Micro needles for Covid-19 Vaccination: A Review Paper on an Efficient Way of Needle-less Vaccine Delivery.

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Abstract

Transdermal Drug Delivery System (TDDS) has not been used in majority of the countries, and the ones that use them have this system not as primary, but secondary choice of use. It is mainly because of the limitations they have previously faced in some cases. But, as a result of progressive evolution of TDDS from 1st Generation to 3rd Generation, there have been major changes and improvements which resolved the older limitations. Now days, TDDS and more specially the type Micro needle (MNs), could also deliver vaccines, and there are many researches and clinical trials occurred and are being proposed time to time, which are showing successful results. Over the past researches and clinical trials, the results depict that using MNs for vaccine delivery have many advantages, especially in view of any calamity or pandemic, like COVID-19. This review article has a main purpose of focusing that MNs would be the most prominent choice for COVID-19 vaccine delivery over injection or syringes, which will be a life changing happening for health care against fighting with pandemics using cost effective, easy and efficacious drug delivery system.

Keywords: Micro needle, COVID-19, Transdermal Delivery, Vaccination, Drug Delivery.

Accepted on 30 December, 2022

Introduction

Conventional methods of vaccination have been used from a long time, but seeing the current scenario of COVID-19, we should intellect with the novel methods that have the potential to cope with the rising demands.

As likely, transdermal patches are not so new but have been unrealised and negotiated by the majority, which led to decrease its use. But with the evolution of the 3rd generation of transdermal patches, it has become one of the greatest tools for refining the health and development system, known as microneedle patches.

Moreover, TDDS has the advantage of neglecting the GIT route, providing higher amount of drug to the bloodstream, especially Micro needle, which could even deliver up to 100% of the Drug to the Bloodstream.

Transdermal Drug Delivery System (TDDS)

Transdermal drug delivery system, also known as TDDS is a mode of drug delivery through the dermal route of the body. It is also known as "Transdermal Patches", which is a medicated adhesive patch placed on the skin to deliver a predetermined and specific amount of dose of medication into the bloodstream via the skin (Figure 1.) [1]. It acts as an alternative to the oral route of drug delivery, reducing the load of oral route on GIT and liver. Moreover, there are several physical methods which enhance the delivery of drug through the TDDS.

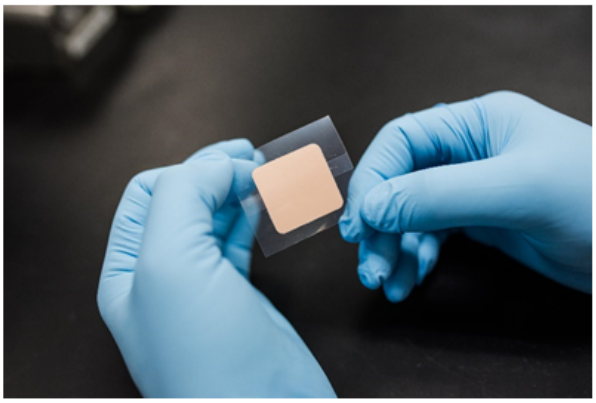

Figure 1. *Transdermal Patch.*

Exigency of TDDS

Skin is the largest organ of the human body, receiving 1/3 of the blood circulation and it is readily available. Skin acts as a barrier to any attacks over body, which can be physical, chemical or biological. Skin has some important roles in human body like it has a key role in regulating the blood pressure, maintaining body temperature, protection from UV rays, *etc*. Moreover, skin separates the underlying circulation of blood network from the outside environment. These are the factors which lead us to use skin for delivering the drug inside the body which could prove essential for the pharma and biotech industries to work more on Transdermal Drug Delivery System.

Anatomy of Skin

Skin is divided into three areas, "Epidermis" as the topmost or outermost layer, "Dermis" in the middle, and "Hypodermis" beneath the Dermis (Figure. 2) [4].

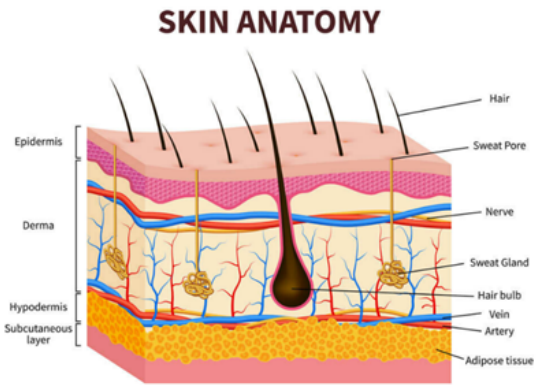

Figure 2. *Anatomy of Skin.*

Epidermis

Epidermis, having a major role for the TDDS, is further divided into two layers; the first one is called as Stratum Corneum, which is the rate limiting barrier for transdermal delivery system of drug. The second one is the viable layer, situated between the Stratum corneum and Dermis. Stratum corneum is the outermost layer which comprises of dead cells of the epidermis. It is 10 millimetres thick when dry, comprised of 75 to 80 % protein, 5 to 15 % lipids, and 10 % Ondansetron material on dry basis [2]. The Viable layer of epidermis is situated beneath the Stratum Corneum, which may arise in thickness, 0.06 mm in eyelids, whereas 0.08 millimetres in palms [2]. This layer is divided into four sublayers which are Stratum Lucidum, Stratum Granulosum, Stratum Spinosum and Stratum Basale [3]. Stratum Basale constantly renews the epidermis by Mitosis.

Dermis

Dermis also called as Corium, is a [3-5] mm thick layer, which is composed of connective tissues like blood vessels, lymph, *etc* [2]. Dermis provides nutrients and oxygen to skin while removing the toxins and waste products. In terms of Transdermal Drug Delivery System, this layer provides minimal barrier to the delivery of most polar drugs that is why this layer is often viewed as essentially Gelled Water. It contains two sublayers, namely, the Papillary Dermis and Reticular Dermis [3]

Hypodermis

Hypodermis is the third layer of skin, which is situated beneath the dermis layer. The major role of hypodermis is to support the dermis and epidermis layer, by providing nutritional support and mechanical protection. It is the fat storage area of the skin, which carries principal blood vessels and nerves. It also helps to regulate the temperature of the body.

Percutaneous Absorption

The penetration of substances into various layers of skin, while permeation across skin into the systemic circulation of the body is called as percutaneous absorption. For the Transdermal Drug Delivery System to work efficiently, the delivered drug has to be absorbed to an adequate extent and rate for achieving and maintaining uniformity of therapeutic levels throughout the duration of use

Factors that influence the Transdermal Drug Delivery

1. Release of Medicament from vehicle

2. Skin barrier penetration

3. Activation of pharmacological response

Generations of Transdermal Drug Delivery System

The generations of TDDS shows how the novel concepts of drug delivery process is evolved. By the newer generations, many limitations of TDDS have been resolved and the further is yet to come (Figure.3) [6].

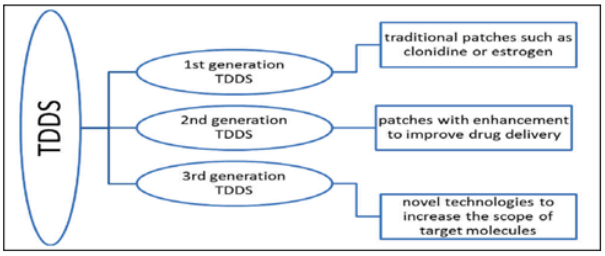

Figure 3. *Generations of Transdermal Patches.*

1st Generation: In the first generation of TDDS, there are two types of systems, mainly, the "Liquid Reservoir System" and the "Adhesive Matrix System". The liquid reservoir consists of a protective and adhesive backing material, a liquid reservoir, and a release membrane. The adhesive matrix system involves the adhesive and the drug in a combined layer, between an outer protective packing material and an inner protective layer touching the skin surface

2nd Generation: The working of the second generation of TDDS is to enhance the effect of drug delivery into the skin, mainly through the stratum corneum. This is done by using some physical or chemical mechanism to disrupt the horny layer (or Stratum Corneum). Gentle heating, iontophoresis, *etc* are some examples of it.

3rd Generation: The goal of the third generation of TDDS is to allow larger molecules to pass through the stratum corneum, into the blood circulation. This method is based on releasing the drug in the area between the ending of the viable epidermis, and the dermis, so that the horny layer is crossed, whereas there is no harm to the nerves and veins. Some 3rd Generation TDDS methods are Micro needle, thermal ablation, ultrasound, microdermabrasion, *etc*

Micro needle -An Array of Advanced Vaccination

Micro needle are 3rd generation TDDS, which serves to deliver the drug through the skin surface, by disrupting the stratum corneum layer through the micron size needles, it contains (refer to Figure 4) [7]. The motive to develop MNs is to resolve the painful hypodermic needle, and at the same time, enhance the drug delivery of the transdermal patches [8]. The advantage of MNs over the hypodermic needles or older transdermal patches is to bypass the stratum corneum and releasing drug between the viable epidermis and the dermis, 100%, without any pain.

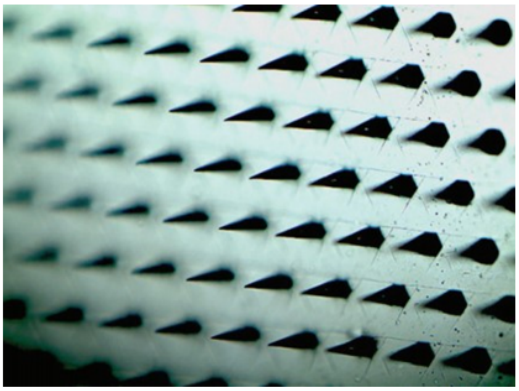

Figure 4. *Micro needle.*

Dimensions

The MN patches have very small micron sized needles, which is the reason for its faster and enhanced action. They are produced having a needle length of up to 1,500 µm, as the epidermis is also 500-1500 µm thick. The thickness of the MNs ranges from 50-250 µm, having 1-25 µm tip thickness [9]. As Waghule T, Singhvi G said in their paper on Micro needle, the tips of Micro needle can be cylindrical, triangular, pointed, pentagonal, octagonal, *etc* [9].

Mechanism

Before MNs, the problems with the older transdermal system are to not provide the desired amount of drug into the systemic circulation. It is due to the stratum corneum, which is also called as the rate limiting barrier of the skin. To resolve this problem, many chemical and physical methods are used, which helped in increasing the rate of drug release through this limiting barrier of skin. Thus, the idea of MN is developed, which works by disrupting the stratum corneum, delivering the drug directly between the viable epidermis and the dermis (refer to Figure 5.) [10]. Therefore, MNs have a high efficacy of action.

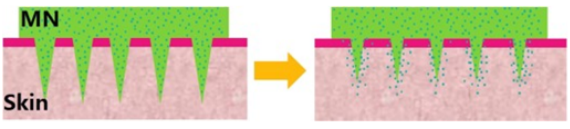

Figure 5. *Dissolving Micro needle.*

Types of Micro needle

Classification of MNs depends on their mode of drug delivery [7]. In common, there are 4 types of MNs available (Figure 6) [10]

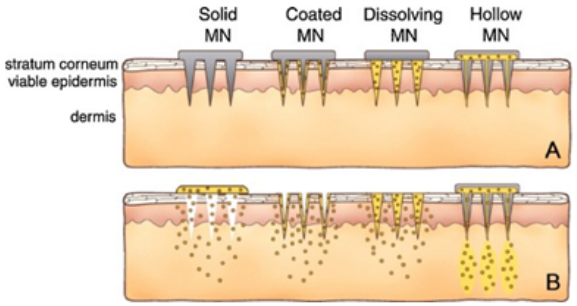

Figure 6. *Types of Micro needle.*

A Solid MNs

Solid MNs are used to puncture the stratum corneum. These MNs do not contain any drug. After the puncture, the drug in the patch is released into the skin, which passes inside the dermis through the punctured pores.

The residue patch of solid MNs should be disposed carefully, or it could come in contact with others and may cause harm.

B Coated MNs

These are also like solid MNs, but these MNs have drug coating over them. When coated MNs are used, the coated drug dissolves inside the skin after puncturing stratum corneum.

C Hollow MNs

In the hollow MN system, the drug is filled inside the needles, allowing the drug to flow and dissolve into the underlying skin surface after disrupting stratum corneum. These MNs have a close resemblance to hypodermic injections [11,7]

D Dissolving MNs

These MNs are very much common to hollow and coated MNs, but here, all the needles are water soluble or biodegradable. These MNs leave no waste or remnants at all in the skin after removing the patch. It has an advantage of transferring larger doses of drug, but fixed amount of drug delivery is somehow difficult [11].

MN Fabrication Materials

Many types of materials are used for the fabrication of MNs like synthetic polymers, biodegradable polymers, metals, glass, ceramics, *etc*. Synthetic polymers generally silicon is referred to use for their mechanical strength. Stainless steel, titanium, gold, palladium, *etc* are used as metal Micro needle. Glass and ceramics are also used for MN fabrication. Sugars such as maltose, mannitol, *etc* are used [7].

COVID-19: Scenario and Science

The Severe Acute Respiratory Syndrome Coronavirus 2, also called as SARS-CoV-2, created a devastating calamity to the world (Figure 7. [13]. Started in a city called Wuhan, in China, the virus spread to the whole world from person to person. With 3050 deaths up to March-1-2020, the deaths increased to 50069 at April -1, 242846 at May-1, 384926 at June-1, 860310 at September-1 2020 and the figure still continues to increase as the pandemic is still persisting [12].

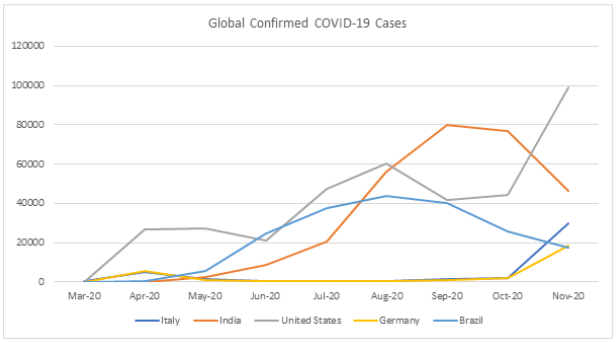

Figure 7. *Global Approaching Cases.*

SARS_CoV_2 have its isolates belonging to the Betacoronavirus genus of the Coronaviridae family [15]. This Coronaviridae family has two subunits, name ly Letovirinae and Orthocoronavirinae, where Orthocoronavirinae includes Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus, in which, SARS_CoV, MERS_CoV, and SARS_CoV_2, all these three belongs to Betacoronavirus [14]. Being a single-stranded RNA virus, it contains four major viral structure proteins: Spike(S), Membrane (M), Envelope (E), and Nucleoplasid(N) proteins [15]. The common symptom it causes includes fever (not in everyone), cough, sore throat, fatigue, headache, myalgia, and breathlessness [16]. Although there are two types of person attacked by this virus, symptomatic ones show the symptoms, while asymptomatic ones don't show properly, but both of them could have serious impact, even death.

COVID-19: Vaccine

What is Vaccine?

Vaccine is a biological preparation which trains the immune system to develop antibody against one or more disease, when given. [17] Basically, vaccines could be subcategorised under several types, depending upon the disease origin or the treatment process, which came as Virus vaccine, Bacterial vaccine, DNA or RNA vaccine, *etc* [19]. Usually, a vaccine has a presence of the agent causing disease, either in weekend form, dead form, its toxins, proteins, *etc*

Generally, Virus vaccines are of four types

a) Live Attenuated Vaccine: -Having a weakened form of the germ

b) Inactivated Vaccine: -Having the dead form of the germ

c) Subunit/Recombinant Vaccine: -Having a specific part of the germ

d) Toxoid Vaccine: -Having the toxins of the germ

SARS_CoV_2 Vaccine and its Working

Generally, a vaccine works by producing 2 types of white blood cells, T-cells and B-cells. T-cells are the one which are attacked by the germ, and B-cells produce Antibody. In the case of live vaccines, the living virus is used but its disease-causing parts were removed. In case of SARS_CoV_2 vaccine development, there is a novel concept of messenger RNA vaccine (mRNA 1273) [20]. Scientists have examined that the spike proteins of coronavirus are the key point to study and work on. Coronavirus enters the human body through the spike proteins, by combining to the ACE-2 receptor of human body. In the mRNA Vaccine of SARS_CoV_2 (refer to Fig. 8 [21]), the nucleic acid sequence of the spike protein is encoded into an mRNA, which when enters the body replicates itself and produces spike proteins from normal cells. After that, the B-cells will learn about the spikes and will create antibody, leading to the end of those cells. The leftover B-cells will remain in the body, which will be helpful for future protection from this disease, as these B-cells now know about these Spike proteins.

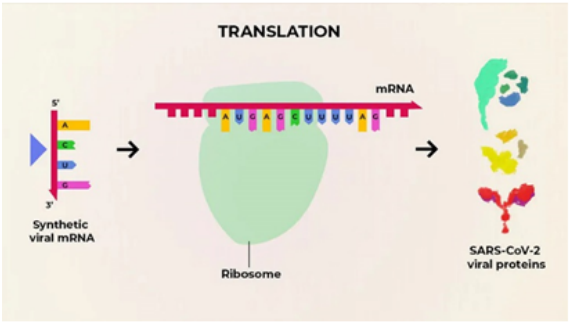

Figure 8. *Mechanism of mRNA vaccine action.*

On-going Covid-19 Vaccine Trials

Indian Biotech giant, Bharat Biotech with collaboration of Indian Council of Medical Research (ICMR) and National Institute of Virology (NIV) created COVAXIN. From the reports and data of the company, the SARS-CoV-2 Strain was isolated in NIV, Pune before it was transferred to Bharat Biotech. The modelling of this Vaccine is an inactivated pathogen derived from an asymptomatic patient. In addition, there are many other Vaccine trails on going; some of them are listed on Table-1 [23],

Table 1. *Covid-19 Vaccine Track.*

Brand Name of Vaccine	Type of Vaccine	Research Organisation/ Institute	Clinical Trial Stage
BNT162	mRNA-based vaccine	Pfizer, BioNTech	Phase 3
mRNA-1273	mRNA-based vaccine	Moderna	Phase 3

Ad5-nCoV	Recombinant vaccine (adenovirus type 5 vector)	CanSino Biologics	Phase 3
CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	Phase 3
Covaxin	Inactivated vaccine	Bharat Biotech; National Institute of Virology	Phase 3
Sputnik V	Non-replicating viral vector	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Phase 3
AZD1222	Replication-deficient viral vector vaccine (adenovirus from chimpanzees)	The University of Oxford; AstraZeneca; IQ*VIA*; Serum Institute of India	Phase 3

Necessity of Micro needle over Injections

1. Safe & Easy Handling

With the ease in understanding the use of MNs, they are also very easy and safe to use/handle. All the work done needed is to remove the outer protective layer so the microneedle patch could be applied on the skin. Is as simple as is said, doing your chores after that also will not bother you.

2. No Compliance

Due to its painless behaviour, it could be used for small children too. As for the adults, they didn't have to spend the time to get injection from a trained physician. It is also very useful for needle phobic persons, and its accidental damage chances are also zero.

3. Less Wastage

After using a MN, the only residue left is the used patch which is very small in size, and at the same time, not harmful for anyone. People however could transfer the used MN patch directly to the dustbin.

4. High Potential

Vaccination using MNs for immune response has shown an inclined path over the time [24]. It has a high potential of drug supply mechanism.

5. Controlled Delivery

Unlike injections, the dosage delivery of vaccine from MNs could be done in a controlled way as CDDS. There could be an acute initial dosage and a sustained release afterwards. CDDS methods are better and safer. They have lesser side effects with better therapeutic action.

6. Cost Effective

For the injection system of vaccine, single injection should be used for any single person, also having a small bottle/vial containing the vaccine. The manufacturing prices of the total injections are and the bottles will be high. MNs overcome these limitations due to its small size, and the only thing it requires is a small patch containing micron-sized needles and the drug.

7. Biodegradable

Using biological methods for treatment is far better than others. Micro needle are also produced having biodegradable nature, especially the Dissolving MNs [7]

8. Time Efficient Process

Using MNs lowers the time interval of the drug delivery process, especially compared to injections and syringes, which helps to provide an efficient time management process for higher number of patients.

Advantages of using MNs in developing countries in COVID-19 situation

1. Budget Option: The first and foremost quality for choosing a newer method is to be budget friendly. As the covid-19 impact on every country, the GDP had gone a negative gradient, which doesn't seem to go up in this current scenario. MNs are cheaper in price and have low manufacturing cost as compared to others, but at the same time, are stable and promising. This is why; producing MN patch will not take much money to spend on, whereas giving better results.

2. No Population Barrier: There should be no restriction of vaccine usage in any area due to population. Reacting towards it, MNs stand out ahead because -

a. There is no expert needed for every person.

b. There is no heavy understanding needed to use this method.

c. People will not have to wait in the queue to get the vaccination.

d. There will be no headache for both the medical staff and the patient.

e. People will not have to break the rule of social distancing in COVID-19.

f. There will be a better and hassle-free way of data management and MN patch delivery to every patient.

3. No Need of Expert (per head): In this time of a pandemic, maximum of the medical staff is working on treating the covid-19 patients, sanitizing as much as possible, data maintaining and management, *etc*. It will be more problematic to them if given the duty of injecting the Vaccine to the entire country. Injections are a time consuming and expert needed work to do. To break this barrier, MNs should be used in place of injections, so that there will be no need of expert to work on every single person.

New Researches on MN Patch Petcock

In an on-going research in the University Of Pittsburgh School Of Medicine, scientists have created MN Patch that can deliver COVID-19 Vaccine to mice [25]. This research has shown a success sight with positive results, leading to acknowledge the potential of MN Vaccination, which furthermore tells us that MN Vaccination for COVID-19 is not a problem at all.

VaxiPatch™

A recent approach by Verndari, Inc. in production of self-administered MN patch for COVID-19 Vaccination is showing a positive result and is said to have more efficacy and improved and easy vaccine delivery.

Another goal of this MN Patch is to eliminate Refrigeration of the Vaccine. This MN Patch could be used for older, recent as well as future vaccines.

MIMIX™

Following the acceptance and advantages of MN patch, Vexes Technologies, Inc. is on the way of emerging their own MN patch, developed at Tufts University, MIT, and Vexes, reported to provide single-dose, self-applied patch, promises to be used with any mechanism/form of COVID-19 Vaccine. This patch works on Sustained Release mechanism of drug delivery, enabling vaccine delivery for 2-3 weeks, with only 5 minutes of wear time.

Glucose Monitor

Recently, a method of Paper Microneedle Patch is developed for self-diagnosis of Glucose level in the body [28]. A simple concept of porous microneedle is combined with Paper Biosensor to give the glucose level results. It could be a great tool, providing Glucose Monitor for us in the near future market with the possibility of discovering newer approaches. Furthermore, future researches into these MN patch monitors could be a great achievement into monitoring more diseases, viruses, health levels of the body.

Previous Researches on Microneedle Array Vaccine

A microneedle has been tested for many diseases occurred in the past, and it has shown a stable positive rate in nearly all of them in the clinical trials, and is the reason it has been accepted worldwide now. Not only the results gathered public attention, but also the way of instalment of the patch, due to its reliability. Previous results and knowledge are essential for using and maintaining an upper gradient in the newer study results, which also helps to deal with future problems.

Micro needle vaccination for Influenza Virus

Influenza or “the flu” is the major cause of sudden flu pandemics, is caused by Influenza Virus of Orthomyxoviridae family [29]. It contains several genera, but Influenza virus A, B & C are known to have the potential of “Birds and Mammal Infection”, where type A & B are the most severe source of Infection causing large number of deaths [29]. Micro needle Patch has been used on Influenza Virus with a goal to overcome the immune tolerance during pregnancy, and the results showed a successful skin penetration and antigen release [30]. Furthermore, it also demonstrated that offspring of the immunized mice using MN Patch has higher levels of anti-influenza antibodies compared to IM route [30]. Moreover, there is a large amount of investment consumed in the research of Influenza virus, and its vaccine also requires an annual re-vaccination [31], which is why MN is a better choice of candidate for the manufacturers for the ease ability of usage.

Microneedle vaccination for Measles

Measles, caused by a virus of Paramyxovirus family, is a very contagious disease, which is caused by infection in the respiratory tract [32]. Spreads directly by air, sneezing & coughing is the simple way of getting infected by this virus. Despite having an effective vaccine, millions of people died due to measles during 2018 [32]. Micro needle patches, therefore, have been said to be an easier and better tool for measles vaccination, according to Georgia Tech and CDC's Global Immunisation Division and Division of Viral Diseases [33]. It is also said that this patch could be used in remote areas and at varying temperatures due to its stability [33]. Several clinical trials conclude the safety and efficacy of micro needle patch used for the immunization of measles virus and is said to be more efficient in terms of the desired levels of drug needed, compared to SC injection [34]. Moreover, Micro needle array have been tested for many virus and diseases, severe to normal, but this delivery has shown a positive result in every study. It is also studied for MERS-CoV, where similar results came with desired action [35]. Studies has also shown that there is proper amount of pressure received in the skin when Micro needle is used by public volunteer to test and apply, indicating successful insertion of MN Patch into skin, covering entire region of patch [36]. This data depicts the usefulness of MN array for any disease. Current market of drugs contains MN mediated drug delivery for many diseases and infections, but the use of this delivery should gain a good view, considering the advantages it has, as compared to conventional drug delivery methods.

Proper way to provide this MN patch to everyone

Seeing the vast population of any country, it could be difficult to provide injection-based vaccine to a huge population. It will need a long interval of time, a much organised way of vaccination that could be broken anytime why people getting mentally impatient. To provide MN based vaccine, there is some good organised way to provide vaccination to everyone in a very short time,

1. Door to Door Delivery

There should be an area specific person who will then further divide smaller areas to different person, simply going to

everyone's house, noting their data and providing them with a number of MN patch as the family size. The staff persons could either tell them the usage (remove the outer layer and simply attach it) or could do the same by themselves.

2. Centre Specific Delivery

There could be any temporary locations created for smaller areas, needing 2-3 staff working on data management and MN patch delivery to people. People could normally walk there, taking any of their document and could simply take one patch or a number of, depending upon their family size. Furthermore, the easy usage of the MN patch could be simply demonstrated to every people via advertisement for videography.

Conclusion

The For the betterment and an improved health development, and to overcome the high population barrier, Micro needle could be a great tool if used for vaccination. It has every property of a good vaccine delivery method, with a prerequisite and unrealized high potential effort. Moreover, it stands out in aspects, quality and quantity manufacturing, due to its high scale of action and low-cost requiring manufacture. At last, using newer technologies which have the right potential, at the same time could easily handle the rising demand, should be a better option than the conventional methods.

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