

Review Article

Lipid Nanoparticles in Drug Delivery: Advances, Challenges, and Clinical Prospects

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Abstract

Lipid nanoparticles have emerged as a highly promising platform for drug delivery, offering remarkable advantages such as biocompatibility, ease of preparation, scalability, and the ability to encapsulate a wide range of therapeutic agents including hydrophilic and hydrophobic drugs as well as nucleic acids. Over the past decades, significant progress has been made in the design and optimization of various types of LNPs, including liposomes, solid lipid nanoparticles, and nanostructured lipid carriers, each tailored to balance stability, drug loading, and release profiles. Advances in lipid chemistry, helper lipids, and surface modification strategies have enhanced delivery efficiency and reduced toxicity, enabling clinical successes such as FDA-approved mRNA vaccines and RNAi therapies. Despite these advances, challenges remain in achieving long-term stability, overcoming biological barriers such as the blood-brain barrier, managing immunogenicity, and ensuring reproducible large-scale manufacturing. Future directions focusing on improved targeting through ligand and receptor engineering, integration with advanced gene editing tools like CRISPR, and next-generation LNPs with enhanced functionalities are poised to expand the therapeutic potential and personalized applications of this versatile platform. Thus, lipid nanoparticles stand as a transformative technology with broad clinical prospects in infectious diseases, cancer, genetic disorders, and beyond, heralding a new era of precision medicine. The aim of this review is to comprehensively encapsulate the advancements, challenges, and clinical potential of lipid nanoparticles as drug delivery systems.

Keywords

Lipid Nanoparticles, RNA therapies, Phosphatidylethanolamine, Liposomes, Drug Delivery

1. Introduction

Lipid nanoparticles (LNPs) have become a cornerstone in the field of drug delivery due to their unique ability to encapsulate and protect therapeutic agents such as small molecules, nucleic acids, and proteins, facilitating targeted and controlled delivery [1]. These spherical vesicles, typically ranging from 10 to 1000 nanometers, are composed of a mixture of solid and liquid lipids stabilized by surfactants, which enhances their stability and biocompatibility [2-4].

What distinguishes LNPs from traditional liposomes is their complex composition, which often includes phospholipids, cholesterol, ionizable and cationic lipids, and polyethylene glycol (PEG)-modified lipids, allowing for optimized drug loading, protection, and release mechanisms [5].

The history of LNP development began with the discovery of liposomes in the 1960s, which laid the foundation for the next-generation solid lipid nanoparticles (SLNs) and

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nanostructured lipid carriers (NLCs) that offer improved stability and targeting abilities [6]. These advancements have been pivotal in overcoming challenges related to drug solubility, stability, and delivery efficiency, especially for sensitive biomolecules. The clinical relevance of LNPs surged with the successful deployment of mRNA vaccines for COVID-19, demonstrating their capacity to deliver nucleic acid payloads safely and effectively in humans [7, 8]. Beyond vaccines, LNPs have been extensively explored for cancer therapeutics by enabling targeted delivery of chemotherapeutic drugs and RNA molecules to tumor sites, thereby enhancing therapeutic efficacy while minimizing systemic toxicity [9-11]. Additionally, they play a crucial role in gene therapy and genome editing applications, delivering siRNA, miRNA, and CRISPR components into cells to modulate gene expression. The continual evolution and adaptation of LNP technology underscore their vital role in advancing nanomedicine and precision therapeutics in diverse clinical settings [12].

2. Types and Composition of Lipid Nanoparticles

Lipid nanoparticles (LNPs) used in drug delivery primarily include liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), each differing in composition, structure, and drug delivery characteristics [7, 13]. Liposomes are spherical vesicles consisting of one or more phospholipid bilayers enclosing an aqueous core, allowing them to encapsulate both hydrophilic and hydrophobic drugs [14]. They are composed mainly of natural or synthetic phospholipids and cholesterol, which stabilize the bilayers and enhance membrane fluidity. Although liposomes offer excellent biocompatibility and versatility, their relatively fragile bilayer structure can limit stability and drug retention [15].

Solid lipid nanoparticles (SLNs) represent the first generation of lipid nanoparticles and are composed of lipids that remain solid at both room and body temperature [16]. These particles feature a solid lipid core matrix stabilized by surfactants, providing improved physical stability compared to liposomes [17]. However, SLNs often suffer from low drug loading capacity and the risk of drug expulsion during storage due to the highly ordered crystalline structure of the lipid core. This can lead to an initial burst release of the encapsulated drug, which may undermine controlled delivery efforts [13, 18].

Nanostructured lipid carriers (NLCs) were developed as a second generation of lipid nanoparticles to address the limitations observed in SLNs [19]. NLCs are composed of a mixture of solid and liquid lipids, resulting in a less ordered, imperfect lipid matrix that offers enhanced drug loading capacity and reduced drug expulsion [20]. The presence of liquid lipids creates spaces within the solid lipid matrix, allowing for higher payload incorporation and a more controlled and

sustained release profile [20, 21].

Key lipid components common to these systems include phospholipids, cholesterol, ionizable and cationic lipids, and polyethylene glycol (PEG)-conjugated lipids. Phospholipids form the structural basis for bilayers in liposomes and contribute to biocompatibility, while cholesterol modulates membrane fluidity and stability [15, 22]. Ionizable and cationic lipids play a critical role in nucleic acid delivery by facilitating complexation with the negatively charged genetic material and promoting endosomal escape [23, 24]. PEGylated lipids are often incorporated to confer steric stabilization, improve circulation time, and reduce recognition by the immune system [25-27].

The structural differences between these lipid nanoparticles impact their drug loading capacities and release behaviors significantly [28]. Liposomes, with their aqueous core and bilayer membrane, excel in encapsulating a range of molecules but may have limited long-term stability. SLNs provide enhanced physical stability due to their solid core but are constrained by lower drug loading and potential drug leakage. NLCs, with their hybrid solid-liquid lipid matrix, offer a balanced improvement in both drug loading capacity and controlled release, making them highly attractive for more effective drug delivery applications [19]. Overall, the choice among these lipid nanoparticle types depends on the nature of the therapeutic agent, desired release kinetics, stability requirements, and clinical application, underscoring the importance of understanding their unique composition and structure-function relationships [13, 14].

3. Mechanisms of Drug Delivery

Lipid nanoparticles (LNPs) serve as effective drug delivery vehicles through several key mechanisms that enable encapsulation, protection, cellular uptake, and targeted release of therapeutic agents [29]. LNPs can encapsulate a wide variety of drugs, including hydrophilic, hydrophobic molecules, and nucleic acids, by incorporating them within their lipid bilayers or core matrices [30]. This encapsulation shields the payload from enzymatic degradation and improves its stability and bioavailability. Upon administration, LNPs interact with cellular membranes primarily through lipid membrane fusion and endocytosis pathways such as clathrin-mediated, caveolae-mediated endocytosis, or micropinocytosis. A critical step in effective drug delivery is the escape of LNPs from endosomal compartments into the cytoplasm [6]. This is partly facilitated by ionizable and cationic lipids that become positively charged in the acidic endosomal environment, promoting fusion with and disruption of the endosomal membrane to release the cargo safely inside the cell.

To enhance delivery specificity, LNPs can be surface-modified with targeting ligands such as antibodies, peptides, or aptamers that recognize and bind to receptors overexpressed on target cells, allowing for active targeting [31]. Additionally, polyethylene glycol (PEG)-modified lipids on

the LNP surface confer steric stabilization, prolonging circulation time by reducing opsonization and clearance by the immune system, though PEG can be designed to shed in certain environments for timely release [27]. Passive targeting through the enhanced permeability and retention (EPR) effect is especially exploited in cancer therapeutics, where LNPs accumulate preferentially in tumor tissues due to leaky vasculature and poor lymphatic drainage [32].

Together, these mechanisms enable LNPs to protect therapeutic agents, facilitate cellular internalization, escape intracellular trafficking barriers, and deliver drugs selectively to the desired sites, maximizing therapeutic efficacy and minimizing off-target effects [29]. Optimization of lipid composition, surface chemistry, and ligand conjugation is thus critical to tailor LNPs for specific drug delivery challenges.

4. Advances in Lipid Nanoparticle Technologies

Recent advances in lipid nanoparticle (LNP) technologies have significantly bolstered their effectiveness as drug delivery systems, particularly for mRNA and RNA therapies exemplified by the success of COVID-19 vaccines [33]. One major improvement lies in the formulation process, where microfluidic and flow chemistry techniques have enabled precise control over particle size, uniformity, and drug loading efficiency [34]. These methods maximize encapsulation rates and produce homogenous LNPs typically in the 60–100 nm size range, which is optimal for cellular uptake and biodistribution. Stability enhancements have been achieved by optimizing the lipid composition, including the use of ionizable lipids that remain neutral during circulation but gain positive charge in acidic endosomal environments to promote endosomal escape and reduce systemic toxicity [35].

Helper lipids such as dioleoyl phosphatidylethanolamine (DOPE), cholesterol, and phosphatidylcholine are integral to these formulations, contributing to particle integrity, membrane fusion capacity, and intracellular release dynamics [36]. For instance, DOPE aids in destabilizing endosomal membranes to facilitate payload release, while cholesterol enhances in vivo stability and circulation time. The incorporation of PEGylated lipids extends half-life by reducing opsonization but can be engineered for reversible shedding to balance circulation and cellular uptake [37].

Novel fabrication approaches, including continuous flow reactors like vortex tube reactors, have emerged to address scale-up production challenges by offering better process reproducibility, higher throughput, and lower batch-to-batch variability [38]. These platforms also enable fine-tuning of formulation parameters such as flow rates and lipid ratios, leading to improved drug loading capacities and enhanced therapeutic efficacy [14]. Collectively, these advances reflect an ongoing trend toward customizable, scalable, and safer lipid nanoparticle delivery systems capable of meeting the

rising demands of next-generation nucleic acid and drug therapies.

5. Challenges in Lipid Nanoparticle Drug Delivery

Lipid nanoparticle (LNP) drug delivery faces several significant challenges that influence their effectiveness and clinical translation [6, 39]. A primary concern is the stability of LNP formulations during storage and in vivo circulation. Lipid crystallization and polymorphic transitions can lead to structural changes, resulting in drug leakage and reduced encapsulation efficiency [40]. This instability is exacerbated by environmental factors such as temperature fluctuations, pH variations, and enzymatic degradation, which are particularly problematic for oral and systemic delivery routes [41]. Overcoming biological barriers, especially the blood-brain barrier, remains a major hurdle due to its selective permeability, requiring sophisticated targeting strategies and nanoparticle engineering to enable CNS delivery.

Another major challenge lies in balancing PEGylation, which extends circulation time by reducing immune clearance but can simultaneously hinder cellular uptake and endosomal escape, thus impairing therapeutic efficacy [8]. Designing PEG molecules that can be reversibly shed or optimized in density and chain length is essential to strike this balance. Toxicity and immunogenicity of LNP components, particularly cationic lipids, also pose safety concerns [42]. While ionizable lipids reduce toxicity compared to permanently charged cationic lipids, immune activation and complement system engagement must be carefully managed to avoid adverse reactions [43].

Manufacturing and reproducibility issues further complicate clinical applications. Large-scale production requires stringent control of particle size, composition, and batch consistency, as minor variations can significantly affect pharmacokinetics and bioactivity [44]. Advanced fabrication techniques such as microfluidics have improved process precision but cost and scale remain limiting factors.

6. Clinical Prospects and Applications

Lipid nanoparticle (LNP) technology has rapidly advanced into a pivotal platform for clinical therapeutics, with multiple FDA-approved drugs and vaccines highlighting its transformative impact [45]. Currently, five LNP-based medicinal products have received FDA and/or EMA approval, including three mRNA vaccines for COVID-19, an RNA interference (RNAi) therapy for hereditary transthyretin amyloidosis, and a vaccine for Respiratory Syncytial Virus (RSV) [14, 46]. These successes have validated LNPs' role in delivering nucleic acid therapies safely and effectively, fostering rapid immune responses or targeted gene silencing. Beyond infectious diseases, LNPs are increasingly explored in cancer

therapeutics through mRNA vaccines and gene therapies that aim to stimulate antitumor immunity or correct genetic mutations [32, 47]. Genetic disorders such as primary hyperoxaluria type 1 and other rare diseases are also emerging targets, where LNPs facilitate precision gene editing using CRISPR-Cas systems [48].

Looking forward, LNPs hold great promise for personalized medicine by enabling tailored nucleic acid delivery customized to individual molecular profiles, as well as for combination therapies that couple gene editing, chemotherapy, and immunomodulation within a single nano-system [6, 33]. Ongoing clinical trials are expanding the therapeutic landscape, including multivalent vaccines and novel gene therapies targeting cardiovascular, metabolic, and neurodegenerative diseases [49, 50]. The scalability and modularity of LNP platforms, along with continuous improvements in lipid compositions and targeting strategies, position them as a cornerstone of next-generation precision therapeutics with broad clinical prospects [46, 51].

7. Future Prospective

The future of lipid nanoparticle (LNP) drug delivery is poised for transformative advancements driven by innovations in targeting, therapeutic integration, and regulatory evolution [52]. Improved targeting is expected through sophisticated ligand and receptor engineering, enabling highly selective delivery to specific cell types or tissues beyond the liver. This precision targeting will rely on advancements in lipid chemistry, ligand conjugation techniques, and molecular recognition strategies, potentially aided by artificial intelligence to optimize ligand selection and nanoparticle formulation [33, 53].

Integration of LNPs with cutting-edge therapies such as CRISPR-Cas gene editing represents a major frontier. Next-generation LNPs are being designed to enhance the efficiency of genome editing tools, facilitating safe and effective delivery of gene editors to target cells for treatment of genetic disorders and personalized medicine applications [54, 55]. These developments include engineering of ionizable lipids with optimized stereochemistry for reduced toxicity and enhanced endosomal escape, as well as modular LNP platforms tailored for multi-functional payload delivery [43, 56].

Enhanced functionality of future LNPs will also be achieved through stimuli-responsive lipids enabling controlled and on-demand drug release, multi-ligand targeting for complex diseases, and formulations that improve pharmacokinetics and biodistribution [14]. Advances in scalable, sustainable manufacturing processes, including continuous flow technologies and AI-driven quality control, will aid in overcoming current commercialization barriers [57].

Regulatory frameworks are evolving to accommodate the unique attributes of LNP-based therapies, fostering accelerated approval pathways while ensuring safety and efficacy [58]. Collaboration between academia, industry, and regula-

tory bodies will be critical to streamline clinical translation, enabling wider access to these promising therapeutics [59]. Overall, the convergence of nanoparticle engineering, gene editing technologies, and regulatory innovation are paving the way for LNPs to become central to next-generation precision therapeutics in oncology, genetic diseases, infectious diseases, and beyond.

8. Conclusion

Lipid nanoparticles (LNPs) have revolutionized drug delivery, offering a versatile and adaptable platform that addresses a wide spectrum of therapeutic needs. Significant advances have been made in optimizing the lipid composition and formulation processes, enabling improved stability, enhanced drug loading, and targeted delivery capabilities. Despite these achievements, challenges such as in vivo stability, overcoming biological barriers, immune responses, and manufacturing scalability remain critical areas of ongoing research. The clinical impact of LNPs is evident in their successful application in FDA-approved mRNA vaccines and RNA-based therapies, with expanding prospects in cancer, genetic disorders, and infectious diseases. Looking forward, innovations in ligand-mediated targeting, integration with gene editing technologies like CRISPR, and the development of next-generation lipid nanoparticles with multifunctional features hold promise for personalized and combination therapies. Continued regulatory advances and manufacturing improvements will be essential for broader clinical translation. Overall, lipid nanoparticles represent a powerful and evolving drug delivery platform poised to transform future therapeutics through enhanced efficacy, safety, and precision.

Abbreviations

AI	Artificial Intelligence
DOPE	Dioleoyl Phosphatidylethanolamine
EPR	Enhanced Permeability and Retention
FDA	Food and Drug Authority
LNPs	Lipid Nanoparticles
mRNA	Messenger Ribose nucleic acid
NLCs	Nanostructured Lipid Carriers
NLCs	Nanostructured Lipid Carriers
PEG	Polyethylene Glycol
RNAi	RNA Interference
RSV	Respiratory Syncytial Virus

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Alebachew Molla is the sole author. The author read and approved the final manuscript.

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