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Emerging era of micro needle mediated transdermal drug delivery

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ABSTRACT

Many advantages exist for drug delivery through the skin, including the exclusion of hepatic first-pass metabolism, the monitoring of steady plasma levels, safety, and compliance over orally administered routes. However, the biggest challenge for transdermal delivery is that only a limited number of potent drugs with ideal physicochemical properties can passively diffuse and intercellular permeate through skin barriers and achieve therapeutic concentration by this route. The Microneedle technique is the most advanced physical method that easily bypasses, the stratum corneum and allows the drug to each viable dermis. Microneedle technology possesses tremendous potential considering the variations in types and materials it offers with ease of fabrication and is the next generation of therapeutics. This review focuses on the types of microneedles, and techniques involved in the insertion and delivery of microneedles. The study explores the wide applications of microneedle as potential drug targeting therapy.

Keywords: TransdermalDrug delivery, Microneedle, Solid microneedle insertion, Hydrogel microneedle.

INTRODUCTION

TRANSDERMAL DRUG DELIVERY USING MICRONEEDLES

The overarching goal of microneedles is to provide a minimally invasive method of transporting molecules into the skin. With this goal in mind, a variety of specific strategies for using microneedles for transdermal delivery have been developed. [1] The majority of research has concentrated on creating microscopic holes in the skin by inserting solid microneedles made of silicon or metal. The ‘‘poke with patch’’ approach uses microneedles to make holes and then applies a transdermal patch (or some prototype) to the skin surface. If an electric field is applied, transport can occur via diffusion or possibly iontophoresis. Another method is "coat and poke," in which needles are first coated with a drug before being implanted into the skin. There is no drug reservoir on the skin's surface; all of the drug to be delivered is contained within the needle itself. [2] A variation on this second approach is ‘‘dip and scrape,’’ where micro lead to much faster rates of delivery that can be modulated over time.

Solid microneedles can be used to create micron-scale holes in the skin through which molecules can be more easily transported. The first microneedle arrays published in the literature were etched into a silicon wafer and developed in vitro for intracellular delivery. The above needles have been inserted into cell lines and microorganisms to enhance molecular take-up and gene transfection. Microneedles for transdermal delivery applications were developed shortly after this work was published, and they have been shown to insert into the skin and deliver a variety of different compounds in vitro and in vivo. [3]

FIRST STUDIES OF TRANSDERMAL DELIVERY

The first study to determine if microneedles could be used to increase transdermal drug delivery. An array of solid micro- needles was embedded in cadaver skin, which caused skin permeability to a small model compound, calcium, to increase by three orders of magnitude.

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Enhanced transport was thought to occur via leakage pathways between the needles and the skin. [4] Skin permeability increased by an order of magnitude after the needles were removed, thereby unplugging the holes they created.

A subsequent study examined the permeability of cadaver skin to a variety of different compounds and discovered that insulin, bovine serum albumin, and latex nanoparticles as large as 100 nm in diameter could cross the skin after microneedle treatment. Mathematical modelling of the data revealed that these compounds were transported via simple diffusion. [5]

Microneedles were created from a silicon wafer using lithography and reactive ion etching in these studies. The needles that resulted formed a 20-by-20 array, with each needle measuring 80 Am at the base and tapering to a height of 150 Am with a radius of curvature near 1 Am at the tip. [6]

The significance of these studies is that they demonstrate increased transdermal transport using micro- needles and show that skin permeability can be increased by orders of magnitude. They do provide detailed guidance on how to make needles for transdermal drug delivery.

Mechanics of micro needle insertion into skin

The majority of microneedle research has focused on fabrication techniques and drug delivery capabilities. The mechanics of micro needle insertion have received only limited attention, but are critically important to practical applications. Hardly microneedles with the appropriate geometrical and physicochemical parameters can penetrate skin. A few needle designs can only be inserted by hand, whereas others, as previously mentioned, benefit from high-velocity insertion. [7] When the force required for insertion is too great, needles can break or bend prior to insertion.

Davis et al. addressed the problems explicitly by measuring the force required for fracture, the force required for insertion, and their ratio (termed the margin of safety) as a function of needle geometry and physical properties. Individual hollow metal microneedles with tip radii of 30-80 Am, wall thicknesses of 5 Am to solid tips (equivalent to 58 Am wall thickness), and a constant length of 500 Am were used in this study.

To determine the effect of micro needle geometry on the force of insertion, Davis et al. addressed the problems explicitly by measuring the force required for fracture, the force required for insertion, and their ratio (termed the margin of safety) as a function of needle geometry and physical properties. Individual hollow metal microneedles with tip radii of 30 – 80 Am, wall thicknesses of 5 Am to solid tips (equivalent to 58 Am wall thickness), and a constant length of 500 Am were used in this study. Insertion force was found to be independent of wall thickness. This implied that the skin was not flexible enough to beveled edge into the needle bore. The measured fracture forces were between 0.5 and 6 N over the range considered. The fracture pressure increased strongly with increasing wall thickness and weakly with increasing wall angle, but was unchanged by tip radius. These results agreed with analytical and finite element modelling.

The ratio of the fracture force to the insertion force can be considered the margin of safety; values greater than one identify needles that will insert into skin without breaking. [8]

Lack of pain caused by microneedles

Microneedles are appealing primarily because they promise painless drug delivery. Because the stratum corneum barrier of the skin lacks nerves, skin anatomy allows needles to be pierced across the stratum corneum without stimulating nerves. There is no evidence in current practise of microneedles penetrating just 10 – 20 Am across the stratum corneum without entering the viable epidermis, where nerves are found, where nerves are found. Rather, as discussed previously, microneedles are inserted at least into the epidermis and sometimes into the superficial dermis. Nonetheless, microneedles are still reported as painless, most likely due to their small size, which reduces the chances of striking a nerve or stimulating it to produce a painful sensation. [9] A limited trial was performed to see if human subjects perceived microneedles to be painless. Microneedle arrays were implanted into the skin of 12 subjects and compared to the negative control of pressing a flat surface against the skin and inserting a 26-gauge hypodermic needle into the skin surface (positive control). The subjects couldn't tell the difference between the painless sensation of the flat surface and that caused by microneedles. The sensation caused by the hypodermic needle was much more painful for all subjects. Other studies have found that microneedles can be used on humans without causing pain. [10]

ANATOMY AND PHYSIOLOGY OF THE SKIN

The epidermis is the body's largest organ, accounting for approximately 15% of total adult body weight. It performs many vital functions, including protection against ex-ternal physical, chemical, and biologic assailants, as well as prevention of excess water loss from the body and a role in thermoregulation. The epidermis is continuous, with mucosal tissue lining the skin surface.[11]

The epidermis and its derivative structures comprise the integumentary system. The skin is com- posed of three layers: the epidermis, the dermis, and subcutaneous tissue (Kanitakis, 2002). The epidermis, the outermost layer, is composed of a specific constellation of cells known as keratinocytes, which function to synthesise keratin, a long, threadlike protein with a protective function. The dermis, the middle layer, is primarily composed of the fibrillar structural protein collagen. The dermis is located beneath the panniculus, which contains small lobes of fat cells known as lipocytes. The width of certain layers varies widely depending on the geographic location of the body's anatomy. The eyelid, for example, has the thinnest epidermal layer (less than 0.1 mm), whereas the palms and soles of the feet have the thickest epidermal layer (approximately 1.5 mm). [12] The dermis is denser on the

back, where it is 30 to 40 times thicker than that of the epidermis.

Epidermis

The epithelial tissue is a stratified, squamous epithelium layer primarily composed of keratinocytes and dendritic cells. Keratinocytes differ from dendritic cells in that they have intercellular bridges and a lot of stainable cytoplasm. The epidermis includes a variety of cell populations, including melanocytes, Langerhans cells, and Merkel cells, but the keratinocyte cell type accounts for the vast majority of the cells. According to keratinocyte morphology and position as they differentiate into horny cells, the epidermis is commonly divided into four layers: the basal cell layer (stratum germinativum), the squamous cell layer (stratum spinosum), the granular cell layer (stratum granulosum), and the cornified or horny cell layer. The stratum malpighii and rete malpighii are the lower three layers that comprise the living, nucleated cells of the epidermis.
The epidermis is an ever-renewing layer that gives rise to derivative structures such as pilosebaceous apparatuses, nails, and sweat glands. The epidermis' basal cells go through proliferation cycles that allow the outer epidermis to regenerate. The epidermis is a dynamic tissue in which cells are constantly moving in unison, as different individual cell populations pass not only one another but also melanocytes and Langerhans cells as they move toward the skin's surface. [13]

Keratinocytes

Ectodermally derived keratinocytes account for at least 80% of epidermal cells. The distinguishing process occurs as cells transit from the stratum basale to the skin's structure resulting in keratinization, a technique in which the keratinocyte first undergoes a synthetic phase, followed by a degradative phase (Chu, 2008). The cell tends to accumulate a cytoplasmic supply of keratin, a fibrous intermediate filament arranged in an alpha-helical coil pattern that serves as the cell's cytoskeleton, during the synthetic phase. Desmosomes are intercellular attachment plates formed when bundles of these keratin filaments converge on and terminate at the plasma membrane. During the degradative phase of keratinization, cellular organelles have been lost and the cell's components are integrated into a mixture of filaments and amorphous cell envelopes, giving rise to the term "horny cell" or "corneocyte." Terminal differentiation refers to the process of maturation that results in cell death. [14]

Basal Layer

Column-shaped keratinocytes attach to the basement membrane zone with their long axis perpendicular to the dermis in the basal layer, also known as the stratum germinativum. Through desmosomal junctions, the above basal cells constitute a continuous layer and adhere to one another as well as to more superficial squamous cells. Basal cells could also be defined by their dark-staining oval or elongated nuclei, as well as the existence of melanin pigment transferred from adjacent melanocytes. [15]
The basal layer is the key region in the epidermis of progenitor cells capable of giving rise to cells of the outer epidermis. Moreover, not all basal cells are capable of dividing (Jones, 1996; Lavker & Sun, 1982). Under optimal conditions, epidermal stem cells in the basal layer are clonogenic cells with a long lifespan that progress through the cell cycle very slowly. Damage as well as other hyperplasiogenic conditions can expand the amount of cycling cells in the epidermis by stimulating stem division of cells. Carcinogenic agents can cause DNA damage that can mutate cell proliferation machinery and alter the speed of cellular division. In humans, it takes at least 14 days for a basal cell to migrate from the basal layer to the cornified layer, and another 14 days to transit through the cornified layer to the outermost epidermis.

Squamous Cell Layer

Elements that make up the basal cell layer is a 5Y10 cell thick epidermis layer known as the squamous cell layer or stratum spinosum. [16] The epithelial tissue layer is composed of a variety of cells that vary in shape, structure, and subcellular properties depending on where they are located.

Routes to percutaneous drug absorption

The stratum corneum seems to be well defined as the primary barrier to the percutaneous absorption of exogenous additives, which include the substances pursuing on using the skin as a portal via transdermal drug delivery. In hypothesis, there seem to be three different ways for a drug to cross the intercellular lipid barrier, allowing it to reach viable tissue and, eventually, the skin microcirculation. From here, the drug enters the systemic circulation to complete the absorption process. The available routes are trans-appendageal, via the hair follicles and sweat glands (sometimes referred to as the shunt route); Transcellular diffusion occurs through and across corneocytes, while intercellular diffusion occurs through the ordered domains of intercellular skin lipids. [17] The physicochemical properties of the permeating molecule, the fractional area of the route, and whether drug permeation is facilitated in any way by disruption of the skin barrier govern the relative contributions of the pathways to overall drug flux.

Classification of Microneedles [6]

Microneedles are categorised as according their implementation (medicine, pharmacy, and cosmetology), material (metal, polymer, glass, silicon, ceramic, hydrogel, and sugar), manufacturing technique (etching, injection moulding, micromachining, micro-molding, and lithography electroforming replication), or design (hollow or solid). Microneedles ought to have the right types of mechanical strength, toughness, and hardness to disrupt the SC without fracturing or buckling. Furthermore, the size of the microneedle must be small enough to ensure

painlessness and minimal invasiveness. Moreover, the drug delivery efficiency should also be fully considered during microneedle design. [17]

Microneedles by Material

Microneedles can be fabricated from a wide diversity of materials [18], for example,

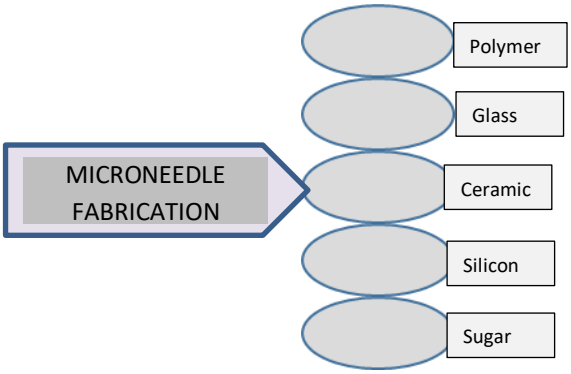

Fig 1: Micro Needles Fabrication

Silicon

Because of its relatively high hardness, this material has been developed for several decades. However, the manufacturing methods of silicon are expensive and need clean room processing. Furthermore, because silicon is a fragile material, silicon microneedles are prone to fracture during transport and application. As a result, microneedles made of brittle materials such as silicon, ceramic, and glass may cause problems during application. Furthermore, silica glass causes skin granulomas. There is currently insufficient evidence to support the biocompatibility of silica glass and silicon for microneedle manufacturing.

Metal

The metals used in the manufacture of microneedles are stainless steel, titanium, and nickel, palladium, and palladium-cobalt arrays. Metal microneedles usually have quite well- integrated mechanical properties, including high toughness, strength, and hardness, which can protect microneedles against mechanical failure microneedles can be manufactured at relatively low cost using a variety of methods (electroplating, photochemical etching, micro-milling, and laser cutting). Titanium is a feasible alternative to stainless since it is strong enough for biomedical applications. Titanium has been used mainly for biosensors and as transdermal delivery systems. Titanium alloys have good biocompatibility with excellent corrosion resistance. Metals are likely a more proper material to substitute silicon in microneedle production. Nevertheless, metal microneedles produce sharp bio-hazardous tip waste.

Polymer

Polymer microneedles typically have a high toughness to support them and prevent brittle fracture during insertion into the skin.
Some polymers are biodegradable, such as poly-glycolic acid (PGA), poly-lactide-co-glycolide acid (PLGA), poly-Lactic Acid (PLA), and chitosan, or water-soluble, so that drugs can be encapsulated in these dissolvable microneedles. Drugs will be released after insertion into the skin due to the degradation or dissolution of these dissolvable microneedles. Biodegradable polymeric microneedles induce almost no harsh side effects; thus, these microneedles are considered the most promising materials due to their biocompatibility, biodegradability, low toxicity, strength against breaking, and low cost. The main materials used for this kind of microneedle are poly(methyl methacrylate), poly (carbonate), poly (vinylpyrrolidone (PVP)), poly (vinyl alcohol (PVA)), polystyrene, poly (methyl vinyl ether-comaleic anhydride) and poly (methyl vinyl ether-comaleic acid).

Ceramic

The main type of ceramic is alumina. The major benefit of this material is its resistance and good biocompatibility; however, ceramic is brittle under tensile stress. Other types of ceramic used to prepare microneedles include calcium sulphate dihydrate and calcium phosphate dihydrate. These materials have good mechanical and drug-loading properties.

Glass

Silica glass is physiologically inert, allowing the visualization of fluid flow. Moreover, microneedles can be produced with different geometries and dimensions. However, glass is a brittle material. Since it has a reduced elastic modulus, borosilicate glass is more elastic. Glass microneedles, in general, take longer to produce because they are made by hand; thus, these microneedles are not recommended for use in industry.

Sugar

Maltose is the most common sugar used to prepare microneedles. Carbohydrates (trehalose, sucrose, mannitol, xylitol, and galactose) seem to be good

alternatives since they are cost - effective and safe for human consumption. Nonetheless, sugar microneedles pose challenges in terms of processing, storage, and application to the skin.

Types of Micro needles Design

The mode of drug delivery determines the classification of MNs. Solid MNs contain no medication and are only used to poke the skin. Additional application of the drug formulation is required post insertion and removal of solid MNs. In comparison, the existence of a shaft, as in hollow MNs, or coating solid MNs with drug formulation allows MN application and drug delivery to occur in a sequential manner. [19] Drugs can also be incorporated in a biodegradable matrix. This eliminates the need to physically remove any remnants. When two MN arrays are mounted on each other to enhance penetration they form rapidly separating MNs.

Solid Microneedles

Solid MNs are an array of a single uniform material with micron scale protrusions, and do not contain any drug or excipient associated with the array. They are generally used as skin pre-treatment. After insertion and removal, the tips of these MNs generate micron-sized pores on the skin surface. Once the formulation is applied over the pores, it allows drugs to permeate into the skin for either local or systemic effect. The formulation can take the form of a topical patch or a semisolid formulation such as gel, ointment, cream, or lotion.

Hollow Microneedles

Hollow MNs have close resemblance to hypodermic injections, with a distinctive feature of micron range size. They comprise of a conduit at the centre of each protrusion. They are used to infuse liquid formulations into the skin or to diffuse drugs from a drug reservoir.

Coated Microneedles

They are solid MNs coated with suitable drug formulation, which serve the purpose of drug delivery supplementary to piercing of the skin. After insertion of MNs, the coating dissolves in the skin, following which the MNs are removed.

Dissolvable/ Biodegradable/ Hydrogel forming Microneedles

MNs can be made out of water-soluble or biodegradable materials like polymers or sugars that encapsulates the drug within the MN matrix. These MNs completely dissolve or degrade in the skin within a week of application, releasing the encapsulated drug payload while leaving no hazardous residues. The polymer needle tips of hydrogel-forming MNs swell by absorbing body fluid, allowing drug release. At the same time, they form conduits, enabling the drug released out from reservoir to enter the microcirculation. They leave almost no polymer residue after removal from the skin.

Rapidly separating Microneedles

One such type consists up of a liquid matrix that encloses the drug. It is attached to another array made of an insoluble polymer that acts as a spacer and helps to overcome skin deformation during insertion. Once drug-loaded MNs are inserted into the skin, they come into contact with interstitial fluid and dissolve. The remnant patches can be peeled off against the skin.

Techniques to insert microneedles into the skin

Drugs can be released from microneedles in a variety of ways. [20] The first is a novel technique known as "poke with patch," in which solid silicon or metal microneedles are used to create microchannels before applying a transdermal patch to the skin's surface. Drug diffusion is responsible for drug transport. The second method is known as "coat and poke," and it involves coating the needles with the drug before inserting them into the skin. Following that, the drug is released. The "dip and scrape" method is a variation of the second method in which the microneedles are first immersed in a solution containing the drug and then the entire surface of the skin is scraped to introduce the drug into the micro-abrasions created by the needles. The third is “Poke and flow” for hollow microneedles delivering a drug like a micro-injection. Eventually, "poke and release" refers to a process of dissolving microneedles made of polymers or polysaccharides while releasing the drug during the dissolution of the microneedles.

Various techniques involved in the mechanism of micro needle insertion are

A) Solid microneedles using poke with patch,
B) Solid microneedles coat and poke,
C) Biodegradable microneedles with the mechanism of poke and release,
D) Hollow microneedles for injection poke and flow.

Solid microneedle using poke with patch

Solid microneedles are mostly used for pre-treating the skin by forming pores. Pointed tips of the needles penetrate into the skin; create channels of micron size, through which the drug directly enters the skin layers on the application of a drug patch, thus increasing the permeation. The drug is taken up by the capillaries to show a systemic effect. It can be used for a local effect also, solid microneedles deliver the drug with passive diffusion to skin layers. Narayanan et al fabricated solid silicon long and tapered microneedles using tetramethylammonium hydroxide etching process. Microneedles with an average height of 158 μm and base width of 110.5 μm were successfully fabricated. Later he also fabricated the gold-coated solid silicon microneedles with the dimension of 250 μm in height, the base width of 52.8 μm, the aspect ratio of 4.73, tip angle and diameter of 24.5° and 45 μm.

The results demonstrated improved bioavailability and mechanical strength. Li et al studied polylactic acid microneedles and found that biodegradable polymer solid microneedles have sufficient mechanical strength to pierce the stratum corneum and can enhance the absorption of the drug. The microneedles having 800 μm depth and density of 256 MNs per cm2 was found to enhance the drug permeation. Stainless steel microneedles are also studied by various researchers. Enhanced delivery of captopril and metoprolol tartrate was studied after application of stainless steel MN arrays.

Solid microneedle coat and poke

The microneedles are surrounded with the drug solution or drug dispersion layer. Subsequent dissolution of drug from the layer takes place and the drug is delivered quickly. The amount of drug that can be loaded depends on the thickness of the coating layer and the size of the needle which is usually very less. Baek et al loaded lidocaine on poly L-lactide (PLLA) microneedle arrays. The loaded lidocaine released rapidly in phosphate buffer saline and was found to be stable for 3 weeks. Coated microneedle also explored for delivery of multiple agents through same formulation. Coated each microneedle with different formulations and drugs thus allowing co-delivery of multiple agents with different properties. These delivered water soluble and water insoluble dyes simultaneously. Chen and co-workers coated PLA microneedles and found the drug delivery efficiency to be approximately 90%. The in-vitro studies in mice confirmed the continuous drug delivery. [21]

Biodegradable microneedles with the mechanism of poke and release

Dissolving microneedles are fabricated with biodegradable polymers by encapsulating the drug into the polymer. After inserting micro needle in the skin, dissolution takes place which releases the drug. The application involves only a single step as the micro needle is not to be removed out after insertion as in other cases. The polymer gets degraded inside the skin and controls the drug release. The bio-acceptability and dissolution of the polymer inside the skin make it one of the best choices for long-term therapy with improved patient compliance. Effective needle drug distribution is an important factor which faces problems while developing dissolving microneedles. Hence, polymer-drug mixing is a critical step in such fabrication developed tip dissolving microneedles which showed rapid and efficient drug delivery without skin irritation. Dissolving microneedles take time to dissolve and complete insertion is difficult, rapidly separating micro needles mounted on solid microneedles which gave sufficient mechanical strength to the micro needles and approximately 90% delivery efficiency was observed in 30 s. Wang et al introduced the addition of bubbles to the dissolving microneedles to prevent drug diffusion in the entire microneedles. These were found to achieve about 80% of drug delivery efficiency in 20 s. Separable arrowhead microneedles were developed by Chu et al. Sharp polymer tips encapsulated with the drug were mounted on blunt metal shafts which separate or dissolve on insertion in the skin within a few seconds. These modifications in dissolving microneedles showed that possibilities of the rapid drug delivery with controlled release kinetics.

Hollow microneedle poke and flow

Hollow microneedles have an empty space inside which is filled with the drug dispersion or solution. They have holes at the tips. On inserting into the skin, the drug is directly deposited into the epidermis or the upper dermis layer. Mostly it is used for high molecular weight compounds such as proteins, vaccines, and oligonucleotides. The drug flow rate and release pressure can be adjusted if the drug is to be given by a rapid bolus injection. These microneedles are capable of administering a large dose of the drug as more amount of drug can be accommodated into the empty space inside the needle. Maintaining a constant flow rate is essential here. Increase in the microneedle bore can increase flow rate but lead to reduced strength and sharpness. Sometimes a metal coat is applied on the microneedle to increase the strength of the microneedle but this can make the needles sharp. Mishra et al developed hollow microneedles aligned on the silicon substrate having a length of 500–600 μm and 100 μm outer diameter. The flow rate of 0.93 μl was achieved at 2 K Pa pressure difference. Maaden and co-workers fabricated fused silica hollow microneedles using hydrofluoric acid etching. These microneedles were able to inject very less amount of vaccine into the skin in an automated manner thus overcoming the drawbacks of the hypodermic needle. Interestingly Suzuki and colleagues developed hollow microneedles which were mimicking the action of mosquitoes and the designed microneedles showed improved penetration in the skin.

Applications of microneedles

Microneedles are used in a variety of health-related fields due to the multiple benefits they provide. Microneedles are a convenient way to deliver a variety of medications (anti-cancer treatments, oligonucleotides, vaccines, proteins, DNA, and even nanoparticles) to the skin. Microneedles has numerous applications in the realms of pharmacy, medicine, and cosmetics. Microneedles have become more widely used in medicine, allowing other significant applications have been in the use of lasers in various medical operations, such as the treatment of glaucoma. Various biomarkers are being monitored. [22]

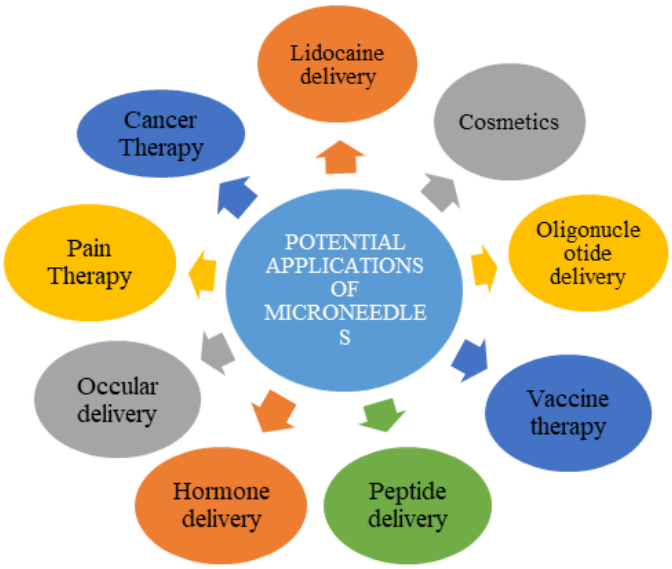

Fig 2: Potential Applications of Microneedles

Delivery of oligonucleotides

Short DNA or RNA molecules are known as oligonucleotides. It's tough to get oligonucleotides to their intracellular sites of action. As a result, numerous ways for improving delivery have been devised. The poke with patch method was used to deliver oligonucleotides using solid microneedles made of stainless steel or titanium. In comparison to intact skin, more medication was observed to reach the site of action. When iontophoresis was combined with a microneedle technique, the results were better than when iontophoresis was used alone.

Vaccine therapy

A biological preparation is a vaccination. It delivers disease-specific active acquired immunity. Vaccines are made up of a disease-causing microbe that has been killed or weakened, as well as its toxins or one of its surface proteins. Vaccine therapy activates the body's immune system and provides protection from future microbe encounters. In vaccination therapy, the microneedle method was proven to be effective. [23]
A microneedle was used to administer the DNA vaccination. Immune responses were far superior to those found with standard doses. There was also an attempt to create a microneedle patch that might be used to administer influenza vaccine. When compared to intramuscular injection, a lower dose is required when the medicine is delivered via hollow microneedles. Hollow microneedles were used to administer anthrax and rabies vaccines.

Peptide delivery

When peptides are taken by mouth, they are enzymatically destroyed. Although transdermal delivery prevents this, it allows for a less amount of peptide to cross the skin. Peptide administration by microneedles can aid in peptide penetration into the skin. Desmopressin is a strong peptide hormone that is synthesised from vasopressin. It's employed to Low amounts of vasopressin must be replaced. This drug is used to treat diabetes insipidus, bedwetting in children, and other conditions. [24] Microneedle delivery of desmopressin was tested in patients with haemophilia A, and it was discovered that microneedle delivery of desmopressin was effective. When compared to other routes, delivery was safer and more efficient.

Hormone delivery

Insulin is a hormone that is made up of peptides. The drug is intended to help people with high blood sugar levels. The use of a microneedle to deliver insulin was found to be more effective in lowering blood glucose levels. Li et al created solid microneedles and investigated how they affected blood glucose levels and insulin delivery in diabetic mice. The results showed a reduction in blood glucose levels to 29% of the starting level after 5 hours, indicating that microneedle therapy enhanced insulin permeability to the skin. Microneedles coupled with pancreatic-cell capsules that sense blood glucose levels and produce insulin were studied by Ye and co-workers. However, the patch was determined to be ineffective. As a result, a microneedle matrix comprising synthetic glucose signal amplifiers (GSAs) was constructed, with nanovesicles containing GSAs.

Cosmetics

The use of microneedles in cosmetics is gaining popularity, particularly for improving skin look and treating blemishes and scars. The microneedle method was used to administer various cosmetic active substances such as ascorbic acid, eflornithine, and retinyl retinoate.

Delivery of lidocaine

Lidocaine is a local anaesthetic agent. Using a micro-needle to administer lidocaine generates less pain than using a needle. As a result of the hypodermic injection, patient compliance is improved. In vitro, these microneedles showed constant skin penetration and improved drug delivery in 2 minutes. [25] Hence, Microneedles can be used for local anaesthetic that is painless and quick. When compared to the topical formulation, microneedles coated with PEG lidocaine dispersions showed better drug delivery within 3 minutes in one trial.

Pain therapy

Poly-di-methyl siloxane moulds were used to make Meloxicam loaded polymeric microneedles. In-vitro penetration investigations revealed that approximately 100 percent of the medication was released in 60 minutes. The drug deposition was determined to be 63.37 percent, and the transdermal flux was improved to 1.60 g/cm2/hr. When compared to a free drug solution, penetration increased 2.58 times. Neuropathic pain is notorious for being difficult to manage. The present treatments do not give adequate pain relief and have some negative side effects. The use of dissolved microneedles to alleviate neuropathic pain was investigated. These supplied a selective calcitonin gene-related peptide (CGRP) antagonist peptide with good receptor selectivity. There were no skin irritation or negative effects from the analgesic microneedle patch. On the application, about 75% of the microneedle dissolved in 20 minutes, this assures the use of microneedles to deliver therapeutics effectively.

Ocular delivery

Targeted medication delivery can be used to treat a variety of posterior segment conditions. Nanoparticles were delivered through the suprachoroidal space using iontophoresis. The particles were observed to localise at the surface without iontophoresis. Injection location More than 30% of nanoparticles were transported to the posterior when coupled with microneedles.

Cancer therapy

Every year, millions of individuals throughout the world are diagnosed with cancer, and cancer treatment is fraught with difficulties. Microneedles have been studied for the delivery of anticancer medicines. Microneedles made of biodegradable materials were used. Anti-PD-1 (aPD1) delivery in a sustained manner is being studied for melanoma treatment. PD-1 inhibitors and hyperglycaemia. Through a microneedle, oxidase-loaded pH-sensitive dextran nanoparticles were administered. A topical cream with 5-HTP. Basal cell cancer is treated with fluorouracil. 5-fluorouracil has a high permeability. [26]
Microneedle technology has the potential to deliver large molecules with significant therapeutic interest, such as insulin, proteins produced by the biotechnology industry, and nano particles that could encapsulate a drug or demonstrate the ability to deliver a drug, by fabricating microneedles in a variety of shapes, sizes, and materials.

Potential of micro needle technology

Microneedles could be useful in immunisation efforts in developing nations, as well as mass vaccination and drug administration. Bioterrorism incidents could occur because people with only rudimentary medical expertise could use them. Extremely small microneedles could deliver extremely focused drug delivery to single cells.
Because of their small size, thousands of needles can be produced on a single wafer by manufacturing them on a silicon substrate. This results in high accuracy, repeatability, and a low fabrication cost.

CONCLUSION

Several MN systems with distinct delivery mechanisms have been developed and used for the delivery of small or macromolecules over the last few decades. Overcoming the stratum corneum barrier is critical to effective MN-mediate transdermal and oral delivery. Intradermal administration. This paper provides an overview of MNs technology in the transdermal drug delivery era. Extensive research Due to the benefits of MNs, research has been conducted in their fabrication. Various MN design types, materials, and colours are available. This paper illustrates design and manufacturing methods. Recent research has shown that temporarily disrupting the skin microchannel lifetime improves transdermal absorption. As highlighted in this article, the delivery efficiency of small molecular drugs, salt forms, excipients, and other formulation factors is efficient when mediated through micro needles.

REFERENCES

1. Bhatnagar S, Dave K, Venuganti VVK. Microneedles in the clinic. J Control Release. 2017;260:164-82. doi: 10.1016/j.jconrel.2017.05.029.
2. Kim YC, Park JH, Prausnitz MR. Microneedles for drug and vaccine delivery. Adv Drug Deliv Rev. 2012;64(14):1547-68. doi: 10.1016/j.addr.2012.04.005, PMID 22575858.
3. Bediz B, Korkmaz E, Khilwani R, Donahue C, Erdos G, Falo LD Jr, Ozdoganlar OB. Dissolvable microneedle arrays for intradermal delivery of biologics: fabrication and application. Pharm Res. 2014;31(1):117-35. doi: 10.1007/s11095-013-1137-x, PMID 23904139.

4. Indermun S, Luttge R, Choonara YE, Kumar P, du Toit LC, Modi G, Pillay V. Current advances in the fabrication of microneedles for transdermal delivery. J Control Release. 2014;185:130-8. doi: 10.1016/j.jconrel.2014.04.052, PMID 24806483.
5. Ita K. Transdermal delivery of drugs with microneedles—potential and challenges. Pharmaceutics. 2015;7(3):90-105. doi: 10.3390/pharmaceutics7030090, PMID 26131647.
6. Tuan-Mahmood TM, McCrudden MT, Torrisi BM, McAlister E, Garland MJ, Singh TR, Donnelly RF. Microneedles for intradermal and transdermal drug delivery. Eur J Pharm Sci. 2013;50(5):623-37. doi: 10.1016/j.ejps.2013.05.005, PMID 23680534.
7. Bhatnagar S, Chawla SR, Kulkarni OP, Venuganti VVK. Zeinmicroneedles for transcutaneous vaccine delivery: fabrication, characterization, and in vivo evaluation using ovalbumin as the model antigen. ACS Omega. 2017;2(4):1321-32. doi: 10.1021/acsomega.7b00343, PMID 30023631.
8. Donnelly RF, Majithiya R, Singh TR, Morrow DI, Garland MJ, Demir YK, Migalska K, Ryan E, Gillen D, Scott CJ, Woolfson AD. Design, optimization and characterisation of polymeric microneedle arrays prepared by a novel laser-based micromoulding technique. Pharm Res. 2011;28(1):41-57. doi: 10.1007/s11095-010-0169-8, PMID 20490627.
9. Lee JW, Han MR, Park JH. Polymer micro needles for transdermal drug delivery. J Drug Target. 2013;21(3):211-23. doi: 10.3109/1061186X.2012.741136, PMID 23167609.
10. Park JH, Allen MG, Prausnitz MR. Polymer microneedles for controlled-release drug delivery. Pharm Res. 2006;23(5):1008-19. doi: 10.1007/s11095-006-0028-9, PMID 16715391.
11. Zhu Z, Luo H, Lu W, Luan H, Wu Y, Luo J, Wang Y, Pi J, Lim CY, Wang H. Rapidly dissolvable microneedle patches for transdermal delivery ofexenatide. Pharm Res. 2014;31(12):3348-60. doi: 10.1007/s11095-014-1424-1, PMID 24867426.
12. Milewski M, Brogden NK, Stinchcomb AL. Current aspects of formulation efforts and pore lifetime related to microneedle treatment of skin. Expert Opin Drug Deliv. 2010;7(5):617-29. doi: 10.1517/17425241003663228, PMID 20205604.
13. Larrañeta E, Lutton REM, Woolfson AD, Donnelly RF. Microneedle arrays as transdermal and intradermal drug delivery systems: materials science, manufacture and commercial development. Mater Sci Eng R Rep. 2016;104;Suppl:1-32. doi: 10.1016/j.mser.2016.03.001.
14. Gill HS, Prausnitz MR. Coating formulations for microneedles. Pharm Res. 2007;24(7):1369-80. doi: 10.1007/s11095-007-9286-4, PMID 17385011.
15. Donnelly RF, Raj Singh TR, Woolfson AD. Microneedle-baseddrug delivery systems: microfabrication, drug delivery, and safety. Drug Deliv. 2010;17(4):187-207. doi: 10.3109/10717541003667798, PMID 20297904.
16. Shukla R, Cheryan M. M. Zein: the industrial protein from corn. Ind Crops Prod. 2001;13(3):171-92. doi: 10.1016/S0926-6690(00)00064-9.
17. GAO S, Singh J. In vitro percutaneous absorption enhancementof a lipophilic drug tamoxifen by terpenes. J Control Release. 1998;51(2):193-9.
18. Fontana G, Maniscalco L, Schillaci D, Cavallaro G, Giammona G. Solid lipid nanoparticles containing tamoxifen characterization and in vitro antitumoral activity. Drug Deliv. 2005;12(6):385-92. doi: 10.1080/10717540590968855, PMID 16253954.
19. Heel RC, Brogden RN, Speight TM, Avery GS. Tamoxifen: areview of its pharmacological properties and therapeutic use inthe treatment of breast cancer. Drugs. 1978;16(1):1-24. doi: 10.2165/00003495-197816010-00001, PMID 352663.
20. Chawla JS, Amiji MM. Biodegradable poly (ε-caprolactone) nanoparticles for tumor-targeted delivery of tamoxifen. Int J Pharm. 2002;249(1-2):127-38. doi: 10.1016/s0378-5173(02)00483-0, PMID 12433441.
21. Jena SK, Singh C, Dora CP, Suresh S. Development oftamoxifen-phospholipid complex: novel approach for improving solubility and bioavailability. Int J Pharm. 2014;473(1-2):1-9. doi: 10.1016/j.ijpharm.2014.06.056, PMID 24992316.
22. Haq MI, Smith E, John DN, Kalavala M, Edwards C, Anstey A, Morrissey A, Birchall JC. Clinical administration of microneedles: skin puncture, pain and sensation. Biomed Microdevices. 2009;11(1):35-47. doi: 10.1007/s10544-008-9208-1, PMID 18663579.
23. Gill HS, Prausnitz MR. Coated microneedles for transdermal delivery. J Control Release. 2007;117(2):227-37. doi: 10.1016/j.jconrel.2006.10.017, PMID 17169459.
24. Gittard SD, Ovsianikov A, Monteiro-Riviere NA, Lusk J, Morel P, Minghetti P, Lenardi C, Chichkov BN, Narayan RJ. Fabrication of polymer microneedles using a two-photon polymerization and micromolding process. J Diabetes Sci Technol. 2009;3(2):304-11. doi: 10.1177/193229680900300211, PMID 20144361.
25. Martin A, McConville A, Anderson A, McLister A, Davis J. Microneedle manufacture: assessing hazards and control measures. Safety. 2017;3(4):4-14. doi: 10.3390/safety3040025.
26. Tanwar H, sachdeva R. A review of transdermal drug delivery system. Int J Pharm Sci Res. 2016;7(6):2274-90.