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Microneedles In Drug Delivery and Therapeutics

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ABSTRACT

The restricted barrier properties of the upmost layer of the skin, the stratum corneum (SC) impose significant limitations for eminent systemic delivery of a broad vary of therapeutic molecules, significantly macromolecules and genetic material. Microneedle delivery has been projected as a method to interrupt the SC barrier perform so as to facilitate effective transport of molecules across the skin. Microneedles are used for the dermal and transdermic delivery of a broad vary of medicine, like tiny relative molecular mass medication, oligonucleotides, DNA, peptides, proteins and inactivated viruses. This strategy involves the employment of metric linear unit sized needles fictitious from completely different materials and victimisation different geometries to make transient binary compound pores across the skin. Following a quick introduction regarding microneedles and its history, this review describes completely different fabrication ways for solid, coated, dissolving and hollow microneedles similarly as their applications and conjointly focuses on recent and potential future developments in microneedle technologies. this can embrace the particularization of progress created in microneedle style, a research of the challenges moon-faced during this field and potential forward methods to embrace the exploitation of microneedle methodologies, whereas considering the inherent safety aspects of such therapeutic tools. Finally, we have a tendency to offer our read on analysis and development that's required to render microneedles as novel dermal drug delivery technologies clinically helpful within the close to future.

Keywords*:* Microneedles (MN), microelectromechanical systems, fabrication, casting

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INTRODUCTION

When oral administration of medicine isn't potential as a result of poor drug absorption or catalyst degradation within the digestive tract or liver, parentral route is that the commonest various i.e. injection employing a painful needle. As this route is price effective, fast and direct thanks to deliver drug molecules into the body. However, hypodermic needles aren't user friendly and additional restricted as a result of pain and needle-phobia experiment by most patients. associate degree approach that's a lot of admirable to patients, is drug delivery through miniature needles.

As per standard word, a microneedle could be a needle that represents components (e.g. diameter) on the micrometer length scale. The definition is very daring because it includes most of the criterion hypodermic needles utilized in practice. Though there square measure several examples in literature for "microneedles" with lengths of a couple of millimeters, easy understanding of microneedles is that the length of the needle is shorter than one metric linear unit, and considerably less in size than normal needles, particularly concerning the length[1].

As the needles square measure miniature in size, they are doing not reach the nerve-rich regions of the below components of the skin. As associate degree outcome, the stimulation caused by microneedle insertion into the skin is poor and perceived as painless. With the emergence of microfabrication producing techniques over the past many decades, microneedles square measure being developed by several tutorial laboratories and pharmaceutical industries.

Historical Perspective

The idea of use of microneedles in drug delivery systems dates back to 1970's and a patent filed in 1971 from Gerstel and Place at Alza house[2]. The patent describes concerning a drug delivery device having small projections (i.e. microneedles) and a drug reservoir is claimed. Becton Emily Dickinson (BD), Alza Corporation and also the Georgia Institute of Technology place isolated efforts parallely on active investigation within the field of microneedles in mid-1990's. within the early 1990's,the thought of rising layer needle for parenteral route by baccalaureate visualized the event of small projections with effective clinical outcomes by microfabrication techniques. together with University of American state at Berkeley, and also the University of Utah many various producing processes were developed[3-5], with primary focus on short hollow steel needles [6] and blunt-tipped, solid microneedles that causes abrasion to the skin and will increase permeation ability to vaccines given through topical route[7].

In 1990's, Alza Corporation combined microneedles with EMDA of transcutaneous drug delivery system [8], and teamed with ISIS prescription drugs to check EMDA of oligonucleotides exploitation solid metal microneedles[9].

The third pioneer in analysis field of microneedles for drug delivery, Georgia technical school developed novel microfabrication techniques. They printed the primary journal article on drug delivery systems exploitation microneedles[10]. variety of different firms concerned in microneedle analysis programs within the late 1990's and early 2000's. Today, with the enlarged novel fabrication approaches the analysis field achieved associate degree transformation purpose. huge applications of microneedles, with the progression of human trials and demonstrable in vitro and animal models, created the novel approach of delivery into practice.

Fabrication of Microneedles

Yield of microneedles raised with the development of microtools for fabrication by micro electronics industry during 1990's.The first microneedle arrays as per literature were fabricated as a silicon wafer and employed for intracellular delivery by Hashmi et al[11], and different materials including metal, polymer, glass and ceramic, with varied shapes and sizes were employed in fabrication as intended for vast applications of drug delivery. Micromolding, photolithographic processes, silicon etching, laser cutting and ablation, metal electroplating, metal electropolishing are the conventional techniques employed in fabrication[12.] In general these miniaturized projections are categorized as solid microneedles, dissolving microneedles, drug-coated microneedles, and hollow Microneedles (Figure.1).

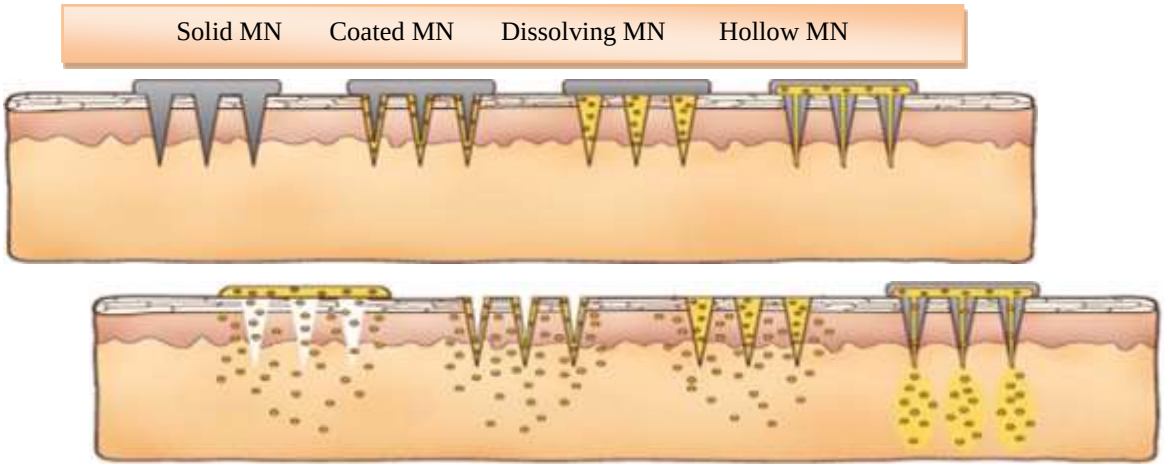

Figure 1.Different types of microneedles: solid, coated, dissolving and hollow

Fabrication of solid microneedles

Solid microneedles are fabricated in a range of 750-1000µm in length. They are employed in skin pretreatment, this type of microneedles upon insertion and removal leads to formation of micron-scale pores on the skin surface, through which drug diffuses slowly into the body. Solid microneedles fabrication has primarily focused on enhancing mechanical strength and to increase the sharpness of needles in order to reduce the force required to apply.

Silicon microneedles were first fabricated[11] and other materials employed in fabrication include biodegradable polymers such as poly-lactic-co-glycolic acid (PLGA), polyglycolic acid (PGA) and polylactic acid (PLA)[13]; non-degradable polymers like as photolithographic epoxy[14]#715; [15] #738; , metals including stainless steel [16,17], titanium [18], a copolymer of methylvinylether and maleic anhydride (PMVE/MA)[19], polycarbonate [20] and polymethyl methacrylate (PMMA) [21]; water soluble compounds including maltose[22];tantalum [23] and nickel [24]; and ceramics[25,26]. Fabrication of solid microneedles employing silicon is expensive and it may break due its brittleness. Metal microneedles show good mechanical strength and cost effective (Figure 2).

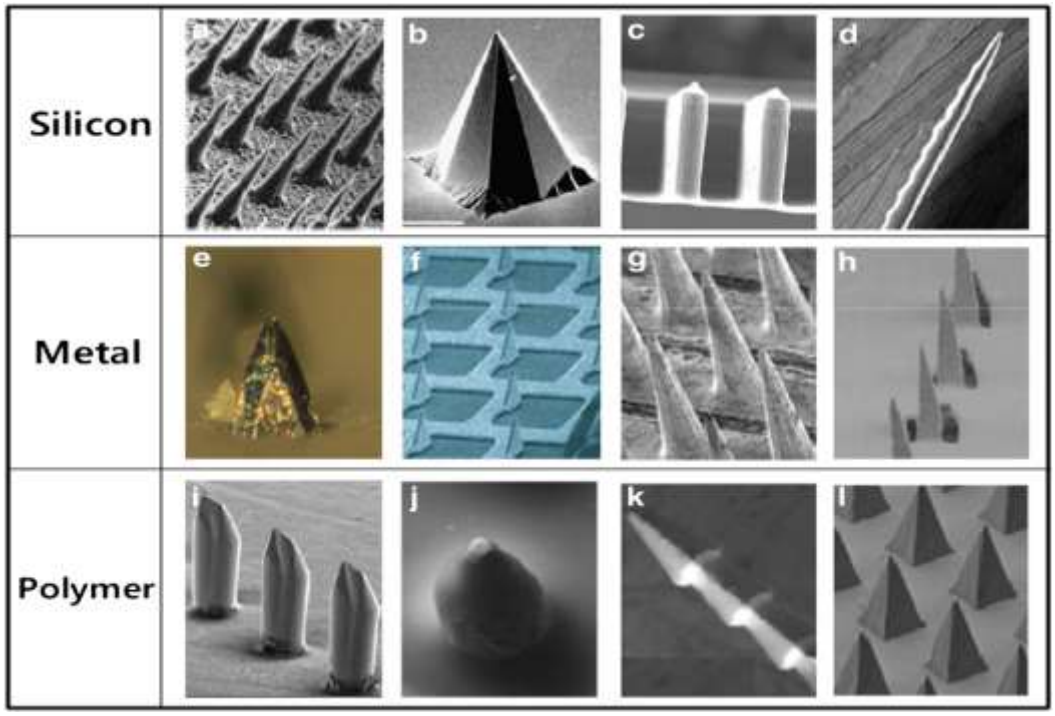

Figure 2.Varied size and shapes of solid microneedles made of silicon, metal, and polymer.

Silicon microneedles

The fabrication of solid microneedles depends on the material employed and geometry intended. Dry-etching process, an isotropic etching and anisotropic wet etching are employed to obtain solid microneedles [27-29]. Compared to dry etching, Wet etching methods can lower fabrication cost but microneedles geometry is restricted. To overcome this, isotropic dry etching and

anisotropic wet etching methods have been combined. In addition an approach to fabricate sharpened probe tip microneedles is done by dicing a silicon substrate and creating a grid pattern of deep grooves and followed by acid etching[12].

Metal microneedles

Three-dimensional laser ablation, laser cutting, wetching, and metal electroplating methods [12]are employed in fabrication of metal microneedles. Two dimensional arrays of miniaturized needles are fabricated by cutting the stainless steel and titanium metal sheets and then bending them at a 90° angle out of the plane. They are also prepared by electroplating or electroless-plating of metal onto positive or negative microneedle molds [30].

Polymer microneedles

Microneedles have been made by photolithography using optically curable polymers, which are then typically employed as master structures for replication by molding. The ultraviolet (UV)-curable polymer SU-8 has been utilized extensively to fabricate microneedles[31–33]. A two-photon-initiated polymerization method was utilized to fabricate three-dimensional microstructures including microneedles. In this approach, a near-infrared ultra short-pulsed laser was focused into a photocurable resin to form three-dimensional microstructures using a sequential layer-by-layer fabrication technique[34-35].

These UV-curable polymers have weaker mechanical strength compared to silicon and metal; thus, they have been used primarily as master structures for making molds. Typically, a silicone polymer(polydimethylsiloxane, PDMS) is poured onto the microneedle master structure to make an inverse mold after curing. Polyvinyl alcohol(PVA), silicon and aluminum have also been used as mold materials to replicate polymer microneedles[36,37]. The mold can then be filled at elevated temperature with molten or softened thermo plastics such as polycarbonate and PMMA[38] to produce non degradable microneedles upon cooling and solidification. In addition, a variety of biodegradable polymers and water-soluble polymers have been micromolded primarily to encapsulate drugs within the microneedle matrix for subsequent release in the skin.

Solid MN design considerations

A number of studies have been reported on the effectiveness of using solid MNs to increase the transport of molecules with varying physicochemical properties into and across the skin. These have included studies using insulin, calcein, naltrexone, and bovine serum albumin (BSA) . The influence of different parameters, such as MN insertion force, tip sharpness and MN density on solid MN- mediated skin permeation of therapeutics has been reported in the literature. For example, Wei-Ze *et al* evaluated the effect of different MN insertion forces (1, 3, 5, 7 and 8

N/array), MN tip sharpness (sharp and flat tip)and MN densities (8 × 8, 10 × 10, 12 × 12) on the performance of super-short silicon MNs(70-80 μm in height) used to enhance the transport of a model compound, galanthamine (GAL), across full-thickness rat skin (Wei-Ze *et al.*, 2010). It was demonstrated that the application of forces in the range between 1 and 5 N/array resulted in increased transdermal GAL transport. However, a further increase in the insertion force beyond this range did not lead to any further permeation enhancement. This indicated that insertion force has a significant effect on the transport of molecules, but only when complete MN penetration has not been achieved. GAL permeation was increased after skin pre-treatment with flat-tipped MNs in comparison to sharp-tipped MNs. In addition, the results revealed that increasing the number of MNs per unit area resulted in increased flux of GAL. However, there was no statistical difference in the cumulative amount of GAL permeated across skin treated with10 × 10 and 12 × 12 MN array [39].

Insulin delivery

The influence of different insulin concentrations (100 and 500IU/ml), duration of MN insertion (10sec, 10 min and 4 h), in addition to the influence of the number of MN array insertions (1 insertion and 5 insertions) on the transdermal delivery of insulin to diabetic rats using solid stainless steel MNs (105 needles, 1000 μm in height) was investigated by Martanto *et al*. When the duration of MN insertion was increased, this resulted in a lower reduction in blood glucose levels, when compared to shorter insertion times. This observation was attributed to the blockage of micro channels by MN arrays left *in situ* thus leading to the delivery of lower insulin concentrations, thus highlighting a limitation in the use of solid MN arrays when delivering therapeutics. Moreover, the insertion of a single MN array was found to be more effective in reducing blood glucose levels than multiple insertions of MN arrays. The authors hypothesized that his phenomenon was due to local damage of the skin which resulted in altered insulin clearance and its absorption by the capillary bed[40].

Combinatorial approaches

Solid MNs, used in combination with other enhancement strategies, such as iontophoresis and/or nanovesicles, have been shown to produce synergistic effects in the facilitation of the transdermal delivery of numerous molecules. The treatment of the skin with solid silicon MNs and iontophoresis was reported to enhance skin permeation of insulin, which had been incorporated into transdermal patches. The result of this was the maintenance of a sustained basal dose of insulin for the continuous reduction of blood glucose levels and also on-demand bolus dosing for mealtime coverage *via* the iontophoresis “switch on” effect [41].

Synergistic enhancement effects of MN pre-treatment using a solid MN device (484 needles;150 μm in height) in combination with a docetaxel-containing liposome delivery system was shown to enhance transdermal flux across porcine skin *in vitro* [42]. The authors suggested that this approach could be used to achieve higher and more stable transdermal delivery rates of drugs with high molecular weights and poor water solubility.

Vaccine delivery

Successful transcutaneous in transdermal vaccination, with or without adjuvant, has also been demonstrated using solid MNs. Ding *et al* investigated immune responses in mice following MN-mediated transcutaneous immunization using a model antigen, diphtheria toxoid (DT). Stainless steel MN arrays (4 ×4, 300 μm in height) were used to pierce the mouse skin and DT formulation with or without cholera toxoid as adjuvant was administered. The application of DT on untreated skin resulted in low serum IgG titres. However, MN pre- treatment led to significantly higher serum IgG titres, which were further increased in the presence of cholera toxin[43].

In a more recent study, the combined effect of solid MN pre- treatment (4 × 4 MNarray, 300 μm in height) with hepatitis B surface antigen encapsulated vesicle formulations for potential transcutaneous vaccination was evaluated in female BALB/c mice . The antigen-loaded vesicles alone failed to induce an immune response in the mice, however MN-treated skin resulted in a robust immune response and incorporation of adjuvant resulted in further improved immune response in mice[44].The results of these studies serve to enhance the profile of MN administration in the convenient, safe and efficacious delivery of vaccines.

Clinical studies in humans

In addition to *in vitro* and *in vivo* studies conducted in animal models, some clinical studies in humans have also been carried out using solid MNs. The first study was carried out by Wermeling *et al.,* to demonstrate the MN based transdermal delivery of an opioid blocker, naltrexone (NTX). This compound was deemed to be an ideal candidate for MN administration due to the fact that passive transdermal delivery of it is limited by its hydrophilic nature. Skin on the upper arm of healthy volunteers was pretreated with two solid stainless steel MN arrays (5 × 10 MNs, 620μm in height) which was followed by NTX patch application and collection of blood samples over a 72 h sampling period. Results showed variable absorption of NTX (1.6 to 8.1ng/ml) achieved within a wide timeframe (1.5 to 18 h) of patch application, followed by steady-state plasma concentrations of ~ 2.5 ng/ml which were maintained for at least 48 h. Application of NTX patches to untreated skin did not result in detectable drug plasma

concentrations. This study served as a platform to demonstrate the feasibility of using MNs to enhance the transdermal delivery of hydrophilic molecules[45].

Taken together, these various studies suggest a potential role for solid MNs in promoting successful enhanced transdermal and intradermal delivery of various low and macromolecular therapeutic compounds, genetic materials and vaccines. Commercialization of silicon-based solid MNs in the field of cosmetic applications should serve to promote the case for commercialization of other solid MN devices.

Coated Microneedles

Solid microneedles which are coated with drug-containing dispersion are used as vehicles to carry and deposit drug within the skin constitutes coated microneedles. Coating is done with a drug in a formulation suitable for coating and subsequent dissolution. In this way, the desired dose of the drug is delivered into tissue quickly upon insertion of the microneedles. The dose that can be administered by this way is limited to the amount that can be coated onto the tip and shaft of the microneedles, which is typically less than 1 mg for small microneedle arrays [46](Figure.3)

A number of techniques are employed in preparation of coated microneedles. An approach using electro hydrodynamic atomization (EHDA) principle in the preparation of smart microneedle coatings was reported in the literature. The authors used this technique to prepare nano- and micrometer-scaled pharmaceutical coating. Fluorescein dye (serving as potential drug, sensory materials or disease state markers) and polyvinylpyrrolidone (PVP, polymermatrix system) formed the remaining components of the coating formulation. Based on these excipients and by varying the coating process, particles (100 nm to 3 μm) and fibers (400 nm to 1 μm)were deposited directly on MNs in controlled and selectable fashion[47].

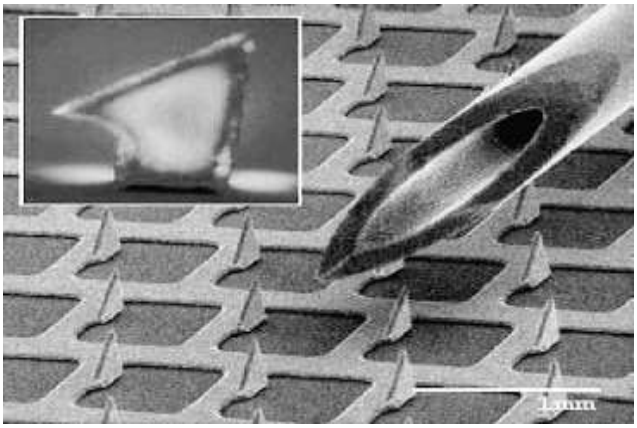

Figure.3 Solid microneedles (‘‘micro projection array’’, 330 Am tall) acid-etched from a titanium sheet were coated with protein antigen for vaccine delivery in vivo; similar needles were used to deliver oligonucleotides in vivo

Ma and Gill used a polyethylene glycol matrix containing a water insoluble drug lidocaine to coat solid microneedles. Uniform coatings were obtained on microneedle surfaces. *In vitro* dissolution studies in porcine skin showed that microneedles coated with PEG-lidocaine dispersions resulted insignificantly higher delivery of lidocaine in just 3 min compared with 1 h topical application of 0.15 g EMLA®, a commercial lidocaine-prilocaine cream [48].

Coating methodologies

Microneedles have been coated by a variety of processes, most of which involve dipping or spraying the microneedles using an aqueous solution often formulated to have increased viscosity to retain more of the formulation on the microneedles during drying; a surfactant to facilitate wetting of the microneedle surface; a drug, vaccine or

other active agent; and in some cases a stabilizing agent to protect the drug from damage during drying and storage. Coating has been carried out by dipping once or repeatedly into a large bath

of coating solution, into micro wells of coating solution for each individual microneedle and into a thin film of coating solution formed on the surface of a roller . The latter two approaches were designed to better localize the coating to the microneedles or just their tips without contaminating the base substrate. Layer-by-layer coating techniques have also been applied to microneedle coating. DNA or protein molecules were coated onto metal and polymer microneedles by alternately dipping into two solutions containing oppositely charged solutes, such as negatively charged DNA and positively charged polymer, to form a polyelectrolyte multilayer. As another alternative, coating solution has been sprayed onto silicon microneedles. In one approach, an angled gas jet was used to spray the surface of individual microneedle shafts from a reservoir created on the microneedle array substrate at the base of the microneedles. In another approach, spray coating was applied using an atomizer[12].

Gene delivery

The use of coated MN for delivery of genetic materials for various clinical indications (e.g. genetic immunizations) has been reported by Pearton *et al.*[49]. In this study, genetic material, in particular plasmid DNA (pDNA), was dry-coated onto in plane stainless steel MNs 750 μm in length. The reliable loading capacity of pDNA onto the MNs, its stability and the performance of the MNs in skin penetration were reflected by successful gene expression in excised, but viable human cutaneous tissue. However, the authors highlighted the need to further investigate the dissolution characteristics of this coated pDNA prior to investigation in a live animal model [50]. More recently, the same research group also demonstrated successful proof-of-concept gene silencing using steel MN coated with small interfering RNA (siRNA) [51].

Vaccine delivery

Coated MN have been extensively studied to facilitate transcutaneous vaccination using MNs. An abundance of immune-presenting cells (APCs)makes the skin an extremely attractive site for antigen presentation. Antigens can be introduced into the skin *via* coated MNs to target Langerhans cells in the epidermis or dendritic cells in the dermis in order to induce a more pronounced immune response[52]. The limited drug quantities that can be coated onto MNs does not infact hinder their application in vaccine delivery as only minute quantities of antigen are necessary to elicit an immune response[53]. Stability concerns associated with conventional injectable vaccines such as the need for the cold chain preservation of vaccine potency during storage and transport is a critical issue. The storage of vaccines in a dry state coated onto MN arrays may circumvent this issue however as it allows the preservation of vaccine stability to a greater extent than storage in the form of an injectable [52]. Most importantly, coated MN-mediated vaccinations manufactured from different fabrication materials (metals or polymer), with or without adjuvant and/or in combination with other enhancing technologies have been demonstrated to induce superior or comparable immunogenicity with attractive advantages of dose sparing compared to the conventional vaccination routes such as subcutaneous or intramuscular administration.

Dissolving microneedles

In counterpoint to coated microneedles, polymer microneedles have been fabricated in order to get completely dissolved in the skin without any bio hazardous sharps waste left behind. These are made of safe, inert, water-soluble materials, such as polymers and sugars which get dissolved in the skin after insertion. Dissolving microneedles are used in skin pretreatment to increase permeability, drugs are often encapsulated inside the microneedle for release into the skin similarly to coated microneedles.

Dissolving microneedle fabrication methods

Dissolving microneedles fabrication constitutes micromolds filled by solvent casting (with water as the usual solvent), filled with a polymer melt allowed to solidify in the mold, and in-situ polymerization of liquid monomer in the mold. Drawing methods of fabrication have also been used with polymer/sugar melts and polymer/sugar solutions. Various materials including dextrin, PVP,PVA, PLGA , fibroin , CMC , chondroitin sulfate , dextran, and sugars have been dissolved in water, filled into the mold cavities and allowed to dry, sometimes with the additional use of vacuum and/or centrifugal force. Melted maltose has been filled in the cavities of a mold and solidified upon cooling. Using a related approach, N-vinylpyrrolidone and/or methacrylic acid

were added as liquid monomers into a mold and polymerized under ultraviolet radiation. In contrast to these highly water-soluble, rapidly dissolving microneedles, polymeric microneedles designed for low biodegradation in the skin have also been fabricated by micromolding polylactic acid, polyglycolic acid and their copolymers as melts using PDMS and silicon molds[54].

Another fabrication method draws up liquid formulations to form tapered microneedle structures that solidify in position. Maltose microneedles were formed as multi-needle arrays using a controlled, stepwise drawing technique enabled by a microfabricated device[55]. An ultrasonic welding method was also introduced to form biodegradable polymer microneedles out of polymer particles welded together without bulk heating of the polymer, which resulting in minimal damage to encapsulated compounds.

Dissolving microneedle formulations and designs

Heat-sensitive compounds like proteins and antigens should be encapsulated in microneedles and solidified at moderate conditions that will not damage their activity. For example, dissolving microneedles were fabricated out of hydrophilic polymers cast in an aqueous solution at room temperature and at atmospheric pressure or under vacuum. CMC microneedles were fabricated under centrifugation to avoid formation of small voids in the microneedle matrix that weaken the structure. Erythropoietin (EPO) and insulin were encapsulated in other hydrophilic polymers such as dextrin and chondroitin by forming threads using pipette tips at room temperature[56,57].

Most dissolving microneedles in the literature need to be inserted into skin for at least 5 minute fully dissolve. To shorten this time, arrowhead microneedles were designed to separate from the shaft within seconds and remain embedded in the skin for subsequent dissolution[58]. In contrast, biodegradable polymer microneedles must be inserted and remain in the skin for at least several days to effectively utilize their controlled-release degradation properties to provide controlled-release delivery in skin for up to months[59].

Microneedles encapsulating hydrogel microparticles were designed for successful separation of microneedles within less than 1 h of insertion into skin by swelling of the hydrogel microparticles[60].Because microneedles may not insert fully into skin, it is sometimes desirable to encapsulate drugs only in the microneedle tips. Drug has been localized in microneedle tips by forming multilayered microneedles using sequential applications of different compositions of polymer solutions and using a particle-based molding method[61]. Drug was also localized in tips by the addition of an air bubble at the base of each microneedle during fabrication, which prevented drug diffusion from the microneedles into the patch backing.

Hollow microneedles

In similar to hypodermic injection, hollow microneedles provide a defined path for drug delivery into the skin or other tissue, they enable pressure-driven flow of a liquid formulation .The liquid formulation may simplify use of existing injectable formulations for delivery using microneedles, but misses the opportunity of solid microneedle delivery methods to administer dry-state drug formulations without reconstitution to improve drug stability and the patient convenience of a patch-based delivery method. Hollow microneedles have also been used as a path for drug diffusion into the skin from a non-pressurized drug reservoir (Figure.4).

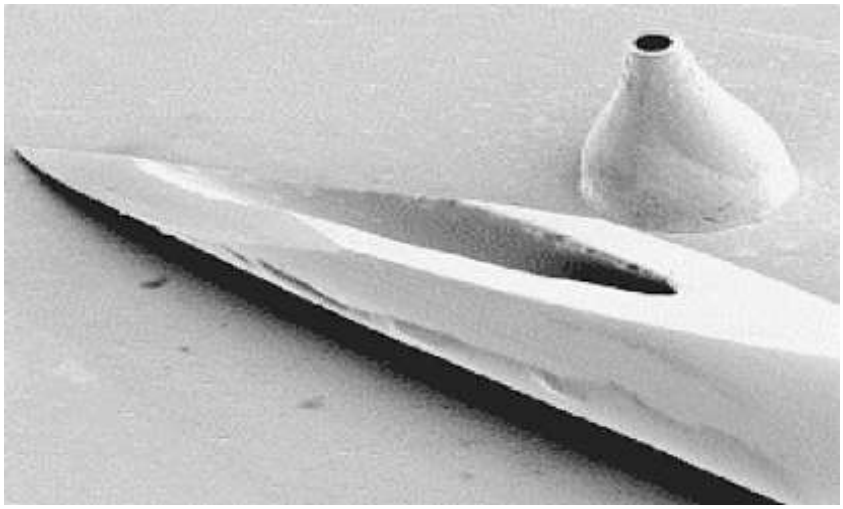

Figure 4. Hollow microneedles (500 µm tall) formed by electrodeposition of metal onto a polymer mold were used for needle insertion and fracture force measurements.

Hollow microneedle fabrication methods

Hollow microneedles have been fabricated directly from a material substrate using microelectro mechanical systems (MEMS)techniques including laser micromachining, deep reactive ion etching of silicon[62,63], an integrated lithographic molding technique[64], deep X-ray photolithography[65], and wet chemical etching and microfabrication[66]. Other hollow microneedle fabrication methods require multiple substrates with different chemical or physical properties to serve as sacrificial layers to obtain shell structures indirectly from a microneedle substrate. Hollow silicon microneedles were fabricated by adapting silicon-based MEMS techniques including lithographic processes, wet etching and micromachining. A SiO2 mask, wetching and deep reactive ion etching were utilized in combination to fabricate cylindrical hollow microneedles[67] and out-of-plane hollow microneedles. To obtain hollow silicon microneedles, the Bosch process was utilized to create hollow shell structures with high aspect ratio, after which isotropic and wet etching processes were added to obtain shaper tips. Bosch deep reactive

ion etching was used to fabricate cylindrical hollow microneedles out of silicon [68]. Isotropic etching and Bosch deep reactive ion etching were used together to fabricate hollow microneedles with a tapered shape[69,70]. Bosch deep reactive ion etching was combined with wet etching to obtain hollow silicon microneedles with sharp tips.

Deep anisotropic etching, isotropic etching and mask technique were used to fabricate cylindrical microneedles with a side-opening orifice[71]. In addition to chemical etching methods, a dicing saw was used together with deep reactive ion etching to obtain hollow silicon microneedles with sharp tips[72].Hollow microneedles made of glass, polymer and metal have been prepared from substrates by conventional fabrication methods. Hollow glass microneedles were made by adapting traditional drawn glass micropipette techniques[73]. Hollow metal microneedle arrays were assembled from commercially available 30 gauge hypodermic needles. Hollow polymer microneedles were formed by drilling to make the bore hole and milling to createthe beveled tip shape out of polyphony sulfone polymer[74].

A digital micro mirror stereo lithography instrument was used to fabricate hollow polymer microneedles by polymerization of liquid resin[75]. The LIGA technique was utilized to form hollow microneedles by exposing X-ray through a mask onto PMMA[76,77]. Direct two-photon polymerization in a laser-based rapid prototyping system was used to form hollow polymer microneedles. Many hollow metal microneedles were fabricated using indirect methods depending on sacrificial substrates. Hollow metal microneedle arrays were made using a multiple step process, which involved backside exposure of SU-8 photo resist and conformal electroplating. A micro machined polymer mold was prepared using an ultraviolet laser; the mold was then coated with nickel by electro deposition onto a sputter-deposited seed layer, and the resulting metal microneedle arrays were released by selectively etching the polymer mold. Another design of metal hollow microneedle was made by drawing lithography and metal electroplating[78].

Hot embossing combined with an ultraviolet excimer laser beam technique was introduced to make polymer hollow microneedle arrays with side opening orifices[79]. Another hollow nickel microneedle device was fabricated by a sequential process of electroless copper and nickel plating and copper wet chemical etching[80]. Hollow silicon dioxide microneedles were fabricated based on electrochemical etching of n-type silicon in hydro fluoric acid solutions. Hollow metal microneedles were fabricated from a silicon needle template using micro-imprinting, hot embossing, electroplating and polishing[81].

Injection using hollow microneedles

To generate the flow of liquid through hollow microneedles, various methods of actuating flow have been devised. Hollow microneedles are commonly used with a syringe to inject liquid formulations. However, some hollow microneedle systems were integrated with an actuator. Hollow microneedles were attached to a PDMS reservoir filled with a drug[82]. Flow of liquid through hollow microneedles was controlled by CO2 gas pressure, a spring, a piezoelectric micro pump, a piezoelectric linear servo motor, a syringe pump and a micro-gear pump[83,84].Currently, there are generally two types of hollow microneedle designs. One type utilizes a single microneedle, which mimics the conventional hypodermic needle. The other type is an array of multiple hollow microneedles. The latter type can deliver liquid formulations to a wide area all at once and, in some cases, more quickly than subcutaneous injection and with higher bioavailability and possible lymphatic targeting[85].However, if one of the microneedles has a leak, then pressure cannot be equally applied to all of the needles and fluid will not flow through all of the microneedles equally. A micro fluidic interconnector was also designed and fabricated out of PMMA, and integrated with a SU-8 hollow microneedle system[86].Rather than fabricating a microneedle, another approach involves using a 30gaugehypodermic needle that is housed in a syringe device that exposes only 1.5 mm of the needle, thereby effectively making a short needle[87]. This device consists of this microneedle connected to a prefilled syringe designed for perpendicular insertion into the skin to achieve intra dermal localization of the injection. The resulting distribution of fluid in the skin was shown to be larger than the conventional mantoux injection control. This system also caused less injury to the papillary dermis, less pain than mantoux injection, and was administered easily by untrained personnel.

In contrast to drug delivery applications, hollow microneedles have also been developed to extract fluids from the body. Glass and silicon hollow microneedles were used to obtain interstitial fluid, and stainless steel hollow microneedles were used for blood sampling.

Different approaches of drug delivery by hollow and solid microneedles

Different approaches of drug delivery by hollow and solid microneedles[88] are

a) poke and flow approach

b) poke and patch approach

c) poke and release approach

d) coat and poke approach.

Hollow microneedles are used with the ‘poke and flow’ approach, whereby a drug in solution is actively or passively delivered through the bore of the microneedle. Solid microneedles are used in three different manners. By the ‘poke and patch’ approach micropores are generated in the

skin by microneedles, and after removal of the microneedles a patch is applied on top of these micropores, allowing the drug in the patch to diffuse through the skin. The 'poke and release' approach uses either dissolving microneedles or porous microneedles, which respectively release the drug by dissolution of the microneedles in the skin, or by diffusion of the drug in solution from the pores into the skin. Finally, with the 'coat and poke' method microneedles are pierced through the skin, and then the drug-containing coati ng is released into the skin through hydrati - on of the coating(Figure.5).

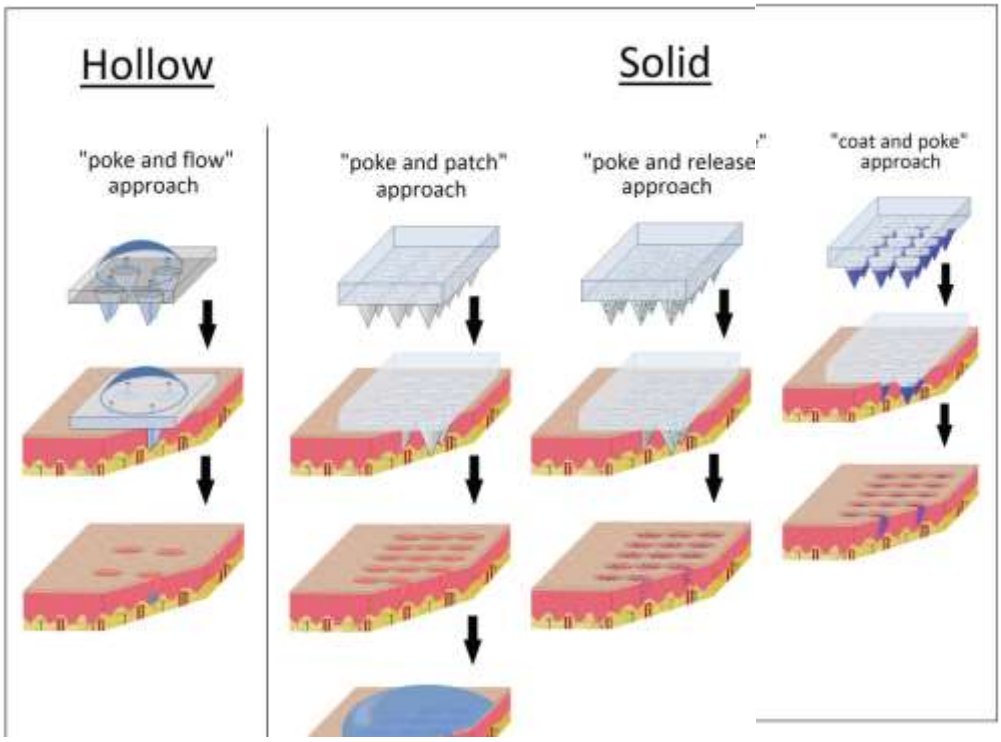

Figure 5. Different approaches of drug delivery by hollow and solid microneedles

APPLICATIONS

Microneedles have been used in many different applications, ranging from neuro stimulation to gene delivery into individual cells. A common goal is to create a pathway to an object by physically circumventing some kind of barrier. In most applications this barrier is the skin. The rationale of using microneedles, as opposed to macroscale devices, is motivated either by the size of the target or the benefit of piercing in a minimally invasive manner.

One of the earliest reported microneedles in the scientific literature was an out of- plane silicon needle array featuring 100, 1.5 mm long, needles on an area of 4.2 mm×4.2 mm (figure 2b)[89].

These extremely slender needles were used as electrical electrodes and designed to stimulate the visual cortex of the brain in order to regain sight. Related to this application, in-plane, microneedle probes have been used for activity recording and cellular chemo stimuli of brain

tissue[90,91]. Solid, out of- plane, microneedles have been used to penetrate the stratum corneum to facilitate EEG (Electroencephalogram) measurements for anesthesia monitoring[92,93]. Here, arrays of 200µm long needles were used to circumvent the electrically insulating layer of the skin. Similar microneedle probes have also been used for diagnostic purposes, where the needles were used for impedance measurements of skin lesion in order to detect skin cancer[94]. The technique is currently being commercialized by SciBase AB and expected to reach market[95] in 2007–2008. Another application for microneedles is sampling of body fluids. Resembling the proboscis of a mosquito, Oka et al. fabricated a millimeter-long, jagged, hollow in-plane microneedle for blood collection[96].

Sampling of interstitial fluid through capillary action has been demonstrated with arrays of 350m long, hollow, out-of-plane microneedles[97]. Microneedles have also been fabricated for micro dialysis, where a hollow in-plane needle equipped with a semi-permeable membrane filters the sampled liquid [98].

Although other application fields exist for microneedles, the vast majority of published microneedles concern drug delivery in various forms.

VISION

A microneedle-based drug delivery system may feature all the favorable properties that made the classical transdermal patch a success. Like the ordinary patch, the system would be easily attached to, for instance, the upper arm and worn for a shorter time while medicating. The advantages of such a system are:

- Pain-free administration
- Easy to use—OTC-compliant
- Discreetness
- Continuous release
- Controlled release
- Safer handling

Pain-free administration:

Microneedles with a length of a few hundred micrometers, only penetrates the superficial layers of the skin where the density of nerve receptors is low. As a consequence, insertion of microneedles into skin is perceived as painless.

Easy to use:

Like an ordinary transdermal patch, an envisioned system can be applied by the patient himself virtually without any training. However, to achieve this, special insertion tools and procedures

are highly unwanted. Hence, the insertion force of the microneedles needs to be low and the insertion procedure needs to be reliable and robust. If this is achieved, it is reasonable to believe that the system, for certain medication, can be sold over the counter (OTC).

Discreetness:

Incorporating a microneedle-array with a planar and compact dosing system yields a patch-like, unobtrusive device that can be discreetly worn under clothing.

Continuous release: An unobtrusive device may be worn for longer times, thus enabling continuous and sustained delivery at therapeutic levels.

Controlled release:

Drug release through a separate mechanism allows the release rate to be precisely controlled. This may be accomplished through integration of passive elements, e.g. flow restrictors or membranes, or active devices. Active dosing systems offer the possibility to modulate the delivery in time and in amplitude. Even more advanced, active elements permit the use of closed-loop systems.

Safer handling:

Microneedles protruding a few hundred micrometers from a surface pose a far less risk of accidental needle sticks than hypodermic needles do. Since microneedles do not reach into the blood, the risk of transmission of blood-borne pathogens is also further reduced.

CONCLUSION

The field of microneedles has dramatically grown over the past 15 years. Microfabrication technology has enabled a variety of different microneedle designs for drug delivery to the skin and other targets. Microneedles have been fabricated out of many different materials including silicon, metals, polymers, and ceramics using a variety of different fabrication methods including lithography, wet and dry etching, laser cutting and micromolding.

Microneedles have been studied for a diversity of medical applications, where delivery of bio actives to the skin has been the primary focus. Animal and human studies have demonstrated microneedle-based delivery of low molecular weight drugs including naltrexone, lidocaine, phenylephrine and compounds for photodynamic therapy; biotherapeutics including parathyroid hormone and insulin among other protein and peptide drugs; and vaccines including influenza, rabies, BCG, West Nile virus, HPV and other vaccines. Functional use of microneedles has also received extensive attention. Patients and healthcare workers have seen value and expressed preference for microneedle based delivery compared to hypodermic injections in surveys.

Human subjects report little or no pain associated with most microneedle designs. A variety of drug and vaccine applications have been shown in animals and humans. Patients, healthcare providers and companies have demonstrated interest in the technology. Micro needles are poised to make expanded impact on clinical medicine over the coming years.

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