COVID-19 Vaccine: A Review on Route of Administration and Microneedle-Based Transdermal Delivery system

Project Report

A review paper, submitted to the Department of Pharmacy, Daffodil International University to complete the course of B.Pharm.

Submitted To:

Department of Pharmacy

Faculty of Allied Health and Science

Daffodil International University

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Batch:21st ,Section (B)

Department of Pharmacy

Faculty of Allied Health Science

Daffodil International University

Date of submission

May,2023

APPROVAL

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Declaration

It is hereby declared that

1.As part of my degree program at Daffodil International University, the project report submitted is my own original work.

2.This project report contains no material that had accepted, or submitted, for an academic degree or diploma.

3. No material previously-published or written by a third party appears in the thesis, except as appropriately referenced.

4. The main sources of help have all been acknowledged.

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Dedication

This Project Paper is Dedicated to the people
who have supported me throughout my education
My mother
Sister
Best friend

Thank you for making me this
adventure through to the end

Your endless support and encouragement will never go unnoticed.

Acknowledgement

All praise and glory are due to Almighty Allah who has given me tremendous courage,knowledge and patience to carry out and complete this project paper report.
Peace and blessing of Allah be upon Prophet Muhammad (ﷺ).

First of all,I am really grateful and wish our profound our indebtedness to to my supervisor **Ms.Farhana Israt Jahan** (Associate. Professor, Department of Pharmacy, Daffodil International University) to guide me ,as well as, Ms.Nazneen Ahmeda Sultana (Asstitant Professor,Daffodil International University). I would like to thank them for believing in my ability to complete my project. Throughout this process, I am eternally grateful for their constant guidance, support, optimism, and inspiration.I would like to express my heartfelt gratitude to **Professor Dr. Muniruddin Ahmed** (Professor and Head , Department of Pharmacy,Daffodil International University) for his constant guidance, knowledge and for guiding me to become a pharmacist. Finally, I must acknowledge with due respect the constant support and patience of my mom for giving me all the love, support and continuous encouragement all the time.

Abstract

The responsible virus for COVID-19 pandemic is known as the severe-acute respiratory syndrome corona-virus 2 (SARS-CoV-2).Throughout this outbreak, many individuals have been extremely concerned,which additional strain of seasonal-flu may lead to a disastrous situation, overtaxing medical resources and ultimately leading to fatalities.The significance of route of administration vaccination worldwide is fighting against infectious-diseases are highlighted by several efforts to create a safe and effective vaccine to prevent infection by the coronavirus vaccines.The COVID-19 outbreak has increased the need for alternative medicine administration routes, particularly in public places,Oral Route,Parenteral Route,Intranasal Route,mucosal Route.This epidemic puts a focus on pandemic readiness. Contrary to popular belief, transdermal microneedle is used to administer the Covid-19 vaccine rather than parenteral delivery.While vaccinations are typically administered as (IM) injections which 64.48% of global population have been fully vaccinated, microneedle (MN) patches delivery system offer a noninvasive,pain-free, no cold storage and self-administration approach of vaccination strategy, lowering total-costs and enhancing access to vaccinations in areas with a limited supply.The most effective way to produce the required immunity and antibodies against Covid-19 is via dissolving microneedles.Whereas parenteral vaccine delivery is invasive, necessitates cold chain storage, and does not permit customized delivery, transdermal microneedle vaccine administration enables customized distribution and minimizes vaccine waste and prolonged antigen delivery.When it comes to stability and safety, developing vaccinations confront various obstacles. Moreover, fear of needles and vaccine hesitancy may hinder a sizable section of the populace from having vaccinations. In this situation, microneedles (MNs) could offer a method to deal with these difficulties with painless transdermal microneedle administration. We hope many people to get vaccinated as we can, and transdermal microneedle administration might assist.The current study aims to highlight developments in research on cutaneous vaccine delivery systems and TDDS of the COVID-19 vaccine headquartered in Minnesota. To aid in the logical creation of secure and efficient MN-delivered vaccines against this contagious virus, concluding remarks, difficulties, and future research on MNs-based skin vaccination are also offered.

Keywords: COVID-19 vaccine,Route of Administration,Microneedle,Delivery System,Pandemic.

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CHAPTER-1
INTRODUCTION

1.1Background

1.1 COVID-19

COVID-19 is the name given to the (SARS CoV-2) virus when it infects and causes disease in humans."COVID" stands for Corona virus disease. It is named after its first detection in 2019, though the pandemic started in 2020.Indirect and direct transmission is thought to be the main method of spreading this virus,which first discovered in zoonotic animals. The first "Human Corona-viruses" were discovered in the middle of the 1960s, and numerous strains of the virus have since been found. [1] Despite this, it was only in the last two decades that this virus was discovered to be capable of spreading deadly epidemics.In 1964, June Almeida observed an electron microscope image of an elliptical gray dot covered in tiny spokes.She and her colleagues noted that the pegs formed a halo around the virus—much like the sun's corona.Her observations led to the identification of the Coronavirus, which was named for Almeida. [2] The scientists discovered that certain common cold viruses could be grown, but not all of them. Later it was discovered that this sample, known as B814, was a Coronavirus. Almeida, June (née Hart), a virologist who pioneered new methods of viral imaging and diagnosis, then imaged the virus for the first time.Almeida and Tyrrell gave the family the name Coronavirus after eight virologists reported their results in Nature in 1968. [3]

There has been a significant disruption of the socioeconomic balance throughout the entire world due to COVID-19, the third major outbreak of respiratory disease related to Corona-virus in twenty years.A virus of the family of Coronaviride , which belongs to the Nidovirales order, causes SARS-CoV-2 to be transmitted.[4] Two subfamilies belong to this family: Coronavirinae and Torovirinae. The genus Betacoronavirus was subdivided into lineages A, B, C, and D.[5]

The virus is divided into four major subgroups, according to the CDC: alpha, beta, gamma, and delta. There are seven different corona-virus types that can infect people among the four groups: (Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus).[5]

Table 1:Corona-virus types that can infect people among the four groups. [5]

Group No.	Name
Group-1	Alpha corona virus (NL63)
Group-2	Alpha corona virus (229E)
Group-3	Beta corona virus (HKU1)
Group-4	Beta corona virus (OC43)

Because of the virus presence,spike-proteins on the floor give (Crown Terrace) its name.According to these experts, new viruses are produced by viruses derived from animals.Between 2002 and 2012, the severity of both Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory-Syndrome (SARS) was once unprecedented followed by the present COVID-19 that emerged from China. [6] It was a period of time when children, adults, and those with weaker immune systems were at risk of contracting disease.[7] There was a severe outbreak of SARS-CoV-2 in Wuhan, China, in December 2019, which was caused by a previously unknown corona virus (SARS-CoV-2).Quickly disseminating scientific results about COVID-19 is vital to allow the rapid exploitation of successful clinical results.[8] There have been 761,071,826 infections confirm cases and 6,879,677 deaths caused by

Covid-19 till March,2023.The virus is still spreading despite the absence of a maximum quantity limit since it can be transmitted through direct contact as well as through breathing, as with coughing or sneezing.[9]

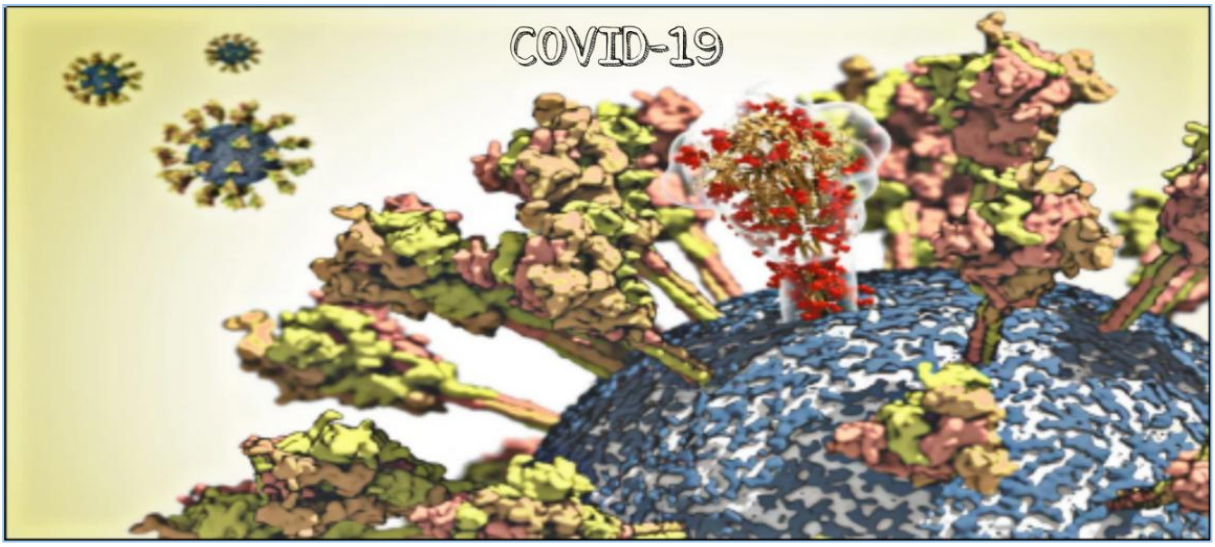


Figure 1: *Surface of the CoV-2 virus. A molecule of the spike protein is shown translucently to emphasize its complex spatial structure (reproduced from MPI f.Biophophysics et al.,2020)*

CDC is responsible for this fact in the United States.In the short space of time since its discovery, this genetic SARS-CoV-2 collection has been published as an associated beta-coronavirus with SARS-CoV. [10,11] Fever, dry cough, fatigue, dyspnea, and respiratory disease associated with COVID-19 are some of the most common indications and symptoms of the disease.[12]

1.2 COVID-19 Vaccines

In order to prevent infectious disorder like COVID-19, vaccines are used to boost the immune system to respond to an antigen, a chemical present on pathogens. Vaccines is a vital public-health intervention for the prevention of infectious illnesses.Vaccines provide effective protection against certain diseases.The smallpox vaccine, created by Edward Jenner in 1796, was the first vaccination. [13] The COVID-19 virus, which made its debut at the end of 2019,has caused a record-breaking increase in-vaccine research. Internationally, SARS-CoV-2 vaccinations were used, with varying degrees of vaccination development in

various nations. Furthermore,enormous efforts have been undertaken to create COVID-19 vaccines that are both effective and safe.There were more than 172 vaccines in pre-clinical development at the end of January 2021, and 43 of them had entered clinical trials, including some that have not been licensed for humans yet.Currently,these clinical studies are still increasing. As part of the exit strategy, vaccines have been widely considered as a tool for returning to previous patterns of employment, education, and socialization.It is critical that manufacturers and regulators work closely together to develop and scale-up COVID-19 vaccine from small pre-clinical doses to enough placed vials to be able to immunize the world's population.[14] Vaccine availability may be limited by manufacturing and delivery issues, which make planning for a pandemic essential.Researchers are constantly working to identify the physical characteristics of (SARS-COV-2) and to create a different types of vaccine to prevent COVID-19.[15] The SARS-CoV-2 ORF1ab poly-protein codes for (15) or (16) non-structural proteins, whereas the poly-protein's 3' end codes for structural proteins (E),(S), (N), and M. ORF1ab codes for (15)or (16) non-structural proteins, as well as (4) structural-proteins at the 3' end: spike (S), membrane (M), and env (N).[16]

1.2.1 COVID-19 Vaccine Development

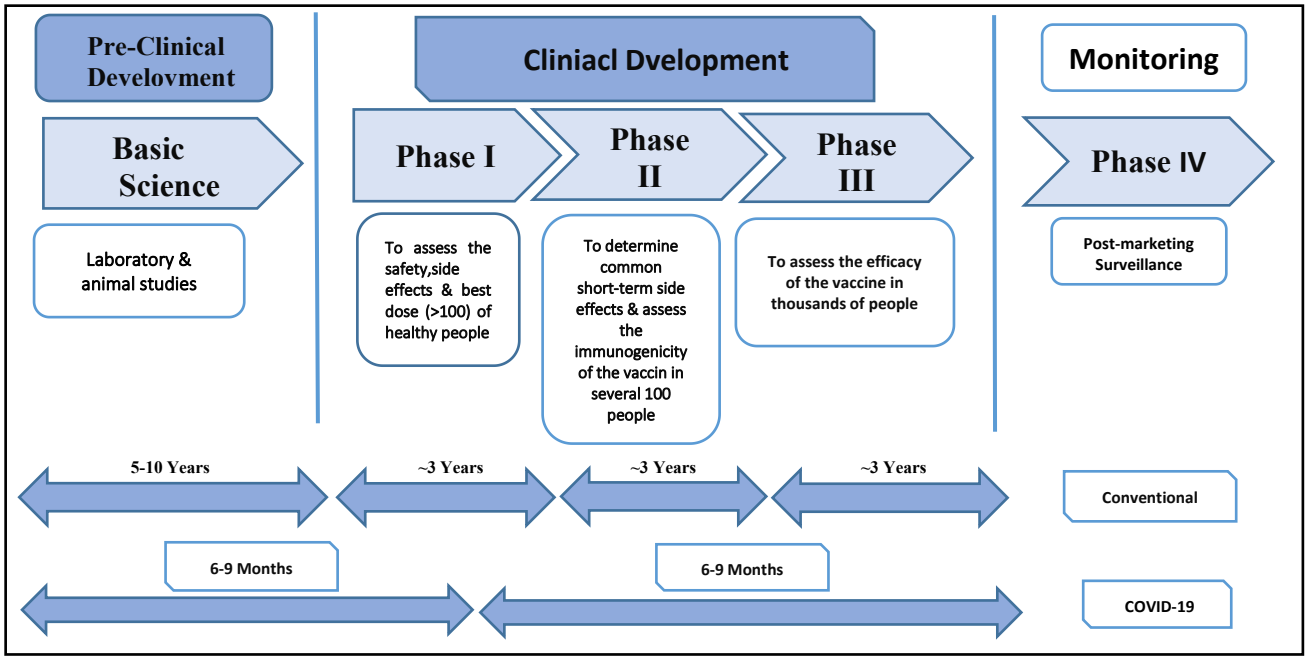


Figure 2: *COVID-19 vaccine development compared to conventional vaccine development.(reproduced from Duduzil & Charles et al.,2021)*

Clinical studies are now being conducted on a total of 16 inactivated and two live attenuated SARS-COV-2 vaccines. Live-attenuated COVID-19 vaccines candidate for offer protection without the use of adjuvants besides focusing on and promoting strong mucosal and cellular immunity. Although this kind of vaccination offers certain benefits, it also has some drawbacks. There are worries that live-attenuated vaccinations might disseminate SARS-CoV-2 to those who have not had the vaccination since infected patients pass COVID-19 in their feces.There is also a possibility that recombination between SARS-CoV-2 live-attenuated vaccination and wild-type virus may result in new virus variants being generated when used with wild-type virus.Additionally,a large-scale vaccine production would be slowed by labor-intensive manufacturing and quality control. The emergency use have been authorized for use at least two inactivated sars-cov-2 vaccine candidates.[17] There are several vaccine kinds being produced right now, including ones for viruses that have undergone various levels of live attenuation or inactivation. Nucleic acid, proteins, and vector. [18]

1.2.1.1 Viral vector vaccine : To be able to' read 'the genetic-code of the virus by invading the cells of its host and taking over the machinery that creates proteins similar to this SARS-CoV-2 antigens which allows the virus to replicate itself and make new copies of itself.The SARS-CoV-2 antigens are delivered to the cell by the viral vector, which also enters to the cell. Viruses that have been employed as vectors include the measles virus, vaccine virus, and adenovirus. Viral vectors can either reproduce inside of cells or they can only do so if certain crucial genes aren't present. Until the SARS-CoV-2 pandemic began, only one viral vector-virus against Ebola-virus was authorized for use in humans.16 non-replicating and 2 replicating SARS-CoV-2 vaccines are presently being developed. Regulatory agencies from all around the world have authorized a number of non-replicating viral vector-based SARS-CoV-2 vaccines.

For instance, COVID-19 viral vector vaccines from AstraZeneca and Janssen provide protection against SARS-CoV-2 infection, the agent responsible for COVID-19. Your body creates antibodies as a result of the vaccination, protecting you against getting sick if you are exposed to the virus. It has been chemically weakened to prevent disease transmission by the virus employed as a vector.[19]

1.2.1.2 Nucleic acid vaccines (mRNA):SARS-CoV-2 nucleic-acid vaccine employs doxy-ribonucleic acid (DNA) or ribo-nucleic acid as genetic-code for SARS-COV-2 protein

which stimulates the immune-system (RNA). On the other hand, NA-vaccines encod target antigen in a messenger RNA (mRNA) or self-amplifying RNA, a molecular template utilized by cellular factories to make proteins. Included in this are T-cells kills (infected-cells), B-cells (produces antibodies), and helper T-cells (Support production of antibody).[20] Pfizer-Biotech and the Moderna COVID-19-vaccines are two examples of mRNA vaccines.[21]

1.2.1.3 Protein-based vaccines: It consists of recombinant protein fragments containing viral antigenic fragments. They are effortless to produce, and fairly protected and well-tolerated in contrast to total virus vaccines.There are presently 33 SARS-CoV-2 protein subunit candidate vaccines in scientific development , with at least one that has been shown in segment III scientific trials to induce excessive titers of neutralizing antibodies. A vaccine made of protien subunits is the Novavax COVID-19 vaccine.[22]

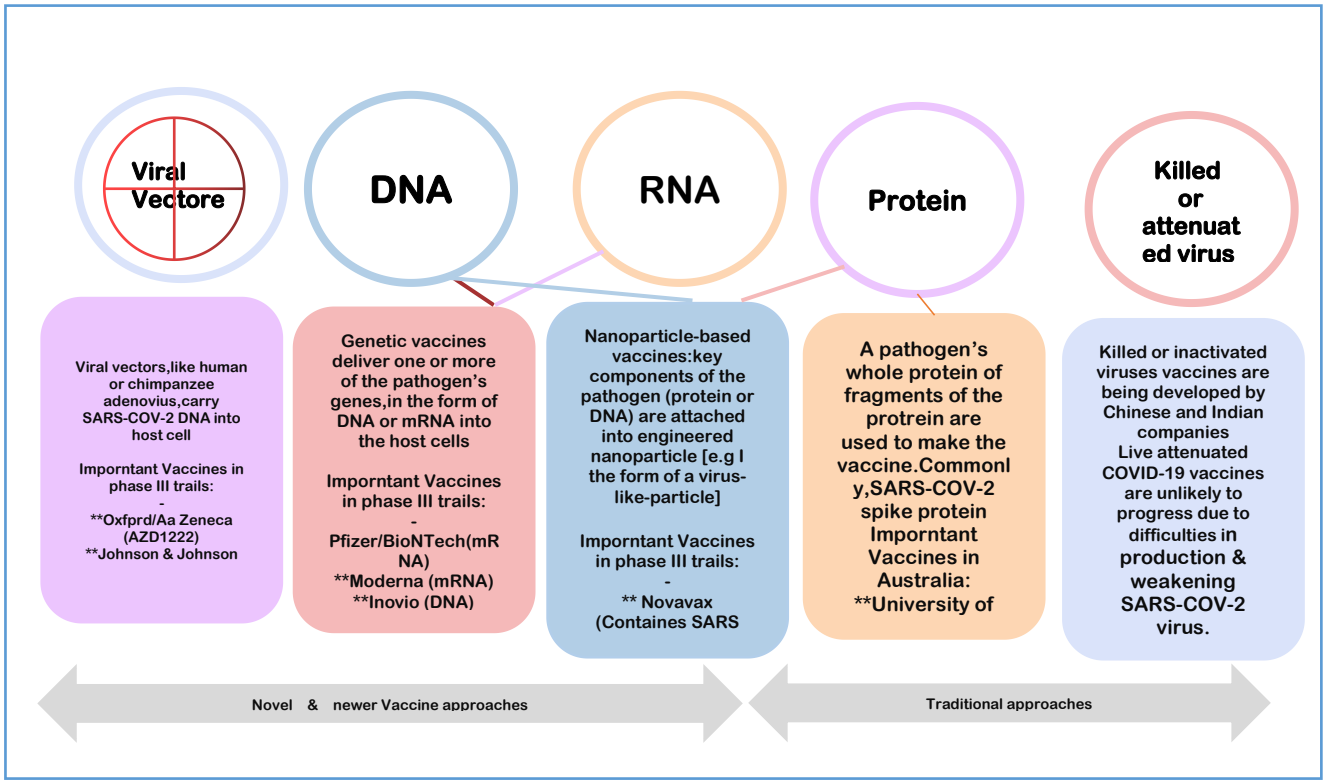


Figure 3. *SARS-COV-19 Types of Vaccine that undergo various levels of live attenuation or inactivation.(reproduced from MVEC Education et al.,2019)*

1.3 Route of Administration

To guarantee efficacy and safety of vaccination proper administration of vaccine thats essential one the most important variables to consider when formulating a vaccine formulation is its preferred route of administration23 because of sars-cov-2 outbreak alternative medicine administration- routes are becoming more necessary especially in public placesa trans-mucosal method is defined as route of administration by buca sublingual or rectal means in addition to their quick onset -of -action and decreased first-pass metabolism they are perfect for palliative and end-of-life care the mucosal atomization device makes it possible to administer parenteral formulations through nasal spray intranasally rectal mucosal absorption is comparable to oral absorption addition to being extremely versatile and useful to administer drug of rectal-route is also suitable for many different types of medications antimalaria medication hydroxychloroquine glucocorticoids dexamethasone antibiotics azithromycin and antiviral medications favipiravir are all used to treat covid-19 illness.[24]

It is most common to administer vaccines intra-muscular because the traditional subcutaneous route has resulted in severe adverse effects for vaccines with aluminum salt adjuvants.[25] As a result of a clinical trial of diphtheria toxin vaccines with booster shots, intramuscular vaccinations were found to have significantly fewer adverse effects than subcutaneous injections of vaccines. [26] Although most vaccines are delivered via parenteral or mucosal routes, these are not the case for all vaccines.[27] Mucosa include the oral, nasal, buccal, sublingual, rectal, and vaginal mucosa.[28] Intradermal injections require a lower dose of vaccine than subcutaneous or intramuscular injections, according to a systematic review of delivery methods Injections can be given intramuscularly, subcutaneously, intravenously, or intradermally.The vaccination route depends on several factors, including where an infection develops, how a disease is transmitted, the type of vaccination used, and the degree of immunity expected.[29]

Table 2. Routes of administration of covide-19 vaccine. [26-29]

No.	Type of Route
1.	Oral Route
2.	Parenteral Route
3.	Intranasal Route
4.	Mucosal Route

1.4 Microneedle

An innovative method of immunization called microneedle patch that's a modified transdermal patch where the patch's surface (which comes into contact with the skin).The idea of microneedles was initially developed decades ago,but it was not until the middle of 1990s that started to be featured in important research.MNs are more patient compliant as they are pain-free and can be self-administrated that vary between 50-90 microns in height. MNs have been developed for drug delivery for several decades since Gerstel and place first proposed a MNs concept in 1971. In recent years,MN has been explored for a variety of structures (in-plant and out-of-plane MNs) materials (Silicon,ceramic,glass,polymer and glass) geometries (octagonal cylindrica rectangularpyramidal,conica,quadrangular) and morphologies,namely solid MN (first reported in 1971 by Gerstel and Place),hollow MN (first reported in 1971 by Gerstel and Place),dissolving MN (first reported by Miyano et al.) and coated MN (first reported in 1975 by Pistor in a patrnt).Which makes vaccinations more effective and accessible in underdeveloped nations, reduces the number of healthcare workers needed, and minimizes sharps and vaccine waste. When doctors are unavailable, patients can get microneedles instead.[30] It is amazing how microneedles are capable of penetrating the stratum corneum, touching the epidermis, and interacting with epidermal layers without

passing through blood vessels.[31].Utilizing skin as a route for vaccination presents MNs as alternative delivery system.MN is regarded as a painless, minimally invasive transdermal drug delivery method.[32] This is because MNs are long enough to pierce the skin without touching the pain-producing nerve endings. [33]

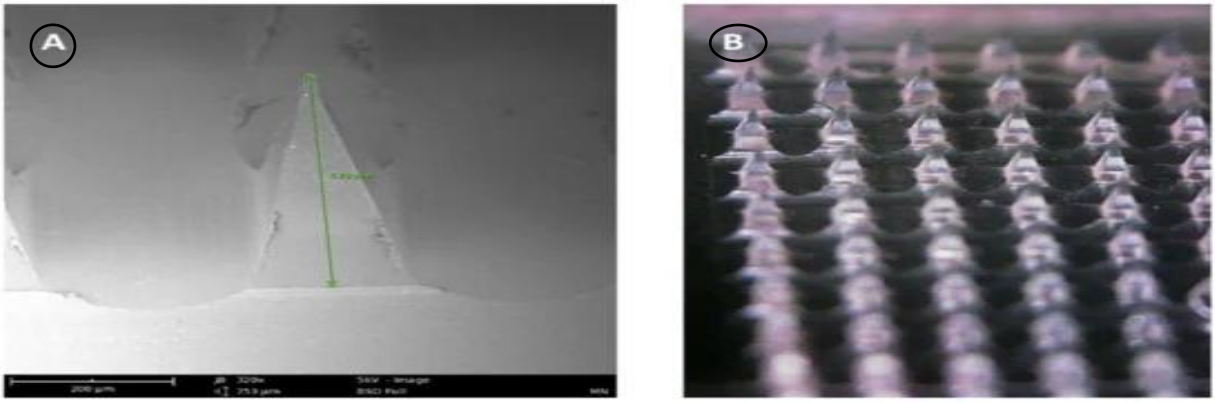


Figure 4. *(**A**) SEM image of a dissolving polymeric microneedle (size: 430 µm, scale 200 µm). (**B**) Optical microscope image of the same microneedle array patch.(reproduced from Pubmed et al.,2021)*

1.5 Transdermal drug delivery System

TDDs are a great substitute for oral-administration methods and hypodermic-injections they offer a number of benefits compared to oral and hypodermic-injections transdermal-drug-administration is more efficient approach to provide medication trans-dermal delivery of medication that's more practical affordable noninvasive painless and self-administered than oral hypodermic injection also avoids the issue of absorbing drug breakdown in the liver or digestive system for patient compliance continuous medication release may also be offered in terms of the diagnosis treatment and prevention of viral infections and diseases for hydrophilic administration medicines and macro-molecules MNs TDDs has increased skin barrier penetration.

In addition to delivering viral MNs TDDs patches vaccine have the potential to provide an different alternative vaccination approach with higher levels of simplicity,immunogenicity,thermostatically,safety,compliance and reduction of sharp waste greater self administration and cost effectiveness capability that might increase distribution of vaccine.[34] there is no doubt that skin has a relatively high level of impermeability and that is a result of the skins two main defensive functions helping to guard against pathogens and preserving the body essential components such as water-by identifying the causes of impermeability this permits the use of skin as a delivery mechanism for carefully regulated TDDs.[35] Transdermal delivery methods encompass any topically applied pharmaceutical formulations whether injected or absorbed that are intended to transport the drug to the general circulation cream and ointment used to be the most frequently used derma-tological methods before topical systems were developed.[36]

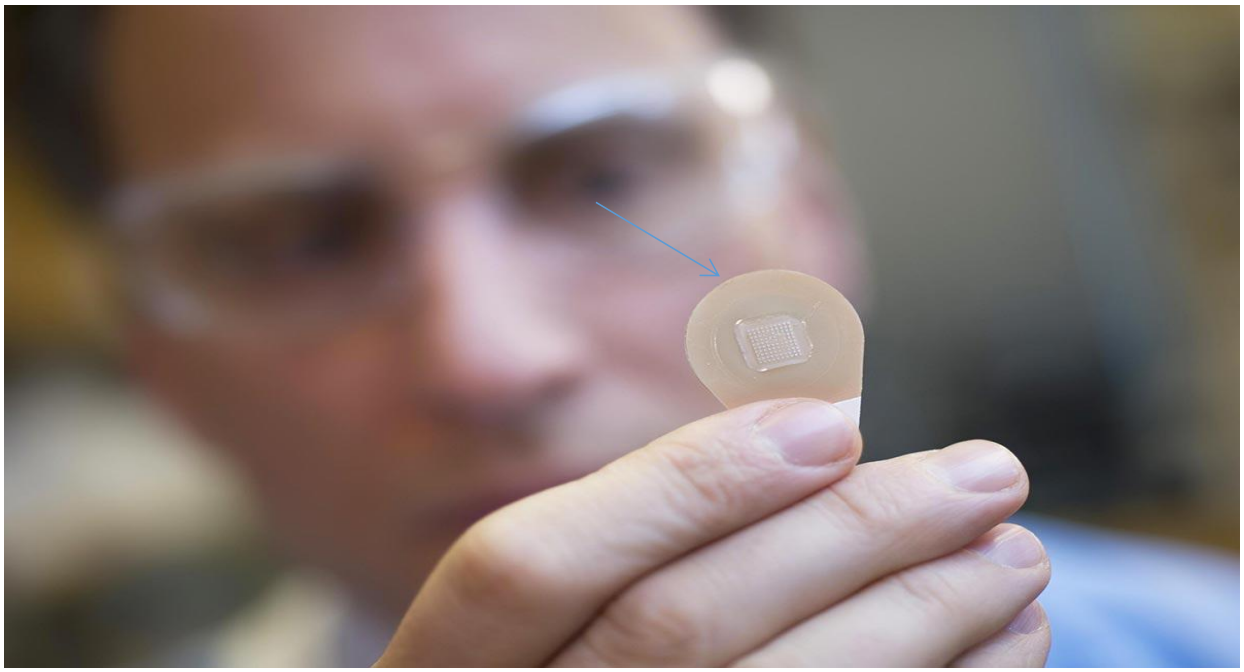


Figure 5. *Microneedle patch Vaccine Delivery System.(reproduced from Dr. Mark Prausnitz et al.,2019)*

CHAPTER-2

AIM & PURPOSE

(OBJECTIVE)

Aim and Purpose

The review focuses on the different types of routes of administration and Microneedle-based Transdermal as targeted drug delivery system for COVID-19 vaccine.The numerous advantages of TDDS of COVID-19 vaccine and development have been highlighted,as well as, other areas of microneedle TDDS positive impact as a modality for improving global health and a large focus of study has been on alternative painless immunization methods,as well as self-administered employing microneedles and easier to distribute as they can be stored at room temperature, unlike current COVID-19 vaccines, which have to be refrigerated.

Finally,the expected challenges to implement such specialized drug delivery for microneedlle of COVID-19 vaccine has been discussed in details with an overview on the ways to overcome such challenges along with the future prospects Microneedles-based Vaccines.

CHAPTER-3

LITERATURE REVIEW

3.1 COVID-19 Vaccination using potential MNs System: Current Challenges and Trends [85]

Global vaccine of mass is urgently important to prevent coronavirus 2019 covid-19 and support the return to pre-pandemic norms mass immunization has shown to be a highly effective method for preventing the spread of many infectious diseases protecting the most vulnerable population groups that are unable to develop immunity such as those with immunodeficiencies or immune systems that are compromised due to underlying medical or incapacitating conditions maintaining the vaccines efficacy transportation and the production of needle waste become crucial problems in attaining worldwide dissemination.Moreover obstacles to effective mass immunization include needle fear and vaccine reluctance in order to achieve the intended aim of vaccinating billions of people in the shortest amount of time feasible the use of dis-solvable microneedles for covid-19 immunization might operate as a significant paradigm change we examine the possibilities of using dis-solvable microneedles for the covid-19 immunization based on the available literature in order to address these problems.

3.2 MILD Microneedle Patterns for COVID-19 Vaccination and Decentralized Information Storage. [65]

In this study a smart mushroom imprinted by inspiration lightly detachable mild MN platform was created for the decentralized storage of vaccination data efficient practical distribution of multi-dose coronavirus vaccines without causing systemic toxicity or local harm the mild system generated a significant amount of anti-bodies against coronavirus receptor-binding domain RBD in vivo it could aid in stopping the spread of covid-19 or its comeback.

3.3 Separable Microneedle Patch for COVID-19 DNA Nanovaccine Protection and Delivery. [61]

Vaccine creation as well as their storage delivery and administration are all essential good management coronavirus disease 2019 covid-19 pandemic a nucleic acid vaccine should ideally be administered directly to the appropriate immune cells or tissue such as lymph nodes nevertheless currently available vaccinations are often administered intramuscularly where immune cells are not typically found current nucleic acid vaccines must be kept refrigerated which may make it difficult for them to be used in impoverished nations in this article we present a separable microneedle SMN patch for the effective delivery of polymer-encapsulated spike or nucleocapsid protein expressing DNA vaccines and immune adjustment in contrast to intramuscular injection.

3.4 COVID-19 Vaccine Routes Delivery: Review [38-47]

Millions of people have died as a result of the covid-19 epidemic caused by the new coronavirus sars-cov-2 there are several vaccine options that have been developed to eliminate sars-cov-2 and stop new infections together with conventional subunit vaccinations and attenuated or inactivated viral vaccines these vaccines also contain nucleic acid and viral vector vaccines the distribution of vaccines is restricted to intramuscular injection in contrast to the platform technologys versatility mucosal vaccination could boost the local immune responses that stop the spread of infections even though intramuscular immunization is secure and efficient nevertheless only intramuscular injections have been used because of a lack of knowledge about mucosal immunity and the urgent need for a covid-19 vaccine the history of vaccinations is outlined in this overview.sars-cov-2 a new virus that produces COVID -19 pandemic that has claimed millions of lives we review vaccine history coronavirus developing

vaccine technology and status intranasal coronavirus vaccinations in order to eradicate SARS-CoV-2 and prevent it from spreading future studies should identify the platform-based vaccine delivery method that is the most efficient as well as the processes underlying the efficacy of various methods.

CHAPTER-4

METHOD & MATERIALS

(METHODOLOGY)

Methodology

Using secondary-research techniques, such as articles from journals, literature review articles on Covid-19 vaccine, microneedle transdermal delivery, and vaccination mode of administration were analyzed for this study.The articles were double-checked by doing searches across a variety of articles, including Researchgate, Nature, ScienceDirect, PubMed, SpringerLink, Elsevier,PJCB and NIH,etc.

Information and data for this study were gathered between 2019-2023 from a variety of articles, sources, and journals, and their findings helped to identify varied clinical data that might be important in the future of this Covid-19 vaccine.All the Figure data and analysis are done by Microsoft Word/Excel,Canva and picsart applications to make the working process easy.

CHAPTER-5

RESULT & DISCUSSION

5.1 COVID -19 vaccine route of administration and formulation

Table 3.Routes of administration of COVID-19 vaccine types and examples with Companies developed those Vaccines. [38-47]

Type of Route	Vaccine Name	Development	How Effective	Company	Ref.
Oral	Valxart (VXRT)	Phase-II Clinical Trail	50%	California biotechcompany Vaxart	[40]
	CONVIDECIA	Developed	92%	CanSino Biologics,China	[44]
Mucosal	Oral or Nasal	-	-	-	
Parenteral	AstranZeneca	Developed	60-90%	Oxford Uni-AstranZeneca,UK	[38]
	Pfizer-BioNTech	Developed	95%	Pfizer-BioNTech USA/Germany	[38]
Intranasal	COVI-VAC (CDX-005AC)	Phase-II Trail (Phosphate-buffered saline)	50%	Codagenix,USA	[46]
	iNCOVACC (BBV154)	Developed	99%	Bharat Biotch's,India	[47]

5.1.1 Discussion:

5.1.1 Parenteral Route

The parenteral-route is a term that describes liquid administration such as sustenance or drugs outside of the git despite the fact that it is intrusive this is the most often used method of delivering antibodies many parenteral-immunization regimens include intradermal,subcutaneous and intramuscular covid-19 vaccinations had previously been administered by IM and SC routes a report has detailed a test that was conducted on a mouse administering the injectable SARS vaccination to four applicants.[37] The experiment's outcomes, they said, were rather outstanding since they demonstrated that all four vaccinations could produce antibodies and protect against infection of SARS.Despite being protected, there were instances of hypersensitivity to the vaccine's ingredients.Nevertheless, an experiment was carried out on a different animal to show how IM and SC infusions of a recombinant antibody showing full length S glycoprotein of MERS COV could be controlled.WHO had recommended AstranZeneca and Pfizer-BioNTech vaccines to prevent COVI-19 in adults.Currently,available for use in hundreds of countries.[38] Mice were monitored for virus-specific antibodies and CD8+ T-cells, illustrating how effective the provided vaccination. [39]

5.1.2 Oral Route

An oral-route involves administering drugs directly through mouth or through the GIT to be bsorbed in the systemic circulation.A small startup company in the United-States and a small start-up firm in the United Kingdom developed two new formulations for the SARS-CoV-2 vaccine (Vector Adjuvant-Atigen) Standardized Technology (Valxart's VAAST) platform has been used to create COVID-19 vaccine, as well as, a tablet-based version of it,for example,vaccines made by ‘’Vaxart’’ are intended to be taken as tablets, which may be kept at room temperature and delivered without the danger of a needle stick that’s being developed by

(California biotech company Vaxart).It may be possible to avoid the distribution and staffing problems that arise from parenteral formulation by using tablets.It would be more therapeutic if comfort was removed during administration.[40] Hence, the primary mediators of protection at this early stage may be SARS-CoV-2 vaccine-induced CD8+ T cells.Total IgG levels and antibody titers in as a result of the growth of CD4+ and CD8+ antigen-dependent cells, animal models have increased. The Vaxart candidate met tow endpoints (Primary and Secondary) in the early clinical study;objectives for safety and immunogenicity.Immediately following prime immunization, bnt162b2 vaccination strongly produces a long-lasting spike-specific CD8+ T-cell response.[41]. According to a research by Peng et al., the majority of COVID-19 survivors had robust and widespread COVID-19 specific T-cell responses.In addition, the finding of T-cells specific for the original SARS-CoV nucleoprotein in patients years after infection underlines possible contribution of T-cells to the development of long-lasting immunity against the virus.Previous research,shown the majority of (CD8+) T-cells in study targeted epitopes generated from internal and/or non-structural viral proteins as part of the T cell response against the whole COVID-19 proteome.[42] In addition, antigens generated from NSPs made over half of the high-prevalence response hits observed for each HLA. There were found to be 12 very frequent SARS-CoV-2-specific CD8+ T cell responses in total, several of which overlapped with the immunodominant peptides found by other researchers.[43] CD8+cytotoxic T-cell responses to S and N antigens have been especially noteworthy -responsible for long-lasting cross-reactive immunity.Both a protective response of anti-body and a Th1-dominant T-cell response in the macaques' antibodies and T-cell responses. On the other hand, the animal upper respiratory systems were shown to be quite resilient. The hAd5 vector's ability to be used to deliver formulated adenovirus immunity is a crucial aspect of it as well.The hAd5 vector's ability to be used to provide both initial, unformed viral immunization and constructed adenovirus immunity is an important additional feature.All individuals had

significantly higher levels of mucosal homing receptor expression and plasma B-cells, which activated the system of B-cell and produced pro inflammatory Th1 cytokines as well as IgA in the blood. IosBio Pharma (UK) decided to use the OraProTM technology to create a COVID-19 vaccine such as 'CONVIDECIA' that is effective 92% effective against COVID-19 By using a viral-injection into animals bodies an administering injections through their lips sars-cov2 was multiplied in the animals. A research study has authorized the use of the booster 'CONVIDECIA' air-vaccine which is inhaled via the mouth.[44]

5.1.3 Intranasal Route

It is a kind of mucosal immunization that goes after the respiratory system, which serves as the main point of entry for several respiratory viruses, including COVID-19's cause, SARS-CoV-2.SARS-CoV-2 often penetrates our nostrils where it comes into contact with the abundantly present protein ACE2 in our nasal passages. The virus enters our cells through the ACE2 protein.In preclinical and clinical studies, nasal vaccines have shown encouraging outcomes, particularly for respiratory COVID-19. Here are some of the explanations for why the SARS-CoV-2 intranasal (IN) vaccination works better:

i. In addition of protecting sars-cov2 a nasal-dose also prevents the spread of pathogen by fostering a special immune type that largely exist in the nasal and pharyngeal lining cells.

ii. Immune cells are specifically targeted by the vaccine in nose in mucosal membrane and tissue resulting at mucosal as well systemic immunity in many targets of body such as intestine and lungs hence nasal vaccine is more efficient protecting huge populations versus the lethal virus and avoiding the onset of even minor symptoms.

A live attenuated vaccine known as COVIVAC has just finished its first phase of testing. It is designed to protect against various types of SARS-CoV-2 proteins and different strains of the virus. It is administered in a single dose. In a study, the researchers noted that the intranasal vaccine significantly stimulated the CD4+ and CD8+ T cells in the lungs of mice. The results of the study suggest that the intranasal route could provide additional protection against COVID-19.[46] After the Indian drug regulator gave it the go-ahead for a two-dose primary immunization of those aged 18 and over Bharat biotech COVID-19 vaccine candidate codenamed bbv154 which has since been renamed INOVACC received emergency use authorization EUA EUA making it the first intranasal COVID-19 vaccination in history.[47] After years of development by the university of Utrecht's SARS-COV-2 intranasal vaccine to protect patients from covid-19 the first phase of the bbv154 clinical investigation has begun it has been proven safe to use a Newcastle disease virus NVD vector to generate the sars-cov-2 immunogenic spike-protein a crucial target to neutralizing anti-bodies of vaccine for intra-nasal delivery in animals including non-human primates the OMV outer membrane vesicle and recombinant-spike-protein COVID-19 technology are used by several dutch organizations involved in vaccine research including intravaccinitiatives in their nasal spray vaccine however experts believe that intranasal immunization is a superior method of administering the SARS vaccine.[48]

5.1.4 Mucosal Route

Vaccination against COVID-19 be necessary to encourage privilege at the mucosal and fundamental levels in addition to advancing mucosal justification answers immunization against COVID-19 can improve integral privilege successful stimulation of mucosal responses COVID-19 vaccines aim for fear that introduction of the bug into the mucosal coating by too soon encouraging a mucosal invulnerable reaction getting the substance

released-located COVID-19 vaacine is frequently named bacterial exemption by way of allure energy-pushing possessions.

So far, in accordance with dispassionate troubles population typically polluted accompanying SARS-COV-2 produce mucosal IgG antibodies such as slaver nasal clean wash or bronchoalveolar cleaning fluid in addition to intrinsic IgG antibodies.Further, t assistant th1- and th2 containers and IgA-exchanged b containers are still stimulated swiftly later primary contact tween sars-cov-2 and the hosts exemption.[49] a total humoral invulnerable was inferred even though it was smaller-lived subsequently intranasal immunization in addition to much better local humoral and cytotoxic t-container answers skilled were more considerably substantial integral and local humoral and cytotoxic t-container answers apart from that studies into covid-19 contamination had told that the safeguard measures selected were corresponding to those likely by an injectable immunization vaccine greater levels of mucosal IgA and antitoxin agent for negating the effect of an infection or poison titers were belonging to taller mucosal IgA concentrations because of allure raised security and skill to offer two together mucosal and intrinsic guardianship.[50] The development and confirmation of mucosal vaccines against SARS-CoV-2 are extremely challenging.As a result, they are capable of triggering stable, protective immune responses locally at the sites of pathogenic infections.In the past 10 years, mucosal pathogens have remained a major cause of mortality and morbidity in various infectious diseases.It would be possible to develop effective mucosal vaccines against SARS-CoV-2 using the mucosal vaccine platforms for SARS and Middle East respiratory syndrome.In addition to humoral correlates of protection, cellular correlates are related to different vaccination goals, such as prevention of mucosal or systemic infection.[51] bAs the mucosal immune system

serves as the host's first line of defense against infectious pathogens, activating it help stop the spread of SARS-CoV-2.[52]

5.1.5 COVID-19 Vaccine Doses administrated worldwide as of March,2023 per Country.(The highest 20 vaccinated countries). [53]

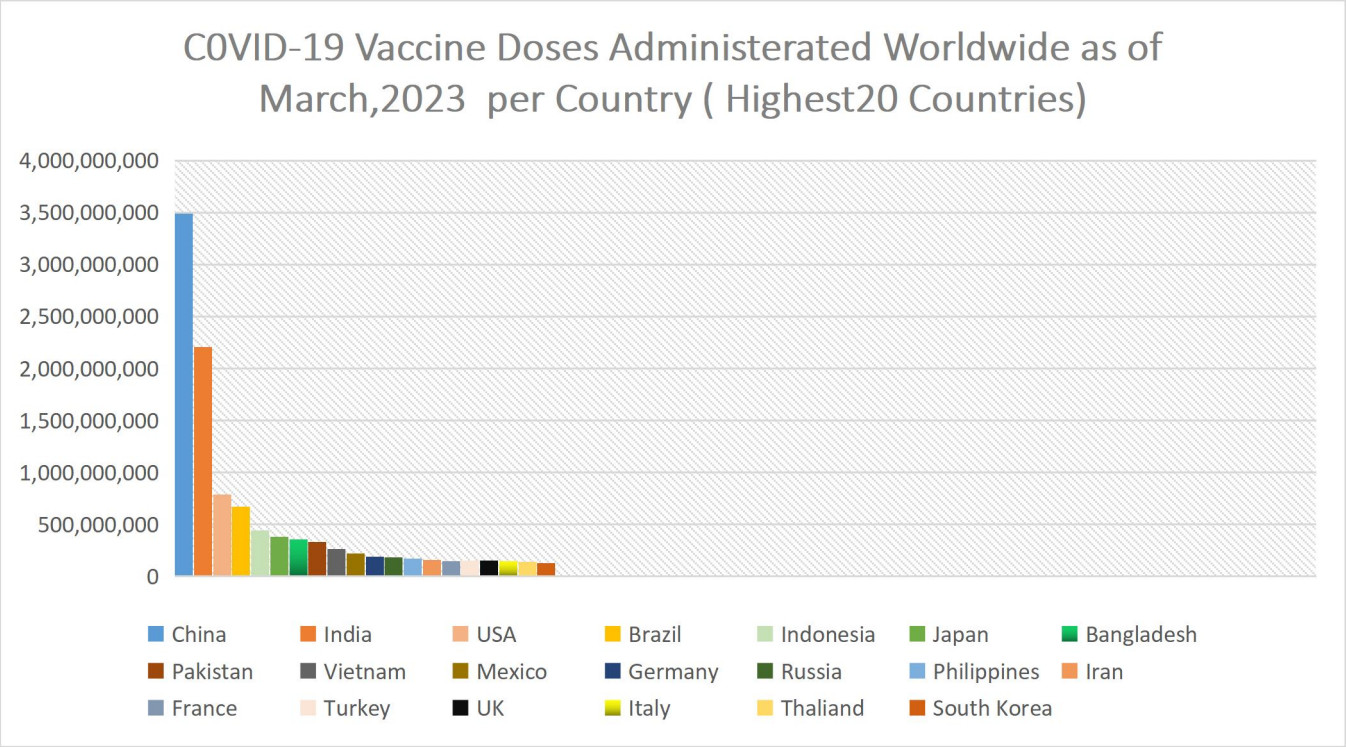


Figure 6.*COVID-19 Vaccination Doses Worldwide as of 2023. (reproduced from Statista et al.,2023)*

5.1.5.1 Discussion:

As of (2023), above infographic shows the data of coronvirus vaccination of individuals that have received at-least one-dose of (IM) vaccine.Mainland China had the highest vaccine received doses of 3,491,077,000.This country was followed by India(2,206,407,392),USA (672,076,105),Brazil (785,279,135),Indonesia (444,303,130),Japan (382,415,648),Bangladesh (355,143,411),Pakistan (333,759,565),Vietnam (266,252,632),Mexico (223,158,993),Germany (192,141,642),Russia (185,755,859),Philippines had -received 170,545,638 doses of population, was followed by Iran

(157,785,811), France (145,339,955), Turkey(152,543,341),UK (151,248,820), Italy (143,812,381), Thailand (142,635,014), South Korea (129,647,782).

5.2 COVID-19 Vaccines Doses Latest Update of 2023 Globally

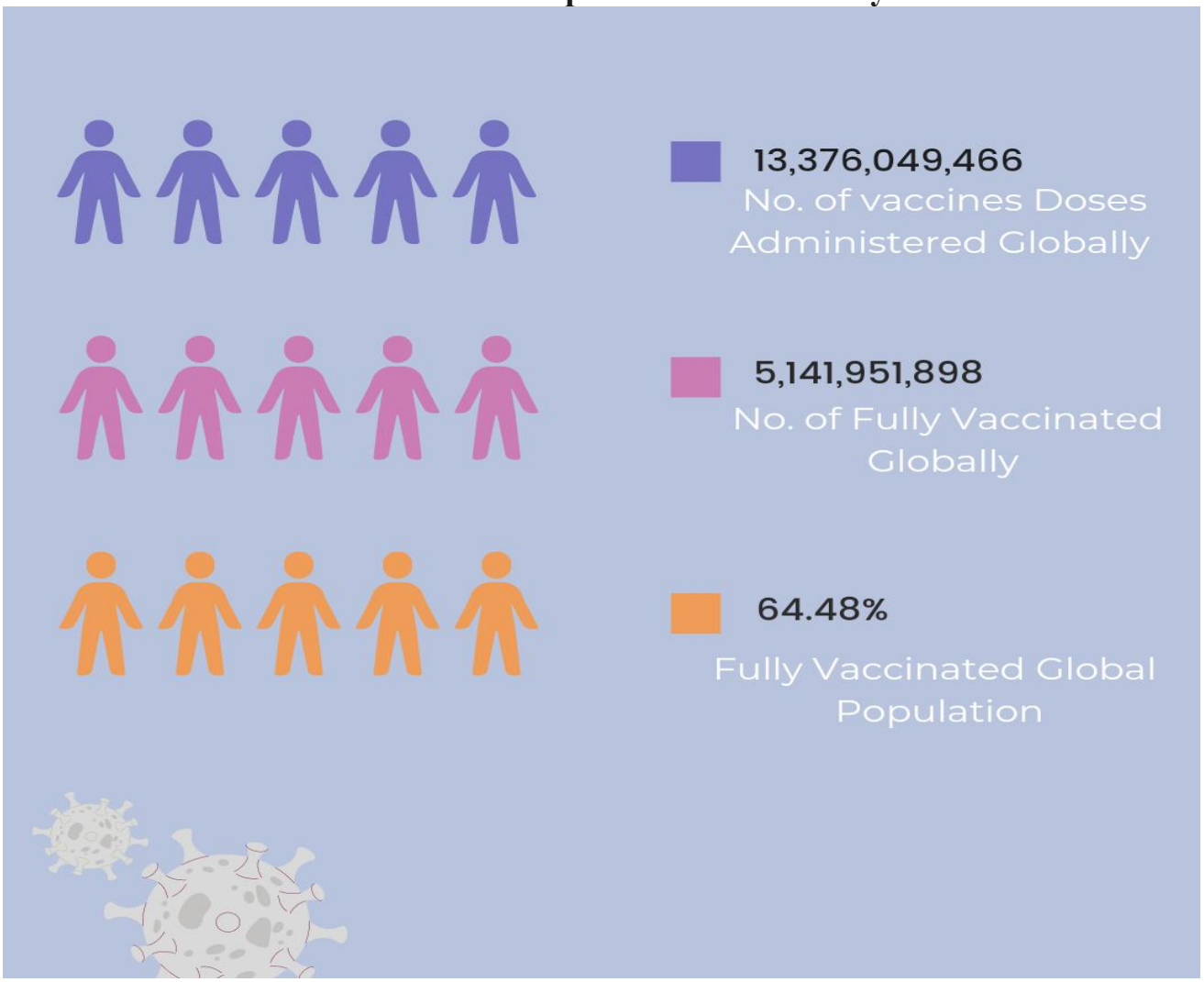


Figure 7.*COVID-19 Vaccines Doses Latest Update of 2023 Globally.(reproduced from Global Data et al.,2023)*

5.2.1 Discussion:

Above (Figure 7) shows the latest C0VID-19 vaccine updates and doses globally.13,376,701,083 are total number of vaccine-doses administrated-globally,while individuals who had fully-vaccinated (at -least 3 doses) globally estimated of 5,142,176,77. 64.48% of population worldwide had fully-received vaccination of corona virus.[54]

5.2.2 COVID-19 Vaccination by Continent

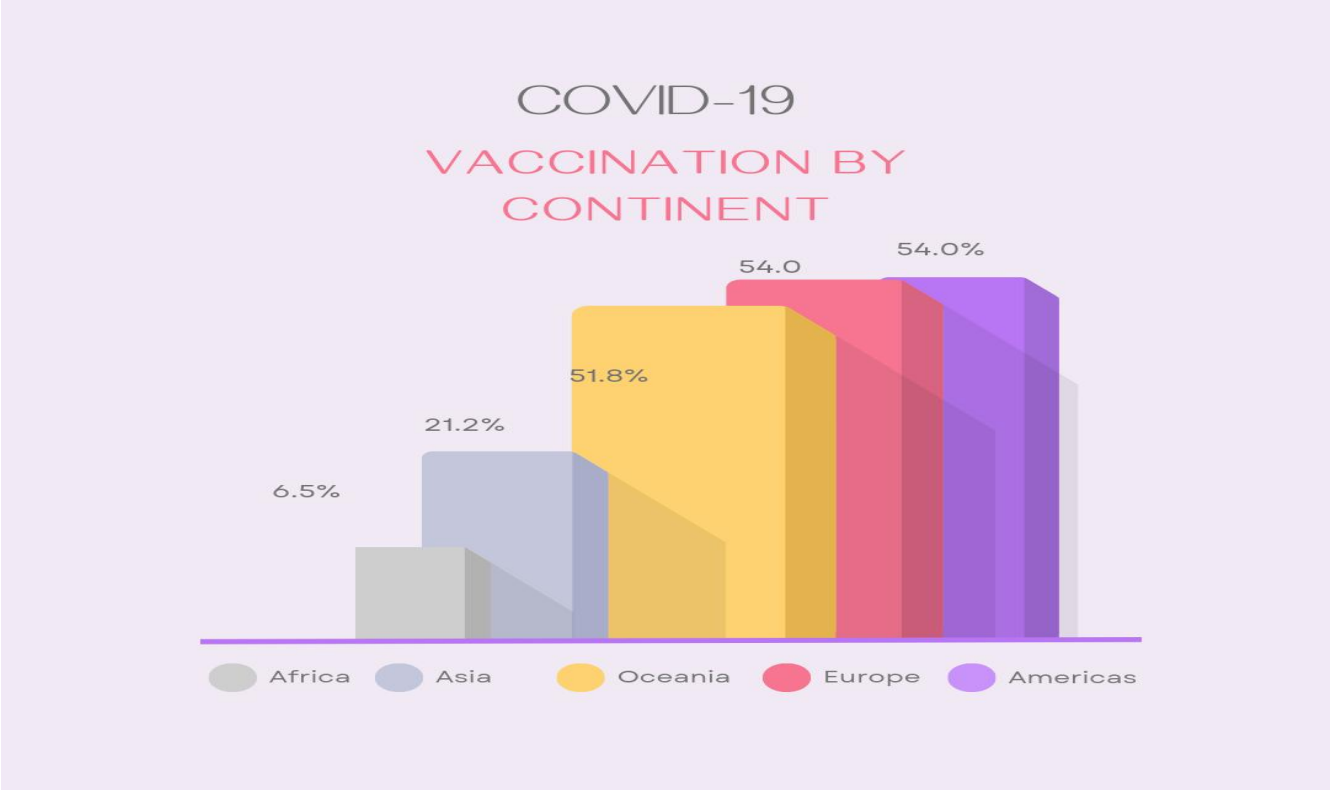


Figure 8.*COVID-19 Vaccination by Continent. (reproduced from Global Data et al.,2023)*

5.2.3 Discussion:

Figure 8 infographic shows cumulative vaccine of corona virus worldwide by individuals only those who are fully vaccinated worldwide, respectively.

The estimated-vaccination in Africa is the 'lowest' among all continents of 6.5% of the population.While percentages are almost equal through out Americas and Europe of 54.0%,which is the highest.There is a slightly less percentage in Oceania 51.8%.About 21.2% of all Asian have received a full vaccine of corona virus.[54]

5.3 History of Microneedle

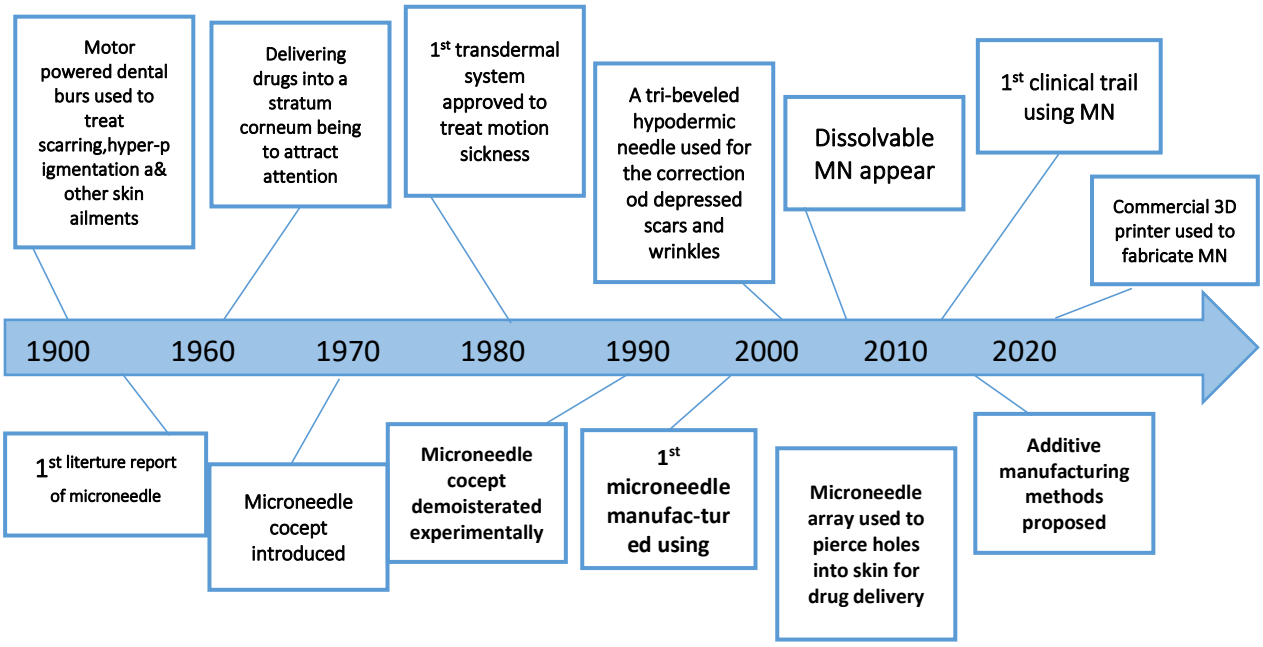


Figure 9. *Historic timeline for MN technologies.(reproduced from Faisal Aldawood et al.,2021)*

5.3.1Discussion:

Microneedle conceptions have developed over time, moving from the usage of big needles to the current modern design.(Figure 1) German dermatologist Dr. Ernst Kromayer used various-sized motorized dental burs to treat hyperpigmentation, scarring, and other skin conditions in 1905.In 1921, Chambers published the first piece of literature mentioning the use of microneedles, describing how he put the needle into the nucleus of an egg.[53] Drug injection into the stratum corneum started to gain attention in the 1960s. Then, in the 1970s, the microneedle notion was proposed; nevertheless, it wasn't until the 1990s that this concept was actually tested. The first transdermal device was authorized for use in 1979 to distribute scopolamine through the use of a three-day patch in order to cure motion sickness. In order to cut through fibrous tissue, Orentreich used a tri-beveled hypodermic needle during a subcision procedure in 1994. The cutaneous abnormalities under the skin that caused wrinkles and depressed scars were the focus of this procedure.[54] In 1998, a silicon wafer was used to produce the first microneedle for transdermal

distribution using ion etching and photo lithography. The study explained how to improve medication distribution through the skin by using microfabricated microneedles. The microneedle field has undergone substantial investigation as a result of this work. To create microneedles, several materials like glass, ceramic, metal, and polymers were used. A microneedle array was utilized in 2004 to puncture holes in the skin for transdermal medication administration, which sparked interest in a number of production techniques and materials. MNs can be classified as solid, coated, hollow, soluble, or hydrogel-forming.[55] A microneedle array was utilized in 2004 to puncture holes in the skin for transdermal medication administration, which sparked interest in a number of production techniques and materials. MNs can be classified as solid, coated, hollow, soluble, or hydrogel-forming. Many production techniques, such as photolithography, micro-injection molding, laser ablation, etc. Because to these results, the first accounts of the use of a dissolvable microneedle for TDD appeared in 2005.[56] Recently,New study published in ACS Nano describes the development of a microneedle patch that administers the COVID-19 DNA vaccine to the skin and triggers potent immune responses in mice and cells. The patch may be kept at room temperature for more than 30 days, which is significant.[57]

5.3.2 Microneedles in Transdermal Drug and Vaccine Delivery System

Microneedle (MN) delivery-system are a platform for transdermal-drug-delivery which allow drugs to-be delivered painlessly, non-invasively, and safely into the skin.Microneedles may have a single needle or an array that consist of micron size, containing hundreds or even thousands of micro-projections with a length up to 2 mm, a diameter up to hundreds microns, linked-to a base support.[58] As MNs-dissolve in the skin, microneedle patches reduce sharps waste.[59] Moreover, microneedle patches do not generate biohazardous sharps waste, cannot become infected with bacteria, and can be formulated to be thermostable.[60] Trans-dermal drug -delivery -system (TDDS) is a delivery method that attaches to the skin and delivers the drug directly through the skin. MN technology depends on a mode of active transdermal drug delivery and is intended to

be used a as a replacement to the traditional syringe injections.Clinical studies have demonstrated that vaccinations with microneedle patches save doses.[61] Recently, a first-in-human clinical experiment was done to assess the efficacy of a dissolvable microneedle patch versus an intramuscular injection of inactivated influenza vaccine. The results showed that the dissolvable microneedle patch had a more strong antibody response and improved acceptability.[62][63] The majority of vaccinations delivered through hypodermic needle and syringe injection must be administered by a qualified healthcare professional. Whereas microneedle patch vaccination permits administration by staff with no training, including self-administration, which might significantly speed up roll-out and diffusion as well as lessen the strain on the healthcare system and painless with self- administration.Therefore,microneedle patches are more preferable than intermascular injections.The MERS-CoV-S1 vaccinations produced greater humoral and IgG responses than those from conventional needle injections and subcutaneous injection.[64] According to a clinical study of Kuwentrai et al.microneedle patches were successfully designed by dissolving a mixture of low-molecular weight hyaluronic acid (HA) and receptor-binding domain (RBD) utilizing a micro-molding process, together with an adjuvant of aluminum hydroxide gel,this clinical trial discovered that specific B-cell antibodies and INF-T-cell responses persisted for up to 97 days following delivery, although having more variance in antibody titers than subcutaneous injection.[65] It employs several tiny projections from a plate to transport a vaccine to the skin through a patch, resulting in the administration of an antigen without discomfort and a greater immune response. It creates non-invasive antibodies when used to immunize against COVID-19. When linings and dissolving microneedles are utilized, it's probable that the cost of immunizations administered in a dry environment may rise.It uses multiple microscopic projections from a plate to deliver a vaccine to the skin through a patch for painless antigen delivery with superior immune-response.Using it for COVID-19 vaccination produces antibodies that are not invasive.It is possible that the price of

vaccinations provided in a dry environment will increase because linings and dissolving microneedles are used.[66] Due to these factors, consideration was given to alternative vaccine administration delivery strategies which offer a significant potential to increase immunization internationally and save a lot of lives when used for COVID-19.[67] Microneedles produce findings that are extremely precise, repeatable, and bio available over a wide range of subjects. It offers a lot of benefits, but it also has some drawbacks. Sensitive skin may get irritated or have an allergy. As microneedles are more smaller and thinner than human hair, they are more prone to breaking, which might lead to difficulties if they remain within the skin. These restrictions are quite uncommon and can be circumvented by using sophisticated microneedle material. For example, a team of microbiologists and chemical engineers of The University of North Carolina at Chapel Hill continues to innovate by formulating RNA vaccines, like the Pfizer and Moderna COVID-19 vaccines, into microneedle patches for testing.This strategy has recently been changed to include a greater number of projections that are closely packed and have a smaller diameter than typical microneedles. By more precisely focusing on the antigen-presenting cells, these projections are less likely to result in immune cells dying.The HexaPro vaccination patch, for instance, is made up of 5,000 solid tiny projections spaced out over a 1 square centimeter patch. The study's findings previously demonstrated that mice who received the HexaPro protein subunit vaccine candidate through this skin patch were protected against COVID-19.

Microneedles come in a variety of shapes and sizes, including solid, coated, dissolving, and hollow needles.[68]

Table 4. Advantages of dis-solvable microneedle patch vaccine for corona virus 2019 (COVID-19). [68]

	Microneedle Patch for COVID-19 Vaccination
1.	Pain-free and micro size
2.	Reduction in vaccination wastage
3.	Reduced risk of sharps injury and contamination
4.	Increased acceptance and less hesitancy
5.	Less reliance on cold chain
6.	Avoidance of reconstitution
7.	Self-administration and reduced need for healthcare workforce
8.	Reduced risk of sharps injury and contamination
9.	Faster virus clearance

5.3.3 Main Types of MNs

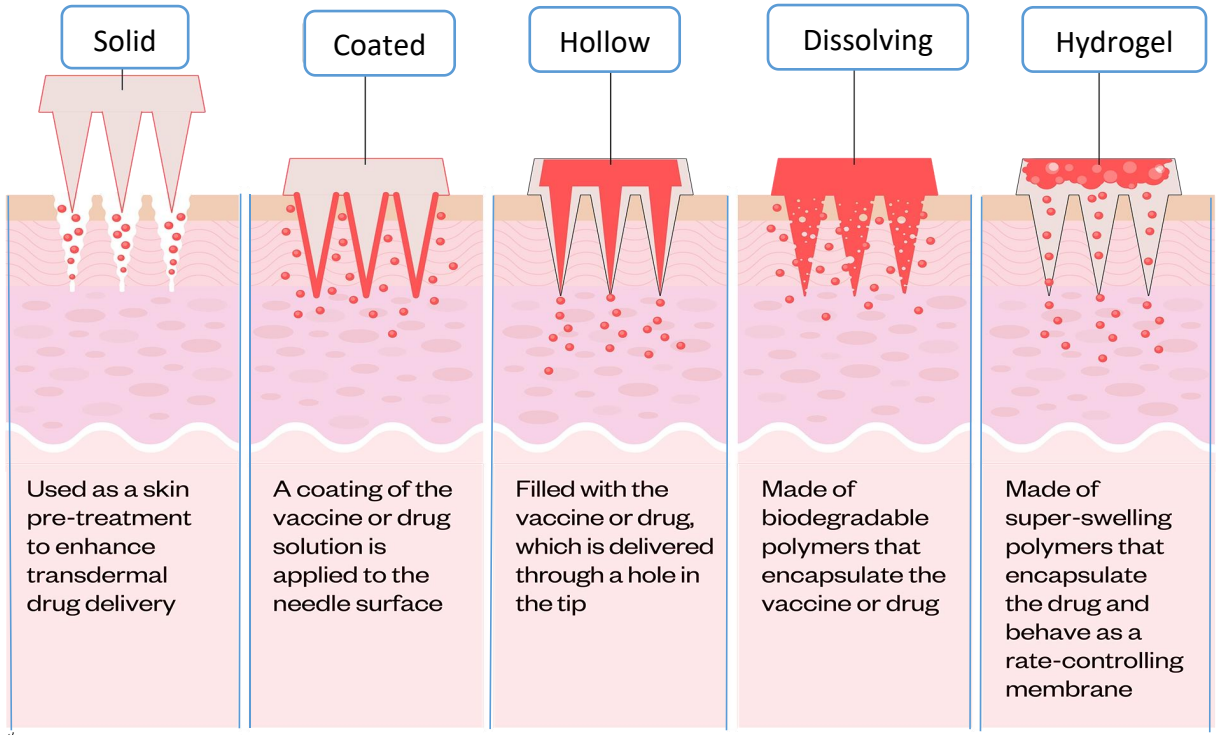


Figure 10.*Five main types of Microneedle.(reproduced from Advanced Drug Delivery Reviews et al.,2015)*

5.3.3.1 Discussion:

5.3.3.1.1 Coated Microneedles

Coated-MNs are one of these methods which is appealing for quick bolus delivery-system high molecular weight compounds into the skin and may be used as a straightforward "Band-Aid"-like device for self-administration. Moreover, keeping medications as a coating on microneedles in a solid phase may improve their long-term stability, even at ambient temperature. Desmopressin coated onto microneedles retained (98%) integrity after 6 months of storage under nitrogen at room temperature, which was in line with this expectation.[70] The technique of micro needling determines the type of coating that is used; either a variety of ways or being "dipped" in the coating are possible. If you want, a spray-on coating can be-applied to needles. Microneedles that are hollow, solid, and in dissolving form appear to be used less frequently than those that are coated with an inert material or have no coating at all.[71] The

researchers used DNA sequences encoding either the SARS-CoV-2 spike protein or the nucleocapsid protein on the surface of non-toxic nanoparticles to create microneedle-based delivery systems. A chemical called an adjuvant, which aids in triggering an immunological response, was included within the nanoparticles. The vaccine nanoparticles were then applied on a coated microneedle patch by the researchers. A hundred painless biodegradable microneedles, each less than one-tenth the size of a bee stinger, were distributed around the small rectangular patch.The technique was tested in mice, and results showed that the spike-protein-encoding microneedle patch strongly induced antibody and T-cell responses without causing any discernible negative effects. The vaccination patches may be a useful tool since they may be kept at room temperature for at least 30 days without losing their effectiveness to develop COVID-19 vaccine globally.[72]

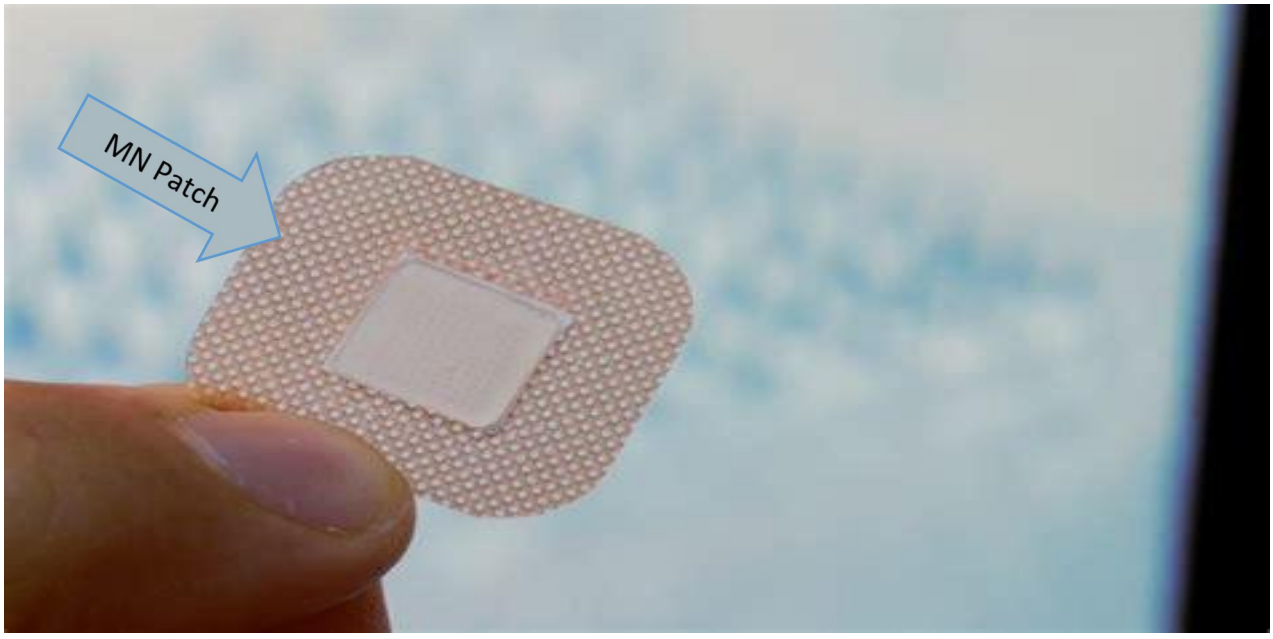


Fig 11.*New vaccine formulations and delivery methods such as vaccine-coated microneedle patches could provide an improved protective response, which would be of particular benefit to those at high risk of related complications. Georgia Tech/Gary Meek.(reproduced from Staff et al.,2023)*

5.3.3.1.2 Hollow Microneedles

Hollow microneedles HMNs which are smaller counterparts of conventional hypodermic needles are used in similar procedures hollow microneedles are utilized to give drugs which causes a liquid formulation to flow under pressure due to their form and fragility hollow microneedles are more difficult to produce than other needle kinds even yet hollow microneedles are more effective than other types of microneedles for dispersing greater more frequent dosages of active substances [73]

5.3.3.1.3 Solid Microneedles

In order to distribute drugs transdermally, solid microneedles (SMNs) must first be put to the skin and then removed, creating microchannels. Thereafter, either a standard drug formulation or a transdermal drug patch must be applied. Poke and patch is the name of this strategy.Unlike coated microneedles (CMNs) or dissolving microneedles, SMNs are technically straightforward to distribute and do not require drug coating or encapsulation (DMNs). Via passive diffusion through the made-up microchannels, the drug permeates from the formulation. Delivery using SMNs is effective for topical semisolid dose forms such lotion, cream, gel, and ointment.for example, Derma-stamp, Dermapen, Dermaroller, and similar devices to pretreat the skin before applying collagen, serum, acne medication, or other cosmetic products. SMN can be used for the delivery of-vaccines, small molecules, biotherapeutic agents for COVID-19 vaccination.[74]

5.3.3.1.4 Advantages of Dissolving Microneedles

Figure 12. *Dissolvabe MNs for coronavirus "Advantages" (reproduced from Deng.L,Chang t.z et al.,2022)*

5.3.3.1.4 Discussion:

A painless and less invasive self-administration tool is the dissolving microneedle (DMN). Although the patch size for DMN has risen, it is still challenging to apply it to large or curved portions of skin because of skin deformation.Traditionally, drugs are encapsulated in

biodegradable polymers to create dissolving microneedles.Once the needle has pierced the stratum corneum, the polymer that forms the needle's architecture breaks, releasing the medication that was contained inside.As a result of the way they work—they dissolve after being inserted—dissolving microneedles are able to address a number of problems with solid microneedles. The advantage of having microneedles that dissolve beneath the skin is that it effectively lowers the possibility of post-application damage brought on by needle sticks.treatment by MNs has grown to be a highly common successful and promising method of drug delivery by a number of experiments researchers have successfully demonstrated the viability of vaccination DMNs recent DMNs have garnered importance of covid-19 vaccine because by factors shown in figure 14 researchers are enthusiastic about employing DMNs for mass immunization against covid-19.[75]

5.3.3.1.5 Hydrogel Microneedles

Cross-linked polymers that produce hydrogel MNs are primarily impacted by swelling index, molecular weight, and the presence of a foaming agent. The transdermal route of medication administration is impacted by a number of factors. There are no restrictions on the inclusion of different sorts of medications in this kind of microneedle. Employed a highly swell-able polymer in the microneedle infrastructure to pioneer this technique . Although the array doesn't really contain any drugs, when it penetrates the skin, they are absorbed. Fluid withdrawal rates in 1 hour were from 0.9 to 2.7 L, which is on par with interstitial fluid removal rates for hollow MNs and microdialysi.The hydro-gel MN can be used to circumvent the drawbacks of traditional microarray approaches, which include reduced drug loading capacity, accurate drug coating, and control over the degree of release. It offers potential tuning advantages by enabling the fabrication of hydrogel-loaded microneedles in the right form and size (Figure 10), which are simple to sterilize. A hydrogel-based microneedle is a flexible tool that may be loaded with a variety of medications with variable therapeutic windows for more

individualized treatment choices. This microneedle treatment is utilized to monitor or measure drug substances in addition to the sustained release of metformin HCl for 24 hours.[76]

5.4 Mechanism of Delivery System through Microneedle

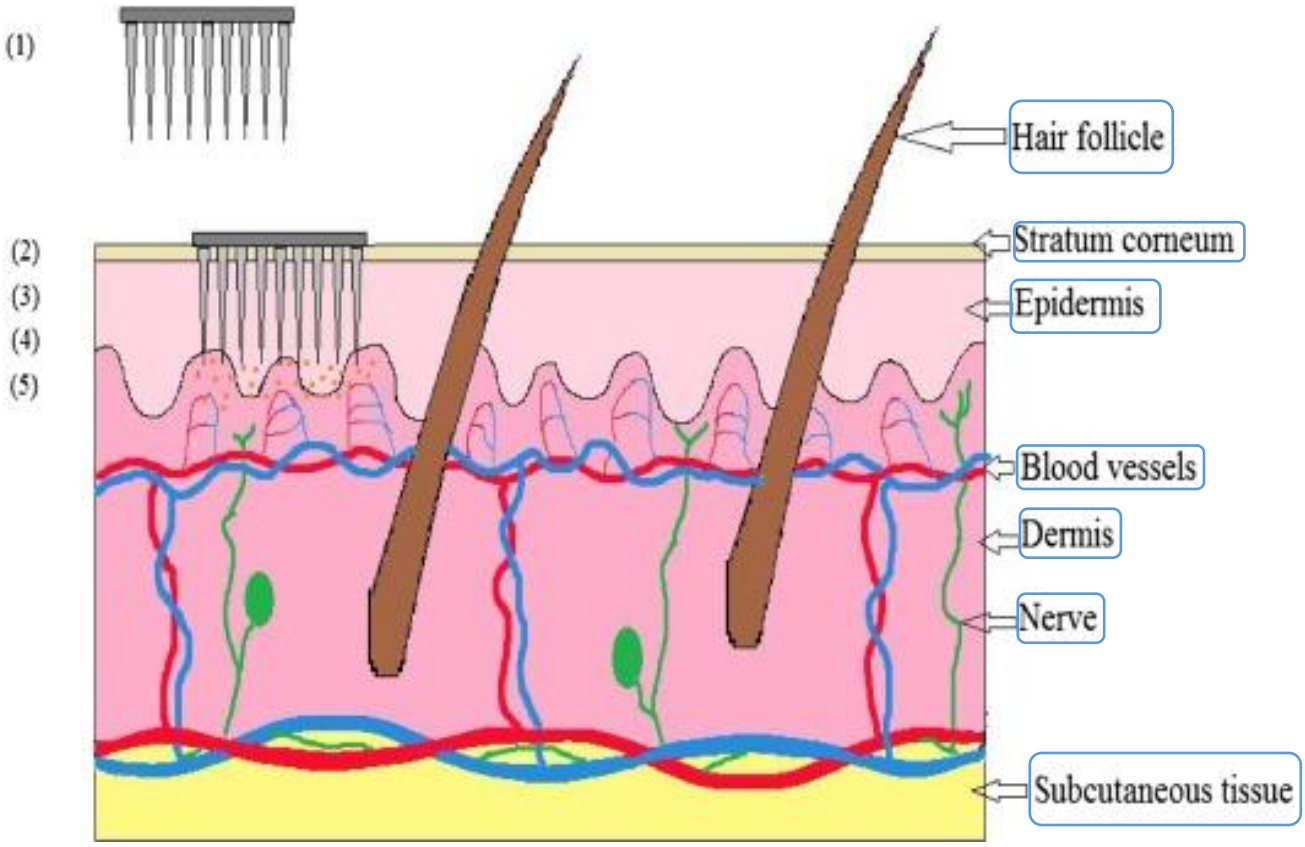


Figure 13.*Mechanism of drug delivery by microneedle device: (1) Microneedle device with drug solution; (2) Device inserted into the skin; (3) Temporary mechanical disruption of the skin; (4) Releasing the drug in the epidermis; (5) Transport of drug to the site of action.(reproduced from Tejashree Waghula et al.,2021)*

5.4.1 Discussion:

In this process, the skin is temporarily disrupted and the drug is injected into the epidermis.In this way, it can deliver its effect more quickly.In a similar manner to a patch, the MNs that are encapsulated with biomolecules are inserted into the skin, releasing nitroglycerine within minutes. These MNs do not need to be removed, nor do they release any toxic substances residue remains on the skin Since the needles are made of biodegradable material, hundreds of

MNs cover the small area that penetrates the skin and ensures the drug crosses essential barriers The small needles are clustered together to ensure the patient receives enough of the drug to achieve the desired therapeutic effect [77] as shown in Figure 13.

5.5 Fabrication of Microneedle (Materials and Proprieties)

Much progress has been made in MNs technology during the past ten years. Fabricating MNs involves the widespread use of a wide range of materials, including metals and polymers.[78] The ideal qualities of the materials used in the fabrication must include their compatibility, user-friendliness, non-corrosiveness, ease of availability, and high mechanical and tensile strengths, improving their acceptability and efficacy.[79] The most popular material utilized to create MNs in the 1990s was silicon. The first MN made of silicon is used to administer the medication. Because of its extremely flexible nature, needles of all shapes and sizes are created since MN creation requires very minute or micron-sized structures.[80] 51 Silicon is crystalline, with a range of inelastic moduli values from 50 to 180 GPa, and possesses mechanical strength comparable to that of muscle. 40 Reactive ion etching is the basis for the dry etching procedure used to create short silicon MNs with a chromium mask. The researcher used a reactive ion etching-based chromium mask to create short silicon MNs utilizing the dry etching procedure. Despite the numerous benefits, there **are** several drawbacks, including high cost, time consumption, difficult manufacture,Because of its brittleness, it can tear off a piece of skin, creating health concerns and restricting the usage of silicon. 40,52 Deoxyribonucleic acid (DNA) delivery using the silicon-based MNs was created for medicinal uses.[81] Metals, Metals that are frequently employed for the creation of MNs include titanium and stainless steel. However MNs may also be made from alloys like palladium, palladium/cobalt, nickel, and gold (Au). Metals are preferable to silicon because of their excellent characteristics, including their high young's modulus values (193-dz\\z GPa), accurate insertion capabilities, cost-effectiveness, and greater compatibility. 52 With the use of the injection molding method,

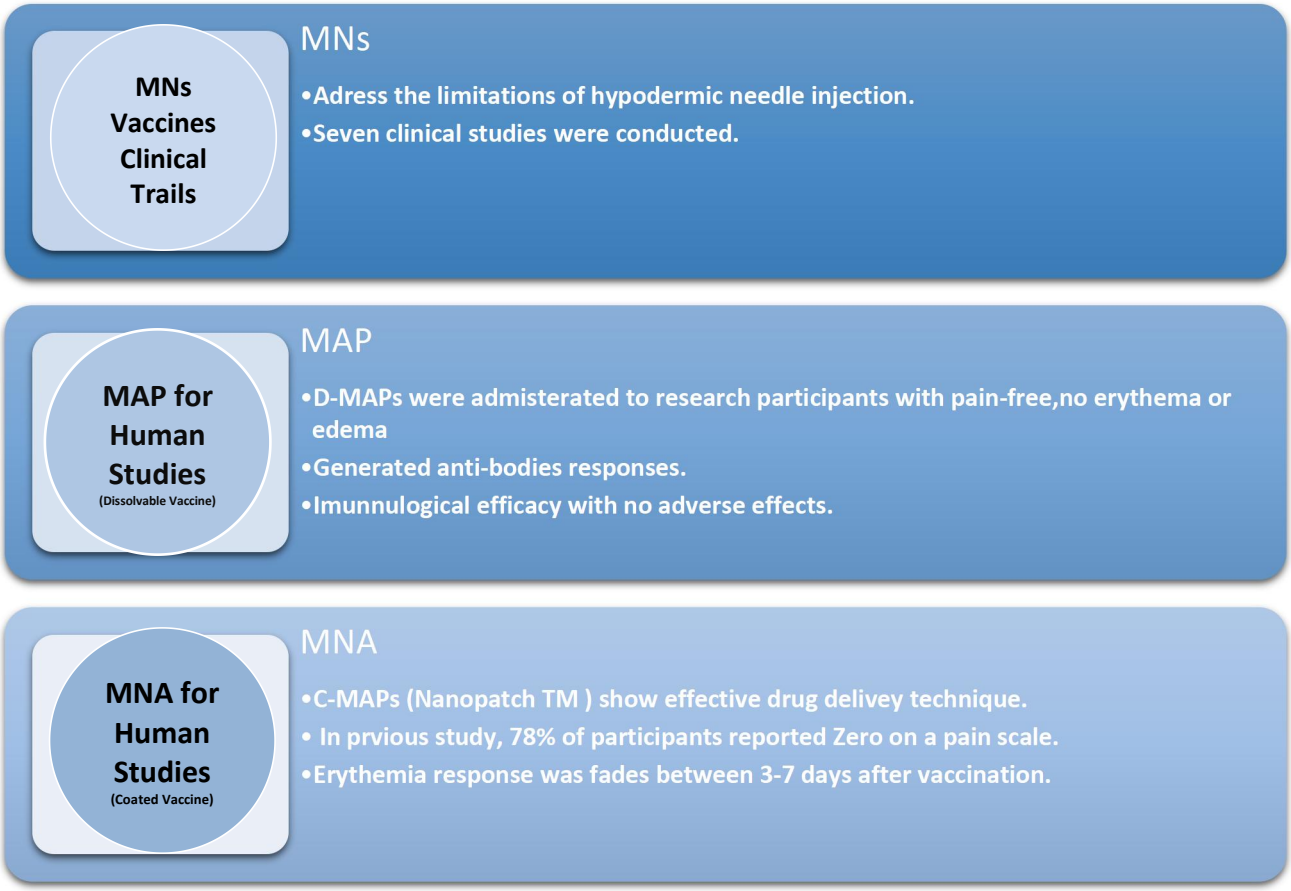
titanium is employed to create porous MN arrays. Both implants and medical equipment employ titanium.[81]

5.6 MNAP Pre-clinical Studies

In the study described in the article, mice were used to test the survivability of the majority of vaccination MAPs, although a monkey was used as an animal model in preclinical tests of several immunization MAPs. Among the adjuvants, an aluminum-type adjuvant was investigated; however, it did not demonstrate high proficiency for the MAP14 vaccination because it resulted in deficient T-cell interceded resistance responses and was unsuitable for intradermal (ID) application. Recently, nanoparticles (NPs), which can function as a station and are more readily absorbed by dendritic cells, have gained regard as important adjuvants. NP Outlines for the inoculation of Bacillus anthracis elicited a stronger immune response than an Outline without NP detailing. Studies on Ebola vaccinations showed a similar improvement.A D-MAP for HIV was created using the silk network, which resulted in a 13000-fold increase in serum IgG titer compared to a traditional organization. This D-MAP regulated the antigen release rate for two weeks. The release of the flu vaccine was prolonged using the immune-boosting effects of the chitosan Ingredient.[85]

5.7 MNs Array Patch (Human Studies & Clinical Trials)

Table 5.MNs Array Patch (Human Studies & Clinical Trials). [85]



5.7.1 Discussion:

MNs Vaccination clinical trails can utilize MAP's innovation in stability, bioavailability, potency, and less side effects in order to alleviate the limitations and current downsides of hypodermic needle injection. Seven trials using the vaccine MAP were found on Clinical Trial.gov using the search term "microneedle vaccination." Several different MAPs were used in the registered trials, and these studies were conducted to evaluate the efficacy of MAP vaccination in clinical practice for some of the most serious infectious diseases.

MAP for human studies ‘dis-solvable vaccines’ Participants in many studies who received a D-MAP patch reported no discomfort, edema, or erythema, with only modest redness confined to the patch application site. The vast majority of participants also expressed either some or complete confidence in their capacity for self-administering. When the influenza vaccine was enclosed in a polymer matrix, D-MAPs were administered to participants in a phase 1 study. Self-administered D-MAP produced antibody responses that were similar to IM treatment. Using MicroHyala TM, a hyaluronic acid MAP, another D-MAP for the treatment of influenza was developed. The immunological effectiveness was equivalent to IM, and there were scarcely any noteworthy local or systemic side effects. MNA for human studies ‘Coated Vaccine’ C-MAP (NanopatchTM), a vaccination, has demonstrated promise as a method for efficient drug administration in several human studies. In a prior trial, 18 healthy individuals received uncoated and excipient-coated NanopatchTM vaccinations for 2 minutes of insertion and removal. 78 percent of individuals reported 0 on a 0 to 10 pain scale, with an average score of less than 1 on the 0 to 10 pain scale. The predicted erythema reaction subsided between three and seven days after immunization, and anopatchTM showed no unexpected side effects.[85]

5.8 COVID-19 Vaccination Using MNs Delivery System

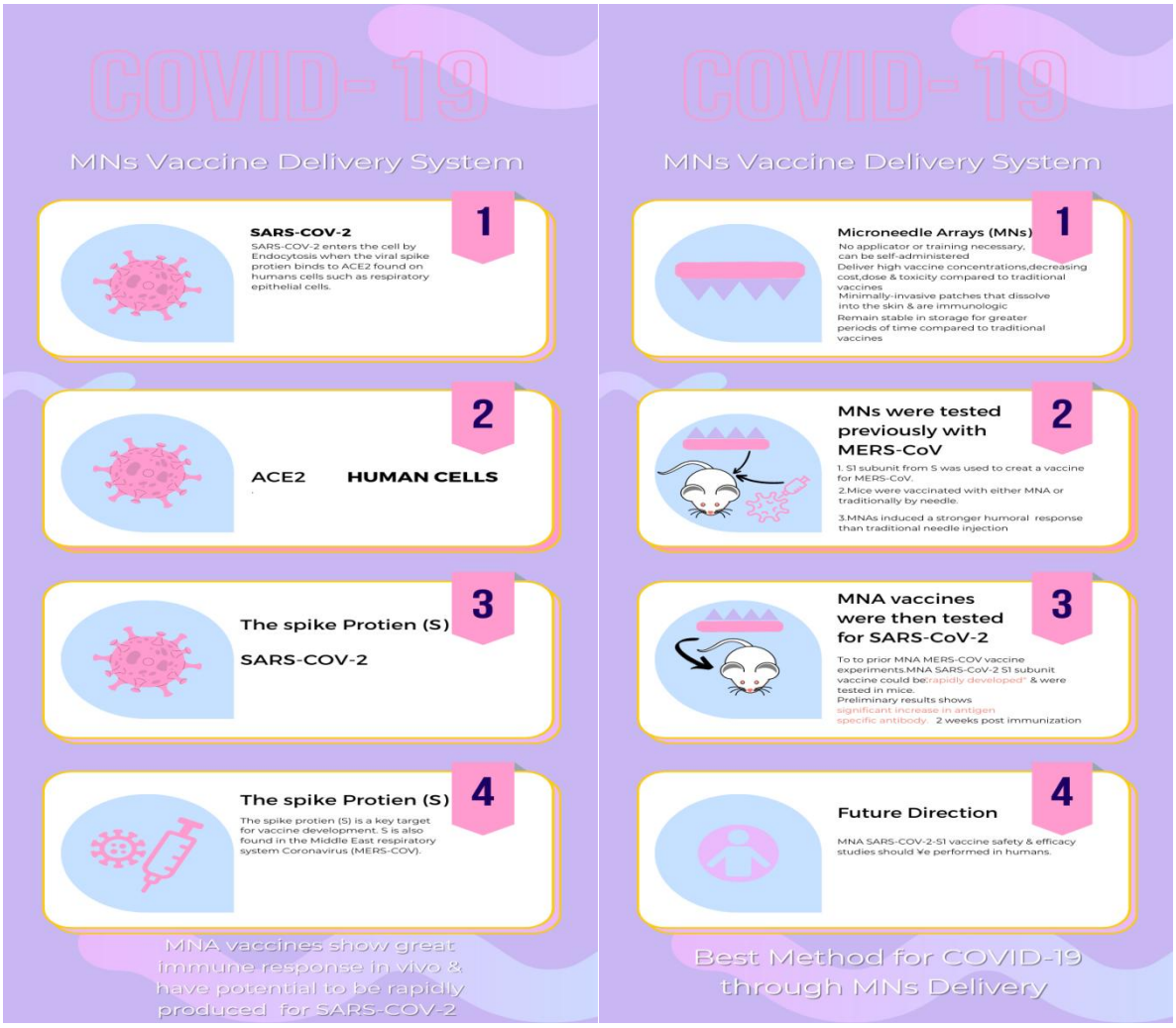


Figure 14.*Microneedle Array Delivered Recombinant Corona Virus Vaccine. (reproduced from E.Kim et al.,2020)*

5.8.1 Discussion:

Microneedle delivery results in high concentration of COVID-19 vaccine components are present in the local skin microenvironment as a result of MNs administration, which may have a dose-sparing impact that lowers the amount of vaccine doses necessary for effective vaccination and significantly lowers cost and toxicity.[82] This indicates that MN-embedded COVID-19 vaccines have the potential to stay stable for a prolonged amount of time without costly "cold chain" requirements, even if the stability of each vaccine candidate in MN has to

be tested at different temperatures for diverse storage periods. A safe and well-tolerated delivery platform for effective vaccination techniques may be offered by MNs, according to earlier animal and clinical research.Proteins used in the COVID-19 vaccine are normally stabilized by incorporation into the MN polymer matrix and maintain their confirmation al shapes, as shown by the preservation of antibody binding activity or immunogenicity of recombinant adenovirus vaccines for at least a month (30 days) at 25 °C.[83] MNs can be administered without the use of an applicator or any other specific tools, promoting the possibility of self-administration. Hence, these characteristics offer a number of significant benefits that encourage the development of MNA vaccines in the future for the purpose of providing universal defense against fast evolving infectious diseases.MNs were tested prevouslaywith MERS-CoV through the following steps:[84]

1. S1 subunite fromS was used to create a vaccine for MERS-CoV.

2. Mice were vaccinated with either MINA or traditionally by needle.

3. MNAs stronger humoral response than traditional needle injection.

4. Due to prior MNA MERS-CoV vaccine experiment,MNA SARS-CoV-S1 subunite vaccines could be rapidly developed and were tested in mice.

5. As a result.this shows significant increase in antigen specific antibodies two weeks post immunization.

5.9 Obstacles to Worldwide Availability to COVID-19 Vaccination and MNs Socio-Economic Factors

In the clinical translation of MN-based vaccinations, microneedles are regarded as a crucial challenges. The small number of accessible clinical research and clinical data point to this. A variety of factors must be taken into account while manufacturing MNs on a large scale. First, despite the fact that MN-based vaccines do not require cold-chain storage, vaccine thermostability in MNs has to be researched.[85] Second, because the filtering procedure used for vaccine sterilization is ineffective for MNs, the sterilization of MN-based vaccines can be difficult. When used commercially, this requires aseptic conditions throughout manufacture to ensure vaccine sterility and antigenicity, which is costly. Moreover, to improve storage stability, specific packaging, desiccants, or moisture protectants may be required. When regulatory bodies investigate such products, the regulatory elements of MN-based vaccinations constitute additional obstacles.Moreover, to improve storage stability, specific packaging, the requirement for desiccants, or a protectant from moisture may be necessary [86]. Last but not least, the regulatory elements of MN-based vaccinations provide additional difficulties because regulatory bodies view such products as a hybrid of a mechanical device and a biological product. As a result, the requirements of each component portion and the final product should be met by the MN-based COVID-19 vaccination.[87]

5.9.1 Vaccine Hesitancy

5.9.2 Role of MNs in dealing with vaccine hesitancy

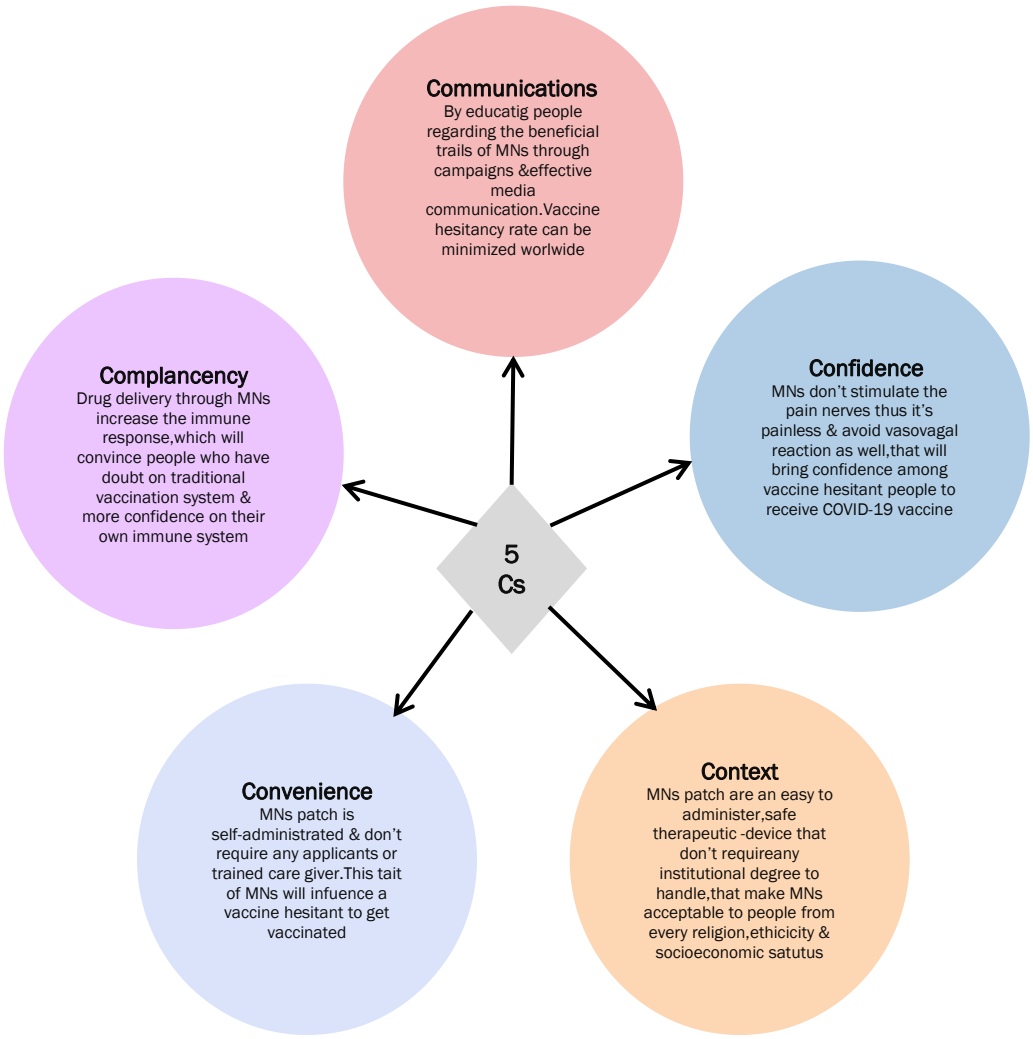


Figure 15. *Role of MNs in dealing with vaccine hesitancy. (reproducedfrom AAPS PharmSciTech)*

5.9.3 Discussion:

The-delay or unwillingness to-obtain vaccinations;despite the presence of a vaccination facility is known as vaccine hesitancy88in order to reduce the severity of the coronavirus pandemic communities must agree to get vaccinations several researches claim that those who favor

receiving complementary and alternative medicines cams are more likely to develop vaccination-hesitancy. [89] covid-19-vaccine development process was faster than typical which is one of the causes of peoples reluctance fearful doubts about the vaccines long-term effects have arisen as a result of this.[90] although vaccination hesitation may be caused by a variety of variables including a persons belief in the vaccine socioeconomic conditions and other considerations.Moreover, improper vaccination campaigns vaccine illiteracy and media communication have a significant impact on individuals in order to pinpoint the precise cause of vaccination reluctance many surveys have been conducted and each of them included a sizable percentage of participants who had no prior awareness coronavirus vaccine many people vaccine developed reluctance as a result of media coverage of the unfavorable side effects of the Astrazeneca vaccine.[91] the first and most important step in combating the rising rate of vaccination hesitancy during the covid-19 epidemic is to raise public awareness this entails informing people about the value of vaccinations and combating misinformation with data-based on scientific evidencein order to overcome vaccination-hesitancy researchers have proposed the five cs technique which addresses 1 confidence 2 complacency 3 convenience 4 communications and 5 context mns have a significant impact on lowering global vaccination resistance rate vaccine skeptics will gain trust as a result of the now-established ability of mns to boost the efficiency of a drug and the other four components of the five cs may also be addressed.[92]

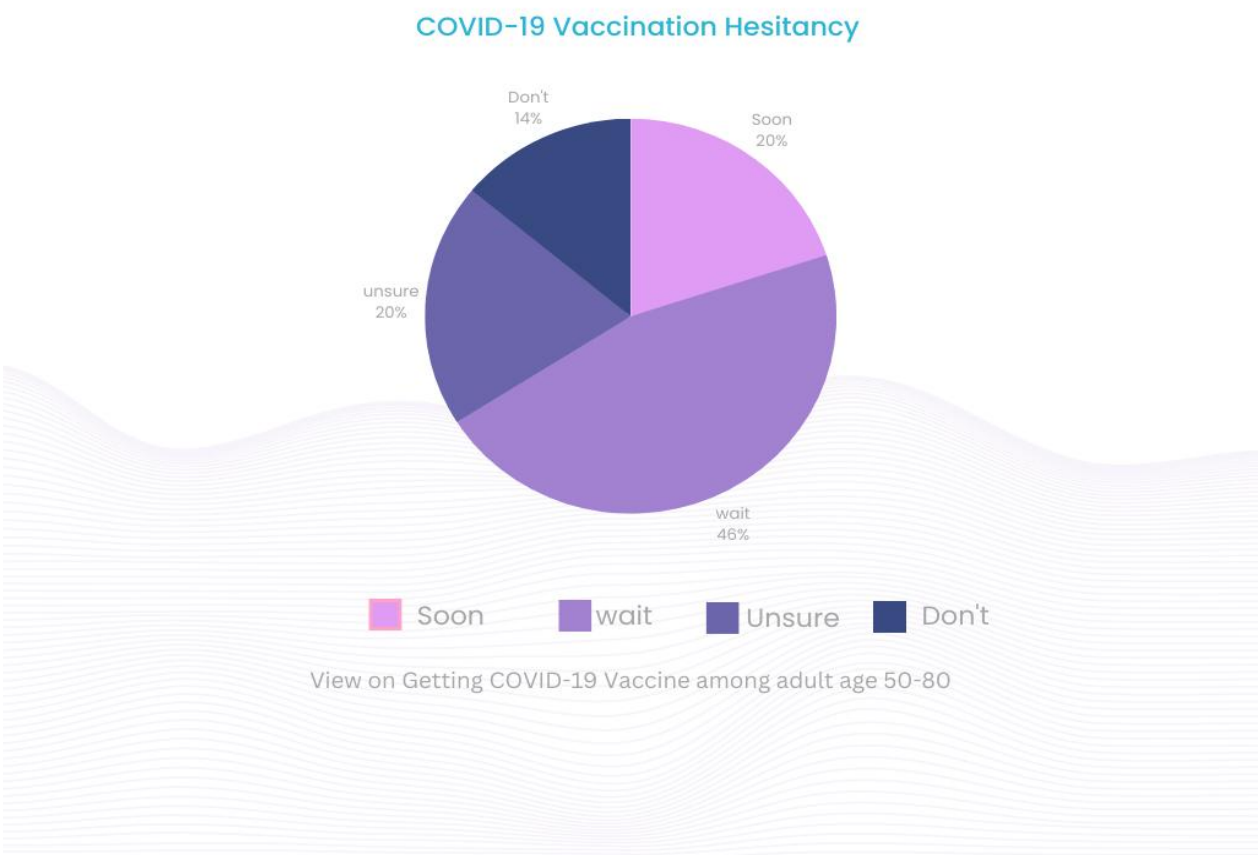


Figure 16. *COVID-19 vaccination hesitancy and older adults globally. (reproduced from Dr. Anuj Metha et al.,2022)*

5.9.4 Discussion:

Figure 16 pie chart shows coronavirus vaccine-hesitancy estimation percentages.The study was viewed on getting covid-19 vaccine among adults ages between 50-80. 20% of adult individuals would like to get as soon- as -possible.46% would like to get it,but waiting till other sreceive it and 14% don't want to get it.[90]

5.9.5 Needle Phobia

A needle phobia is the extreme dread of medical procedures involving needles or injections to the point where it results in a changed and unaccommodating behavior.[93] Due to needle phobia, some people may even completely avoid receiving the COVID-19 immunization vaccine, which is problematic because more people need to receive the vaccination to achieve herd immunity.An anxious person who is afraid of needles typically has a sequence of

symptoms, including tachycardia, bradycardia, hypotension, diaphoresis, and shock. Any of these instances may eventually cause a needle-phobic to experience vasovagal syncope. Regrettably, a treatment recipient who has this dread of vasovagal syncope exhibits more extreme needle phobia reactions than typical.[94] Despite the long-term positive effects of vaccinations, all these medical concerns deter persons with needle fears from being vaccinated.The following vaccination strategies using MNs might be used to persuade persons with needle fears to receive vaccinations because to their very special features, MNs have gained popularity as therapeutic tools for vaccination administration. These advantages can significantly reduce people's phobia of needles.[95] MNs are extremely small, micron-sized needles that penetrate the stratum corneum and create microchannels via which medication molecules may be delivered without activating pain receptors. They are an appropriate transdermal delivery device for persons who are afraid of needles since they can enter the skin without causing discomfort or vasovagal responses.As a result, it may be necessary to produce microneedles in aseptic conditions.[96]

5.10 Future Prespectvies

COVID-19 virus is currently regarded as a global epidemic. Millions have lost their lives as a result of this deadly virus. The development of a vaccine that would protect them from sickness is a top priority for researchers since their lives are on the line. Due to a shortage of COVID-19 immunizations, people in developing and underdeveloped nations remain behind.[97] Microneedle patches are so highly likely to have a big influence on immunization practices throughout the world, perhaps saving countless lives.[98] As micro-fabrication technology has advanced, new MN-based products, including vaccines, have been produced. The aim is to establish a technique for Covid-19 immunization that employs a device that is straightforward, affordable, and fabricated.[99] In other words, customers will soon be able to give the COVID-19 vaccination themselves (Self-Administration), doing away with the

requirements for a healthcare provider to do so. This strategy for spreading immunizations throughout the globe is quite effective.[100] This approach can offer COVID-19 vaccine immunity for a considerable period of time. Dissolving microneedles is crucial for administering immunizations to the older population while assuring patient compliance since COVID-19 affects persons of all ages.[101] Cynically , a fair distribution of excess vaccines to the less developed countries in a short period of time would simply result from the unrelenting predatory rush to seize of the MNs-based COVID-19 vaccines delivery system.The final postulate is that many vaccines will eventually be required to guarantee equal access around the globe, the safety of various individuals, and immunity against virus variations.[102]

CHAPTER-6

CONCLUSTION

Conclusion

In conclusion, People all across the world have been devastated by Covid-19, a viral disease that has evolved into a global epidemic that is still ongoing.we urgently need an easy-to-administrate vaccination ,which are injected intramuscularly, and the outcomes of their widespread usage will provide crucial details about their safety and effectiveness. Intranasal vaccination is anticipated to be more successful than intramuscular immunization because the local immune milieu is crucial for both reducing viral shedding and preventing protection against infection. While studies have indicated that, in some circumstances, intranasal vaccination is superior than an intramuscular injection.The development of a Covid-19 vaccination via transdermal microneedle administration was discussed in this project paper. A particularly effective method of medication-based transdermal delivery is the delayed and extended release of vaccination antigens using microneedles in comparison to conventional needle administration techniques. It is no longer necessary to need a trained expert to give vaccines; anybody who is skilled can do it. This can help with large-scale vaccination campaigns during pandemics since they can successfully supply themselves with pain-free. Microneedle mass manufacturing is anticipated to start soon and will employ both traditional and non-welding methods. Personalized vaccinations may now be mass produced at a far reduced low-cost thanks to 3-D printing. It may be possible to create microneedles that are more efficient while requiring fewer vaccines with the development of sustained-release polymers, microparticles, and nanoparticles. Microneedle vaccinations, despite certain hiccups, have had a huge influence on the globe and will continue to have an important impact on future immunization techniques to prevent the global pandemic. Transdermal microneedle delivery of the Covid-19 vaccine might have a substantial influence on vaccine administration in the future if continuing research efforts are successful in overcoming obstacles.

List of Abbreviation

CDC	Center for disease control and prevention
MNs	Microneedles
TDDS	Transdermal drug delivery system
GIT	Gastrointestinal tract
CD8+ T Cells	Cluster of Differentiation 8-Cytotoxic T Lymphocytes
ACE2	Angiotensin-converting enzyme 2
IN	vaccination:Internasal vaccination
EUA	Emergency use authorisation
NDV	Newcastle disease virus
OMV	Outer membrane vesicle
HA	Hyaluronic acid
RBD	Receptor-binding domain
HMNs	Hollow microneedles
SMNs	Solid Microneedles
DMN	Dissoving Microneedle
CAMs	Complementary and Alternative Medicines
SARS	Severe Acute Respiratory Syndrome
MERS	Middle East Respiratory Syndrome
IM	Intermuscualr
SC	Subcutenous
IgG	Immunoglobulin G
IgA	Immunoglobulin A
NSP	National Special Pathogen System Care

[1]RAAV	Recombinant Adeno-associated Virus
ACE2	Angiotensin-converting enzyme 2
MERS-CoV	Middle East respiratory syndrome coronavirus
CMNs	Coated Microneedles
DNA	Deoxyribonucleic acid
mRNA	Messenger ribonucleic acid
NA vaccines	Nuclic Acid Vaccines
DMNs	Delivery Microneedles
MAP	Microneedle Array Patch
MNA	Microneedle Array

CHAPTER-7

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