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MICRONEEDLE BASED DRUG DELIVERY DEVICE

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ABSTRACT

The main objective of the review is to update the microneedles for the supply of medicines and vaccines. Applicators of therapeutically active drugs cannot cross the stratum corneum effectively. Microneedle patches have been developed to penetrate the stratum corneum with micro scale pores that are large enough to allow medications. The microneedles are manufactured using a microelecromechanical system that uses silicon, metals, polymers or polysaccharides. Five main type of microneedle design have been described, namely solid, coated, solvent, hollow and hydrogel forming microneedles. Microneedles can be used to administer macromolecules such as insulin, growth hormones, immunobiological proteins and peptides. Microneedles containing cosmeceuticals are currently available to treat acne, pigmentation, scars, wrinkles and to improve skin tone. Microneedle technology is capable of dosing very precisely, complex release patterns, local administration and improvement of the biological stability of the drug by storing in a micro volume that can be precisely controlled. The proposed revision of the microneedle for the supply of drug and vaccines revealed that it improves the dosage and the supply of micro volume of medicines and has made more progress in cilinical practice to allow better pharmaceutical therapies, vaccination and other application.

KEYWORDS: Microneedles, Transdermal drug delivery, materials, fabrication methods.

1. INTRODUCTION

Skin is the largest and one of most complex organ evolved to protect the body against unwanted influences, such as excessive water loss, invasion of harmful chemicals and to prevent the pathogens.[1] There are 3 layers in human skin, which include epidermis, dermis and hypodermis. Stratum corneum is the outer most layer, is the primary barrier of skin,[3,4] it imposes significant restrictions on the successful delivery of drug, especially the high molecular weight drugs.[1] Transdermal drug delivery system have demonstrated tremendous potential for their increasing role in medical care. Compared with oral and hypodermic administration, transdermal drug administration can overcome the problem of absorption and degradation of drug that occur in the gastro intestinal tract or liver, it is convenient, economical, non- invasive, painless and self-administered ; as well as can provide a sustained release of medications to improve patient compliance.[5,6]

Microneedles are an attractive strategy for minimally invasive supply of molecules through barriers. When used for transdermal delivery, they penetrate the skin to the upper layer of the dermis without causing pain or bleeding.[7] There sharp micrometer sized needles can deliver molecules directly through the skin, cornea or back of eye, or even the intestinal membrane.[8] These are designed to be minimally invasive high performance ducts, through which pharmacological solution can be pass to the body. To be minimally invasive, the needles are designed to be extremely sharp, with sub micron tip radii. This allows the needles to be effectively inserted into the skin. Microneedles often an attractive way for advanced drug delivery system by mechanically penetrating the skin and injecting the drug just absorb it quickly into the blood stream.[9,10]

Microneedles attracted a lot of attention in the pharmaceutical sector, particularly during the last decade due to its ability to facilitate the administration of medicines and vaccines through skin, but also depending on its use in the extraction of biological fluids for monitoring purpose.[2] Depending upon its design and mode of use, the microneedles can be classified into four basic types: hollow microneedles, dissolvable microneedles, poke and patch microneeldes and coated microneedles. Hollow microneedles is similar to a conventional hypodermic needle but is noticeably much shorter. They have a hole and liquid can be injected through them.

Dissolvable microneeeldes are made of a drug or a matrix in which the drug is dispersed. Soluble microneedles after insertion into the skin may dissolve in

minutes or may degrade after a long time. Microneedles, which are intended to pretreat the skin to increase its permeability. The microneedles are first inserted into the skin to create perforation of the size of microns after which the formulation of the medication or transdermal patch is applied to the pretreated skin. Finally, in coated microneedles is inserted in a matter of minutes, the coating dissolved, after which the microneedle can be removed and discarded safely.

Application of microneedles studied to date have emphasized drug and vaccine delivery to the skin. Conventional transdermal delivery is limited by the barrier properties of the stratum corneum.[11] several chemical, physical and biochemical methods have been studied to increase skin permeability. However, chemical and biochemical methods do not appear to be widely useful for the administration of biotherapuetics and vaccines through the skin. While physical methods are more promising for the delivery of micromolecules, they generally involve the use of sophisticated devices that are relatively large, expensive and require training in their use. Microneedles, on the other hand, can be prepared as a low cost patch that is simple for patients to request the supply of biomacromolecules. Targeting vaccine administration to antigen- presenting cells in the skin using microneedles is also of particular interest.[12]

Other applications of microneedles have also been explored. The supply of drugs to the eye, especially through the supercoroid space, has received recent attention.[13] As a extension of micropipette techniques, microneedles have been used to deliver molecules to cells and their nuclei, among other laboratory application.[14,15]

2. CLASSIFICATION OF MICRONEEDLES

Generally microneeedles are categorized as solid microneedles for skin pretreatment, coated microneedle, dissolving microneedle and hollow microneedles.

2.1 SOLID MICRONEEDLES FOR SKIN PRETREATMENT

Microneedles can be used a pretreatment for pore formation in the skin. Sharp microneedles penetrate into the skin in order to make holes through which the drug can transport, either for local effect in the skin or for systemic delivery after uptake by skin capillaries. The drug can be applied to the skin surface over the pores using a drug loaded patch or using semi solid topical formulations, such as ointments creams gel or lotion.[16]

2.2 COATED MICRONEEDLES

Solid microneedles can be used not as piercing structures, but also as vehicles to carry and deposit drug within the skin or other tissue. This is done by coating microneedles with a drug in formulation suitable for coating and subsequent dissolution. By this way, the desired dose of the drug is delivered into tissue quickly upon insertion of microneedles. The drug dose administered this way is limited to the amount that can be coated onto the tip and shaft of the microneedle, which is less than 1mg for micronnedle array.[17]

2.3 DISSOLVING MICRONEEDLES

Polymer microneeldes have been developed in contrast to coated microneedles, to completely dissolve in the skin and thereby leave behind no biohazardous sharps waste after use. These microneedles are made of safe, inert, water-soluble materials, such as polymers and sugars that will dissolve in the skin after insertion. Dissolving microneedles can also be used as skin pretreatment to increase permeability, drugs are often encapsulated in the microneedles for release into the skin similarly to coat microneedles.

2.4 HOLLOW MICRONEEDLES

Hollow microneedles provides a defined conduit for the administration of the drug to the skin or other tissue. Similar to hypodermic injection, hollow microneedles allow the pressure-driven flow of a liquid formulation. The pressure and, thereby flow rate, can be modulated for a rapid bolus injection, a slow infusion or a variable rate of administration over time. The liquid formulation may simplify the use of existing injectable formulations for delivery using microneedles, but loses the opportunity of solid miucroneedles delivery methods to administer dry drug formulation without reconstitution to improve drug stability and patient convenience of a patch based delivery method. Hollow microneedles have also been used as a conduit for diffusion of the drug into the skin from a non- pressurized drug reservoir.

3. MATERIALS OF MICRCONEEDLES CONSRUCTION

3.1 SILICON AND SILICA GLASS

Silicon is hard and brittle crystalline solid. The first microneedle for drug id made up of silicon. Glass microneedles are generally prepared by micropipette pulling. The use of hollow glass microneedles was suggested for drug delivery and diagnostic purposes.

3.2 METALS

Metals and their alloys have been used in the biomedical field for generations. Hypodermic needles are mainly made from stainless steel while titanium is widely used in implants and prostheses. Stainless steel was the first metal used in the production of microneedles. Hollow microneedles are also made up of metals.[18]

3.3 CERAMICS

Ceramics are solid materials composed of inorganic compounds of a metals, non- metals or metalloids. Most commonly used ceramics as biocompatible materials are those between aluminium and oxygen (alumina, Al2O3), calcium and oxygen (CaO), and silicon and nitrogen (silicon nitrate). Ceramics microneedles are typically prepared using micromoulding of ceramic slurry followed followed by sintering at high temperatures.[19]

3.4 CARBOHYDRATES

Melts, slurries and solutions of carbohydrates can be easily form microneedles by micromolding in matel or PDMS mold. Carbohydrates are cheap and safe alternative for glass and metals. Maltose is the most commonly use sugar for the preparation of microneedles. Other sugars like trehalose, sucrose, mannitol, fructose, raffinose amd sorbitol in combination with polymers are also used in preparation of microneedles.[20]

3.5 POLYMERS

Polymers have revolutionized the field of drug delivery. The first instance of polymer science is the derivatization of naturally occurring cellulose to celluloid and cellulose acetate.

Polymers attract wide attention of microneedle fabrication due to their biocompatibility, biodegradability and low cost. A number of naturally occurring polymers are used for casting of microneedles. These include naturally occurring proteins, polysaccharides, semisynthetic and synthetic polymers. Polymers are used to prepare solid dissolvable or swellable microneedles or used as a coating on structures made of other materials. Polymer microneedles are majorly fabricated using a lithographic or molding process.[21]

4. FABRICATION OF MICRONEEDLE

4.1 FABRICATION OF SILICON BASED MICRONEEDLES

The most commonly used technique for fabrication of silicon-based microneedles starts with lithography. A photosensitive layer is coated onto a substrate (generally a silicon wafer with a silicon dioxide layer on the top). A variety of materials can be coated onto the substrate based on the coating method used. A physical vapour decomposition method is used to heat the material and condense its vapours onto the substrate. Alternatively, in chemical vapour deposition, material is deposited as a thin film produced by chemical reaction between the hot substrate and inert-carrier gases in the chamber. A photoresist is layered on the silicon oxide substrate by spin coating. Spin coating ensures uniform thickness of coating. Any residual solvent on the spin- coated layer is removed by heating. The photoresist layer is illuminated by UV light through a mask. The mask behaves like a stencil not allowing UV radiation to pass through certain regions. This procedure allows near-perfect transfer of structure from mask to the photoresist layer. With UV exposure, the exposed regions of the mask are altered chemically and can now be easily solubilized and removed. A positive or negative photoresist can be developed based on requirements. With positive resists, UV illumination weakens the bonds allowing their easy removal, while in developing a negative resist, UV light strengthens the chemical bonds. The photolithographic process depends on thick photoresist polymer used. SU-8 and poly-methyl- methacrylate (PMMA) are versatile materials, which are used to produce a pattern for high-aspect-ratio microstructures. SU-8 can provide a sophisticated structure by controlling the light path and the focus, resulting in the production of solid tapered MNs and hollow polymer MNs.[22] Following lithography, it is necessary to etch the oxide layer and even the substrate. For wet etching, the wafer is immersed in a liquid bath containing a chemical etchant to remove the desired material. Etchants generally used for silicon are potassium hydroxide (KOH) and tetramethyl ammonium hydroxide (TMAH). Dry etching may be performed as reactive ion etching (RIE) or ion beam milling (IBM).

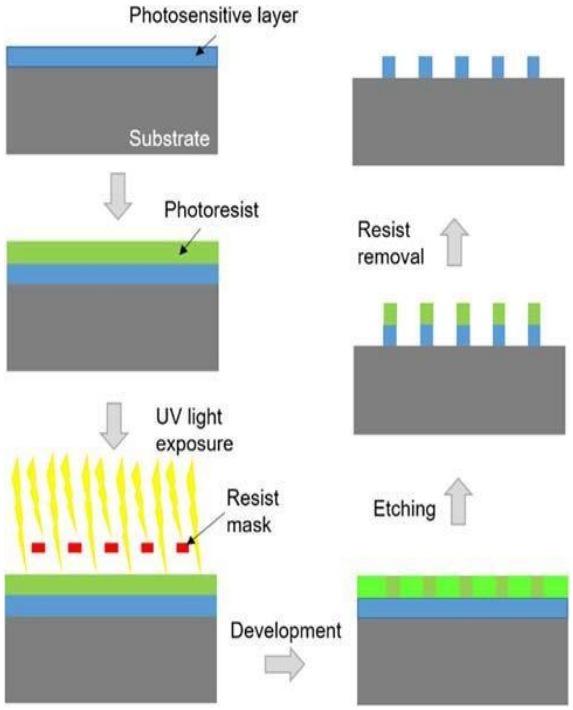

Figure 3: Steps in lithography/etching procedure for fabrication of silicon MNs.

4.2 FABRICATION OF METAL MICRONEEDLES

The easiest way to manufacture metal based microneedles arrays by assembling hypodermic needles or wires. The length of the cable or pipe can be adjusted according to the needs of the end user. Simple needle-based cosmetic device, such as dermaroller, consist of metals pins arranged in a cylindrical drum. Microneedles can be done in he plane using a lithographic/etching process and then foldes at 90 degree to create needles out of the plane. In addition, microneedles designs and complex shapes are prepared by laser metal cutting followed by electroplating.

4.3 FABRICATION OF GLASS AND CERAMIC MICRONEEDLES

Glass microneedles are manufactured by pulling borosilicate glass pipette using micropipette puller. A length of glass tubing is heated at its centre and the two ends are drawn apart by toothed wheels are driven using a spring. The tips are beveled at the required angle and cleaned with solvent. Ceramic microneedles are prepared

by micromolding with ceramic slurry filled into mold cavities under vacuum followed by sintering at high temperature.

4.4 FABRICATION OF POLYMERIC MICRONEEDLES

The most common manufacturing technique for microneedles is micromoulding method, including hot embossing, injection, and casting. After the master mold for microneedles are fabricated, microneedles can be produced efficiently and stably via micromoulding techniques until the mold breaks. These master molds with desired microstructures were usually produced via techniques such as LIGA (lithography, galvanoformung and abformung). Other methods such as photolithography, heat imprint lithography, and laser writing, were also used to fabricate polymeric microneedles. Recently the 3 dimensional printing has been developed for polymeric microneedles. All these methods have been achieved based on the advantage of versatility of polymer, including viscosity, dissolution properties, and postmodification.

5. APPLICATION OF MICRONEEDLES

Microneedles are convenient, safe, and painless enough to achieve the comfort of patient and now widely used in transdermal, ocular, and intracellular delivery.

5.1 MICRONEEDLE DELIVERY OF VACCINE

Traditionally, most vaccines are administered intramuscularly or subcutaneously, and the route of administration is relatively painful. Today, MNs array system has been widely studied for delivery of vaccine and is comparable to the conventional routes of administration. DNA vaccines are considered to be the effective candidates of conventional vaccines because they can generate strong cellular Nand humoral immune responses, are inexpensively, and can be manufactured easily.[23] However, DNA vaccines often exhibit an immune response weaker than expected when administered intramuscularly to patients because of the low efficient delivery of plasmid DNA into host cell, which induces the low expression of encoded antigen.159 Thus, a suitable DNA vaccines delivery system is considered a key method to improve the immunization results. Microneedles can deliver DNA vaccine into the skin to improve the immune responses induced by the enhancing expression of encoded antigen and become an effective delivering method for DNA vaccines.

The MNs array system has been investigated for influenza immunization due to the efficient and precise delivery of vaccine. MN array system provides an important advance in the delivery of vaccine to enhance the strong cellular immunity, indicating that MNs will have a great influence on drugs used for vaccination in the future.

5.2 MICRONEEDLE DELIVERY OF INSULIN

Diabetes mellitus is a complex metabolic diseases caused by abnormal insulin level in the whole world. Its main manifestations are increased glucose production in the liver an decreased clearance of glucose into muscle and fat, resulting in obvious hyperglycemia in the blood.[24] Insulin administration is required to control blood glucose levels for patients suffering from various types of diabetes. Traditionally, the delivery of insulin is conducted by methods ranging from smaller gauge needles to insulin pen to insulin jet injector and to insulin pump. However, the exogenous insulin delivered by these methods does not closely match the physiological release of insulin, which often causes inadequate glycemic control and subsequent negative consequences. For example, too low dose of insulin will induce the blindness and kidney failure for patients, while too high dose of insulin will induce hypoglycemia, which will cause seizures, loss of consciousness, and even death. Microneedle delivery system is the expected technique to deliver the insulin, closely matching the need of patient. MNs for insulin delivery are expected to pave the way for noninvasive regulation of glucose level for diabetic patients.

5.3 MICRONEEDLE DELIVERY OF OTHER DRUGS

Lidocaine is a class drug for local anesthesia and is usually delivered for pre- and postoperative anesthesia either alone or in combination with other drugs.[25] Transcutaneous injection are often used to deliver lidocaine. However, the traditional method can cause local and systemic effect to the patients, including unpleasant feeling (eg, fear, pain, anxiety),erythema, and edema occurred in topical application, increasing risk of unexpected diffusion and inadequate placement of lidocaine.[26] Hence, MN delivery system has been investigated to be an alternative traditional delivery method of lidocaine.

Acetyl salicylic acid (ASA, aspirin) is commonly used for pain relief and anti- inflammatory and cardiovascular treatment.

Due to the gastrointestinal side effects and low bioavailability of oral administration, MNs delivery system is becoming an alternative method for the delivery of ASA.[27]

In addition, MNs are widely used to deliver other largemolecular- weight drugs, such as protein,[28] DNA,[29] and peptides,[30] and small-molecular-weight drugs, such as dyclonine developed for topical anesthesia,[31] zolmitriptan developed for acute treatment of migraine,[32] naltrexone used to treat opiate and alcohol dependence, and so on. Besides, MNs can be also one of the methods used to detect the tumors and to continuously real time monitor alcohol, glucose, and so on for patients, since they can be penetrated into skin with negligible damage or pain.

5.4 BLOOD AND INTERSTITIAL FLUID EXTRACTION

Microneedles have been used mainly for delivery into the skin, but several studies have investigated the role of microneedles as a diagnostic tool to extract analytes from the skin for ex vivo analysis or by integrating a sensor into the microneedle for in situ sensing in the skin. In one approach, up to a few microliters of interstitial fluid were extracted under suction from skin pretreated with microneedles; measured glucose concentrations in the extracted interstitial fluid showed excellent correlation with corresponding blood glucose levels in rats and human subjects.[33]

A microneedle for microdialysis has also been developed to selectively collect analytes below a molecular weight cut off to prevent biosensor fouling with high molecular weight compounds.[35] Integrated diagnostic systems including a microneedle, as well as supporting microactuators, microfluidic controls and sensors, have also been developed to collect blood from the skin for glucose monitoring.[36]

5.5 COMBINATION OF MICRONEEDLES AND OTHER METHODS

Microneedle technology has been combined with iontophoresis, electroporation and other methods to provide synergistic effects. In one of the first papers on drug delivery using microneedles, skin was pretreated with microneedles and then oligonucleotides were driven through the permeabilized skin by iontophoresis in hairless guinea pigs. This approach reduces the skin barrier using microneedles and then provides a driving force for enhanced transport by iontophoresis.

Microneedles have also been developed as micro-electrodes for skin electroporation. In one study, insertion of microneedles combined with application of short electrical pulses designed to cause skin electroporation increased delivery of dextran into the skin.[35 b] In other studies, arrays of independently addressable, solid microneedle electrodes were fabricated by a novel metal-transfer micromolding technique and shown to electroporate cells to increase uptake of calcein and bovine serum albumin and to increase DNA transfection.

5.6 DELIVERY TO THE EYE

In addition to applications in the skin, microneedles have also been used for drug delivery to the eye. Hollow microneedles can be used to make minimally invasive injections of soluble molecules, as well as nano- and microparticles, into the sclera. Intrascleral injection was influenced by scleral thickness, infusion pressure, microneedle retraction depth, and concomitant use of enzymes. By inserting hollow microneedles to the base of the sclera, fluid injection could be targeted to the suprachoroidal space, which is a potential space between the sclera and choroid of the eye.[35] Fluid injected in this way was able to flow circumferentially around the eye and even reach the macula after injection near the limbus. Soluble molecules, as well as nano- and microparticles, were injected, which was influenced by microneedle length, intraocular pressure, infusion pressure, and particle size.

5.7 DELIVERY INTO CELLS

Single, hollow microneedles have been used for intracellular injection for decades, facilitating applications in the bioscience laboratory, animal cloning and clinical medicine (e.g., in vitro fertilization).[36] This extremely low-throughput approach uses pulled glass micropipettes that are carefully inserted into individual cells under a microscope for intracytoplasmic **or** intranuclear injection of proteins, DNA, spermatozoa or other materials.

5.8 *OTHER APPLICATIONS*

For medical applications, solid microneedles have been developed for drug delivery into blood vessel walls, for example to treat restenosis. Such microneedles were shown to puncture across the internal elastic lamina in rabbit arteries ex vivo. To aid tissue engineering, hollow microneedles were developed to improve cell viability in tissue culture by better perfusing slices of harvested brain tissue.[37]

CONCLUSION

Microneedle for drug delivery was invented in 1971, after the microneedles have been developed over 4 decades. When compared to traditional drug delivery system, microneedles have been demonstrated to be safe and successful to deliver various drugs. Microneedles have been made of variety of materials such as polymers, metals, silicon, ceramics, glass and sugars. Researcgers have made great achievements in the fabrication techniques based on these materials. Solid, coated, dissolved, and hollow microneedles have been developed to deliver drugs along with wide range of molecules.

Very small microneedles could provide highly targeted drug administration to individual cells. Microneedles are capable of accurate dosing, complex release patterns, local delivery and biological drug stability enhancement by storing in a micro volume can be precisely controlled. There are some microneedles devices on the market, which have brought good clinical outcomes for the delivery of insulin, influenza vaccine, and lidocaine. Many microneedles are still in experimental phases. Microneedles are designed to balance the pain, mechanical strength, quantity of drugs, and stable drug formulation. Microneedles should be fabricated in low cost to obtain sufficient and reproducible penetration; and be easily handled by all patients.

In spite of these problems, due to the unique properties of microneedles, more efficient and advanced microneedles system will be developed for the market in the future. Microneedles system for transdermal drug and vaccine delivery will have a great impact on the future.

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