Drawing lithography takes the viscous polymer in the glass transition process as a crucial point to achieve the manufacturing performance of a 3D microstructure. In the thermal drawing of microneedles, the biodegradable thermoplastic poly(lactic-co-glycolic acid) (PLGA) is vertically stretched by a metal pillar while the speed is controlled. The top is broken by fast drawing to form a microneedle structure, and the shape of the microneedle can be adjusted by changing the temperature and fracture speed after cooling. In this process, it is necessary to ensure that the properties of the material remain unchanged after heat treatment. For example, a magnetorheological drawing lithography method is proposed by Chen et al. to form a flexible microneedle array. It only needs one step, which is formed from the

compressed droplets of curable magnetorheological fluid on a flexible substrate. Then, the MN was solidified in an oven for 1 h with a temperature of 90 ◦C, and the penetration of calcium protein through rabbit skin increased after the application of this microneedle. In addition, drawing lithography is suitable for mass production due to its one-step manufacturing process.

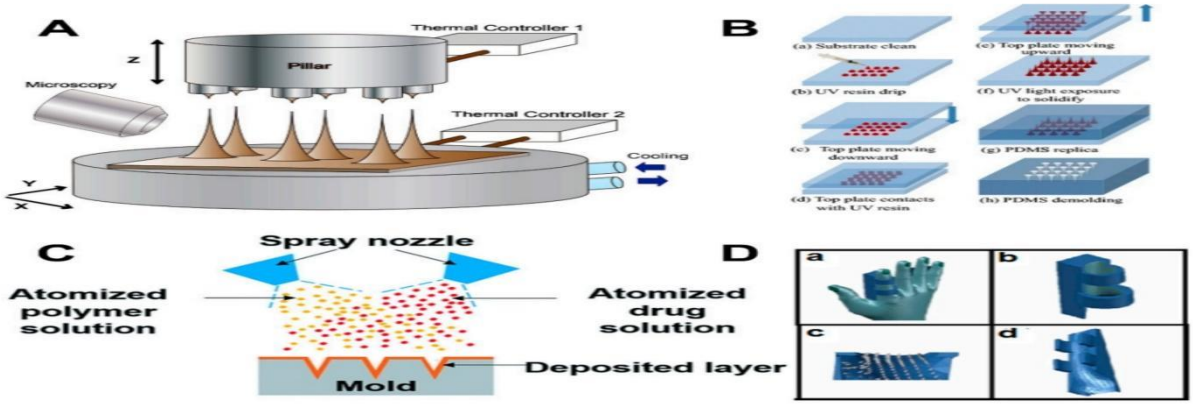

Fig. 15: Manufacturing process of microneedle

6. Three Dimensional (3D) Printing Technology

Three-dimensional printing is an emerging manufacturing technique based on 3D model data in computers; it uses a method of layer-by-layer accumulation of materials. This printing technique has the advantages of high accuracy, high precision, high flexibility, fewer manufacturing steps and less waste. Currently, the 3D printing techniques used to manufacture microneedles for transdermal drug delivery mainly include 3D projection inkjet (3DPI), fused deposition molding (FDM),photopolymerization-based approaches (stereolithography (SLA); two/multi-photon polymerization (2PP/MPP); digital light processing (DLP)) and laser-assisted bioprinting (LAB). Although MPP has the highest resolution, it was limited by speed and materials. Meanwhile, SLA has a higher resolution but with more impact by oxygen inhibition than DLP. Three-dimensional printing has been integrated into microneedle fabrication via photopolymerization. According to Shin et al., DLP-based 3D printing was adopted to construct molecules in an aqueous solution with lower concentration by photo-crosslinking, combining silk fibroin with riboflavin to form a flexible MN. Given the low drug load of microneedles and the high flexibility of 3D printing, Seng et al. fabricated a dual-function microneedle array on personalized curved surfaces for drug delivery and splint to treat the affected finger by DLP. The microneedles can withstand twice the average thumb force without breaking, and the amount of drug that penetrated the skin significantly increased. Inkjet printing is a non-contact process for the on-demand delivery of biological materials containing small amounts of proteins and nucleic acids, which can be used to manufacture microneedles with improved coat uniformity, stability and reproducibility. For instance, Pere et al. made MNs with biocompatible resin by using a stereolithography printer, and then printed the insulin solution to the surface of MNs through the inkjet printer, which is similar to the atomized spray process mentioned above10.

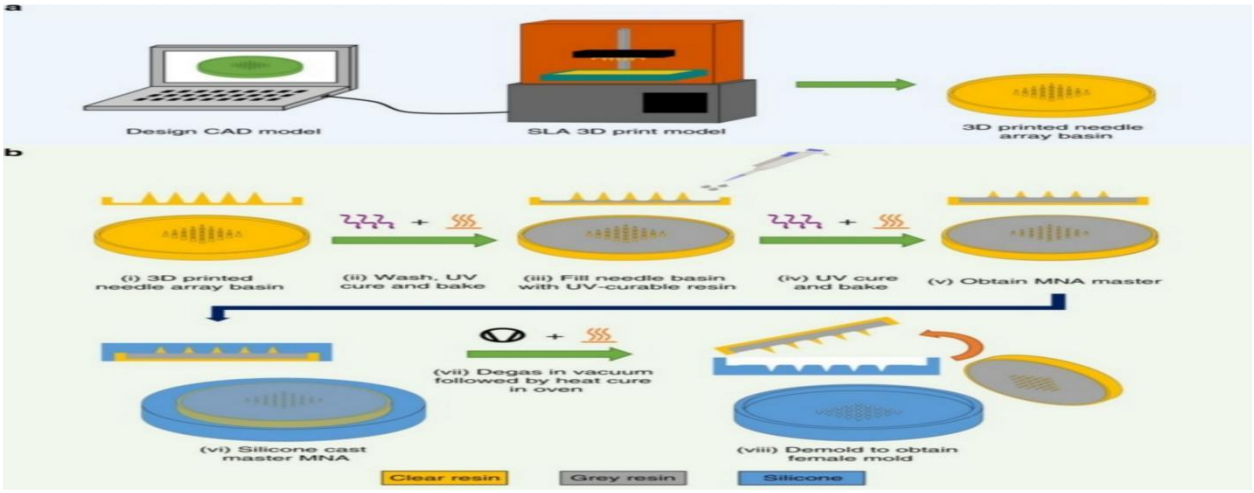

Fig.16: 3D printing technology

Fabrication of different microneedles

1. Fabrication of silicon microneedles

Silicon MNs are produced mainly using MEMS [Micro-electromechanical systems] technology. This type of technology utilises diverse tools and methodologies to create small 3D structures, with dimensions ranging from subcentimetre to sub-micrometre. Originally, this technology was developed for production of integrated circuits. A MEMS process involves a series of sequential operations. The three basic techniques in MEMS technology are: application of a patterned mask on top of a film by photolithographic imaging; deposition of thin films of material on a substrate; and etching the films selectively to the mask .

Lithography and etching. The majority of processes in microelectronics and micromachining fabrication starts with lithography. This technique is used to transfer a master pattern onto the surface of a substrate (e.g. silicon wafer). For this purpose, this surface is previously coated with a photosensitive material by selective exposure to a radiation source (e.g. UV light). Indeed, the most widely used type of lithography is photolithography. In general, the subsequent steps are involved in the mask transfer onto the photosensitive-coated substrate.

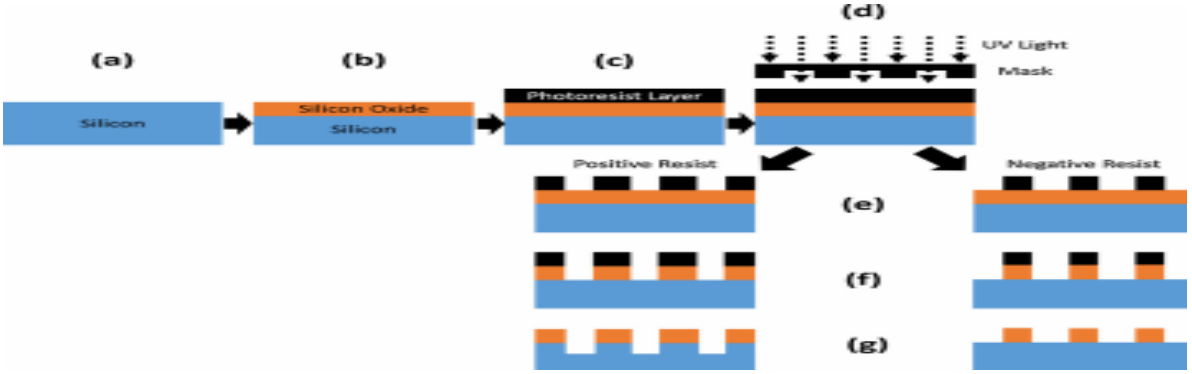

Fig.17: Fabrication of silicon microneedle

Two main types of resists can be used: positive resists and negative resists. In the first one, the chemical bonds within the resists are weakened when exposed to UV light and, subsequently, the exposed resists become more soluble in the development solutions. In negative resists, these chemical bonds are strengthened when exposed to UV radiation. Normally, the mask used in photolithography is typically an optically flat glass or quartz plate, transparent to near UV, with a metal absorber layer. Additionally,

there are other technological alternatives to create a desired pattern on a substrate, such as X-ray and charged-particle beam lithography.

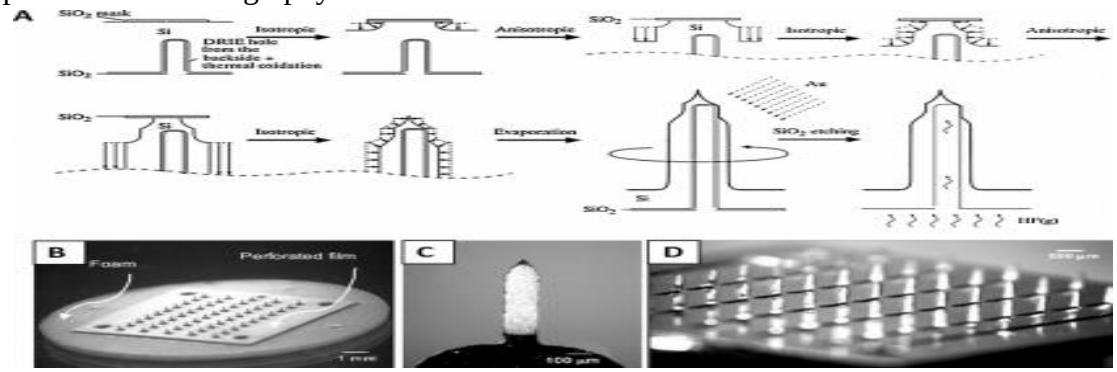

Fig.18: Fabrication method of microneedle

(A) Process flow of the fabrication of circular side-opened hollow silicon microneedles. (B) 50 out-of-plane microneedle array. Vitamin B coated (C) single and (D) 50 stainless-steel microneedle out-of-plane array.

2. Fabrication of metal and glass microneedles

In order to produce metal MN, a wide number of approaches have been proposed, such as electroplating (e.g. palladium), photochemical etching (e.g. titanium), and laser cutting (e.g. stainless steel). These techniques allow, in a similar way to silicon, routine fabrication of both solid and hollow MNs.

The simplest method to obtain metal MNs is by assembling conventional stainless-steel hypodermic needles or stainless-steel wires yielding hollow or solid MN respectively. Currently, the smallest used hypodermic needles are 30 G for conventional syringes (305 mm outer diameter) and 31 G for insulin delivery injectors (254 mm outer diameter.)

3. Fabrication of ceramic microneedles

Ceramic MNs are produced mainly by micromolding techniques. These techniques will be explained in detail in the next section. A ceramic slurry is cast inside a mould followed by a sintering process. This type of process allows device production at a low cost, as this technology can be easily scaled up. Bystrova and Luttge prepared MN arrays using this process, obtaining a wide variety of array geometries. The first step of the process consists of casting an alumina slurry into a PDMS microneedlemould. Additionally, the multiple replication of the PDMS mould offers a low cost production mould which can be reused for ceramic micromolding. Such a micromolding process was used by Cai et al. to prepare calcium sulphatedihydrate and calcium phosphate dihydrate MN arrays . Two types of needles, each with different dimensions, were designed densely arranged pyramids 100 mm in height, 150 mm in base width and with 160 mm between tips, and sparsely-arranged pyramids 200 mm in height, 285 mm in base width and with 820 mm between tips.

4. Fabrication of carbohydrate and polymeric microneedles

Polymeric MNs have been produced using a wide variety of mould-based techniques. Some examples of these techniques are: casting , hot embossing , injection moulding , investment moulding , drawing lithography , laser micromachining and X-ray methods. Drawing lithography, on the other hand, is a unique additive process to fabricate MNs.

This method produces 3D polymeric structures extended directly from 2D viscous polymeric materials. The polymer is cooled down until it becomes a viscous glassy liquid. After contact of the drawing pillars on a coated glassy liquid surface by plate moving, 3D structures are selectively elongated from the 2D glassy liquid-plate as a result of the longitudinal upward movement of the drawing pillars. Then, the polymer is cured and finally isolated .

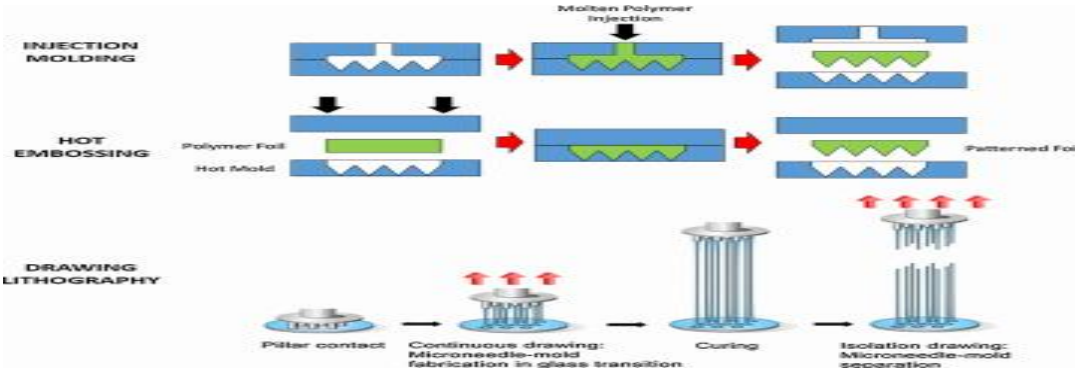

Fig. 19: Types involved in microneedle fabrication

Microneedle mechanical characterization

A crucial step in the development of successful MN devices is mechanical characterisation. MNs normally experience a wide range of stresses, including those experienced during insertion or removal. Therefore, it is mandatory for such devices to possess inherent strength to avoid failures . There are a wide number of failure modes that these stresses can cause, including MN bending, buckling and base-plate fracturing . Therefore, mechanical characterisation should be performed in order to ascertain that the designed MN are safe prior to use.

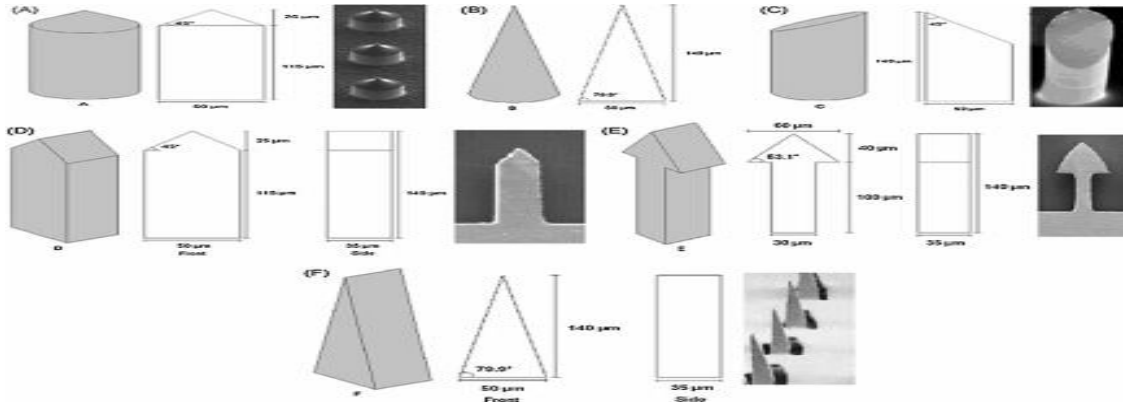

Fig. 20: Microneedle mechanical characterization

Different Microneedles Designs

One of the first MN mechanical tests described was developed by Zahn et al. This test consisted of a single, hollow, silicon MN and a force gauge that gradually increased the vertical force being exerted at the MN tip (0–20 g range) until it fractures. Since then, numerous methods and tests have been developed for MN mechanical characterization .

Axial force mechanical tests

Axial force mechanical tests involve applying a force to the MNs perpendicular to the base-plate This type of test normally needs the use of a mechanical test station, which records both displacement and

force while the MNs are pushed against a hard surface at a defined rate . When MN fracture occurs, a sudden decrease can be observed in the force-displacement curves generated. The maximum force exerted immediately before this drop is normally taken as the MN failure force . Images ofthe MN arrays can be taken before and after fracture to provide insights into the mode of failure . Some axial force tests reported in the literature should be viewed with caution, as they only use a single MN . The failure force of a MN array obviously cannot always be assumed to correlate with that of a single MN. Additionally, it is important to clarify that this test does not accurately simulate the forces experienced by MNs during insertion into the skin.

Transverse force and shear strength mechanical tests

Skin surface irregularities and its natural elasticity often lead to incomplete insertion of MN arrays, with transverse bending of the needles also frequently observed. Therefore, a transverse fracture force test is necessary to probe the behaviour of MNs during application . Using a mechanical test station, a transverse force (applied normal to the MN y-axis) is applied at a defined point on the MN shaft until the MN fractures . Again, a sudden drop in the force-displacement curves indicates MN failure . When this test is applied to a row of MNs rather than to a single MN, the force should be divided by the number of MN in the row to calculate the transverse fracture force per individual MN . The main limitation of this test as reported in the literature is the requirement to align the metal probe with a defined length manually . This can lead to experimental inaccuracies, even if the test is performed with the aid of a microscope camera.

Base-plate strength and flexibility tests

The tests described above are focused on mechanical testing of the needles themselves, but assessment of the MN base-plate strength is also important. Clearly, fracture of the base-plate during patient application is not acceptable. Therefore, base-plates need to be flexible enough to conform to the topography of the skin without fracturing . For this purpose, a three points bending test has been used11.

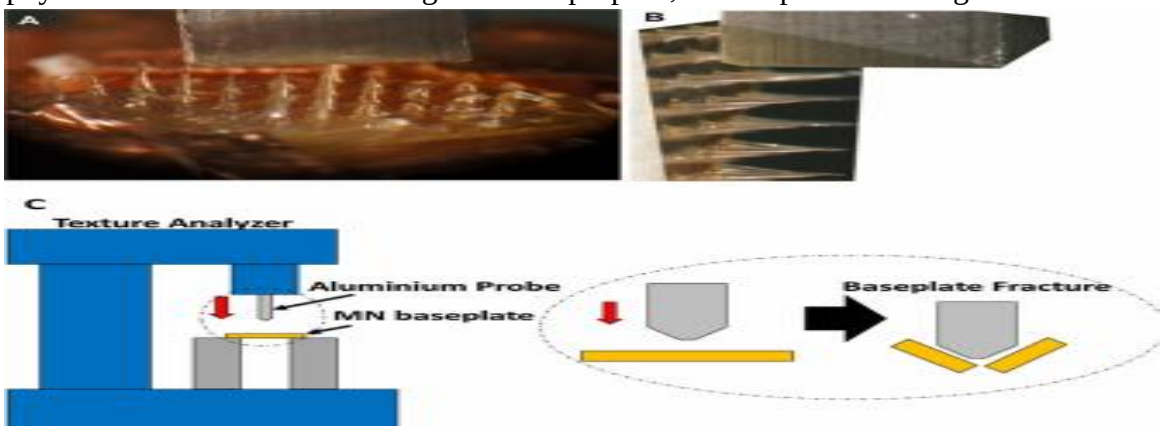

Fig 21: Different designs of microneedles

EVALUATION OF MICRONEEDLES

1. Penetration
2. Skin Resealing
3. Insertion Force

1. Penetration

Pretreatment with solid MNs can improve the permeability of some hydrophilic agents; for example, naltrexone successfully delivered through skin showed a rapid rise or burst of absorption within the first several hours of application. Several factors affect skin permeability; for example, an increase in the tip radius of the MNs caused lower penetration, whereas an increase in MN length resulted in more drug penetration . Different MN shapes cause different insertion depth. The maximum depth of diffusion was found withcone-shaped 200-μm long MNs (170 ± 13 μm), whereas the depth of diffusion of 300-μm long needles with sharp tips and an angle of 15° was 120 ± 10 μm. Another finding showed that micro-channels created by MNs were markedly smaller than the dimensions of the MNs. Velocity of insertion also affects the permeability of the drug; the increase of applicator speed increased the proportion of penetration Injection in different skin areas may affect the depth of holes; for example, inserting a 280-μm solid MN in the volar arm resulted in average depth of 179 ± 14 μm, whereas inserting the same MN in the fingertip gave an average depth of 146 ± 19 μm.

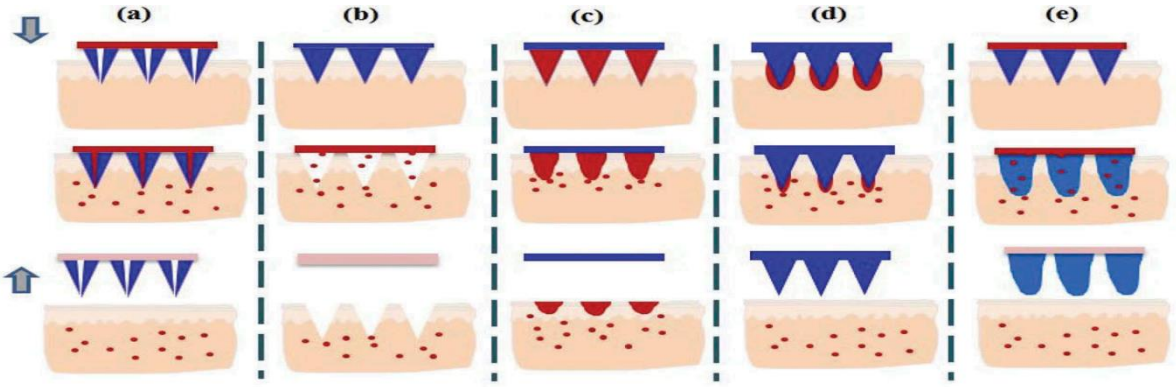

Fig. 22: Penetration process of microneedle

2. Skin Resealing

One of the most significant concerns about solid MN application is the reversible property of the skin's natural repair mechanisms. As soon as the stratum corneum is disrupted, the lamellar body secretory responses create a synthesis of the lipid to restore and maintain the stratum corneum structure. This natural process reduces the delivery of drugs, blunting the clinical utility of this unique technique. One study noted that the insertion points can close as quickly as 15 min, although other studies report closing within 24 h after solid MN application when the injection sites are exposed to the air. A study showed that the insertion points reduced from a depth of 158 ± 20 μm to a depth of 76 ± 13 μm in a time frame of 45 min. The explanation for variation in time frames between the studies could be the difference in insertion methods and the variable MN geometries. For example, with the impedance technique, the authors noted that actual micropore closure time frames may be less drastic than their calculations due to diffificulty in distinguishing between healing curves, relatively large error bars, and differences in initial impedance drops. A new application of the impedance test is the gel direct condition, which was demonstrated to produce less variation between the young and elderly groups. To prolong the skin's resealing time, it was treated with occlusion following the solid MN injection; as a result, the time frame was extended to 40 h in one study and 48–72 h in two other studies. With occlusion, skin repair also depends on MN length; a 2-fold increase in length resulted in 6-fold longer closing time, and a 5-fold increase in the number of needles corresponded to a 10-fold increase in barrier resealing time. An alternative hypothesis is the existence of subclinical local inflammation at the microscopic level; in

support of this idea, one study demonstrated that micropore closing time was extended by using topical antiinflammatory agents such as diclofenac .

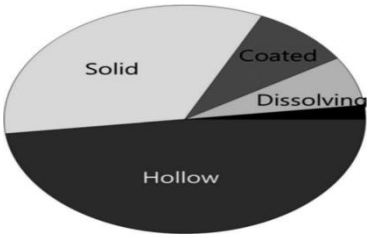

Fig. 23: Evaluation of microneedle

3. Insertion Force

Various geometries of MNs need different applied forces. Research has shown that the dependence between the force necessary for injection and the interfacial area of the needle tip is linear and might be described by the balance between the energy applied to the skin and the energy required to create a tear in the skin. Hydration status has been known to alter the mechanical properties of the skin. With skin in a normal condition, approximately 10 mN of force was needed to insert a novel ultra-sharp tip and a side opening silicon hollow MN array. In term of solid MNs, the conically shaped 300-μm long MN needs an applied force ranging from 0.1 to 3 N. At the force in this range, the fracture discontinuities were rarely apparent; even with forces was as high as 25 N. Most notably, repeated insertion and wear tests failed to result in damage to solid MN arrays12.

Evaluation of Microneedles Characterization of microneedle geometry

Scanning electron microscopy can be used to determine the base radius, tip radius and wall thickness of the microneedles. Interfacial area (i.e. the effective area of contact between the needle and the skin) can be calculated in two ways:

(1) The annular surface area, Aa; at the needle tip

$$Aa = \pi(rtt\text{-}t2/4) \quad (1)$$

(2) The full cross-sectional area, Af; at the needle tip

$$Af = \pi r12 \quad (2)$$

(3) Needle wall angle, α is calculated as

$$\alpha = \tan\text{-}1(rh - rt/h) \quad (3)$$

where rt is the outer radius of the microneedle tip, rb is the outer radius at the needle base, t is the wall thickness and h is the height13.

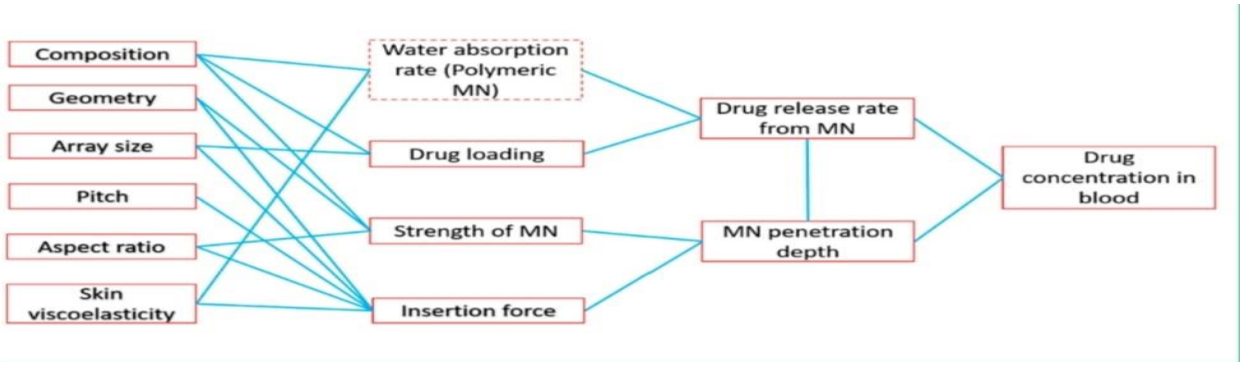

Fig. 24: Geometry of microneedle

DISSOLUTION DATA OF MICRONEEDLES

1. **In vitro testing of MNs**
2. **In vivo testing of MNs**

1.In vitro testing of MNs

The in vitro testing is conditioned to hit upon the permeation or active (drug) release from MNs into the selected dissolution media . In vitro study of smart MNs is generally performed using the diffusion cell apparatus. The pig ear skin is preferred for evaluation of the permeation of active agent . Besides this, the cumulative permeation profile is tested for both cases which include MN treated skin and untreated skin penetration and this compared permeation profile can be helpful for the progress of efficient MNs.

2.In vivo testing of MNs

In vivo testing of MNs was performed for analysis of key objectives such as biosafety (safety and toxicity) and in vivo pharmacokinetic and pharmacodynamic evaluation of the active pharmaceutical ingredient. Here, the hairless animal (for example mice/mouse, rabbits, guinea pigs, and monkeys) can be applied for the in vivo testing study . In addition, we can evaluate the various parameters such as trans epidermal water loss (TEWL), bioavailability, skin irritation, or inflammation. TEWL testing was performed before and after microneedling using the Delfin vapometer14.

Devices used in Microneedle drug delivery

Fig.26: Devices used in microneedle drug delivery system

Regulatory clearance of microneedles

Regulatory approval is the process of approving a medicinal product or medical device for use in humans. Up until now, there is no approved MN vaccine available in market according to regulatory authorities15.

Although there is no such clear guidance from FDA yet on microneedles-based devices as of now, FDA has clearly indicated FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, repackage, and/or import medical devices sold in the United States. In addition, CDRH regulates radiation-emitting electronic products (medical and non-medical) such as lasers, x-ray systems, ultrasound equipment, microwave ovens and color televisions. There are various types of medical devices, encompassing from a surgical glove to a pacemaker, and each device is classified per CDRH.

FDA ruled that any device with microneedles to be claimed as Class I and get an exempt must have needle length of 0.3 mm or less which assures that the needles are short enough to puncture only the outer (dead) layer of skin and does not go past that layer and affect the structure/function of the skin. In addition, these devices cannot claim any therapeutic benefits. The label, design, functions and marketing has to strictly follow the guidelines for Class I and such devices are exempted from regulation by FDA. Requirements for exempt devices are provided on FDA's website . FDA provides a monthly listings of 510(k)s cleared by FDA .

Any microneedles-based device (both manual and motorized) with needles with length exceeding 0.3 mm can alter the form and function of skin and need to be regulated. These include ones that are intended to be used as a delivery system for topical cosmeticeuticals or better absorption of pharmaceutical products16.

Scope

This guidance is being issued to assist industry in understanding when a microneedling product is a device as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. § 321(h), and is, therefore, subject to the device requirements under the FD&C Act and its implementing regulations. This document also provides information on the regulatory pathway to market for microneedling devices for aesthetic use. Throughout this guidance document, the term "we" refers to FDA staff from CDRH. "You" and "your" refers to the sponsor.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidance means that something is suggested or recommended, but not required.

This guidance addresses certain "microneedling products," which is a generic term that encompasses instruments with common technological features that include an array of needles, "micro-protrusion" tips, or pins, which can be blunt or sharp, and of varying lengths. s. The needles1 are incorporated into the body of an instrument that facilitates rolling or stamping of these needles across or into the skin. For example, the needles may be attached to a cylinder that is rolled across the skin, attached perpendicular to a flat surface that is applied to the skin in a "stamping" fashion, or arranged in an array on the tip of a pen-shaped instrument. The application of needles to skin may be done manually, or motorized where the depth and speed of penetration of needles into the skin can be controlled. Other generic terms used to

describe microneedling products include: microneedling or needling instruments, needlers, dermal rollers, microneedle rollers, microneedle stamps, dermal stamps, and variations.

Microneedling products have a wide range of uses from facilitating skin exfoliation and improvement of the appearance of skin, to treatment of scars, wrinkles, and other skin conditions (e.g., acne). In addition, these products may be for single use or multiple use for a single or multiple users, and include, or have available separately, cleaning solutions, additional needle cartridges, and/or additional tips.

Microneedling products have also been promoted with topically applied substances such as creams, ointments, gels, vitamin solutions, drugs, or blood products (e.g., platelet-rich plasma), which may be packaged together with the microneedling product or available separately where the microneedling product provides instructions for use with such topical products. Such microneedling products may be combination products under 21 CFR 3.2(e), which would be regulated by the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and/or the Center for Devices and Radiological Health (CDRH). Microneedling combination products are outside the scope of this guidance; manufacturers of such combination products should contact the Office of Combination Products (OCP) for additional information regarding the regulation of these products.2 Acupuncture needles, hypodermic needles or other needles for injection, tattoo machine needles, needle probes that emit any type of energy (e.g., radio-frequency needles) or deliver any type of energy to a patient (e.g., LASER, ultrasound), and dermabrasion devices are also outside the scope of this guidance.

Definition

The following definitions are intended to be used within the context of this guidance and are not necessarily applicable to any context beyond this document.

- Stratum corneum: The stratum corneum is the superficial or outer layer of the epidermis, consisting of several layers of flat, keratinized, non-viable, peeling cells. The stratum corneum is a dead cell layer of skin, as opposed to living layers of skin.
- Exfoliation: Exfoliation is the detachment and shedding of superficial dead cells of the epidermis, i.e., the stratum corneum.
- Living layers of skin: Living layers of skin are layers of live cells and surrounding tissues (e.g., connective tissue) within the epidermis, dermis, and subcutis, including hair follicles and glandular structures. Living layers of skin exclude the stratum corneum.
- Dermabrasion: Dermabrasion is the abrading or eroding of skin via shear forces with abrasive substrates such as brushes, rasps, corundum, and burrs.

Microneedling Products That Are Devices

A. Statutory Definition of a Device

Under section 201(h) of the FD&C Act, a device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory which is:

Recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animal, or Intended to affect the structure or any function of the body of man or other animal, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon

being metabolized for the achievement of its primary intended purposes. Whether a microneedling product is a device depends, in part, on whether it is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, or intended to affect the structure or any function of the body.

B. Determining Whether a Microneedling Product Is a Device FDA may consider the following, among other relevant sources, in determining whether a microneedling product is a device under the FD&C Act:

Firm's Claims and Statements

FDA may consider, among other things, any written or oral claims or statements in any label, labeling, advertising, and/or promotion of a microneedling product by or on behalf of a firm in determining whether a microneedling product is intended to cure, mitigate, treat or prevent disease or affect the structure or function of the body.

FDA considers claims or statements that indicate penetration or some effect beyond the stratum corneum into living layers of skin by such products to be evidence of a firm's intent to affect the structure or function of the body. The stratum corneum is a dead layer of skin that is naturally shed through the desquamation process. Therefore, claims or statements regarding the removal of the stratum corneum are not considered an intent to affect the structure or function of the body. In contrast, explicitly or implicitly claiming or stating that a microneedling product penetrates living layers of skin (e.g., epidermis and dermis) would be considered an intent to affect the structure or function of the body.

- Treats scars (e.g., acne scars, atrophic scars, hypertrophic scars, burn scars).
- Treats wrinkles and deep facial lines.
- Treats cellulite and stretch marks
- Treats dermatoses
- Treats acne
- Treats alopecia (hair loss)
- Stimulates collagen production
- Stimulates angiogenesis
- Promotes wound healing

Product Design and Technological Characteristics/Features

In addition to examining a firm's claims and statements, FDA may consider the design and technological characteristics/features of a microneedling product in determining whether a microneedling product is a device under the FDAC Act.

In considering the design and technological characteristics of these products, FDA may evaluate the following:

- Needle length and arrangement and whether the specifications facilitate
- penetration into living layers of skin
- Needle sharpness and whether that facilitates penetration into living layers of skin
- Degree of control of manual or motorized microneedling products over the movement of needles and depth of penetration into living layers of skin.

Information regarding design and technological characteristics may be found in various places, including the product's specifications, directions for use, or other materials.

Microneedling Products That Are Not Devices

Microneedling products that are not intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, and that are not intended to affect the structure or any function of the body, are not devices under section 201(h) of the FD&C Act. For example, generally, microneedling products that do not penetrate living skin (e.g., epidermal and dermal layers of the skin) and claim only to do the following would not be devices:

- Facilitate exfoliation of the skin (i.e., disruption or removal of the stratum corneum)
- Improve the appearance of skin.
- Give skin a smoother look and feel.
- Give skin a luminous look

In general, such microneedling products would not be devices; however, the products may still be subject to other requirements of the FD&C Act or other Federal statutes or regulations administered by other Federal agencies.

Classification of Certain Microneedling Devices

Microneedling devices for aesthetic use are classified as class II devices under 21 CFR 878.4430, subject to premarket notification (510(k)) and special controls outlined in the classification regulation (see 21 CFR 878.4430(b)(1)-(10)). Under 21 CFR 878.4430, a microneedling device for aesthetic use is identified as a device using one or more needles to mechanically puncture and injure skin tissue for aesthetic use. This classification does not include devices intended for transdermal delivery of topical products such as cosmetics, drugs, or biologics. FDA classified microneedling devices for aesthetic use into class II under section 513 of the FD&C Act, also referred to as the De Novo classification process. This process provides a pathway to class I or class II classification for devices for which general controls or general and special controls provide a reasonable assurance of safety and effectiveness, but for which there is no legally marketed predicate device. For those submissions where clinical data is necessary to demonstrate substantial equivalence, we recommend considering the following when designing a clinical study: The clinical study protocol should generally ensure that enrolled subjects are representative of the clinical population that the device is intended to treat. This should be reflected in the inclusion and exclusion criteria developed for the study.Safety data should generally be collected to support the safe use of the device. Such data should characterize the risks of infection, nerve and blood vessel damage, scar formation, hyper-/hypo-pigmentation, skin inflammation, allergic reactions, skin irritation, and other adverse events related to the use of the device.The proposed primary effectiveness endpoint should generally be developed to align with the proposed indications for use for your device. Effectiveness should be measured using a method that minimizes subjectivity or bias. FDA recommends use of validated measurement tools to assess device effectiveness. The follow-up period should ensure a reasonable assessment of the short-term and long-term performance of the device, as it relates to the safety and effectiveness endpoints as outlined17.

Applications of microneedles

Skin is not only a potent barrier, but also helpful for delivering bioactive agents. Thus it is well applied in molecular diagnosis and treatment. Microneedles were usually introduced for disease treatment by enhancing penetration and transporting drugs. At present, the application of microneedles is undergoing

expansion to more fields including immunobiological administration, disease diagnosis and cosmetic uses18.

Drug Delivery

The first application of MN for drug delivery was by using a solid silicon MN in 1998 . A dissolvable MN patch was used to deliver human growth hormone for transdermal delivery to hairless rat skin . A dissolvable caffeine loaded MN patch wasable to control the weight of obese mice and work as an anti-obesity treatment plan . A coated MN patch was used to deliver salmon calcitonin . A solid microneedle was used to deliver a protein antigen (ovalbumin) into hairless guinea pig skin . Solid silicon and metal MNs were used for the delivery of calcein , BSA, and insulin . Furthermore, MNs have been used for transdermal permeation for several drugs such as ibuprofen, ketoprofen, and paracetamol . Other drugs administrated via microneedles include L-Ascorbic acid, riboflavin, aspirin, docetaxel, pilocarpine, lidocaine, hydrochloride, ketoprofen, and glycerol . Despite the fact that most studies used microneedle array for drug delivery into mice, pig, human skin, there were other studies which successfully demonstrated microneedle injection into chicken thigh , and brain tissues .

Vaccine Delivery

A dissolvable MN is a common type of MN used for vaccine delivery purposes. The dissolvable MNs were used to replace hypodermic injection needles that were typically used to administer vaccines. Unlike other types of MN, the dissolvable MNs are biocompatible, robust, scalable, and do not generate biohazardouswaste . Dissolvable MNs were used to deliver vaccines for malaria, diphtheria , influenza , Hepatitis B , HIV , and polio . Even though dissolvable MNs are most frequently used for vaccine delivery, coated MNs arrays have also been successfully used for vaccination purposes . A study used a simple, safe, and compliant vaccination method to improve the immune system for pigs by administering bacillus Calmette–Guérin (BCG) vaccine with a coated MN . Another study successfully encoded hepatitis C virus protein in DNA vaccine coated on microneedle. The microneedle was effectively primed for specific cytotoxic T lymphocytes (CTLs) in mice. Furthermore, a coated microneedle carried influenza virus antigen for vaccination application in mice . Hollow MNs have been used to deliver anthrax recombinant protective antigen vaccine to a rabbit instead of regular injection . A hollow microneedle was evaluated for vaccination against plaque in a mouse model . A clinical trial conducted inbhumans using hollow microneedle with influenza vaccination showed similar results with the immune system when compared to intramuscular injection 19.

Light emitting MN devices

Microneedling has previously been used in combination with photodynamic therapy (PDT) to enhance topical delivery of aminolevulinic acid (ALA), in the treatment of actinic keratosis, the dry scaly patches of skin caused by long-term sun exposure . In this study, skin was pretreated with a MN roller, Roll-CIT TM (MN width: 108 lm, MN length: 300 lm) and ALA was then applied to the skin for a defined period. Following this, the use of red light and broadband pulsed light allowed for deeper activation of ALA, resulting in statistically significant improvements in photoageingscores .For a more detailed review of the use of MN in conjunction with PDT. Other research teams have also developed microscale optical diffusers, or fiberoptic MN, for the enhancement of clinical laser procedures and homogeneous light emission, while minimisingphotothermaldamage in non-target tissues . Evolving from these innovations,

new CE-approved devices, termed LED (light emitting diode) MicroNeedling Rollers (MN length = 1000 lm), have been launched. These incorporate titanium MNs and LED light to combat wrinkles and scarring and are used in a fashion akin to that described for the Dermarollerdevice . Worth noting, however, is that despite the fact that these devices are readily available for purchase online, there is very limited technical information available for the same which indicates the benefits of these over other ,non LED roller devices20 .

Application of microneedles in psoriasis

Psoriasis is a polygenic inflaammatory chronic disorder disease of the skin. It is immune-mediated and relapse is common.43 Psoriasis reportedly affects approximately 2% of the world's population, negatively influencing the life quality of patients. The exact cause of psoriasis is still unclear. Despite being studied for a long period, and with some achievements, no firm conclusions on the etiology and pathogenesis of this disease have been reached so far. The immune system is involved in psoriasis development and the key pathogenic factor including but not limited to TNF- a, IL-17A, IL-23 as it's been widely acknowledged. Psoriasis lesions typically feature erythema, scales, red papules, and thickened skin. Itching, desquamation, and visible plaques are the most concerning common symptoms and signs of psoriasis and may have a serious impact on the quality of life; that there is no cure for psoriasis so far is regrettable. Local and systemic drugs have been widely used for a long time in dermatologic disease treatment. Topical drugs, physical therapy, and systemic therapy are used in the treatment of psoriasis to avoid progressive damage to health. However, the topical treatment is time-consuming and messy, with the oiliness and stickiness of topical treatments commonly reported problems.

The physical therapy, constituting a significant part in the psoriasis treatment, has a relatively strict requirement of treating frequency and time. Systemic therapy is often associated with side effects. It is been reported that 74% of drugs delivered orally are not as effective as desired. An alternative injection choice is desirable when poor efficiency arises, which is usually associated with pain and fear. In the systemic therapy, the first-line drugs in the treatment of psoriasis include methotrexate (MTX), cyclosporine A (CyA)and retinoic acid.5 These drugs are effective but bring about harmful side effects such as hepatotoxicity, impaired renal function, and hypertension. Traditional oral, intramuscular, or intravenous drips may also be administered. With the advent of targeted biologics, the efficacy of the targeted attack on pathogenic factors is more significant than that of traditional drugs. The high cost of biologics is an obstacle to extensive promotion. Because of limitations of the existing treating method suchbas relatively poor penetration, low efficacy and side effects as mentioned previously, researchers are committed to performing innovative research into drug delivery methods21.

Cosmetic Application

MNs have widely been used in cosmetic applications such as skin treatment and hair growth . Kim et al. developed a hyaluronic acid-based dissolvable MN patch for the intradermal delivery of ascorbic acid and retinylretinoate. Kumar et al. showed an enhancement of local delivery of eflornithine (used to reduce facial hirsutism) in vitro and in vivo using a solid MN . Further, MN technology was able to treat two patients suffering from alopecia areatadisease . These patients experienced hair growth after treatment. Effective clinical trials have been conducted in atrophic facial scarring , atrophic acne scars , and hypertrophic burn scars using a MN. Microneedles are considered as an effective treatment for

cosmetic applications related to aging, skin lesions, vulgaris, and wrinkles . With an increasing demand of cosmetic products, microneedles (patches and rollers) have a high potential in the future .

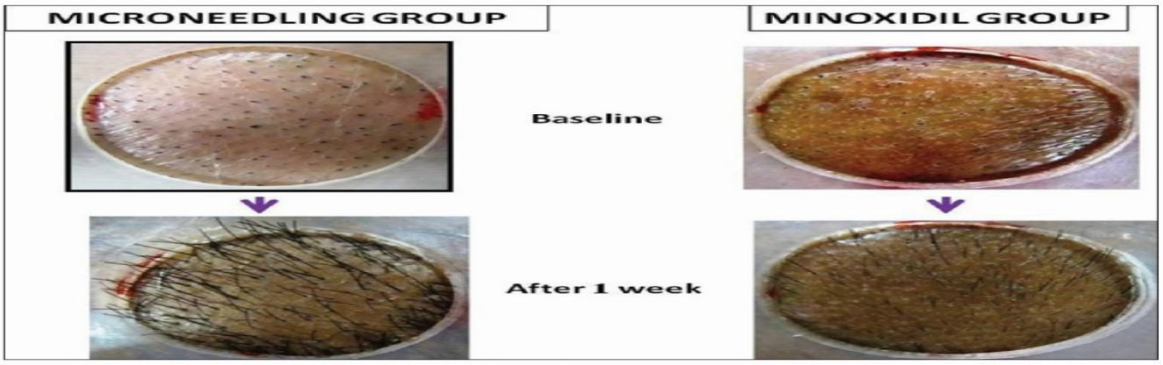

Fig 27: Applications of cosmetics

Cancer immunotherapy by MN patches

Various types of MNs, including solid removable, coated, dissolving, hollow, and hydrogel forming ones, have been proposed , in order to overcome the challenges and drawbacks of cancer immunotherapy by other approaches that have hindered their clinical translation.

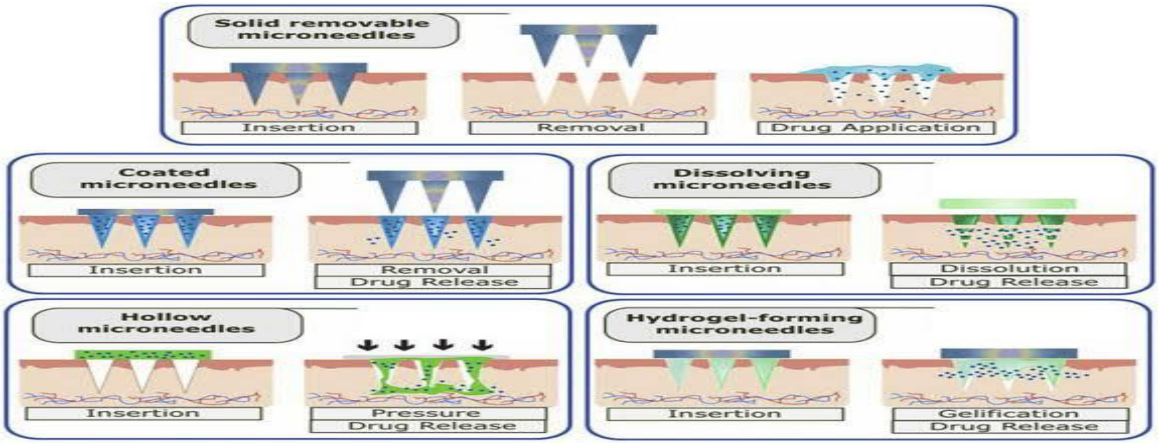

Fig. 28: Cancer related microneedle drug delivery system

Different types of MNs used for the delivery of immunotherapeutic agents and mechanisms of action for the controlled release of payloads.

- Solid MNs: Immunotherapeutic agents are able to pass via the micro-channels created by MN.
- Coated MNs: Immunotherapeutic agents are able to mix with interstitial fluids and then their delivery occurs through diffusion.
- Dissolving MNs: Dissolution and diffusion of immunotherapeutic agents occur into the body along with other components within the structure of MNs.
- Hollow MNs: Immunotherapeutic agents are able to pass through the MNs. Hydrogel-forming MNs: immunotherapeutic agents are able to diffuse into the body after insersion and the swelling of MNs22.

Sample extraction

Other applications of MNAs are in extracting and obtaining samples from patients for bioassays and monitoring setups . Self-monitoring of blood glucose (SMBG) is a simple way to control blood glucose by the patients to prevent adverse ramifications of prolonged hyperglycemia. However, the extraction of

blood with conventional needles is painful, which causes reluctance in patients to collect blood samples regularly. MNAs as a minimally invasive and painless method can facilitate the development of point of-care (POC) blood collection.

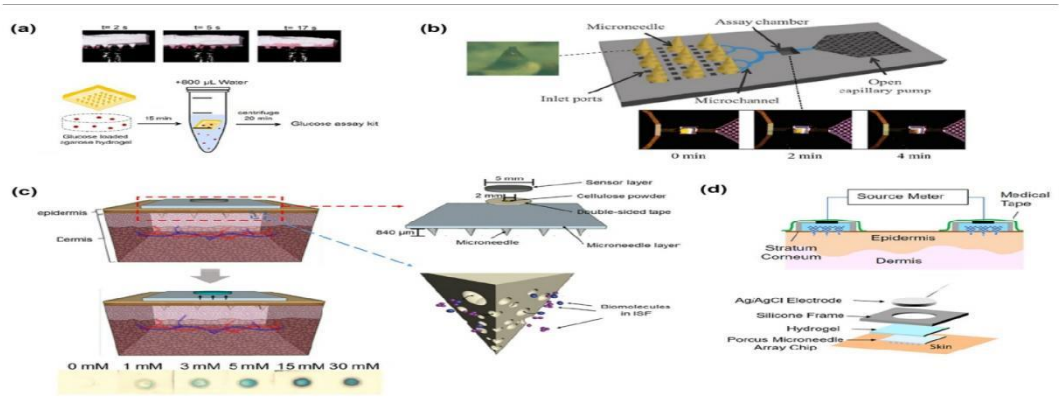

Fig. 29: Sample extraction method in microneedle drug delivery system

A hollow MNA was developed along with a paper-based colorimetric detection method to detect glucose concentrations ranging from 4 to 7 mM L-1 by eye . Using SLA 3D printing, an initial master mold was prepared to build a negative mold, which was used to fabricate 400-mm long hollow MNA. This device could absorb samples in 5 s for POC applications. MNs should be able to withstand 0.028 to 0.030 N during insertion-axial load applied by the user to penetrate into the skin . Therefore, the mechanical properties of MNs should be studied to avoid fracture. The strength of the MNA was evaluated using a 50 N load cell that pushed toward the MN at a rate of 0.01 mm s-1. The reported MN was stiff enough for application in POC diagnostics .

Based on the DLP 3D printing technology, a new setup was built with high precision to print in micro-scale, being utilized for fabrication of MNs with a photosensitive hydrogel, which was cured with different blue light . Alginate hydrogel (5 wt%), which is similar to human skin in terms of mechanical properties, was used as an artificial skin to study drug injection, extraction, and detection by the fabricated MNs. MNs were soaked in deionized (DI) water for 1 day, whereas the artificial skin was soaked in an RhB solution for the same duration, subsequently, MNs were inserted inside the skin. The integrated density of RhB inside the MNs reached more than 20 mg L 1 in 25 min, enabling the successful detection of drugs in the skin.

Using a 3D-printed master mold, porous polydimethylsiloxane (PDMS) MNs with 1,000 mm height were fabricated to extract PBS from an agarose gel-based skinphantom . In another study, drawing lithography, an additive manufacturing method, was used to fabricate a hollow metallic MN for blood sample extraction . Following an examination of various size features and resist thicknesses, a 1,800-mm height MN with a bevel angle of 15 , an inner diameter of 60 mm, and an outer diameter of 120 mm was the most efficient MN for blood extraction 23.

Interstitial fuid extraction and biosensing through porous MNs devices: a porous alumina MNs applied for transdermal extraction of glucose which is recovered by centrifugation for subsequent detection (reproduced with permission, porous PDMS MNs interfaced with microfuidic chip for fuids collection and transport, as well as glucose monitoring system in assay chamber (reproduced with permission , porous PLGA MNs loaded on the paper substrate with a paper-based sensor attached for glues concentration test based on the colorimetric analysis of the reaction zone (reproduced with permission,

porous poly(glycidyl methacrylate) MNs integrated with electrode system for transdermal electrical diagnosis (reproduced with permission .24

Other Applications

Initially, MNs were used to break barriers and enhance transdermal efficiency. Now, the use of microneedles has expanded to many other fields. The prominent studies of biomedical application of MNs. In addition to the treatment or drug delivery of various diseases, as described above, in the skin, MNs have also been used to treat the eye, cells, blood vessels, and so on . In particular, hollow microneedles and porous microneedles are mostly used in biosensor research, and good results have been obtained using them. Takeuchi et al.interfaced porous MNs with a microfluidic chip consisting of a capillary pump for the continuous sampling of ISF, which will lead to minimally invasive and continuous biosampling for long-term healthcare monitoring. With increasing crossover between disciplines, microneedles will be able to take on more functions. Chen et al. combined physical (MNs) and nonphysical (enhancer) modes of drug delivery enhancement for a macromolecule in a large animal model . These systems could potentially enable the delivery of a range of drugs through the generation and maintenance of a privileged region in the gastrointestinal tract25.

CONCLUSION

The review papers on transdermal drug delivery systems (TDDS) provide helpful information on TDDS and its evaluation process as a convenient resource for research scientists working on TDDS. Given that they can be employed to produce prospective deliverable pharmaceuticals from both hydrophobic and hydrophilic active molecules, the information above suggests that TDDS have great potentials. To optimise this drug delivery technique, more understanding of the manufacturing process and polymer processes is required. The TDDS, the subsequent generation of drug delivery systems, has a real-world application.

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