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Microneedles and transdermal drug delivery: A review

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Abstract

Advances in the processing of materials on a micro-scale have led to the development and introduction of devices that employ very small needles. That has significant potential in devices for diagnostics, healthcare monitoring and drug delivery by mechanically perforating the outer skin layer and allowing for transdermal drug absorption or fluid sampling. These processing techniques incorporate one or more technologies that enable the precise machining, extrusion, casting, and/or forming of from one to an array or grid of microneedles. Evolving microneedle systems will be well positioned to address a significant segment of the large molecule biological drugs expected to emerge from the convergence of automated discovery and genome mapping. To overcome the problems of oral route skin has been extensively studied as an alternative route of drug delivery. Skin is a large and easily accessible organ that can be readily used to administer drugs into the blood capillaries lying just tens of microns beneath the skin's surface. Despite the advantages offered by skin for drug delivery, clinical drug delivery through the skin is severely limited by the presence of the top most layers of dead cells called the stratum corneum. This layer is just 10-20 μm in depth, but is the rate-limiting barrier and only allows low molecular weight molecules with moderate oil and water solubility to diffuse through. This in turn restricts the drugs that can be delivered via the skin into a very narrow range. As a result, presently only thirteen active molecules are approved for delivery through the skin by the Food and Drug Administration.

Keywords: Microneedles, stratum corneum, hypodermic needles, microelectromechanical pump.

INTRODUCTION

The success of transdermal drug delivery has been severely limited by the inability of most drugs to enter the skin at therapeutically useful rates. Recently, the use of micron-scale needles in increasing skin permeability has been proposed and shown to dramatically increase transdermal delivery, especially for macromolecules. Using the tools of the microelectronics industry, microneedles have been fabricated with a range of sizes, shapes and materials. Most drug delivery studies have emphasized solid microneedles, which have been shown to increase skin permeability to a broad range of molecules and nanoparticles in vitro. In vivo studies have demonstrated delivery of oligonucleotides, reduction of blood glucose level by insulin, and induction of immune responses from protein and DNA vaccines. For these studies, needle arrays have been used to pierce holes into skin to increase transport by diffusion or iontophoresis or as drug carriers that release drug into the skin from a microneedle surface coating. Hollow microneedles have also been developed and shown to microinject insulin to diabetic rats. To address practical applications of microneedles, the ratio of microneedle fracture force to skin insertion force (i.e. margin of safety) was found to be optimal for needles with small tip radius and large wall thickness. Microneedles inserted into the skin of human subjects were reported as painless. Together, these results suggest that microneedles represent a promising technology to deliver therapeutic compounds into the skin for a range of possible applications. Microneedles find widespread use; researchers must perfect the techniques for optimally inserting them into the skin, and complete the integration of microneedles into a full diagnostic, monitoring or drug delivery system [1-4]. Microneedles are expected to be less painful than conventional hypodermic needles because they are too small to significantly stimulate nerve endings. Before microneedles find widespread use, the researchers must perfect the techniques for optimally inserting them into the skin, and complete the integration of microneedles into a full drug delivery system. The need to minimize variability in needle insertion is being addressed in part by development of an applicator device that would be part of the delivery system. A painless "microneedle" that mimics the way a female mosquito sucks blood has been built by engineers in India and Japan[5].

Design and Mechanism of Working

The needle could be used to draw blood, inject drugs, and as a glucose-level monitor for diabetics. A female mosquito sucks blood by flexing and relaxing certain muscles in its proboscis. This creates suction (or negative pressure) that draws blood into its mouthparts. The new biocompatible microneedle, designed by Suman Chakraborty of the Indian Institute of Technology in Kharagpur and Kazuyoshi Tsuchiya of Tokai University in Kanagawa is based on the same principle. In this case, the sucking action is provided by a microelectromechanical pump, which works using a piezoelectric actuator attached to the needle[6-7].

Current Research in Microneedles Technology

The first microneedle arrays reported in the literature were etched into a silicon wafer and developed for intracellular delivery in vitro by Hashmi et al. These needles were inserted into cells and nematodes to increase molecular uptake and gene transfection. Henry et al. conducted the first study to determine if microneedles could be used to increase transdermal drug delivery. An array of solid Microneedles was embedded in cadaver skin, which caused skin permeability to a small model compound. In a follow-up study, McAllister et al.[14] studied permeability of cadaver skin to a range of different compounds and found that insulin, bovine serum albumin, and latex nanoparticles as large as 100 nm in diameter could cross the skin after treatment withmicroneedles. Mathematical modeling of the data indicated that transport of these compounds was by simple diffusion. Extending in vitro findings to the in vivo environment, Lin et al. used microneedles either alone or in combination with iontophoresis to deliver 20-mer phosphorothioated oligodeoxynucleotides across the skin of hairless guinea pigs[8-12]. A related study further demonstrated microneedle enhanced delivery of desmopressin and human growth hormone using a similar approach.

Using solid microneedles of a different design, Martanto et al., Delivered insulin to diabetic hairless rats *in vivo*. Microneedle arrays were inserted into the skin using a high-velocity injector and shown by microscopy to embed fully within the skin. Matriano et al. examined the use of Microneedles to deliver ovalbumin as a model protein antigen coated onto the needle surface. Microneedles were prepared with a dry-film coating of antigen and then inserted into the skin of hairless guinea pigs in vivo using a high-velocity injector. Mikszta et al. studied delivery of naked plasmid DNA into skin using microneedles. The arrays were dipped into a solution of DNA and scraped multiple times across the skin of mice in vivo to create microabrasions. A variety of hollow microneedles have been fabricated, but only limited work has been published on their possible use to deliver compounds into skin. McAllister et al. used single glass Microneedles inserted into the skin of diabetic hairless rats in vivo to deliver insulin during a 30-min infusion. In related studies, Stoeber and Liepmann demonstrated injection into chicken thigh in vitro using microneedle arrays. Chen and Wise used microneedles to inject chemical stimuli into brain tissue in vivo. Smart and Subramanian used single microneedles to extract nanoliter quantities of blood from the skin to measure glucose levels[13-16]. Kaushik et al carried out a small trial to determine if microneedles are perceived as painless by human subjects. Microneedle arrays were inserted into the skin of 12 subjects and compared to pressing a flat surface against the skin (negative control) and inserting a 26-gauge hypodermic needle into the skin surface (positive control). Subjects were unable to distinguish between the painless sensation of the flat surface and that caused by microneedles. All subjects found the sensation caused by the hypodermic needle to be much more painful. Other studies have also reported that microneedles were applied to human subjects in a painless manner.

Several new and interesting microneedle concepts have been recently proposed which may find great utility in the future. For example, biodegradable polymer microneedles have recently been fabricated and characterized. The advantage of polymer needles is that they may be produced much more inexpensively (compared to silicon) and they should not pose a problem if they break in the skin since they are biodegradable[17-20]. This study addresses microneedles made of biocompatible and biodegradable polymers, which are expected to improve safety and manufacturability. To make biodegradable polymer microneedles with sharp tips, micro-electromechanical masking and etching were adapted to produce beveled- and chisel-tip microneedles and a new fabrication method was developed to produce tapered-cone microneedles using an in situ lens-based lithographic approach. Gill et al (2007) have been studied on coating of Microneedle.

A novel micron-scale dip-coating process and a GRAS coating formulation were designed to reliably produce uniform coatings on both individual and arrays of microneedles. This process was used to coat compounds including calcein, vitamin B, bovine serum albumin and plasmid DNA. Modified vaccinia virus and microparticles of 1 to 20 μm diameter were also coated. In conclusion, this study presents a simple, versatile, and controllable method to coat microneedles with proteins, DNA, viruses and microparticles for rapid delivery into the skin.25 Recently Lee et al (2008) has studied on dissolving microneedles for transdermal drug delivery. This study presents a design that encapsulates molecules within microneedles that dissolve within the skin for bolus or sustained delivery and leave behind no biohazardous sharp medical waste[20-25]

New Microneedle Inspired by Mosquito

Joint collaboration between the Indian Institute of Technology Kharagpur and Tokai University of Japan has resulted in a new hypodermic microneedle, which does not come with an iota of pain. This is due to the fact that it was designed after a mosquito's unique micro-electro-mechanical based suction system. This new design has a diameter of 60 microns, which is way smaller than a conventional needle that currently stands at 900 microns, and is hoped to be developed further for use in glucose monitoring, blood draws, insulin pumps and other drug delivery devices [26-28].

Proboscis-Mimicking Microneedle for Drug Delivery

Precise control over the fluidic transport and the ability to scale down the analysis to very small volumes of liquid are among the most attractive capabilities of these novel health care approaches. Such concepts provide excellent promises in revolutionizing health care protocols for the future, with the possibilities of developing substantially improved and patient-friendly health monitoring systems." The needle has been designed to mimic a mosquito's proboscis in dimensions, the manner that suction is created and rate of flow. As it has an external diameter of only 60µm, as opposed to 900µm for conventional syringes, the microneedle is said to be painless. Microneedles with similar dimensions have been created previously but have primarily been fabricated from silicon dioxide that rendered them brittle making them liable to snap, which could potentially cause a blood clot. This latest model in the needle's development is crafted from titanium and related alloys, giving it the strength needed to administer therapeutics without the risk of snapping. It is capable of penetrating 3mm under the skin to administer therapeutics into the capillaries or extract blood [29-33].

Among the potential applications

Arrays of hollow needles could be used to continuously carry drugs into the body using simple diffusion or a pump system; Hollow microneedles could be used to remove fluid from the body for analysis such as blood glucose measurements and to then supply micro liter volumes of insulin or other drug as required; Microneedles may prove useful for immunization programs in developing countries, or for the mass vaccination or administration of antidotes in bioterrorism incidents because they could be applied by persons with minimal medical training. Very small microneedles could provide highly targeted drug administration to individual cells.

Advantages of Microneedles

The major advantage of microneedles over traditional needles is, when it is inserted into the skin it does not pass the stratum corneum, which is the outer 10-15 µm of the skin. Conventional needles which do pass this layer of skin may effectively transmit the drug but may lead to infection and pain. As for microneedles they can be fabricated to be long enough to penetrate the stratum cornea, but short enough not to puncture nerve endings. Thus reduces the chances of pain, infection, or injury. By fabricating these needles on a silicon substrate because of their small size, thousands of needles can be fabricated on a single wafer. This leads to high accuracy, good reproducibility, and a moderate fabrication cost5. Hollow like hypodermic needle; solid—

increase permeability by poking holes in skin, rub drug over area, or coat needles with drug6. Arrays of hollow needles could be used to continuously carry drugs into the body using simple diffusion or a pump system [34-37]. Hollow microneedles could be used to remove fluid from the body for analysis – such as blood glucose measurements and to then supply micro liter volumes of insulin or other drug as required . Immunization programs in developing countries, or mass vaccination or administration of antidotes in bioterrorism incidents, could be applied with minimal medical training. Very small microneedles could provide highly targeted drug administration to individual cells. These are capable of very accurate dosing, complex release patterns[38].

Different types of microneedles

Hollow Metal Microneedles for Insulin Delivery to Diabetic Rats:
The goal of this study was to design, fabricate, and test arrays of hollow microneedles for minimally invasive and continuous delivery of insulin in vivo.

Electrically Conductive Micro needle Roller:
An electrically conductive micro needle roller includes stacked discs, each of which includes a plurality of radial grooves, a plurality of micro needles that are received in the radial grooves of the disc, an electrically conductive bracket that supports the stacked discs, and a handle that supports the bracket. Electric current flows to the skin via the micro needles and provides electric stimulation. The discs are assembled using UV bond thereby reducing the assembly time. The roller has enhanced service life since the micro needles do not fall off from the roller since radial grooves holding the micro needles have tapered shape.

Collagen Induction Therapy with the Micro needle Derma roller:
The Micro needle Derma roller is a small plastic roller studded with about 200 extremely fine needles of medical grade stainless steel. The skin reacts to these pricks like it reacts to any other wound with the formation of the various growth factors. This process of stimulating collagen tissue production is a normal physiological reaction and is known as Collagen Induction Therapy (CIT).

A Selection of Micro needle Resources
Micro needle Therapy System: MTS-Roller: The Micro needle Therapy System (MTS) is a breakthrough device, simple in concept but yielding magnificent results for the human skin. The MTS consists of a series of devices, which have both cosmetic and medical applications. Their mechanism of action is through the painless piercing of the stratum.

The Derma roller: The Derma roller is the most effective device for deep transdermal Delivery of active substances through the epidermal barrier (stratum corneum).

Skin Care Review: Derma roller: Skin care and rejuvenation information and reviews based on published research and other independent sources.

The Derma roller: The Collagen-Induction-Therapy with the CITDERMAROLLER is a perfect alternative to achieve the same goal: a new collagen-layer on the dermis. The Leaf and Rusher

Derma Roller is a unique rolling device that significantly enhances the action of the Leaf and Rusher Treatment System.

MTS Micro needle Derma roller: Micro channel formation enhances product penetration and stimulates collagen production for rejuvenation and treatments of acne scars and stretch marks.

CIT-findings: The Collagen-Induction-Therapy (CIT) with the needling device called DERMA ROLLER%u2122 is a fairly new procedure for the stimulation of new collagen fibers

Microneedles: The Option for Painless Delivery: Transdermal drug delivery is limited by the extraordinary barrier properties of the stratum corneum, the outer 10-15 mm of skin. Conventional needles inserted across this barrier and into deeper tissue effectively deliver drug, but can lead to infection and cause pain, thereby reducing patient compliance**.** The biomedical industry seeks to replace stainless steel hypodermic injection needles with needles that have smaller diameter and sharper tips, to minimize pain and tissue damage. Since the dawn of microelectronic processing, electronic devices have been fabricated to smaller and smaller scales on a silicon substrate.

As technology improves and smaller devices are created with more robust processes, the complexity of these devices will increase. In the meantime, non-implantable devices, such as the microneedles, are proving to be useful and worthwhile. For over 150 years, syringes and hypodermic needles have been utilized to deliver drugs into patients.1 Because of the transport barriers that exist in other delivery routes; injection is still a prominent method for drug delivery today. Currently, the smallest needles that are commercially available for injections are 30 gauges for conventional syringes and 31 gauge for pen injectors, which are utilized mainly for insulin delivery. The 30 and 31 gauge needles have outer diameters of 305 and 254 um, respectively.

Micro fabrication has been utilized to create micro needles, which are orders of magnitude smaller in diameter, capable of localized and painless delivery of drugs into cells or tissues. Research into the application of micro needles for gene and drug delivery has been divided into three broad areas: cellular delivery, local delivery and systemic delivery. Until very recently, the only drugs that could permeate transdermally were those possessing a very narrow and specific combination of physicochemical properties. However, rapid advances in bioengineering have led to the emergence of various new “active” enhancement technologies designed to transiently circumvent the barrier function of the stratum corneum. These novel systems, using iontophoresis, sonophoresis, electroporation, or microneedles arrays, will greatly expand the range of drugs that can be delivered transdermally. Crucially, the delivery of macromolecules will become possible and the transdermal flux of other molecules could be enhanced by several orders of magnitude. Micro needles are somewhat like traditional needles, but are fabricated on the micro scale. They are generally one micron in diameter and range from 1-100 microns in length. Micro needles have been fabricated with various materials such as: metals, silicon, silicon dioxide, polymers, glass and other materials. An example of micro needles, which was fabricated by creating micron-sized holes on a silicon substrate and by using a KOH solution to create the needle shape**.** Various types of needles have been fabricated as well, for example: straight, bent, filtered, and hollow[39-44].

CONCLUSION

Many people, particularly children, are 'needlephobes'. In addition, there are several patients, such as diabetics who are dependant 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 needle-based 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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