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Review Article

A Review: Transdermal Microneedle.

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ABSTRACT
Transdermal drug deliver have a number of advantages including greater patient compliance, sustained release, prevent gastric irritation and avoidance of pre systematic first-pass effect. It gives attraction to many researcher due to various advantages. Recently, the use of micron-scale needles in increasing skin permeability has been proposed and shown to dramatically increase transdermal delivery, especially for macromolecules. Researchers have focused their attention on the use of microneedles to overcome the barrier of the stratum corneum. Microneedles deliver the drug into the epidermis without disruption of nerve endings. Recent advances in the development of microneedles are discussed in this review. Using the tools of the microelectronics industry, microneedles have been fabricated with a range of sizes, shapes and materials.

KEYWORDS
Microneedle, penetration, transdermal, first pass effect.

1. INTRODUCTION

Drug can be administered through most common routes like the oral, parenteral, ophthalmic and transdermal route, as well as less explored routes such as nasal, pulmonary and buccal. Each of these routes have specific merits and disadvantages. Oral drug delivery systems offer advantages such as patient compliance, large surface area with rich blood supply for absorption, low cost, ease in engineering of drug release in stomach/intestine, etc. However, limitations, like drug degradation in the gastrointestinal tract, first-pass metabolism, poor absorption, local irritation and variability in absorption (due to factors like pH, motility, food, mucus layer, etc.), are associated with these drug delivery systems. The parenteral route offers advantages like quick onset of action, accurate drug delivery and continuous drug delivery by infusion; its limitations include pain associated with the injections, expertise required to deliver the drug, risk of infection and difficulty in obtaining sustained drug delivery. [1]

Transdermal drug delivery involves the transport of drug across the skin. Optimal physiochemical properties are required in drug candidates for delivery via transdermal patches. In human stratum corneum, the main lipid classes are free fatty acids, ceramides and cholesterol which form two lamellar phases. These include the short periodicity phase and the long periodicity phase with repeat distances of approximately 6 and 13 nm, respectively. Below the stratum corneum is the viable epidermis, which is a cellular, a vascular tissue measuring 50–100 μm thick. The viable epidermis consists mainly of keratinocytes and approximately 40% protein, 40% water and 15%–20% lipids. The undulating epidermal–dermal junction consists of papilla that project into the dermis. Cells in the basal layer of the epidermis form the most important structural and functional connection to the dermis below. The stratum corneum and viable epidermis together form the full epidermis. There is a basement membrane at the base of the epidermis and the existence of tight junctions in the viable epidermis has been recently documented. Base membrane and tight junctions may both offer resistance to the transport of molecules across the epidermis. Below epidermis layer is the reticular dermis, made up of thick collagen bundles and coarse elastic fibers.

Standardization of plant crude material is becoming today's necessity. Products of primary

The dermis contains blood vessels, lymphatics and nerves, as well as the various skin appendages. Below the reticular dermis lies the hypodermis (subcutaneous fat tissue), which may have a thickness of up to several millimeters. [5]

To increase skin permeability, a number of different approaches has been studied, ranging from chemical/lipid enhancers to electric fields employing iontophoresis and electroporation to pressure waves generated by ultrasound or photoacoustic effects. Although the mechanisms are all different, these methods share the common goal to disrupt stratum corneum structure in order to create ''holes'' big enough for molecules to pass through. The size of disruptions generated by each of these methods is believed to be of nanometer dimensions, which is large enough to permit transport of small drugs and, in some cases, macromolecules. [9]

1.1. Microneedles

Microneedles are recently developed systems for drug delivery. Microneedles can be defined as solid or hollow cannula with an approximate length of 50–900 mm and an external diameter of not more than 300 mm. These are the microstructure system composed of micro sized array

projection coated with a drug or vaccine. These are considered as a combination of hypodermic needles as well as transdermal patches and effective enough to overcome the limitations being possessed by these two systems. A quick response can be observed due to disruption of stratum corneum by microneedles. First studies of transdermal delivery Henry et al. conducted the first study to determine if microneedles could be used to increase transdermal drug delivery. The ‘‘poke with patch’’ approach uses microneedles to make holes and then apply a transdermal patch (or some prototype) to the skin surface. Transport can occur by diffusion or possibly iontophoresis if an electric field is applied. Another approach is ‘‘coat and poke,’’ where the needles are first coated with drug and then inserted into the skin. There is no drug reservoir on the skin surface; all the drug to be delivered is on the needle itself. Microneedles are more capable of enhancing the transport of drug across the skin as compared with other transdermal delivery methods. [12, 17]

1.2. Advantages of Microneedles [11]

The advantages of microneedles are:

- Painless administration of the active pharmaceutical ingredient.
- First-pass metabolism can be avoided due to local administration.
- Faster healing at injection site than with a hypodermic needle.[23–25]
- No fear of pain due to insertion of needle.
- Ease of administration as it can be self administered.
- Decreased microbial penetration as compared with a hypodermic needle, the microneedle punctures only the epidermis.
- Specific skin area can be targeted for desired drug delivery.
- Enhanced drug efficacy may result in dose reduction.
- Good tolerability without long-term oedema or erythema.
- Rapid drug delivery can be achieved by coupling the microneedles with an electrically controlled micropum,
- The rate of drug delivery can be controlled more effectively by this system as compared with drug delivery via the stratum corneum.

1.3. Disadvantages of Microneedles [39]

The disadvantages of microneedles are:

- Dosage accuracy may be less than with hypodermic needles.
- Careful use of the device may be needed to avoid particles ‘bouncing off’ the skin surface; if the device is not held vertically, the dose may escape or can penetrate the skin to differing degrees.
- The thickness of the stratum corneum and other skin layers varies between individuals and so penetration depth of particles could vary too.
- The external environment, like hydration of the skin, could affect delivery.
- Repetitive injection may collapse the veins.
- The tip of the microneedle may break off and remain within the skin on removal of the patch.

- A small amount of drug (less than 1 mg) can be given by bolus.
- Compressed dermal tissue can block hollow microneedles.

1.4. Mechanism of Drug Delivery through Microneedle [28]

In an earlier phase of research on microneedles, an array of solid microneedles was pierced through the skin to circumvent the barrier effect of the stratum corneum. The needles were made up of silicon wafers and a medicated patch was applied to the treated skin surface thereafter. This approach is known as 'poke and patch'. This technique was also tried to extract the interstitial fluid to measure the glucose level by non-invasive method.

1.5. Preparation of Microneedle [22]

Microneedles fabricated in different forms like as hollow, solid, and dissolving microneedle. Microneedles can be fabricated employing micro-electromechanical systems (MEMS). The basic process can be divided in to three parts: deposition, patterning and etching.

- **Deposition:** specially referred to the formation of thin films with a thickness anywhere between a few nanometers to about 100 micrometers.
- **Patterning:** is the transfer of a pattern into the film. Lithography is used to transfer a pattern into a photosensitive material by selective exposure to a radiation source such as light. This process can involve photolithography, ion beam lithography, electron beam lithography. Diamond patterning is also a good option for lithography.
- **Etching:** is a process of using strong acid or mordant to cut into the unprotected parts of a material's surface to makes a design in it and can be divided into two categories: wet etching or dry etching. The selection of any of the above mentioned methods largely depends on the material of construction and the type of microneedles. Microneedles fabricated in different forms like as hollow, solid, and dissolving given below.

1. Solid Microneedles

Solid microneedles carried out passive diffusion for drug delivery. Henry *et al.* used a deep reactive ion etching process to fabricate silicon microneedles and a chromium masking material was first deposited onto silicon wafers and patterned into dots which had a diameter approximately equal to the base of the desired microneedles. The wafers were then loaded into a reactive ion etcher and subjected to plasma etching. The regions protected by the metal mask remained to form the microneedles. These microneedles have the potential for reduced drug leakage resulting in improvement of drug delivery efficiency and the possibility of introducing multiple drugs. The fabricated solid microneedles with rectangular cup shaped tip are 200 μm in height. The cup shaped tips have dimensions of 60 × 60 μm (length × breadth) with a depth of 60 μm. The cups are filled with drug using a novel drop coating system. Solid microneedles fabricated from silicon, metal and polymer [12].

2. Hollow Microneedles

Hollow microneedles contain a hollow bore in the centre of the needle. These are very expensive to prepare and require expensive micro fabrication techniques. These micro needles contains hollow bore which offers possibility of transporting drugs through the interior of well defined needles by diffusion or for more rapid rates of delivery by pressure driven flow. The 4 × 4 pattern of holes was drilled in a polyether ether ketone mold (diameter 9 mm). Then, the needles

were placed through the holes at a predetermined length of 300, 550, 700 and 900 μm. Subsequently, the needles were cut and glued at the back of the mold. A manual applicator was also designed for the microneedles array [17]. These microneedles are mainly employed to inject the drug solutions directly into the skin.

3. Dissolving Microneedles

Dissolving microneedles are fabricated on the basis of the "poke and release" principle. They are made from polysaccharides or other polymers. These microneedles release encapsulated drug into the skin following application and dissolution. Micromoulding is the preferred fabrication method for making dissolving microneedles. Certain drugs and vaccines are thermolabile so moulds are often filled with solutions of drugs and excipients and then dried under mild conditions. The fabrication process involves pouring the polymer solution into female molds, filling the microcavities of the mould under vacuum or pressure, drying under ambient conditions, centrifugation or pressure.

4. Coated Microneedles

Coated microneedles refer to microneedles which have coating with the drug-containing dispersion. A plethora of techniques has been used in the literature to prepare coated microneedles. Stainless steel (600–900 μm in height) microneedles were coupled to a ground electrode (in the electro hydrodynamic atomization coating set-up) with the deposition distance and collecting methodology varied for an ethanol: methanol (50:0) vehicle system. Fluorescein dye (serving as potential drug, sensory materials or disease state markers) and polyvinylpyrrolidone, (polymer matrix system) formed the remaining components of the coating formulation [7].

1.6. Material Used in the Preparation of Microsphere

Material for constitution of the microneedle should be based on criteria such as gentle fabrication without damage to sensitive biomolecules, sufficient mechanical strength for insertion into skin and controlled or rapid drug release as per the requirement. Microneedles have been produced using glass, silicon and metals (Table 1). The use of polymers to constitute microneedles has also been explored; solid microneedles have been produced using plastic or biodegradable polymers.[18] Metallic microneedles are expensive, non-biodegradable and brittle. Polymer microneedles overcome the limitations of silicon and metal microneedles and may provide advantages like low cost, mechanical strength and safety in case of accidental breakage of needle in the skin.[27] Poly [di(carboxylatophenoxy) phosphagene] (PCPP), having phosphorus-nitrogen backbone and organic side chain, offers potent immunoadjuvant activity. [16]

Table 1: material used for preparation of microneedle.

Synthetic polymers			
Metals	**Biodegradable polymers**	**Non-Biodegradable polymers**	**Natural polymers**
Silicon	Polylactic acid	Polyvinyl acetate	Thermoplastic starch
Stainless steel	Polyglycolic acid	Alginic acid	Carboxymethyl cellulose
Titanim	Polylactide-co-	Gantrez AN-139,	Amylopectin

	glycolic acid	a copolymer of methylvinylether and maleic anhydride	
Mesoporous silicon	Polycarbonate Polyvinylpyrrolidone	Carbopol 971 Polyetherimide	Dextran, galactose, chondroitin sulphate Maltose

1.7. Evaluation of Microneedle Geometry

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

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

$$Aa\ rtt\ t = \pi\ (-2\ /4)\ (1)\text{and}$$

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

$$Af\ rt = \pi\ 2\ (2)$$

Needle wall angle, a, is calculated as

$$\alpha = \tan{-1}(rb - rt\ /h)\ (3)$$

Where rt is the outer radius of the microneedle tip,

rb is the outer radius at the needle base,

t is the wall thickness and h is the height.[44]

Measurement of Insertion Force into Human Skin

A drop in electrical resistance of the skin was used to identify needle penetration since visual observation of needle insertion was extremely difficult. The electrical resistance of skin's outermost layer, the stratum corneum, is much greater than deeper tissues; therefore the resistance of the skin drops dramatically as soon as a needle penetrates. [39]

Margin of Safety

Forvi *et al*. defined the margin of safety as the ratio between the force required for piercing the stratum corneum and the force at which microneedles broke. [31]

Functional Capacity Test

The test setup consisted of a syringe pump system with a dye-filled syringe, a polymer tube and microneedle array. This syringe pump system was used to examine the formation of the microneedle lumens by allowing dye to flow from the syringe to the microneedle orifice. Microscopic inspection of the microneedle tips and the base plate during the microfluidic characterization can be used to detect cracks in the base plate and passage continuity. [7]

Biological Safety Test

Extraction of chemicals from microneedles was done by immersing microneedles in physiological saline at 37°C for 72 h. The extract was then directly applied on shaved intact human skin for checking dermal irritation. Negative result of the test revealed then biological safety of the microneedles. [10, 14]

1.8. Applications of Microneedles in Biopharmaceuticals

Insulin, heparin, and growth hormones are not administered orally due to proteolytic degradation and hindered absorption. The majority of commercially available biopharmaceuticals are administered via the parenteral route and hence a suitable non-invasive route is desirable.

Verbaan *et al*. administered macromolecules Skin is suitable for gene and oligonucleotide delivery because it is well characterized at the cellular as well as the molecular level. [17]

Immunologicals

Microneedles form transient conduits and enhance passage of the vaccine molecule across the skin barrier. Using microneedles, vaccines are able to cross the stratum corneum and stimulate a clinical response. An increase in haemagglutination inhibition (HI) and IgG subtype titres was observed when influenza vaccine and cholera toxoid were co-administered employing microneedles [36]. The clinical response wasmuch higher than that obtained after intramuscular injection of plain vaccine. High purity subunit vaccines are safer than live attenuated or whole inactivated vaccines. The use of pure vaccines results in decreased immunogenicity [37]. Several studies have been carried out to achieve effective immunization of vaccines via microneedle delivery along with adjuvant.

Diagnostic Purpose

Hollow microneedles can be used to withdraw fluid from tissue or blood which can be subsequently analysed to check the status of diseases like cancer, diabetes and many more. Hollow microneedles, along with quantum dots, help in medical diagnosis. Quantum dots are nanoscale crystals with a light-emitting property. The multiphoton microscopy method could rapidly diagnose cancers or other medical problems [22].

Phlebotomy

Phlebotomy is the withdrawal of blood for diagnostic purpose. Analysis of blood samples for specific blood constituents helps in the diagnosis of a disease. Some diseases like diabetes require frequent monitoring of blood for estimation of glucose concentration or disease severity. Painless hollow microneedle-based micro sampling can be used instead of traditional methods for glucose estimation [24].

Cosmetic Products [24]

Generally, only minor fractions (maximum 0.3%) of the active substance present in a cream, gel or lotion can penetrate deeply into the skin. This means that the majority of an active ingredient, about 99.7%, is wasted. Derma rollers and stamps are available on the market for treatment of skin problems as well as to improve looks. Clinical Resolution Laboratory markets MTS Derma roller, a cosmetic aid possessing needles that penetrate the skin up to a depth of 0.2–0.3 mm. The product contains 200 very fine stainless-steel needles to pierce the epidermis, creating a micro-channel effect. Clinical studies from various countries have proven that therapeutic serum absorption is increased by as much as 1000 times when applied using the MTS Derma roller [13]. The majority of cosmetic products lending themselves to microneedle technology are for non-surgical and nonablative treatment of skin conditions such as ageing (wrinkles, lax skin), scarring (acne, surgical), photodamage, hyperpigmentation (age/brown spots) and hair loss (alopecia). The process facilitates and stimulates skin's natural repair without causing permanent epidermal damage.

1.9. Challenges in the Development of Microneedles

Many applications of microneedles have been discussed but very few products have been marketed to date. There is a need to consider safety and efficacy while developing microneedles for delivery of both small and large molecules. With metallic microneedles, traces of metal are

retained beneath the skin which may lead to irritation, erythema, swelling, discoloration or other side effects.[18] Frequent application of the microneedle at the same site may result in the aforementioned problems. Application at different sites every time or variation in skin thickness in individuals may result in variation in bioavailability, which needs to be considered while developing microneedles. [36] Today, research is more focused in the development of new technologies for administration of existing molecules, which are already proven as safe, thus reducing development time and assuring a higher rate of success. This is the main reason why many workers in the pharmaceutical industry strive for successful development of microneedles as transdermal drug delivery systems.

Development of different types of microneedles faces varied challenges. Use of solid metallic microneedles may result in irritation or retention of metallic particle in the skin. Furthermore, they may leave behind biohazardous sharp waste after use and destruction needs to be done carefully[28]. Dissolving microneedles are made of polysaccharides and dissolve in the skin with no waste left after use. Complete dissolution, proper insertion into the skin and loading of drug extensively at the tip only are the foremost challenges to be faced during their development [18, 29]. The use of hollow microneedles is another approach gaining the attention of researchers due to the capacity of the hollow microneedle to administer a larger variety of molecules as compared with other devices. However, this type of microneedle does not possess enough strength, an issue which needs to be focused on by the researcher [31].

The microneedle delivery system can be used for treatment of various genetic diseases related to skin, various types of malignancies and infectious diseases, and for immunization. A dense array of very sharp pyramidal microneedles was used to deliver gene into cells. Microneedle delivery of gene is better than a microinjection technique because many cells can be treated at once. Thus microneedles can be used to deliver bioactive agents systematically as well as locally. Research could focus on antiviral, antidiabetic, genetic, oncological, anti-osteoporosis, vaccine, dermatological, etc., areas for bioavailability improvement by developing microneedle-based transdermal drug delivery systems. [43]

2. CONCLUSION

A review of the literature shows that microneedles can be fabricated by a number of different methods to yield a variety of needle sizes, shapes and materials. Various research reports studied confirmed that microneedles are ought to be the prominent carriers for enhancing the permeation deep into the systemic circulation and providing a painless, effective and safe route for the drug delivery. In future microneedles plays important role in innovation and design of controlled drug delivery for various drugs. Transdermal drug delivery system is an emerging area for systemic as well as local delivery of macromolecules. The biggest drawback of TDDS is poor permeability through stratum corneum and it can be overcome by using microneedles. Hence, researchers focused their attention on development of different types of microneedles for delivery of macromolecules, immunobiologicals and drugs as well as to withdraw the tissue fluids. Physical approaches have also been combined with microneedles to enhance drug delivery through skin. In conclusion, microneedles have been tried by many scientists as a novel means to administer the molecules. Many patents have been filed to cover the invention and this reflects the scope of

development of microneedle as a means to administer the problematic macromolecules. Improved therapeutic response can be obtained using microneedles.

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