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REVIEW

Progress in microneedle array patch (MAP) for vaccine delivery

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ABSTRACT

A microneedle array patch (MAP) has been developed as a new delivery system for vaccines. Preclinical and clinical trials with a vaccine MAP showed improved stability, safety, and immunological efficacy compared to conventional vaccine administration. Various vaccines can be delivered with a MAP. Currently, microneedle manufacturers can mass-produce pharmaceutical MAP and cosmetic MAP and this mass-production system can be adapted to produce a vaccine MAP. Clinical trials with a vaccine MAP have shown comparable efficacy with conventional administration, and discussions about regulations for a vaccine MAP are underway. However, there are concerns of reasonable cost, mass production, efficacy, and safety standards that meet FDA approval, as well as the need for feedback regarding the best method of administration. Currently, microneedles have been studied for the delivery of many kinds of vaccines, and preclinical and clinical studies of vaccine microneedles are in progress. For the foreseeable future, some vaccines will continue to be administered with syringes and needles while the use of a vaccine MAP continues to be improved because of the advantages of less pain, self-administration, improved stability, convenience, and safety.

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1. Introduction

The World Health Organization (WHO) estimates that immunization annually prevents 2–3 million deaths, and vaccination is the most powerful tool to protect people from infectious diseases. Despite the successes of the vaccine era, there were approximately 15 million deaths from such diseases globally in 2010.[1] Thus, vaccine development, vaccine coverage, and mass vaccination continue to be WHO's top priorities because many countries still suffer from the enormous burden of disease owing to influenza, HIV/AIDS, tuberculosis, hepatitis B, and especially the emerging infectious diseases such as the Ebola virus, the Zika virus, and other pathogens. Most conventional vaccinations have been injected with needles and syringes. Syringes and needles have provided successful delivery of predetermined doses of vaccines, and many diseases have been brought under control or virtually eliminated through syringe and needle-based vaccination. However, syringes and needles have several disadvantages such as pain, needle-stick injuries, needle reuse, and poor patient compliance.[2] In addition, the cold chain of manufacturing, delivery, and storage of vaccines increases the cost, the likelihood of misuse, and risk during clinic practice.[3] The cost of vaccination programs in 94 low- and middle-income countries over the decade 2011–2020 has been about 62 USD billion. The delivery cost was 34 USD billion and the supply chain cost was 4 USD billion, corresponding to 54% and 6%, respectively, of total vaccine cost.[4] The high cost of vaccines is one of the main barriers to vaccination coverage in low- and middle-income countries, and according to 2015 survey data, only 60% of eligible children in these countries had received full immunization.[5]

To overcome these limitations, vaccination with a microneedle array patch (MAP) was introduced because a MAP has the advantages of improved stability, delivery, and storage at room temperature, low bioburden, painlessness, minimally invasive nature, self-administration, and intradermal delivery of antigens into the skin, as shown in Table 1.[6] The length of microneedles in a MAP ranges from 100 to 1000 μm, and the vaccine can be delivered into the epidermal and dermal layers of human skin where Langhans cells and dendritic cells are located.[7–9] Three types of MAP – solid MAP (S-MAP), coated MAP (C-MAP), and dissolving MAP (D-MAP) – have been used to test the immunization application. As shown in Figure 1, the S-MAP delivers the vaccine into the deeper layer of the skin through the holes generated by the MAP. A C-MAP delivers the vaccine formulation directly into the skin layer and releases the vaccine immediately after being inserted into the skin. A D-MAP is made of safe, inert, water-soluble materials, and the vaccine is released from the matrix of the D-MAP after it is inserted into the skin.

The first study of immunization by MAP was carried out in 2002,[10] and the significant milestones of MAP for vaccination are displayed in Figure 2. The use of a D-MAP for influenza vaccination was well tolerated and generated robust antibody responses in 2017, and the first clinical trials with vaccine MAPs were conducted in 2015.

In this review, the studies of MAP for vaccination are summarized and analyzed with sections addressing preclinical studies, stability studies, and clinical trials. In addition, manufacturing issues, regulation considerations, and future possibilities are discussed to provide a total view of the application of MAP as the alternative means of vaccination. In this

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Table 1. Microneedle array patch (MAP) solution for vaccine needs.

Limitations of Syringes and Needles	Strengths of Microneedles	Limitations of Microneedles
• Risk of needle waste • Low thermal stability • Cold chain required for delivery and storage • Need of medical expertise to administer	• Low pain • Increase of vaccine coverage • Improved thermal stability during delivery • Long shelf life at room temperature • Reduced risk of biohazardous product • Self-administration	• Uncertain manufacturing cost • Need for mass production • Lack of feedback on proper administration • Efficacy and safety criteria to meet FDA approval not yet established

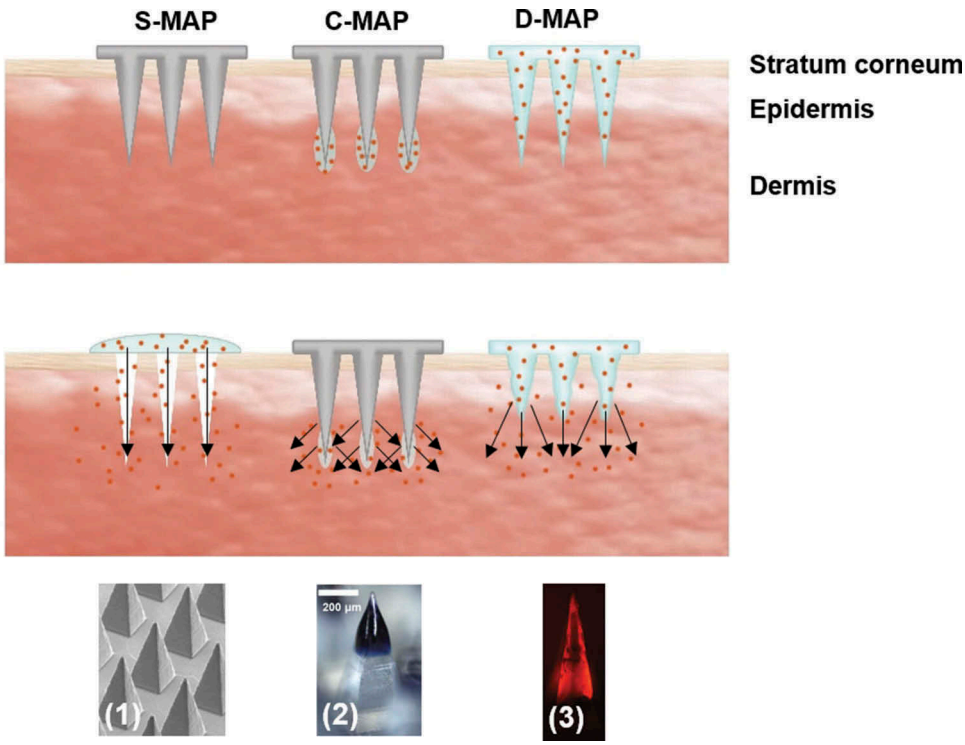

Figure 1. Illustration of vaccine microneedle array patch (MAP) types: (a) solid MAP (S-MAP), (b) coated MAP (C-MAP), (c) dissolving MAP (D-MAP). Arrows show the direction of vaccine diffusion. Representative images of S-MAP (1), C-MAP (2), and D-MAP (3).

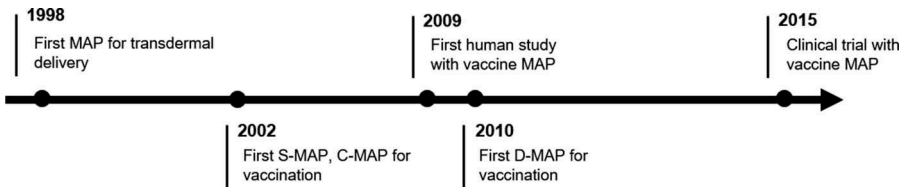

Figure 2. Timeline of studies with microneedle array patch (MAP) for vaccination.

review, hollow microneedles are not discussed. S-MAP, C-MAP, and D-MAP for delivery of vaccine are discussed because these three types of MAP have been developed for the delivery of solidified vaccine formulations.

Table 2 summarizes the criteria when selecting S-MAP, C-MAP and D-MAP. In regard to the manufacturing process, the drug is not loaded or coated onto S-MAPs, so the manufacturing cost is cheaper than for C-MAPs or D-MAPs. However, because S-MAPs have to puncture the skin to deliver the drug, the amount of drug delivered is small and inconsistent. In the case of C-MAPs and D-MAPs, the wear time (i.e., time needed to keep the microneedles attached to the skin) is longer (from a few minutes to 30 min) because sufficient adhesion time is required to deliver all of the drug in the coating formulation of the C-MAP or in the D-MAP matrix. Because the D-MAP matrix is also dissolved in the skin, the mechanical strength and biocompatibility of the microneedle material are critical concerns.[11] Compared to S-MAPs or precoated microneedles of C-MAPs made of water-insoluble

Table 2. Decision matrix for use of solid microneedle array patch (S-MAP), coated microneedle array patch (C-MAP), and dissolving microneedle array patch (D-MAP).

Criteria	S-MAP	C-MAP	D-MAP
Manufacturing cost	5*	3	2
Mass production	5	4	3
Self-administration	5	5	5
Wear time	5	3	3
Biocompatibility of microneedle material	5	4	3
Delivery of right dose	1	4	3
Aseptic process	5	4	3
Stability against humidity	5	5	2
Waste	2	2	5

* 5 is the highest score and 1 is the lowest score for criteria.

polymer, most D-MAPs are made of soluble polymers, which potentially makes them more likely to break down as a result of contact with moisture.[12,13]

2. preclinical and stability studies

2.1. Preclinical studies of vaccine MAP

Preclinical studies of various vaccine MAPs have been conducted and are summarized in Table 3. Mice were used to test the efficacy of most vaccine MAPs, and a monkey was used as an animal

Table 3. Vaccine and model animals regarding type of microneedle array patch (MAP).

MAP	Vaccine	Animal	Reference(s)
S-MAP	Influenza subunit (subunit)	Mouse	54
	Hepatitis B (DNA)	Mouse	10,24,55-57
	DT (inactivated)	Mouse	18,21,54,58
	Tetanus toxoid (inactivated)	Mouse	19
	Anthrax (DNA, inactivated)	Mouse	22,59
	Malaria (recombinant vector)	Mouse	60-62
	Plague (live bacteria)	Mouse	63
	Anthrax rPA (recombinant subunit)	Rabbit	59
	Encephalitis (live attenuated)	Monkey	64
C-MAP	Influenza (DNA, subunit)	Mouse	28-30,32,37-44,65-71,73-80
	Hepatitis C (DNA)	Mouse	81
	Hepatitis B (subunit)	Mouse	82
	DT (inactivated)	Mouse	83
	Rotavirus (live attenuated)	Mouse	84
	Fever (live attenuated)	Mouse	85
	Ebola (recombinant vector)	Mouse	45
	Human adenovirus (recombinant vector)	Mouse	86
	Chikungunya virus (inactivated)	Mouse	46
	West Nile virus (DNA-delivered attenuated)	Mouse	46
	Herpes (inactivated)	Mouse	49,50
	Zika (inactivated)	Mouse	51
	Dengue (recombinant subunit)	Mouse	87
	Francisella novicida (live attenuated)	Mouse	88
	Malaria (recombinant vector)	Mouse	89
	Leishmania spp. (recombinant vector)	Mouse	90
	Measles (live attenuated)	Rat	91
	IPV (inactivated)	Mouse	92,93
	Influenza (subunit)	Guinea pig	94
	HIV (recombinant vector)	Rabbit	95
	Hepatitis B (subunit)	Pig	96
	BCG (live attenuated)	Mouse	97
	HIV (recombinant vector)	Monkey	98,99
	Hepatitis B (subunit)	Mouse	100
	Influenza (subunit)	Young mice	101
D-MAP	Influenza (inactivated)	Mouse	31,33,102-109
	Hepatitis B (recombinant subunit)	Mouse	20,110,111
	HIV (recombinant vector)	Mouse	47,48,112-114
	Dengue virus (live attenuated)	Mouse	115
	Ebola (DNA)	Mouse	23
	Enterovirus (VLPs)	Mouse	52
	Rotavirus (inactivated)	Mouse	116
	Polio virus (inactivated)	Mouse	117
	Streptococcus (inactivated)	Mouse	118
	Staphylococcus (recombinant subunit)	Mouse	119
	Shigella (BLP)	Mouse	107
	Clostridium (toxoid)	Mouse	107
	BCG (live attenuated)	Mouse	120
	Neisseria gonorrhoeae (inactivated)	Mouse	121
	Pseudomonas aeruginosa (inactivated)	Mouse	122
	Orientia tsutsugamushi (recombinant subunit)	Mouse	123
	Malaria (recombinant subunit)	Mouse	124
	Influenza, DT, Tetanus toxoid (inactivated)	Rat	124
	BCG (live attenuated)	Mouse	125
	Influenza (inactivated)	Guinea pig	126
	Hepatitis B (recombinant subunit)	Pig	127
	Hepatitis C (VLPs)	Mouse	128
	Rabies (DNA)	Dog	129
	IPV (inactivated)	Monkey	130
	Measles (live attenuated)	Mouse	131
	Hepatitis B (recombinant subunit)	Mouse	111
	Tetanus toxoid (inactivated)	Pregnant mouse	132
	Measles, Rubella (live attenuated)	Infant monkey	53

rPA: recombinant protective antigen; IPV: inactivated poliovirus vaccine; HA: hemagglutinin; VLPs: virus-like particles; BCG: Bacille Calmette–Guerin; DT: diphtheria toxin; TIV: trivalent influenza vaccine; HIV: human immunodeficiency virus; DT: diphtheria and tetanus.

model. Among the adjuvants, an aluminum-type adjuvant has been studied; however, it did not show high efficacy for a vaccine MAP[14] because it induced low T-cell mediated immune responses and it was not suitable for intradermal (ID) use.[15] The preclinical studies of adjuvants for MAPs are summarized in Table 4. Recently, nanoparticles (NPs) have been considered an effective adjuvant because they can act as a depot and are more efficiently taken up by dendritic cells.[16,17] NPs prepared from chitosan induced an equally strong immune response compared to subcutaneous injection of diphtheria and tetanus (DT) vaccine[18] and generated a higher IgG2a titer than commercial tetanus toxin vaccine.[19] Liposome NPs are a candidate for vaccine MAP application; the mucosal injection elicited robust systemic and widespread immune response in hepatitis B MAP.[20] However, a study with the liposome formulation of DT did not induce a higher antibody than free DT.[21] NPs were fabricated from polymer as poly(lactic-co-glycolic acid)-PLGA with anthrax vaccine, and NPs were encapsulated in a MAP. An anthrax vaccine NP MAP induced a stronger immune response than a MAP without an NP formulation.[22] A similar enhancement was observed in Ebola vaccine research.[23] Another polymer NP formulation was prepared from pluronic-modified polyethyleneimine, and hepatitis B DNA vaccine was encapsulated in NPs. DNA NP MAPs generated higher humoral and cellular immunity than DNA MAPs.[24]

The immune response was improved by the sustained release of vaccine and exposure of antigens to lymphoid tissues by using an implantable MAP. The D-MAP for HIV was fabricated with the silk matrix to control the release rate of the antigen for 2 weeks, and the serum IgG titer was increased 1,300-fold compared to conventional administration.[25] The release of influenza vaccine was extended by using the chitosan MAP, which induced an immune-enhancing effect.[26] The extended release of vaccines for daily vaccination provided an improved vaccination effect.[27]

To demonstrate the successful protection of immunity by MAP vaccination, a number of studies of pathogen challenges were carried out, and the results were promising. In particular, studies of influenza vaccination that compared MAP injection and a no-treatment group found that the MAP application conferred greater protective immunity.[28,29] Similar observations were documented when comparing MAP injection with subcutaneous injection[30,31] and intranasal administration.[32] Notably, the MAP application induced not only comparable protective efficacy[33-37] but also better protection event[38-41] compared to intramuscular (IM) administration. Of equal importance, such protective efficacy continued for several months after vaccination (6 months,[42] 14 months[43]). Another study demonstrated cross-protection when mice vaccinated with A/PR8 influenza hemagglutinin DNA did not contract pandemic 2009 H1N1.[44] Besides the influenza vaccine, some vaccines targeting virus outbreak pandemic pathogens, such as the Ebola virus,[45] the Chikungunya virus,[46] HIV,[47,48] and the herpes simplex virus,[49,50] were successfully delivered into the skin by MAP and conferred suitable protection after viral challenge. The Zika virus was especially challenged in the neonatal mouse model.[51] The enterovirus MAP vaccination induced full protection against lethal challenge with only 10% of the delivered antigen dose compared to IM injection.[52] Most of the challenge tests were studied in mice, but one study of a measles vaccine was applied in infant rhesus macaques. The results showed complete protection in the MAP administration group compared to the group that received the vaccine by a subcutaneous route.[53]

Vaccine development for bacteria-derived pathogens plays a critical role in decreasing the burden on the health-care system throughout the world. Several such severe antigens were researched to be delivered by MAP, and mice were challenged after vaccination to prove the strong induction of protective immunity against *Pseudomonas aeruginosa*,[122] *Clostridium difficile*,[107] *Streptococcus suis*,[118] and *Francisella novicida*.[88] The anthrax vaccine was tested, and the results showed 100% protection from aerosol spore challenge in rabbits.[133] A tetanus vaccine was studied in another neonatal mouse group, and the group administered with MAP vaccination was totally protected, while none of the mice administered via the IM route survived.[132] Finally, live adenovirus-vectored malaria vaccine was researched and an equivalent protective efficacy was reported when comparing intradermal (ID) immunization by MAP with the administration via hypodermic needles.[61] A large number of preclinical research studies have been carried out with MAP for vaccine application; the target animals were wide ranging from mice to monkeys. More importantly, it was demonstrated that MAP-based vaccination generated strong desired immune response to specific antigens and conferred protective efficacy not only for a short time but also for a long time after vaccine administration. Different vaccines for infectious diseases were investigated, and the results indicate that it is feasible to use MAPs to combat diverse pathogens. In addition, it was found that the S-MAP gradually received less attention than the other MAP types because of the S-MAP's complex application steps and the difficulty in measuring the right dose for delivery. Therefore, the most promising MAP types for ID vaccination are C-MAP or D-MAP applied as patches.

Table 4. Preclinical studies of vaccine microneedle array patch (MAP) with adjuvants.

Adjuvant Type	Vaccine	Ref.
Cholera toxin	Diphtheria toxin, hepatitis B	21,54,56,58
dmLT (double mutant heat-labile toxin)	Clostridium, shigella	107
Fms-like tyrosine kinase 3 ligand	Hepatitis B	55
CpG oligonucleotide	Hepatitis B	110
Monophosphoryl lipid A	HIV	113
Poly(I:C)	Influenza	29,79
Saponin-based	Ebola, hepatitis B, influenza	45,73,127

HIV: human immunodeficiency virus.

2.2. Stability studies of vaccine MAP

Keeping antigens stable during processing and storage has been one of the challenges for MAP vaccination. The possible loss of antigenicity can occur in the drying and storing stages. The thermostability of the MAP vaccine can be improved by the addition of a stabilizer; the appropriate

stabilizer depends on the kind of vaccine being administered, as shown in Table 5.

3. Clinical trials and human studies of vaccine map

3.1 Clinical trials of vaccine MAP reported at ClinicalTrial.gov

The innovation of MAP in stability, bioavailability, potency, and less adverse reactions is incorporated into the vaccine to overcome the limitations and current disadvantages of hypodermic needle injection. Using "microneedle patch" as the keyword, we found three trials registered at Clinical Trial.gov that have applied the vaccine MAP (Table 6). Three kinds of MAPs have been used in the registered trials, and these studies have been conducted to address some of the most dangerous infectious diseases to determine the feasibility of MAP vaccination in clinical practice.

3.2. Vaccine C-MAP for human studies

In several human studies, a vaccine C-MAP (Nanopatch^{TM}) has shown promise as a system for effective drug delivery. Both uncoated and excipient-coated Nanopatch^{TM} were administered to 18 healthy adults for 2 min of insertion and removal. On a pain scale from 0 to 10, 78% of the participants scored 0, and the average score was less than 1. No unexpected adverse events directly related to Nanopatch^{TM} were observed, and the expected erythema response faded between 3 and 7 d after vaccination.[138] When Nanopatch^{TM} with 15 μg of inactivated influenza virus (H1N1) was administered to healthy volunteers, adverse events were mild or moderate, and more than half (55%) of the volunteers preferred the Nanopatch^{TM} to IM administration.[139] In addition, the antibody response using a Nanopatch^{TM} was comparable to that with conventional IM administration.[139]

3.3. Vaccine D-MAP for human studies

When a D-MAP patch was applied to the participants in one study, there was no pain swelling, and only mild erythema was localized to the site of patch administration. Moreover, the large majority of subjects were somewhat or fully confident with self-administration.[140] Consequently, influenza vaccine was encapsulated in the polymer matrix and D-MAPs were applied to volunteers for a phase 1 trial. The antibody response by self-administered D-MAP was comparable to that by IM administration.[141]

Another D-MAP for treating influenza was prepared from a hyaluronic acid MAP named MicroHyala ^{TM}. No severe local or systemic adverse events were detected, and immunological efficacy was comparable to that of IM administration.[142]

4. Concerns about vaccine MAP

4.1. Commercialized MAP

Several pharmaceutical companies have developed MAP devices for drug delivery systems, as shown in Figure 3. Onvax^{TM} (BD company) consists of an array of plastic microprojections with a height of approximately 200 μm. Rubbing the skin surface with such devices led to disruption of the skin

Table 5. Stability studies of vaccine MAP.

MAP	Vaccine	Stabilizer	Temperature	Period	Ref.
S-MAP	Hepatitis B (Recombinant subunit)	Mannitol	4°C	3 weeks	57
C-MAP	Influenza (Plasmid DNA)	Trehalose	25°C	After coating	44
	Influenza (inactivated)	Trehalose	4°C, 25°C, 37°C	1 month	134
	Influenza (inactivated)	Trehalose	23°C	6 months	76
	Influenza (Subunit)	Sucrose	4°C, 25°C	8 weeks	94
			Freeze-thawing	3 cycles	
	Hepatitis B (recombinant subunit)	Trehalose	4°C, 25°C, 37°C	28 d	82
			Freeze-thawing	10 cycles	
	Malaria (live attenuated)	Trehalose + sucrose	37°C	10 weeks	89
D-MAP	Influenza (inactivated)	Trehalose	4°C, 25°C, 37°C	3 months	135
	Influenza (inactivated)	Trehalose	40°C	6 months	102
	Influenza (inactivated)	Trehalose	35°C	12 months	108
	Rabies (DNA)	Sucrose	4°C	3 weeks	129
	Hepatitis B (recombinant subunit)	-	4°C	3 months	20
	Hepatitis B (recombinant subunit)	Sucrose	45°C	6 months	127
	Influenza (Subunit)	Arginine + heptagluconate	25°C	24 months	136
			Freeze-thawing	5 cycles	
	BCG (live attenuated)	-	25°C	2 months	120
	Tetanus toxoid/Diphtheria toxoid (Divalent subunit)	-	4°C	24 weeks	137
	Scrub typhus (recombinant subunit)	-	25°C	4 weeks	123

HbsAg: hepatitis B surface antigen; HA: hemagglutinin; BCG: Bacille Calmette–Guerin.

Table 6. Clinical trials of vaccine MAP registered at ClinicalTrial.gov.

MAP	Disease	Phase	Number of Participants	Age	Processing	Number of Identifier
S-MAP	Hepatitis B	2,3	120	>21	Recruiting	NCT02621112
D-MAP	Influenza	1	100	18–49	Completed	NCT02438423
	Safety vaccination		34	6 weeks to 24 months	Completed	NCT03207763

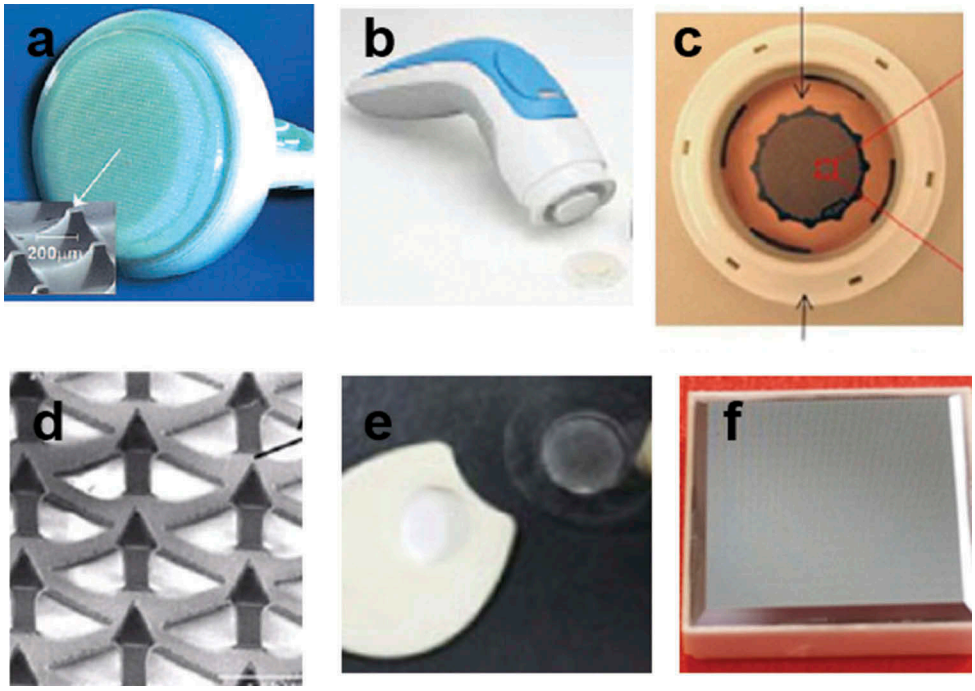

Figure 3. Commercial microneedle array patch (MAP) devices: (a) Onvax by BD, (b) Microstructured Transdermal System (MTS) by 3 M, (c) ZP MAP by Zosano Pharma, (d) scanning electron microscopic image of ZP MAP, (e) MicroHayla by CosMED Pharmaceutical Ltd., and (f) Nanopatch by Vaxxas.

and delivery of the vaccine into the epidermal layer.[59,143] A Nanopatch™ has been produced by Vaxxas and is a solid high-density microprojection array coated with the influenza vaccine formulation. A Nanopatch™ needle length is 250 μm and is administered with a spring-loaded applicator.[62] The ZP MAP system from Zosano Pharma consists of 1,300 microneedles in a 2 cm^2 area. The drug is coated on a 190-μm-long MAP, and the ZP MAP is applied with a hand-held reusable applicator. This system administers the drug formulation into the outer skin layers and provides the desired outcome.[144] CosMED Pharmaceutical Ltd. has developed a D-MAP (MicroHyala™) made of hyaluronic acid. The D-MAP is approximately 800 μm in length and efficiently delivers various materials into the epidermis and dermis below the stratum corneum.[142,145] 3M has developed a C-MAP based on a Microstructured Transdermal System (MTS) of 500 μn; an applicator is used to deliver the drug agent into the skin. A one square-centimeter microneedle array is molded from durable medical grade polymer, and the array is attached to an adhesive patch.[70,71] MicroCor™ was designed by the Corium company. MicroCor™ is a D-MAP with an applicator device integrated as a single piece into the MAP.[126,147]

4.2. Manufacturing issues

Concerns for vaccine MAP are dosage uniformity, reasonable cost, mass production, and production according to Good Manufacturing Practice (GMP). In regard to cost and scalability, MAPs require large-scale manufacturing machines and processes to be established.[148] Substantial investment is necessary for machining, casting, and forming of MAPs at the initial stages of mass production. However, after the successful establishment of these initial stages, the cost of manufacture can be predicted to be less than for injectables.[149] The polymer-based MAP casting technique might offer low cost because some polymers, such as cellulose derivatives, engineering plastics, and sugars, are typically inexpensive. However, because of reliance on master molds and inherently multi-step filling, handling processes can be a challenge to scale up. Furthermore, temperature may increase due to the drying process during the manufacture of vaccine MAP. Thus, a low-temperature process can be required to produce thermo-sensitive antigens. Special packaging or desiccants can be required to increase storage stability, but the addition of material to protect from moisture can increase the cost of packaging. Moreover, sterilization also is essential for vaccine MAP. Even though MAP has a low bioburden, the cost for the aseptic process should be considered. Also, validation of vaccine MAP products should be considered as a cost factor. Standardization of MAPs is also crucial for quality control during manufacturing and marketing. Manufacturers must develop an effective pharmaceutical quality assurance system, which must be a comprehensively designed and correctly implemented according to a Pharmaceutical Quality System incorporating Good Manufacturing Practice and Quality Risk Management.[150] Finally, the successful manufacture of vaccine MAP depends on current guidelines for conventional drugs as well as specific standards for each type of MAP.[151]

Some previous studies have mentioned the vaccine MAP preparation environment. HBsAg D-MAP was fabricated in an aseptic Grade A isolator in a GMP pilot facility,[127] and influenza C-MAP developed from 3 M's solid microstructured transdermal system was produced by a GMP-scalable process.[94] 3 M's proprietary GMP manufacturing and aseptic coating technology has a capacity of manufacturing up to 10,000 patches per day.[152] Lohmann Therapie-Systeme (LTS) AG and Corium Inc. have manufacturing licenses for MAP

Table 7. Microneedle manufacturers developing vaccine microneedle array patch (MAP).

Company	Type of MAP	Vaccine Target	Location
Micron Biomedical	D-MAP	IRV-IPV Measles	USA
Vaxxas	C-MAP[154]	Influenza	Australia
QuadMedicine	C-MAP[71,82]	Influenza Hepatitis B	Korea
Vaxess	D-MAP[155]	Influenza	USA
Raphas	D-MAP[156]	Tumor	Korea
3 M	C-MAP[94]	Influenza	USA
JUVIC	D-MAP[157]	scrub typhus	Korea

D-MAP: dissolving microneedles, C-MAP: coated microneedles.

patches as drug delivery systems.[153] However, companies usually have not released detailed information about their manufacturing technology and environment.

A reasonable and affordable price of commercial MAP is important for successfully launching novel pharmaceutical dosage forms to the market. However, issues related to mass production, GMP, and costs during manufacturing are all challenges currently hindering the development of such innovative products for clinical use. Currently, seven microneedle manufacturers are developing vaccine applications (see Table 7).

4.3 Regulatory issues

The most recent document from the U.S. Food and Drug Administration (FDA) describes a vaccine MAP as a product that is a combination of a biological product and a mechanical device. A product is composed of two or more regulatory products. The prefilled syringe, autoinjector, or MAP patch preloaded with a biological product are examples of this type of product (21 CFR 3.2e).[158] A vaccine MAP has been focused on because of the advantages of MAP. Vaccine and MAP were combined as a single entity. The regulation of vaccine MAP should consider the safety and effectiveness questions associated with each constituent part and the product as the whole (21 CFR Part 4 Subpart A: sec. 4.4 (b)). A vaccine MAP also should fulfill the requirements for current GMP and for postmarketing safety to transition from the laboratory to clinical use.

The National Regulatory Authorities (NRAs) of each country where the authorized vaccine MAP will be used to require the extension of current marketing authorization or a new one because vaccine MAP changes the route of drug administration. The studies comparing conventional and new vaccine products could reduce the regulatory steps.[159] In low-income countries, the novel vaccine must be licensed by the NRA, FDA, or European Medicines Agency, which are following the essential regulatory functions of the WHO Vaccines Pre-Qualification Program. Such organizations authorize the use of suitable vaccines for the target population and the program.[160] Because another advantage of vaccine MAP is self-administration, regulatory guidelines for the validity and proper use of self-vaccination will be necessary.[148]

5. Conclusion

Preclinical studies of vaccine MAP have been conducted in a wide range of animal models, from rodents to primates. Various vaccines, including new outbreak pandemic vaccines, have been tested using the MAP system, and comparable or superior antibody response has been shown compared to IM and other routes of vaccination. Clinical studies have also been conducted to prove the stability, safety, and immunological efficacy of vaccine MAP, and positive and comparable results compared to IM administration have been demonstrated. However, concerns remain about mass production, reasonable cost, aseptic process, and reproducible quality. Vaccine microneedles are a vaccine product, and the standards for the vaccine product will be applied to the preparation of vaccine microneedles. Therefore, it will take time for the final clinical product of vaccine microneedles to come out. Furthermore, the need for a suitable applicator of vaccine MAP and additional packaging for vaccine MAP are additional cost factors. But several microneedle manufacturers with mass-production capabilities have already developed vaccine MAP in cooperation with vaccine companies, and improved immunological results have been reported. If the above-mentioned limitations are overcome, various vaccines will be incorporated into a microneedle system and administered by MAPs. In the near future, MAPs will be used as a vaccine delivery system together with syringes and needles.

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