THE SCIENCE WORLD
A Monthly e Magazine
ISSN:2583-2212
Review Article
December, 2025 Vol.5(12), 11114-11122

From Needles to Nanocarriers: Recent Advances in Vaccine Delivery Technologies

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DOI:10.5281/ScienceWorld.18048461

Abstract

Empty viral capsids vaccines, which are also termed Virus-like particles (VLPs), lack nucleic acid. VLPs offer various advantages, high safety and efficacy, enhanced DIVA capability, reduced need for a biosafety level III facility, and economy. Technology presents an alternative platform for developing effective vaccines to combat infectious diseases of serious concern, and it is moving in parallel with mRNA and viral-vector based vaccines. Empty capsid vaccines present repetitive antigenic epitopes on their surface in a more authentic confirmation that the immune system can readily detect these antigens. Chimeric VLPs are also produced which display foreign peptide antigens from other infectious agents. Cloning viral structural genes of interest, expression in prokaryotic or eukaryotic system, harvesting, purification and vaccine formulation are important steps in ECVs production. Various expression systems are available and newer methods of production are being explored. Various products such as VLPs based hepatitis B and human papillomavirus vaccines have been delivered to the market. Although many advantages, technology suffer many challenges, mitigation of these challenges is important prospect of empty capsid vaccines technology.

Key Words: Empty capsid vaccines, VLPs, expression systems, efficacy, Challenges, chimeric VLPs.

1. Introduction

Viral infectious diseases always pose threat to human and animal health. Vaccination is the most effective and cost-efficient method for preventing and controlling infectious diseases. This strategy has evolved significantly since its origin, at the end of the 18th century. Initially, vaccination was done using live attenuated or inactivated pathogenic agents as

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vaccines. This approach has found to be very effective to protect against various infectious diseases. But reversal of virulence and incomplete inactivation of pathogens are important safety concerns associated with these vaccines and may have serious consequences. Although effective, due to the safety concerns newer vaccine technologies have been explored to address these issues. In this regard various protein subunit and nucleic acid-based vaccines with better safety are developed and found to provide good level of protection against various infectious diseases of humans and animals. Despite these characteristics, such as an improved safety profile and, in general, simpler production methods, subunit and nucleic acid-based antigens have been found to be weak immunogens. This is mostly due to the limited recognition of these molecules by the immune cells, a fact that makes the use of powerful adjuvants mandatory in order to obtain a protective immune response (Cordeiro & Alonso, 2015). For this reason, different adjuvants have been developed in the past few decades.

Conventional delivery poses certain drawbacks such as fear of injection in human and animal patients, trained personnel required, pain associated with injections, booster dosing requires repeated injections, stringent storage conditions such as continuous cold chain, unsterile injection may increase iatrogenic infections. Various approaches such as nanotechnology, sustain release kinetics, pulsatile release kinetics and delivery of antigen in most representative form to the antigen presenting cells are being explored and various technologies are available to date.

2. Osmotic Pump

It is a most precise device to control the sustained release kinetics and doses of vaccines. It consists of an inner core that contains both cargo and osmotic materials and an outer shell composed of a semipermeable membrane. Osmotic materials absorb water that flux into the pump through their outer membranes. Release kinetics is largely independent of cargo materials and the physiological environment (Naguyen *et al.,* 2020). Tam *et al*., 2016 implanted an osmotic pump under the skin of mice to administer human immunodeficiency virus (HIV) antigens and found more effective antibody response than conventional delivery. Similarly, Cirelli *et al*., 2019 used osmotic pumps to deliver HIV envelope proteins in rhesus monkeys with constant dosing for two or four weeks and found effective than older methods.

3. Hydrogels

Hydrogels are crosslinked polymer networks with high water content. Due to their high-water content, broad structural diversity and good safety profiles hydrogels are can be used in wide variety of biological applications. Natural polymers such as alginate, chitosan, dextran, hyaluronic acid, proteins, peptides and some synthetic polymers such as polyethylene

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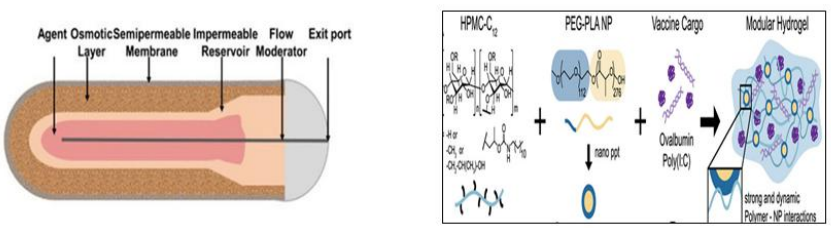
glycol (PEG), polyvinyl alcohol, and zwitterion polymers are used for formation of hydrogels (Cordeiro & Alonso, 2015). The crosslinking density and polymer structure determine the mesh size of the hydrogel network, which further affects the diffusion rate of encapsulated cargo (Fan & Xiao, 2008). First, preformed hydrogels must be implanted surgically. Many injectable hydrogels that have been formed in situ have been developed to avoid surgery (Dimatteo *et al*., 2018).

4. Transdermal delivery

Skin houses large number of immune cells particularly antigen presenting cells (i.e. Dentrictic cells primarily). Due to the easy accessibility and the prevalence of a profoundly complex and functionally rich network of immune cells in the skin, it is becoming preferred choice for vaccine administration. The ideal targeting of cutaneous APC populations by a skin-compatible adjuvant agent appears to be indispensable for the induction of a powerful adaptive immune response and the initiation of immunological memory (Pielenhofer *et al*. 2020). In order to be successful in vaccine delivery by transdermal route, vaccine molecules must have a low molecular weight, be reasonably lipophilic and have a very high potency (Luo *et al*., 2023).

4.1 Microneedles

The most explored method of transdermal delivery is in the use of microneedles, which consist of 10s to 1000s of pointed micro size projections fabricated onto a surface (Kim *et al*., 2012; Luo *et al*., 2023). Various microneedle systems have been developed such as solid, hollo, coated and dissolving microneedles (Wallis *et al*., 2019). Solid microneedles have been fabricated from a range of materials such as silicon, polymers, water-soluble compounds, metals and ceramics and can be used to make the skin permeable before topical application of the vaccine. Coated microneedles use solid microneedles as vehicles to deliver drug or vaccine deposited on their surface into the dermal layers; this may be a quick method to administer the desired dose. The use of microneedles to administer large-dose pharmaceuticals requires further investigation. Finally, the safety of microneedles must be thoroughly investigated by



(a) (b)

Figure 1. 1(a) Osmotic Pump 2(b) Hydrogel

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performing clinical trials, particularly when vaccines are administered to infants (Li *et al*., 2022).

4.2 Iontophoresis and Electroporation

Electricity has also been used to facilitate the delivery of drugs and vaccines trans-dermally in two differing methods, iontophoresis and electroporation. Iontophoresis relies on the application of an electrical current to drive charged particles into the skin through electrostatic effects (Kalia *et al*., 2004). Electroporation uses electrical pulses in the order of hundreds of volts for 10µs–10ms to temporarily disrupt cellular membranes (Schoellhammer *et al*., 2014).

4.3 Sonophoresis

It is the use of ultrasound to improve transdermal drug and vaccine delivery (Ita, 2017). Main mechanism that drives the enhanced delivery of sonophoresis is cavitation. This process involves the application of focused ultrasound to achieve expansion and collapse of gas bubbles which, in turn, creates microstreaming and shockwaves. Sonophoresis has been used to either increase the permeability of the skin before topical application of the vaccine or as a method of concurrently applying both cavitation and vaccine, thereby actively pushing the vaccine particles into the skin (Wallis *et al*., 2019).

4.3 Gene gun, Jet injector, Tattooing

Gene gun is a biolistic device that enables the DNA to directly enter into the cell following bombardment of target DNA in the gene gun chamber kept against the target site. The gene gun immunization is found to be more effective over IM injection as DNA from gene gun method is directly shot into the target cells whereas DNA from the IM must enter the cell before protein (antigen) synthesis. A jet injector is a needle-free injecting medical

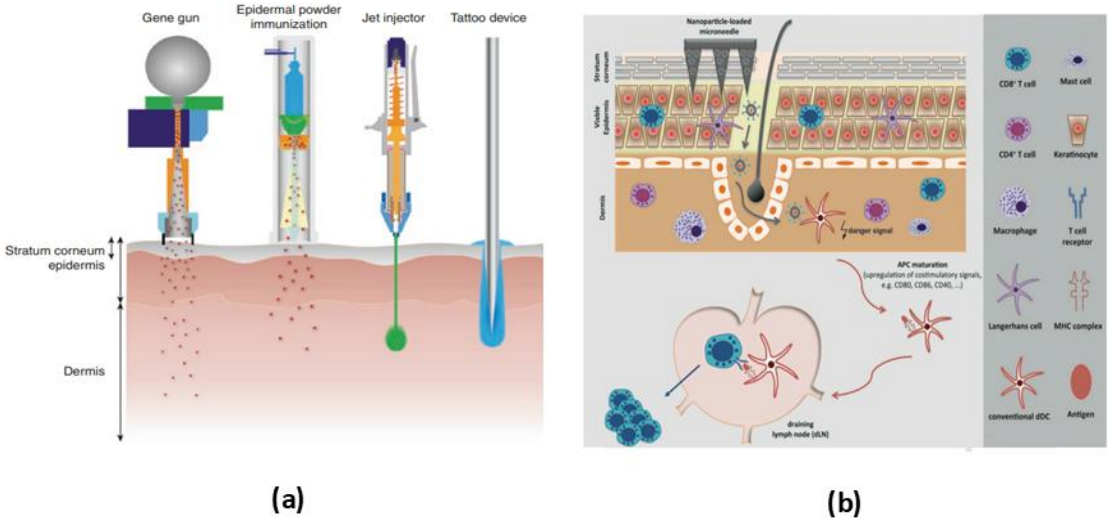

Figure 2. 2(a) Transdermal vaccination methods 2(b) Transdermal delivery process

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device that uses a high-pressurized narrow stream liquid to penetrate across the skin barrier and has been used to deliver various macromolecules such as vaccines (Kim, 2017). Recently jet injector-based world's first DNA-based Coronavirus vaccine has received emergency permission from India's medicines authority. Zydus Cadila, a pharmaceutical firm, created the three-dose, needle-free vaccination. It is also the first vaccine to be authorized for teenagers. Zydus Cadila said that the vaccine, known as ZyCoV-D, generates the spike protein from the Coronavirus, which stimulates an immune response to treat the disease (Samal *et al*., 2021) this vaccine administered exclusively using PharmaJet Tropis® System.

5. Mucosal delivery

The majority of pathogens invade via mucosal surfaces such as the respiratory, gastrointestinal or reproductive tracts. These surfaces come into direct contact with the air, water and food from our surrounding environment, giving a first point-of-contact for opportunistic pathogens (Wallis *et al*., 2019; Su *et al*., 2016). Oral vaccination is a preferred route for vaccination, as it is painless, safe, low cost and does not require trained personnel for administration. In order to induce immunity through the oral gastrointestinal route, a relatively large amount of vaccine must be administered due to factors such as dilution while passing through the gastrointestinal tract, degradation within the stomach or failure to breach the epithelial tight junctions (Wallis *et al*., 2019). Currently, Calf-Guard (Bovine rotavirus and coronavirus) for calves and various poultry vaccines such as Burse BLEN-M, UNIVAX-BD, Bursine-2 etc. are available for oral administration (Wilson *et al*., 2020).

Intranasal vaccination is a popular choice for alternative vaccination methods, as it uses a site that is easily accessible and has the potential for self-administration. As nasal vaccination delivers the antigenic material directly to the targeted site, a relatively small dose is required when compared to alternative forms of vaccination (Wallis *et al*., 2019). Currently the only licensed intranasal vaccines for use in humans (Flumist), which consists of a live attenuated virus delivered by nasal spray (Wallis *et al*., 2019) while Bovilis (IBR- Bovine herpesvirus 1 BHV1), TSV-2 (Infectious bovine rhinotracheitis- IBR) virus and parainfluenza3 (PI3) virus, INFORCE 3 (BRSV, IBR, and PI3) and Flu Avert I.N. (Equine influenza virus type H3N8 strain) are available for use in animals by intranasal route (Wilson et al., 2020).

6. Oral bait vaccines

The successful vaccination of terrestrial wild mammals with oral baits depends upon a number of technical considerations that include an effective vaccine formulation that can be used safely to reduce or stop disease transmission, a container that delivers the vaccine orally,

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a bait that specifically attracts and is accepted by the target species, a bait delivery system that reaches a high proportion of the susceptible population, and acceptable costs for development and use (Ballesteros *et al.,* 2007). Baer *et al*., 2007 developed an oral rabies vaccine for foxes in which- plastic elongated polyethylene tube holds vaccine and vaccine-containing bait is an ampoule surrounded by meat, when the bait is bitten, the vaccine is released into the oropharyngeal mucosa. Currently Raboral V-RG, ONRAB and RABIGEN SAG2 oral bait vaccines available against rabies (Wilson *et al*., 2020).

7. Edible vaccines

Edible vaccines are subunit vaccines where the selected genes are introduced into the plants and the transgenic plant is then induced to manufacture the encoded protein. Foods under such application include potato, banana, lettuce, corn, soybean, rice, and legumes (Saxena & Rawat, 2014). Rabies virus in Tobacco, spinach, Hepatitis B in Potato, Tobacco, Banana and HIV in Tomato are some edible vaccines developed against these viral infectious diseases (Saxena & Rawat, 2014).

8. Nanotechnology based advanced delivery for nucleic acid and protein sub unit vaccines

Cationic liposomes, polymeric nanoparticles, inorganic gold nano rods, peptide nanofibers, and carbon nanoparticles have been studied for the delivery of DNA vaccines against viral infectious diseases. Mannose-conjugated zwitterion lipid was used as a component of cationic liposomes and has been studied for the delivery of DNA and RNA vaccines encoding viral antigens. Mannose receptors are known to be overexpressed on the surfaces of antigen-presenting cells (Wilson *et al*., 2019). Intramuscular administration of the lipoplexes of mannose-modified cationic liposomes loaded with DNA encoding HIV-1 env was shown to provide higher immune responses (Qiao *et al*., 2016).

Dendrimers have also been used as a platform to deliver mRNA against Ebola virus and infuenza H1N1 virus. Modified poly (amido amine) dendrimer was complexed to a Venezuelan equine encephalitis virus replicon RNA encoding the HA protein of H1N1 infuenza virus or an RNA encoding Ebola virus glycoprotein. Notably, this study demonstrated that antigen proteins could be expressed in vivo after intramuscular administration of an mRNA platform (Chahal *et al*., 2016). Virus-mimetic polymeric nanoparticles have been studied for influenza-A virus nucleoprotein delivery in which introduction of a pH-responsive moiety to the polymeric nanoparticle that can increase the endosomal escape of an antigen to the cytoplasm so there by facilitate enhanced immune response (Knight *et al*., 2019).

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9. Challenges and conclusions

In case of Lipid-based delivery systems, the oxidation of lipid component is major challenge that needs to be addressed. While formulation of nanoparticles precipitation and size changes alter the efficacy and safety so this needs to be taken care. One of the purposes of advanced delivery systems is stability of vaccine candidates under humid and hot conditions so this issue should be taken into consideration while formulation. Newer systems need to be examined for most suitable route of administration also non-invasive forms required to be explored more. Liposomal escape of antigens can be enhanced by using various methods. In case of mucosal vaccines IgA production should be taken as evaluation parameter rather than IgG. Lastly cost of production is very important factor that needs special attention.

Traditional 'three Is' model (isolate, inactivate, inject) of vaccine development is increasingly being phased out as conventional vaccines poses certain limitations. Newer vaccines technologies such as subunit proteins and nucleic acid based vaccines emerged as promising tools to address issues with conventional ones. Even effective and safer than conventional vaccines these newer vaccines suffer from some limitations which can be overcome by development of advanced vaccine delivery systems. Nano-particles, microneedles patches, edible vaccines, mucosal vaccines and hydrogels and many more advanced technologies are in research and are potential future of vaccinology. Mitigation of challenges associated with these systems and development of safer and more potent immunogenic vaccines candidates remain as future prospect.

10. Acknowledgements

We acknowledge the contributions of all researchers whose work has been cited in this review, as well as the countless individuals who have contributed to the advancement of knowledge in this field.

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