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Review Article

Microneedle drug delivery system-Overview

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ABSTRACT

Transdermal patches offer a convenient way to administer drugs without the drawbacks of injections and oral dosage forms. However, the stratum corneum allows only low molecular weight drugs to diffuse through and acts as a barrier that limits the penetration of drug substances through the skin. Recently, the use of microneedles for skin permeability has been proposed and shown to dramatically increase transdermal delivery. Microneedles are long and robust enough to penetrate across the barrier, but short enough to prevent nerve stimulation which projections of solid silicon or hollow drug-filled metal needles which are fabricated in several shapes and sizes. With the use of hollow microneedles it allows the delivery of medicines, insulin, proteins, or nanoparticles that would encapsulate a drug or demonstrate the ability to deliver a virus for vaccinations. Microneedle use is simple, pain-free, and causes no bleeding, with further advantages of convenient manufacture, distribution, and disposal.

Keywords: Microneedle; Micromold; MEMS Technology.

INTRODUCTION

The last decade has seen a proliferation of interest in Transdermal Drug Delivery to the systemic circulation.

This can be attributed to the following factors:

- It provides constant blood levels in plasma for drugs with a narrow therapeutic window, thus minimizing the risk of toxic side effects or the lack of efficacy.
- It avoids first-pass metabolism, which allows drugs with poor oral bioavailability and/or short biological half-lives to be administered once a day, resulting in better patient compliance.
- Problems of drug degradation in GIT and gastric irritation are avoided.
- Removing the transdermal system from the skin can terminate the therapy.
- It provides noninvasive alternative to parenteral, subcutaneous and intramuscular injections.
- It is suitable for patients who are unconscious or vomiting (Finnin BC *et al*., 1999)
- Other epithelial routes of administration, i.e., nasal, buccal, oral, rectal, vaginal and pulmonary, exhibit enzymatic activity comparable to that in the small intestines (LeeVHL *et al*., 1988) whereas skin,although it contains aminopeptidases, exhibits less enzymatic activity (Amsden BG *et al*., 1995).

Despite these advantages, very few drugs can be administered transdermally at therapeutic levels due to the excellent barrier properties of skin because of its low permeability and lipophilic nature (Prausnitz MR *et al*., 1992) Therefore, scientists are constantly focusing on strategies to overcome the barrier properties of skin. A number of innovative methodologies have been devised that include chemical penetration enhancers, biochemical enhancers, iontophoresis, electroporation, sonophoresis, magnetophoresis and laser treatment.

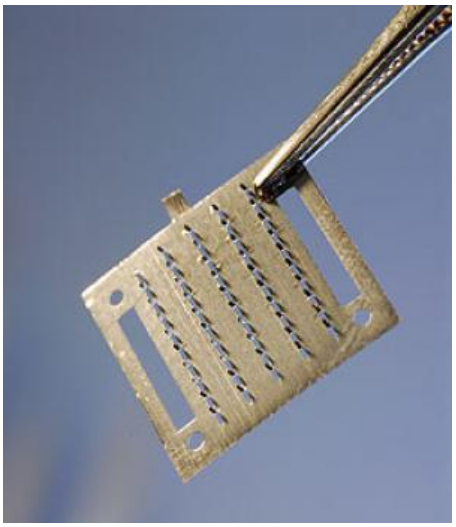

Figure 1: A microneedle-based drug-delivery patch

The objective of this article is to highlight a novel technology that makes use of microneedles having a width less than that of human hair and we describe fabrication techniques used to make needles out of silicon, metal, polymer, and glass that have a range of geome-

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tries, can produce needles ranging from in-plane to normally protruding from substrates, and can be formed in large two-dimensional arrays. These methods mostly require just one or two fabrication steps or a single molding step and use technologies that are readily scalable for inexpensive mass production.

METHODS

Fabrication of Silicon Microneedles

Solid microneedles were etched from silicon substrates (Henry S *et al*., 1998). Briefly, chromium was sputter deposited and then lithographically patterned (e.g., 20 _ 20 arrays of 80-_m-diameter dots with 150-_m center-to-center spacing) onto 2-inch (5-cm), _100_ oriented silicon wafers (McAllister, D. V., Cros, F *et al*., 2000). Reactive ion etching was then carried out with 20 standards cm3_min SF6 and 15 cm O2 at a pressure of 20 Pa and Power of 150 W for a run time of _200 min. Microneedle Fabrication was finished when the chromium masks became fully undercut and fell off the needle tips.

To form the bores of hollow micro needles, polymer photoresist was spin-coated and then lithographically patterned (e.g., 10 _ 10 arrays of 60-_m-diameter holes with 300-_m center to- center spacing onto 2-inch, _100_ oriented silicon wafers. Inductively coupled plasma reactive ion etching (ICP-RIE; Plasma Therm) was then carried out by using a modified Bosch Process to yield straight-walled holes completely through the 350-_m-thick wafer. With the addition of a lithographic alignment step, microneedles were etched around the holes as for solid silicon needles.

Fabrication of Microneedle Masters

To serve as masters for subsequent fabrication of micromolds, microneedle structures were etched into silicon and polymer substrates (Park, J.-H *et al*., 2003). To make molds for symmetrically tapered needles, the solid silicon microneedles described above were used as masters. To prepare asymmetrically beveled microneedle masters, cylinders of SU-8 epoxy photoresist were lithographically defined (e.g., 50-_m radius, 250–600 _m tall, and 600–1,500 _m center-to-center spacing) on top of 2-inch silicon wafers; the spaces between cylinders were filled with melted Polylactic-*co*glycolic acid.

The surface was then coated with Al or Cu by electron beam deposition and lithographically patterned as 900 _ 9,000 _m rectangular masks asymmetrically positioned with multiple cylinders located under the wide edge of each mask. As described above for silicon needle fabrication, RIE was carried out such that under etch beneath the masks occurred, which provided a beveled shape at the top of each cylinder. After the remaining PLGA was removed with methylene chloride, these masters were used to make polymer micromolds.

Fabrication of Microneedle Molds

Silicon, metal, and polymer micromolds can be fabricated uniquely by using different techniques (McAllister, D. V *et al*., 2000).

Silicon micromolds

Silicon molds were made by directly etching arrays of cylindrical holes through the entire thickness of a silicon wafer by using inductively coupled plasma RIE, as described above, to generate hollow lumens for silicon microneedles. These molds were used to fabricate hollow straight walled microneedles made of metal.

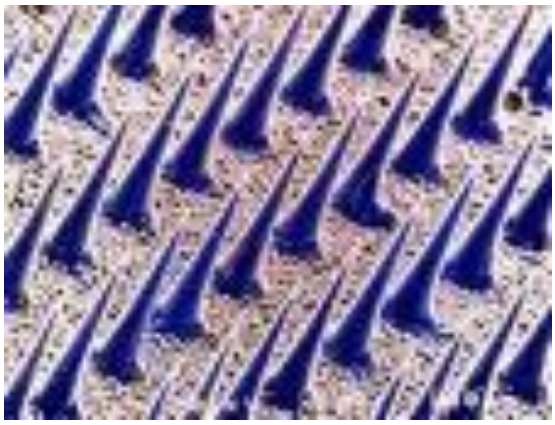

Figure 2: Array of silicon microneedles

Metal micromolds

Metal micromolds were fabricated by electroplating NiFe onto solid silicon microneedle masters. After Depositing a seed layer of Ti_Cu and covering the back side of the array with Scotch tape to protect it from being electroplated, we placed the needle master in a NiFe plating bath (200 g_liter NiSO4_H2O, 5 g_liter NiCl2_H2O, 3g_liter saccharin, 8 g_liter FeSO4_H2O, 25 g_liter H3BO3).

Plating for 6 h at 10–20 mA_cm2 provided a 50- to 100-_m coating of NiFe. Complete removal of the silicon master by reactive ion etching (as above) yielded a NiFe micromold suitable for making solid polymer needles by injection molding.

Polymer micromolds for solid needles

Polymer micromolds were fabricated by a number of different methods. In one approach, polydimethylsiloxane (PDMS) micromolds were fabricated from silicon or polymer masters. A mold was formed by coating a microneedle master with silicone oil, pouring a layer of PDMS, up to 8 mm thick onto the master, applying vacuum to remove any entrapped air bubbles, curing at 90°C for 1 h, cooling, and gently peeling off the mold.

These molds were used to fabricate solid microneedles from both another approach involved spin casting SU-8 epoxy onto a glass slide at a thickness that was _50 _m taller than the height of the microneedle master. After

inserting the master into the epoxy, the epoxy was cured by baking on a hotplate and exposure to UV light. Complete removal of the silicon master by RIE (as above) yielded a polymer mold suitable to make solid metal microneedles by electroplating.

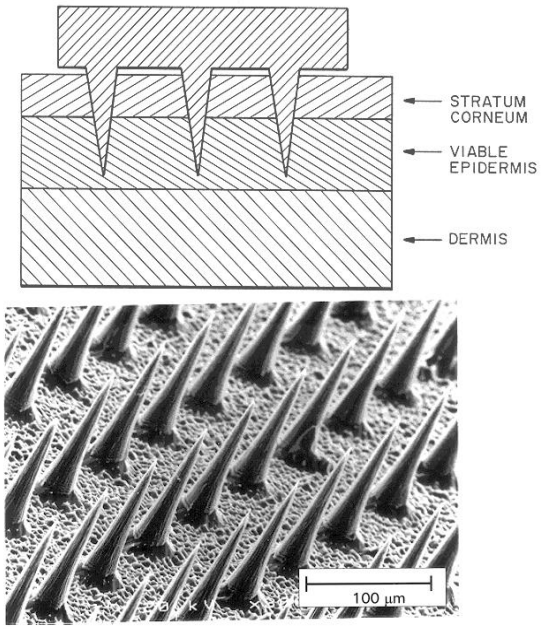

Figure 3: Solid metal microneedles

Polymer micromolds for hollow needles

To make molds for hollow metal microneedles based on silicon masters, SU-8 epoxy was spun on at a thickness slightly taller than the microneedle master, cured by baking and exposure to UV light, and then etched back in an O2_CHF3 plasma RIE to expose the tips of the silicon microneedle master. The samples were then flipped over and etched by SF6 plasma RIE to remove all of the silicon. The resulting polymer mold had conical holes bored completely through, suitable to make hollow metal microneedles by electroplating.

Molds for hollow metal microneedles were also made without the need for microneedle masters (McAllister, D. V., Cros,F *et al*., 2000). Straight-walled molds were made by spin coating SU-8 Epoxy onto a silicon wafer or glass slide coated with a 100-nm layer of titanium.

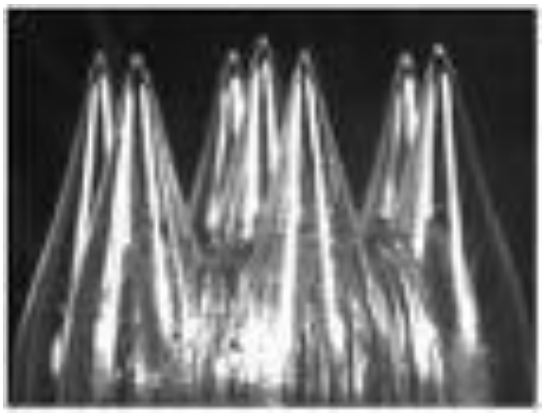

Figure 4: Hollow microneedles

After soft baking, an array of holes was lithographically patterned into the epoxy, which was then baked after exposure and developed in trichloroethylene. The mold was separated from the substrate by etching the titanium layer with hydrofluoric acid (5%), which yielded a polymer mold with cylindrical holes bored completely through, suitable for electroplating hollow metal microneedles with straight walls.

To fabricate hollow metal microneedles with tapered walls without the need for masters, polymer molds were formed by drilling holes of the desired geometry into polyimide or polyethylene terephthalate sheets by using an excimer laser(Micromaster, Resonetics, Nashua, NH) (Davis,S. P *et al.*, 2003). This method yielded tapered holes bored completely through, which were used for electroplating hollow metal microneedles with tapered walls.

Fabrication of Metal Microneedles

Metal microneedles were fabricated by electrode position onto polymer or silicon micromolds sputter coated with a Ti_Cu seed layer (Davis,S. P *et al*., 2003). On hollow microneedle molds, the outer surface of the mold adjacent to the needle tips was covered with powder coating tape to protect it from being electroplated. A Ni or NiFe bath was used at a current density of 10 mA_cm2 to deposit a 5- to 50-_m-thick layer of metal to form the microneedle walls of hollow microneedles. To make solid microneedles, plating was continued until the molds were filled.

Although PDMS molds could be gentled peeled off the resulting needles, molds made of polyimide and polyethylene terephthalate were removed in an alkaline bath (1 M NaOH, boiling), silicon was removed in a 20% KOH bath, and SU-8 was removed with O2_CHF3 plasma (RIE).

Fabrication of Polymer Microneedles

Polymer microneedles were made by melting polyglycolic acid (inherent viscosity _ 1.71 dl_g), polylactic acid (1.48 dl_g) or polylactic-*co*-glycolic acid (50_50;0.49 dl_g) into PDMS micromolds at120–250°C, applying vacuum, and peeling the molds off (McAllister, D. V *et al*., 2000).

Characterization of Microneedles Containing Drug

In Vitro Release Test in Skin

To study the dissolution and release of drug in skin, microneedles encapsulating calcein were inserted into full thickness human cadaver skin and placed in a sealed chamber at 4-C. Refrigeration was used to avoid dehydration and degradation of the skin. Recognizing that skin properties and drug delivery kinetics are different at the experimental temperature of 4-C and the body temperature of 37-C, This experiment was conducted to qualitatively verify microneedle insert and that encapsulated drug is released in the skin.

After 8 h, the needles were removed and any residual calcein on the skin surface was cleaned off with wet tissue paper. The spatial profile of calcein released in the skin was then imaged by confocal microscopy (LSM 510; Zeiss, Thornwood, NY, USA). Human cadaver skin was obtained from the Emory University Body Donor Program with approval from the Georgia Tech and Emory University Institutional Review Boards.

In Vivo Microinjection Studies

The ability of microneedles to inject compounds into skin was assessed in diabetic, hairless rats by using a protocol approved by the Georgia Tech Institutional Animal Care and Use Committee. Hairless rats (healthy, male, adult, 300–400 g, Charles River Breeding Laboratories) were injected i.v. with 100 mg/kg streptozotocin (Sigma) in a volume of 700 micro litre. Over the next day, diabetes developed because of destruction of pancreatic islet cells by streptozotocin. Before microinjection studies, rats were anesthetized by i.p. injection of urethane (Sigma) and verified to have successful induction of diabetes by verifying blood glucose levels of 350–500 mg/dl.

A glass microneedle was then filled with either PBS or 100 units/ml insulin (Humulin-R) and drilled with a circular motion to a depth of 500–800 micro metre into the dorsal skin. A pressure of 10 psi (1 psi = 6.89 kPa) was applied for 30 min to inject fluid into the skin.

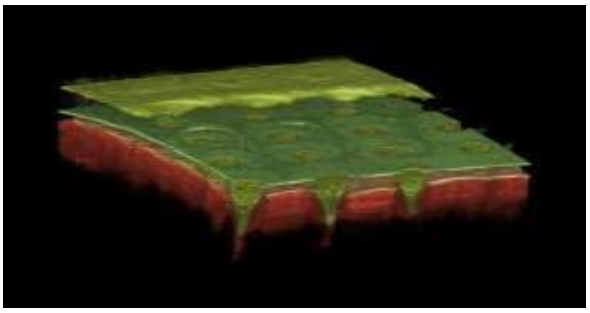

Figure 5: OCT image of microneedles penetrating the skin

Blood was collected periodically by tail vein lacertion and assayed for glucose concentration (Accu-chek Compact blood glucose meter, Roche Diagnostics).

Microneedle Failure Force Measurement

To determine the effect of calcein encapsulation on microneedle mechanical properties, the microneedle failure force was measured (S. P. Davis *et al*., 2004; J.-H.Park *et al*., 2005). Briefly, stressYstrain curves were generated using a displacement force test station while pressing an array of 35 microneedles against a stainless steel surface at a rate of 1.1 mm/s until a preset maximum load (19.6 N) was reached. Microneedles had a base radius of 100 mm, tip radius of 12 mm, and height of 1 mm. Microneedle failure was indicated by a sudden drop in applied force. After each test, microneedles were visually inspected by microscopy to confirm that all microneedles had deformed and failed uniformly. Failure force was determined at calcein contents of 0, 2, and 10% prepared using a single encapsulation method.

RECENT ADVANCEMENTS

Nanoject microneedle drug delivery system

Nanoject (Debiotech S.A *et al*.,2010) is debiotech's latest innovative nano technology, based on a patented bio compatible MEMS technology, for the design and manufacturing of microneedle arrays. This technology is intended, in particular, for the improvement of intradermal and hypodermic drug delivery and/or interstitial fluid diagnostics.

Table 1: Properties of microneedle arrays based on design

DESIGN	PROPERTIES
Extremely sharp	Robust and skin friendly
Projected side holes	Non coring during penetration
Controlled length	Pain less with low dead volume

MEMS TECHNOLOGY

Nanoject is based on MEMS (Micro Electro Mechanical System) which is an area in which debiotech has an established worldwide leading reputation within the medical field. MEMS technology leads, in particular, to extremely precise devices with very strong and excellent biocompatible properties. MEMS also allows precision in replication of microneedle from one to the next, as well as high precision and yield in the manufacture of each needle,while being compatible with large scale batch production at low cost.

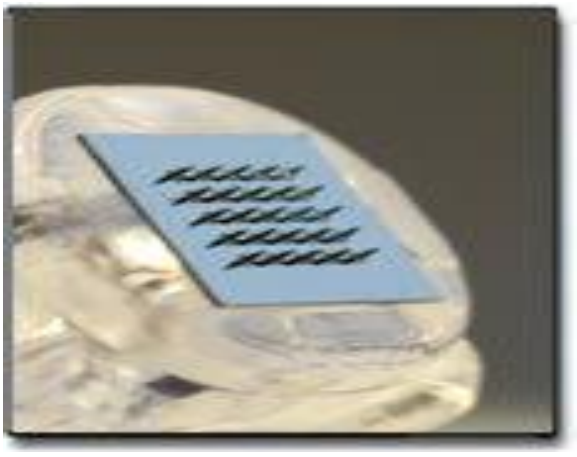

Figure 6: Nanoject: An innovative microneedle

A New pain less drug delivery and access mode

A nanoject is intended to offer a new range of totally painless drug delivery capabilities. It can be made by design, to offer unique hypodermic injection properties and functionalities while maximizing the bio availability and efficacy of certain drug substances currently delivered subcutaneously. A nanoject can also be used for the continuous extraction of interstitial fluid for diag-

nostic purposes without limitation due to coring effect currently existing with other microneedle technologies.

Sharpness and Side Holes

The nanoject is characterized by its side holes which prevents the coring effect which normally blocks the inner through whole channel of the micro-needle during skin penetration. The side hole of each nanoject is protected against any such coring while leaving the entire tip part of the needle available for a better circular penetration of the skin with unmet sharpness characteristics. Skin penetration with nanoject needles ensures minimal damage to the skin, as no tissue is removed at the insertion of the needles and eventually a better and quicker healing of the injection site.

Length and Dead Volume

The length of nanoject is designed in such a way that almost no pain is felt during the insertion of needles. The nanoject could be designed between 300 and 1'000 microns in length to avoid most pain receptors in skin. Each nanoject microneedle is equivalent to gauge 39, resulting in an important reduction of the dead volume usually found in regular needles (from microliters to nanoliters) and thus saving significant amounts of drug compound. The total fluid resistance of a nanoject patch, comprising a typical array of 25 microneedles, is not different from the one observed with an existing gauge 24 needle for subcutaneous injection.

Fields of Application

Nanoject can be used in various fields of drug delivery, from painless injection of substances to the sampling of biological fluids for diagnostics. Nanoject is particularly appropriate for intradermal delivery of vaccines, allowing significant dose reduction while increasing the immune response (e.g. one fifth of the standard intramuscular dose of influenza vaccine)

DEBIOTECH is developing this technology for immediate use, including with its various drug delivery techniques. This microneedle technology can be used in combination with the MEMS micropump for painless controlled insulin delivery.

Microneedle application for drug delivery

Unlike the application of traditional patch-based delivery systems, the application of MNs requires the assistance of external energy to ensure efficient penetration of MNs into biological tissue at desired depths. This assistance can be by either utilizing an applicator device, which serves the function of presenting the MN arrays to the biological tissue, such as skin, or by using a manual application method. Understandably, it is difficult to produce consistent penetration depths and uniform pressures by manual application methods. Incontrast, applicator devices can provide consistent penetration into biological tissue, with minimum inter-individual variability. MN arrays can either be integrated within an applicator device which, upon activation, can deliver the MN array into the skin surface, or the MN arrays can be applied to the skin and the device then activated to push the MN through the *SC*. The literature shows that these types of applicators are for either single-use or multiple-use.

Recently, various applicator designs have been disclosed, but many are in their development stage. The simplest type of single-use disposable applicator termed 'MicroCor™' was presented by Corium international ltd. In this system, the MNs are present under the surface. The applicator is applied with light finger pressure and worn for a few minutes or less and removed. Drug delivery could be quick or continuous depending on MN formulation (Cleary, GW , 2009).

Zosano's Macroflux® transdermal micro projection delivery system allows administration of therapeutic molecules from coated MNs patches, which are designed to be stable at ambient conditions. The reusable-applicator consists of an integrated MN-loaded adhesive patch which upon activation by pressing against skin surface, delivers the patch at the site of application (Zosanopharma, 2009).NanoBioSciences LLC has developed a proprietary MN shape termed Advanced microneedlePatch (ADMIN PATCH®) MN array.

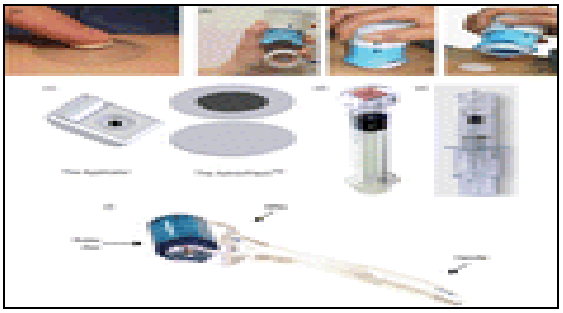

Figure 7: Macroflux® transdermal micro projection delivery system

The claimed advantages of this design are that the shape of the MN allows continuous delivery of drugs when inserted in the skin. TheMNs are formed from a standard metal film, which allows very robust and inexpensive manufacture, and a conventional transdermal drug-in-adhesive patch can be simply laminated on the back surface of the ADMINPATCH® MN array (Nanobiosciences, 2009).

Nano Pass Technologies Ltd designed the MicronJet® MN device, which consists of hollow type MNs mounted on a standard syringe barrel. This system requires minimal expertise for intradermal delivery of therapeutic molecules. The MicronJet® MN device contains an array of 'Micro Pyramids', each less than 500 high.

Similarly, BD Soluvia™ described a prefillable microinjection system that is integrated with a miniature BD™ MN. This device is similar in appearance to hypodermic syringes. However, the needle height is much shorter (BD, 2009).

BD Soluvia™ claim that the MN system is barely perceptible, safe, easy to use, and showed reproducible injections to the dermal layer, irrespective of the subject's gender, age, ethnicity, and body mass (Laurent et al., 2007 a; b).

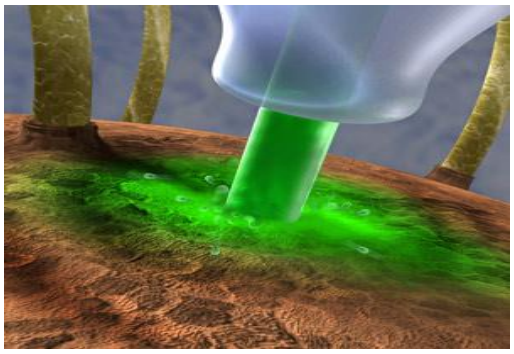

Figure 8: MicronJet® MN device

The Microneedle Therapy System (MTS)-Rollers™ from Clinical Resolution Laboratory Inc. Uses steel MNs with heights ranging from 0.2–2.0 mm mounted onto radial discs. The discs are held together with the help of handle. This discs-integrated MN roller is then rolled over the skin surface to produced micropores. This technology is, at present, available in different models, as for personal use, for medical use, and for clinical use. They are used in treating alopecia, skin 'restoration', active ingredient delivery, and various other cosmetic applications (Microneedle, 2009),similar to the MTS-Rollers™.

Figure 9: Micro Needle Roller 1.5mm OEM (Dermaroller)

Nanogen is marketing Scalproller™, a specially designed roller to help treat thinning hair (Nanogen, 2009).

Figure 10: Scrap roller with titanium microneedle 0.3mm

The Scalproller™ uses titanium needles unlike the steel needles used in MTS-Rollers.

CONCLUSION

In conclusion, practical microfabrication techniques were developed to yield silicon, metal, and polymer microneedles of micrometer dimensions in various geometries. Solid microneedles were shown to pierce skin and thereby increase skin permeability by orders of magnitude to levels that may permit clinical delivery of macromolecules across skin. Together, these results suggest that microneedles are a useful approach to transdermal drug delivery. Many people, particularly children, are 'needle-phobes'. In addition, there are several patients, such as diabetics who are dependent on multiple injections on a daily basis. Many other disease conditions also require the delivery of therapeutic agents to the skin, while the outbreak of a pandemic would necessitate mass vaccinations. A solution to the problems posed by needlebased injections is the development of micro needles. This technology will help realize the development of new and improved devices, which will be smaller, cheaper, pain-free and more convenient with a wide range of biomedical and other applications. The future of drug delivery is assured to be significantly influenced by micro fabrication technologies. These micro fabricated drug delivery devices can enable efficient drug delivery that was unattainable with conventional drug delivery techniques, resulting in the enhancement of the therapeutic activity of a drug.

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