Micro Needle Assisted Drug delivery: A review

Nishant Thakur1*, Bhupinderkaur1, Chandan Sharma1, Manish Goswami1

1. University Institute of Pharma Sciences, Chandigarh University.

*Corresponding Author:
Nishant Thakur
University Institute of Pharma Sciences, Chandigarh University
Gharuan Mohali. Pin Code: 140413

ABSTRACT
Skins pose the barrier to the entry of the foreign particles into the body. However, it is the largest organ of the body. Transdermal drug delivery provides the benefit of the deliver the drug locally and avoids the first pass metabolism. But large drug molecules cannot be delivered by transdermal patches. Microneedles can overcome the skin barrier and deliver drug directly into the blood. Microneedle patches can be detachable or dissolving type and provides the ease of application and use. Thus, potent molecules can be easily administered with greater patient compliance by the transdermal patches.

Keywords: Microneedle, Transdermal Patches, polymers, Biodegradable


INTRODUCTION
Topical Drug delivery offers many benefits over other drug administration routes. (1). The drug delivery by transdermal route is painless and reduces the first pass metabolism (2). Outermost layer of skin offers strict barrier against the permeation of the lipophilic molecules (3). Hence the delivery of larger and ionic molecules should be designed with safe and in scientific manner. (4). Transdermal route offers better patient compliance because it is non invasive and self administration along with sustained delivery is possible.(5). Larger molecules cannot be delivered through transdermally (6). Transdermal delivery is possible only with molecules less than 500 da, and adequate lipophilic balance.(7) transdermal delivery is good option in case of the drugs which are difficult to formulate oral route.(8). Sustained delivery for a longer time with better patient compliance make it lucrative for patients (9).In transdermal delivery the drug is carried across the skin from applied patches by different mechanisms.(10). Traditionally reservoir and matrix type of systems are there.(11). Skin is the largest organ in the body and offers the better patient compliance and sustained delivery over a long period of time. With avoiding first pass metabolism etc (12).

Technically the drug can pass the skin barrier actively or passively depending upon the various external permeation enhancement (13). Penetration enhancers are used to deliver the drug through skin and takes a longer time.(14). But
active fast transport is a choice for researchers (15). Many such investigatory methods are under clinical trials. (16) Micro Jet injectors, drug permeation by changing ion charge, electroporation, sonophoresis, microneedles, powdered injection, surface ablation, jet injectors and stripping by tape are active method of delivery of drugs (17). These methods also enhance the delivery and ease of administration of larger molecules (18). This type of delivery offers immediate delivery and avoiding the lag time (17). The device related parameters can be adjusted as per individual needs.

**Microneedles for the immediate release of the drugs via transdermal route:**

Microneedles deliver the pain transdermally effectively painless (19). Microneedles donot stimulate the underlying pain stimulating needles (20). Microneedles are adjusted as per the need of the drug molecule and their effective delivery (21). Microneedle presents a good method of delivery of larger molecules, peptides and vaccines (22). Microneedles has proven to be a method for delivering a number of compounds more accurately (23). While designing a microneedle strategy, design specification and cost effectiveness is also as much important (24). Many experiments and strategies have been developed in this regard (25). Microneedles utilize microscopic needles which protrude into skin and then delivers the medicament for a prescribed time period (26). Microneedle comprises a solid micronized array of needles which may be dissolve in the skin (27).

**Henry and co workers.** conducted the first trials for the microneedle and delivered calcein into the body at three different rates howevr the experiment was interrupted due to the leakage from the microneedle array (28). After this, **McAllister and co-workers** administered insulin and other molecules by theis method into the cadaver skin and determined the permeation (29). Slicon wafers with reactive ion technology was used for the preparation of the microneedles (25).

**MICRONEEDLES**

Microneedles are hollow cannulas inserted into the body with at 50 mm to 500 mm external length (31). Microneedle patches are tested for the delivery of vaccine and larger peptides in the (32). Active response is observed while delivering medicine by the drugs via microneedles. (33). Microneedles are made up from the low cost silicon materials (34, 35). Micro needles are able to deliver the medication at the depth of 70–200 μm (36). Microneedle deliver the drug in to the body at a specific rate and painlessly (37).

**MICRONEEDLES BENEFIT IN THE DRUG DELIVERY (38)**

The benefits of microneedles are:

- Bigger moieties and peptides can easily be delivered.
- Self-administration.

- Hepatic metabolism is avoided.
- Faster delivery and healing of the site.
- No fear of needle.
- No microbial infection because only epidermis is penetrated
- Targeted delivery
- Increased efficacy.
- Good tolerability.
- Acceptable with other method of drug delivery.

**DISADVANTAGES OF MICRONEEDLES(34)**

- Dose accuracy.
- Careful use on the skin to avoid bouncing off.
- Skin thickness is different in different individuals.
- External factors like hydration and occupation
- Effects veins in continuous use.
- The tip may braek into the skin
- Dermal tissue compression effects the drug delivery.

**MECHANISM OF MICRONEEDLES**

Microneedles have hindred of needles on the array.(39) Microneedles are pressed in to the body and then they protrudes and start te d delivery of the drug(40). This can deliver the vaccine and other drugs(41)after the removal of the microneedle patch the residual holes on the skin remains for two hours to a day.(41)some time dissolvable microneedle are used which dissolve sinside the skin and occlusion and other problems can be avoided(42). The occlusion over the needle hole can delay the release of the drug or medicament and different polymers like PLGA, Sodium CMC are used.(43) This method include the piercing by needles and then delivery of then delivering the medicament slowly.(44).

**MICRONEEDLE COATING METHODS**

**Dip Coating**

The plunge covering process is the least complex methodology to cover microneedles(23). Microneedles are first dunked into the detailing and afterward pulled back. This progression delivers a film of fluid on microneedle. The spreaded fluid is then permitted to evaporate to frame a strong film coating(26). The plunge covering strategy has
been used to convey hydrophilic and hydrophobic medications. A few molecules have been covered onto microneedles utilizing this strategy, e.g., proteins, bio pharmaceuticals and DNA(45).

**Gas flash drying:**

The moderate drying method related with plunge covering method is restricted for all intents and purposes, particularly for bended microneedles (30). While the medication covering arrangement is as yet wet on the microneedles surface, the arrangement can possibly move and migrate off the microneedle surface, lessening and differing the ideal portion. Indeed, even the multi-plunge covering approach is possibly hazardous as multi-layer covering (of arrangement) aggregates and dries at the base substrate. Chen et al. gas flash drying particularly for extremely less than<90μ length and intently ~20.000 cm$^{-2}$ separated micro needles(46). Strong silicon microprojections were sputter covered with a slim layer of gold. Total 6-8 μL micro projectors were used which had perfect surface pressure and consistency properties. The covering arrangement contained methylcellulose

**Splash Covering**

The splash covering process is like ordinary covering draws near (e.g., utilized for covering tablets)(47) to accomplish millimeter thicknesses. The micron estimated structure of microneedles (ordinarily ~60 to 700 μm in tallness) requires a covering thickness in and beneath the micron go less than < 280 μm(48). Shower covering of microparticles onto microneedles experiences three stages. Right off the fine atomization, which is the age of detailed microdroplets from the splash coater. Besides there is testimony and adherence of beads onto the outside of microneedles. At long last there is the mixture of beads on the substrate to frame a flawless film coating(40).

**EHDA Based Processes**

The electro hydro -dynamic atomization (EHDA) process produce small scale and nano sized scaled designs in a single step. The standard procedure was depicted by Grace and Marijnissen (1994)(49). Here, atomized beads are delivered by an electrically forced moving fluid that fly through a hair like spout exit and are in this way gathered over a ground cathode situated underneath the spout tip(50). The fluid utilized is a polymeric arrangement, or detailing, containing three primary segments (a dissolvable, polymers and dynamic medication) and potentially other excipients(51).

**Piezoelectric Inkjet Printing**
The piezoelectric ink printing produces the ink liquid drops (1–100 picoliters) onto a subject (e.g., microneedles) before solidification(52). It require low viscosity (53). The selected excipients are dissolved in a suitable solvent and then sprayed with the help of a piezoelectric vibrations or probe and then dried leads to thermal inkjet printing(54).

**MICRONEEDLES COATING TECHNIQUES (55)**

**TYPES OF MICRONEEDLES**

Microneedles can create pores on the skin and enable the drug to pass to the epidermis layer to the dermal tissue directly(24). Unlike regular hypodermic needles, the microneedle has the ability to improve patient compliance as it does not hurt nerves(26). Structurally, micro needles are classified into four types, namely

- solid microneedles,
- coated microneedles,
- dissolving microneedles
- hollow microneedles(56).

The drug delivery principle of these microneedles (respectively) are the “poke and patch” approach, the “coat and poke” approach, the “poke and release” approach, and the “poke and flow” approach(23).

**Solid Microneedles**

Microneedles can make pores on the skin and empower the medication to pass through the epidermis layer to the dermal tissue directly (24). In contrast to customary hypodermic needles, the microneedle can improve tolerant consistence as it doesn't hurt nerves(26). Morphologically, microneedles are ordered into four kinds, in particular strong microneedles, covered microneedles, dissolving microneedles and empty microneedles(56). The medication conveyance systems of these microneedles (separately) are the "jab and fix" approach, the "coat and jab" approach, the "jab and discharge" approach, and the "jab and stream" approach(23).

**Coated Microneedles**

The appearance of coated microneedles, which are coated with drugs at their tips via dipping, gas-jet drying, ink-jet printing or spraying methods, has solved complexity problem of solid microneedles(60). The “coat and poke” approach is the drug delivery mechanism of coated microneedles. In detail, the microneedle patch is inserted into the skin, then the drug coated on the microneedle tips released into the skin.
Dissolving Microneedles

Compared with strong or covered microneedles, dissolving microneedles have different focal points, for example, that they are effortlessly made, advantageous, and high medication loading (61). Usually, dissolving microneedles are conformed to the premise of "jab and discharge" conduct: when the microneedle fix infiltrates the skin, the medication stacked in the dissolving microneedle tips is released (31). Micromolding, photopolymerization, and drawing lithography are a few normal techniques for assembling dissolving microneedles, which are getting progressively well known in different fields (62).

Hollow Microneedles

Hollow microneedles, which have the most noteworthy accuracy in portion, are somewhat unique in relation to the next microneedle frameworks depicted previously (63). Medications can be conveyed into the skin legitimately through the gaps in empty microneedles, which can give measures of liquids into the skin at various weight driven stream rates (64). These microneedles are commonly produced using a metal or silicon substrate by means of microelectromechanical frameworks (MEMS) systems, for example, laser micromachining, incorporated lithographic embellishment procedure, microfabrication, and X-beam photolithography methods (65). Additionally, as the conveyance conduct of empty microneedles seems to be "poke and flow," they are reasonable for blood extraction (66).

Micro Needles Testing And Evaluation

Micro needle assesment (43)

SEM is used for the surface characterization and measurements along with morphology study. The main measurements are (1) the total surface area, Aa; at the needle tip and (2) the total cross-sectional area, Af; at the needle tip

\[
Aa = \pi (rt^2 - t^2) / 4 \ldots 1
\]

\[
Af = \pi rt^2 \ldots 2
\]

wherert is the exterior radius of the microneedle tip, rb is the exterior radius at the needle base, t is the wall thickness and h is the height

working or functional capacity test (67)

Wang et al. assessed the practical limit of micro fluid lumens utilizing a designed flow test arrangement. The experiment design comprised of a syringe pressure system with a color filled syringe, a polymer tube and micro
This syringe siphon framework was utilized to look at the arrangement of the microneedle lumens by permitting color to spill out of the syringe to the microneedle hole. The movement of the microneedle and the base plate can be easily investigated for splits and coherence in the base.

**Skin penetration force (68)**

A displacement–force test design was used by Shawgo et al. to explore the power applied to a needle, needle position and skin opposition during the arrangement of the needle's interpretation, diversion of tissue around the needle and addition into the skin of human subjects. A drop in electrical obstruction of the skin was utilized to recognize needle entrance since visual perception of needle addition was incredibly troublesome. The electrical opposition of skin's peripheral layer, the stratum corneum, is a lot more noteworthy than more profound tissues, in this manner the obstruction of the skin drops drastically when a needle infiltrates.

**Safety evaluation (69)**

Forviet al. characterized security as the proportion of the power required for piercing the stratum corneum and the power at which micro needles will break. They theorized that on the off chance that the proportion is 1:1, at that point microneedle cluster can be utilized in clinical application. They checked edge of security for silicon micro needles using automated device. For compressive disappointment power estimation, Enduratec station was used in which microneedles were put among punch and burden cell. A proper edge of security was found for test silicon microneedle exhibits.

**Fracture force determination (70)**

Davis et al. studied the force required for breaking downa microneedle, employing an axial load check station that drove the microneedle in opposition to a square piece of aluminium at a rate of 0.01 mm/s until a predetermined displacement of 500 mm become achieved. Microneedles had been attached to the checking out floor the use of adhesive tape around the base of the needle. Microneedle breakdown changed into found through an connected microscope to assess the mode of failure. The fracture pressure is evaluate by the pressure and displacement profile.

**Penetration/diffusion test**

**In-vitro and ex-vivo test**

In vitro and in vivo tests are done to evaluate the penetration of the needle. confocal laser scanning microscopy (CLSM) is used to demonstrate penetration of Rhodamine B in human (71). hey announced the centralization of the color to be exceptionally frail underneath 80 mm profundity. They additionally assessed the infiltration of model
medication utilizing Franz dispersion cell over the microneedle-treated and untreated skin and detailed upgrade in entrance by 104 to multiple times with utilization of microneedles. Comparable perceptions were additionally announced by different analysts. Then again anyway the entrance of the ascorbic corrosive don't increment by microneedle strategy.(72). They punctured the skin more than once to show the impact of microneedle reuse..

**In-vivo test**

Teo et al(73) reported that the delivery of insulin via rat skin pores and found that the in vitro and in vivo models do not correlate much with each other. If correlation is installed among ex-vivo and in-vivo models, the drug improvement system will be made extra economic and shorter. Bal et al. reported penetration of fluorescent dye via human skin after microneedle software with the assist of confocal laser scanning microscopy (CLSM)(74). further, Enfield et al. used optical coherence tomography (OCT) for imaging of tissue shape. both those strategies provide tissue imaging without the want for tissue pre-remedy or removal(75)

**Transepidermal water loss (TEWL)**

DermaLab TEWL probe and Tewameter TM 210 probes are used to determine the skin permeability and the water loss from the epidermal layer. A gross sampling before application and after the application of the microneedle showed increase in the permeability.(76).

**Biological safety test**

DermaLab TEWL probe and Tewameter TM 210 probe have been utilized at some point of their research on microneedles. TEWL can tell about the intact animal skin and skin pores. These probes are held for a longer duration with the clamps and the samplings are done at different point of time. The researchers concluded that there was an growth in pores and skin permeability after the usage of microneedle(76).

**Applications (77)**

**Microneedles are used in the delivery of the**

- **Immunobilogicals** eg influenza vaccine, hepatitis vaccine, Human IgG, Antharax, tetanus toxoid

- **Biopharmaceuticals** eg Recombinant human growth hormone and desmopressin, calcein

- **Drugs** : Aspirin(22), Docetaxel (80), Pilocarpine (81), Riboflavin(47)
### COMMERCIAL MICRONEEDLES IN MARKET(84), (85), (86)

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Company</th>
<th>Product</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Echo. Therapeutics, Inc.</td>
<td>Symphony®</td>
<td>Glucose monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuous Glucose Monitor</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Becton Dickinson/Sanofi Pasteur</td>
<td>.Intanza®</td>
<td>Pre filled injection system</td>
</tr>
<tr>
<td>3</td>
<td>Corium International, Inc.</td>
<td>MicroCor®</td>
<td>Dissolvable microneedle Device</td>
</tr>
<tr>
<td>4</td>
<td>NanoPass Technologies, Ltd.</td>
<td>MicronJet®</td>
<td>Hollow microneedle Device</td>
</tr>
<tr>
<td>5</td>
<td>Seventh Sense Bio systems, Inc.</td>
<td>TAP 20C®</td>
<td>Microneedle penetration/blood sampling</td>
</tr>
<tr>
<td>6</td>
<td>TheraJect</td>
<td>TheraJect® Patch</td>
<td>Dissolvable microneedle device</td>
</tr>
<tr>
<td>7</td>
<td>Valeritas, Inc.</td>
<td>Micro-Trans®</td>
<td>Microneedle device</td>
</tr>
<tr>
<td>8</td>
<td>Vaxxas, Inc.</td>
<td>The Nanopatch®</td>
<td>Vaccine-coated microneedle device</td>
</tr>
<tr>
<td>9</td>
<td>ZosanoPharma</td>
<td>ZP Patch</td>
<td>Drug-coated microneedle Patch</td>
</tr>
</tbody>
</table>

**Reference:**


10. SHINGADE GM. REVIEW ON: RECENT TREND ON TRANSDERMAL DRUG DELIVERY SYSTEM. J Drug DelivTher. 2012;


http://doi.org/10.36295/ASRO.2020.231540


42. Serrano-Castañeda P, Escobar-Chávez JJ, Rodríguez-Cruz IM, Melgoza-Contreras LM, Martínez-Hernández J. Microneedles as enhancer of drug absorption through the skin and applications in medicine and cosmetology. J Pharm Pharm Sci. 2018;


47. Gill HS, Prausnitz MR. Coating formulations for microneedles. Pharm Res. 2007;


84. Inal Ö, Yapar EA, Baykara T. Modern transdermal therapeutic systems in medication. Ankara UnivEczacFakDerg. 2008;


86. Ö. I, E.A. Y, T. B. Modern transdermal therapeutic systems in medication. Ankara UnivEczacFakDerg. 2008;