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Review on Microneedle Transdermal Drug Delivery System

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ABSTRACT

Transdermal drug administration is very advantageous because it allows medications to be given through the skin without having first-pass metabolism, giving the patient an ongoing steady state of drug in their bloodstream, and therefore increases the safety and comfort of patients. However, there are some difficulties associated with transdermal drug delivery because the skin presents such a barrier to drug passage. The stratum corneum, or outermost layer of skin, acts as a significant barrier to drug entry. It only allows a small number of drugs to pass through it naturally. Microneedles are a new, simple, yet non-invasive solution to this issue. Microneedles create micro-channels (or micro-pathways) in the skin that allow the drug to be able to penetrate through the top layers of skin without providing a significant amount of pain. Multiple designs have been developed for microneedles, such as solid, coated, hollow, dissolving and hyaluronic gel-forming types. These designs utilise a variety of materials including metals, silicon or biocompatible polymers. The purpose of this review article is to provide an overview of the different microneedles' key characteristics, methods of fabrication, primary assessment method(s), and growing usage in relation to the administration of pharmaceuticals, vaccines and/or diagnostics. Although there is great potential for further applications within the healthcare field, there are still many challenges that exist, including improvements to the mechanical integrity of needles; improvement of drug storage capabilities; prolonged release of target drug; reduction in production costs; and scaling-up for mass production.

Keywords: Skin ; Transdermal Route; Polymeric Needles; Drug Delivery; Microneedle

1. INTRODUCTION

1.1. Drug Delivery System

From ancient days, herbal remedies to today's modern dosage forms - tablets, injections, implantable systems - drugs have been introduced to the body. Oral delivery has been the most popular choice for convenience, but first-pass metabolism can result in an extended burden on the organs. Parenteral delivery can provide rapid relief or an immediate effect, but it is not the most comfortable route of administration. Inhalation therapy can also be used to treat respiratory conditions; however, it may require many doses

throughout the day and increase the chance that patients will not administer their medications properly. With all of these drawbacks associated with the conventional routes of administration, transdermal drug delivery (TDD) has gained considerable interest as an alternative method of delivering medication through the skin (which has approximately 1.8 square meters of surface area) for non-invasive drug delivery. Transdermal systems may enhance patient compliance, produce fewer gastric side effects than orally delivered drugs, prevent first-pass metabolism by the liver, and provide continuous delivery of medication. The primary disadvantage to using TDD is that the stratum corneum of the skin creates a significant barrier to the penetration of most drugs, particularly hydrophilic molecules and macromolecules. Using microneedles may be a solution to help overcome the barrier presented by the stratum corneum. Microneedles have been formed in various ways (solid, coated, hollow, dissolving, hydrogel-forming) as a method to provide temporary "micro-channels" in the skin that allow drugs to permeate the deeper layers of the dermis with little or no pain and minimal damage to the surrounding tissue.

Drug Delivery Routes across Human Skin

Drug molecules can penetrate by three pathways:

1. Sweat ducts
2. Hair follicles
3. Sebaceous glands

OR

Directly across the stratum corneum.

1.2.Anatomy of the skin

The skin, as the largest organ, comprises three layers: a defense for external factors, including toxins, trauma, and pathogens, while playing a large role in the immune system through the presence of immune cells. The outer or epidermis layer consists of five sheets, of which the stratum corneum is the outermost and accounts for about 150-200 µm of the epidermis and consists of about 10-20 µm of keratinised or dead cells.

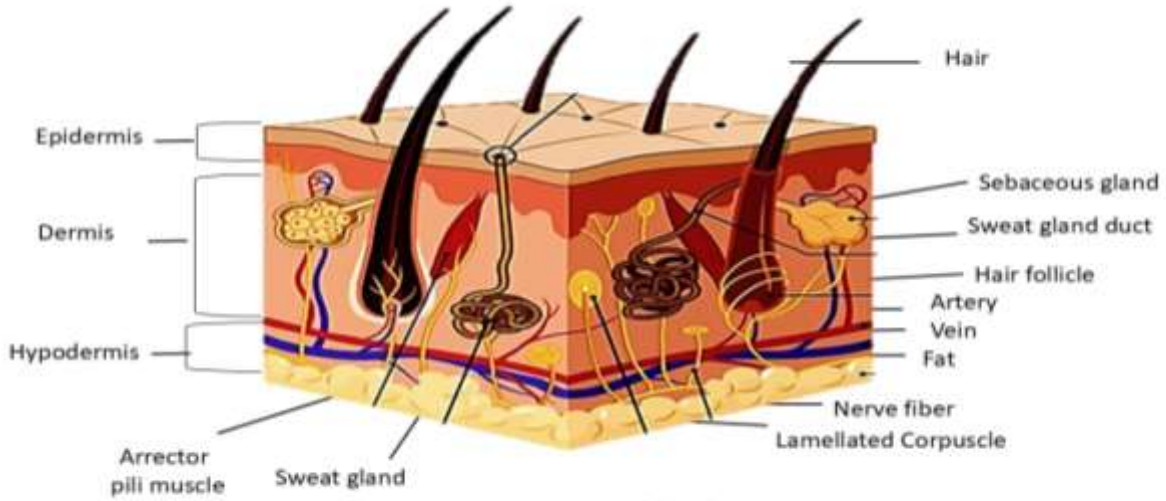

Fig 1: Anatomy of the skin

Therefore, the stratum corneum provides the most effective barrier against drug penetration. Moreover, the viable epidermis contains cells responsible for soaking drugs into the skin (keratinocytes and melanocytes), in addition to immune cells involved with drug penetration. The dermis lies beneath the epidermis and contains a variety of components such as connective tissue, blood and lymphatic vessels,

sweat glands, hair follicles, and immune cells. Therefore, the dermis plays an important role in providing structure or strength to the skin and overall function. The innermost layer of the skin is called the hypodermis and consists primarily of fat cells. The route of drug absorption through the skin is from the dermis into the skin cells (intracellular), between the skin cells (intercellular) or through the skin layers.

1.3. Transdermal drug delivery (TDD)

Transdermal drug delivery systems (TDDS) work by placing the drug on the surface of the skin and allowing it to diffuse through the various layers of skin into the systemic circulation. The diffusion process will begin in the stratum corneum, move through the epidermis and dermis, and ultimately into the bloodstream. TDDS are preferred because they can provide continuous and controlled delivery of drugs, increase bioavailability of drugs, reduce the frequency of administration, and eliminate first-pass metabolism, which is beneficial in reducing adverse effects. The major disadvantage of TDDS is the presence of the stratum corneum as a barrier. The stratum corneum is a thin yet very effective barrier for preventing most drugs from penetrating into the deeper layers of skin (example: high dose drugs and large molecule drugs like peptides and proteins). Therefore, only drugs with the proper properties (low molecular weight and appropriate lipophilicity) can be delivered to the systemic circulation by using passive transdermal patches.

To enable delivery of more drugs across the skin, many different enhancement methods have been developed over time. The first generation consisted of diffusion-based patches, the second generation consisted of chemical enhancers along with iontophoresis, and the third generation was composed primarily of more sophisticated physical methods like electroporation, thermal ablation, and microneedles. Of these methods microneedle technology, which creates microchannels in the skin through the use of miniature needles, offers some of the greatest potential for enhancing transdermal delivery with minimal pain and invasive nature attached to it.

Examples of the various types of transdermal drug delivery systems are given in Figure 2.

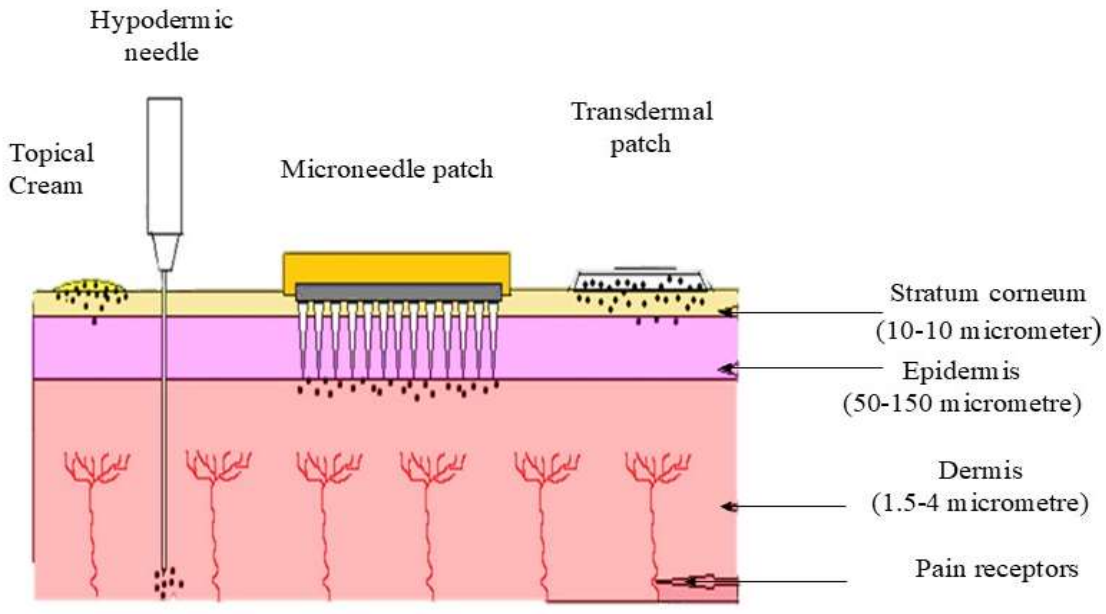

Figure 2. Various Examples of Transdermal Drug Delivery Systems Reprinted from Biomedicine & Pharmacotherapy, 109, Tejashree Waghule et al., Microneedles: A Smart Approach & Increasing Potential

for Transdermal Drug Delivery Systems, 1249 - 1258, Copyright (2019), Reproduced with Permission from Elsevier

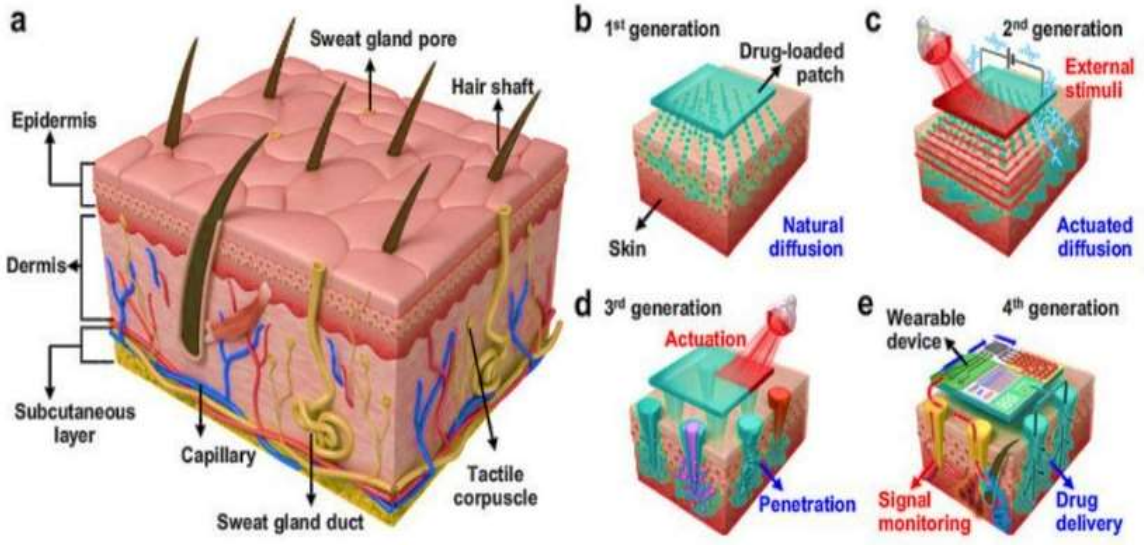

Figure 3. Schematic representation of human skin (a), First generation (bigs' name) transdermal drug delivery device (or systems) via natural drug diffusion. Second generation (or systems) of transdermal devices (Thermally (or actuation)) for drug delivery based on external stimulation, e.g. electronic (or mechanical) stimulation. Third generation (or systems) of transdermal devices based on microneedle media for better transportation of drugs through created perforations, and using the microneedle technology's multiple applications. Fourth-generation (or systems) of transdermal drug delivery devices for patient-targeted therapy by integrating into fitness wearable devices (e.g., Fitbit). Reproduced from Advanced Drug Delivery Reviews, volume 127, Hyunjae Lee et al., Device-assisted transdermal drug delivery, pages 35-45, copyright (2018) with the permission of Elsevier.

The main components of a transdermal patch are :

1. **Polymer matrix:** The transdermal drug delivery system (TDDS) employs a polymeric matrix that serves as the base material of the TDDS and controls the release of the drug from the TDDS into the body at various rates and in different amounts depending upon the requirement of the patient. Acceptable polymers used in the TDDS include, but are not limited to, cellulose-based derivatives, zein, gelatin, shellac, waxes, gums, and polybutadiene. Additional acceptable polymer materials include all types of rubber such as (but not limited to) polyisobutylene; silicone rubber; nitrile rubber; acrylonitrile rubber; neoprene rubber; polyvinyl alcohol (PVA); polyvinyl chloride (PVC); polyethylene (PE); polypropylene (PP); polyacrylate (PA); polyamide (PA); polyurea (PU); polyvinyl pyrrolidone (PVP); polymethylmethacrylate (PMMA). A desirable polymer used as the matrix for the TDDS must not chemically react with the drug; must be stable during the long-term storage of the TDDS; must be non-toxic, and must have a reasonable (or inexpensive) cost.
2. **Drug:** Drugs that can be absorbed through the skin (transdermal administration) offer a potentially attractive option if they meet specific requirements, including their pharmacokinetics and physical characteristics. Transdermal administration can offer significant benefits for the delivery of drugs that

have a high rate of first-pass "metabolism" (i.e., Fentanyl and Nitroglycerin), drugs with narrow therapeutic indexes, or drugs with very short "half-lives" (i.e., Fentanyl and Nitroglycerin**).**

3. **Permeation enhancers:** Permeation enhancers, one of the three classes of permeation enhancers (lipophilic solvents, surface active agents and two-component systems) can provide more therapeutic levels of medication through enhanced permeability of the stratum corneum. One example would be the use of DMSO.
4. **Adhesive:** The goal of using this type of adhesive is to provide high levels of therapeutic drug delivery through the stratum corneum**.**
5. **Backing laminates:** Should have high Flexibility. e.g., vinyl, polyethene.
6. **Release liner:** Protects the patch during storage. The liner is removed prior to use.
7. **Other excipients like plasticisers and solvents.**

1.4. Microneedle drug delivery system

Transdermal drug delivery via Microneedles (MN) is an exciting new active mode of drug delivery to the skin, offering solutions to the limitations of traditional transdermal patches and painful injections. Microneedles are very small (25-2000 µm long) needle-like structures, which puncture the stratum corneum layer to form micro-channels through which drugs penetrate into the epidermis or dermis with little pain and minor tissue damage. MNs improve drug penetration through the skin and will allow for self-administration. Therefore, microneedles provide a patient-friendly drug delivery method. Microneedles have been researched for many applications including the delivery of drugs, vaccines, cosmetics, and diagnostics. There are five categories of MNs: solid, coated, hollow, dissolving, and hydrogel-forming. Each category provides different patterns of drug release/delivery. MNs can be produced from a number of materials including metals, silicon, ceramics, glass, and polymers. However, the trend is to use biocompatible and biodegradable polymers, as they have better safety profiles. The delivery of drug by MNs depends on patient-specific factors such as skin condition and environmental conditions (e.g. temperature, humidity, pH, and patch adhesion). Such factors can affect the rate of drug release and penetration and highlight the importance of the design and formulation of each MN fluid delivery system. Overall, MN drug delivery systems are a promising method to provide an effective, safe, and controlled means of drug delivery.

Advantages and Disadvantages

Advantages:

There are various benefits of using microneedles for drug delivery. Directly injecting drugs into the bloodstream enables better delivery, higher bioavailability, more precise dosage, quicker onset of effect, and eliminates first-pass metabolism. The dermis has a large concentration of immune cells, therefore it is ideal for administering vaccines as well. In addition, microneedles are typically painless to use; less reliant on the practitioner's ability; and minimize biohazardous waste increasing patient compliance and safety. Finally, as microneedles remain solid and do not need refrigeration, plus the all-in-one patch format reduces the packaging size, this method results in better manufacturing efficiencies and cost savings. Because MNs are considered one of the best methods available for transdermal drug delivery since drugs delivered through MNs never reach critical human organs like the liver. In addition, they eliminate the pain of traditional injectable routes, making them an attractive alternative for individuals who have a fear of needles (trypanophobia). The application of microneedle transdermal delivery systems allows patients

themselves to apply microneedles without the need for professional assistance, thereby making it user-friendly to apply. Furthermore, microneedle administration reduces the risk of introducing microorganisms into the body. The stratum corneum layer

Disadvantages:

Despite its advantages, microneedles also have some disadvantages regarding drug delivery. The size of microneedles limits the amount of medication that can be administered. Additionally, there is a risk of experiencing allergic reactions or temporary skin rashes. Furthermore, microneedle patches require ongoing development of more advanced technologies for making the microneedles. The integrity of the patches must be maintained when they are being shipped and distributed; they must be stored properly as well. Finally, when the patch has been applied, there is a risk that some of the microneedles will break off and remain lodged under the skin. Some disadvantages associated with using MNs for transdermal drug delivery include the time it takes to apply numerous patches to a single area, the mechanical properties required of the MNs, and the compatibility of the MN materials with the body (i.e., transdermal MNs). According to Rzhevskiy, the lack of sufficient pharmacokinetic evidence to support the MN delivery route with regard to doses and potential side effects creates an issue when attempting to obtain clinical research. Additionally, how far the MN patch penetrates into the skin is impacted by the variation in thickness found in the stratum corneum and the rest of the skin, and this must also be considered between different racial/ethnic groups. The ability for drugs to be delivered effectively and for the drugs to permeate the skin is highly dependent on the proper placement of the MNs.

Economic Value and Statistics :

Microneedles (MN) have also been evaluated based on recent economic outcomes from their use in the United States' Influenza Vaccination Program. The success of MN has been supported by SEIR-based transmission modelling that shows MN-based vaccination strategies are more cost-effective than traditional injectable vaccines. Based on multiple sources, ICERs have been established at less than or equal to USD 23,000 per QALY (quality-adjusted life year) with a moderate to high level of market penetration (i.e., approximately 10% to 60%); however, financial benefits from self-administration have relatively lowered reported ICERs to less than or equal to USD 1,500, thereby reducing logistical and personnel costs associated with traditional injectables. From a commercial perspective, the microneedle market has seen steady growth over the past 22-23 years. Initial microneedle market analyses indicate gradual growth since early 2000, while recent advances in TDD (Transdermal Drug Delivery) technology have contributed to increasing growth rates. The TDD market worldwide is expected to reach between USD 90-100 billion by 2025, further driven by the increasing demand for less invasive and more patient-friendly drug delivery methods. In addition, the growing commercial interest behind this entire industry vertical

Microneedle History :

Over the past 100 years, microneedles have improved drastically, evolving from crude instruments created to penetrate the skin (as first demonstrated by Dr Ernst Kromayer in 1905) to highly sophisticated methods of micro-fabricated devices today. For instance, Dr Kromayer treated scars, discolouration, etc. by using motorised instruments to penetrate into the skin. Similarly, in 1921, a doctor named Chambers led an experiment that injected thin needles into egg yolks in order to insert needles into egg nuclei, making this experiment one of the first scientific references to microneedles. Microneedle research for drug delivery

(to/through) the stratum corneum began in the 1960s, with the first formal introduction of microneedles by the scientific community occurring in 1970. However, actual development of successful microneedles didn't occur until the 1990s as microfabrication technology advanced. Furthermore, transdermal drug delivery systems were developed, culminating in ophthalmic (scopolamine) being approved by the Food and Drug Administration (FDA) as the first transdermal patch in 1979 for motion sickness. Finally, there were significant advancements in microneedle development in 1998, with silicon-based microneedles being fabricated, demonstrating tremendous potential (to provide-) for transdermal drug delivery systems. Therefore, microneedles have been instrumental in the delivery of drugs through/into target tissues since they were invented.

Types of microneedles

A variety of materials can be used to produce microneedles, including silicon, metal, sugar and polymer. Microneedles can either be produced as a solid structure (not coated or hollow), a coating on another object or a structure that will dissolve/hydrate after use. In addition to providing the desired drug delivery method, all of these environments for microneedles will determine their ability to provide a consistent level of drug delivery, both as compared to one another and with regard to the drug itself. Microneedles are arranged into an array (typically with an adhesive backing) for insertion into the body through the skin. These arrays can range in size from tens of thousand square millimeters to hundreds of thousand square millimeters and can range significantly in size across each of the categories: solid versus coated versus dissolving versus hydrogel versus hollow Each microneedle's physical size is determined by three dimensions: a length of 150 to 1500 μm; a width between 50 μm and 250 μm; and a tip diameter of 1 to 25 μm. The drug to be administered would typically be embedded (or coated) onto the needle. All microneedle arrays are made up of microneedles that are designed to work with the specific drug and delivery system used; microneedles generally work by forming micro-channels through the skin, and then the drug is either applied topically or otherwise contained within the microneedle at the time of insertion. Based on the design and method of drug administration, there are five classification groups of microneedles: solid, coated, dissolving, hydrogel-forming and hollow microneedles. Solid microneedles are most commonly used to make micro-channels through the skin and do not deliver the drug until they have first been inserted; whereas, coated microneedles deliver drugs by direct contact (when the microneedle is inserted into the skin). Dissolving microneedles encapsulate the drug using a biodegradable substrate, then eliminate the sharp after the drug has been delivered. Finally, hydrogel-forming microneedles encapsulate the drug in a hydrated gel state in order to provide sustained-release delivery of the drug.

Solid Microneedles:

Solid microneedles, or "microneedle arrays" are made of little tapering sharp needles (of only one type of material) that do not have any drug incorporated into the needle structure. Microneedles will create temporary microchannels through the stratum corneum (this is the major barrier to transdermal drug delivery) in the skin by inserting the needles into the skin. After the insertion/Removal of the microneedles from the skin, the drug formulation/patch may be applied to the area that had been treated with microneedles to facilitate passive diffusion of the drug through the viable epidermis and upper dermis into systemic circulation and result in enhanced bioavailability. This method of "poke and patch" may also enhance drug permeation while at the same time causing minimal damage to the skin. In unique cases, microchannels produced by the use of solid microneedles could remain open for longer periods of time

and permit extended release of the drug. Solid microneedles can be utilized with systems that have diffusion-based systems and/or assisted delivery methods (e.g., iontophoresis) and have been utilized to increase the efficacy of vaccine delivery via stronger immune response compared to traditional intramuscular methods due to the ability of solid microneedles to bypass the stratum corneum. Solid microneedles may contain materials such as silicon and/or metals (e.g., stainless steel).

Figure no 4 : Solid microneedles

Coated microneedles :

Drug delivery via microneedles works best with solid microneedles that have been coated with a thin film of drug, which has been dissolved in a water-soluble excipient. When a solid microneedle is inserted into the skin, it will dissolve and release the drug contained within it into either the epidermal level or the superficial dermal layer very quickly. The volume of drug delivered upon insertion of the solid microneedle will depend on the thickness of the coating, the size of the microneedle used, and the uniformity of the coating over the solid microneedle. For example, the use of a solid microneedle for the delivery of potent drugs, such as peptides, proteins, DNA or vaccines, where rapid onset is required, works well with coated microneedles that operate using a "poke and release" mechanism. The poke-and-release mechanism of a coated solid microneedle provides a quicker route to delivering a drug than can be achieved with a solid microneedle for the purpose of providing a skin pre-treatment. Precise and reproducible coatings of solid microneedles utilising a coating process will provide for consistency in dosing for better patient care and minimal wasted drug from the coating process. Efficacy rates for delivering vaccines with coated microneedles are as good as those for delivering vaccines intradermally or intramuscularly; however, there are challenges associated with limited drug loading capacity (residual drugs remaining in the coating process), and a greater risk associated with cross-contamination of materials by technology developers.

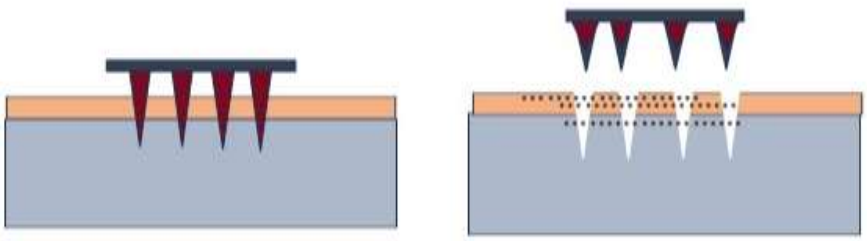

Figure no 5: Coated microneedles

Dissolving microneedles :

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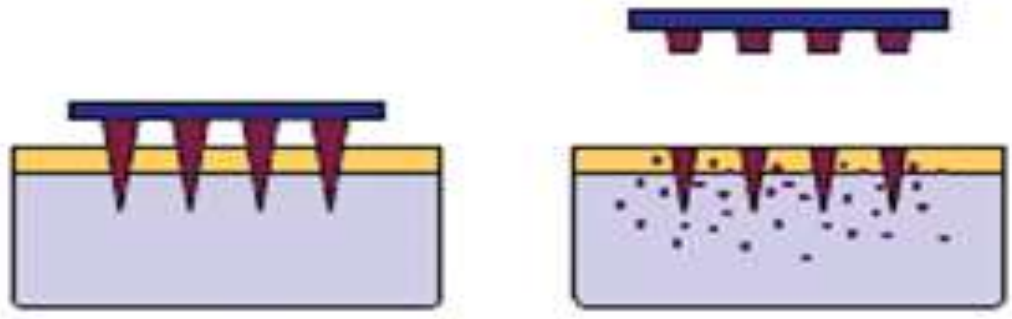

Figure no 6: Dissolving microneedles

Hydrogel Microneedles:

Microneedles have been developed using a hydrogel formation technique, which allows for the dispersion of the drug throughout the entire microneedle patch (including the microneedle tips and backing layer), and are made of highly swelling and hydrophilic crosslinked polymeric materials. When the hydrogel-forming microneedles are inserted into the skin, the crosslinked polymer absorbs interstitial fluid (in addition to numerous other polymers that swell in response to the addition of liquid), causing the polymer to swell without dissolving. Swelling creates continuous pathways (or channels) providing a fluid communication between the drug-containing hydrogel-forming microneedle patch and the microcirculation of the dermis. Once fluid reaches the channels that were formed during the swelling of the polymer, drug delivery to the dermal microcirculation will occur due to diffusion of the drug from the drug reservoir into the channels. This technique therefore, acts to provide controlled and sustained drug delivery. Hydrogel-forming microneedles can deliver larger amounts of any drug than either coated or dissolvable types of microneedles, because of the flexibility of the membrane created by the swelling hydrogels around the drug, as well as ease of sterilisation and the ability to remove the microneedles from the skin without any residual effects. However, the rate of drug release is controlled by the hydrogels due to the fact that the hydrogels create membranes surrounding the drugs, as well as the swelling hydrogels, therefore providing design flexibility and their continued use for skin delivery of drugs.

Hollow microneedle

Micro needles with a hollow center that open at one end (-) accelerate micropuncturing skin and can provide access to either the epidermis or dermis of skin using the hollow core. A hollow microneedle can be viewed as a very small needle placed into the skin allowing for injection of very hydrophilic compounds (e.g. many types of biopharmaceuticals) and similar proteins (e.g. bovine serum albumin) and various vaccines (e.g. herpes simplex virus), peptides and oligonucleotides. The hollow microneedle thus works similarly to other types of hypodermic syringes as they are typically available in a variety of small diameters to produce larger volumes of sterile product and longer than traditional hypodermic syringe dimensions that would have been necessary only to deliver a volume equivalent to that which can be delivered by a standard length hypodermic needle.

Drug can be delivered into the skin through hollow microneedles either by:

Passive diffusion

Where the drug travels from higher concentration that is typically contained in the drug formulation to a lower concentration through the hollow microneedle.

Pressure infusion mode:

Drug may be expressed into the hollow microneedle on 2-3 mL syringes or 20-50 mL compounding type syringes using a standard I.V. pump (10-20 lbs/in2) until sufficient pressure to push the drug into the hollow microneedle is generated as a result of excessive pressure created by the pump on the liquid drug formulation being expressed from the syringe into the hollow microneedle.

Hollow microneedles are a good option for rapid delivery of liquid drug products, as well as for providing continuous dosing of liquid products. However, hollow microneedles may be more easily manufactured than non-hollow microneedles due to the fact that hollow microneedles are weaker mechanically than non-hollow microneedles; therefore, improper use of hollow microneedles is common due to the design being either less complex or simpler than non-hollow microneedle designs, thus, there are difficulties associated with the usage of hollow microneedles due to their mechanical fragility compared to solid microneedles.

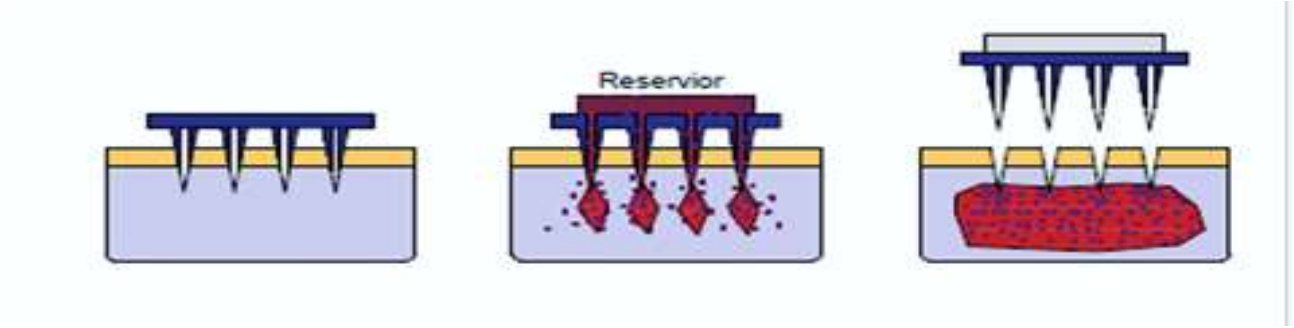

Figure no 7: Hollow microneedles

Materials used for Microneedles :

Many materials can be used to make microneedles. They can be made from different metals, polymers, or ceramics, and the porosity or composition of the microneedle will also determine what material can be used. Microneedles must have sufficient mechanical strength to penetrate the dermis without bending or breaking to work correctly. Microneedles that completely dissolve after delivering their pharmacological agent are generally made of non-toxic, biocompatible, and chemically stable materials for the entire length of the microneedle insertion/penetration into the skin; whereas, coated and dissolvable microneedles will usually be made from either water-soluble or biodegradable polymers. Depending on the medication being

delivered through transdermal drug delivery systems (TDDSs), it is essential that the material used to fabricate microneedles be compatible with the drug during both manufacture and TDDS. By selecting microneedle materials appropriately, the development of safe and effective methods of using microneedles in medication delivery could be rapidly advanced.

Silicon :

Microneedles made up of silicon were one of the first materials to be made into microneedles, as they investigated microneedles a lot during the 1990's, as well as having a large library of silicon microneedles due to its ability to manufacture use photolithography and deep reactive ion etching with a lot of precision and accuracy. The pointed tip of many silicon microneedles, as well as having a very defined geometry, allows silicon microneedles to be used for all three types of microneedles (solid, coated, and hollow). Due to the strong nature of silicon microneedles, a lot of force is generally not needed to penetrate through the skin when inserted into the skin. However, due to the very expensive nature of creating silicon microneedles, the low speed of production

Metals :

Metal is used to manufacture microneedles because it is very strong, very elastic (flexible), and has an excellent quality because metals are biocompatible (compatible with living tissues) in general. Microneedles made out of silicone are considerably less durable and more likely to break than metal. Metal microneedles have the advantage of allowing for safe and effective penetration through the skin (into the body) without damage during use (i.e., breaking or bending). The primary metal used to make microneedles is stainless steel, which has traditionally been the most commonly used metal for microneedles. Titanium is the second most common material used to form microneedles and has better mechanical characteristics than stainless steel, but it is considerably more expensive than stainless steel. Microneedles made from metal can be fabricated as solid, coated, hollow or hybrid based on the structural requirements and the needs for insertion. The manufacturing processes available to produce microneedles from metal include laser cutting, photochemical etching and electroplating. In addition to the mechanical characteristics of metal microneedles, an additional risk is that some people may experience an allergic reaction or inflammation to metal, while it is likely that stainless steel microneedles will be subject to more corrosion than titanium alloys.

Ceramic :

Alumina and the use of other ceramic materials in making microneedles is partially due to their biochemical characteristics and to their ability to withstand compression (Bystrova et al.); however, although alumina has a lot of strength against compression, it is not as strong in terms of tensile strength compared to some of the other materials used to make MN (Joseph, 2020; Morales et al., 2020). The MN are also considered to be biocompatible through the use of their mechanical properties. There have been studies done that show that when MN is manufactured from alumina, and pressure is applied to the skin with an MN manufactured from alumina, the MN will break when the MN is inserted into the skin. Supporting studies include the study by Ita (2018), as well as other studies (Bystrova et al.) that have investigated the manufacture and use of MN made out of ceramics, which indicate that there is no other material that has been more commonly used than ceramics to manufacture MN materials. An example of the common use of ceramics to prepare MN materials would include gypsum, brushite, calcium, alumina, and Ormocer. Gypsum (calcium sulfate) and brushite (calcium phosphate) can produce MN with good mechanical qualities and also good biocompatibility; only MN manufactured with alumina can provide a chemically inert (or resistant) MN.

Glass :

Hollow glass microneedles are produced primarily from borosilicate or silica glass that brings considerable advantages over other types of microneedles made from metal. These microneedles can be precisely shaped into a very sharp tapered tip using one of several methods, including micropipette pulling or wet etching techniques. The biocompatibility and biological inertia of the glass material enable it to be sterilised easily because of its stability to high temperatures and pressures. While borosilicate glass is more elastic than silica, which allows it to be stronger than pure silica, glass materials are still significantly more brittle than normal metal, which poses a primary disadvantage to the use of glass microneedles.

The risk of creating additional small pieces of glass in tissue after the glass microneedles have been removed from the skin may lead to an inflammatory or granulomatous type of response to the foreign body. This disadvantage emphasises the need for improved production approaches since the lengthy manual methods used to produce glass microneedles make their use much more prevalent in research than for commercial utilisation.

Carbohydrate :

Carbohydrate-based microneedles are created from sugar and sugar-related substances such as maltose, trehalose, sucrose, mannitol, xylitol and galactose. There are many positive attributes of carbohydrate-based materials, including cost, toxicity and compatibility with human biological tissue. The rate of release of therapeutic agents from carbohydrate-based microneedles is a continuous and predictive function of the dissolution of the carbohydrate--thus indicating the rate of release. There are two methods for making carbohydrate-based microneedles: (i) forming drug-containing carbohydrate mixtures in either silicon or metal master molded templates; and (ii) forming drug-containing carbohydrate mixtures into solid state forms of microneedles being formed from other materials. However, as mentioned previously, carbohydrate-based microneedles are very heat and moisture-sensitive, which complicates their production and storage. The major challenges for the broader commercialisation of carbohydrate-based microneedles are their tendency to degrade due to extremes in thermal conditions and low mechanical strength.

Polymers :

In recent years, there has been significant interest in using polymeric microneedles as alternatives to traditional silicon and metal microneedles. Their attractiveness comes from their biocompatibility, biodegradability, low toxicity and low costs.

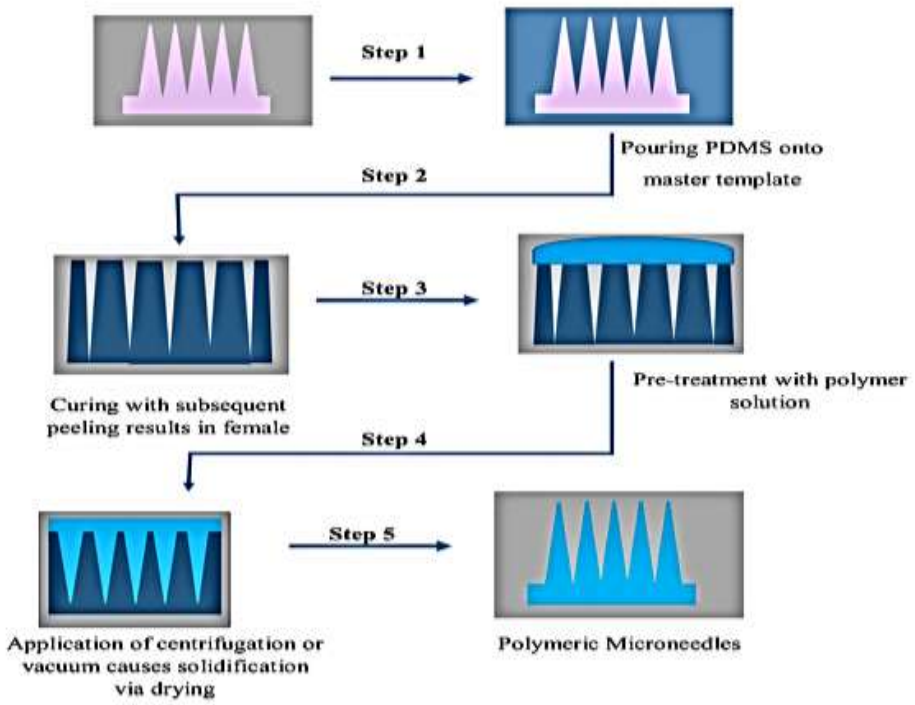

Figure 8. Schematic illustration of polymeric microneedle fabrication via polydimethylsiloxane

The selection of polymer materials for microneedle manufacture must consider the ability of the polymer to penetrate
through the stratum corneum while still being safe and non-irritating to skin tissues. Generally, water-soluble or biodegradable polymers are preferred because they dissolve or degrade within the body without generating sharp waste or causing an adverse biological response. Polymeric microneedle manufacturers generally use solvent casting and micromoulding as their primary methods of manufacture. When using solvent casting, a polymer or drug/polymer solution is poured into an inverse microneedle mould and dried under controlled conditions. Once complete, the dried microneedle array is demoulded (removed from the mould) and removed from the microneedle moulds. The solvent casting method is easy to use, scalable and allows for the development of temperature-sensitive drugs, including proteins, peptides and vaccines. Other fabrication methods being studied as means of producing polymeric microneedles include, but are not limited to, photolithography, hot embossing, replica moulding, micromachining and more recently, three-dimensional (3D) printing and two-photon polymerisation. A broad range of different types. polymers have been used in the manufacture of microneedles. Some of the most commonly used types of water-soluble and biodegradable polymers include hydroxypropyl methylcellulose (HPMC) and hyaluronic acid.

Microneedle fabrication techniques:

Before fabricating a microneedle, it is necessary to characterise the active drug, which includes determining the dose, molecular structure, pharmacokinetic/pharmacodynamic profile, and intended use. After evaluation and characterisation of the drug properties, design and material selection for the microneedle can proceed. Once a material is chosen based on the intended use of the microneedle, a fabrication technique must be selected based on the microneedle design, the selected material and the production goals. Various fabrication processes have been described to create microneedle arrays: laser

ablation; micro-moulding; solvent casting; injection moulding; additive manufacturing (3D Printing); surface and bulk micromachining; chemical etching; and lithography/electroforming replication methods. Solvent casting and micro-moulding techniques usually provide simple, low-cost manufacturing processes to fabricate polymer microneedles, while micro-electromechanical system (MEMS) techniques normally allow for accurate production of silicon and metal microneedles. Ultimately, the selection of the fabrication process will depend upon a combination of factors such as precision, reproducibility, scalability, and production costs.

A) Laser-Based Fabrication Methods:

1) Laser Cutting :

The preparation of microneedles from metals and polymers may be accomplished swiftly and effectively using laser cutting technology. A stainless-steel flat substrate is cut to create the shape of each microneedle according to a two-dimensional design produced from computer-aided design (CAD) software, and the microneedle structure is created by means of a focused laser beam vaporising some of the material away from the substrate to create the desired dimensions. After fabrication, the microneedles have typically been bent at 90 degrees mechanically to give them a three-dimensional shape. Microneedle shapes have been made using several types of laser technologies, such as carbon dioxide (CO2), ultraviolet (UV) excimer, and femtosecond. The surfaces of microneedles may be enhanced further after microneedles are fabricated through various post-processing techniques (i.e., electropolishing) for the purpose of enhancing the surface. Therefore, laser cutting provides an efficient and rapid method for producing large volume quantities of flexible metal microneedles that can be manufactured.

2)Laser ablation :

Microneedles are formed by the process of creating the microneedle using a laser beam to remove material from the metal or polymer substrate, thus allowing the creation of three-dimensional microneedles or negative moulds of microneedles from the materials used to manufacture the microneedle. The term laser ablation refers to the heating of the area to be ablated, which is achieved by focusing a wide beam of the appropriate wavelength of laser light (usually either CO2 or UV lasers) onto the substrate, where the heat generated by the laser on the substrate will cause the substrate to vaporize or sublimate, resulting in the formation of three-dimensional microneedle shapes or negative molds of microneedles. Generally, the interaction time of the laser with the substrate is very short, on the order of nanoseconds, which allows for microneedles to be created with very precise amounts of material removed from each microneedle. Because microneedles can be fabricated using laser ablation, microneedles can be made from a variety of materials (metal or polymer), and there are very low total heat inputs to the substrate due to the laser ablation method used for the fabrication of the microneedles. However, localized thermal effects on the cutting face of the microneedle can impact the physical and mechanical characteristics of the microneedle and can lead to defects (for example, formation of cracks or lower fatigue strength) in the microneedle. Due to the capital cost of laser-based equipment and the limited scalability of the laser ablation method, the use of laser ablation to produce microneedles**.**

B) Photolithography :

The lithography technique is used in the method to manufacture microneedles as a method of accurately transferring a geometrically defined two-dimensional shape (pattern) onto a substrate (material onto which the pattern will be placed). Specifically, in the process, lithography is used as a method to manufacture solid and hollow microneedles (typically made of silicon), and for manufacturing dissolvable and hydrogel

microneedles as molds by the inverse cast method. The process begins by coating a silicon wafer with a photomask, exposing it with UV light through a photomask (the desired shape for the microneedle), developing the photoresist, and removing the photoresist from the areas not exposed to UV light. The areas of the substrate that were exposed to UV light are then etched away, thus transferring the pattern from the photomask to the surface of the substrate. The lithography method is capable of producing microneedle products that have a very high degree of dimensional accuracy (precise measurements), smooth, vertical sidewalls, and geometric dimensions that are very well controlled, and can be produced using a very diverse range of materials (glass, metal, ceramic and polymer). Even though lithography provides for the rapid, accurate, and efficient manufacture of these products; due to the requirement for an advanced or 'class 100' clean room environment, proper photoresist processing techniques, high dollar costs associated with the process, and limitations due to being used only on a limited number of substrates, it is primarily used as the most common method of manufacturing microneedles.

C) Etching :

Microneedle manufacturing involves etching as an essential method of creating microneedles. Microneedle shapes, heights, and tapers are all created using photolithography, which provides for the definition of microneedle shape, height, and taper during the microneedle construction phase. The spacing between microneedles and the base width of the microneedles are also defined before starting to create the microneedles using the etching process. The etching process will remove all parts of the exposed substrate to create the final microneedle shape previously determined. There are two types of etching: wet and dry. Each of these techniques can yield either isotropic or anisotropic removal of material based on the type of etching process used. The controlled etching conditions will ensure that identical dimensional parameters and well-defined tips are created, making the etching process a critical step in the development of microneedle structures with high precision and functionality.

1)Dry Etching :

There are different methods for producing microneedles: using a combination of both techniques; ion milling and sputter, which utilize dry-etching processes (producing high-precision and precise structures) on various substrates (material) - most commonly silicon-based. Ion milling and sputter both involve directing the flow of accelerated inert gases (Argon, Sulfur Hexafluoride) at the surface of the substrate so as to cause anascipsoitronic (anistropic) material removal. Chemical etching, on the other hand, produces a gas plasma that chemically interjects the substrate's exposed surface producing a gaseous by-product which results in isotrophic production. The Reactive Ion Etching process incorporates both the physical bombardment and chemical reaction principles of both physical and chemical etching and therefore provides a larger number of variables on which to control depth and direction of etching. Optimizing the production parameters of dry etching creates a reliable means for manufacturers to produce microneedles with specific geometric dimensions and smooth tips**.**

2)Reactive Ion Etching:

This technique combines chemical and physical techniques to produce precise, isotropic or anisotropic results, allowing for the fabrication of sharp tips.

3)Wet Etching:

Wet etching is a method of microneedle fabrication or etching, using chemicals as etchants to remove material. Wet etching produces silicon and metal microneedles by removing material from a substrate using liquid etchants. Liquid etchants, such as aqueous potassium hydroxide (KOH), remove the material in a selective manner based on the crystal structure of the material that is being etched, enabling tapering

of the etched surface in a specific direction at a point. The wet etching process can be characterised as being non-uniform, rapid and cost-effective compared to dry etching; however, it does not allow any control over the generation of fine features or pattern accuracy. Therefore, it is not suitable for the fabrication of highly accurate or complex microneedle shapes. Nevertheless, wet etching remains one of the best methods for fabricating microneedles with low cost and a large area.

D) Micro-Moulding:

To create micro-moulded replicas, you first have to produce a master mould. After the master mould is created, a casting mixture of a polymer and an active drug component is added to an aluminium cast to provide the micro-moulded device (see Figure 13). One of the biggest advantages of using the micro-moulding process is that it is very cost-effective and conducive to mass production [146]. MN manufacturing often incorporates either pure polymers or polymer composite materials into the fabrication of MN devices [147]. In relation to the micro-moulding method, the PDMShaving provides a multitude of benefits that can provide a lower-cost solution while also providing ease of use due to the low surface energy and thermal stability of the polymers involved [148,149]. The main disadvantage of the micro-moulding method is that there are some restricting factors to making MNs with this process, including controlling the depth of penetration, drug load capacity, and controlling the mechanical properties of the polymer used [147**].**

E)Injection Moulding:

Injection moulding is one of the techniques utilised for the production of micro needle devices (MN's), with the aid of a true polymeric MN as illustrated in Figure 14. Polycarbocyanate (PC) was used by the researchers to manufacture a hollow polymeric 4 × 4 MN and demonstrated that the MN's could be inserted into the tissue without dulling the needles after many insertions. The injection mould building process for creating solid MNs through the use of micro-injection moulding (MIM) has also been successfully demonstrated for the delivery of high molecular weight hydrophilic substances. This can be accomplished by MIM and would provide the opportunity to use working polymeric drug delivery devices (drugs) produced in moulds made of plastic into chicken/beef liver, and after the µL of liquid was obtained, a small piece was taken from the polymer NR (NN). This is done cheaply with mass production as MNs will be created using this process. Copyright for this publication is Copyright John Willy and Sons, 2019. Micro hydraulic structure compression can produce MNs with reproducibility, accuracy of dosage, and fast rates of injection, while providing separation of the plasticising and polymer melting injections. Issues with using injection moulds are the ability to maintain injection velocity accurately.

F)Additive manufacturing, or 3D printing:

A new approach to the fabrication of microneedle arrays with high design flexibility and low-cost prototyping is offered in the 3D printing community. The fabrication of microneedles is done in a layer-by-layer process that allows for the creation of customised and complex geometries that cannot be achieved using conventional manufacturing processes. There have been important advances in the techniques for making microneedle structures using high-precision fabrication technologies such as SLA, DLP, and FDM. Besides reducing the time required for product development and minimising the need for tools, 3D printing also enables rapid design optimisation and small-scale production. “Print-and-fill” techniques have recently been developed for making master moulds of microneedles, thus offering a chance to make copies of the microneedles using polymer casting. Although there are still challenges associated with the creation of ultra-sharp tips of microneedles and high strengths of microneedles, 3D printing is still an attractive and scalable technology for the fabrication of next-generation microneedles

G) Microstereolithography (μSL) :

The μSL technique has been widely studied as a technique for the fabrication of tissue scaffolds, nerve guidance conduits, and cardiovascular stents by biomedical/tissue engineers (Dharadhar et al. 2019), the creation of 3D objects relies on the photopolymerization of a liquid resin that has been exposed to a light source such as UV light through computer-controlled processes that position each layer in the correct position to form the 3D object. The laser or digital light projector that shines light on the surface of the resin to form the 3D object has been accurately controlled such that each layer of the resin is exposed to form a structure on the building platform (Krieger et al. 2019; Melchles et al. 2010). Microneedles were fabricated from poly(propylene fumarate) using the μSL technique for the treatment of skin cancer and were found to have enhanced mechanical strength through their composition with diethyl fumarate (Lu et al. 2015). This microneedle delivery system will enable the controlled release of drugs or other compounds into the patient.

H)Digital Light Processing (DLP):

(mentioned in CLIP but not specifically covered in a separate section.) One technique mentioned is fused deposition modelling, or FDM.

I)CLIP, or Continuous Liquid Interface Production:

Unlike the traditional building up of materials in additive machines, the CLIP (Continuous Liquid Interface Production) is a technology that will make use of the photopolymerization of photopolymer resins with an image projection made by a general DLP (Digital Light Processor) chip in designing an object (Johnson et al. 2016). Although CLIP makes use of the same general principle as in DLP printing, it overcomes the challenge of the peeling of the already cured resin after the addition of each layer to the object, compared to other printing technologies that involve separation and rearrangement of the object after the addition of each layer (Schmidleithner et al. 2018). The microneedles were fabricated using CLIP technology that took approximately 2 to 10 minutes (a 25 to 100-fold reduction in time) compared to conventional extrusion-based additive manufacturing technologies. (Schmidleithner et al. 2018). Johnson et al. (2016) offered biocompatible photoresins for the fabrication of microneedle arrays (which include: trimethylolpropane triacrylate, polyethene glycol dimethacrylate, polycaprolactone trimethacrylate, and polyacrylic acid).

J)TPP, or two-photon polymerisation:

Two Photon Polymerisation (TPP) is a highly sophisticated form of 3D printing that has a very high level of detail replication (approx 100nm) (Takada et al. 2005). The process of TPP is based on the use of a laser, specifically a near-infrared spectrum (for example, a titanium sapphire laser), that does not employ UV light, which causes a photoinitiator to react and initiate the curing process from within the resin itself. In the TPP process, the curing process only occurs at the focal point where the laser energy is actually being directed, as opposed to the entire surface area of the laser beam, as is the case with the standard SLA process, when an entire surface area of laser energy simultaneously fills a volume. This means that there are virtually unlimited sources of 3DCAD available to select from in creating more complex and elaborate 3D models (Balmert et al. 2020, Park et al. 2009) (fig. 5).

Drug delivery by microneedles

Proteins Delivery Using Microneedles

The application of protein-based therapeutics in cancer, immunization, and genetic & metabolic disorders is vast, but it is limited in a clinical setting because protein therapeutics are generally poorly stable, poorly

absorbed, and of high molecular weight. Protein denaturation may occur during storage and administration, poor skin penetration may occur, and poor bioavailability may lead to reduced therapeutic potential. Hence, there has been extensive research on the transdermal application of microneedle delivery systems to enhance the delivery of protein-based therapeutics. The application of proteins using microneedles has been explored for a variety of proteins such as insulin, desmopressin, erythropoietin, lysozyme, glucagon, glucagon-like peptide-1, parathyroid hormone, and growth hormone. Microneedles can enhance protein absorption by bypassing the stratum corneum, offer a less painful mode of administration, and enhance patient compliance. Although these advantages exist, the problem of protein stability persists during the preparation of microneedle-based protein delivery systems. To overcome the problem of protein stability, the current study focuses on the application of optimised formulation approaches and processing conditions, along with the incorporation of stabilisers, to maintain the bioactivity of proteins and their therapeutic potential

Vaccines/antibodies Delivery Using Microneedles :

Most vaccines are normally administered through a needle injection, either intramuscularly or just beneath the skin, which requires the intervention of health care professionals to administer them, are stored in special coolers, and so on. Most people will not get their vaccine because of the pain associated with needles; hence, there have been many reasons for the public health sector to investigate alternative ways of vaccine administration over the years. Microneedles are becoming a popular alternative for vaccine administration through the skin. The reason that microneedles can be used as a method of vaccine delivery is because of the fact that the skin is rich in immunological cells, including many types of antigen-presenting cells, such as dendritic and Langerhans cells. This makes it possible for vaccines using microneedles to be injected directly into the epidermis and/or dermis, which promotes the uptake and faster/increased local responses to the vaccine compared to standard vaccine injections. By injecting the vaccine into the skin, then less vaccine needs to be administered, yet more antibodies are produced, which is thus very beneficial for populations trying to receive vaccinations rapidly. Another important factor that is contributing to the microneedle vaccine is the fact that the vaccine

Evaluation of microneedle

1) Characterisation methods :

Characterisation of the microneedle patch is significant in order to ensure the safety, quality, and efficacy of the microneedle patch as a drug delivery system. Microneedles can be characterised based on their morphology using either Scanning Electron Microscopy (SEM) or Optical Microscopy to determine their geometry, the sharpness of the profile, the surface homogeneity, and the level of homogeneity in the structure and how these factors will influence the penetration of the microneedles into the skin. In order to determine the chemical compatibility of the drug with the microneedle matrix, FTIR and XRD can be used. These methods will be used to determine the chemical compatibility of the drug with the microneedle matrix and will help in identifying the potential chemical interactions and changes in the physical state of the active pharmaceutical ingredient (API). The structure of the microneedle, i.e., the properties of the microneedle surface such as surface roughness and wettability, will be determined using surface profilers and contact angle measurement. The quantification of the content and homogeneity of each API is usually done using quantitative analytical techniques (HPLC or GC-MS analysis) to ensure that the amount of active ingredient in each dose can be accurately and precisely measured.

2) Dimensional evaluation :

Dimensional analysis helps in ensuring that the microneedles are manufactured with precise size and shape specifications, which have a direct bearing on the penetration depth, comfort, and efficacy of drug delivery. Needle length, tip radius, and base diameter are generally measured by high-resolution optical microscopy or scanning electron microscopy (SEM). These specifications are of utmost importance because needles of shorter lengths may not be able to penetrate the viable epidermis, while needles of longer lengths may be painful or undesirably penetrate the dermis. The tip sharpness is also of utmost importance because a blunt tip may require higher force for penetration, thus increasing the chances of discomfort or incomplete penetration. Needle density, which is the number of needles per unit area of the patch, also requires optimization to ensure that there is sufficient drug delivery without causing undue trauma to the skin. The thickness of the base plate is also measured to ensure that it is thick enough to provide adequate mechanical support to the needles during the insertion process. Dimensional consistency between batches is also measured to ensure that there is consistency in performance. Tolerances are maintained within very tight limits because even minute changes may impact the mechanical.

3)Mechanical Properties or Insertion Forces :

Mechanical property testing is an essential requirement to ensure that microneedles are safe for skin penetration without bending or breaking. Fracture force testing, also performed by texture analyzers, determines the force at which the microneedle breaks. Insertion force testing evaluates the minimum force needed to overcome the stratum corneum, which depends on the sharpness, geometry, and strength of the needle. Successful microneedles should be able to withstand forces much lower than their fracture forces. The in penetration capability of microneedles is usually evaluated by animal or human skin models removed from the body, with the penetration depth determined by histological staining or optical techniques. For flexible or wearable microneedle patches, flexibility testing is required to ensure that the skin is properly adapted to without compromising mechanical properties. A key design factor is the safety factor, which is the ratio of the fracture force to the insertion force and should be sufficiently high to ensure safe and successful application. In general, mechanical testing is required to ensure that microneedles possess the necessary strength, sharpness, and stability for successful transdermal drug delivery.

4)In Vitro Skin Permeation Studies:

In vitro skin permeation tests assess the permeation of drugs through the skin after microneedle treatment. This research is very helpful before embarking on in vivo research. The most effective technique is the Franz diffusion cell technique, which involves the use of excised human or animal skin as a barrier between the donor compartment, which contains the drug-loaded patch, and the receptor compartment, which is filled with a buffer solution. The research involves the collection of drug samples from the receptor compartment at set time intervals, which are then analysed using high-performance liquid chromatography (HPLC) to assess the rates of permeation. The research also involves the assessment of the skin barrier function by measuring the transepidermal water loss (TEWL) before and after microneedle treatment. This is an effective means of assessing that the stratum corneum has been successfully opened. Degradation or dissolution tests for biodegradable microneedles involve the assessment of the rate at which the material degrades in the skin to release the drug. In addition, fluorescent dyes or nanoparticles can be added to microneedles and tracked using confocal laser scanning microscopy (CLSM). This is an effective means of assessing the routes of penetration and distribution.

5)In-vivo animal model studies :

In vivo studies are required to assess the safety, efficacy, and biological activity of microneedle patches. Hairless rats are considered better models due to easy accessibility of the skin and the similarity of skin responses to those of human skin. The animals are anesthetized before the application of microneedles. The barrier property of the skin is assessed by the TEWL test before and after microneedle application, typically by the use of a Delfin Vapometer to confirm that the stratum corneum has been properly penetrated. Pharmacokinetic assessments include the measurement of the plasma concentration of the drug after microneedle application to assess the absorption and bioavailability of the drug, while pharmacodynamic assessments assess the therapeutic activity of the drug in disease models. Safety assessments include the assessment of local skin reactions and histopathological analysis of the skin to assess the inflammation and damage caused by the microneedle patch. Biodistribution studies can be performed to assess the localization and clearance of the drug.

MN Applications

Microneedles (MNs) have received immense attention from researchers, scientists, and people from the industry. Many studies have revealed their potential for use in different areas, such as drug delivery, vaccine delivery, disease diagnosis, and cosmetics.

Drug Delivery: The first application of microneedles for drug delivery was demonstrated in 1998 using solid silicon microneedles, which was a major milestone in transdermal drug delivery. Since then, various types of microneedles have been explored for the delivery of a range of therapeutic compounds. Dissolving microneedle patches have been successfully employed for the delivery of macromolecules like human growth hormone across rat skin and have also been explored for the management of metabolism, as exemplified by the use of caffeine-loaded microneedles for anti-obesity treatment in animal models. Coated microneedles have facilitated the effective delivery of peptide drugs like salmon calcitonin, whereas solid microneedles have been used for the delivery of protein antigens like ovalbumin for immunological studies. Silicon and metal microneedles have been demonstrated to be effective for the delivery of small molecules and proteins like calcein, bovine serum albumin, and insulin. In addition, microneedles have enhanced the transdermal permeability of a range of common drugs like ibuprofen, ketoprofen, and paracetamol, as well as a number of vitamins, anesthetics, and anticancer drugs. Although most of the applications of microneedles have been in skin-based delivery in animal and human models, microneedle-based delivery has also been demonstrated to be feasible in non-skin tissues.

Vaccine Delivery : Dissolving microneedles are the most investigated type of microneedles for vaccine delivery and have been recognized as a promising new technology for vaccine delivery that can potentially replace traditional hypodermic injections. These microneedles are biocompatible, mechanically robust, scalable, and do not create a biohazardous sharps waste issue. Dissolving microneedles have been shown to be successful in vaccine delivery for diseases such as malaria, diphtheria, influenza, hepatitis B, HIV, and polio, and have demonstrated successful immune responses through intradermal delivery. While dissolving microneedles are the most dominant in vaccine research, coated and hollow microneedles have also demonstrated immense promise. Coated microneedles have been used for vaccine delivery of BCG and DNA-based hepatitis C vaccines, which demonstrated enhanced cellular immune responses. Hollow microneedles, which enable controlled fluid delivery, have been investigated for vaccines such as anthrax and influenza, and clinical trials have demonstrated that they can induce immune responses comparable to intramuscular injection but at a lower dose. Therefore, microneedle-based vaccine delivery has

demonstrated immense promise in terms of enhanced immunogenicity, reduced dosing, enhanced patient compliance, and ease of administration, and is a promising next-generation vaccine delivery platform.

Peptide delivery: Peptide drugs have been shown to undergo significant degradation when administered orally due to enzymatic reactions in the gastrointestinal tract. Although transdermal delivery creates a barrier against enzymatic degradation, the stratum corneum layer prevents peptide diffusion. Microneedle-based delivery systems have been identified as an effective strategy to overcome this barrier by creating temporary microchannels in the skin, thereby facilitating peptide diffusion. Desmopressin, a vasopressin analogue, has been studied for its use in the treatment of diabetes insipidus, nocturnal enuresis, and haemophilia A. Its use in microneedle-based delivery systems has been explored. The results showed that microneedle-assisted delivery of desmopressin was safe and effective for efficient delivery compared to conventional delivery systems. Cyclosporine A, a high molecular weight and poorly water-soluble cyclic peptide, has been used in dermatological disorders. It has been used in dissolving microneedle-based delivery systems. Microneedles containing 10% cyclosporine A showed significant dissolution upon insertion into the skin, resulting in successful drug delivery. In another study, swelling microneedles composed of polyethene glycol diacrylate were developed for the delivery of GAP-26, a gap junction-blocking peptide. The microneedles facilitated peptide diffusion by the swelling mechanism and were therapeutically effective by inhibiting keloid fibroblast proliferation and collagen I expression

Hormone delivery : Insulin, a peptide hormone used for the treatment of diabetes, has been found to have increased therapeutic potential when delivered through microneedles. Insulin delivery through microneedles has been found to cause a more effective reduction in blood glucose levels than other methods of delivery. Experiments performed on diabetic animal models using solid microneedles resulted in a significant reduction in blood glucose levels, thus confirming the increased skin permeability of insulin. More advanced microneedle technology involving pancreatic β-cell capsules with the capacity to measure glucose concentrations has also been explored. Although the early models were not very effective, further research and development using synthetic glucose signal amplifiers mixed into microneedle matrices led to a significant improvement in the secretion of insulin by making it more glucose-sensitive. Microneedle delivery of parathyroid hormone (1-34) has also been found to have faster absorption and a shorter half-life than conventional injection methods, thus indicating rapid efficacy. These findings, therefore, indicate the potential of microneedles as an effective delivery system for hormonal therapies. Moreover, microneedle delivery systems can be designed for sustained hormone release using appropriate polymers, and other techniques such as iontophoresis may also be employed to further enhance the efficacy of hormonal delivery.

Oligonucleotide delivery : Oligonucleotides, which are short DNA or RNA sequences, have many challenges in reaching their target cells inside the body because of poor skin permeability. To address this issue, microneedle-based delivery systems have been considered. Solid microneedles made of stainless steel or titanium were employed for the delivery of phosphorothioated oligodeoxynucleotides using a poke-and-patch method, which showed significantly increased drug transport compared to full skin. Moreover, the use of iontophoresis in combination with microneedles further improved the delivery of oligonucleotides, showing better results than iontophoresis alone**.**

Lidocaine delivery : Lidocaine, a commonly used local anesthetic drug, has been proven to ensure better patient compliance when administered through microneedles due to the painlessness associated with the administration of lidocaine through microneedles compared to hypodermic injections. It has been proven that lidocaine-coated microneedles are capable of penetrating the skin rapidly and successfully, leading to

the successful administration of the drug within a few minutes. Experiments carried out using PEG-lidocaine-coated microneedles have further proved that the administration of the drug through microneedles is painless and rapid.

Pain therapy : Microneedle-based systems have been proven to have immense potential in pain management as they enable rapid and efficient transdermal drug delivery. Polymeric microneedles loaded with meloxicam exhibited close to complete drug release in one hour, with significant skin drug deposition and significantly enhanced transdermal flux compared to conventional drug solutions. This was enough to demonstrate the efficacy of microneedles in enhancing skin permeability of analgesic drugs. In the context of neuropathic pain management, dissolvable microneedles have been suggested for
delivery of specific calcitonin gene-related peptide (CGRP) antagonist peptides. These microneedles exhibited high receptor specificity, rapid dissolution rate upon administration, and analgesic activity without causing skin irritation or systemic toxicity. Overall, the successful analgesic drug delivery using microneedles clearly indicates their immense potential as a safe and patient-friendly modality for future pain management therapies.

Bacterial Disease : Microneedles have recently been identified as a promising transdermal technology for antimicrobial therapy and wound management because of their least invasive nature and enhanced patient compliance. Dissolvable polymeric microneedles functionalized with graphene oxide have been demonstrated to have enhanced mechanical strength, water resistance, and natural antibacterial and anti-inflammatory properties, in addition to minimizing microbial contamination during storage and use. Microneedle patches have also been demonstrated to have great potential for use in wound healing. Chitosan-based microneedle systems enabled controlled and temperature-dependent release of therapeutic agents such as vascular endothelial growth factor, which stimulated angiogenesis and tissue repair at the inflamed wound site. Hyaluronic acid microneedles loaded with green tea extract also had broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria. Bio-inspired microneedles with advanced multifunctional adhesive and antibacterial properties have been demonstrated to have great skin adhesion properties in both dry and wet conditions, in addition to effective bacterial inhibition. Microneedle-based delivery systems have also been investigated for novel antimicrobial uses such as bacteriophage and nanoparticle-assisted antibiotic delivery, which greatly enhanced drug retention and biofilm penetration.

Viral Disease : Microneedle-based drug delivery systems have demonstrated great potential for antiviral therapy and vaccine delivery. Dissolving microneedle array patches have been explored for the intradermal delivery of long-acting antiretroviral drugs like rilpivirine, providing a discreet and needle-free approach to oral and intramuscular drug delivery for HIV prevention and treatment. These patches showed good skin penetration, physical stability, and potential for improved patient compliance and safety from needle-stick injuries and biohazardous waste. Herpes microneedles have also been explored for improving the local delivery of acyclovir for the treatment of simplex infections. Dissolving polymeric microneedles showed a significant increase in acyclovir accumulation in the basal epidermis, reaching concentrations far exceeding those needed for viral inhibition. Similarly, microneedle-assisted transdermal delivery of lamivudine-loaded nanoparticles showed a greatly increased drug flux compared to passive diffusion, overcoming the limitations posed by the short drug half-life. Moreover, microneedle patches are being developed as promising vaccine delivery systems. Studies using influenza vaccines incorporated into microneedle tips showed preserved antigen stability and excellent immune responses in animal

models. In summary, these studies emphasise the versatility, minimally invasive nature, and efficacy of microneedles as antiviral therapy and vaccine delivery systems.

Diabetes : Transdermal insulin therapy using microneedles has been found to be extremely promising in overcoming the limitations of conventional injection therapy. Experiments carried out on diabetic animal models have revealed that the insulin released from microneedles is readily taken up, resulting in a significant reduction in blood glucose levels within an hour of administration. Both solid and dissolvable microneedles have been found to enhance the diffusion of insulin through the skin, leading to hypoglycemic effects similar to those of subcutaneous injections. Dissolvanle microneedles prepared from biocompatible polymers such as gelatin, starch, hyaluronic acid, alginate, and maltose were found to have fast dissolution rates, high bioavailability, and retention of the pharmacological activity of insulin. More advanced systems, such as microneedle rollers, iontophoresis-assisted delivery, glucose-responsive vesicles, swelling microneedles, and hydrogen peroxide-responsive nanoparticles, have further improved the diffusion and glucose-controlled release of insulin. Recent developments in the form of 3D-printed microneedles and phase-transition microneedle systems have made it possible to produce microneedles on a large scale and achieve sustained insulin release.

Cancer therapy : Cancer therapy is still faced with problems of systemic toxicity, patient compliance, and a lack of drug localization. Recently, microneedle-based drug delivery systems have emerged as a new approach for localized and minimally invasive drug delivery of anticancer drugs. Self-degradable microneedles have been investigated for the treatment of melanoma, enabling the sustained release of immune checkpoint inhibitors such as anti-PD-1 from pH-responsive nanoparticles. Similarly, pre-treatment of the skin with solid microneedles significantly enhanced the permeability and antitumor efficacy of topical 5-fluorouracil in basal cell carcinoma. Microneedles have also been investigated for the localized delivery of chemotherapeutic agents such as tamoxifen and gemcitabine for the treatment of breast cancer, thus helping in the alleviation of systemic toxicity. Polymeric microneedle systems have also shown potential in skin cancer therapy by enhancing drug penetration and retention in the target tissue. Additionally, microneedles are increasingly being investigated for cancer vaccines and immunotherapy, as they effectively penetrate the stratum corneum and deliver drugs in a controlled manner. Microneedles offer painless delivery, reduced irritation, enhanced safety, and enhanced stability of vaccine formulations compared to hypodermic needles. In conclusion, microneedle-based systems are a versatile and patient-friendly approach for cancer therapy.

Ocular Microneedle Delivery : Ocular drug delivery also has challenges due to the presence of several anatomical and physiological barriers, resulting in low bioavailability of conventional eye drops and ointments. Microneedle-based ocular drug delivery systems have been investigated as a promising alternative for the localised, minimally invasive, and targeted delivery of drugs to ocular tissues. Solid and dissolving microneedles have demonstrated enhanced penetration across corneal and scleral tissues, resulting in a substantial increase in the delivery of small molecules and macromolecules with less frequent dosing. Recent developments in microneedle technology, including fenestrated titanium microneedles and dissolving polymeric microneedles, have addressed the issues of drug loading and sustained release. The detachablefurther enhanced patient comfort by enabling rapid tip separation and uniform drug delivery to ocular tissues. Additionally, microneedle-assisted iontophoresis has demonstrated enhanced targeting of drugs to the posterior segment of the eye via the suprachoroidal space, with substantially higher drug distribution compared to the passive delivery approach. In summary, microneedle-based ocular drug

delivery systems offer a patient-friendly, effective, and home-compatible therapeutic approach for both anterior and posterior eye diseases, highlighting their vast potential for future ocular therapies.

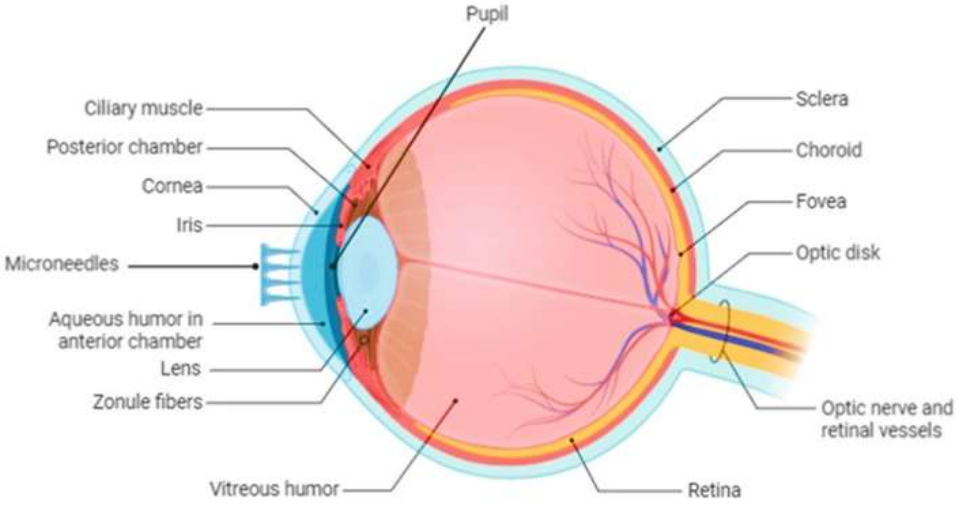

Fig Human eye: anatomical features with the microneedles array.

Cosmetic Application: Microneedles have gained popularity in the cosmetic and dermatological industry due to their ability to deliver active substances directly into the skin with minimal invasiveness. Dissolvable microneedle patches have been successfully used for the intradermal delivery of cosmetic actives such as ascorbic acid and retinyl retinoate, resulting in improved local skin availability. The use of eflornithine for the treatment of facial hirsutism has also been improved using solid microneedles in in vitro and in vivo studies. Additionally, the therapeutic strategy using microneedles has shown promising results in hair growth, with documented improvement in patients with alopecia areata. Clinical studies have also confirmed the efficacy of microneedles for the treatment of atrophic facial scars, acne scars, and hypertrophic burn scars. In summary, microneedles are currently acknowledged as a safe and effective strategy for cosmetic therapies related to aging, wrinkles, skin lesions, and acne vulgaris. With the rising demand for advanced cosmetic products, microneedle patches and rollers have vast potential for future cosmeceutical applications.

Scale-up and manufacturing considerations: The rising acceptance of microneedle-based systems by patients has resulted in the acceleration of research, patenting, and early commercialisation activities during the past two decades. Although several microneedle-based systems are already on the market, drug/protein-loaded microneedle systems have not yet reached the full commercialisation stage. The clinical studies performed so far have primarily focused on skin penetration, delivery efficiency, immunogenicity, sensory feedback, and patient acceptance, with early human studies, particularly for vaccine delivery, showing promising results. However, despite the progress, many challenges still remain. Scalable, low-cost manufacturing of polymeric microneedles is still faced with challenges of batch processing, material hygroscopicity, and the need for specialised processing environments. In addition, the absence of pharmacopoeial standards and harmonised regulatory requirements also constitutes a barrier to industrialisation. Safety concerns regarding repeated polymer deposition, skin irritation, and tissue accumulation over long periods also require further human clinical studies of longer duration. Scalable manufacturing, harmonised regulatory requirements, and a better understanding of tissue-specific interactions will be essential for the advancement of microneedle technology in the future. Tissue-specific

microneedle design, materials, and drug loading will be the key to successful clinical translation of microneedle-based drug delivery systems.

Approved products: The first microneedle product was the derma roller. Many microneedle products are coming to the market and are approved for medical and cosmetic use [2,29,78]. Many companies in Germany, the US, Europe, and Japan are selling microneedle products [9].

Clinical trials and safety: Although many preclinical studies have already demonstrated the efficacy of microneedles, only a few have advanced to the level of successful human clinical trials. The initial human clinical trials have consistently shown that microneedles caused significantly less pain and discomfort than the traditional hypodermic needle. The initial human clinical trials demonstrated that microneedles were well-tolerated with minimal or no skin irritation and were preferred by the patients due to their painless nature. The following human clinical trials demonstrated the improved efficacy of drug delivery systems, such as the rapid onset of local anaesthesia after pretreatment with microneedles and enhanced therapeutic effects in the case of skin diseases such as psoriasis when using a combination of microneedles and topical drugs. It is worth noting that the studies also highlighted the good patient acceptance and feasibility of self-administration. In conclusion, the available human clinical data support the safety, tolerability, and therapeutic efficacy of microneedle-based drug delivery systems.

Current research, challenges, and future trends: Historically, microneedle technology started with silicon-based microneedles, which were explored for their potential to enhance transdermal drug delivery. Early studies performed on cadaver skin demonstrated that microneedles could significantly enhance the diffusion of large biomolecules such as insulin and albumin, thus establishing their potential beyond conventional transdermal drug delivery systems. Since then, research on microneedles has been moving at a very rapid pace, with new and innovative microneedle designs being developed that are expected to play a pivotal role in future drug delivery systems. However, despite the rapid progress achieved in microneedle technology, there are still a number of challenges that this technology needs to overcome before it can be widely accepted in the clinical environment. These include the low drug loading capacity of the microneedle, the potential for skin irritation, the difficulty of delivering hydrophilic and high molecular weight drugs, and the need to balance the mechanical strength of the microneedle with painless insertion. In addition, infection and handling risks also need to be considered. To overcome these challenges, new and innovative microneedle designs, including hollow microneedles and the integration of microneedles with physical enhancement techniques such as ultrasound, have been developed.

Conclusion:

Historically, the microneedle technology began with silicon-based microneedles, which were investigated for their application in the improvement of transdermal drug delivery. The initial research work that was conducted on cadaver skin suggested that microneedles had the potential to greatly improve the diffusion of large biomolecules such as insulin and albumin, thus proving their potential application beyond the conventional transdermal drug delivery systems. Since then, research work on microneedles has been progressing at a very rapid pace, with new and innovative microneedle designs being developed that are expected to play a pivotal role in future drug delivery systems. However, despite the rapid progress that has been made in microneedle technology, there are still a number of challenges that this technology needs to overcome before it can be widely accepted in the clinical setting. These include the low drug loading capacity of the microneedle, the possibility of skin irritation, the difficulty of delivering hydrophilic and high molecular weight drugs, and the requirement to balance the mechanical strength of the microneedle

with painless insertion. Infection and handling risks also need to be addressed. To address these challenges, new and innovative microneedle designs such as hollow microneedles and the use of microneedles in combination

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