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Review

PAINLESS MICRONEEDLES

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Abstract

People generally have aversion to take injection, due to the pain caused. To overcome this pain, painless injection chips are being developed. Once such device is a painless vaccine chip, which consist of a round shaped chip of 1.5 cm diameter and possesses 300 micro needles that allow the drug to penetrate the body through the dermis. These micro needles are made up of water soluble polymer which on insertion releases the dose, which is absorbed in the circulatory system. Each of the needles is 0.5 mm long and 0.3 mm wide at the base. The needle dissolves and administers the vaccine, after penetrating just 0.5 mm in the skin so the patient feels no discomfort and there is absolutely no bleeding. Earlier efforts to develop painless needles had been a failure because the micro syringes used were made up of sugar, which degraded at temperature above 100 degrees centigrade. Now the sugar moiety has been replaced by a water soluble polymer which dissolves while injecting the vaccine, eliminating the chances of degradation and making the system very efficient.

Key Words: Skin, Hypodermis, Transdermal, water soluble polymers

Introduction

Drugs, which are administered orally, are considered to be not suitable for every situation due to its enzymatic reaction in gastric tract or in liver. While, parenterals are considered to be the best choice for any situation & can be given for quick release of drug, but injecting a drug into the body involves lot of pain which affects the compliance of the patients.^{1,2} Utilization of the micro needles which are considered painless or suppose to cause the minimum pain while delivering the drug is considered a better alternate to the parenterals. Till date, various research studies has been conducted to enhance the painless activity of the micro needles and to improve the permeation of the drug molecules across skin, with good success. This technology has also shown the promising results for

the delivery of the high molecular weight drugs such as oligonucleotides like Insulin and vaccines etc. Today, there are three research institute working on same problem of pain caused by injection are now nearing to give painless vaccine system. It was during the mid 90's when the idea of Microneedles is proposed but the technology was considered promising candidate for broad range of drugs in early 2000s with widespread use.

Micro needles can be employed in number of ways for the delivery of the drugs through transdermal route of drug delivery. Out of these the most employed technique is focused on making the microscopic holes in the skin by penetrating the micro needles made up of Silicon or metal. Micro needles can be utilized by two different approaches, as follows:^{3,4}

1. Coat and poke approach: In this the drug is loaded in the microneedle reservoir and pierced into the skin. The release of the drug into body takes place by diffusion.
2. Poke with patch approach: In this, microneedles are first pierced into the skin, and then the drug patch is applied on that part of the skin. Transport of the drug occurs via diffusion or by iontophoresis.
3. Dip & scrape technique : This approach is a variant of the coat and poke approach, where the microneedles are dipped in the drug solution and is scrapped on the skin, while the drug left behind the abrasions made by these microneedles.
4. Hollow microneedles : Hollow microneedles possess better design and approach in comparison to patch.⁵

Structure of skin

Skin is the outer protective covering of the body, consists of the dermis layer (or corium) and the epidermis layer.

- The Epidermis is the layer which provides waterproofing and acts as a barrier to infection.
- The Dermis is the layer which provides the location for the appendages of skin.
- The Hypodermis (Fig.1)

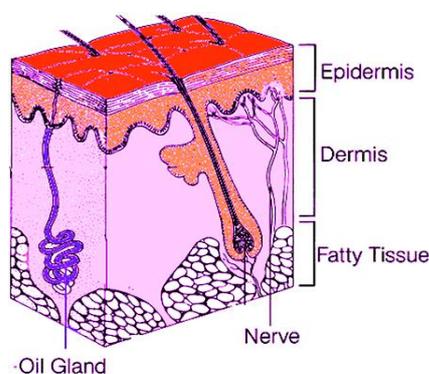


Fig. 1. Structure of skin

Epidermis

Epidermis is the outermost layer of the skin. It forms the waterproof, protective covering over the body surface which is made up of stratified squamous epithelium with an underlying basal lamina. The epidermis does not contain blood vessels, and cells which are present in the deepest layers are nourished by diffusion from blood capillaries extending to the upper layers of the dermis. The main type of cells which make up the epidermis are Merkel cells, keratinocytes, with

melanocytes. Langerhans cells are also present. The epidermis can be further subdivided into the following strata (the outermost layer): corneum (present in palms of hands and bottoms of feet), granulosum, spinosum, basal. Cells are formed by the mitosis at the basal layer. The daughter cells climb up the strata changing shape and composition as when they die due to isolation from their blood source. The cytoplasm is released and the protein keratin is introduced. They now reach the corneum and slough off. This process is called keratinization and which occurs within about 27 days. This layer is responsible for keeping water within the body and keeping other harmful chemicals and substances like pyrogens out, making skin act as natural barrier to infection. This layer helps the skin to regulate body temperature.⁶

Dermis

The dermis is the layer which is present beneath the epidermis and consists of connective tissue and act like cushions for the body from stress and strain. The dermis is closely connected to the epidermis by a basement membrane. It also contains many mechano receptors that provide the sense of touch and heat. It contains the hair follicles, sweat glands, sebaceous glands, apocrine glands, lymphatic vessels and blood vessels. The blood vessels in the dermis provide nourishment.⁶ The dermis is structurally divided into two areas: uppermost area next to the epidermis, called the papillary region, and a deep lined area known as the reticular region.

Hypodermis

The hypodermis is not part of the skin but it lies below the dermis. Its purpose is to connect the skin to bone and muscle as well as supplying it with blood vessels and nerves. It contains 50% of body fat. Fat serves as padding and insulation for the body. Another name for the hypodermis is the subcutaneous tissue.

Microorganisms like *Staphylococcus epidermidis* colonize the skin surface. The density of skin flora depends on region of the skin. The disinfected skin surface gets recolonized from bacteria residing in the deeper areas of the hair follicle, gut and urogenital openings.

The skin has various layers however if only the epidermis layer is pricked, there will be little or no pain would be caused. This micro needle system on the other hand, is made up of water soluble polymers which will dissolve in epidermis and the

upper layer of dermis measuring only 0.5 mm deep into the skin. The skin has various layers however if only the epidermis layer is pricked, little or no pain would be caused. This micro needling system on the other hand, are made up of water soluble polymers which will dissolve in epidermis and upper layer of dermis ranging to only 0.5 mm deep into the skin.

Microneedles

These are small arrays of needles mostly about the size of a dime which are made of silicon, glass, or biodegradable polymers using techniques such as microlithography and etching. This technique is widely employed in the manufacture of electronics products. There are two major points which are considered for the success of painless drug delivery. They are sharpness and length of the needles.

For the successful fabrication of micro needle the tip should be finer than a human hair by ten times and the needle should very short in length. Thus the pain is not felt while piercing as it does not reaches the dermis layer.⁷

There are four different modes by which drug can be delivered into the skin using micro needles. These modes are:⁸

1. Solid micro needles pierced into the skin is then followed by application of a drug patch at the treatment site.^{9,10}
2. Micro needles are coated with drug and inserted into skin for its better application & dissolution inside the skin for absorption in circulatory system.¹¹
3. Encapsulating drug within biodegradable, polymeric micro needles followed by insertion into skin for controlled drug release.¹²
4. Drug is injected through hollow micro needles.¹³

Types of micro needles

There are two types of micro needle used:

1. Solid micro needles
2. Hollow micro needles

Solid micro needles: For the easy transportation of molecule through the skin a micro hole is done with help of solid micro needles.⁷ Initially, micro needles were made up of silicon wafers for intra cellular delivery, for the enhancement of the molecular uptake and gene transfect ion they were inserted into the cell and nematodes .When this work was done and published many new compounds were synthesized for insertion into the skin.¹⁴

Hollow micro needles: To enhance the rate of flow of drug new micro needles were used having cavity in them, they were hollow from inside which offer the possibility of delivering the drug without wasting it. For more rapid rate of insertion we can use the pressure driven flow. Single glass fabricated micro needles were used to insert the insulin in the diabetic hairless rat for 30 min diffusion, the study demonstrated that glucose drops to 70% in 5 h span. These micro needles were fabricated with the help of micropipette puller and beveller of 60 Am radius. This study demonstrates micro needle-based drug injection into the skin.¹⁴

Why micro needles do not cause pain?

Due to the advantage of providing drug without causing pain micro needles are preferred over other delivery system, as micro needles only penetrate through the stratum corneum which is devoid of nerve fibers. Hence there is no pain sensation occurs. Though during the actual practice penetration of the micro needles up to the epidermis and sometimes to the dermis as well is seen, which contains only slight amount of nerve fibers. But still the microneedles are considered painless, due to lack of interaction with these nerves.¹⁵

In order to determine the painless characteristics of the micro needles, a clinical experimental trial was conducted involving 12 human volunteers, where the pain caused by inserting the micro needles is compare with pressing of the skin against the flat surface and with the hypodermic needle of 26 gauges. The study shows that the subjects reported the sensation of the pain due to hypodermic needle but there is no sensation was found with the flat surface and the micro needles. Other studies have also been carried out till date in order to quantify the activity of the micro needles.^{16,17}

Fabrication of micro needles

Process of micro needle formation involves following steps (Fig. 2).¹⁸

Laser cutting: Earlier micro needles were prepared by cutting the stainless sheets by IR (Infrared laser) using AutoCAD software in which details of the micro needle shape and the dimensions are feeded. Infrared laser were operated at a frequency of the 1000-1100 Hz, with energy density of 18-22 Joules per square meter area to cut micro needles which involves passing of the laser beam thrice through stainless steel sheet with a cutting speed of 2-2.5 mm/s and air removal at 140000 Pa, pressure.

Cleaning and bending: Cleaning of the laser cut micro needles was done manually with the detergent for removing the grease, slag and oxides from the surface which are deposited during the laser cutting, followed by the rinsing in running water.¹⁸

Electro polishing: To enhance the sharpness of the tip and to debur and cleaning of the edges of the microneedles, they are electropolished in the solution of glycerin, ortho-phosphoric acid (85%) and water in a ratio of 6:3:1 v/v. This operation is performed at 700 C in 300 mL beaker and stirring it at 150 rpm. In this, copper plate is used as cathode and microneedle as the anode, which is kept on vibrating at the 10 hz by using vibrating device throughout the electropolishing procedure. This helps in removal of bubbles which are produced due to electropolishing at the anodic end. The size of the micro needle is reduced to 50 μm due to electropolishing. They are dried using compressed air.¹⁸

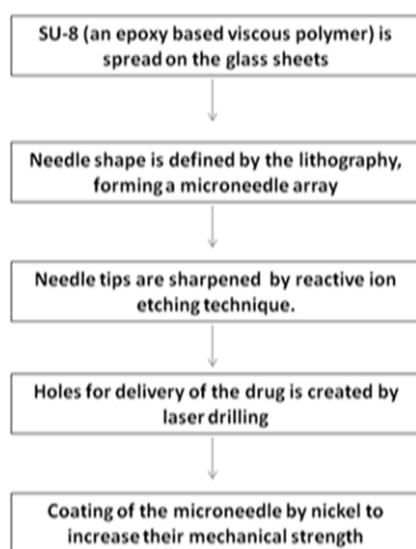


Fig.2. Stages involved in fabrication of micro needles

Polymers used in micro needle technology

The polymers used in micro needle technology are given in Table 1. The polymers should be completely water soluble and must also provide a wide range of functionalities and benefits to a variety of applications. They should also be easier to work with.

Delivery from coated micro needles

Since it was found that the efficiency of the coated micro needles is more as it get deposited inside the skin and there is no residue seen on the skin surface

suggesting the high bioavailability, delivered through the small surface area of micro needle. Vaccine delivery via coated micro needle is considered to be effective because delivery focuses on the dendritic cell which is responsible for better immune response. Storage and delivery of vaccine in solid-state coatings should increase the stability of antigen, which may help in eliminating the need for cold-chain storage.¹⁸

Table 1: Polymers used in common marketed preparations

Marketed Product	Polymer
CELLOSIZETM	Hydroxy ethyl cellulose (HEC)
DOWTM	Latex powders (DLP)
ETHOCELTM	Ethyl cellulose polymer
KYTAME R TM	PC polymers
METHOCEL TM	Cellulose ethers
POLYOX TM	Water soluble resin

Advantages of micro needles

Some of the advantages offered by micro needle technology are listed below:

- Penetration of skin is easy²⁰
- Delivery of drug is effective²⁰
- They do not hurt¹⁹
- They are biocompatible¹⁹

Current research on micro needle technology

Takada and coworkers have developed a round vaccine *chip* that is 1.5 cm in diameter and it contains as many as 300 micro needles. The unique feature of this device is that it can deliver drugs to the body without breaking the dermis layer of skin.⁸ It penetrates just 0.5 mm before the needles dissolve and administer the vaccine, and hence, the patient feels no discomfort and pain. Moreover, there is no bleeding.⁷

It took six years to develop the new drug delivery system by Professor Takada to rectify earlier efforts by other researchers that used micro needles made out of sugar. Previous procedure failed because sugar degrades at temperatures above 100 °C. To overcome this shortcoming, Professor Takada replaced sugar with a water-soluble polymer that dissolves when pressed into the epidermis, releasing

the vaccine to be absorbed into the circulatory system.⁸

Applications of Microneedles

1. *Blood glucose measurements*: As it is mentioned earlier that the micro needles penetrates up to 10-15 μm which does not cause pain thus it can be effectively used in the taking of blood samples. Since there is huge no. of population suffering from the diabetic disease they require the regular drawing of blood sample, hence they will be the most benefited part of it. Kumetrix is an example of the company fabricating such devices.

2. *Transdermal drug delivery*: In transdermal drug delivery system the limitation of drug molecule is to be small, because of the stratum corneum does not contains any nerves. So that the micro needles could easily penetrate across this layer. It does not stimulate the nerves due to its shortness in length, and help in introducing painless system. Use of the hollow micro needle help in delivering medicines, insulin, protein and nanoparticles

3 *Molecular and cell biology*: Micro needles are used to deliver DNA, oligonucleotides, proteins and delivery of impermeable membrane molecule into the host. Micro needles are widely used to deliver DNA into plant and mammalian cells helping in growth of molecular biology.

Microneedle technology has shown potency and positive sign for the use in painless injections. It is just similar to laser technique with minimum of damage in the skin. Clinical resolution labs utilize micro rollers for the treatment, where penetration of micro needle is done to epidermis breaking the old collagen strands leading to youthful skin.

Conclusion

In last many year there were different technique which were used but they failed due many reasons, no. of experiments were conducted for determining the reasons of their failure which were not so successful, but this method will prove to be one the of the major success in medical era by killing the pain. Many people particularly children they have great fear of injection but now they will feel like toying with it. It will also help the diabetic people who were require taking multiple injections on daily basis. This technology will help in production of new improved devices which will be smaller, painless and cheaper. The future of drug delivery is assured to be significantly influenced by micro fabrication technologies.

Declaration of Interest

It is hereby declared that this paper does not have any conflict of interest.

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