International Journal of Research in Pharmacy and Pharmaceutical Sciences
ISSN: 2455-698X
Impact Factor: RJIF 5.22
www.pharmacyjournal.in
Volume 3; Issue 2; March 2018; Page No. 38-42

Microneedles: A review on painless micro injections

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Abstract
In the modern days everything this world is getting small but has more powerful and desired functions than its predecessors. In the same way Micro and Nano technologies of drug delivery have been emergent to meet the desired needs of the drug in comparatively smaller doses and with least inconvenience of administration to the patient. This article quotes about the various advantages of Microneedles over the conventional dosage forms with less pain and required target action. Microneedles are typically needle like structures of micro sizes that are dissolvable and are pain less method of injecting the drug into the epithelial layers. The patch of microneedles that are 100–1000 μm in size poke through the skin and allow micron-scale drugs to pass into the blood stream. This proves a carrier in the transport of drugs to the skin deep into the systemic circulation. This article discusses about the types, mechanism of action, methodology, merits and demerits and approaches of the microneedles.

Keywords: microneedles, quadruplet microneedles, biodegradable microneedles

Introduction
There are various drug delivery systems for the administration of the drug into the body. Among them, the oral route of drug delivery is the most preferred and convenient route. But there are some cases in which oral or conventional route of drug administration may not satisfy the purpose of medication. So for satisfying the needs, other routes of administration have been developed after a humongous research over them. In that transdermal drug delivery systems is one of the routes of administration which deliver the drug through external epithelia. During the recent times, there is a tremendous advancement in transdermal drug delivery systems in providing health care services. These types of drug delivery systems are preferred because they have several advantages over the conventional route of drug delivery like preventing the unpleasant taste of the drug, avoids fast pass metabolic activities by the liver and also helpful in giving the immediate response of the drug by steady release. And it is more effective and easy for administration. In transdermal drug delivery systems, the drug is administrated by different pathways like transcellular and intracellular pathways. In both the pathways the drug is delivered to the site of action by simple diffusion. The other important pathway is by micro-needling through microchannels. In the mechanism of micro-needling, the skin is temporarily disrupted by placing the microneedle in the epidermis and the drug is released and delivered to the site of the target. According to recent research, the technology advancement has put forward in delivering large molecular weights of hydrophilic compounds for a single time [1-5].

Microneedles are manufactured in different shapes and sizes by using different materials to deliver drugs. They are made by fabrication of different materials like metals, silica, glass, polymers etc. on a micro scale. The microneedle ranges from 1-100 microns in length and 1 micron in diameter. These are made in very small size because it should not create any pain and should not cause any damage to skin when it is penetrated into epidermal layer. Microneedles are used along with transdermal patches. These transdermal patches deliver the drug by simple diffusion. When hallow needles are penetrated into the skin through these patches holes are formed and thereby permeability is increased, this type of mechanism is known as the pumping mechanism. So by this diffusion through pumping mechanism facilitates continuous drug delivery. Many approaches have been developed and utilized in order to increase skin permeability, ranging from chemical/lipid penetration enhancers to non-cavitation ultrasound, thermal ablation, iontophoresis, sonophoresis, microdermabrasion, electroporation, cavitational ultrasound, and microneedles [6-8].

The microneedles are shown in the figures1 and 2.

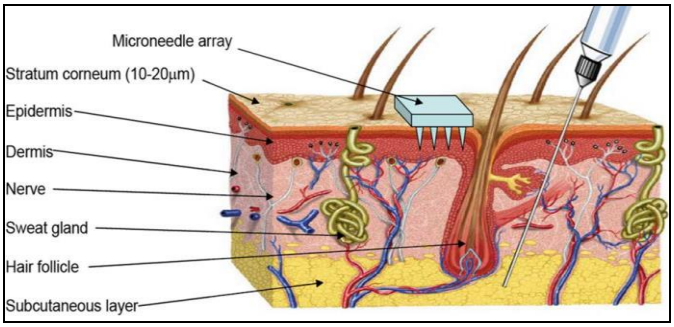

Fig 1: Anatomy of Skin

Fig 2: Microneedles

Advantages

The advantages include: [9-11].

- Cause minimal pain and irritation.
- Has a good pharmacokinetic and pharmacodynamics response.
- Do not cause extensive rupture of skin.
- Does not damage the nerves and nerve endings.
- Quick delivery of drug substances.
- Target delivery is possible.
- Large molecules can be administered.
- First pass metabolism can be avoided.
- Faster healing than the conventional methods.
- Decreased microbial penetration when compared to the conventional hypodermic needle.

Disadvantages

The disadvantages include: [12-15].

- Careful handling is must.
- Few external factors like hydration of skin might affect the drug delivery.
- Repetitive administration may damage the veins.
- The tip if microneedles may break and remain in the skin while removing the patch.
- Sterility of the preparation might be a problem if not carefully handled.

Salient Features

Microneedles have a large number of distinct features that make it a desired delivery system. They are: [16-19].

- Pain-free administration of the drugs
- Easy to use preparation.
- Discreetness of the product.
- Continuous release of the drug is possible by incorporating necessary agents in the formulation.
- Controlled release of the drug can be achieved.
- Safer handling of the active ingredient
- Patient compliance is relatively good.

General mechanism of action

The mechanism of action of micro needles is not only by simple diffusion but it also involves the process of temporary mechanical disruption of skin and release of drug in to the epidermis to reach the target site. Microneedles help in increasing the permeability of the skin by which drug can easily travel through the patch and enter in to epithelial layer. Before administration drug is incorporated in to the needles and is mechanically inserted in to the skin. Then the drug starts releasing in to the blood stream and reaches target site. And there is no need to remove these patches, the needles will also get dissolved and absorbed after giving therapeutic response at the site of action as they are made of safe and biodegradable substances [20-22].

Methods of drug delivery

There are different delivery methods employed to use microneedles for transdermal drug delivery system. They are as follows [23-27].

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

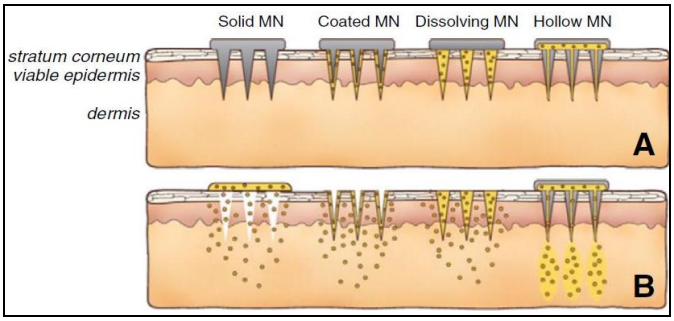

Fig 3: Approaches of Microneedles

Coat and poke approach of transdermal drug delivery

In this approach of drug delivery the microneedles are coated with drug containing dispersion. Different techniques are used for preparing the coated microneedles. The electro dynamic atomization is one of the common technique used for the preparation. The ethanol and methanol are used as vehicle system in the coating formulation. Fluorescein dye and polyvinyl pyrrolidine are used as adhesives in the formulation. Then finally the microneedles are coated with this coating solution and are inserted in to the skin for drug delivery through dissolution mechanism.

Dip and scrape approach of transdermal drug delivery

In this method the microneedles undergo the process of dipping in drug solution then followed by scraping across the skin surface to leave behind the drug within the micro abrasions which were created by the microneedles.

Solid microneedles in transdermal drug delivery

In this method of drug delivery, the array of projections are first penetrated into the skin for making holes in stratum corneum and are applied before the administration of drug and later they are discarded. The solid microneedles will create micron sized holes in the skin through which the drug is easily transported. This type of approach is helpful in case of inserting microneedles under specific period of time. Then after insertion micro channels are formed through which the drug is transported to different layers of epidermis. Before inserting into the skin these solid microneedles are coated with the drug. After removing these solid microneedles drug deposition takes place within the skin membranes. There are also some limitations to this process of approach, sometimes

improper delivery of drug takes place due to poor flow. Thick layer of drug formulations are not preferable for this kind of drug delivery as it affect the sharpness of the needles and also creates pain during insertion.

Hollow microneedles in transdermal drug delivery
This method involves the process of injection of drug through a hollow bore. This hollow bore is located at the center of the needle. When the microneedles is pierced in to the skin, the hollow bore present inside bypasses the stratum corneum layer and creates a direct channel to the other lower layers of epidermis. This kind of approach is mainly employed for injection of drug solution in to the skin directly. The hollow bore helps in interior transport of drugs through the needles either by diffusion method or by pressure driven flow. This method of approach is more reminiscent of an injection than a patch.

Biodegradable microneedles in transdermal drug delivery
For preventing the skin barrier properties that restrict the flow of transdermal drug delivery, the arrays of microneedles are fabricated by silicon or other metals. For meeting the better standards, safety measurements and the quality of product, the microneedles are made of different biocompatible and biodegradable polymers. For preparing the biodegradable polymer microneedles with sharp tips different techniques like micro-electromechanical masking and etching were done. Polylactic acid, chitosan, polyglycolic acid, or poly (lactide-co-glycolide) (PLGA) are some of the polymers used as biodegradables and these polymer will form a matrix and get degraded after its application in to the skin. These are conventional for sustain delivery of drugs by choosing proper polymers. These are mechanically evaluated by inserting in to the skin and tested their biodegradable property.

Types of Microneedles
There are different types of microneedles made up of different materials [26-30].
1. Single-tip microneedles
2. Quadruplet microneedles
3. Hollow microneedles
4. Solid microneedles

Single-tip microneedles
Single-tip microneedles are the first type of microneedles that has a sharp tip. Single-tip microneedles are in straight shape and 200µm in length. The sharp tip consists of different angles of 150, 300, 450, 750.

Quadruplet and Hollow microneedles
Quadruplet microneedles are the second type and Hollow microneedles are the third type. The Quadruplet microneedles and Hollow microneedles are good in strength and are not expensive. The Hollow microneedles offer the possibility of active injection of the drug into the tissue. The advantage of this is that larger amount of drug can be given at a time. The Hollow microneedles have lumen diameter 30µm and height 250µm. They carry the drug continuously by diffusion. Removal of fluid from the body for analysis can be obtained.
Classification of microneedles is usually based on the fabrication process. Microneedles are either prepared as in-plane microneedles or out-of-the-plane microneedles.

In-plane microneedles
In-plane microneedles are parallel to the substrate surface. The advantage of this type of microneedles is that length of the needle can be accurately controlled. The disadvantage of this type of microneedles is that it is difficult to fabricate two-dimensional array.

Out-of-the plane microneedles
Out-of-the plane microneedles protrude out of the substrate surface. Various factors become a significant challenge in the fabrication of these type of needles like length and high-aspect ratios.

Solid microneedles
The solid microneedles are the fourth type. This type of microneedles creates holes in subcutaneous and is applied before application of medicine and thereafter removed. Increase the permeability by poking the holes in and rub the drug over the area. The solid microneedles are fabricated in 750-1000µm in length, 190-300µm in base area and 150-200 tapering tips angle.

Other types
Another type is the Dissolving microneedles. These involve targeting the drug within the dissolvable by insertion into the skin for drug release. Polymers used for this type of microneedles are PLA, PGA, PVP, Polycarbonate.
For fabrication different type of materials are used they are Silicon, Glass, Metal, Polymers. Silicon when used in solid microneedles the fabrication is costly because silicon is brittle and may break through the skin. Metal when used in solid microneedles have good mechanical strength and cost is low.

Evaluation Parameters
The evaluation parameters can be classified into two types i.e. *In vitro* & *In vivo*. They are [30-35]:

***In vitro* study**
In vitro study of microneedles is accomplished by various mediums like menthol and agarose gel to insert the microneedles. The *In vitro* test is used to determine the characters of a new test device. The main objective of this type of *In vitro* involves optimization of microneedles, evaluation strength of microneedle, finding penetration force and bending force, determination of dissolution rate of coating materials, estimation of efficiency of drug delivery. Various methods are conducted as follows
Method A- This method follows the efficacy of microneedles. In this microneedles are integrated with polydimethylsiloxane biochip and black ink is injected by microneedle into the Petridish, which contains menthol.

Method B- Rhodamine B dye injected into microneedles to 1% agarose gel to evaluate the penetration force and flow of solution after penetrating into 1% agarose gel.

Method C- In this method, we insert microneedle into porcine

cadaver skin and pig cadaver skin from 10s-20s and 5min are evaluated by this method. This method is used to determine the delivery efficiency and dissolution rate of coating materials, which are coated on microneedles tip with vit.B and calcein.

***In vivo* study**

In vivo study of microneedles is accomplished by conducting a preclinical study on mice, guinea pigs and rabbits monkey etc. are used. The main objective of the *In vivo* is the determination of safety and toxicity of the tested compound. *In vivo* testing of microneedles of include to perform skin toxicity test, mechanical stability, penetrating force in a different skin, bending and breaking force, determination of various parameters like skin sensitization, chronic dermal toxicity, carcinogenicity.

Method A- Involves testing of microneedles by injecting into the tail of hairless mice. It is used for the determination of penetration force into the skin.

Method B- In this method of testing of microneedles, Rhodamine B is injected into hairless tailed mice and anaesthetized for determining penetrating force and bending breakage force.

Method C- This method is used for the evaluation of vaccine delivery by microneedles and can be done by administering Ovalbumin, a model protein antigen into the hairless guinea pig by using solid metal microneedles at the rate of 20µg ovalbumin in 5s up to 80µg.

Method D- This method involves the use of rabbits for vaccine delivery. Anthrax vaccine containing the recombinant protective antigen of Bacillus anthracis is injected into the rabbit by hollow and solid microneedles.

Conclusion

As per the today's research advancement in pharmaceutical technology, microneedles that are made up of silicon, glass, plastics and metal have been effectively used in the transdermal drug delivery including the biodegradable and biocompatible substances. The polysaccharide biomaterials are also utilized for controlled delivery of drugs. In this way the microneedles have been succeeded in increasing the permeability of skin through transdermal patches. Much more extensive studies have to be done for utilizing microneedles for higher number of drugs. And also sufficient care must be taken in preventing skin irritations and risk of infections. As of now microneedles have been proven to be an effective novel drug delivery system in administering various drugs to get the desired action much more efficiently and an effective research and study in this field will definitely help in the development of a drug delivery system of desired characteristics.

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