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Microneedles: A Astute Approach and Increasing Efficacy for Transdermal Drug Delivery System

Vikrant Nikam[1]*, Shubhangi Damale [1], Rushikesh Ingale [1], Jyoti Khapare[2]
[1]Amrutvahini College of Pharmacy, Sangamner 422 608 (MS), India
[2]Matoshri College of Pharmacy, Eklahare, Nashik 422 105 (MS), India

***Corresponding author:**
Vikrant Nikam; vikrantnikam@gmail.com

Abstract:
While the world's population increase and live longer, monitoring health becomes an important issue. Actual methods use hypodermal syringe creating fear and pain among patients. According to medical science the skin is full of immune cells and scientists now know that this is a very effective area for the application of vaccines and other life saving drugs. Microneedle is the fantastic opportunity waking up by the pharmaceutical industry. Recently microneedle opened a new way to biomonitoring drug delivery. Microneedle patch contains lot of small needles and these needles are very very short so that it does not cause pain. When applied to the skin these small needles create lots of passage across the skin so that the drug can be delivered. Five types of microneedle patch exist such as coated, solid, hollow, hydrogel and dissolving. Currently this microneedle patch can be used in two areas one is for drug delivery and other one is for cosmetics. Microneedle patch is an innovative dosage form suitable for wide variety of molecules such as biologics, vaccines and small molecules.
Keywords: Microneedles, Transdermal, Drug delivery, Drug reservoir.

Introduction:

The method of administering pharmaceutical substances in order to achieve therapeutic effect in humans or animals is referred as drug delivery (1). There are various methodsof drug delivery which includes oral (through the mouth), topical (through the skin), trans-mucosal (nasal, buccal, sublingual, vaginal, ocular, rectal), parenteral (into the systemic circulation), and inhalation routes (2). There areseveral methods for transdermal administration hypodermic needle, topical creams, transdermal patches. The concept of microneedle came into existence in 1970s.

It is a combination of the benefits of hypodermic needle injections and transdermal patches.

Microarray patches are the next generation of intradermal and transdermal therapeutic systems. Microneedle based transdermal drug delivery is painless, less invasive, easy to self administration and imparts high drug bioavailability (3).Large number of active substances absorption is enabled through the skin. The patches consist of an adhesive film and microscopic polymer needles in which the active ingredient is embedded.Fig.1 shows parts of transdermal patch.

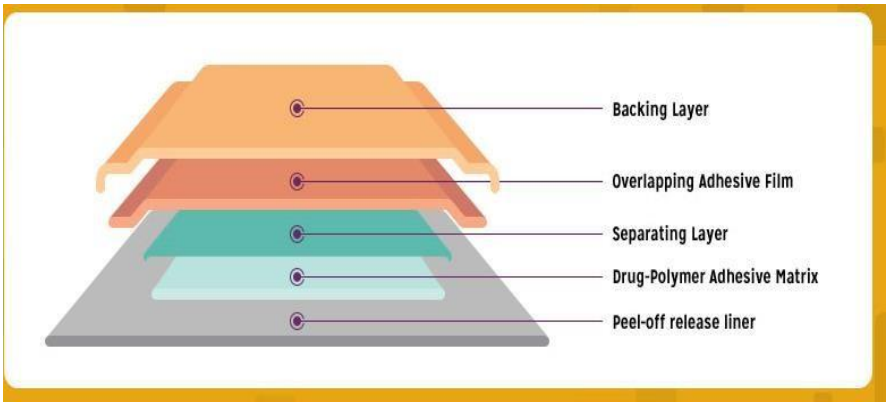

Fig 1. Parts of transdermal patch

Normally a microneedle could be 150-1500µm in length,50-250µm in width, and the thickness of the tip is 1-25µm. Normally a microneedle is made from metal, silicon, polymer, glass or ceramic. The microneedle has a tapered shape. The number, shape and length of the needles their arrangement and the mechanical properties of the patch can be optimally adapted to the respective active ingredient. Microneedle patch is securely fixed to the skin (3). The needles containing the active ingredient penetrate the outer barrier of the skin the stratum corneum without causing pain or damaging the blood vessels. The needle tips dissolve in the epidermis and release their active ingredient. The active ingredient is then absorbed by the body and transported directly to its site of action. The first

pass effect is avoided and provides sustained release of drug (4). Fig 2 shows microneedle transdermal patch with drug reservoir.

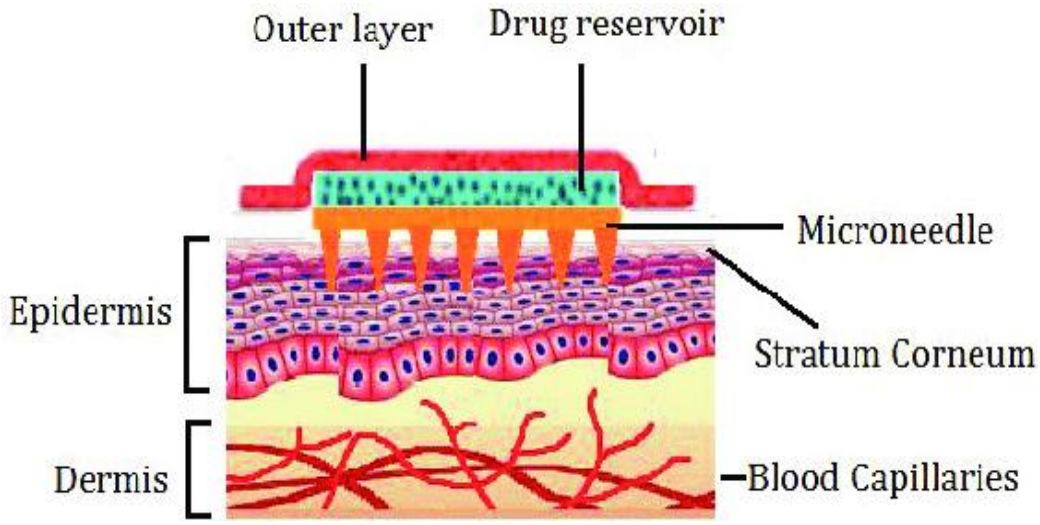

Fig 2. Microneedle transdermal patch with drug reservoir

Microarray patches are suitable for biologicals, vaccines and small molecules and reduce the risk of needle injuries and infections. Advantages of microneedles as compared to a conventional hypodermic syringe then we have the minimally invasive nature of the microneedles as we are no longer having a device that will cause pain and potentially bleeding. There is no issue of disposal that would have with conventional needle and syringe.

Advantages: (3, 5)

- Improved drug delivery as the drugs are delivered directly into the body through the skin.
- It shows rapid onset of action.
- By controlling microneedle formulation accurate dose of drug can be delivered at the site of action.
- Microneedles bypass the presystemic metabolism.
- Microneedles based drug delivery is painless, less invasive as they are small in size and length.
- Microneedle patches are cost effective.
- Dose reduction and enhance drug efficacy as specific area of skin can be targeted for desired drug delivery.

Types of microneedles:

The microneedles can be classified as solid microneedles, coated microneedles, dissolving microneedles, hydrogel microneedles and hollow microneedles (6). Fig. 3 Types of microneedles

Microneedles as an alternative to conventional oral administration of medicine from tablets to capsules there is not only an opportunity to improve the bioavailability of macromolecules like proteins and peptides but also to control the administration of a whole range of drugs over several days. This could be particularly important in elderly patients. There are several advantages and disadvantages of microneedle based drug delivery;

Disdvantages:

- The external environmental conditions such as hydration of skin could affect drug delivery.
- Limited dose of drug is delivered as the size of microneedle is small.
- Insertion of microneedle in the skin can cause allergy or temporary inflammation.
- There are chances of breaking of microneedle which could remain within the skin.
- Manufacturing of microneedle patch requires sophisticated technologies.
- To maintain hygiene of the microneedle patch special storage conditions are required which may increase manufacturing cost.

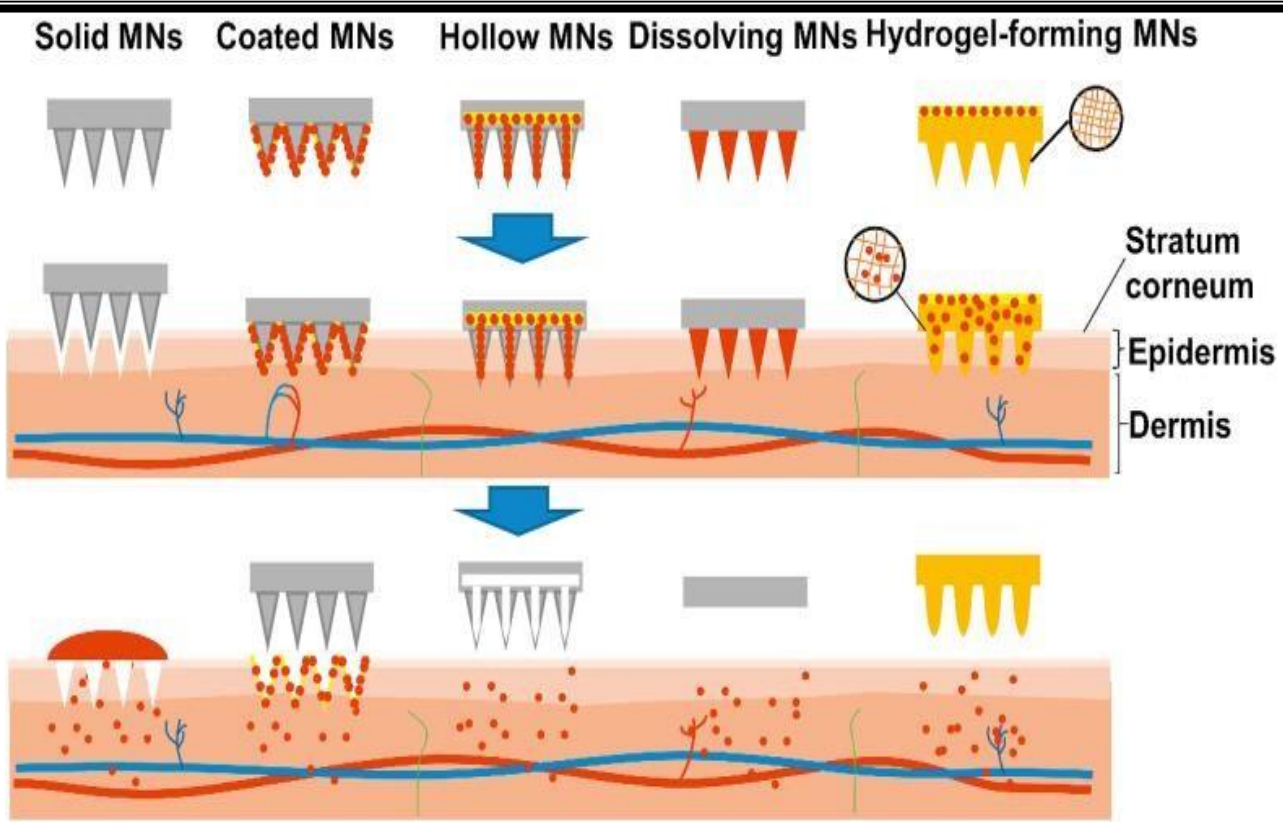

Fig 3. Types of microneedles

Solid microneedles:

Solid microneedles are array generally made from metal material without any drug or excipients. Generally they are used for the pretreatment of the skin. Solid microneedles are mostly used to form pores. They are known to use poke with patch approach for the delivery of active ingredient. Firstly solid microneedles create microscopic holes in the stratum corneum which is followed by application of drug from patch. By this mechanism drug enters the skin and then drug is taken up by the capillaries to show a systemic effect (3, 7). Fig. 4 represents poke and release approach for drug delivery.

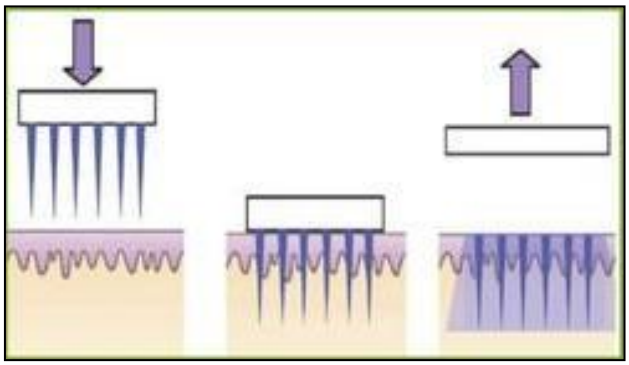

Fig. 4 Represents poke and release approach

Coated microneedles:

Coated microneedles are the microneedles that are coated with drug reservoir solution. Coated microneedles use coat and poke approach for delivery of drug. Coated microneedles incorporate the needle and the drug together by coating the needle with the drug. The microneedle patch is applied to the skin and the drug will be delivered simultaneously to the intradermal space directly. After insertion of the microneedle into the skin the drug gets dissolved rapidly and is absorbed by the body. Advantage of coated microneedle is that it shows rapid release of drug. The amount of drug that can be loaded depends on the thickness of the coating layer and the size of the needle. Coated microneedles are advantageous as it only requires a single patch application which would likely to increase patient compliance. The disadvantage to coated microneedle is the limitation on the thickness of the drug

layer. If the drug layer is too thick it may lead to decrease delivery efficiency due to increased sharpness (3, 7).

Hollow microneedles:

Hollow microneedle is a great advancement from the coated microneedles as it solves the problem with the limitation of quantity of drug allowed to be loaded. As the name indicates 'hollow' means void space. Hollow microneedles has a hollow center in each of the needles with the drug patch placed on the top of the hollow needles where the drug would then diffuse through the needles into the skin when applied. The ability to load higher quantity of drug allows the application of this technology to a bigger variety of drugs. The only issue with hollow microneedles is that it requires a consistent flow rate for the vaccine to diffuse. However during penetration the tip could be blocked by the dense dermal tissue. Polio and influenza are the two most anticipated vaccines for the usage of hollow microneedle technologies (3, 7).

Dissolving microneedles:

Dissolving microneedles are made from pure silk fibrin or polyvinyl alcohol. The drug is infused into the polymer material and will diffuse into the intradermal space once penetrate the skin. Dissolving microneedle patches allow sufficient loading of the drug dose while also being quick and easy to use. However the polymer materials have low mechanical strength which prevents consistent and reliable skin penetration (3, 7).

Hydrogel microneedles:

Hydrogel microneedles are newly developed microneedles. They are prepared from a hydrogel forming material. This is essentially similar material to what soft contact lenses are made from. Hydrogel microneedle is hard in the dry state and can penetrate beneath the stratum corneum and into the viable skin layer. It rapidly takes fluid from the viable skin and swells to form a more jelly like material. It is through this jelly that drug is released or delivered. In this way either the medication is delivered or biomarkers and medicines are picked up that are already in the person's body for monitoring purpose (3, 7).

Advanced skin needling innovation for the treatment of acne scars: Dermapen (8)

A fractional microneedling device that works to tighten, lift and rejuvenate the skin. Effective in reducing fine lines and wrinkles, minimizing pores, stretch marks, surgical and acne scars. Damage to the elastic support structure beneath the skin is what causes acne scars. Skin is comprised of three layers. The epidermis is the outer protective layer from which skin cells generate and are shed as they move to the surface and the underlying layer is known as the dermis. The dermis is comprised of loosely organized mesh like network of collagen and elastin fibres that provide skin with structural support and elasticity. Scars are created in response to skin damage. Cells called fibroblast enter the site that was damaged by acne and create new collagen. However instead of regenerating a mesh like network f collagen and elastin fibres in the same manner that existed before the new collagen is produced in a fashion where collagen fibres are linked in a single direction, resulting in fibrous tissue that lacks the smooth elastic properties of normal skin. This scaring process can result in pits and depression, ridges or thickenings. Dermapen microneedle that penetrate the skin puncture some of the cells but do not damage the entire region. Damage from the microinjuries allows small amounts of cellular material to leak out and influx of ions that disrupt the normal state of the cell. Rather than rapid catastrophic cell death that results in an extensive immune response, the dermapen treated cells begin a process of programmed cell death where the cell start to shrink, lose its attachments and breaks into small compartmentalized units. The result is a minimal immune response. Immune cells that cleanup the cell debris are attracted and release cellular signals draw a better blood supply to the region. Dermapen treatment locally increase levels of transforming growth factor beta-3 which plays an important role in scar free wound healing. Fibroblasts are attracted and begin new collagen production.

Methods of delivering drug:

Number of methods can be used to deliver the drug into the epidermis layer. First approach is to punch the skin with the microneedles to create holes, followed by removal of the microneedle and application of the drug-containing patch over it. This creates a direct transport pathway for a drug to travel into the skin. The electric field can be applied for better effect. The second approach is to cover the microneedle surface with a coating layer containing the drug. The coated microneedles are inserted into the skin where drug dissolution takes place from the coating (9). The third approach is to dip the microneedles into the solution containing drug and scrape the needles on the skin. The drug is left behind into the abrasions. Another approach is to incorporate the drug into a biodegradable polymer and fabricate the microneedles from the mixture. (8,10).

Evaluation of microneedles:

Characterization of microneedles:
Normally drug can be loaded into the microneedles either in suspension/dispersion form or coated with the polymer solution or can be applied as a patch. (5,11). Number of physicochemical characterizations including particle size, polydispersity index, viscosity, and zeta potential can be evaluated for loaded drug depending on the type of formulation used in the microneedles [50]. Drug release, adhesion, permeation tests are performed for a patch which is applied after pre-treatment. The size, internal structure, and crystallinity of the liposomes or nanocarriers can be performed using a dynamic light scattering, X-ray scattering, and transmission electron microscopy technique. Stability studies of drug dispersion and microneedles can be studied at a different temperature, pH and simulated in-vivo physiological conditions (cell line or tissues). Other tests like solubility studies, drug content, in-vitro release tests, and biocompatibility studies are also performed on designed microneedle

Dimensional evaluation of microneedle:
Various methods are used to evaluate the tip radius, length, height, geometry of the microneedle. Most common methods are optical or electrical microscopy. Scanning Electron Microscope (SEM) and confocal laser microscope have been used for this purpose. SEM produces an image of a sample by making use of a focused beam of electrons which interact with the atoms in the sample while scanning and produce various signals which give information about sample surface topography and composition. Confocal laser microscope produces high-resolution images (12,13).

Mechanical properties:
A microneedle must be sharp and slender enough so that it can easily penetrate into the skin and also be strong enough so that it does not break when inside the skin. Mechanical tests which are performed on microneedles include insertion force & depth. The ratio of these two forces is called as the 'safety factor'. The ratio is preferred to be as high as possible (14).

In-vitro skin permeation studies:
In-vitro skin permeation of the drug performed on diffusion cell apparatus. Pig ear skin is mostly used in the experiment which is mounted between the receptor and donor compartment. The cumulative permeation profiles of microneedle treated and untreated skin are compared (15).

In-vivo animal model studies:
In-vivo animal studies performed on hairless rats. A suitable technique to anesthetize the animal shall be used. One of the parameters considered is trans-epidermal water loss which is measured before and after micro needling. (15).

Patient compliance and safety:

Skin recovery process:
Normally microneedle device is inserted into the skin and removed after the treatment, it produce holes of micron size. It may take time to close these pores. These holes need to be closed quickly, otherwise may cause infection. Pore closing can be studied by electrical impedance measurement. It can take 2–40 hrs to recover depending on whether the skin is occluded or not and also the geometry of the needle. Tissue staining can be used to study pore closing (15,17).

Skin irritation:
The transdermal injections show a small inflammation around the site because a foreign material is being inserted into the skin (18).

Skin irritation and infection:
Sensitive skin use of microneedles can cause mild to moderate skin irritation or allergy. Redness, pain, swelling can be seen. Itching can cause patient discomfort [55]. Holes caused by inserting microneedles into the skin can be a site of infection unless the needles are sterile. Although the pores created by microneedles are very small as compared to that of a hypodermic needle, thus show less microbial penetration (19).

Pain:
The microneedles produce less pain as compared to that of a hypodermic needle. The strength of pain depends on the number of microneedles on a patch, length of the microneedle and the tip angle or needle shape (20).

Applications:
Microneedles have a wide range of theragnostic applications in the field of molecular medicine, cell biology, human biology, biomedical engineering, and genetic engineering. Potential applications of microneedles are shown in Fig. 5. Microneedles are used for the local drug administration and development of personal medication on the basis of introducing an RNA medicine, DNA, peptide, and proteins (21-30). These molecules play an essential role in medicine. These molecules as drugs are target delivery and to maximize the drug concentration reached to the affected site (31-38). Normally microneedles use in cosmetics, Oligonucleotide delivery, Vaccine therapy, Peptide delivery, Hormone delivery, Lidocaine delivery, Pain therapy, Ocular delivery, Cancer therapy (39-46).

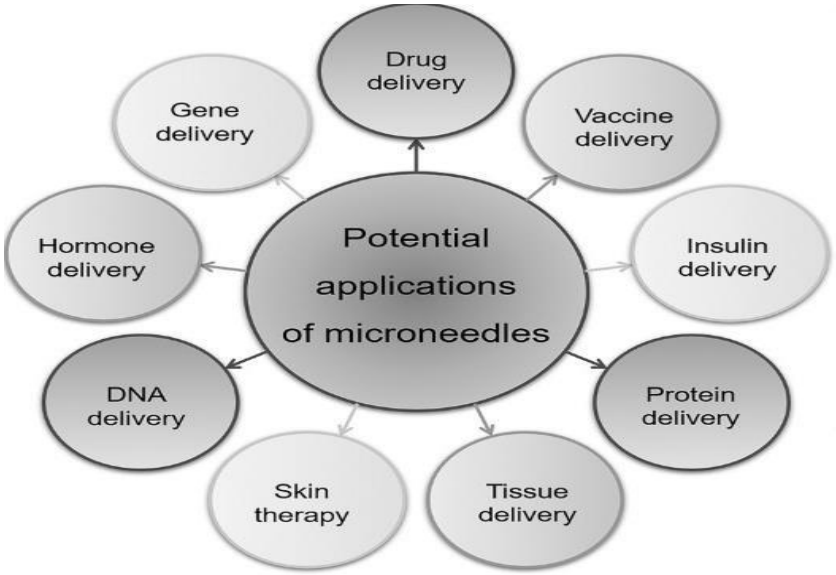

Fig 5. Applications of Microneedles

Conclusion:
Today's oral administration and hypodermic syringes are the most commonly used delivery methods but they possess several disadvantages such as painful side effects of using hypodermic syringes or drug bioequivalence problem with oral administration. Transdermal patches as an alternative method as they provide controlled release of medicine to the patient but they cannot permeate large molecules to pass the subcutaneous layer thereby limiting the medical application to patients. Microneedles have been proposed to overcome this limitation and provide the transdermal delivery of large molecular weight proteins. The microneedles can be made from polymers, metals, glass and silk. But the main problems associated with the microneedles technology include, skin allergy, redness and irritation. A limited amount of drug can be loaded into the microneedle. Passing hydrophilic and large compounds through the skin is a major challenge. A proper material has to be selected in the fabrication of these needles, which has adequate mechanical strength and insertion force. The main objective is to increase the permeation without causing pain. A number of technologies are developing to deliver the drug through the skin. Various modifications have been investigated in the conventional microneedles. Microneedles can be fabricated with a variety of modifications in order to smartly deliver the drug through the skin providing a new direction and revolution in the field of transdermal drug delivery systems. Microneedles have a wide range of theragnostics applications for the development of targeted drug delivery systems toward cancer, diabetes, CNS disorders, immune disorders and genetic disorders.

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Consent for publication: Not applicable
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