A review on dissolving microneedle mediated transdermal insulin delivery

By

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material that has been accepted or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis title “A Review On Dissolving Microneedle Mediated Transdermal Insulin Delivery” submitted by Khadija Akter (16346052), of Summer, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This project does not involve any human or animal trial.

Abstract

Microneedles (MNs) are microscopic applicators used to deliver vaccines or other drugs across various barriers. Whereas the most favorite use of MN is transdermal applications. Generally, four types of MN are present. These are solid MNs, hollow MNs, coated MNs and dissolvable MNs. They can deliver drugs through different mechanisms. The vision of this report was to create a dissolving MNs application system. By which way insulin loaded dissolving MNs were made on a chip. By this lesson we can gain optimal relative bioavailability for insulin delivery using a gelatin/CMC MNs patch in comparison with traditional hypodermic injection. It may be a satisfactory delivery device for those drugs which are employed for diabetes and these drugs are not permeable. By insertion tests on human cadaveric skin it is indicated that dissolving MNs could deal as proficient devices for transdermal drug delivery in medical use. Also, to get total absorption of insulin, two-layered dissolving MNs array chips were equipped and delivered to the abdominal skin of rats. Glucose levels of plasma were calculated for 6h. The relative pharmacological availability was determined by comparing the hypoglycemic effect which was attained after subcutaneous injection.

Keywords: microneedle; transdermal; insulin; diabetes mellitus; hypodermic

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Table of Contents

List of Table

List of Figures

List of Acronyms

DMN	Dissolving Microneedle
DNA	Deoxyribose Nucleic acid
ELISA	Enzyme-Linked Immunosorbent Assay
PVA	Poly Vinyl Alcohol
PVP	Poly Vinyl Pyrrolidone
TDDS	Transdermal Drug Delivery
SC	Subcutaneous
HMN	Hollow Microneedle
PLA	Poly Lactic Acid
ITP	Iontophoresis
CMC	Carboxymethyl
PCL	Polycaprolactone
IP	Intraperitoneal
MEMS	Micro Electro Mechanical System
CLT	Cisplatin
IDSs	Insulin Delivery System
PDMS	Polydimethylsiloxane
PET	Polyethylene Terephthalate
NIR	Near Infrared
FDA	Food and Drug Administration
CD	Cyclodextrin

Chapter 1

Introduction

The skin, as the biggest organ, could be a superior alternative for sedate conveyance in numerous illnesses. Be that as it may, due to the low permeability of therapeutics most transdermal delivery is difficult. To promote the therapeutic efficacy of the drugs administered numerous advancements in transdermal drug delivery appeared. As a new therapeutic vehicle through transdermal routes, these micron sized needles are of great interest to scientists especially for vaccines, drugs, small molecules, etc. These micron-sized needles, ranging from 25 to 2000 μm in height, are made of a variety of materials and shapes. Transdermal drug delivery has given a choice to the injectable and oral administration of drugs (Haj-Ahmad et al., 2015). Transdermal delivery of drugs means delivery of drugs through the skin and then they reach within the systemic circulation (Moochhala, 2005).

The needles of the micro needles ought to be solid enough to administer drugs (Jung, 2013). There are few more layers in the skin like dermis, epidermis and hypodermis conventional injection utilized to target the hypodermis for drug delivery but as it is painful so scientists made micro needles (Maaden et al., 2012). There are few issues in case of vaccination by utilizing hypodermic needles, like for many of the infections a booster dose is required to preserve the viability. Furthermore, these immunizations for the most part do not work well in patients with vitamin deficiency. Again, a prepared wellbeing care supplier is required for good vaccination that is rare in developing countries. Also, needle stick injuries are really very common and it is really very painful. For bio therapeutics such as chemo-agents, vaccines, small molecules, liquid formulations, etc hypodermic injections appeared broadly acknowledged as a conveyance strategy. As they are micron sized, application of these may potentially prevent pain and deliver any kind of therapeutics such as a small particulate or liquid formulation by the patient him/herself, imparting a precise localized delivery into tissues,

corneas, cell nuclei, etc. The microneedles do not reach the pain receptors which are deep into the dermis, thus cause less pain as compared to that of a hypodermic needle. The intensity of pain depends on the number of microneedles on a patch, length of the microneedle and the tip angle or needle shape Application of MNs to the skin can create micron-sized transport pathways that allow enhanced delivery of extensive extent of drug molecules. Most of the MN related research has been based on the transdermal routes. Microneedle is a microscopic applicator. There are some types of microneedles like solid microneedle, hollow microneedle and dissolving microneedle. In this paper I have tried to find out their advantages and disadvantages so that we can use the perfect microneedle for our coating purpose. Also, different microneedles deliver drugs in different ways like poke and patch, poke and release coat and poke and poke and flow. We also have tried to discuss that.

They are developed through different strategies more often than not include photolithographic processes or micro molding. To administer in the body Some microneedles are composed of a drug but are shaped within a needle to penetrate the skin. Microneedles are ordinarily connected through little clusters. As microneedles require less training to apply it is a simpler strategy for doctors also they are not as hazardous as other needles. Microneedles made the administration of drugs to patients safer and caused a little pain. Hence in this research it was found that microneedles have expanded patient compliance and Transdermal delivery has evolved as a great choice for delivering drugs through the skin (Chávez et al., 2016).

1.1 Microneedle and its History

The first recorded use of a micro needling procedure was in 1905 by German dermatologist Ernst Kormaed. Various-sized dental burs powered by motor-driven flexible cord equipment was used to treat scars, birthmarks and hyperpigmentation. In 1921 the term “microneedle”

was first introduced. The concept of microneedle was first used by two scientists. Hollow and solid microneedles were used for this purpose. The first drug coated microneedles were also introduced. It was used for significant evaluation and for proof of concept that silicon microneedles prepared by micro fabrication technology was used for the delivery of calcine. The first in vivo evaluation of pain was reported by them. The safety issues of microneedles were first evaluated by misztkaet et. al. Solid and hollow microneedles were used to deliver insulin albumin and latex beads for the first time and the result is reported. The first cosmetic microneedle based application was used in 2005. Microneedle roller was used at that time (Duarah et al., 2019).

Microneedle as we think today was first used in 1995 by Dr. Desmond Fernandez in Philadelphia to treat wrinkles and scars with hypodermic needles. At the same time, Dr. Fernandez developed a small needle stamp to induce collagen production. With more investigation, micro needling was found to be effective in treating other skin conditions other than scars. Capitalizing on the body's natural healing method, a micro needling procedure induces collagen and elastin generation to dispose of wrinkles and lines, smooth out the skin, and treat pigment issues and brown spots. (Volume 260, 28 August 2017).

1.2 Classification of Microneedle

To promote transdermal delivery of small and large molecules, microneedles (MN) are nowadays being exploited. Through the former several decades' microneedle became manifested by theoretical research and pharmaceutical companies with the advancement of microfabrication synthesizing technology. To promote delivery of the drug across the skin, transdermal microneedles invent micron sized pores in the skin. (Pharmaceutics 2015, 7)

There are 4 types of MN have been categorized showing in (Fig 1): hollow, solid, coated and polymer.

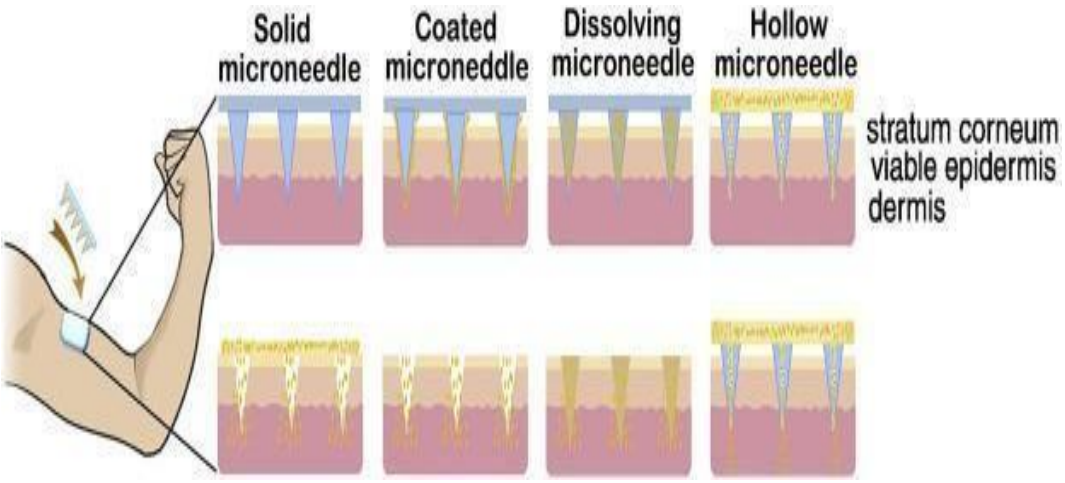


Figure 1: Classification of Microneedles (Lee et al,2020)

In figure1, it represents the classification of microneedles. There are four types of microneedles. They are solid, hollow, coated and dissolving microneedles.

1.2.1 Classified by Drug Delivery Methods

Solid Microneedle

Solid microneedles deliver drugs among skin. Solid MNs crumble up the stratum corneum of skin. This creates a transitory microchannel. After that a patch with the drug formulations is applied onto the skin. So the drug can diffuse gradually into the skin through the transitory microchannel. Delivery of drugs with a wide range of molecules is promoted enough by using solid microneedles. The delivery of peptides is also promoted by using solid MN, but the peptides porousness diminished with the increment with molecular weight of peptides. (N. Dang,2017)

Solid microneedles are the simplest form of microneedle devices and were used for most of the early work on microneedle delivery of vaccines. The solid microneedle array enters the intense obstruction of the SC, creating channels for active molecules diffusion. After removal of the microneedles, the vaccine formulation is topically applied onto the skin over the pretreated

area. The creation of pores within the skin makes a difference the transport of a variety of molecules through the gaps of minutely damaged skin and after that coming to the epidermis and dermis. (N. Dang,2017)

Coated Microneedle

They are coated by the scattering of drugs. They are especially popular for rapid bolus delivery which are high atomic masses such as vaccines, proteins, peptides and DNA. The drug is quickly released from the coating into the tissue when inserted into the skin. Still, there is one serious limiting factor which is they have extremely small surface area in achieving a significant drug release profile. It conducts to the limited quantity of drug that might be perfectly coated onto them. However, there are further issues such as consistency, the quality of being uniform, the ability to reproduce and the state of being stable of the MN coating materials. On the other hand, necessary measures should be taken so that there is minor harmful drug loss through the method of coating and also prior to insertion into the skin. Coated MNs have also indicated the successful and delivery of therapeutic nucleic acids with less pain, less scars such as small interfering RNA (siRNA) etc. In a recent research, drug-coated poly (L-lactic acid) (PLLA) MN arrays were manufactured to convince quick and painless local anesthesia in the skin (Duarah et al., 2019).

Hollow microneedles (HMNs)

Hollow microneedle comprises hollow needles that act as conduit structures that are particularly utilized to infuse fluid and liquid formulations. Hollow MNs (HMNs) are of interest for pharmaceutical application because they empower exchange of a wide range of molecules transdermal with the advantages of hypodermic injection such as rapid onset action without the disadvantage (e.g. pain, skin reaction). The flow rate can be balanced for a rapid bolus injection, a slow infusion or a time-varying delivery rate. HMNs can be coordinated into a smart biomedical device consisting of a biosensor and blood sampling and drug delivery

systems (Maaden et al. 2012). HMN arrays are also used as minimally invasive monitoring devices for biological fluid collection and assay (when integrated with other devices). HMN permits the delivery in a persistent manner, where drug solution can flow through the MN bore by different methods such as diffusion, pressure, or electrically driven flow. For these characteristics HMN permits the modulation of flow rate for a rapid bolus injection. Besides, delivering larger amounts of drug substances are possible in comparison with solid, coated, and dissolving MN. (Maaden et al. 2012). Besides, there are some disadvantages like low stability, reduced shelf life, and low patient compliance compared with other types of MNs. The basic restriction of HMN is the possibility for needle clogging through introduction into the skin. Moreover, due to the compression of thick dermal tissue around the MN tips through insertion there might be clogging from the flow resistance. Instead of the tip the clogging of MN might be ignored by using a very sharp MN with bore-opening on the side of MN. Although partial withdrawal of MNs potentially alleviate skin compaction and boost the flow conductivity. Another drawback is the possibility for leakage in the adjoining area. (Maaden et al. 2012). Ordinarily, there are two types of HMNs, 1st is use of a single MN, which imitate ordinary hypodermic needle, another is multiple hollow MNs. This type HMNs may administer the formulation to an extensive surface area at once. Also it should be noticed if there is one leakage, the pressure cannot be applied equivalently to all. Which can lead to dissimilar flow through the MNs. (Duarah et al., 2019).

Dissolving Microneedle

They have amazing biocompatibility, low cost and relatively simple. The matrix of MNs dissolves at a certain rate after insertion which contacts body fluid to release the incorporated insulin. After detaching it does not leave any biomedical waste. At the beginning, insulin-loaded MNs used dextrin. The matrix had been prepared for the percutaneous delivery of insulin. It proved the feasibility of self-dissolving MNs. The MNs contains various insulin

doses (0.5, 1.0, and 2.5 IU/kg). The doses were administered to male mice individually. After 1 hour of the administration plasma glucose level reached the lowest hence dose-dependent hypoglycemic effect was observed. After being inserted MNs remain on the skin and after that When MNs completely degrade or dissolve in the skin the releasing of drug is realized. These MNs are easily-made, convenient, and high drug loading. To date, for transdermal drug delivery minimally invasive dissolvable MNs are more efficient and advantageous. Li et al55, for insulin delivery the dissolving MNs made of polylactic acid (PLA). For this thermal micro molding technique was followed. It was concluded that shorter the MNs better the mechanical stability, while the longer MNs were more appropriate for drug permeation. The in vivo study revealed that to reduce the blood glucose levels to 29% dissolving the MN system promoted insulin absorption. In this paper we will discuss elaborately about dissolving microneedles for transdermal drug delivery.

Materials used for DMs

As we mentioned earlier MNs can be categorized in three categories. First one is solid MNs. Second one is dissolvable MNs. Third one is hollow MNs and lastly coated MNs. The materials that need to be selected to produce microneedles based on some criteria. The first criteria is that the microneedle that will deliver biomolecules need to be fabricated gently. Secondly, if the microneedle needs to disrupt the skin then sufficient mechanical strength is needed. For those microneedles that require controlled or rapid drug delivery. The materials need to be selected based on this idea. Some materials are used to fabricate microneedles most often. In these materials glass, silicon and materials glass, silicon and metals are used. Polymers are also used to make microneedles. Generally, solid microneedles are made of polymers that are biodegradable. There are some reasons to choose the polymers as materials for production of microneedles. The advantages those polymers have are firstly, the cost of this polymer is very low. Secondly, polymeric microneedles are not so brittle like metal microneedles. Thirdly,

polymers are safer because the incident of accidental breakage of needles is very rare. Another type of material like polysaccharides is also used to make microneedles that are dissolvable. Carbohydrates can also be used to fabricate microneedles but they are rarely used because of some limitations**.**

DMs consist of water-soluble materials like maltose, poly vinylpyrrolidone, chondroitin sulfate, dextran, hyaluronic acid, and albumin. Drugs can be administered into the skin by forcing the dissolving microneedle with the finger. DMs usually dissolve within biological tissues. Mechanical forces are associated with application of dissolving MN which prevent damage. Dissolving microneedles are more profitable than silicon and metal needles.

1.3 Different types of release from microneedle

Microneedle is a recent noninvasive physical technique widely used for intra- and transdermal delivery of small drugs, nanoparticles, macromolecules, and extraction of fluids. In a microneedle array, there are a number of micron size needles and are used to create transient aqueous pores across the SC without any contact with nerve fibers. Solid microneedles are intended to pierce the skin to increase drug permeation whereas hollow microneedles possess hollow cores to retain liquid formulation for active injection. Based on the mode of application microneedles are categorized into four classes.

- Poke and patch or poke and flow (microporation followed by application of a drug-loaded patch or a liquid formulation).
- Coat and poke (coating solid microneedles with a drug formulation).
- Poke and release (soluble microneedles with drug encapsulated in them).
- Poke and flow (hollow microneedles).

1.3.1 Solid Microneedles for “Poke and Patch

Solid microneedles first introduced the poke and patch approach. The poke and patch approach is also used by the dissolvable microneedle. In this method microneedles are first applied and then removed. Since a drug formulation that is reserved in a patch is introduced in the skin so the drug can deliver. It is very important to remain open at the time of drug application. It perforates the skin and gets to the deepest layers of the epidermis (Fig 2) by creating a microchannel. The passive transport of drugs through the skin is remarkably upgraded by this procedure. This method follows two steps: Firstly, microneedles make a hole the epidermis, then eliminate. Secondly, applied in a traditional dosage form. Like solution, cream, or patch works as an external drug reservoir. It is simple for use. Its easy application makes it highly attractive in a clinical setting. However, there are also some controversies about this approach and presents several disadvantages.

A very common drawback is that the micro pores stay unclosed for a specific period of time, and stop the delivery of the active substance prematurely. Also the risk of infection increases by using formulations like patches or tapes in this condition. It also causes skin irritation.

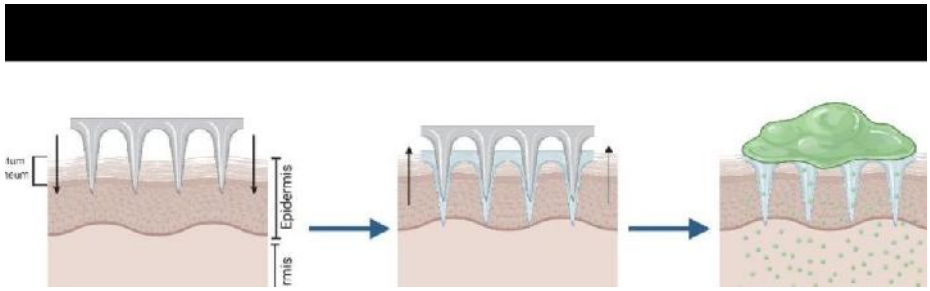


Figure 2: Poke and patch (Maaden et al., 2012).

Figure 2 represents the poke and patch approach. Which is mainly used for solid microneedles.

1.3.2 Coated Microneedles for “Coat and Poke”

Another approach is the “coat and poke”. It is basically the coating of the solid microneedles. After MNA insertion drug diffuses across a cell membrane from a region of high concentration to low from coating surface to the deeper epidermal layer’s (Fig 2). If there are any coating related issues it may restrict the effectiveness of this method. Like, if the amount of drug which can be encapsulated in the coating layer is relatively low. Furthermore, the coating depth may reduce the intensity and control their capability to enter the skin. Despite this, coated MNA are most important in vaccination.

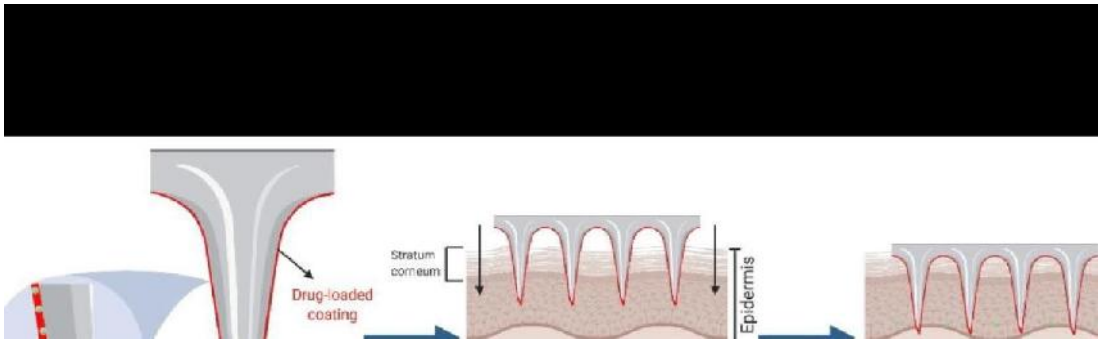


Figure 3: Coat and poke approach (Maaden et al., 2012).

Figure 2 represents the coat and poke approach. Which is mainly used for coated microneedles.

1.3.3 Dissolving Microneedles for “Poke and Release”

Dissolving MNA might be constituted of water-soluble materials which get disintegrated by the action of microorganisms like bacteria, fungi. As microneedles dissolve after insertion the drugs can be loaded and released. This approach is more advantageous than “poke and patch”. The advantages are:

Controlled drug release can be maintained over a longer period of time. Can control the dissolution rate of the formulation. As they are able to pierce the skin it can reduce the drug

administration procedure to one step. Also, dissolving MN keeps away the production of sharps Pharmaceutics excess, reducing the price associated with its regulation and minimizing needle-stick damages. Also, it has some drawbacks. Like a limited drug loading and a potentially lower ability to perforate the stratum corneum.

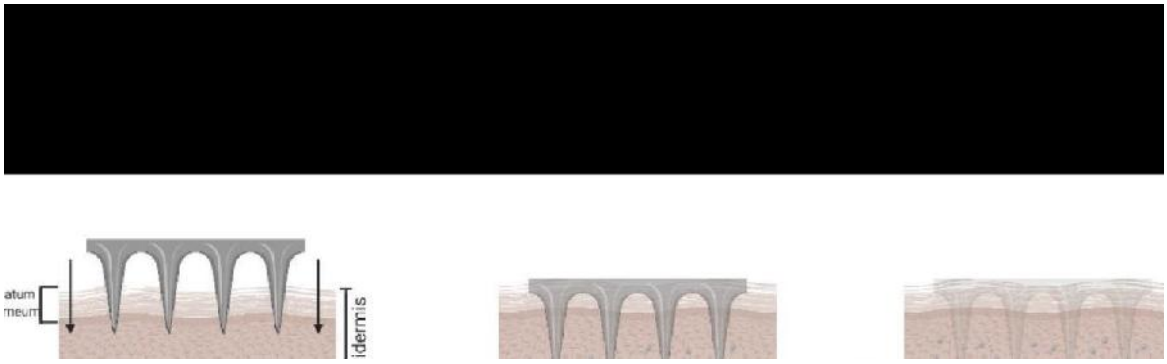


Figure 4: Poke and release approach (Maaden et al., 2012).

Figure 2 represents the poke and release approach. Which is mainly used for dissolving microneedles.

1.3.4 Hollow Microneedles for “Poke and Flow”

An important benefit of hollow microneedles over solid microneedles is the possibility to facilitate force-driven fluid flow, thereby allowing faster rates of drug delivery. Furthermore, the dose of the desired drug in solution can be more easily controlled according to the need of the patient. This method of drug delivery can be achieved via passive diffusion through the bore of the microneedle. Other methods are also possible whereby the drug in solution is actively delivered through the bore of the microneedle. The latter requires a driving force through pressure. (Maaden et al., 2012).

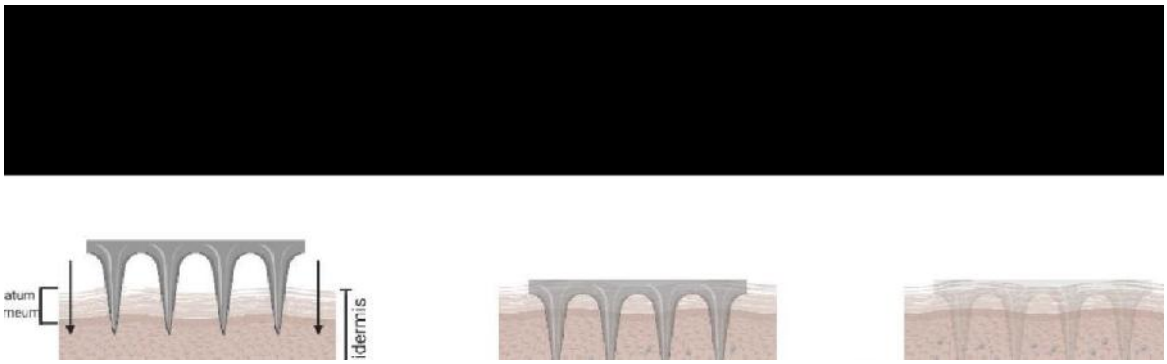


Figure 5 : Poke and flow approach (Maaden et al., 2012).

Figure 2 represents the poke and flow approach. Which is mainly used for hollow microneedle.

1.4 Fabrication of Dissolving Microneedles

There are several techniques for fabricating dissolving MNs. These techniques are mold based. Among these techniques are laser machining, hot embossing, microinjection molding and solvent casting. Among these techniques, solvent casting is the most popular method. This technique is also very simple. In this technique at first the polymers are dissolved in appropriate solvents. In the next step it is mold cavities that are used. These mold cavities are used for filling purposes. After that these are kept for drying. After drying the centrifugal forces are added. There are other types of MNs named tapered MNs. These tapered MNs are actually made by fabrication methods. To fabricate tapered MNs at first a liquid preparation is made. In the next step the liquid preparation is drawn. Then the liquid preparation is solidified and the tapered MNs are made. The tapered MNs are very useful to coat different types of drugs. The drugs that can be coated in tapered MNs are dextrin, albumin etc. these materials are coated on tapered MNs. For this tapered MNs coating every needle of tapered MNs are fabricated by drawing a liquid preparation. The liquid preparation is drawn by using pipettes. Another technique is called ultrasonic welding. This technique is also used to fabricate hollow MNs. The mechanism of this technique is discussed below:

At first the polymers are fused together. The fusion process of these polymers has a condition. The condition is that the polymers need to be fused without the help of any heating process. Actually this process has a benefit as a very less amount of damage is done to the materials that are encapsulated in the dissolving MNs.

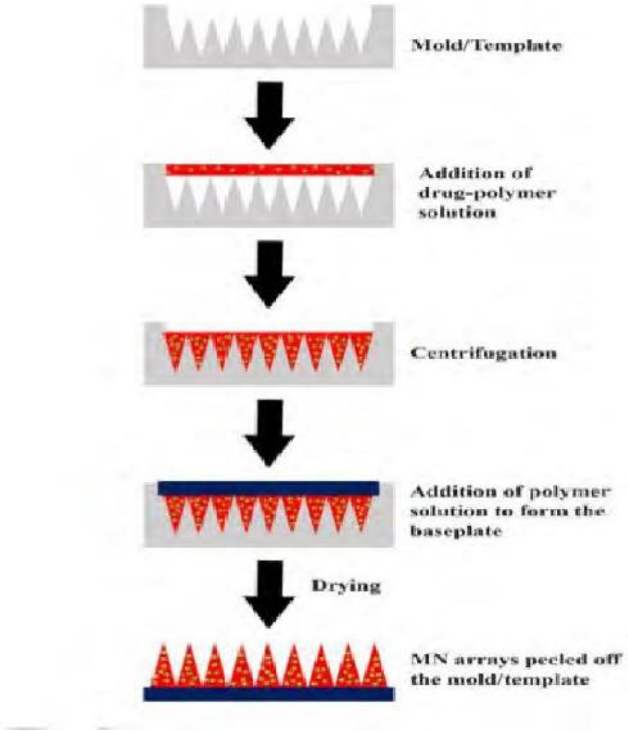


Figure 6: Process in fabricating dissolving MNs (Duarah et al., 2019)

It represents the process of fabricating dissolving microneedles. There are several steps in fabricating dissolving MN.

1.5 Application of Dissolving Microneedle

The use of microneedles in the delivery of different agents is vast. Microneedle with different virus coated is under development (Donnelly, 2016).

Immunobiologicals

Generally, the immunobiologicals are delivered via the skin. In this purpose generally hypodermic needles were used. Before the use of microneedles immune biologics were generally delivered in intramuscular or subcutaneous routes. As we all know, using hypodermic

needles has many drawbacks. The main problem is the pain that is created by the hypodermic needle. The problem of the hypodermic needle is needle phobia. On the other hand, microneedles have various advantages. The first advantage is the lack of pain. Commonly, microneedles create very little pain or no pain. Second advantage is that microneedles are self-administrable so no extra person is needed. The other advantage of microneedles is drugs can be rapidly delivered. Another advantage of microneedles is generally the conventional vaccines require cold conditions to store them and this liquid vaccine has a very short half-life. On the other hand, the vaccines that are coated into microneedles also have the ability to cross the upper layer of skin that is stratum corneum and give clinical response. It has been seen in different studies that microneedles can create a better immune response at lower dose than the hypodermic needles. (Larrañeta, 2016)

Bioactive Macromolecules

Generally, insulin, heparin and growth hormone are considered as bioactive materials. Commonly, the bioactive materials are delivered through the parenteral route. This parenteral route delivery has some limitations. As a result, a method of delivering bioactive materials is needed that is noninvasive and that Can deliver bioactive macromolecules. (Larrañeta,2016).

Drugs

Very few drugs have the ability to cross the skin barrier and show its action. Actually the main reason behind that is the lack of physicochemical properties that are needed to deliver drugs via the skin. The physicochemical properties are the hydrophilic lipophilic balance, the solubility and finally the molecular weight. All these challenges can be overcome by using microneedles.

(Larrañeta,2016).

Phlebotomy

Phlebotomy is the process by which blood samples can be withdrawn. This withdrawal blood sample can be used in the diagnosis process. A microneedle named hollow microneedle is used for this purpose. Diabetes is the proper example of phlebotomy. In diabetes the blood sample is collected and after that the glucose amount is measured. In phlebotomy, using a microneedle is very helpful because a microneedle can reach the depth that is required for the purpose of collecting the blood sample and it does not cause too much pain. (Donnelly,2016).

Safety Issues in Microneedle

Most of the studies found that microneedle is very safe to use. However, the safety issues of microneedles are a great concern because it can create micro channels by which the drug is delivered. As micro needles disrupt the skin so the safety issues need to be monitored.

Ocular Drug Delivery by Microneedle

Human eyes are very sensitive. If the intraocular pressure is increased, then the glaucoma is caused. This can cause blindness (Sharma, 2019). The needles of the microneedle need to be strong enough to administer drugs in the eye (Lee et al., 2013). Microneedle is an emerging tissue for delivering drugs in the posterior segment of the eye (Agrahari, 2013). Microneedle has a significant potential in delivering drugs into the eye. Microneedles can penetrate but not through the sclera or cornea. As a result, it is very safe to use (Rao,2016).

1.6 Dissolving Microneedle for transdermal delivery

Dissolving MNs (DMNs) are composed of biocompatible material such as rapidly dissolving sugars (e.g., trehalose and raffinose) and biodegradable polymers (PVP and polyvinyl alcohol (PVA). Sugars have been used in many applications due to its biocompatibility and controlled release profile, the hygroscopic nature of sugars limits its applicability in DMNs as it can lead to physical and chemical degradation of DMNs. Coating the DMNs could provide a strategy to prevent the loss of active and improve DMNs storage and handling stability throughout its life

cycle. Tranexamic acid and the biodegradable PVP MN has been formulated with 34% local drug release with the remaining successfully permeating through skin with no dermal toxicity. They are consisting of polysaccharides or other polymers. These MN follow dissolution to release encapsulated drug into the skin. Proprietary electro-discharge-machining technology was used for master structures. Polydimethylsiloxane (PDMS) molds were created for master structures. All master structures were sputter-coated with platinum to prevent adhesion to PDMS molds. Sputter coating is a physical vapor deposition method which is used to apply a very thin and functional coating on a substrate. The process starts by electrically charging a sputtering cathode. PDMS molds were fabricated by pouring PDMS solution and then offering the polymer to recover overnight at ambient temperature. Then peeling of the recovered PDMS from master structure. Thermal drawing is mostly used technic for preparing microneedle structure by using ultra-high aspect ratio. Still, continually producing MNs with similar conformation by using thermal drawing is complicated. Because of fluctuations in temperatures, drawing speeds or drawing heights this incident occur. Lee et al. manufactured master molds several times by thermal drawing and reproduce high aspect ratio silk fibroin microneedles from these master molds. The authors utilize poly (lacticco-glycolic acid) to manufacture MN masters for micro molding. PLGA MN masters was fabricated by using a non-linearly distinct thermal drawing system. Then PDMS resin was poured on the PLGA MN masters and cured at a room temperature for 24 h. After curing, negative PDMS molds were produced. Lastly, an aqueous solution was poured on the negative PDMS molds and dried at room temperature for 24 h.

Because of the low permeation rate of the drug across the skin and the inconvenience of attaining therapeutic concentration still transdermal delivery of insulin is a great barrier in the technological community

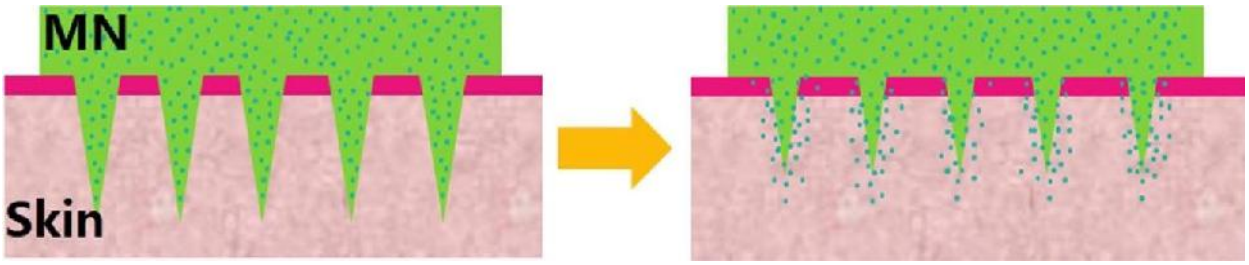


Figure 7: Dissolving Microneedle (Ita et al. 2015).

Figure 7 represents the dissolving microneedle. It dissolves in the skin interstitial fluid to release drugs in the skin.

Microneedles are used as another method for the injection of drugs. This can be used for those drugs which have poor permeability and can drastically raise the skin permeability. Besides, 200–300 two-layered DMs are formed as an array on a chip. Which have a diameter of 15. 0mm.Each DM is 500 lm long and 300 lm in diameter at its base. The DMs were inserted into the region of the epidermis with fingers. After the microneedle array chip was administered to the skin, the base polymer dissolved immediately, and the formulated drug was released within 5min.A two-layered DM array chip with insulin showed relative pharmacological availability (RPA) of 33.2–35.2% in rats. The acral portion must be inserted fully in order to obtain complete absorption of insulin. (Prausnitz et al. 2012).

1.7 Dissolving microneedle patch

It is a substrate of polymers that dissolve in vivo blended with active ingredients and molded into the shape of fine needles. The patch form can be placed directly on the skin. Dissolving polymeric microneedle (MN) patches consist of gelatin and sodium carboxymethyl cellulose (CMC). These patches are utilized to place insulin. These patches have in vitro skin insertion power. It is decided by operating tissue-marking dye. These dye are utilized to stain the skin after patches withdrawal. Scanning electron microscopy(SEM) was used to establish changes in the MN overtime. To observe their real-time penetration depth optical coherence

tomography (OCT) was used. Skin areas received FITC-insulin-loaded MNs. By using an in vivo imaging system (IVIS) it presents strong fluorescent signals. After1 h of application it is reduced greatly. Experiments show that dissolving MNs quickly release FITC-insulin, and then it slowly diffuses into the skin. Different biomolecules are labeled by using FTC insulin, e.g. immunoglobulins, lectins and other proteins, peptides, nucleic acids, nucleotides; oligo-and polysaccharides. FITC-Insulin is one of Nano fluorescent insulin conjugates that was labeled by Fluorescein dye. Insulin is one of important proteins that regulate carbohydrate and fat metabolism in human cells. For studying insulin biological functions fluorescently labeled insulin conjugates are used. This study demonstrates that insulin delivery by using a gelatin/CMC MN patch attains a pleasing relative bioavailability than traditional hypodermic injection. To treat diabetes, it is most encouraging a delivery device.So dissolving MNs serve as effective devices for transdermal drug delivery in medical practice which is revealed by insertion tests on human cadaveric skin. (Chen et al.2018).

Figure 8: Dissolving microneedle patch.

Figure 8 represents the dissolving microneedle patches. The patch is a substrate of polymers that dissolve in vivo blended with active ingredients and molded into the shape of fine needles. The patch form can be placed directly on the skin.

1.8 Dissolving polymer microneedle patches for rapid and efficient transdermal delivery of insulin

Dissolving microneedles (DMNs) are polymeric, microscopic needles. It delivers encapsulated drugs in a minimally invasive manner. Nowadays, DMN arrays are placed onto patches to facilitate their insertion into skin. The arrays were fabricated on the patch because of the wide variety of skin elasticity and the amount of hair on the skin. These are often not fully inserted and delivery of large amounts of loaded materials cannot be possible. The advantages are that their production cost is cheaper than silicon microneedles. If they break off in the skin, there is no risk of infection. The reason is the needles can thoroughly and safely dissolve or degrade within the skin. These microneedles are not reusable. They are composed of metal or silicon. Drugs can be surrounded by the polymer matrix of microneedles and for this drug loading capability is increased. This study presents a dissolving microneedle patch, which consists of starch and gelatin. After insertion into the skin which can rapidly dissolve in the interstitial fluid of the skin. As they dissolve these microneedles release their encapsulated insulin. Starch is a naturally occurring, non-cytotoxic, and biodegradable polysaccharide. It can also be used in subcutaneous form. Starch is commonly used as an excipient for solid dosage formulations. It can be utilized as filler, disintegrate, and binder. It has several disadvantages like low cost, biodegradability, non-polluting nature, and renewability. Nevertheless, pure starch is an inflexible and fragile polymer with weak film-forming properties. Besides, these microneedles have some disadvantages like the chemicals used in the patch materials can cause skin irritation and/or allergic reactions, trouble in attaching to flexible body joint areas and to hairy skin. Nevertheless, patients must wait for long periods of time to dissolve entirely.

Nowadays, several techniques have been manifested to overcome the limitations connected with DMN-mediated drug delivery. Two-layered DMNs which consist of a therapeutic

polymer layer and a shaft. It has been established to deliver drug-based polymer tips with greater efficiency. (Chen et al.2013).

1.9 Two-layer dissolving MN patches

Two-layer dissolving polymeric MN patches consist of gelatin and sodium carboxymethyl cellulose (CMC). It is produced by two methods like two-step casting and centrifuging. These 2 processes limit the insulin in the needle to attain effective transdermal delivery of insulin. In this process in vitro skin insertion capability was determined by staining with tissue-marking dye after insertion, and the real-time penetration depth was monitored using optical coherence tomography. (Lee et al.2016)

Fabrication of two-layer dissolving gelatin/CMC MN patches

In this study, MN molds were created with PDMS to prepare two layer dissolving MN patches by using 3M MN mold (Fig 8). The two-step preparation process follows previous studies but there are some modifications. Various types of polymer solutions are used such as 10% gelatin solution with the incorporation of drugs into polymer matrix. Then the solution poured into PDMS molds and then centrifuged in swinging bucket rotors at 4000 rpm for 30 minute MN patch mold cavities were filled by centrifuged solution and the residual solutions on the mold surfaces were removed. Later, a second layer of different types of polymer solution were used, such as the 10% CMC solution, without incorporation of drug into the polymer matrix which was placed on the first layer (Fig 8). Then centrifugation the solution at 4000 rpm for 10 min. The MN patch molds were then dried at room temperature overnight.

Microneedle patches may be soundly applied in diabetic mice and human cadaveric skin models. The gelatin/CMC MN patch is a perfect choice for conventional insulin injection. It is a trouble free and suitable approach and efficient for controlling blood sugar. After release from MNs insulin reserves its pharmacological activity. It can produce a notable hypoglycemic

effect in diabetic mice. Human cadaveric skin tests show that the volar aspect of the forearm is potentially the ideal location for the clinical application of MN patches. These collective results indicate that dissolving gelatin/CMC MNs are potentially favorable devices for the transdermal delivering several biomolecules.(Lee et al. 2016)

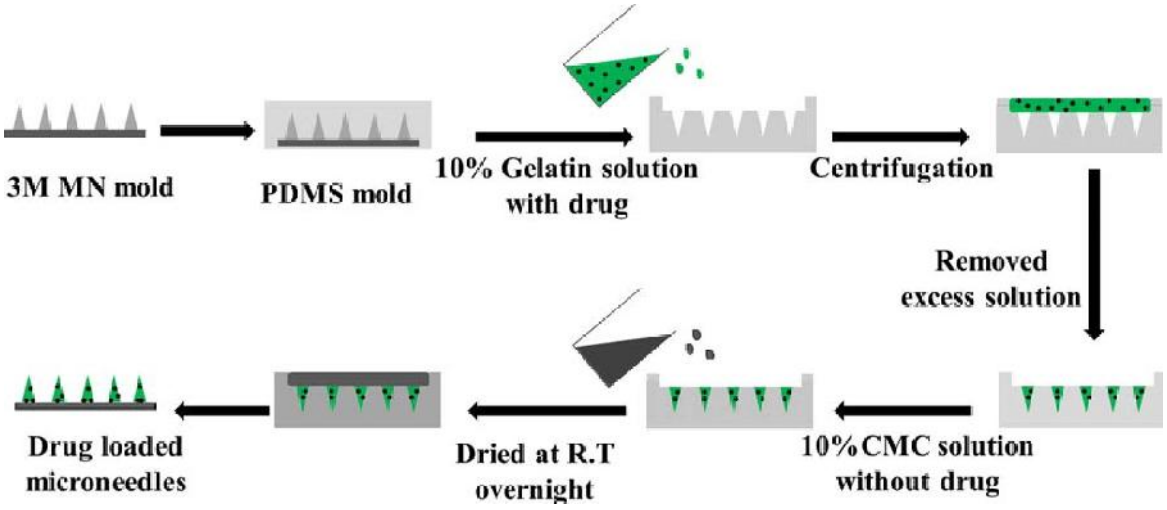


Fig 8: Fabrication process of the two-layer gelatin/CMC MN patches (*Lee et al. 2017)*

Figure 8 Represents the schematic illustration of the fabrication process of the two-layer gelatin/CMC MN patches. The model drug and insulin were located and centralized in the tip of the needles.

1.9 Advantages of dissolving microneedle

Dissolving microneedles have some advantages over the conventional needle available in the market. Such as:

- Dissolving microneedles can deliver a variety of drugs.
- Dissolvable microneedles can deliver drugs at a higher dose than solid microneedles (Bariya et al., 2012).
- Dissolvable microneedles can deliver some substances at a higher rate (Duarah et al., 2019).

- In case of dissolving microneedles there is very low chances of remaining any tips that are biohazardous (Duarah et al.2019).
- Another advantage of dissolving microneedles is it is easy to use and also self-administrable without medical training. (Duarah et al., 2019).
- The materials used for the dissolving microneedles are cost-effective.
- In dissolving microneedle system there are lower rates of microbial invasion into delivery sites.
- Swallowing a pill or giving an injection can be completed within seconds. However, for complete drug delivery, MNPs must typically be worn for minutes. Reducing patch wear time would shorten the time required to administer the drug and thereby should increase patient compliance.
- Hypodermic injection of drugs generates biohazardous sharps waste (i.e., used needles). This poses a safety risk of disease transmission due to accidental or intentional reuse of needles. It also incurs additional costs and requires logistics for safe sharps disposal.
- Dissolving microneedles as well as needles and syringes are single use, single dose, and fully disposable, all of which reduce the risk of disease transmission associated with medical equipment reuse. However, drug and vaccine vials are sometimes multiuse and multidose. This can lead to vaccine wastage.
- Dissolving microneedles capture the stability advantages of a dry formulation and do not need to be reconstituted because they are “reconstituted” by the skin’s fluids upon patch application.

1.10 Disadvantages

This is not sure that when a microneedle is applied the drug has fully entered into the skin or not. Despite many other advantages, dissolving microneedles have some disadvantages, limitations and challenges. They are:

- The risk of drugs not properly entering into the skin and will not be effective. (Olatunji et al 2017).
- The disadvantages of using dissolvable microneedles are that a large amount of drug introduction is a limitation for dissolving microneedles (Bariya et al., 2012).
- Dissolving microneedles poses incomplete penetration and this leads to drug wastage. (Olatunji et al.2017).
- Microneedles can leak onto a person's skin either by damage of the microneedle or by incorrect application by the physician. This is why physicians must be trained to perfectly apply the arrays. (Olatunji et al.2017).
- Another limitation is that if microneedles incorrectly applied it could leave foreign material in the body.
- Even if there is a little risk of infection but because of their small size these microneedles are more breakable than a typical hypodermic needle. So they have a possibility of breaking off and remaining in the skin.
- The microneedle arrays are difficult to store and process. (Duarah et al., 2019).
- Another drawback is that the dissolving microneedle has dose limitations.
- As titanium is used to construct the microneedles, the needles would cause irritation because titanium cannot be absorbed by the body.
- Another serious problem is hygroscopicity, which is broadly noticed in polymers such as PVP. To lessen the hygroscopicity problem should increase the mechanical robustness. (Chen et al. 2018).

1.10.1 Side effects

The most common side effect is minor skin irritation immediately following the procedure. You may also see redness for a few days.

It has severe side effects, such as:

- bleeding
- bruising
- infection
- peeling

You may not be an ideal candidate for microneedling if you are pregnant, have certain skin diseases, such as psoriasis or eczema, have open wounds, have had radiation therapy recently. Have a history of skin scars. Some redness or mild irritation can appear in the first few days — that's just the skin recovering. The redness should go away within three days. You might also notice that your skin feels tight, swollen, dry, or sensitive to the touch in the days immediately following the treatment, or it might flake away within the week.

If we perform at-home microneedling more often than prescribed, you will notice that skin problems you wish to overcome only get worse. To avoid skin inflammation, hyperpigmentation issues, and slow healing, it is advised to stick to the instructions that come along with the skin pen.

Microneedling is generally safe and effective, but it's not recommended for people who take or have had radiation in the past year, are pregnant, have a skin disease, or have a history of scarring or poor wound healing, according to Emory Aesthetic Center.

1.12 Patient compliance

1.12.1 Pain

Pain is not a safety concern and does not affect the patient compliance. In some initial studies we have seen that microneedle length from 50-200 mm and with 400 arrays of micro needles 26 and they are generally painless (Kaushik et al. 2001; Mikszta et al. 2002). Then again in some studies we have noticed that the pain is mainly associated with the length of the microneedle. Again, tip angle, thickness, width do not have any correlation with pain. In all cases it has found that

microneedles create less amount of pain than the hypodermic needle (Laurent et al. 2007). Microneedle with a length of a few hundred micrometers, only penetrates the superficial layers of the skin where the density of nerve receptors is low. As a consequence, insertion of microneedle into skin is perceived as painless (Shakeel et al., 2011). A table has been given below to see the relation between microneedle and pain.

MNS materials	Length of MN	Comment
Silicon	150	painless
Stainless steel	200 & 400	painless
Silicon	180 & 280	Lower pain
Stainless steel	620	One fourth pain of the hypodermic needle
Silicon	200	painless
Borosilicate glass	1	Less painful
Insulin	550,750,1 mm & 4mm	Painless if volume is more than 1mm then pain is caused

Table 1: Relation between pain and microneedle (Duarah, Sharma, & Wen, 2019)

Infection

Because of the contaminated needles the risks of infection mainly occur. But in this case microneedles are considered as a safer option than hypodermic needles. Most microorganisms are generally found in the upper layers of the skin. So those microneedle arrays that contain thousands of microneedles can be problematic. On the other hand, it is clinically proven that the infection caused by microneedle is minimal. In case of human studies, it is found that no infection occurred due to microneedles is reported and no serious adverse effect occurred (Adams et al. 2005; Barker and Ryan 1995).

Bleeding

This is a microneedle which has needles that are very small in size and used for the delivery of drugs (Wu, 2017). First of all, there is no vasculature in the upper layer of skin. The capillary that is superficial is generally placed above the dermis. So the microneedle whose length is 100 nm can cause bleeding. Generally, in the experiments those were done to see whether MNs create bleeding or not showed that MNs generally are not associated with bleeding. However, in the study 150 mm microneedle can produce pinpoint bleeding, and 600 mm microneedle can cause significant bleeding. But in the case of human subjects bleeding can occur for microneedles that range from 500-100 mm length. However, for solid microneedles it is reported that 1.5 mm length can sometimes cause bleeding or injection where hollow microneedles are used (Gill et al. 2008).

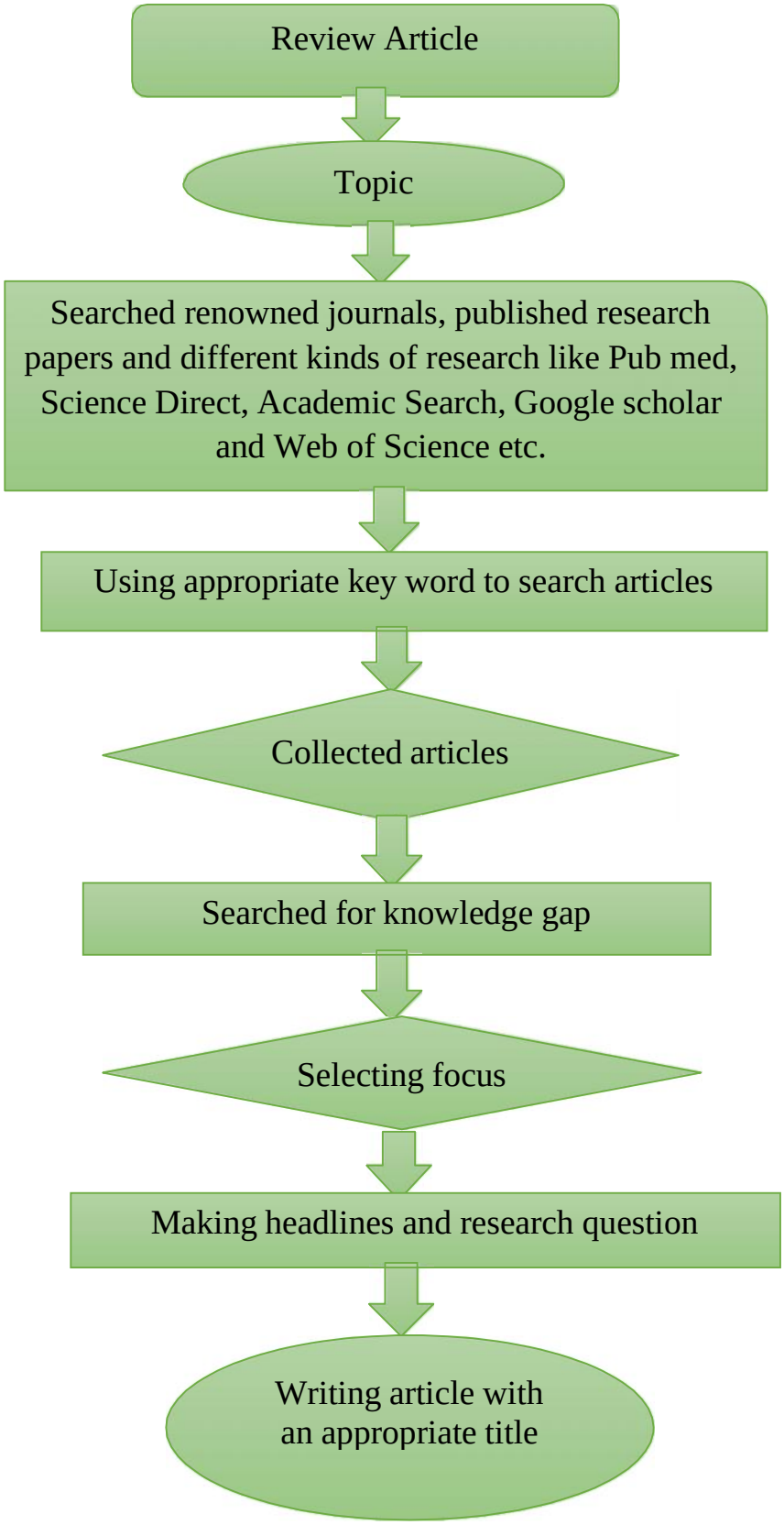
Skin Irritation

No noticeable skin irritation has occurred in case of using microneedles in humans. However, in some experiments some localized red spots have been seen but that generally is not a matter of concern. In a recent study it has been seen that using a 1.5 mm length microneedle can cause some sort of irritation but that generally passes away after some minutes (Laurent et al. 2007).

Chapter 2

Methodology

I have searched renowned journals, published research papers and different kinds of research databases like Pub med, Science Direct, Academic Search, Google scholar and Web of Science etc. I have gone through all the articles that I have collected for writing a review on dissolving microneedle technology. I have gone through around 100 articles and collected information from around 55 articles that seemed relevant to my topic to know about this revolutionary technology and after that assembled them. Here I have summarized some of the methods that were used in different articles. I have searched for knowledge gaps and research question



There are arrays of three microneedle exhibits utilized in this examination. The first Is microneedle and they are collective and those have different needle lengths. Another type is

made of steel and it is stainless, and finally the third one is microneedle arrays but they are hollow. From one article I have found information about the overall microneedle and those have different needle lengths. Later I collected information about the history of microneedles from another article. Then I gathered information about the classification and the basis of classification. (Chávez et al., 2016).

From another article I came to know about different types of microneedle release of microneedle. Basically there are 4 types: 'poke and patch', 'coat and poke', 'poke and release',' poke and flow'. (Maaden et al., 2012). Afterwards I collected information about fabrication of different microneedles and their materials. (Duarah et al., 2019). In this work the solid microneedle was made of the polylactic acid particles. These were biodegradable. A material named polyvinyl acid was given so that the concentration of the solution can be controlled. From another article I collected information about fabrication of dissolving microneedles There are several techniques for fabricating dissolving MNs. These techniques are mould based. Among these techniques, solvent casting is the popular method. Thus I gathered data about dissolving microneedles for transdermal delivery of drugs from the article "Transdermal Insulin Application System with Dissolving Microneedles". Here the author spoke about the dissolving microneedle (DM) application system, where 225–300 insulin loaded DMs were formed on a chip. (Prausnitz et al.2012).

Also I have found some articles regarding preparation of dissolving microneedle patches. These are:

- "Rapidly Dissolvable Microneedle Patches for Transdermal Delivery of Exenatide" (Wang et al. 2014).
- "Dissolving polymer microneedle patches for rapid and efficient transdermal delivery of insulin to diabetic rats." (Chen et al.2013).

- "Dissolving Microneedle Patches for Transdermal Insulin Delivery in Diabetic Mice: Potential for Clinical Applications." (Chen et al.2018).

In this article the author argued about the materials used in the preparation, how they work etc. Later from the article "Transdermal Delivery of Drugs with Microneedles—Potential and Challenges" I collected information about advantages and disadvantages of dissolving microneedles. (Ita et al. 2017).

Chapter 3

Discussion & Result

According to the literature a dissolvable MNs has some advantages. Firstly, a broad range of drug can be given by this. Secondly, it is also applicable for the sustained release of drugs. Now, there is some special fabrication technology for fabricating MNs. It needs to be kept in mind that the dissolving microneedle needs to be designed in such a way that it can meet the regulatory aspect alongside with its own superiority than the other methods. Again, according to this experiment a manufacturing method will be useful if it meets certain criteria. Some of the examples of this criteria are that they need to be applicable for specific material such as Dissolving polymer microneedle patches and the fabrication capability need to be reproducible. Now, many of these requirements can be solved by a technique named solvent-casting technique. This technique has some advantages. Firstly, it is cost effective. Secondly, it can be used for a broad range of materials. Thirdly, it can be processed at a low temperature. However, the techniques that are used for the fabrication of master molds have some limitations like they are applicable for only some materials, e.g. silicon, silicon dioxide etc., also it is also mentioned that they are also applicable for only some fixed geometries fabrication. Now for these shortcomings mechanical micro milling is suggested as an alternative for fabricating master molds. There are some advantages of this technology like its capacity to create any micro scale geometry, low unit cost, shorter lead-time for fabrication and metals, most polymers,

compositor ceramics can be processed through it so this study found micro milling as a very good alternative to photolithographic processes. A very useful advantage of it is that it has no post process method. Micromilling is very helpful in this purpose. Finally, reproducibility of the dissolvable MNs are very important for regulatory approval and clinical adaptation. Cosmetics, vaccines etc can be induced by other MNs instead of injection. This literature shows that the needle length of the microneedles needs to be minimized because if the needle is larger in length then the needle can be deformed. (McCrudden et al.).

However, as with dissolving and coated microneedles, this system is disadvantageous for delivering large doses. Several studies are being directed for increasing the amount of drug that can be incorporated in these microneedles. In this study, dissolving polymeric microneedle (MN) patches were made of gelatin and sodium carboxymethyl cellulose. These patches are applied to placed insulin. These patches have in vitro skin insertion power. (Chen et al.2018).

An investigation revealed that the in vivo penetration depth of the microneedles was 200–250 lm. This result is reciprocal with earlier research which revealed that as a result of their broad needle structure and minor mechanical quality they are tough to introduce completely. The pain and skin irritation (erythema) caused by microneedles initially depends on the inclusion profundity. The suggested technique can lessen skin damage and pain sensation because the penetration depth corresponds to insertion into the superficial dermis. (Jones, 2013).

Chapter 4

Future directions

Vaccine delivery by using conventional needles can cause problems like needle phobia, needle injury, skin irritation etc. Now, after the invention of microneedles for vaccination these problems actually pass away. Studies have shown that microneedles are superior to conventional needles in terms of dose sparing, immunogenicity etc. Some studies are going on based on the increasing vaccine stability and delivering of that vaccine to different body areas apart from skin (Shin, 2017).

1. Polymeric MN devices have opened a new era in MN technology. Polymeric MNs can solve many problems that occur with silicon made solid MNs. Also it is nontoxic and biocompatible.

2. There are many pharmaceutical companies that are trying to commercialize MN technologies. Among these companies Zosano pharma, Coriunm 3M etc can be mentioned. If some problems can be addressed, then this technology can be the pharmaceutical dosage forms and monitoring device in near future. Moreover, Zosano pharma are trying to deliver parathyroid hormone by using microneedles for the treatment of osteoporosis but this is in phase 3 trial now (Mahmood et al.,2013).

3. One more thing is that though polymeric microneedles can solve many limitations associated with other types of microneedles, the therapeutic efficiency of polymeric microneedles is still not satisfactory. It will be very useful in the future if nano medicines containing drugs are incorporated into functional nanoparticles. If it is done then this problem associated with polymer microneedle can be solved (Xu, 2017).

4. In the future it is urgent to come up with some good adjuvant that will increase the immunogenicity. Moreover, there is a very good chance that the research community will give more chances to the microneedle product for clinical trials (Ita, 2016).

Conclusion

This study presents a dissolving microneedle design including fabrication. Which was held under mild conditions that may be suitable for protein delivery and inclined to mass generation. It was created by selecting FDA-approved polysaccharides and altering a casting method with centrifugation. To have enough mechanical strength to embed into skin, dissolving microneedles were formulated by using a low aspect ratio and pyramidal geometry. Microneedle patches provided bolus release of a model drug over the dissolution of the microneedle matrix inside skin by using a low aspect ratio and pyramidal geometry. By altering microneedle formulation model drug release rate was controlled. Overall, dissolving microneedles may be valuable as a strategy for patients to self-administer drugs without the pain or hazards of hypodermic needles. (Mahmood et al.,2013).

Yet, marketing policy will also be important in acquiring the highest market share relative to existing and widely accepted conventional delivery systems. In the meantime, academia and industry must work together to address concerns, and push MN technology into the clinic, where its potential can be truly realized. Finally, it needs to be said that microneedles can invent a revolutionary change in the vaccination process. Moreover, the needle spreading is expanding at an alarming rate. So the microneedle can be a very good preventive factor for needle spreading disease.

References

[1] Ashraf, M. W., Tayyaba, S., Nisar, A., Afzulpurkar, N., Bodhale, D. W., Lomas, T., … Tuantranont, A. (2010). Design, fabrication and analysis of silicon hollow microneedle for a transdermal drug delivery system for treatment of hemodynamic dysfunctions.

[2]Bariya, S. H., Gohel, M. C., Mehta, T. A., & Sharma, O. P. (2012). Microneedle: *An emerging transdermal drug delivery system. Journal of Pharmacy and Pharmacology, 64*(1), 11–29. https://doi.org/10.1111/j.2042-7158.2011.01369.x

[3] Bhatnagar, S., Saju, A., Cheerla, K. D., Gade, S. K., Garg, P., & Venuganti, V. V. K. (2018). Corneal delivery of besifloxacin using rapidly dissolving polymeric microneedle. *Drug Delivery and Translational Research, 8*(3), 473–483. https://doi.org/10.1007/s13346 017-0470-8

[4] Bouwstra, J., Ossendorp, F., van der Maaden, K., Terwisscha van Scheltinga, A., Pontier, M., Heuts, J., … Camps, M. (2017). Hollow microneedle-mediated micro-injections of a liposomal HPV E743–63 synthetic long peptide vaccine for efficient induction of cytotoxic and T-helper responses. *Journal of Controlled Release, 269*(November 2017), 347–354. https://doi.org/10.1016/j.jconrel.2017.11.035

[5] Quinn HL, Kearney M-C, Courtenay AJ, McCrudden MTC, Donnelly RF.2014.The role of microneedles for drug and vaccine delivery. *Expert Opinion Drug Delivery* 11:1769–1780.

[6] Henry S, McAllister DV, Allen MG, Prausnitz MR. 1998. Microfabricated microneedles: *A novel approach to transdermal drug delivery. J Pharm Sci* 87:922–925.

[7] McCrudden MTC, Alkilani AZ, McCrudden CM, McAlister E, McCarthy HO, Woolfson AD, Donnelly RF. 2014. Design and physicochemical characterisation of novel

dissolving polymeric microneedle arrays for transdermal delivery of high dose, low molecular weight drugs. *J Control Release* 180:71–80.

[8] Gill, H.S.; Prausnitz, M.R. Coated microneedles for transdermal delivery. *J. Control. Release 2007, 117,* 227–237. [CrossRef] [PubMed

[9] Garland MJ, Migalska K, Tuan-Mahmood TM, Thakur RRS, Majithija R, Caffarel-Salvador E, McCrudden CM, McCarthy HO, Woolfson AD, Donnelly RF. 2012. Influence of skin model on in vitro performance of drug-loaded soluble microneedle arrays. *Int J Pharm* 434:80–89.

[10] Gomaa YA, Garland MJ, McInnes F, El-Khordagui LK, Wilson C, DonnellyRF.2012. Laser engineered dissolving microneedles for active transdermal delivery of nadroparin calcium. *Int J Pharm* 82:299–307.

[11] LingM-H, ChenM-C.2013.Dissolving polymer microneedle patches for rapid and efficient transdermal delivery of insulin to diabetic rats. *Acta Biomater* 9:8952–8961.

[12] Ito Y, Murano H, Hamasaki N, Fukushima K, Takada K. 2011. Incidence of low bioavailability of leuprolide acetate after percutaneous administration to rats by dissolving microneedles. *Int J Pharm* 407:126– 131.

[13] Ito Y, Hasegawa R, Fukushima K, Sugioka N, Takada K. 2010. Self-dissolving micropile array chip as percutaneous delivery system of protein drug. *Biol Pharm Bull* 33:683–690.

[14] Lee JW, Choi S-O, Felner EI, Prausnitz MR. 2011. Dissolving microneedle patch for transdermal delivery of human growth hormone. Small 7:531–539.

[15] Siddiqui, O.; Sun, Y.; Liu, J.C.; Chien, Y.W. Facilitated transdermal transport of insulin. *J. Pharm. Sci.* **1987**, *76*, 341–345. [CrossRef] [PubMed]

[16] Gill, H.S.; Prausnitz, M.R. Coated microneedles for transdermal delivery. *J. Control. Release* 2007, *117,* 227–237. [CrossRef] [PubMed]

[17] Lee, I.C.; He, J.S.; Tsai, M.T.; Lin, K.C. Fabrication of a novel partially dissolving polymer microneedle patch for transdermal drug delivery. *J. Mater. Chem. B* **2015**, *3*, 276–285. [CrossRef]

[18] Lee, I.C.; Lin,W.M.; Shu, J.C.; Tsai, S.W.; Chen, C.H.; Tsai, M.T. Formulation of two-layer dissolving polymeric

microneedle patches for insulin transdermal delivery in diabetic mice. *J. Biomed. Mater. Res. Part A* **2017**, *105*, 84–93. [CrossRef] [PubMed]

[19] Kaestli, L-Z, Wasilewski-Rasca A-F, Bonnabry P, Vogt-Ferrier N. 2008.Use of transdermal drug formulations in the elderly.DrugsAging 25:269–80. MorrowDIJ, McCarronPA, WoolfsonAD, DonnellyRF.2007 Innovative strategies for enhancing topical and transdermal drug delivery. *Open Drug Deliv* J 1:36–59.

[20] Kim, Y.C.; Park, J.H.; Prausnitz, M.R. Microneedles for drug and vaccine delivery. *Adv. Drug Deliv. Rev.* 2012, *64*, 1547–1568. [CrossRef] [PubMed

[21] Xie, X.; Pascual, C.; Lieu, C.; Oh, S.; Wang, J.; Zou, B.; Xie, J.; Li, Z.; Xie, J.; Yeomans, D.C.; et al. Analgesic microneedle patch for neuropathic pain therapy. *ACS Nano* 2017, *11*, 395–406. [CrossRef] [PubMed]

[22] Ita, K.B. Chemical penetration enhancers for transdermal drug delivery—Success and challenges. *Current. Drug Delivery.* 2015, *12*, 645–651. [CrossRef] [PubMed]

[23] Henry S, Mcallister DV, Allen MG, Prausnitz MR. Microfabricated microneedles: a novel approach to transdermal drug delivery. *J Pharm Sci.* 1998;*87*(8):922–5. https://doi.org/10.1021/js980042+.

[24] Donnelly RF, Majithiya R, Thakur RRS, Morrow DIJ, Garland MJ, DemirYK, MigalskaK, RyanE, GillenD, ScottCJ, WoolfsonAD.2011. Design, optimization and characterization of polymeric microneedle arrays prepared by a novel laser-based micromoulding technique. *Pharm Res* 28:41–57.

[25] Sullivan SP, Koutsonanos DG, del Pilar Martin M, Lee JW, Zarnitsyn V, Choi S-O, Murthy N, Compans RW, Skountzou I, Prausnitz MR. 2010. Dissolving polymer microneedle patches for influenza vaccination. *Nat Med* 16:915–920.

[26] McCrudden MTC, Alkilani, AZ, Courtenay AJ, McCrudden CM, McCloskey B, Walker C, Alshraiedeh N, Lutton REM, Gilmore BF, Woolfson AD, Donnelly RF. 2014. Considerations in the sterile manufacture of polymeric microneedle arrays. *Drug Delivery Transdermal Res*5:3–14.

[27] Larra˜neta E, Moore J, Vicente-P´erez EM, Gonz´alez-V´azquez P, Lutton R, Woolfson AD, Donnelly RF. 2014. A proposed model membrane and test method for microneedle insertion studies. *Int J Pharm* 472:65–73.

[28] Donnelly RF, Morrow, DIJ, McCarron PA, Woolfson AD, Morrissey A, Juzenas P, Juzeniene A, Iani V, McCarthy HO, Moan J. 2009. Microneedle arrays permit enhanced intradermal delivery of a preformed photosensitizer. *Photochem Photobiological* 85:195–204.

[29] (Xuan Jin, Dan Dan Zhu, Bo Zhi Chen, Mohammad Ashfaq, Xin Dong Guo , Insulin Delivery Systems Combined with Microneedle Technology.)

[30] Thakur RRS, Garland MJ, Migalska K, Caffarel-Salvador E, Shaikh R, McCarthy HO, Woolfson AD, Donnelly RF. 2012. Influence of a pore-forming agent on swelling, network parameters, and permeability of poly (ethylene glycol)-crosslinked poly (methyl vinyl ether-comaleic acid) hydrogels: Application in transdermal delivery systems. *J Appl Polym Sci* 125:2680–2694.

[31] Chen, Y., Chen, B. Z., Wang, Q. L., Jin, X., & Guo, X. D. (2017). Fabrication of coated polymer microneedle for transdermal drug delivery. *Journal of Controlled Release*, *265*(September 2016), 14–21. https://doi.org/10.1016/j.jconrel.2017.03.383

[32] Paudel, K.S.; Milewski, M.; Swadley, C.L.; Brogden, N.K.; Ghosh, P.; Stinchcomb, A.L. Challenges and opportunities in dermal/transdermal delivery. *Ther. Deliv.* 2010, *1*, 109–131. [CrossRef] [PubMed]

[33] Donnelly, R. F., Mooney, K., Caffarel-salvador, E., Torrisi, B. M., Eltayib, E., & Mcelnay, J. C. (2014). *Microneedle-Mediated Minimally Invasive Patient Monitoring*. 10–17.

[34] Duarah, S., Sharma, M., & Wen, J. (2019). Recent advances in microneedle-based drug delivery: Special emphasis on its use in paediatric population. *European Journal of Pharmaceutics and Biopharmaceutics*, *136*, 48–69. https://doi.org/10.1016/j.ejpb.2019.01.005

[35] Escobar-Chávez, J. J., Bonilla-Martínez, D., Villegas-González, M. A., Molina-Trinidad, E., Casas-Alancaster, N., & Revilla-Vázquez, A. L. (2011). Microneedle: A valuable physical enhancer to increase transdermal drug delivery. *Journal of Clinical Pharmacology*, *51*(7), 964–977. https://doi.org/10.1177/0091270010378859

[36] Kim, Y. C., Park, J. H., & Prausnitz, M. R. (2012). Microneedle for drug and vaccine delivery. *Advanced Drug Delivery Reviews*, *64*(14), 1547–1568. https://doi.org/10.1016/j.addr.2012.04.005

[37] Wang, M., Hu, L., & Xu, C. (2017). Recent advances in the design of polymeric microneedle for transdermal drug delivery and biosensing. *Lab on a Chip*, *17*(8), 1373–1387. https://doi.org/10.1039/C7LC00016B

[38] Zhu, Z., Luo, H., Lu, W., Luan, H., Wu, Y., Luo, J., … Wang, H. (2014). Rapidly dissolvable microneedle patches for transdermal delivery of exenatide. *Pharmaceutical Research*, *31*(12), 3348–3360. https://doi.org/10.1007/s11095-014-1424-1

[39] Henry, S.; McAllister, D.V.; Allen, M.G.; Prausnitz, M.R. Microfabricated microneedles: *A novel approach to transdermal drug delivery. J. Pharm. Sci.* 1998, *87*, 922–925. [CrossRef] [PubMed]