International Journal of Biological and Pharmaceutical Sciences Archive

ISSN: 0799-6616 (Online)

Journal homepage: https://ijbpsa.com/

(REVIEW ARTICLE)

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Biodegradable nanoparticles for targeted drug delivery in viral infections

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International Journal of Biological and Pharmaceutical Sciences Archive, 2025, 09(01), 048-076

Publication history: Received on 12 February 2025; revised on 23 March 2025; accepted on 25 March 2025

Article DOI: https://doi.org/10.53771/ijbpsa.2025.9.1.0031

Abstract

Viral infections continue to pose significant global health challenges, contributing to high morbidity and mortality rates, as seen in diseases such as HIV/AIDS, hepatitis, influenza, and SARS-CoV-2. Despite advancements in antiviral therapies, conventional treatment strategies face critical limitations, including drug resistance, systemic toxicity, and poor bioavailability. Biodegradable nanoparticles (BNPs) have emerged as revolutionary drug delivery systems, offered targeted and controlled release of antiviral agents while enhanced therapeutic efficacy and minimizing adverse effects. This review explores the diverse types of biodegradable nanoparticles, including polymeric, lipid-based, and protein-based nanoparticles, detailing their composition, drug-loading mechanisms, and biodegradability properties. The mechanisms of biodegradation and drug release, including enzymatic, hydrolytic, and oxidative degradation, are analyzed to highlight how BNPs enhance antiviral drug pharmacokinetics. Moreover, various targeting strategies—such as receptor-mediated targeting, pH-responsive nanoparticles, and nanoparticle-based immunomodulation—are discussed for their ability to improve drug localization and immune response activation. Recent advances in clinical translation and regulatory considerations, including the success of mRNA-based lipid nanoparticle vaccines and ongoing clinical trials, underscore BNPs' potential for widespread therapeutic applications. However, challenges such as scalability, cost of production, toxicity concerns, and regulatory hurdles remain major obstacles to clinical adoption. The review further highlights emerging trends, including CRISPR-loaded BNPs for viral genome editing, biohybrid nanoparticles for vaccine development, and biomimetic nanoparticles for enhanced drug delivery. By bridging scientific, clinical, and regulatory perspectives, this review aims to provide a comprehensive understanding of biodegradable nanoparticles as next-generation antiviral therapeutics, with a focus on enhancing their scalability and real-world application.

Keywords: Biodegradable Nanoparticles; Antiviral Therapy; Drug Delivery; Nanomedicine; Targeting Strategies; Mrna Vaccines; CRISPR Nanoparticles; Clinical Translation

1. Introduction

1.1. Overview of Viral Infections as a Global Health Challenge

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Viral infections continue to pose significant challenges to global health, with diseases such as HIV/AIDS, hepatitis, influenza, and the recent SARS-CoV-2 pandemic leading to substantial morbidity and mortality worldwide [1]. These infections not only strain healthcare systems but also have profound socio-economic impacts, particularly in low- and middle-income countries. HIV/AIDS remains a major global public health issue, having claimed an estimated 42.3 million lives to date. About 39.9 million individuals have HIV as of 2023, with 65% of them living in the WHO African Region. An estimated 1.3 million new infections and 630,000 HIV-related deaths occurred in 2023 alone [2,3].

Hepatitis B and C infections are also of significant concern, leading to chronic liver diseases and hepatocellular carcinoma. Viral hepatitis and influenza contribute to substantial morbidity and mortality, with hepatitis B and C affecting over 354 million people globally. Influenza viruses contribute to annual epidemics, resulting in substantial morbidity and mortality, particularly among vulnerable populations. The outbreak of SARS-CoV-2 has further emphasized the global vulnerability to viral pandemics, producing enormous health and economic catastrophes, leading to millions of deaths across the globe and imposing unprecedented demand on medical institutions [4,5].

Viral infections continue to impose a significant burden on global public health, contributing to widespread morbidity, mortality, and economic disruption. Despite advancements in antiviral therapies, many viral diseases remain difficult to manage due to limitations such as drug resistance, treatment accessibility, and the inability to completely eradicate the infection. According to WHO (2023), HIV/AIDS, hepatitis B and C, influenza, and SARS-CoV-2 are among the most prevalent and deadly viral infections worldwide, affecting millions of individuals annually [6,7]. Current treatment strategies, including antiviral medications and vaccines, have provided relief but are often hindered by challenges such as the need for lifelong treatment, high costs, and the emergence of resistant viral strains [7]. Table 1 presents a brief summary of the global burden of these major viral infections, highlighting their prevalence, annual infections and deaths, and the limitations associated with existing therapeutic interventions.

Table 1 Global Burden of Major Viral Infections and Limitations of Current Therapies

Viral Infection	Global Prevalence	Annual New Infections	Annual Deaths	Current Therapies	Limitations
HIV/AIDS	39.9 million people living with HIV in 2023. Ref [8]	1.3 million in 2023. Ref [2]	630,000 in 2023. Ref [2]	Antiretroviral therapy (ART)	Lifelong treatment required; no cure; access and adherence challenges
Hepatitis B	Over 296 million people living with chronic HBV infection. Ref [9]	Data not specified	Approximately 820,000 annually. Ref [9]	Antiviral medications; vaccine available for prevention	No definitive cure; treatment can be lifelong; limited access to vaccination in some regions
Hepatitis C	Approximately 58 million people with chronic HCV infection Ref [9]	1.5 million new infections per year. Ref [9]	Approximately 290,000 annually. Ref [9]	Direct-acting antivirals (DAAs)	High cost of treatment; limited access in low-resource settings
Influenza	Affects 20-30% of children and 5-10% of adults every year. Ref [9]	Data not specified	290,000 to 650,000 respiratory deaths annually. Ref [9]	Antiviral medications; annual vaccines	Vaccine effectiveness varies; antigenic drift requires annual reformulation
SARS-CoV-2 (COVID-19)	Data not specified	Data not specified	7.1–36.5 million deaths as of 2025. Ref [10]	Antiviral medications; vaccines	Emergence of variants; vaccine distribution inequities

Note: Data for SARS-CoV-2 are continually evolving due to the ongoing nature of the pandemic.

Conventional antiviral therapies, while essential, face several limitations. Extended exposure to antiviral drugs, as well as continued replication of viruses arising from immunosuppression, play important roles in the buildup of antiviral drug resistance, which can emerge as persistent or rising viremia or illness despite treatment. Resistance to drugs has

a wide range of implications, from the toxicity of using second-line antivirals to severe sickness and even death from increasing viral infection when no viable alternative therapies are available [11].

Additionally, many antiviral drugs suffer from poor bioavailability, affecting their therapeutic efficacy. For instance, In the instance of acyclovir, certain patients exhibited absorption rates down to 15% of the given dosage. Bioavailability is influenced by solubility and permeability, necessitating higher doses that may lead to toxic effects. These difficulties emphasize how urgently creative ideas are needed to improve antiviral treatment. By enhancing medication delivery, lowering toxicity, and minimizing the evolution of drug resistance, biodegradable nanoparticles have become a viable method to get beyond these constraints [12,13].

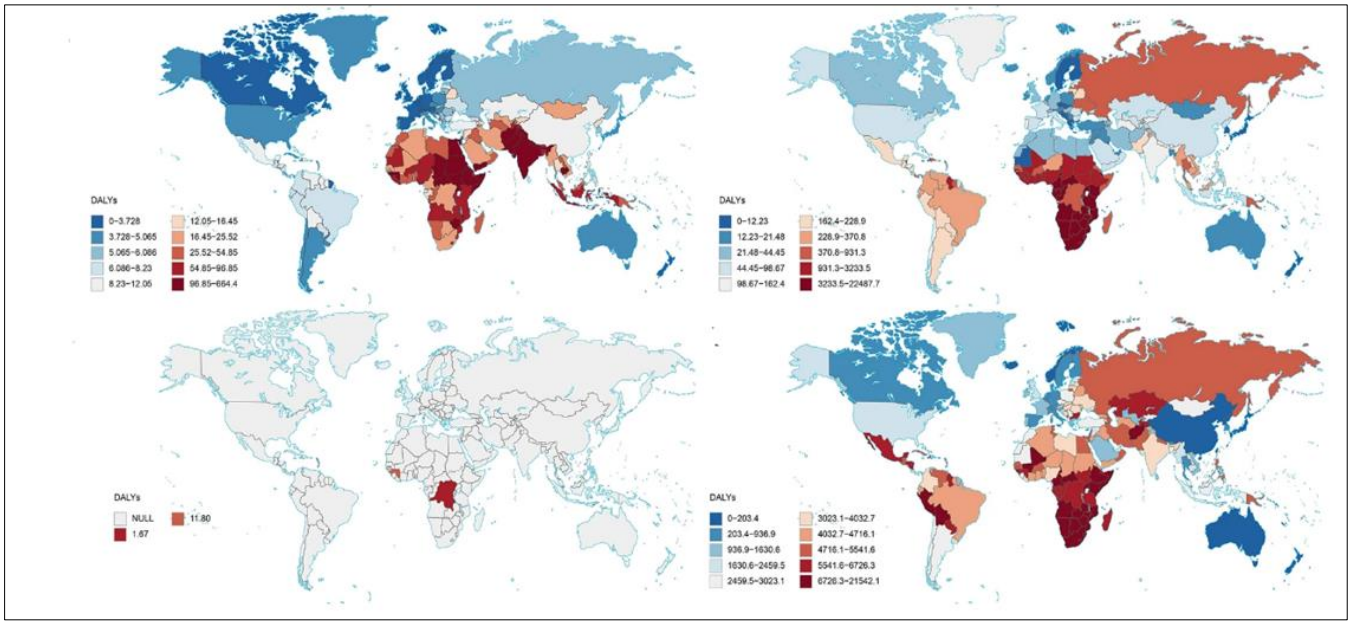

Figure 1 Global distribution of age-standardized DALY rates for six viral infectious diseases of poverty for all ages and both sexes in 2021 (a acute hepatitis, b HIV/AIDS, c EVD, and d COVID-19). *The rate is per 100,000 population. DALY disability-adjusted life year. Map approval number: GS(2024)3052. Modified from Ref. [12] with permission

1.2. Nanobiotechnology Roles in Antiviral Drug Delivery

Nanobiotechnology has emerged as a transformative approach in antiviral drug delivery, offering significant advantages over traditional drug carriers. One significant advantage it has is the capacity to provide tailored delivery of therapeutic agents. According to Maus et al. [14], nanocarriers can be designed to recognize and attach to precise receptors on virus-infected cells, making sure that antiviral drugs are administered specifically to the site of infection. Beyond the optimization of the therapeutic efficacy of the drugs, this targeted technique also reduces off-target effects, therefore lowering possible adverse effects.

Controlled release is another critical advantage offered by nanobiotechnology in antiviral therapy. Nanoparticles can be tailored to deliver their payload in a continuous and regulated pattern, maintaining highly efficient drug concentrations in the bloodstream over prolonged periods. As highlighted by Mitchell et al. [15], this controlled release system lowers drug administration frequency and increases compliance among patients. Furthermore, it helps in maintaining consistent therapeutic levels of the drug, which is crucial in managing chronic viral infections.

The ability of nanoparticles to biodegrade is crucial for their safety and efficacy as drug delivery systems. Nanoparticles that are biodegradable are made to degrade into metabolites that are harmless to the body and may be eliminated with relative ease. This characteristic markedly diminishes the risk of prolonged toxic effects linked to the build up of materials that are non-biodegradable in the body. Kumari et al. [16] indicate that the degraded products of these nanoparticles are generally metabolized and eliminated via natural physiological pathways, thereby improving their biocompatibility.

Moreover, the use of biodegradable materials in nanoparticle formulation improves drug clearance rates. From the findings of Kadam et al. [17], it was observed that biodegradable nanoparticles exhibited reduced apparent clearance,

leading to enhanced drug exposure. This implies that the drug stays in the therapeutic zone for an extended period of time, thereby possibly facilitating reduced dosages to produce the intended therapeutic result. Additionally, the improved clearance reduces the likelihood of drug accumulation and associated toxicities.

This review work seeks to give a detailed examination of biodegradable nanoparticles as new carriers for antiviral drug delivery. The focus will address the numerous types of biodegradable nanoparticles, their methods of action, practical applications, and the problems involved with their utilization. First, we will examine the many types of biodegradable nanoparticles, such as lipid-based, polymer-based, and other naturally occurring systems. Understanding the unique features of each kind is vital for selecting the optimal carrier for various antiviral medicines. Next, we will delve into the mechanisms by which these nanoparticles enhance antiviral efficacy. This includes their capacity to increase drug solubility, preserve therapeutic molecules from early degradation, facilitate targeted delivery to sick cells, and offer regulated release patterns. These pathways collectively contribute to overcoming the limits of conventional antiviral therapies. Additionally, the practicality of biodegradable nanoparticles in the treatment of different viral diseases will be investigated. We will review recent advancements in preclinical and clinical studies, highlighting how these nanocarriers have been utilized to improve therapeutic outcomes in diseases such as HIV, hepatitis, influenza, and emerging viral pathogens.

Despite their promising potential, the implementation of biodegradable nanoparticles in clinical settings faces several challenges. These include issues relating to large-scale manufacturing, assuring consistent quality and performance, possible immunogenicity, and navigating the complicated regulatory landscape for approval [18,19]. Addressing these obstacles is critical for the effective translation of nanoparticle-based therapeutics from the laboratory to the clinic. The goal of this review is to close the gap between clinical application, scientific research, and regulatory issues. By combining knowledge from these fields, we hope to present a comprehensive picture of the present situation and potential applications of biodegradable nanoparticles in antiviral drug delivery. Such an interdisciplinary approach is crucial for stimulating creativity and facilitating the discovery of safe and effective antiviral medicines.

2. Various Biodegradable Nanoparticles in Antiviral Drug Delivery

Biodegradable nanoparticles have come to prominence as a crucial discovery in antiviral medication delivery, presenting remedies to the constraints of existing therapeutic techniques. These nanoparticles, derived from materials that can naturally decompose within the body, serve as carriers that enhance the efficacy and safety of antiviral agents [20,21]. Their design allows for improved drug solubility, targeted delivery to infected cells, and controlled release profiles, thereby minimizing systemic toxicity and reducing the potential for drug resistance. This section digs into the numerous kinds of biodegradable nanoparticles applied in antiviral therapeutics (see Figure 2), evaluating their distinct features and contributions to enhancing medical treatments. The selection of an appropriate biodegradable nanoparticle system for antiviral drug delivery depends on several factors, including biocompatibility, drug-loading capability, durability, and modulated release features. Different nanoparticle types, such as PLGA-based, chitosan-based, PEGylated, liposomal, and protein-based nanoparticles, offer distinct advantages and limitations in antiviral applications. PLGA nanoparticles, for instance, are widely used due to their FDA approval and ability to provide sustained drug release, whereas chitosan-based nanoparticles are preferred for their mucoadhesive properties, enhancing drug absorption. PEGylation is commonly employed to extend circulation time and reduce immune clearance, while liposomal and protein-based nanoparticles offer high biocompatibility and drug-loading potential [20,22,23]. Table 2 provides a comparative analysis of these biodegradable nanoparticle types, highlighting their compositions, advantages, disadvantages, and common applications in antiviral therapy.

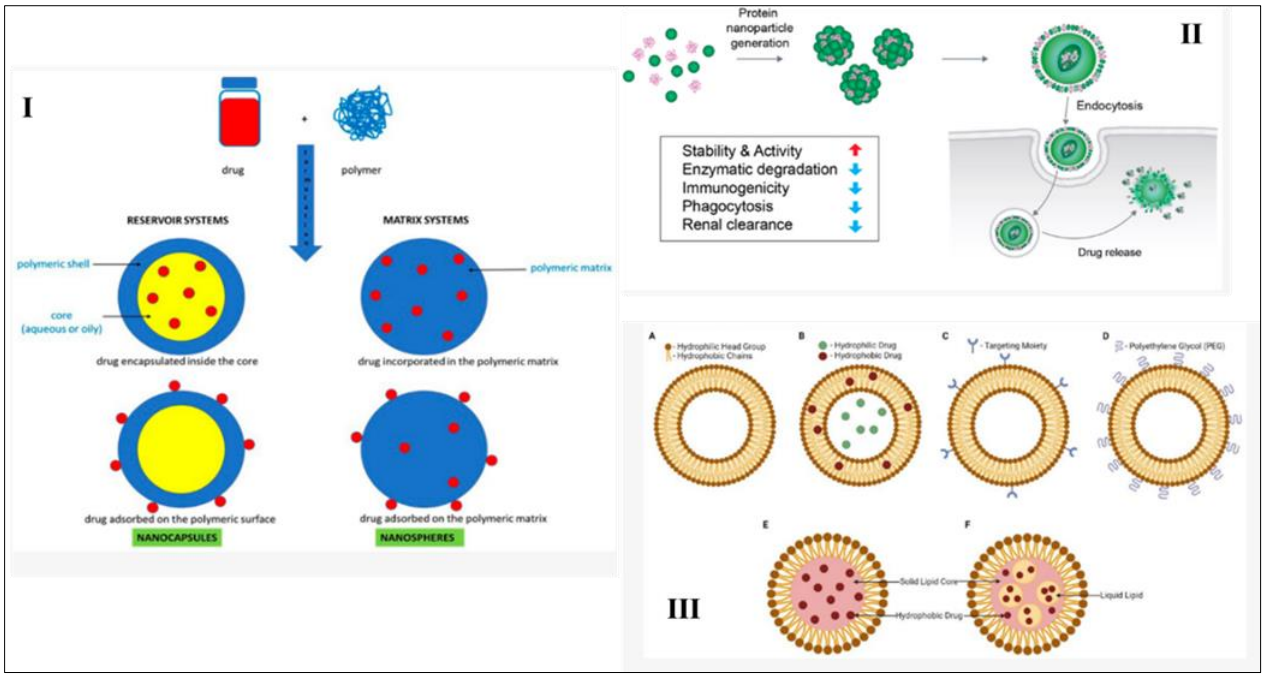

Figure 2 (I) Types of polymeric nanoparticles according to the composition. Reproduced with permission from Ref [21]. (II) Delivery of protein nanoparticle to the cell. Intracellular delivery of insoluble drugs by protein nanoparticles. Reproduced with permission from Ref [23]. (III) Visual illustration of the structures and composition of various LNPs. (A) Liposome. (B) Drug-loaded liposome. (C) Targeted liposome. (D) PEGylated liposome. (E) Solid lipid nanoparticle. (F) Nanostructured lipid carrier. Reproduced with permission from Ref [19]

Table 2 Comparison of Biodegradable Nanoparticle Types for Antiviral Drug Delivery

Nanoparticle Type	Composition	Advantages	Disadvantages	Applications
PLGA (Poly(lactic-co-glycolic acid))	Copolymer of lactic and glycolic acids	- Biodegradable and biocompatible - Regulated and prolonged drug delivery - FDA-approved for various applications	- Potential for acidic degradation products - Possible initial burst release	Delivery of small molecules, proteins, and vaccines
Chitosan-Based Nanoparticles	Derived from chitin, a natural polysaccharide	- Biodegradable and biocompatible - Mucoadhesive properties enhance drug absorption - Intrinsic antimicrobial activity	- Limited solubility at neutral pH - Variable degree of deacetylation affects consistency	Oral and nasal delivery systems
PEGylated Nanoparticles	Nanoparticles coated with polyethylene glycol (PEG)	- Increased circulation time - Reduced immunogenicity - Enhanced solubility of hydrophobic drugs	- Potential for PEG-related immune reactions - Possible interference with cellular uptake	Prolonged systemic delivery
Liposomal Nanoparticles	Phospholipid bilayer vesicles	- Biocompatible - Capable of encapsulating both hydrophilic and	- Potential for rapid clearance by the reticuloendothelial system	Delivery of nucleic acids and chemotherapeutic agents

		hydrophobic drugs - Enhanced drug stability	- Stability issues during storage	
Protein-Based Nanoparticles	Proteins such as albumin, gelatin, or silk fibroin	- Biodegradable - Ability to bind various drugs - Generally recognized as safe (GRAS) status for some proteins	- Potential for immunogenicity - Stability concerns under physiological conditions	Targeted drug delivery and vaccine carriers

Note: The selection of a specific nanoparticle type should be based on the desired drug release profile, target site, and potential immunogenicity.

The development of biodegradable nanoparticles as drug delivery systems has undergone significant transformation over the past few decades, driven by advances in materials science and nanotechnology. From early implant devices and synthetic biodegradable polymers to more sophisticated micelles, liposomes, and nanoparticles, these systems have evolved to enhance drug bioavailability, control drug release, and improve targeted delivery. Figure 3 illustrates this chronological progression, underscoring the transition from bulk drug delivery systems to nanoscale platforms that are revolutionizing antiviral therapies.

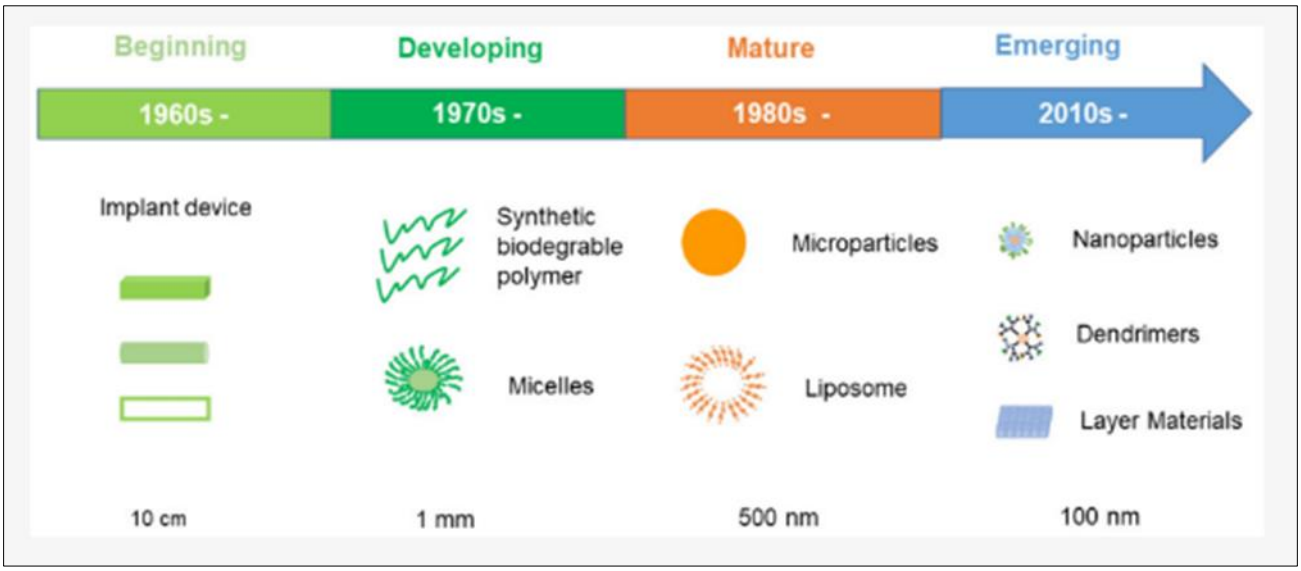

Figure 3 Evolution of biodegradable drug delivery systems over the decades, showing the transition from early implant devices in the 1960s to advanced nanoscale platforms such as nanoparticles, dendrimers, and layer materials in the 2010s. Reproduced from Ref [23] with permission

2.1. Polymeric Nanoparticles (PNPs)

Polymeric nanoparticles (PNPs) have received substantial research focus in antiviral drug delivery systems owing to their flexibility, biocompatibility, and capacity to boost therapeutic effectiveness. PEGylated nanoparticles, chitosan-based nanoparticles, and poly (lactic-co-glycolic acid) (PLGA) are notable among the several kinds of PNPs due to their special features and uses [24].

2.1.1. PLGA (Poly (lactic-co-glycolic acid)) Nanoparticles

The United States Food and Drug Administration (FDA) has authorized PLGA, a biodegradable and biocompatible copolymer, for a variety of therapeutic uses [25]. Its excellent safety profile and customizable degradation rates make it a good choice for medication delivery systems. PLGA nanoparticles can encapsulate a wide spectrum of antiviral medicines, preserving them from premature breakdown and permitting regulated release. This regulated release method assures prolonged therapeutic levels of the medicine, potentially lowering dose frequency and boosting patient compliance. The versatility of PLGA-based nanoparticles has been demonstrated in various studies, highlighting their potential in delivering antiviral therapeutics effectively [14,24,26].

2.1.2. Chitosan-Based Nanoparticles

Chitosan, a natural polysaccharide derived from chitin, possesses unique properties that make it advantageous in antiviral drug delivery. Its cationic nature enables strong mucoadhesive interactions, particularly beneficial in targeting mucosal surfaces where many viral infections initiate [27]. By extending the nanoparticles' residence duration at the infection site, this mucoadhesive characteristic improves drug absorption and efficacy in therapy. Furthermore, better drug permeability is made possible by chitosan's biocompatibility and sealed junctions across epithelial cells. Studies have shown that chitosan-based nanoparticles can effectively deliver antiviral agents, improving their bioavailability and therapeutic outcomes [28,29].

2.1.3. PEGylated Nanoparticles

PEGylation, or the treatment of nanoparticles with polyethylene glycol (PEG), is a calculated tactic to enhance their pharmacokinetic characteristics. PEGylation gives a hydrophilic coating surrounding the nanoparticle, limiting opsonization by serum proteins and subsequent identification and clearance by the mononuclear phagocyte system. This "stealth" property prolongs the circulation period of the nanoparticles, allowing for greater accumulation at the target location. In the context of antiviral therapy, PEGylated nanoparticles can increase the transport of antiviral medicines to diseased tissues, boosting therapeutic efficacy while avoiding systemic adverse effects. Research indicates that PEGylated nanoparticles can evade immune detection effectively, making them promising carriers for antiviral drugs [30,31].

2.2. Lipid-Based Nanoparticles (LNPs)

Lipid-based nanoparticles, or LNPs, have become a popular and efficient antiviral drug delivery system with special benefits for improving therapeutic effectiveness and safety. LNPs utilized as mRNA vaccine carriers, liposomes, and solid lipid nanoparticles (SLNs) have demonstrated the most promise among the several types of LNPs.

2.2.1. Liposomes

These are sphere-shaped vesicles made of one or more bilayers of phospholipid enclosing an aqueous core. Their structural resemblance to biological membranes enables for effective encapsulation and distribution of both hydrophilic and hydrophobic medicines. A famous example is AmBisome, a liposomal version of amphotericin B, principally used as an antifungal drug. AmBisome's liposomal encapsulation enhances drug stability and reduces toxicity, enabling higher dosing with improved safety profiles. While its primary indication is for fungal infections, the liposomal delivery system exemplifies the potential of liposomes in antiviral therapies by improving pharmacokinetics and minimizing adverse effects [32,33].

2.2.2. Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles are submicron-sized particles composed of biocompatible and biodegradable lipids that remain solid at both room and body temperatures. SLNs offer several advantages, including high drug loading capacity, improved stability, and controlled drug release. Their solid lipid matrix protects encapsulated antiviral agents from degradation, enhancing bioavailability and therapeutic efficacy. Studies have demonstrated that SLNs can effectively deliver antiviral drugs, improving their pharmacokinetic profiles and reducing systemic toxicity. For instance, SLNs have been investigated for antiretroviral drug delivery, showing enhanced drug stability and sustained release properties, which are crucial for effective HIV treatment [34,35].

According to Pandey et al. [35] surfactants play a crucial role in stabilizing the lipid matrix of SLNs by reducing interfacial tension between the lipid core and the surrounding aqueous phase. They form a protective layer around the lipid nanoparticles, preventing particle aggregation and enhancing colloidal stability (see Figure 4). This stabilization is crucial for maintaining the structural integrity and functionality of SLNs in drug delivery applications. Additionally, surfactants can improve drug loading efficiency and control the release of encapsulated molecules by modulating the surface properties of the lipid carriers.

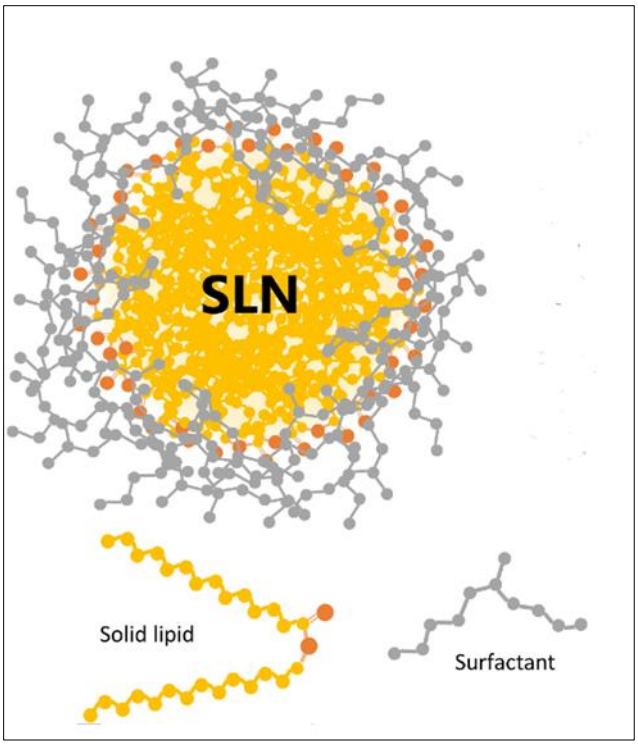

Figure 4 Schematic illustration of a SLN and a NLC stabilized through steric hindrance by a neutral surfactant (gray). Oxygen atoms present in the solid and liquid lipids are depicted in orange. Reproduced with permission from Ref [33]

2.2.3. mRNA Vaccine Carriers

Lipid nanoparticles are essential mRNA delivery carriers, as demonstrated by the present effectiveness of mRNA vaccinations against COVID-19. LNPs shield the fragile mRNA compounds from enzymatic breakdown and enable their absorption by host cells, where the mRNA is converted into viral antigens, prompting an immunological response. The SARS-CoV-2 spike protein mRNA is encapsulated and delivered by LNPs in the Moderna COVID-19 and Pfizer-BioNTech vaccines. Usually made up of cholesterol, phospholipids, ionizable lipids, and polyethylene glycol (PEG)-lipid conjugates, these LNPs improve stability, delivery effectiveness, and biocompatibility [15,36,37]. The design and composition of these LNPs have been optimized to achieve robust immune responses with a favorable safety profile.

2.3. Protein-Based Nanoparticles

Consequent to their great biocompatibility and intrinsic biodegradability, protein-based nanoparticles have attracted a lot of interest in the field of antiviral medication delivery. Interestingly, protein-based nanoparticles like albumin and gelatin have shown a great deal of potential as antiviral drug carriers.

2.3.1. Albumin-based nanoparticles (ANPs)

Albumin, a naturally occurring serum protein, offers several advantages when utilized as a nanoparticle for drug delivery. Its non-immunogenicity and biocompatibility make it a good choice for therapeutic uses. Additionally, albumin's capacity to bind different medicines boosts the dissolvability and stability of hydrophobic antiviral agents, enhancing their efficient transport to target areas [38,39]. The nanoparticle albumin-bound (nab) technology leverages these properties, enabling the noncovalent binding of hydrophobic chemotherapy drugs to albumin, thereby improving their therapeutic efficacy [38].

2.3.2. Gelatin-based nanoparticles (GNPs)

GNPs, or gelatin-based nanoparticles, have also become popular as flexible drug delivery vehicles. Derived from collagen, gelatin has good biocompatibility and is biodegradable, which makes it appropriate for use in medicine. Antiviral medications are among the many therapeutic compounds that GNPs can encapsulate. By modifying the manufacturing procedure, their drug release profile, surface charge, and size can be customized for particular uses [40,41]. This flexibility makes it possible to administer antiviral drugs effectively, which may improve their therapeutic effects.

Protein-based nanoparticles have been investigated as a potential solution to the problems with traditional HIV treatments. Protein-derived nanoparticles are one of the nanotechnology-based strategies being researched to enhance the administration of anti-HIV medications. By reducing systemic toxicity, targeting certain cells, and increasing drug absorption, these tactics may improve patient outcomes. Likewise, the use of protein-based nanoparticles presents a viable therapeutic intervention option for hepatitis infections [41]. These nanoparticles may increase the effectiveness of therapy against hepatitis viruses by enabling the controlled release and targeted administration of antiviral medicines. The biocompatibility and biodegradability of protein-based carriers further support their potential use in clinical settings, aiming to reduce adverse effects and enhance patient compliance.

2.4. Stimuli-Responsive and Hybrid Nanoparticles

Stimuli-responsive and hybrid nanoparticles have generated a lot of research interest in antiviral drug delivery because of their capacity to adapt to specific environmental cues and so improve therapeutic efficacy. Among these, pH-sensitive nanoparticles and nanozymes stand out for their innovative approaches in targeting infected cells and mimicking enzymatic antiviral activities, respectively.

2.4.1. pH-Sensitive Nanoparticles

By design, the unique pH differences between healthy and diseased tissues are exploited by pH-sensitive nanoparticles. Targeted medication release is made possible by these nanoparticles' ability to adapt structurally to the acidic milieu seen in infected or inflammatory tissues while remaining stable at physiological pH. According to Binauld and Stenzel [42], such pH-responsive behavior ensures that antiviral agents are preferentially released at sites of infection, thereby minimizing systemic side effects. For instance, since the pH at the replication sites of viral infections is frequently lower, pH-sensitive carriers can be made to release their payload only in these acidic environments, increasing the antiviral drugs' therapeutic index.

Polymers that degrade in acidic conditions or suffer structural changes are frequently used in the construction of pH-sensitive nanoparticles. pH-responsive polymeric carriers have been demonstrated to increase the effectiveness of drug administration in vivo, enabling targeted drug distribution and fewer adverse responses, according to Yang et al.'s findings [43]. Since the nanoparticles may be engineered to release their therapeutic cargo in response to these precise pH changes, this method is especially advantageous for treating illnesses when the pathogen modifies the local pH.

2.4.2. Nanozymes: Catalytic Nanostructures Mimicking Enzymatic Antiviral Activity

Nanozymes are nanomaterials with intrinsic enzyme-like properties capable of catalyzing biochemical reactions. In antiviral therapy, nanozymes can be designed to mimic natural enzymes that degrade viral components or inhibit viral replication. Nanozymes are incredibly powerful for antiviral applications because of their small size, which increases their contact with microbial organisms [44]. For example, certain nanozymes have been developed to mimic proteases that cleave viral proteins essential for replication, thereby halting the infection process. Additionally, nanozymes can be engineered to produce reactive oxygen species that damage viral particles, offering a broad-spectrum antiviral strategy [45].

The versatility of nanozymes extends to their stability and tunable activity under various physiological conditions, which are advantageous over natural enzymes that may be sensitive to environmental changes. From the findings of Singh et al. [46], nanozymes have demonstrated significant potential in viral diagnostics and therapy, offering a promising avenue for the development of novel antiviral strategies. Their ability to be engineered for specific catalytic activities allows for the customization of treatments against a wide range of viral pathogens.

3. Mechanisms of Biodegradability and Drug Release

Understanding the mechanisms of biodegradability and drug release in biodegradable nanoparticles is essential for optimizing antiviral therapies. To ensure safe removal, these nanoparticles are designed to break down within the body into non-toxic metabolites. Environmental circumstances, molecular weight, and polymer composition all affect the breakdown process, which in turn affects the rate and pattern of drug release. By adjusting these parameters, antiviral medicines can be released in a controlled and sustained manner, improving therapeutic efficacy and lowering systemic side effects [16,21]. This section delves into the intricate processes governing the biodegradation of nanoparticles and the subsequent dispensing of drugs in capsules, providing insights into their design and application in antiviral treatments.

Different biodegradable nanoparticles employ various drug release mechanisms depending on their composition and intended therapeutic use. Some nanoparticles rely on diffusion-controlled release, where the drug gradually migrates through the polymer matrix, while others degrade enzymatically or react to outside stimuli such variations in temperature or pH [47]. Table 3 provides a comparative summary of the major biodegradable nanoparticle types used in antiviral therapy, highlighting their composition, drug release mechanisms, and key findings from the literature.

Table 3 Drug Release Mechanisms of Biodegradable Nanoparticles in Antiviral Therapy

Nanoparticle Type	Composition	Drug Release Mechanism	References
PLGA (Poly (lactic-co-glycolic acid))	Copolymer of lactic and glycolic acids	- **Diffusion**: Drug molecules migrate through the polymer matrix. - **Erosion**: Hydrolytic degradation of the polymer backbone releases the drug. - **Swelling**: Polymer matrix absorbs water, facilitating drug release.	Ref [48]
Chitosan-Based Nanoparticles	Natural polysaccharide derived from chitin	- **Ionic interactions**: Electrostatic attraction between the positively charged chitosan and negatively charged drug molecules. - **pH-sensitive release**: Drug release rate varies with pH changes, enhancing release in acidic environments.	Ref [49]
Liposomal Nanoparticles	Phospholipid bilayer vesicles	- **Encapsulation**: Drugs are contained within the aqueous core or lipid bilayer. - **Fusion with cell membranes**: Liposomes merge with cellular membranes, releasing the drug into the cytoplasm. - **pH-triggered release**: Acidic environments induce drug release.	Ref [15]
Protein-Based Nanoparticles	Proteins such as albumin, gelatin, or silk fibroin	- **Enzymatic degradation**: Proteolytic enzymes break down the protein matrix, releasing the drug. - **pH-responsive release**: Changes in pH alter protein structure, triggering drug release. - **Thermal sensitivity**: Elevated temperatures can induce conformational changes, facilitating drug release.	Ref [50]

Note: The choice of nanoparticle and its drug release mechanism should align with the specific antiviral therapy requirements, considering factors like the drug's physicochemical features and the target location environment.

3.1. Enzymatic Degradation

Poly (lactic-co-glycolic acid) (PLGA) nanoparticles are widely used in antiviral drug delivery systems, and their biodegradability and drug release processes depend heavily on enzymatic breakdown [51]. PLGA is a copolymer made up of lactic and glycollic acid monomers connected by ester linkages. The degradation of PLGA primarily occurs through hydrolysis of these ester linkages, leading to the breakdown of the polymer into its constituent monomers. These monomers are subsequently metabolized via the Krebs cycle into carbon dioxide and water, which are naturally eliminated from the body. Esterases, enzymes that catalyze the breaking of ester bonds, frequently assist hydrolytic degradation, speeding up the process [51,52].

The rate of PLGA disintegration, and thus the release profile of the encapsulated antiviral drug, can be adjusted by adjusting the copolymer ratio of glycollic acid to lactic acid. For instance, a higher glycolic acid content generally results in a more hydrophilic polymer, which absorbs water more readily, leading to faster hydrolytic degradation. Conversely, elevating the lactic acid level improves the polymer's hydrophobicity and crystallinity, decreasing the degradation rate. This programmable degrading feature enables the construction of PLGA-based nanoparticles with regulated drug delivery kinetics, which is critical for sustaining therapeutic drug levels over a chosen period [51,53].

In the setup of antiviral treatment, the enzymatic breakdown of PLGA nanoparticles guarantees that antiviral drugs are released at the target location in a sustained and controlled manner, increasing therapeutic efficacy while reducing systemic side effects. Furthermore, the biodegradability and biocompatibility and of PLGA make it a promising alternative for designing safe and effective drug delivery systems [54].

3.2. Hydrolytic Degradation

Hydrolytic degradation is a crucial process in the performance of pH-sensitive nanoparticles (NPs) intended for antiviral medication delivery, especially in acidic virus environments. These nanoparticles are made to remain stable at physiological pH values, but rapidly degrade in acidic environments, such as those present in tissues that are infected or intracellular compartments where viruses multiply [55]. This tailored degradation guarantees that antiviral medicines are released exactly at the site of infection, increasing treatment efficacy while reducing widespread side effects.

The process of hydrolytic degradation involves the cleavage of chemical bonds within the nanoparticle matrix in the presence of water, a reaction that is significantly accelerated in acidic environments. According to Lim et al. [56], pH-sensitive nanoparticles are designed to exploit the pH differences between healthy and diseased tissues, facilitating site-specific drug release. For instance, polyketal-based nanoparticles have been developed to degrade rapidly under acidic conditions, releasing their therapeutic payload in response to the lowered pH typical of viral infection sites. This method not only improves the drug's bioavailability at the target site, but also decreases the potential toxicity to healthy cells [57].

From the findings of Bazban-Shotorbani et al. [58], the incorporation of acid-labile linkages within the polymer backbone of nanoparticles has been shown to enhance the precision of drug release in acidic environments. These connections remain stable at neutral pH, but hydrolyze quickly under acidic circumstances, causing the nanoparticle to disassemble and release the encapsulated antiviral drugs. This strategy is particularly advantageous in treating viral infections where the pathogen induces an acidic microenvironment, as it allows for a more targeted therapeutic intervention [58].

3.3. Oxidative and Stimuli-Responsive Degradation

Oxidative and stimuli-responsive degradation mechanisms have emerged as critical approaches in the development of biodegradable nanoparticles for antiviral medication delivery. These systems are designed to respond to particular triggers, like reactive oxygen species (ROS), which are commonly seen in sick tissues. ROS-sensitive nanoparticles can accomplish localized and regulated drug release by leveraging the specific microenvironment of sick locations, increasing therapeutic efficacy while minimizing widespread adverse effects.

3.3.1. Reactive Oxygen Species-Sensitive Systems in Infected Tissues

Infected and inflamed tissues produce an excess of ROS, such as superoxide anions, hydrogen peroxide, and hydroxyl radicals. This abnormal ROS buildup can be used to cause the destruction of specially engineered nanoparticles. According to Ballance et al. [59], ROS-responsive polymer carriers provide tailored drug delivery, decreasing toxicity and adverse effects on normal cells while also managing drug release. When exposed to ROS, these polymers cleave their backbone or side chains, causing the nanoparticle to disassemble and release the encapsulated antiviral medicines. This focused release method guarantees that the therapeutic payload is mostly active in the diseased areas, increasing drug efficacy while reducing off-target consequences.

The design of ROS-sensitive nanoparticles often involves incorporating ROS-cleavable linkages, such as thioketals, into the polymer matrix. From to the findings of Ballance et al. [59], these connections are robust under normal physiological settings but rapidly breakdown when exposed to elevated ROS levels, allowing for controlled drug release. This method has been shown to improve therapeutic outcomes in a variety of disease models by limiting medication release to diseased areas with high ROS concentrations.[59].

3.4. Implications for Safety and Clearance

The biodegradability of nanoparticles plays a pivotal role in ensuring their safety and effective clearance from the body, thereby minimizing potential accumulation and associated toxicities. Biodegradable nanoparticles are engineered to break down into non-toxic byproducts that can be readily eliminated through physiological pathways, such as renal excretion. This degradation process is influenced by factors such as the surface features, size and composition of the nanoparticle.

According to Wei et al. [60], the nanoparticles' surface features, as well as the size significantly affect their blood residence time and organ-specific accumulation. Nanoparticles with optimized surface modifications can evade rapid clearance mechanisms, thereby enhancing their circulation time and therapeutic efficacy. However, it is crucial that these particles are eventually degraded and cleared to prevent long-term accumulation. From the findings of Mitchell et al. [15], creating nanoparticles with optimal clearance characteristics minimizes toxicity risks and reduces concerns of nanoparticle interference by decreasing the duration of exposure to these agents. This is particularly important in antiviral therapies, where prolonged presence of non-degradable nanoparticles could lead to adverse effects [15].

Furthermore, the safety profile of biodegradable nanoparticles is reinforced by their approval for pharmaceutical applications Regulatory bodies like the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) [61]. As noted by Singh et al. [62], the nanoparticles' composition, surface modifications, and size are critical factors influencing their biodistribution and clearance, which in turn impact their safety and efficacy profiles.

4. Targeting Strategies for Viral Infections

Effective antiviral therapies often hinge on the precise delivery of therapeutic agents to infected cells or tissues, thereby maximizing efficacy while minimizing systemic side effects. Targeting strategies in antiviral drug delivery are designed to enhance the specificity of treatment by directing antiviral agents to the exact location of viral activity [63]. These strategies encompass a range of approaches, including the exploitation of unique viral or host cell markers, receptor-mediated targeting, and the utilization of stimuli-responsive delivery systems. By employing such targeted methodologies, it is possible to improve the therapeutic index of antiviral drugs, reduce off-target effects, and potentially overcome challenges associated with drug resistance [63]. This section delves into the various targeting strategies employed in antiviral therapies, highlighting their mechanisms, applications, and the advancements that have propelled their development.

4.1. Receptor-Mediated Targeting

A key tactic in antiviral therapy is receptor-mediated targeting, which takes advantage of the inherent connections between viral infections and host cell receptors to improve the specificity and effectiveness of systems for drug delivery. Therapeutic drugs can be precisely targeted to infected cells by creating nanoparticles that bind to these receptors, enhancing treatment outcomes and reducing off-target effects [64]. This approach has been notably applied in the development of ACE2-targeted lipid nanoparticles (LNPs) for SARS-CoV-2 and CD4-targeted nanoparticles for HIV drug delivery. Different viral infections exploit unique host receptors for cell entry, and the specificity of antiviral treatment can be greatly improved by leveraging these receptor-ligand interactions. It is possible to design biodegradable nanoparticles to target receptors such as ACE2 (SARS-CoV-2), CD4 (HIV), and ASGPR (Hepatitis B), improving drug localization while minimizing off-target effects [64,65]. Table 4 provides a comparative summary of receptor-mediated targeting strategies for antiviral drug delivery, detailing the specific viral receptors, nanoparticle compositions, targeting ligands, and key findings from recent studies.

Table 4 Receptor-Mediated Targeting of Biodegradable Nanoparticles in Different Viral Infections

Targeted Receptor	Virus/Disease	Nanoparticle Composition	Targeting Ligand	Key Findings	References
ACE2 (Angiotensin-Converting Enzyme 2)	SARS-CoV-2	Solid Lipid Nanoparticles (SLNs)	Spike S1 Receptor Binding Domain (RBD)	Virus-mimicking particles (VMPs) functionalized with Spike S1 RBD can bind to ACE2 receptors, blocking SARS-CoV-2 entry into host cells.	Ref [66]
CD4 (Cluster of Differentiation 4)	HIV	Lipid-Based Nanoparticles (LNPs)	Anti-CD4 Antibodies	CD4-targeted LNPs enhance delivery of antiviral drugs like Indinavir to CD4+ T cells, increasing therapeutic efficacy.	Ref [67]

ASGPR (Asialoglycoprotein Receptor)	Hepatitis B	PLGA Nanoparticles	Galactose	Galactose-functionalized nanoparticles target ASGPR on hepatocytes, improving liver-specific drug delivery.	Ref [50]
Transferrin Receptor (TfR)	Neurotropic Viruses	PLGA Nanoparticles	Transferrin	Enhanced drug delivery to the brain by targeting TfR, improving therapeutic efficacy against neurotropic viruses.	Ref [49]
LDLR (Low-Density Lipoprotein Receptor)	Hepatitis C	Lipid-Based Nanoparticles	Apolipoprotein E (ApoE)	Increased uptake by liver cells due to LDLR-mediated endocytosis, leading to improved antiviral activity.	Ref [68]
Folate Receptor	Viral Infections in Folate-Rich Cells	Chitosan Nanoparticles	Folic Acid	Improved cellular uptake and antiviral efficacy in folate receptor-positive cells.	Ref [69]
Integrin Receptors	Various Viruses	Liposomal Nanoparticles	RGD Peptide	Increased binding and uptake by infected cells, enhancing antiviral drug potency.	Ref [70]

Note: The selection of targeting ligands and nanoparticle compositions is critical for enhancing the specificity and efficacy of antiviral therapies by directing therapeutic agents to virus-specific receptors.

4.1.1. ACE2-Targeted Lipid Nanoparticles for SARS-CoV-2

The main entrance receptor for SARS-CoV-2 is the angiotensin-converting enzyme 2 (ACE2), which promotes viral attachment and subsequent host cell infection. Leveraging this mechanism, researchers have developed ACE2-targeted LNPs to inhibit viral entry. According to Yathindranath et al. [64], LNP formulations designed to bind the SARS-CoV-2 spike protein demonstrated a 90% inhibition of pseudovirus infection in Calu-3 cells, a human airway epithelial cell line. These LNPs, referred to as LNP-Trap, were biocompatible at concentrations up to 1 mg/mL and effectively localized in the nasal cavity following intranasal administration in mice, suggesting a potential for localized treatment of SARS-CoV-2 in the upper respiratory tract [64].

In addition to direct viral inhibition, another approach involves downregulating host cell receptors essential for viral entry. Yathindranath et al. [64] also developed LNP-Trim formulations capable of reducing ACE2 and TMPRSS2 expression at both mRNA and protein levels by approximately 70% and 50%, respectively. This reduction resulted in over 90% inhibition of pseudovirus infection in vitro, highlighting the potential of receptor-targeted strategies in mitigating SARS-CoV-2 infection.

4.1.2. CD4-Targeted Nanoparticles for HIV Drug Delivery

The Human Immunodeficiency Virus (HIV) typically attacks CD4+ T cells by attaching to the CD4 receptor. Exploiting this pathway, researchers have engineered nanoparticles that specifically target CD4+ cells to deliver antiretroviral drugs more effectively [71]. CD4-targeted lipid nanoparticles containing the protease inhibitor Indinavir, for example, showed improved binding and distribution to CD4+ HIV host cells, according to research by Freeling et al. [72]. This targeted delivery significantly improved the anti-HIV efficacy of Indinavir, even with limited exposure time, suggesting a promising strategy for enhancing antiretroviral therapy [72].

Further advancements include the development of CD4+ T cell-mimicking nanoparticles designed to neutralize HIV-1 and deliver cytotoxic agents specifically to infected cells. According to Campbell et al. [73], these nanoparticles, termed TNP, demonstrated substantial breadth and potency against diverse HIV-1 strains, including those resistant to multiple broadly neutralizing antibodies. By mimicking the natural target of HIV-1, TNPs offer a novel therapeutic direction that exploits the virus's dependency on CD4 binding, potentially minimizing the development of viral resistance [73].

4.2. pH-Responsive and Smart Nanoparticles

Smart and pH-responsive nanoparticles have become a viable way to target viral illnesses, especially those caused by viruses like Ebola and influenza. By taking use of the acidic microenvironments found in specific intracellular compartments, these nanoparticles are designed to improve therapeutic efficacy and enable targeted drug delivery.

4.2.1. Targeting Acidic Intracellular Compartments in Influenza and Ebola-Infected Cells

Influenza and Ebola viruses utilize the host cell's endocytic pathways for entry and replication. During this process, viral particles are internalized into endosomes, which subsequently acidify to facilitate viral fusion and release into the cytoplasm. This acidification presents a unique opportunity for targeted drug delivery. Huang et al. [74] claim that pH-responsive nanoparticles may be made to stay stable at physiological pH while undergoing structural alterations in acidic environments, like endosomes, which allows the encapsulated antiviral medicines to be released exactly where they are required.

To stop viral replication early, pH-responsive nanoparticles can be designed to discharge their payload in these acidic endosomal compartments. For example, the Ebola virus enters host cells through macropinocytosis and moves through endosomal compartments where a drop in pH causes conformational changes necessary for viral fusion and entry into the cytoplasm [75]. From the findings of Jhaveri & Torchilin [68], mesoporous silica nanoparticles functionalized for pH-sensitive binding have demonstrated potential in delivering therapeutic agents directly into the acidic intracellular compartments, effectively targeting the viral replication sites.

Similar to this, influenza viruses can enter host cells by endocytosis facilitated by receptors. Once endosomes are acidified, the virus can uncoat and release its RNA into the cytoplasm of the host cell. It is possible to disrupt this process by using pH-responsive nanoparticles. Recent developments indicate that influenza virus reproduction can be effectively inhibited by using nanoparticles that are engineered to dismantle or release their therapeutic payload when exposed to the acidic pH of endosomes. This is achieved by preventing the virus from undergoing the essential acid-induced conformational changes [76,77].

The design of these smart nanoparticles often involves materials that undergo pH-induced transformations, which includes the cleavage or protonation of acid-labile bonds, thereby triggering the release of the antiviral drug specifically in acidic environments. By lowering off-target drug release, this tailored strategy beyond increasing the therapeutic agent's concentration at the infection site it also reduces systemic side effects. The use of pH-responsive polymers in nanoparticle design has been demonstrated to increase the specificity and effectiveness of drug delivery systems in acidic intracellular settings, according to Dai et al.'s findings [78].

4.3. Nanoparticle-Based Immunomodulation

A promising method for boosting antiviral immune responses is nanoparticle-based immunomodulation, especially with the creation of vaccination adjuvants based on nanoparticles. These adjuvants are designed to improve the body's immune reaction to vaccines by enhancing antigen presentation and stimulating both innate and adaptive immunity [79]. One notable example is the Matrix-M adjuvant, developed by Novavax, which comprises nanoparticles formulated from saponins extracted from the bark of the *Quillaja saponaria* tree, combined with cholesterol and phospholipids. This composition forms immune-stimulating complexes that enhance the immune system's ability to present and deliver antigens. The Novavax COVID-19 vaccine is one of the vaccine candidates that has used the Matrix-M adjuvant. It has been shown to improve the immune response by boosting the recruitment of antigen-presenting cells and encouraging a strong generation of neutralizing antibodies [80].

According to research, nanoparticles can be used in vaccine formulations for two purposes: as adjuvants to boost the vaccines' immunological effectiveness and as carriers to carry and protect antigens. To strengthen the body's defence against viral infections, for example, it has been reported that gold nanoparticles, carbon nanotubes, silica particles, polymers, and liposome nanoparticles can trigger cytokine and antibody responses. Nanoparticle-based adjuvants boost immune responses by improving antigen transport to immune cells and potentiating innate immune responses.

Nanoparticles can replicate pathogen-associated chemical patterns, triggering pattern recognition receptors on immune cells, resulting in a more powerful and prolonged immune system responses [80,81].

5. Applications in Specific Viral Diseases

The application of biodegradable nanoparticles in antiviral therapy has shown significant promise across various viral diseases. These nanocarriers can be designed to improve the transport and effectiveness of antiviral medicines, providing targeted and long-term therapeutic benefits. Generally, biodegradable nanoparticles have revolutionized drug delivery by offering versatile platforms for the treatment of various diseases. Their ability to encapsulate therapeutic agents, improve bioavailability, and enable controlled drug release makes them suitable for addressing both chronic and infectious diseases. Beyond antiviral therapy, these nanoparticles have shown immense potential in delivering drugs for diabetes, cancer, cardiovascular diseases, and vaccine development. Figure 5 presents a comprehensive overview of the wide-ranging biomedical applications of biodegradable nanoparticles, underscoring their significance in modern medicine. However, this section investigates the specific use of biodegradable nanoparticles in the remediation of certain viral infections, focusing on their mechanisms of action, therapeutic advantages, and obstacles in clinical applications.

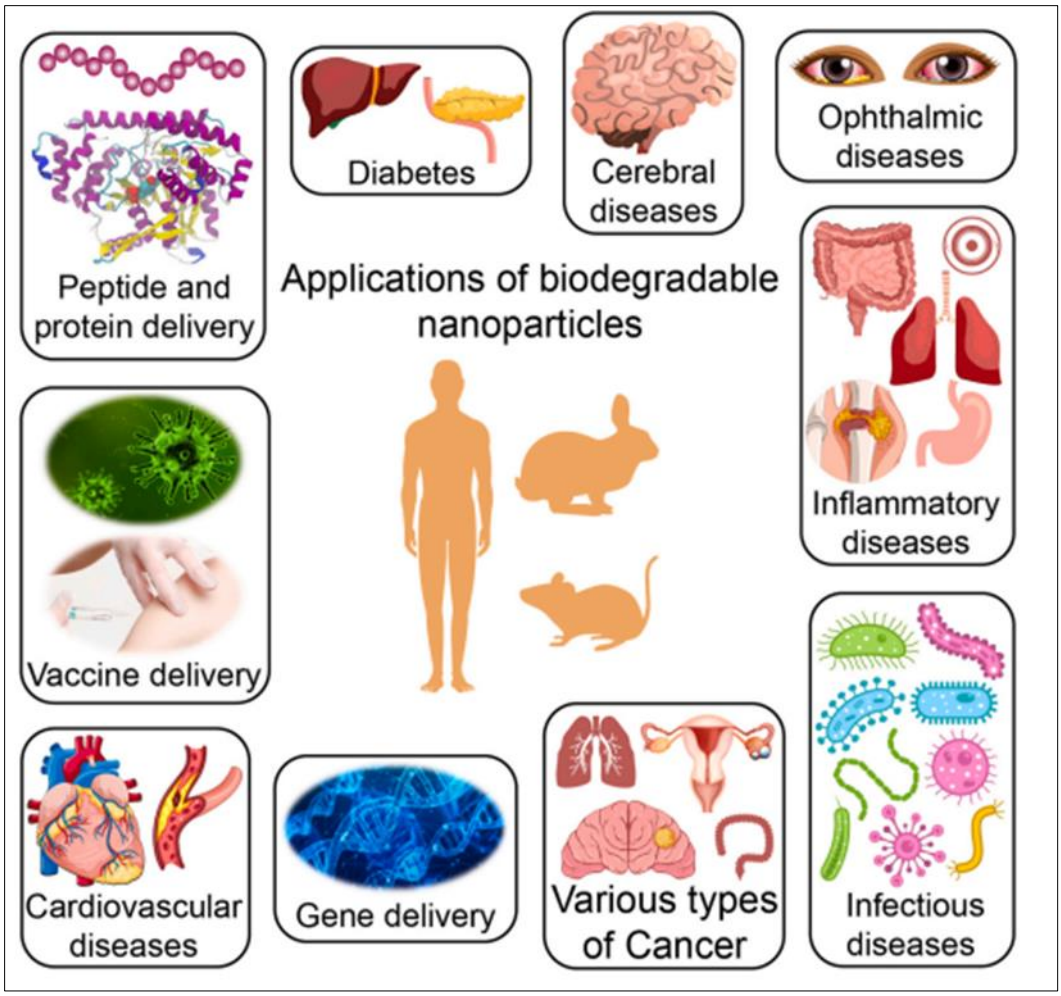

Figure 5 Biomedical applications of biodegradable nanoparticles in drug delivery systems, highlighting their multifunctional roles in the treatment of various diseases. Reproduced from Ref [82] with permission

5.1. Applications in HIV/AIDS

The integration of biodegradable nanoparticles into HIV/AIDS therapy has opened new avenues for enhancing the efficacy and delivery of antiretroviral treatments. While lipid nanoparticles (LNPs) have been looked at for delivering small interfering RNA (siRNA), poly(lactic-co-glycolic acid) (PLGA)-based nanoparticles have been researched for prolonged antiretroviral medication release [83].

5.1.1. PLGA-Based Nanoparticles for Sustained Antiretroviral Drug Release

PLGA, a biodegradable and biocompatible polymer, has been utilized to develop nanoparticles that encapsulate antiretroviral drugs, aiming to provide sustained release and improve therapeutic outcomes. In a study by Destache et al. [84], PLGA nanoparticles were formulated to contain a combination of antiretroviral drugs: ritonavir (RTV), lopinavir (LPV), and efavirenz (EFV). The nanoparticles exhibited an average size of 262 nm and a drug loading efficiency of 4% (w/v). When these nanoparticles were introduced to peripheral blood mononuclear cells (PBMCs), intracellular drug levels peaked on day 4 and remained detectable up to day 28, with no observed cytotoxicity. This sustained release profile suggests that PLGA-based nanoparticles could reduce dosing frequency and enhance patient adherence to antiretroviral therapy [84].

Yang et al. [85] conducted another investigation showing the possibility of PLGA nanoparticles in delivering many antiretroviral drugs with different physicochemical characteristics. Their study highlighted that core-shell type PLGA nanoparticles could effectively encapsulate and release combinations of antiretroviral drugs, supporting the feasibility of this platform for sustained HIV-1 prevention and treatment.

5.1.2. Functionalized PLGA Nanoparticles for Targeted HIV Therapy

While PLGA nanoparticles provide sustained drug release, their effectiveness can be enhanced by incorporating targeting moieties such as antibodies, peptides, or small molecules that bind selectively to HIV-infected cells. CD4+ T cells, macrophages, and dendritic cells serve as major viral reservoirs, making them key targets for nanoparticle-based drug delivery. According to Xu et al. [86], functionalizing PLGA nanoparticles with mannose residues significantly enhances their uptake by HIV-infected macrophages, which express mannose receptors. Their study demonstrated that ritonavir-loaded mannose-functionalized PLGA nanoparticles exhibited 4.3-fold greater intracellular drug accumulation compared to non-targeted nanoparticles, effectively suppressing viral replication in infected macrophages.

To improve drug transport to infected T cells, Tang et al. [87] also investigated the use of monoclonal antibodies (mAbs) targeting CD4 receptors attached to PLGA nanoparticles. Their results showed that CD4-targeted nanoparticles delivered tenofovir with 7-fold greater specificity to infected T cells compared to non-functionalized particles, reducing viral loads more efficiently in vitro.

5.1.3. Lipid Nanoparticles for siRNA Delivery to Block Viral Replication

Through the targeting and degradation of certain viral mRNA sequences, RNA interference (RNAi) techniques—in particular, siRNA—have been investigated as a means of inhibiting HIV replication. However, stability and delivery issues are obstacles to siRNA's clinical use. Lipid nanoparticles have shown promise as carriers to deal with these problems. LNPs have the ability to encapsulate siRNA, preventing its degradation and enabling its transport to target cells, according a review by Friedrich & Aigner [88]. Functionalization of LNPs allows for targeted delivery, enhancing the therapeutic efficacy of siRNA-based interventions against HIV.

Clinical studies using LNP-mediated siRNA transport have demonstrated promise in reducing viral replication and modifying immune responses. For example, research has shown that LNPs may efficiently transfer siRNA to immune cells, which in turn can inhibit HIV-1 replication in vitro [89,90]. Although these results are promising, further clinical research is required to completely determine the safety and effectiveness of LNP-based siRNA treatments in HIV-positive patients.

5.1.4. LNPs for Targeting Ligands in the Delivery of siRNA

The capacity of nanoparticles to deliver siRNA molecules to HIV-infected cells specifically while sparing healthy tissues is essential for the efficacy of siRNA therapy in HIV treatment. Because of their biocompatibility and capacity to bond with cell membranes, LNPs have been extensively investigated as effective siRNA carriers. LNPs conjugated with anti-gp120 antibodies effectively targeted HIV-infected T cells, according to a research by Cisneros et al. [89]. These LNPs encapsulated siRNA designed to silence the CCR5 co-receptor, a key protein involved in HIV entry. The targeted LNPs showed 6-fold greater siRNA uptake in HIV-infected cells compared to non-targeted controls, effectively reducing viral replication in vitro.

Agbosu et al. [91] looked into another promising strategy in which LNPs functionalized with cell-penetrating peptides (CPPs) like Tat peptide enhanced siRNA distribution across the blood-brain barrier (BBB), focusing on HIV reservoirs in the central nervous system (CNS). Their study showed that Tat-conjugated LNPs delivered siRNA with 9-fold higher

efficiency to HIV-infected glial cells in the brain compared to conventional LNPs, providing a potential strategy to treat HIV-associated neurocognitive disorders [91].

5.2. Hepatitis B and C

Significant progress has been made in treating Hepatitis B and C with nanotechnology, especially in the areas of liposomal delivery systems and PEGylated nanoparticles, which improve target specificity and therapeutic efficiency.

5.2.1. Liposomal Delivery Systems

Liposomal encapsulation of antiviral agents, such as tenofovir and interferon, has been explored to help enhance drug transport and treatment results for Hepatitis B and C infections. Antiviral therapies can have their bioavailability increased, their degradation prevented, and their targeted delivery to hepatocytes facilitated by liposomal formulations [21,54]. One research by Liu et al. [92], for example, showed that apolipoprotein A1-modified liposomes significantly increased the hepatic uptake of baicalin, a compound with anti-HBV activity, thereby enhancing its antiviral efficacy.

5.2.2. PEGylated Nanoparticles for Liver-Targeted Delivery

Polyethylene glycol (PEG) modification, or PEGylation, of nanoparticles has been employed to improve the pharmacokinetics and liver-targeting capabilities of antiviral therapies. PEGylation improves nanoparticle stability and circulation duration, enabling more effective liver delivery [93]. Clinical trials have investigated the combination of PEGylated interferon alfa with tenofovir disoproxil fumarate in patients with chronic Hepatitis B-related liver fibrosis, aiming to enhance therapeutic outcomes.

5.2.3. Clinical Case Studies

In a phase 2 clinical trial, 232 chronic Hepatitis B patients were randomized to receive either JNJ-56136379 monotherapy, nucleos(t)ide analogue (NA) monotherapy, or a combination of JNJ-56136379 and NA. The purpose of the study was to assess how well various therapies worked to inhibit the virus [94]. Another clinical study compared tenofovir monotherapy with PEGylated interferon and tenofovir in persons with chronic Hepatitis B [95]. Data of 143 CHB patients were analyzed in this study. The study compares the effectiveness of pegylated interferon (Peg-IFN) monotherapy and its combination with tenofovir (TDF) in chronic hepatitis B patients. Results show that combination therapy significantly improves virological suppression, biochemical response, and HBsAg loss compared to monotherapy. Key predictors of treatment response include baseline liver inflammation, HBV DNA levels, age, ALT levels, and fibrosis severity. The findings suggest that Peg-IFN plus TDF enhances treatment outcomes and is better suited for patients with favorable response factors [95].

These investigations highlight how delivery methods based on nanoparticles may improve the effectiveness of antiviral treatments for Hepatitis B and C. The formulations of liposomal and PEGylated nanoparticles provide prospective paths towards more efficient treatment of these persistent viral infections by enhancing targeted administration, drug stability and bioavailability.

5.3. Influenza and Emerging Viral Infections

The prevention and treatment of influenza and newly developing viral illnesses including SARS-CoV-2, Zika, and Ebola have greatly improved with the use of biodegradable nanoparticles. The customized delivery methods provided by these nanocarriers improve the effectiveness of medications and vaccinations.

5.3.1. Solid Lipid Nanoparticles (SLNs) for Pulmonary Drug Delivery in Respiratory Infections

Since the respiratory tract is the main site of infection for SARS-CoV-2 and influenza, solid lipid nanoparticles (SLNs) have been investigated as a potentially effective method of delivering antiviral drugs directly to this organ. Antiviral medications can be encapsulated in SLNs, which are made of biocompatible and biodegradable lipids. This prevents the pharmaceuticals from breaking down and allows for regulated release. Their lipid-based nature allows for efficient fusion with pulmonary surfactant, enhancing drug absorption in the lungs [96].

Studies have demonstrated that SLNs can improve the bioavailability of antiviral drugs administered via the pulmonary route. For instance, research on SLN formulations for delivering antiviral agents against respiratory infections has shown enhanced drug retention in the lungs and improved therapeutic outcomes [97,98]. These results imply that by guaranteeing greater local drug concentrations at the infection site, SLNs may be a useful treatment approach for respiratory infections.

5.3.2. RNA-Based Nanoparticle Vaccines

The development and use of RNA-based vaccines, especially those that use messenger RNA (mRNA) encapsulated within lipid nanoparticles (LNPs), have increased since the advent of SARS-CoV-2 [99]. As delivery vehicles, these LNPs shield the delicate mRNA strands from deterioration and make it easier for host cells to absorb them. Once within the cells, the mRNA triggers an immune response by telling the cellular machinery to manufacture viral antigens. Two well-known examples of this technique are the COVID-19 vaccines produced by Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2) [36]. Clinical research has shown how effective they are for preventing COVID-19. For example, the BNT162b2 mRNA vaccine was found to be efficacious for a variety of COVID-19-related outcomes in a statewide mass immunization research conducted in Israel [100].

Rare side effects have been documented, despite the fact that these vaccinations have been crucial in containing the pandemic. Following mRNA COVID-19 immunization, cases of myocarditis and pericarditis have been reported, especially in younger boys [101,102]. These occurrences are uncommon, according to the Centres for Disease Control and Prevention (CDC), and the majority of patients recover completely with the right care [103]. RNA-based nanoparticle vaccines are being researched for additional newly developing viral diseases in addition to COVID-19. mRNA vaccine platforms' versatility enables quick creation in reaction to epidemics. For instance, using the same LNP technique to produce protective immunity, research is being done to create mRNA vaccines against the Zika virus [104,105].

6. Clinical Translation and Regulatory Factors

A thorough grasp of both therapeutic effectiveness and regulatory frameworks is essential for the successful clinical translation of biodegradable nanoparticles for antiviral drug delivery. As these nanotechnologies progress from laboratory research to clinical applications, it is imperative to address challenges related to safety, scalability, and compliance with regulatory standards [106]. This section explores the critical considerations involved in the clinical adoption of biodegradable nanoparticle-based antiviral therapies, including the evaluation of biocompatibility, the design of clinical trials, manufacturing practices, and compliance with the rules established by regulatory organizations.

6.1. Biodegradable Nanoparticles in Clinical Trials

Significant progress has been made in the clinical translation of biodegradable nanoparticles for antiviral drug delivery, especially since regulatory bodies like the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have approved products based on nanomedicine [106]. These authorizations highlight how nanotechnology can improve antiviral drugs' safety and therapeutic effectiveness. According to recent reports, the FDA and EMA have approved almost 100 formulations based on nanomedicine, indicating the increasing use of nanotechnology in medical treatments [107]. These formulations cover a variety of treatment fields, such as vaccinations, infectious disorders, and cancer. The bulk of these authorized nanopharmaceuticals are lipid-based and protein-based drug delivery systems, demonstrating their adaptability and efficacy in clinical settings [107].

The creation and licensure of mRNA vaccines that use lipid nanoparticles (LNPs) as delivery vehicles is a noteworthy achievement in this field. The promise of nanoparticle-based platforms in treating newly developing infectious illnesses is demonstrated by the quick development and implementation of mRNA vaccines during the COVID-19 pandemic [108]. The LNPs' function in shielding the mRNA and promoting its entry into host cells is primarily responsible for the vaccines' great effectiveness and safety.

In addition to vaccines, liposomal formulations have been explored for antiviral therapies. Liposomal drug delivery systems can enhance the bioavailability and therapeutic index of antiviral agents by improving their solubility and stability, and by facilitating targeted delivery to infected cells [21,96]. Although a number of liposomal formulations have been licensed for the treatment of cancer, research is still being done to determine how well and safely they work in antiviral therapy.

Nanomedicines are subject to stringent regulation to guarantee their efficacy, safety, and quality. To help developers prepare applications for marketing authorization of nanomedicine products, the European Medicines Agency (EMA) has created scientific guidelines. These guidelines address considerations specific to nanomaterials, including their characterization, manufacturing processes, and non-clinical and clinical evaluation [109]. Similarly, the FDA has released guidance focusing on the identification and management of risks associated with drug products containing nanomaterials. This includes recommendations on the characterization of nanomaterials, assessment of their safety and efficacy, and considerations for product quality [110]. Such regulatory frameworks are crucial for ensuring that novel

medicines based on nanomedicine fulfil accepted standards for patient care by easing their transition from research to clinical practice.

6.2. Challenges in Translating BNPs to Clinics

Translating biodegradable nanoparticles (BNPs) from research settings to clinical applications presents several significant challenges, particularly in scalability and manufacturing, toxicity and immune response concerns, and cost-effectiveness.

6.2.1. Scalability and Manufacturing Hurdles

It is a difficult undertaking to increase BNP output while preserving constant quality and functioning. Large-scale repeatability and consistency are sometimes hampered by the intricacy of nanoparticle manufacturing procedures such emulsification, solvent evaporation, and spray drying [111]. The stability, drug loading effectiveness, and therapeutic efficacy of the nanoparticles can all be greatly impacted by changes in important process variables, such as temperature, humidity, and mixing speed. Large-scale production attempts are further complicated by the specific tools and strict environmental regulations needed for nanoparticle synthesis. To overcome these obstacles and enable the practical translation of BNP-based treatments, reliable, scalable, and economical production processes must be established [112].

6.2.2. Toxicity and Immune Response Concerns

For BNPs to be used safely in clinical settings, their biocompatibility must be guaranteed. The breakdown products, particle size, surface charge, and other physicochemical characteristics of BNPs might cause toxicity or unexpected immune responses, even though biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) are often thought to be biocompatible [113]. According to studies, certain nanoparticles have the ability to trigger the innate immune system, which might result in inflammation or other negative consequences. For example, it has been shown that the immunogenicity of lipid nanoparticles affects the effectiveness of mRNA-based treatments, highlighting the necessity of thorough immunotoxicological assessments during the development of BNP [114]. Addressing these concerns requires meticulous design and thorough preclinical testing to assess and mitigate potential adverse effects associated with BNPs.

6.2.3. Cost-Effectiveness of Biodegradable Nanoparticle Formulations

The economic feasibility of BNP-based therapies is a critical factor influencing their clinical adoption. The intricate and resource-intensive manufacturing processes contribute to the high production costs of BNP formulations [111]. Storage needs, scalability, and manufacturing complexity are important variables influencing medicine prices. Investigating ways to improve production stability and efficiency is crucial to cutting costs. Additionally, the need for specialized storage conditions and the potential for limited shelf life further escalate costs, posing challenges for widespread clinical implementation. Balancing the benefits of BNPs with their production and distribution costs is imperative to ensure that these advanced therapies are accessible and sustainable within healthcare systems.

6.3. Regulatory Frameworks for Biodegradable Nanoparticles

Following strict regulatory guidelines set by organizations like the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) is essential for the clinical translation of biodegradable nanoparticles for antiviral treatments. These frameworks are intended to guarantee the quality, safety, and effectiveness of pharmaceuticals based on nanoparticles.

6.3.1. FDA Guidelines on Nanoparticle-Based Therapies

The FDA has issued comprehensive guidance documents addressing the development of drug and biological products containing nanomaterials. In its guidance titled "Drug Products, Including Biological Products, that Contain Nanomaterials," the FDA outlines considerations for the characterization, manufacturing, and evaluation of such products [115]. The document emphasizes the importance of understanding how nanomaterials influence product attributes and performance, recommending a thorough physicochemical characterization and assessment of biological interactions. To ensure that products incorporating nanomaterials fulfil established safety and effectiveness requirements, the FDA further emphasizes the need for suitable in vivo and in vitro evaluations to assess pharmacokinetics, toxicity, and immunogenicity [115].

6.3.2. EMA Guidelines on Nanomedicines

In a similar vein, the European Medicines Agency (EMA) offers scientific recommendations to help developers prepare applications for marketing authorization of nanomedicines [116]. These recommendations include a range of development-related topics, such as clinical, non-clinical, and quality factors. For example, the European Medicines Agency (EMA) has published reflection papers on data requirements for liposomal formulations and intravenous iron-based nano-colloidal treatments, including the research required to show comparability with reference products [116]. The significance of thorough characterization, reliable manufacturing procedures, and thorough safety and effectiveness assessments catered to the particular characteristics of nanomedicines are emphasized in these publications.

6.3.3. Challenges in Approval Pathways

Despite the availability of these guidelines, several challenges persist in the regulatory approval of nanoparticle-based therapies. One significant hurdle is the complexity of characterizing nanomaterials, given their diverse physicochemical properties and dynamic behaviors in biological systems. Standard analytical methods may be insufficient, necessitating the development of specialized techniques to accurately assess critical quality attributes [117]. Moreover, the scalability of manufacturing processes poses challenges, as maintaining consistent quality and performance during scale-up requires meticulous control and validation. Regulatory agencies also face difficulties in establishing standardized testing protocols and evaluation criteria that adequately address the unique aspects of nanomedicines [117]. In order to improve current frameworks and create standardized standards that enable the transition of nanoparticle-based antiviral therapies safely and efficiently into clinical applications, regulatory agencies, industry stakeholders, and the scientific community must continue to work together.

7. Emerging Trends in Biodegradable Nanoparticle Research

The field of biodegradable nanoparticles (BNPs) in targeted drug delivery is rapidly evolving, with innovative approaches enhancing therapeutic precision and efficacy. Emerging trends such as CRISPR-loaded BNPs for viral genome editing and biohybrid nanoparticles for vaccine design are at the forefront of this advancement.

7.1. CRISPR-Loaded Biodegradable Nanoparticles for Viral Genome Editing

With its ability to precisely alter genetic material, the CRISPR/Cas9 technology has completely changed genome editing. Delivering CRISPR components to target cells in a safe and efficient manner is still quite difficult, though. A potential remedy for this delivery problem is biodegradable nanoparticles. Xu et al. [118] claim that CRISPR/Cas9 designs may be effectively transported using nanoparticle-based delivery methods, improving their stability and cellular absorption. By customizing these nanoparticles to target certain tissues or cell types, off-target effects and possible immunogenicity may be reduced. For example, CRISPR components have been encapsulated in lipid nanoparticles (LNPs) to enable efficient in vivo genome editing [118]. From the findings of Liu et al. [119], LNPs have demonstrated low immunogenicity and high delivery efficiency, making them suitable carriers for CRISPR-mediated therapies. This approach holds significant promise for treating viral infections by enabling the direct editing of viral genomes within host cells, potentially eradicating persistent infections [119].

7.2. Biohybrid Nanoparticles for Vaccine Design

Vaccine development has greatly benefited from nanotechnology, particularly through the use of biohybrid nanoparticles that mimic natural pathogens to elicit robust immune responses. These virus-mimicking nanoparticles are designed to present antigens in a manner similar to actual viruses, thereby enhancing antigen recognition by the immune system. According to Xu et al. [120], biohybrid nanoparticles can be engineered to display viral antigens on their surface, effectively simulating the structural characteristics of viruses. This mimicry facilitates the activation of both cellular and humoral immune responses, leading to improved vaccine efficacy. For example, erythrocyte-mediated delivery of virus-mimicking nanoparticles has been explored as a vaccination strategy. From the findings of Lenders et al. [82], these nanoparticles, when attached to red blood cells, can circulate longer within the bloodstream, providing sustained antigen exposure and a stronger immune response. This novel technique has the potential to improve the success of vaccines against different viral pathogens by better antigen presentation and immune system activity.

The field of BNPs for targeted drug delivery is continually advancing, with several emerging trends poised to enhance therapeutic outcomes. Beyond CRISPR-loaded BNPs and biohybrid nanoparticles, notable developments have followed

7.3. Co-Delivery Systems

Co-delivery systems employing BNPs are garnering interest for their capacity to concurrently administer numerous therapeutic drugs, which is particularly advantageous in treating complicated disorders needing combination therapy. For instance, gelatin nanoparticles have been exploited to co-deliver chemotherapeutic and immunotherapeutic drugs, potentially increasing cancer therapy effectiveness [121,122]. These systems can increase drug solubility, stability, and targeted administration, ultimately enhancing therapeutic effects.

7.4. Stimulus-Responsive Drug Delivery

Stimulus-responsive BNPs are developed to release their therapeutic payload in response to certain physiological stimuli such as pH changes, temperature fluctuations, or enzyme activity. This tailored release method guarantees that medications are given exactly at the site of action, reducing systemic adverse effects and boosting therapeutic effectiveness. Research into gelatin-based nanoparticles has demonstrated their potential in creating stimulus-responsive delivery systems, which can be tailored for various medical applications [123,124].

7.5. Natural Polymer-Based Nanoparticles

Consequent to their low toxicity, biodegradability, and biocompatibility, natural polymers like chitosan are becoming more and more popular for use in the production of BNPs. By improving the stability and bioavailability of encapsulated medications, chitosan-based nanoparticles have demonstrated potential in antiviral drug delivery systems [125]. These natural polymer-based carriers can be engineered to improve mucosal adhesion and facilitate targeted delivery, which is crucial in antiviral therapies [125,126].

7.6. Biomimetic Nanoparticles

Biomimetic nanoparticles, designed to mimic natural biological structures, are being explored to improve drug delivery efficiency and immune system evasion. For instance, therapeutic drugs can be delivered to target areas more effectively when nanoparticles coated in red blood cell membranes circulate in the circulation for a longer period of time. This approach has been investigated for delivering cancer-fighting drugs, demonstrating the potential of biomimetic strategies in improving therapeutic outcomes [127,128].

While these cutting-edge innovations demonstrate the capacity of biodegradable nanoparticles to transform in targeted therapeutic deliveries, several challenges still hinder their large-scale application. Factors such as manufacturing scalability, production costs, toxicity concerns, and regulatory hurdles continue to pose significant barriers to widespread clinical adoption. Despite the promising advancements in nanoparticle-based antiviral therapies, the ability to scale up production while maintaining cost-effectiveness and regulatory compliance remains a critical challenge. Addressing these barriers is essential for translating laboratory success into commercially viable medical treatments. Table 5 offers a thorough summary of the main obstacles in scaling up biodegradable nanoparticle production, highlighting empirical data from industry reports and recent research studies.

Table 5 Challenges in Scaling Up Biodegradable Nanoparticle Production

Challenge	Description	Empirical Data	References
Manufacturing Complexity	Scaling up production while maintaining nanoparticle quality and consistency is complex.	The global lipid nanoparticle manufacturing market is projected to grow from USD 0.37 billion in 2024 to USD 2.53 billion by 2035, indicating significant investments in overcoming production challenges.	Ref [129]
Cost of Production	High production costs hinder widespread adoption.	The nanoparticle contract manufacturing market is expected to reach approximately USD 5.21 billion by 2033, reflecting ongoing efforts to reduce production costs through outsourcing.	Ref [130]
Toxicity Concerns	Potential toxicity of nanoparticles raises safety issues.	Comprehensive biocompatibility assessments are required to address safety concerns, adding complexity to development.	Ref [131]
Regulatory Challenges	Lack of standardized regulatory frameworks	Nanomedicines face additional development and regulatory considerations compared to	Ref [132]

	complicates approval processes.	conventional medicines, with efforts underway to establish specific guidelines.	

Note: Addressing these challenges requires interdisciplinary collaboration, investment in scalable manufacturing technologies, comprehensive safety evaluations, and the development of clear regulatory guidelines.

8. Conclusion

Biodegradable nanoparticles (BNPs) are at the forefront of revolutionizing targeted antiviral therapy. They are perfect carriers for antiviral drugs because of their special qualities, which include increased bioavailability, regulated release, and the capacity to pass through biological barriers. BNPs, for example, have been used to increase the therapeutic efficiency of antiviral medications by enhancing their stability and distribution.

BNPs must overcome several difficult obstacles on their path from research to clinical use, including as large-scale production, biocompatibility, safety, intellectual property concerns, and regulatory compliance. A multidisciplinary strategy that closes the gaps between clinical development, scientific innovation, and regulatory frameworks is needed to address these issues. For BNP-based treatments to be successfully implemented in clinical settings, cooperation between researchers, physicians, and regulatory agencies is crucial.

Future studies should concentrate on creating scalable and economical processes for producing BNP. Reaching this objective is essential to ensure that BNP-based antiviral treatments are widely available and reasonably priced. Simplified regulatory procedures and manufacturing process innovations will be essential to introducing these cutting-edge medicinal treatments to the world market.

Wrapping it all up, BNPs offer a promising avenue for enhancing targeted antiviral therapy. By fostering integration across research, clinical, and regulatory domains, and focusing on scalable production, the full potential of BNPs can be realized in combating viral infections.

Compliance with ethical standards

Acknowledgments

The authors wish to acknowledge the collaborative effort of all contributing scholars and colleagues who jointly authored and edited this review paper. This work was conducted entirely through the intellectual and academic contributions of the authoring team, without external funding or assistance from any individual, institution, or organization.

Disclosure of conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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