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A Review on Dissolvable Microneedle Patches To Enable Increased Access to Vaccines against Sars-Cov-2 and Future Pandemic Outbreaks

Anagha.A[1], Niyuktha.S[1] , Vimal K.R[1] , Nethaji Ramalingam[1] , Babu Ganesan[2]
[1]*DEPARTMENT OF PHARMACEUTICS, DEVAKI AMMA MEMORIAL COLLEGE OF PHARMACY, CHELEMBRA,MALAPPURAM,KERALA-673634,INDIA*
[2]*DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, DEVAKI AMMA MEMORIAL COLLEGE OF PHARMACY, CHELEMBRA,MALAPPURAM,KERALA-673634,INDIA*

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ABSTRACT
Vaccines are an essential component of pandemic preparedness but can be limited dueto challenges in production and logisticalimplementation.The COVID-19 pandemic is a serious threat to global health and the global economy. The development ofa safe and efficacious vaccine to prevent infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent for COVID-19, highlightsthe importance of vaccination to combat infectious pathogens.The highly accessible cutaneous microenvironmentis an ideal target for vaccination since the skin harbours a high density of antigen-presenting cells and immuneaccessory cells with broad innate immune functions.Microarray patches (MAPs) are an attractiveintracutaneous bio cargo delivery systemthat enables safe, reproducible, and controlled administration of vaccinecomponents (antigens, with or without adjuvants) to defined skinmicroenvironments.Dissolvable microneedle patches areadvantageous for many possible reasons: improved immunogenicity; dose-sparing effects; expectedlow manufacturing cost; elimination of sharps; reduction of vaccine wastage; no need for reconstitution;simplified supply chain, with reduction of cold chain supply through increased thermostability;ease of use, reducing the need for healthcare providers; and greater acceptability compared to traditionalhypodermic injections.When applied to coronavirus disease 2019 (COVID-19) and futurepandemic outbreaks, microneedle patches have great potential to improve vaccination globally andsave many lives.

KEYWORDS:COVID-19,Dissolvable microneedle patch, Drug delivery, Skin vaccination, Vaccine delivery

I. INTRODUCTION

Now, the coronavirus disease 2019 (COVID-19) pandemic, caused by severeacute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to 100 million confirmedinfections and more than 2 million deaths worldwide**[1]**.Rapidlyexpanding public health strategies help control the spread of COVID-19.

The remarkable history of immunization against infectious pathogensunderscores the importance of vaccination to combat emerging infectiousdiseases. Indeed, since the release of the genomesequence of SARS-CoV-2 inmid-January 2020, there has been unprecedentedprogress toward the development of a safe and effective vaccineagainst SARS-CoV-2 infection. Prominent advances in biomedicalscience and technology have enabled rapid development of severalCOVID-19 vaccine candidates using different or inactivated virus,nucleic acid, and live viral vectored antigen strategies[2].

The COVID-19 pandemic has overwhelmed both health and economic systems. Most vaccinesfor SARS-CoV-2 are injected using a hypodermic needle and require multiple doses administered by specially trainedhealthcare providers and have cold chain distribution requirements ranging from -70^0Cto 8^0C, which presents significant logistical limitations[3]. The founding of the COVID-19 Vaccines Global Access (COVAX) Facility by Gavi, the Coalition for Epidemic Preparedness Innovations (CEPI), and the World Health Organization (WHO) is an attempt to garner resources and unite higher- and lower-income countries for a coordinated, rapid, transparent, and equitable access to COVID-19 vaccines worldwide.

The WHO identified vaccine hesitancy as one of the top ten global health threats in 2019.

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Vaccine hesitancy is further magnified by needle-phobia, pain, fear of complications,and fear of leaving quarantine to a healthcare setting. National surveys during theCOVID-19 pandemic report that roughly 30% of adults are not sure whether they wouldbe vaccinated and 10% did not intend to be vaccinated. The spread of bloodbornepathogens by needle re-use is also a major concern, along with a shortage of healthcareproviders, especially in developing countries. New and innovative vaccine technology anddelivery mechanisms may assist in addressing these challenges.

As a possible solution for pandemic countermeasures, dissolvable microneedle patchesshould be considered as a vaccine delivery method. The patches consist of micronscalesolid conical structures made of dissolvable excipients on a skin patch backing thatdeliver vaccine antigens across the stratum corneum barrier into the viable epidermisand dermis of the skin. As microneedles are less than one millimeter long, they causelittle or no pain and are strongly preferred over traditional immunization by injection.Further,microneedle patches require no special training to be administered, do not generatebiohazardous sharps waste, and can be formulated for thermostability[4],[5].

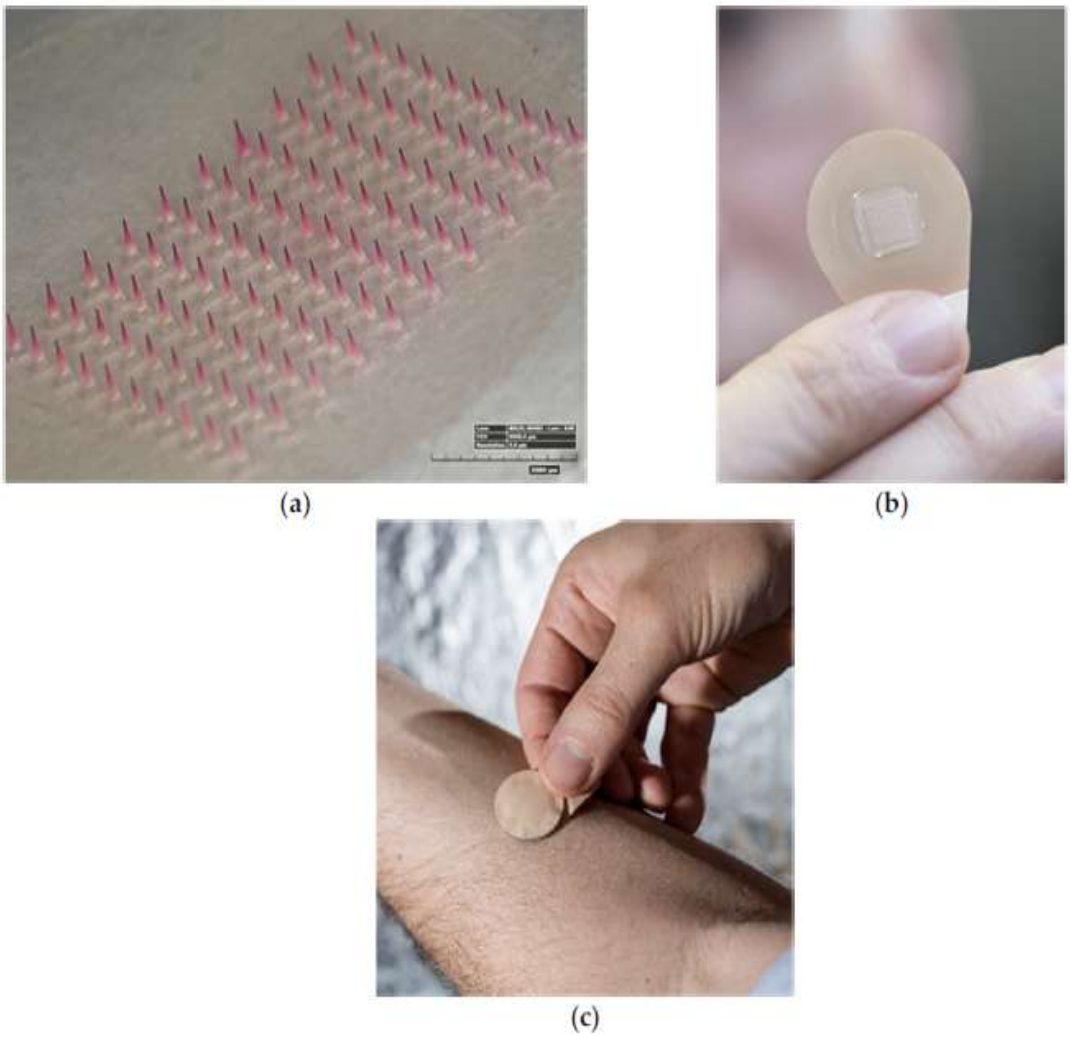

Figure 1 Dissolvable microneedle patch for simplified vaccination. (a) An array of microneedlescontaining pink dye to simulate vaccine. A microneedle patch (b) showing the microneedle array,adhesive backing, and non-adhesive tab for handling. (c) A microneedle patch being applied to theskin.

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II. STRUCTURAL PROPERTIES OF SARS-COV-2

The knowledge gained from the two precedingcoronaviruses (SARS-CoV and MERS-CoV) outbreaks and our emergingunderstanding of the SARS-CoV-2 virus and infection have enabled theidentification of rational targets for COVID-19 vaccine development. SARS-CoV, MERS-CoV, and SARS-CoV-2 areBetacoronaviruses (Beta-CoVs), which are enveloped, single-strandedpositive sense RNA viruses. The nucleocapsid (N), envelope (E),membrane (M), and spike (S) proteins are important structural componentsofBetaCoVs.TheEandMproteins arecritical fortheformationor assembly of coronavirusparticles.TheNproteininteractswiththeR NAgenomeofcoronavirusesandparticipates inviral transcriptionand assembly of BetaCoVs. The S protein of SARS-CoV-2 is amajor player in the infection of host cells, and in turn, replication ofSARS-CoV-2. Therefore, the S protein has received significant attentionas a potential target for safe and effective intervention strategies[6]. Specifically, the SARS-CoV-2 spike glycoprotein consists of S1and S2 subunits that mediate viral entry to host cells. The S1 subunitbinds to the angiotensin-converting enzyme 2 (ACE2) receptor of hostcells through its receptor-binding domain (RBD), and the S2 subunit enablesviral fusion with the target cell membrane. The SARSCoV-2 S glycoprotein is cleaved by host proteases at the boundary betweenthe S1 and S2 subunits, separating S1 fromS2. This furin cleavagesite is unique to SARS-CoV-2 and is not found in SARS-CoV. SARS-CoV-2and other CoVs undergo further cleavage at a second site found withinthe S2 subunit, through a process that activates the S protein to promotemembranefusion.The S proteinis a knowntarget ofneutralizingantibodiesgenerated in coronavirus infections, which can block the virusfrom binding to the ACE2 receptor.

Ultimately, this emergingknowledgeaboutcoronaviruses suggeststhat theSproteinof theviralenvelopeis an attractive target for the rational design and development ofCOVID-19 vaccines. This is further supported by previous effortsdemonstrating the immunogenicity of the S protein of SARS-CoV andMERS-CoV. Several vaccine candidates targeting the Sprotein of SARS-CoV-2 (e.g., either full S protein, S1 subunit, or RBDdomain)have been developed using different antigen formats, includingnucleicacid(DNAorRNA), attenuatedliveviralvectors (e.g.,adenovirus),and recombinant protein. Recently, other structural componentsof coronaviruses, such as the N andMproteins, have also beensuggested as potential vaccine targets due to their ability to elicit virusspecificcellular immuneresponses thatmaybeimportant for thebreadthand durability of the immune response. Thus, progressive scientificefforts on elucidation of the structure of BetaCoVs are identifyingmany vaccine targets against COVID-19[7].

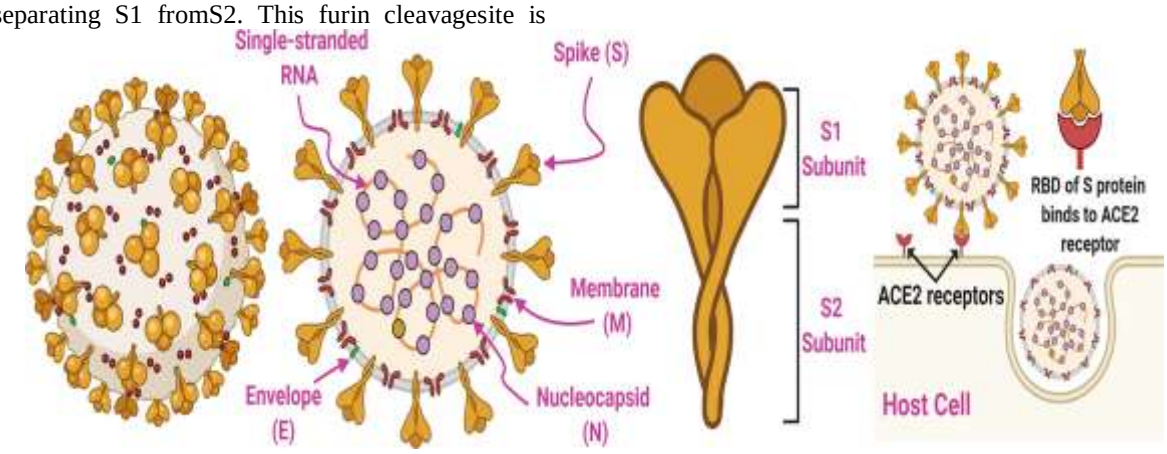

Figure 2 Structural properties of the enveloped, positive-sense, single-stranded RNA virus SARS-CoV-2 and mechanism of SARS-CoV-2 entry into host cells. Critical viral components include Envelope (E), Membrane (M), Nucleocapsid (N), and Spike (S) proteins. The S protein consists of two subunits (S1 and S2) and plays a major role in the infection of host cells, as the receptor-binding domain (RBD) of the S protein binds to the angiotensin-converting enzyme 2 (ACE2) receptor on host cells.

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III. SKIN VACCINATION

The readily accessible, immunologically active skin microenvironmenthas long been considered an attractive target tissue for vaccination. Specifically, the immunization campaign against smallpox that utilized intracutaneous vaccination with vaccinia virus was the first successful demonstration of a large-scale effective vaccine that induced protective immunity in human populations[8]. Since then, progress in developing skin-targeted vaccines has been relatively slow, partly because of inaccessibility created by the outermost skin barrier, the stratum corneum, and the lack of technologies capable of reproducibly introducing antigen into the skin microenvironment[9]. Interestingly, intramuscular (IM) and subcutaneous (SC) vaccination routes have been empirically used for the majority of vaccines without strong mechanistic evidence supporting their rationale other than reproducible delivery. Recently, there has been a substantial increase in hypothesis driven efforts to gain a fundamental understanding of the effect of immunization routes on vaccine efficacy. Advances in skin science, coupled with evidence of successful induction of sustained humoral and cellular immune responses, even at distant organs(e.g., lungs), through skin-targeted vaccination are providing the much-needed mechanistic underpinnings for rationally designed skin vaccination strategies[10]. A growing body of evidence suggests that intracutaneous immunization is mechanistically superior to traditional vaccination methods due to the more immune-responsive microenvironment present in the skin compared to subcutaneous and muscle tissues. Further, greater efficiencies seen with skin immunization could offer dose-sparing (i.e., requiring less vaccine doses to induce protective immune responses) for both antigens and adjuvants, reducing cost and in the later instance increasing safety. Although these advantages need to be confirmed for each antigen and adjuvant candidate, they could translate into more effective global immunization programs against infectious pathogens.

Intracutaneous vaccination utilizes innate immune mechanisms toprovide environmental context (e.g., danger signals) to tune skin APCfunctions to promote internalization and processing of skin-deliveredantigens,migration to the skin-draining lymph nodes, and presentationto adaptive immune cells. Skin APCs can interact with lymph node-resident T cells directly, or indirectly by transferring antigens and activation signals to lymph node-resident APCs, both of which result in priming and amplification of adaptive immunity. Further, in addition to delivering antigen to skin-resident APCs, skin-targeting could result in direct delivery of antigen to lymph node-resident APCsby way of passive diffusion through the draining lymphatics[11].This rich population of APCs in the cutaneous microenvironment, their capacity to adapt their function based on environmental conditions, and their effective communication with cells in the skin-draininglymph nodes, together uniquely enable efficient priming of antigenspecificT and B cells. Together, these mechanisms enable skin targeted vaccines to induce efficacious systemic immunity that is both antigen specific and durable.

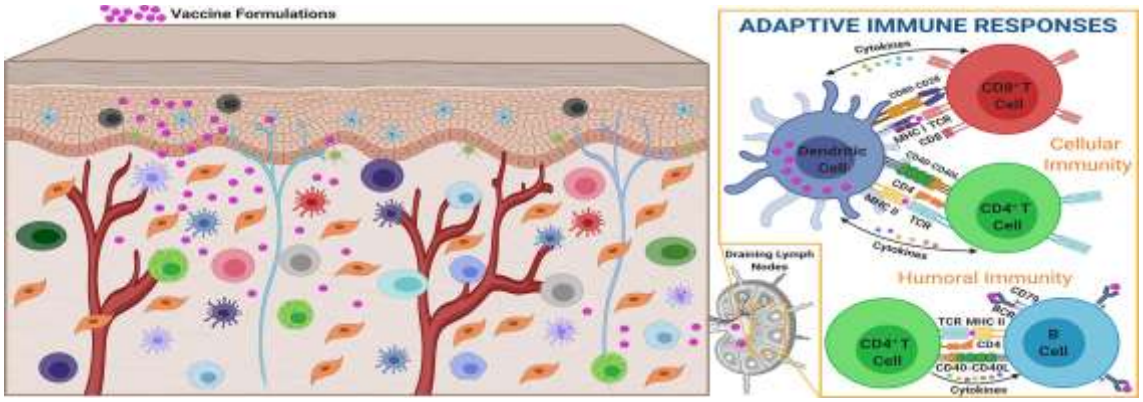

Figure 3 Skin vaccination induces antigen-specific cellular and humoral immune responses. Introduction of vaccine components into the skin microenvironment results in antigen loading and functional skewing of skin-resident APCs capable of directly or indirectly inducing CD4+ and CD8+ T-cell responses in the draining lymph nodes. The magnitude, breadth, and longevity of these responses are influenced by vaccine dose, spatiotemporal

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vaccine release kinetics, and immunoregulatory signals delivered with the antigen or released by other skin cells.

Several key factors contribute to antigen presentation function ofskin APCs, which impact the magnitude, quality, and longevity of vaccine-induced protective immunity. In addition to the structure and dose of antigen, spatiotemporal presence of antigen plays an importantrole in shaping the ensuing antigen-specific immune responses. Importantly, microenvironmental signals (e.g., chemokines and cytokines),which are secreted by skin-resident cells and influenced by the antigen delivery method (e.g., disruption of the skin barrier), as well as antigen type, dose, and kinetics, regulate local immune mechanismsto elicit systemic protective immunity. Further, a thorough investigation of the correlation between local cutaneous mechanisms and resulting antigen-specific systemic adaptive immune responses is necessary for more predictable skin-targeted vaccines.

Despite the theoretical advantages of the skin microenvironmenttargeting, there are currently only a few clinically approved skin targeted vaccines. This is also reflected in current COVID-19 vaccine efforts in which there are only a few skin-targeted SARS-CoV-2 vaccines to date (e.g., an intradermal plasmid DNA vaccine, an intradermalmRNA vaccine, and a MAP-delivered subunit vaccine). On the other hand, the vast majority of vaccine candidates being developedagainstCOVID-19aredeliveredvia traditional routes. For instance, antibody-dependent enhancement of natural infection and cell-mediated immunopathology resulting from sub-optimal humoral or cellular immune responses is an important safety concern for coronavirus vaccines[12]. Collectively, the skin offers an attractive target for the development ofmore effective immunization approaches against SARS-CoV-2 and other infectious pathogens. However, critical knowledge and technology gaps remainand must be addressed to realize the fullpotential of intracutaneousvaccination. Thus, the coming years are likely to bring an increasing number of academic and/or industrial efforts to address these gaps forthe rational development of skin-targeted vaccines against a broad range of infectious diseases.

IV. MICROARRAY PATCHES

Microarray patches (MAPs) are among the most promising skin targeted vaccine delivery systems. One of the major road blocks to the success of intracutaneous immunization has been the lack of safe, effective, convenient, patient-friendly, and inexpensive delivery technologies that can reliably administer vaccines to targeted skin microenvironments. The hydrophobic stratumcorneum, which consists of several layers of dead keratinocytes embedded in an organized lipid structure, is a major obstacle to reliable delivery of hydrophilic antigensand structurally complex immunomodulators. Therefore, macromolecule antigens and adjuvants applied to the skin topically or viatraditional transdermal patches are typically unable to penetrate the stratum corneum, as required for effective immunization. Combining the simplicity of topical application or conventional transdermal patches with the delivery benefits of traditional hypodermic needle injections, while considerably improving the precision and reproducibility of the skin-targeted bio cargo delivery, MAPs are a rapidly emerging technology platform for convenient, painless, and controlled vaccine delivery to the skin[13].

Microarray patches typically contain several micron-scale protrusions attached to a backing substrate, and these sharp-tipped micro protrusions, designed and fabricated with diverse geometries using various materials, mechanically penetrate the skin (the stratumcorneum)to deliver bio cargos (e.g., vaccine components).Unlikeprevailing hypodermic needle injections, MAPs deliver vaccine componentsintoviable skin layers that are considered more suitable immunotargets for vaccination, thereby resulting in improved antigen-specific immune responses[14] . Due to these advantages, there has been great interest in the development of several types of MAPs, and in functional testing of MAPs for numerous vaccine candidates. Collectively, the design, biomaterials, manufacturing, skindeliverymechanisms and efficiency, storage,acceptability,andcostofMAPsystemsarekeyfactorscontributingtothesuccess of MAP-based vaccination.

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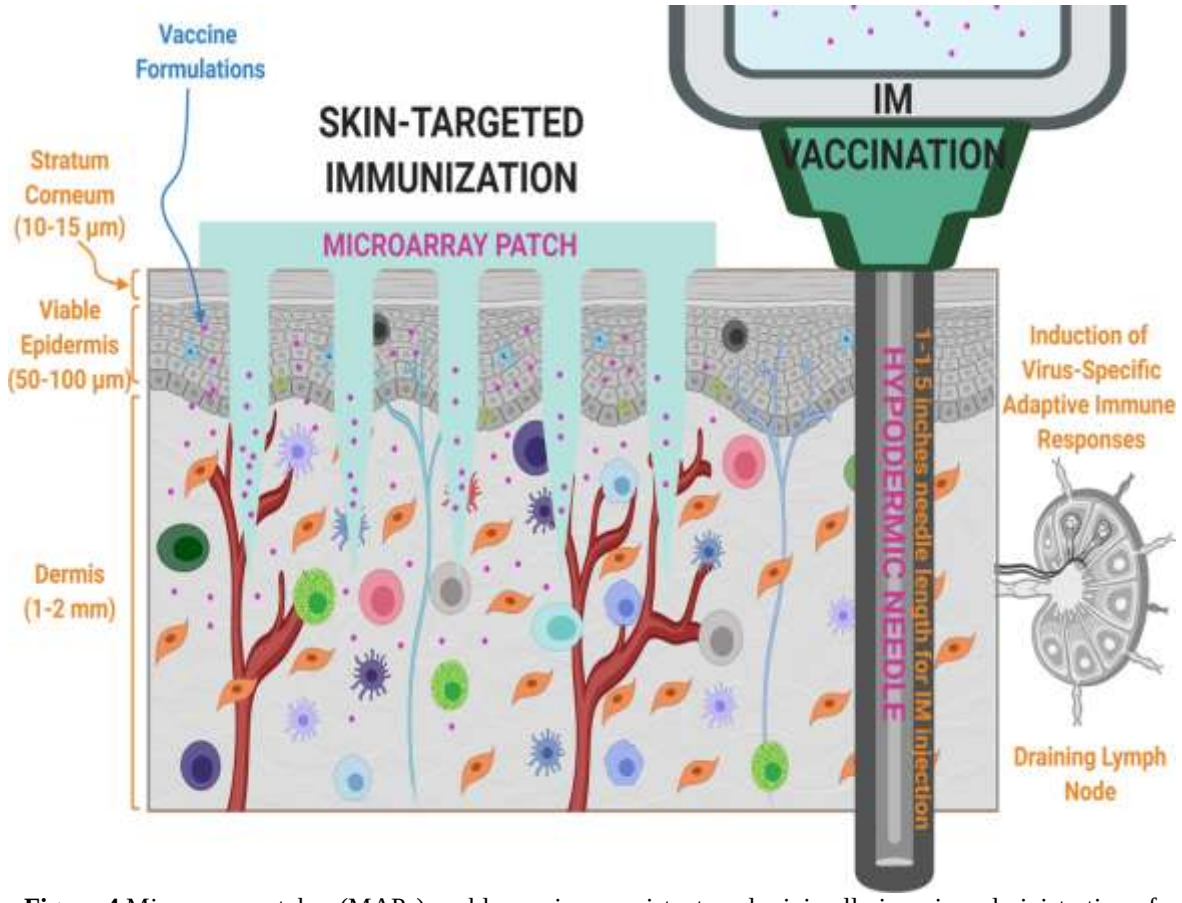

Figure 4 Microarray patches (MAPs) enable precise, consistent, and minimally invasive administration of vaccine formulations (antigen ± adjuvant) to immunologically rich cutaneous microenvironments, whereas conventional intramuscular (IM) immunization bypasses the skin immune system, results in systemic exposure to vaccine ingredients, and causes pain.

4.1.DISSOLVABLE/BIODEGRADABLE MAPS

Biodissolvable/biodegradable MAPs have been widely investigated. These MAPs integrating bio cargos (e.g., vaccine components)are fabricated from biocompatible natural or synthetic polymers that either rapidly dissolve, or slowly degrade after skin application, thereby releasing antigens and adjuvants into the cutaneous microenvironment. The skin residence of vaccine depends on the polymer choice, and several different polymers and sugars have been utilized to createbiodissolvable or biodegradable MAP systems[15]. Besides release kinetics, these materials control the manufacturability, strength and failure-free insertion ability, retention of vaccine bioactivity, skin delivery efficiency, and long-term stability of MAP-embedded vaccines. In addition to these advantages, other benefits of dissolvable MAPs, such as simple and low-cost fabrication, convenience ofstorage and application, precise and consistent dosing, relatively higher vaccine dose capacity, controlled drug delivery, and ease of disposal, make them a promising alternative for effective skin-targeted vaccination.

4.2.DISSOLVING MICRONEEDLE FORMULATIONS AND DESIGNS

Heat-sensitive compounds like proteins and antigens should been capsulated in microneedles and solidified at moderate conditions that will not damage their activity. For example, dissolving microneedleswere fabricated out of hydrophilic polymers cast in an aqueous solution at room temperature and at atmospheric pressure or under vacuum. CMC microneedles were fabricated under centrifugation to avoid formation of small voids in the microneedle matrix that weaken the structure. Human growth hormone was encapsulated in sodium chondroitin sulfate microneedles in a vacuumdryer[16]. Erythropoietin (EPO) and insulin were encapsulated in other hydrophilic polymers such as dextrin and

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chondroitin by forming threads using pipette tips at room temperature.Most dissolving microneedles need to be inserted into skin for at least 5 min to fully dissolve. To shorten this time, arrowhead microneedles were designed to separate from the shaft within seconds and remain embedded in the skin for subsequent dissolution.In contrast, biodegradable polymer microneedles must be inserted and remain in the skin for at least several days to effectively utilize their controlled-release degradation properties to provide controlled-release delivery in skin for up to months. Microneedles encapsulating hydrogel micro particles were designed for successful separation of microneedles within less than 1 h of insertion into skin by swelling of the hydrogel micro particle.Because microneedles may not insert fully into skin, it is sometimes desirable to encapsulate drugs only in the microneedle tips. Drug has been localized in microneedle tips by forming multi-layered microneedles using sequential applications of different compositions of polymer solutions and using a particle-based moldingmethod[17].

In this scenario, the patient applies the patch to the skin, possibly using an applicator, and then leaves the patch in place probably for a few minutes before discarding it. Microneedles have to be formulated using safe excipients that quickly dissolve in the fluids of the skin and protect drug stability during fabrication and storage; and may need to be manufactured under aseptic conditions.A microneedle patch enables rapid bolus delivery. If sustained release delivery is preferred, the microneedle formulation can be adjusted to have slow drug release from a skin depot formed by the dissolution products of the microneedle or its coating. Perhaps the greatest limitation of the microneedle patch is the small dose that can be coated on or encapsulated in microneedles. Although it depends strongly on drug propertiesespecially water solubility, since dissolving microneedles and microneedle coatings are typically prepared in aqueous solutiona general rule of thumb is that on the order of 0.1–1 μg of drug can be administered per microneedle, which corresponds to 10–1000 μg for a patch containing 100–1000microneedles. Some of the very small microneedles may not support so much drug per microneedle, but can generally be packed at higher density such that this same dose range applies for a patch of up to a few square centimeters in size.

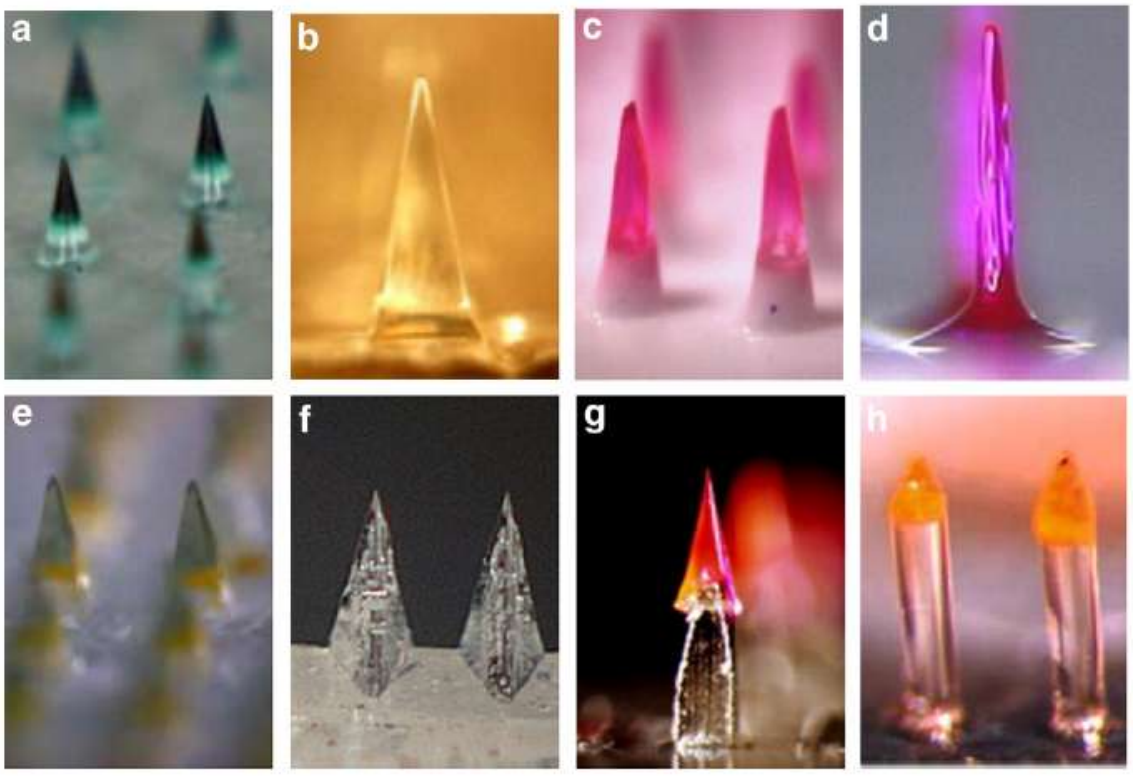

Figure 5 Dissolving microneedles made of water-soluble polymers and biodegradable polymers

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V. OVERCOMING BARRIERS TO EFFECTIVE VACCINATION

There are several barriers for effective vaccination campaigns in all resource settings, including the need to increase vaccine immune response, simplify the supply chain, eliminatebiohazardous waste, improve cost-effectiveness, and reduce reliance on trained healthcareproviders.Microneedle patches have been studied for their potential application against many pathogens, including other respiratory viruses. For seasonal influenza, vaccination by microneedle patches resulted in faster virus clearance in the lungs of murine models. For pandemic influenza, higher immunogenicity was noted in animal models compared to intramuscular injection. Delivering vaccines in the epidermis or dermis puts the antigen in close contact with the skin's rich population of antigen-presenting cells and can result in lower doses of antigens being used. Vaccinations using microneedlepatches have demonstrated dose-sparing in clinical studies. The use of microneedledevices ensures a more accurate, effective, and reproducible delivery of vaccine to the skin compared to injections.Most vaccines that are administered by hypodermic needle and syringe injection requirea trained healthcare provider to administer the vaccine. Microneedle patch vaccination allows for administration by minimally trained personnel, including self-administration, which could reduce the burden of healthcare system.Microneedle patches reduce the risk of sharp waste because the microneedlesdisappear after dissolving in the skin. The risks with sharps include unintentionalre-use, needle stick injuries, and cross contamination. The spread of blood borne pathogens is a major concern, withan estimated 1.3 million deaths resulting from needle re-use according to WHO estimates, especially in developing countries. Further, dissolvable microneedle patches are a safe delivery method, with no reports of accidental infection in controlled studies and widespread use in commercial cosmetic products[18].Standard hypodermic needle vaccination may be wasteful via multi-dose vials and the need for reconstitution. In general, vaccine wastage rates increase as the number of vaccine doses per vial increases. Estimates suggest wastage rates for 10-dose vials maybe as high as 25% for liquid vaccines and 40% for lyophilized vaccines[19]. Single-usemicroneedle patches remove this waste. Some vaccines need vaccine reconstitution with a diluent, which not only requires a trained healthcare provider to perform but also adds more needles, syringes, and vials that need to be safely stored and transported. Microneedle patches do not require reconstitution.Microneedle patches have improved stability and can often be stored at ambient temperature, eliminating the cold chain, and allowing for easier stockpile and storage. Further, the patches are much smaller in size than vaccine vial and needle-syringe systems, facilitating storage and distribution, and thereby simplifying the supply chain.The cost of vaccination is the cost of vaccine plus the logistical costs associated with making the vaccine available for use. Healthcare providers, waste disposal, vaccine storage, transportation, cold chain, and vaccine wastage all contribute to the cost of vaccination. While vaccine manufacturers often sell vaccines at significantly reduced cost for use in developing countries, the logistical costs to vaccinate can remain a significant barrier. Analyses suggest that the use of self-administered microneedle patches could not only improve vaccination coverage but would also be cost-effective.

Limitations of dissolving microneedle patch delivery systems for vaccines exist, including theoretical issues with dosage accuracy; inability to deliver large doses of medications(which could be an issue if using certain adjuvants require milligram doses); possibility of skin irritation and external environment affecting delivery, such as hydration of the skin or excessive sweating; and uncertainty about cost and capability of large-scale manufacturing. Potential advantages of dissolvable microneedle patch vaccine for coronavirus disease 2019 (COVID-19) includeIncreased Immunogenicity, Faster virus clearance, Dose-sparing effect, Reduction in vaccination wastage, Avoidance of reconstitution,Increased acceptance and less hesitancy, Little or no pain, Self-administration and reduced need for healthcare workforce, Reduced risk of sharps injury and contamination, Improved stability,Less reliance on cold chain.The patches are intended to be shelf-stable, self administered, and self-boosting by releasing the spike protein into the body as pulses or continuously over a few weeks. This approach could eliminate the need for repeated vaccinations[20].

Microneedle patches for SARS-CoV-2 vaccination are currently not available due to a lack of existing manufacturing and regulatory infrastructure needed for rapid development. Continued and expanded investment in innovative

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vaccine delivery platforms such as microneedle patches is needed to ensure the technology and infrastructure are in place for the pandemic needs of the future.

VI. CONCLUSION

The COVID-19 pandemic clearly demonstrates that emerging infectious pathogens pose a major global public health problem. Vaccination is the most effective strategy for reducing the burden of infectious disease, preventing millions of deaths each year, as estimatedby the WHO. Realizing the true potential of immunization against a novel pathogen will require: 1. Identification of a rational vaccine target and production of a safe and effective vaccine, 2. determination of an ideal vaccine administration route, and3. development of an easy-to-use, cost-effective, patient-friendly, andbroadly deployable vaccine delivery system. The expanding knowledge of skin immunobiology suggests that targeting vaccines to the skin microenvironment is an attractive alternative to prevailing immunization routes and is more suitablefor mass vaccination. Advances in skin science and vaccine delivery technologies are facilitating the rational selection of safe and potent adjuvants for intracutaneous immunization, and enabling reproducibleand controlled delivery of vaccine components to the skin microenvironment. MAPs are rapidly emerging skin-targeted vaccine delivery systems with several unique advantages.Ultimately, immunogenicity, simplicity, safety, compliance,thermostability, cost, versatility, and supply chain advantages of MAP-based vaccines makethem an exciting alternative for global immunization programs. Microneedle patch immunization has the potential to overcome many factors affecting the uptake and distribution of traditional hypodermic intramuscular injection campaigns. Dissolvable microneedle patches are advantageous for many possible reasons: improved immunogenicity; dose-sparing effects; expected low manufacturing cost; elimination of sharps; reduction of vaccine wastage; no need for reconstitution; simplified supply chain, with reduction of cold chain supply through increased thermostability; ease of use, reducing the need for healthcare providers; and greater acceptability compared to traditional hypodermic injections. When applied to COVID-19, microneedle patches have great potential to improve vaccination globally and save many lives. While the timeline for COVID-19 microneedle patch vaccine deployment may be a missed opportunity for the current pandemic, there is a need for investment today to be better prepared for tomorrow's pandemic needs.

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