Microneedles as Enhancer of Drug Absorption Through the Skin and Applications in Medicine and Cosmetology

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ABSTRACT - The microneedles technology has found applications in many health-related fields. For example, their application in drugs and vaccines delivery as well, as the determination of biomarkers, has been reported. They also have a place in the dermatology and cosmetic areas such as the treatment of wounds from burns, scars, acne, depigmentation, and alopecia will be shown. Microneedles are used in therapeutic applications and are manufactured using materials such as metal (steel, titanium, nickel), polymer (oly-glycolic acid (PGA), poly-lactide-co-glycolide acid (PLGA), poly-L-lactic acid (PLA), chitosan), glass, silicon, ceramic, carbohydrates (trehalose, sucrose, mannitol). Examples of application of microneedles and their advantages and disadvantages are discussed.

INTRODUCTION

At present, the human skin is a route for delivering drugs with either local effect or with systemic therapeutic effect, and it represents a highly attractive alternative compared to conventional dosage forms including injections, capsules, and tablets (1). This route of drug administration has advantages, such as avoiding first-pass metabolism, controlled drug release, and reduction of dosages. It is painless, easy to administer, and noninvasive (1-4). Nevertheless, the principal limitation for a transdermal drug delivery system is the skin itself (1, 5-6). The external layer of the skin is the stratum corneum (SC), which is the principal barrier of protection from microorganisms and other dangerous agents (1-7). For this reason, it is necessary to use chemical or physical penetration enhancers with the intention of increasing permeability of different substances through the skin (8-18).

In the case of physical enhancers, microneedles have been shown to increase the drug permeability through the skin by up to 3 orders of magnitude by passing the SC. Microneedles can allow transdermal delivery of many drugs and macromolecules, such as insulin, peptides, and other biomolecules that normally

cannot diffuse through the skin (6, 18-20). In addition, the microneedles enter the upper layer of the skin without reaching the nerves, making the drug delivery painless (6, 18-20).

The aim of this review is to offer an overview of the use of microneedles as a drug delivery system in medicine, pharmacy, and cosmetology and to show the principles, limitations, and pharmacological profiles for each field.

SKIN STRUCTURE

Human skin has several functions such as photoprotection, thermoregulation, hormonal synthesis, sensory perception, and protective function as a barrier for chemical, physical, and microbial agents (5, 21-22). Anatomically, the skin

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has three main layers, the epidermis, dermis, and hypodermis (subcutaneous tissue). Figure 1 shows the component layers of the skin (23).

The epidermis thickness is around 0.12 mm and comprises five layers: the basal or germinative layer, the stratum spinosum, the granular layer, the lucidum layer, and the SC (24-28). The SC is the main barrier that shields the skin from the entry of foreign substances. The SC has an average thickness of 20 µm; this layer is composed of corneocytes (dead anucleated epidermal cells), which are filled with keratin filaments and embedded in a continuous multilamellar lipid matrix. The lipid composition is complex, it includes components like long-chain ceramides, fatty acids, and cholesterol compared to most other biological membranes that basically have phospholipids (24). Moreover, the SC is a selective membrane that controls the penetration of substances into the skin and prevents water loss. The lower three sublayers (stratum granulosum, stratum spinosum, and stratum basale) constitute the viable part of the epidermis that has cells like melanocytes, Langerhans cells, and Merkel cells (5, 21-24).

The dermis has a thickness of 3-5 mm. This matrix is formed of connective tissue, and it is made up of collagen fibers and elastin (25). This tissue is vascularized, presenting blood vessels and nerves and includes apocrine glands, sweat glands, and pilosebaceous follicles (5, 26-27). The dermis is constituted by the subcutaneous fascia and chorion layers.

The hypodermis is the innermost layer of the skin, where the function of transporting nutrients and migrating cells is observed. It acts as an isolator, which helps the body to retain heat. This layer is constituted of adipose tissue. This skin layer is where more irrigation exists because there are many blood vessels in addition to numerous nerve endings (5, 24-27).

It is important to mention that the skin thickness is different according to gender, race, age, and anatomical region (24-27). Moreover, the thickness of the skin is a critical factor in transdermal drug delivery.

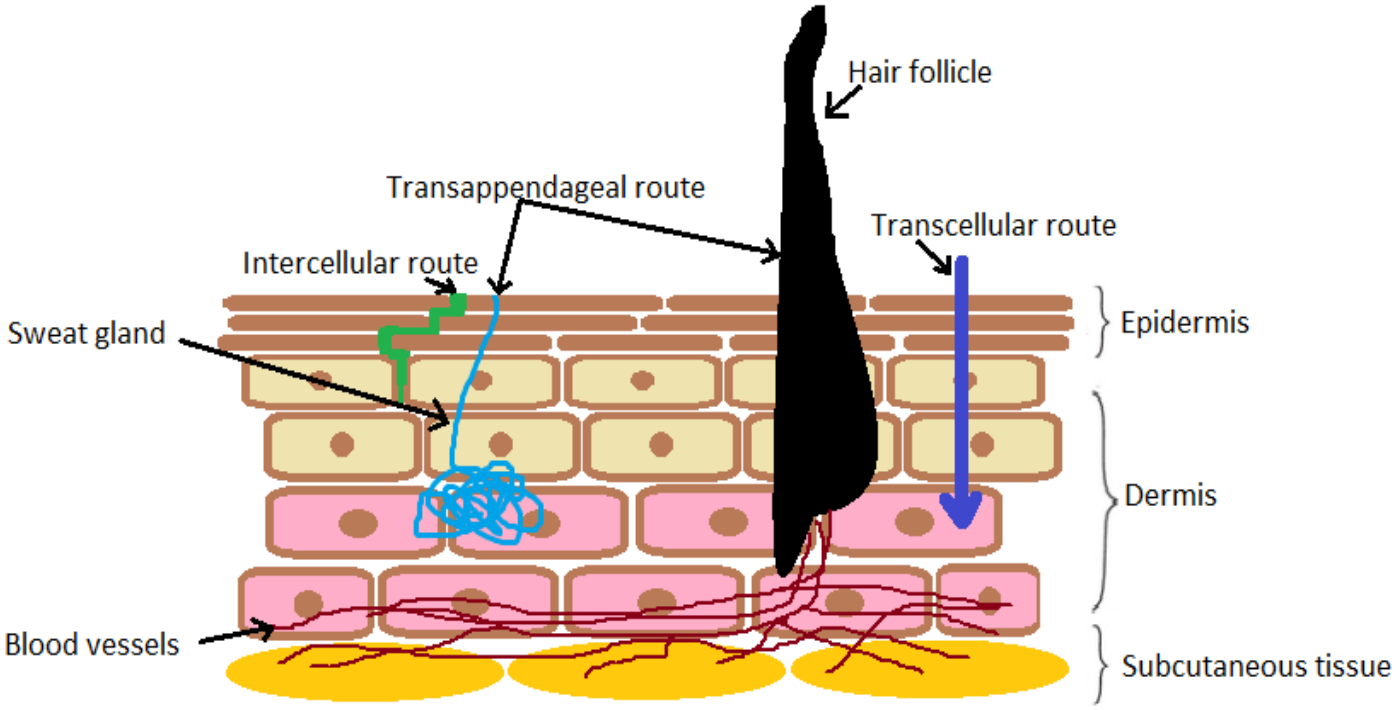

Figure 1. Layers of the skin and penetration routes.

PENETRATION DRUG ROUTES THROUGH THE SKIN

Human skin is an interesting route for drug therapy since it offers an accessible route, avoiding the first-pass hepatic metabolism. The main routes of penetration through the SC barrier are trans-appendageal, intercellular, and intracellular routes.

The *trans-appendageal route* is the transport via of pores, embracing sweat glands and hair follicles with their associated sebaceous glands; nonetheless, the classical concept considers that the trans-appendageal route is not a significant transdermal route because hair follicles and sweat glands occupy 0.1% of the surface of the human skin (29-30). However, it is an important mode of entrance for large polar molecules and ions, which can barely pass through the SC.

The *intercellular route* is the principal route of entry for lipophilic drugs due to the dense packing of proteins within the corneocytes, which make them almost impermeable (31-32).

In the *intracellular route*, the drug is mainly driven by its partition coefficient (log P). Hydrophilic drugs can diffuse via the intracellular route. In contrast, lipophilic drugs preferably cross the SC via the intercellular domain (5, 29, 31-32).

Transdermal penetration through the SC is illustrated in Figure 1. As seen, transdermal penetration may occur between the cells (intercellular) or through cells (transcellular route). The relative contribution of these pathways depends on the solubility, partition coefficients, and diffusivity of the drug within proteins or lipids. These skin diffusion processes are mediated by a limiting process of passive diffusion. The rate and extent of transport follow Fick's law (2, 5, 33).

Only molecules with appropriate physicochemical properties can passively diffuse through the skin membrane. In recent years, many different chemicals and physical permeation enhancers have been developed. Among the most recent and promising techniques is the use of a microneedle based on improving the skin transport of molecules.

MICRONEEDLES

Microneedle technology for drug delivery was first developed in 1971 for an invention by Gerstel and Place (34-36), but until the 1990s, microneedle drug delivery advanced with microelectronics technology (6, 35). Microneedles are micron-sized needles that are used to open holes into the skin to create micro-channels for the subsequent delivery of drugs and thus cross the SC (6). The microneedles enter the upper layer of the skin without touching the nerves, thus delivering drugs transdermally in a painless manner. Microneedles usually have a diameter of a few hundred microns, which recedes toward the sharp tip and has a length of 50 to 900 μm (37).

Classification of Microneedles

Microneedles can be classified based on applications (medicine, pharmacy, and cosmetology), material (metal, polymer, glass, silicon, ceramic, hydrogel, and sugar), manufacturing technique (etching, injection molding, micromachining, micro-molding, and lithography electroforming replication), or design (hollow or solid).

Microneedles should have the appropriate combination of mechanical strength, toughness, and hardness to disrupt the SC without fracture and buckling failure. In addition, microneedle size must be small enough to ensure painlessness and minimal invasiveness. Moreover, the drug delivery efficiency should also be fully considered during microneedle design (38).

Microneedles by Material

Microneedles can be fabricated from a wide diversity of materials, for example, metal, polymer, glass, silicon, ceramic, hydrogel, and sugar.

Silicon. This material has been developed for several decades because this material has relatively high hardness. However, the manufacturing methods of silicon are expensive and need clean room processing (39). Moreover, silicon is a fragile material; thus, silicon microneedles are prone to fracture in transportation and application (38-39). Therefore, microneedles made from brittle materials like silicon, ceramic, and glass could present problems at the time of application. In addition, silica glass causes granulomas in the skin. Currently, there is insufficient evidence regarding the biocompatibility of silica glass and silicon for microneedle manufacture (35-39).

Metal. The metals used in the manufacture of microneedles are stainless steel, titanium, 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 (38). Metal

microneedles can be manufactured at relatively low cost using a variety of methods (electroplating, photochemical etching, micro-milling, and laser cutting). Titanium is a viable alternative to stainless steel because this material is adequately strong for biomedical applications. Titanium has been used mainly for biosensors and as transdermal delivery systems. Titanium alloys have good biocompatibility with excellent corrosion resistance (39). Metals are likely a more proper material to substitute silicon in microneedle production. Nevertheless, metal microneedles produce sharp bio-hazardous tip waste (38-39).

Polymer. Microneedles made of polymers generally have high toughness to support the polymer microneedles to avoid brittle fracture during their insertion into the skin. Some polymers are biodegradable, such as poly-glycolic acid (PGA), poly-lactide-co-glycolide acid (PLGA), poly-L-lactic acid (PLA), and chitosan, or water-soluble, so that drugs can be encapsulated in these dissolvable microneedles. After insertion into the skin, drugs will release with 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-co-maleic anhydride) and poly (methyl vinyl ether-co-maleic acid) (35-39).

Ceramic. The main type of ceramic is alumina. The main advantage of this material is the resistance and good biocompatibility; nevertheless, under tensile stress, ceramic is brittle. Other types of ceramic used to prepare microneedles include calcium sulfate dihydrate and calcium phosphate dihydrate. These materials have good mechanical and drug-loading properties (36-39).

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. Borosilicate glass is more elastic because it presents a lower value of elastic moduli. In general, glass microneedles required more time for production because they are created by hand; thus, these microneedles are not recommendable for the industry (38-39).

Sugar. Maltose is the most common sugar used to prepare microneedles. Carbohydrates (trehalose, sucrose, mannitol, xylitol, and galactose) are good alternatives because they are affordable and safe for human health (38). Nevertheless, sugar microneedles present problems in the processing, storage, and application on the skin. Moreover, the main disadvantage of this microneedle is that it needs thermal treatment in manufacturing (35-39).

Microneedle Design

Solid Microneedles

These microneedles penetrate the upper layer of the skin and thus allow passage of the drug through the lower layers of the skin (35-40). The drug can be coated on the surface of solid microneedles to be inserted into the skin and then the drug dissolves into the skin. Subsequently, the needles are removed from the skin. Regarding manufacture, solid microneedles are easier to make than hollow microneedles, and they have better mechanical strength and sharper tips. Solid microneedles can be fabricated with metals or polymers, such as PLGA, PLA, PGA, hyaluronic acid, PVP, PVA, sodium alginate, chitosan, zein, carboxymethyl cellulose (CMC), and hydroxypropyl cellulose (HPC), as well as silk, chondroitin sulfate, ceramics, and sugars, such as maltose, galactose and dextrin (35-40).

Hollow Microneedles

Hollow microneedles allow the flux of the drug through the holes in the needles. Injection of drug solutions using hollow microneedles can provide control over the time and the amount of drug delivered (35-39). Once the injection is applied on the skin, the drug diffuses through the epidermis to be absorbed by the blood vessels in the dermis. One of the main benefits of the hollow microneedles is that they allow continuous diffusion through the skin (35-39). Solid and hollow microneedles have been manufactured from silicon, metal, and glass. Biodegradable microneedles can be made of biopolymers like chitosan, sugar glass, PLGA, hyaluronic acid, PVA, and PVP (19, 40-55).

ADVANTAGES AND DISADVANTAGES OF MICRONEEDLES

The advantages and disadvantages of using microneedles as a physical penetration enhancer are summarized in Table 1.

TECHNIQUES TO INSERT MICRONEEDLES INTO THE SKIN

There are diverse ways of releasing drugs from microneedles. The first is a novel technique called "poke with patch" (18-19, 59, 65-69) where solid silicon or metal microneedles are used to create micro-channels and then applying a transdermal patch to the surface of the skin. The transport occurs by drug diffusion. The second is called "coat and poke" (70-72), where the needles are first coated with the drug and then inserted into the skin. After that, the drug is released. A variation of this second method is "dip and scrape" where 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 (18, 32). The third is "Poke and flow" for hollow microneedles delivering a drug like a micro-injection (73-74). Finally, "poke and release" is for dissolving microneedles fabricated from polymers or polysaccharides, releasing the drug during the dissolution of microneedles (See Figure 2) (67, 75-79).

APPLICATIONS OF MICRONEEDLES

Microneedles are used in different areas related to health, based on the numerous advantages they offer (48, 66) (Table 2). Microneedles are an attractive candidate to administer several drugs (anti-cancer drugs, oligonucleotides, vaccines, proteins, DNA, and even nanoparticles) throughout the skin (6, 80-81). Moreover, microneedles have many applications in the pharmacy, medicine, and cosmetology fields.

The use of microneedles in medicine has grown and allowed to administer drugs through different medical procedures such as the case of treatment for glaucoma, other important applications have been in the use of diagnostics such as monitoring of various biomarkers.

Table1. Advantages and disadvantages of microneedles.

Advantages	Disadvantages
Microneedles are a minimally invasive technique for transdermal drug delivery (37).	Microneedles can only be inserted into the skin if they have the correct shape and adequate physical properties (37).
Microneedles are very small (length of 50 to 900 μm) (37).	Microneedles need to be applied with the required force to avoid breaking or bending before insertion (64).
Microneedles avoid first-pass effect (34).	Microneedles made of metal, stainless steel, or silicon have fracture risks. They can leave fragments in the skin (54).
Microneedles can penetrate the SC without stimulation of nerves (18, 54-55).	Microneedles can cause skin irritation and in some cases allergy (55).
With a constant rate and a prolonged period, the drug can be administered, allowing the correct dose of drugs (56). There is a reduction of adverse reactions (56). Microneedles are easy and safe to use. Microneedles can be produced with high precision, accuracy, and low cost (18, 55). Hollow needles can be used with patches and timed pumps to deliver drugs at precise times (57-58). Hollow microneedles offer continuous infusion through the skin (35-39). Small microneedles could target drugs to each cell (6). They are biologically nontoxic (55, 57). Microneedles have less microbial penetration than conventional needles (55). Microneedles can be removed immediately if adverse reactions occur (58-63).	Microneedles need micro-tools and microelectronics to be produced in bulk (55).

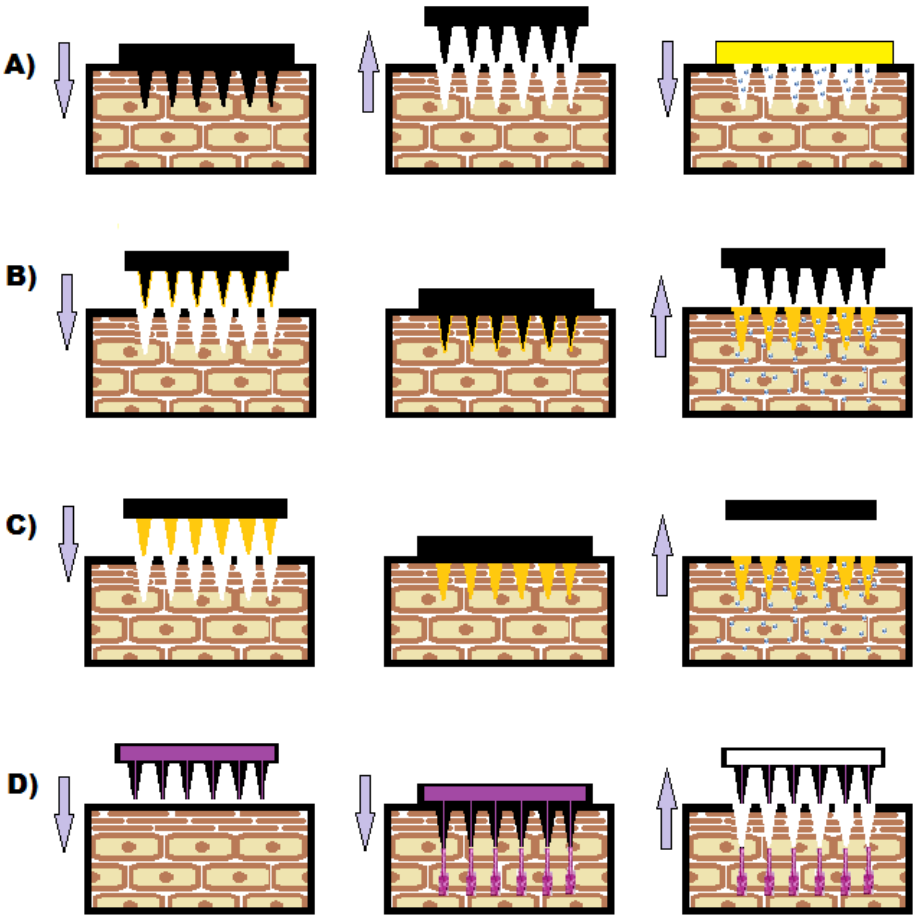

Figure 2. Schematic representation of different microneedles and mechanisms of application for transdermal drug delivery: A) solid microneedles using poke with patch, B) solid microneedles coat and poke, C) biodegradable microneedles with the mechanism poke and release, D) hollow microneedles for injections (poke and flow).

Therapeutic Applications

Antiglaucoma

Kim et al. used hollow microneedles to introduce drugs into the supraciliary space. They show dramatic dose sparing of antiglaucoma agents compared with eye drops. Targeted delivery in this way increases safety, diminishes side effects, and permits a single injection with enough drug for prolonged-term sustained delivery (82). Microneedles have a safe, simple, and efficacious ocular drug delivery. However, the limited drug carrying capacity of devices demonstrated to date may limit the potential for clinical translation. Omid et al. developed microneedles which serve as reservoirs for passive delivery, the capacity of the microneedles can up to five-fold relative to solid microneedles (83).

Diagnostics

It is impossible to make a good therapy without a proper diagnosis. This is basic and essential for the success of therapy; thus, the use of microneedles has helped in this field. Sun et al. developed microneedles that can be used to release protein antigens and therapeutic proteins in the skin for allergen skin testing or immunotherapy. The microneedles with PVP deliver intact proteins or peptides to the skin for diagnostic or therapeutic applications (84).

On the other hand, Skoog et al. developed *in vivo* biosensors that enable continuous real-time detection of biomolecules for monitoring patient health. They fabricated nitrogen ultra-nanocrystalline diamond-coated titanium alloy microneedle arrays that are capable of electrochemical detection of dopamine and uric acid (85). Moreover, Li et al. fabricated

hollow microneedles with the drawing lithography technique, and a sharp tip was generated with a laser-cutting system. Their results demonstrated that hollow microneedles can extract mouse blood *in vivo* (20 µl) at a good rate. Those microneedles with correct geometry can penetrate the skin without problems (86). Hollow microneedles can be combined with other technologies, such as biosensors and microfluidic chips to create blood analysis systems for diagnostics that would be minimally invasive, or they can be inclusively used for electrochemical detection of drugs *in vivo* (86-87). Dae et al. Obtain biochemical information, they develop a micro-scale needle for minimally invasive and painless blood sampling. The challenge was to combine the features of a sharp tip shape, appropriate length, and a hollow structure simultaneously (1.8 mm, an inner diameter of 60 µm, an outer tip of 100 µm, and a 60 ° bevel angle), these microneedles can be used to collect blood volumes up to 840 µL at a pressure 0.4 kPa, microneedles facilitate efficient and minimally invasive blood extraction or drug injection. Microneedles have potential applications in various blood analysis or sensor systems in point-of-care diagnostics (88).

The advantage that the microneedles offer in the diagnosis is that they can penetrate deeper layers of the skin, allowing the monitoring of bio-signals with greater reliability and thereby reducing the interferences with other substances.

Glucose monitoring

The commercial continuous glucose monitoring sensors are implanted subcutaneously for a period of 7-14 days. The subsequent biofouling effects have implications on the performance of the sensors over time, especially at low glucose concentrations. In adding, the sensors are sensitive to the presence of interfering substances like acetaminophen. Sanjiv et al. develop microneedles to eliminates this interference the microneedles operate at a lower potential (400 mV) in contrast with the commercial glucose monitoring (700 mV), reducing the interferences (89). Chua et al. made hollow silicon microneedle arrays for minimally invasive continuous glucose monitoring (90). Vacuum pump-assisted interstitial fluid sampling using microneedles in humans was studied. Microneedles show a good determination of glucose levels following insulin injection with a time lag of fewer than 20 minutes (91). The microneedles penetrating deeper layers of the skin compared to other devices for monitoring insulin, besides they allow glucose monitoring without interference and they give us greater sensitivity.

Cancer diagnosis

Keum et al. made a dual-diagnostic system with an endo-microscope and microneedle sensor that has high-resolution imaging combined with electrical real-time detection of nitric oxide released from cancer tissues. This system can be used for simple, fast, and accurate detection of cancer in biomedical applications (92). In comparison with the traditional endomicroscopy that can only identify microscopic pathological features and often requires biopsy sampling of suspicious lesions for additional histopathological examination of cancers.

Biomarkers

Li et al. have shown that surface-modified microneedle arrays could reliably and quickly quantify biomarkers in the upper dermis after laser treatment. It could be safely performed by brief laser irradiation of the microneedle array application site. The assay was independent of the length of the microneedles or molecular mass, as IgG can be measured by this noninvasive procedure (93-94).

Other applications are being monitored, such as in *electrocardiography (ECG)*, *electromyography (EMG),* and *electroencephalography (EEG)*, which are important for understanding pathological and physiological conditions in humans. The electrodes are currently used, but they have disadvantages that can result in wrong results if not properly applied and need the use of the gel. Therefore, Forvi et al. developed microneedles based on dry electrodes for an alternative to the conventional wet electrodes in recording bio-signals in clinical examinations. Their microneedles were tested on ECG, EEG, and EMG in the short term, and they were better than conventional wet electrodes under static conditions in signal acquisition and under dynamic conditions where the wet electrode is more susceptible to motion artifacts. These microneedles are comfortable, easy to apply, and do not require preparation of the skin (95). Renxin et al. improved the microneedles for monitoring EEG microneedle electrode arrays (MNEAs parylene-based) have been used as dry electrodes that could be capable of EEG monitoring without skin abrasion and gel. In the study, they develop a flexible MNEAs that can be adapted to the skin which could provide not only conformal but also robust contact, in comparison

with the conventional devices (96). Lee et al. prepared microneedles of silicon for infusion of drugs in the brain used to identify neuronal connections and activities. They conclude that the proposed thin microneedles can deliver drugs in specific regions of the brain. They want to incorporate multiple inlets and outlets for delivering various drugs simultaneously and adding neural probes with drug delivery capability to detect neural spike signals (97).

Perivascular delivery

In order to inhibit intimal hyperplasia (IH) caused by abnormal growth of smooth muscle cells (SMCs) in tunica media, various perivascular drug delivery devices are reported for delivery of anti-proliferation drugs into vascular tissue. However, there still remain conflicting requirements such as local and unidirectional delivery vs device porosity, and conformal tight device installation vs pulsatile expansion and constriction of blood vessels. For these reasons, Lee et al. developed wrappable microneedles of PLGA for treat intimal hyperplasia (IH). Microneedles showed significantly reduced neointimal formation (11.1 %) compared with structure coated with 1 μg of sirolimus and microneedles with 1 μg of sirolimus (23.7 and 22.2 %) after 4-week in vivo animal study. Additionally, wrappable MN meshes effectively suppressed side effects such as IH due to mechanical constriction, loss of toxic drug to the surroundings, and cell death that were frequently observed with other previous perivascular drug delivery devices (98).

Vaccines

New vaccine technologies using microneedles offer an efficient and painless method for introducing antigens into skin that, in the future, could solve some problems in the traditional vaccination. Today vaccination programs have cold chain storage, generate vaccine waste and hazardous waste, and require trained personnel. These factors add significant costs to immunization programs. Vaccine development programs aim to reduce the cost of each dose of the vaccine, and self-administered administration does not require trained staff. Microneedle dermal vaccines avoid these problems. Moreover, stabilization of a vaccine and the problems associated with reconstitution in a liquid solution for administration are solved (60, 79).

Matsuo et al. used microneedles for permeation of peptides with different molecular weights and observed that microneedles can remarkably enhance the transdermal delivery of all hydrophilic peptides. The skin permeation of peptides depends on their molecular weight and decreases as the molecular weight increases. In addition, the enhanced skin permeation of peptides produced by microneedle pretreatment may be caused by the generation of convection. They demonstrated that microneedles provide an attractive route to deliver low molecular weight peptides to the skin (79).

Hirobe et al. created a microneedle patch MicroHyala (MH) with hyaluronic acid, and the vaccination with MH induced a strong immune response against various antigens in mice. They studied the clinical safety and effectiveness of the transcutaneous influenza vaccine (flu-MH), which contains trivalent influenza hemagglutinins (15 mg each), and showed that the administration of influenza vaccines in humans using the MH system induced high levels of immunity (54).

Edens et al. examined the formulation of microneedles with a patch to vaccinate rhesus macaques against measles. The microneedles were inserted in the skin with thumb pressure. They were dissolved in the skin in 10 min, and they caused only mild to transient skin erythema. The groups of macaques generated antibody responses to measles. In addition, the microneedles have an adequate level of potency after storage at elevated temperatures, indicating thermostability compared with the standard vaccine. They concluded that the microneedle vaccine for measles was immunogenic in primates and may be used as a vaccine in humans (99).

Hiraishi et al. developed a vaccine with the bacillus Calmette-Guérin (BCG). The prevention and control of tuberculosis would benefit from a novel method of BCG vaccination that eliminates dangerous residues that conventional vaccines have. In this work, they reported that the design and engineering of a BCG-coated microneedle vaccine patch improved intradermal delivery of the vaccine. The microneedles induced a robust cell-mediated immune response in the lungs and spleen of guinea pigs (100). Levin evaluated the device (MicronJet^{TM}) that can inject antigens close to the skin's dendritic cells. A dose-sparing study was in 280 healthy adults using trivalent virosomal adjuvant influenza vaccine. The MicronJet^{TM} provides better response in comparison with the conventional vaccine (101).

Damme et al. studied the same device (MicronJet^{TM}) and a low-dose influenza vaccine

delivered intradermally with microneedles. They showed that this gadget has a similar dose of intramuscular vaccination. The device shows that microneedles are effective, secure, and reliable (102). Microneedle delivery of nucleic acids as plasmid DNA (pDNA) into the skin is a potential method for the clinical management of genetic skin diseases and cutaneous cancers and for intracutaneous genetic immunization. Zhu W et al. developed a microneedle to increase the immunogenicity of conventional influenza vaccines. A new 4M2e-tFliC fusion protein construct containing M2e sequences from different subtypes was generated and loaded on microneedles. The results demonstrated that mice receiving a conventional inactivated vaccine followed by the treatment with microneedles boost could better maintain the humoral antibody response than the only the use of conventional vaccine alone. Compared with an intramuscular injection, the mice with receiving microneedles showed significantly enhanced cellular immune responses, hemagglutination-inhibition (HAI) titers, and neutralization titers. The results of this study demonstrate that receiving 4M2e-tFliC microneedles of carboxymethylcellulose boosting immunization after the conventional influenza vaccine prime is an efficient and speedy approach to acquire extra protection against homologous influenza virus infection and cross protection against heterologous viral strains (103).

Mikszta et al. studied the delivery of naked pDNA into skin using microneedles. They used the technique "dip and scrape" *in vivo* to create micro-abrasions. They reported that, in a mouse model, the topical gene transfer was increased 2800-fold by microneedles, in contrast with topical application alone. Using DNA plasmid encoding hepatitis B surface antigen, microneedles induced stronger immune responses compared with hypodermic injection and required fewer immunizations for full seroconversion. The importance of this study was that the DNA vaccine delivery generated an immune response using the microneedles. It also established the feasibility of using blunt-tipped microneedles to scrape the skin for increased delivery (104).

Stimulation of CD4+ and CD8+ T cell immunity it's an inefficient process. The delivery of prophylactic vaccines is mainly mired by low transfection efficacy, poor immunogenicity, and safety issues from the materials employed. For this reason, to improve the immunogenicity Huu et al. developed a polyelectrolyte multilayer assembly on microneedles loaded with DNA vaccine. The charge reversal pH-responsive copolymer, composed of oligo (sulfamethazine) -b-poly (ethylene glycol) -b-poly (amino urethane) (OSM-b-PEG-b-PAEU), was used as a triggering layer in the polyelectrolyte multilayer assembly on microneedles. Charge reversal characteristics of this copolymer exhibit is a positive charge at low pH (pH 4.03) and negative charge (pH 7.4), allowing the facile assembly and disassembly of polyelectrolyte multilayers. The microneedles can delivery of a DNA vaccine to antigen-presenting cells and their subsequent stimulation of CD4+ and CD8+ T cell immunity. *In vivo* immunization of BALB / c mice, the results demonstrated that targeted delivery of a DNA vaccine encoding Aβ fusion protein to antigen present cells induced a robust antigen-specific immune response (105).

Chen et al. Evaluated the potential of a chitosan microneedle patch loaded with antigen ovalbumin (OVA at a dosage of 200 μg) for low-dose immunization. This system comprises antigen-loaded chitosan microneedles made of polyvinyl alcohol/polyvinylpyrrolidone. The microneedles allow a sustained release OVA for up to 28 days. We found that rats immunized with microneedles had persistently high antibody levels for 18 weeks, which were significantly higher than intramuscular injection of OVA at a dosage of 500 μg, demonstrating at least 2.5-fold dose sparing. Moreover, OVA-encapsulated chitosan MNs had superior immunogenicity to OVA plus chitosan solution, indicating that MN-based delivery and prolonged skin exposure can further enhance chitosan's adjuvanticity (106).

Insulin and macromolecules

Microneedles have been proposed to be a kind of delivery system that permits the entry of drugs, therapeutic proteins, and insulin with minimal skin invasiveness (48). Zhang et al. investigated the utility of solid microneedle (150 mm in length) in enhancing transdermal peptide delivery. Four model peptides were used: (Gly-Gln-Pro-Arg [tetrapeptide-3,456.6Da], Val-Gly-Val-Ala-Pro-Gly [hexapeptide, 498.6Da], AC-Glu-Glu-Met-Gln-Arg-Arg-NH_2 [acetyl hexapeptide-3,889Da], and Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2 [oxytocin, 1007.2Da]). The penetration was evaluated using porcine ear skin with Franz diffusion cells. Peptide permeation across the skin was significantly enhanced by microneedle

pretreatment, and permeation rates were dependent on peptide molecular weights. They concluded that solid microneedles are effective to enhance skin delivery of peptides (107).

Ling et al. made dissolving microneedles with starch and gelatin for rapid and efficient transdermal delivery of insulin in diabetic rats. The dissolution of the microneedles was 5 min after application. They quickly released their encapsulated payload into the skin. Pharmacodynamic and pharmacokinetic results showed a comparable hypoglycemic effect in rats receiving insulin-loaded microneedles and a subcutaneous injection of insulin. The bioavailability of insulin was around 92%, demonstrating that insulin has pharmacological activity after encapsulation and release from microneedles. Storage stability was more than 90% of the insulin even after storage at 25°C or 37°C for 1 month, generally, the insulin should be stored at 4°C- 8°C. These results supported that encapsulation of biomolecules in microneedles has great potential for transdermal delivery of diverse biomolecules (108). Other studies using microneedles with insulin lispro showed that they can deliver insulin effectively to treat diabetes (108-110). Yu et al. To reduce the painful subcutaneous injection of insulin, developed biodegradable microneedle patches that fabricated from 3-aminophenyl boronic acid-modified and crosslinked alginate was prepared for transdermal drug delivery of insulin. Microneedles exhibited a strong mechanical strength to penetrate the skin and good degradability to release the insulin. In vivo had been applied the microneedles using diabetic mice. The insulin in microneedles maintain the high pharmacological activity, having a sustained hypoglycemic effect in diabetic mice with relative pharmacologic availability and relative bioavailability of insulin from microneedle were 90.5±6.8% and 92.9±7% in mice compared with that of subcutaneous injection route with same insulin dose (111).

Drug Delivery

Statin or HMG-CoA reductase inhibitor. Serrano et al. used a dermaroller to increase the permeation of sodium pravastatin patch. They evaluated pravastatin penetration using microneedles of two different lengths (250 μm and 2250 μm). The result gives a therapeutic dosage equivalent of a 10 mg tablet with the constant drug release. The authors state the advantage of the route to be avoidance of the presystemic hepatic loss of the drug that is expected after oral administration (112).

The μ-Opioid receptor antagonist. Wermeling et al. conducted a clinical study using microneedles for delivering naltrexone formulated in a transdermal patch. Application of the naltrexone patch in the skin over 72 h produced undetectable drug plasma levels. However, pretreatment of skin with microneedles achieved steady-state plasma concentrations within 2 h of patch application, and they were maintained for at least 48 h. The microneedles arrays were painless upon administration and did not damage the skin during insertion, and microneedles were not broken off in the skin (6, 113).

Anti-cancer agents. Cancer is the principal cause of death worldwide. Localized intratumoral anti-cancer injections can be an attractive treatment, but conventional hypodermic injections result in poor distribution of the drug in the tumor and leakage of the drug into the systemic circulation. For these reasons, Ma et al. developed coated microneedles for delivery of intratumoral anti-cancer drugs. Moreover, PLGA nanoparticles encapsulating doxorubicin were prepared and coated on microneedles. The hypodermic injection of different volumes into porcine buccal tissue confirmed significant leakage (about 25% of the injected 80 μl). This study confirmed that microneedles can deliver anti-cancer drugs on localized oral cancers reducing the percentage of leakage. (114). Vemulapalli et al. investigated transdermal iontophoretic delivery (0.4 mA/cm^2 applied for 60 minutes) of methotrexate, alone or in combination with maltose microneedle array, *in vivo* and *in vitro* using rats. Delivery was enhanced with iontophoresis and microneedles (*in vitro* and *in vivo*). A synergistic 25-fold enhancement of *in vivo* drug delivery using microneedles and iontophoresis was obtained compared with each physical enhancer alone. This result is due to the fact that both methods are penetration enhancers and each of them has different mechanisms one based is in microabrasions (microneedles) and the other by the use of electric current. (6, 115).

Calcium channel blockers. Kaur et al. studied the effect of microneedle rollers and stainless-steel microneedles on the percutaneous penetration of verapamil hydrochloride and amlodipine. Verapamil is a calcium channel blocker. It regulates hypertension by decreasing myocardial contractility,

heart rate, and impulse conduction. Amlodipine is a calcium channel blocker too, used to treat hypertension and ischemic heart disease. *In vitro* passive diffusion studies of verapamil and amlodipine across the skin using vertical static Franz diffusion cells with porcine ear skin as a membrane was low. They conclude that it is possible to develop transdermal microneedle patches for these drugs because the use of microneedles increased the diffusion of verapamil and amlodipine (116). In another study, Kolli and Banga characterized maltose microneedles and evaluated the capacity to enhance transdermal drug delivery of nicardipine hydrochloride *in vitro* and *in vivo* in rats. Microneedles penetrated the skin creating micro-channels, and nicardipine hydrochloride *in vitro* was increased after pretreatment (flux 7.05 mg/cm^2·h) compared with the untreated skin (flux 1.72 mg/cm^2·h). The same case was observed *in vivo* (117). The advantages of using microneedles are that by avoiding the first hepatic metabolism, more drug enter to the bloodstream, allowing it to do its therapeutic effect, and besides avoiding side effects due to the dose presented by the tablets.

Heparin. This drug is used to prevent clots in patients with certain medical conditions or in medical procedures that increase the chance of their formation. Heparin has another use to prevent the growth of clots formed in blood vessels, but cannot be used to decrease the size of these clots. Gomma et al. developed a laser-engineered dissolving microneedle array made with aqueous blends of 15% w/w poly (methylvinylether-co-maleic anhydride) for transdermal delivery of nadroparin calcium. The microneedles were loaded with 630 IU of nadroparin. The technique "poke and release" was used. Microneedles allowed permeation of 10.6% of the nadroparin over a 48-h study period. The cumulative amounts of nadroparin permeated at 24 h and 48 h were 12.28 ± 4.23 IU/cm^2 and 164.84 ± 8.47 IU/cm^2, respectively. Skin permeation of nadroparin can be modulated by the length and array density of microneedles (118). The microneedles have a good potential for transdermal delivery of nadroparin at a low cost.

Ito et al. generated dissolving needles loaded with a polysaccharide with heparin. They used three polymers, chondroitin, dextran, and dextrin, as the base of the microneedles. The insertion was in rat skin with doses of 25, 50, and 100 IU/kg. The values of C_{max} were 0.40 ± 0.03, 0.46 ± 0.03, and 0.47 ± 0.06 IU/ml. The physiological availabilities were 102.3%, 81.5%, and 97.7%, respectively (119). These results confirm the use of biodegradable microneedles for the percutaneous administration of polysaccharide drugs like heparin. These studies demonstrated that it is possible to load the microneedles with high molecular weight biomolecules and allow the passage of these through the skin, maintaining the advantages of transdermal administration.

Local anesthesia. Lidocaine is indicated as a local anesthetic. It is used on the intact skin for minor surgery (superficially) and preparation for infiltration anesthesia. The poor patient acceptance of injections, principally in the case of the pediatric population, makes microneedles an interesting choice to eliminate pain associated with conventional needles. They can give a drug administration, eliminating the pain associated with conventional needles.

Caffarel et al. developed biodegradable microneedles loaded with lidocaine. Their results suggested that microneedles can dissolve quickly in the skin around 15 min upon application. They concluded that microneedles are a viable alternative to administer lidocaine in pediatric patients, avoiding needle phobia for children (120).

Central nervous system stimulant *(CNSS)*. Caffeine is a CNSS drug, but another use of caffeine is to treat the apnea of prematurity in infants. Nevertheless, the only pharmaceutical preparation of caffeine for treatment of apnea in infants is an intravenous infusion and an oral dosage form. For these reasons, Caffarel et al. developed biodegradable poly(methylvinylether/maleic anhydride) microneedles using caffeine. They obtained a gradual and sustained increase in plasma caffeine concentration during a period of 24 h, but at 2h, they have therapeutic concentrations. Their results suggested that a single application of biodegradable microneedles has a continuous delivery of caffeine, maintaining therapeutic concentration for more than 24 h. The advantage is in simplifying treatment (2–3 days dosing) instead of the current dosage (once daily) oral or intravenous route. Microneedles can benefit neonates who commonly cannot tolerate the enteral administration of caffeine, particularly in the early postnatal period. Another advantage is that microneedles could be easy to remove in cases of suspected toxicity and it is not necessary to apply

intravenously that it is sometimes complicated in neonates to apply an intravenous and sometimes causing more damage if it is not done correctly (120).

Anti-obesity. Manita et al. developed 500 µm long microneedles loaded with caffeine made of Carboxymethylcellulose CMC, polyvinyl pyrrolidone, polyvinyl alcohol and applied to obese mice for weight loss (121).

Cosmetology Applications

The application of microneedles into human skin emerged as a popular tool in the cosmetic area because microneedles are useful in bettering conditions like seborrheic keratosis (122), scars (125), striae, anti-aging, wrinkles, or depigmentation (123). The original instrument used is the "dermaroller," which consists of a handle with a cylinder with stainless steel needles (0.5-2 mm length). Treatment with a dermaroller requires four to eight weeks to have the desired effect on the skin. Microneedles or dermaroller treatment is popular in the world, not only in the treatment of post-acne but also in anti-aging therapy with no sequelae (123).

Burn scars. The treatment is a simple method for treating burn scars using microneedles in comparison with laser treatments. The procedure is safe and applicable in areas where a laser cannot be used (124). Microneedle procedures effectively manage hypertrophic scars. Microneedles provoke the collagen fiber rearrangement in scar tissue (125). An important advantage of using microneedles compared to a laser is that the treatment is cheaper.

Acne scars and stretch marks. The use of microneedles is a simple procedure. The area to be treated is previously anesthetized (45 min to 1 h). After that, the dermaroller is passed 15 to 20 times in horizontal, vertical, and oblique directions. The pretreated zone is cleaned with wetted saline pads. The complete procedure continues for 15 to 20 min. A minimum of six weeks is recommended between two treatments for new natural collagen to form. Approximately 3 to 4 treatments are needed for moderate acne scars (126). Skin needling is a simple and cost-effective technique used for the treatment of acne scarring (125, 127). The dermabrasion used to improve the quality of the skin is based on the "ablation" (destruction or injury of the superficial layers of the skin), the dermabrasion induced by microneedles generate an equilibrate cell proliferation facilitates the repair of the skin without leaving scars that other techniques cannot do efficiently.

Anti-aging, wrinkles, depigmentation or pigmentation. Microneedle fractional radiofrequency (RF) is a noninvasive method. Growth factors can be used as a novel anti-aging treatment. Seo et al. evaluated the effectiveness and security of microneedle RF for rejuvenation using stem cells that have many growth factors and cytokines. They concluded that RF is safe and effective in skin rejuvenation and has better results combined with stem cells (128). The therapies with percutaneous collagen offer to rejuvenate and repair the skin appearance without risk of depigmentation (129).

In the case of melasma that is a common acquired symmetrical hypermelanosis characterized by irregular light to-dark-brown macules and patches on sun-exposed areas of the skin. The tranexamic acid (TXA) is administered orally, and locally or via localized intradermal injections, results in lower melasma severity. TXA seems to inhibit the synthesis of melanin by interfering with the interaction of melanocytes and keratinocytes. Also, TXA can reverse the abnormal dermal changes induced by melasma, such as increased vasculature. Machekposhti et al. generated microneedles (1200 µm height, 280 µm base width, 36 microneedles in the array) of PVP and methacrylic acid loaded with tranexamic acid. These microneedles had adequate properties to be applied to the skin and have a release in the TXA with the possibility of being an alternative for the treatment of melasma (130). Another case of pigmentation is the seborrheic keratosis or senile lentigo are commonly seen on people >50 years of age, the treatment is with all-trans retinoic acid (ATRA), ATRA has some drawbacks such as its poor water solubility and photostability, and skin irritation reactions limit its topical use. Because the skin permeability is relatively low Sachiko et al. developed an ATRA-loaded microneedle patch (ATRAN-MN) to increase the permeability of ATRA and microneedle patch loaded with retinoic acid. ATRA-MN was applied to the lesion site of each subject for 6 h once per week for 4 weeks. The use of microneedles did not induce severe local or systemic adverse effects. The treatment with microneedles is promising as a safe and effective therapy for seborrheic keratosis and senile lentigo (131).

Alopecia areata. Alopecia areata (AA) is a chronic autoimmune disease that may be mediated by T cells, affecting hair follicles and sometimes nails, but the mechanism is not clear. The disease can present as a single demarcated patch (hair loss zones), as the total hair loss (called alopecia), and as the loss hair of the head and body (called alopecia universalis) (132). The AA is usually difficult to treat. Topically applied corticosteroids are useful but painful in large patches (hair loss zones) because they are injected. Microneedles are a good option to apply corticosteroids in large hair loss zones without pain. Moreover, they increase blood supply to the hair follicles providing them with more nutrients. Another hypothesis is that the microinjury generated by microneedles helps in recruiting and inducing growth factors (133). All the applications of microneedles are summarized in Table 2.

Table 2. Applications of microneedles

Medical and Pharmaceutical Applications		
Study	Outcome	Reference
Transfer-molded Wrappable Microneedle Meshes for Perivascular Drug Delivery	Developed a wrappable MN mesh of poly(lactic-co-glycolic acid) (height of 640 μm) to deliver the anti-proliferative drug into an injured blood vessel for IH reduction with minimal mechanical stress (98).	Lee et al. (2017)
A microneedle electrode array on flexible substrate for long-term EEG monitoring	The use of microneedles (silicone height of 190 μm) has been used that could be capable of EEG monitoring. Microneedles can be adapted to the skin providing robust contact with the skin (96).	Renxin et al. 2017
Fenestrated microneedles for ocular drug delivery	They develop fenestrated microneedles (lengths 500 – 1500 μm) which serve as reservoirs for passive delivery, the capacity of the microneedles can up to five-fold relative to solid microneedles (83).	Omid et al. 2016
Microneedle for Minimally Invasive and Painless Blood Sampling	Develop microneedles to obtain biochemical information (1.8 mm, an inner diameter of 60 μm, an outer tip of 100 μm, and a 60 ° bevel angle), that can extract blood volumes up to 840 μL (88).	Dae et al. (2018)
Microneedle array electrodes for continuous glucose monitoring sensors	The use of microneedles eliminates this interference to detect glucose in comparison with other devices glucose (89).	Sanjiv et al. (2017)
Silicon microneedles for deep brain drug infusion.	Microarray prepared on silicon for infusion of drugs in the brain to identify connections and neuronal activities (93).	Lee et al. (2015)
Targeted delivery of antiglaucoma drugs to the supraciliary space using microneedles.	Use of hollow microneedles loaded with a drug for the treatment of glaucoma applied in the eye (space intraciliary) as a new alternative for the treatment (82).	Kim et al. (2014)
Nitrogen-incorporated ultra-nanocrystalline diamond microneedle arrays for electrochemical biosensing.	Nitrogen-incorporated ultra-crystalline diamond-coated titanium alloy microneedle arrays can detect electrochemical signals (dopamine and uric acid) (84).	Skoog et al. (2015)
Hollow microneedles for minimally invasive blood extraction. Microscopic gel-liquid interfaces supported by a hollow microneedle array for voltammetric drug detection.	Hollow microneedles can be incorporated with other technologies, such as biosensors and fluidic chips, to create blood analysis system (85-86).	Li et al. (2013) Vázquez et al. (2014)
Influence of microneedle shapes on skin penetration for continuous in vivo glucose monitoring. Microneedle-based automated therapy for diabetes mellitus.	Hollow microneedles of silicon that can determine the amount of blood glucose through a sample of interstitial fluid (87-88).	Chua et al. (2013) Khanna et al. (2008)
Microneedle biosensor for real-time electrical detection for in situ cancer diagnosis.	Microneedle sensor has high-resolution imaging combined with electrical real-time detection of cancer. The system can be a new platform for detection of cancer (89).	Keum et al. (2015)

Table 2. Continued...

Preliminary technological assessment of microneedle-based dry electrodes for biopotential monitoring in clinical examinations.	Microneedle-based dry electrodes tested in ECG, EEG, and EMG are comparable to wet electrodes in static conditions and better in ECG dynamic conditions (92).	Forvi et al. (2012)
Microneedle with charge reversal pH-sensitive copolymers improve antigen presenting cells-homing DNA vaccine delivery and immune responses	Microneedles with charge reversal copolymer that can stimulate the CD4+ and CD8+ T cell immunity. *In vivo* demonstrated the delivery of a DNA vaccine encoding Aβ fusion protein to antigen present cells induced a robust antigen-specific immune response (105).	Huu et al. (2018)
A boosting skin vaccination with dissolving microneedle patch encapsulating M2e vaccine broadens the protective efficacy of conventional influenza vaccines	The results of this study demonstrate that receiving 4M2e-tFliC microneedles of carboxymethylcellulose boosting immunization after the conventional influenza vaccine, the array has 100 microneedles (250 and 650 μm, diameter and length, respectively) (103).	Zhu W et al. (2017)
Chitosan microneedles patch to enhancing immunogenicity of antigens	A strong and persistent antibody responses for at least 18 weeks by microneedles loaded with OVA and resulted in at least a 2.5-fold antigen dose reduction (106).	Chen et al. (2017)
Microneedles of alginate and hyaluronate for transdermal delivery of insulin	Microneedles (650 μm) patches made with alginate and hyaluronate loaded with insulin. The relative pharmacologic availability and relative bioavailability of insulin from microneedle were 90.5±6.8% and 92.9±7% in mice (111).	Yu et al. (2017)
Anti-obesity effect of caffeine-loaded in microneedle patch	Microneedles of PVP, PVP, and PVA (500 μm long) loaded with caffein, has a weight loss of 12.8 ± 0.75% in obese C57BL/6J mice (121).	Manita et al. (2017)
A transcutaneous immunization system by microneedle array for soluble and particulate antigens.	Use of microneedles for permeation of peptides with different molecular weights. Microneedles can remarkably enhance the transdermal delivery of all hydrophilic peptides and be used for safe vaccination. (79).	Matsuo et al. (2002)
Clinical study of transcutaneous influenza vaccination using a dissolving microneedle patch.	Microneedles of hyaluronic acid with hemagglutinins of influenza for vaccination, inducing a strong immune response (54).	Hirobe et al. (2015)
Microneedle patch containing the measles vaccine is immunogenic in non-human primates.	Vaccination with a microneedle loaded with an antibody of measles that was immunogenic in non-human primates (94).	Edens C. et al. (2015)
Bacillus Calmette-Guérin (BCG) vaccination using a microneedle patch.	Vaccination patch coupled with microneedles, preloaded with BCG for the treatment and prevention of tuberculosis (95).	Hiraishi et al. (2011)
Clinical evaluation of a microneedle device for the intradermal delivery of an influenza vaccine. Safety and efficacy of a microneedle device for influenza vaccination in healthy adults.	Silicon microneedles using 0.45 mm long (MicronJet^{TM}) for injecting the influenza antigens very close to the skin´s dendritic cells. MicronJet^{TM} gives a superior response to influenza vaccination and warrants further clinical evaluation. The microneedle injection device is effective, safe, and reliable (96-97).	Levin et al. (2014) Damme et al. (2009)
Droplet-born air blowing: made dissolving microneedle.	Developed biodegradable microneedles by the blowing method that are loaded with insulin (57).	Dong et al. (2013)
Coated microneedles for transcutaneous delivery of live virus vaccines.	Silicon microneedles coated by a method of spray, containing adenovirus antigen and virus Ankara that stimulated CD8 cells of the immune system (60).	Vrdoljak et al. (2012)
Enhanced delivery of hydrophilic peptides in vitro by transdermal microneedle pretreatment. Improved genetic immunization via micromechanical disruption of skin.	An array of solid microneedles of 150 μm in length was used to make the skin more permeable (pig's ear) and facilitate transport of peptides (61, 98).	Zhang et al. (2014) Mikszta et al. (2002)

Table 2. Continued...

Development and a characterization of a pravastatin transdermal patch coupled with solid microneedles.	Used a dermaroller® to increase the permeation of sodium pravastatin formulated in a transdermal patch. The pravastatin penetration using microneedles (250 μm and 2250 μm of lengths), and obtained viable results to achieve a therapeutic equivalent dose of a 10 mg tablet (103).	Serrano et al. (2014)
Transdermal delivery of microneedles to the skin in medication to humans.	Clinical study of microneedles for enhanced delivery of naltrexone in a transdermal patch. This human proof-of-concept study demonstrated the systemic administration of hydrophilic medication using a microneedle for enhanced transdermal delivery (104).	Wermeling et al. (2008)
Drug-coated microneedles for treatment of oral carcinomas.	Development of coated microneedles for direct and minimally invasive intratumoral delivery of anti-cancer drugs (105).	Ma et al. (2015)
The effect of iontophoresis and microneedles for transdermal delivery of methotrexate.	Synergistic 25-fold enhancement of delivery in vivo in combination (microneedle-iontophoresis), compared to each one alone (106).	Vemulapalli et al. (2008)
Microneedle delivery of verapamil hydrochloride and amlodipine besylate.	Microneedles increased penetration of verapamil hydrochloride and amlodipine. It is possible to generate transdermal microneedle patches for these drugs (107).	Kaur et al. (2014)
Characterization of solid maltose microneedles and their use for transdermal delivery.	Increase transdermal drug delivery of nicardipine hydrochloride *in vitro* and *in vivo* across hairless rat skin (108).	Kolli et al. (2008)
Laser-engineered dissolving microneedles for active transdermal delivery of nadroparin calcium.	Development of laser-engineered dissolving microneedle arrays fabricated by 15% w/w poly (methylvinylether-co-maleic anhydride) with nadroparin calcium. The microneedles offer immense potential as a relatively low-cost functional delivery system (109).	Gomma et al. (2012)
Evaluation of dissolving microneedles containing low molecular weight heparin in rats.	The use of biodegradable microneedles for the percutaneous administration of polysaccharide drugs like heparin (110).	Ito et al. (2008)
Potential of hydrogel-forming and dissolving microneedles for use in pediatric populations.	Application of biodegradable microneedles allows continuous delivery of caffeine into systemic circulation, maintaining the therapeutic concentration for more than 24h. Microneedles are a viable alternative for pediatric administration (111).	Caffarel Salvador et al. (2015)

Cosmetology Applications

Study	Outcome	Reference
Microneedle for transdermal delivery of tranexamic acid	Microneedles of PVP and methacrylic acid loaded with tranexamic acid. They concluded that polymer microneedle as a highly efficient method for delivering tranexamic acid for treat melasma (130).	Machekposhti et al. (2017)
Clinical study of a retinoic acid-loaded microneedle patch for seborrheic keratosis or senile lentigo	Microneedles of sodium hyaluronate (800 μm length) loaded with ATRA to treat seborrheic keratosis and senile lentigo. The treatment with microneedles is promising as a safe and effective therapy for seborrheic keratosis and senile lentigo (131).	Sachiko et al. (2017)
Management of hypertrophic scar after burn wounds using microneedles. Skin needling as a treatment for acne scarring.	Use of microneedles for treating acne scars in which the skin is prepared using local anesthesia and a dermaroller passed several times in different directions. Skin needling is a simple technique for treating acne scars (115-117).	Kim et al. (2009) Doddaballapur et al. (2009) Harris (2015)

Table 2. Continued...

Skin rejuvenation by microneedle fractional RF and a human stem cell conditioned medium. Percutaneous collagen induction: minimally invasive skin rejuvenation without risk of hyperpigmentation.	Fractional RF was used with microneedles in the skin using stem cells for skin rejuvenation. The therapy with percutaneous collagen offers a modality with which to rejuvenate (118,119).	Seo et al. (2013) Aust et al. (2008)
Alopecia areata (AA): successful outcome with microneedles and triamcinolone acetonide AA: a new treatment plan.	Application of corticosteroids using microneedles, promoting blood supply to hair follicles for treatment of AA. Helps in recruiting growth factors and inducing hair growth (132,133).	Chandrashekar et al. (2014) Alsantali (2011)

CONCLUSIONS

Microneedles allow painless insertion with minimum tissue damage, better control over the dosage of the drug, do not generate infectious waste and are more acceptable and comfortable for patients. Consequently, microneedles have been growing in fields of drug development, therapeutics and cosmetology. It is possible to administer peptides, avoiding multiple daily injections like the case of insulin. In addition, the use of microneedles is growing in medicine. They are being used in the diagnosis, treatment for glaucoma, and in monitoring bio-signals. Finally, the use of microneedles has been shown to be very useful for the treatment of alopecia, anti-aging, and scars. Due to all the advantages and alternatives that the use of microneedles offers, increased research on them concerning their applications in many fields of health and beauty is likely.

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