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Microarray patches for transdermal drug delivery: a critical narrative review of technological innovations, CMC challenges, clinical translation, and global health implementation

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Microarray patches (MAPs), alternatively known as microneedle patches, is a paradigm shift in the administration of pharmaceutical agents and vaccines. By utilising micron-scale projections to breach the stratum corneum, MAPs bridge the gap between the convenience of transdermal patches and the efficacy of hypodermic injections. This critical narrative review synthesises advances in MAP technology for transdermal drug delivery, focusing on technological innovations, chemistry, manufacturing, and control (CMC) challenges, clinical translation, regulatory considerations, and global health implementation. Special emphasis is placed on CMC challenges, including sterilisation and stability profiling, as well as the landscape of Clinical Trials, highlighting recent frameworks for pivotal Phase III studies in measles and rubella. We conclude by evaluating the programmatic suitability of MAPs for low- and middle-income countries (LMICs), addressing critical barriers such as cold-chain logistics and trypanophobia. A coordinated evolution from product-by-product model to platform-industrialisation model involving vaccine, polymer and device producing companies, regulators, global-health agencies including World health organization (WHO), and technology enablers is necessary. The Measles-Rubella programme provides an important template. MAPs' value is not about replacing a syringe but enabling equitable distribution of vaccination; a strategy to make vaccination less dependent on infrastructure. As scientific innovations, upscaling, unified regulatory frameworks and equitable access advance, MAPs will achieve global relevance.

KEYWORDS
clinical translation, CMC challenges, global health implementation, microarray patches, technological innovations

Introduction

Hypodermic needles and syringes have remained the standard for administering vaccines and biologics for over 170 years [1]. Although effective, this modality is fraught with logistical and compliance hurdles. Parenteral administration typically requires trained healthcare professionals, necessitates a rigorous cold chain, poses risks of needle-stick injuries, and also generates biohazardous sharps waste [2]. Also, trypanophobia (the fear of needles; pain associated with injections) contribute significantly to vaccine hesitancy and non-compliance [3–5]. So, the vaccine coverage varies widely among nations. Marginalised, vulnerable, fragile and conflict-affected community children have low access to immunisation service [6]. Recent outbreaks of measles, vaccine-derived polioviruses, etc. demonstrate the benefit of sustaining high levels of vaccine coverage to eliminate and eradicate the vaccine-preventable diseases.

Microarray patch (MAP) is aninnovative cutting-edge technology that mayincrease global immunisation coverage significantly. It has emerged as a transformative alternative designed to overcome the limitations. MAPs consist of arrays of micron-scale projections, the height typically ranging from 50 to 900 μ, attached to base support. The projections, upon application, painlessly penetrate the stratum corneum, outermost skin barrier, to deliver payloads directly into the viable epidermis and dermis [7–12]. The skin is an immunologically active organ, rich in antigen-presenting cells (APCs) like the Langerhans cells and dermal dendritic cells [13, 14]. Unlike intramuscular (IM) injections, that deposit vaccines into muscle tissue with relatively low immunogenicity, MAPs target the potent immune effector cells directly. This targeting capability allows for 'dose sparing', a phenomenon where protective immune responses is achieved with a fraction of the standard dose needed in conventional injections [1].

Beyond vaccines, MAP has diagnostic, chemotherapeutics and biotherapeutics (like antibody) delivery applications [15]. From proof-of-concept to addressing manufacturing, regulatory approval and clinical validation translational hurdles, the focus has shifted as the technology advanced [16]. This critical narrative review aims to provide a multidisciplinary perspective on the current and emerging landscape of MAP technology, integrating pharmaceutical, engineering, manufacturing, clinical, regulatory, and global health considerations. It also examines key barriers and opportunities for the scalable development, manufacturing, clinical adoption, and equitable deployment of these technologies. Table 1 summarises these considerations.

Methodology for the study

This study was a critical narrative review of MAP for transdermal drug delivery. The review adopts a thematic, integrative, and critical approach to synthesise and interpret the existing scientific and technical literature, rather than following a systematic or scoping review methodology. Accordingly, the purpose is not to provide an exhaustive or quantitatively pooled assessment of all available studies, but to critically examine the field's evolution, integrate evidence across multidisciplinary domains, and identify key technological, translational, and implementation challenges.

The literature was critically examined and synthesised across key thematic domains relevant to the development and translation of MAP technology, including technological innovations, MAP design and fabrication, drug and vaccine delivery applications, CMC, manufacturing scalability, product quality and stability, clinical development, regulatory considerations, and global health implementation. Particular attention was paid to the relationship between technological development and the practical requirements for manufacturing, quality assurance, clinical translation, regulatory approval, and implementation across diverse healthcare settings.

The evidence was organised thematically and critically interpreted to highlight advances in the field, ongoing uncertainties, technical and manufacturing barriers, translational challenges, and opportunities for innovation. Where appropriate, findings from different technological and application areas were synthesised to provide an integrated perspective on the development pathway from MAP design and formulation through to manufacturing, clinical evaluation, regulatory translation, and eventual implementation.

Rather than merely summarising individual studies, this review critically evaluates the field's strengths, limitations, opportunities, and unresolved challenges, and considers how these factors may affect the scalability, accessibility, affordability, and real-world adoption of MAP technologies. Particular emphasis is placed on identifying research and development priorities that could facilitate the transition of promising MAP platforms from laboratory and early-stage development towards clinically viable, manufacturable, regulatory-compliant, and globally implementable products.

Classification and fabrication of microarray patches

Since the initial conceptualisation of microneedles in the 1970s and filing of the first patent in 1976, the approach has evolved into five distinct categories based on drug release mechanism and the fabrication material [22]. These five distinct categories are detailed below (Figure 1).

Solid MAP (S-MAP)

Solid MAPs are among the earliest designs, often fabricated from silicon, metal (*e.g.*, stainless steel, titanium), or non-degradable polymers [22–25]. These primarily adopt 'poke and patch' approach: solid array pierces the skin to create transient microchannels, followed by topical formulation application [1]. While effective for small molecules, this two-step process relies on passive diffusion and has limited reproducibility and patient compliance heavily.

Coated MAP (C-MAP)

Coated MAP is an improvement of solid MAPs by drying formulated vaccine or drug directly onto the solid micro-projection surface ('coat and poke' approach). The coating dissolves in interstitial fluid after skin insertion and release the

TABLE 1 General considerations for programmed vaccine delivery by MAPs.

MAP attribute	General consideration	References
Ease of use	MAP-vaccine delivery is needleless and doesn't require reconstitution; immunisation performed by minimally trained or community health volunteers; enables delivery in settings with weak health systems by house-level campaigns, makeshift and fixed posts, making MAPs well suited for supplementary immunisation, outbreak response, and routine immunisation	[17]
Safety in reconstitution/administration	Risks from reconstitution errors, wrong diluents, contamination, and needle-stick injury is eliminated	[18]
Single-dose presentation	Single-dosing reduces hesitancy to open vials and missed vaccination opportunities compared with the multi-dose vaccination that is common in EPI settings	[19]
Thermostability	Improved stability may enhance thermostability beyond usual needs; removes cold-chain equipment at health posts, and storage of vaccines at ill-equipped facilities	[19, 20]
Painless/reduced pain vaccine delivery	Reduced administration pain would lower vaccine hesitancy and increase acceptability compared with needle-and-syringe vaccination	[21]
Disposal	MAPs generate less biohazardous waste; disposed by the usual non-sharps biohazardous waste system	[18]

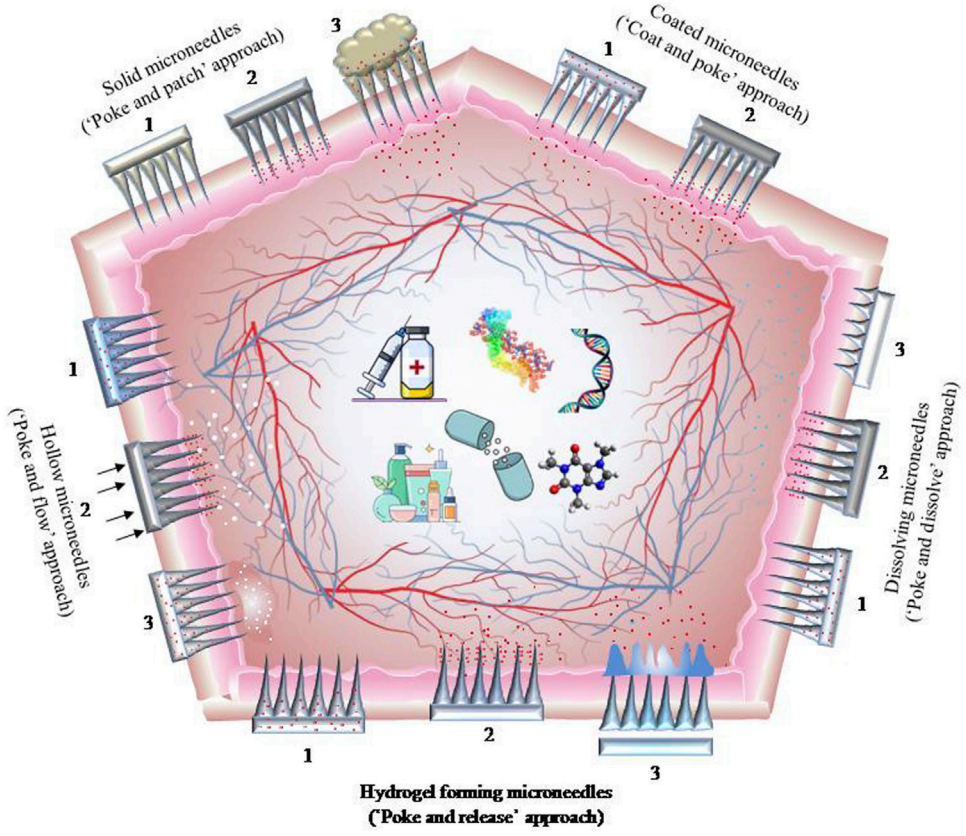


FIGURE 1
Illustrated vaccine MAP types: solid MAP (S-MAP), coated MAP (C-MAP), dissolving MAP (D-MAP), hydrogel-forming MAP, and hollow MAP; the arrows show the vaccine diffusion direction.

payload. While useful for potent vaccines, coated MAPs inherently suffer from limited payload capacity, often restricted to less than 1 mg/array [26]. Further, solid projections remain intact after use, necessitating safe disposal of the sharps waste.

Dissolving and biodegradable MAP (D-MAP)

Dissolving MAP (D-MAP) is a significant safety and convenience advancement [27]. The active ingredient in the patch is encapsulated by fabricated biocompatible, aqua-soluble sugar or polymer (*e.g.*, cmc: carboxymethylcellulose, PVP: polyvinylpyrrolidone, PVA: polyvinyl alcohol, sucrose). The needles release the payload after administration and leave no sharps waste behind by dissolving completely in minutes to hours [23, 28, 29]. Recent innovations have focused on polymer matrix optimisation. For instance, the second generation D-MAPs using methylcellulose (MC) replace the cmc. While cmc solution is too viscous for filter sterilisation, MC formulation is filter-sterilisable; critical cGMP (current good manufacturing practice) compliance factor [30].

Hydrogel-forming MAP

Fabricated from cross-linked polymers (like polymethylvinylether-co-maleic acid crosslinked with PEG), hydrogel-forming MAPs are distinct. They do not dissolve upon contact with the interstitial fluid, but rather they swell. Swelling after insertion, the needles form continuous, porous conduit to allow drug to diffuse from a backing reservoir into the skin. As reservoir size is not limited by needle volume, this design allows for higher drug payloads compared to the coated or the dissolving MAPs. The swollen patch is removed intact leaving no polymer residue in the skin [31–35].

Hollow (porous) MAP

Hollow MAPs possess an internal bore to allow pressurised infusion of liquid formulation, a function that is similar to miniaturised hypodermic needles ('poke and flow'). Hollow MAPs allow delivery of larger volumes, and precise flow rate control. However, they are susceptible to clogging and need complex microfluidic fabrication. Porous MAPs contain porous network that allow liquid formulations to diffuse into the skin via capillary activity [22–24, 36].

Innovative fabrication techniques

Fabrication advancements address the persisting low-drug-loading limitation. For maximum cargo capacity, a novel "powder-filling" technique is adopted. Powder filling involves packing lyophilised drug powder directly into the moulded cavity before adding the polymer matrix, unlike traditional solution casting where the drug is dissolved in polymer solution (limiting concentration due to viscosity or solubility). This has achieved up to 4.5 mg antibody loading capacity per a cm^2 patch, a 20-fold increase over solution casting [15, 37, 38]. Also, additive manufacturing (3D printing) to create complex (undercut, "arrowhead" microneedle, etc.) geometries is increasingly being used to improve skin retention.

Vaccine delivery applications

Due to their enhanced immunogenicity and simplified logistics potentials, MAPs are being extensively evaluated for vaccine delivery.Aimed at achieving high delivery efficiency, Choi *et al.* (2024) prepared a five-in-one vaccine microneedle patch (Figure 2) by integrating four microneedle arrays containingHepatitis B, Diphtheria/Tetanus, Pertussis and *Haemophilusinfluenzae* type B vaccine ina single patch [39].

Adjuvanted MAPs were evaluated in lab animal models to address weak immunogenicity of vaccines. The platforms enhance humoral and cellular immunity both with abundantly found antigen-presenting cells (APCs) in the epidermis and dermis in the skin. Preclinical trials explored many antigens and microparticulate adjuvant, chemical or microbial combinations delivered through MAPs. Adjuvanted multiple antigen peptide based vaccine is a tailored and designed immunotherapy where branched peptide dendrimers usually built on an oligo-lysine are linked to an adjuvant that stimulates the immunity. It creates "self-adjuvanting" delivery optimising the APCs uptake, T-cell enhancement or B-cell priming while minimising adjuvant toxicity. Table 2 lists adjuvant-containing MAP-based vaccines that have undergone preclinical evaluation.

Influenza

Influenza is the most extensively studied MAP vaccination target. Preclinical studies in mice have shown that inactivated influenza vaccine delivered through dMNPs induced robust antibody and cellular response, often superior to intramuscular injection. Davies *et al.* and Foster *et al.* [46, 47] utilised dMNPs made of PVP encapsulated inactivated influenza vaccine demonstrating improved protective immunity in mice compared to IM injection [46, 47]. Clinical trials have further validated this, demonstrating that dMNP-delivered influenza vaccines were safe, well-tolerated and immunogenic in human subjects.

Measles and rubella (MR)

Although measles and rubella elimination is a global priority, coverage gaps persist that result in over 90,000 measles deaths each year. MR-MAPs that are amenable to remote settings, to reach "zero-dose" children, are being developed. Rhesus macaque preclinical trial confirmed that MR-MAP induced neutralising antibody titre was comparable to subcutaneous injection [48–50]. Recent Phase I/II trials involving 9-month-old infants and toddlers in Gambia confirmed that MR-MAP was safe and generated comparable immunogenicity to the conventional needle-n-syringe delivery. Stability of MR-MAP is a key advantage; formulations remained stable at elevated temperatures, potentially reducing the reliance on cold-chain logistics [51, 52].

Polio and rotavirus combination

As the world transits from oral polio vaccines (OPV) to inactivated polio vaccines (IPV), the logistics burden of injectable IPV has increased. MAPs could solve it. Studies in rats on IPV and inactivated Rotavirus vaccine (IRV) co-administration via dMNPs were successful. Crucially, no immune interference between the antigens was observed when co-administered. The study has found

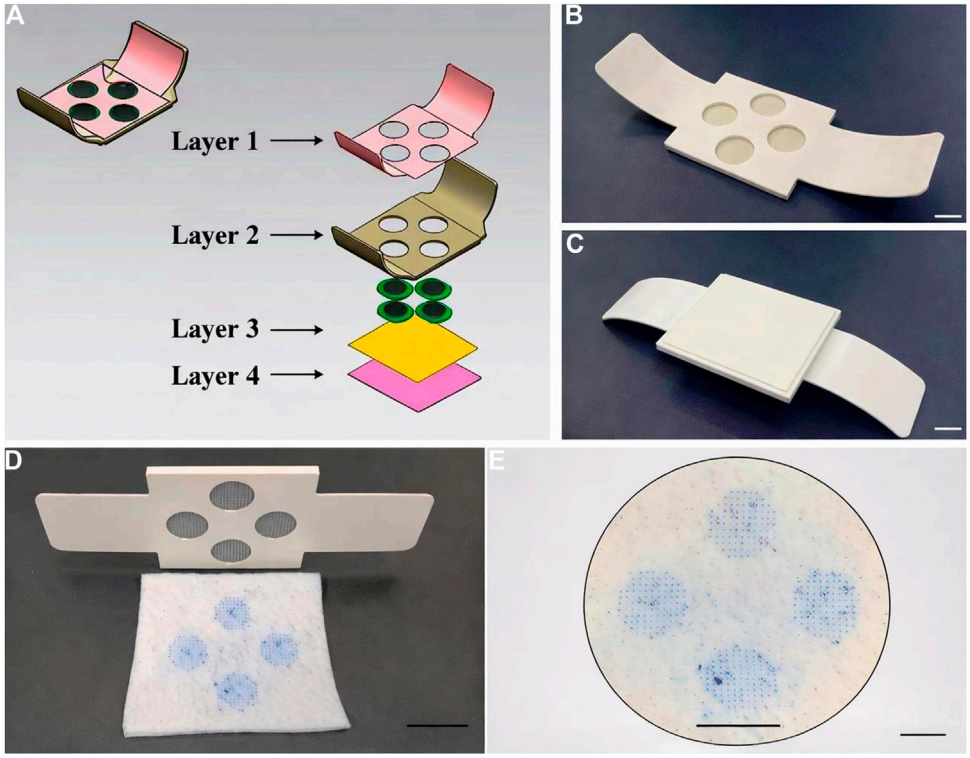


FIGURE 2
Five-in-one layered MAP assembly with four microneedle arrays (C-MN): **(A)** C-MN housing with four layers – 1. Upper adhesive layer, 2. Array-holder layer, 3. Lower adhesive layer, 4. Mechanical support layer; **(B,C)** Fabricating MAP with four C-MN arrays back and forth **(D)** Stained porcine tissue after five-in-one MN patch insertion with all microneedle arrays inserted into skin; **(E)** Enlarged image of treated skin forming the blue dots. Source: Choi et al. [39]. (A),(B) and (C) reproduced from Figure 3 "Concept of 5-in-1 MN patch assembled with four microneedle arrays and four layers: a microneedle patch that integrates combination vaccines into a single application, consisting of four coated microneedle (C-MN) arrays, each coated with different vaccines", (D) and (E) reproduced from "Figure 4. (a) Stained porcine tissue after 5-in-1 MN patch insertion showing that all microneedle arrays (four C-MN arrays) were successfully inserted into the porcine skin. (b) Enlarged image of treated skin showing successful penetration of all microneedles, forming blue dots. Scale bar represents 1 cm" by In-Jeong Choi et al., licensed under CC BY 4.0.

TABLE 2 **Adjuvant-conjugated MAP-based vaccines that underwent preclinical evaluation.**

Adjuvant	Vaccine	References
Cholera toxin	Diphtheria toxin, hepatitis B	[40]
dmLT (double mutant heat-labile toxin)	*Clostridium*, *Shigella*	[41]
Fms-like tyrosine kinase 3 ligand	Hepatitis B	[42]
CpG oligonucleotide	Hepatitis B	[43]
Monophosphoryl lipid A	HIV	[15]
Poly(I:C)	Influenza	[44]
Saponin-based	Ebola, hepatitis B, influenza	[45]

that a combined IRV-IPV dMNP administration induced neutralising antibodies against Poliovirus types 1, 2 and 3 and Rotavirus, comparable to single-antigen patches. Further, there was dose-sparing; a quarter dose of the combined vaccine delivered via 2nd generation dMNP was as potent as a full dose [30, 53, 54].

COVID-19 (SARS-CoV-2)

COVID-19 pandemic scenario triggered MAP research. MAPs that targeted the SARS-CoV-2 spike protein (S1 subunit or RBD) showed robust immune response in preclinical model. For instance, a cmc-based dissolving MAP loaded with the S1 subunit elicited potent antibody responses in mice as early as 2 weeks after being immunised. Another study used a high-density MAP to deliver SARS-CoV-2 spike subunit vaccine that resulted in enhanced T-cell response compared to needle injection. These patches offer critical advantages for pandemic response due to the thermostability (reduced cold-chain dependence) and self-administration potential, which reduces the burden on the healthcare systems [9, 55–58]. Table 3 lists the MAP-conjugated vaccines that are at various development stages.

Other targets

MAPs for Hepatitis B, HPV, Rabies, Dengue, Ebola, Zika and Tuberculosis (BCG) vaccines are also being developed. dMNPs loaded with Hepatitis B surface antigen (HBsAg) showed immunogenicity in mice and Rhesus macaques. dMNP was as immunogenic as IM injections in rabid dogs, potentially simplifying post-exposure prophylaxis [2, 26].

TABLE 3 Microarray patches based vaccines at development stage.

Antigen type	Antigen/ vaccine	References
Recognised antigens for which comparator commercial/emergency authorisation vaccine is available	Pertussis	[39]
	Yellow fever	[59]
	BCG	[60]
	Seasonal influenza	[61]
	Japanese encephalitis	[62]
	Cholera	[63]
	Hepatitis B	[39]
	HPV	[39]
	Measles-rubella	[64]
	Diphtheria	[39]
	Polio	[30]
	Tetanus toxoid	[39]
	Rabies	[65]
	Chikungunya	[66]
	Ebola	[67]
	Rotavirus	[30]
	Respiratory syncytial virus	[68]
	Pandemic influenza	[61]
	Dengue	[69]
	Malaria	[70]
Investigational for which comparator commercial/emergency authorisation vaccine is unavailable	Anthrax	[27]
	Zika	[71]
	Plague	[72]
	HIV-1	[73]
	MERS	[55]
	Lassa fever	[74]
	Hepatitis C	[27]
	Herpes simplex virus 2	[1]
	Enterotoxigenic*E. coli*	[75]
	West nile virus	[66]

Therapeutic applications beyond vaccines

Infectious disease management

MAPs are being employed to treat infections that disproportionately affect the communities in LMICs [76, 77], especially the neglected tropical diseases (NTDs).

Tuberculosis (TB)

The delivery of antibiotics like rifampicin, isoniazid and pyrazinamide using MAPs is being explored. Hydrogel-forming MAP demonstrated the ability to deliver high dose of antibiotics across porcine skin. Further, MAPs to diagnose TB, deliver purified protein derivative (PPD) for skin testing with greater depth control (and less pain than Mantoux technique) are being developed [43, 78–81].

Malaria

Dissolving MAPs loaded with antimalarials like artemether and lumefantrine have shown extended-release profiles and significantly (99.5%) reduced parasitaemiain *P. yoelii* infected murine models. This approach could be particularly beneficial for paediatric patients or those intolerable to oral medication due to vomiting [82, 83].

Skin and soft tissue infections (SSTIs)

MAPs can breach the biofilm barrier and necrotic tissue that often render topical creams ineffective in such as the localised infections caused by Methicillin-resistant *Staphylococcus aureus* (MRSA). Loaded with gentamicin or vancomycin, MAPs have demonstrated high localised drug retention and bacterial clearance in wound models *ex vivo*. Additionally, MAPs fabricated from Manuka honey had inherent antibacterial (MRSA) properties [84, 85].

Antibody delivery

Monoclonal antibodies (mAbs) can critically treat cancers and infectious diseases like HIV. However, high-dose intravenous infusion is typically required. MAPs with "powder-filling" method successfully delivered thermostable human IgG and anti-HIV b12 antibodies. Novel "core-shell" MAP design allows for pulsatile release; polymer shell bursts at pre-programmed intervals (*e.g.*, day-0, 10 and 21) and degrades at specific rates to release antibody, mimicking repeated injections [15, 86].

Are the potential benefits overstated?

It is understood that several potential advantages of MAPs are overstated. Claims regarding painless administration, cold-chain elimination, self-administration, waste elimination, and increased vaccine coverage should be expressed more cautiously because these outcomes depend on the MAP design, formulation, packaging, applicator, and implementation setting. Beyond vaccines, MAPs are promising in their applications in therapeutics. However, their potential advantages are often overstated as against the reality. Some such claims include, eliminating the cold-chain, the scope to self-administer, painless administration, eliminating the generation of biohazard waste, and increase in vaccine coverage. MAP does not guarantee thermostability; a formulated therapeutic could still lose its efficacy without proper specialised packaging, particularly at tropical temperatures. The MAP product is dependent on the microneedle type (like dissolving, coated, hollow, solid, etc.) the

sugar/polymer matrix material that encases the vaccine/drugor the needle matrix (hyaluronic acid, PLGA, metal, etc.) and the overall formulation (like attenuated vs. mRNA). In this context, the need of the cold-chain could not be eliminated. Further, the scope of MAP to self-administer is also overstated. An extremely foolproof implementation design (like manually applied by thumb pressure, mechanical applicator, etc.) is necessary for self-administration in its true sense. High user error rates, which would lead to under-dosing, could occur without proper sensing system to intuitively visualise or physically specify that the MAP was optimally pressed and stayed attached long enough for effective performance.

Similarly, patient perception could be heavily influenced by the design of the applicator as the MAP microneedles are typically too short and are incapable of reaching the pain receptors located deep. The spring-loaded device/clicker that ensures uniform penetration into the skin could inflict acoustic shock or discomfiture which the patients could perceive as hurting. Thus, the claim of painless drug administration could be overstated. Although MAPs reduce sharp-biohazard waste as compared to the traditional needles and syringes, they really do not eliminate waste production. Instead, MAP introduces new waste streams like the discarded applicator, additional protective backings and contaminated patches which require proper disposal procedure as biohazard materials. Thus, biohazardous wastes are not really eliminated but rather reduced, at the best. The deep reach of MAPs to cover the remote population is grossly dependent on the implementation strategy. MAPs will face the same logistical bottlenecks as traditional vaccines if it needs complex applicators, special trainings for successful delivery, or stringent humidity-controlled wrapping. Thus the claim of increased vaccine coverage also is an overstatement.

Chemistry, manufacturing and control (CMC)

The MAPs translation from the laboratory to the clinic hinges rests on robust chemistry, manufacturing and control (CMC) strategies. Table 4 lists the companies working on microarray patch-based vaccine development. Besides this, an Indian start-up Innovodigm has also developed coated microneedle MAP for Hepatitis B which is under preclinical trials.

Manufacturing and scale-up

Translation of MAPs from promising laboratory platforms into commercially viable vaccine products is heavily dependent on maturity of CMC strategies. A MAP is a more complex dosage formulation, unlike conventional liquid vaccines, wherein formulating the vaccines, the matrix polymer, geometry of the microneedles, backing layer, packaging and applicator determine product performance collectively. Therefore, CMC development must demonstrate not only antigen identity, purity, potency and stability, but also exhibit consistent physical performance of the finished patch and reliable delivery of the intended dose into the skin. Figure 3 depicts the critical criteria for the designing of MAPs.

Currently, most vaccine MAPs are produced on a small scale for early-stage clinical trials. Scaling up to commercial levels (millions of units) requires establishing Good Manufacturing Practice (GMP) facilities. Processes must be scalable and cost-effective. For example, injection moulding and screen printing are being explored for high-throughput fabrication. A critical challenge is maintaining "lot-to-lot" consistency regarding antigen content, dissolution rates and mechanical strength [1, 3, 27, 93–95].

Critical quality attributes (CQAs) and dose uniformity

Defining the CQAs is central to MAP development. CQAs may include antigen identity and potency, antigen loading, content uniformity, residual moisture, polymer composition, microneedle dimensions, tip sharpness, mechanical strength, insertion efficiency, dissolution or dissolution time, microbial quality, sterility and package integrity, depending on the platform and vaccine. These attributes need to be linked to critical material attributes and critical process parameters through a science-based control strategy.

Dose uniformity is particularly important as MAPs generally contain relatively small quantity of antigen distributed across an array of individual microneedles. Variability in antigen deposition, drying, filling or coating can thus translate directly into variability in delivered dose. Analytical methods must be able to measure antigen content and potency at both the patch and manufacturing-lot levels. Sampling strategies could account for spatial variability across the patch and between patches, rather than relying solely on bulk measurements. Manufacturing processes like micro-mould filling, coating, printing or powder deposition consequently require tight control of formulation viscosity, solids concentration, deposition volume, drying rate and environmental conditions [1, 27, 95].

Insertion efficiency and mechanical performance

Therapeutic performance of MAPs depends on successful skin penetration. The efficiency of insertion is influenced by microneedle height, base width, tip geometry, aspect ratio, polymer composition, mechanical strength, skin characteristics and the force and speed applied during administration. A MAP that contains the correct antigen dose but fails to insert adequately may result in incomplete delivery and inconsistent clinical performance.

Thus, mechanical strength is a critical CQA. Microneedles must withstand manufacturing, packaging, transportation and application without bending or collapsing. At the same time, excessive mechanical strength or inappropriate geometry can make dissolution or drug release undesirably slow. Mechanical testing could evaluate compression and fracture forces, dimensional integrity and performance following exposure to temperature and humidity excursions. Importantly, laboratory mechanical testing may be correlated with skin insertion studies rather than being treated as an independent specification.Skin layers and accessing each layer as drug delivery strategies is presented in Figure 4. The epidermis and dermis of skin have 1–2 orders of magnitude more immune cells (antigen presenting cells; APCs) per unit volume compared to the subcutaneous muscle layer.

Needle fracture represents a specific patient-safety and product-quality concern. Fracture can occur when polymer microneedles are subjected to excessive application force, inappropriate geometry,

TABLE 4 Various global companies working on microarray patch-based vaccine development.

Company	MAP type	Vaccine target	Location	References
Micron biomedical	D-MAP	IRP-IPV (rotavirus, polio)	USA	[87]
Micron biomedical	D-MAP	Measles	USA	[88]
Vaxxas	C-MAP	Influenza	Australia	[61]
QuadMedicine	C-MAP	Influenza, hepatitis B	Korea	[89]
Vaxess	D-MAP	Influenza	USA	[90]
Raphas	D-MAP	Tuberculosis	Korea	[91]
Raphas	D-MAP	Tumour	Korea	[92]
3 M	C-MAP	Influenza	USA	[27]
JUVIC	D-MAP	Scrub typhus	Korea	[27]

[D]MAP: dissolving microneedle; C-MAP: coated microneedle.

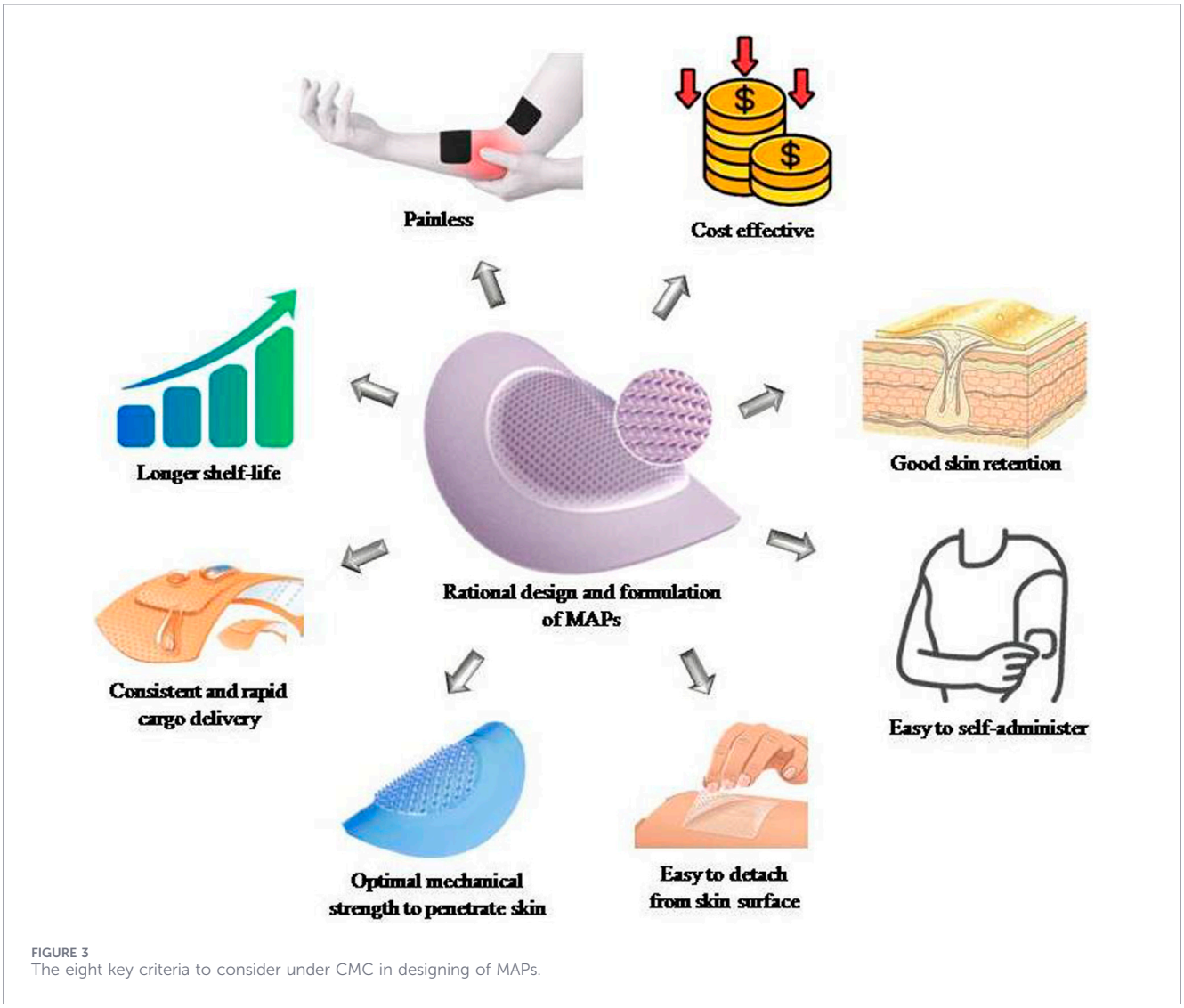


FIGURE 3
The eight key criteria to consider under CMC in designing of MAPs.

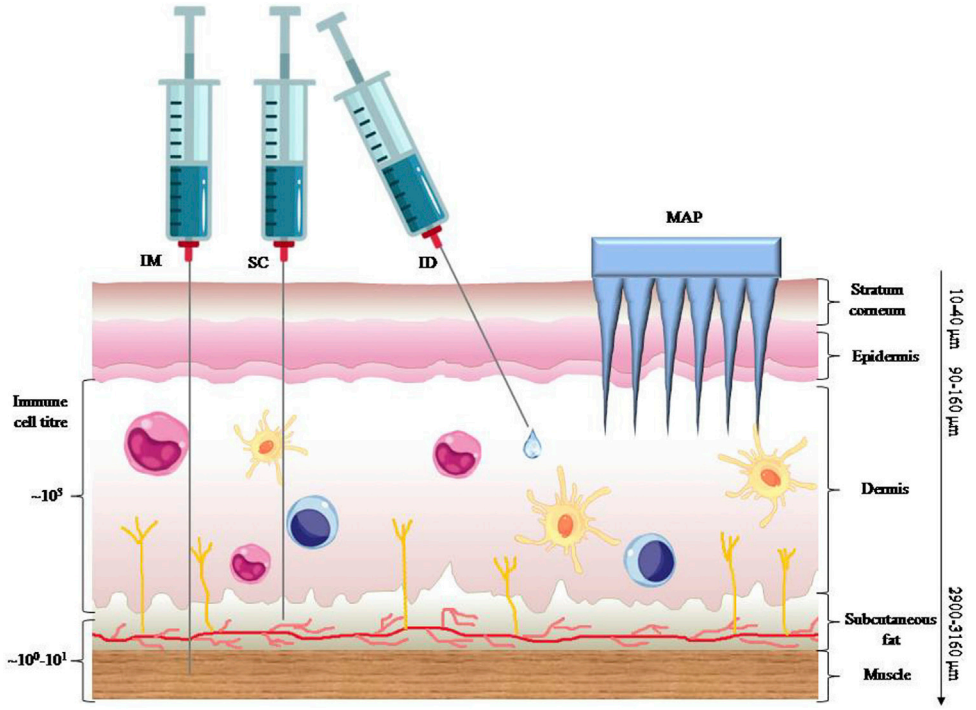


FIGURE 4
The skin layers and accessing each layer as drug delivery strategies. The epidermal and dermal layers have more immune cells (APCs) per unit volume tissue at 1–2 orders of magnitude compared to subcutaneous layer (IM: intramuscular; SC: subcutaneous; ID: intradermal; MAP: microarray patch). ID access enables interstitial fluid (ISF) collection. The scale to the right indicates the depth of each skin layer.

material defects or mechanical damage during handling. Robust strategies could establish acceptable fracture limits and demonstrate that selected formulation and applicator provide adequate mechanical robustness under field conditions. Microscopic inspection, mechanical testing and skin insertion studies combined could facilitate appropriate design.

Residual moisture and stability

Moisture uptake may affect both potency and delivery performance. It is a vital attribute as MAPs often depend on a relatively dry polymer matrix to maintain structural integrity and vaccine stability. Excess moisture can accelerate antigen degradation, promote polymer relaxation or swelling, alter mechanical strength and increase premature dissolution risk. Manufacturing processes need to control humidity during formulation, moulding, coating, drying and packaging. Moisture specifications should be established based on demonstrated relationships between water content and product performance instead of simply accepting conventional pharmaceutical limit. Moisture sorption studies, accelerated stability testing and real-time stability data are needed to determine appropriate limits.

A major attraction of MAP technology is its potential for improved thermostability. Dry-state stabilisation using excipients like trehalose and sucrose can protect sensitive antigens during drying and subsequent storage [96–99]. Influenza MAPs have demonstrated encouraging stability at elevated temperatures, while IPV MAPs have shown prolonged stability under conditions that would challenge conventional liquid formulations [30, 100]. Nevertheless, the results must be translated into product-specific stability specifications and regulatory claims. Controlled-temperature-chain and other temperature-excursion claims should be supported by validated stability data for the final commercial formulation and package.

Extractables and leachables

Extractables and leachables need attention as MAPs combine vaccine formulations with polymer, adhesive, backing material, mould-release agent, coating and packaging component. From MAP, the risk extends to substances originating from manufacturing equipment or primary packaging may also migrate into the product. Extractables studies would characterise potential chemical species released from product-contact materials under appropriately exaggerated conditions, while leachables studies would evaluate substances that migrate into the product during actual storage. Particular attention for materials that are in direct contact with the vaccine formulation is needed. Toxicological relevance of the identified compounds, together with their potential impact on antigen stability and potency, need to be assessed. Instead of addressing only after manufacturing (quality control), material selection may be integrated into formulation development (as a part of quality assurance).

Process validation and manufacturing consistency

Commercial-scale manufacturing will need process validation that is capable of producing millions of patches with consistent

performance. The transition from laboratory fabrication to high-throughput scaled-up manufacturing is not simply about increasing production speed. Altered mould dimensions, filling dynamics, drying conditions, coating uniformity, humidity or polymer processing conditions can affect performance of the final product. Manufacturing technologies like injection moulding, micromoulding, screen-printing, coating and powder filling offer potential routes to scale-up, but each introduces different process controls and sources of variability. Process validation should demonstrate reproducibility across batches and establish relationships between critical process parameters and CQAs. In-process controls, automated inspection and statistically just sampling will be increasingly important as the production volume increases [3, 95].

Applicator performance

The applicator is not a simple accessory. It determines whether the MAP achieves insertion depth and contact for effective delivery. Varying application force, application time, angle or patch contact can produce differences in dose delivery, particularly when MAP administration is performed by minimally trained personnel. Consequently, applicator performance of the overall product system could be characterised and validated. Human-factor study could assess whether intended users can consistently apply the patch correctly, while mechanical testing should demonstrate reproducible force delivery and reliable engagement of the MAP with the skin. For the applicator, its simplicity, robustness and failure risks are critical in performance of the patch in successful mass vaccination campaigns.

Packaging and combination-product considerations

Packaging must protect MAPs throughout its productive life from moisture, oxygen, light and mechanical harm. High-barrier foil pouch, desiccant and controlled packaging environment are needed [30, 101]. Packaging choice may also consider applicator compatibility, usability and opening traits. Integrity testing and transport simulation of packaging are integral to CMC programme. As the final MAP product may contain biological drug or vaccine, a polymeric delivery device and possibly a dedicated applicator, such vaccines may present regulatory challenges. Based on the jurisdiction and product design, combination-product and regulatory requirements applicable to both medicinal product and medical device may be considered. Regulatory strategies need to be defined early with clear responsibility allocation for vaccine quality, device performance, manufacturing controls, usability and post-market surveillance.

Ultimately, the CMC objective is to demonstrate that every MAP that reaches the 'bed-side' contains the intended vaccine dose, remains stable throughout its labelled shelf-life, possesses sufficient mechanical integrity for safe application, inserts reproducibly into the skin and can be manufactured at commercial scale with consistent quality and performance. Achieving this control level is essential for converting MAPs from an innovative drug-delivery technology into a reliable vaccine presentation that is suitable on the field for routine immunisation under the mass global health and wellbeing programmes.

Table 5 provides the comparisons among the five MAP platforms (1. solid "poke-n-patch" MAP, 2. coated MAP, 3. dissolving MAP, 4. hollow MAP, and 5. hydrogel-forming MAP) and performance mechanisms regarding parameters and attributes related to stability, payload capacity, manufacturing feasibility, dose accuracy and reproducibility, physicochemical and thermal stability, biocompatibility and safety profile, clinical maturity (clinical development stage), regulatory status, cost of production, and suitability for deployment in the low-resource settings such as the LMICs.

Sterility

Sterility is a major regulatory requirement. Unlike liquid vaccines that can be sterile-filtered, solid MAPs often cannot. Terminal sterilisation methods, like gamma or electron beam irradiations, are preferred but can degrade sensitive biologics. Studies show that certain trehalose and sucrose formulations protect antigens during irradiation. Alternately, aseptic manufacturing process may be required, though it significantly increases the production cost. Recent innovations include "self-sterilising" MAPs incorporating AgNPs to prevent bacterial growth at insertion site [72, 102, 103].

Stability and thermostability

A key value proposition of MAPs is their potential in eliminating the cold-chain. Formulating vaccines in a dry state within the patch matrix inherently improves stability. Excipients like trehalose and sucrose are critical to stabilise protein during the drying process and subsequent storage [96–99]. Influenza vaccine MAPs have demonstrated stability at 60 °C for 4 months [100], and IPV MAPs maintained potency for a year at 40 °C [30]. Similarly, antibodies loaded via powder-filling maintained functionality after exposure to 100 °C for an hour [15]. It is important to note that regulatory requirements for labelling, like vaccine vial monitor (VVM) standards (*e.g.*, stability at 37 °C for 30 days) and controlled temperature chain (CTC) standards (*e.g.*, 40 °C for 3 days), must be validated for MAPs [50, 104–106].

Quality attributes, performance, process validation and regulatory compliance

Other important criteria under the chemistry, manufacturing and control of MAP also include the underlying critical quality attributes such asdose/dosage uniformity, the efficiency of insertion, mechanical strength of MAP, needle fracture, residual moisture level, and process validation aspects like the leachables and extractables, applicator performance, and the regulatory framework for the combination-product (conjugated MAP), and design controls.

Dose uniformity

It involves ensuring precise drug distribution across all the needles in a patch. It could be validated across different

TABLE 5 Comparisons among the MAP platforms with regard to their stability and performance.

Criterion	Solid MAP ('poke-n-patch')	Coated MAP	Dissolving MAP	Hollow MAP	Hydrogel-forming MAP
Mechanism	Creates transient microchannels; drug applied as separate topical formulation	Drug/vaccine film-dried onto MAP shaft; dissolves in skin in minutes	Drug capsulated in biodegradable polymer matrix (*e.g.*, hyaluronate, carboxymethylcellulose, PVP, PVA) that dissolves in skin fully, leaving little sharps waste	Microneedle acts as conduit; formulated liquid infuses actively/passively in the dermis through a bore/lumen	Cross-linked (non-dissolving) polymer like Gantrez S-97/PEG imbibes interstitial fluid upon skin contact and swells, forming a continuous, unblocked microchannel; drug diffuses from an attached reservoir/patch backing; array is removed intact
Payload capacity	Not applicable in the classic sense; device decouples from drug; capacity limited only by isolated topical reservoir	Low, restricted by surface area of microneedle; typical loads of tens to low hundreds μg per patch. Apt fabrication (hot-compaction + dam-board reservoirs) raised loading to ≈118 μg/array, 'hundreds of times' the usual baseline; coating often is surface-area limited	Moderate–high drug distributed through the needle matrix and/or base-plate reservoir; milligram-range loading achieved (*e.g.*, 3.84 mg diclofenacNPss/patch in a bimodal DMN; loading is limited by viscosity/crystallinity limits of the casting polymer and needle volume	High; lumen/reservoir is decoupled from the mechanical/geometric constraints of needle, allowing continuous larger liquid volume (hundred μL to mL range) infusion, suiting biologics and high-dose small molecules	High for potent/high-dose drugs; payload is limited by size of an attached, separately formulated reservoir (tablet, lyophilised wafer or gel disc) as hydrogel matrix itself carries no drug. Demonstrated delivery of ~44 mg ibuprofen sodium and ~1.24 mg ovalbumin over 24 h from a lyophilised-wafer reservoir
Production feasibility	Simple, etching, micromoulding or metal-stamping (silicon, stainless steel, titanium) standard process; high mechanical reproducibility	Moderately complex; needs precision secondary coating (dip-coating, printing, spray-coating) after fabrication; shaft coating (sans baseplate) only for reproducibility and uniformity is technically demanding	Moderate to highly complex; need micromolding/casting, vacuum or centrifugal filling and controlled drying; compatible with roll-to-roll and injection-moulding scale-up. LTS LohmannTherapie-Systeme AG secured MN manufacturing licensure, showing industrial-scale feasibility	Highly complex; need bore/lumen micro-machining (etch, 3D microfabricate or laser drill), and integrated pump/reservoir/actuator; few related literature (the least standardised for mass manufacture)	A scalable injection-moulding process (custom metal master → silicone mould → aqueous polymer casting) is validated explicitly for 14X14 arrays; is 'easily scalable' with GMP/commercialisation; novel 'scalable' PVA/PVP hydrogel MAPs infrared-crosslinking methods have been standardised
Dose accuracy/reproducibility	Dosing accuracy depends on topical formulation applied later, and variable/dynamic recovery of created microchannels, which can itself cause inconsistent permeation	Poorest among the five; non-uniform coating thickness and patchy/irregular deposits recur, documented problems, directly causing inaccurate dosing; dosage and drug uniformity are still the bottlenecks for coated MAPs	Good; homogeneously distributed drug (or tip-localised) in a solid, pre-formed matrix produced under controlled micro-moulding/metrology, unit-to-unit dose variability is markedly lower than coated MAP; tip-loading strategies further improve reproducibility and dissolution kinetics	Good to excellent when actively pumped; flow-rate/volumetric control of infused liquid enables precise, titratable dose, though back-pressure from compressed dermal tissue occludes the bore, compromises delivery consistency	Very good; dose set by (manufactured, easily assayed separate) drug reservoir rather than by MAP itself, and the hydrogel channels are not blocked by compressed tissue (unlike hollow MAP), giving more predictable and sustained pharmacokinetics

(*Continued*)

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TABLE 5 Continued

Criterion	Solid MAP ('poke-n-patch')	Coated MAP	Dissolving MAP	Hollow MAP	Hydrogel-forming MAP
Physico-chemical/thermal stability	High; device (metal/silicon/ceramic) is drug-free and shelf-stable indefinitely under normal conditions	Moderate; dried coating improves short-term stability of some antigens over liquid formulations, but coat film offers limited protection against humidity/oxidative degradation	High; key comparative advantage; dehydrated polymer matrix confer vaccine/protein thermostabilisation, and reduce/eliminate cold-chain dependency; explicitly cited as a principal LRS/vaccine deployment driver; 'improved thermostability' is the core value proposition	Low; hollow MAP offers little benefit over conventional injectables and cold-chain requirements as formulation is liquid	High; thermostable reservoir components (lyophilised wafer, dry tablet) formulated, independent of the (drug-free) hydrogel-forming matrix
Biocompatibility/safety profile	Good; break and retained needle in skin risks metal/silicon fragment; a real recognised safety concern for non-degradable materials	Good; risk profile similar to solid MAP (non-degradable substrate) plus potential local reactions against the coated excipient	Favourable and self-disabling; fully biodegradable/bioresorbable, no sharps waste, and cannot be reused; reducing needle-stick and cross-contamination risk; hydrogel-forming variants additionally show intrinsic antimicrobial properties against ingress pathogens	High risk profile among all; larger bore MAPs pose pain/discomfort as solid/coated/dissolving arrays; blocked needle by compressed dermis may need applying higher insertion force	Excellent; removed intact (no polymer residue on skin, unlike D-MAP), not blocked by compressed tissue (unlike hollow MAP), and possesses demonstrated antimicrobial activity at the insertion site, offering 'enhanced patient safety potentials'
Clinical maturity	Long clinical history to pretreat skin (used since the '90s, but rarely used these days as a standalone monotherapy platform	Advanced; vaxxas' coated high-density (HD) MAP is the most clinically mature platform: Completed phase I trials for split inactivated influenza vaccine; 2.5 μg dose (1/6 standard IM dose) induced immunogenicity comparable to full-dose IM injection	Advanced for paediatric/LMIC vaccination; micron biomedical measles-rubella MAP completed phase 1/2 randomised, age de-escalation trial in Gambia (infants, toddlers, adults); first paediatric efficacy/safety data for a DMAP vaccine patch; 93% measles and 100% rubella seroconversion in infants, broadly subcutaneous injection comparable; induration is the main local reactogenicity signal	Least clinically advanced; less human trials than solid/coated/dissolving MAPs due to the difficulties in standardising the manufacturing	Preclinical-to-early-clinical indications (metformin, enfuvirtide, photodynamic-therapy precursors, melanoma therapy); no hydrogel-forming MAP products yet commercially marketed despite more than 20 years of R&D, and hundreds of cumulative MAP clinical trials across platforms
Regulatory status	Governed by existing device/topical-drug frameworks	No MAP vaccine product yet fully licensed; vaxxas HD-MAP progressing under FDA IND pathway	No fully licensed MAP vaccine product yet; MR-MAP in phase 1/2, with WHO full-value vaccine assessment underway to inform policy/regulatory planning	Regulatory pathway least defined among the five, reflecting low product count	'Microneedling products' specific FDA framework exists, but is oriented toward cosmetic/topical use, not as drug/vaccine MAPs; dedicated pharmacopeial/GMP standards for MAP class being developed

(*Continued*)

TABLE 5 Continued

Criterion	Solid MAP ('poke-n-patch')	Coated MAP	Dissolving MAP	Hollow MAP	Hydrogel-forming MAP
Cost	Lowest per-unit device cost; simple fabrication	Low–moderate device cost, offset by precision/yield loss at the coating step	US$0.50–5.00/patch manufacturing cost (scale & polymer choice based); US$0.24–0.61/dose (probability ≥87%) is projected operational (non-device) savings due to reduced cold-chain, labour and waste disposal costs; <US$30/dose price points may raise cost-effective MAP adoption; australian influenza-programme analysis projected an annual US$108 million national savings from full MAP substitution	Base device cost is comparable to solid/coated MAP, but added reservoir/pump/actuator hardware increases total system cost and reduces the 'low-resource' cost advantage as compared to D-MAP	Cost is similar to D-MAP at lab scale; achieving the validated industrial injection-moulding process could reduce the unit cost at scale; only ~13 MAP products (mostly cosmetic) have reached the market despite >4,000 filed MAP-related patents, reflecting a persistent translation-to-commercialisation gap across all polymer-based MAP types
Suitability for low-resource settings	Limited; requires a second, separate drug-application step and standard cold-chain for most biologics; offers few specific advantages in low resource settings	Moderate; one-step, needle-free application is favourable for lay/community-health-worker use, but low payload and dose-uniformity issues; lacks thermostability data too	Best suited among the five; single-dose, applicator-free (in few cases), self-disabling, thermostable and requires minimal training, directly matching the WHO/PATH's stated immunisation priorities for LMICs; validated in a real LMIC field trial setting (The Gambia) across infant, toddler and adult cohorts	Poor fit; requires more complex hardware (pump/reservoir), less mature manufacturing base; no demonstrated thermostability benefit over needle-and-syringe undermines cold-chain elimination, the primary LRS value proposition	Good potential (self-administration, no sharps waste, mechanically robust); 20 N compression caused ~14% reduced height only; currently held back by early clinical-stage status and absence of field-deployed LMIC trial data comparable to the MR-MAP programme

production batches and on individual needles through mass spectrometry or HPLC (high-performance liquid chromatography).

Efficiency of insertion

This evaluates the percentage of the microneedle that penetrates the skin barrier successfully. The repeatability of the delivery depth is evaluated and confirmed using either optical coherence tomography (OCT) or *in vitro* skin (like porcine skin) models.

Mechanical strength of MAP microneedles

It is to determine the force that is needed to compress/break the needle. To ensure that the needle would survive handling, packaging and insertion into the skin without its premature failure, texture analyser is used to conduct the tests related to the axial and transverse forces.

Needle fracture

It is necessary to define the mode when the needle could fail. The dissolving microneedle is dissolved completely in the skin first instead of breaking it off dry to ensure wet-fracture of the needle. The non-dissolving microneedle is tested against the risk of the impulsive breaking off of the tip, and leaving the foreign material within tissue.

Residual moisture level

The moisture level in the dissolving or the polymer-based microneedle is monitored. Excess moisture might affect the structural integrity and accelerate degradation of the conjugated drug. Similarly, over-drying of the needle could make it brittle. It is needed to be controlled through strict environmental measures during microneedles drying and packaging, which is quantified through the Karl Fischer titration technique.

Process validation

A robust framework is required to be established for the manufacturing line, to validate the process. Consistency of moulding/casting process, reproducibility of demoulding/separation step, and drying phase uniformity are the key parameters included, and all these are documented along with temperature, humidity and curing time as critical process parameters (CPPs).

Leachables and extractables

The potential chemical contaminants from the needle polymers, adhesive, patch backing or primary packaging that could potentially migrate are profiled. Controlled extraction assays are carried out

using various solvents. It follows routine leachable monitoring throughout the shelf life of the product.

Applicator performance

The brevity of the mechanical applicator, particularly if the system has to rely on one for insertion, is validated. The velocity, impact force and the reliability of the firing mechanism across thousands of actuations are tested to ensure that the insertion pressure is the same for every receiving patient.

Regulatory classification for combination product

The system needs to be first correctly classified based on the primary mode of action. For instance, a drug-led combination product it is typically regulated based on the therapeutic effect achieved through the drug (*e.g.*, CDER reviewed in consultation with the CDRH, of the USFDA). The same applies to the international regulatory guidelines too.

Design controls

The mechanical components in the patch and the applicator control designs need to comply the 21 CFR Part 820 which refers to the USFDA's current good manufacturing practice requirements of the quality management system (QMS) for medical devices. Maintenance of a design history file, performance of risk management (ISO 14971) rigorously to address the mechanical failure or user error, and conducting usability engineering or human factors studies are included under it.

Clinical trials: frameworks and recent progress

Clinical development of MAPs has moved beyond laboratory and animal studies to safety, tolerability, immunogenicity, usability and acceptability in humans. The evidences should be carefully described. Available literature demonstrate clinical proof-of-concept with influenza and measles-rubella vaccines, including a Phase I/II trial in infants and young children, but MAP vaccines do not yet have any established clinical efficacy trials against any human disease in a completed Phase III trial. Thus, the next major development step is a pivotal efficacy-immunogenicity programme, particularly against measles-rubella, instead of the MAP technology that is already clinically validated for routine vaccine efficacy.

Clinical evaluation of MAPs has progressed with time from the safety and acceptability studies to the efficacy trials. It is important to distinguish the *in vitro* or animal studies, clinical trials, modelling studies, institutional reports and commercial information more clearly first. The evidence types do not have equivalent scientific weight as is often contemplated. Supporting data across numerous such studies have scientific weight which varies considerably across various evidences. However, distinguishing the early-stage laboratory findings and rigorous human trial data, while evaluating the safety and efficacy considerations for the true readiness of MAPs, are critical. Although *in vitro* and modeling studies are crucial while developing the early-stage formulation, they would not guarantee clinical efficacy of MAPs. For instance, a patch that delivers a drug through a synthetic lipid bilayer membrane (mimicking the typical natural cell membrane) effectively *in vitro* might fail to exhibit desired immune response on human skins.

Further, animal models are essential for toxicological studies. However, laboratory animals like mice and pigs would display large variations in their skin anatomy as compared to the humans, such as the hair follicle density and the epidermal thickness. Thus, animal data could at best serve as an initiation point and not a reliable confirmation. Similarly, the summarised data of commercial press releases and institutional reports are often optimistically presented to highlight the global healthcare potentials of the product to attract potential investors and global market. This requires that such reports or press releases always require validation and verification through relevant peer-reviewed clinical data, as cross-references. Table 6 below breaks down the hierarchy of evidence for MAPs, ranked from the highest scientific weight to the lowest.

Completed clinical trials

The initial MAP-vaccine human study involved influenza. Rouphael *et al.* (2017) conducted a randomised Phase I trial on 100 adult volunteers of a dissolving MAP containing inactivated influenza vaccine [107]. Acceptable safety and tolerability was demonstrated, and antibody responses following patch administration were comparable with conventional intramuscular vaccination. Participants also showed high acceptability of the patch, establishing an early clinical foundation for vaccine delivery through dissolving microneedles.

A subsequent Vaxxas's study evaluated polymer-based high-density microarray patches (HD-MAPs) for influenza vaccination. 210 healthy adult volunteers received various influenza haemagglutinin doses by HD-MAP and conventional intramuscular injection during the randomised Phase I trial. 2.5 μg HA HD-MAP dose had inhibition and microneutralisation effect on haemagglutination that insignificantly varied from those produced by conventional 15 μg intramuscular dose. Although the study was designed primarily for safety and immunogenicity rather than clinical protection against influenza infection, it also provided antigen dose-sparing clinical evidence. Another first-in-human influenza study evaluated the high-density microprojection array (Nanopatch) and reported safety, tolerability, acceptability and immunogenicity of intradermal delivery. The findings supported feasibility of delivering vaccine through a high-density microprojection system without the conventional needle-and-syringe administration.

Garg *et al.* [108] recently reported a Phase I trial of MIMIX dissolving MAP system in 45 healthy adult volunteers who received 7.5 or 15 μg of H1N1 influenza vaccine [108]. No serious adverse events were reported, and both dose cohorts generated substantial haemagglutination-inhibition and microneutralisation responses that persisted at least 180 days. The results demonstrated that different microneedle architectures can reach first-in-human evaluation, and broadened the clinical evidence beyond a single MAP platform.

Measles-rubella (MR) vaccination represents the most important paediatric clinical milestone. A Phase I trial evaluated

TABLE 6 The evidence hierarchy from the least to the highest for MAP studies.

Scientific weight	Evidence type	Major limitation	Core focus and utility
Least	Commercial press release	Marketing and business development driven; lacks peer review and biasing prone	On scalability, patch design proprietary and mass produce; provided by the manufacturer
Contextual	Institutional report	Focus on feasibility, logistics and policy; does not generate fresh clinical data	Issued by global health bodies; focus on deploying public health, logistics, regulatory framework
Least to moderate	*In silico* (modeling) study	Accurate to baseline data fed to model and mathematical assumptions	Predicts simulated skin penetration, drug release kinetics and stress distribution
Moderate	*In vitro* study	Unable to replicate blood flow, systemic biological interactions and complex immune responses	Lab tests (like skin model, cell culture) of mechanical strength, dissolution rates, cell toxicity
Moderate to high	*In vivo* animal study	Altered physiology, immune system impact or skin girth won't translate perfectly to humans	Evaluates systemic delivery, toxicity and biological response in living organisms like mice or nonhuman primates
Highest	I–III clinical trial phases	Sample size is small in early phases; limited safety data on the long-term effect for novel polymers	Exhibits drug pharmacokinetics, tolerability, immune response or safety in humans

MR vaccine delivered by Vaxxas HD-MAP in adults to demonstrate acceptable safety and immunogenicity, together with encouraging vaccine stability under controlled temperature excursions. Subsequent Phase I/II trials conducted in The Gambia was particularly significant as it evaluated MR-MAP vaccination across age-groups de-escalation, from adult to toddler and finally to measles-rubella-naïve 9–10-month infant. Randomised, double-blind, double-dummy, active-controlled study assessed safety, immunogenicity and tolerability against conventional subcutaneous vaccination. It provided the first clinical proof-of-concept for MR-MAP administration in infant population. However, it could be described as evidence of safety and immunogenicity rather than clinical efficacy, and could support progression toward pivotal development.

Usability, acceptability and human-factors studies

MAP development also required studies where the vaccine itself is not the principal study variable. These investigations addressed whether a patient could reliably apply the device, whether the applicator provides reproducible insertion and whether intended users accept the resulting skin response. Norman *et al.* (2014) conducted a randomised study involving 91 adults using placebo microneedle patches to simulate influenza vaccine [109]. Self-administration with a snap-based applicator produced approximately 93–96% microneedle insertion, thus demonstrating that an appropriately designed applicator can substantially improve reliability. The study also found increased stated willingness to receive influenza vaccination when self-administered microneedle vaccination was offered.

Human tolerability and usability were further examined by Arya *et al.* (2017), who evaluated dissolving microneedle patch administration in human subjects [110]. The work demonstrated that controlled application could achieve reliable skin insertion while producing acceptable local responses, providing important evidence for subsequent clinical translation. Guillermet *et al.* [111] examined anticipated acceptability of Nanopatch among potential end-users and healthcare workers in Benin, Nepal and Vietnam, at the community level [111]. The study used simulated vaccination and qualitative methods rather than actual vaccine administration, defining it as acceptability and implementation study rather than a clinical vaccine trial. Davies *et al.* [46] subsequently evaluated HD-MAP applicator usability among healthcare professionals and other healthcare workers [46]. Sixty-one participants received simulated MAP applications including self-administration, and the majority met essential usability criteria. The application time was identified as a potential issue, reinforcing the importance of human-factors engineering in the final combination product.

Proposed phase III trial framework for measles-rubella

Phase III study for MR-MAP is the next major clinical milestone. The WHO-led frameworks propose individually randomised, active-controlled non-inferiority trial comparing MR-MAP with conventional subcutaneous MR vaccination in healthy measles-rubella-naïve infant aged approximately 9–10 months [50]. Sero-response and safety after first dose are the principal endpoint assessments, with a follow-up period to characterise immunogenicity and adverse intervening events. The framework also considers a second dose at about 15–16 months to examine MAP and conventional vaccination route interchangeability.

This framework is important as regulatory approval and WHO prequalification need more evidence than MAPs being safe or immunogenic. The pivotal programme needs to establish non-inferiority or otherwise clinically acceptable immunogenicity against an established vaccine, characterise safety in the target population, demonstrate administration reliability and generate manufacturing and product-quality evidence that is appropriate for licensure. Taken together, the clinical literature supports a more measured conclusion than the statement that MAPs have already progressed to efficacy trials. MAP technology has successfully entered human clinical development with Phase I and Phase I/II studies demonstrating safety, tolerability, usability and immunogenicity across influenza and MR vaccines. The strongest current evidence is the Phase I/II paediatric MR study

in The Gambia. Preclinical studies have additionally demonstrated protective efficacy in animal models. The field is now approaching the pivotal Phase III stage, with the MR-MAP framework providing a defined pathway toward regulatory approval, WHO prequalification and eventual programmatic use. Distinction between immunogenicity, usability and true clinical efficacy compared to routine vaccination campaign approaches is critical while assessing MAP vaccine's performance. Zehrung *et al.* [50] proposed a robust Phase III trial framework to support global licensure and WHO prequalification [50]. It included the following aspects.

Target population

The pivotal trial should enrol measles-rubella susceptible infants of 9–10 months. To ensure generalisability, special populations like HIV-positive and/or malnourished infants should also be included. However, they could also be separately analysed to avoid non-inferiority skewed data.

Study design

The study design could have a 1:1 individually randomised, non-inferiority (NI) open-label trial to facilitate a healthy comparison between the MR-MAP and MR-Subcutaneous (SC) injection.

Primary endpoint

The primary immunogenicity and safety endpoints should be assessed 6 weeks after the administration of the first dose. The metric for immunogenicity is the sero-response rate (SRR) with the non-inferiority margins set typically at 5% or 10%, depending on the regulatory requirements.

Secondary endpoints

In order to evaluate the MAPs and N&S injections interchangeability (*e.g.*, MAP prime followed by SC boost, or the vice versa), a specified children cohort could be administered with the second dose at 15–16-month stage.

Safety monitoring

Solicited adverse events could be monitored for up to 14 days after the administration of the vaccine, with specific attention to skin discoloration in dark-skinned individuals. Critical adverse events should be monitored for up to 6 months.

Vaccine-free application studies

A particularly useful category of evidence comes from studies using vaccine-free, excipient-coated MAPs. These studies isolate the performance of the patch and applicator from the immunological effects of the vaccine. A 2025 study evaluated vaccine-free HD-MAP self-administration in 44 adults aged 50 years and older. The volunteer participants received the patches applied by a trained user, and subsequently self-administered the patches to the forearm and upper arm. Skin engagement, trans epidermal water loss, tolerability, usability and acceptability were assessed. Fluorescent dermatoscopy demonstrated comparable skin engagement between trained-user and self-administration, and all participants considered the applicator easy to use. The study provides evidence relevant to administration performance, although it cannot establish vaccine efficacy or immunogenicity.

Structured clinical development of MAPs

MAPs development involves clinical trial, usability study, vaccine-free application study, proposed Phase III framework and preclinical proof, and it has progressed to efficacy trials. It is provided below in a structured manner referring to Table 7, separating each evidence phase clearly. It is to note that efficacy metrics focus on immunogenicity and surrogate biomarkers of protection at the present MAP development stage (not mass disease prevention).

Preclinical evidence

In vivo immunogenicity

Laboratory animal models like mice and non-human primates have demonstrates that MAPs deliver vaccines effectively to the rich antigen-presenting dermal and epidermal cells.

Dose sparing

Preclinical data have exhibited over and over again that MAPs could achieve comparable or superior immune responses even with a fraction of the antigen dose required in case of conventional intramuscular injections.

Stability profiles

Laboratory studies have confirmed that the altered formulation allowed the vaccine to stabilise even at elevated temperatures, thereby reducing the logistics dependence on cold-chains.

Vaccine-free application studies

Skin tolerability

Focusing purely on the mechanical delivery system, the placebo patch studies have shown that micro-projections (on the MAP) could safely penetrate the stratum corneum with no physical contact with the pain receptors.

Dermal recovery

Application site assessments demonstrated that the dermal and epidermal micro-punctures closed rapidly in hours, thus reducing secondary infection risk or sustained skin irritation.

Biocompatibility

Analyses of the structural materials, like dissolving polymers or carboxymethylcellulose, confirmed that they dissolved safely in the skin interstitial fluid with no localised toxicity.

Usability and acceptability studies

Self-administration audit

Studies on the human factors indicated that a layperson or a minimally trained individual should be able to apply MAPs correctly using an integrated applicator or simple hand pressure.

TABLE 7 An outline of the MAPs development landscape across the five core data categories.

Category	Focus area and key indications	Current data landscape and evidence	Key takeaways and regulatory status
Key preclinical evidence	• Penetration mechanics • Pharmacokinetics (PK) • Thermostability	• Extensive *ex vivo* and animal model data confirm that microneedles cleanly bypass the stratum corneum without stimulating deep dermal nerve fibres (pain-free delivery) • Preclinical PK modeling for bilayer configurations demonstrates a >30% delivery efficiency, maintaining therapeutic plasma thresholds for over 30 days	• Excellent structural integrity, precise dosage accuracy and structural stability across a range of temperature, minimising cold-chain reliance
		Bench-side manufacturing breakthroughs, material innovations, and mechanical performance validations	Establishes the viability of solvent casting to dissolve patches, optimise needle geometry (tip radius/Young's modulus), and solutions to sterilisation/packaging degradation challenges
Device usability studies	• Human factors engineering • Application acceptability • Force feedback technology	• Assessing usability of premier designs (*e.g.*, micron biomedical and vaxxas) utilise integrated force feedback indicators to visually confirm microneedle insertion • Multi-national surveys using MAPVac scale show overwhelmingly positive responses from parents, older adults and healthcare professionals	• Validates feasibility of self-administration or deployment by lesser-trained healthcare workers in low-resource settings
		Assessments focusing on patient/investigator application, pain profiles and self-administration viability	Studies prove MAPs cause considerably less pain than hypodermic needle (reduce up to 7-fold) and result in comparable delivery efficiencies when self-administered
Vaccine-free application trials	• HIV PrEP (cabotegravir) • Insulin delivery • Radiation injury countermeasures • Cosmetic dermatology	• Progressed into long-acting, small-molecule systemic delivery (*e.g.*, bilayer arrays for month-long HIV pre-exposure prophylaxis) • In mid-2026, a US$4.5 million NIAID contract was awarded to develop MAP-based countermeasures against radiation injury • Self-dissolving hyaluronic acid and peptide patches are fully commercialised in consumer skincare	• Displaces the limitation that MAPs are exclusively for vaccines • Successfully expands utility into chronic disease management and emergency response
		Clinical and commercial expansion into therapeutics, diagnostics, cosmetics, and drug monitoring	Focus includes daily abaloparatide MAPs for osteoporosis, anti-wrinkle hyaluronic treatments, Alzheimer's therapies and real-time therapeutic drug monitoring (*e.g.*, vancomycin tracking)
Completed clinical trials	• Measles-rubella (MR) • Seasonal influenza • Japanese encephalitis	• Phase I/II age-de-escalation trials evaluated safety and immunogenicity successfully in adults, toddlers and infants using dissolving microneedles • Trials demonstrated robust immune responses equivalent to traditional needle and syringe (N&S), with mild erythaema being the primary side-effect	• Proof-of-concept established for vulnerable infant target populations • Clinical data confirm much low pain scores and high safety profiles
		Evaluation of safety, immunogenicity, and early phase efficacy for vaccine and macromolecule delivery	Favourable safety and immunogenicity profiles demonstrated across multiple targets like influenza, SARS-CoV-2, and measles-rubella; coated and dissolving MAPs have shown excellent tolerance

(*Continued*)

TABLE 7 Continued

Category	Focus area and key indications	Current data landscape and evidence	Key takeaways and regulatory status
Future phase III frameworks	• Pivotal regulatory design • WHO prequalification • Global standardisation	• World health organisation (WHO) and partners established a definitive phase III clinical trial framework for MR-MAPs • Framework mandates non-inferiority design comparing MR-MAPs against subcutaneous injection in 9–10-month-old infant, assessing immunogenicity till 6 weeks after the dose	• Standardises the clinical roadmap required for global regulatory approval, policy decisions and target procurement to reach 'zero-dose' children
		Design roadmaps established to meet regulatory approval, WHO prequalification, and commercialisation requirements	Frameworks emphasise non-inferiority trials in infants (*e.g.*, measles-rubella MAP vs. subcutaneous injection) and evaluating long-term infection risks from tens of thousands of repeat patch applications

Pain assessment score

MAP application was perceived as nearly painless compared to the conventional needle-and-syringe injection, revealed through visual analogue scale from the human cohort data. Visual analogue scale (VAS) is a measurement tool for participants to continuously rate experiences like pain, mood, or fatigue that are subjective and could not be measured directly by physical biomarkers.

Logistical preference

As the sharps waste are eliminated, the biohazardous wastes generation is low in volume, and due to the ease of storage, field surveys involving healthcare workers and patients highlighted a strong preference for MAPs.

Completed clinical trials

Phase I (safety and immunogenicity)

MAP candidate Phase I influenza and measles-rubella trials had favourable safety profiles, low systemic adverse events, and encouragingly high neutralising antibody responses in small human trial cohorts [50, 64].

Phase II (efficacy and dose-finding)

Early Phase II trials established optimal dosing beyond doubt, and confirmed the immune response comparable to intramuscular injection.

Proposed phase III frameworks

Target population expansion

The Phase III designs in the future aim to evaluate MAPs across broader demographic cohorts in endemic regions, including infants, elderly populations and the immunocompromised.

Field efficacy endpoint

The laboratory immunogenicity to real-world clinical efficacy transitions in the proposed framework would track actual reduction in disease incidence compared to a control group.

Deployment logistics

Mass trial would integrate field stability monitoring, analysing how well the patches would perform when distributed beyond the cold-chain setting.

Transitioning from robust preclinical proof-of-concept to standardised Phase III regulatory frameworks, the MAP landscape includes a rapidly evolving array of applications. Initially centered on pain-free vaccine delivery, the landscape includes highly diverse vaccine-free therapy, commercial dermatology and critical medical countermeasures. Table 7 outlines the current landscape of MAPs development across five core data categories, key preclinical evidence, device usability studies, vaccine-free application trials, completed clinical trials, future Phase III frameworks, and based on recent literature, clinical progress, and regulatory guidelines.

Preclinical evidence supporting clinical translation

Clinical programmes need to be supported by extensive preclinical evidence across multiple vaccine antigens. Edens *et al.* [112] demonstrated in Measles-Rubella (MR) vaccination that dissolving measles vaccine MAP generated neutralising antibody responses in Rhesus macaques that was comparable to subcutaneous injection, and the acceptable potency level was retained even when stored at an elevated temperature [112]. More compelling evidence came from Joyce et al. [113] who evaluated MR vaccination in baby Rhesus macaque [113]. All those who received MR MAP-vaccine achieved protective measles neutralising antibody titres, and all in the principal study group remained protected against wild-type measles virus challenge. The results were important bridge between formulation, delivery and biological protection before paediatric clinical evaluation. Preclinical studies have also demonstrated broader applicability of MAP technology. MAPs produced immunogenic responses with inactivated poliovirus and rotavirus vaccines, while influenza MAP studies have demonstrated enhanced stability and protective immune responses in animal models.

Human factors and acceptability

Clinical trials have consistently shown high acceptability. In the Vaxxas influenza trial, participants reported less pain with MAPs than IM injections and expressed a preference for the patch [47]. Similarly, in the Gambia MR trial, parents preferred MAP due to the lack of needles and ease of use. Ensuring consistent application force (often requiring an applicator or feedback mechanism) remains a critical self-administration human factor.

Global health implications and programmatic suitability

MAPs hold immense promise for strengthening the immunisation drives especially in the low and medium income countries (LMICs).

Cold chain elimination

'Cold chain' logistics requirement accounts for significant vaccine cost (US$200–300 million yearly) and wastage. The thermostability of MAP allows for storage at ambient temperatures, enabling distribution to remote areas without electricity and refrigeration facilities [8–12, 114].

Task-shifting: self-administration

Current vaccination drives rely on trained healthcare workers. MAP is designed for easy use, allow for "task-shifting" to self-administer or minimally trained community healthcare worker. It is particularly vital in mass vaccination campaigns or pandemic-like emergencies where healthcare systems are stretched to limits. Studies showed that self-administered MAPs yield similar delivery efficiency and immune responses [50, 115].

Waste disposal and safety

Unsafe injection practices lead to millions being infected, with HIV, Hepatitis B/C, etc., annually. Dissolving MAPs eliminate the biohazardous sharps waste generation, as needles dissolve in the skin and the backing can be disposed as non-sharps waste. It reduces the risk of needle-stick injuries and disease transmission significantly [3].

For safety and regulatory compliance, disposal needs for microarray patches must be clearly differentiated based on physical composition, active ingredients and potential biohazard risks, similar to any other biomedical biohazardous waste that is generated. Structured breakdown of the waste disposal needs is provided in Table 8, categorised primarily by the four standard MAP technologies.

Reaching "zero-dose" children

MAPs need to reach the "zero-dose" children—those who could not receive routine vaccine—often in the conflict zones, remote rural regions or urban slums. This could primarily be addressed by overcoming the logistics barriers. Modelling has suggested that the introduction of MR-MAPs has the ability to reduce the measles burden by 27–37% in 70 LMICs as compared to the prevailing strategies [116].

Discussion

Evolving MAPs represent a most significant technological advancement in transdermal drug delivery since the introduction of hypodermic syringe over 170 years ago. However, the true disruptive potential of MAPs extends beyond needle replacement. Rather, it challenges long-standing paradigms in pharmaceutical product design, vaccine deployment, patient-centric healthcare, and global health logistics. The central hypothesis underpinning MAP technology is that the efficacy is maintained—or even enhanced—with simultaneously simplified administration, reduced dependence on healthcare infrastructure and improved accessibility. Although the gathered preclinical and clinical evidence increasingly supports this hypothesis, its universal validity across all therapeutic modalities remains to be critically examined. Figure 5 is the timeline of studies related to MAP technology for delivery of vaccines and therapeutics.

From scientific perspective, the greatest strength of MAP technology is in exploiting unique immunological and physiological properties of the skin. Unlike conventional intramuscular injection, the epidermis and dermis contain dense antigen-presenting cell network (including Langerhans cells and dermal dendritic cells) that enable efficient immune activation with largely low antigen doses. This biological advantage is consistently demonstrated across multiple vaccine platforms and provides a compelling rationale for dose-sparing strategies to dramatically expand vaccine availability during pandemics or supply-constrained situations. Nonetheless, the advantage is not indiscreetly generalised. With key inter-individual variation due to age, ethnicity, hydration status, disease, anatomical site and skin barrier integrity, the skin is a highly heterogeneous organ. Such variability introduces uncertainty in dosing, absorption kinetics, and therapeutic reproducibility, particularly for high-dose biologics and chronic therapies where narrow therapeutic windows demand exceptional precision.

Technological innovation has significantly broadened applicability of MAPs beyond usual vaccine delivery. Recent advances in dissolving matrices, hydrogel-forming systems, coated metallic arrays, powder-filled microneedles, and implantable biodegradable platforms have expanded the range of deliverable payloads from small molecules to monoclonal antibodies, nucleic acids, viral vectors, and cell-derived therapeutics. Yet, these innovations increase the product complexity too. Unlike usual dosing, MAPs integrate pharmaceutical formulation, medical device engineering, polymer science and manufacturing science into a single product combination. Consequently, product performance depends on formulation characteristics as also microneedle geometry, mechanical strength, insertion efficiency, dissolution kinetics, applicator design, packaging integrity, and end-use technique. This multidimensional interdependence challenges traditional chemistry, manufacturing and controls paradigms and necessitates new quality-by-design frameworks capable of linking critical material attributes and process parameters with clinically meaningful performance.

TABLE 8 A MAP waste disposal breakdown, categorised by the four standard technologies.

Category	Product constituent	Risk profile	Disposal need
Solid MAP (coated or layered)	Solid MAPs typically feature non-degradable silicon, metal or rigid polymer projections that remain intact after skin removal	The patch contains sharp projections that have breached stratum corneum and been exposed to blood/interstitial fluid; they carry needlestick-like injuries and cross-contamination risks	Treated as biohazardous clinical sharps waste. They must be discarded immediately into puncture-resistant, yellow sharps containers for incineration
Coated MAP (non-dissolving backing)	Coated MAP uses a solid, non-degradable array structure where the formulated drug is only applied to the tips that dissolve into the skin	Biological fluid contaminated sharp, rigid micro-structure remains intact after coated drug delivery; residual active pharma ingredients or biologics may still remain	Treated as biohazardous clinical sharps waste; disposed in puncture-resistant sharps bins
Dissolving MAP	Dissolving MAPs are fabricated from water-soluble polymers or sugars that dissolve entirely within the skin to release the payload, leaving no sharp structures behind	Remaining backing matrix is soft, non-sharp, and cannot cause mechanical puncture injuries; it is in direct contact with patient's skin and may retain microscopic traces of API or biologics	Remaining backing matrix is discarded as non-sharps clinical waste, provided the needles fully dissolve; local regulations may permit disposal as regulated domestic waste if used in home-care setting, but clinical applications require biohazard segregation
Hydrogel-forming MAP	Hydrogel MAP contains arrays that swell on absorbing interstitial fluid, creating a conduit for drug diffusion from attached patch reservoir	Microprojections become soft and gelatinous, and lose structural rigidity after application, eliminating sharps hazard; the hydrogel is saturated with patient's interstitial fluid and contains significant residual medication or biological agents	Treated as biohazardous non-sharps waste; disposed of in designated clinical waste bags or pharma waste containers to incinerate, preventing environmental contamination

The principal barrier to widespread commercialisation is thus no longer proof-of-concept but industrialisation. Manufacturing billions of MAPs with consistent micron-level dimension, uniform drug loading, sterility assurance and acceptable production economics represent a challenge that is unprecedented in pharmaceutical sector. Existing laboratory fabrications often lack the throughput, automation and process robustness needed in commercial supply. Future manufacturing systems will require highly integrated digital process control, advanced in-line metrology, automation and real-time release testing to ensure consistent product quality of global standard. Establishing harmonised international standards to characterise, mechanical testing, insertion performance, dissolution behaviour, and stability assessment is equally important to facilitate regulatory convergence across jurisdictions.

From a clinical translation perspective, recent success of MR-MAPs is a major milestone instead of the end of development. These programmes provide the first realistic regulatory template to evaluate safety, immunogenicity, usability and manufacturing consistent MAP-based vaccines. However, broader therapeutic adoption requires evidence extending beyond immunogenicity to add long-term pharmacokinetics, pharmacodynamics, device reliability, patient adherence, real-world efficacy, and health-economic value. Regulatory agencies must also address unique questions surrounding human factors engineering, combination product classification, self-administration and lifecycle management that have limited precedent under the prevailing pharmaceutical regulations.

Perhaps the greatest opportunity for MAP technology lies in global health implementation. The convergence of thermostable formulations, simplified administration, reduced sharps waste, elimination of reconstitution steps, and decreased dependence on highly trained healthcare professionals aligns closely with the needs of immunisation programmes in low- and middle-income countries (LMICs). Nevertheless, technology alone will not guarantee public health impact. Successful implementation needs coordinated funds for manufacturing, procurement, reimbursement framework, technology transfer, workforce training, integrated supply-chain, and public acceptance. The risk of MAPs becoming another technologically superior innovation with limited global reach is high without deliberate strategies addressing affordability and equitability.

The future of MAPs may not be measured solely by the ability to replace existing injections but ultimately by theability to dictate how medicine is developed, manufactured, distributed, deployed and delivered. The major contribution lies in shifting healthcare from infrastructure-dependent delivery toward patient-centric, decentralised therapeutic administration. Realising this vision requires exceptional collaboration among scientists, engineers, pharmaceutical manufacturers, regulators, global health organisations, funding agencies, and policymakers. If the multidisciplinary challenge is addressed with the same pace as technological innovation, MAPs can potentially become not merely an alternate dosage form, but basic technology platform that reshapes pharmaceutical delivery and strengthens resilient and equitable global healthcare systems.

Limitations

Like any investigation for scientific insights, this narrative review also has limitations which need to be mentioned. The first aspect related to this is that the literature considered under the study is restricted only to the articles in English language; no vernacular

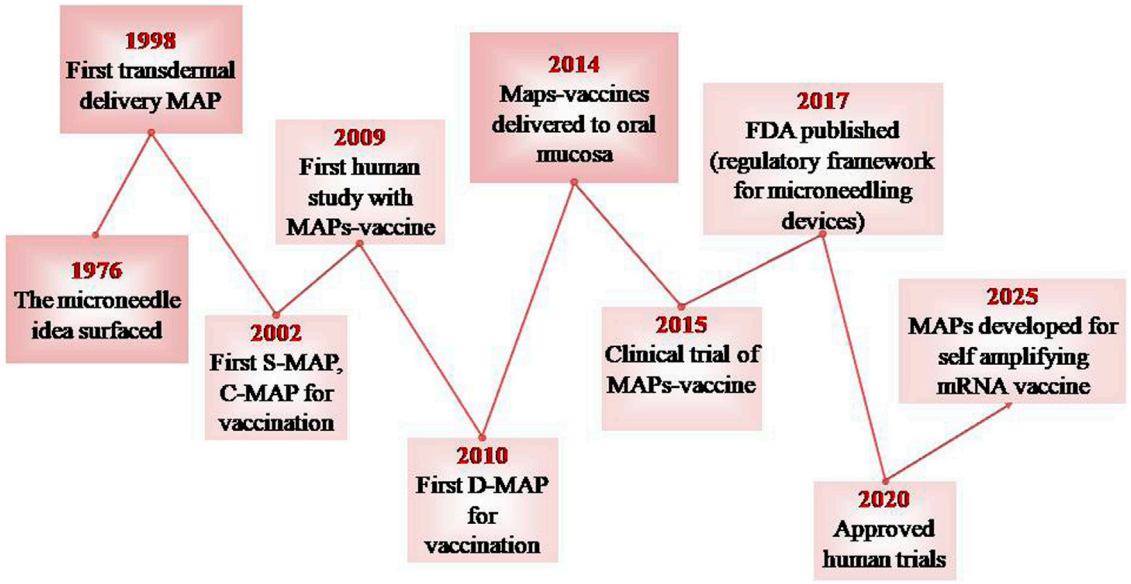


FIGURE 5
Timeline of studies with microneedle array patch (MAP) for vaccination.

language literature was included. There might be publication bias as only a selected lot of literature was investigated in detail under the study without PRISMA guideline (for systematic review). Further, a formal primary assessment of the quality, which was beyond the scope of the study, is lacking. Also, evidences from the various sources were heterogeneous, and might lack coherence, collateral corroborations and validation. Similarly, the studies as evident from the available literature are predominantly preclinical trials, which show that there is a long journey to travel before such products are finally available for lab-to-bedside translation. Rapidly changing commercial development scenario across MAPs and conjugated MAPS also limits the scope of this current study. Similar scenario also applies to the changing landscape of standardised and unified international regulatory frameworks.

Conclusion

MAPs are no longer simply experimental alternatives to hypodermic needle. The evidence reviewed here indicates that they represent a potential revisit and redesigning of the vaccine delivery, combining dermal immunology, polymer science, precision microfabrication, pharmaceutical formulation and human factors engineering in a single dosage platform. Their biological rationale is compelling: the epidermis and dermis in skin contain dense antigen-presenting cell populations, creating opportunities for dose-sparing and efficient immune activation. Across influenza, measles-rubella, polio and other vaccine models, preclinical and early clinical studies have demonstrated encouraging immunogenicity, while human studies also established safety, tolerability, acceptability and the feasibility of reliable application. Yet the central challenge has shifted; instead of isolated proof-of-concept studies for another decade, MAPs need coordinated industrial (scaled-up) translation.

The capability to manufacture billions of patches (MAPs) with reproducible microneedle geometry, dose uniformity, mechanical integrity, sterility, moisture control and validated insertion performance while maintaining acceptable cost are the defining barriers. The available literature similarly identifies manufacturing scale-up, aseptic processing, quality standardisation and regulatory definition as the principal commercialisation constraints. The field should therefore adopt a bold change in priority; MAP development should move from a product-by-product model to a platform-industrialisation model. A coordinated acceleration programme involving vaccine manufacturers, polymer and device companies, regulators, WHO, global health agencies and technology developers should establish common standards for critical quality attributes, insertion efficiency, mechanical strength, sterility, stability, applicator performance and human factors. Also, investment should shift toward automated high-throughput manufacturing, in-line metrology, digital process control and real-time quality monitoring. Such initiatives would serve multiple vaccines rather than being designed around a single antigen.

The measles-rubella programme provides an important template. The proposed Phase III framework demonstrates that regulatory translation is now sufficiently matured to define a credible pivotal pathway, but successful licensure will require integration of clinical evidence with manufacturing consistency, device reliability and user performance. Most importantly, the value of MAPs should ultimately be judged not by whether they replace a syringe, but by whether they facilitate vaccination to reach to the remotely located deprived and needy people. Thermostable, single-dose, needle-free patches that require minimal training could support decentralised and house-to-house delivery, reduce dependency on cold-chain logistics and simplify outbreak response. The strategic objective, thus, should be nothing less than to make vaccination less dependent on specialised infrastructure. MAPs will achieve global significance only when

scientific innovation, industrial scale, regulatory convergence and equitable access advance together.

Author contributions

PP: Conceptualization, Supervision, Writing – original draft, Writing – review and editing; LT: Methodology, Validation, Writing – original draft; MA, AA, MA, TJ, HA, and GA: Data curation, Validation, Writing – original draft; SM: Supervision, Writing – review and editing, RM: Data curation, Project Administration, Writing – review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Glossary

AgNPs	Silver nanoparticles
APCs	Antigen presenting cells
BCG	*Bacillus* Calmette-Guerin
CDC	Center for Disease Control and Prevention
CHWs	Community health workers
C-MAPs	Coated MAPs
cmc	Carboxymethyl cellulose
CMC	Chemistry, manufacturing and control
CTC	Controlled Temperature Chain
D-MAPs	Dissolving MAPs
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
IM	intramuscular
IPV	Inactivated polio vaccines
IRV	Inactivated Rotavirus Vaccine
LMICs	Low- and middle-income countries
mAbs	Monoclonal antibodies
MAPs	Microarray patches
MC	Methylcellulose
MR-MAPs	Measles and Rubella MAPs
MRSA	Methicillin-resistant *Staphylococcus aureus*
OPV	Oral polio vaccines
PEG	Polyethylene glycol
PPD	Purified Protein Derivative
PVA	Polyvinyl alcohol
PVP	Polyvinyl pyrrolidone
RBD	Receptor-binding domain
SAEs	Serious adverse events
SRR	Sero-response rate
TB	Tuberculosis
VVM	Vaccine Vial Monitor
WHO	World Health Organisation