

Virus-like Particles

Subjects: [Biotechnology & Applied Microbiology](#)

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Nanotechnology is a fast-evolving field focused on fabricating nanoscale objects for industrial, cosmetic, and therapeutic applications. Virus-like particles (VLPs) are self-assembled nanoparticles whose intrinsic properties, such as heterogeneity, and highly ordered structural organization are exploited to prepare vaccines; imaging agents; construct nanobioreactors; cancer treatment approaches; or deliver drugs, genes, and enzymes. However, depending upon the intrinsic features of the native virus from which they are produced, the therapeutic performance of VLPs can vary.

nanomedicine

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virus-like particles

1. Introduction

Nanotechnology is an interdisciplinary field devoted to engineering and developing structures ranging from 1 to 500 nm. Structures that correspond to this scale are defined as nanoparticles (NPs). NPs possess promising optical, chemical, and physical properties attractive for biomedical purposes, such as diagnostic, chemical sensing, cellular imaging, drug delivery, therapeutics, and tissue engineering ^[1].

Given the unique physical, optical, chemical, and therapeutic properties of NPs, there has been an increasing interest in designing methods to develop and characterize them. NPs are prepared through top-down and bottom-up approaches, including laser ablation, sputtering, etching, and mechanical milling techniques. The latter encompasses spinning, chemical reduction, molecular condensation, and green synthesis processes ^[2]. Instead of reducing a bulk material into nanometric objects, bottom-up methods stimulate the self-assembly of atoms into bioactive NPs. For example, in nanomedicine, the amino acid side chains and functional groups of distinct proteins (e.g., collagen, elastin, gelatin, keratin, silk, and zein) are used as scaffolds to induce the self-assembly of nanofibers, nanotubes, and nanobelts to deliver drugs or develop materials for tissue engineering ^{[3][4]}.

Among protein-based nanomaterials, virus-like particles (VLPs) are self-assembled platforms commercially approved by the US Food and Drug Administration (FDA) since the 1980s ^[5]. Since VLPs resemble the capsid morphology, structural organization, and cellular tropism of wild-type viruses ^{[6][7]}, they have been exploited to prepare monodisperse nanocarriers (20–500 nm) for drug delivery, enzyme delivery for enzymatic replacement therapy ^{[8][9]}, and gene therapy applications. In addition, they have been widely used to construct human vaccines against various pathogenic viruses (e.g., human papillomavirus and zika virus) and distinct types of cancer, such as colorectal, pancreatic, and cervical cancer ^{[5][10]}.

In contrast to other organic NPs, VLPs are convenient, because they exhibit higher biocompatibility, the capacity for cell internalization, and ease of functionalization for cell targeting. In fact, for the latter, they can be tailored by chemical or genetic methods with various biomolecules (i.e., transferrin, folic acid, and single-chain antibodies) to enhance their bioavailability and, herein, evoke both humoral and cellular immune responses ^{[11][12]}. However, these phenomena rely on the physicochemical and biochemical characteristics of VLPs.

Nowadays, there is a constant effort to develop analytical methods that, alone or in combination with others, enable scientists to assess the influence of physicochemical parameters in the biological activities of nanomaterials. For instance, the therapeutic performance, stability, and morphology ^{[13][14]} of VLPs can vary in accord with pH ranges ^[15], choice of the expression system ^{[16][17]}, and purification procedures ^{[18][19]}.

Since the novel coronavirus SARS-CoV-2, there has been an increasing interest in reviewing VLPs as a powerful approach to producing vaccines and nanocarriers ^[20]. However, there is a need to complement those studies and recent ones ^[21], with basic principles about expressing, manipulating, functionalizing, and characterizing VLPs.

Therefore, the literature regarding the structure classification, production, morphology, and functionalization of VLPs for biomedical applications was consulted in this entry. The research engines PubMed, Google Scholar, Web of Science, and Wiley Online Library databases were used to compile the literature. In addition, the same databases were used to integrate the main aspects of viruses and how the geometry is indispensable to constructing VLPs-based platforms.

2. Brief Description of Viruses

Viruses are entities characterized by the lack of machinery for self-replication and energy production. Their replication relies on hijacking the cellular systems of the host cells to produce the molecules necessary for their assembly and subsequent escape from the cells. Infectious viruses that have not been internalized in the host cells (not in a replication phase) and residing outside the cell host are called virions.

Viruses are ubiquitous entities containing a DNA- or RNA-based genome protected or not by a protein shell known as a capsid and other accessory biomolecules, such as proteins and membranes [22]. The capsid shell is assembled through covalent and electrostatic interactions conferring a robust and flexible structure and made by small subunits known as capsomers [23]. These capsomers are critical components of the VLPs and constitute the basis for their self-assembly into complex structures [24].

The general structures of viral capsids show a diversity of conformations, including icosahedral conformation. Icosahedral capsids comprise 20 triangular subunits, whereas helical capsids are proteins assembled to form helical cylinders [25]. Despite the structural variabilities between both shapes, the functions of the viral capsid rely on the packaging, sequestering, and protection of the viral genetic material, preventing its degradation in the environment or exposure to chemical hazards [25][26].

Besides the capsids, viruses are surrounded or not by a viral envelope that facilitates their fusion and infection of the host cell. In addition to the presence of proteins and glycoproteins, this envelope can contain lipidic membranes acquired from the host. Viral envelopes are necessary to protect the viral genome, increase the packaging capacity, confer structural flexibility, and enable the new viruses to exit from their host cell and avert immune responses [27].

Viruses with envelopes are known as enveloped viruses, such as the varicella-zoster virus [28], lymphocytic choriomeningitis virus, tick-borne encephalitis virus, human immunodeficiency virus 1 [29], and severe acute respiratory syndrome coronavirus [30][31].

3. Key Concepts about Virus-like Particles (VLPs)

The assembly of VLPs uses exclusively viral proteins and excludes the genetic material. Thus, VLPs can be produced from a myriad of wild-type viruses, such as hepatitis B and E, tobacco, and papaya mosaic viruses [32], and from the capsids of various bacteriophages (Q β , MS2, P22, and PP7) [33][34][35][36].

The production of VLPs using bacteria, mammalian cells, plants, yeast, and insect cell lines is well-documented [37][38][39]. However, current efforts are devoted to understanding their capsid self-assembly mechanisms to improve the cargo loading capacity, potency, and efficacy.

The capsid self-assembly of VLPs is a spontaneous natural process by which highly ordered structures arise from the interactions between protein monomers, also known as building blocks. The self-association between building blocks is facilitated by a thermodynamic equilibrium based on van der Waals, hydrogen bonding, hydrophobic, and electrostatic interactions during the nucleation and growth phases [40][41]. As a result, VLPs can adopt different structural arrangements, such as helical, icosahedral, spherical, or complex shapes [42][43] (Figure 1).

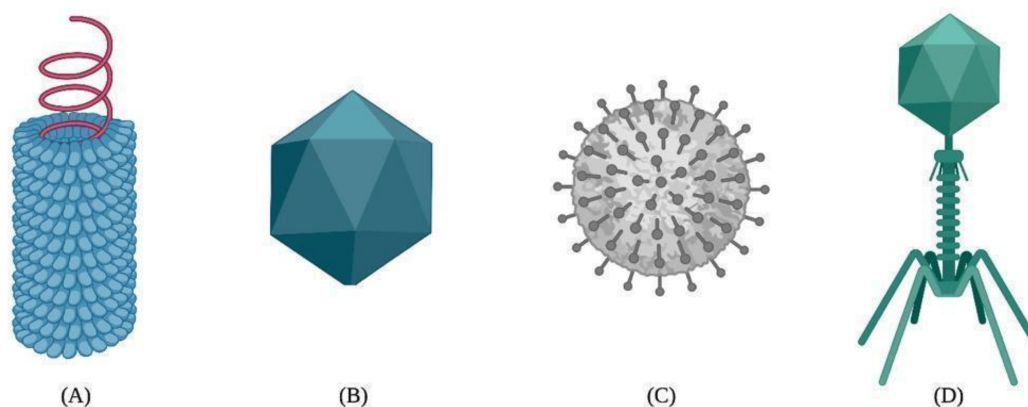


Figure 1. Different types of viral capsids: (A) helical, (B) icosahedral, (C) spherical, and (D) complex.

The self-assembly of VLPs is assisted by small molecules such as scaffolding proteins and nucleic acids [40]. In this regard, scaffolding proteins and nucleic acids can be used to aid the *in vitro* capsid self-assembly process of many VLPs, such as the cowpea chlorotic mottle virus, hepatitis C virus, bacteriophage MS2, simian virus 40, beak and feather disease virus, and adeno-associated virus serotype 2 VLPs [40].

Since the self-assembly of VLPs can be perturbed by changes in the salt concentration, denaturant agents, pH, and temperature [29], excipients such as polysorbate 80 are used to avoid the aggregation and preserve the stability of the VLPs [40]. On the other hand, molecules such as 2-phenoxyethanol have been used as a preservative agent to produce licensed VLP-based vaccines such as the Engerix®-B hepatitis B vaccine [44]. Comparably, buffering agents such as L-histidine and sodium borate have been used to manufacture the Gardasil® human papillomavirus vaccine [44].

VLP-based nanocarriers could be produced by producing viruses in their natural host, followed by virion purification, disassembling, and nucleic acid removal (see Figure 2). Then, the disassembled coat proteins are transferred into assembling conditions in the presence of any cargo to be encapsulated. Finally, the VLPs containing the load could be functionalized with any ligand or chemical moiety and covered with polymers or other compounds to reduce or enhance their immunogenicity or facilitate cell internalization. Molecules used to decorate the VLP surface include T-cell receptor ligands; polysaccharides; enzymes (e.g., α -glucosidase); and canonical amino acids (i.e., aspartic acid, cysteine, glutamic acid, lysine, and tyrosine); among others [45][46][47][48].

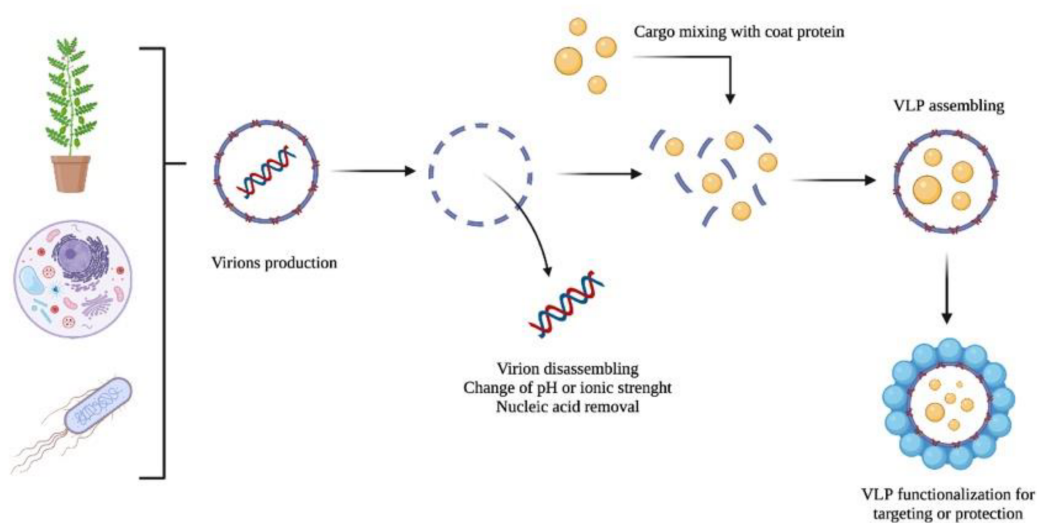


Figure 2. A schematic representation of the VLP production of virions as nanocarriers: (i) production, (ii) disassembling and nucleic acid removal, (iii) cargo encapsulation, and (iv) VLP functionalization.

The coat proteins of the VLPs can be heterologously produced and purified from an industrial microorganism and reconstituted under suitable conditions in the presence of their cargo. In this regard, the cargo loading could be obtained by simple encapsulation when the charges of the inner portion of the VLP and the cargo surface are complementary. However, as described in detail below, the loading could also be reached by chemical or genetic modification of the coat protein on both the inner and outer surfaces.

Although most VLPs are deficient in viral genetic material, they retain properties from the native virus from which they are produced. These features include their affinity for cellular receptors, host cell entry mechanisms, and immunogenicity [49]. As native viruses, VLPs elicit both humoral and cellular responses in the host system. These responses are stimulated by VLP-based systems due to their repetitive antigenic epitopes, resembling pathogen-associated molecular patterns (PAMPs), and low polydispersity [50]. The introduction of antigens (e.g., proteins or small peptides) on the VLP surface is necessary to enhance the immune response and is achieved through chemical and genetic approaches [51][52][53]. It is worth mentioning that the immune response only occurs against the antigen, not the rest of the nanostructure produced [54].

Functionalized VLPs can trigger an immune response by activating PAMPs. These patterns are conserved molecular motifs associated with pathogen infections [55]. PAMPs are recognized by pattern-recognition receptors (PRRs), nucleotide-binding oligomerization domain-like receptors, and Toll-like receptors (TLRs) on the surface of phagocytic cells [56]. Due to the similarity of VLPs with wild-type viruses, the morphology of these NPs stimulates adaptive and innate immune responses, including cellular uptake. For example, VLPs can be taken up by enterocytes, specialized intestinal epithelial cells, dendritic cells (DCs), and macrophages [57]. This process depends upon the size, shape, and surface charge of the VLPs [58].

Like other NPs, the surfaces of VLPs can be modified with various ligands to improve their therapeutic efficacy, bioavailability, and cellular interactions. The introduction of multiple molecules on the VLPs surface is known as multivalence. Then, VLPs are multivalent engineered nanoplatfoms that form independent ligand-receptor bonds, elicit therapeutic responses, and mitigate endemic diseases. For example, Garg and coworkers developed a VLP-based multivalent vaccine (CJaYZ) against four arboviruses, including the zika, chikungunya, yellow fever, and Japanese encephalitis viruses. Even though the CJaYZ

vaccine promoted a neutralizing antibody response against the four viruses in Balb/c mice models, further studies are required to assess the precise antigen amount of individual VLPs and their efficacy in other animal models [59]. The general features of VLPs are depicted in Figure 3.

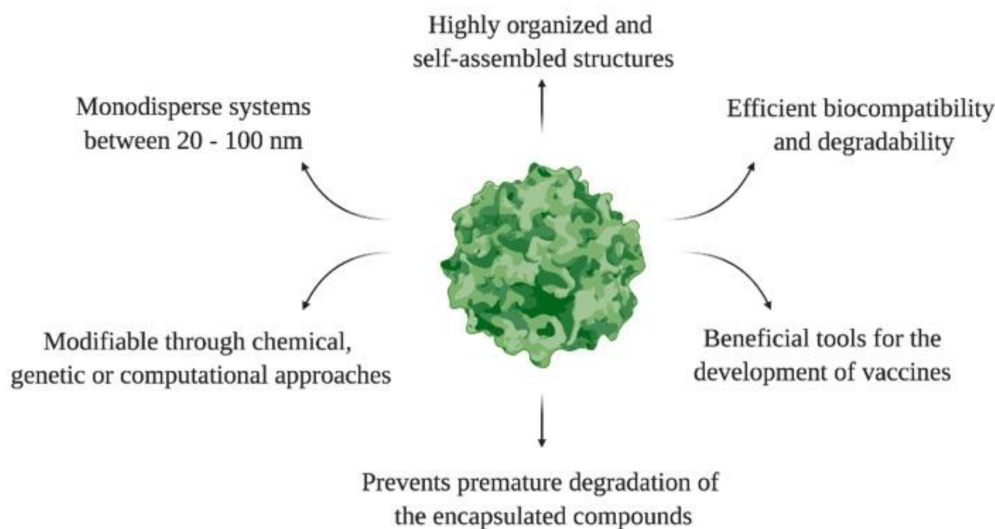


Figure 3. General features of VLPs.

4. Structure Classification of VLPs

Given the structural diversity of VLPs, they have been categorized into three main groups: enveloped, nonenveloped, and chimeric. For example, enveloped VLPs (eVLPs) are expressed using eukaryotic systems and as wild-type viruses. eVLPs are complex structures that own a host-cell-derived membrane and one or more glycoproteins. The viral envelope in eVLPs can be engineered to display heterologous adjuvants and antigens; however, this process might alter their downstream processing due to the possible presence of host cellular contaminants [60].

As vaccines, eVLPs stimulate immune responses and are manipulated with chemical or genetic methods. In this regard, a handful of eVLPs have been produced from pathogenic viruses for vaccine development. Some examples include eVLPs derived from the West Nile virus (WNV), dengue virus (DENV), JEV, Rift Valley fever virus (RVFV), and Ross River virus (RRV), among others [61][62]. For drug delivery applications, Rous sarcoma virus (RSV) eVLPs displaying a single-chain variable fragment (scFv) of humanized CC49 antibody (hCC49) have been expressed on silkworm larvae to deliver doxorubicin into human colon carcinoma cells [63]. In addition, doxorubicin was loaded into hCC49 scFv-displaying RSV VLPs by electroporation.

Non-eVLPs are single or multiple capsid protein nanoconstructs that lack cell membranes. Members of this category are produced on eukaryotic or prokaryotic expression systems. The surfaces of non-eVLPs can also be manipulated with chemical and genetic approaches to display epitopes or peptides on their surfaces and, herein, elicit wider immunological responses [64]. For instance, non-eVLPs derived from the coxsackievirus B3 antigen have enhanced humoral immune responses and protected murine models against myocarditis [65]. Additionally, rotavirus non-eVLPs (Ro-VLPs) were produced in *Nicotiana benthamiana* plants. The immunogenicity and tolerance of Ro-VLPs were evaluated in adults, toddlers, and infants [66].

Chimeric VLPs (cVLPs) are nanoplatfroms from structural components originating from at least two different viral serotypes [67]. In these nanoplatfroms, the VLP core can be modified with antigens that cannot self-assemble or present polyproteins from distinct viruses [68]. In contrast with the other two categories of VLPs, cVLPs are useful to present foreign epitopes; entrap multiple therapeutic or diagnostic molecules; and target cells, tissues, or organs [42]. However, the production of cVLPs depends upon various factors, such as the type of conjugation between proteins, glycosylation patterns, cell type, length of the fused antigen, and steric effects.

For biomedical purposes, cVLPs have been prepared from major structural components of influenza viruses (e.g., M1 protein) and human immunodeficiency virus type-1 (HIV-1) (e.g., Group-specific antigen; Gag) to target colon carcinoma cell lines and for vaccination purposes [69]. In another study, murine polyomavirus cVLPs were manipulated to elicit CD8⁺ and CD4⁺ T cells and antibody responses [70]. The immune response against other cVLPs has also been evaluated recently, specifically for the

foot-and-mouth disease virus cVLP vaccine, based on the co-expression of the HIV-1 Gag protein and rabies glycoproteins [\[74\]](#).

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