International Journal of Current Innovations in Advanced Research
(International Multidisciplinary Tri-annual Research Journal)
Content Available at www.ijciar.com ISSN (O) 2636-6282 ISSN (P) 2659-1553

ROLE OF MICRONEEDLE TECHNOLOGY IN TRANSDERMAL DRUG DELIVERY SYSTEM

Kodirekkala Kavya*, Thummamaluru Anil Kumar, Uggirala Mounika and Chandu BabuRao.
Priyadarshini Institute of pharmaceutical Education and Research, 5th Mile, Pulladigunta, Guntur -522017, Andhra Pradesh, India.

***Corresponding Author**
Kodirekkala Kavya

DOI: https://doi.org/10.47957/ijciar.v7i2.185

Received: 21 May 2024 Revised: 06 June 2024 Accepted: 27 June 2024

Abstract
In order to safely, noninvasively, and painlessly transfer medications into the skin, microneedle (MN) transdermal drug delivery systems have undergone significant development. Newer production processes have led to the development of different varieties of MNs over the past few decades. In summary, the morphological characteristics of MNs can be categorized as solid, coated, dissolved, or hollow, according on the drug delivery strategies used for transfer: "shove and patch," "coat and poke," "shove and release," and "poke and flow." Other features of microneedles depend on their composition and design. Despite the benefits of using the skin to deliver drugs, the appearance of the stratum corneum—the topmost layers of dead cells—seriously restricts practical drug delivery through the skin. Utilizing silicon, metals, polymers, or polysaccharides, solid-coated microneedles can be used to puncture the outer layer of skin after application and popularization. Microneedles are manufactured using microelectromechanical systems.

Keywords: Microneedles, Transdermal drug delivery, Administration, Stratum Corneum, Application.

Introduction

The successfulness of transdermal drug delivery has been seriously limited by the incapability of most drugs to enter the skin at therapeutically utility rates. Recently, the use of micron-scale needles enlarge skin porous has been proposed and exhibit to dramatically increase transdermal delivery, extremely for macromolecules. Utilize the tools of the microelectronics industry, microneedles have been fabricated with a range of sizes, shapes and materials. Most drug delivery studies have accentuate solid microneedles, which have been shown to increase skin permeability to a wide ranging of molecules and nanoparticles in vitro.Microneedle manner has been prosperously used to deliver a variation of compounds as well as macromolecules and hydrophilic drugs into the skin. As microneedle system by passes the stratum corneum barrier of the skin, permeability magnification of two to four orders of immensity has been observed for small molecules like calcine and also for the relatively larger compounds like proteins and nanoparticles.[1] On the other hand, physical means of transdermal drug delivery comprises of iontophoresis, electroporation and sonophoresis. Chemical approach increases the lipophilicity and therefore increase the permeability of drugs across skin,whereas the physical approaches into confusion the upper layers of skin the stratum corneum (SC) and reduce the aversion to the passage of drugs by creating minute holes in the skin that are large enough for passage of smaller drug molecules but in all probability small enough not to injury the skin. Microneedle technology has been developed as modern technique for perforation of large molecular weight and/or hydrophilic compounds. (1)

1. Need of Using Microneedles:

When oral administration of drugs is not plausible because to unfortunate medication retention or enzymatic degradation in the gastrointestinal tract or liver, injection using a painful hypodermic needle is the most well-known other option. However, transdermal delivery is seriously restricted by the inability of the large part of drugs to cross skin at therapeutic rates because of the extraordinary barrier imposed by skin's outer stratum corneum layer. To increase skin permeability, a number of different approaches has been considered, going from synthetic/lipid enhancers to electric fields employing iontophoresis and electroporation to pressure waves produced by ultrasound

or photo acoustic effect. Although the mechanismsare various, these methods share the common objective to disturb stratum corneum structure in order to create "holes "large enough for molecules to pass through. An alternative methodologyincludes creating larger

- can be administered.
- First pass metabolism is avoided.

1. Disadvantages:

- Skin irritation may result because of allergy or sensitive skin.
- Local inflammation may result if the concentration of drug is high under theskin.
- Compressed dermal tissue can block hollow microneedle.
- transport pathways of micro dimensions using arrays of microscopic needles.

2. **Advantages of Microneedles:**

- Rapid onset of action.
- Painless administration of the active pharmaceutical ingredients.
- Large molecules

1. Applications of Microneedles:

Microneedles are convenient, safe, and painless sufficient to achieve the comfort of patient and now widely used in transdermal, ocular, and intracellular delivery. Here into, transdermal drug delivery is the main area for the application of microneedles. (2)

- Immunobiologicals
- Bioactive macromolecules (Biopharmaceuticals)
- Drugs also used
- Phlebotomy
- Diagnosis
- Cosmetic products
- Decompression delivery
- In transdermal drug delivery

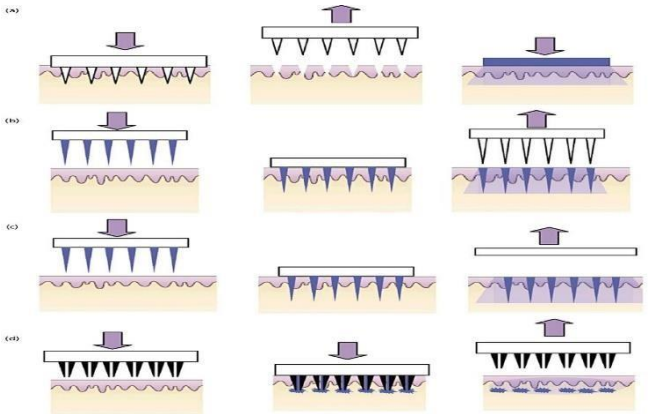
2. Mechanism:

3. The mechanism of action based on the type of microneedle composition. The general mechanism of delivery via microneedles is depends on mechanical disturbance of the skin andapplication of the drug or vaccine within the epidermis, from where it can more readily reach its targeted site of action. The drug is capture within the microneedles, which when inserted into the skin and releases the drug into the layers of skin which are highly vascularized. In

some cases the needles dissolve within minutes, releasing the entrapped drug at the deliberate site of delivery from where they reach the target site. Model drugs have been encapsulated within polylactic co-glycolic acid (PLGA) microneedles-controlled release over hours to months and subsequential within water soluble carboxymethyl-cellulose, polyvinyl- pyrrolidine and maltose for rapid release within minutes. (3)

4. Drug Delivery Through Microneedles:

In an earlier phase of analysis on microneedles, an formation of solid microneedles was penetrate through the skin to get round the barrier effect of the stratum corneum. The needles were made up of silicon a drug patch was applied to the treated skin surface thereafter. This approach is known as 'poke and patch'. This technique was also tried to extract the interstitial fluid to measure the glucose level by non-invasive method. Subsequent analysis in microneedletechnology focused on development of solid microneedles coated with drug solution using a dip-coating method. The skin was pierced before the release of the drug. A limited amount of drug could be coated over the microneedles (only about 1 mg) and extensive optimization wasrequired for uniform coating in this 'coat and poke' approach. (4)



5.1 Proteins:

Protein drugs can be applied to various cancer treatments, vaccinations, and treatment of genetic diseases. Rapid development is expected; however, drug delivery is limited due to the

issue of low stability and absorption. For example, during dosing and storage, protein denaturation, drug absorption, microneedle technology has been advance for proteins including using insulin, desmopressin, erythropoietin, lysozyme, glucagon, glucagon-like peptide-1, parathyroid hormone, and growth hormone.

5. Classification of Microneedles:

The main purpose of MNs is to penetrate into skin via the micro projections, without hurting any nerves to improve the patient comfort and ensure the safety. Microneedles can be classified into different types based on the parameters, including drug delivery methods, materials and structures. (5)

- Solid Microneedles
- Coated Microneedles
- Dissolving Microneedles
- Hollow Microneedles
- Hydrogel Microneedles

6.1.Solid Microneedles:

Solid microneedles are developed to deliver drugs into skin based on the mechanism of"poke-and-patch" approach. In this approach, solid MNs are penetrated into the skin to disrupt the stratum corneum and create transient microchannels and then a patch with thedrug formulations is applied onto the skin so that the drug can diffuse slowly into the skin through the transient microchannel. The "poke-and-patch "method to enhance the permeation of lidocaine hydrochloride.

6.2 Hollow Microneedles:

Hollow MN deliver drugs via the "poke-and-flow "approach. Similar to the hypodermicinjection, the liquid drug can continuously flow into the skin via the holes in the

hollow microneedle driven by the pressure. Hence, the flow rate of drug can be accurately controlled by special equipment, such as micropump. Comparing with the solid microneedle hollow microneedles are likely to promote force-driven fluid flow, thereby allowing faster drugdelivery rates. Hydrogel Microneedles: In hydrogel microneedles, the drug is contained in all areas of the microneedles tip, base substrate, and patch backing and is released at a slow rate while the patch is applied to the skin. The microneedle patches are primarily composed of hydrogel, and when they encounter fluids in the skin, they are hydrated but not dissolved. A high amount of the drug in the hydrogel is delivered to the skin through diffusion. (6)

6.3 Based on structure of microneedles:

Microneedles can be divided into 2 types based on the structures, including in-plane and out- of-plane microneedles. The out- of plane microneedles show that the length of microneedles is perpendicular to the substrate. It is easy to enhance the efficiency of drug delivery on large areas of skin by out-of-plane microneedles. The through increasing the density of microneedle arrays. Out-of-plane microneedles can be hollow or solid microneedels. Furthermore, it is alsoeasy to manufacture the out-of-plane microneedles and the out-of plane microneedles have widely used to deliver drugs.

6.4 Based on materials of microneedles:

Traditionally, materials used for microneedles are inorganic materials, metals and polymer. We subsequently introduce each type of materials in detail.

6.5 Metal:

Various metals, such as SS, Ti and nickel (Ni), have been used as structural materials to fabricate solid MNs, coated microneedles and hollow microneedles. Metals have strong mechanical strength and toughness for the transdermal drug delivery system. However, metals are non-biodegradable, which may produce unwanted bio hazardous tip waste induced by the broken microneedles left behind in the skin, even though some metals, such as SS and Ti, havebeen safely used as bio materials in medical treatment for decades. (7)

6. Methodology For Drug Delivery:

A number of delivery strategies have been employed to use the microneedles for transdermaldrug

delivery. These include

- Poke with patch approach
- Coat and poke approach
- Biodegradable microneedles
- Hollow microneedles
- Dip and scrape

7.1 Poke with patch approach:

It involves piercing an array of solid microneedles into the skin followed by application of thedrug patch at the treated site. Transport of drug across skin can occur by diffusion or possiblyby iontophoresis if an electric field is applied.
Eg: Insulin Delivery

7.2 Coat and poke approach:

In this approach needles are first coated with the drug and then inserted into the skin for drug release by dissolution. The entire drug to be delivered is coated on the needle itself. (8)
Eg: Protein vaccine delivery.
Eg: Insulin Delivery

7.3 Dip and scrape:

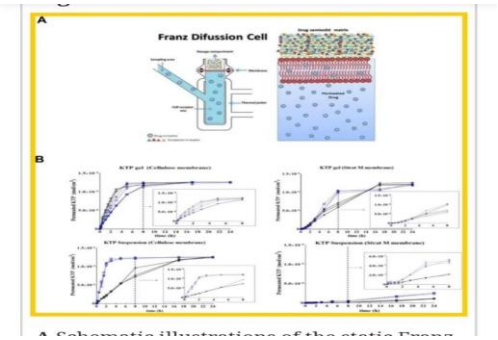
Dip and scrape approach, where microneedles are first dipped into a drug solution and then scraped across the skin surface to leave behind the drug within the micro-abrasions created by the needles. The arrays were dipped into a solution of drug and scraped multiple times across the skin of mice in vivo to create micro-abrasions. (9)

7. Methods for Characterizing Transdermal Drug Delivery System:

The evaluation of delivery efficiency and effectiveness is a very important process intransdermal drug delivery system. There are various methods used for this, depending on the
type and purpose of the drug to be delivered. Materials and Methods of Microneedles:
Various materials, from metal to polymer, are used in microneedles, depending on the design or components of the patch. Generally, microneedle materials should have sufficient mechanical strength for skin insertion. Non-dissolving microneedles are inert, bio-compatibleand sufficiently strong for skin insertion without causing an immune response. In contrast, the matrices of the coated and dissolving microneedles should generally be water-soluble and bio-compatible.

8.1 Silicon:

First the microneedles were fabricated using silicon to have sharp and hard microneedle because of greater mechanical strength. Fabrication by microneedle is costly because itrequire cleanroom microfabrication for processing. Silicon is brittle and may break in the skin.



8.2 Metal:

Metal are used for fabrication as they have good mechanical strength, cost is low, metal usedare stainless steel, titanium, nickel, iron. (10)

8.3 Polymers:

Biodegradable polymer used are Polylactic acid and Polyglycolic acid because they are cost- effective. This biodegradable polymer is used owing to the chance of microneedle breaking offin the skin.

8.4 Glass:

Fabrication is also done by glass. They are physically capable of insertion into the tissue and they have high drug loading capacity and one can see how much amount of drug is delivered after use. Glass microneedles are primarily hollow and prepared using wet etching or micropipette puller.

8.5 Fabrication of Inorganic Material MNs:

Since the first solid MNs made of silicon by reactive ion etching (RIE) was reported, the techniques to fabricate the silicon MNs have been developed for years. Not only wet-etching and dry-etching but also electrochemical micromachining have already been used to fabricatesilicon MNs, such as solid, hollow, in-plane, and out-of-plane MNs.
Fabrication of Metal MNs:

8.6 Dry etching: Dry etching is primarily used to create solid or hollow microneedles. It is classified into physical methods and chemical methods. Physical methods include ion milling and sputtering. In dry etching, an inert gas (e.g.,

Ar or SF6) is ionized by high energy and unidirectional electrodes. Because the ions strike the silicon substratum at a high speed in a single direction, anisotropic etching is performed. (11)

8.7 Wet etching: Wet etching is also used for fabrication of metal or silicon microneedles. Inthis process, a pattern is produced on the substrate using a chemical etchant.

8.8 Fabrication of silicon microneedle:

Cleaning the wafer to remove the hydrocarbon and the mist. Depositing the Oxide and Nitridewith the depths are 1 and 0.2 µm respectively. Coating the photoresist. Photolithographic and
develop the microneedles. Remove the susceptible Oxide and Nitride by Reactive Ion Etching, RIE. KOH wet-etching: The KOH solution is also 30 wt% at 80°C.

8. Microneedle Fabrication Technique:

When designing a microneedle, the objective of the microneedle is considered first. The drug type and dose, delectable pharmacokinetics/pharmacodynamics and targets for use are considered. Next, the most optimized microneedle design and materials are determined. The manufacturing method for microneedles variegate depending on the arrangement or material.

Evaluation of Microneedles:

9.1 Characterization of microneedle geometry:

Scanning electron microscopy can be used to influence the base radius, tip radius and wall consistency of the microneedles. Interfacial area (i.e. the effective area of contact between the needle and the skin) can be deliberate in two ways the annular surface area, at the needle tip.

9.2 Functional capacity test: Evaluated the functional capacity of micro-fluidic lumens usinga custom fluidic test setup. The test setup consisted of a syringe pump system with a dye-filledsyringe, a polymer tube and microneedle arrangement.

9.3 Measurement of Insertion Force into Human Skin:

A displacement–force test station was used to measure the force applied to a needle, needle position and skin resistance during the sequence of the needle's translation, deflection of tissuearound the needle and insertion into the skin of human subjects.

9.4 In-vitro and ex-vivo test:

In-vitro/ex-vivo tests are performed on isolated animal/human dermatomed skin to study penetration or diffusion of drug from a dosage form to its site of application. These tests can also be used to compare the depth of penetration of the molecule used confocal laser
scanning microscopy (CLSM) to demonstrate the depth of penetration of Rhodamine B in human dermatomedskin using microneedles of 150 mm length. (12)

9.5 In-vivo test:

For a transdermal drug delivery system, it is practically unachievable to predict the skin permeability of formulations using in-vitro experiments alone. Significantly different results might be observed while performing in-vivo study. This is reflected by a study epithelialduct. They reported that the diffusion of insulin through rat skin was found to increase by 10–20 times in an in-vitro study, while during their in-vivo study, microneedles failed to deliver drug systemically. Thus, along with in-vitro/ex-vivo testing, in-vivo tests should always be performed.

9.6 Combination of Iontophoresis and Microneedles:

In iontophoresis a small electrical current is used for transportation of drug across the stratum corneum of the skin. The current may be turned on and off by the patient and can deliver small drug molecules and biomolecules having a molecular weight up to a few thousandDaltons. Studied the administration of insulin unicellular nanovesicles through microneedles along with iontophoresis. The positive zeta-potential and small diameter of the nanovesicles increased the penetration of insulin with the help of iontophoresis and microneedles.

9.7 Combination of Sonophoresis and Microneedles:

Sonophoresis uses ultrasound (frequency, 20 kHz to 10 MHz; intensity, up to 3 W/cm2) for enhancing installation of drugs by forming cavitation and change in the lipid arrangement of the stratum corneum. Drug permeation can be controlled by controlling the frequency of the ultrasound. As the sound frequency increases from 20 kHz to ªMHz, skin perturbation increases1000-fold found that an increase in the rate and magnitude of delivery of calcein (623 Da) and bovine serum albumin (66.430 kDa) could be achieved by using a combination of Sonophoresisand microneedles.

9.8 Nanoemulsions:

Nanoemulsions are a mixture characterized by low viscosity and isotropic, thermodynamic, and dynamic stability. The small particle size, large specific surface area, and low surface tension of nanoemulsions provide fantabulous wettability that ensures close contact withthe skin. 3D Printing (additive manufacturing):

3D printing is an accumulative processing technology that rapidly prototypes a designing at low cost and high output. Recently, the 3D printing technology has been expanded to include the production of microstructures such as microneedles. The existing manufacturingtechnology is limited to the production of a simple structured microneedle, while the new 3D printing technology can produce a more sophisticated and complex-shaped microneedle structure. Microneedles are manufactured using high imprecision stereo lithography (SLA), digital light processing (DLP) method, or fused deposition modeling (FDM). (13)

9. Safety Issues of Microneedle:

Microneedles have been used for the safe and prompt delivery of drugs and vaccines by creating changeable microchannels in the skin. Disruption of the stratum corneum by using conventional needles for the delivery of drugs and vaccines may cause pain, bleeding, skin irritation, skin redness and infection. Challenges in the Development of Microneedles:

Many applications of microneedles have been unregenerate but very few products have been marketed to date. There is a need to consider safety and efficacy while developing microneedles for delivery of both small and large molecules. With metallic microneedles, traces of metal are retained above the skin which may lead to irritation, erythema, swelling, discoloration or other side effects. Frequent application of the microneedle at the same site may result in the mentioned problems. Application at different sites every time or fluctuation in skin

thickness in several may result in variation in bioavailability, which needs to be considered while developing microneedles.(14)

Conclusion

Because they provide patients with more immediate and tolerant access to medications than traditional methods of administration, research on microneedles, a transdermal drug delivery technology, is expanding quickly. Solid, coated, dissolving, and hydrogel formulations are the several types of microneedles. To impart distinct shapes, sizes, and features, a variety of manufacturing procedures are used. Through clinical trials, microneedles are being developed further to apply different medications. Progress in these TDDS could serve as a catalyst for managing the onset of diseases related to the cardiovascular and central nervous systems, diabetes, neuromuscular disorders, genetic disorders, and infectious and confine infectious diseases. Additionally, it could lead the way in spearheading vaccination advancements and bolstering patient preferences for long-term self-administration of medications. popularized.

Author contributions

All authors are contributed equally.

Financial support

None

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Acknowledgements

None

Reference:

1. Langer R. Drugs on target. Science. 2001 Jul 6;293(5527):58-9. https://www.science.org/doi/10.1126/science.1063273
2. Miller ML, Molinelli EJ, Nair JS, Sheikh T, Samy R, Jing X, He Q, Korkut A, Crago AM, Singer S, Schwartz GK. Drug synergy screen and network modeling in dedifferentiated liposarcoma identifies CDK4 and IGF1R as synergistic drug targets. Science signaling. 2013 Sep 24;6(294):ra85-. https://www.science.org/doi/10.1126/science.1063273
3. Sung YK, Kim SW. Recent advances in polymeric drug delivery systems. Biomaterials Research. 2020 Jun 6;24(1):12.
4. Sung YK, Kim SW. Recent advances in polymeric drug delivery systems. Biomaterials Research. 2020 Jun 6;24(1):12.
5. Bora P, Kumar L, Bansal AK. Microneedle technology for advanced drug delivery: Evolving vistas. Curr Res Inf Pharm Sci. 2008 Jan;9(1):7-10. https://www.researchgate.net/publication/228754367_Microneedle_technology_for_advanced_drug_delivery_Evolving_vistas.
6. Katakam P, Reddy MB, Hwisa NT, Assaleh FH, Dey B, Murthy SV, Chandu BR, Adiki SK. Formulation and evaluation

of sustained release venlafaxine tablets using hydrophilic-hydrophobic polymer combinations by melt granulation. J. Sci. Innov. Res. 2014;3:49-59.
(PDF) Formulation and evaluation of sustained release venlafaxine tablets using hydrophilic-hydrophobic polymer combinations by melt granulation (researchgate.net)

7. Mali AD. An updated review on transdermal drug delivery systems. skin. 2015;8(9). https://nlistsp.inflibnet.ac.in/vufind/Search2Record/10.52711_2231-5713.2022.00027/Details
8. Gowri SP, Lakshmi HV, Bhanu VN, Brahmaiah B, Nama S, Rao CB. Proniosome: a novel approach to vesicular drug delivery system. The Pharma Innovation. 2013 May 1;2(3, Part A):166.
9. Lambert PH, Laurent PE. Intradermal vaccine delivery: will new delivery systems transform vaccine administration?. Vaccine. 2008 Jun 19;26(26):3197-208.
(PDF) Formulation and in vitro evaluation of lamivudine multiunit floating dosage forms using novel lipoidal polymers (researchgate.net)
10. Milewski M, Brogden NK, Stinchcomb AL. Current aspects of formulation efforts and pore lifetime related to microneedle treatment of skin. Expert opinion on drug delivery. 2010 May 1;7(5):617-29.
https://www.tandfonline.com/doi/full/10.1517/17425241003663228?scroll=top&needAccess =true
11. Escobar-Chávez JJ, Bonilla-Martínez D, Angélica M, Molina-Trinidad E, Casas-Alancaster N, Revilla-Vázquez AL. Microneedles: a valuable physical enhancer to increase transdermal drug delivery. The Journal of Clinical Pharmacology. 2011 Jul;51(7):964-77. https://accp1.onlinelibrary.wiley.com/journal/15524604
12. Miller ML, Molinelli EJ, Nair JS, Sheikh T, Samy R, Jing X, He Q, Korkut A, Crago AM, Singer S, Schwartz GK. Drug synergy screen and network modeling in dedifferentiated liposarcoma identifies CDK4 and IGF1R as synergistic drug targets. Science signaling. 2013 Sep 24;6(294):ra85-.
https://www.science.org/doi/10.1126/science.1063273
13. Sung YK, Kim SW. Recent advances in polymeric drug delivery systems. Biomaterials Research. 2020 Jun 6;24(1):12. https://www.science.org/doi/10.1126/science.1063273
14. Lambert PH, Laurent PE. Intradermal vaccine delivery: will new delivery systems transform vaccine administration?. Vaccine. 2008 Jun 19;26(26):3197-208.
(PDF) Formulation and in vitro evaluation of lamivudine multiunit floating dosage forms using novel lipoidal polymers (researchgate.net)