MICRONEEDLE PATCH (MNP): A GAME CHANGER AND NEW EMERGING APPROACH TO VACCINATION

Abstract

In medical history, vaccination has been one of the most successful interventions, reducing mortality and morbidity from a variety of infectious diseases to almost zero. Many vaccines are typically administered through subcutaneously or intramuscularly injections, which can cause pain, discomfort, and fear in individuals with a fear of needles. However, the skin offers a promising alternative for vaccine delivery due to its accessibility and abundance of immune cells. Microneedles leverage skin-based immunization while addressing the issues associated with traditional needle-based vaccination, such as needle injuries, pain, and the risk of needle reuse. Microneedle patches are currently under extensive investigation as a vaccination delivery system, aiming to replace traditional injections and syringes. Their potential for self-administration, efficiency, and cost-effectiveness is being closely examined. This chapter seeks to provide an overview of the benefits and the potential transformative influence of microneedle patches in the context of vaccine delivery.

Keywords: Microneedle Patch, Vaccination, Immunity

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I. INTRODUCTION

In developing countries million people die each year from infectious diseases which could massively be avoided with the aid of vaccination. Since the launch of Expanded Program on Immunization (EPI), immunization rate has increased but still there is enormous scope to overcome the challenges coming in the way to a more accomplished vaccination program in developing countries [1]. As per world health organization valuations, millions of children succumb to death every year from vaccine-preventable diseases for which there are vaccines proposed by WHO and among 1–59 months old children, 29% of deaths are vaccine preventable [2]. Currently, vaccines are administrated in mainly two scenarios: routine and mass vaccination ventures. Routine vaccination aims at high coverage on an on-going basis, though occasionally fall short by itself owing to infrastructural challenges. On the contrary mass vaccination ventures specifically target large population in particular regions more effectively. These campaigns are performed at fixed-post clinics, or rather carried off door-to-door steps, generally administering non-injectable vaccines by minimal trained manpower [3].

While multiple vaccines are exceptionally effective and endeavor life-long immunity, other vaccines offer merely moderate protection, specifically in developing nations where nutrition values are low and individuals might have compromised body's defense mechanism due to existence of other infections [4]. Majority of vaccines require administration of booster doses to shoot up immune response which anticipates vaccinating the same person couple of times that might be laborious to execute in those places having poor healthcare framework and recordkeeping [5]. Most of the immunization occurs *via* intramuscular or subcutaneous route that cause pain, discomfort or avoidance by individuals having needle-phobia. Few other methods like thermal microporation, transfollicular delivery, powder and fluid jet injection, sonoporation and microneedles have been put forward to release antigens into the skin [6]. In recent years, microneedles (MNs) have gathered the attention as an alternative to injectable dermal vaccination. MNs are needle-like microstructures, up to 1 mm in length which are basically incorporated on a patch. They penetrate the underlying tissue or stratum corneum and release the antigen into the dermis or epidermis layer, meanwhile they won’t reach to pain receptors and consequently avoid the pain sensation also [7].

Although, skin is intended to design in order to protect human body from foreign or toxic substances. Stratum corneum, the top-layer of skin (thick in humans) forms a physical barrier against vaccine delivery. Moreover, intradermal delivery of vaccination is considered convenient when compared with conventional intramuscular administration. Therefore, the release of high-molecular weight (>500 Da) substances like antigens need different methods to penetrate into skin [8]. MNPs are principally designed either with silicon/polymer microneedles or as solid dissolvable microneedles formed from water-soluble materials enveloped with vaccine formulations which are released in the skin upon microneedles dissolution. moreover , innovative microneedles vaccine delivery system offer additional advantages for instance thermo stability, fewer booster doses, less stress on healthcare personnel and increase in the vaccination adherence [9].

II. BARRIERS IN THE WAY OF EFFECTIVE VACCINATION

The commonest routes for administration of vaccines are oral and parenteral with disadvantages for each. In view of enzymes and acids in digestive system, the bioavailability of oral vaccine is significantly reduced. And the serious effects of needle injection such as needle injury, needle-borne infectious disease and blood-borne disease transmission also affect the physiological factors, efficacy and systemic functions [10]. For example, Type 1 diabetic patients have to daily administer insulin shots to get better quality of life, but routine injection prompt pain and trauma to skin, making it troublesome for diabetic patients to uphold sufficient compliance [11]. Almost the entire vaccination campaigns are carried off with hypodermic needle and syringe injection. Consequently, for the safe administration of vaccines, professional healthcare personnel are needed as well as to cautiously dispose off the resulting sharp waste needles (figure 1) [12]. In developing countries lack of trained healthcare staff remains a significant barrier to achieve huge vaccination campaigns. Both healthcare workers and patients are at risk due to unsafe injection practices. A study evaluated that due to unsafe injection practice every year up to 315,000 hepatitis C, 1.7 million hepatitis B and 33,800 HIV infections occurred [2]. Accordingly these hypodermic needles need to be cautiously discarded to avoid the needle-stick infections to healthcare personnel. Also, bio hazardous sharp waste generated during the process need to be disposed off carefully to ensure that their reuse are avoided either accidentally or intentionally. With these formidable obstacles during any vaccination campaigns in developing countries, it becomes more difficult to overcome the challenges of safe collection and disposal of hypodermic needles [13].

An added difficulty which comes in the way is that vaccines have to be kept at cold chain or usually refrigerated during storage, distribution and when used after reconstitution. Unusual freezing as well as heating temperatures both are ruinous to most vaccine formulations [14]. Due to the limited transportation infrastructure in developing nations, there is a shortage of proper cold chain storage during vaccine distribution, leading to significant vaccine wastage. Therefore, it is crucial to optimize the supply chain by considering the size and volume of vaccine containers, such as vials and syringes [15]. For example, variations in the space required for different vaccine presentations within the cold chain highlight the importance of this aspect. For instance, one dose of a vaccine in a 10-dose vial occupies only 3 cm3 of cold chain space, whereas another vaccine in a single-dose vial takes up 12.9 cm3 of cold chain capacity [16]. Moreover, the cost of establishing and maintaining the cold chain infrastructure is estimated to be between $200 to $300 million annually. This expense can be sustained in industrialized countries with well-established cold chain systems, but it poses a significant challenge in developing countries with less robust cold chain networks. This vulnerability underscores the potential for substantial losses in these regions [17].

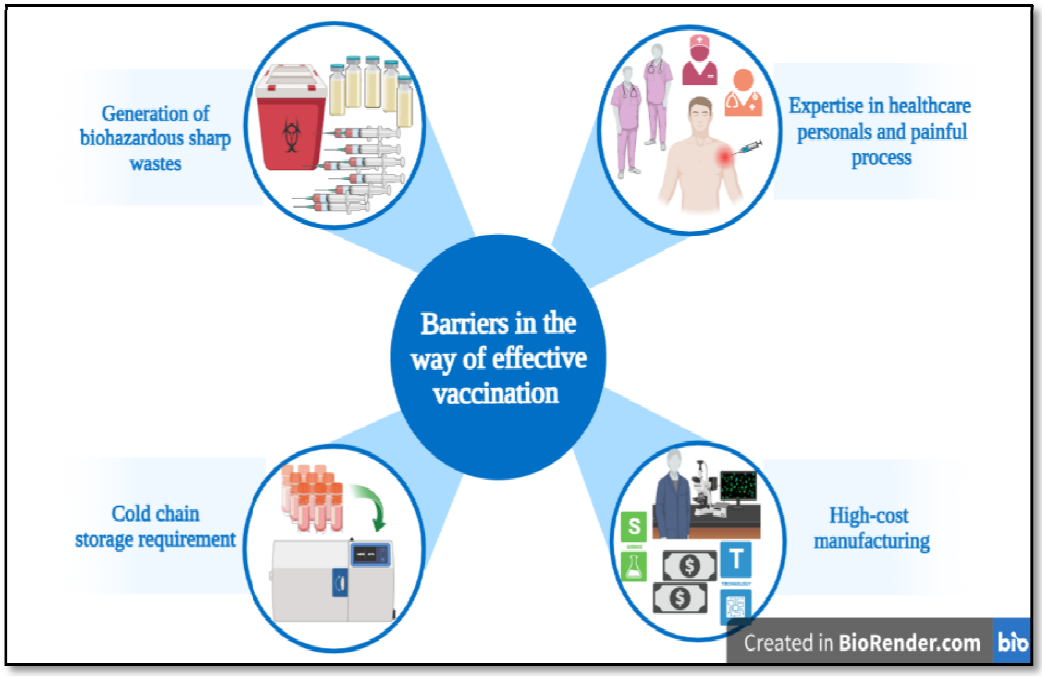

Figure 1: Barriers in the way of Effective Vaccination

III. POTENTIAL OBJECTIVES OF MNP (MICRONEEDLE PATCH)

1. **Targeted Skin Delivery:** Skin, being an immune-competent organ is easily accessible and attractive alternative to dermal vaccine delivery. Since dermal vaccination accesses diverse physiology and anatomy in contrast to hypodermic injection, oral delivery or unlike other conventional ways, the vaccine efficacy might get altered [18]. The dermis and epidermis layer of skin embrace a myriad of antigen presenting cells (APCs) including dermal dendritic cells (dDCs) and Langerhans cells (LCs) (figure 2). These APCs trap the antigens and eventually migrate them to draining lymph nodes for the presentation of antigen to T-cells to activate Ag-specific systemic immune response [19]. Apart from dDCs and LCs, epidermal keratinocytes are too engaged in generating immune response via chemokines and cytokines (e.g. TNF-α and IL-1β) by reinforcing the maturation of APCs and migration to the lymph nodes. As a result of considerable numbers of APCs displayed in the skin, vaccine delivery via dermal route might contribute to dose-sparing effects, thereby triggering enhanced immune response with lower doses of vaccines [20].

   Dissolvable microneedles are inherently designed to target these immune cells, suggesting a unique opportunity to enhance vaccine immunogenicity and dose tolerability. For instance, the effective lymphatic drainage and rich capillary beds in the skin give quick access to systemic circulation and faster vaccine onset times [21]. Over and above, skin is the most important defense against pathogen infiltration in the body and, consequently, provides an abundant proportion of immune cells that are excellent targets for vaccination. In routine administration sites, needles measuring hundreds of microns are aimed at skin with a thickness of 1–2 mm [22]. As a mean of protection, animals immunized against influenza employing microneedle patches showed better

clearance of virus from the lungs after inoculation with live virus than intramuscular vaccination. Additionally, MNP induced protection and immune response is supposed to last longer as compared to intramuscular vaccination [23].

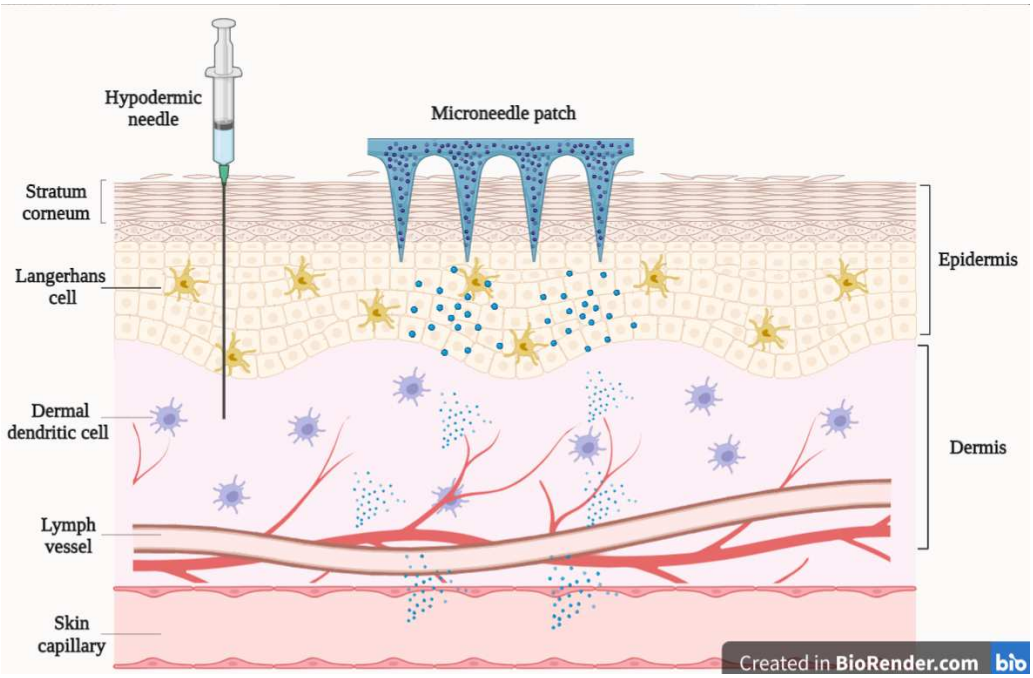

Figure 2: Targeted skin delivery by microneedle patch

2. **Reduced Expertise for Healthcare Personals:** The basic and minimal invasive technique of MNP delivery allow self-administration or management by personnel with minimal training or may be with or without the healthcare providers. This could also crash the limitation of requirement of trained healthcare personnel who currently vaccinate the people at fixed-post clinics and shifts the focus on house-to-house campaigns by minimally trained personnel [24]. In today's scenario, administration of vaccines by a trained health care personnel and to access facility-based care in developing countries imposes a serious challenge. DMNs (dissolvable microneedles) could resolve the necessity of professional healthcare workers as they are quite easy and effortlessly inserted by applicator device or hand (figure 3) [25]. This will be more beneficial during mass vaccination campaigns, where vaccination by patients themselves or lesser-trained personnel would expand access to lifesaving vaccines and concurrently could have significant cost savings [26]. For instance, in type 1 diabetes individuals are self-trained to take insulin shot as there is no other therapeutic alternative, measles vaccine is currently delivered by subcutaneous injection using hypodermic needle and syringe. At centralized locations, these delivery methods poses the requirement of professionally trained healthcare workers to administer each vaccine dose [27].

Decreasing the logistical challenges concerned with delivery of measles vaccine could enhance vaccination coverage and decrease vaccination campaign costs. Contrary to measles vaccine, the global campaign to uproot polio has been achievable because of the simplicity of administrating the vaccine orally by minimally trained personnel [28].

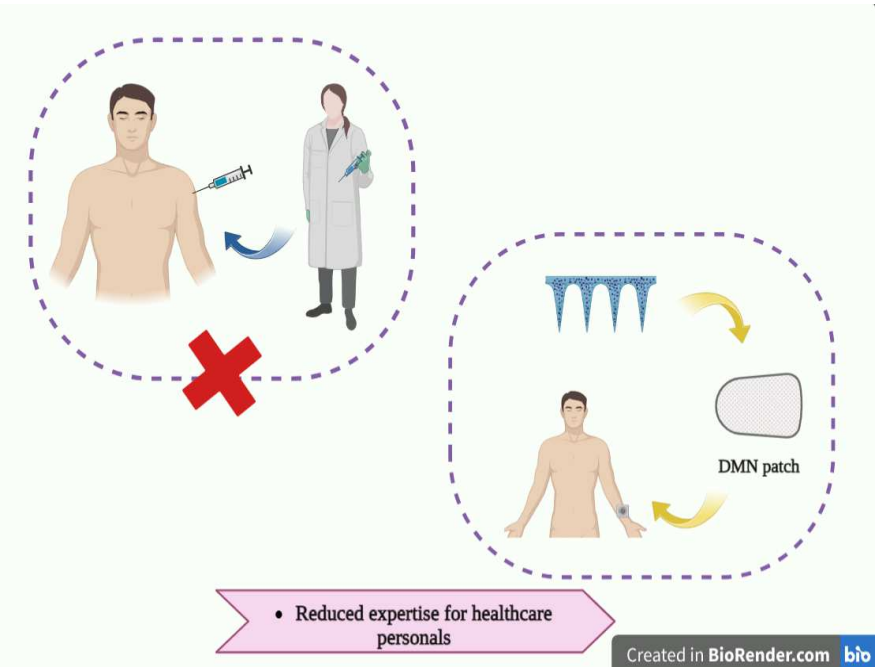

Figure 3: Reduced expertise for healthcare personals

3. **Reduced Risk of Sharp Hazardous Wastes:** Application of hypodermic needles in vaccination campaigns creates hazardous medical waste that needs to be demolished safely. Preventing needle theft and reuse through reliable disposal method adds up considerable huge costs to vaccination programmes [29]. For instance, in Philippines, a small-scale measles vaccination programme generated across 130,000 kg of sharp needle wastes. This arouse safety issues and risk of transmission of infectious diseases by either intentional or accidental reuse of needles [30]. All of these challenges incur extra expenditure and demands logistics regarding disposal of sharp wastes. Quite the reverse, DMN patches are created on the basis of water-soluble and biocompatible materials that disintegrate into the skin after insertion, consequently contributes in overcoming the dilemma of biohazardous sharp needle (figure 4) [31] and any other stuff that remains on skin might be discarded as non-sharp waste. Hence, the risk of infections and disease transmission arising from reused or discarded needles is circumvented by DMN patches [32].

4. **Elimination of Cold Chain Storage:** The next crucial challenge associated with the conventional vaccination framework is the requisite of cold chain storage and transport. Post reconstitution, multi-dose vials have to be used within two hours or might be discarded that results not only in bulk wastage of vaccines but also increases the program cost [33]. Most vaccines compel storage at precise temperature from the view point of manufacturer terms and condition, transportation and administration. Particularly in developing countries, this comes down to significant economic barrier, where it's difficult to meet the infrastructure requirements of cold chain storage [34]. Whilst due to cold chain failure, vaccines may be exposed to temperature outside its recommended range that leads to decreased vaccine potency or consequent lack of protection against vaccine-preventable ailments. In contrast DMNs patches are smaller than typical hypodermic needles or syringes, thereby conferring simplistic supply chains, storage and distribution

[35]. DMNs are fabricated in such a way that the vaccine is in its dried form and in some cases combined with ideal excipients to enhance thermo stability. Because of the solid-state formulations in DMNs, they can be stored at room temperature, conquering the necessity of cold chain storage either completely or partially (figure 4) [36]. In the case of the latter whereby only partial thermo stability is attained, DMNs can be stored in refrigerators but might not seek cold storage amid allocation to remote areas or during mass vaccination campaigns. A delivery system that knocks out the need of reconstitution, cold storage, transport and decreased cost per delivered dose could facilitate more effectual usage of vaccine [37].

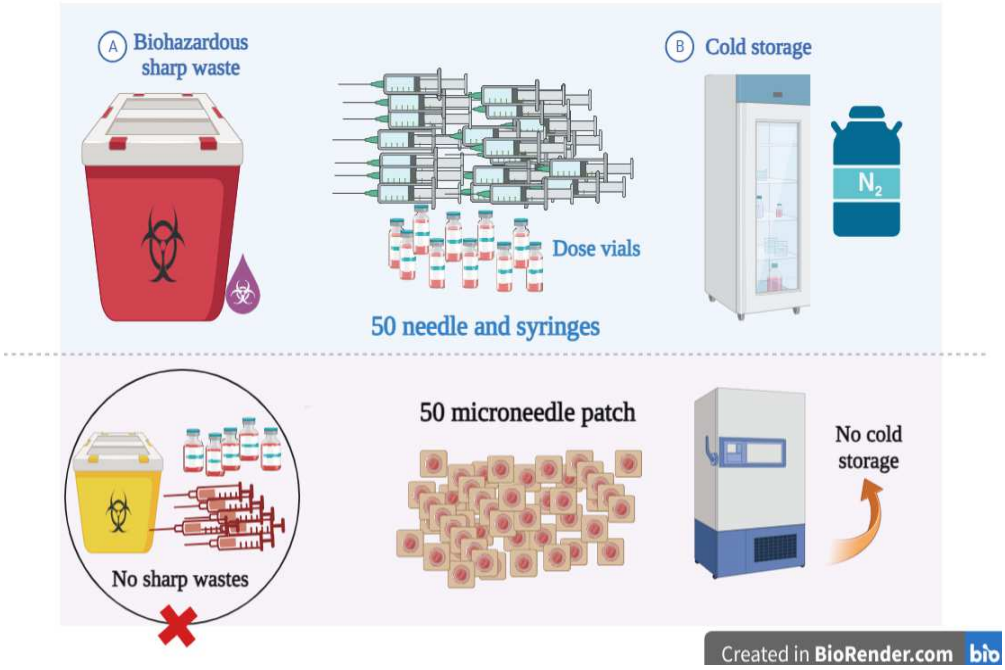

Figure 4: Elimination of cold chain storage and sharp hazardous wastes

5. **Single Use and Fully Disposable:** Microneedle patches are employed once, single shot and are fully disposable, which curbs the likelihood of contagion transmission closely linked with reuse of medical gear. Meanwhile, traditional vaccines are sometimes used multiple times and multidose administrated [38]. It entails vaccine wastage, such as when only few of doses are used before the vaccine expires, and to missed immunizations, for instance, when health care provider choose not to vaccinate the individual because doing so would demand the opening of a new vial when there are not enough patients to utilize the entire vaccine vial [8]. Such problems are common in the developing world, and can be avoided by using single dose DMNs. In conclusion, Medical devices with a reconfigurable component in combination with the single use component are more complex because they have to be kept until their next use. This complexity is circumvented by fully disposable DMNs [39].

6. **Reduction in the Cost of Vaccination (Low-Cost Manufacturing):** It is plausible that MNPs prompt reduction in vaccination cost owing to simplified supply chain, bump off hazardous needle wastes and to the prospect of reduced expertise of healthcare personnel

or can say self-vaccination [40]. Packaging of syringes and vials in aseptic conditions costs more than the pressing patches, with costs in dollars versus pennies. It is anticipated that DMNs production cost might compete with injectable drugs in manufacturing costs [41]. Although, it would be interesting to expand an understanding about MNPs manufacturing regulations and its subsequent costs, which are tend to be vaccine specific, to have a comparison of MNPs with the conventional vaccination approaches [42].

IV. POTENTIAL EFFECTS OF MICRONEEDLE PATCHES IN DEVELOPING COUNTRIES

In 2010, Prausnitz group reported the first successful vaccination using dissolvable micro needles. They fabricated DMNs with 650 µm needle height, comprised of liquid vinyl pyrrolidone monomer and 3 µg of lyophilized inactivated influenza virus. Dissolvable MNPs were inserted into mouse skin with gentle pressure and disintegrated within minutes [43]. It was further reported that immune response induced by DMNs was protective and greater than observed in intramuscular immunization with the equivalent doses. Particularly, even after lethal challenge with influenza virus DMNs showed enhanced humoral and cell mediated protective immunity. Going down the same road, Kendall and his co-workers formulated the NanopatchTM and authenticated the successful realease of Quil-A adjuvanted ovalbumin and influenza vaccine [44]. Concurrent with the reports by Prausnitz group, Kendall also confirmed that MNPs performed better at arousing humoral immune response against ovalbumin in mice in comparison to the traditional intramuscular route. In addition, both the authors also reported that the robust antibody responses induced in mice vaccinated with DMN, was achieved by using much lower dose with respect to intramuscular injection control [45]. Following these preliminary proclamations which marked the aspiring potential of the technique, a myriad of of studies have alleged the successful delivery of varied antigens, with an appreciable progress being directed in the field of DMN vaccination [31].

V. DIRECTIONS FOR FUTURE RESEARCH AND DEVELOPMENT

The forthcoming phase of microneedles research seems to be bright: indeed more researchers are coming forward and publishing multiple number of articles in this field. Meanwhile, it’s an exciting time for DMN research but it is of utmost importance to study the valuation of the imprint of microneedles before it is translated into use in clinical medicine for the welfare of patients. This transition will require not merely good science and engineering, but also constant funding from a vigilant pharmaceutical sector for the product development and clinical trials. Although two leading outstanding questions raise are (i) benefits of DMNs to people and (ii) reliable, scalable and low-cost manufacturing of MNPs. Particular attention should be paid to vaccine stability, microneedle skin insertion, biomechanics of DMNs application, precise transit of vaccine molecules in the skin capillaries for systemic distribution to immune cells and safe disposal of used DMNs. Besides, it also expands the vaccination programmes in developing countries, plausibly promote better vaccine stability, reduced vaccine wastage and thereby reduce burden on healthcare personnel.

The accreditation of MNPs in clinical practice require a handful of queries to be addressed. A vast array of manufacturing protocols for DMN fabrication on small-scale laboratory settings have been registered; still there are certain barriers to adopt these

techniques on industrial scale. Usually, assembly of DMN requires numerous fabrication steps to localize vaccine antigen and adjuvant in specific sections of DMN array, for heightened immune response and delivery efficacy. Embracing of such technologies at industrial level necessitate a considerable investment in equipment's, DMNs formation and characterization, expertise and guidance in good manufacturing practices, processing capabilities and pharmacopoeial standards. The world's largest manufacturer of transdermal patches, well known as LTS Lohmann Therapie-Systeme AG, now possesses a manufacturing license for the production of MNPs. In view of the fact that MNPs comprise vaccine within matrix of the array, each and every patch could possess distinct characteristics that makes it indispensable to test each DMN to ensure if it is authentic for the purpose.

The ongoing paucity of management guidance in this particular area poses a challenge to achieve the goal of DMN production at large scale. If DMNs are to be executed at clinical practice, regulatory instructions referring to patient welfare are warranted. The PATH Centre of Excellence for Microarray Technology aspires to meet regulatory affair and quality control tests in order to move forward this technology. Similar facts that need consideration apart from above discussed concerns are packaging, ease of use, subsequent delivery and validation of insertion. Despite that, couple of other improvements are yet to be figured out in some field of DMNs development ahead of regulatory acceptance and industrial scale-up. DMN fabrication require further optimization of certain methods to accredit minimal antigen wastage that is quite often claimed, though barely reported in the literature or not even verified on at least pilot scale production level. Analytical hardship cover potency and stability testing amidst storage, quantification and fidelity of antigen or adjuvant disintegration into the skin. Henceforth, for the future better organized research like selection of suitable adjuvant and to analyze its effect on DMN geometry are necessary for the optimization of DMN immunization. Till now, three clinical phase 1 studies have been briefed, pointing out that patch application and skin irritation are the leading issues to be resolved in future implementation. Undoubtedly, an ideal MNP does not exist thereby steps should be taken to further strengthen DMNs into safe, affordable and efficacious product.

VI. CONCLUSION

Microneedles were first manufactured in late 1990's, since then it has been an exemplar shift in the context of modulating vaccines delivery route to trigger paramount immune response with the highly economical doses. Past few years have witnessed a plethora of research initiatives to examine the framework of microneedle-mediated delivery of vaccine in response to elicit antigen-specific humoral and cell mediated immunity, patient compliance, stability and efficacy compared with standard subcutaneous or intramuscular routes. The spectrum of MNPs practice in therapeutic vaccines is diverse, ranging from multitudinous viral vaccines, bacterial vaccines and novel concept of DNA vaccines that are yet to be utilized for human use. In a similar vein, microneedle constitution has emerged and diversification has also been observed ranging from solid one to hollow injectable and implantable type microneedles. The polarity in microneedle types would prove authentic in governing the kinetics of vaccine release. Eventually, the intent behind the prototype of the inception of microneedles was to facilitate administration of vaccine release to profuse network of APCs underneath the skin, but the ongoing research in basic immunology also focuses on the biological mechanisms responsible for the optimistic results seen in various microneedle studies so far.

Moreover, clinical studies in influenza vaccination using microneedles have reported greater serological protection in contrast to traditional subcutaneous route and confirmed the safety and pain free action of microneedles, whilst there were no prominent adverse effects noted except for a mild local erythemia in some patients. In conclusion, it is conceivable that MNPs, owing to its dose-sparing lead, improved patient compliance, safety and better serological conversion rate would surely establish a firm stand ahead as one of the very best effective and easily practiced vaccine delivery routes.

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