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Microneedle Patch: An Approachto Enhance Systemic Delivery of Drugs Through the Skin

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Abstract

Transdermal administration offers the benefit of avoiding the first-pass impact and enabling continuous medication release. The largest obstacle to transdermal distribution, however, is the fact that only a small number of strong medications with optimal physicochemical characteristics can pass through skin barriers, intercellularly penetrate, and attain therapeutic concentration through this mechanism. One strategy for achieving high patient compliance is microneedle medication administration. The use of microneedles improves medication administration by this method and helps to solve a number of issues with traditional formulations. One of the microscale physical enhancement techniques that significantly broadens the range of medications available for transdermal and intradermal administration is the use of microneedles.

The main idea is that the skin layer is disrupted, which opens up micron-sized passageways that carry the medication straight to the upper dermis or epidermis, where it can enter the systemic circulation without having to pass through the barrier. The design of the microneedles and the drug compositions can regulate the dosage, rate of distribution, and effectiveness of the medications. The types of microneedles, their designs, the materials utilised in their construction, and their production processes are all introduced in this review.

Key words: Microneedles, transdermal drug delivery, systemic circulation, enhanced permeation.

Introduction

The skin serves several functions, and its ability to act as a barrier protects the underlying organs from environmental threats such as chemicals, physical strains, and microbes. It is a desirable option to provide treatments, including medications, vaccines, biomolecules, and tiny molecules that are challenging to administer, through the skin. For drug delivery through the skin, topical creams and hypodermic needles are the most often utilised methods. Patients are less likely to accept needles because of the agony they cause, and topical creams have a lower bioavailability. The main obstacle to drug delivery by topical application is the skin. Three basic layers comprise skin: the middle epidermis, the thickest layer, the dermis, and the outermost stratum corneum. Due to its ability to filter out specific compounds, such as lipophilic and low molecular weight medicines, the stratum corneum layer functions similarly to a main barrier. When creating topical formulations, the layer's comparatively lower permeability causes a number of issues.

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Types of microneedles

A variety of materials such as silicon, stainless steel, sugar, and polymers have been used to fabricate solid, coated, dissolvable, or hydrogel microneedles. Each type of the microneedle has their unique characteristics, advantages, disadvantages, applications, and material type. A typical microneedle has the shape of a tapered sharp tip with a length of 150–1500 μm, a width of 50–250 μm, and a tip thickness of 1–25 μm. The drug is generally placed in or on the microneedle tip, which is fixed to the base substrate underneath to form an arrayshown in figure1.[4]

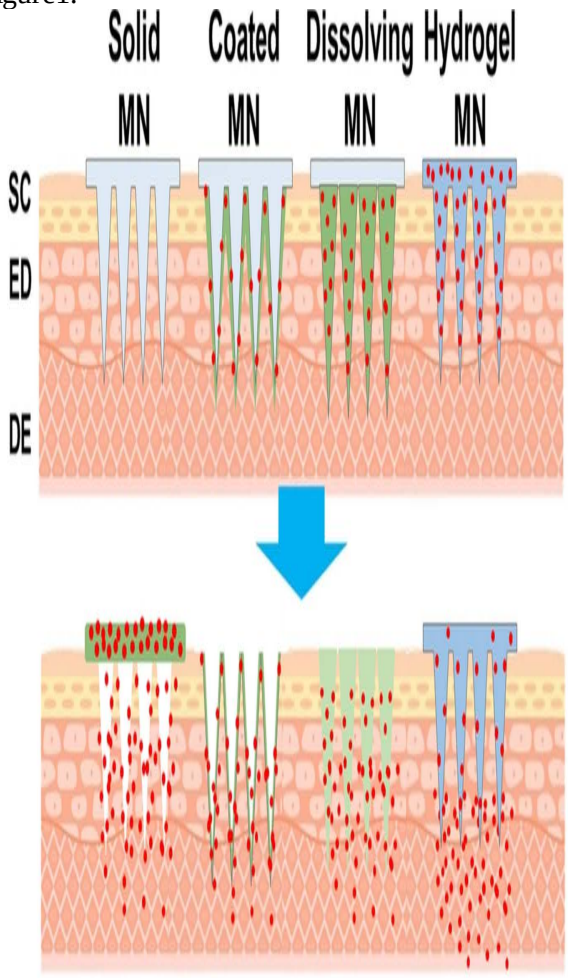

Fig. 1: **Diagrammatic representation of the several kinds of microneedles and how drugs are delivered to them.** (MN- microneedles, ED-epidermis, DE-dermis, and SC-stratum corneum.).[5]

Solid microneedles

This type of microneedle structure is designed to penetrate the stratum corneum in order to enhance drug delivery to the dermis to improve the bioavailability and kinetic transport across the skin.They are an array containing microscale tapered sharp tips composed of a single material without any drugs or excipients, They are inserted into the skin, creating micron-sized pores on the skin surface. When the drug is placed on the treated area, the drug passes through the stratum corneum, the largest barrier of the skin, through these pores; it is easily transferred to the capillaries in the superficial dermis, increasing the bioavailability of the drug.[6] The agent may be formulated as a conventional transdermal patch or topical skin formulation. Drugs can be delivered over and extended time by including reagents that keep the pores open for a longer duration.[7]

Coated microneedles

In coated microneedles, the surface of a solid microneedle is coated with a water-soluble matrix so that the drug dissolves rapidly into the skin after microneedle insertion. The coating formulation should form a film on the surface of the microneedle and maintain adhesion during storage and insertion into the skin. To achieve this purpose, the coating formulation should have adequate viscosity. The location where the coating formulation is placed should be considered. Generally, it is economical to place the drugs only at the tip where the microneedle enters the actual skin. In the case of dip coating, the drug-coated area can be controlled via regulating the depth to which the microneedle is dipped into the coating formulation shown in figure2. The drug-coated area can be determined by controlling the surface tension of the coating formulation, thus regulating the spreading of the microneedle. In coated microneedles, the drug can quickly dissolve in the skin, resulting in a fast onset of drug action. The thickness of the coating can be increased by repeating the formulation coating; however, it is not suitable for drug delivery as it requires a large dose due to dose limitations.[8]

An advantage of a coated MN is rapid delivery of the drug to the skin; however, the remnant drug at the tip of the needle might infect other patients.

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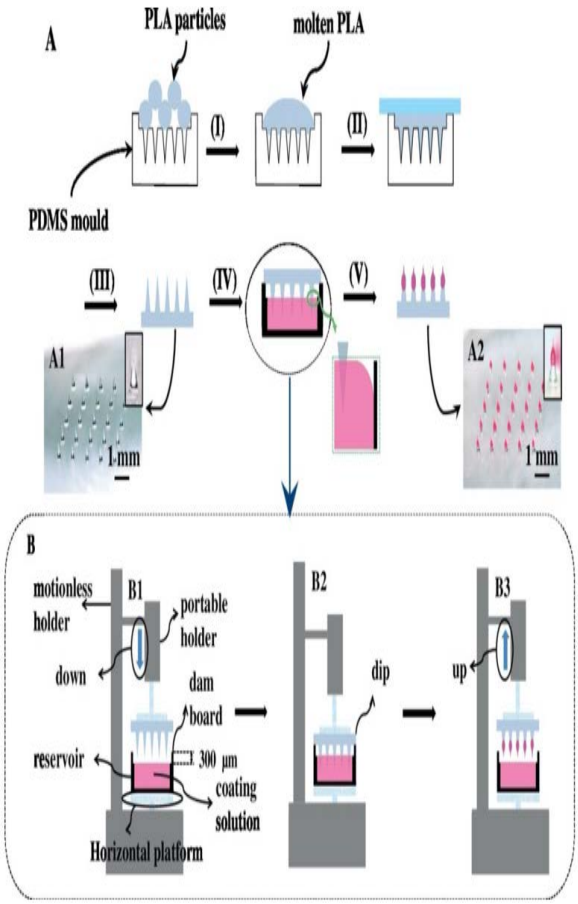

Fig. 2: Production of the coated polymer MNs: (A) A flowchart showing the steps involved in producing the coated polymer MNs. The process used to create the coated polymer MNs was as follows: (I) covering the polydimethylsiloxane (PDMS) cavities' surface with heated and melted PLA; (II) filling the mold cavities with melted PLA; (III) applying pressure to the melted PLA and allowing it to cool; (IV) dipping the PLA MNs into the coating solution; and (V) drying the coated polymer MNs. PLA MNs with a length of 650 µm are depicted in figure (A1). The 650 µm long MNs coated with formulation III are shown in image (A2). A schematic diagram of the movable, elevating and lowering apparatus is shown in Image (B). Images (B2) and (B3) depict the PLA MNs dipped in the coating solution and the portable holder emerging from the reservoir, respectively.[8]

Dissolving microneedles

Microneedles themselves can be made of water-soluble or biodegradable materials that contain the drugs and possess sufficient mechanical strength to penetrate the skin. Insertion of a dissolving microneedle into the skin does not generate sharps waste because it rapidly dissolves or disintegrates upon contact with the skin fluid. Dissolving microneedles are primarily manufactured using a water-soluble biodegradable polymer via a solvent casting method. Biodegradable, cellulose-based polymers such as carboxymethyl cellulose (CMC) and methyl cellulose are frequently used. Saccharides (e.g. trehalose and sucrose) are also included in the microneedles; they promote disintegration of the formulation and stabilize biomolecules.[9,10] The formulation of the drug-containing tip should exhibit compatibility with the drug, provide mechanical strength, and have a sufficiently low viscosity for filling the microscale mold space well without air bubbles shown in figure 3. The base substrate containing no drug may have a higher viscosity than the tip, may be mechanically weak, or may be a water-insoluble material.

However, this type of MN requires complete insertion which is often difficult to accomplish, and also undergoes a delay in dissolution.

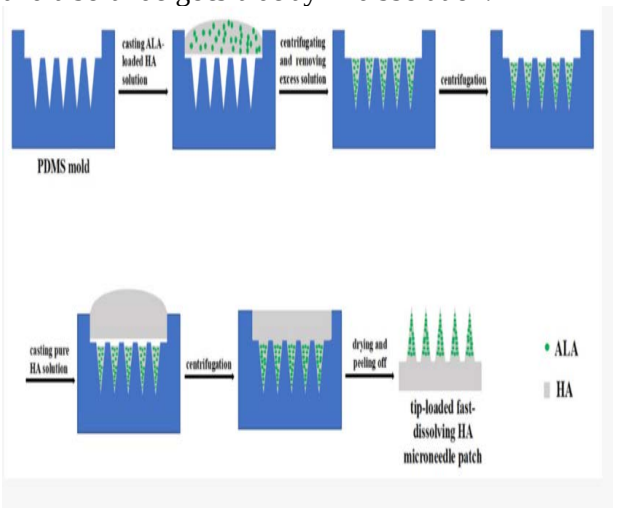

Fig. 3: Schematic illustration of the process to fabricating the tip-loaded fast-dissolving HA MN patch.[11]

Hydrogel microneedles

In hydrogel microneedles, the drug is contained in all areas of the microneedle tip, base substrate, and patch backing and is released at a slow rate while the patch is applied to the skin.The microneedle patches are primarily composed of hydrogel, and when they encounter fluids in the skin, they are hydrated but not dissolved.[12] A high amount of the drug in the hydrogel is delivered to the skin through diffusion. Since the

drug can be incorporated in the entire microneedle patch, this system is suitable for large dose delivery; however, its disadvantage is that the patch-wearing time is long because the drug delivery rate is slow.

Materials for microneedles

The primary reason behind the production of MNs is their ability to penetrate the skin without breaking or bending. Several factors, such as material, manufacturing method, and design, have been considered in tackling the MN manufacturing challenge. A variety of materials have been used to fabricate different types of MNs. Examples of these materials are silicon, metals, ceramic, and polymers. A combination of different material types have been utilized for biomedical applications in the area of delivery drugs, tissue engineering, and biomedical implants.

Metal

Metals are utilized in the manufacture of MNs as they have good biocompatibility and mechanical properties. Metal materials exhibit high mechanical and tensile strength; therefore, they can easily pass through the skin. They are used to produce solid, coated, and hollow microneedles.[13] In general, stainless steel are typical metal materials used in microneedles. Stainless steel is the most used metal material for microneedle production; however, it exhibits a faster corrosion rate than titanium alloy.

Polymer

Polymers offer a promising material alternative for MN. They have excellent biocompatibility, low toxicity, and low cost. The polymers used for microneedle manufacture should be water-soluble, biocompatible, and mechanically strong for skin insertion. The most common method for producing polymer microneedle is the solvent casting method. This method involves obtaining an inverse mold from the microneedle structure, pouring a polymer formulation on it, drying it, and peeling it from the inverse mold. Dissolving or hydrogel microneedles are manufactured using the solvent casting method with various types of polymers such as hydroxypropyl methylcellulose, hyaluronic acid, CMC, polyvinyl pyrrolidone, and poly.[14]

Ceramic

Since ceramic materials such as alumina, calcium phosphate, and calcium sulphate exhibit biocompatibility and provide sufficient mechanical strength, studies have explored their use in the preparation of microneedles.[15]

Silicon

In the 1990s, the first MN was fabricated from silicon material. Silicon microneedles can be precisely manufactured with small sharp tips with lengths of 100 μm or less using deep reactive ion etching and photolithography. However, the equipment used is expensive, the process is expensive, and the production speed is slow. The silicon microneedle can cause safety problems when it breaks from the skin and fragments remain in the tissue.[16]

On the other hand, there are limitations associated with using silicon such as time-consuming fabrication, high cost, and the possibility of causing fractures in the skin.

Glass

Glass microneedles are primarily hollow and prepared using wet etching or micropipette puller. It exhibits sufficient strength for skin insertion, enabling easy processing of the tapered shape. It is easy to sterilize because it isstable at high temperature and pressure; the material itself is biocompatible. However, it breaks easily; specifically, if the tip of the microneedle is broken and it remains in the skin tissue, it can cause inflammation or granulomas.[17]

Method of preparation of microneedles

When designing a microneedle, the objective of the microneedle is considered first. The drug type and dose, desirable pharmacokinetics/pharmacodynamics, and targets for use are considered. Next, the most optimized microneedle design and materials aredetermined. The manufacturing method for microneedles varies depending on the design or material.When focusing on theeconomic aspect, a method such as solvent casting, which is easy to set up, is used. In contrast, if the focus is on the accuracy, precision, and reproducibility of needle production, production of metal or silicon microneedles based on MEMS(Micro-Electro-Mechanical Systems technology) can be considered. We have

summarized various methods reported till date for microneedle manufacture.

Laser-mediated fabrication techniques

Laser ablation

Laser ablation incorporates the use of a focused optical light beam in eliminating material from a substrate to create MN arrays.[18] Lasers have been used to process different materials ranging from micro- and nano-scale for several applications.

Laser ablation is also used for fabricating metal or polymer microneedles. Laser cutting involves cutting a metal or polymer plate into a 2D shape, whereas laser ablation engraves the plate into a 3D shape. Basically, when the substrate is irradiated with a laser beam (e.g., CO_2 laser beam), it absorbs the laser energy and heats, resulting in its evaporation or sublimation. Through this process, an inverse mold can be produced by generating a microneedle pattern.

Laser cutting

Laser cutting is primarily used for manufacturing a metal or polymer microneedle; the most used material is stainless steel. The 2D shape of a microneedle is generated through cutting on a flat 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^o to create a 3D microneedle. Needle tips or rough surfaces can be cleaned using electropolishing.[19, 20]

Photolithography

Photolithography is used to elaborately create solid or hollow microneedles. This method is used to manufacture silicon microneedles or dissolving/hydrogel microneedles via making an inverse mold based on the microneedle structure. When fabricating silicon microneedles using photolithography, a sacrificial layer is deposited in the form of a thin film on cleanly treated silicon. Subsequently, a photo resist, a photosensitive polymer, is coated on the silicon via spin coating. If the photomask with a desirable pattern is aligned on the substrate and exposed to strong UV radiation, the desired pattern is generated in the part exposed or not exposed. The pattern is generated in the photoresist through the development process; subsequently, the exposed substrate without the photoresist is etched through the etching step. Consequently, a desirable pattern is transferred from the photomask to the photoresist to the silicon.[17, 21]

Etching

When a microneedle is fabricated using general photolithography, etching is an important process for determining the tapered shape of the microneedle tip. Before the etching process, the size of the microneedle base and the gap among the microneedles are determined. Subsequently, the length and shape of the microneedles are determined through the etching process. The etching process is classified as dry etching and wet etching. It results in isotropic or anisotropic etching, depending on the method utilized.[22]

Dry etching

Dry etching is primarily used to create solid or hollow microneedles. It is classified into physical methods and chemical methods. Physical methods include ion milling and sputtering. In dry etching, an inert gas is ionized by high energy and unidirectional electrodes. Because the ions strike the silicon substrate at a high speed in a single direction, anisotropic etching is performed. In the manufacturing process, the area protected by the oxide film (sacrificial layer) or photoresist is hardly etched, while the area exposed on the silicon is etched. Chemical methods include high pressure plasma etching, in which a chemically reactive plasma gas is generated using strong energy. The plasma reacts with the surface of the substrate, and it is converted into a volatile material, which is blown away, thereby resulting in isotropic etching of the substrate. Reactive ion etching combines physical and chemical methods; both plasma and sputter etching can be used to control isotropic and anisotropic etching. Through the optimization of this process, a precise microneedle sharp tip can be manufactured.

Wet etching

Wet etching is also used for fabrication of metal or silicon microneedles. In this process, a pattern is produced on the substrate using a chemical etchant. In the case of a silicon wafer, a potassium hydroxide aqueous solution is used; a sharp tip shape can be produced by applying different rates of etching, depending on the direction of the silicon crystals. Wet etching is primarily isotropic etching via a chemical reaction; the etching rate is significantly faster than that in dry etching. Although the cost required for the entire process is

low, the poor accuracy of this method is a disadvantage for the fabrication of fine patterns.[23]

Additive manufacturing (3D printing)

3D printing is an additive processing technology that rapidly prototypes a design at low cost and high throughput. Recently, the 3D printing technology has been expanded to include the production of microstructures such as microneedles. The existing manufacturing technology is limited to the production of a simple structured microneedle, while the new 3D printing technology can produce a more sophisticated and complex-shaped microneedle structure. Microneedles are manufactured using high precision stereolithography (SLA), digital light processing (DLP) method, or fused deposition modeling (FDM).

Microstereolithography (μSL)

Microstereolithography has been widely used in the production of tissue scaffolds, nerve guidance conduits, and cardiovascular stents in biomedical and tissue engineering. The manufacturing of 3D objects using the μSL method is based on the photopolymerization of a liquid resin using a light source such as UV radiation and the process of controlling the space to manufacture the 3D object. The building stage and laser beam or digital light projector are precisely controlled by a computer so that the light is illuminated on the resin surface. A layer-by-layer is created on the surface of the building platform, forming the structure. A microneedle based on poly(propylene fumarate) was prepared using μSL technology for the treatment of skin cancer. To improve mechanical strength, a biodegradable polymer, poly(propylene fumarate), was mixed with diethyl fumarate. This microneedle system enabled controlled release of dacarbazine, an anti-cancer drug, for 5 weeks through modification of the drug dose and molecular weight of the polymer monomer.[24]

Continuous liquid interface production (CLIP)

Continuous liquid interface production is different from the traditional layer-by-layer approach to additive manufacturing. CLIP fabricates an object through photopolymerization of a photoreactive resin using the light reflected from a general DLP chip. The basic principle of the CLIP is the same as that for the DLP method; however, CLIP addresses the problem of peeling of the cured resin layer. Because the separation and rearrangement steps, which are rate limiting in the conventional process, have been eliminated, the microneedle could be produced in approximately 2 to 10 min (i.e., reducing the output time by approximately 25 to 100 times compared to that for the conventional method).[25]

Two-photon polymerization (TPP)

Two-photon polymerization is a sophisticated additive manufacturing method with a resolution of approximately 100nm. TPP initiates polymerization of the resin through multiphoton absorption, which occurs through excitation of the photoinitiator. TPP employs a near-infrared wavelength laser, such as a titanium-sapphire laser, instead of UV light. In the TPP method, unlike in the conventional SLA method, the curing reaction does not occur in the illumination path of the entire laser beam but only at the focal point. Therefore, it is possible to manufacture elaborate and complex 3D structures.[26]

Evaluation of microneedles

***In-vitro* skin permeation studies**

Diffusion cell apparatus is used to find the permeation of the drug through the skin. Pig ear skin is mostly used in the experiment which is mounted between the receptor and donor compartment. The cumulative permeation profiles of microneedle treated and untreated skin are compared. [27]

***In-vivo* animal model studies**

Hairless rats can be used for the study. A suitable technique to anesthetize the animal shall be used. One of the parameters considered is trans-epidermal water loss (TEWL) which is measured before and after micro needling. Delfin vapometer is used to measure this parameter.[27]

Dimensional evaluation

Various methods are used to evaluate the needle geometry and to measure the tip radius, length, height of the microneedle. The most common methods are optical or electrical microscopy. Analysis of a 3D image gives a better picture of needle geometry and helps in quality control. Scanning Electron Microscope (SEM) and confocal laser microscope have been used for this purpose. SEM produces an image of a sample by

making use of a focused beam of electrons which interact with the atoms in the sample while scanning and producing various signals which give information about the sample surface topography and composition. Confocal laser microscope produces high-resolution images.[28, 29]

Mechanical properties or insertion forces

A microneedle must be sharp and slender enough so that it can easily penetrate into the skin and also be strong enough so that it does not break when inside the skin. Two important factors for a safe and efficient design of microneedles are the force at which the microneedle loses its structural integrity and the insertion force. The ratio of these two forces is called as the 'safety factor'. The ratio is preferred to be as high as possible.[30]

Characterization methods

The drug can be loaded onto or into the microneedles either in suspension/dispersion form or encapsulated form (liposomes, nanoparticles, nanoliposomes). The drug can be coated with the polymer solution or can be applied as a patch. Various physicochemical characterizations including particle size, polydispersity index, viscosity, and zeta potential can be evaluated for loaded drug depending on the type of formulation used in the microneedles. Drug release, adhesion, permeation tests are performed for a patch which is applied after pre-treatment. The size, internal structure, and crystallinity of the liposomes or nanocarriers can be performed using a dynamic light scattering, X-ray scattering, and transmission electron microscopy technique. Stability studies of drug dispersion and microneedles can be studied at a different temperature, pH and simulated *in-vivo* physiological conditions (cell line or tissues). Other tests like solubility studies, drug content, *in-vitro* release tests, and biocompatibility studies are also performed on designed microneedles.[31, 32]

Conclusion

This review summarizes MNs technology in the transdermal drug delivery era.Over the past few decades, a variety of MN systems with distinct delivery mechanisms have been developed and used for the delivery of small or macromolecules. Microneedles can be classified as solid, coating, dissolving, and hydrogel formulations. They are composed of various materials such as silicon, metal, polymer, glass, and ceramic. Moreover, MN mechanical tests and their characterization are explored in the literature.Novel manufacturing methods, micromachining and 3D printing technologies in particular, are envisaged to lower the costs and simplify fabrication procedures in the near future.This technique has the potential to provide therapeutic effects in multiple fields.

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