COVID-19 VACCINE FOR TRANSDERMAL DELIVERY: FORMULATION CONSIDERATION AND MICRONEEDLE ACCESSION

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)

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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

The thesis/project titled "COVID-19 VACCINE FOR TRANSDERMAL DELIVERY: FORMULATION CONSIDERATION AND MICRONEEDLE ACCESSION "submitted by

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Ethics Statement

There were no unethical works involved in doing the thesis. This study does not involve any kind of human or animal trial.

Abstract

Covid-19, a worldwide disease, affects millions of people. As of now, there is no effective technique to avoid infection. This outbreak emphasizes pandemic preparedness. Contrary to popular belief, the Covid-19 vaccination is delivered via transdermal microneedling rather than parenteral administration. Dissolving microneedles are best suited to eliciting the necessary immunity and antibody against Covid-19. It also allows for delayed and sustained antigen delivery, making it an effective pharmacological approach for immunizing. Why Transdermal microneedle vaccine administration allows for individualized distribution and reduced vaccine waste, while parenteral vaccine delivery is intrusive, requires cold chain storage, and does not allow for customised delivery. The challenges of clinical translation and sterilization are simply overcome by greater research. Vaccins are also avoided due to needle phobia, which is eliminated with painless transdermal microneedle delivery. Transdermal microneedle delivery may help us reach our aim of vaccinating as many individuals as possible.

Keywords: Formulation; Transdermal Microneedle; COVID-19 Vaccine

Dedication

This thesis project is dedicated to my beloved parents.

Acknowledgement

It will be covered in the next revision.

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Chapter 1

Introduction

1.1 Covid-19 background

Corona viruses were discovered by humans in the 1960s (Walsh et al., 2020). Crown Terrace is named from the spike proteins on their floor, which are visible because to the presence of the virus. Animal viruses, according to these experts, are the genesis of the new viruses. Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) reached unprecedented heights between 2002 and 2012 (Noor et al., 2021). During this historical period, children, adults, and anyone with weaker immune systems were at danger of contracting life-threatening illnesses as a result of these viruses (Walsh et al., 2020). Unfortunately, in December 2019, a previously unknown coronavirus (SARS-CoV-2) first emerged in Wuhan, China, causing severe sickness in a large number of individuals. Covid-19 has infected 167,602,538 people and claimed the lives of 3,479,991 people. Even if there is no maximum limit to the quantity of this virus, it is still spreading since it is transferred via direct touch as well as breath, such as sneezing or coughing. The Centers for Disease Control and Prevention (CDC) in the United States is responsible for this fact. This genetic SARS-CoV-2 collection is published shortly after its discovery and is regarded as a beta-coronavirus related to SARS-CoV (David et al., 2021). The most common COVID-19 indications and symptoms that are within the normal range include fever, dry cough, fatigue, dyspnea, and the respiratory disease that occurs concurrently (Wu et al., 2020).

1.2 Covid-19 Vaccines

There is no question that planning for a pandemic is essential, but manufacturing and delivery issues may limit the availability of vaccinations. Researchers are working around the clock to create a vaccine against COVID-19 and to establish the physical appearance of SARS-COV-2 (David, 2021). The genome of SARS-CoV-2 is made up of an ORF1ab polyprotein that encodes 15 or 16 non-structural proteins, with the 3' end encoding four structural proteins that include S,

M, E, and N; the 5' end of the genome is made up of an ORF1ab polyprotein that encodes 15 or 16 non-structural proteins, as well as the 3' end encoding four structural proteins that include spike (S), membrane (M), env (N) (Fernando et al., 2020). The vaccine inventors want whole-cellular antigens and structural proteins to prevent the immunization from being targeted (Shingai & Charles, 2021). Because it combines floor advertising and a direct detection mechanism in the body's immune system, S protein is the most promising SARS-CoV-2 antigen vaccine (Tamam et al., 2021).

1.3 Microneedles

Micro-needle vaccination is a new technique that makes immunization more powerful and accessible in impoverished nations, lowers the number of people needed for professional healthcare workers, and minimizes the danger of sharps and vaccine waste (Larraneta et al., 2016). If doctors are unavailable, patients may be given microneedles. Microneedles are similar to the structure of needle, available in a variety of materials with macroscale diameters and lengths up to one millimeter (Woolfson et al.,2016). One of the most amazing characteristics of microneedles is their capacity to penetrate the stratum corneum, touch the epidermis, and interact with epidermal layers without passing through blood vessels (Nagarar et al., 2020). They produce antibodies with little invasiveness when used for CVID-19 immunization. Because of the use of lining and dissolving microneedles, the price of a vaccine provider that provides vaccinations in a dry condition may increase (Lutton et al., 2016)

1.4 Transdermal drug delivery

It has been around for a while of making the transdermal drug delivery systems simpler to use. Prior to the more recent usage of topical systems, the most often used systems for dermatological disorders were creams and ointments (Tomoda & Machino, 2014). Because of skin absorption, several of these formulations have systemic deleterious effects. The skin has received systemic treatment with a variety of medications (Bibi et al., 2017). Transdermal delivery methods encompass any topically applied pharmaceutical formulations, whether injected or absorbed, that are intended to transport the drug to the general circulation (Mishra et al., 2019). Transdermal

systems have been developed to deliver medicines to the bloodstream in a regular and controlled manner via the skin (Alchilani et al., 2015). The relative impermeability of skin is generally acknowledged, and this is thought to be related to skin's two main defensive functions: protecting the body from pathogens and ensuring that essential bodily components, such as water, are not wasted. This enables the use of skin as a conduit for controlled systemic drug delivery by elucidating factors that contribute to impermeability (Zhang et al., 2021).

1.5 Formulation

Because the skin contains a large number of immune cells, it is an excellent target for novel vaccine delivery techniques (Faden et al., 2001). Other dissolving microneedle technologies are capable of reading this. It also employs FT-FIR (along with Nano indentation, pores and skin transport assays, and synchrotron radiation), among other techniques, to gain a comprehensive understanding of the important bulking agents and excipients, namely polyols, and how they influence various fabric attributes such as size, shape, strength, failure properties, diffusion, and dissolution (joyce et al., 2017 & Flynn et al., 2021). However, despite the fact that mannitol was no longer having an impact on the micro-systems, the researchers decided to examine mannitol, sucrose, trehalose, and sorbitol concentrations ranging from 1:1 to 30:1 in combination with CMC (Stern et al., 2005). Additional crystalline systems (sorbitol, sucrose, and trehalose) were found, and synchrotron radiation was used to study FT-FIR infrared Fourier remodeling (Criscuolo, 2019). Sorbitol formulations had a bimodal distribution because crystalline systems showed much higher elastic moduli (8–12 GPa vs. 0.05–11 GPa) (Rappuoli, 2014).

The conventional vaccine formulations are most commonly used methods for vaccination. Nanoparticles based vaccine formulations are also using nowadays. But both the methods have some problems including needle phobia, expertise requirement, wastage of medicines as well as cold chain storage etc. These problems of conventional vaccine formulations and nanoparticles formulations can be avoided by using microneedle vaccine formulation. Microneedle vaccines are short and narrow sufficient to avoid he dermal nerve stimulation which resulted in the no pain during the vaccination. Microneedle also includes better immunological response than the conventional formulation by producing more antibodies in compare to the conventional one at the

similar dose. Moreover, microneedle vaccine reduces the production of harmful medical waste and improve the compliance of vaccine as well as the safety. In addition, conventional vaccine requires expert for vaccination process which is not necessary for microneedle approach and self-administration is possible in most of the cases. Microneedle has also the advantage of reducing vaccine wastage which is a common for conventional formulation. The final and most important advantage of microneedle over the conventional vaccine is that it does not require cold chain storage which is very expensive as well as requires a recommended temperature for the distribution for preserving the vaccine potency

By analyzing the common problems of conventional vaccine and advantages of the microneedle vaccine delivery as well as considering the current situation of the Covid-19, the purpose of this article is to focuses on the Covid-19 vaccine formulation for transdermal microneedle delivery.

Topic of Discussion	conventional vaccine	microneedle vaccine
1. Invasiveness	**1.** More invasive	**1.** Less invasive
2. Expertise Requirement	**2.** Require	**2.** Not require except some particular cases.
3. Wastage of medicine	**3.** Yes.	**3.** No.
4. Cold Chain Storage	**4.** Require	**4.** Not require.
5. Immunological response	**5.** Lower than Microneedle Vaccine.	**5.** Higher than Conventional Vaccine.

Chapter 2

Methodology

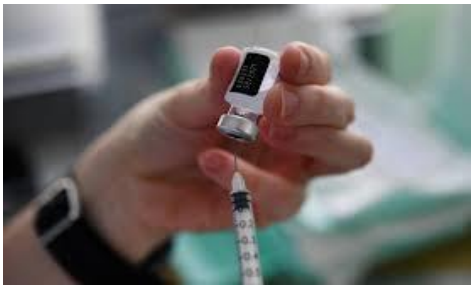
Extensive literature review on Covid-19 vaccine, microneedle transdermal delivery and vaccine formulations were analyzed for this study by using secondary research methods including research articles, articles from different journals such as PubMed, ScienceDirect, Elsevier, Nature, NIH etc. Information and data related to this study were collected from different articles, sources and journals with their findings which assisted in the identification of variable clinical data that could play a significant role in the future aspects of this Covid-19 vaccination.

Chapter 3

COVID -19 vaccine formulation and route of administration

3.1 Formulation

Antigens that are included in immunizations fall into many types, including live attenuated, inactivated, subunit, and mRNA-based vaccines (Stern et al., 2005). The formulator's decisions ultimately have an impact on the end result. When establishing a formulation, one of the most important variables to consider is the desired route of administration (Rappuoli, 2014). Vaccine delivery strategies have always necessitated careful consideration of how the balance of mucosal and systemic immune responses is impacted (Faden et al., 2001). It is critical to have mucosal immunity tolerance, but it is also crucial to be well-prepared for systemic immunity. Although most vaccines are administered by parenteral or mucosal routes, this is not the case for all vaccines (Lyche et al., 2012). Mucosal locations include the oral, nasal, buccal, sublingual, rectal, and vaginal mucosa (Criscuolo et al., 2019). Intramuscular, subcutaneous, intravenous, and intradermal injections are all possible. Several factors influence the vaccination route, including where the infection develops, how the disease is transmitted, the type of vaccination used, and the amount of immunity expected (Zhang, 2015)



3.2 Intranasal route

Some of the most promising vaccine candidates include COVI-VAC (live attenuated) vaccine candidates from Codage-nix in the United States and Serum Institute in India, as well as a replicating viral vector-based RBD expressing vaccine being developed by the University of Hong Kong and Beijing Wantai Biological Pharmacy (China). These CIGB-669, AdCOVID, Razi Cov Pars, and BBV154 were created by the Cuban Center for Genetic Engineering and Biotechnology, as well as a collaboration between Altimmune Inc. and the University of Alabama, and a new product is being developed by Bharat Biotech India (licensed from Washington University, School of Medicine in St. Louis, USA) (Teijaro JR, 2021). COVIVAC is a live attenuated intranasal

vaccine that has just completed phase 1 testing. It is administered as a single dose (Chung JY & Thone MN, 2021). Not only does the COVI-VAC protect against all SARS-CoV-2 proteins, but it also protects against a wide variety of SARS-CoV-2 strains (Teijaro & Farber DL, 2021). The University of Alabama and Altimmune, Inc. are developing an AdCoVID single-dose human adenovirus vectored intranasal vaccine that includes the SARS-CoV-2 spike protein and provides mucosal and systemic protection. AdCOVID causes significant serum neutralizing antibodies, a T-cell response (CD4+ and CD8+ cells), and mucosal IgA in the respiratory tract, according to an early pre-print paper. At room temperature, AdCOVID remains stable for months. Phase 1 investigations are being done, and anyone interested in signing up can check at the study's website (Peel Jn et al., 2020). Bharat Biotech India has received a license to use Adenovirus vector vectored SARS-CoV-2 spike protein gene delivery (done via intranasal injection) (name BBV154). The BBV154 clinical trial has begun with the first stage. individuals were shown to have significant neutralizing antibodies and T-cell responses after a one-month exposure to the SARS-CoV-2 virus Also, a vaccination method that utilizes codon optimization for GMP manufacturing will be required in addition to AttenuBlock technology to produce a nasal vaccine for SARS-CoV2. (Hassan AO e al.,2021). The firm created a respiratory syncytial virus vaccine candidate using the same technology that was used to create an intranasal vaccine. While Utrecht University, Wageningen Bio-veterinary Research University, and Intravacc Netherlands are working on an intranasal vaccine for SARS-CoV-2 using reverse genetics techniques and the Newcastle Disease Virus as the vector for generating the SARS-CoV-2 spike protein, a medical start-up company is working on an oral vaccination that incorporates the same manufacturing process. Intravacc, one of several organizations in the Netherlands working on vaccine research initiatives, is utilizing the OMV (outer membrane vesicle) and recombinant spike protein (SARS-CoV-2) technology in their nasal spray vaccination (Feldmann F et al., 2021). The vaccine candidate offered good protection when hamsters and mice were injected with the chemical, according to the study team. Researchers instead use a less invasive kind of viral vector, such as those developed by BlueWillow Biologics in the US and Medigen Vaccination Biologics Corporation in Taiwan (pre-clinical stage) (Curiel DT et al., 2021). The SARS-Cov-2 S-2P ectodomain delivery technology is being jointly developed with NanoVax® and BlueWillow, with the latter acting as a key collaborator to implement the SARS-Cov-2 S-2P ectodomain delivery technology in the development of a systemic and mucosal immune response to the SARS-Cov2 S-

2P ectodomain. Because to the S-2P-NE-01 vaccine, IgA levels have increased in both serum and bronchoalveolar lavage. This is a condensed version of the information on intranasal vaccines that was given before (Ochumura A et al., 2021).

3.3 Oral route

Two new SARS-CoV-2 vaccine formulations are being developed by small start-up firms in the United States and the United Kingdom. Using its VAAST (Vector ADjuvant-Atigen Standardized Technology) platform, Vaxart created a tablet-based version of the non-replicative COVID-19 vaccine. The distribution and staffing issues that arise with parenteral formulation may be avoided with tablet formulation. Comfort would be removed during administration, which would be a significant therapeutic advantage (Moore AC et al., 2020). Antibody titers and total IgG levels in animal models have risen as a consequence of the expansion of CD4+ and CD8+ antigen-dependent cells. In the early clinical trial, the Vaxart candidate fulfilled the main and secondary safety and immunogenicity goals (dated February 3, 2021). The SARS-CoV-2 strain NCT04563702 controls and generates a strong CD8+ T-cell response. Both the outer spike protein (S) and the nucleocapsid protein (N) are present in the vaccination vaccine product VXA-CoV2-1 (N). Due to its high conservation, the N protein is less susceptible to mutation. With this new genetic engineering, it may be possible to protect people against various types of bacteria. Next, researchers are theorizing that a substance known as N protein may be a better T-cell response target. There were no noteworthy adverse effects on over 500 individuals who got the vaccination. the company's news release describes how CD8+cytotoxic T-cell responses to S and N antigens have been particularly notable (responsible for long-lasting cross-reactive immunity). The number of plasma B cells and the expression of the mucosal homing receptor were substantially enhanced in all participants, resulting in activation of the B-cell system, production of pro-inflammatory Th1 cytokines, and the presence of IgA in the blood. The OraProTM technology has been selected by IosBio Pharma (UK) for the development of a COVID-19 vaccine (Dora EG et al, 2020). In recent years, collaborations with companies such as iosBio Pharma and Therm-SB, Immunity Bio, and an American biopharmaceutical organization have resulted in the development of a COVID-19 vaccine using a human Adenoviral (hAd5) vector. to develop a novel vaccination strategy

incorporating the spike protein gene (S-fusion) and the nucleocapsid protein gene, which contains an enhanced T-cell activation domain (N-ETSD). SARS-CoV2 was increased in the animals by injecting the virus into their bodies and giving injections via their lips (Peinovich et al., 2020). They studied the antibodies and T-cell responses of the macaques and found that they exhibited both a protective antibody response and a Th1-dominant T-cell response. The upper respiratory tracts of the animals, on the other hand, were shown to be very resistant. Another significant feature of the hAd5 vector is that it may be utilized to provide formulated adenovirus immunity as well as initial, unformed viral immunization. ClinicalTrials.gov Identifier: NCT04732468 and ClinicalTrials.gov Identifier: NCT04591717 have started phase 1 study on this vaccine candidate. The immunogenicity was shown to be substantial in pre-clinical studies on mice (Peinovich et al., 2020).

3.4 Mucosal Route

Mucosal membranes are more porous and thus a conduit for disease-causing substances than other membranes. This method's disadvantages include antigen instability at the mucosal site and the difficulty in eliciting a significant IgA antibody response. In terms of vaccination dissemination, the oral approach is the most successful. The use of virus-like particles as an oral vaccination method has been demonstrated to be effective (Lyche et al., 2012). COVID-19 vaccines made from virus-like particles are being widely produced for a new generation of patients. In the past, a SARS-CoV-2 vaccine had been created by administering oral probiotic pills. Nasal route vaccination is an efficient method of immunization because of its large surface area, thin mucous layer, and good vascularization. In an experiment to evaluate the efficacy of this vaccination, mice were injected intranasally with a recombinant adeno-associated virus (RAAV) that had SARS-CoV S-protein RBD (SARS-CoV specific viral glycoprotein). Intranasal immunization elicited a stronger overall humoral immune response, but it lasted less time (Balmert et al., 2021). There were significantly larger systemic and local humoral and cytotoxic T-cell responses, as well as significantly higher local humoral and cytotoxic T-cell responses. Apart from that, research conducted on COVID-19 infection had shown that the measures used for prevention were equivalent to those administered through intramuscular vaccine. Mucosal IgA concentrations were correlated with both greater levels of mucosal IgA and serum antibody titers. The experts think that intranasal vaccination is a

superior delivery route for SARS vaccine because of its improved safety and the potential of providing both mucosal and systemic protection. After intravenous injection, the formulation rapidly disseminates throughout the respiratory system, which has a large surface area, a thermal expansion, and a high density of antigen-presenting cells, including alveolar macrophages, dendritic cells, and B cells (Erdos et al., 2021). Drugs delivered to the alveolar regions of the lungs, on the other hand, are difficult to utilize because they must struggle with physiological defensive systems and aerodynamic resistance (Falo et al., 2021). We are still in the early stages of this research, but we intend to develop an inhalation vaccine that leverages mRNA-encoded neutralizing anti-COVID-19 antibodies to manufacture antibodies in the lungs (Carey et al, 2020).

3.5 Parenteral route

This can be the foremost broadly utilized course for the antibody to be conveyed, in spite of the fact that its obtrusive in nature. The different courses of parenteral immunization are- intradermal, intramuscular and subcutaneous. Till presently, covid-19 immunizations have been conveyed through subcutaneous and IM courses. A study has specified around a test which was done on a mouse giving four candidates od SARS immunizations by means of the intramuscular course (Lobaina et al., 2010). They further added that, the results of the experiment were quite impressive since they proved to induce antibodies and shield from SARS infection with all the four vaccines. Despite having the protection, there were observed hypersensitivity to the vaccine components (Johansen et al., 2015). On the other hand, a try was done on another mouse demonstrate regulating a recombinant antibody illustrating full length S glycoprotein of MERS CoV through intramuscular and subcutaneous infusions (Clements et al.,2016). Virus-specific antibodies and CD8+ T lymphocytes were managed in mice, showing adequacy of the given vaccine (Herzog et al., 2014). Presently, various intramuscular and intradermal SARS-CoV-2 vaccines are being industrialized by various manufacturers (Johansen et al.,2015).

Chapter 4

Microneedles for Transdermal delivery

This microneedle array utilizes micron-sized needles implanted in the stratum corneum to provide the relevant measurements. A variety of geometric and metal microneedles, as well as silicone and polymer microneedles, exist in micron ranges of 50 to 900 microns (Larraneta et al., 2016). Because of the tiny liquid holes created by using microneedle patches to provide medicines to the epidermal layer of the skin, injections may now be administered to this area with a single administration (Woolfson et al., 2016). However, according to a new study, microneedles have only been widely used within the last century. They are painless and self-administered, and the fact that they are microneedles adds an extra level of patient compliance. A microneedle is about one micron in size, which means you may make almost any drug or small particle formulation without causing any pain (Nagarar et al., 2020). Another advantage of microneedle delivery was the ability to treat diverse parts of the body, such as the skin or the eye. Microneedles come in a variety of shapes and sizes, including solid, coated, dissolving, and hollow needles (Nguyen et al., 2020).

Drug delivery approach	Description	Type of microneedle	Reference
Poke and patch	Drug releases through micropores generated by microneedles	Solid microneedle	(Henry *et al.*, 1998)
Coat and poke	Detachment of coating from the microneedle	Drug-coated microneedle	(Mcgrath *et al.*, 2011)
Poke and release	Drug diffuses and dissolves through the pores	Dissolving microneedle	(Chen *et al.*, 2008)
Poke and flow	Drug flows out through the bore	Hollow microneedle	(Bal *et al.*, 2010)

4.1. Solid Microneedles

When it comes to skin preparation, the needles are rock firm. They are injected into the skin and subsequently retrieved from pores as small as 1 micron in size (Singh et al., 2020). To apply the patch's medication solution to the surface with the microspores, the patch is removed and the solution is applied (Prausnitz et al., 2012). A different method used a roller with solid microneedles

that rolled across the skin, repeatedly making microscopic holes in the stratum corneum (Parc et al., 2012).

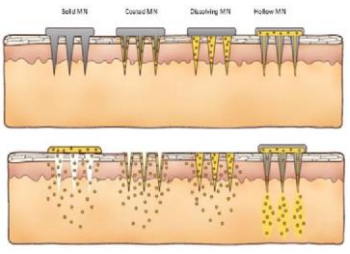
4.2. Hollow Microneedles

Hollow microneedles, like ordinary hypodermic needles, are micro-sized replicas of standard needle (Larraneta et al., 2016). The use of hollow microneedles for medication delivery results in pressure-driven flow of a liquid formulation. Because of their form and fragility, hollow microneedles are more difficult to produce than other needle types. Even yet, as compared to other types of microneedles, hollow microneedles can be utilized to distribute greater, more constant dosages of active substances (Lutton et al.,2016).

4.3. Dissolving Microneedles

These microneedles dissolve using medication-laden polymers and sugars, such as an infusion of drugs into the polymers or sugar. When the needles are placed against the skin, they disintegrate, releasing the payload (CFR, 2021). The distinction between dissolving needles and solid and hollow microneedles is that dissolving needles build and apply the patch in a single process. Microneedles are rigorously examined to determine their ability to deliver vaccines to the skin (Parc et al., 2012).

4.4. Coated Microneedles



The coating of a solid microneedle is a pharmaceutical solution or dispersion, while an uncoated microneedle is one that has not been coated with a pharmacological solution or dispersion (Nagarar et al., 2020). The kind of coating that is employed is determined by the technique of micro needling; either a range of ways or being "dipped" in the coating are possibilities. The needles may be coated with a spray-on coating if that is what you want. It seems as if hollow, solid, and dissolving microneedles are employed less often than microneedles that are coated with an inert substance or are not coated at all (Nguyen et al, 2020)

Chapter 5

Composition of Microneedles

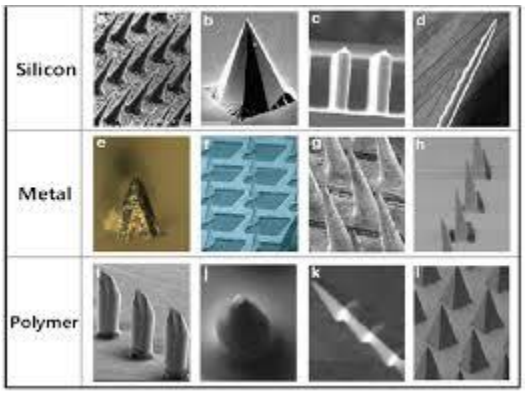
Diverse allowed materials are frequently used to manufacture microneedles, which are composed of various combinations of these materials (Hu et al., 2020). The first chemical utilized was Si. The advantages of pattern silicon include its high flexibility, which allows for the creation of needles in a wide range of forms and sizes (Hutton et al., 2020). The major drawbacks of Si microneedles include manufacturing costs, lengthy production schedules, and multiphase manufacturing. Steel and aluminum are also used in the production of microneedles (Haagmans et al., 2020). Titanium and chrome steel are both commonly used materials (Fernando et al.,2020). Metal microneedles are sometimes referred to as biocompatible due to their biocompatibility. Metals' mechanical properties make them particularly appealing for production (Lim et al., 2018). Ceramics have been used in conjunction with other materials to create microneedles. When compared to wholly different materials, these may be used at a lower cost (McConville & Davis, 2016). Microneedle patches are often constructed using silica glass, which enables a multitude of needle forms to be manufactured and assembled quickly to suit different purposes. Hand-made chemical compound glass, on the other hand, is frequently fragile and tends to be manufactured (Alarcon JB et al.,2007). Carbohydrates are most commonly used in the production of microneedle patches by utilizing hot melts or slurries of the carbs. Because the patches are simple to make and disintegrate when applied to the skin, they are suitable for usage in humans (Raphael et al., 2016). Maltose, trehalose, sucrose, and mannitol are examples of unusual sugars used to make dissolving microneedles. The biggest downside of this type of needle is that it restricts the sorts of drugs that can be included in the mix (Crichton et al., 2016). Furthermore, temperature and moisture are known to substantially compromise the needles' integrity (Sheridan et al.,2019). On a more mundane note, polymers that have been approved for use in space manufacturing seek to create microneedles. As a result, PVA, PVP, polysaccharide, and polylactic acid are among the few polymers in use (Lin, 2020).

Chapter 6

Vaccination using microneedle

It was cutaneous or intramuscular vaccination that constituted the real idea of vaccination. In general, painful injection through the IM route or the SC approach are the most often used procedures (Rodgers et al., 2018). Langerhans cells and dermal dendritic cells are abundant in the skin and serve as antigen-presenting cells. Because of the relevance of the skin as a site of immunization, as well as the concept of transdermal administration through microneedle, skin vaccination is becoming increasingly important (Jones et al., 2011). A 30-gauge metallic microneedle inserted into the skin just under the skin's surface (at about 1.5 mm) delivered vaccine antigen and was implanted in the dermis layer of the skin (Zehrung et al., 2011).

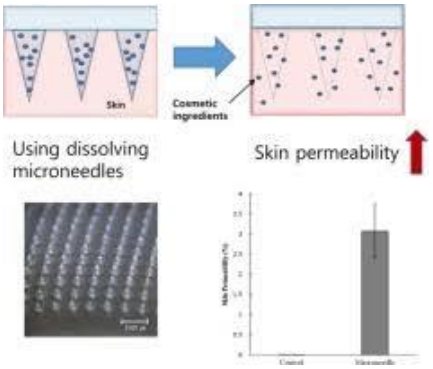
6.1 Solid microneedle for Vaccine Delivery



Concerning the earlier mentioned three sorts of microneedles, I'd like to stress that there are three types: solid, hollow, and dissolving. This microneedle technology is being researched as a viable technique of immunization. In the manufacture of solid microneedles for use in vaccine delivery, almost all stainless steel is used. Additional solutions-based antigens are coated on these stainless-steel microneedles, which have been impregnated with nanoparticle-based antigens (Jonnalagadda et al., 2020). To apply antigens using microneedles, the injections are performed in the dermis. Once the microneedle coating is included, metal microneedle vaccination is far more likely to succeed. As a consequence, microneedle manufacturing was more efficient, and the use of Nano patterns was also developed (Jung et al., 2017). Dip coating antigens has been shown to improve the hydrophilicity of the microneedle surface by improving the hydrophilicity of the surface of the Nano patterning. The Nano patterned microneedle method increased the loading of plasmid DNA (Rejinol et al., 2017). The observed increase in immunological response was ascribed to clinical microneedles, which

had never been utilized previously, due to an apparent increase in loading. Previously, the antigen coating on solid microneedles was changed in an attempt to enhance it (Chim et al., 2017). By boosting the antigen-presenting cell response, the charged polymer pH-sensitive copolymers offered a more effective DNA vaccine delivery (Duong et al., 2018). Initially, the HPV vaccination was administered using solid microneedles grouped in a Nano patch. This significantly increased the number of antigens, causing the test to show a larger reaction. In addition, the novel technique improved HPV vaccine transfer efficiency by 20 percent (Thambi et al., 2018). Additionally, the Nano patch was utilized in a clinical study in which an influenza vaccination was delivered through microneedles and into the patient. In a randomized, placebo-controlled, double-blind trial, 82% of patients found the microneedle injection better than their prior IM injection (Meyer et al., 2019). Solid microneedles for vaccine administration and cancer immunotherapy are being studied for the use of novel production techniques. The development of an effective technique of delivering vaccinations using microneedles composed of silk fibroin was done in order to resist Clostridium difficile and Shigella infections (Williams et al.,2019). SILK FIBROIN-based microneedles offered an excellent level of protection against influenza, but were inadequate when it came to fighting Clostridium difficile infection. The authors point out that the antigen applied to mice after inoculation is smaller than the amount of antigen coating given. It is difficult to administer microneedle vaccination precisely because of the broad range of dose (Dubey et al., 2019).

6.2 Dissolving Microneedles for Vaccine Delivery

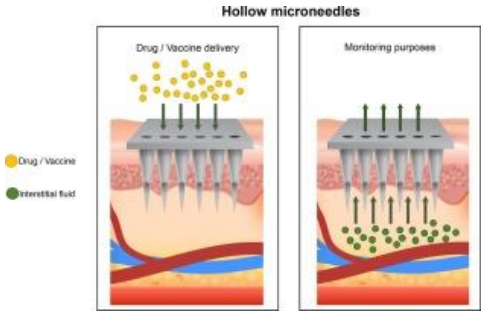


Despite its effectiveness in triggering a robust immunological response, hollow microneedles leave behind non-biodegradable remains on the skin. These disadvantages of dissolving microneedles are offset by advantages in other applications (Arya et al., 2016). Because microneedles may be loaded with vaccine antigens as well as nanoparticles, the latter can be employed in the same way that the former was used in the first (Chiang et al., 2016). These microneedles disintegrate as soon as they inserted, allowing the vaccination to be absorbed in the body (Joyce et al., 2017). Using microneedle that contain micro particles to dissolve them has the benefit of releasing the antigen gradually over time,

allowing the immune response to continue for an extended length of time (Flynn et al., 2021). The initial stage in administering the influenza vaccine was the use of microneedles to dissolve the needles that were used for vaccination. The lyophilized encapsulated antigen was dispensed in 5 minutes using this polyvinyl pyrrolidone microneedle technology (Duong et al., 2020). Several microneedles have since been created to dissolve various vaccinations with various polymers and sugars. The approach for antigen stability preservation at room temperature (25°C) has also been shown to be successful when using soluble microneedles (Ali et al., 2020). The vaccination against influenza remained stable at 25 C and 60 C for up to 24 months and four months, respectively, using dissolving microneedles composed of polyvinyl alcohol (PVA) and sucrose (Duong et al., 2020). The malaria antigen was more stable in a dissolving microneedle patch than it was in liquid form. Furthermore, PVA-based microneedles disintegrate quickly, allowing for powerful immune responses after pathogen exposure (Lanza et al., 2021). Prophylactic DNA vaccines are also an excellent delivery strategy for these vaccinations for cervical cancer treatment. In situations of tetanus toxin exposure during pregnancy, other means of administration, such as intramuscular injections, have also been examined; this research is focused on maternal protective immune responses (Cole et al, 2017). When infected with Streptococcus suis bacteria, PVA microneedles activate TH1 cytokines (IFN- and IL-12) and offer long-term protection by generating IgG2a antibodies specific to S. suis. Bacteria (Ali et al., 2020). In patients infected with Plasmodium falciparum, dissolving microneedles were found to generate a superior antibody response to AdHu5–PfRH5 malaria immunization (Arshad et al., 2019). A study found that, when compared to prime-dose intramuscular injections, low-dose dissolving microneedle injections elicited a higher immune response. As a result, utilizing microneedles instead of the traditional intramuscular technique improves the efficiency of the immune response (Nazariet al., 2019). In the face of a Neisseria gonorrhea invasion, PVA and sugar-coated microneedles elicited an enhanced immune response. Vacunene-loaded cationic liposomes encapsulated with cationic liposomes, like hollow microneedles that disintegrate, have also been employed to investigate cationic liposomes encapsulated with vacunene (Esser et al., 2019). Leishmania Donovan (LD) vaccine may be prevented by a cationic liposome-based microneedle vaccination known as CLLMV. In contrast to the BCG vaccination, which is delivered by hypodermic needle, the BIK vaccination is given by a hypodermic needle and is an intradermal vaccine (Arshad et al., 2019). One research found that the microneedle technique performed equally as well as the injection

method when using sodium alginate and sugars as adjuvants (Lanza et al., 2020). Hyaluronic acid is another often used biodegradable polymer for microneedle injection. Injection of hyaluronic acid microneedle tips was used to provide a canine influenza vaccine.The microneedles, also known as insertion-responsive microneedles, have detachable tips (Zhou et al., 2020). When the vaccine was stored at 50 degrees Celsius for three weeks, the microneedle proved to be more thermally stable than the liquid version, which was likewise protected against H3N2 wild type virus exposure (Yang et al., 2020). This third study on an insertion-responsive microneedle injection system for canine influenza vaccination, which worked without the need to shave dogs' hair, demonstrated that the technology could be used to vaccine dogs and provided greater compliance for both the animal and its owners (Yeom et al., 2020). While intratumoral injection of free, programmed death-1 was as effective as a single injection of hyaluronic acid microneedle induction, it was not more effective than intradermal injection of hyaluronic acid microneedle induction (Lim et al., 2020). Microneedles have also been created using sustain-release polymers. The cores and shells of vaccines were micro molded utilizing poly (lactic-co-glycolic acid) microneedle technology (Frew et al., 2020). Streptococcus pneumonia was prevented in the Prevnar-13 clinical trial, which included this vaccine (Huang et al., 2020). Additionally, it was found that microneedle vaccination, which employs very fine needles, elicits a reaction comparable to that produced by multiple SC injections (Ingrole et al., 2021).

6.3 Hollow Microneedles for Vaccine Delivery



It is critical to effectively target APCs in order to elicit an effective immune response. Particulate vaccines, according to research, are better absorbed by APCs. A powerful tool for immunization is provided by combining APC targeting with pain-free administration (Du et al., 2017). Much research is now being conducted on the use of microneedles to encapsulate antigens in polymeric particles. Particle-based vaccines are frequently administered by hollow microneedles (Chu et al., 2019). The vaccination antigen is put into hollow needles, which are then inserted into the skin, where the vaccine antigens are dispensed (Niyomtham et al., 2017). An automated syringe containing microneedles that control the flow of antigen-containing gel inside

a round-ovalbumin as well as an adjuvant known as enveloped adjuvant (EAA) were used in the antigen oval-bumin delivery model with and without the assistance of optimized nanoparticles such as poly (lactic-co-glycolic acid) (PLGA) nanoparticles, liposomes, and mesoporous silica were used (GNPs) (Niu et al., 2017). It was discovered that the injection of PLGA nanoparticles and liposomes to cells via a microneedle that penetrated 120 microns produced a humoral and cellular immune response (Camps et al., 2018). The results were similar when the experimental ovalbumin and adjuvant were encapsulated in PLGA nanoparticles and applied using hollow plastic microneedles attached to an applicator (Martin et al., 2010). Hollow microneedles have also been utilized to administer DNA vaccines that are contained inside a microneedle and surrounded by nanoparticles, according to the National Institute of Health. While bare DNA would only excite the immune system briefly, the DNA vaccine that encodes for ovalbumin was encapsulated in inclusion-formyl peptide (Niosomes) to elicit a greater and more robust immunological response (Sullivan et al., 2010). Furthermore, the DNA vaccine encapsulated in the noisome was found to be more effective at eliciting an immunological response than the SC route (Arya et al., 2016). Traditional intradermal injection required a lot more antigen, whereas a digitally controlled hollow microneedles injection approach utilized for therapeutic cancer vaccine required a lot less (Mistilis et al., 2017). A team was able to successfully administer multiple (0.25–10L) sub-microneedle injections of a synthetic long peptide using this novel hollow microneedle method based on the creation of an HPV-encapsulated cationic liposome-containing lipopeptide (Pontier et al, 2018). Immunization with an antigen generated a robust CD8 cytotoxic cell response in addition to a robust CD4 T-helper cell response (Esser et al., 2016).

Chapter 7

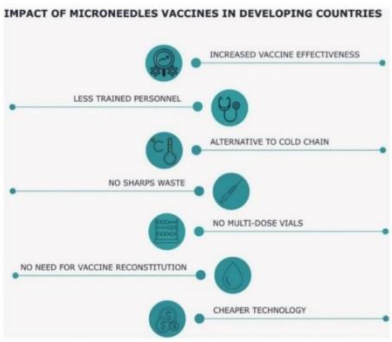
The Obstacles to Microneedles-Based Vaccines

Much effort has gone into developing microneedles for immunization. A PubMed search revealed 236 recent publications on microneedle vaccination, in addition to these recent publications. Clinical and preclinical investigations, as well as review papers, were covered. A quick search on clinicaltrias.gov using the terms “microneedle vaccine” and “indicated” yielded a list of studies with 100 participants in the Phase 1 trial and 33 individuals in the Phase 2 research. The findings of all studies are available. Aside from these, seven other microneedle-based vaccine trials are either in the last stages of development or being considered (Indermun et al., 2014). Furthermore, the microneedle research trend is continuing to accelerate, and it has now reached a "tipping point." Furthermore, it appears that translating microneedle-based vaccines into clinical practice will be a substantial problem (Luttge et al., 2014). While clinical evidence is limited, it is also possible that the lack of clinical usage of microneedles vaccines is due to increased microneedle scale-up (Choonara etal., 2014). In the case of large-scale microneedle manufacturing, this means that a number of critical issues will need to be addressed in subsequent reviews (Rodgers et al., 2019). There are numerous effective methods for preventing and treating infectious diseases, but vaccines are the most dependable. The predominance of compliance in the outbreak in Côte d'Ivoire has demonstrated this point (Cordeiro et al., 2019). When it comes to vaccinations, many people are afraid of needles and hence avoid them. If microneedle immunization is painless, patients are more likely to accept treatment (Donnelly e al., 2010). Vaccine storage may be a barrier to immunization in areas where cold-chain storage is difficult, and microneedles, which do not require cold-chain storage, may boost vaccine coverage (Woolfson et al., 2010). The thermostability of the vaccines in these patches must be thoroughly investigated in order to meet the objective of vaccination patches that do not require cold chain storage (Singh et al., 2010). Microneedle-based vaccination systems should be able to include consistency data up to Category 7 VVM, according to WHO guidelines. A higher category, such as VVM 14 or VVM 30, may be appropriate for vaccines stored at room temperature (WHO, 2021). Because the microneedle matrix is dry and amorphous, microneedles can provide superior stability (Donnely e al., 2010). Some microneedles can be self-administered, but others must be specially designed to accommodate the shift in pressure utilized

during administration (Pillay et al., 2014). Only a coordinated immunization program will be able to prevent a COVID-19 pandemic. Prior to clinical trials, COVID-19 showed remarkable promise with microneedle vaccinations (Gallagher et al., 2021). Furthermore, some companies are investigating the use of microneedle technology to deliver therapies for a variety of viral illnesses and cancer. The majority of human vaccinations are pyrogen-free and sterile (US Pharmasist, 2021). The antigens in vaccines are an exception. The approval of microneedle-based vaccinations will improve if sterility is controlled. The bulk of vaccinations need distinct sterilization methods since microneedles are solid patches that cannot be sterilized by sterile filtration (Indermun et al., 2014). Furthermore, radiation sterilization may diminish the efficacy of the antigen included in the microneedle patch. As a result, it may be necessary to produce microneedles in aseptic conditions (Woolfson et al., 2010). Microneedle vaccinations, which are widely employed to address disease outbreaks that necessitate mass vaccination, may be more challenging to mass-produce (Vescovo et al, 2014). Microneedle vaccinations will be considered a combination product for regulatory purposes, as stipulated in FDA 21 CFR 3.2. Combination products are those that combine two or more regulated products, such as ceramics and jewelry. All of the microneedles have controlled their diameter, toughness and ability to absorb epidermal levels, as well as their control for the supply of microneedles (manual or robotic) (Cordeiro et a., 2019). In addition, vaccinations for microneedle, microneedles and combination products will need regulatory applications (Rodgers et al.,2019).

Chapter 8

Future Anticipation



COVID-19 is now considered a worldwide pandemic. As a result of this lethal vaccine, millions of people have died. Their lives are on the line, and researchers are working around the clock to develop a vaccine that will save them from illness (Jitendra et al.,2021). Those living in poverty and developing countries are lagging behind due to a lack of vaccines. As a result, there is a considerable likelihood that microneedle patches will have a significant impact on worldwide vaccination practices, potentially saving many lives. New MN-based goods, including vaccinations, have been developed as microfabrication technology have advanced (Vora, 2021). To put it another way, in the future, consumers will be able to administer their own covid-19 vaccine, eliminating the need for a healthcare professional to do so. This method of disseminating vaccinations around the world is highly efficient (Baishali et al., 2019). Using this strategy in the case of COVID-19 can provide herd immunity for a lengthy period of time. Because covid-19 affects people of all ages, dissolving microneedles are essential in giving vaccinations to the elderly (Prausnitz et al., 2020). As a result, we should be able to develop a microneedle-based vaccine delivery system that will allow us to vaccinate against this devastating disease while ensuring patient compliance (Hare, 2021).

Chapter 9

Discussion

Because of the invasive and stringent cold chain storage requirements, the parental route is commonly used, despite the fact that it is invasive. We'll overcome these challenges by using a non-invasive vaccine delivery method as well as an alternative vaccine delivery mechanism. Several countries have emergency use approval for the delivery of a large scale of vaccination. The intramuscular technique is used to create the most commonly administered vaccinations. In addition, this article cites two independent studies that outline design criteria for microneedle patches used to deliver Covid-19 vaccination in the nasal and oral mucosa. The Covid-19 vaccination is increasingly being administered through the skin, with the justification that this is a more persistent and powerful form of administration. As a result, superior transdermal microneedle dispersion leads to improved total systemic immunity, which is more effective in combating SARS-CoV-2 and also advantageous in combating the Covid-19 pandemic.

Chapter 10

Conclusion

Covid-19, which has turned into a global epidemic, has had a devastating impact on many people all over the world. We desperately require a simple-to-administer immunization because we are in the midst of a pandemic. While the current situation of the world leaves little room for optimism, this paper performed a good job in developing a Covid-19 vaccine that uses transdermal microneedle delivery. When compared to traditional needle administration systems, delayed and prolonged release of vaccine antigens via microneedles is a very successful drug delivery approach. Vaccines can now be administered by anyone who is capable, eliminating the need for an experienced professional. Because they can effectively supply themselves, this can work for large-scale immunization efforts during pandemics. The usefulness of microneedles in eliciting a robust immune response has also been established in the treatment of cancer immunotherapy patients, as well as patients with diverse viral and bacterial infections. This strong immune response is believed to be due to the concentrated Langerhans cells, dermal dendritic cells, and other immunological machinery located in the skin. To generate microneedles with customizable features, a biodegradable polymer and additives are coupled with microneedles having configurable characteristics.

Beginning in the near future, microneedle mass production is expected to use both conventional and non-welding techniques. 3-D printing has made it possible to mass-produce personalized vaccines at a far lower cost. With the development of sustained-release polymers, microparticles, and nanoparticles, microneedles that are more effective while requiring fewer vaccinations may be feasible. Despite a few setbacks, microneedle vaccines have had a big impact on the world and will have a significant impact on future immunization procedures to combat the worldwide pandemic. If ongoing research efforts are successful in overcoming hurdles, transdermal microneedle delivery of Covid-19 vaccine could have a significant impact on vaccine administration in the future.

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