



Nanoparticle-Based Vaccines: From Design and Immune Modulation to Clinical Translation

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Abstract

Vaccines are among the most significant advancements in modern medicine, and their role in combating and even eradicating infectious diseases cannot be overstated. Through a series of immunological processes, vaccines induce immunological memory, characterized by the formation of memory cells and antibodies. Since the introduction of the first vaccine against smallpox, substantial efforts have been made to enhance vaccine efficacy, overcome existing limitations, and develop vaccines against emerging pathogens. The use of nanotechnology in vaccines offers multiple advantages, as it can overcome many of the limitations associated with traditional vaccine platforms. Moreover, nanotechnology has paved the way for the development of several vaccine formulations and is expected to contribute further to future advancements. Nanoparticles exist in several types, each with distinct advantages and limitations. The physicochemical characteristics of these nanoparticles, namely particle size, particle shape, particle rigidity, surface charge, and hydrophobicity, affect the immune response potency. Optimization of these properties can enable the development of vaccines that elicit strong immune responses. Such strategic optimization has facilitated the production of effective vaccine formulations against several major pathogens currently in use. Notable nanoparticle vaccines include those for human papillomavirus, malaria, hepatitis B, and severe acute respiratory syndrome coronavirus 2. This comprehensive review examines the immunological cascade induced by vaccines, nanoparticle-based vaccine platforms, their advantages and limitations, and the influence of their physicochemical characteristics on vaccine efficacy. Furthermore, this review highlights nanovaccine formulations that have been approved for clinical use.

Keywords:

nanovaccines; lipid nanoparticles; virus-like particles; vaccine delivery; immune modulation

1. Introduction

Vaccines are powerful medical interventions that play a critical role in preventing infectious diseases [1]. They exert their protective and preventive effects by training the immune system to resist infectious microorganisms upon subsequent exposure through the establishment of immunological memory. This immunological memory en-

ables rapid antibody production and activation of memory lymphocytes upon subsequent exposure to pathogens [2]. The importance of vaccines cannot be overstated. Diseases such as smallpox have been eradicated thanks to widespread vaccination efforts [3]. Similarly, poliomyelitis, another debilitating disease, is on the verge of

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eradication as a result of global vaccination programs [4]. Vaccines also protect against a multitude of other serious illnesses, including whooping cough, tetanus, measles, mumps, diphtheria, rubella, and influenza [5]. By preventing these diseases, vaccines not only safeguard individuals from potentially life-threatening illnesses but also reduce healthcare costs and ensure a healthier, more productive population [6].

Vaccines contain components known as antigens and adjuvants. Antigens are substances that trigger an immune response, whereas adjuvants are added components that enhance this immune response [7]. Vaccines are available in various forms, including live attenuated vaccines, which use a weakened, non-virulent form of a live pathogen, and inactivated vaccines, which contain a non-replicating form of the virus or bacterium [8]. Live

attenuated vaccines may carry a risk of reversion to virulence, whereas inactivated vaccines may require adjuvants or booster doses to achieve sufficient immune protection. Toxoid vaccines, formulated from bacterial toxins, have the drawbacks of low immunogenicity and multiple dose requirements. Protein subunit vaccines are generally less immunogenic than live attenuated vaccines. Recombinant vector vaccines are developed by incorporating the antigen-encoding sequence into an attenuated virus or bacterium. However, their efficacy may be reduced because of the potential for mutations. Nucleic acid vaccines are newer vaccine platforms that offer several advantages, including rapid production, flexible design, and improved stability under appropriate formulation conditions [9,10]. Figure 1 illustrates the various types of vaccines.

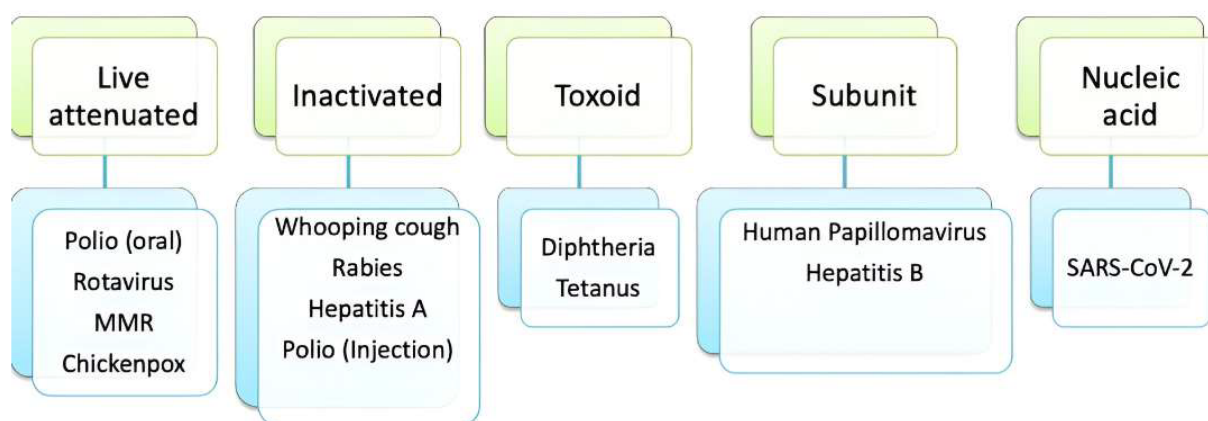


Figure 1: Types of vaccines and their examples.

Nanotechnology has revolutionized the field of vaccine development. In essence, nanotechnology-based vaccines use nanoscale-engineered particles to deliver antigens, the components of viruses or bacteria that trigger an immune response, into the body. These nanoparticles (NPs) can be fabricated from a variety of materials, including lipids and polymers [11]. Several types of nanotechnology-based vaccines are currently being investigated. Some nanovaccine platforms encapsulate the antigen, protecting it from degradation and enhancing its delivery to immune cells. Others can be engineered to target specific immune cells, thereby eliciting a more robust immune response. Additionally, researchers are developing nanotech vaccines that can combine antigens from multiple pathogens, potentially offering broader protection in a single shot [12].

The potential advantages of nanotechnology-based vaccines are substantial. Compared with conventional vaccines, they may offer improved stability, facilitating storage and transportation, particularly in resource-limited settings. Additionally, nanocarriers can enhance the immune response, potentially leading to longer-lasting protection with fewer doses. Furthermore, the targeted delivery of antigens with nanocarriers could minimize side effects by reducing exposure to unnecessary components (Figure 2) [13,14].

In this review, the vaccine immunological cascade is thoroughly discussed, along with the various nanoparticle platforms, their advantages and drawbacks, and the influence of their physicochemical properties on vaccine efficacy. Moreover, approved applications of nanotechnology in vaccine formulations are highlighted.

Traditional Vaccine Challenges

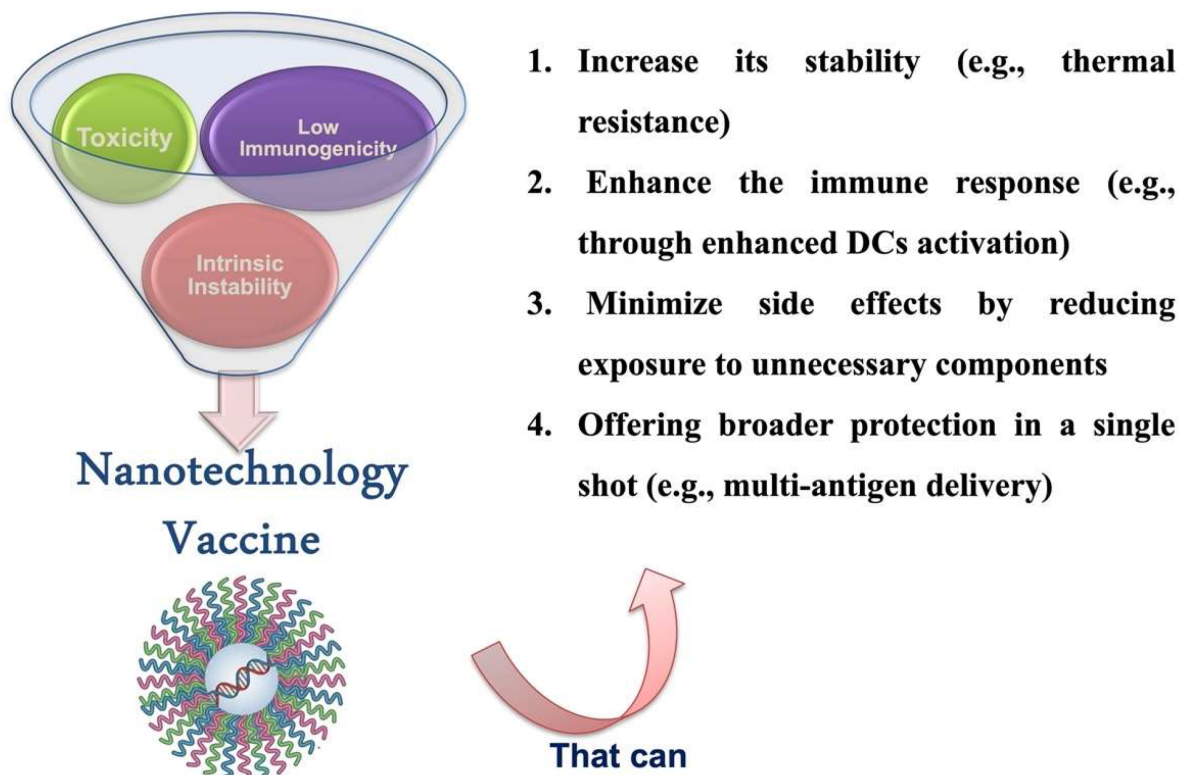


Figure 2: The disadvantages of the currently available vaccines that can potentially be overcome through nanotechnology.

2. Vaccine Immunological Cascade

Vaccines are designed to protect against pathogen infection by inducing the production of antibodies and the formation of memory cells. By stimulating the immune response, vaccines establish immunological memory that provides protection upon subsequent exposure to the pathogen [15]. There are different routes for vaccine administration. These routes include oral, intranasal, subcutaneous, intradermal, and intramuscular (IM) routes. Oral and intranasal routes are considered mucosal routes of vaccine administration that provide a needle-free alternative while eliciting immune responses at both the mucosal and systemic levels [16]. Despite these advantages of mucosal vaccines, only a limited number are currently licensed for clinical use [17]. The formulation and administration of antigen subunit mucosal vaccines remain challenging because the physiological barriers of mucosal tissues promote vaccine degradation and limit cellular uptake [18]. In contrast, the IM route is the most frequently used route for vaccine administration. The IM route offers the advantages of good tolerability and minimal adverse

reactions at the injection site, both of which are desirable characteristics for vaccine licensure [19]. Following vaccine administration, localized muscle injury at the injection site initiates the immune response required for vaccine efficacy. Skeletal muscle cells and muscle-resident immune cells initiate a local inflammatory response. This localized inflammation is essential for triggering the cascade of immunological events that activates the adaptive immune response required for effective vaccination [20]. Skeletal muscle injury causes damaged cells to release endogenous danger molecules, known as danger-associated molecular patterns (DAMPs), into the extracellular space and the bloodstream.

Circulating immune cells recognize DAMPs through pattern-recognition receptors (PRRs), which promote their recruitment to the site of injury [21,22]. Furthermore, damage-activated resident immune cells release signaling proteins known as cytokines, which promote immune cell migration and further recruitment to the site of injury [21]. A subset of immune cells internalizes the vaccine antigen. Antigen uptake occurs through several mechanisms, including receptor-mediated endocytosis, phagocytosis, and macropinocytosis [23]. Subsequently,

these cells degrade the antigen, process it into antigenic fragments, and present these fragments on their surface bound to major histocompatibility complex class II (MHC-II) molecules [24]. These immune cells are known as antigen-presenting cells (APCs), and their primary function is to present antigens to T lymphocytes (T cells), thereby initiating the adaptive immune response [25]. The APCs consist of macrophages, B lymphocytes (B cells), and dendritic cells (DCs), which are the specialized and proficient APCs [26]. Following antigen uptake, DCs undergo maturation and migrate to the T-cell zones of secondary lymphoid tissues to present the processed antigen [27].

Antigen presentation is essential for initiating the adaptive immune response [25]. B and T lymphocytes are the cells mediating the response. The B cells undergo differentiation into plasma cells that release antibodies. There are two subsets of effector T cells: cytotoxic (Tc) T cells and helper (Th) T cells. Cytotoxic T cells, also known as CD8⁺ T cells, eliminate infected cells through direct cell-to-cell contact, whereas helper T cells, or CD4⁺ T cells, secrete cytokines that enhance both B- and T-lymphocyte responses [28,29]. Secondary lymphoid organs (SLOs) serve as sites of antigen presentation and immune surveillance [30]. The SLOs comprise the lymph nodes (LNs), tonsils, spleen, and intestinal Peyer's patches [31]. The LNs are distributed throughout the body at strategic locations to maximize the sampling of foreign antigens [32]. Furthermore, LNs are anatomically divided into three compartments: the cortex, the paracortex, and the medulla. Each of these compartments contains distinct subsets of immune cells. The cortex, which serves as the B-cell zone, contains B cells organized into follicles, whereas the paracortex, the T-cell zone, contains T cells and DCs. In addition, the medulla contains macrophages and plasma cells [33]. The LNs are surrounded by a channel lined with macrophages and DCs called the subcapsular sinus (SCS) [34].

After migrating from the administration site, the DCs and soluble antigens drain from the lymph into the LNs via afferent lymphatic vessels [35]. Upon entering the LN, DCs migrate from the subcapsular sinus to the T-cell zone [36]. Soluble antigens enter the SCS and, depending on their size, either diffuse into the B- and T-cell zones or are engulfed by SCS macrophages. Small antigens can enter the B-cell zone, where B cells capture the antigens and present them to T cells. Alternatively, the antigens can pass through fibroblastic reticular cell conduits into the T-cell zone, where LN-resident DCs present them to T cells. In contrast, large antigens are internalized by SCS macrophages and transported to the B-cell zone,

where they are recognized by B cells or subsequently transferred to the T-cell zone for antigen presentation [37,38].

In antigen presentation to Th cells, naïve CD4⁺ T cells residing in the LN T-cell zone recognize the antigen presented by the DCs' MHC-II molecule and interact with the antigen via the T cell receptor (TCR) [39]. Subsequently, the costimulatory receptor CD28 on T cells binds to the ligands CD80 and CD86 on DCs, enhancing TCR signaling and thereby promoting T-cell proliferation and effector cell differentiation. Finally, DCs secrete a mixture of cytokines to regulate immune activation [40]. After the presentation, T cells are differentiated into effector Th cells, which function to secrete cytokines that mediate the response of other immune cells [41].

In contrast, during antigen presentation to Tc cells, CD8⁺ T cells recognize antigens presented on major histocompatibility complex class I (MHC-I) molecules expressed by host cells and DCs [42,43]. DCs can cross-present antigens through both MHC-II molecules to CD4⁺ T helper cells and MHC-I molecules to CD8⁺ T cells [42]. Then, T cells interact with antigen fragments via the TCR, while co-stimulatory signaling through the CD28 receptor is activated, triggering the cytotoxic machinery and driving differentiation into effector cytotoxic T cells. Tc cells eliminate infected or antigen-bearing target cells through the release of perforin and granzymes [43,44]. Following antigen elimination, most effector CD8⁺ T cells undergo apoptosis, whereas a small subset survives and differentiates into long-lived memory T cells [45]. Upon re-encounter with the antigen, memory T cells rapidly differentiate into effector cells, enabling a swift and efficient immune response to eliminate the antigen [46].

To mount an antibody response, B cells bind antigens through the B-cell receptor (BCR) and, as APCs, internalize, process, and present the antigen via MHC-II. At the border between the B- and T-cell zones, the antigen is recognized by CD4⁺ T cells through the TCR. Subsequently, CD4⁺ T cells secrete cytokines that promote B-cell activation and proliferation [47]. Once activated, some B cells undergo differentiation into short-lived plasma cells or memory B cells [48]. A subset of B cells returns to the follicle to form germinal centers (GCs). In the GCs, B cells proliferate and differentiate into long-lived memory B cells and plasma cells [49]. Consequently, plasma cells derived from GCs migrate to the bone marrow, where they continue to secrete antibodies, providing long-term protection [48]. Antibodies produced by plasma cells are predominantly immunoglobulin M during the initial acute exposure to an antigen. Subsequently, through class switching and affinity maturation, plasma cells produce immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies [50]. These antibodies

protect against antigens through several mechanisms, including neutralization by preventing antigen binding to and entry into host cells, complement-mediated lysis, and antibody-dependent cellular cytotoxicity [51]. Upon subsequent exposure to the antigen, memory B cells rapidly differentiate into plasmablasts, generating a rapid and effective antibody response [47].

The DCs, in particular, are recognized as the most effective activators of naïve T cells [52], although recent studies indicate that macrophages may also play a crucial role in T-cell priming following particulate vaccination [53]. Cross-presentation, the process by which anti-

gens are processed and loaded onto MHC-I molecules to prime CD8+ T cells, which is crucial for antiviral and anti-cancer vaccines, is induced by the internalization of particulate immunogens by DCs [54]. Particle vaccines are frequently administered via the subcutaneous or intradermal route, after which they either drain through the lymphatic system to the LNs or are rapidly engulfed by DCs at the injection site. APCs that have engulfed vaccine nanoparticles must efficiently release their antigen cargo to enable antigen presentation and T-cell priming [55]. **Figure 3** demonstrates the immunological cascade following the IM administration of vaccines.

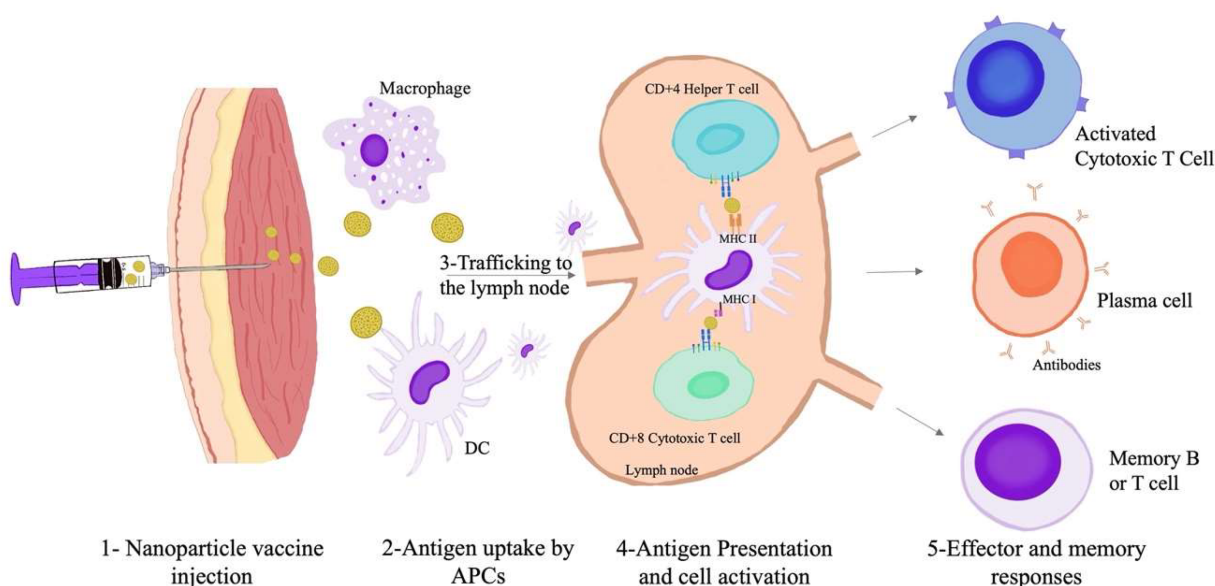


Figure 3: Immunological cascade after intramuscular administration of vaccines.

3. Nanoparticles and Vaccine Delivery

In recent years, nanoparticles have attracted significant attention as potential vaccine delivery vehicles. The vaccine antigen can be conjugated to the surface of nanoparticles or encapsulated within them. Antigen encapsulation within nanoparticles prevents degradation upon administration and thereby improves immunogenicity. In contrast, when antigens are conjugated to the surface of nanoparticles, they can be presented to the immune system in a manner that closely resembles the native pathogen, thereby eliciting a comparable immune response. Additionally, nanoparticles composed of certain materials can provide sustained antigen release, thereby prolonging immune system exposure. Researchers are

currently investigating the potential of using nanoparticles to deliver vaccines through non-traditional routes, such as transdermal and inhalational administration, as well as developing single nanoparticle-based vaccines that incorporate multiple antigens capable of eliciting immunity against multiple pathogens [12,56,57]. **Figure 4** illustrates the advantages of various nanoparticles in vaccine delivery.

NPs used as vaccine delivery systems can be engineered from a range of materials, including natural and synthetic polymers, lipids, viral components, and inorganic compounds. In the following sections, the various nanoparticle platforms used to deliver vaccines will be covered, along with their advantages and limitations. Moreover, the influence of the physicochemical properties of nanocarriers on vaccine efficacy is discussed.

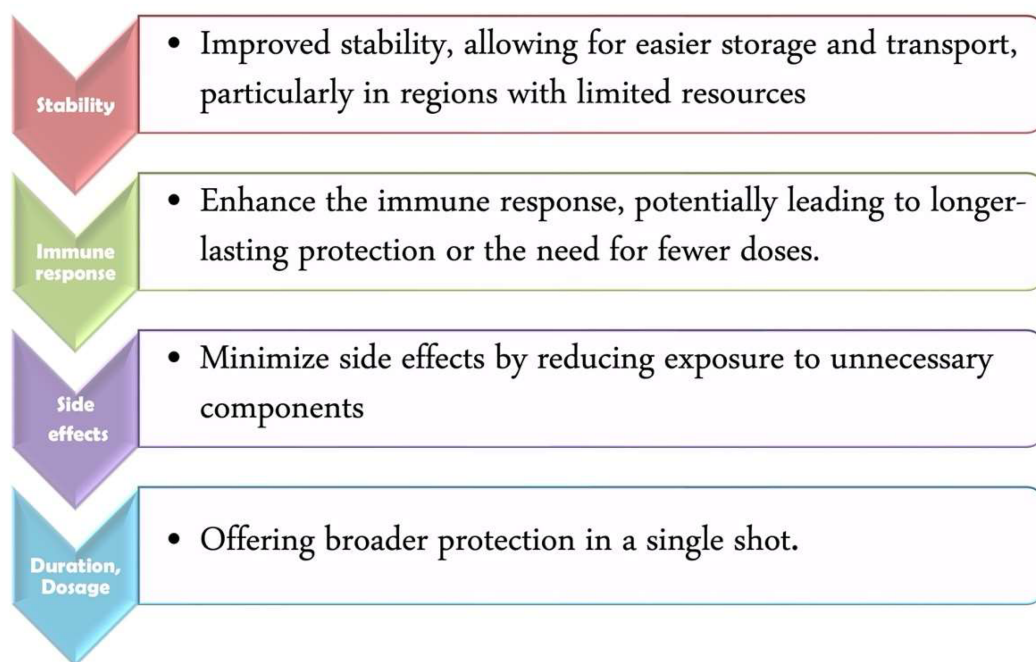


Figure 4: The advantages of various nanoparticles in vaccine delivery.

3.1. Platforms of Nanoparticles Used in Vaccine Delivery

3.1.1. Inorganic Nanoparticles

Inorganic nanoparticles are composed of inorganic materials (i.e., gold, mesoporous silica, and iron oxide). These nanoparticles possess several advantages, including high drug-loading capacity, stability, small particle size, and tunable physicochemical properties. However, despite these advantages, inorganic nanoparticles generally exhibit poor biocompatibility, are non-biodegradable, and may cause high cellular toxicity [58].

3.1.2. Polymeric Nanoparticles

Polymeric nanoparticles are formulated from polymers in which the active compound is either encapsulated within or adsorbed onto the polymer matrix. Polymeric nanoparticles comprise nanospheres and nanocapsules, which differ in structure [59]. Polymeric nanoparticles can be composed of naturally occurring polymers such as chitosan, inulin, albumin, heparin, pullulan, gelatin, and mannan. Additionally, synthetic polymers, including poly (lactic-co-glycolic acid) (PLGA), poly (D, L-lactide-co-glycolide), poly (ethylene glycol), polyphosphazenes, polyanhydrides, polymethacrylates, and poly (D, L-lactide), can be used to fabricate polymeric nanoparticles [60]. Polymeric nanoparticles are versatile, biocom-

patible, and offer sustained release. However, polymeric nanoparticles have several drawbacks, including the toxicity of preparation solvents, challenges associated with large-scale production, and the biphasic release of encapsulated materials [61].

3.1.3. Liposomes

Liposomes are spherical vesicles comprised of phospholipid bilayers separated by water-containing spaces. The phospholipid bilayers of these nanoparticles are primarily formed from cholesterol and other naturally occurring phospholipids. The composition of the phospholipid bilayer influences the characteristics of liposomes, including their size, rigidity, fluidity, and surface charge. phosphatidylcholine, phosphatidylglycerol, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, cholesterol, stearylamine, and dicetyl phosphate are examples of phospholipids used in liposome preparation [62]. Liposomes offer several advantages, including low toxicity, minimal immunogenicity, biocompatibility, and biodegradability. However, they also have several limitations, including high production costs, poor stability, and a short half-life [63].

3.1.4. Immune-Stimulating Complexes (ISCOMs)

The ISCOMs are micellar structures composed of colloidal saponins, cholesterol, and phospholipids. The

primary saponin used in the preparation of ISCOMs is Quil A and its purified components. The main phospholipids used are phosphatidylcholine and phosphatidylethanolamine. ISCOMs are self-adjuvanting vaccine delivery vehicles. Moreover, they can be used as adjuvants without the incorporation of viral proteins; in such cases, these complexes are referred to as ISCOMATRIX or empty ISCOMs [64].

3.1.5. Virus-Like Particles (VLPs)

Virus-like particles (VLPs) are self-assembling nanoparticles composed of viral structural proteins that function as vaccine antigen delivery vehicles. They are molecularly and morphologically similar to native virions. Nevertheless, due to the absence of genetic material, VLPs are incapable of replication or infection [65]. Moreover, VLPs are classified into enveloped and non-enveloped types based on the presence or absence of a lipid envelope. VLPs are biocompatible and biodegradable and can be produced in mammalian, plant, insect, and bacterial expression systems. However, VLP production is associated with several limitations, including low yield and a complex purification process [66,67].

3.1.6. Lipid Nanoparticles (LNPs)

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are the two kinds of LNPs. SLNs are first-generation lipid nanospheres composed of lipids that remain solid at both room temperature and physiological body temperature. SLNs can be comprised of waxes, glycerides, or triglycerides [68]. SLNs combine the advantages of liposomes and polymeric nanoparticles while overcoming many of their limitations. They are easy to prepare, can be produced without the use of organic solvents, are cost-effective, and are suitable for large-scale production. SLNs also exhibit excellent biodegradability and biocompatibility, high physical stability, a favorable drug release profile, chemical versatility, and a non-toxic lipid matrix. Additionally, SLNs are less toxic and generally face fewer regulatory hurdles than polymeric carriers [69]. However, SLNs have limitations, including low drug entrapment efficiency due to their highly ordered crystalline structure and the likelihood of drug expulsion during storage [70]. To tackle these limitations, the second-generation lipid nanoparticle NLCs were designed [71]. NLCs are composed of a combination of solid and liquid lipids and possess a higher drug-loading capacity than SLNs due to their imperfect crystalline structure. Moreover, by preventing lipid crystallization during manufacturing and storage through the incorporation of liquid lipids, NLCs minimize the expulsion of encapsulated ma-

terials. Furthermore, compared with SLNs, NLCs provide more controlled release and greater solubility of the encapsulated cargo within the lipid matrix [70,72].

3.2. Physicochemical Characteristics That Influence the Potency of Nanoparticle Vaccines

3.2.1. Particle Size

The two primary objectives of vaccination are to mimic a pathogenic infection and to establish immunological memory against potential future exposures. Before a vaccine can trigger an immune response, it must successfully transfer antigen from the injection site to secondary lymphoid tissue, which is home to APCs, B cells, and T cells. Antigens can be transported directly to lymphoid organs, such as the spleen and LNs, via the interstitial fluid and collecting lymphatic vessels. Nevertheless, particulate vaccines can enter the lymphatic system and interact with T and B cells within LNs following uptake by APCs at the injection site [73,74]. Therefore, the ability of vaccines to reach and distribute within the LNs is strongly influenced by particle size.

The transmission of the vaccines to the LNs is significantly influenced by their particle size. Large vaccine particles must be actively transported to the LNs by immune cells, primarily DCs. Conversely, smaller particles are thought to move more readily through interstitial flow. As a result, small, non-liposomal nanoparticles (<50 nm) are transported more efficiently into lymphatic capillaries and drain to the LNs than particles larger than 100 nm due to interstitial flow, which facilitates the drainage of fluids from the interstitial space [75,76]. Importantly, DC migration to draining LNs may enhance the retention of smaller particles while representing an additional factor influencing the amount of antigen delivered to the LNs for larger particles (>50 nm) [77].

The antigen must overcome multiple biological barriers before reaching secondary lymphoid tissues through different routes of administration. Consequently, distinct DC subsets are distributed across different tissues, including Langerhans cells in the skin, CD103⁺ DCs in connective tissues, and mucosal DCs in the gastrointestinal tract [78]. In one study, orally administered biodegradable polylactic acid (PLA) microparticles with diameters ranging from 1 to 26 μm were used. The uptake of these particles by intestinal lymphoid structures, known as Peyer's patches, increased with particle size up to 11 μm , after which it declined. Larger particles remained in the spleen, but smaller particles were later carried from the Peyer's patches in the jejunum by the lymphatic system [79]. The

authors hypothesized that the reduced splenic localization observed when the microparticle size exceeded the threshold was due to the lower efficiency of phagocytic uptake of particles larger than 10 μm [80,81]. It has been demonstrated that nanoparticles are more effective than microparticles for oral delivery because they are more efficiently absorbed by intestinal epithelial cells and can penetrate deeper into Peyer's patches [82]. Therefore, particulate vaccines should ideally be designed within the nanometer size range to maximize their ability to cross the intestinal barrier.

Regarding nasal administration, it has been demonstrated that decreasing the size of non-liposomal particles enhances their transport across the rat nasal mucosa, resulting in increased IgG and IgA responses, which are indicators of systemic and mucosal immune responses, respectively [83].

Particle size is a critical factor influencing nanoparticle internalization. The range of nanoparticle sizes, typically thought to be between 10 and 100 nm, is based on how well the nanoparticles are distributed and cleared in vivo. Although smaller particles may facilitate more rapid cellular uptake, no apparent upper size limit for cellular internalization has been observed for particles up to 5 μm . A series of polyethylene glycol hydrogels ranging from 100 nm to 5 μm was evaluated for their ability to penetrate HeLa cells [84]. Large microparticles were generally observed to have slower internalization rates than small nanoparticles. These particles are internalized via clathrin- and caveolae-mediated endocytosis, as well as clathrin- and caveolae-independent pathways. Overall, particles smaller than 50 nm can rapidly drain into and penetrate more effectively within the LNs. Larger particles may be retained more effectively within the LNs, highlighting the need for further research to determine the optimal particle size for achieving both efficient lymphatic drainage and prolonged LN retention. Additionally, the dispersion might be impacted by the mode of administration, which should be considered while designing vaccines.

3.2.2. Particle Shape

Along with particle size, particle shape is a key determinant of the immune response. The aspect ratio (AR), defined as the ratio of particle height to width, is commonly used to describe particle shape. Huang et al. reported that the biodistribution of mesoporous silica nanoparticles following injection into mice is influenced by their shape [85]. They observed that both the liver and spleen accumulated the long-rod particles (720 nm, high AR) and the short-rod particles (185 nm, low AR). However, ac-

cumulation in the spleen was more pronounced for the long-rod particles than for the short-rod particles. Additionally, the body eliminated short-rod particles more rapidly through urine and feces than long-rod particles. These findings indicate that particle shape influences uptake by tissue-resident cells, thereby affecting tissue distribution and retention. However, in this study, the influence of particle size cannot be completely excluded [85]. In another study, tubular-shaped filomicelles with a high AR were found to persist in the bloodstream of rats and mice for up to one week following injection [86]. Short tubular micelles were cleared from the circulation within two days. Human macrophages were able to phagocytose filomicelles shorter than 3 μm but not those exceeding this length. Researchers suggest that the extended circulation time of long filomicelles is due to their reduced frequency of interaction with phagocytes and the blood vessel wall. Shorter cylindrical particles are more readily taken up by phagocytes and are less influenced by blood flow, resulting in more efficient uptake and more rapid clearance from the circulation. However, because these particles were administered intravenously, the focus of this investigation was on circulatory uptake rather than lymphatic trafficking [86]. Following oral administration of mesoporous silica nanoparticles, decreasing the AR from 5 to 1.75 and 1 increased absorption in the small intestine while reducing urinary excretion [87]. Interestingly, particles with the lowest AR exhibited the highest accumulation in the spleen, whereas the other particles were predominantly distributed in the liver, lungs, and kidneys. These findings underscore the importance of the route of administration in determining how particle characteristics influence immunogenicity, suggesting that the biodistribution profile of spherical particles is more favorable than that of non-spherical particles following oral administration.

3.2.3. Particle Rigidity

Along with size and form, rigidity can affect how quickly particles are eliminated and biodistributed. Merkel et al. developed hydrogel particles known as red blood cell mimics (RBCMs), which mimic the shape, size (6 μm), and mechanical properties of red blood cells [88]. They found an inverse relationship between particle rigidity and circulation time, with the most rigid RBCMs being cleared from the circulation significantly more rapidly than the least rigid ones. This was probably due to the ability of less rigid particles to pass through regions with limited blood flow, thereby extending circulation periods. Hydrogel nanoparticles based on "soft" polyethylene glycol (PEG) were produced to resemble hard particles. Compared with rigid particles, these particles exhibited longer

elimination and distribution half-lives [88,89]. Tissues were examined after 30 min and 12 h, revealing that soft particles were present at higher levels in nearly all tissues, including the heart, lungs, brain, blood, kidneys, and spleen, with the exception of the liver. The altered biodistribution was attributed to the prolonged circulation time of soft nanoparticles, which increased their retention in highly perfused organs. Their decreased retention in this tissue could be explained by the degradation of soft nanoparticles in the liver. They observed that the less rigid particles passed through the pulmonary circulation and were predominantly distributed to the spleen, whereas the more rigid particles accumulated within the pulmonary capillaries. These findings suggest that more rigid particles become trapped within the first microvascular bed they encounter [88].

Compared with liposomes composed of phosphatidylcholine exhibiting a low transition temperature, liposomes incorporating phosphatidylcholine with a high transition temperature corresponding to increased membrane rigidity have been shown to exhibit prolonged circulation in the bloodstream. There was also a decrease in the uptake by the spleen and liver [90,91]. Senior et al. reported similar findings and proposed that the prolonged circulation was due to reduced interactions between high-density lipoproteins in the blood and the liposomes [92]. Evidence indicates that high-density lipoprotein apolipoproteins ApoA-I and ApoA-II can interact with phosphatidylcholine and cholesterol-containing liposomes, promoting accelerated clearance from circulation [93]. Rigid cationic liposomes remained at the injection site for a longer duration than less rigid liposomes following IM injection. This was consistent with the higher number of non-rigid liposomes in the draining LNs [94]. Kaur et al. found that the cholesterol content of cationic liposomes, which also influences membrane stiffness, had no effect on transport to LNs or drainage from the injection site following IM injection [95]. It appears that particles with increasing rigidity may have greater difficulty passing through small lymphatic capillaries, thereby hindering lymphatic trafficking, similar to the effect observed with increasing particle size.

3.2.4. Surface Charge

For use in vaccination systems, polymeric particle platforms with varying surface charges, including both positively and negatively charged formulations, have been developed. Surface charge plays a significant role in protein adsorption in circulation and nonspecific cellular internalization. Zeta potential, defined as the electric potential at the slipping plane, is widely used to estimate the surface

charge of particles and is generally considered meaningful within an appropriate measurable range. One of the main benefits of charged particles is their ability to enhance adsorption through electrostatic interactions with other vaccine ingredients, especially the antigen and adjuvant. Protein antigens can occasionally be preserved more effectively by adsorption via electrostatic interactions than by encapsulation. The introduction of surface charge into injectable polymeric particle vaccines may enhance immune responses, as demonstrated in both *in vitro* and *in vivo* studies.

In general, cationic particles exhibit higher efficiency than anionic particles in terms of uptake and activation of APCs, particularly macrophages and DCs [96, 97]. Yet, there are several qualifications to this generality. First, several studies have shown that this effect is enhanced by increased surface charge. In contrast to neutrally charged particles, particles with sufficiently strong negative charge may also improve uptake by APCs and subsequent activation [98]. Second, in addition to differences in uptake and response, anionic and cationic particles may interact with APCs through distinct mechanisms. For example, cationically surface-modified polystyrene particles were associated with reduced phagosomal acidification compared with more neutral polystyrene particles or those with anionic surface modifications [99]. Lastly, cationic PLGA particles formulated with polyethyleneimine (PEI) and plasmid DNA containing CpG motifs did not induce CD83 expression in human DCs, whereas treatment with anionic PLGA particles or plasmid DNA alone did. However, DC activation, as assessed by CD83 or CD86 expression, was not observed in a comparable experiment using PLA particles instead of PLGA particles [100]. The impact of charged particles may vary depending on the type of polymer used to make them, and the charge may not be sufficient to activate APCs [101]. This may not be directly applicable to biodegradable polymers, as much of the early evidence suggesting superior APC interactions with cationic particles was generated using non-degradable polystyrene particles. Enhancement of antigen presentation may represent another advantage of the “proton sponge” effect in polymeric particles containing polycations. Endolysosome disruption is thought to be aided by increased chloride ion influx from polycationic polymers such as PEI, which have a considerable H⁺ ion buffering capacity. It is believed that this disruption enhances MHC-I presentation and promotes cross-presentation in different particle systems [102–104]. Notably, however, studies of adaptive immune responses have focused on a narrower range of particle surface charge magnitudes. Antigen is not always required in *in vitro* assays that focus solely on particle-

APC interactions, and antigen adsorption can reduce the effective surface charge of the particles.

3.2.5. Hydrophobicity

In general, hydrophobic particles are more rapidly and efficiently phagocytosed by cells than hydrophilic particles [105]. Liu et al. investigated the impact of surface chemistry on immune activation by synthesizing microparticles from poly(D, L-lactic acid), poly(D, L-462 lactic-co-glycolic acid), and poly(monomethoxypolyethylene glycol-co-D, L-lactide). Despite having uniform sizes and shapes, these particles varied in their surface hydrophobicity. Results indicated that the most hydrophobic particles prompted the highest expression of MHC-II and CD86 in DCs, as well as peak cytokine production in splenocytes. This enhanced response is attributed to the stronger adhesion of hydrophobic surfaces to cell membranes, facilitating the internalization of both particles and their associated antigens. They concluded that the hydrophobicity of microparticles is one of the main parameters in optimizing the immunogenicity of particulate vaccine delivery systems [104].

According to the hazard theory, which proposes that hydrophobic patterns act as danger signals that activate the immune system, particles with higher hy-

drophobicity exhibit enhanced immunogenicity [105]. To investigate the complex immunological effects of polyanhydride nanoparticles with varying degrees of hydrophobicity, the Narasimhan group used copolymers based on 1,6-bis(p-carboxyphenoxy) hexane (CPH), 1,8-bis(p-carboxyphenoxy)-3,6-dioxaoctane (CPTEG), and sebacic acid (SA). The less hydrophobic, SA-rich particles were found to be more efficiently absorbed by DCs than the more hydrophobic particles (i.e., CPH-rich) [106]. Additionally, more hydrophobic particles induced expression of MHC-II and CD86 but did not stimulate DCs to produce IL-6, IL-1, or TNF. In contrast, less hydrophobic particles elicited higher levels of secreted cytokines but did not induce expression of surface markers. The particles that were least hydrophobic (20:80 CPH/SA) broke down and triggered an immune reaction the fastest. Formulations with a high CPH content (20:80 CPTEG/CPH, 50:50 CPTEG/CPH) were retained in the lungs for at least 63 days, degraded more slowly, and induced higher antibody titers with broader epitope specificity [107]. The delayed, sustained release of antigen was considered responsible for the induction of longer-lived plasma cells and the enhanced inflammatory response associated with particle hydrophobicity. Figure 5 summarizes the physicochemical characteristics of nanoparticles for ideal vaccine delivery.

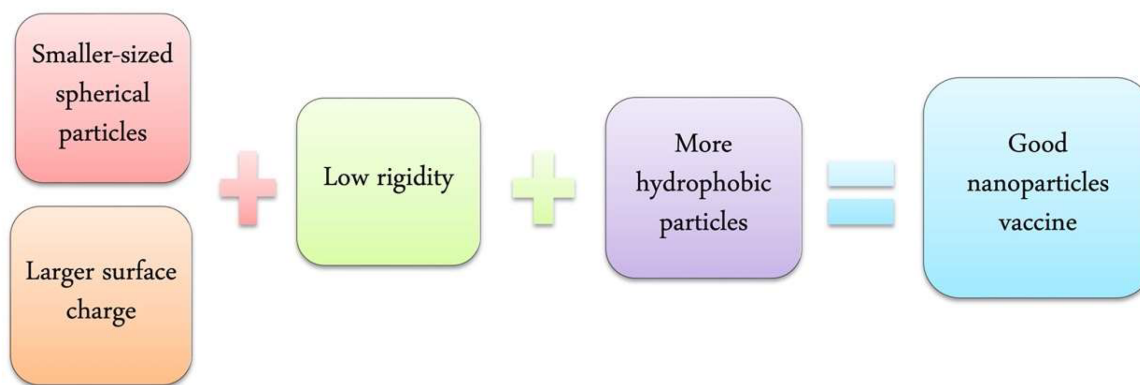


Figure 5: Physicochemical characteristics of nanoparticles for ideal vaccine delivery.

3.3. Clinically Approved Nanovaccines

Several nanovaccines have completed clinical evaluation and received authorization for use. The most widely known nanoparticle-based vaccines include those developed against hepatitis B, human papillomavirus (HPV), malaria, and severe acute respiratory syndrome coron-

avirus 2 (SARS-CoV-2). These vaccines are categorized according to the type of nanoparticles used, including lipid nanoparticle vaccines, virus-like particle vaccines, and immune-stimulating complex vaccines. Table 1 summarizes the currently approved nanovaccines and their corresponding nanoparticle platforms.

Table 1: Summary of clinically approved nanovaccines and their corresponding nanoparticle platforms.

Pathogen	Vaccine	Type of NP	Antigen	Particle Size (nm)	Reference
Severe acute respiratory syndrome coronavirus 2	<i>Comirnaty</i>	LNP	spike protein	~100	[108]
	<i>Spikevax</i>				
	<i>Covifenz</i>	VLP		100–150	[109]
	<i>Nuvaxovid or Covovax</i>	ISCOM		27.2	[110]
Hepatitis B virus	<i>Recombivax HB</i>	VLP	small S antigen	20	[111–113]
	<i>Engerix-B</i>				
	<i>Heplisav-B</i>		pre-S1, pre-S2, and S		
	<i>PreHevbrio</i>				
Malaria	<i>Mosquirix</i>	VLP	<i>Plasmodium falciparum</i> circumsporozoite protein, hepatitis B surface antigen	~20	[114,115]
Human papillomaviruses	<i>Cervarix</i>		L1 protein of virus types 16 and 18	55	[116–118]
	<i>Gardasil</i>		L1 protein of virus types 6, 11, 16 and 18		
	<i>Gardasil 9</i>		L1 protein of virus types 6, 11, 16, 18, 31, 33, 45, 52, and 58		
	<i>Cecolin</i>		L1 protein of virus types 16 and 18	50–60	[119]
Hepatitis E Virus	<i>Hecolin</i>		genotype 1 antigen	20–30	[120,121]

3.3.1. Lipid Nanoparticle Vaccines

Lipid nanoparticles are used to deliver nucleic acid cargo, such as messenger RNA (mRNA) encoding vaccine antigens [65]. The encapsulation of mRNA cargo in LNPs protects it from RNase degradation and enhances its cellular transport [122]. Pfizer-BioNTech's *Comirnaty*TM and Moderna's *Spikevax*TM are Food and Drug Administration (FDA)-approved mRNA-lipid nanoparticle-based vaccines against SARS-CoV-2 [123]. The mRNA encodes the viral spike (S) protein, which mediates viral attachment to and entry into host cells. The LNPs are approximately 100 nm in size and demonstrate potent immunostimulatory properties when complexed with mRNA, thereby eliminating the need for an additional adjuvant [108,124]. Furthermore, mRNA containing modified nucleosides is used to minimize the mRNA immunogenicity and enhance the translational capacity [65,125]. The LNP facilitates uptake via endocytosis by disrupting endosomal membranes and enabling delivery of mRNA into the host cell cytosol [126]. Inside the ribosomes, the mRNA is translated into the spike (S) protein [127]. The unprocessed S protein is presented as a membrane-bound

antigen on the cell surface, serving as an antigen for B cells. Consequently, the S protein is degraded by lysosomes in APCs and presented via MHC-II to T cells [128]. It is also degraded by the proteasome for presentation via MHC-I to cytotoxic T cells [129,130].

3.3.2. Virus-Like Particle Vaccines

Virus-like particle-based vaccines are the most widely available class of nanoparticle vaccines. Commercial VLP-based vaccines include those against hepatitis B virus (HBV), malaria, HPV, hepatitis E virus (HEV), and SARS-CoV-2.

The first generation of hepatitis B vaccines was plasma-derived vaccines, which have now been effectively replaced by recombinant VLP vaccines. Hepatitis B vaccines are enveloped recombinant subunit vaccines against the hepatitis B virus surface antigen (HBsAg) with a particle size of approximately 20 nm [111,112]. The HBsAg comprises three envelope proteins: the small hepatitis B surface antigen (S antigen), the middle hepatitis B surface antigen (Pre-S2 antigen), and the large hepatitis B surface antigen (Pre-S1 antigen) [131]. *RecombivaxHB*[®] and *Engerix-B*[®] are second-generation HBV

vaccines. Both are yeast-derived recombinant vaccines that comprise the small S antigen and are used worldwide to vaccinate neonates and adults [113]. They differ in the antigen concentration and the type of aluminum adjuvant [132]. *Heplisav-B*TM is another small S antigen yeast-derived vaccine that differs from the other two vaccines in the type of adjuvant used. It utilizes CpG 1018, a toll-like receptor 9 agonist adjuvant, to enhance the immune response and reduce the number of required doses (two doses compared with three for *Engerix-B*[®]). *Heplisav-B* is FDA-approved for adults aged 18 years and older [133,134]. A third-generation vaccine, *Pre-Hevbrio*[®] (Sci-B-Vac), targets all three HBsAg envelope proteins (pre-S1, pre-S2, and S). It is derived from mammalian cells and is approved by the FDA for individuals aged 18 and older. It elicits a faster and stronger immune response than second-generation HBV vaccines; consequently, it demonstrates greater efficacy in high-risk groups, immunocompromised individuals, and non-responders to conventional second-generation vaccines. Furthermore, it has been suggested that it may be used as a therapeutic vaccine for the treatment of persistent HBV infection [111,113].

Mosquirix[®] is a yeast-derived World Health Organization (WHO) approved vaccine against malaria and is currently the only vaccine approved for it. It has an approximate particle size of 20 nm and contains the *Plasmodium falciparum* circumsporozoite protein, fused to and combined with HBsAg [114,115].

Human papillomavirus vaccines target the virus's major capsid protein (L1). *Cervarix*[®] vaccine is an insect cell-derived vaccine containing capsid protein of HPV types 16 and 18. Unlike *Cervarix*[®], *Gardasil*[®] and *Gardasil 9*[®] are yeast-derived vaccines that contain proteins of four (i.e., 6, 11, 16, and 18) and nine (i.e., 6, 11, 16, 18, 31, 33, 45, 52, and 58) HPV types, respectively [118]. These vaccines have a particle size of approximately 55 nm and are FDA-approved for females aged 9 to 25 years for *Cervarix*[®], up to 26 years for *Gardasil*[®], and up to 45 years for *Gardasil 9*[®] [116,117,123]. Another bivalent type 16 and 18 vaccine, *Cecolin*TM, is authorized for use in China and is prepared using the *Escherichia coli* expression system [111,135]. It has a particle size ranging from 50 to 60 nm [119].

Hecolin[®] is a HEV vaccine of genotype 1 with a particle size of 20-30 nm. It is produced using an *Escherichia coli* expression system and is approved for use in China [120,121].

Covifenz[®] or CoVLP is a plant-based SARS-CoV-2 vaccine measuring approximately 100–150 nm in size. It was developed using *Nicotiana benthamiana* and consists of recombinant spike proteins derived from SARS-CoV-2.

The vaccine was authorized in Canada for adults aged 18–64 years in 2022; however, the sponsor voluntarily withdrew its authorization in 2023 [109,136].

3.3.3. Immune-Stimulating Complexes Vaccines

Nuvaxovid[®] or *Covovax*[®] is a recombinant subunit SARS-CoV-2 vaccine with protein-protein micellar nanoparticles based on the virus S protein. It is the most recent SARS-CoV-2 vaccine to receive WHO approval and is authorized and used in multiple countries worldwide. The vaccine is 27.2 nm in size and has a polydispersity index (PDI) of 0.25–0.29 [110]. It uses Matrix-MTM 40 nm adjuvant nanoparticles composed of *Quillaja saponins*, cholesterol, and phospholipids to enhance the immune response to the spike glycoprotein [137].

4. Conclusions

Vaccines are essential healthcare tools for maintaining global health and preventing disease outbreaks. Nanoparticles, through their physicochemical properties, strongly influence vaccine-induced immune responses; therefore, optimizing these properties can enhance vaccine efficacy. This review addresses vaccine-elicited immune responses, different nanoparticle types, and how the immunogenicity of nanovaccines is influenced by physicochemical properties, namely size, shape, rigidity, surface charge, and hydrophobicity. Based on the available evidence, this review concludes that these properties should be carefully considered in vaccine development. Nanotechnology has contributed to significant advancements in vaccinology, as evidenced by the number of approved vaccines discussed in this review, and is expected to play an increasingly important role in future vaccine development.

List of Abbreviations

APCs	Antigen-Presenting Cells
AR	Aspect Ratio
B cells	B Lymphocytes
CPH	1,6-bis (p-carboxyphenoxy) Hexane
CPTEG	1,8-bis(p-carboxyphenoxy)-3,6-Dioxacatane
DAMP	Danger-Associated Molecular Patterns
DCs	Dendritic Cells
FDA	Food and Drug Administration
GCs	Germinal Centers
HBsAg	Hepatitis B Virus Surface Antigen
HBV	Hepatitis B Virus
HEV	Hepatitis E Virus
HPVs	Human Papillomaviruses

IgA	Immunoglobulin A
IgG	Immunoglobulin G
IM	Intramuscular
ISCOMs	Immune Stimulating Complexes
LNPs	Lipid Nanoparticles
LN	Lymph Nodes
MHC-I	Major Histocompatibility Complex Class I
MHC-II	Major Histocompatibility Complex Class II
mRNA	Messenger RNA
NLCs	Nanostructured Lipid Carriers
NPs	Nanoparticles
PDI	Polydispersity Index
PEG	Polyethylene Glycol
PEI	Polyethyleneimine
PLA	Polylactic Acid
PLGA	Poly(lactic-co-glycolic) Acid
PRRs	Pattern-Recognition Receptors
RBCMs	Red Blood Cell Mimics
SA	Sebacic Acid
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCS	Subcapsular Sinus
SLNs	Solid Lipid Nanoparticles
SLOs	Secondary Lymphoid Organs
T cells	T Lymphocytes
Tc	Cytotoxic T Cells
TCR	T Cell Receptor
Th	helper T Cells
VLPs	Virus-Like Particles
WHO	World Health Organization

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Conflicts of Interest

The authors declare no conflicts of interest.

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AI Declaration

The authors confirm that ChatGPT (OpenAI, San Francisco, CA, USA) was used solely for English language editing. All content was critically reviewed and approved by the authors, who take full responsibility for the accuracy, originality, integrity, and scientific content of the manuscript.

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