The Accessibility of Covid-19 Vaccine Toward Commercialization Using Microneedles

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Bachelor of Pharmacy (Hons.)

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Declaration

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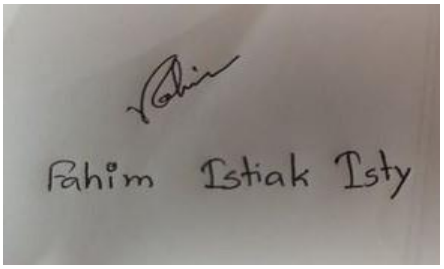

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Approval

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Ethics Statement

The thesis was done without unethical work. No human or animal tests are involved in this study.

Abstract

The abrupt development in December 2019 of a novel coronavirus (COVID-19 or 2019-nCoV or SARS-CoV-2) still harms the whole humankind and has damaged not just the medical system but the global economic and social balance. The World Health Organization soon named COVID-19 as a global pandemic. However, since its breakout we understand COVID-19 substantially and have tried or are presently in research numerous therapies and pharmacology treatments to reduce its risks. Infectious illness prevention is the most efficient technique. As novel immunization methods, microneedles have become more attractive. Based on its mechanism for action, painlessness and convenience of usage, microneedle is a very effective technique that delivers transdermal vaccines. The dissolving microneedle is important in achieving herd immunity and is advantageous for the population. Also, viable options for the fabrication of covid- 19 vaccine are solid microneedles, Hollow microneedles. Because of safety, effective stability, this platform has become very lucrative and user pleasant and at a commercial cost, and as a Covid-19 vaccine delivery system may play an increasingly important role.

Keywords: Microneedle; Commercialization; Patient Safety: Covid -19.

Dedication

Dedicated to my Parents, who have sacrificed their *worldly happiness in fulfilling my ones to their best and to my beloved sibling and friends.*

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Chapter 1

1. Introduction:

1.1 General Introduction

COVID-19 is a respiratory disease caused by the serious acute respiratory syndrome coronavirus-2 (SERS-CoV-2), a tedious virus of a family of single-stranded, positive-sense RNA viruses known as coronavirus. The acronym of "Coronavirus disease - 2019." SARS-CoV-2 targets the respiration system, like the influenza virus, and produces diseases such cough, fever, tiredness, and respiratory illness (Chamola et al., 2020). Because of its quick expansion and high fatality rate, the current coronavirus disease 2019 (COVID-19) outbreak is a worldwide emergency (Zhu, N. et al.,2020). Worldwide, the number of persons infected with COVID-19's causal agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As a result of COVID-19 infection, patients might get pneumonia. (Huang, C. et al., 2020) Alpha, beta, gamma, and delta are the four classes of the coronavirus family, all featuring a single-stranded positive-sense RNA genome. The membrane envelops encapsulating the viral genome are decorated with glycoprotein spike transmembrane proteins (Chauhan et al., 2020).

COVID-19 typically involves fever, dry cough, and tiredness, often with lung infections. The high COVID-19 transmission rate resulted in the present significant cost on public health and the global economy and underlined that a rapid and efficient strategy for preventing or treating fatal infections is necessary (Chen et al., 2021). Over the last 100 years, the expectations of vaccinations have substantially risen, and the culture and economy have been reshaped. The severe consequences of many infectious illnesses have diminished as vaccination is widely available and applied. (Chung et al., 2021)

Several SARS-CoV-2 vaccines, including Pfizer-BioNTech and Moderna-mRNA vaccines, are already licensed in several countries, including Janssen's Ad-based Vaccine and Novavax's Nanoparticle Formulation and the Adjuvant Sublimated Vaccine, and approval is being sought for additional vaccine applicants. In the final analysis, these and other vaccine developments should enable successful worldwide vaccination to fight the pandemic of COVID-19 (Korkmaz et al., 2021). A safe, reproductive, adaptable, patient-friendly, cost-efficient, and widely used vaccine administration strategy must be effective and extensively immunized. Most vaccines, including most advanced COVID-19 candidates, are presently administered by hypodermic needle injection through typical parenteral routes (for example, subcutaneous (SC) or

intramuscular (IM)). There have been limitations to these approaches. The efficacy of many of the conventional vaccinations is likely to vary from manufacturing to injection, hence requiring an expensive cold chain for distribution and storage. Many also need correct administration from qualified healthcare personnel and might suffer from significant non-compliance with immunization owing to pain, dread of the needle and discomfort (Zafar et al., 2020).

1.2 Importance of Vaccination

Vaccination is the adaptive immune system immunologic preparation for a particular illness. It decreases the incidence and lengthens the service life of infectious illness in children. Therefore, in our community immunizations are often utilized (Soiza et al., 2021). Several features, such as safety, stability, economic efficiency, easy dispensation, and capacity to generate an efficient immune response, should be taken into consideration for production of vaccines (Amara, 2021). Working (neutralizing antibody response or particular T cell development) and helping are always connected in vaccine development (the prevention of a disease in a population base with an acceptable safety profile) (WHO, 2020). As a result, more than 160 vaccinations have been developed in parallel (WHO, 2020).

1.3 Potential of vaccination using Microneedles

The needle used to deliver vaccines is called a hypodermic needle (Kim et el.,2012). This technique of vaccination distribution is quick and direct (Kermode, 2004). Although the hypodermic needle is well-known and widely used, it is connected with needle stick injuries, the transmission of blood-borne diseases (Hauri, 2004), as well as phobias, discomfort, and anxiety (Nir et al., 2003). In addition, these needles are difficult to self-administer unless the user has undergone specialized training on injection technique and needle disposal (Giudice and Campbell, 2006). Oral vaccination is an attractive alternative (Wang and Coppel, 2008). There are a few oral vaccinations that have been authorized for human use (Liebowitz et al., 2015). These vaccines are less efficient, however, since they must be digested in the gastrointestinal system before they can induce a sufficient immune response (Wang and Coppel, 2008). In addition, research on their application has been confined to mucosally transmitted diseases, with a few notable recent exceptions in this regard (Liebowitz et al., 2015). However, intradermal delivery is technically challenging, and it has been associated with side effects such as discomfort, inflammation (Al Jarad et al., 1996), and abscesses (Ormerod & Palmer, 1993). Microneedles were developed as a remedy to the constraints of parenteral, oral, and conventional transdermal and intradermal immunization. Microneedles

can be 1mm in diameter and range from 50mm to 1000mm in length, while mini-needles range from 1000mm to 1500mm (Donnelly and Singh, 2015). In addition to being regarded as painless, Microneedles are related with a decrease in bleeding, according to research (Birchall et al., 2011) (Escobar-Chavez et al., 2011). As well as the capacity to avoid first pass metabolism (Birchall,2006), microneedle-mediated delivery offers enhanced patient compliance (Norman and Prausnitz, 2012) and dosage sparing, as well as the opportunity for self-administration (Mistilis et al., 2015).

1.4 Review article objectives

Intramuscular, intradermal, and subcutaneous injections provide numerous benefits, but there are a lot of disadvantages in the administration of this vaccination. The construction of a new supply chain of vaccines was therefore necessary for a long time. The newly introduced vaccinations were recently attracted by microneedles. Due to its mode of action, painlessness and convenience of use, microneedle is a very efficient transdermal vaccination administration technology. we discuss our current perspective on the opportunities and challenges for future development of microneedle vaccination strategies against COVID-19 pandemics.

Chapter 2

Types of Microneedles

2.1 Solid Microneedles

For pre-treatment of the skin through pores, solid microneedles are usually employed. Sticky points of the needles penetrate the skin; form a micro-sized channel via which the medication penetrates the skin layers directly when applying a drug patch, therefore improving permeability. The medication is used for systemic effects by capillaries (Waghule et al., 2019). The solid microneedles are enough to improve medication supply through a variety of compounds. For example, Zhanget al31 has produced solid silicon microneedle panels for the delivery of peptides with a length of 150mm. The skin of the pig ear was prepared with solid microneedles, and the drug permeability was illustrated using four types of peptides of varying molecule weights. The results indicated the solid microneedle ranges were used to improve peptide transport but that the permeability of peptides was reduced by increasing peptide molecular weight (He et al., 2019). In recent years, the popularity of solid microneedles has declined due to the need for multi-step administration, consistencies, and growing benefits of alternative microneedle systems, notwithstanding the immunogens (Marshall et al., 2016). Furthermore, solid microneedles may be used to remove interstitial fluid (IFF) simply by generating micropores and removing dermal ISF with the use of an optional vacuum chamber. This technique, however, has severe restrictions on the supply of drugs and the extraction of ISF, which leads to high risk since it prolongs the period of occlusion and increases the chance of micro-organism infection (Xie et al., 2020).

2.2 Coated Microneedles

The creation of coated devices was a step forward in solid microneedles (Marshall et al., 2016). Recent advances in the distribution and sensing of coated microneedles permit extensive use. Coated microneedles can increase dissolution of microneedle-coated bio-moles (e.g., medicines, proteins, vaccines, and DNA) (Li et al., 2018). A functional coating layer can alter the biocompatibility and mechanical strength of coated microneedles. The biocompatibility and mechanical strength of microneedles was enhanced using a gold layer (Xie et al., 2020). In a composition suited for coating and dissolving, Solid microneedles are pre-coated with a vaccine, leading to one-step delivery. In the area where the vaccine is dissolved, vaccine coated microneedles are implanted. Limited to the size of the shaft and tip is the administration of vaccines through microneedles. Influenza, human papillomavirus, chikungunya, rotavirus,

herpes simplex virus and hepatitis C in mice, Calmette- flu virus and bacillus Calmette - Guinea pigs, pig hepatitis B virus, and measles and polio viruses in rats are successful in coating microneedles (Marshall et al., 2016).

2.3 Hollow Microneedle

Hollow microneedles enable the administration by injection by the inserted hollow needles of a certain medicine on the skin. These types of microneedles permit molecules across the skin to continue delivery through the microneedle bore by various methods: diffusion or electrically powered flow. These methods might supply more chemicals than solid, laminated, and dissolving microneedle in compared to solid, coated, and dissolving microneedles (Lutton et al., 2016). There are numerous hollow microneedle systems available on the market; Micron Jet is clinically evaluated and Soluvia is licensed to use. Soluvia is a pre-fill micro-insert system with a single hollow silicon Microneedle of 1500mm whereas Micron Jet consists of four silicon microneedles of 600mm hollow organized on a conventional syringe barrel adapter. Hollow Microneedles were constructed effectively with the aim of immunizing humans with polio or influenza vaccinations, immunizing mice against pesticide disease and administering polio to rats (Marshall et al., 2016).

2.4 Dissolving Microneedles

Finally, biologically degradable products such as different polymers and sugars loaded with medicines produce dissolving microneedles. The needles are dissolved to release the payload into the skin once the needle is introduced to the skin. In contrast to solid and hollow microneedles, the benefit of dissolving microneedles is the simplicity of production and the simple application of the patch. Dissolving microneedles for administration of skin vaccinations have been studied extensively(Menon et al., 2021). Influenza Virus, hepatitis B, tetanus, diphtheria, malaria, and HIV vaccinations have been created to be included in mice and measles and polio in rhesus macaques to provide a self-sufficient platform for long term thermostatic management. Dissolving microneedles Although an intriguing platform, dissolvable vaccine-supply microneedle (DMICRONEEDLE) devices take more time than hollow or solid microneedles to achieve clinical studies. The usual categorization of the hollow and solid microneedle devices is the medical device. Dissolving Microneedle patches are probably considered, by contrast, as a hybrid product of a medical product (vaccine) and a gadget from a regulatory standpoint (Marshall et al., 2016). So, for these purposes dissolving microneedles would be the microneedle selected for Covid-19 vaccination.

Chapter 3

Methodology

The publication of papers in the Google, GOOGLE SCHOLAR, PubMed/MEDLINE, Science Direct databases was searched systematically to find significant research relating to microneedle systems and their impacts on vaccine delivery. The most relevant articles have been discovered using advanced search method. The identification of systemic and thorough review papers in comparable domains was also emphasized. To provide optimum coverage for searching the article, many databases have been employed. The search was conducted using the following keywords: Microneedle, commercialization, patient safety, Covid -19, fabrication techniques, microarray patch, transdermal delivery along with preclinical and clinical data have been selected in the scope of review paper.

3.1 Fabrications techniques, advantages, and disadvantages for different types of Microneedle system Ref: 23,24,25

Table 1: Fabrication techniques, advantages, and disadvantages for different types of Microneedle system

Microneedle Types	Fabrication Process	Advantages	Disadvantages
Solid Microneedles	Silicon Microneedles fabrication techniques are isotropic etching, anisotropic wet etching, silicon dry-etching process, dicing silicon and acid etching, and 3D laser ablation. Metal microneedles fabrication techniques are wet etching, metal electroplating methods, laser cutting. Ceramic Microneedles fabrication techniques are ceramic micro molding and sintering lithography. Polymer Microneedles fabrication techniques are mostly based on photolithography	Mechanically and physically strong and stable.	Low drug loading, chance of infection, biologically incompatible and inaccurate dose administration
Coated Microneedles	Microneedles can be dipped or sprayed with drug solution and then dried.	Moderate drug (less than 1 mg)	Drug may peel off during

	Microneedles can be dipped into a microwell containing vaccine solution once or more than once and then dried. A layer-by-layer coating technique has also been used.	loading capacity and efficacy, mechanically strong	administration, drug may migrate from the microneedle system at the time of fabrication and storage
Hollow Microneedles	Several techniques are used for this category which includes micro projection array, micro fabrication, wet chemical etching, lithographic, X-ray photolithography, micro-electromechanical systems, techniques-laser micromachining, and deep reactive ion etching of silicon.	Suitable for diverse molecules, comparatively higher drug loading and accurate dosing	Fracture due to low mechanical strength, clogging, chance of infection due to repeated application
Dissolving Microneedles	Micro molding	Easy and cost-effective fabrication process, high drug loading and sustained delivery. chance of infection is low	Fracture due to low mechanical strength, clogging, chance of infection due to repeated application.

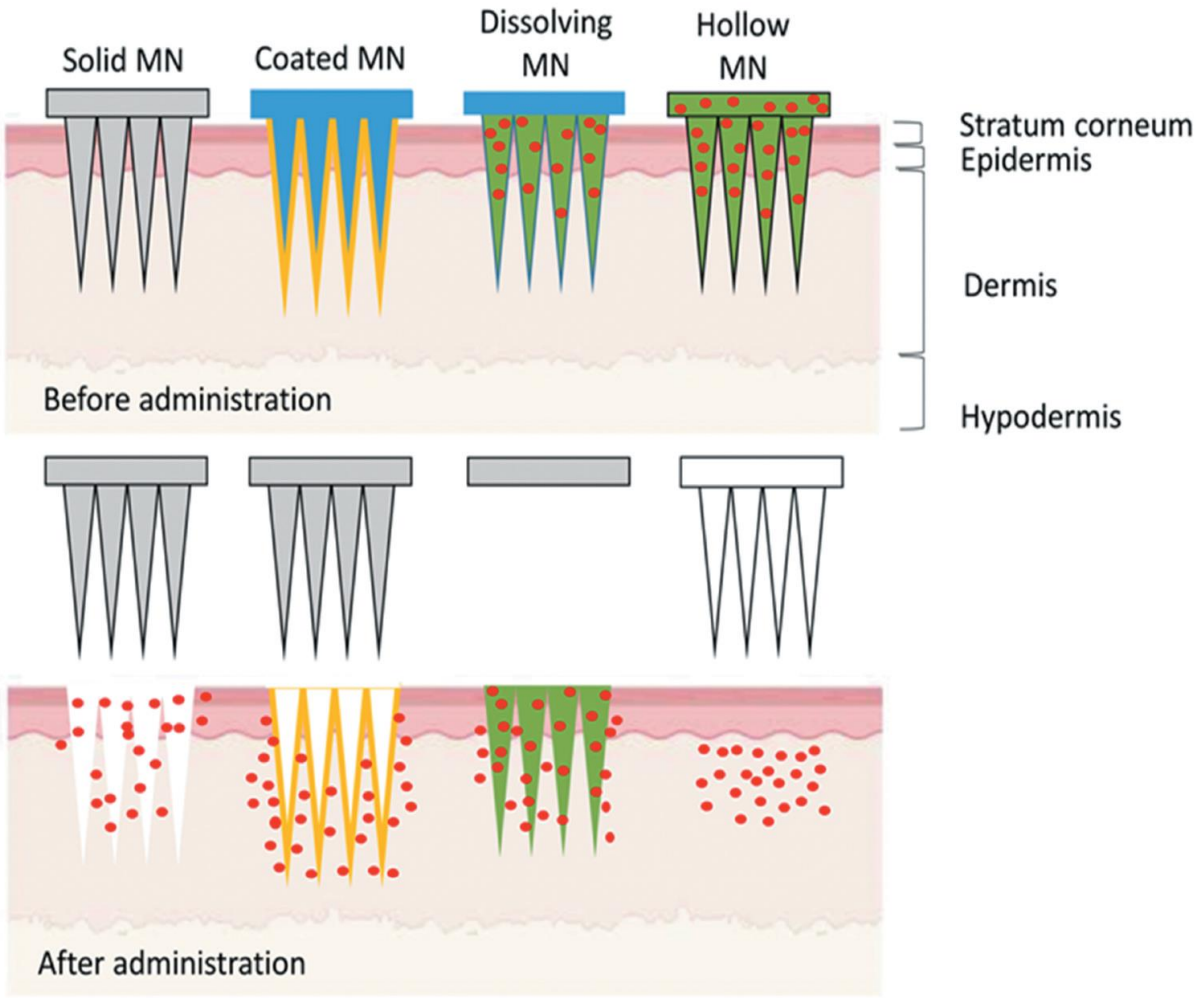

Figure 1 Mechanism of vaccine delivery by various type of Microneedle systems

Chapter 4

Evaluation of Microneedles

4.1 Visual Characterization Methods

Inclusion/penetration may be affected by the shape of the Microneedle. By optical or electric microscopy and optical inspection, geometry and measurement of tip radius, height, and length were assessed. The 3D image acquisition was utilized to obtain a confocal laser microscope and electron microscopy (SEM), which helps to control quality (Zhao et al., 2017). SEM offers composition and surface topography info. With fluorescent-labeled modules the molecules included in the microneedles were identified and observed by means of optical examination, fluorescence microscopy, and confocal laser scanning microscopy(Gupta et al., 2021)

4.2 Mechanical Properties

To enter the skin without generating fractures, microneedles should have enough mechanical strength and hardness. Including force/shift testing, tint marks or electrical measures, mechanical tests performed for measurable insertion forces. Criteria are histological stains, cryosections, optical microscopy and confocal microscopy for assessing insertion depth (Li et al., 2017).

4.3 In Vivo Permeation Studies

Drugs may penetrate the skin using Franz diffusion cell systems. Pig ear skin is widely utilized when mounted between the two compartments, the receiver, and the donor. The profiles for the cumulative release of drugs were determined to ensure the duration for treatment with microneedles and untreated skin. (Uppuluri et al., 2017).

4.4 In Vivo Studies

For in vivo investigations based on hairless rat animal model, the different rebuilt skin models are employed. One of the characteristics assessed with the Delfin Avometer is the trans epidermal water loss (Gupta et al., 2021).

4.5 In Vitro/In Vivo Correlation Studies

The Franz diffusion cell installed hairless pig skin, maintained pH and dissolving media temperature replicated in vivo and the medicament's penetration profile studied in the in vitro experiment, in the in vitro correlation research. Therefore, the in vivo study connected all factors and circumstances of the in vitro investigation (Gupta et al., 2021).

4.6 Skin Irritation Studies

Transdermal delivery can generate numerous adverse effects on the application site, including as moderate or severe erythema. To quantify the degree of skin irritation, we employed the Draize technique. Before and after the application at the place of activity, dermatological changes were detected (Sabri et al., 2019).

Chapter 5

Preclinical and Clinical Update on Vaccine Delivery through Microneedle

Microneedles started to be produced in the nineties and several microneedles have been authorized for various disorders following 30 years of considerable scientific work. In preclinical and clinical vaccination research particularly for infectious illnesses via microneedle system, a considerable number of information are accessible. A few research have also studied and achieved considerable progress in the use of the microneedle system for the creation of immunotherapy for cancer, dermatological disorders, allergies, and other complex medical problems.

Table 2: Preclinical studies of vaccine delivery by Microneedle system

Vaccine type	Microneedle System	Study Outcome	Ref.
Live attenuated viruses	Microabation and microneedle penetration	ChimeriVax exhibited a superior immunogenicity compared to IM injections when accompanied by microabration live attenuated vaccine.	60
Inactivated viruses	Hollow dissolving-type microneedle	The dissolving Microneedle administration of hepatitis B antigen showed comparable immune responses in relation to conventional IM administration	61
	Metal Microneedles coated with inactivated H1N1 A/PR/8/34 virus	The inactivated H1N1 A/PR/8/34 virus delivery by the coated Microneedles method shows improved serological antibody titers, robust Th1 bias and viral protection in comparison with IM injections.	62
	Dissolving microneedles patch with polyvinylpyrrolidone (PVP)	The administration of inactivated influenza antigens (A/PR/8/34) against H1N1 using dissolving Microneedle's patch demonstrated superior antibody responses compared to IM injection.	63

Inactivated viruses	Intradermal delivery (ID)using microneedle	An ID and IM injection were used for assessing the immune response of inactivated virus strain; ID route showed a 1/100th dosage better response than IM injection. Similar outcomes were shown at 1/10th of IM dosage for ID administration of trivalent human vaccination (H1N1). The investigation was performed in the model of rats.	64
	Microneedle (MICRONEEDLE) patch	Two alternative pathways in the mouse model were investigated with inactivated Rota virus antigen. Vaccine-coated microneedle patch had shown greater IgG-specific Rota virus compared to IM.	65
Subunit Vaccine	Coated microneedles (prepared from stainless steel sheets)	Two separate ways assessed the immunogenicity reaction of the HA influenza component A/Aichi/2/68. Vaccine-coated MICRONEEDLEs showed stronger IgG reaction than subcutaneous injections.	66
	Nano patch (micro projection array patch)	Fluvax (split virion influenza) administered by Nano patch revealed a 1/100th standard dosage with good immunogenicity in comparison to IM injection. In this work, the nano patch was vaccinated and carried out in the mouse pattern	67
	Dissolving Nano patch	Fluvax vaccination was assessed in two ways in a mouse train immunogenicity response. Nano patch dissolved showed higher effectiveness in comparison with IM injection	68
	Coated micro-scale needle shafts by dip coating approach	Two strategies have been followed by a vaccination dosage comparison investigation in the Mice model. Fluvax vaccination and IM injection were used to cover Microneedle	69

		types. Most vaccines were released within two minutes after application to the skin and elicited a far stronger immune response compared with IM injection.	
	Coated microneedle patch (Metal type)	In this study, an influenza subunit vaccine (A/Brisbane/59/2007 vaccine) was coated in metal MICRONEEDLEs and compared with IM injection. Superior immune response was observed with coated MICRONEEDLEs compared to IM injection in mice model.	70
	Dissolving MICRONEEDLE array for COVID 19 vaccine	A preclinical study has been conducted to evaluate the efficacy of a subunit coronavirus vaccine in mice. Vaccine was administered by traditional needle and syringe and Microneedle array. The efficacy of the vaccine was determined by measuring the COVID 19 specific IgG in serum. The dissolvable Microneedle array assisted recombinant COVID 19 vaccine demonstrated potent antibody response and laid the foundation of clinical trials.	71
Virus-like particles (VLPs)	Nano patch (Micro projection assay)	In a mouse model two pathways were used to assess an immunogenic response to a preventive human cervical cancer vaccination (L1 VLP human papillomavirus capsid). Compared to IM injection, Nano patch showed greater antibody response.	72

	Solid metal MICRONEEDLEs	The immunogenicity response of Influenza VLPs expressing the HA subunit was assessed in mice model via two routes. microneedles were coated with vaccine and upon administration to skin showed comparable immune response when compared with IM injection and provide protection from virus challenge.	73,74
	Arrays of solid metal MICRONEEDLEs	The immunological reaction of two VLP Vaccines H1(A/PR/8/34) and H5 (A/Vietnam/1203/04) was studied in these mechanism studies. The vaccine transmitted by microneedles effectively stimulates Langerhans's cells, and this is demonstrated by changes in cell shape and by the lower cell count of the epidermal zone.	75
Bacterial vaccine	Microneedle	In the rat model, the dose-saving impact of Bacillus anthracis recombinant protective antigen (RPA) was assessed. In comparison to IM injection with the lower dosage, the microcannula microneedle vaccination was highly immune.	76
	Solid-state biodegradable microstructures	Biodegradable microneedles have been covered by Bacillus anthracis recombinant protective antigen (rPA) and have been assessed in the rat model using two ways to assess immune response. Similar responses to IM injection induced by MICRONEEDLEs mediated vaccination	77
	Microneedle array	The bacterial vaccine's immune responses were examined using transcutaneous method with or without microneedle arrays	78

		pretreatment. Diphtheria toxoid was pretreated in groups with MICRONEEDLEs with 1000 higher IgG titers (DT).	
	Microneedle arrays (300 μm length	A nanocarrier system to check its influence on generation of antibodies was studied in this study. Treated with microneedles to boost the immune response, N-trimethyl chitosan nanoparticle containing DT was supplied. When administered as a solution, the system has exhibited better immune response.	79
	Bio needle	Starch was created for the ability of a hollow dissolving bio needle to elicit anticorps reactions in the mouse model. Tetanus toxoid was employed in this study for the effectiveness assessment of the bio needle and a higher response to antibody than IM.	80
	Microneedle's array	Two methods of the guinea pig model assessed the effectiveness of Bacillus Calmette-Guerin (BCG). In comparison to the hypodermic injection, Microneedles arrays with BCG demonstrated a better immune response.	81
	Hollow stainless-steel Microneedles	In monkey models the effectiveness of a 4-protein vaccination solution was investigated. The hollow MICRONEEDLE vaccination and protection against anthrax, botulism, pestilence, and staphylococcal toxic shock proven.	82
DNA vaccines	Nano patch (Microneedles Array)	In the Nano patch mice model, the effectiveness of the DNA vaccination was assessed. Nano patch has shown high immune response in a mouse model with a DNA	83

		vaccine (Particles of West Nile Virus). The Nano patch seems incredibly safe, painless and cost effective.	
	Coated Microneedles	The effectiveness of a hepatitis C-virus-expressing DNA vaccine was assessed by employing a system of coated microneedles compared to standard delivery techniques. In comparison to certain intrusive procedures like hypodermic injection and gene gun, the system's vaccinations were superior to the antibodies of the virus.	84
	Micron-Scale Silicon Projection	The effectiveness of hepatitis B-surface antigen DNA vaccines was in vivo with the help of the micro microneedles system enhancement. The first documented in vivo trial with micro enhancer microneedles was the vaccination topically delivered.	85
	Nano patch	The efficacy of vaginal herpes simplex virus (HSV) protein gD2 was evaluated using Nano patch in mice model. Nano patch was able to generate excellent immune response and enhanced the survival of treated mice	86
	Dissolvable Microneedles	DNA vaccines were used as a model of the human immunodeficiency virus antigen to examine the efficacy of the dissolved microneedle system built of multilayer poly electros. This technique enhances local transfection and increases the durability of the vaccination antigen in the skin after application to the skin.	87

Table 3: A summary of the clinical studies of vaccines using microneedle systems

Vaccine type	Microneedle System	Study Outcome	Ref.
Monovalent influenza vaccine	Nano patch (HD-MAPs	The effectiveness of A/Singapore/GP 1908/2015 H1N1 hemagglutinin, a monovalent, inactivated influenza virus vaccine, has been assessed with 60 healthy humans utilizing nano patch (HD-MPAs). Influenza-coated nano patch was well tolerated, was less uncomfortable, stable at 40°C and showed greater immune response to 1/6th usual dosage IM injection.	Phase 1 clinical trial. Trial reference number at Australia New Zealand Clinical Trials Registry ACTRN12618000112268 (88)
Placebo/Coating materials	Nano patch (HD- MPAs)	This study examined the adequacy of utilizing Nano patch in 18 people who were healthy with a placebo recipe as an alternative to hypodermic injection. This study indicated that Nano patch was chosen by 83% of participants in comparison with hypodermal. No discomfort (pain score less than 1) on a pain range of 0 to ten were observed and no	36

		Nano patch adverse effects were noted.	
Influenza (split, monovalent) A/ California/07/2009 (H1N1)-like virus antigen	Nano patch	In this study, Nano patch has been assessed in healthy human volunteers for the safety and immune response capability of inactivated influenza vaccines (Fluvax) at various doses. A hypodermic needle for comparison data generated the vaccination. On day 0, 7 and 21, the immunological response was assessed. Nano patch preferred to IM injection about 55 percent of subjects using Nano patch (Placebo/HA). Most of the participants accepted Nano patch safely and successfully. On day 7 and 21 in the nano patch group the immunological rest was greater compared to IM injection (HAI titers)	Australian, New Zealand Clinical Trials Registry (ANZCTR. org.au), trial ID ACTRN12616000880448 [89]
Trivalent inactivated influenza vaccine (TIV)	ID Microneedles system	The safety and immunogenicity of an influenza vaccine was assessed in a Phase II study in 978 healthy humans via two routes. The subjects treated with 9 micrograms of TIV intradermally	(37)

		demonstrated superior immune responses against H1N1 and H3N2 compared to IM injection at the dose of 15 microgram HA	
Trivalent Influenza vaccine, (inactivated, split-virion vaccine)	Micro projection system	In a randomized experiment in 1150 healthy human volunteers on two routes, the safety and immunogenicity impact of a trivalent influenza vaccination was examined. The 9 μg of hemagglutinin/ strain subjects treated by ID microinjection showed a viable alternative to traditional IM injection	Phase 2 clinical trials (NCT00703651) 38
Influenza vaccine	Micron Jet	180 healthy human volunteers have been assessed for the safety and immunogenicity of the influenza vaccination (α-RIX®, GSK). The intradermally dose-low vaccination with Micron Jet was delivered and a similar reaction was exhibited compared with full IM injection	39
Bacillus Calmette-Guerin (BCG	Micron Jet 600	Two approaches have been used by healthy volunteers	ClinicalTrials.gov Identifier: NCT04064554

		to examine the safe and immunogenic nature of a BCG vaccination. Themes using Micron jet 600 and IM injection have been addressed intradermally. The study was finished in 2019. No result has been published yet	
S-OIV H1N1 Influenza Vaccination	Micron Jet 600	In healthy human workers with Micron Jet 600 and IM injection, safety and immunogenicity of a low-dose influenza vaccine (ID S-OIV H1N1) were assessed via ID route. This was completed in 2010, and there have been no results yet.	ClinicalTrials.gov Identifier: NCT01049490
TIV 2010/2011 influenza vaccine	Micron Jet	The study was performed to assess the use and comparison of intra-muscular influenza vaccine using Micron Jet. In 2011 it was finished. There is still no outcome provided.	ClinicalTrials.gov Identifier: NCT01304563
IPOL (Sanofi Pasteur) inactivated polio vaccine booster dose	Nano Pass Micron Jet 600 microneedle device	In healthy individuals, the immunogenicity effects of Inactivated Polio Vaccine (IPV) were assessed. Sujets were intradermally treated with a modest dosage of IPV with Micron Jet 600 and an entire dosage with IM	ClinicalTrials.gov Identifier: NCT01686503 (90)

		injection. In comparison to IM injection, a similar response to a 60 percent reduction in the normal dosage may be obtained from the vaccination system using Micron Jet	
Measles Rubella Vaccine (MRV-SC	Dissolving microneedle patch	This is a two-blind study in phase I and II. The effectiveness of Measles Rubella (MRV-SC) vaccine utilizing a dissolvable MICRONEEDLE patch is assessed in this study in comparison with intramuscular injections. The study has yet not started	ClinicalTrials.gov Identifier: NCT04394689
Inactivated influenza vaccine	Dissolvable microneedle patch	The study examined the safety and immunogenicity of an inactivated flu vaccine via two methods of administration in a Phase I research. Themes treated with dissolvable microneedle patches revealed no major adverse effects and did not occur with chronic disease.	ClinicalTrials.gov Identifier: NCT02438423 (91)
Intradermal HBVv with imiquimod	Microneedles	This study was carried using two modes of administration to assess the safety and immunogenicity of hepatitis B immunization. Those	ClinicalTrials.gov Identifier: NCT02621112 (Phase 2 &3)

		individuals were treated using the MICRONEEDLEs and IM injection systems. The study was finished in 2019 and there were no results yet.	
Zostavax	Microneedles	This study was conducted to evaluate the safety and efficacy of an intradermal live-attenuated against Varicella Zoster Infection in sibling donors undergoing HSCT. The study was completed in 2019 and no results have yet been posted	ClinicalTrials.gov Identifier: NCT02329457
Influenza vaccine	Microneedles	This study aimed to evaluate the efficacy of an influenza vaccine via TC, ID and IM routes of administration in 60 healthy human volunteers. The study has been completed and no results have yet been posted	ClinicalTrials.gov Identifier: NCT01707602

Chapter 6

Commercially Available Microneedles

Number of microneedle systems are licensed for medical and cosmetic use in the US, Japan, the EU, and certain other countries because of considerable study in this field (Waghule et al., 2019). However, Intanza® and Fluzone® are presently the only commercially available microneedle vaccination distribution method (Bragazzi et al., 2019). In 2010, MicronJet600 for the provision of medicines and other substances was authorized by the US FDA (Donnelly et al., 2012). A list of commercially available microneedle vaccine delivery system has been illustrated in Table 3. Although the scientific community is highly enthusiastic about microneedle-mediated vaccine administration, just a few microneedle systems are available on the market to be vaccinated, and even less are on the road to marketing (Nguyen et al., 2021).

Table 4: Commercially Available Microneedles

Product name	Manufacturer	Product description	Vaccine	Remarks
Intanza (BD Soluvia)	Becton Dickinson	This is a prefilled syringe with a length of 1.5 mm (0.06 inches	Influenza vaccine (split virion, inactivated)	Got marketing authorization in EU in 2009
Fluzone	Sanofi Pasteur Inc	This is a prefilled syringe with a length of 1.5	High dose (Quadrivalents)influenza vaccine containing strain A &B	US FDA approved (2009)

		mm (0.06 inches)		
MicronJet600	Nano Pass Inc. Sanofi Pasteur Inc.	Syringe type microneedle system with 3 needles of 600 µm length	Intradermal delivery of vaccines. Number of clinical trials were conducted using MicronJet600 and got promising results	This device was approved by US FDA in 2010
Pandemrix	Nano Pass Inc. GSK	This microneedle system consists of 3 needles of 600 µm length	Influenza vaccine (H1N1)	This vaccine was developed in 2006 by GSK and discontinued from 2015 due to lack of demand

Chapter 7

Discussion

The skin is a target model for immunization. FDA-approved polymers are used to make dissolving microneedles, which can be loaded with vaccination antigens or nanoparticles carrying the antigens. When these microneedles are injected into the skin, they disintegrate entirely, releasing the vaccine. Antigens are released slowly from dissolving microneedles filled with microparticles, allowing for prolonged antigen release, which aids in a strong adaptive immune response. Initially, influenza vaccination was administered using microneedles that dissolve. Using a polyvinyl pyrrolidone microneedle technology, the lyophilized antigen could be delivered in 5 minutes (Arya et al., 2016). A variety of polymers and sugars have been used to create dissolving microneedles for vaccinations since then (Mistilis et al., 2017). To combat the COVID-19 epidemic, dissolving microneedles have also been investigated. Antigen-specific antibodies were discovered to be generated by microneedles coated with the SARS-CoV-2-S1 protein (Ingrole et al., 2021).

Chapter 8

Advantages of Microneedles

8.1 Opportunity for vaccine administration by untrained personnel.

Currently, vaccination administration requires a health practitioner to deliver. This is a difficulty when healthcare professionals and facility-based care have restricted access, especially in nations in the poor world (Norman et al., 2014). Microneedles can overcome the need for skilled individuals to give the right vaccination simply by inserting them by hand or using an application device (Donnelly et al., 2016). This may be particularly useful during, for example, mass vaccination camps that would extend access to life-saving vaccinations by patients or less-trained health workers. At the same time, if patients or lower-trained employees self-administer the vaccinations, a considerable cost reduction might occur (Lee et al., 2019). Considering this, authors have developed different studies to explore the opinions of health care professionals and the public on the use of microneedles (Birchall et al., 2016). In especially for pediatric populations, Marshall et al presented a literature evaluation of the perception and acceptance of the microneedle vaccines technology. Overall, the research emphasizes the positive opinions of both the public and health experts of the technology and lists several advantages usually linked. (Marshall et al., 2019). In this way, the end users will benefit from a novel method of monitoring DMICRONEEDLE administration, ensuring accurate use, and helping to transfer technology into clinical application in the future. Feedback on the microneedle application has been assessed using a low-cost sensor-indicating film (Vicente-Pérez et al., 2016).

8.2 Overcoming pain and needle phobia

In many situations, adherence to vaccination regimens might be hindered by needle phobias (Nir et al., 2019). A needle gauge and needle mechanics, including hypodermic needle force and mechanical effort, are being correlated with the frequency of discomfort (Gill et al., 2019). Since microneedles are small and thin enough to avoid activation of dermal nerves, vaccination management via this method does not cause discomfort (Ripolin et al., 2017). As a result, patient adhesion to microneedle vaccination programs is anticipated to grow and microneedles are generally accepted by patients as previously pointed out (Quinn et al., 2018).

8.3 Potential for reduced cost vaccination

Costing is always an important consideration for any kind of delivery platform (Savitz et al., 2016). For these reasons, vaccine administration by hypodermic injection was always deemed costly. These include the requirement for: cleanroom facilities, autoclaving, freezing, complicated and sophisticated distribution channels. Cold chain supply systems, needles, syringes, injection water to rebuild the freezing-dried pulse (Adhikari et al., 2016). As an alternative to conventional hypodermic injections, microneedle supported vaccine administration has shown to be cost-effective because of many important benefits. Clean room facilities, cold chain systems or skilled healthcare personnel are not required to adhere to microneedle patches. They also employ cheaper polymers, plastics, metals, and others and offer lower dosage frequency and dose saving. All these variables significantly reduce the overall cost (Corrie et al., 2017). However, the cost of these two vaccine supply systems were compared in few studies. Bishwa et al. evaluated the cost efficiencies of delivering traditional vaccinations to microneedle-medicated measles using syringe and needle in their investigation. This study revealed that the administration of microneedle aided vaccines at a 95 percent vaccination level cost USD 1.66 per case as against USD 2.64 per case, which was roughly 40 percent cheaper for traditional subcutaneous injection (Bishwa et al., 2016). It has been estimated that microneedles could save US 950 USD million to third party payers and US 2.6 USD billion to society over an influenza season (Lee et al., 2015). The dose-saving capacity of the Nanopatch® mediated vaccinations in clinical testing was outstanding and the unit vaccination costs are projected to be reduced with commercialization of this platform (Corrie et al., 2017). For individuals living in underdeveloped and resources-limited nations, it will thus be particularly advantageous.

8.4 Elimination of hazardous sharps waste

As microneedle is made of water-soluble, biocompatible materials dissolved in the skin upon insertion, they overcome the production of biologically dangerous sharp waste and may be disposed of in non-sharp waste (Rodgers et al., 2019). This avoids the possibility that used or infected needles may transmit injuries and diseases (Arya et al., 2016).

8.5 Improved thermostability, simplified supply chain and subsequent increased vaccine coverage

Smaller than conventional hypodermic needles and syringes, microneedles enable simpler supply chain storage and delivery (Rodgers et al., 2019). Most vaccines require storage, shipping, storage, and delivery at a particular temperature from the time of production. This creates major economic problems, when cold chain storage infrastructure needs are generally difficult to satisfy in third world countries. Furthermore, cold chain failures and vaccine exposure beyond authorized limits might result in reduced vaccine power and a subsequent lack of vaccine-preventable disease protection (Wedlock et al., 2019). In many situations in conjunction with appropriate excipients, microneedles were manufactured to increase the thermostability of the vaccine within the microneedles, in its dried form (Hanson et al., 2017). Microneedles can thus be stored at environmental temperatures because of its solid-state formulation, and it is fully or partially necessary for cold chain storage (Kolluru et al., 2019). Several studies have shown the thermostability of microneedle vaccinations. As an example, a thermostable influenza vaccine micro-adhesive was created by Mistilis et al. During storage at room temperature up to 6 months a number of microneedles were proven to remain stable (Mistilis et al., 2015). Following that study the long-term stability of influenza vaccine microneedle including cold chain storages and the possible strains identified during manufacture and storage were evaluated in the same research team. The study was more current. In summary, flu vaccine in microneedle has shown that over 4 months' exposure to 60oC, numerous freeze-thaw cycles, or electron beam irradiation no substantial activity has been lost (Mistilis et al., 2017). Furthermore, in comparison with traditional liquid inactivated polio vaccine, Kolluru and the co-employees created a thermostable microneedle for inactivated polio vaccines with increased thermostability (IPV) (Kolluru et al., 2019). A number of excipients were examined for their stability improvement and maltodextrin and D-sorbitol combinations in histidine buffers have been shown to preserve IPV activity. With more than 40 percent of activity maintained post-storage for 2 months and over 20% after a single year, the resulting microneedles retained IPV stability in storage at up to 40ºC (Wedlock et al., 2019).

Chapter 9

9.1 Future Aspects of Covid -19 Vaccine Delivery using Microneedles

An international epidemic has been proclaimed due to Covid-19's spread. All around the world, there have been claimed to be millions of deaths. In order to reduce the number of deaths and immunize individuals against the virus, experts are working on developing a vaccine. If we talk about the future, microneedle-based vaccine delivery can play a strong impact in the world. As vaccination needs a professional health practitioner, they have restricted access especially in the poor nations. Again, costing is always an impactful problem for the poor nations. So, through microneedle-based vaccine delivery we can recover from these problems as it does not need any health practitioner and it is also cost effective. As long as the technology is employed to combat Covid 19, herd immunity will be enhanced.

9.2 Conclusion

The abrasive growth of the new coronavirus (COVID-19 or 2019-nCoV or SARS-CoV-2), which took place in December 2019, is still harmful to the entirety of mankind. COVID-19 was shortly called a worldwide pandemic by the World Health Organization. Since its emergence, however, COVID-19 is widely understood, and various therapeutic and pharmacological treatments are or have been currently in the study to decrease its dangers. The most efficient approach is infectious disease prevention. Microneedles are becoming intriguing as new vaccination techniques. Microneedle is a powerful method for transdermal vaccinations based on its mechanism for action, painlessness, and usage comfort. The microneedle dissolve is crucial for herd immunity and is beneficial for the population. Solid microneedles, Hollow microneedles are also feasible solutions for the manufacture of a covid-19 vaccine. This platform is very lucrative, user-friendly, and cost efficient because to its safety and efficient stability and is becoming an increasingly significant part of the administration of Covid-19 vaccines.

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