

Review Article

Engineering Lipid Nanoparticles for Enhanced Drug Encapsulation and Release: Current Status and Future Prospective

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Abstract

Lipid nanoparticles have emerged as a versatile and effective platform for drug delivery, offering significant advantages such as biocompatibility, scalability, and the ability to encapsulate diverse therapeutic agents including nucleic acids, proteins, and small-molecule drugs. This review comprehensively explores engineering strategies for enhancing drug encapsulation efficiency and achieving controlled release within LNPs. Key formulation components such as ionizable and PEGylated lipids, along with lipid matrix design, play pivotal roles in optimizing nanoparticle stability, payload capacity, and release kinetics. Advances in fabrication methods including microfluidics and solvent mixing techniques have enabled reproducible production of high-quality LNPs tailored for specific therapeutic applications. The critical role of engineered LNPs is exemplified by their success in RNA therapeutics, notably COVID-19 mRNA vaccines, and expanding applications in cancer therapy and protein delivery. The review also highlights challenges like balancing stability and drug loading, minimizing toxicity, and scaling up manufacturing, alongside emerging solutions. Future perspectives emphasize the development of novel lipid materials, hybrid nanocarriers, and integration with personalized medicine and gene editing. These advances position LNPs as a cornerstone for next-generation nanomedicine platforms aimed at safe, efficient, and targeted delivery for a broad spectrum of diseases. The aim of this review is to comprehensively examine the engineering principles and formulation strategies employed to enhance drug encapsulation efficiency and achieve controlled release in lipid nanoparticles.

Keywords

Lipid Nanoparticles, Drug Encapsulation, Controlled Release, Ionizable Lipids, PEGylated Lipids, Solid Lipid Nanoparticles, Nanostructured Lipid Carriers

1. Introduction

Lipid nanoparticles (LNPs) have revolutionized the field of drug delivery with their unique ability to encapsulate a wide range of therapeutic agents, including small molecules, proteins, and nucleic acids, while protecting them from degradation and improving their bioavailability [1]. As biocompatible

and biodegradable nanocarriers, LNPs offer advantages over conventional drug delivery systems due to their tunable size, lipid composition, surface properties, and scalable manufacturing processes [2, 3]. These attributes have enabled their rapid clinical translation, prominently exemplified by the

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success of mRNA vaccines against COVID-19, underscoring their potential across various therapeutic areas [4, 5].

Despite these advances, challenges remain in optimizing the encapsulation efficiency and achieving controlled and targeted drug release to maximize therapeutic efficacy and minimize side effects [6, 7]. The lipid composition, nanoparticle morphology, and surface functionalization critically influence drug loading capacity, release kinetics, stability, and tissue targeting [2, 8]. Innovations in engineering LNPs focus on overcoming biological barriers, enhancing extrahepatic delivery, and enabling sustained and stimuli-responsive release profiles [9]. The integration of natural bioactive lipids and novel ionizable lipids has further expanded the functional versatility of LNPs [10].

This review presents a comprehensive overview of the current status of LNP engineering strategies aimed at enhancing drug encapsulation and improving controlled release. It discusses key formulation principles, production technologies, and functional modifications that contribute to optimizing LNP performance. Furthermore, the future prospective of LNPs in expanding therapeutic delivery, including their application in gene therapy, immunotherapy, and precision medicine, is critically evaluated to guide ongoing research and clinical development.

2. Drug Encapsulation Mechanisms in Lipid Nanoparticles

Lipid nanoparticles (LNPs) encapsulate drugs primarily based on interactions between the drug molecules and the lipid components, which depend heavily on the drug's physicochemical properties and the lipid matrix structure [2, 11]. In solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), drug molecules can localize at different sites depending on the lipid matrix crystallinity and the degree of structural imperfections [12]. SLNs consist of highly crystalline lipid cores where drugs are mainly entrapped in imperfections or defects within the solid lipid matrix. NLCs, by incorporating both solid and liquid lipids, create a less ordered matrix with more space for drug accommodation, enhancing the drug loading capacity compared to SLNs [13].

Drug lipophilicity and chemical properties critically influence encapsulation efficiency. Highly lipophilic drugs tend to partition deeply within the lipid matrix, improving loading and retention, while hydrophilic drugs require specialized approaches such as ionizable lipids or amphiphilic molecules to stabilize their encapsulation [14]. The crystallinity and phase behavior of the lipid matrix govern drug release rates: higher crystallinity often results in reduced drug mobility and slower release, while a more disordered or partially amorphous lipid phase allows faster drug diffusion and controlled release [15]. Fine-tuning lipid composition and processing conditions thus enables modulation of drug release profiles [16].

Amphiphilic lipids and reverse micelle structures within LNPs play a crucial role in enhancing drug loading, especially for hydrophilic or charged molecules such as nucleic acids [17]. Ionizable lipids can acquire positive charges at acidic pH, facilitating strong electrostatic interactions with negatively charged drug molecules for efficient encapsulation. The internal core of LNPs can form reverse micelles or non-lamellar phases that sequester and protect these cargos until delivery [18].

3. Lipid Components and Formulation Strategies

Ionizable lipids are fundamental to achieving high drug encapsulation efficiency in lipid nanoparticles (LNPs) due to their pH-dependent charge switching properties [7, 18, 19]. At acidic pH, these lipids become positively charged, allowing strong electrostatic interactions with negatively charged therapeutic molecules such as nucleic acids, thereby enhancing payload loading and stability [20, 21]. Upon reaching physiological pH in circulation, the lipids become neutral, reducing toxicity and promoting cellular membrane fusion for effective intracellular delivery [22-24].

PEGylated lipids, although used in small molar ratios (typically around 1.5%), play a crucial role in improving LNP stability during formulation and storage by creating a steric barrier that prevents particle aggregation [25, 26]. PEG chains extend from the nanoparticle surface, decreasing protein binding and immune recognition, which prolongs circulation time and enhances drug protection in vivo [27-29]. The length of the PEG chain and the hydrophobic tail structure of the PEG-lipid influence desorption rates and thus impact circulation half-life and biodistribution [25]. For instance, longer alkyl tails (C16-C18) in PEG-lipids improve LNP stability and extend circulation time compared to shorter tails (C14) which desorb faster and promote liver accumulation [26].

The lipid composition including the type of lipids, their molar ratios, and incorporation of liquid lipids significantly influences nanoparticle size, drug encapsulation, and release characteristics [2, 30]. Adjusting the balance between solid and liquid lipids modulates the internal lipid matrix structure, creating more space for drug loading and allowing controlled release [31]. This compositional tuning also affects nanoparticle morphology, colloidal stability, and biodistribution profiles, enabling optimization of delivery for targeted therapies.

4. Methods for Enhancing Drug Loading and Encapsulation Efficiency

Several advanced techniques are employed to enhance drug loading and encapsulation efficiency in lipid nanoparticles (LNPs), each leveraging different physical and chemical principles for optimized drug incorporation [2, 32, 33]. High-pressure homogenization and microemulsion tech-

niques are commonly used to produce stable nanoparticles with uniform size distribution. High-pressure homogenization applies intense shear forces to reduce particle size while promoting drug entrapment within the lipid matrix. Microemulsion methods use isotropic mixtures of lipids, surfactants, and water to create thermodynamically stable nanoparticles with high drug payloads [16].

Solvent evaporation techniques involve dissolving both the drug and lipid in organic solvents, followed by solvent removal to form solid lipid nanoparticles with encapsulated drugs [34]. This method allows precise control over drug distribution within the lipid matrix, particularly suitable for hydrophobic drugs.

For RNA drug encapsulation, techniques like T-junction mixing and ethanol dilution have gained prominence [7]. These enable rapid and controlled self-assembly of ionizable lipid-coated nanoparticles by mixing aqueous RNA solutions with lipids dissolved in ethanol under specific flow conditions, resulting in high encapsulation efficiency and reproducibility essential for nucleic acid therapeutics [35].

To prevent burst release and improve drug retention, strategies include optimizing lipid composition to create a more compact and ordered matrix, using nanostructured lipid carriers (NLCs) that incorporate liquid lipids to reduce crystallinity and drug expulsion, and employing surface modifications like PEGylation to stabilize nanoparticles and control release kinetics [16, 36]. These approaches enable sustained and controlled drug release, enhancing therapeutic efficacy and reducing toxicity.

Collectively, these methods provide a comprehensive toolkit for designing LNPs with enhanced encapsulation efficiency and controlled release suited to diverse therapeutic applications. Drug Encapsulation Mechanisms in Lipid Nanoparticles involve localization of drugs at different sites within the lipid matrix, influenced by drug properties and lipid crystallinity [2, 7]. Solid lipid nanoparticles (SLNs) possess highly crystalline cores where drugs are entrapped mainly in lattice imperfections, while nanostructured lipid carriers (NLCs) incorporate liquid lipids creating a less ordered matrix enhancing drug loading capacity [35, 37]. Drug lipophilicity affects encapsulation, with lipophilic drugs deeply partitioning into lipid matrices, whereas hydrophilic drugs require amphiphilic lipids or reverse micelle structures within the LNPs for stabilization [14, 38]. Lipid matrix crystallinity governs drug release more crystalline matrices restrict drug mobility leading to slower release, while less ordered phases facilitate faster release [16]. Amphiphilic lipids and formation of reverse micelles enhance loading especially for charged molecules like RNA by electrostatic interactions inside LNP cores [17].

Lipid Components and Formulation Strategies include ionizable lipids that enable high encapsulation efficiency through pH-dependent charge interactions, becoming positively charged at acidic pH to bind negatively charged drugs, then neutral at physiological pH to reduce toxicity and en-

hance delivery [21]. PEGylated lipids improve nanoparticle stability, prolong circulation time, and protect drugs by steric hindrance preventing aggregation and immune recognition [11, 27]. The length of PEG chains and alkyl tail hydrophobicity affect PEG desorption rates and biodistribution. Lipid type, molar ratios, and incorporation of liquid lipids critically influence nanoparticle size, internal structure, drug loading, and release kinetics by tuning lipid matrix fluidity and imperfections for controlled release [26, 39, 40].

Methods for Enhancing Drug Loading and Encapsulation Efficiency include techniques like high-pressure homogenization, microemulsion, and solvent evaporation which produce uniform nanoparticles with high drug loading by controlling particle size and lipid-drug interactions [2, 16]. For RNA drugs, precise techniques such as T-junction mixing and ethanol dilution facilitate rapid nanoparticle self-assembly and efficient nucleic acid encapsulation with reproducibility [41]. To prevent burst release and improve drug retention, strategies involve optimizing lipid composition to reduce crystallinity, using NLCs for structural imperfections enhancing drug accommodation, and surface modifications like PEGylation to stabilize nanoparticles and control sustained release profiles [2, 16, 42].

5. Controlled and Targeted Drug Release

The design of the lipid matrix in lipid nanoparticles (LNPs) fundamentally governs drug release kinetics by modulating drug mobility and matrix stability [10]. Solid lipid nanoparticles (SLNs), characterized by a solid lipid core at physiological temperature, restrict drug diffusion to enable sustained release, while variations in lipid crystallinity and polymorphic transitions affect drug retention and release profiles [16, 43]. Incorporation of liquid lipids in nanostructured lipid carriers (NLCs) introduces imperfections in the lipid matrix, facilitating controlled and tunable drug release by altering the lipid phase behavior [44-46].

Endosomal escape is a critical step for intracellular delivery of nucleic acids and other macromolecules, is facilitated by ionizable lipids within LNPs [20, 47]. These lipids become positively charged in acidic endosomal environments, promoting membrane fusion and disruption that enable cargo release into the cytoplasm. Helper lipids exhibiting cone-shaped geometry, such as dioleoyl phosphatidylethanolamine (DOPE), contribute to formation of non-lamellar phases that enhance membrane fusion and endosomal release efficacy [20].

Surface modifications further advance targeted delivery and controlled release. PEGylation extends circulation time by reducing opsonization and immune clearance; however, excessive PEG can hinder cellular uptake and endosomal escape, which is addressed by using cleavable or reversible PEG-lipids [25, 28]. Targeting ligands attached to LNP surfaces enable receptor-mediated uptake by specific cells or tissues, while stimuli-responsive moieties allow triggered

drug release in response to environmental cues such as pH, enzymes, or redox conditions [48-50]. Together, lipid matrix engineering, ionizable lipid design, and strategic surface modification converge to finely control drug release kinetics, enhance intracellular delivery, and achieve tissue-specific targeting, underscoring the sophisticated versatility of LNP-based drug delivery systems [2, 16].

6. Challenges and Solutions

Balancing nanoparticle stability and drug payload represents a critical challenge in lipid nanoparticle (LNP) formulation [2]. High drug loading can destabilize the lipid matrix, causing aggregation or premature drug leakage, while formulations that are overly stabilized may hinder effective drug release [51, 52]. Achieving an optimal balance requires precise tuning of lipid composition, molar ratios, and lipid-drug interactions to maintain colloidal stability without compromising encapsulation efficiency.

A significant issue is drug expulsion during lipid crystallization transitions as solid lipids undergo polymorphic phase changes that can expel the drug from the lipid matrix [30]. Nanostructured lipid carriers (NLCs), which combine solid and liquid lipids, mitigate this by creating structural imperfections that accommodate greater drug payloads and reduce expulsion risks [45]. Careful selection of lipid types and processing parameters further minimizes this challenge [53].

Toxicity associated with surfactants and cationic lipids poses another hurdle. Conventional cationic lipids improve nucleic acid encapsulation but can cause cytotoxicity and immune activation [54-56]. Ionizable lipids that switch charge depending on pH have largely addressed this by being neutral in circulation but positively charged in acidic endosomes, reducing systemic toxicity while enabling efficient encapsulation and endosomal escape [21, 57]. Optimizing surfactant choice and concentration is also essential to reduce toxicity while preserving nanoparticle stability.

Scale-up and reproducibility for clinical translation demand robust manufacturing processes with tight control over particle size, polydispersity, and drug loading [11, 58]. Techniques like microfluidics and T-junction mixing have improved batch-to-batch consistency and scalability [59]. Regulatory compliance requires thorough characterization and quality control to ensure safety and efficacy of LNP therapeutics. Overcoming these challenges entails a multidisciplinary approach involving rational lipid design, innovative formulation strategies, advanced manufacturing technologies, and comprehensive safety evaluations to realize the full clinical potential of lipid nanoparticles.

7. Challenges and Solutions in Lipid Nanoparticle Engineering

Balancing nanoparticle stability and drug payload is a

critical challenge in lipid nanoparticle (LNP) formulation. High drug loading can destabilize the lipid matrix, causing aggregation or premature drug leakage, while formulations with excessive stability may impede effective drug release [51]. Careful tuning of lipid composition, molar ratios, and lipid-drug interactions is essential to maintain colloidal stability without sacrificing encapsulation efficiency [60].

Drug expulsion during lipid crystallization transitions is another major issue, as the solid lipid matrix undergoes polymorphic phase changes that can expel the drug [2, 30]. Nanostructured lipid carriers (NLCs), which combine solid and liquid lipids, create matrix imperfections that accommodate higher drug loads and reduce expulsion. Optimizing lipid types and processing parameters minimizes this risk [44, 45, 53].

Minimizing toxicity from surfactants and cationic lipids is vital. Traditional cationic lipids improve nucleic acid encapsulation but cause cytotoxicity and immune responses [18, 61, 62]. Ionizable lipids that are neutral at physiological pH yet positively charged in acidic endosomes reduce systemic toxicity while enhancing encapsulation and endosomal escape [23]. Careful choice and optimization of surfactants are also crucial for safety and stability.

Addressing scale-up and reproducibility for clinical translation requires robust and scalable manufacturing methods, such as microfluidics and T-junction mixing, to control particle size, polydispersity, and drug loading with consistent quality [63]. Rigorous characterization and quality control ensure safety and efficacy, facilitating regulatory approval [18].

8. Applications and Case Studies

Lipid nanoparticles (LNPs) have demonstrated remarkable success in enhancing drug encapsulation and controlled release for diverse therapeutic modalities including RNA therapeutics, cancer drugs, and protein delivery [64]. For RNA therapeutics, LNPs achieve high encapsulation efficiency often exceeding 85-90% due to optimized ionizable lipid components that interact electrostatically with the negatively charged nucleic acids [60]. This has allowed the effective delivery of small interfering RNA (siRNA), antisense oligonucleotides, and messenger RNA (mRNA) with protection from enzymatic degradation and improved cellular uptake [65]. Advanced techniques such as T-junction mixing and ethanol dilution facilitate reproducible production of RNA-loaded LNPs with well-controlled size and morphology [7, 66].

In cancer therapy, engineered LNPs enhance encapsulation and controlled release of chemotherapeutics, improving therapeutic index by reducing systemic toxicity and enabling tumor-targeted delivery through surface functionalization [67]. Nanostructured lipid carriers (NLCs) with mixed lipid matrices accommodate higher drug payloads and offer sustained release, effectively managing drug resistance and im-

proving treatment outcomes [45, 46, 68]. Proteins and peptides, which are typically unstable and prone to degradation, have also been successfully encapsulated in LNPs using specialized formulation strategies that preserve their bioactivity and allow controlled release [69, 70].

The most prominent real-world application of engineered LNPs is their critical role in COVID-19 mRNA vaccines by Pfizer-BioNTech and Moderna [71, 72]. These vaccines utilize ionizable lipid-based nanoparticles to encapsulate and protect the mRNA encoding the spike protein, enabling efficient cellular delivery and protein expression that induces robust immune responses [73, 74]. The success of this platform has validated LNPs as versatile, scalable carriers, accelerating ongoing development of RNA-based therapeutics and vaccines across medical fields [50, 71, 75].

9. Future Perspectives

The future of lipid nanoparticles (LNPs) in drug delivery is poised to be shaped by novel lipid materials and hybrid nanocarriers. Development of advanced solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and polymer-lipid hybrid nanoparticles is expanding the toolbox for achieving higher drug loading, improved stability, and precision-controlled drug release [76]. These hybrid systems combine the biocompatibility of lipids with the enhanced stability and multifunctionality of polymers, enabling new applications in sustained release, targeted therapy, and theranostics [77].

Advanced fabrication techniques, including microfluidics, high-throughput automated mixing, and artificial intelligence (AI)-guided formulation optimization, are transforming LNP production [78, 79]. These technologies improve reproducibility, scalability, and batch-to-batch uniformity essential for clinical translation. Integration of sophisticated characterization tools such as cryo-electron microscopy, small-angle X-ray scattering, and high-resolution mass spectrometry allows detailed insights into LNP structure-function relationships, guiding rational design of formulations with optimal performance [7, 80].

LNPs are increasingly integrated with personalized medicine approaches and cutting-edge gene editing technologies like CRISPR-Cas systems [11]. Tailored LNP formulations designed for patient-specific genetic profiles can enhance therapeutic efficacy and reduce off-target effects [2, 58]. Furthermore, LNPs facilitate delivery of complex gene editing tools, enabling precise, efficient, and minimally invasive gene therapy applications [81, 82]. Research is also exploring non-invasive delivery routes, multi-drug combination therapies, and stimulus-responsive LNPs that release cargo under physiological triggers [7, 12, 83]. Together, these innovations forecast an expanding role for lipid nanoparticles as versatile, scalable, and highly tunable drug delivery platforms driving next-generation therapeutics for cancer, rare diseases, infectious diseases, and genetic disorders, with a strong emphasis

on safety, efficacy, and personalized care.

10. Conclusion

Engineering lipid nanoparticles (LNPs) for improved drug encapsulation and controlled release relies on key principles including the careful selection and optimization of lipid components such as ionizable lipids, PEGylated lipids, and the balance of solid and liquid lipids to modulate matrix crystallinity and drug loading capacity. Advanced formulation and manufacturing techniques, including microfluidics and solvent mixing methods, enable high encapsulation efficiencies, especially for challenging cargos like RNA therapeutics. Controlled release is achieved through tailored lipid matrix design, leveraging phase behavior, lipid polymorphism, and surface modifications to regulate drug release kinetics and enhance intracellular delivery via endosomal escape.

These engineering strategies are critical to advancing effective nanomedicine platforms that provide improved therapeutic efficacy, reduced systemic toxicity, and precise tissue targeting. The success of LNP-based COVID-19 mRNA vaccines exemplifies the transformative impact of these technologies in clinical translation. With ongoing innovations in lipid materials, hybrid nanocarriers, and integrated fabrication and characterization tools, LNPs hold tremendous promise for next-generation personalized medicine, gene therapy, and beyond. This synthesis of principles and emerging trends underscores the importance of continued multidisciplinary research and development to fully realize the potential of lipid nanoparticles as versatile, scalable, and precision drug delivery systems for a broad spectrum of diseases.

Abbreviations

AI	Artificial Intelligence
COVID-19	Coronavirus Disease 2019
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
DOPE	Dioleoyl Phosphatidylethanolamine
LNPs	Lipid Nanoparticles
mRNA	Messenger RNA
NLCs	Nanostructured Lipid Carriers
PEG	Polyethylene Glycol
siRNA	Small Interfering RNA
SLNs	Solid Lipid Nanoparticles

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Conflicts of Interest

The author declares no conflicts of interest.

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