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A REVIEW ON MICRONEEDLES: RECENT ADVANCEMENTS AND ITS APPLICATION

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ABSTRACT

In comparison to other drug delivery system the novel drug delivery system has various advantages and benefits over other drug delivery system. The drug delivered through the novel drug delivery system does not undergo first pass metabolism due to which there is zero chance of irritation of gastro intestinal tract as well as the large amount of drug can easily be absorbed into systemic circulation because when the drug undergoes first pass metabolism some amount of drug gets metabolised but in case of novel drug delivery system it does not occur. In case of transdermal drug delivery system there is a one major disadvantage that is the resistance created by the stratum corneum to The drug flow to the systemic circulation. Here what happens when the drug is applied trans dermally the stratum corneum act as barrier for the drug flow from the skin to the systemic circulation. To overcome this major disadvantage of the transdermal drug delivery system, there started a development of another type of novel drug delivery system namely "Microneedle Drug Delivery System" In microneedle drug delivery System, the drug is delivered by micron sized needles which get penetrated into the skin. So, That the drug can easily be delivered. In this case when the microneedle containing drug is penetrated into skin it crosses the uppermost layer of skin known as Stratum corneum. As the microneedles are in micron sized it crosses the Stratum corneum and delivers the drug to the epidermis and upper dermis layer. As we know that the lower art of the dermis contains the nerve endings and the microneedle delivers the drug to the epidermis and the upper dermis layer. Hence it does not create any major pain and also does not harm any healthy tissue during the penetration of the microneedles into the skin. So, this advancement of microneedle drug delivery system in the field of pharmacy was boon for the society. This microneedle has various advantages and benefits over the transdermal drug delivery system like it does not harm the healthy tissue, there is less chance

of microbial attack, it is patient compliable, it does undergo first pass metabolism, it is almost painless and having no other side effects. The microneedles are mainly classified into – Solid Microneedles, Coated Microneedles, Dissolving Microneedles, Hollow Microneedles and Hydrogel forming microneedles. This article also contains the descriptive information about the fabrication materials as well as the different fabrication methods. Each method is identical for the particular type of material used for the production of microneedles. This review article contains a brief information about the microneedle drug delivery system and its importance in the present scenario. It also contains a descriptive and detailed information about the researches which were done in the field of microneedles as well its different fabrication technique used for the manufacture of the microneedles. Although a lot of research work need to be done for more improvement and advancement in the drug delivery through microneedles.

KEYWORDS: Solid Microneedles, Coated Microneedles, Dissolving Microneedles.

INTRODUCTION

The skin is the outer most layer of our body which act as protecting sheath or covering which protect our body from various intolerable and obnoxious particles, microorganisms, antigen etc. which may harm our body.

Hence, we can say that the skin act as “first line of defense” for our body by protecting it from the obnoxious substance and also maintains our body temperature.

Skin is the largest organ of our body which covers about 1.858 sq. meters of total body area (William, 2019).

The skin consists of three layers:

- Upper and outermost layer – Epidermis
- Middle layer – Dermis (which is present just below the epidermis)
- Innermost layer – Hypodermis

The blood vessel, nerve ending, hair follicles and sweat glands are present in the dermis layer (middle layer of the skin) which is present below the epidermis.

Transdermal drug delivery system delivers the drug through the skin. Drug delivered through transdermal route is not only effective but also comfortable for those patients who had a fear of needle piercing and pain caused by the parenteral drug delivery.

The transdermal drug delivery is pain free drug delivery system and can deliver the drug without harming the healthy tissue.

But there is one minus point of transdermal drug delivery system i.e., when it applied on the skin, the drug has to cross the hydrophobic layer of Stratum corneum (which is the outermost layer of the skin) which prevent or limit the absorption or transport of the drug through the skin. To overcome this issue, use of Microneedles came into existence, which delivers the drug to epidermis and superior dermis layer with effectively, painlessly and without harming any healthy tissue.

This review article contains an elaborative information about the microneedles, its application and advancement in present scenario.

Microneedles

By its name we can know that in this delivery system the drug is deliver through the micron sized needles.

Dimensions of Microneedles

LENGTH – 150-1500 µm

WIDTH – 50-250 µm

DIAMETER – 1-25 µm

Microneedles deliver the drug directly into the epidermis by penetrating through the stratum corneum (upmost layer of skin) and to the overlying dermis layer.

The microneedles can easily deliver the hydrophilic drug molecule of higher molecular weight.

It is regarded as almost the painless device because it delivers the drug to epidermis and to upper dermis layer. As we know that the dermis layer contains the nerve endings. Hence, it delivers the drug to the epidermis (outermost layer of the skin) for which it does not hurt or create pain.

A number of materials are used for manufacturing of microneedles such as polymer, sugar glass, ceramics, silicon metal and some are also made from the drug which is to be administered in which the drugs are shaped into needles so that it can easily penetrate through the stratum corneum.

The microneedles should be of appropriate shape and size so that it can perfectly delivers the medication to the epidermis or to the upper dermis layer and also it should have sharp needle tip so that it can easily penetrate through the stratum corneum layer.

The microneedle drug delivery system has some distinctive features which makes it different from other drug delivery system (Abhijita Dash et al., 2018). Some of its features are given below: -

- Faster onset of action.
- Increase drug permeability.
- High efficacy and efficiency.
- Increased patient compliance.
- Painless as compared to parenteral drug delivery system.
- Drug delivered by it does not undergo hepatic first pass metabolism.
- Better stability.
- Economical.

Types of Microneedles

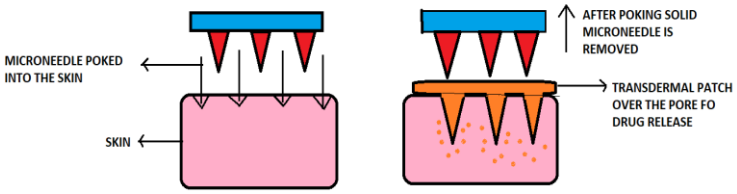
Various types of microneedles are used now a days. In recent years various approaches of microneedles were developed such as -

- Solid microneedle.
- Coated microneedle.
- Hollow microneedle.
- Dissolving microneedle.
- Hydrogel forming microneedles.

The details of all types of microneedles are discussed below including some of the recent research work and development made foe the improvements in the following types of microneedle.

The following types of microneedles are discussed as follows: -

Solid microneedle



Solid microneedles are basically based on the principle of poke and patch. In this approach first the microneedle arrays are introduced into the skin due to which very small cavities are made into the skin and after poking the microneedle, a transdermal patch containing the medicaments is placed over the cavities and through this minute cavities the drug gets transported from the patch to the epidermis or to the upper layer of the dermis of the skin.

Now a days the solid polymeric microneedles are commonly used. Here the microneedles are made from biocompatible polymers like PVP (poly vinyl pyrrolidine), PVA (poly vinyl alcohol), etc.

IN recent years various researchers performed their study on solid polymeric microneedle. Some of the recent research works on solid polymeric microneedles are as follows: -

- In 2018, Andersen, Andersen, Petersen and others uses poly-e-caprolactone (PCL) (Andersen et al., 2018).

Purpose – Furosemide drug delivery by hot embossing method using biodegradable polymer microneedle fabrication.

- In 2018, Bhatnagar, Saju, and others uses PVA (poly vinyl alcohol) and PVP (poly vinyl pyrrolidine) (Bhatnagar et al., corneal delivery of besifloxacin using rapidly dissolving polymeric microneedle, 2018).

Purpose – Anti biotic drug delivery over the cornea by using first dissolvable microneedles fabrication by PVA and PVP.

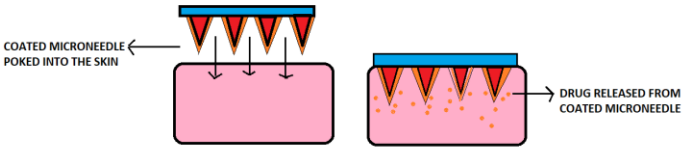
- In 2019, Park, Kim, and others uses PLGA (poly-lactic-co-glycolic acid) and PVP (Park et al., spray formed layered polymermicroneedle for controled biphasic drug delivery, 2019).

Purpose – Fabrication of spray formed polymer microneedle transdermal drug delivery system by controlling the kinetics of drug release.

- In 2019, Arshad, Hasan, Hussain and others uses chitosan (Arshad et al., 2019).

Purpose – Delivering cetirizine hydrochloride through polymer microneedles to the patient skin suffering from swelling and nausea problem.

Coated Microneedles



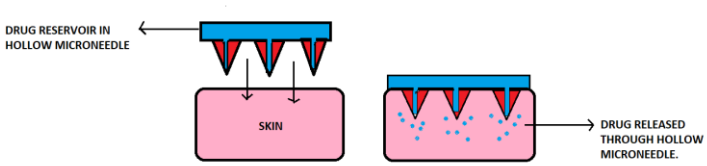
The coated microneedles are based on the principle of coat and poke. Here the drug which is to be administered is coated over the microneedle before introducing it into the skin.

After poking the coated microneedle into the skin, the drug start liquify inside the skin and get deposited into the epidermis or the upper layer of dermis.

Some of the recent research work on coated microneedles are as follows: -

- In 2020, AF. Moreira, Rodrigues and others have used the chitosan and poly vinyl alcohol (PVA) for the delivery of gold core silica shell and doxorubicin (Moreira et al., 2020).
- Recently in 2019, D.H. Shim, T.T. Nguyen and others associates prepared botulinum toxin A coated microneedles for treating palmar hyperhidrosis (Shim et al., Development of Botulinum Toxin A-Coated Microneedles for Treating Palmar Hyperhidrosis., 2019)

Hollow Microneedle

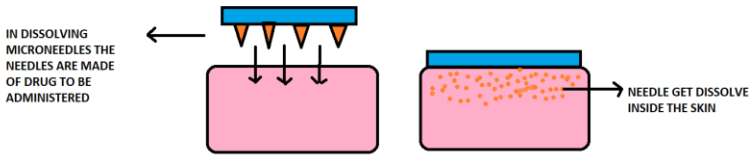


It is based on the principle of poke and flow. Basically, the microneedle in this type is hollowed inside or there is a passage inside it.

Here the hollow microneedle is introduced into the skin and the drug enters to the epidermis or to the upper layer of dermis through the passage or the hole present inside the hollow microneedle.

E.g. 3M^{TM} Hollow micro constructed transdermal system (3M's HMTS) marketed by 3M companies, USA, in the year 2017.In this product the medical grade polymer is used for cancer vaccine (Dick et al., 2019).

DISSLOVING MICRONEEDLE



Dissolving microneedle are basically based on the principle of poke and release. The dissolving microneedle is considered to be the most effective one.

In this approach the microneedle is itself prepared from the drug which is to be administered and degradable polymer.

It is considered to be most effective than other types because as the drug is directly incorporated into the skin in the form of needle. So, it can release the drug for longer period of time and in a controlled manner.

The liquification of drug mainly depends upon the depletion and release of the polymer in the skin.

In this approach some of the researches have been done in the recent years such as-

- In 2019, polymeric dissolving microneedle was evolved by the Bhatnagar's research group in which they used poly vinyl pyrrolidine (PVP) and poly vinyl alcohol (PVA)for delivering docetaxel and doxorubicin (Bhatnagar et al., Dissolvable microneedle patch containing doxorubicin and docetaxel is effective in 4Txenografted breast cancer mouse model, 2019).
- In 2020, Mao's research group evolve polymeric dissolving in which they used PVP (poly vinyl pyrrolidine) with rifamycin which has enhanced anti-anginal effect (Mao et al., Transdermal delivery of rapamycin with poor water solubility by dissolving polymeric microneedle for anti angiogenesis, 2020).

Hydrogel forming microneedle

Here in this type the polymeric microneedles are used which soak up the inner tissue fluid from the skin and due to soaking of the tissue fluid it gets expand and swells up and get converted into hydrogel.

The cross-linking power of hydrogel regulate the release of drug. Here the drug is released slowly and in a controlled way (Bhatnagar et al., 2019).

Microneedle Patches

The microneedle patches are now a days regarded as the matter of interest in which the drug is delivered to the damaged tissue directly.

The microneedles patches provide greater action with minimal side effects and also makes the drug delivered easily in comparison to conventional drug delivery system.

As we know that the stratum corneum is the protective hydrophobic layer present at the outer surface of the epidermis and resist the drug transport into the skin. So, to overcome this issue,

the microneedles play an important role in delivering the drug into the skin without damaging the healthy tissue and painlessly.

The microneedles present in the patches crosses the stratum corneum. So, the drug can easily be transported into the skin.

The microneedles patches are generally use for the transdermal drug delivery but in present there are various study and researches are in under progress for the betterment and advancement in microneedles.

Several researches are based upon designing of the microneedle patches to not only delivering the drug into the skin but also delivering the medicaments to different tissues like mouth, eye, vagina, GIT etc.

Certain researches are also in the path of progress for maximizing effectiveness with minimal side effects of microneedle through performing the pre-clinical and clinical studies.

Some problems were also faced by the researchers during administration process of microneedles to different tissues.

In our body several types of tissues are found, some tissues are wet, some are soft tissues and some tissues are very sensitive to pain. So, in those cases extra care and precaution should be taken during the administration of microneedles.

The early researches which were done in the field of microneedles patches will play an important role in further development of microneedles intended to be used in different tissue in our body.

Some new researches should also be done by using advance techniques for the betterment of microneedle administration to different tissues by emphasizing on the biological, physiological and anatomical mechanism of tissue where the administration of microneedles to be done through microneedle patches (Prausnitz, Drug delivery using microneedle patches: not just for skin, 2018).

Materials Used in the Fabrication of Microneedles

- **Silicon**

In 1990's first silicon fabricated microneedle was made. The silica is anisotropic and crystalline in nature due to which it is suitable for microneedle production.

The silicon is so much flexible that it can easily be shaped into needles of various dimensions. But due to its high cost and time-consuming process of fabrication makes it unsuitable for microneedle production. As it is very much fragile it can easily break inside the skin which is very much harmful.

The silica has its different elastic moduli (50-180Gpa) of the silica is due to its allying crystal latices (Larranta et al., 2016); (Hong et al., 2013); (Waghule et al., 2018).

- **Ceramics**

Ceramic microneedles are also commonly used. Here the slurry of ceramic is molded into micro mold and this process is said to be micro molding technique. This process is easy for scale-up and can be done in very low cost.

In ceramics, alumina is mainly used for the production of microneedle due to its stability and resistive power against the chemicals.

The covalent and the ionic bond between the aluminum and oxygen atoms of alumina increases the stability.

Now a days a three-dimensional cross-linked copolymer 'Ormocer' is used which is an organically modified ceramic (Gittard et al., 2009) ; (Waghule et al., 2018).

- **Carbohydrates**

Carbohydrate can also be used for the production of microneedles as it is safe for human use and are of very low cost but it can easily be degraded in increased temperature due to which its fabrication is difficult (Larranta et al., 2016).

Maltose is widely used for the production of carbohydrate microneedles (Lee et al., dissolving microneedles for transdermal drug administration prepared by stepwise control drawing of maltose, 2011). For the production of carbohydrate microneedle, the carbohydrate

slurry is casted or molded using the silicon templates to form microneedles (Miyano et al., 2005).

- **Silica Gel**

The silica glass microneedles are not widely used for the production of microneedle commercially but it is used for the experimental purpose.

There is declination in the use of silica glass microneedle as due to its brittleness it can easily be broken inside the skin after introduction which may be fatal. Although it is cost effective and inert, it's brittle nature makes it unsuitable for the production of microneedle (Gupta et al., 2009).

- **Polymers**

The polymer microneedles are generally dissolved or get degraded inside the skin.
The hydrogel forming microneedles are also made from the polymer.

Various polymers are used for the production of microneedles such as – poly vinyl alcohol (PVA) (Chu et al., 2010), poly vinyl pyrrolidine (PVP) (Chu et al., 2010), poly glycolic acid (PGA) (McAllister et al., 2003), poly lactic acid (PLA) (Aoyagi et al., 2007), etc.

The mechanical strength of polymer is less but much higher than ceramic and glass (Larranta et al., 2016).

Metals

Stainless steel and titanium are mainly used in the manufacturing of microneedles despite of these palladium, cobalt-palladium alloy, nickel is also used for the production of microneedle.

As we know, in metals the atoms are closely packed to each other which gives metal its strength and the metal became strong due to which the microneedle made up of metal does not break inside the skin after introduction.

As compared to other its mechanical strength is more and it is also biocompatible.

Stainless steel is the first metal which is used for microneedle production. Later the use of titanium for the production of microneedle was also started (Larranta et al., 2016) (Waghule et al., 2018).

Fabrication of Microneedles

There are various fabrication techniques which are used in the manufacturing of microneedles and such fabrication techniques are discussed below (Bhatnagar et al., Microneedle based drug delivery: Materials of construction, 2019).

1. Silicon-Based Microneedle Fabrication

Lithography is the most commonly used fabrication technique for the silicon-based microneedles.

Here basically the silicon wafer (substrate) is coated by silicon dioxide layer (photosensitive layer).

Through this process different kind of coating materials can be used to coat substrate basing upon the methods used for coating.

The coating can also be done by the process of spin coating in which a photosensitive layer is uniformly coated over the silicon oxide (substrate) Any extra solvent which remains on the coated layer can be removed by heating.

The UV- light up the photoresist layer by means of mask. The mask act as a partial screen for UV-light due to which the UV -light cannot cross the mask through some region.

When the UV-light is focused on the mask. The region of the mask exposed to the UV-light can easily be removed or solubilized as there is an alteration in the chemical bonding occur.

The photoresist is of two types one is positive and another one is negative.

So, when the UV-light falls on the positive photoresist the bond get debilitate and the photoresist layer can easily be removed.

While in case of negative photoresist the UV-light tends to make the bond stronger due to which there is no removal of the photoresist layer.

The photoresist polymer plays a very important role in the photolithographic process.

SU-8 (negative photoresist) and poly methyl methacrylate (PMMA) are very much adaptable for the purpose out of these two SU-8 gives more advanced and complicated results as

compared to PMMA which makes it suitable for the production of hollow and solid microneedle (Lee et al., polymer microneedle for transdermal drug delivery, 2013).

In this lithography technique the etching is the most important process in which the layer of oxide as well as the substrate both are etched. The etching can be done by two process –

-Dry etching

-Wet etching

Dry Etching

The dry etching is again can be done by two process

- **Reactive Ion Etching (RIE)**
- **Iron Beam Milling (IBM)**

Reactive Ion Etching (RIE)

In this process the material is etched by the reactive ions. Here firstly the reactive ions are produced in the chamber and are moved towards the material to be etched.

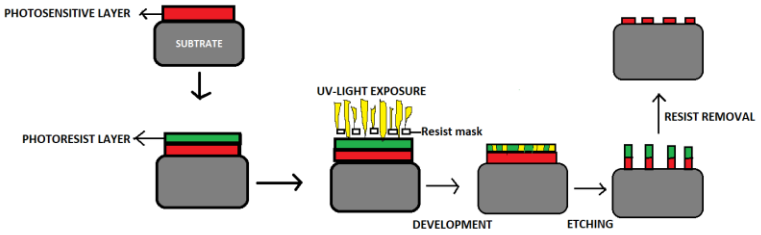
Ion Beam Milling (IBM)

In this process the material to be etched is physically removed by inert ion accelerating from the source towards it.

Wet Etching

In wet etching the material to be etched (wafer) is submerged in the container contain chemical etchant for the removal of the material.

In case of silicon potassium hydroxide (KOH) and tetra methyl ammonium hydroxide (TMAH) is commonly used as etchant material (Shikida et al., 2000).



2. Fabrication of Metal Microneedles

The hypodermic needles are assembled for the fabrication process of metal microneedle making it the easiest way to fabricate the metal microneedle.

The dimensions like length and width can be set up according to the user need.

Now a day's various cosmetics devices consisting the metal microneedle arrays are used. One of the such product is derma roller. It is a device which are used or roll over the skin to remove the scars, acne marks etc. The derma roller consist of cylindrical body in which small metal microneedles are arranged.

The lithography or the etching technique are used for making the microneedles in plane but when it is bend at 90 º the microneedle made are outside the plane.

The design of the microneedle is made by means of laser. After the design of the microneedle is confirmed then the cutting of the microneedles is started and after that the electroplating of the metal microneedle is done.

The fabrication of the metal microneedle the dimensions are very much précised as well as accurate but the fabrication process is very much costly as very complicated machines were used for the fabrication and it is also a time-consuming process.

3. Fabrication of Glass Microneedles

Earlier the hollow microneedles are generally used but now a days the glass microneedles are used.

Here the borosilicate glass pipette is passed by means of the micropipette puller for the fabrication of microneedles.

In this fabrication process the glass is heated from the center and the two-ending point of the glass tube is stretched apart by means of toothed wheels which are runed by a spring.

The slopy tips are made at a required angle and the solvents are used for the cleaning purpose.

As it is a time-consuming technique and calibrations for the dimensions of microneedle should be done precisely and hence making it unsuitable for the industrial purpose.

4. Fabrication of Ceramic Microneedles

The **ceramics** are also used for the fabrication of the microneedles in which the mold cavities in the microneedle are filled with ceramic slurry and at under vacuum at high temperature it was sintered. This process is known as micro molding.

5. Fabrication of Polymer Based Microneedles

The molding techniques are most commonly used for the fabrication of the polymer-based microneedles.

The polymer-based microneedle is done mainly by three process:

- Injection molding.
- Hot embossing.
- Micro molding.

The molding is the process in which the female molds are used for giving the polymer a shape of microneedle.

The female molds consist of small holes which corresponds the final microneedle of specific dimensions.

Different materials are used for the manufacturing of molds but the PDMS molds are very commonly and widely used.

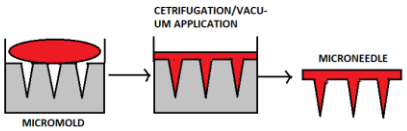
The PDMS molds are very much cost effective, accurate and flexible as well as there is consistency and clarity in the product outcome (Park et al., Polymer particle based micromolding to fabricate novel microstructures, 2007).

The PDMS used for preparing them old is economical and large number of molds can be manufactured and used simultaneously.

Another method was used that is by using the laser beam for the micro molding process (Donnelly et al., 2011). In this process the laser beam is used for the manufacture of silicon or metal female molds. Here the laser beam gives a perfect and detailed shape to the female mold. However, as it requires complicated machines and due to its high cost, it is considered to be unsuitable for industrial use

Different casting and molding techniques –

❖ **Micromolding**



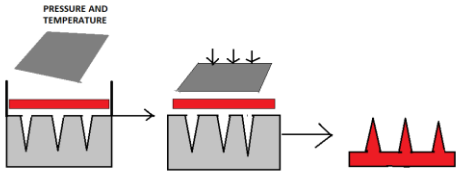
The micro molding process is carried out for the preparation of carbohydrate-based microneedle.

In this technique the sugar is first converted to viscous liquid and then the viscous sugar is streamed into the molds by means of applying vacuum pressure or by giving centrifugal force and after cooling the viscous sugar liquid takes the shape of microneedles.

The main problem with the sugar microneedle is that it is very much fragile and can easily break and another point is that, during the casting of the sugar microneedles some air bubbles can get trapped inside it which is difficult to remove.

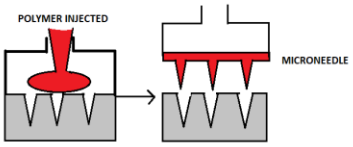
❖ **Hot Embossing**

The hot embossing technique is used for the preparation of polycarbonate microneedle. In this process the polycarbonate substance is taken and the plastic sheet is pile over it and both are compressed together into the silicon rubber mold in such a way the silicon rubber mold can completely and perfectly filled. The process was carried out in temperature maintaining at 170ºC (Trautmann et al., 2005).



❖ **Injection Molding**

It is another technique through which the microneedles are fabricated. Luton and others prepare a hydrogel forming microneedles by means of siloxane injections molds by applying centrifugal force after pouring the polymer into the molds (Luton et al., 2015).



How does microneedlle delivers drug?

The drug delivery through microneedles is very much effective and almost painless. Here the drug is delivered through hundreds of microneedles which are inserted into the skin for drug release.

In microneedle drug delivery system, the microneedle device consists of patch which contains many micron sized needles which are arranged in a specific manner in arrays.

Here the patch is used to deliver the sufficient amount of drug for producing a required therapeutic action.

The microneedle is poked into the stratum corneum (upmost hydrophobic layer of skin) and delivers the drug to epidermis or superior dermis layer.

After delivering to epidermis and the superior dermis layer the drug goes to the systemic circulation and produces a required therapeutic action on the site of action.

Drug Delivery through Microneedle

There are various approaches in the field of microneedle for the delivery of drug.

As we earlier discuss about the types of microneedle like solid microneedles, coated microneedle, hollow microneedle, dissolvable microneedle, and hydrogel forming

microneedle. They all are based on certain approaches which are specific to them. So, such approaches are discussed below (Bhatnagar et al., Microneedle - based drug delivery: Materials of constrruction, 2019).

Poke and Patch Approach

In this approach by using the solid microneedles made of silicon wafers, punctures are made into the skin and after poking the patch containing the medication was placed over the punctured area.

This technique was attempted for measuring glucose level by extracting the tissue fluid without harming any healthy tissue.

The poke and patch approach was done in the primary stages of microneedles development.

Coat and Poke Approach

As the time passed many advancements are made in the fields of microneedles. After the poke and patch approach, the coat and poke come in the form of advancement in microneedles.

Here the thin film of drug is coated over solid microneedle by dip coating technique and poked into the skin. Only approximately 1 mg of drug can be coated over the microneedle due to which the amount of drug in various cases is not sufficient for the treatment.

Poke and Release Approach

It paths of development of microneedle after several researches the poke and release approach microneedles are introduced.

Here the microneedle is made up of the drug which is to be delivered and the degradable polymer.

In this approach the microneedles get dissolve inside the skin slowly after perforation. In this case also the large amount of drug will not be delivered.

Poke and Flow Approach

Basically, the hollow microneedles are based on poke and flow approach. Here the hollow microneedle is first introduced into the skin and then the drug stored in to reservoir flows through the channel or hole present in the microneedle into the skin.

In this case a huge or sufficient amount of drug can be delivered into the skin which makes it more advantageous than other approaches.

- Wang et.al. delivered he hollow microneedle with drug reservoir.

Advantages of Microneedles Over Conventional Drug Dellivery System

- It is comfortable for the patient suffering from Aichmophobia (fear from sharp objects).
- As compared to injections it is less painful.
- Produces less harmful waste product than traditional needles.
- Economical as compared to traditional injections methods.
- It is non-invasive in nature.
- It does not harm the sensitive parts of our body.
- It is easy for use.
- In case of traditional injections therapy the needles form a puncture or tiny hole in the skin which may remain for up to 2 days and due to which there is a possibility of microbial attack through that puncture.

But in case of drug delivery through the microneedles the puncture made by microneedle is up to 10-15µm deep which makes microorganisms entry difficult.

Some Drawbacks of Microneedles

- Dose accuracy is less as compared to traditional needles.
- The thick ness of the skin layers differs from person to person; hence the puncturing depth also defers.
- Skin hydration can affect drug delivery.
- The tip of microneedles can be blocked by the skin tissue which resist the drug flow.
- The microneedle tip can get break inside the skin layer during its removal.
- Repeated introduction or perforation of microneedles may damage the veins in the skin.
- Very trained physicians are required for introducing the microneedle into the skin safely and cautiously.

Applications of Microneedles

Now a days the microneedles are not only used for the transdermal delivery of drug but also used for delivering the drug to other parts off the body, as it is very much safe as well as can deliver the drug almost without causing any pain and it also does not damage any other healthy tissues.

Some of the applications of microneedles are discussed below:

1. Ocular Delivery Through Microneedles

Various researches and advancements in the field of microneedles makes the ocular delivery of through microneedle possible (Yadav, 2019).

Now a days the microneedles deliver the drug to treat the diseases of the posterior segment by penetrating into the sclera.

The drug delivery through microneedle in case of ocular drug delivery is non – invasive and it does not have any severe effect.

2. Delivery of Insulin Through Microneedle

Insulin is hormone which is used as medication in case of diabetic patient to re duce the glucose level in blood.

In the year 2017 Li et. al studied the blood sugar level of diabetic mice after administration of insulin through fabrication of solid microneedles (Lee et al., formulation of two layer dissolving polymeric microneedle patches insulin transdermal delivery in diabetic mice, 2017).

The study shows that 29 percent of the blood sugar level decreased at initial stage just in five hours after administration.

This process proves that insulin can also be easily administered through microneedles.

3. Lidocaine Delivery Through Microneedles

Lidocaine is the drug which is used as local anesthetic. Lidocaine administration through microneedle is comfortable for the patient and also less painful in comparison to conventional injections.

In 2017, Baek et. al. basing upon coat and poke approach. Baek with his group coated the tip of the microneedle lidocaine and performed the invitro study by penetrating it into the skin.

This lidocaine coated microneedle showed a speedy delivery of drug just in two minutes (Baek et al., 2017).

Through this study we know that the microneedle can be used for delivering local anesthetics rapidly and painlessly.

4. Cancer Treatment Through Microneedles

Cancer is becoming very common disease condition which was taking thousands of lives every year all over the world.

It is becoming a challenge for the whole health system to fight against it. As its treatment process was very much challenging. So, now a day's various study was going on for establishing a complete and easy treatment process.

Some of the study says that the transdermal delivery of drug by microneedles has some effective result on treating cancer.

In the year 2016, Wang and their research group treated the skin cancer by giving anti PDI through a biodegradable polymer-based microneedle.

They fabricated the microneedle patch by using HA with pH-responsive dextran NPs (Wang et al., Immune therapy by microneedle patch assisted delivery of anti PDI, 2016).

In the year 2019, Bhatnagar and others studied for the treatment of breast cancer by delivering the doxorubicin and docetaxel through a PVA and PVP fabricated dissolving microneedle (Bhatangar et al., 2019).

5. Delivey of Nanoparticles

Nanoparticles are the medicines which consist of nanoparticles or nanoscale material and are used for treating and diagnosing disease.

The nanomedicines are made by using the nanotechnology. The nanomedicine is used in the manufacturing of drug as it reduces the drug degradation and can protect the mucosal surface interaction.

A study shows that the efficacy can be enhanced by using peptide which is pre-formulated with the drug through polymer fabricated microneedles which gives a better result in efficient delivering of nanomedicine to the desired site or organ (Wang et al., Recent advances in the design of polymeric microneedles for transdermal drug delivery and biosensing, 2017).

6. Delivering BCG Vaccine Through Microneedles

BCG stands for Bacillus Calmette Guerin vaccine. It is basically used as preventive measures for tuberculosis. It is named after the scientist Albert Calmette and Camille Guerin.

Earlier the BCG vaccine was given through various routes like orally, through intradermal injections and also through percutaneous route. Out of these routes the intradermal route of administration of the BCG vaccine is said to the safest route and this route of administration was also recommended by the World Health Organization (WHO).

The use of conventional needles for delivering of BCG creates various technical and safety issues and also there are various challenges faced during the disposal of the needles. To overcome these issues Hiraishi and others studied on the use of BCG coated microneedle vaccine patch which can easily administered the drug intradermally without producing any technical or safety issues (Hiraishi et al., 2011).

7. Delivering The Etanercept, An Anti – Rheumated Arthritic Drug Through Microneedle

Rheumatic arthritis is an auto immune disease in which the immune system of our body attacks own tissue recognizing them as foreign substance.

In these diseases the inflammation occurs at joints of hand and feet.

Till date there are only five TNF inhibitors are present (Tumor Necrosis Factor inhibitors) which are approved and present the market and used to treat rheumatic arthritis. Such TNF inhibitors are – infliximab, adalimumab, certolizumab pegol, golimumab and etanercept. Out of these five the etanercept is very much used for treating the rheumatic arthritis and it was a protein drug due to which it can only be given through the subcutaneous route. Jian Cao and others developed a hyaluronic acid microneedle to deliver the etanercept with increased bio-compatibility and bio-equivalence (Cao et al., 2019).

8. Rabies Vaccination In Dogs Using A Dissolving Microneedle Patch

Rabies is one of the deadliest viruses and can be transmitted through the bite of the infected animals, as the rabies virus remain on the saliva of infected animals. So, when animals bite the virus get transmitted from the saliva of an infected animals.

Usually, the rabis virus get transmitted through the bite of the stray dogs. If the symptoms of rabies arise in the body, then there is no cure for the disease. The rabies symptoms include aerophobia, hydrophobia, illusions, etc. So, it is better to prevent the disease to be occurred.

To prevent the transmission of the rabies virus it is very much necessary to imply mass vaccination and population control strategies for the stray dogs as well as to educate people about the harmful effects caused by the rabies virus and by the dog bite. It is very much difficult to vaccinate a large population of the stray dogs due to which Jaya M Arya et al. developed a dissolving microneedles patches of the rabies vaccine. This formulation is very much stable and can be stored at low temperature at about 4ºC for 3 weeks. To vaccinate the dog the dissolving microneedle patch should be inserted inside the inner ear of the dog by hand without use of any applicator (Arya et al., 2016; wikipedia).

CONCLUSION

The use of microneedles in the health care system have been increased in the last 20 years. Various researches and development programs made the drug delivery through microneedle more efficient and easy year-by-year.

As the researches were progressed the different types of microneedles were also invented. Firstly, the solid microneedles were developed but due to some of tits disadvantages the coated microneedle came into existence after the coated microneedles the hollow microneedles were developed and after some further development the dissolving as well as the hydrogen forming microneedles came into existence. But now a days the microneedles patches were extensively used in the treatment processes.

As the development were made the fabrication methods and materials to be fabricated were also changed. Previously, metals and ceramics were extensively used for the preparation of microneedles but later on after the several studies the use of silicon and polymers came into existence.

Not only the fabrication materials were changed but also the fabrication techniques were also developed. Different fabrication techniques such as dry and wet etching, laser cutting, lithography and micro molding were used for the fabrication.

As time passed the different delivering techniques were also developed this delivery approaches were specific for a specific type of microneedles such as:

Poke and patch approach is done by solid microneedle

Coat and poke approach is also done by solid microneedle

Poke and release approach is done by dissolving microneedle

Poke and flow approach is done by use of hollow microneedle

This development brings a new era of microneedles and the use of microneedle in the drug delivery increases incredibly.

Now a days the microneedles are not only used for deliver the drug to the skin but also these are used to deliver the drug to different sensitive part of the body including eye and so on. It is a fact that various developments have been done for the advancement in the microneedle but it is very much necessary to conduct further researches and developments program to make the microneedle drug delivery more efficient and more advantageous than any other drug delivery.

REFERENCES

1. Abhijita Dash et al., D. Microneedle as an new drug delivery system: An overview. *International Journal of Pharmaceutics and Health Care Research*, 2018; 108-116.
2. Andersen et al., A. drug loaded biodegradable polymer microneedles fabricated by hot embossing. *Microelectron Engineering*, 2018; *195*: 57-61. doi:10.1016/J.mee.2018.03.024
3. andersen, andersen, petersen. drug loaded biodegradable polymer, 2018.
4. anderson. drug loaded biodegradablepolymer microneedles, 2018.
5. anderson, andeson, peterson. drug loaded biodegradable polmer microneedle, 2018.
6. Aoyagi et al., A. laser fabrication high aspect ratio thin holes on biodegradable polymer and its application to a microneedle. *Sensors and Actuators A : Physica.l*, 2007; *139*: 293-302. doi:10.1016/j.sna.2006.11.022
7. Arshad et al., A. Increased transdermal delivery of cetrizine hydrochloride by using polymeric microneedle. *DARU Journal of Pharmaceutical Science*, 2019; *27*: 673-681.
8. Arya et al., A. Rabies vaccination in dogs using a dissolving microneedle patch. *Journal of Controlled Release*, 2016; *239*: 19-26.
9. Baek et al., B. Drug coated microneedle for rapid and painless local anaesthetics. *Biomedical Devices*, 2017; *19(1)*: 2.
10. Bhatangar et al., B. Disolvable microneedle patchusing doxorubicin and docetaxel., 2019.

11. Bhatnagar et al., B. corneal delivery of besifloxacin using rapidly dissolving polymeric microneedle. *Drug delivery and translational research,* 2018; *8*: 473-483. doi:10.1007/s13346-017.
12. Bhatnagar et al., B., 2019.
13. Bhatnagar et al., B., 2019.
14. Bhatnagar et al., B., dissolvable microneedle patch containing doxorubicin and docetaxel effective in blood cancer, 2019.
15. Bhatnagar et al., B. dissolvable microneedle patch containing doxorubicin and docetaxel is effective in 4T xenografted breast cancer muse model, 2019.
16. Bhatnagar et al., B. Dissolvable microneedle patch containing doxorubicin and docetaxel is effective in 4Txenografted breast cancer mouse model. *International Journal of Pharmaceutics,* 2019; *556*: 263-275. doi:10.1016/j.ijpharm.2018.12.022
17. Bhatnagar et al., B. Microneedle - based drug delivery: Materials of constrruction. *Journal of Chemical Sciences,* 2019; *131(9)*: 1-28.
18. Bhatnagar et al., B. Microneedle based drug delivery: Materials of construction. *Journal of Chemical Sciences,* 2019; *131(9)*: 1-28.
19. Cao et al., C. Microneedle assisted transdermal delivery of etanercept for rheumatoid arthritis treatment. *Pharmaceutics,* 2019; *11(5)*: 235.
20. Chu et al., C. fabrication of dissolving polymer microneedle for control drug encapsulation and delivery. *Journal of Pharmaceutical Sciences,* 2010; *99*: 4228-4238. doi:10.1002/jps.22104
21. Dick et al., D. Innovative drug delivery technology to meet evolving need of biologics and small molecules. *ON Drug Delivey Magazine,* 2019; *56*: 4-6.
22. Donnelly et al., D. Design, optimisation and characterisation of polymeric microneedles arrays prepared by a novel laser based microneedling technique. *Pharmaceutical Research,* 2011; *28(1)*: 41-57.
23. Gittard et al., G. pulse layer deposition of antimicrobial of silver coating on ormocer. *Biofabrication,* 2009; *1(4).*
24. Gupta et al., G. Minimally invasive insulin delivery in subjects with type 1 diabetes using hollow microneedle. *Diabetes Technology & Therapeutics,* 2009; *11(6)*: 329-337. doi:10.1089/dia.2008.0103
25. Hiraishi et al., H. Bacillus calmette Guerin vaccination using a microneedle patch. *Vaccine,* 2011; *29*: 2626-2636. doi:10.1016/j.vaccine.2011.01.042

26. Hong et al., H. dissolving and biodegradable micronedle technology for transdermal sustained delivery of drug and vaccine. *Drug Des Devel Ther.,* 2013; *7*: 945-952. doi:10.2147/DDDT.S44401
27. Larranta et al., L. Microneedle arrays as transdermal and intradermal drug delivery system. *Material Science and Engineering: R: Reports,* 2016; *104*: 1-32. doi:10.1016/j.mscr.2016.03.001
28. Lee et al., L. dissolving microneedles for transdermal drug administration prepared by stepwise control drawing of maltose, 2011.
29. LEE et al., L. dissolving microneedles for transdermal drug administration prepared by stepwise controlled drawing of maltose, 2011.
30. Lee et al., L. polymer microneedle for transdermal drug delivery. *Journal of Drug Targeting,* 2013; *21*: 211-223. doi:10.3109/1061186X.2012.741136
31. Lee et al., L. formulation of two layer dissolving polymeric microneedle patches insulin transdermal delivery in diabetic mice. *Journal of Biomedical ResearchPart A,* 2017; *105(1)*: 84-93.
32. Luton et al., L. A novel sealable manufacturing process for the production of hydrogel microneedles, 2015.
33. Mao et al., M. transdermal delivery of rapamycin with poor water solubility by dissolving polymer microneedles, 2020.
34. Mao et al., M. Transdermal delivery of rapamycin with poor water solubility by dissolving polymeric microneedle for anti angiogenesis. *Journal of Material Chemistry B,* 2020; *8*: 928-934. doi:10/1039/C9TB00912D
35. McAllister et al. microfabricated needles for transdermal delivery of macromolecules and nanoparticles :fabrication methods and transport studies. *Research Article*, 2003; *100(24)*: 13755-13760. doi:10.1073/pnas.2331316100
36. Miyano et al., M. sugar microneedle as transdermic drug delivery system. *Biomedical Microdevices,* 2005; *7*: 185-188.
37. Moreira et al., M. Poly (vinyl alcohol)/chitosan layer-by-layer microneedles for cancer chemo-photothermal therapy. *International Journal of Pharmaceutics,* 2020; *576*: doi:10.1016/j.ijpharm.2019.118907
38. Park et al., P. Polymer particle based micromolding to fabricate novel microstructures. *Biomedical Microdevices,* 2007; *9(2)*: 223-234.
39. Park et al., P. spray formed layered polymermicroneedle for controled biphasic drug delivery. *polymers,* 2019; *11*: 369. doi:10.3390/polym11020369

40. Prausnitz, L. a. Drug delivery using microneedle patches: not just for skin. *Expert Opinion on Drug Delivery*, 2018; *15*: 541-543. doi:10.1080/17425247.2018.1471059
41. Prausnitz, L. a. Drug delivery using microneedle patches:not just for skin, 2018.
42. Shikida et al., S. Difference in anisotropic etching proprety of KOH and TMAH. *Sensors and ActuatorsA:Physical*, 2000; *80(2)*: 179-188.
43. Shim et al., S. botulin toxin A coated microneedle for treating palmar hyperhydrosis, 2019.
44. Shim et al., S. Development of Botulinum Toxin A-Coated Microneedles for Treating Palmar Hyperhidrosis. *Molecular Pharmaceutics*, 2019; *16(12)*: 4913-4919. doi:10.1016/acs.molpharmaceut.9b00794
45. Shim et al., S. Development of Botulinum Toxin A-Coated Microneedles for Treating Palmar Hyperhidrosis, 2019.
46. Shim et al., S. Development of Botulinum Toxin A-Coated Microneedles for Treating Palmar Hyperhidrosis, 2019.
47. Trautmann et al., T. Replication of microneedle arrays using vacuum casting and hot embossing. *TRANSDUCERS'05*, 2005; *2*: 1420-1423. doi:10.1109/SENSOR.2005.1497348
48. Waghule et al. Microneedle ; a smart approach and increasing potential for transdermal drug delivery. *Biomedicine and Pharmacotherapy*, 2018; *109*: 1249-1258. doi:10.1016/j.biopha.2018.10.078
49. Wang et al., W. Immune therapy by microneedle patch assisted delivery of anti PDI. *Nano LETTERS*, 2016; *16(14)*: 2334-2340.
50. Wang et al., W. Recent advances in the design of polymeric microneedles for transdermal drug delivery and biosensing. *Lab on a Chip*, 2017; *17(8)*: 1373-1387.
51. wikipedia. (n.d.)
52. William, B. a. The art of science of dermal formulation development. *CRC Press*, 2019.
53. Yadav, G. Application of microneedle in delivering drug for various ocular disease. *Life Sciences*, 2019; *237*. doi:10.1016/j.lfs.2019.116907.