A REVIEW ON MICRONEEDLES: AN EMERGING TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT
Though oral delivery is the most convenient route of drug administration, it is limited to few drugs because they may either degrade in the gut or be poorly transported across gastrointestinal epithelium. An alternative way to such drugs is transdermal drug delivery. Among the different approaches available for drug release through this route, microneedles are the best choice as they pierce the barrier layer of stratum corneum more effectively without causing pain to the patient. Microneedles are an array of micro structured projections. They can be classified as solid or hollow microneedles. In this article we will describe the need of microneedles, their types and applications. This review also covers the different methods of drug delivery like poke and patch, poke and release, coat and poke, poke and flow. A lot of research is being done on microneedles which allow integration with other devices in order to release the drug in a more controlled manner and overcomes the possible limitations.

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INTRODUCTION
Oral delivery of drugs is associated with some problems like poor bioavailability, hepatic first pass metabolism and chances of degradation in the digestive system. Transdermal drug delivery overcomes all these problems as it provides potential for improved patient compliance and controlled release of medicament for enhanced duration of action and reduced side effects. But skin constitutes a major barrier for permeation of pharmaceuticals [1, 2]. A relatively novel approach to disrupt the skin barrier in a controlled manner is the use of microneedle arrays [3].

Microneedles are sub-millimeter sharp pointed devices that are designed to pierce through stratum corneum, the outermost layer and deliver compounds to the viable epidermal layer of skin [4]. They can transport therapeutics ranging from small molecules to nanoparticles through the skin. Their low complexity enables self-administration by patients [5]. They donot penetrate deep into the skin to stimulate the nerves and are relatively pain-free. The pores created by microneedles were found to close within 72h after their removal and are thus very appealing to patients with impaired healing and those requiring frequent injections [6].

Transdermal microneedles are now emerging as a credible way to deliver drugs, vaccines, proteins and polypeptides [7]. Microneedles hold great potentials to be used in various medical applications like drug delivery, local cell treatment, bio-sampling, control release etc. [8].

STRUCTURE OF THE SKIN
Skin is the largest organ in the body. It is a physical barrier towards environment and regulates body temperature and fluid loss. It consists of three layers (Fig. 1):

Epidermis
It is the superficial layer of skin which is composed of stratified keratinized squamous epithelium. It consists of a thick, horny outer layer called stratum corneum and a deeper germinative layer. Cells on the surface are constantly rubbed off and replaced by cells which originate in germinative layer. Stratum corneum forms major constituent of water barrier in the skin [9].

Dermis
This represents the bulk of the skin and mainly consists of collagen fibers and a smaller amount of elastin. This fibrous network gives tensile strength and elasticity to the skin. It also provides support to nerves and vascular networks [10].

Hypodermis
It is the layer of loose connective tissue and fat which lies beneath the dermis. It supplies the underlying bone and muscle with blood vessels and nerves [11].

Stratum corneum is the main rate limiting layer for transdermal drug delivery. Due to its limited permeability, for the drugs to pass it should possess high lipophilicity, small molecular weight and small dose up to milligrams [12].

ENHANCEMENT OF PERMEATION
Various enhancement techniques could be used to improve the drug delivery through the skin (Fig.2). All these techniques work on the principle of disrupting the stratum corneum to allow easy passage of molecules. These include:

Fig.1. Structure of skin
Iontophoresis
It involves use of small electric potential across the skin to transport hydrophilic and charged molecules through it. Amount of current used in humans is currently set at 0.5mA cm$^{-2}$[13].

Sonophoresis
Sonophoresis or phonophoresis is application of ultrasound of a suitable frequency to enhance the transdermal transport of drugs. It employs ultrasound waves ranging from 20 kHz to 10 kHz with intensities of up to 3W cm$^{-2}$. Application of ultrasounds to the skin, makes some defects in the skin which facilitate delivery of active medicaments via stratum corneum [14].

Electroporation
In this technique, high voltage pulses of very short duration are applied to the tissue, leading to cell membrane permeabilization and electrophoresis of large charged molecules. This technique is generally used to deliver DNA [15].

**Techniques for permeation enhancement through skin**

**Physical Techniques**
- Iontophoresis
- Electroporation
- Sonophoresis
- Magnetophoresis
- Thermophoresis
- Microneedles
- Needle-free injections

**Chemical Techniques**
- Pro-drug
- Salt formation
- Chemical Enhancers

**Fig.2. Techniques for enhancement of permeation through skin**

**NEED FOR MICONEEDLES**
An alternative approach involves creation of larger pathways of microns dimensions using an array of microscopic needles. These pathways readily permit transport of macromolecules, microparticles and even few supramolecular complexes [16]. Microneedle devices have been developed for controlled transdermal drug delivery with minimum invasion. No pain is induced as the needles do not reach the nerves in deep dermis[17]. Advantages of microneedles include:
- Controlled release of drug
- Rapid onset of action
- Possible self-administration
- Painless delivery
- Good stability
- Improved patient compliance

**MECHANISM OF ACTION**
Microneedles are used to draw blood, insert drugs and also as a glucose level check for diabetics. They penetrate the skin barrier of stratum corneum without reaching the nerves in the dermis (Fig.3). Hence they should be at least 50µm in length but not more than 150µm[18].
METHODOLOGY FOR DRUG DELIVERY

Poke and patch approach
The skin is pierced with an array of solid microneedles and then a drug formulation or patch is applied to the treated site. The initial piercing makes the stratum corneum more permeable. Here microneedles can be used alone or in combination with iontophoresis which increases transdermal flux.
E.g. oligonucleotide delivery, Insulin delivery

Coat and poke approach
Solid microneedles are coated with drug formulations which dissolve off within the skin after microneedle insertion.
E.g. protein vaccine delivery, desmopressin delivery

Poke and release approach
Here microneedles are made of dissolving or degrading polymers which encapsulate the drug and then release it within the skin with predetermined kinetics.

Poke and flow approach
This approach facilitates micro infusion of a liquid drug formulation [19, 20].

TYPES OF MICRONEEDLES
Based on the fabrication process, microneedles are classified as:

In-plane microneedles
These are fabricated with the shaft being parallel to substrate surface using UV lithography technique and are made long enough to ensure sufficient penetration depth. Here the length, needle width and round of a corner can be accurately controlled but fabrication of two-dimensional arrays is difficult [21, 22].

Out-of-plane microneedles
These protrude from the surface and are straight forward to fabricate in arrays. These are micro machined in two-dimensional arrays, making them ideal for patch-like transdermal drug delivery applications. The challenge in fabrication of these needles is the difficulty to integrate planar microfluidic components on chip [23].

FABRICATION OF MICRONEEDLES
Microneedle arrays are fabricated using micro fabrication technology adapted from microelectronics industry. A variety of materials like silicon, metals and polymers are being used for their fabrication [24]. The steps involved include a series of photolithography, thin-film deposition and reactive itching techniques [25].

EVALUATION OF MICRONEEDLES
Characterization of microneedle geometry
Scanning electron microscopy is used to determine base radius, tip radius and wall thickness of microneedles. Interfacial area which is the effective contact area between needle and skin can be calculated using these values.

Margin of safety
It is the ratio between the force required for piercing the stratum corneum and the force at which microneedles broke. If the ratio is <1, it is hypothesized that the microneedle array can be used for biomedical application.
Biological safety test
Chemicals were extracted from microneedles by immersing them in physiological saline at 37°C for 72h. The obtained extract was applied on shaved intact human skin. Absence of dermal irritation revealed biological safety of microneedles.

Diffusion test
This test was performed on isolated animal skin to study diffusion of drug from dosage form to its site of application. Penetration of model drug was evaluated using Franz diffusion cell across microneedle treated and untreated skin.

Trans Epidermal Water Loss (TEWL)
Probes were held in a clamp above the application site and readings were taken over three minutes at various time intervals before and after application of microneedle array [26, 27].

APPLICATIONS OF MICRONEEDLES
Delivery of biotherapeutics
Large drug molecules like peptides, proteins, DNA and RNA which cannot be orally administered, can be delivered with a microneedle patch. As the doses of these biotherapeutics are often low, they can be administered either coated onto microneedles or encapsulated within dissolving microneedles. Commonly administered biotherapeutics include insulin, low molecular weight heparin, desmopressin and human growth hormone[28].

Diagnostic purpose
Hollow microneedles can be used to remove fluid from the body from analysis like blood glucose measurements and to supply micro liter volumes of insulin.

Targeted drug delivery
Very small microneedles could be used to provide highly targeted drug administration to individual cells. They are capable of very accurate dosing[29].

Immunization programs
Microneedles are useful for immunization programs in developing countries or for mass vaccination or administration of antidotes in bioterrorism incidents[30].

CONCLUSION
In this review we suggest the use of this innovative technique of microneedles. They can be fabricated using a wide range of materials and different techniques. Microneedles have found applications in the field of medicine to aid in drug delivery, mass vaccinations and also in diagnosis. Recently, microneedles are being used in association with other techniques like iontophoresis and electroporation to enhance their permeation into skin.

Key advantage of microneedles is that they allow integration into a patch like device which allows the drug delivery in a controlled manner.Research is also going on to integrate microneedles with displacement pumps or with an electrically controllable dispenser. All these techniques allow drug release in a pre-determined manner and also aid to improve the therapeutic response.

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