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REVIEW ARTICLE

MICRONEEDLES: NOVEL APPROACH TO TRANDERMAL DRUG DELIVERY SYSTEM

***Pawar RG,** Pawar SD, Gadhave MV, Jadhav SL, Gaikwad DD
Department of Pharmaceutics, Vishal Institute of Pharmaceutical Education & Research, Ale, Pune, MH, India-412411
Corresponding Author's Email ID: ravipawar79@yahoo.co.in

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ABSTRACT

Excellent impervious nature of skin is the greatest challenge that has to be overcome for successfully delivering drug molecules to the systemic circulation by this route. Various formulation approaches used to systemically deliver drug molecules include use of prodrugs/lipophilic analogs, permeation enhancers, sub saturated systems and entrapment into vesicular systems. Further, the adhesive mixture, physical system of the delivery system and release liner influence drug release and its permeation across the skin. The novel microneedle dual-delivery method combines the advantages of hypodermic syringes and transdermal patches. Composed of dozens to hundreds of hollow microneedles, a (1–2) cm2 transdermal patch is applied to the skin to increase its permeability. Arrays of microneedles that are 100–1000 μm in length poke through the top layers of skin and allow micron-scale drugs to pass into the body. The needles are too small to stimulate nerve endings; patients wouldn't feel any pain when a microneedle injection is performed. This review gives an overview of microneedles for drug delivery applications. The concept of miniaturized needles is presented and defined. Specific requirements for microneedles aimed for transdermal drug delivery are discussed and the scope is delimited. Some of the basic microfabrication methods used to fabricate microneedles is introduced and microneedles for drug delivery presented so far are reviewed and commented.

Keywords: Transdermal drug delivery, microneedles, transcutaneous permeation, percutaneous permeation, Microelectromechanical Systems.

INTRODUCTION

Transdermal drug delivery means that a pharmaceutical compound is moved across the skin - the *dermis* - for subsequent systemic distribution. Hence, strictly semantically this does not only include the more commonly understood "patch", but also traditional subcutaneous administration by means of a hypodermic needle and a syringe as well as novel techniques such as microneedles.

Following conventional terminology, a *microneedle* is a needle with representative parts (e.g. diameter) on the micrometer length scale. However, this definition is rather bold as it includes most of the standard hypodermic needles used in medical practice. Although there are many examples of "microneedles" with lengths of a few millimeters described in the literature, a common understanding of microneedles is that the length of the needle is shorter than 1 mm. What can be said is that microneedles are significantly smaller than ordinary needles, especially concerning the length.

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. 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 microneedle insertion into the skin is weak and perceived as painless [1, 2]. By combining microneedles with a patch-like structure, a system can be realized which essentially has all the favorable properties of a traditional transdermal patch, i.e. continuous release, ease-of-use, unobtrusiveness and painlessness. Unlike the standard patch, a microneedle-based patch enables delivery of virtually any macromolecular drug (including insulin and vaccine). Such a patch would not only offer a discreet and patient-friendly drug administration system, but also an efficient and possibly safe way to administer drugs with minimum involvement from health-care professionals. A number of companies are actively developing microneedle technology for transdermal drug delivery [3].

SKIN ANATOMY

The skin is the largest organ of the human body and has several functions. It is a physical barrier towards the environment, it regulates body temperature and fluid loss, it conveys sensory information to the nervous system, and it processes immunologic information to the immune system. The skin can be divided into three main layers: the superficial *epidermis*, *dermis* and *hypodermis*, see figure 1. The epidermis is approximately 50–150 m^2 thick and consists largely of constantly renewing, outward moving cells called keratinocytes. Apart for these cells, most of the antigen-presenting Langerhans' cells are located in the epidermis. The outermost layer of the epidermis is the *stratum corneum*, a 10– 20 m^2 thick layer of 15–30 stacked, dead, cornified cells. These so-called corneocytes are flat, hexagon-shaped and partly overlapping cells with a diameter of approximately 30 m^2. The cells are mechanically coupled to each other through special protein rivets and together with stacked layers of lipids they form an interlinked mechanical scaffold [4]. The stratum corneum

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forms the major constituent of the water barrier in the skin [5]. The dermis represents the bulk of the skin and the predominant components are collagen fibers and a smaller amount of elastin. This fibrous network gives tensile strength and elasticity to the skin and also provides support for nerve and vascular networks.

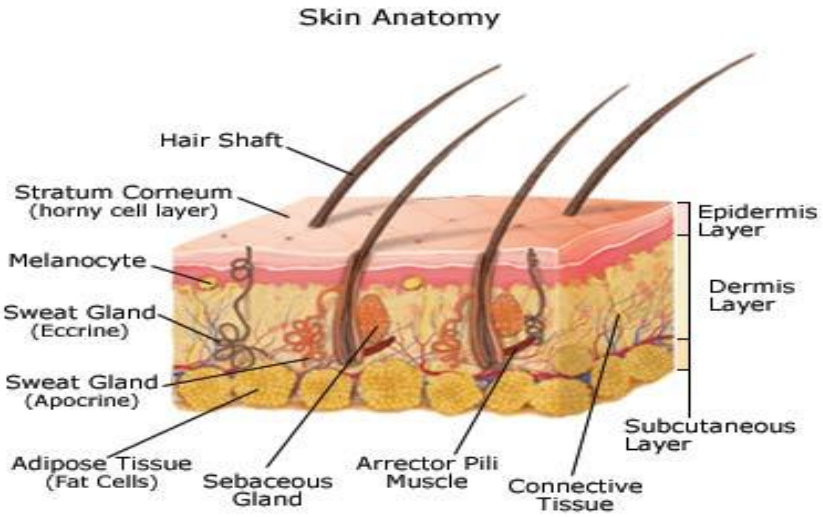

Figure 1: Anatomy of skin from [28]

In the upper, papillary, region of the dermis the collagen fibers are small and loosely distributed. The deep, reticular region contains densely packed, bundled, collagen fibers mainly running parallel to the skin surface and along certain directions, called Langer's lines.[5, 6]

The dermis rests on the hypodermis (subcutis) which is composed of loose fatty connective tissue. Its thickness varies considerably over the surface of the body as well as between individuals [4].

MICRONEEDLES FOR DRUG DELIVERY

The concept of an array of miniaturized needles for drug delivery purposes essentially dates back to 1976 and a patent (filed 1971) from Gerstel and Place at Alza corp. [22]. In this patent, a drug delivery device featuring miniaturized projections (i.e. microneedles) 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 to the backing of the reservoir. Figure 8 shows a drawing from the original document illustrating the device. Although not fully to the point, some predecessors to Gerstel and Place's patent exist, especially for vaccine delivery.

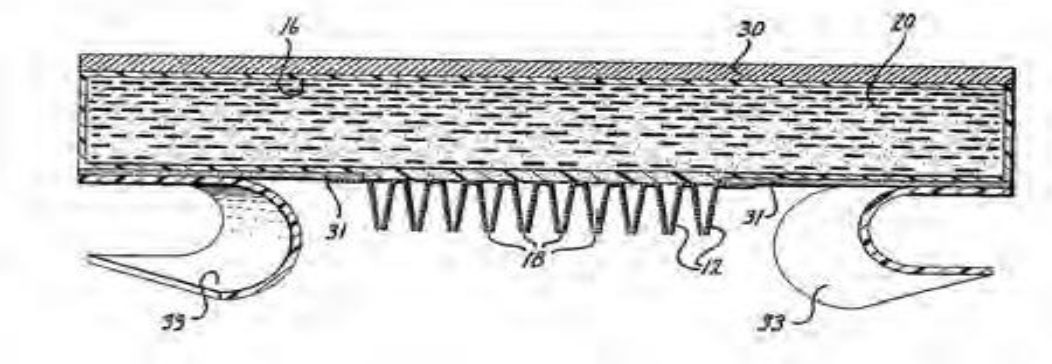

Figure 2: The original concept of a microneedle-based transdermal patch from the patent of Gerstel and Place 1976 [22]. The device contains microneedles [12], a drug reservoir [16], adhesives [31] and optionally a rate-controlling membrane.

To achieve physiologically relevant delivery rates, microneedle-based drug delivery is preferably made with arrays of needles over a certain area. To insert microneedle arrays with a large number of needles into the skin without using a special insertion tool (e.g. a high-velocity plunger), the insertion force needed to pierce the tissue has to be minimized. In addition, since the patch is aimed to deliver drugs, it should penetrate regardless of skin type or age of the subject, or the present humidity. All these factors may change the needed penetration force considerably. Thus, it is reasonable to believe that safety margins of 3–5 times may be required, demonstrated experimentally by Davis et al., penetration of microneedles into the skin is strongly linked to the interfacial area between the microneedle and the skin [7]. A small interfacial area gives a low insertion force. In other words, a sharp needle, where the interfacial area is minimal, will penetrate the tissue better than a blunt needle.

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It can be argued that an array of hollow microneedles, aimed for convective drug delivery, require far fewer needles to achieve therapeutic delivery rates. Thus, since fewer needles can be used, the insertion force of the needles does not necessarily need to be minimized. This is basically true. However, if a small number of needles are used, the delivery rate per needle needs to be higher than in the case of many needles. While a high flow rate may lead to significant flow resistance in micrometer-sized needle bores [8], the main fluid dynamical limitation lies in the tissue.

A microneedle inserted into skin will cause a large deformation of the tissue around the insertion area. As a consequence, the tissue will be highly compressed, which leads to a concurrent reduction of the fluidic permeability in the tissue. By partially retracting the needle after insertion, and thus relieving the compressed tissue, the flow resistance is decreased [9–10].

In summary, to achieve therapeutic delivery rates with microneedles without leakage, the delivery has to be made over a certain area using many needles. In turn, to allow insertion by hand, an array with many microneedles requires a sharp needle where the insertion force is low.

MICRONEEDLE TYPES

A classification for microneedles usually used in literature is based on the fabrication process: *in-plane* or *out-of-plane microneedles*. In-plane microneedles (figure 3a) are fabricated with the shaft being parallel to substrate surface. The advantage of this arrangement is that the length of the needle can be very accurately controlled. A disadvantage is that it is difficult to fabricate two-dimensional arrays. Out-of-plane microneedles (figure 3b) on the other hand, protrude from the substrate and are straightforward to fabricate in arrays. Instead, the length and high *aspect-ratios* become significant challenges in the fabrication of these kinds of needles. Another useful point of distinction is whether the microneedles are *solid* or *hollow*. Hollow needles with a needle *bore*, or *lumen*, allow an active liquid transport through the microneedle.

(a) (b)

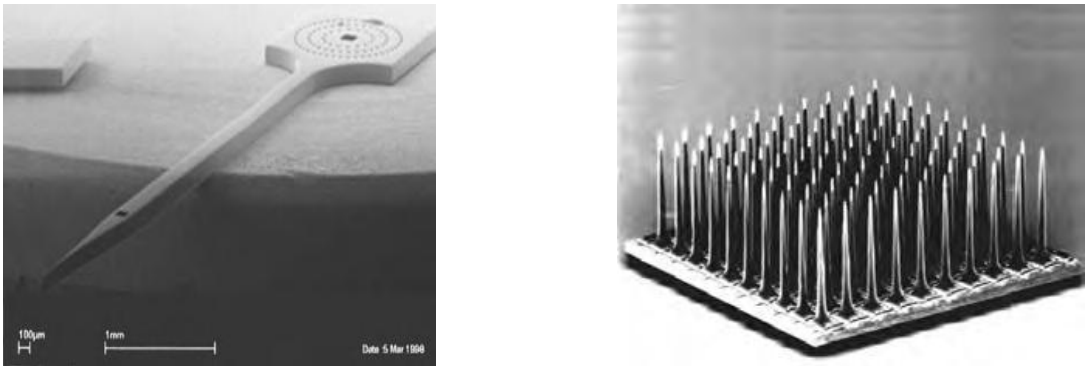

Figure 3: (a) 6 mm long, hollow, in-plane microneedle. From Talbot and Pisano [23]. (b) Individually addressable, 1.5 mm long, solid, out-of-plane microneedles used as electrodes. From Campbell et al. [24]

The following sections will give an overview of drug delivery microneedles, related fabrication techniques and design principles.

1. 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 microdevices. As such, MEMS devices can be made to interact with the surroundings, control fluidic flows or simply be used as small-scale mechanical devices. Typical MEMS devices are 4 Estimated cost at UNICEF for disposable needle and syringe including safety disposal; i.e. the cost is based on very high volumes.

2. Solid microneedle arrays

One of the first microneedle 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 microneedles. 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.

3. Hollow microneedle arrays

In contrast to solid microneedles, 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 microneedles were presented by McAllister et al. in 1999 [27].

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APPLICATION:

Microneedles have been used in many different applications, ranging from neurostimulation 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) [12]. 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 chemostimuli of brain tissue [13, 14]. Solid, out of- plane, microneedles have been used to penetrate the stratum corneum to facilitate EEG (Electroencephalogram) measurements for anesthesia monitoring [15, 16]. 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 [17]. The technique is currently being commercialized by SciBase AB and expected to reach market in 2007–2008 [18]. 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 [19].

Sampling of interstitial fluid through capillary action has been demonstrated with arrays of 350m long, hollow, out-of-plane microneedles [20]. Microneedles have also been fabricated for microdialysis, where a hollow in-plane needle equipped with a semi-permeable membrane filters the sampled liquid [21].

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 microneedles require a very low insertion force to be inserted into skin, potentially allowing arrays with hundreds of such microneedles to be inserted into skin by hand without any aids. It can penetrate human skin *in vivo* at clinically relevant sites. It can be hermetically sealed through thin membranes and be opened at the time of delivery by applying pressure or inserting the sealed needles into skin tissue. It can be fabricated with high process yield.Microneedles also combines the advantages of transdermal patch as well as needles.

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