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Nanostructured Lipid Carriers in HIV Therapy: Unlocking the Future of Long-Acting and Targeted Antiretroviral Delivery

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Abstract

Nanostructured lipid carriers (NLCs) have emerged as a transformative platform in HIV therapy, addressing critical limitations such as poor adherence, systemic toxicity, and restricted drug penetration into viral reservoirs. The composition of NLCs integrates solid lipids, liquid lipids, and surfactants within a biocompatible matrix, enhancing drug solubility and stability while enabling sustained and controlled release of antiretrovirals. The classification of NLCs—imperfect type, multiple type, and amorphous type—offers structural versatility for optimizing drug entrapment and release profiles. Various preparation methods, including high-shear homogenization, ultrasonication, and microwave-assisted synthesis, contribute to scalable and reproducible formulations.NLCs are increasingly explored as long-acting delivery systems for HIV therapy, exhibiting extended drug half-life and reduced dosing frequency, which improves patient adherence and minimizes resistance. In vivo studies have demonstrated prolonged systemic retention and enhanced bioavailability compared to conventional formulations. Additionally, targeted delivery strategies facilitated by NLCsenable selective accumulation in HIV reservoirs such as the central nervous system (CNS), lymphoid tissues, and macrophages, overcoming biological barriers like the blood-brain barrier (BBB).Case studies illustrate the successful application of NLCs in specific antiretroviral drugs, including zidovudine, lopinavir, atazanavir, etravirine, and ritonavir, showcasing improved pharmacokinetic profiles, higher entrapment efficiencies, and extended half-lives. Notably, co-loaded NLC formulations have demonstrated synergistic effects, enabling combination therapy within a single nanocarrier for enhanced therapeutic efficacy. As research advances, priorities should include clinical translation, manufacturing scalability, and exploration of NLCs alongside latency-reversing agents and immune modulators. With continued innovation, NLC-based systems hold immense promise in advancing global HIV therapeutic interventions toward a functional cure or eradication.

Keywords: Nanostructured Lipid Carrier, HIV, Targeted therapy, Bioavailability, Sustained drug delivery

Introduction

Human Immunodeficiency Virus (HIV) is a lentivirus belonging to the Retroviridae family that selectively infects and depletes CD4+ T-helper lymphocytes, a critical component of the adaptive

immune response[1]. The progressive attrition of these immune cells culminates in acquired immunodeficiency syndrome (AIDS), characterized by heightened susceptibility to opportunistic infections and certain malignancies[2]. Despite considerable advances in virological research and public health interventions over the past several decades, HIV continues to pose a significant global health burden, affecting an estimated 38 million individuals worldwide. The advent and widespread implementation of antiretroviral therapy (ART), particularly in the form of combination antiretroviral therapy (cART), has transformed HIV infection from a terminal illness into a manageable chronic condition by effectively suppressing plasma viral load and partially restoring immunological competence[3,4].

Nevertheless, the virus exhibits a remarkable ability to establish latent infection in anatomical and cellular reservoirs, including the central nervous system (CNS), lymphoid tissues, gastrointestinal tract, and monocyte-macrophage lineages. These sanctuaries remain pharmacologically inaccessible to conventional antiretroviral regimens due to biological barriers such as the blood-brain barrier (BBB), limited intracellular penetration, and subtherapeutic drug concentrations[5]. As a result, these latent reservoirs serve as persistent sources of viral rebound upon treatment interruption and represent a formidable obstacle to achieving a sterilizing or functional cure. This persistence underscores the need for novel therapeutic modalities and advanced drug delivery strategies capable of achieving targeted, sustained, and efficient distribution of antiretroviral agents to these elusive viral niches[6].

Conventional antiretroviral therapies (ART), while effective in suppressing systemic viral replication, are associated with numerous pharmacological and therapeutic limitations that hinder optimal clinical outcomes. These include inherently low oral bioavailability, abbreviated plasma half-lives, and the necessity for lifelong, strict adherence to daily dosing regimens[7]. Such constraints often culminate in subtherapeutic drug concentrations within pharmacologically privileged compartments—such as the central nervous system (CNS), lymphoid tissues, and macrophage-rich reservoirs—where the virus can persist in a latent state. Inadequate drug penetration into these sanctuary sites significantly compromises the ability to achieve complete viral suppression, facilitating the persistence of viral reservoirs and predisposing patients to viral rebound and therapeutic failure[8].

Furthermore, a substantial proportion of antiretroviral agents are subject to extensive hepatic first-pass metabolism, which markedly diminishes their systemic bioavailability and necessitates higher or more frequent dosing to maintain therapeutic drug levels. The limited permeability of the blood-brain barrier (BBB) presents an additional challenge, restricting the entry of many antiretrovirals into the CNS, thereby impeding effective management of HIV-associated neurocognitive disorders (HAND)[9]. Compounded by the potential for adverse effects and the risk of developing drug resistance due to inconsistent adherence, these pharmacokinetic and pharmacodynamic challenges underscore the exigent need for advanced drug delivery platforms. Such systems should ideally enhance drug stability, prolong systemic circulation, enable site-specific targeting of latent reservoirs, and provide controlled or sustained release profiles to improve patient compliance, minimize dosing frequency, and ultimately optimize long-term virological suppression[10].

Enhancing adherence, drug targeting, and reservoir penetration is paramount for the long-term success of HIV therapy. Poor adherence to antiretroviral regimens remains a major contributor to virological failure and the emergence of drug-resistant viral strains, particularly due to the requirement for lifelong,

daily dosing. Simultaneously, effective targeting of antiretroviral agents to anatomical and cellular reservoirs—such as the central nervous system, lymphoid tissues, and macrophage-rich sites—is critical for achieving durable viral suppression and preventing latent reactivation[11]. Traditional drug formulations often fail to reach these sanctuaries at therapeutic concentrations due to physiological barriers like the blood-brain barrier and intracellular sequestration. Therefore, advanced delivery systems that promote precise targeting, improve pharmacokinetics, and facilitate sustained release hold immense potential to enhance treatment efficacy, reduce dosing burden, and ultimately move closer to functional cure strategies in HIV management[12].

Nanostructured lipid carriers (NLCs) have emerged as a next-generation lipid-based drug delivery system, designed to overcome the limitations of traditional formulations, particularly in the context of poorly water-soluble drugs such as antiretrovirals. Unlike their predecessors—solid lipid nanoparticles (SLNs)—NLCs are composed of a blend of solid and liquid lipids, which results in a less ordered internal structure[13]. This imperfect matrix enhances drug loading capacity, minimizes drug expulsion during storage, and allows for controlled drug release. The nanoscale size of NLCs (typically <200 nm) facilitates enhanced permeation across biological barriers and improves cellular uptake, making them particularly advantageous for targeting viral reservoirs where conventional therapies demonstrate limited efficacy.The versatility of NLCs also lies in their ability to be surface-modified or functionalized to achieve site-specific targeting, reduce systemic toxicity, and bypass efflux transporters that often limit antiretroviral bioavailability. In HIV therapy, NLCs offer a promising strategy to improve central nervous system (CNS) delivery by crossing the blood-brain barrier, thereby addressing one of the major challenges in eradicating HIV from latent CNS reservoirs[14]. Furthermore, their potential to sustain drug release can reduce dosing frequency, which is critical for improving patient adherence and reducing the risk of resistance development. With scalable production methods and excellent biocompatibility, NLCs represent a transformative platform in the development of long-acting, targeted antiretroviral therapies[15].

The aim of this review is to comprehensively examine the potential of nanostructured lipid carriers (NLCs) as an innovative drug delivery platform to overcome the pharmacological challenges inherent in conventional HIV therapy. Specifically, the review seeks to elucidate how NLCs can enhance the bioavailability, targeting efficiency, and sustained release of antiretroviral agents, thereby improving drug penetration into viral reservoirs such as the central nervous system and lymphoid tissues. By critically analyzing recent advances in formulation strategies, preclinical and clinical studies, and surface modification techniques, this review aims to highlight the prospects of NLCs in enabling long-acting, site-specific antiretroviral delivery that can enhance patient adherence, minimize systemic toxicity, and ultimately contribute to more effective and durable HIV management.

2. Challenges in conventional antiretroviral therapy

Conventional antiretroviral therapy (ART) has profoundly transformed HIV pharmacotherapy, achieving sustained viral suppression and enhancing patient longevity. Nevertheless, critical biopharmaceutical constraints continue to impede optimal therapeutic efficacy. These include limited drug permeability, accelerated systemic clearance, restricted biodistribution within latent viral sanctuaries, and the stringent necessity for perpetual adherence to intricate multidrug regimens. Such pharmacokinetic and pharmacodynamic limitations precipitate suboptimal virological responses, therapeutic resistance

emergence, and persistent reservoir retention, accentuating the imperative for next-generation precision-driven drug delivery paradigms.

2.1 Enhancing therapeutic compliance through regimen streamlining

Achieving ≥95% adherence to Highly Active Antiretroviral Therapy (HAART) is imperative for sustained virological suppression and mitigation of antiretroviral resistance emergence. However, lifelong compliance with multicomponent therapeutic regimens poses significant pharmacotherapeutic hurdles, driven by excessive pill burden, high-frequency dosing requirements, and cumulative drug-induced adverse effects.Adherence-enhancing strategies encompass tailored pharmacist-led interventions, cognitive-behavioral reinforcement techniques, and therapeutic regimen rationalization to optimize patient compliance. Fixed-dose combination (FDC) formulations, exemplified by Atripla, have markedly streamlined medication adherence by reducing pill burden. Advanced once-daily FDC constructs, integrating tenofovir, emtricitabine (FTC), elvitegravir, and darunavir, are under development, primarily addressing treatment-naive cohorts. However, there remains an urgent imperative to extend these regimen simplifications toward treatment-experienced patients exhibiting multidrug-resistant HIV strains, thereby augmenting adherence rates and enhancing long-term therapeutic outcomes[16].

2.2 Workforce management concerns

In resource-constrained healthcare settings characteristic of low- and middle-income countries (LMICs), the deficit of highly specialized medical practitioners and the financial burden associated with professional training and remuneration constitute formidable systemic barriers to efficient healthcare provision. While disease-specific intervention frameworks have significantly expanded accessibility to antiretroviral therapy (ART), an increasing emphasis is placed on fortifying the foundational healthcare infrastructure, human resource allocation, and systemic sustainability to holistically address multifaceted medical challenges beyond ART delivery. A pivotal strategy in mitigating service disparities involves the decentralization of healthcare operations, transitioning toward community-centric medical models and redistributing specialized responsibilities through task-shifting initiatives, wherein physician-led interventions are delegated to trained nursing personnel and lay health practitioners. This adaptive realignment has demonstrated marked efficacy in enhancing ART accessibility, augmenting patient adherence rates, and ensuring comprehensive longitudinal follow-up, thereby reinforcing continuity of care and optimizing therapeutic outcomes[17].

2.3 Poor bioavailability

Many antiretroviral pharmacotherapeutics exhibit limited oral bioavailability, predominantly due to intrinsic hydrophobicity and extensive hepatic first-pass metabolic clearance. This biopharmaceutical limitation significantly compromises systemic drug permeation, reducing therapeutic potency and impairing antiviral efficacy. The restricted aqueous solubility of several antiretroviral agents hampers intestinal absorption, leading to suboptimal plasma drug concentrations and attenuated therapeutic index. Additionally, the cytochrome P450 enzymatic system, particularly the CYP3A subfamily, actively metabolizes numerous protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs), further diminishing systemic drug retention and accelerating renal and biliary excretion pathways. To address these pharmacokinetic hurdles, several formulation strategies have been explored, including

lipid-based nanoformulations, solid dispersions, self-emulsifying drug delivery systems (SEDDS), and polymeric nanocarriers. These advanced delivery platforms aim to enhance drug solubility, prolong systemic retention, and facilitate targeted biodistribution within viral reservoirs, thereby optimizing therapeutic efficacy. Moreover, the co-administration of pharmacokinetic enhancers, such as ritonavir, functions as a metabolic inhibitor, reducing CYP-mediated degradation and prolonging drug half-life, ultimately improving patient adherence and clinical outcomes[18].

2.4 Short plasma half-life

The accelerated elimination of antiretroviral agents from systemic circulation results in abbreviated plasma half-lives, necessitating multiple daily dosing to maintain therapeutic drug concentrations. This frequent dosing requirement often leads to inconsistencies in drug administration, causing fluctuations in plasma drug levels that may fall below the minimum effective concentration. Such subtherapeutic exposures not only compromise sustained viral suppression but also create a pharmacological environment conducive to the selection of resistant viral strains. Consequently, the rapid systemic clearance of these agents poses a significant barrier to long-term treatment efficacy and highlights the critical need for drug delivery strategies that prolong circulation time and ensure stable plasma concentrations[19].

2.5 Emergence of drug resistance

Fluctuating plasma drug concentrations, arising from suboptimal adherence or restricted tissue permeability, promote the selection and propagation of resistant viral variants, thereby compromising therapeutic efficacy and constraining future pharmacological interventions. These pharmacokinetic inconsistencies accelerate viral evolutionary adaptation, leading to reduced drug susceptibility, therapeutic failure, and progressive limitations in antiretroviral regimen flexibility[20].

2.6 Limited penetration into viral reservoirs

Physiological barriers within anatomical reservoirs, including the central nervous system (CNS) and lymphoid structures, significantly impede antiretroviral drug permeation, thereby facilitating persistent HIV latency despite systemic pharmacotherapy. The blood-brain barrier (BBB), characterized by highly selective endothelial tight junctions and efflux transport systems, presents a formidable challenge to therapeutic drug penetration, limiting effective viral suppression within neural compartments. Similarly, lymphoid tissues, including secondary lymphoid organs such as lymph nodes and the spleen, exhibit restricted vascular permeability and reticuloendothelial sequestration, contributing to viral reservoir maintenance.These pharmacological constraints underscore the necessity for advanced drug delivery modalities, such as lipid-based nanocarrier systems, targeted prodrug strategies, and efflux transporter inhibition, to enhance CNS and lymphoid bioavailability and mitigate viral persistence within these immune-privileged sites. Optimizing drug physicochemical properties and leveraging transporter-mediated uptake mechanisms remain critical to circumventing these anatomical barriers, ultimately improving long-term virological suppression and therapeutic outcomes[21,22].

2.7 Need for long-acting and targeted strategies

The imperative for next-generation, long-acting and precision-targeted drug delivery systems is underscored by the necessity to maximize pharmacotherapeutic efficacy while minimizing dosing

frequency and mitigating systemic adverse reactions. The advent of sustained-release delivery modalities ensures consistent plasma drug concentrations, facilitating enhanced therapeutic index, reduced dosing burden, and improved patient compliance—key factors in the long-term management of chronic pathologies such as HIV and oncology-based disorders.These bioengineered drug delivery platforms capitalize on nanotechnology-driven enhancements, leveraging biodegradable polymeric carriers, lipid-based nanocarriers, and ligand-functionalized nanoparticles to enable site-specific drug deposition at pathological reservoirs, thereby optimizing therapeutic targeting and restricting off-target toxicities. Furthermore, strategic pharmacokinetic modulation through approaches such as prodrug engineering, transporter-mediated uptake mechanisms, and controlled-release depot formulations augments drug residence time, ensuring prolonged exposure at the intended site of action.In the context of antiretroviral therapy (ART), the integration of long-acting injectable formulations and nanostructured lipid carriers (NLCs) presents significant advancements in viral suppression by sustaining intracellular drug concentrations within critical anatomical sanctuaries, including the central nervous system (CNS) and lymphoid tissues. Similarly, oncology-focused drug delivery paradigms, particularly tumor-targeting nanoparticle systems and antibody-drug conjugates (ADCs), optimize cytotoxic payload delivery, mitigating systemic toxicological manifestations while precisely eliminating malignant cell populations.The translational relevance of prolonged drug exposure and selective targeting strategies extends beyond HIV and cancer, offering paradigm-shifting improvements in autoimmune disease management, neurodegenerative disorders, and antimicrobial therapy. Consequently, the continued evolution of innovative nanocarrier frameworks, bioresponsive drug delivery platforms, and pharmacokinetic optimization approaches remains pivotal in refining therapeutic precision, reducing treatment burden, and enhancing clinical outcomes in chronic disease management[23].

3. Nanostructured Lipid Carriers

3.1 Composition of Nanostructured Lipid Carriers (NLCs)

Nanostructured Lipid Carriers (NLCs) represent an advanced lipid-based nanocarrier paradigm meticulously engineered via strategic coalescence of solid-phase lipids and liquid-phase lipids in the presence of amphiphilic surfactants, fostering enhanced molecular entrapment dynamics. **Table 1.**presents a comprehensive overview of diverse excipients and their respective functional contributions in Nanostructured Lipid Carriers (NLCs).The solid lipid constituents, including stearic acid, glyceryl monostearate, and cetyl palmitate, function as primary matrix-stabilizing agents, imparting structural robustness and crystalline integrity to the formulation. Conversely, liquid-phase lipids—typically lipophilic excipients such as oleic acid, medium-chain triglycerides (MCTs), or isopropyl myristate—are incorporated with strategic intent to disrupt the highly ordered crystalline lattice, thereby introducing molecular imperfections that augment drug entrapment efficiency and optimize loading capacity.**Figure 1** illustrates the structure of NLCs. Surfactants, including polysorbate 80, lecithin, and sodium dodecyl sulfate (SDS), serve a critical stabilizing function, modulating interfacial tension and preempting colloidal aggregation, ensuring dispersion homogeneity and long-term stability of the lipid matrix. The solid-to-liquid lipid ratio, surfactant selection, and processing variables exert profound influence on particle dimensionality, encapsulation efficacy, and release kinetics, collectively dictating the pharmacokinetic and physicochemical performance of the finalized NLC construct[24–27].

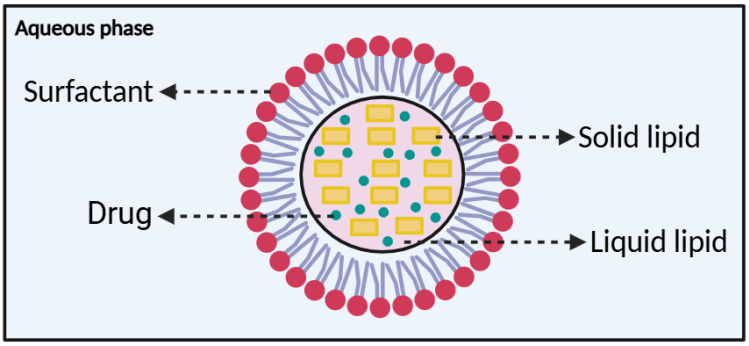

Figure 1. Structure of NLCs

Table 1 Various excipients and their functional roles in Nanostructured Lipid Carriers (NLCs)

Component	Examples	Function
Solid lipids	Stearic acid, Glyceryl monostearate, Cetyl palmitate, Behenic acid, Tripalmitin, Precirol ATO 5, Compritol 888 ATO, Dynasan 114 (Glyceryl trimyristate), Dynasan 118 (Glyceryl tristearate), Palmitic acid	In Nanostructured Lipid Carriers (NLCs), solid lipids provide structural rigidity, ensuring controlled drug release and enhanced stability by maintaining a semi-crystalline matrix.
Liquid lipids	Oleic acid, Medium-chain triglycerides (MCTs), Isopropyl myristate, Caprylic/capric triglycerides, Squalene, Castor oil, Miglyol 812, Labrafaclipophile, Ethyl oleate, Soybean oil	Liquid lipids introduce structural imperfections that improve drug entrapment efficiency and increase loading capacity by disrupting crystallinity.
Surfactant	Polysorbate 80, Lecithin, Sodium dodecyl sulfate (SDS), Poloxamer 188, Poloxamer 407, Cremophor EL, Span 20, Span 80, Tween 20, Tween 80	Surfactants are essential for stabilizing the dispersion, reducing interfacial tension, and preventing aggregation, ensuring homogeneous nanoparticle formation and long-term formulation stability. These components collectively determine particle size, drug bioavailability, and release kinetics, optimizing NLC efficacy in pharmaceutical applications.

3.2Types of Nanostructured Lipid Carriers

Nanostructured Lipid Carriers (NLCs) are systematically categorized into three distinct structural types—imperfect-type, multiple-type, and amorphous-type—based on their internal physicochemical

arrangement. Imperfect-type NLCs are formulated by integrating structurally incompatible lipid constituents, resulting in a partially disrupted crystalline matrix that facilitates enhanced drug encapsulation and mitigates drug expulsion during storage. Multiple-type NLCs, characterized by oil nanocompartments embedded within a solid lipid framework, establish a multi-phase "oil-in-solid lipid-in-water" system, optimizing co-delivery of hydrophilic and lipophilic therapeutic agents. In contrast, amorphous-type NLCs are specifically designed to retain a non-crystalline lipid phase, thereby circumventing drug expulsion linked to crystallization phenomena during extended storage durations, ensuring consistent pharmaceutical stability. These distinct structural configurations play a pivotal role in determining optimal drug delivery performance, influencing parameters such as drug loading efficiency, sustained release kinetics, and long-term formulation stability[14,28,29].

Table 2. Classification of Nanostructured Lipid Carriers (NLCs)

NLC Type	Structure Description	Advantages
Imperfect Type	Partially disordered matrix	Higher drug loading, reduced expulsion
Multiple Type	Oil droplets within solid lipid matrix	Suitable for multiple drugs, sustained release
Amorphous Type	Non-crystalline matrix	Prevents crystallization, enhanced stability

3.3 Methods of preparation

The fabrication of Nanostructured Lipid Carriers (NLCs) encompasses multiple strategic methodologies, each possessing distinct operational merits and inherent constraints.**Table 3** illustrates the various methods used for preparation of NLCS. Among these, High-Pressure Homogenization (HPH) stands out as a widely implemented technique, leveraging intensified mechanical shear forces to modulate particle dimensionality and achieve homogeneous colloidal dispersion. This shear-induced particle refinement can be executed under thermal or cryogenic conditions, contingent upon the thermosensitivity of the encapsulated pharmacological agent.Conversely, the solvent evaporation approach necessitates the dissolution of lipid constituents within an organic solvent, followed by emulsification in an aqueous phase. Subsequent solvent evaporation facilitates nanoparticle generation, ensuring optimized drug encapsulation dynamics. Another effective strategy, melt emulsification, involves thermal liquefaction of the lipid phase, subsequent emulsification within an aqueous surfactant milieu, and progressive solidification via cooling, thereby yielding a stabilized NLC matrix.Additional nanotechnological methodologies include ultrasonication, wherein acoustic cavitation energy is employed to precisely fragment lipid aggregates, thereby achieving narrowed size distribution and enhanced formulation homogeneity. Similarly, microemulsion-based techniques operate through self-assembly phenomena, wherein pre-formed nanoemulsions undergo controlled aqueous dilution, culminating in spontaneous NLC formation[30,31].

Table 3. Method of preparation of NLCs

Sr. No.	Method of Preparation	Procedure

1.	High-Pressure Homogenization	High-Pressure Homogenization (HPH) represents a widely utilized nanoformulation technique for the fabrication of Nanostructured Lipid Carriers (NLCs), wherein the lipid phase is intricately emulsified within an aqueous surfactant-containing matrix. The resultant colloidal dispersion is subjected to intensified mechanical forces, typically operating within a pressure range of 500–2000 bar, compelling lipid droplets to traverse a highly constrained homogenization gap, thereby achieving nanoscale particle fragmentation and enhanced dispersion uniformity. HPH can be conducted under thermal or cryogenic conditions, contingent upon the melting characteristics and thermosensitivity of the selected lipid excipients. This highly scalable methodology is extensively employed in large-scale pharmaceutical production, offering precise particle size control, reproducibility, and formulation robustness.
2.	Emulsification-ultrasonication method	This lipid-based nanocarrier fabrication approach, akin to High-Pressure Homogenization (HPH), entails molecular integration of the active pharmaceutical agent with both solid-phase and liquid-phase lipid matrices. The lipid blend undergoes thermal liquefaction, wherein it is heated 5–10 °C above the solid lipid's phase transition temperature, ensuring uniform molecular dispersion. Concurrently, the amphiphilic surfactant is dissolved within a thermally stabilized aqueous medium, which is subsequently incorporated into the lipid phase, yielding a pre-emulsified colloidal system. This dispersion is then subjected to intensified homogenization forces followed by ultrasonic cavitation, facilitating nanoscale droplet refinement. The resultant homogeneous lipid emulsion is diluted in distilled water and gradually cooled to ambient conditions, thereby solidifying the lipid nanoparticles into a structurally stable Nanostructured Lipid Carrier (NLC) system.
3.	Solvent diffusion or solvent evaporation method	The solvent evaporation or diffusion technique is employed in the fabrication of Nanostructured Lipid Carriers (NLCs), wherein solid and liquid lipid components are solubilized within an organic solvent matrix. Following this, the organic phase undergoes controlled solvent elimination or diffusive migration into an aqueous surfactant-containing system, inducing lipid precipitation and nanoparticle formation. The resultant

		colloidal dispersion is then subjected to intensified homogenization or ultrasonic cavitation, facilitating precise particle size reduction and enhanced formulation uniformity. This method is recognized for its operational simplicity, cost-efficiency, and versatility in encapsulating both hydrophobic and hydrophilic pharmacological agents.
4.	Hot melt extrusion	Hot melt extrusion is a thermal-processing technique utilized in the fabrication of Nanostructured Lipid Carriers (NLCs), wherein solid-phase and liquid-phase lipids are subjected to elevated temperatures exceeding their respective melting thresholds, resulting in the formation of a homogeneous molten lipid matrix. The active pharmaceutical ingredient (API) is integrated within this liquefied lipid phase, ensuring uniform molecular dispersion. The molten blend is subsequently extruded through a precision-controlled nozzle, facilitating nanoparticle generation via controlled solidification dynamics. As the extrudate undergoes progressive cooling, the lipid matrix solidifies, yielding a structurally stabilized NLC system. This highly scalable methodology offers enhanced drug incorporation efficiency, consistent particle size distribution, and optimized bioavailability, making it particularly advantageous for encapsulating poorly water-soluble pharmacotherapeutics.
5.	Microemulsion	The microemulsion technique generates a thermodynamically stable oil-in-water dispersion, comprising lipid components, amphiphilic surfactants, and active pharmaceutical agents, which undergo controlled cooling to facilitate Nanostructured Lipid Carrier (NLC) formation. This solvent-free, mild formulation approach accommodates both hydrophilic and lipophilic drug entities, though its intricate formulation dynamics present challenges for large-scale industrial implementation.
6.	Melt-dispersion method	The melt-dispersion technique entails thermal liquefaction of solid-phase and liquid-phase lipid components, followed by dispersion into a surfactant-stabilized aqueous system. Upon controlled cooling, the lipid matrix solidifies, yielding Nanostructured Lipid Carriers (NLCs). This method is recognized for its operational simplicity, solvent-free nature, and cost-

		efficiency, making it particularly advantageous for thermo-sensitive pharmaceutical compounds.
7.	Coacervation method	Lipids and surfactants are dissolved in an organic solvent, then mixed with an aqueous phase to form drug-loaded coacervates, which solidify into NLCs. Though it allows control over particle size and drug loading, its complexity and use of solvents limit its popularity.

4.NLCs as long-acting delivery systems for HIV therapy

4.1 Mechanism of controlled and sustained drug release

Nanostructured lipid carriers (NLCs) represent an advanced lipid-based drug delivery system that enables controlled and sustained release of antiretroviral agents, addressing key limitations of conventional HIV therapies. The biphasic lipid matrix of NLCs—composed of a blend of solid and liquid lipids—creates a less-ordered internal structure, allowing for higher drug loading and slower drug expulsion. Upon administration, the drug is released in a regulated manner either by diffusion from the lipid matrix or through gradual degradation of the lipid components. This prolonged release maintains plasma drug concentrations within the therapeutic window for extended durations, reducing dosing frequency and improving adherence[32–34].

In the context of HIV, sustained drug release from NLCs ensures consistent antiretroviral exposure at systemic and cellular levels, including in hard-to-reach viral reservoirs such as the central nervous system and lymphatic tissues. Moreover, the nanoscale size and lipidic nature of NLCs enhance bioavailability and facilitate cellular uptake, enabling more effective intracellular delivery. By modulating release kinetics through lipid composition, surfactant type, and production parameters, NLCs can be tailored to optimize pharmacokinetics and therapeutic outcomes. This approach holds particular promise for developing long-acting antiretroviral formulations, potentially transforming HIV treatment paradigms by minimizing resistance risks and enhancing patient quality of life[35–37].

4.2*In vivo* studies showing extended half-life and reduced dosing frequency

Nanostructured lipid carriers (NLCs) significantly contribute to the extension of antiretroviral drug half-life in HIV therapy by enabling sustained and controlled drug release. Their unique matrix—comprising both solid and liquid lipids—creates a disordered lipid network that slows drug diffusion and degradation, maintaining therapeutic plasma concentrations over extended periods. This prolonged systemic presence reduces the need for frequent dosing, thereby enhancing patient adherence and minimizing the risk of viral resistance. Additionally, the lipid-based nanoscale structure of NLCs promotes improved bioavailability and cellular uptake, particularly into HIV reservoirs, further supporting extended pharmacological activity and improved therapeutic outcomes.

Arshad Ali Khan et al. (2019), conducted a study on freeze-dried lopinavir-loaded Nanostructured Lipid Carriers (NLCs) aimed at enhancing intracellular drug uptake and optimizing pharmacokinetic performance. The findings demonstrated that the lopinavir-encapsulated NLCs significantly prolonged the elimination half-life, achieving 16.5 ± 2.36 hours, in contrast to the free lopinavir suspension, which

exhibited a markedly lower half-life of 5.4 ± 0.0904 hours. This notable pharmacokinetic enhancement is attributed to the lipid matrix-based encapsulation, which modulates drug release kinetics, reduces hepatic first-pass metabolic degradation, and augments systemic drug residence time, ultimately improving bioavailability and therapeutic efficacy[38].

Abdul Muheem et al. (2024) conducted a study on the fabrication of TPGS-functionalized Etravirine-loaded lipidicnanocarriers, designed as a novel bioavailability-enhancing strategy for targeted lymphatic delivery. The findings demonstrated a significant prolongation in the elimination half-life of both Etravirine–TPGS–NLCs+CYHD (23.92 hours) and ERVN–TPGS–NLCs (54.45 hours), indicative of extended systemic drug retention and optimized pharmacokinetic performance. This enhancement is primarily attributed to the lipidic matrix-based encapsulation, which modulates drug solubilization dynamics, mitigates hepatic first-pass metabolism, and facilitates lymphatic drug trafficking, ensuring sustained therapeutic exposure. The incorporation of d-α-Tocopheryl polyethylene glycol succinate (TPGS) plays a pivotal role in augmenting cellular uptake, inhibiting P-glycoprotein-mediated efflux, and improving drug permeation, further contributing to the enhanced bioavailability profile[39].

Satish Rojekar et al.(2021), designed and optimized Etravirine-loaded Nanostructured Lipid Carriers (NLCs) for precision-targeted drug delivery across multiple anatomical HIV-1 reservoirs, aiming to enhance pharmacokinetic performance and therapeutic efficacy. The study demonstrated a significant prolongation of the elimination half-life, wherein Etravirine-NLCs exhibited an extended systemic retention of 172.22 ± 11.32 hours, markedly surpassing the half-life of the conventional Etravirine solution (59.50 ± 10.20 hours). This pharmacokinetic augmentation is attributable to the lipid-based encapsulation strategy, which modulates drug release kinetics, mitigates hepatic first-pass metabolism, and facilitates targeted biodistribution, thereby optimizing antiviral exposure within persistent HIV reservoirs. The findings underscore the potential of lipid nanocarrier systems in maximizing drug bioavailability, reducing dosing frequency, and improving long-term virological suppression, solidifying NLCs as a viable strategy for advanced antiretroviral therapy (ART) applications[40].

5. Targeted delivery using NLCS: reaching HIV reservoirs

Targeting the central nervous system (CNS), lymphoid tissues, and macrophages is of paramount importance in HIV therapy, as these sites constitute key anatomical and cellular reservoirs where the virus can persist in a latent or low-replication state, even under suppressive antiretroviral therapy (ART).**Table 4**. Illustrates different strategies developed utilizing NLCs to target HIV reservoirs. The blood-brain barrier (BBB) limits the penetration of many conventional antiretroviral drugs into the CNS, allowing HIV to persist in perivascular macrophages and microglial cells. This contributes to the development of HIV-associated neurocognitive disorders (HAND), which continue to affect a significant proportion of people living with HIV despite systemic viral suppression. Similarly, lymphoid tissues provide a niche for viral persistence due to limited drug accessibility and the abundance of target cells such as CD4+ T cells and follicular dendritic cells.

Macrophages also play a central role in HIV pathogenesis by serving as long-lived viral reservoirs and vehicles for virus dissemination across various tissues, including the CNS. Their resistance to the cytopathic effects of HIV and ability to evade immune detection make them particularly challenging to target. Inadequate drug concentrations within these compartments not only allow the virus to endure but also promote the emergence of drug-resistant strains. Therefore, the development of drug delivery

systems that can efficiently target and penetrate these reservoirs—such as nanostructured lipid carriers (NLCs)—is essential for achieving comprehensive viral suppression, preventing viral rebound, and moving toward the ultimate goal of HIV eradication.

Table 4. Strategies developed using NLCs for targeting HIV reservoirs

Author	Description	Targeting site
Ketan Mahajan et al. (2021)[41]	Fabricated Layer-by-Layer Engineered Nanostructured Lipid Carriers for CD-44 Receptor-Mediated Targeting in HIV-Infected Macrophages to Enhance HIV-1 Suppression.	Macrophages
Satish Rojekar et al. (2022) [42]	Fabricated Mannose-Conjugated Nano-Selenium Encapsulated Nanostructured Lipid Carriers of Etravirine for Targeted HIV Reservoir Delivery.	Brain, ovary, lymph nodes
Babita Garg et al. (2019) [43]	Fabricated Nanostructured Lipid-Based Carriers of Lopinavir for Optimized Therapeutic Intervention in HIV-Associated Neurocognitive Dysfunction	Brain
Ketan Mahajan et al. (2021)[44]	Formulated Efavirenz-encapsulated nanostructured lipid carriers to enhance and sustain viral suppression in HIV-infected macrophages.	Macrophages
Satish Rojekar et al. (2021)[40]	Fabricated a nanostructured lipid-based carrier system encapsulating Etravirine to achieve comprehensive organ-specific targeting of latent HIV-1 reservoirs, validated through in-vivo proof-of-concept experimentation.	Liver, ovary, lymph nodes, and brain

6. Case Studies: NLCs for Specific Antiretroviral Drugs

6.1 Ritonavir-loaded NLCs

This study focuses on the development of nanostructured lipid carriers (NLCs) encapsulating ritonavir to enhance its oral bioavailability and minimize adverse effects. Ritonavir, a protease inhibitor within the highly active antiretroviral therapy (HAART) regimen, is currently used as a pharmacokinetic booster rather than a direct antiviral agent due to its low bioavailability and side effects. The NLCs were formulated using a combination of solid and liquid lipids, including alpha-tocopherol, employing a hot-emulsion and ultrasonication technique. Characterization studies assessed particle size (273.9–458.7

nm), polydispersity index (PDI: 0.314–0.480), zeta potential (−52.2 to −40.9 mV), and entrapment efficiency (47.37–74.51%). In vitro drug release indicated higher release in acidic conditions compared to neutral pH, while in vivo pharmacokinetic evaluation demonstrated a sevenfold increase in the area under the curve (AUC) and a tenfold enhancement in maximum plasma concentration (Cmax) compared to pure drug suspension, underscoring the potential of NLCs in optimizing ritonavir's therapeutic efficacy[45].

6.2 Lopinavir-loaded NLCs

This study focuses on the formulation of lopinavir-incorporated nanostructured lipid carriers (NLCs) using high-shear homogenization, followed by freeze-drying with trehalose as a cryoprotectant. In vitro drug release assessments conducted in simulated gastric and intestinal fluids revealed an initial burst release. The optimized freeze-dried formulation (LPV-NLC-7-Tres) exhibited a nanoscale dimension of 286.8 ± 1.3 nm, a polydispersity index of 0.413 ± 0.017, a zeta potential of −48.6 ± 0.89 mV, and an entrapment efficiency of 88.31 ± 2.04%. Morphological analysis via transmission and scanning electron microscopy confirmed a spheroidal topology, while differential scanning calorimetry ruled out physicochemical incompatibilities between the drug and lipid matrix. Cellular uptake investigations using Caco-2 cells demonstrated superior internalization of LPV-NLC-7-Tres compared to free LPV suspension. Stability assessments over six months indicated a minimal expansion of particle size (~40 nm), with negligible deviations in dispersity, charge potential, and drug retention at refrigerated conditions (5 °C ± 3 °C). Pharmacokinetic profiling in male Wistar rats underscored a remarkable 6.98-fold augmentation in oral bioavailability relative to conventional LPV suspension, emphasizing the viability of NLCs in enhancing the systemic absorption of protease inhibitors[38].

6.3 Zidovudine-loaded NLCs

This study presents an innovative microwave-assisted approach for synthesizing lipid nanoparticles, characterized by its one-pot, single-step process that is rapid, cost-effective, scalable, and free from organic solvents. This method was utilized to formulate nanostructured lipid carriers (NLCs) encapsulating the hydrophilic antiretroviral drug zidovudine (AZT). A comparative evaluation of NLCs produced via hot ultrasonication and microwave-based synthesis was conducted using a Quality by Design (QbD) framework. The optimized formulations exhibited favorable physicochemical attributes for oral delivery, including a nanoscale size range (100–300 nm), low polydispersity index (<0.3), and a stable negative zeta potential (>−20 mV). Morphological assessments using transmission electron microscopy (TEM) confirmed a spherical architecture, aligning with findings from dynamic light scattering (DLS). The AZT-loaded NLCs remained physically stable over 45 days and demonstrated cytocompatibility with Jurkat T cells. Controlled drug release profiles under simulated gastric and plasma conditions underscored the formulation’s potential for sustained delivery, reinforcing the viability of microwave-assisted synthesis in enhancing antiretroviral drug bioavailability[46].

6.4 Atazanavir-loaded NLCs

This study explores the formulation of Atazanavir-loaded nanostructured lipid carriers (NLCs) to enhance brain bioavailability for improved NeuroAIDS management. Given Atazanavir’s limited central nervous system penetration when administered orally, the study employs a Quality by Design approach, optimizing the formulation using the Box–Behnken design. The optimized NLCs exhibit a nanoscale

dimension of 227.6 ± 5.4 nm, high entrapment efficiency (71.09% ± 5.84%), and substantial drug loading capacity (8.12% ± 2.7%). Drug release follows a biphasic pattern, with an initial rapid release (60% within 2 hours) followed by sustained delivery. Pharmacokinetic evaluations reveal a 2.75-fold increase in peak brain concentration (Cmax) and a fourfold enhancement in brain bioavailability compared to conventional drug suspension. These findings underscore the potential of NLCs as a viable strategy for encapsulating hydrophobic drugs and facilitating targeted brain delivery, thereby improving Atazanavir's therapeutic efficacy in NeuroAIDS treatment[47].

6.5 Etravirine-loaded NLCs

This study presents a nanocarrier-based strategy for enhancing the bioavailability and therapeutic potential of Etravirine in HIV treatment, addressing the inherent limitations of conventional antiretroviral therapies. Due to unfavorable physicochemical properties restricting brain penetration, a monophasic hot homogenization approach was employed to formulate nanostructured lipid carriers (NLCs), generating polydisperse nanoparticles (50–1000 nm) through ultrasonication. The NLC formulation exhibited superior anti-HIV1 efficacy, demonstrating enhanced therapeutic index and improved cellular uptake, as confirmed by confocal microscopy and flow cytometry. Pharmacokinetic evaluations highlighted substantial improvements over the plain drug solution, attributed to molecular dispersion within the lipid matrix. Biodistribution studies in rats revealed a significant increase in Etravirine concentration across multiple organs, including the brain, liver, ovary, and lymph nodes. These findings underscore the promise of ETR-NLC systems as a viable strategy for multi-site targeted drug delivery, potentially advancing HIV/AIDS eradication efforts[40].

7. Future prospects

The development of nanostructured lipid carriers (NLCs) represents a promising frontier in antiretroviral drug delivery, particularly in the context of overcoming biological barriers and achieving long-acting, site-specific delivery. Future research should aim to optimize the physicochemical properties of NLCs—such as particle size, surface charge, and lipid composition—to enhance their ability to cross the blood-brain barrier and accumulate in lymphoid tissues and macrophage-rich sites, which are major viral reservoirs. Additionally, functionalization of NLCs with targeting ligands (e.g., transferrin, mannose) offers a strategic route for cell-specific delivery, minimizing systemic toxicity and maximizing therapeutic efficacy.

Advanced formulation techniques incorporating stimuli-responsive or "smart" lipids may further allow for on-demand drug release in response to physiological triggers, such as pH or enzyme activity within infected microenvironments. Integration of NLC-based systems with next-generation antiretrovirals, including long-acting injectable and latency-reversing agents, could potentially revolutionize the landscape of HIV treatment by facilitating both suppression and eradication strategies. Moreover, the combination of NLCs with CRISPR-Cas or RNAi technologies may offer innovative tools for directly targeting proviral DNA or gene silencing within latent reservoirs.

To translate these promising strategies into clinical application, future studies must focus on large-scale manufacturing, regulatory standardization, and comprehensive safety and pharmacokinetic profiling. Collaborative efforts between pharmaceutical scientists, clinicians, and regulatory bodies will be

essential to accelerate the clinical adoption of NLCs, with the ultimate goal of achieving functional cure or complete eradication of HIV.

Conclusion

Nanostructured lipid carriers (NLCs) represent a promising leap forward in the advancement of HIV therapy, offering a highly adaptable platform that addresses critical limitations of conventional antiretroviral treatment. This review highlights the significant strides made in leveraging NLCs for long-acting and targeted drug delivery—two pillars essential for overcoming challenges such as poor adherence, frequent dosing, systemic toxicity, and inadequate penetration into viral reservoirs. By combining solid and liquid lipids within a biocompatible matrix, NLCs improve drug solubility and stability, allowing for sustained and controlled release of antiretrovirals. This long-acting behavior not only maintains therapeutic plasma concentrations over extended periods but also reduces the dosing frequency, thereby improving patient adherence and minimizing the risk of resistance.Furthermore, the targeted delivery capabilities of NLCs—enabled by surface modifications such as PEGylation or ligand conjugation—facilitate selective accumulation in key HIV reservoirs, including the central nervous system (CNS), lymphoid tissues, and macrophages. These strategies enhance NLCs' ability to traverse biological barriers like the blood–brain barrier (BBB) and preferentially deliver payloads to infected cells, addressing a major obstacle in achieving viral suppression in sanctuary sites.This review also presents several case studies illustrating the application of NLCs for specific antiretroviral drugs, such as zidovudine, lopinavir, atazanavir, etravirine, and ritonavir-loaded formulations. These studies demonstrate improved pharmacokinetic profiles, higher entrapment efficiencies, favorable particle sizes, and extended half-lives in vivo. In particular, NLCs co-loaded with multiple drugs have shown synergistic effects, enabling combination therapy within a single nanocarrier and further enhancing therapeutic efficacy.Overall, this review underscores that NLCs are not only capable of optimizing current antiretroviral strategies but also open new avenues for future therapeutic interventions. As research progresses, priorities should include clinical translation, manufacturing scale-up, and exploration of NLCs in conjunction with novel agents such as latency-reversing agents or immune modulators. With continued innovation and rigorous validation, NLC-based systems have the potential to significantly advance the global fight toward a functional cure or eradication of HIV.

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