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Review Article

MICRONEEDLES IN TRANSDERMAL DRUG DELIVERY: AN UNIQUE PAINLESS OPTION

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ABSTRACT
The outermost layer of skin, the stratum corneum, has developed unnerving physical and immunological barrier properties that prevent infiltration of noxious chemicals and pathogens. Consequently, transdermal delivery of medicaments is currently restricted to a limited number of low molecular weight drugs to enter the skin at successful therapeutic rates. As a result, there has been significant recent interest in providing strategies that disrupt or dodge the principal physical barrier, the stratum corneum, for the efficient cutaneous delivery of macromolecular and nucleic acid based therapeutics. 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, micro-needles have been fabricated with a wide range of sizes, shapes and materials. These strategies include: Micro-needles, Macroflux ®. A micro-needle-based drug delivery system is pain free administration, easy to use, discrete, continuous and controlled release system. This review compile the current advancement and literature regarding the fabricated micro-needles used for enhancing Transdermal Drug Delivery System and other structure based techniques.
KEYWORDS: Transdermal Drug Delivery, Micro-needle, Macroflux, Microelectromechanical Systems (MEMS)

INTRODUCTION

Transdermal drug delivery is the delivery of drug across the intact skin into systemic circulation. It is a device which provides an alternative route for administering medication. Nowadays, the transdermal route has become one of the most successful and innovative focus for research in drug delivery, with around 40% of the drug candidate being under clinical evaluation related to transdermal or dermal systems. The technology has a proven record of FDA approval since the first transdermal patch was approved in 1981[1]. However, the efficiency of transdermal delivery is greatly limited by the poor permeability of the hard layer of skin at the stratum corneum which is the outmost layer of skin that forms the primary transport barrier[2]. The rate of diffusion also depends in part on the size and hydrophilicity of the drug molecules. So far, a number of chemical enhancers, electroporation, physical enhancers have been proposed to promote the transdermal drug delivery[3,4]. As one of the enhancers, the micro-needle array devices have been well developed for controlled transdermal drug delivery in a minimum invasion and convenient manner[5,6]. The micro-needles are used to penetrate the stratum corneum and generate pathways or micro-channels, so as to deliver drugs into the epidermis layer. No pain is induced as the needles do not reach the nerves in deep dermis.

Advantage of Transdermal Drug Delivery System (TDDS)

The advantages of transdermal delivery over other delivery modalities are as follows:

• Avoidance of 'first-pass' metabolism of drugs and providing a large surface area and ease of accessibility for drug administration.
• Peak plasma levels of drugs are reduced, leading to decreased side effects.
• Reduction of fluctuations in plasma levels of drugs.
• Utilization of drug candidates with short half-life and low therapeutic index [7].
• Easy termination of drug delivery in case of toxicity.
• Reduction of dosing frequency and enhancement of patient compliance [8].

Different chemical and physical methods like chemical enhancers, ultrasound, electric energy, pressure driven flow, and lasers have been tried to disrupt the mass transfer resistance barrier of stratum corneum to deliver larger molecular weight and/or hydrophilic compounds. However, these methods have found limited success. 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. Micro-needles have been shown to increase transdermal flux of large molecular weight compounds by many folds. One of the ways in which this is achieved is to coat the compound onto micro-needle shafts and insert them into the skin where they deposit their payload.

Advantages of Micro-needles

1. The major advantage of micro-needles over traditional needles is, when it is inserted into the skin it does not pass the stratum corneum, which is the outer 10-15μm of the skin[9]. Conventional needles which do pass this layer of skin may effectively transmit the drug but may lead to infection and pain. As for micro-needles they can be fabricated to be long enough to penetrate the stratum corneum, but short enough not to puncture nerve endings. Thus reduces the chances of pain, infection, or injury.
2. 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 cost[10].
3. Hollow like hypodermic needle; solid-increase permeability by poking holes in skin, rub drug over area, or coat needles with drug[11].
4. Arrays of hollow needles could be used to continuously carry drugs into the body using simple diffusion or a pump system[12].
5. Hollow micro-needles 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[12].
6. Immunization programs in developing countries, or mass vaccination or administration of antidotes in bioterrorism incidents, could be applied with minimal medical training.
7. Very small micro-needles could provide highly targeted drug administration to individual cells.
8. These are capable of very accurate dosing, complex release patterns, local delivery and biological drug stability enhancement by storing in a micro volume that can be precisely controlled[13]. Some recently approved Transdermal drug delivery systems are given in Table 1. Several new active transport technologies have been developed for the transdermal delivery of 'troublesome' drugs (Flow chart 1) as the development of modified novel physical techniques have overcome the limitations of chemical enhancement techniques[14,15].

Micro-needles for Drug Delivery Applications

In recent years, attention has been drawn to a new type of delivery method where arrays of miniaturized needles are used to penetrate the skin layer. A micro-needle is a needle with representative parts (e.g. diameter) on the micrometer length scale. Since the needles are short, they do not reach the nerve-rich regions of the lower parts of the skin. As a consequence, the stimulus caused by micro-needle insertion into the skin is weak and perceived as painless[16, 17]. Micro-needle has all the favorable properties i.e. continuous release, ease-of-use, unobtrusiveness and painlessness.

Types of Micro-needles

A classification for micro-needles usually used in literature is based on the fabrication process i.e. in-plane or out-of-plane micro-needles.

a) In-plane microneedles[18] are fabricated with the shaft being parallel to substrate surface. The advantage of in-plane micro-needles is that the length of the needle can be very accurately controlled and disadvantage is that it is difficult to fabricate two-dimensional arrays.

b) Out-of-plane microneedles[19]on the other hand, protrude from the substrate and are straightforward to fabricate in arrays. Another useful point of distinction is whether the micro-needles are solid or hollow. Hollow needles with a needle bore, or lumen, allow an active liquid transport through the micro-needle.

Micro-needles For Drug Delivery

The concept of an array of miniaturized needles for drug delivery purposes essentially dates back to 1976 and a patent filed in the year 1971 (Gerstel and Place at Alza corp)[20]. In this patent, a drug delivery device featuring miniaturized projections (i.e. micro-needles) and a drug reservoir is claimed. The needles are small enough to penetrate only the stratum corneum and can be either solid or hollow. Delivery from the device may occur through diffusion or through convection by applying a force on the backing of the reservoir.

Micro-fabrication techniques, evolving strongly in 1900s, enabled these micrometer-sized needles to be precisely fabricated in a potentially cost-effective manner. Given the

governing goal to deliver a substance across the skin for subsequent systemic distribution, and the means (micro-needles), several possible strategies can be employed to accomplish this. The simplest way, as also proposed by the early vaccinations strategies mentioned above, is to perforate the skin with micro-needles and then apply the drug onto the skin for subsequent diffusive spread into the body. The drug can be applied to the skin surface as a gel or through a medicated patch to achieve prolonged release. Another way is to pre-coat the micro-needles with the drug before they are inserted into the skin. A third option is to fabricate the micro-needles in a biodegradable material that incorporates the drug[21]. When the needles are inserted into the skin, they dissolve and the drug is subsequently released. If the micro-needles are hollow, the drug can be actively injected into the tissue. Hollow needles can also be used with passive and diffusion-driven, delivery. In that case, the needles merely functions as controlled and sustained paths or channels into the body.

A few but basic requirements for micro needles can be defined:

Suited To The Purpose: For micro-needles to function properly the needles need to have a certain length and certain sharpness, and they should be fabricated in a material which can withstand the forces of matter[22].

Batch Compatible: As a minimally invasive medical device, micro-needles for drug delivery will need to be disposable, single-use, devices to gain acceptance in medical practice. Hence, for general drug delivery applications such as vaccinations or insulin delivery, fabrication methods need to be batch compatible to be commercially competitive[23].

Biocompatible: Micro-needles are designed to be inserted into human tissue and as such they need to be compatible with the local environment, both in terms of toxicity and intended function. The duration of contact with the tissue range from minutes to days at the most (insulin infusion-sets are typically changed every third day). Hence, if the material is non-toxic in the short term, malfunctioning due to biological host response through e.g. biofouling is unlikely to occur. For hollow micro-needles there is a risk of blocking the needle bore with cored tissue during insertion into the skin. Concerning toxicity, well-known, bio-inert, materials such as titanium, stainless steel or gold, or biodegradable polymers such as PLGA (polylactic-Co-glycolic acid), may be used with confidence as micro-needle material[24].

MEMS

Microelectromechanical Systems (MEMS) or Microsystem Technology (MST) refers to devices with sub-millimeter features. MEMS extend the fabrication techniques developed at the microelectronics industry to add mechanical structures onto micro devices. Typical MEMS devices are various sensors, e.g. pressure, flow, acceleration sensors; microfluidic systems such as ink-jet print heads or chemical analysis systems, or micromechanical devices such as micromirror arrays or microswitches.

Characteristic attributes of MEMS fabrication are miniaturization, parallelization and integration. Miniaturization allows fabrication of compact and energy-efficient, fast-responding, devices. Parallelization refers to batch fabrication methods inherited from the microelectronics industry in which thousands or millions of devices are concurrently produced. Integration refers to monolithic integration of electronics and to packaging techniques.

General Fabrication Techniques

Typical MEMS fabrication techniques include very precisely controlled deposition and etching of materials. By utilizing differences in selectivity to the etchant between different types of materials, structures can be formed in a controlled manner. The structures to be fabricated are defined by a two-dimensional pattern. This pattern is transferred from an original photomask to a photosensitive film on a substrate by photolithography. The substrate is typically a silicon wafer with a thickness of 300–700μm. Also in case that polymer replicated microdevices are desired, a common method is to fabricate the master device in silicon due to the precision achievable through silicon micromachining. Once a structure is defined on the substrate, materials can be etched with respect to each other. By consecutively redepositing, patterning and etching materials, intricate three-dimensional structures may be created. Common techniques to add material to the substrate are spin coating, physical vapor deposition (e.g. evaporation or sputtering) or chemical vapor deposition (CVD). Etching may be accomplished through wet etching (dipping into liquid solution) or dry, plasma-based, etching. In plasma-based etching a gas is excited into a reactive state, enabling reactions between the gas and the substrate to take place. By controlling the gas pressure, the relative amount of ions over reactive radicals can be adjusted, which in turn affects the degree of isotropy of the etch. An electric field (bias) may accelerate the ions and further increase the directivity

of the etch. Such an anisotropic plasma-based etch is referred to as Reactive Ion Etching (RIE).

Solid Micro-needle Arrays

One of the first micro-needle arrays for drug delivery, although not transdermal, was presented 1993 by Dizon et al[25]. The array, featuring pyramidal-shaped silicon spikes at densities of thousands per square centimeter represents one of the most basic designs of micro-needles. The needles are etched in potassium hydroxide (KOH) solution and the geometry is defined by controlled undercutting of the etch mask in combination with the anisotropic etch rates in monocrystalline silicon. Through the controlled etch (with intersecting crystal planes), the needles have an extremely sharp apex with a tip radius below 100 nm[26]. The array was used to transfect cells by coating the needles with foreign DNA before pressing the array onto cell cultures. Successful delivery of DNA into tobacco leaf cells[26] and animal nematode cells were demonstrated[27].

In 2001, the first delivery results using micro-needle arrays *in vivo* were published. A research group at Alza corp. reported successful intra-dermal delivery of oligodeoxy-nucleotide (20 bases) into hairless guinea pigs using a micro-needle array made of stainless steel[28]. The array, called Macroflux, was fabricated by etching the needle contour through a 30μm stainless steel foil followed by a 90° raise, to realize out-of-plane projections[29]. Using a 2 cm^2 array featuring 480 micro-needles, 430μm long, up to 14 mg/day of the substance could be delivered. It was found that a configuration with the needles inserted into the skin, with the drug in close contact to the array, gave a better drug uptake than if the drug was placed on bare micro-needle-perforated skin. The micro-needle array was manually inserted to the skin using finger force.

Macroflux® technology is another novel transdermal drug delivery system that ALZA Corporation has developed to deliver biopharmaceutical drugs in a controlled reproducible manner that optimizes bioavailability and efficacy without significant discomfort for the patient.

Three types of Macroflux ® have been designed and tested in preclinical studies. They include-

• *Dry-Coated Macroflux* ® system for short duration administration that consist of a drug coated microprojection array adhered to a flexible polymeric adhesive backing.

• *D-TRANS® Macroflux® system* for short duration administration that consist of a microprojection array coupled with a drug reservoir.

• *E-TRANS® Macroflux* ® system for pulsatile or on demand delivery that include a microprojection array coupled with an electrotransport system[30]. Therapeutic peptides, proteins and vaccines such as desmopressin, human growth hormone (HGH), TH 9507 (a human growth hormone releasing factor analog), ovalbumin (45000 Da protein) are in the developmental stage for transdermal delivery by Macroflux®[31].

Hollow Micro-needle Arrays

In contrast to solid micro-needles, hollow needles offer the possibility of active injection of the drug into the tissue. The apparent advantage of this is that a considerably larger amount of drug can be delivered for a given time, thus opening for applications where relatively large amounts are needed to obtain a therapeutic effect. Additionally, pressure-driven delivery adds the possibility to precisely steer the flow rate and to obtain a more controlled delivery. The first hollow out-of-plane micro-needles was presented by McAllister et al. in 1999[32]. By combining the fabrication process of solid silicon micro-needles with the Bosch process to form a needle bore, 150 μm long hollow micro-needles and microtubes could be fabricated. It also describes the fabrication of hollow metal micro-needles which were produced by a lost-mold technique, where the needles were electroplated. Solid silicon needles were used as the mold insert to facilitate the bore. These nickel-iron needles had a bore opening of 10μm in diameter and were shown to penetrate epidermal tissue *in vitro*.

Applications of Micro-needles

Micro-needles have been used in many different applications, ranging from neuro stimulation to gene delivery into individual cells. A common objective is to create a pathway to an object by physically circumventing some kind of barrier. Some of the applications are stated below:

1) Blood Glucose Measurements

Glucose self-testing by diabetics represents the largest single potential market. Kumetrix has designed a silicon-based "micro-needle" with a diameter smaller than that of a human hair, enabling diabetics to withdraw blood painlessly. To take a measurement, a patient will load the cartridge into the electronic monitor and simply press the monitor against the skin. This action will cause the micro-needle to penetrate the skin and draw a very small volume of blood (less than 100 nanoliters) into the disposable cartridge. Chemical reagents in the disposable cartridge react with the glucose in the blood to produce a color. The blood-glucose concentration will be measured either electrochemically or optically, and the resultant value will be displayed on the monitor. These micro-needles/probes penetrate human skin reliably and painlessly, and can be

used in instruments for single-use or continuous monitoring of analytes in blood[33].

2) Drug Delivery To The Eye

Solid metal micro-needles measuring 500 to 750 μm in length were coated with model drugs, protein, and DNA; inserted into non preserved human cadaveric sclera; and imaged. Micro-needles coated with sodium fluorescein were then inserted into rabbit cornea in vivo. After needle removal, fluorescein concentration in the anterior segment of the rabbit eye was measured for 24 hours. Similar experiments were performed using pilocarpine-coated micro-needles, and the rabbit pupil size was monitored afterward. In vitro insertion tests showed that micro-needles were mechanically strong enough to penetrate into human cadaveric sclera and that the drug coating rapidly dissolved off the needles within the scleral tissue within 30 seconds after insertion. In vivo delivery from fluorescein-coated micro-needles showed that fluorescein concentrations in the anterior chamber were 60 times greater than those achieved by topical application without micro-needles. Similarly, micro-needle delivery of pilocarpine caused rapid and extensive rabbit pupil constriction. There were no measurable inflammatory responses caused by micro-needle insertion. This study demonstrated for the first time that coated micro-needles can deliver drugs into the eye via intrascleral and intracorneal routes. This minimally invasive approach may avoid the complications associated with intraocular injection and systemic administration[34].

3) In Transdermal Drug Delivery

The success of transdermal drug delivery has been severely limited by the inability of most drugs to enter the skin at therapeutically useful rates because the stratum corneum does not have any nerves. Since micro-needles that are long enough and robust enough to penetrate across this layer, but short enough to not stimulate the nerves in the deeper tissue, have the potential to make transdermal delivery a painless and much more viable option[35]. With the use of hollow micro-needles 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. An array of needles ranging from 300-400 needles can be designed to puncture the skin and deliver the drug.

4) Targeted Drug Delivery

Additionally, micro-needles have been utilized to target drug delivery to a specific region or tissue in the body, thus avoiding unfavorable effects that can result from administering certain drugs systemically. The target to specific region can reduce side effects, minimize the dose of an expensive drug, and/or provide a means of delivery to a location that is difficult to treat[36]. For instance, a multichannel silicon microneedle has been microfabricated to deliver bioactive compounds into neural tissue while simultaneously monitoring and stimulating the neurons *in vivo*[37]. In addition, microneedles have been used to penetrate vessel walls of normal and atherosclerotic rabbit arteries in vitro demonstrating potential use for targeted delivery of anti-restenosis drugs[38] into coronary arteries. By incorporating the solid spikes onto stents, the spikes could penetrate compressed arterial plague as well as the elastic lamina, and thus enable a viable path for local drug therapy[39].

CONCLUSION

Transdermal drug delivery is a viable option to improve the bioavailability and increase the range of drugs. It is a convenient route of administration for a variety of clinical indication. The technology no longer is just a adhesive patches. Due to the recent advances in technology and the incorporation of the drug to the site of action without rupturing the skin membrane transdermal route, it is becoming the most widely accepted route of drug administration and its upcoming market is undoubtedly bright.

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Table 1: Recently approved Transdermal drug delivery systems

Product	Company	Indication	Approved
Fentanyl generic	Watson pharmaceuticals	Analgesic	August 2007
Fentanyl generic	Actavis	Analgesic	August 2007
Exelon (rivastigmine)	Novartis pharmaceuticals	Alzheimers and Parkinsons dementia	July 2007
Neupro (rotigotine)	Schwarz Bioscience	Parkinsons	May 2007
IONSYS (Fentanyl ionophoretic)	Alza Corp.	Patient-controlled pain management	May 2006
Daytrana (methylphenidate)	Noven pharmaceuticals	ADHD	April 2006
Emsam (selegiline)	Somerset pharmaceuticals	Depression	February 2006

Flow chart 1: Recent techniques based on active transport for enhancing TDDS