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Transdermal Drug Delivery: Microneedles, Their Fabrication and Current Trends in Delivery Methods

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Authors' contributions

This work was carried out in collaboration between both authors. Author MO was involved with the literature search and the writing of the manuscript. Author HKO drafted the study design and edited the review. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The past few decades have seen a tremendous growth in the use of microneedles in the transdermal delivery of therapeutics. This is due to the several advantages that microneedles offer in the delivery of compounds. Therapeutics are delivered in a simple, minimally invasive and painless manner. This has led to the employment of different materials such as silicon and polymer in the fabrication of this device. Also, methods have been introduced in the fabrication of microneedles to meet the high demand this technology raises. This review article is meant to give a foundational knowledge about this rapidly evolving tool with detailed emphasis on their fabrication and delivery methods as well as future prospects of microneedles in the medical industry.

Keywords: Stratum corneum; silicon; polymer; hydrogel.

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1. INTRODUCTION

The most common routes in the administration of drugs are the oral and hypodermic methods of delivery. But there are several limitations to the use of these methods such as pre-systemic metabolism (first pass effect), acidic pH and irritation of the stomach, pain associated with hypodermic injection and a certain degree of variability in the absorption of the drugs [1,2]. An attractive alternative approach is the patient friendly transdermal delivery of drugs. This mode of delivery overcomes the limitations mentioned above, is less expensive, non-invasive, can be self-administered and also be used in the sustained delivery of the active drug [3].

Although the transdermal method of delivery offers exciting promises, there is still a major hurdle in the delivery of several medications. The stratum corneum (SC) of the skin is a major barrier in the permeation of materials. It has a thickness of approximately 10 - 15μm, and is a key agent that regulates strongly the influx of drugs into the skin [4]. The barrier set up by the stratum corneum has therefore led to the exploration of various tools to promote the transfer of materials. Approaches such as electroporation, ultrasonic enhancement or chemical enhancers have been employed to decrease the permeation barrier of the skin [5]. There are several drawbacks experienced in the utilization of these techniques such as irritation of the skin and they are also mostly used for small molecules [6].

There is however a significant advantage in the use of microneedles for the delivery of substances as it can be used to form micro-conduit in the skin [5]. Also, the use of their sharp tips and short ends ensure that the nerves endings are not damaged, thus, this provides a non-invasive way to deliver molecules into the intradermal layer of the skin without inducing pain [5].

In addition, microneedles seldom cause infection during administration of drugs or nanoparticles. Further, it has been tested to increase the rate of permeation of compounds through the skin [7]. Hence, microneedle array technology is an evolving technique that combines the ease of use of transdermal patch and the effectiveness of syringes through the use of multiple projections from a backing plate that enhance penetration and provides a unique form of delivery [8].

Microneedles were first proposed in the 1970s but it found its application in the 1990s. It was first mentioned by Vandervoot and Ludwig [9]. Since then, it has been a potential replacement for hypodermic needles. This has led to an increase in the interest of scientists in this field and a lot of work has been done in the area of fabrication and its use in drug delivery [9]. The first patent of microneedles as a drug delivery device in the United States was filed by inventors, Gerstel and Place in 1971. They used the term 'puncturing projections' to describe this invention.

However, the first proof of concept of microneedles emerged in 1998 when Henry et al. [10] utilized silicon microneedles to deliver calcein across the human skin. The authors found out that the silicon microneedles increased the permeability of calcein by a magnitude of four orders [11].

Till date, microneedles have been used to successfully deliver substances across biological membranes which include the skin, mucosal tissue and sclera [4]. In addition, microneedles have been successfully used to deliver large molecules such as peptides, proteins, oligonucleotides, insulin, vaccines and other compounds through the skin employing a number of different strategies to deliver these compounds in a non-invasive manner [4].

Therefore, the focus of this article is to first introduce the role of the skin in the transdermal delivery of drugs, give a deeper understanding of microneedles and its fabrication methods. In addition, discuss on the major delivery types, clinical studies that have been carried out and future work.

2. BASIS OF TRANSDERMAL DRUG DELIVERY; THE SKIN

The skin is the outer layer that covers the entire body. It is the largest organ in the human anatomy with more than 10% body mass [2,9]. The skin enables the body to be able to interact more closely with the environment [7]. It is also associated with protection against excess water loss and unwanted agents [12], contain and protect internal organs. It provides insulation, regulation of internal body temperature, homeostatic balance and sensing of external stimuli [2,7]. It is seemingly popular to use the skin as a site of systemic delivery because of its large surface area [12]. However, the surface

area of the skin constantly undergoes changes which depend on factors such as age, height, sex, thickness [2], weight loss and gain of the individual [12].

The skin is divided into three layers: epidermis, dermis and hypodermis [1]. The main characteristics of the epidermis are the presence of active striated cells and the absence of capillaries [13].

The stratum corneum (SC) is the thick barrier that prevents substances from getting into the skin [1]. It is about 10 to 20 µm thick and is highly dense (about 1.4 g/cm^3 in the dry state). Factors such as the degree of hydration and location of the skin determine the thickness of the SC [9,14-15]. The SC is made of rich keratin cells known as corneocytes. The corneocytes are held together by corneodesmosomes that help to maintain the structural integrity of the SC. Also, the corneocytes are surrounded by a mixture of four main compounds which are cholesterol, cholesterol sulphate, ceramide and free fatty acids which assemble into a multiple layer of lamellar structure [9,15]. A common representation of the SC layer is the brick and mortar model. The corneocytes are the “bricks” because they are flat, polygonal and elongated, and the structure impacts a high tortuosity to substances transversing through the skin and the “mortar” is the continuous interstitial lipid matrix that forms a water-tight barrier to the already formed tortuous path [14,16]. In addition to the SC, the epidermis contains living cells, though it is not vascularized [7]. This layer is right below the SC, and is about 130–180 µm [12]. It gets nutrients by passive diffusion from the interstitial fluid [7].

The dermis is a fibro-elastic structure that sustains the mechanical integrity of the skin. It is vascularized and has nerve endings [1]. It is found under the epidermis and is about 2000µm thick [12]. Drugs are usually taken up by capillaries in this layer [2]. The pain associated with the delivery of drugs parentally is due to the damage done to the nerve fibers in the dermis layer [1].

The hypodermis is the deepest layer, also known as subcutis [14]. The hypodermis contains adipose tissue important for thermal insulation and energy reserve [17]. Other appendages that can also be found in the skin are sweat ducts, hair follicles, apocrine glands and nails [7]. The skin appendages facilitate the penetration of different agents into the skin. Despite the large openings they provide on the skin surface, their density is low and therefore it is not a suitable means for drug delivery [14].

Despite the barrier provided by the SC, the use of the skin for drug delivery offers a potential for the controlled and steady release of substances which avoid fluctuations of drug dosage concentration in the blood, poor efficacy and subsequent toxicity. In addition, drug absorption and stability problems that occur in the gastrointestinal tract can be prevented. Also, the ability to bypass problems associated with the use of oral route such as the pH effects of the stomach, first-pass metabolism of the liver and the emptying of the stomach makes the transdermal route attractive. The skin also offers an exciting means for vaccination because of the presence of large numbers of immune cells which make for a rapid antigen response upon entry into the body [12].

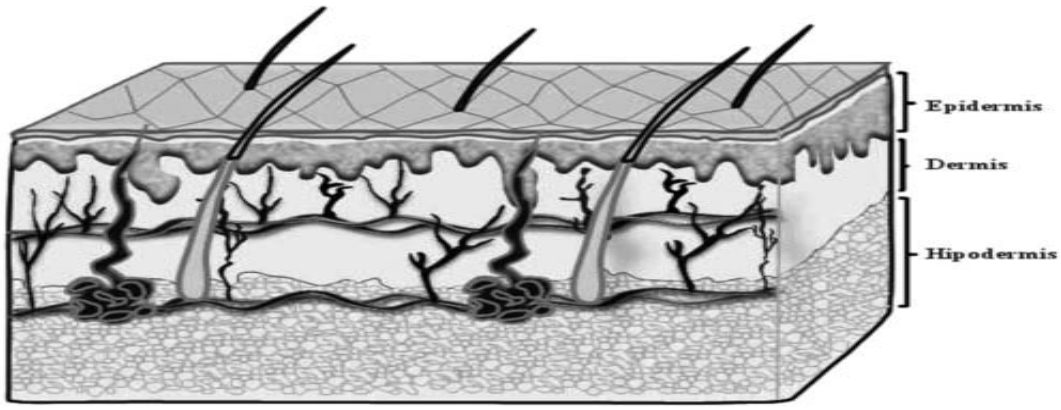

Fig. 1. Schematic representation of the skin layers [1]

3. MICRONEEDLES

Microneedles (MN) can be defined as a canula which is either solid or hollow with an approximate length ranging between 50 – 900 µm and an external diameter of 300 µm [1]. Microneedles have been designed to penetrate into the epidermis which has a depth of 70 – 200 µm. These devices are thin and short and do not penetrate the dermis [1]. Therefore, the main benefit of using microneedles is the promise of painless delivery of small and large molecular weight pharmaceuticals [18]. Another advantage of using MN is that patients can administer the drug in a simple and minimal invasive manner [1]. Further, there is an improvement in patient's compliance in contrast to the use of hypodermic needles because of needle-based phobia experienced by some patients [19]. Also, there is no bleeding or introduction of pathogens following microneedle use [19]. In addition, pharmaceutical agents can be delivered locally with the use of microneedles in skin, suprachoroidal space of the eye and the nucleus of cells [19].

MN vary widely in shape. The shapes range from square, circular, flat tipped, sharp tipped etc. all of which are attached to a base support [2,18]. MNs are designed in arrays to improve the contact of the needle with the surface of the skin [19]. These are basically of two design types which is either as in-plane (the MNs are parallel to the surface of the fabrication) or out-of-plane (the MNs are perpendicular for this design). The MN arrays can be applied through the skin in various ways such as manually, pneumatically, or with the aid of electrical or high velocity applicator [11].

Materials that can be used to fabricate MN are glass, metal, silicon and biodegradable polymers. In addition, the use of fish scales has also been investigated as a potential material for MN [2]. MN creates a pathway of magnitude larger than molecular dimensions which aid the movement of macro or micro molecules into the skin [7].

4. FABRICATION OF MICRONEEDLES

A major property to be considered when fabricating microneedles is that it must possess enough strength to penetrate the skin without breaking or bending before or during insertion [18]. Similarly, factors that affect the performance of MNs such as the type of material used, needle height, tip-radius, base diameter, needle geometry and density must be put into consideration because of their overall effect on the insertion and fracture force of the MN.

4.1 Continuous Liquid Interface Production (CLIP)

This is the use of additive manufacturing (3D printing) to computationally design and rapidly prototype microneedles patches. It is a continuous approach which differs from the traditional layer by layer approach to additive manufacturing. It has advantages of faster production times eliminating the rate limiting separation and realignment steps and it also generates high resolution structure (such as microneedles) that will be typically damaged during the traditional mechanical separation steps [20].

Johnson et al. reported on the use of this method to manufacture microneedle arrays from trimethylolpropane triacrylate and biocompatible materials like polyethylene glycol dimethacrylate, polycaprolactone trimethacrylate and polyacrylic acid. In addition, they tested the CLIP microneedles to penetrate into murine skin and release the drug surrogate rhodamine. They were able to show that these microneedles possess the chemical and mechanical characteristics necessary to penetrate into the skin. The microneedles size and shape were altered with the use of a computer aided design (CAD) file [20].

A microneedle patch is designed with the use of a CAD file. The microneedle is then fabricated using the CLIP method with a time of approximately two to ten minutes. The CLIP was able to generate the microneedle patch through photopolymerization of a liquid, photoreactive resin with light reflecting off a digital light processing (DLP) chip. Continuous fabrication is enabled through a process of oxygen mediated inhibition of the polymerization reaction taking place at the window surface. The CLIP process can be basically used to design any microneedle patch in two to ten minutes [20].

The CLIP approach provides a huge flexibility for microneedle design and a rapid prototyping that enables a varied number of different parameters such as size, shape and composition to be investigated in a throughput way. Also, targeting specific cell population and area could be possible with the use of this technique [20].

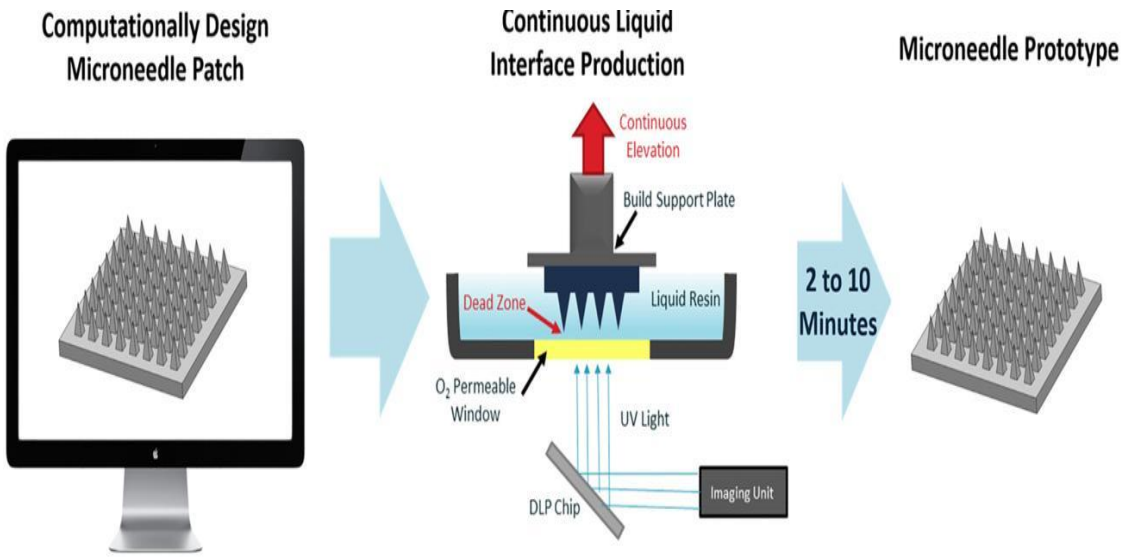

Fig. 2. Continuous Liquid Interface Production (CLIP) process [20]

The CLIP method of fabrication needs to be further investigated for its therapeutic use. Particularly the methods for encapsulating and stabilizing compounds and the resulting biocompatibility of the MN devices need further development and elucidation. Also, there is need for the assessment of the safety profile of the CLIP MN devices in order to avoid toxicity .For instance, unreacted acrylic monomers and oligomers are associated with toxicity, therefore, there should be complete photopolymerization process or perhaps the complete removal of residual monomer is necessary for future device development. In addition, the degradative products of the devices should be further investigated. Hence, it is important to be able to characterize the molecular weight of the degraded products and ensure it has been successfully removed from the body [20].

4.2 Microelectromechanical Systems (MEMS)

Microneedles have become a type of biological injector that doesn't excite the nerve but allows substances to pass through the cuticle without the patient feeling anything. Materials that are suitable for this type of fabrication are PMMA, PDMS, silicon etc [7]. MEMS technology has been shown to be efficiently used in the fabrication of MN arrays. The technology is adapted from the integrated circuit technology [18]. The basic technique of MEMS is divided into the following processes: deposition, patterning, lithography and etching [7].

Deposition: the formation of thin films on a material with a thickness of few nanometers to 100 micrometers [7]. The materials commonly used include silicon dioxide and silicon nitride. Generally, in physical vapor deposition (PVD) technique, the raw materials are extracted from the source and deposited on the substrate surface. In contrast, in the chemical vapor deposition (CVD) technique, thin films are generated through chemical reactions that occur between the hot substrate and the carrier gases in the chamber. The choice of deposition is dependent on factors such as the structure of the substrate, source, apparatus, temperature at which the process operates and the time of production [18].

- **Patterning:** The transfer of a pattern type on the film [7].
- **Lithography:** A process of transferring a pattern of interest onto a photosensitive material by exposure to a source of radiation such as light. This can involve other processes such as electron beam lithography, ion beam lithography or x-ray lithography [7].
- **Etching:** The use of strong acid or mordant to cut into the unprotected parts of a material's surface to make a design of interest. It is divided into two categories: wet and dry etching. The use of any methods above depends on the material type and the microneedle of interest [7].

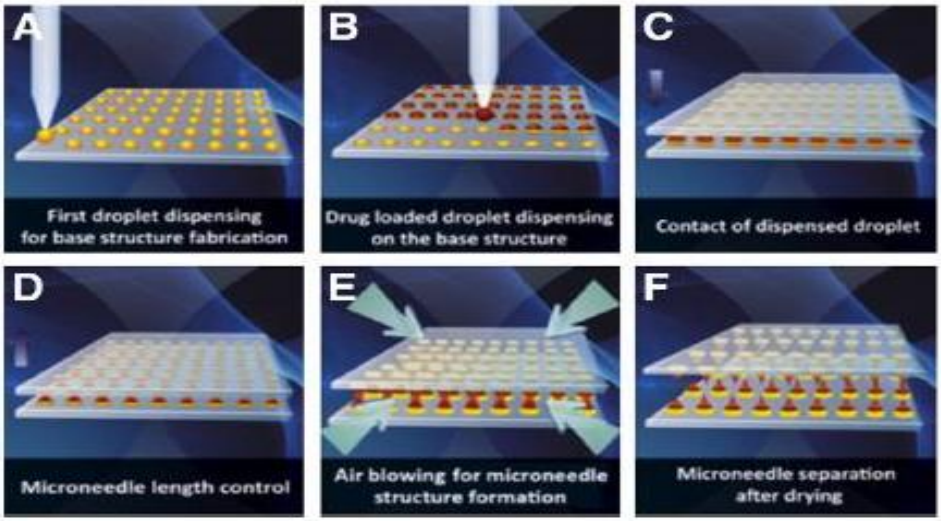

Fig. 3. Schematic illustration of dissolving microneedle fabrication with the use of droplet-born blowing method. (A) Biopolymer is dispensed on the flat surface for base structure fabrication. (B) Drug-containing droplet is dispensed on the base structure, (C) contact of dispensed droplet by the upper plate, (D) control of the length of the microneedle, (E) the solidification to shape of the droplet into microneedle mediated by air blowing, (F) plate separation producing dissolving microneedle arrays on the lower and upper plates [7]

4.3 Droplet-Born Air Blowing (DAB)

The fabrication method was proposed by Kim et al. [19]. In this method, polymer droplet is shaped into the microneedle with the use of air blowing, allowing for gentle condition without the use of heat and UV irradiation. Also, the use of a single polymer drop per MN allows for control over the size and concentration of the droplet and thus for controlled drug loading without the loss of the drug [8]. This process takes an approximate time of 10 minutes and has been used in the fabrication of insulin loaded dissolving microneedles. Kim et al. [19] reported a successful use of insulin loaded dissolving microneedles fabricated with this method to reduce blood glucose levels in diabetic mice. The microneedles were shown to avoid skin damage and are successful in systemic delivery [8].

4.4 Micro-molding of Ceramic MNS Arrays

An advantage of using this process is the low cost it offers and the potential of up-scaling the technology during production of the device. The ceramic microneedle array is fabricated in this process by casting an alumina slurry into a poly (dimethyl siloxane) microneedle mold. This generates a nanoporous microneedle [8].

The nanoporous microneedle array is remarkable for holding a specific volume of the drug for controlled release. Though similar to the reservoir found in a patch, it further enhances the permeability of the compound into the skin by mechanically breaching the structural integrity of the skin. Further, the structure of the nanoporous material allows a connection between the viable epidermis and the drug reservoir i.e. the backing plate of the MN atop of the skin. Similarly, simple diffusion can be used to evoke the release of compounds into the skin. An important thing to note is that the material ensures that the integrity of the microneedle is sustained during insertion into the skin. Also, it avoids the manufacturing complexity of a cannula through the MN instead the reservoir serves as a flow through of compounds injected into the skin. In vitro human skin studies showed a successful breach of the SC and the epidermis was achieved with the use of nanoporous ceramic microneedles. This ultimately led to the injection of antibodies into the skin [8].

4.5 Two Photon Polymerization

The two-photon polymerization is fast becoming an approach with a lot of promise for its prototyping process. The term is used to refer to additive, layer-by-layer fabrication process of three-dimensional structures from media such as

solid, liquid or powder precursors. Advantages of using this kind of approach is the low cost and high throughput it offers. Regardless of the benefits it tends to hold, it has some disadvantages that need to be overcome such as the issues of biocompatibility, geometry control by master structure and poor mechanical properties [21].

Despite the disadvantages, this method is compatible with many photosensitive resins that can be found in the market at relatively low cost. It can also be performed in conventional clinical settings such as an outpatient medical office. However, many conventional microneedle fabrication techniques require a clean room to work with as well as a high-energy consumption rate sometimes up to the value of 10,200 kW/m [2]. In addition, this method is suitable to scale up commercial manufacturing at a high rate [21].

For the selection of the material for this method, two criteria must be met. First, the material must be capable of polymerization by means of two photons in an unmodified state or with the aid of a photo-initiation. Second, the wavelength of the laser must be able to penetrate the transparent material. Materials that fulfill these requirements that can be used for this approach are SU-8 photoresist, zirconium propioxide copolymer, organic ceramic and methacrylate-based polymer [21].

The principle behind two-photon polymerization is the use of ultrashort laser pulses for the polymerization of resins into microscale and nanoscale complex structures. The polymerization is initiated by a process called the two-photon absorption. The two-photon absorption generates an energy that is centered at the laser focal point. Negligible absorption occurs as a result of the nonlinear energy distribution of the two-photon absorption in the immediate environment of the light beam [21].

A notable thing about this method is the making of a desired three-dimensional structure by polymerization of the material within the resin. The desired structure is initially sliced with the aid of a computer-aided design (CAD) model. Next, each layer is written in the photosensitive resin by rastering the path of the laser for the contour to be filled in for each layer [21].

This approach is mostly used to fabricate an array of microneedles. Microneedle arrays is typically favored over the solitary counterpart because of the large surface area they cover when a therapeutic is delivered or a biological fluid is extracted from the skin [21].

5. INNOVATIVE DELIVERY METHODS USING MICRONEEDLES

5.1 Solid Microneedles

A lot of research attention has been given to solid MNs (SMNs) since they were first used for the transdermal delivery of drugs. They can be produced from materials such as glass, silicon and metal. Silicon is mechanically strong and considered relatively safe for use. Although, it has yet to be approved by the FDA for the fabrication of solid MN [2,22]. Metal and glass are relatively non-biodegradable and there are safety concerns in their use in the situation where they break under the skin. Metals used to fabricate MNs are stainless steel, titanium and nickel iron [22]. Solid MN are typically 150-300 μm in length tapered at a tip angle 15-20^{o}. Their wear time ranges from 30 seconds to 10 minutes [2,7].

SMNs were first reported for use in a gene therapy study [2]. However, the feasibility of delivering drugs transdermally was demonstrated by Henry et al. in 1998 [10]. Basically, Henry and his team designed a conical shaped MN which has a length of 150 μm and a tip diameter of 51 μm using a fabrication technique known as deep reactive ion etching [2]. This increased the permeability of the skin by four folds magnitude of the compound. A study conducted by Wei- Ze et al. led to the fabrication of super short MNs with a length between 70-80 mm. They were able to successfully deliver the drug galantamine with the use of this needle into patients suffering from Alzheimer's disease.

The advantage of using solid MNs is that it has sufficient mechanical strength making it not to break under the skin. Also, they can be fabricated using a number of low cost, mass-production technologies [22]. In addition, they have been proven to be safe in terms of skin irritation, microbial penetration and SC restoration after piercing. Further, solid MNs can be either applied manually or through an applicator. A major disadvantage of solid MNs is the generation of biohazardous sharp waste which can be a public health concern if it is not properly disposed [22].

5.2 Coated Microneedles (CMNS)

Coated microneedles (CMNs) are usually microneedles which has drug-containing dispersions coated with it [23]. As a result of this, the desired amount of drug can be delivered upon insertion of the MN into the skin [19]. An advantage of this method is the one-step application of its usage compared to the uncoated solid MNs which is a two-step technique [4]. A limitation of this approach is that a particular dose of the drug can only be coated onto the tip and shaft of the MN (usually less than 1mg for small MN array) [19]. This may restrict the use of coated MN to deliver potent molecules. Also, the loss of drug coating from the MN surface prior to use must be prevented (e.g. during handling) [4].

One approach of coating MN is through the use of electrohydrodynamic atomization (EHDA) [23]. In this method, stainless steel microneedles with a height between 600–900 μm in height were coupled with a ground electrode with a varying system of ethanol: methanol ratio of 50:50. Generally, this technique was reportedly used in the making of nano- and micrometer- scaled coatings of pharmaceutical products [23]. The remaining component that made up the coating formulation was fluorescein dye and polyvinylpyrrolidone (PVP, polymer matrix system). Further, Ma and Gill prepared a coated solid microneedle from polyethylene glycol matrix containing the drug lidocaine. Also, the team performed an in vitro study of coated microneedles with PEG-lidocaine dispersion. This showed a higher delivery of lidocaine in three minutes compared to 1 h topical application of the commercial cream EMLA® (lidocaine-prilocaine at 0.15 g) [23].

Another approach is known as the layer-by-layer coating technique. An instance is the coating of the DNA or protein molecules onto metal and polymer MN by alternately dipping them into two solutions of oppositely charged solutions. Hence, a polyelectrolyte multilayer of negatively charged DNA and positively charged polymer is formed [19].

In one approach, the surface of the individual MN can be coated with an angled gas jet by spraying from a reservoir made from the substrate of the MN array. In addition, spray coating can be applied with the use of an atomizer [19]. Also, coating can be done by dipping either once or repeatedly in coating solution or micro-wells of coating solution for each individual microneedle [19]. Two most important parameters in the dip-coating process are surface tension and the viscosity of the formulation. A lowered surface tension facilitates good wetting and slows down the rate of film formation on the MN surface [19,4].

CMNs have been widely used in the delivery of substances such as drugs, vaccines, DNA, micron-scale particles, such as BaSO4 particles (1 μm) and latex particles (10 μm) and bio-molecules [19,24]. The coating of therapeutics on MNs depends on factors like physical and chemical interaction between the microneedle and the coating compound, the type of coating solution used [24] etc.

5.3 Hollow Microneedles

Hollow microneedles offer a lot of possibilities in terms of drug transport and control. Transport of drugs is mainly through the diffusion process. In addition, it can be controlled by a rapid delivery or by a pressure driven flow. The method used here is that the skin is first punctured with a MN and then the liquid formulation is infused through the holes created [22].

Hollow MN are manufactured using micro-fabrication technique resembling that of hypodermic needles intended to minimally invade the stratum corneum of the skin and efficiently deliver drugs. Hollow MN can be used to deliver drugs at specific times and also to remove fluid from the body for analysis such as glucose measurement, etc [22].

Hollow MN can either be designed as tapered or beveled tip which allows it to deliver micro-liter quantities of drugs at very specific positions [22]. They are typically categorized into two types: single hollow microneedle which resembles hypodermic needle and multiple hollow microneedles. The single hollow microneedle is advantageous in that it can be used to deliver liquid formulations over a wide area in one usage, with a high level of bioavailability and possible targeting of the lymphatic organ [19].

The advantage of using hollow MN includes the ability to apply drug at higher concentration with a single procedure compared with solid MN. Also, there is a possibility of either prolonged infusion of the drug into the skin or the use of external pressure to aid in rapid infusion [22]. This typically makes it to act like a micron syringe

in terms of the delivery of compounds through the SC [2]. However, hollow MNs are not free from disadvantages, some of which include low shelf life, low drug stability and less convenience experienced by patients compared to the use of solid or dissolving MNs [24].

Furthermore, there has been less research attention given to hollow MN in contrast to solid microneedles because they are more difficult to use, as they are relatively weak in terms of their mechanical strength [2,22]. There are additional constraints on the needle design and insertion methods in the use of hollow MN. There is also the problem of flow which is likely due to the resistance encountered from the dense dermal tissue beneath the tip of the MN. In addition, the placement of the bore opening at the tip of the needle reduces its sharpness and makes insertion much more difficult. Hence, solid MN has been considered robust because of its mechanical strength and less complex manufacturing process [2,22]. A range of materials have been used including silicon, polymers, metals and glass to fabricate hollow MN [22]. Although most hollow MNs have been fabricated out of silicon, their safety has not yet been determined for use in humans. Also, there is no report of a proven biocompatibility with the silicon hollow MN. Metals are now promising in use as some MNs have been fabricated using this material. Metals are relatively cheap, stronger than silicon and are biocompatible. This has made metals more attractive for use as hollow needles. The first use of hollow MNs published for human subjects used MNs to deliver methyl nicotinate. It was able to deliver approximately 1 mL of the substance into the skin [22].

5.4 Polymer Microneedles

There is a gain in popularity in the use of polymer in the fabrication of microneedles. Polymer MNs have the potential of increasing the skin's permeability by orders of magnitude. Also, this is due to the properties they possess such as biocompatibility, biodegradability and strength. They have been an alternative to the insoluble metal and major fabrication has been carried out on biodegradable or water soluble polymers. A variety of techniques have been employed for the production of polymer MN such as injection molding, embossing, casting etc. In addition, polymeric materials are relatively inexpensive and have a lasting record of safety in its use as medical devices [11].

Polymer MNs have been fabricated from polylactic acid (PLA), polyglycolic acid (PGA), poly- lactic-co-glycolic acid (PLGA), sodium carboxymethyl cellulose, and poly (methylmetha-acrylate) (PMMA). Also, there has been a long history of the use of PLA, PLGA and their copolymers because of their biocompatibility and this would make them suitable for the production of MN. In addition, polymers have been considered safe to dispose either by dissolving them in a solvent or destroying them mechanically [11].

Polymer MNs have been successfully used to deliver compounds such as calcein and serum bovine albumin suggesting their safety and potential in the delivery of drugs [11]. A study carried out showed that the pretreatment of human skin with polymeric MN improved the stability of the topical formulation, reduced cost and inconvenience experienced by patients [11].

5.5 Dissolving Microneedles

In contrast to polymeric MN, dissolving MNs from the name are basically designed to break into the skin, dissolve and create channels for drugs and other compounds to pass into the skin and interstitial fluid out of the skin. It can also be typically molded into the desired shape before insertion [24]. One major advantage of the use of this MN type is the biodegradable property of the material upon contact with the skin's interstitial fluid. This process allows the drug to be released from its matrix and subsequently introduced for either local or systemic delivery [11].

Dissolving MNs have been made from sugars such as galactose, maltose and dextrin. Maltose was first reported for use and it has generally been recognized as a safe substance appropriate for its utilization in the fabrication of MN. Upon contact with the skin, it dissolved within three hours and its shape is retained for at least three months at 40% humidity. In a study carried out on maltose MN, research proved that it sufficiently pierces the SC of hairless rats, creating a micro conduit for the transport of compounds. Therefore, it can serve as a means of transporting protein macromolecules such as human IgG which passively pass through the skin. In addition, another study showed the improved transdermal delivery of nicardipine hydrochloride with the use of maltose MN in the treatment of hypertension. There is however a disadvantage to the use of maltose MN; the fact that the sugar maltose is a disaccharide, it

absorbs water under high humidity and this therefore leads to the MN bending in the skin, thereby making insertion difficult. Moreover, a high temperature is needed for the production of maltose MN, under this condition the loss of protein/peptide drugs occurs because the drugs at this temperature becomes easily degradable. A way to overcome this challenge that has been proposed by researchers is the development of new, self-dissolving MNs made of dextrin that can be used for administration [11]. Interestingly, the combination of iontophoresis and dissolving MNs performed both in vivo and in vitro lead to 25-fold enhancement delivery when compared to the use of either method alone [11].

5.6 Hydrogel Forming Microneedles

Hydrogel MN array has been manufactured from aqueous blends of polymeric materials (poly (methylvylether/maleic acid) and poly(ethyleneglycol) with a micro molding process which involves laser-based technology. Hydrogel MNs can be defined as an integrated system which consists of cross-linked needles projecting from a solid base plate to which an adhesive drug reservoir is attached. The method of use of the MN array is such that when it is applied to the skin, diffusion of the drug from the patch occurs through the swollen micro projections. Hydrogel MN are typically suitable for the delivery of small hydrophilic drugs such as caffeine, methylene blue and high molecular weight compounds (i.e. insulin and bovine serum albumin) [4].

A study by the Donnelly group showed that the hydrogel system of delivery showed a sustained method of transporting drugs in vitro in neonatal porcine skin where the peptides and protein were delivered over a 24 h period. Further, complementary studies by the same research group showed the crosslink density of the hydrogel matrix can be modulated to control the transdermal delivery of drug. This indicates that the drug delivery method can be personalized on a case by case basis to meet the requirement demanded by the drug of interest. This further confirms the versatility of the hydrogel-MN device [4].

Additional advantages of using hydrogel MN in contrast to dissolving MN is that it remains intact when withdrawn from the tissue leaving no residues behind. In addition, the potential toxic effects have not been elucidated following repeated use of dissolving MN and the overall health impact of the accumulation of residues in the body is unknown. Further, hydrogel MN offers better control of the delivery of compounds in the required amount of dose and they are not blocked by the dermal tissue in contrast to that experienced in the use of hollow MNs [4].

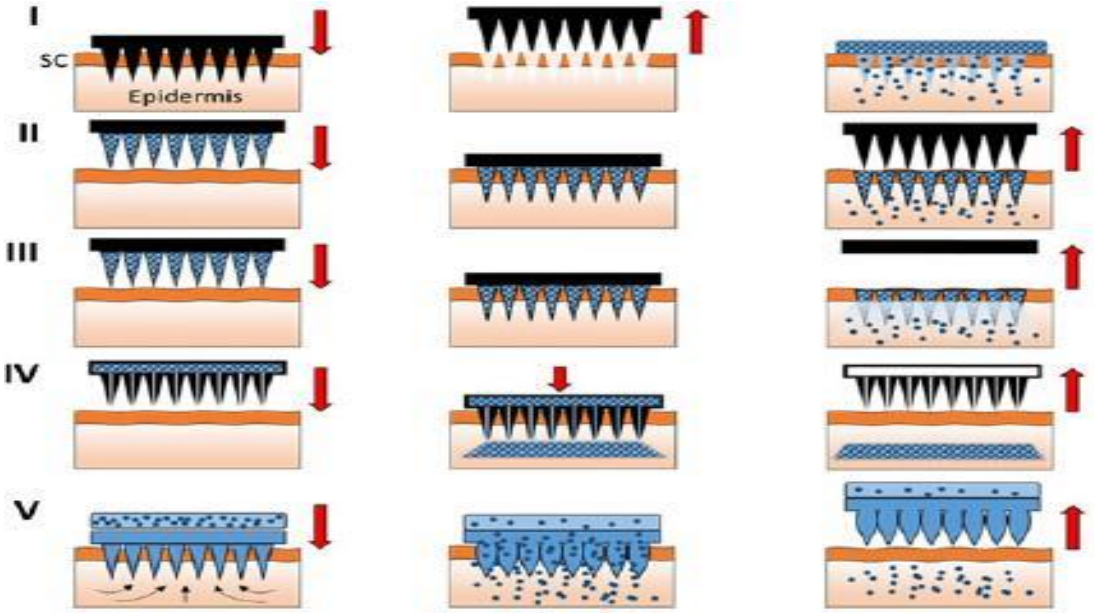

Fig. 4. Solid MNs (I); coated MNs (II); dissolving MNs (III); hollow MNs (IV) and hydrogel-forming MNs (V) [14]

6. CLINICAL STUDIES

Several studies have shown the potential of MN in the transdermal delivery of compounds for both *in vitro* and *ex vivo* models. So far, only few studies reported on the success of its use in human subjects, with most investigations done on either animals or just the fabrication techniques [18,25].

The first reported human study was carried out by Kaushik et al. [26] consisting of 12 human volunteers between the ages of 18-40 years to demonstrate the application of MN is a painless procedure. The MN used in this experiment was 150 µm long with a base diameter of 80 µm and tip radius of 1 µm. The array contains 400 microneedles. A hypodermic needle was used in this study as the positive control, while a smooth silicon wafer was the negative control. The pain-scores were recorded on a visual analog scale from each volunteer and findings showed that the use of MN was painless and also no skin damage or irritation was observed [18,25].

Bal et al. [27] conducted an experiment on the safety and disruption made after the use of MN arrays of different length and types in 18 healthy volunteers of equal pairs of male and female between the ages of 21 and 30. The parameters considered are the barrier function of the skin (measured with the TEWL approach), erythema (measured with Laser Doppler imaging (LDI) and the skin color) and the pain-score. The result showed an increase in TEWL and erythema values with the use of solid MN arrays of 400 µm compared to 200 µm. However, there was no record of pain during use and the irritation experienced was short-lasting [18].

Sivamani et al. [28] studied the pain factor observed with the use of hollow MNs with two different geometries. They used pointed tip microneedles and symmetrically shaped microneedles in this study. Volunteers experienced a sensation of pressure but no pain was experienced with the application of MNs. Similarly, the team also investigated the ability of hollow silicon MN in the delivery of drugs past the SC in five human subjects. They used Laser Doppler imaging to measure the blood flow and Hexyl nicotinate (HN) as the marker for SC penetration. The result obtained showed that MN was capable of delivering the drug into the body past the SC [18,25].

Wermeling et al. [29] carried out the first clinical studies on human subjects with the use of MN in the transdermal delivery of the compound, naltrexone (NTX). A 5 × 10 microneedle arrays with a height of 620 µm and a width of 160 µm was used in this study. Blood samples were collected from the upper arm over a period of 72h from the NTX adhesive patches. The results showed a rapid absorption of the drug (1.6–8.1 ng/ml) for the first few hours, followed by a steady state of plasma concentration (≈ 2.5 ng/ml) over the 72 h period [18].

Further, the application of MN on human volunteers has not shown signs of redness, edema or erythema. MN technology fabricated with biocompatible material is safe, painless and offers exciting opportunities for transdermal delivery compared to hypodermic needles [25].

7. CONCLUSION AND FUTURE WORK

Transdermal delivery of compounds is a rapidly emerging field in the local and systemic delivery of therapeutics. The biggest drawback is the barrier set up by the stratum corneum of the skin. Microneedle has proven to be able to overcome this barrier by increasing the permeability of compounds moving across the skin as well as achieving this in a painless manner. There is a widespread interest in the fabrication and application of this device owing to the minimal tissue damage, avoidance of first pass metabolism, rapid healing at the injection site compared to hypodermic needle, and increased drug dosage concentration [1,4,30].

Despite the many advantages this technology has been found to possess, there are no products currently on the market. Further, there are issue of safety and efficacy relating to the use of this device. The use of metallic microneedles leave traces of this element beneath the skin which may lead to complications such as irritation, erythema, swelling and other side effects. Also, frequent use may likewise result in the aforementioned problems [1].

Silicon was the first material used in the fabrication of MN. Due to the brittle nature of this metal and the potential of it breaking off in the skin, other materials have been sought after for the manufacture of MN. The long-term use of this material has not been fully elucidated but there are rare reports of silicon-related granuloma. In addition, silicon is expensive, thereby making researchers sought after another replacement for it. Other materials that have been used to

fabricate MNs are glass, polymers, titanium, metal and sugars [22].

Animal models have typically been used to test for the *in vitro* transdermal study of MN due to ethical reasons. Pig skin is often used because of the close similarities it has with that of human. The SC of the pig is somewhere between 21-26 µm. Also, the viable epidermis under the SC measures 66-72 µm compared to 70 µm found in human. A study carried out by Barbero and Frasch [31] showed a positive correlation coefficient for permeability of 26 chemicals across the skin of both pig and human. The author reached a conclusion porcine skin could be a good surrogate for the measurement of skin permeability. Similarly, a study carried out by Andega et al. [32] on the permeation of melatonin across both porcine and human skin showed a strong positive correlation in the data collected from both skin types. This further support the fact that porcine skin can be used for *in vitro* transdermal testing of MN delivery [15].

The application of microneedle for transport however can be affected by a variety of properties such as the height, density, material type, duration, aspect ratio and patch size. To understand the effect of these factors on the permeability of the skin, different researchers have theorized on the MN type that can aid in transdermal delivery. Stoeber and Liepmann [33] suggest the length of the MN must be longer than 100 µm for efficient permeation of therapeutics. In contrast, a study done by Shikida et al. [34] proposed that the length of an ideal MN must be between 50 and 200 µm. In addition, Pastorin et al. [35] explained that a length of MN below 50 µm can enhance skin permeability without causing pain. Al-Qallaf et al. [36] used mathematical model to study the effect of parameters such as MN length, duration of the application of the device, surface area of the patch, skin thickness and pharmacological variables on the transport of fentanyl and human growth hormone across the skin. Al-Qallaf and Das [36,37] also proposed a model for increasing the permeability of drugs across the skin. In addition, they observed in this study that the thickness of the skin affects to a great extent its permeability which varies for different skin types (e.g. race, sex, age and geographical location). However, this model has to be experimentally validated to prove this theory [18].

Coated MNs have been used to successfully deliver vaccines and gene through the skin. As a matter of fact, a recent study showed that desmopressin coated MN was able to achieve 79% bioavailability through the skin. In addition, hollow MNs have been used for obtaining body fluids for analysis and also for the injection of drug continuously with the aid of microcircuitry [22].

Future studies will focus on the stability of drugs loaded into the tip or the body of dissolving microneedles. In addition, studies will be done to determine the suitability of drugs or vaccines for use in this type of delivery. Also, studies show that the insertion of solid microneedles during administration elevates the permeability of the skin for five hours. However, there is no report showing how long pores created by microneedle remain open for with or without skin patches *in vivo*. This is essential because longer pore closure time for microneedle insertion will increase the chances of infection. Likewise, investigations need to be carried out more on the relationship between infections and microneedle failure in long term studies [22].

Future research also needs to find ways of incorporating detection and delivery in a microneedle system. This can be an important tool for glucose testing and the release of drug in diabetic patients. Also, microneedles can have a tremendous benefit for the delivery of genes and vaccines. This will invariably have a huge global health impact. In addition to this, the simplicity of administration will make it an accessible tool since this does not require high training. Also, the suitability of microneedle type that will enhance vaccine delivery when coated needs to be properly elucidated [22].

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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