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Nanotechnology as Delivery Vehicles for Antiviral Drug Delivery Systems: A Review

P. Selvakumar[1*], Arvinder Kour Mehta[2], Shiney Chib[3], Santosh Kumar Nathsharma[4], T. C. Manjunath[5] and Sandeep Gupta[6]

[1]Department of Science and Humanities, Nehru Institute of Technology, Coimbatore, TN, India
[2]Department of Management and Humanities, Yeshwantrao Chavan College of Engineering, Nagpur, MH, India
[3]Department of Management, Datta Meghe Institute of Management Studies, Nagpur, MH, India
[4]Department of Chemistry, Stewart Science College, Cuttack, OR, India
[5]Department of Computer Science and Engineering, IoT, Rajarajeswari College of Engineering, Bangalore, KA, India
[6]Department of Electrical Engineering, Graphic Era (Deemed to be University), Dehradun, UK, India
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*drselvakumar05@gmail.com

ABSTRACT

Antiviral drug delivery systems are pivotal in the ongoing battle against viral infections, which remain a significant global health challenge. The complexity of designing effective antiviral drug delivery systems stems from the need to target viral pathogens precisely while minimizing adverse effects on host cells. One of the foremost challenges in antiviral drug delivery is achieving selective targeting of the virus without causing systemic toxicity. It is particularly challenging because many viruses can rapidly mutate, potentially rendering existing drugs less effective. Furthermore, the virus's ability to evade the host immune system complicates the development of effective therapies. Additionally, the potential for immune system interactions or toxicity must be carefully evaluated through rigorous preclinical and clinical testing. Another significant opportunity in antiviral drug delivery is the development of targeted delivery mechanisms that exploit the unique features of viral infections. For example, certain viruses have specific receptors or enzymes that can be targeted by drug-delivery systems, enhancing the efficacy of antiviral agents. Moreover, combination therapies that use multiple drugs or delivery systems could overcome issues related to drug resistance and improve the overall treatment outcomes. Furthermore, the cost of developing and producing sophisticated delivery systems can be prohibitive, limiting their accessibility and widespread use. While advanced delivery systems such as nanoparticles and liposomes hold promise for improving the efficacy and safety of antiviral therapies, their development is complex and requires ongoing research and innovation. Addressing these challenges while leveraging the opportunities offered by new technologies and targeted approaches will be crucial in enhancing antiviral drug delivery and ultimately improving patient outcomes in the fight against viral infections.

Keywords: Nanotechnology; Targeted Delivery Systems; Antiviral Drug Delivery Systems.

1. INTRODUCTION

The emergence and re-emergence of viral infections pose a persistent threat to global public health, often outpacing the development of effective therapeutic interventions. Traditional antiviral drug delivery methods frequently suffer from limitations such as poor bioavailability, systemic toxicity, rapid degradation, and inadequate targeting of infected tissues. The global burden of viral infections—ranging from chronic diseases like HIV and hepatitis to acute outbreaks such as influenza, Ebola, and most recently, COVID-19—has underscored the urgent need for effective antiviral therapies. However, conventional drug delivery approaches often face significant challenges, including poor solubility, rapid metabolism, limited bioavailability, and off-target effects. Nanotechnology offers a transformative solution by providing advanced drug delivery platforms that can enhance the pharmacokinetic and pharmacodynamic profiles of antiviral agents. Viral infections continue to pose significant global health challenges, often leading to widespread morbidity and mortality. Despite the availability of various antiviral agents, their clinical efficacy is frequently hindered by limitations. This review explores the role of nanotechnology in antiviral drug delivery, highlighting current advances, potential applications, and the challenges that must be addressed to translate these systems into clinical practice. The emergence and re-emergence of viral infections, exemplified by global health crises such as the COVID-19 pandemic, have underscored the urgent need for effective antiviral therapies.

From long-standing threats such as HIV and influenza to emerging viruses like SARS-CoV-2, the treatment and prevention of viral diseases continue to challenge modern medicine. These nanoscale carriers can

overcome biological barriers, protect active drug molecules from degradation, and facilitate their uptake by infected cells, thereby improving the overall therapeutic index. It discusses the types of nanocarriers employed, their mechanisms of action, benefits over conventional systems, and the challenges associated with their development and clinical translation. By exploring the intersection of nanotechnology and virology, this paper highlights the potential of nanomedicine to revolutionize antiviral therapy in the coming decades.

2. NANOTECHNOLOGY-BASED ANTIVIRAL DRUG DELIVERY: PRINCIPLES AND APPLICATIONS

One of the fundamental principles is the modification of nanoparticles to optimize their interaction with viral pathogens and infected cells. Liposomes, which are lipid-based nanoparticles, can encapsulate antiviral drugs and improve their stability and solubility. They are used in therapies for various viral infections, including HIV and hepatitis. Similarly, polymeric nanoparticles offer a versatile platform for drug delivery due to their customizable size, surface properties, and drug-loading capacity (Abumanhal *et al.* 2019). Nanoparticles can present viral antigens in a manner that closely mimics their natural presentation, thereby improving the immune response and offering potential benefits for vaccine development. Quantum dots and other nanoparticle-based imaging agents are also being explored for their ability to track viral infections in real time and assess the efficacy of antiviral treatments.

Additionally, the complex manufacturing processes required to produce nanoparticles consistently and at scale pose logistical and economic challenges. Moreover, the regulatory landscape for nanotechnology-based drug delivery systems is evolving, and navigating these regulations can be complex (Azevedo *et al.* 2020). The integration of nanotechnology into clinical practice also demands interdisciplinary collaboration between nanotechnologists, pharmacologists, clinicians, and regulatory bodies to address these challenges effectively (Guo Y et al. 2017). While the potential benefits are substantial, ongoing research and development are crucial to overcoming the challenges related to toxicity, manufacturing, and regulation.

3.. TARGETED ANTIVIRAL DRUG DELIVERY: STRATEGIES FOR ENHANCED EFFICACY

Targeted antiviral drug delivery represents a cutting-edge approach designed to enhance the efficacy of antiviral therapies by directing drugs precisely to the site of infection while minimizing off-target effects. This strategy is driven by the need to improve therapeutic outcomes and reduce systemic toxicity associated with conventional antiviral treatments. One prominent strategy involves the use of nanotechnology (Couch *et al.* 2013). Functionalization of these nanoparticles with ligands or antibodies that bind specifically to viral surface proteins or receptors on infected cells enhances the selective accumulation of the drug at the injection site. Another effective strategy is receptor-mediated targeting. Many viruses exploit specific cellular receptors to gain entry into host cells. This approach not only enhances the efficacy of the drug but also minimizes exposure to non-target cells, thereby reducing potential side effects. A complementary approach involves the use of antibody-drug conjugates (ADCs). Bourquin *et al.* (2018) stated that nanoparticles release their antiviral payload in the acidic environment of an infected tissue or cell and can provide localized drug delivery while sparing surrounding healthy tissues.

Furthermore, the potential for immune system interactions or toxicity of the delivery systems themselves must be thoroughly evaluated through preclinical and clinical studies. Another challenge is the variability in target expression among different individuals or even among different cells within the same individual. This variability can impact the effectiveness of targeted delivery systems and necessitates the development of strategies that can adapt to such differences (Collins and Varmus, 2015).

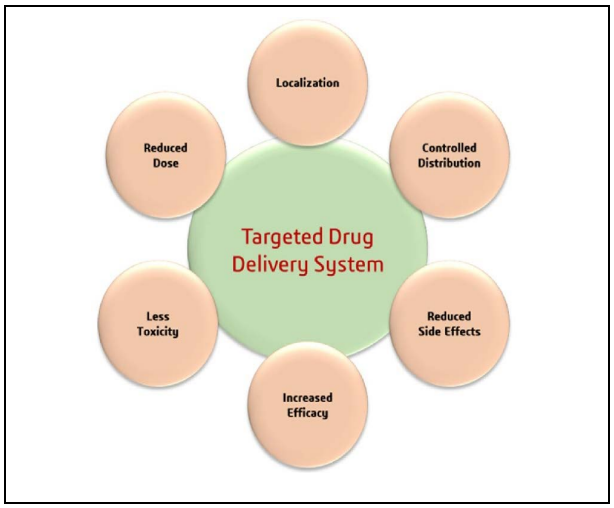


Fig. 1: Advantages of targeted drug delivery system

4. LIPOSOMAL ANTIVIRAL DRUG DELIVERY: FORMULATION AND CHARACTERIZATION

Liposomal antiviral drug delivery represents a significant advancement in pharmaceutical technology, offering enhanced drug efficacy and reduced toxicity through innovative formulation and characterization techniques. The formulation of liposomal antiviral drug delivery systems involves several key considerations, including lipid composition, size, charge, and surface modifications. The formulation of liposomal systems

begins with the selection of appropriate lipids. Phospholipids, such as phosphatidylcholine and phosphatidylserine (Duan *et al.* 2020). The choice of lipids can influence liposome stability, drug release rates, and interactions with biological membranes. For instance, incorporating cholesterol into the lipid bilayer can enhance liposome stability and fluidity, while the use of specialized lipids can provide targeted delivery by altering the liposome's surface properties. Each method offers distinct advantages in terms of encapsulation efficiency, scalability, and the ability to incorporate various types of drugs. For hydrophilic drugs, encapsulation within the aqueous core of the liposome is straightforward, while hydrophobic drugs are integrated into the lipid bilayer. Achieving high drug loading while maintaining liposome stability is a key challenge during formulation. Characterization of liposomal antiviral drug delivery systems is crucial for ensuring their quality, efficacy, and safety (Dunne *et al.* 2020).

Typically, liposomes range from 50 to 200 nanometers in diameter, with smaller sizes facilitating better tissue penetration and larger sizes offering prolonged circulation times. Zeta potential, which measures the surface charge of liposomes, affects their stability and interaction with cells. A neutral to slightly negative zeta potential is often preferred to minimize aggregation and promote biocompatibility. High encapsulation efficiency is desirable to maximize the therapeutic dose while minimizing drug waste (Fang *et al.* 2020). It is vital for expensive or potent antiviral agents. Drug release kinetics are also crucial, as they determine how the drug is released from the liposomes over time. Controlled release profiles can enhance the drug's therapeutic efficacy and reduce the frequency of dosing. DLS provides information on liposome size and size distribution, while electron microscopy offers detailed visual insights into liposome morphology. HPLC is used to quantify drug content and release profiles, ensuring that the liposomes perform as intended.

5. POLYMERIC NANOPARTICLES FOR ANTIVIRAL DRUG DELIVERY: DESIGN AND DEVELOPMENT

Antiviral drug delivery offers innovative solutions to enhance drug efficacy, specificity, and controlled release (Gimbrone and García-Cardena, 2016). The design and development of polymeric nanoparticles involve several critical factors, including polymer selection, nanoparticle formulation, and characterization, each contributing to the overall performance of the drug delivery system. Standard methods include solvent evaporation, nanoprecipitation, and electrostatic assembly (Hong *et al.* 2020). Nanoprecipitation involves the mixing of polymer and drug solutions to induce nanoparticle formation through solvent exchange. Electrostatic assembly leverages the interaction between oppositely charged polymers and drugs to form nanoparticles. Each technique offers unique advantages in terms of encapsulation efficiency, particle size, and drug release kinetics. Characterization of polymeric nanoparticles is crucial to ensure they meet the desired specifications for drug delivery.

Drug loading capacity is evaluated through high-performance liquid chromatography (HPLC) or spectrophotometric methods, ensuring that a sufficient amount of drug is encapsulated. The release profile is studied using in vitro assays to determine how the drug is released over time, which is essential for achieving controlled and sustained drug delivery. Ensuring the stability of nanoparticles in biological environments is crucial, as they can be subject to degradation or aggregation, which can impact drug release and efficacy. Furthermore, scaling up from laboratory to industrial production presents challenges in maintaining consistency and reproducibility (Jiang *et al.* 2022). The regulatory landscape for polymeric nanoparticles also requires thorough navigation, as safety and efficacy must be demonstrated through rigorous preclinical and clinical testing before approval for clinical use.

In conclusion, polymeric nanoparticles offer a versatile and practical approach to antiviral drug delivery, with the potential to enhance drug targeting, control release, and therapeutic efficacy. The design and development of these nanoparticles involve careful selection of polymers, formulation techniques, and comprehensive characterization. Through continued innovation and refinement, polymeric nanoparticles hold the promise of significantly improving antiviral therapies and patient outcomes.

6. DENDRIMER-BASED ANTIVIRAL DRUG DELIVERY: A PROMISING APPROACH

Dendrimers are categorized based on their generation, which refers to the number of branching layers from the core (Kou *et al.* 2018). Higher-generation dendrimers possess more functional groups and a larger surface area, which can be utilized for drug loading and surface modifications. The uniform size and structure of dendrimers allow for a controlled and predictable drug release profile. In addition to their high drug-loading capacity, dendrimers offer several other benefits. Their well-defined size and shape facilitate precise control over pharmacokinetics, including circulation time and tissue distribution. Despite their promising advantages, dendrimer-based drug delivery systems face several challenges. One significant challenge is the potential for toxicity, as the high density of functional groups on dendrimers can lead to interactions with biological systems that may cause adverse effects. Thorough biocompatibility and toxicity studies are essential to address these concerns (Luk *et al.* 2014). Additionally, the complexity of dendrimer synthesis and modification can be cost-intensive, potentially limiting the scalability and commercial viability of dendrimer-based therapies.

7. VIRAL VECTOR-MEDIATED ANTIVIRAL DRUG DELIVERY: GENE THERAPY AND BEYOND

Viral vector-mediated antiviral drug delivery represents an innovative frontier in gene therapy, offering transformative potential for treating a range of viral infections by harnessing the natural capabilities of viruses to deliver genetic material into host cells (Molinaro *et al.* 2018). This approach utilizes engineered viral vectors to introduce therapeutic genes into cells, where they can produce antiviral agents or modulate cellular processes to combat viral infections. Designing viral vectors involves several key modifications to enhance their therapeutic efficacy and safety. One significant modification is the inclusion of tissue-specific promoters, which ensure that the therapeutic gene is expressed only in targeted cells or tissues (Molloy, C. P. 2017).

Additionally, vectors are engineered to evade the host immune system, which can otherwise recognize and neutralize the viral particles before they deliver their payload. The efficacy of viral vector-mediated drug delivery depends on several factors, including the efficiency of gene transfer and expression (Nag and Delehanty, 2019). Assessing the distribution of vectors within the body and their ability to reach the targeted cells or tissues is also critical for optimizing therapeutic outcomes. Safety is a significant concern in viral vector-mediated therapies. Additionally, immune responses against the viral vectors or the expressed therapeutic proteins can pose challenges (Osman *et al.* 2020). Rigorous preclinical and clinical testing is required to evaluate the safety profile of viral vector-mediated therapies, including studies to monitor immune responses, potential toxicities, and long-term effects. The development of these systems involves meticulous design and engineering of viral vectors, careful selection of therapeutic genes, and comprehensive evaluation of delivery efficiency and safety (Pinheiro *et al.* 2021). While challenges related to immunogenicity, insertional mutagenesis, and vector stability remain, ongoing research and advancements in vector technology and gene therapy are likely to enhance the efficacy and safety of these innovative treatments. As the field progresses, viral vector-mediated drug delivery holds the potential to revolutionize antiviral therapies and provide new solutions for combating viral infections.

8. MICRORNA-TARGETED ANTIVIRAL DRUG DELIVERY: A NOVEL STRATEGY

MicroRNA (miRNA)-targeted antiviral drug delivery is an innovative and emerging strategy in the field of antiviral therapy that leverages the unique regulatory roles of miRNAs in gene expression to enhance therapeutic efficacy. This natural regulatory mechanism can be harnessed to design novel antiviral therapies that specifically target viral RNAs or modulate host cell factors involved in viral replication. The concept of miRNA-targeted antiviral drug delivery consists of the design of therapeutic agents or delivery systems that can specifically interact with miRNAs to either enhance their antiviral effects or inhibit the function of miRNAs that promote viral replication. This strategy can be broadly categorized into two approaches (Suk *et al.* 2016). miRNA mimics are designed to replace or augment endogenous miRNAs that have antiviral properties. For example, specific miRNAs are known to target and degrade viral RNAs, thereby inhibiting viral replication. By delivering synthetic mimics of these antiviral miRNAs into infected cells, it is possible to enhance the cellular antiviral response and suppress viral replication more effectively. This approach requires precise delivery of the miRNA mimics to the target cells to ensure their uptake and function. It can be achieved through various delivery systems, such as nanoparticles or viral vectors. Design and Development Considerations: The successful implementation of miRNA-targeted antiviral drug delivery relies on several key considerations (Trac *et al.* 2021). Specificity and Targeting: One of the significant challenges are achieving high specificity for the target miRNA. The design of miRNA mimics or inhibitors must ensure that they interact precisely with their intended targets while minimizing off-target effects. Advances in computational tools and high-throughput screening methods can assist in identifying and validating specific miRNA targets and designing effective therapeutic agents. Stability and immunogenicity Ensuring the stability of miRNA agents in biological environments is critical to maintaining their therapeutic efficacy (Vemula, S et al. 2010). Additionally, the potential for immune responses against synthetic miRNAs or delivery vehicles must be considered and minimized through careful design and optimization. Regulatory and Safety Aspects As with any novel therapeutic approach, miRNA-targeted antiviral drug delivery systems.

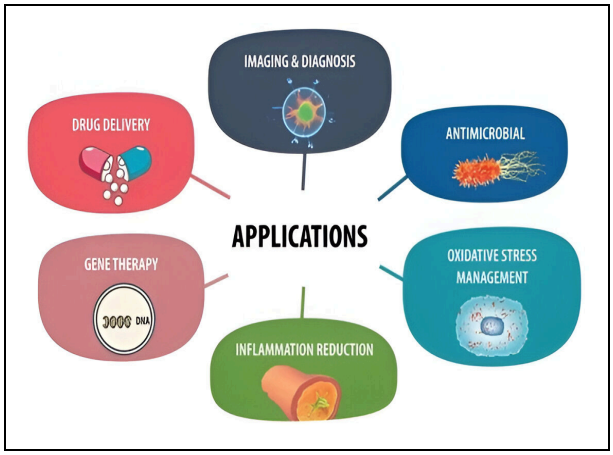


Fig. 2: Nanotechnology and targeted delivery for antiviral drug delivery systems

9. ANTIVIRAL DRUG-LOADED MICROCAPSULES: CONTROLLED RELEASE AND TARGETING

Antiviral drug-loaded microcapsules represent a sophisticated approach to drug delivery, aiming to improve the efficacy and safety of antiviral therapies through controlled release and targeted delivery. Microcapsules are small, spherical particles encapsulating an active pharmaceutical ingredient (API) within a polymeric or lipid shell—design and Fabrication of Antiviral Drug-Loaded Microcapsule. The design of microcapsules for antiviral drug delivery involves selecting appropriate materials and methods to achieve desired release profiles and targeting capabilities. Several techniques are employed to fabricate drug-loaded microcapsules, including coacervation, solvent evaporation, and electrospinning (Wei *et al*. 2021). Coacervation involves mixing polymers in a solution to form a phase-separated system that encapsulates the drug. Electrospinning creates nanofibers that can be further processed into microcapsules, providing a high surface area for drug loading and release. Controlled Release Mechanisms Diffusion-controlled release involves the gradual movement of the drug through the polymeric or lipid shell, providing a steady release over time. For antiviral drug-loaded microcapsules, controlled release is crucial for maintaining therapeutic drug levels and minimizing fluctuations that can lead to drug resistance or side effects. By tailoring the properties of the encapsulating materials and optimizing fabrication processes, researchers can design microcapsules that provide sustained and controlled drug release, improving the overall efficacy of antiviral treatments.

10. ELECTROSPUN NANOFIBERS FOR ANTIVIRAL DRUG DELIVERY: FABRICATION AND APPLICATION

These nanofibers, typically with diameters in the range of hundreds of nanometers to a few micrometers, are fabricated using an electrospinning technique that creates highly porous, fibrous mats with high surface area and tunable mechanical properties. The application of electrospun nanofibers in antiviral drug delivery capitalizes on these attributes to improve drug release profiles, targeting capabilities, and overall therapeutic performance.

Fabrication of Electrospun: Nanofibers as the polymer solution is extruded through a needle, the electric field causes the formation of a jet that stretches and solidifies into nanofibers as the solvent evaporates. The fibers are collected on a grounded collector, forming a nonwoven mat. Several factors influence the fabrication of electrospun nanofibers, including the polymer type, solution concentration, electric field strength, and collector configuration. Common polymers used include biodegradable options. Each polymer offers different characteristics in terms of drug compatibility, release kinetics, and mechanical properties (Weiss *et al.* 2013).

Additionally, the inclusion of drug molecules in the polymer matrix during electrospinning allows for the creation of drug-loaded nanofibers with controlled release profiles. Electrospun nanofibers can be engineered to enhance targeted delivery of antiviral agents. Additionally, nanofibers can be functionalized with cell-adhesive peptides or molecules that promote interaction with infected cells. This approach can address different aspects of viral infection and enhance the overall therapeutic effect. By co-loading different drugs in the nanofibers, it is possible to achieve synergistic effects that improve treatment outcomes. Characterization and evaluation: The performance of electrospun nanofibers in antiviral drug delivery is assessed through various characterization techniques. Key parameters include fiber diameter, porosity, drug loading efficiency, and release kinetics.

11. ANTIVIRAL DRUG CONJUGATES: CHEMICAL LINKAGE AND TARGETED DELIVERY

Antiviral drug conjugates represent a sophisticated approach in drug delivery systems that enhances therapeutic efficacy by chemically linking antiviral agents to targeting moieties. This method aims to improve the selectivity, stability, and overall effectiveness of antiviral therapies while minimizing off-target effects and side effects. By combining antiviral drugs with targeting ligands through chemical conjugation, researchers can create drug conjugates that are specifically designed to deliver therapeutic agents to infected cells or tissues, thus optimizing treatment outcomes. Chemical Linkage in Drug Conjugates: The creation of antiviral drug conjugates involves the covalent attachment of antiviral agents to targeting ligands through a chemical linkage. This linkage is crucial for ensuring that the drug is explicitly delivered to its intended site of action. The chemical bond between the drug and the targeting moiety can be established using various linkers, which are molecules that connect the drug to the ligand. Linkers can be designed to be stable under physiological conditions but capable of releasing the drug upon reaching the target site. Common linkers include biodegradable esters, disulfide bonds, and pH-sensitive linkers that break down in response to specific environmental conditions. The choice of linker affects the stability, release profile, and pharmacokinetics of the drug conjugate (Yu *et al.* 2021). For instance, a pH-sensitive linker can be used to release the drug in the acidic environment of the endosome or lysosome, which is often the site of viral replication. Similarly, biodegradable linkers ensure that the conjugate breaks down in a controlled manner, releasing the active drug over time. The chemical properties of the linker must be carefully optimized to balance stability and controlled release. For example, monoclonal antibodies or peptide

ligands that specifically bind to viral proteins or cell surface markers on infected cells can be used to target moieties.

Characterization and evaluation: The development of antiviral drug conjugates involves thorough characterization to ensure their effectiveness and safety. Key parameters include the conjugation efficiency, drug loading capacity, and stability of the conjugate. In vivo, studies focus on the pharmacokinetics, distribution, and therapeutic efficacy of the conjugate in animal models (You *et al.* 2017). These studies help determine the optimal dosing, safety profile, and therapeutic potential of the drug conjugate.

12. ANTIVIRAL DRUG DELIVERY ACROSS BIOLOGICAL BARRIERS: OVERCOMING CHALLENGES

Overcoming these barriers requires innovative strategies and advanced technologies to ensure that antiviral agents reach their intended sites of action in sufficient concentrations. Understanding these barriers and developing methods to bypass or penetrate them is essential for improving the efficacy and safety of antiviral therapies. Its outermost layer, the stratum corneum, is composed of tightly packed keratinocytes that form a highly effective protective layer. Delivering antiviral drugs through the skin requires overcoming this barrier while minimizing irritation or damage. Transdermal drug delivery systems have been developed to facilitate the transport of antiviral agents across the skin. These systems include patches, microneedles, and iontophoresis. Iontophoresis uses a small electric current to enhance the penetration of drugs through the skin (Yu *et al.* 2023). These methods improve drug absorption while minimizing systemic side effects. Mucosal Membranes Mucosal membranes, such as those lining the gastrointestinal (GI) tract, respiratory tract, and urogenital tract, present unique challenges for drug delivery. These membranes are designed to protect against foreign substances while facilitating the absorption of essential nutrients.

Delivering antiviral drugs to these sites requires strategies that can effectively traverse the mucosal barrier while ensuring drug stability and bioavailability. Techniques such as enteric coating, which protects drugs from stomach acid, and the use of absorption enhancers or prodrugs that become active in the intestinal environment, can improve the efficacy of oral antiviral therapies. Targeted delivery systems that concentrate the drug at the site of infection can help achieve this balance. Future Direction Future research will likely focus on advancing drug delivery technologies to enhance penetration across biological barriers. Innovations in nanotechnology, biotechnology, and materials science will drive the development of new delivery systems with improved targeting, controlled release, and reduced side effects. Personalized medicine approaches that tailor drug delivery systems to individual patient needs and specific viral infections will also become increasingly important. In conclusion, overcoming the challenges of antiviral drug delivery across biological barriers is essential for advancing effective therapies for viral infections.

13. IMMUNOTHERAPY AND ANTIVIRAL DRUG DELIVERY: COMBINATION STRATEGIES

Combining immunotherapy with antiviral drug delivery represents a cutting-edge approach to treating viral infections by leveraging the strengths of both therapeutic modalities. The integration of these strategies offers a synergistic effect that can enhance therapeutic outcomes, address limitations inherent to each approach when used alone, and potentially lead to more effective and durable treatments for viral infections. Immunotherapy involves various strategies designed to enhance or modify the immune system's response to fight infections. Key approaches include monoclonal antibodies, immune checkpoint inhibitors, and cytokine therapies (Zenych *et al.* 2020). Cytokine therapies involve administering immune-modulating molecules such as interferons, which boost the body's natural antiviral defenses. Prodrugs are chemically modified drugs that become active only after reaching the target site, thereby reducing systemic toxicity (Mahadev Madgule et al. 2023). Enhanced efficacy Combining these approaches can result in a more comprehensive attack on viral infections. While antiviral drugs directly inhibit viral replication, immunotherapy can improve the immune system's ability to recognize and destroy infected cells. This dual approach can lead to more effective viral clearance and reduce the likelihood of drug resistance.

Synergistic Effects: Synergistic effects occur when the combined use of immunotherapy and antiviral drugs results in greater efficacy than the sum of their individual effects. For instance, antiviral drugs can reduce viral load and make viral antigens more visible to the immune system, while immunotherapy can help eliminate remaining infected cells more effectively. Optimal Timing and Dosing: Determining the optimal timing and dosing for combining immunotherapy with antiviral drugs is complex. Coordinating the administration of these therapies to maximize their synergistic effects while minimizing adverse interactions is crucial (Zhang, Y et al. 2017).

14. TOXICITY AND SAFETY CONSIDERATIONS IN ANTIVIRAL DRUG DELIVERY SYSTEMS

Types of Toxicity in Antiviral Drug Delivery Systems Systemic Toxicity: Systemic toxicity arises when the drug delivery system affects organs and tissues beyond the intended target. It can result from the

accumulation of drug or delivery system components in non-targeted areas. For instance, the use of nanoparticles or liposomes can lead to unintended interactions with organs like the liver and kidneys, potentially causing toxicity (Leung AKK *et al.* 2014). The systemic distribution of drug carriers must be carefully monitored to avoid adverse effects on vital organs. Local Toxicity Local toxicity occurs at the site of drug administration or where the drug is intended to act. For example, local irritation or inflammation can result from the use of specific delivery systems, such as microneedles or transdermal patches. The materials used in the delivery system must be biocompatible and not induce local inflammatory responses or tissue damage.

Immunotoxicity: Immunotoxicity involves adverse effects on the immune system. The introduction of foreign substances, such as nanoparticles or viral vector components, can trigger immune responses that might lead to hypersensitivity reactions, autoimmune responses, or chronic inflammation. It is crucial to assess the immunogenicity of delivery systems and their components to prevent undesirable immune responses.

Cytotoxicity: Cytotoxicity refers to the toxic effects of a drug or delivery system on cells. High drug concentrations or poisonous materials in the delivery system can cause cell death or damage, impacting healthy tissues. Cytotoxicity assays are essential for evaluating the safety of drug delivery systems at the cellular level. Scalability and Manufacturing The manufacturing process for drug delivery systems must be carefully controlled to ensure consistency and safety. Variations in manufacturing can lead to differences in product quality and safety (Gong Y et al. 2017). These studies assess the safety of the delivery system and its components, including long-term toxicity, reproductive toxicity, and carcinogenicity.

The performance and safety of nanotechnology-based antiviral drug delivery systems are highly dependent on several critical physicochemical parameters, among which particle size, surface charge, shape, and surface functionalization are particularly influential. Particle size plays a key role in cellular uptake, circulation time, and biodistribution. Nanoparticles typically ranging from 10 to 200 nm are ideal for systemic delivery, as they can avoid rapid renal clearance, penetrate tissues effectively. Surface charge (zeta potential) also significantly affects interaction with cell membranes and proteins. Moderate positive charges can enhance cellular uptake due to the negatively charged cell membranes, but overly cationic surfaces may lead to increased cytotoxicity and nonspecific protein adsorption. In contrast, neutral or slightly negative particles may offer longer circulation times but lower cellular uptake. Particle shape (e.g., spherical, rod-like) also influences biological interactions, with non-spherical particles sometimes showing prolonged circulation or enhanced tissue penetration. Careful optimization of these parameters is essential not only for maximizing therapeutic efficacy and targeting specificity but also for minimizing systemic toxicity and immune response, ensuring safe and effective antiviral treatment.

15. TARGETED DELIVERY SYSTEMS TO EFFECTIVELY DIFFERENTIATE BETWEEN VIRUS-INFECTED AND HEALTHY CELLS

A critical advancement in nanotechnology-based antiviral drug delivery is the development of targeted systems capable of distinguishing between virus-infected and healthy cells. For instance, certain viruses induce the expression of specific proteins or alter the cellular microenvironment, which can be exploited for targeted delivery. Additionally, pH-responsive, enzyme-sensitive, and receptor-mediated targeting strategies are being employed to enhance precision at the site of infection. These smart delivery systems not only improve drug accumulation at the infection site but also reduce systemic exposure, thereby offering a safer and more effective approach to antiviral therapy. Continued research into the molecular signatures of virus-infected cells is crucial for refining these targeted delivery platforms and ensuring their clinical success.

The identification of viral receptors and enzymes that play essential roles in viral entry, replication, and pathogenesis is pivotal for the rational design of targeted nanocarrier systems. These receptors can be exploited for targeting by functionalizing nanocarriers with ligands or antibodies that specifically bind to infected cells expressing these surface molecules. Similarly, viral enzymes such as reverse transcriptase in HIV, RNA-dependent RNA polymerase (RdRp) in coronaviruses, and neuraminidase in influenza are critical for viral replication and can be targeted using enzyme-sensitive nanocarriers or inhibitors encapsulated within nanoparticles. By directing drug delivery to these molecular targets, nanotechnology enables precise antiviral action, enhances therapeutic efficacy, and minimizes off-target effects. Understanding the molecular biology of virus-host interactions thus provides a strategic framework for developing more effective and intelligent drug delivery systems.

16. CASE STUDIES FOR THE EFFECTIVENESS OF NANOPARTICLES AND LIPOSOMES IN ANTIVIRAL DRUG DELIVERY

Several case studies have illustrated the potential of nanoparticles and liposomes in enhancing antiviral drug delivery. Conventional acyclovir suffers from low bioavailability, but when encapsulated in liposomes, it demonstrates improved stability and targeted delivery to infected tissues, resulting in

enhanced antiviral activity and reduced dosing frequency. These nanoparticles have shown increased drug loading efficiency, sustained release profiles, and improved cellular uptake, leading to more effective viral suppression. These LNPs protected the fragile mRNA, facilitated cellular uptake, and ensured efficient expression of the viral spike protein, ultimately eliciting a strong immune response. Collectively, these examples underscore the versatility and clinical promise of nanotechnology-enabled delivery platforms in combating viral infections.

Acyclovir, a standard antiviral for treating HSV infections, suffers from poor oral bioavailability and limited skin penetration when applied topically. Liposome-based delivery systems have been developed to overcome these limitations by encapsulating acyclovir within phospholipid vesicles. In a comparative study, liposomal acyclovir demonstrated significantly higher skin permeability and retention, leading to improved antiviral efficacy against HSV-1. The enhanced targeting to infected tissues and sustained drug release helped reduce dosing frequency and improve therapeutic outcomes. The success of the Pfizer-BioNTech and Moderna COVID-19 vaccines represents a groundbreaking application of lipid nanoparticles in antiviral therapy. Upon internalization, the mRNA is translated into antigenic protein, stimulating a strong immune response. The LNPs not only prevent degradation of the mRNA but also facilitate endosomal escape and cytosolic release, proving essential for the effectiveness of these vaccines.

Poly(lactic-co-glycolic acid) (PLGA) nanoparticles have been employed to deliver antiretroviral drugs such as zidovudine (AZT) and tenofovir. In one study, AZT-loaded PLGA nanoparticles exhibited sustained release over 72 hours, improved cellular uptake in HIV-infected macrophages, and reduced cytotoxicity compared to the free drug. These characteristics are crucial for maintaining consistent therapeutic levels, especially in chronic infections like HIV where viral reservoirs are difficult to reach with traditional formulations. In one approach, AuNPs were conjugated with sialic acid derivatives that mimic the natural receptors on host cells. These nanoparticles effectively blocked the binding of the influenza virus hemagglutinin protein, preventing viral entry and replication. The high surface area and tunable chemistry of AuNPs make them excellent platforms for such receptor-targeted antiviral strategies. Lamivudine, used to treat Hepatitis B virus (HBV), has also been incorporated into SLNs to improve its oral bioavailability and hepatocyte targeting. Studies have shown that lamivudine-loaded SLNs not only enhance drug stability but also lead to higher drug accumulation in liver tissue, thereby increasing antiviral efficacy and reducing systemic side effects.

17. COMBINATION THERAPIES OR STRATEGIES TO OVERCOME DRUG RESISTANCE AND ENHANCE TREATMENT OUTCOMES

One of the major challenges in antiviral therapy is the emergence of drug-resistant viral strains, which often arise due to genetic mutations and prolonged monotherapy. Nanotechnology offers a versatile platform to implement combination therapies, where multiple antiviral agents with different mechanisms of action are co-delivered within a single nanocarrier system. For instance, liposomes and polymeric nanoparticles have been used to co-encapsulate reverse transcriptase inhibitors and protease inhibitors for HIV treatment, enabling synergistic antiviral effects, reduced dosing frequency, and better patient adherence. Additionally, nanocarriers can be engineered to incorporate both antiviral drugs and gene-silencing molecules such as siRNA or CRISPR-Cas components that target viral genomes or essential host factors, providing a multifaceted approach to suppress viral replication and reduce resistance. Nanoparticles can also improve drug localization at the infection site, achieving higher local concentrations that surpass the viral mutation threshold and reduce the chance of resistance development. Moreover, stimuli-responsive nanoparticles—which release drugs in response to changes in pH, enzymes, or redox conditions—can provide on-demand release in infected tissues, enhancing efficacy while minimizing systemic exposure. These combination strategies, enabled by nanotechnology, hold great promise in addressing the growing concern of antiviral drug resistance and improving long-term treatment outcomes.

Nanotechnology-based drug delivery vehicles, while offering significant advantages in terms of targeted delivery, stability, and controlled release, also present the potential for immune system interactions that could lead to unwanted side effects. The immune system may recognize nanoparticles as foreign entities, triggering complement activation, phagocytosis by macrophages, or the generation of pro-inflammatory cytokines. This can result in the clearance of nanocarriers from circulation, hypersensitivity reactions, or even chronic inflammation at the site of administration. To mitigate these immune-related challenges, several strategies can be employed. One of the most effective approaches is PEGylation, where polyethylene glycol (PEG) is attached to the surface of nanoparticles, forming a hydrophilic shield that reduces protein adsorption and immune recognition, thereby extending circulation time and minimizing immune clearance. Additionally, the surface charge and size of nanoparticles play a crucial role in immune interactions. Neutral or slightly negative charges tend to reduce non-specific binding to immune cells, while maintaining particle sizes between 20 to 200 nm. Lastly, employing biodegradable and biocompatible materials, such as liposomes, polymers, or lipid nanoparticles, can

further reduce long-term immune activation by ensuring that the nanocarriers are safely broken down and cleared from the body. By carefully designing nanocarriers with these considerations in mind, it is possible to harness the full therapeutic potential of nanotechnology while minimizing adverse immune responses.

A key optimization strategy is to implement phase I trials that not only focus on determining the dose escalation and safety profile of nanocarriers but also on identifying potential immune responses or toxicities specific to nanomaterials, such as complement activation or nanoparticle accumulation in non-target tissues. The design should include detailed biomarker monitoring to assess immune activation, inflammation, and organ function. In subsequent phase II and III trials, assessing the efficacy of these systems should focus on both pharmacokinetics (PK) and pharmacodynamics (PD). This includes understanding the bio-distribution, half-life, and tissue targeting capabilities of the nanocarriers in different populations, such as those with viral infections of varying severity or in immunocompromised individuals. Randomized controlled trials (RCTs) comparing nanotechnology-based delivery systems to conventional antiviral therapies can offer critical insights into the superiority of these novel systems in terms of efficacy, reduced side effects, and patient outcomes. Additionally, incorporating long-term follow-up to monitor the chronic toxicity and the potential for resistance development is vital to ensure the sustainable use of nanotechnology in antiviral therapy. Importantly, trial protocols should be flexible to accommodate the evolving nature of nanomaterials, with continuous monitoring and adaptation of data safety monitoring boards (DSMBs) to address unforeseen adverse effects. Incorporating real-time pharmacovigilance systems that track adverse reactions across diverse populations and environments will further ensure the robustness of clinical trials.

18. FUTURE DIRECTIONS AND EMERGING TRENDS IN ANTIVIRAL DRUG DELIVERY SYSTEMS

As the understanding of viral mechanisms and drug delivery technologies evolves, so do innovative antiviral treatments. Here, we explore several key areas of advancement and emerging trends that are likely to shape the future of antiviral drug delivery systems. Nanotechnology and Nanomedicine Nanotechnology continues to revolutionize antiviral drug delivery through the development of nanoparticles, including liposomes, solid lipid nanoparticles, and polymeric nanoparticles (Sugumaran *et al.* 2024). The use of receptor-mediated endocytosis and other targeting mechanisms is being refined to enhance the delivery of antiviral agents to specific tissues or cellular compartments. Additionally, the development of personalized targeting approaches based on individual patient profiles and viral strains is emerging as a promising strategy to improve treatment outcomes. Vaccines are gaining prominence in antiviral drug delivery. These therapies can specifically target viral RNA or modulate host cell responses to inhibit viral replication. Advances in RNA delivery technologies, such as lipid nanoparticles and viral vectors, are enhancing the stability, efficacy, and targeted delivery of RNA-based drugs. The success of mRNA vaccines against COVID-19 has accelerated interest in applying similar technologies to other viral infections. Advanced Drug Delivery Platforms Innovations in drug delivery platforms are transforming antiviral therapies. Tailoring antiviral therapies based on individual genetic profiles, viral strains, and disease characteristics allows for more effective and targeted treatment. Personalized medicine also involves adjusting drug dosages and delivery methods to suit individual patient needs and improve therapeutic efficacy (Almalik A et al. 2017). Sustainable and green chemistry practices are increasingly being incorporated into the development of antiviral drug delivery systems. Researchers are focusing on using eco-friendly materials, reducing waste, and minimizing the environmental impact of drug manufacturing processes.

19. CONCLUSION

Advances in drug delivery technologies, particularly those involving nanotechnology and targeted delivery systems, are transforming the landscape of antiviral therapies and offering new avenues for effective treatment. As research and development in these fields continue to evolve, they bring forth significant improvements in drug efficacy, safety, and patient compliance, addressing many of the limits associated with traditional antiviral therapies. Targeted delivery systems represent another significant advancement, utilizing various mechanisms to direct antiviral drugs specifically to their sites of action. It includes the use of receptor-mediated endocytosis, where drugs are delivered via ligands that bind to specific cellular receptors and the development of smart delivery systems that respond to environmental stimuli like pH changes or enzyme activity. These systems ensure that drugs are released at the optimal location and time, profiles, and viral strains further refine this approach, enabling more tailored and effective treatments. The integration of these advanced drug delivery technologies into antiviral therapy is addressing many of the challenges faced in treating viral infections. For instance, nanotechnology has improved the pharmacokinetics and pharmacodynamics of antiviral drugs, overcoming issues related to drug resistance and bioavailability. Targeted delivery systems have enhanced the precision of antiviral treatments, reducing the risk of collateral damage to healthy tissues and improving overall treatment outcomes. Looking ahead, the continued evolution of

these technologies promises even more incredible advancements. Innovations in nanotechnology will likely lead to the development of more sophisticated and multifunctional delivery systems, incorporating capabilities such as real-time monitoring and adaptive drug release. Advances in targeted delivery will focus on refining targeting mechanisms, improving specificity, and integrating with other therapeutic modalities to address complex viral infections. Moreover, the convergence of nanotechnology and targeted distribution with emerging fields such as gene editing and personalized medicine will open new frontiers in antiviral therapy. In conclusion, the advances in medicine delivery machineries, including nanotechnology and targeted delivery systems, are reshaping the field of antiviral treatments. These innovations are enhancing the efficacy, safety, and precision of antiviral treatments, offering new hope for effectively managing and curing viral infections.

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