TRANSDERMAL MATERIAL CONSTRUCTION IN COVID-19 VACCINE DELIVERY: A MICRONEEDLE APPROACH

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons)

Department of Pharmacy
Brac University
August 2021

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing 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 which 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

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of Spring, 2021 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons) on 25th August 2021.

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Ethics Statement

There were no unethical activities engaged in the thesis. There will be no human or animal trials in this research.

Abstract

COVID-19 has an impact on people of all ages, races, and ethnicities. Because many infected persons are asymptomatic, the virus is unknowingly transmitted to others, resulting in a rapid spread of illness. Spike protein (S) of coronavirus is a distinctive secondary element of the viral envelope which is regarded as a major target of antibodies designed to detect coronavirus contamination. Microneedle methods, particularly dissolving microneedles, are very helpful and beneficial for achieving herd immunity in the population. There will be increased immunogenicity, less vaccination waste, customized distribution, and so forth. Hollow microneedles and solid microneedles are also viable options for producing the vaccine of COVID-19, and the materials used to make them include ceramic, polymers, carbohydrates, hydrogels, and so on. In order to protect people in this worldwide epidemic, this may be an excellent way of vaccinating against this lethal virus while also ensuring patient compliance.

Keywords: COVID-19; Vaccination; Transdermal; Microneedles.

Dedication

This thesis is dedicated to my loving parents and spouse for their love and unwavering support.

Acknowledgement

All praises to Almighty Allah who is our creator and source of all knowledge and wisdom. Without Allah’s help, I would not have been able to continue my study in full devotion and complete my project paper.

This research would not have been possible without the support and guidance of my honorable supervisor Dr. Md. Jasim Uddin, Associate Professor, Department of Pharmacy, Brac University. His untiring guidance, cooperation and his extensive knowledge in research has helped me in every situation to perform the project work. I would like to forward my gratitude and sincere regards to Dr. Eva Rahman Kabir, Chairperson and Professor, Department of Pharmacy, Brac University for giving me the opportunity to conduct such an interesting project and for enhancing a smooth conduction of my study.

I owe special thanks to my friends and family for their uncountable support, motivation and contribution in my project work.

Thank you.

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Chapter 1

Introduction

1.1 History of covid-19

Corona viruses were first discovered in the 1960s. (Chung et al., 2021). It was called for the virus's shape, which resembled a crown due to the spike proteins on its surface that induce infection. According to studies, these viruses are derived from animals. They further added that, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) were discovered in 2002 and 2012, respectively, and are more transmissible and cause life-threatening illnesses in children, adults, and immunocompromised individuals. Coronaviruses are adherents of the subfamily Coronavirinae which is from the family Coronaviridae and the order Nidovirales. (Cui et al., 2019). They further added that, this subfamily comprises of 4 genera- Beta-coronavirus, Alpha-coronavirus, Delta-coronavirus and Gamma-coronavirus — which is based on their phylogenetic associations and genomic assemblies. Unfortunately, a new coronavirus (SARS-CoV-2) appeared in December 2019 and was initially identified in Wuhan, China. To date (May 24, 2021), there have been 167, 602, 538 total cases (infected) globally, with 3,479,991 death cases. The number continues to rise since the virus is spread via direct contact and respiratory droplets, such as those produced by sneezing or coughing, according to the Centers for Disease Control and Prevention (CDC) in the United States. SARS-genetic CoV-2's sequence was released only weeks after it was discovered, at that time it was identified as a structure of beta-coronavirus with SARS-CoV-like genomic characteristics. Fever, dry cough, tiredness, dyspnea, and breathing difficulties are the most frequent COVID-19 symptoms, whereas severe symptoms are followed by pneumonia and systemic infection. Addition to these symptoms, it was also seen that there were gastrointestinal symptoms of COVID-19 triggered by the viral impairment to the intestine somewhat than the immunopathogenic response to the lung infection of the host. (Tu et al., 2020). They further added that, whenever these symptoms are visible there are certain tests that need to be done for the primary detection and initiating the treatment like- chest X ray, CT scan etc. In a report, it was validated that, by the date January 2, 2020 there were 42 hospital admitted patients who were diagnosed with 2019-nCoV infection which were laboratory confirmed in Wuhan where it all started. (Huang et al., 2020). In terms of pediatric patients, a study was conducted by comparing their physical condition with that of adult patients and it was noticed that these patients had mild symptoms clinically, very few changes were observed in laboratory and radiological testing parameters. (Xu et al., 2020). Radiologists played a vital role in this outbreak. They were involved in the primary detection of the radiological deviation which provides a doubt of pneumonia in infected patients who are at risk. (Kim, 2020).

1.2 Transdermal drug delivery

Since 1981, this method has been used in therapeutic settings. But there is this event that has occurred in 1979, which is the usage of scopolamine transdermal patch and attracted widespread attention owing to its marvelous advantages. (Yang et al., 2020). But, the number of drugs appropriate for patch construction were very few in number due to the physiological blockade of the epidermis. (Lee et al., 2018). It is known to us that the skin is our body's largest organ and provides the greatest route for transdermal and dermal medication administration. As a result, the medicine must possess specific characteristics in order to penetrate beyond the stratum corneum, our skin's outermost layer. (Münch et al., 2017). They furthermore added that, as it does not have to travel through the GI tract, transdermal medication delivery is preferable to oral treatment because of avoidance of the adverse effects of first-pass metabolism. Also, unpredictable bioavailability and problems associated with short half-life can be addressed by transdermal drug delivery method. (Ita, 2015). The main aim of recent transdermal drug delivery study is to explore methods to improve skin dispersion of larger, hydrophilic medicines and macro molecules for treating diseases and vaccination. (Palmer & DeLouis, 2016). A study has also shown that, how transdermal drug delivery unit has assisted in monitoring the glucose level precisely by inventing a wearable device which is sweat-based. (Lee et al., 2017). They further added that, this system is also advantageous for accurately delivering the controlled transdermal drug like- Metformin which is a drug used for treating type-2 diabetes. There were extensive experiments conducted and vaccines against Calmette–Guérin (BCG), influenza and other vaccines have proved that vaccine delivery in our skin is also promising. (Chen et al., 2016).

1.3 Microneedles

It is a new method to use micro-needle patches which enables safer and effective vaccination in low-income countries, while also reducing the need for trained healthcare workers, streamlining the supply chain, and reducing the risk of vaccine waste and sharps. (Münch et al. 2017). Microneedles may be given to patients without the assistance of experts. There structure has similarity with needle with a microscale diameter up to 1 mm in length. Great thing about microneedles is they may go through the stratum corneum and into the epidermis/dermis layers without contacting the pain-sensing neurons or blood vessels, making it a painless procedure. (Amani et al., 2020). They release antibodies directly with minimum invasiveness, which is critical for administering the covid-19 vaccination. The usefulness of dissolving and coated microneedles as vaccine carriers may be enhanced since they can carry vaccines in a dry state. In the recent investigations it was noticed that microneedles have not been functional for the skin only, they have also shown effectiveness in delivering drugs to other tissues like- blood vessels, corneal tissue and scleral tissue. (Lee et al., 2019). Microneedles were also extensively considered for signal monitoring, blood sampling, gene transferring via microneedle-assisted, intrascleral drug administration and biosensor. (Ma & Wu, 2017). On the other hand, infections in skin and soft tissue are the most common infections caused by viruses, fungi, and bacteria globally. (Jamaledin et al., 2020). Biofilms yield an extracellular polymeric material that hampers the effective conveyance of therapeutics. To attain biofilm disturbance and enhance antibiotics dispersion while sustaining painless administration, the CAM@GNPs were further combined into a microneedle array patch delivery method. (Xu et al., 2019). In a study, a degradable active microneedle delivery method was established which was skilled of producing autonomously dynamic convective fluid streams, for a greatly improved drug permeation. (Lopez-Ramirez et al., 2019). For larger patches of microneedles, many fingers, or the whole palm of the hand will be needed to confirm even addition of the needles dispersed over the whole part of the patch. (Ripolin et al., 2017). Also, in a study, the researchers had established a near-infrared (NIR)-light-activatable microneedle system which frequently produces heat and concurrently releases captured anticancer medicines into the tumor when triggered by the NIR laser. (Chen et al., 2015). A study was done developing skin-mounted graphene-hybrid microneedle arrays proficient of not only sweat-based glucose and pH monitoring in combination with a sweat-control layer, but also precise transcutaneous drug distribution via bioresorbable temperature-responsive microneedles. This is a unique method to monitor diabetes. (Lee et al., 2016). One of the interesting examples of microneedle patches is simplified rabies immunization of dogs, especially abandoned dogs in emerging countries, since these patches could be simply applied by the personnel on a dog's ears with little to no training. (Arya et al., 2016).

1.4 Covid-19 Vaccines

Vaccines are a critical component of pandemic preparation, but manufacturing and logistics issues may limit their availability. (O’Shea et al., 2021). In developing countries like Bangladesh, microneedle patches mediated covid-19 vaccination will be beneficial to minimize such logistical problems and will also simplify the supply chain. (Arya & Prausnitz, 2016). Research works are still ongoing vigorously to invent am efficient and safe vaccine against

COVID-19 and attempting to discover the actual structural identity of single-stranded SARS-COV-2 RNA virus. (Zafar et al., 2020). Mass vaccination process using durably effective and safe vaccines for SARS-CoV-2 would curb out COVID-19 pandemic, especially in combination with several associated prevention methods. (Mehrotra et al., 2020). The requirement to make sure that the availability and affordability of any upcoming COVID-19 vaccine is getting enhanced consideration. (Karim, 2020). The different types of Covid-19 vaccines which are under investigations are- mRNA vaccines, subunit vaccines, Whole-Cell Killed and Live-Attenuated Vaccines, Synthetic Peptide or Epitope Vaccine, live vector vaccines and DNA vaccines. (Zhang et al., 2020). Traditional mRNA vaccines incorporate an ORF for the target antigen, flanked by untranslated regions (UTRs) and with a terminal poly(A) tail at their simplest. (Zhang et al., 2019). According to Zafar et al, ORF1ab polyprotein is found in the 5' end of its genome, that comprises of 15 to 16 non-structural proteins. On the other hand, the 3' end comprises of four structural proteins which include spike (S), membrane (M), envelop I and nucleocapsid (N) proteins. (Zafar et al., 2020). The vaccine will tackle structural proteins and whole-cell antigens as its targets. The most probable antigen vaccine participant for SARS-CoV-2 infection is S protein because it includes surface exposure and easy identification by the immune system of host. People shall have the knowledge as to how the vaccination is protecting them from the infection and what exactly the vaccine is protecting them from, so that they have a broad idea of advantages and risk factors associated with the vaccination. Apart from the conventional vaccines, an investigation was done using particles in the form of nanoplatforms which displays related antigenic moieties which is an appealing way too. (Al-Halifa et al., 2019). In a study conducted, it came out that the mRNA-1273 vaccine proved to be 94.1% efficient at curing diseases caused by COVID-19 vaccine, including all other severe symptoms. (Baden et al., 2021).

1.5 Material construction

For the microneedles, we may utilize a variety of materials, including inorganic materials, metals, and polymers. (Bolton et al., 2020). Silicon, glass, and other inorganic materials may be utilized. Silicon is the most popular of these materials since it is readily absorbed by the skin. Ceramic, like glass and silicon, is extensively utilized because it has attracted a large number of scientists. Bio-ceramic biodegradable microneedles have increased mechanical strength to pierce the skin without retaining waste of various types into the skin that are sharp in characteristic and may create problems for the patient. Different metals, such as Titanium and Nickel, have also been utilized to produce various types of microneedles. Metals are excellent for transdermal drug administration due to their great mechanical strength and hardness. Polymeric microneedles are also being utilized to avoid very severe adverse effects in the skin. This has been shown to be a safe method of medication delivery (vaccine). Polymers that may be utilized include carboxy methyl cellulose, poly-ethylene glycol and others.

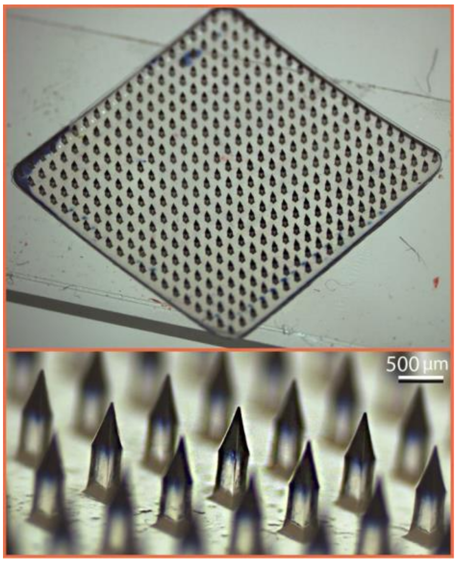

Figure 1: Microneedle Patches

https://www.cmu.edu/ambassadors/may-2020/microneedle-patches.html

As we know, oral drug conveyance is the most prevalent route because of its easy and safe administration, but this route is not always desirable owing to the hepatic first pass outcome, inactivation at gastric pH and enzymatic degradation. (Uddin et al., 2017). Hypodermic needles are conventionally used for most of the vaccines including the COVID-19 vaccine but there are disadvantages associated with these needles like- patients tend to face difficulty while using them by themselves along with inadequate patient compliance because of having needle phobia and pain. (Asfour, 2020). Other than these, there are problems associated like-risk of disease spread, needle-stick injuries, huge cost because of cold chain storage and also the transportation cost is high. (Balmert et al., 2019). Presently, two of the COVID-19 vaccines are very effective (Moderna and Pfizer-BioNTech), being developed recently and these are administered via the intramuscular route. Although the efficiency of IM administered vaccine doses are higher, but microneedles allow for accurate delivery into the dermal layers of the skin. Because the insertion depth is small enough to avoid impinging on innervated tissue, the injection is painless, and patients' needle anxiety is alleviated. (Menon et al., 2021). However, COVID-19 vaccination and treatment via dissolvable microneedle array patches can be meaningfully faster and more effective than using hypodermic needles.

Table 1: Comparison between COVID-19 vaccine delivery methods: Hypodermic needles and microneedle-array patches

Parameters/ Characteristics	**Hypodermic Needles**	**Microneedle-array patches**
Patient Compliance	Good	Better
Cost	High-cost	Low-cost
Trypanophobia	High	Little to no
Need of trained health-care personnel	Yes	No
Efficacy	Comparatively low	High
Pain	Yes	No
Cold-chain storage	Needed	Not-needed
Dose-sparing effect	Absent	Present
Reconstitution	Needed	Not needed

Chapter 2

Research Methodology

After selecting the thesis project topic, a comprehensive literature review was done for this study starting from finding out articles using key words to analyse articles and papers from platforms like Google Scholar, PubMed, Elsevier, Research Gate etc. and from journals like Journal of Controlled Disease, Vaccines, The Lancet, European Journal of Pharmaceutics and Biopharmaceutics, EbioMedicine, Nature Nanotechnology and so on. Then articles were filtered out in the criterion of impact factor being more than three (03). Also, qualitative method was used along with the aforementioned secondary method to conduct this review. Data were collected and implied from the filtered articles and journals which assisted in various decision-making process, selection and analysis that could provide a vital impact in the future prospects of this study. Finally, the study was corrected several times with the assistance with the supervisor and revised accordingly.

Chapter 3

Microneedles: History, characteristics and types

3.1 History of microneedles

Virgil A Place and Martin S Gerstel were the first to develop and propose the idea of medication administration through microneedles in the 1970s. However, it became a priority in the late 1990s due to advances in microfabrication technology that improved the manufacturing process. (Larran˜eta et al., 2016). McAllister et al. published the first publication on the transdermal drug-delivery of macromolecules and nanoparticles which is MN-based in 2003, where they utilized two kinds of microneedles (Solid MNs and Hollow MNs) to administer insulin, albumin, and other drugs. Over the last decade, there has been a lot of research done on MN innovation using a wide range of MN designs and materials.

3.2 Properties of microneedles

It is well known that microneedles have always been the minimum intrusive devices that may be applied into the surface area of skin without causing discomfort and penetrate the epidermis by making pores through which the medication diffuses to the dermal microcirculation, resulting in systemic administration. These are made adequately long to penetrate the dermis, yet thin and short enough not to stimulate dermal nerves or burst dermal blood vessels. According to statistics, there have been no instances of skin infections caused by MNs, and MN may be replicated into skin by patients without the use of any applicators. In vivo experiments have demonstrated that many medicines such as oligonucleotides, hormones, and insulins may be administered safely. The main advantages associated with the microneedles are that- they are proficient in localized and controlled drug delivery. (Bilal et al., 2020). As we know, a number of drugs need continuous refrigeration and that too while transporting the drug which in turns increase the cost of logistics. Therefore, microneedles can offer enhanced stability without the need of refrigeration, especially for biomolecules like vaccines and proteins. (Prausnitz, 2017).

3.3 Types of Microneedles

There are four distinct kinds of microneedles that are extensively utilized in the field of transdermal medication administration. Various sorts of molecules, including vaccines, are included in the categories of medicines. In every kind of microneedles, needle measurement (length) is to be accustomed properly which should be sufficient to penetrate the stratum corneum and not to lesion nerve endings. (Halder et al., 2020). A research was also done proposing a novel technique to manufacture purpose-oriented microneedles which are based on universally applicable RNA membrane. (Kim et al., 2020)

3.3.1 Solid microneedles characteristics

The “poke-and-patch” technique lies at the heart of this approach. Solid MNs transport medicines across the skin's layers by forming microchannels and thereby increasing skin permeability. (He et al., 2019). At the same time, the drug of interest encapsulated in a patch must be applied to the channels. Nevertheless, the skin must retract to seal microchannels immediately after MN patch is removed from skin. It will help to avoid infection from pathogenic microorganisms and protect from the entry of harmful chemicals. A number of materials have been utilized in the fabrication process of solid MNs. Another version used a roller made of solid microneedles that poked holes in the stratum corneum many times as it moved over the skin. Several variables influence the absorption of medicinal compounds through solid MNs, including MN penetration force, MN density, and tip sharpness. The combination of solid MNs with additional permeation increasing methods, such as iontophoresis, has also been shown to be helpful in the transdermal administration of many active compounds.

3.3.2 Hollow microneedles characteristics

Hollow microneedles are made from a broad variety of materials and in a wide variety of geometrics and heights. (Duarah et al., 2019). These are miniature replicas of standard hypodermic needles. (Menon et al., 2021). Hollow bore microneedles allow for drug dissemination or pressure-driven drug flow via a core lumen, while polymeric MN release their medicate payload as they decay or biodegrade inside the reasonable skin layers. These MNs allow for the delivery of a particular medication into skin by infusing formulation of a liquid via the implanted hollow needles. The main limitations of hollow MNs are the possibility of tissue obstruction in the needle holes during flow resistance and skin penetration caused by thick dermal tissue squeezed around the MN tips when insertion. The main constraint may be addressed by using an alternate strategy to locate the bore-opening on the MN tip's side. Because of their shape and fragility, these microneedles are more difficult to produce than other kinds of microneedles. They split the stratum corneum, allowing for deep drug administration, albeit ultrasonic increased dispersion rates via cavitation effect inside the epidermis as well as within the MNs hollow drug repository. According to research, the drug flow rate is primarily related to the hollow microneedles inside diameter and inversely proportionate to the needle's length. Flow rates may be adjusted by adjusting factors such as infusion pressure, MN tip size, and penetration depth. As a result of this, we may achieve regulated medication delivery. Nonetheless, the effectiveness of hollow MNs may be damaged by the possibility of tissue obstructing the bore-opening of needle during the skin penetration process. Luckily, this has been avoided by suggesting another one-of-a-kind design that puts the bore-opening off-center by a small margin, rather than at top point. This helps to avoid needle clogging while also increasing the medication exposure area to tissue and retaining the sharpness of tip.

Furthermore, flow resistance caused by dense dermal tissue's compression which surround the MN tip is a significant drawback of hollow MNs. According to one research, gently retracting the needle once it has penetrated the skin improves fluid infusion. Typically, this is due to the unwinding of compacted tissue, which increases the skin stream conductivity beneath the tip of MN.

3.3.3 Dissolving microneedles characteristics

Drugs are transported into the skin by dissolving MNs using the "poke-and-release" technique. This technique is distinct from the "poke-and-patch" method. (He et al., 2019). They further added that, drugs are often encased in MNs in this technique. After being embedded into the skin, these MNs remain on the skin, and the drug discharge is understood when the MNs fully disintegrate or break apart inside the skin. The benefits of utilizing dissolving microneedles are their ease of manufacture, ease of usage, and high drug loading capacity. Dissolving MNs have been shown in studies to improve the dermal and transdermal distribution of many therapeutic compounds including as heparin, insulin, 5-aminolevulinic acid, ovalbumin, adenovirus vector, sulforhodamine B, thymopentin (TP5) and many types of vaccination antigens. Dissolvable microneedles have also been discovered to deliver the drug doxorubicin for treating T-cell lymphoma. (Bhatnagar et al., 2017). So, in the instance of the COVID-19 vaccine, research may be conducted utilizing dissolving microneedles to get the optimum results. The majority of polymeric materials have excellent biodegradability and biocompatibility profiles, which provide them potentiality in the area of drug conveyance technology. As we all know, patient compliance is critical, thus utilizing MN made of biodegradable and water-soluble sugars or polymers reduces the risk of biohazardous, toxic, and sharp waste into the skin. This procedure also decreased the likelihood of infection in skin, as well as the danger of infection transfer. Because being a one-step procedure, it is very much helpful as well as easy for the patients to utilize. In addition to the numerous benefits, there are also drawbacks that are mostly connected to the creation and design of dissolving MN. In certain instances, drug stacking and manufacturing techniques may jeopardize the mechanical integrity and solidity of MNs or the given macromolecule or drug. Furthermore, dissolving microneedles made of sodium hyaluronate produced a better immune response in mice against influenza hemagglutinin, ovalbumin, diphtheria toxoid and tetanus toxoid. Investigations on the relationships between MN dimensions, duration of administration, drug concentration and drug viscosity revealed that the shorter dissolvable MNs had higher mechanical strength, while longer ones were significantly more suited for drug permeation. Increase in the concentration of drug triggered the expansion of the drug penetration but had no effect on the drug permeation rate. Furthermore, the quantity of drug penetration is related inversely to drug viscosity. Extension of treatment duration on the skin to one hour resulted in a consistent quantity of drug penetration that was essentially unchanged after an hour. According to studies, dissolving MN system increased insulin absorption, lowering blood glucose levels to 29 percent of the initial level after 5 hours. In an ex vivo study, MNs dissolved 89 percent + 3 percent by mass after 5 minutes, and after 15 minutes in an in vivo study, MNs dissolved 83 percent + 6 percent by mass, eliciting a humoral and powerful immune response of cellular with a low antigen dose after a single immunization, which can cover protective immunity against critical viral challenges. Studies have shown that dissolving microneedles which are manufactured from biocompatible polymers (FDA approved) are of great importance. Therefore, investigations showed that, polyvinylpyrrolidone (PVP) being FDA-approved biocompatible polymer and also been extensively used as a blood plasma expander and in the industry of pharmaceuticals for numerous purposes e.g., tablet binder and in manufacturing dissolving MNs for transdermal drug delivery. An assumption was made that, a simple and cost-effective technique in manufacturing rapidly dissolving microneedles by means of biocompatible polymers which can effectively load drugs of innumerable molecular weights and also strong enough to infiltrate the ocular tissues which will then quickly dissolve to distribute the drug to both anterior and posterior segments of our eyes in a negligibly invasive means. (Thakur et al., 2016). A study was conducted on Ag85B DNA vaccines which can be delivered to the skin with the help of dissolving microneedles to prevent tuberculosis. (Yan et al., 2018). Other than these, dissolving microneedles were also studied for unadjuvanted TT and this induced a more significant immune response including strong protection against tetanus toxin compared to the intramuscular immunization.

3.3.4 Coated microneedles characteristics

The "coke-and-poke" mechanism is used to make coated microneedles. Microneedles coated with specified formulation of drug are inserted into the layer of skin, the medication is dissolved in the skin, and then the needles are taken out of the skin. (He et al. 2019). They went on to say that, like dissolving MNs, administering the medication via the skin is a one-step procedure. One of the main drawbacks of utilizing coated microneedles is that the drug delivery effectiveness is extremely poor due to the limited number of medicines that may be coated in the MNs. However, they are especially useful for large molecules' bolus delivery to the skin, such as vaccinations, peptides, proteins, and DNA. Coated MNs are striking candidates for vaccine administration into the skin because antigens may be delivered into skin or dermis' dendritic cells to produce greater immune response by targeting the Langerhans cells located in epidermis. As a result, using coated microneedles to administer CVID-19 vaccination would be both easy and efficacious. There are several concerns regarding the factors that must be addressed, such as the consistency, repeatability, stability, and homogeneity of the MN coating materials. Furthermore, appropriate measures must be taken to guarantee that there is little hazardous medication loss during the coating process from the MN surface and also before to penetration in the skin. An experiment was carried out utilizing ovalbumin as a model antigen, and investigations revealed that while antigens were coated into microneedles and injected into skin of guinea pigs, a significant immune response was seen. A little quantity of antigen was required to elicit an immunological response, and that modest quantity has no bearing on their use of vaccine delivery. Recently, it was shown in a research that MN arrays coated with medication produced painless and rapid local anesthetic into the skin. Because of their severe restrictions, they are not as prevalent as the other kinds of MNs. The medication may also be sprayed coating, which is an effective way of coating the needles.

Chapter 4

Vaccine Delivery Methods of COVID-19

There are many ways for vaccine delivery, and an optimal route is required for effective vaccine administration in terms of practicability, immunogenicity, and safety. For traditional vaccine administration, routes such as parenteral, mucosal, and transcutaneous have been utilized.

4.1 Parenteral vaccination

Although it is invasive, this is the most often utilized method for vaccine delivery. (Zafar et al., 2020). Parenteral immunization may be administered through intradermal, intramuscular, or subcutaneous methods. COVID-19 vaccinations have been administered subcutaneously and intramuscularly so far. (Saman et al., ND) described an experiment on mice in which four candidates for SARS vaccinations were administered intramuscularly. They went on to say that the findings of the trial were very remarkable, as they demonstrated the ability of all four vaccinations to produce antibodies and protect against SARS infection. Despite having immunity, there was hypersensitive reaction to the vaccination components. In another mice model, a recombinant vaccine showing full length MERS CoV S glycoprotein was administered through subcutaneous and intramuscular injections. In mice, CD8+ T cells and virus-specific antibodies were provided, suggesting that the vaccination was effective. Several firms are currently developing intramuscular and intradermal SARS-CoV-2 vaccines.

4.2 Transcutaneous vaccination

When compared to the IM and subcutaneous methods, this route is much more convenient and effective for vaccination administration. (Zafar et al., 2020). As previously said, our skin layers include antigen-presenting cells, which makes it a favorable one. Our skin's specialized antigen-presenting cells include macrophages, monocytes, and dendritic cells (Kashem et al., 2017). Saman et al. insisted that vaccine administration using this technique is invasive to a minimum level and immune induction is considerably safer than traditional methods since no direct interaction between the systemic circulation and hazardous adjuvants has been found. They went on to say that there are two methods that are ideal for transcutaneous administration in order to overcome the restriction (stratum corneum). Electroporation and microneedles are two of them. According to research, this method is often utilized for DNA vaccinations. The vaccination stimulated the recruitment of melanocytes, dendritic cells, and granulocytes in conjunction with the local production of IL-8, IL-1, and IL-17 responses. In contrast to intradermal vaccination with a needle and microneedle patches, vaccine administration by surface electroporation produced the strongest and greatest IFN T-cell and IgG responses. Microneedles have recently created one of the popular methods for vaccine administration, with many benefits such as customized drug delivery in addition to the cold chain independence for proteins and so on. Vaccines have been delivered using coated, dissolving, and hollow microneedles. The spin-casting technique was used to create a dissolvable microneedle patch using carboxymethylcellulose (CMC) (Saman et al., 2020). A research found that vaccine administration of microneedle-facilitated SARS-CoV-2 S1 subunit resulted in a significant response from antigen-specific antibody in a mouse model after 2 weeks of vaccination. The results show that microneedle is an appropriate contender for administrating recombinant protein subunit vaccines against the coronavirus and other current or emerging viral infections.

4.3 Mucosal Vaccination

The majority of substances that cause diseases enter the body via the mucosal pathway, because of the slender surface and high penetrability of mucosal surface. (Zafar et al., 2020). In mucosal vaccination, there is also a classification of routes of mucosal administration like-nasal roues, sublingual route, vaginal and rectal routes. (Corthesy & Bioley, 2018). Maximum amount of presently licensed mucosal vaccines for human are made up of attenuated strains of viruses or pathogenic bacteria that maintain their immunogenicity while passing through the upper gastrointestinal tract and can aim inductive immune positions in the large and small intestine, as well as the upper respiratory tract. (Miquel-Clopés et al., 2019). This method has several drawbacks, for example antigen instability at mucosal location as well as the problem in producing a sufficient IgA antibody response. For the objectives of vaccine administration, the oral route is always the most fruitful. Oral vaccine administration by the usage of virus-like particles has been shown to be efficacious. Several virus-like particle-based COVID-19 vaccines are being developed. A SARS-CoV-2 vaccine on the basis of an oral probiotic capsule is now being developed. As the surface area is large enough, mucous layer is thin enough, and vascularization is strong, the nasal route is an efficient vaccination route. In a recent research, mice were vaccinated in the nasal route with recombinant adeno-associated virus, thus creating the RBD of SARS-CoV S-protein. The reports showed that the overall humoral immune response created by the intranasal vaccination was stronger than the intramuscular vaccination but lasted less time. Cytotoxic T lymphocyte reactions (both systemic and local) and humoral responses (both local and systemic) were much stronger. The efficacy against the COVID-19 infection given by intramuscular immunization was also compared. There was an increase in mucosal IgA as well as neutralizing serum antibody titers. The scientists concluded that intranasal vaccination could be a better method for SARS vaccine administration owing to its increased safety and potential to produce mucosal as well as systemic protection. Following pulmonary injection, the formulation enters the respiratory system, which has high permeability, an expanded surface area, and a plethora of antigen-presenting cells such as B cells, alveolar macrophages, and dendritic cells. Nonetheless, drug delivery to the alveolar sections of the lungs is challenging due to aerodynamics and preventive physiologic processes, which, when combined with particle geometry, restrict drug candidates' access to the absorptive regions. At the moment, vaccine inhaled formulation based on neutralizing anti-COVID-19 antibodies which are mRNA-encoded and are capable of producing antibodies straight into the lungs has been established.

Chapter 5

Microneedles: Material Construction

One of the microneedle categories is based on the materials used in their manufacture. This is an essential issue to consider in terms of vaccination administration and effectiveness in order to guarantee compliance and patient safety. In addition to the more common materials such as inorganic compounds, metals, and polymers, sugars may produce microneedles (trehalose, sucrose, maltose etc.). These are mainly viable for the production of dissolving MNs. Maltose-based MNs, in particular, dissolve quickly and improve medication administration through the skin.

5.1 Inorganic materials

There are many inorganic materials that may be utilized to make microneedles. They are as follows: silicon, glass and ceramic. (He et al., 2019).

5.1.1 Silicon

Silicon is the most prevalent of the inorganic materials listed above. For etching the silicon in the process of microneedle production, an inductively coupled high density plasma etch system was used. (Bolton et al., 2020). Silicon has proved to be useful in the creation of microstructures and microelectrochemical systems (MEMS). (Larran˜eta et al., 2016). This is due to the ease with which microstructures of all shapes and sizes may be produced. The use of monocrystalline or polycrystalline silicon allows for the tailoring of specific configurations to a broad variety of requirements. One significant advantage is silicon substrates are capable enough for batch manufacturing, which reduces costs in the long run. Because silicon's properties are dependent on location in relation to crystal lattice, resulting in different elastic moduli in the range of 50 Gpa to 180 Gpa. (Larran˜eta et al., 2016). Silicon is a hard material in nature, which allows it to readily enter the skin. However, there is cause for worry since silicon microneedles are very brittle. They are quickly degraded during the penetration phase into the skin. As a result, there is a significant danger connected with the use of silicon since it may remain under the skin and cause irritation. Furthermore, silicon, unlike other metals and certain polymers, is not biocompatible, which limits its usage. (He et al., 2019).

5.1.2 Glass

Because glass is medically inactive, it enables the flow of fluid and can be manufactured with microfabricated MN's dimensions. (Larran˜eta et al., 2016). However, He et al. noted that glass is unsuitable material since it may cause problems similar to silicon. (He et al., 2019). If they break off after insertion, they may remain under the skin and cause irritation. Borosilicate glass has lower levels of flexible moduli (64 Gpa), resulting in a more elastic material. Manufacturing glass MNs takes a long time since it is done by hand, thus it is inefficient. Larran˜eta et al. also said that Glass MNs are being utilized in recent times, but mainly in experiments and unsuitable for commercial application in medication or vaccine administration.

5.1.3 Ceramic

Scientists discovered that ceramic is a viable alternative for manufacturing MNs, and by more research study, it was discovered that ceramic is widely explored in the manufacture of microneedles. (Larran˜eta et al., 2016). Furthermore, zirconia, calcium sulfate hemihydrate, and alumina are often utilized in the production of MNs. However, this has a significant drawback since most sintered ceramics are brittle and nonreformable, causing irritation when they enter the skin. To address this problem, biodegradable ceramic MNs with increased mechanical strength have been developed and shown to be effective when put into the skin. This will assist to keep biohazardous and potentially dangerous sharp waste off of the skin.

Furthermore, BCMNs can regulate drug release by adjusting factors like as surface, porosity and degradation.

5.2 Metals

Metals provide high mechanical strength and robustness in the context of transdermal medication administration. MNs have been made from a variety of metals, including Ti,81,83,120 SS,51,61,84,88, and nickel (Ni),92. In spite of Ti and SS being carefully used as biomaterials in medical therapy for years, nonbiodegradable characteristic is one of the main constraints with metal, which may produce biohazardous tip waste formed by the broken residual MNs under the skin.

5.3 Polymers

Polymeric MNs have recently piqued the attention of researchers because to their biocompatibility and biodegradability. (AL-Japairai et al. 2020). They have a low toxicity and a cheap cost. In such scenario, they are a safe device to use, since they prevent dangerous side effects in the skin, which is advantageous for both medication administration and vaccination distribution. The polymeric microneedles have a classification according to formulations, materials, construction of microneedles and in vivo results of the performance. (AL-Japairai et al. 2020). Polymeric MNs have been widely utilized in the production of the four kinds of microneedles: hollow MNs, solid MNs, coated MNs, and dissolving MNs.

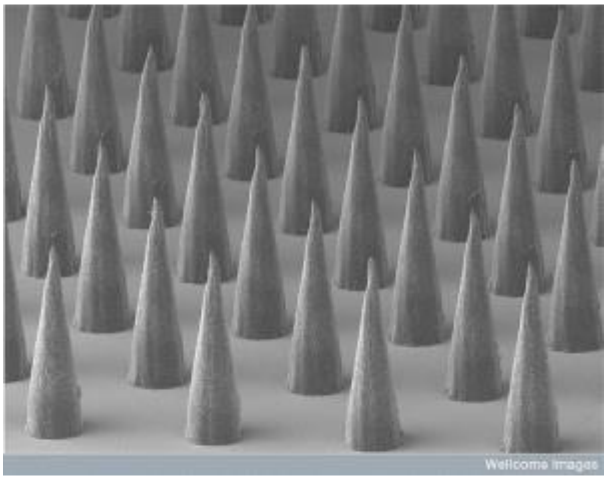

Figure 2: Polymer Microneedles Developed for Vaccine and Drug Delivery (https://www.polymersolutions.com/blog/polymer-microneedles-for-vaccine-and-drug-delivery/)

Polymers typically have lesser strength than ceramic, metals, glass and silicon, but are more robust than glass and ceramics. Polymers that are extensively utilized are polyglycolic acid,[101,98] PLA,[55,94,112] polymethyl methacrylate,[21,97,] polycaprolactone (PCL),[102,127,124] PVP,[22,54,104,126] polylactic-co-glycolic acid),[95,125] carboxymethyl cellulose (CMC),[106,128,129] and PVA.[103,105] MNs are produced using complicated structural elements such as PVA-PLA131, 106 PVP-cyclodextrin,130, 127 CMC-amylopectin and so on to increase mechanical strength during insertion. According to research, the geometrical properties of polymeric MNs are also known to improve the mechanical strength of MNs. Polymers are often utilized in the fabrication of hydrogel-forming and dissolving microneedle arrays. Following the dissolution/biodegradation process, the drug molecules were freed from the matrix for local or systemic administration. Polysaccharides are used in macromolecular dissolving MN systems. Carboxymethylcellulose, hydroxypropyl cellulose, dextrin, hyaluronic acid, amylopectin, and alginate are the most important. (Luzuriaga et al. 2018). MN arranged with these macromolecules have sufficient mechanical properties to penetrate the skin and deliver their cargos (insulin, model molecules and lysozyme). Synthetic polymers such as polymethyl vinyl ether-co-maleic anhydride (Gantrez AN-1391) together with polysaccharides are utilized to make dissolving microneedles. PVA and PVP are also often utilized. Circumventing the stratum corneum is a significant issue, and research has proven that microneedles produced with Gantrez AN-1391 are sufficiently powerful to do so. Because polymers are plastic in nature, these MNs can withstand compression pressures of maximum 0.7N per needle without breaking. The microneedles made of PVA and PVP are adequately strong to penetrate into skin as well as deliver their dosages. Biodegradable MN arrays, on the other hand, are made mostly of PLA, chitosan, PGA, or PLGA. The biodegradable MN has been used to deliver treatments ranging from tiny compounds to macromolecules to nanoparticles over the skin. These biodegradable polymeric microneedles serve as a painless device and also these are sanitary substitute to syringes. (Luzuriaga et al. 2018). In addition to dissolving/biodegradable MN arrays, hydrogel-forming MN arrays are important types of polymeric MN arrays. These provide medication release as a consequence of polymer swelling while captivating bodily fluid, leaving zero polymer residues following skin removal. Mechanical properties of those materials allow mechanical resistance and skin penetration to break in the dry state, which makes this kind of hydrogel a strong contender for the production of hydrogel-forming MNs. By accumulating NaHCO3, a pore producing chemical, the swelling of this kind of material may be changed. If we see the diverse fabricating means of polymers in the microneedle mold, the micro molding technique can be differentiated into hot embossing method, casting method, injection molding and investment molding etc. Usually, casting technique casts the drug loaded polymer solution into the microneedle mold and loads the polymer solution into the dumps of microneedle mold by vacuum, centrifugation or ultrasound to eradicate bubbles, and dry the mold to attain the anticipated microneedle. (Liu et al. 2020).

5.3.1 Hydrogel forming MN arrays: Construction

MN clusters that form hydrogels were assembled using tiny scale silicone molds which were laser-engineered. (Courtenay et al., 2020). MN arrays were made up of 121 needles with needle heights of around 600 m, base widths of around 300 m, and base interspacing of around 150 m. The needles were conical with an approximate base area of 0.5 cm^2. Aqueous mixtures of 20% w/w Gantrez® S-97, 7.5 percent w/w PEG 10,000, and 3% w/w anhydrous sodium carbonate were used to create hydrogel-forming MNs that contained no medication. (Courtenay et al., 2020). Following the stated procedure, the authors noted that .5 gram of aqueous mixture was poured into molds while centrifuged at around 3000 revolutions per minute (RPM) for 15 minutes and dried at optimal temperature for two days. Following that, the molds containing the aqueous mixture were heated at 176 °F for a whole day to facilitate a cross-linking esterification process between the hydroxyl functional groups of PEG 10,000 and the carboxylic acid groups of Gantrez® S-97. After the cooling process, hydrogel-forming MN clusters were drained from molds. The sidewalls of the hydrogel-forming MN arrays were emptied using a warmed surgical blade edge.

For transdermal drug delivery, hydrogel microneedles which forms novel in situ using a non-ionic biocompatible triblock amphiphilic thermosensitive copolymer were evaluated. (Sivaraman & Banga, 2016).

5.3.2 Hydrogel-forming MN arrays: Characteristics

To determine the penetration properties into skin of hydrogel-forming microarrays, Parafilm M® was used in an experiment as a model membrane. (Aaron J. Courtenay et al., 2020). For a short period of time, single sheet of Parafilm M® was carefully folded to form eight layers, each of which was about 1 mm of thickness. Following that, it was placed over a polyethylene sheet as a backing.

TA.XT.Plus Texture Analyzer was used to apply hydrogel-forming MN arrays perpendicularly onto Parafilm M®, an eight layer film (approximate thickness 1 mm). The Surface Analyzer being in compression mode, was adjusted to a lower speed of around 1.19 mm/s and a constraint of 62 N/minute. After passing half of a minute, the probe was moved ascendent at a post-test haste of around 10 mm/sec. Penetration of MN array using a texture analyzer had been compared to MN array penetration in manual process. Inclusion of manual studies were conducted by the application of thumb pressure on hydrogel-forming MN cluster in Parafilm M® for around half minute. After this period of time, the hydrogel forming MN clusters were carefully drained from the Parafilm M®, the layers of Parafilm M® were unfolded, and the number of gaps in each Parafilm M® layer was calculated in both instances. The intriguing feature of the hydrogel MNs is that they may be used to subjugate ingest interstitial fluids for compounds extraction process from skin for subsequent examination. In case of wound healing, a research was done by exploring chitosan hydrogel micro-needle array patch having controlled drug release property. (Chi et al., 2020). Microemulsion-based hydrogels for lidocaine (anesthesia) delivery have a tendency to have an extended lasting effect compared to the emulsion-based systems and yield nearly 50–100% larger fluxes of lidocaine than the emulsion-based EMLA® cream. (Zhang et al., 2020). A study has also shown that, the hydrogel-forming microneedles have the potential to deliver lithium TDM using the interstitial fluids which works as a sampling reservoir. (Eltayib et al., 2016)

5.4 Carbohydrates

MNs may be efficiently organized by molding slurries of carbohydrate or hot melts with metal or silicon MNs as a form of ace patterns. Prior to casting of the formulation in the molds, the drugs to be transmitted are mixed into the mixture. Such MNs should degrade upon skin contact in order to release the pharmacological payload. Carbohydrates are superior to the previously mentioned resources since they are less costly and safer for human health. Maltose is one of the most frequent sugars utilized in the fabrication of microneedle arrays. Additional sugars such as trehalose, xylitol, galactose, sucrose and others have been explored for use in the production of microneedles. Polysaccharides like hyaluronic acid, dextran have been used alone or in combination with different biopolymers like- amylopectin to fabricate microneedles for administering drugs like- doxorubicin and biopharmaceuticals (insulin) or natural extract and vaccines. (Fonseca et al., 2019). However, the mechanical strength of these sugars has received little attention. Galactose MN showed a noticeable decrease in MN stature when subjected to a little amount of stress on a block of aluminum. Although they are able to pierce the skin for delivering the medication, they do have several significant limits. The microneedles produced by these carbohydrates are difficult to process, store, and utilize. The main drawback of this kind of MN is that the need for heat treatment during manufacturing restricts the portion of compounds that may be stacked inside the arrays. Furthermore, when the medication is released, partially dissolved sugar blocks the MN-induced pores, limiting drug distribution. Furthermore, storage in circumstances of temperature and relative mugginess has a negative impact on this type of MN. These drawbacks are unacceptable and impede commercial production or clinical use of carbohydrate-based MNs.

Table 2: Strengths of materials used to make microneedles

Material	Young's Modulus (GPa)	Ultimate tensile strength (MPa)
Silicon	110	7000
Stainless steel	200	1000
Nickel	214	586
Titanium	110	241
Palladium	117	186
PMMA	3	170
Platinum	147	117
Glass	85	50
Ormocer®	17	30
Maltose	31.1	-
SU-8	3	-

Source: Data obtained from [N.A. Monteiro-Riviere, Toxicology of the Skin, CRC Press, Boca Raton, 2010.]

Chapter 6

Fabrication: Microneedles of different type

6.1 Solid microneedles fabrication

First solid microneedles were made from silicon by the usage of microfabrication technology. This method was widely used by other scientists at the time to create solid microneedles that are silicon-based of variable diameters. (Duarah et al., 2019). Microfabrication technology such as MEMS is deployed reliably in the fabrication of micron-scale devices as well as microprocessors. MEMS is now being used as a manufacturing technology of MN devices. (Duarah et al., 2019). They further added that, the method for fabricating silicon MNs varies depending on the shape and material of the needle. Despite the fact of being advantageous for higher throughput MN fabrication, microfabrication methods are not particularly cost-effective, require handling by a specialist, and include complicated handling. This technology provides a sequence of regulated actions and methods. The three basic elements used in MEMS are photolithographic imaging on top of the films to place a patterned mask, selectively engraving films into the mask, and deposition of material on a substrate which is thin in nature. Photolithography imaging is used to replicate optically treatable polymers to provide master structures, which are then used to build robust polymeric MNs in molding process. SU-8, widely known as the UV curable polymer, is widely used in the production of MNs. Silicon MNs have been created via receptive ion carving and isotropic carving. In addition, anisotropic crystalline silicon's wet carving of anisotropic characteristic has been used in the creation of strong MNs. There are also plans to combine anisotropic wet carving and isotropic dry carving techniques in MNs production. Acid etching process is authorized for honing the points of props gained by a silicon substrate dicing. Solid microneedles are produced by utilizing metals like titanium, palladium, and others via a variety of methods such as photochemical etching (titanium), 3-D laser ablation (stainless-steel), and electroplating (palladium). A new drawing lithography of magnetorheological technique was successfully applied to produce solid microneedles. A bead of reparable magnetorheological liquid is extracted to provide a 3D microneedle under an outward magnetic field. In most cases, a one-step approach eradicates the need for calibration of temperature.

6.2 Hollow microneedles fabrication

Using MEMS methods in conjunction with deep reactive silicon ion etching, laser micromachining, wet chemical print and microfabrication, deep X-ray photolithography and a combined lithographic molding technique, a diversity of hollow microneedles has been invented. Bosch process is used in fabricating high aspect ratio hollow shell structures followed by wet engraving procedure and isotropic procedure in order to obtain tip sharpness. Hollow microneedles having sharp tips were achieved other than the usage of chemical etching techniques by utilizing dicing saw including ion etching in deep reactive process. Conventional manufacturing approaches are used by arranging hollow MNs. For creating hollow glass MNs the glass micropipette strategy is utilized. Various techniques are used in fabrication of hollow polymeric MNs. Grinding was used to create a beveled tip out of polyphenylsulfone polymer after holes were punctured. Lithographic methods were used in fabrication of hollow MNs made of PMMA. On the other hand, polymerization of liquid resin was applied in the groundwork of polymeric hollow microneedles where a stereolithography device was used. For creating hollow polymer microneedles by coordination of two-photon polymerization, a laser-based quick prototype framework was also utilized. In another circumstance, electroplating of metal and lithography drawing was utilized to design metal MNs. In another design, UV laser was used to organize a polymeric microfold, which was afterwards nickel coated by electrodeposition. The formed metal MNs arrays are released by successive polymer mold's selective etching. Successive procedure of electro-less copper in addition to wet chemical etching of copper and nickel plating were also used to equip hollow nickel MN arrays.

6.3 Dissolving microneedles fabrication

A wide range of mold-based techniques are utilized in fabrication of dissolving MNs including drawing lithography, solvent casting, laser machining, droplet-borne air blowing, microinjection molding, ultrasonic repairing and hot embossing.

Most common technique for dissolving microneedles fabrication is solvent casting. In this method the polymers and any other components are being broken in appropriate solvents, which are then poured in mold cavities and allowed to dry for a while in addition to vacuum or centrifugal hindrance. (Duarah et al., 2019). In the alternative fabricating technique, liquid formulations which later solidify in position are drawn in the formation of pointed MNs. This strategy was applied in preparation of MNs containing albumin, chondroitin sulfate and dextrin, where pipette tips were drawn in fabrication of each needle. (Park et al., 2016) Ultrasonic welding method was also utilized in fabrication of dissolving MNs in which without heating the polymers are stuck together and as a result produce insufficient impairment to the molecules which are encapsulated. In the recent time, it was observed from a comparison that less stress is exerted from centrifugal lithography than droplet-born air blowing during the process of fabrication procedures and as a result the encapsulated medicines' activity has decreased. As a result, this technique may be used to create dissolving microneedles containing delicate biological medicines. In a research, it was also shown that, the prepared dissolvable microneedles were strong and sharp enough to penetrate the porcine skin in case of cosmetic products and they dissolved in the phosphate-buffered saline and the skin. (Park et al., 2016)

6.3.1 COVID-19 vaccination using dissolvable MN patches

Dissolving MN patches are skin patches with micron size solid conical structures composed of dissolvable excipients that assist transport vaccination antigens into skin's dermis and epidermis. (O'Shea et al., 2021). Falo, in one of his papers, said that when the dry sharp needle is penetrated to the skin, they absorb moisture and dissolve the vaccine materials. (Falo, 2020). O'Shea et al. complimented that, because microneedles <1mm, they cause negligible discomfort and are highly preferred over traditional injection-based vaccination. MN patches are ideal option for COVID-19 immunization as they do not need specific expertise to be administered, no generating of biohazardous sharp along with toxic waste, and may be thermostable. Some constraints for effective vaccination campaigns exists in every asset context, including the requirement to increase vaccination resistance response, waste disposal, cut costs, and reduce reliance on prepared healthcare professionals. Carrying antibodies in the dermis or epidermis brings the antigen into direct contact with skin's cells which carry antigen, resulting in reduction of doses. In comparison to injections, a more precise, reproducible and effective vaccine delivery to the skin is safeguarded by the usage of dissolvable microneedle devices. During the ongoing COVID-19 pandemic situation, a massive medical team is mandatory to do the campaign arrangement for mass vaccination, that may cause crowding and worsen the overall circumstances. In recent situations, it has been observed that the produced COVID-19 vaccinations are given by syringe injection and hypodermic needle, which necessitates the use of a skilled healthcare practitioner. Vaccination of COVID-19 by the usage of MN patches unlocks the potential of administration by employees with little training as well as self-administration, potentially accelerating roll-out and propagation while reducing the strain on the healthcare system. As the microneedles vanish after dissolving in the skin, dissolvable microneedle patches thus decrease the risk of sharp wastes too. A report shows spread of bloodborne infections already resulted in roughly 1.3 million fatalities as a consequence of needle re-use, particularly in poor countries such as Bangladesh. Dissolvable microneedle patches have been proven in controlled trials to be innocuous and safe for delivery procedures, with no instances of mortality due to accidental infection. Typical hypodermic needle vaccination may be inefficient due to the use of multi-dose vials and the necessity for rebuilding. Microneedle patches, on the other hand, do not need any kind of reconstitution. Vaccine waste rates are generally increasing because of vaccine doses per vial increment. According to research, waste rates for liquid vaccines in ten dose vials can get high as twenty-five percentage and forty percentage for lyophilized vaccines. As a result, one-time usage of MN patches reduces the wastage. Often vaccinations require vaccine reconstitution, which necessitates a well-qualified medical professional. It also necessitates additional vials, needles, and syringes, which necessitate safe transit to the warehouse. Because microneedle patches offer greater stability, they may frequently be kept at room temperature, enabling a simpler storage management system. Furthermore, smaller size of patches paves the way for easier distribution. Vaccination expenses include the estimated expenses related to make the vaccine available. Medical professionals, management of waste disposal, immunization storage, transport and supply chain make the expense of vaccination more costly. The estimated expense to immunize remains as a worrying impediment. According to studies, the usage of self-administered MN patches may enlarge the immunization coverage while lowering costs. The fabrication expenses of MN patches are calculated to be less than that of pre-filled syringes. A sample MN array has weight < 1gm. MERS-CoV-S1 vaccinations elicited more effective response than needle injections, as well as more effective IgG responses. The government of US has allocated around two million USD to three organizations working on MN patches via the Biomedical Advanced Research and Development Authority (BARDA). These will include spike protein, which is the fundamental of almost all COVID-19 vaccines. They are designed to be self-administered and self-stabilized with the release of spike protein. This technique may extinct the requirement and struggle for immunizations after periodic intervals. Boundaries of conventional vaccination techniques can be removed by microneedle patch vaccination, particularly where resource is limited.

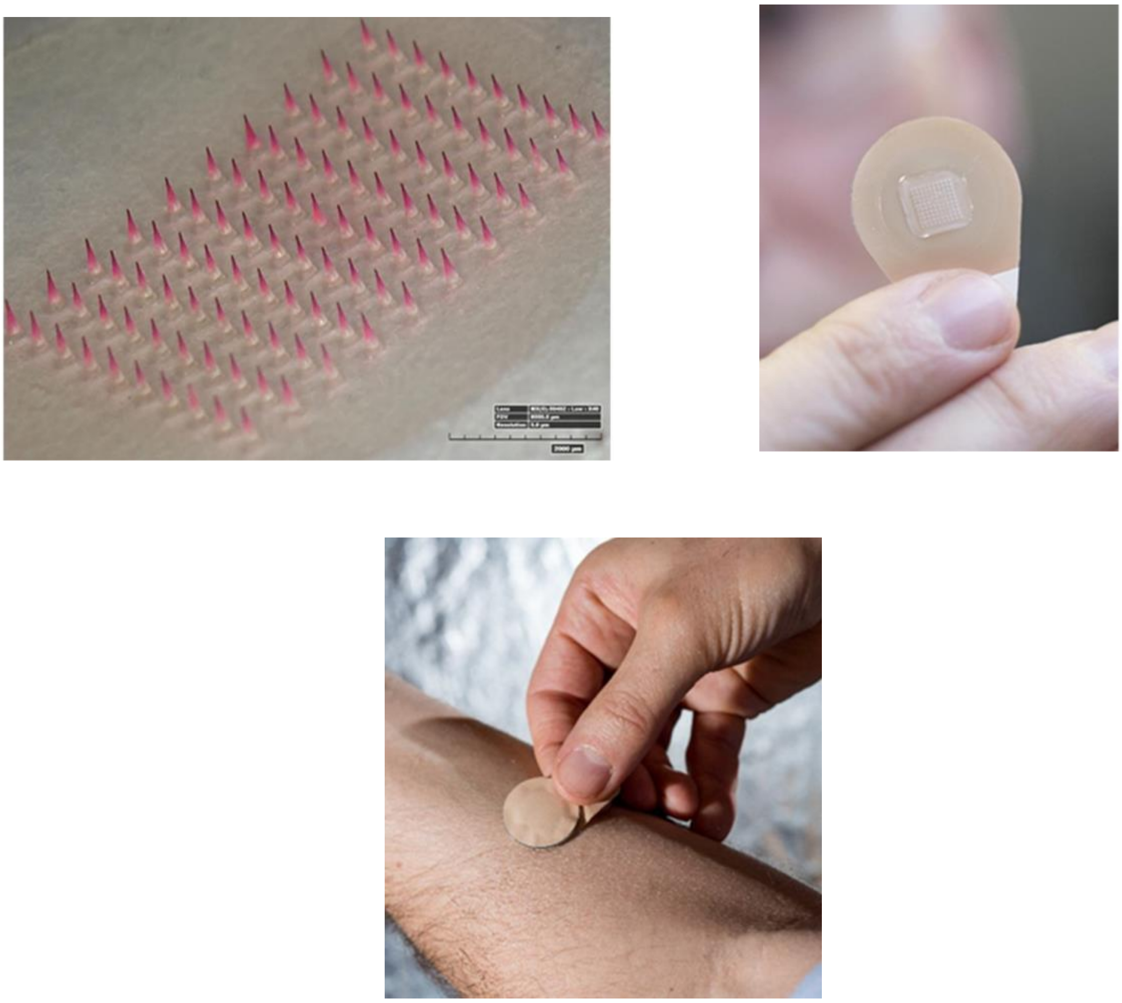

Figure 3 Dissolvable microneedle patches for vaccination [2]

6.3.2 Benefits of dissolvable COVID-19 microneedle patch vaccine

There are many potential benefits to using a dissolvable microneedle patch to vaccinate the public against COVID-19. (O'Shea et al., 2021). Notable ones are- dose-sparing effect, quicker virus clearance, evading of reconstitution, rate of vaccination wastage dropped, little or no pain, enhanced acceptance and less uncertainty, minimal risk of contamination along with injury through sharp materials and minimal requirement of medical staff, less dependence on cold chain and enhanced stability.

6.3.3 Limitations of dissolvable COVID-19 MN vaccination

There is a possible chance of wasting the antigen during the manufacturing methods like-micro-molding. The backplate material ought to have higher consistency than that of the needles to diminish the dissemination of the antigen from the dissolvable MNs amid arrangement and drying. (M. Leone et al. 2017). Therefore, while testing the stability testing the presence of the antigens in the needle and also the lacking of antigen in the backplate shall be observed to check loss of diffusion of antigen while storing to the backplate.

While manufacturing the dissolvable microneedles, another major challenge is antigen deterioration as these can be degraded due to the high temperature. In drawing and soft lithography, the optimum temperature is 100º C and which is why they can cause damage to the thermolabile antigens which are attached to the covid-19 vaccine matrix.

6.4 Coated microneedles fabrication

Processes are in place to ensure that MN arrays are effectively coated with specific medicines. A suggestion was made for a dip-coating process by the application of various aqueous or liquid preparations. It was structured for the deposition of various compounds with different physio-chemical characteristics on MNs' surface. The essential characteristics are viscosity of coating solution and surface tension to monitor during the dip-coating process. MNs have also been coated using layer-by-layer coating techniques. A versatile but easy gas jet coating method was also discovered to reliably coat a wide variety of compounds on micro projections. An alternative research utilized a piezoelectric inkjet printing method to apply pharmacological coatings on the surface of polymeric microneedles for antifungal purposes.

Chapter 7

Microneedle patches as a future prospect in COVID-19 vaccine delivery

COVID-19 vaccine dissemination is designated a worldwide epidemic. Fatalities are recorded throughout the globe as a result of this powerful vaccination. The experts are working around the clock to create a vaccine that will give vaccination in order to save people's lives. Because of a shortage of vaccines, individuals in emerging and underdeveloped nations are falling behind. In the upcoming days, MN patches can escalate immunization processes all across the globe and thus rescue thousands of people. The design and development of products based on microneedles incorporating the vaccines is encouraged by the progress of technologies in fabrication. Individuals will give the vaccination by themselves, eliminating the requirement of a medical expert. It is a dynamic way of globalizing the vaccination. If this technology is utilized, it may be used for a long time and, in the case of COVID-19, it will be extremely helpful for giving herd immunity. As we all know, covid-19 attacks people of all ages, therefore one of the most significant advantages of utilizing microneedles for immunization is that dissolving MNs may be used as per the dosage needed for various category of people. For this reason, if MN based vaccine delivery is developed, control of this fatal illness is very much possible as well as keep patient compliance.

Chapter 8

Discussion

The skin serves as a model for vaccination. Because, our skin contains a huge network of immunologically antigen-presenting cells and active cells which are responsible for generating adaptive immune response. Many experiments were performed to assess the immunogenicity of these vaccine variations, which were administered by traditional needle. MERS-CoV-S1 vaccine delivery by MN array resulted in more effective responses than traditional injection, according to research. In a particular university, named Carnegie Mellon University, the professors are looking for researchers who are preparing the viable vaccines against COVID-19 saying they can manufacture hundreds of microneedle arrays with viable vaccines and test them in the university lab delivering to thousands if succeeded. A month after the SARS-CoV-2 S1 sequence was identified, dissolvable microneedle patches were designed made of carboxymethyl cellulose which contained SARS-CoV-2 and MERS-CoV-S1 which were proficient of causing effective antigen-specific IgG responses. Thousands of people are dying from the outbreak of COVID-19 and if we can implement personalized vaccine delivery promoting microneedle array patches for vaccination, this will be a win-win situation for the world specially the developing countries. The materials that can be used to fabricate these microneedles are- silicon, carbohydrates, polymers etc. Dissolvable polymeric microneedle are the best microneedle array patches for delivering the COVID-19 vaccines.

Chapter 9

Conclusion

COVID-19's intriguing, unexpected pathological, and epidemiological natures need unusual conceptions of efforts and assets, particularly in the improvement of compelling and safe vaccines. People all across the globe are frightened in the midst of a worldwide pandemic (the COVID-19 outbreak), and IM vaccines are causing stress, anxiety, agony, and unanticipated particular immune reactions. Given the cosmic COVID-19 casualty rate among aged and other high-risk patient groups, the advancement of a compelling vaccine has been a worldwide imperative. (Sadarangani et al., 2021). Although the MN patch vaccine arrangement might be an untapped possibility in the present widespread, there is a requirement for enterprise at present to be well prepared for epidemic requirements of future. If various types of microneedles-solid, hollow, dissolving, and so on-are used and taken into account while producing the vaccine, the globe will steadily heal from COVID-19. Obtaining herd immunity is a problem that must be addressed as quickly as possible, and microneedle arrays will assist in this endeavor. Though data are not yet available, pre-clinical trials are being conducted at several institutions and businesses across the globe to deploy SARS-CoV vaccination utilizing microneedle patches. The resources needed to build the materials, such as hydrogel, silicon, and others, must be abundant in order to expedite the process and cure the planet as quickly as possible.

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