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MNext-generation viral nanoparticles for targeted deliver of therapeutics

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Introduction

Viral nanoparticles (VNPs) are virus-based nanocarriers that have been studied extensively and intensively for biomedical applications. However, their clinical translation is relatively low compared to the predominating lipid-based nanoparticles. Therefore, this article describes the fundamentals, challenges, and solutions of the VNP-based platform, which will leverage the development of next-generation VNPs.

Although the administration of drugs on the skin is a safe and noninvasive therapeutic alternative, producing formulations capable of disrupting the cutaneous barriers is still a challenge. In this scenario, extrusion-based techniques have emerged as disruptive technologies to ensure unique drug-excipient interactions that facilitate drug skin diffusion for systemic or local effect and even mean the key to obtain viable industrial products.

Areas covered

Different types of VNPs and their biomedical applications are reviewed comprehensively. Strategies and approaches for cargo loading and targeted delivery of VNPs are examined thoroughly. The latest developments in controlled release of cargoes from VNPs and their mechanisms are highlighted too. The challenges faced by VNPs in biomedical applications are identified, and solutions are provided to overcome them.

This article presents a comprehensive overview of extrusion-based techniques in developing pharmaceutical dosage forms for topical or transdermal drug delivery. First, the theoretical basis of how extrusion-based techniques can optimize the permeation of drugs through the skin is examined. Then, the current state-of-the-art of drug products developed by extrusion-based techniques, specifically by hot-melt extrusion (HME) and fused deposition modeling (FDM) 3D printing, are discussed and contrasted with the current pharmaceutical processes.

Expert opinion

In the development of next-generation VNPs for gene therapy, bioimaging and therapeutic deliveries, focus must be given to reduce their immunogenicity, and increase their stability in the circulatory system. Modular virus-like particles (VLPs) which are produced separately from their cargoes or ligands before all the components are coupled can speed up clinical trials and commercialization. In addition, removal of contaminants from VNPs, cargo delivery across the blood brain barrier (BBB), and targeting of VNPs to organelles intracellularly are challenges that will preoccupy researchers in this decade.

A wide variety of pharmaceutical products can be obtained using HME and FDM 3D printing, including new dosage forms designed for a perfect anatomical fit. Despite the limitations of pharmaceutical products produced with HME and FDM 3D printing regarding thermal stability and available excipients, the advantages in industrial adaptability and improved bioavailability allied with patient-match devices certainly deserve full attention and investment.

For neophytes in this technique, the PCR method consists of a complex system based on enzymatic engineering that can read targeted DNA and incorporate complementary oligonucleotides by nucleophilic substitution. From very low oligonucleotide concentrations found in real samples, concentrations may be increased to levels that could be detected and quantified by a colorimetric technique. This could be regarded as the most well-known methodology used on the market; however, it is time-consuming and produces high costs linked to the use of specific biological and chemical reagents. For these reasons, the development of modified methodologies and other derivative methods based on PCR arouses increasing interest. This technique allows the provision of an important solution to detect and quantify low genomic concentrations in real samples. This is achieved by the amplification of the genomic material involving the copy of DNA by an enzymatic strategy; hence, a resulting concentration improves the signal increase in the presence of tuned nanostructures. Many cycles could be repeated to control the desired quantity. However, the extra procedures add more time to the method. In addition, to improve time and procedures, other related PCR-based methods have also been developed, such as efficient polymerase chain reaction assisted by metal–organic frameworks. It was demonstrated that UiO-66 and ZIF-8 not only enhanced the sensitivity and efficiency of the first round of PCR but also increased the specificity and efficiency of the second round of PCR. Moreover, the modified PCR method could widen the annealing temperature range of the second round of PCR, probably due to the interaction of DNA and Taq polymerase with MOFs. A potential candidate for enhancing PCR is thus offered, yielding insights into mechanisms for improving nano-PCR and exploring a new application field for MOFs.

Accordingly, the accurate and controlled aggregation by highly specific and targeted DNA interactions could yield particles of varied sizes at the nanoscale and towards the microscale and higher dimensions. In this regard, recent high-tech developments have taken place in DNA sequencing that are closely related to NGS technologies offered on the market, such as nano-ball technology. This technology was initially developed from design of self-assemblies and nano-arrays, as in the case of the human genome sequencing using unchained base reads in self-assembling DNA nanoarrays. Regarding to the higher sized micro-structures previously mentioned, fluorescent structural DNA nanoballs have been reported for sequencing in NGS. Nanoballs are DNA self-assemblies at the nanoscale and higher scales within the microscale, with particular properties such as nucleotide transporters and bright light sources after targeted interactions. The design considers the incorporation of intercalating fluorophore in DNA strands. It could also be used as a source of nucleotides for DNA polymerization reactions, thus amplifying local concentrations of genomic materials in real time. Highly labeled DNA nanoballs functionalized with phosphate-linked nucleotide triphosphates (dNTPs) were developed as nanoplatforms of dNTPs for DNA polymerase. The particles were prepared by strand-displacement polymerization from a self-complementary circular template. Imaged by atomic force microscopy, these functionalized particles appear as condensed, fuzzy balls with diameters between 50–150 nm. They emit a bright fluorescent signal detected in 2 msec exposures with a signal-to-noise ratio of 25 when imaged using a TIR fluorescence microscope.

In order to highlight fluorescence techniques, it should be noted that fluorescence signaling in all cases showed intrinsic high-sensitive intensity. This particular property is not shown as high from non-labeled genomic materials; for this reason, it should be added in some part of the method. This addition was by using varied fluorophores, laser dyes, and emitters with different nominations depending on the current status of the development in this research field. The fluorescence signal was thus tracked after full complementary nucleotide interactions. Both steps showed to be key phenomena to detect complementary nucleotides. In view of this, the method should rely on previous information such as known genomic probe and non-classical light wavelength to measure the targeted detection, and optimally, a signal modification should be produced after genomic material detection. These three conditions could vary according to the strategy of detection, even if fluorescence is applied as a unique detection technique. Challenges posed in these three steps are connected with real-sample cleaning and experimental procedures such as chemical conjugation, labeling, and interference. Potential molecular optical active biomolecules could quench emissions and hinder oligonucleotide detections. Thus, the application of fluorescence varies by developing labeling or biolabeling with bioconjugation techniques. Associated methods such as direct fluorescence emissions, FRET, FISH, incorporation of more complex enzymatic bio machineries, as well as the development of accurate targeted aggregation have proven to be new ways to overcome difficulties in genotyping.

To conclude this section, fluorescence techniques have been used to accomplish sequencing from the molecular level to higher-sized nanochemistry control and participate in nucleotide chemistry and DNA interaction. In this particular research field, it is very important to examine strategies already developed and transfer high-impact research in real applications to provide innovative ways to address the current challenges linked to low DNA concentrations in real samples for detection and quantification.

Article highlights

- Virus nanoparticles (VNPs) have been exploited as vehicles for gene therapy, immunotherapy, bioimaging, and drug delivery.

- Currently, less than one-tenth of the commercialized nanomedicines are related to VNPs, of which none are for bioimaging and drug delivery applications.

- The obstacles faced by VNPs in biomedical applications, cargo loading, targeted delivery, and cargo release are described.

- Solutions are provided to resolve the issues pertaining to VNPs including immunogenicity, stability, contamination, and particle formation.

- Future directions of VNPs including modular virus-like particles, cargo delivery across the blood brain barrier, and targeting of VNPs to organelles intracellularly are discussed intensively.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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