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Lipid Nanoparticle (LNPs) As Drug and Gene Delivery Carries

Vaibhav Panwar*
M.Pharm (Pharmaceutics) II[nd] Semester
Faculty of Pharmacy, Medicaps University, Indore (M.P)

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Abstract –
Lipid nanoparticles (LNPs) have emerged as an advanced platform for drug and gene delivery, enabling the transition from conventional therapeutics to nucleic acid–based treatments. Solid lipid nanoparticles (SLNs), composed of biocompatible lipids, provide enhanced stability, reduced toxicity, and controlled drug release. The evolution from liposomes to modern systems such as nanostructured lipid carriers (NLCs) and ionizable LNPs has significantly improved the delivery of fragile biomolecules like mRNA and siRNA. Despite advantages, challenges such as immunogenicity, stability, and limited tissue targeting remain. Ongoing research into novel lipids and formulation strategies continues to expand LNP applications in gene therapy, cancer treatment, and personalized medicine.

Keywords: Lipid nanoparticles (LNPs), Nanostructured lipid carriers (NLCs), Drug delivery, Gene delivery, mRNA vaccines, Ionizable lipids, Controlled release, Nanomedicine, Targeted therapy

I. Introduction

Solid lipid nanoparticles are sub-micron particulate vehicles that are 50 to 1000 nm in size. They are made up of lipids that stay solid at normal body temperature. They were made to get rid of many of the problems with current systems, like their high cost, complex manufacturing process, and need for organic solvents. They were also made to combine the best parts of liposomes and polymeric nanoparticles. By putting drugs or genetic material into a solid lipid matrix, these carriers can help drugs stay in the body longer and protect them better from chemical decomposition. [1)

The creation of Lipid Nanoparticles (LNPs) is a big step forward in the field of pharmaceutical sciences. It means that we are moving away from simple small-molecule drugs and toward more complicated genetic treatments. For decades, researchers have looked into lipid-based delivery systems. The success of mRNA-based COVID-19 vaccines showed that these systems are safe and can be used on a large scale, bringing their clinical validation to a new level around the world.[2)

LNPs are intricate nanocarriers made up of many parts that are meant to carry and protect sensitive medicine. Modern LNPs are built in a way that gets around the biological hurdles that stop nucleic acids like DNA, siRNA, and mRNA from being delivered. This is different from early liposomal formulations. These molecules are hard to get through the anionic cellular membrane because they are big and anionic. This makes them easy for body-wide enzymes to break down quickly.(3)

II. Advantages of Lipid-Based Carriers

Lipid nanoparticles offer several distinct pharmaceutical benefits over other colloidal systems:

- **Reduced Toxicity:** SLNs exhibit decreased cellular toxicity because they are composed of natural lipid, avoiding the long term buildup issue often associated with certain polymeric delivery system.
- **Protection of Cargo:** The solid lipid matrix provides a barrier against chemical degradation for incorporated drugs or biochemicals.
- **Scalability:** Mostly benefits is the high pressure mixing allows these carries to be easily manufactured on a large bulk scaleup.
- **Avoidance of Organic Solvents:** The SLNs production techniques bypass the use of organic solvent, enhancing safety and streamlining the path to regulatory clearance.
- **Controlled Release:** SLNs allow for the controlled release of active ingredients over an extended period, which is more difficult to achieve with traditional emulsions.[1,2][8]

2.1 Disadvantages and Challenges

Although their success, several hurdles remain for broader clinical adoption:

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- **Stability Concerns:** It remains difficult to maintain the long-term physical and chemical integrity of the LNP and its genetic cargo (like RNA) while in storage.
- **Immunogenicity:** Frequent use of PEG-coated LNPs can cause the body to create anti-PEG antibodies, leading to rapid clearance from the blood and allergic-like reactions.
- **Poor Targeting Specificity:** Unless specific molecules are added to guide them, LNPs tend to gather in the liver naturally because of how they interact with certain proteins and receptors.
- **Extrahepatic Delivery:** Achieving precise delivery to organs beyond the liver and spleen, such as the brain, heart, lungs, and musculoskeletal tissues, remains a major research focus.
- **Incomplete Structure-Function Understanding:** The morphological and structural characteristics of LNPs, particularly their internal composition and distribution, remain elusive, arising from challenges in characterization, the dynamic nature of LNPs, and poorly understood formulation-structure relationships.
- **Scale-up Challenges:** Maintaining batch-to-batch consistency during industrial manufacturing requires precise control over formulation parameters.[1,3]

III. Classification of Lipid Nanoparticles

Lipid nanoparticles are broadly classified based on their structure, composition, and evolutionary development:

3.1 Liposomes

Liposomes are the first type of lipid-based carriers. They have an aqueous core that is surrounded by one or more phospholipid bilayers. They can hold both hydrophilic (in the aqueous core) and hydrophobic (in the lipid bilayer) drugs. The liposomal doxorubicin formulation Doxil was the first nanocarrier to be approved by the FDA. It set the stage for other lipid-based delivery methods.[5] [7] [4]

3.2 Solid Lipid Nanoparticles (SLNs)

SLNs are very small colloidal carriers that are made of lipids that stay solid at room and body temperatures. They are usually between 50 and 1000 nm in size. They were made to have the best of both polymeric nanoparticles (which are stable in the physical world) and liposomes (which are safe for living things), while avoiding problems like high cost, complicated production, and the use of organic solvents. But SLNs have problems, such as not being able to hold a lot of drugs and leaking drugs while they are being stored because of their very ordered crystalline structure.[4,1] [5,1] [7,1]

3.3 Nanostructured Lipid Carriers (NLCs)

NLCs are the second generation of lipid nanoparticles. They use a mix of solid and liquid lipids to make an imperfect crystal matrix. This change to the structure makes more room for drugs to be added, which means that the drug loading capacity is higher and the stability is better than with SLNs. The disordered matrix keeps drugs from leaking out while they are being stored.[4,2] [5,2] [7,2]

3.4 Ionizable Lipid Nanoparticles

PH-sensitive non-viral delivery vectors are made just for delivering nucleic acids and are the best way to do gene therapy right now. They have ionizable lipids that stay neutral at neutral pH (which lowers systemic toxicity) but become positively charged in the low-pH internal cellular compartments (pH 5.5–6.5). This helps them interact with nucleic acids through electrostatic forces and cytosolic release. The COVID-19 mRNA vaccines use this technology with synthetic lipids like SM-102 (Moderna) and ALC-0315 (Pfizer/BioNTech).[4,3] [5,3] [7,3]

3.5 Hybrid LNPs

Hybrid systems combine lipids with polymers or metals (such as gold or silver) to achieve multifunctionality and enhanced biocompatibility. These platforms can integrate therapeutic, diagnostic, and targeting capabilities within a single carrier system. [4,4][5,4] [7,4]

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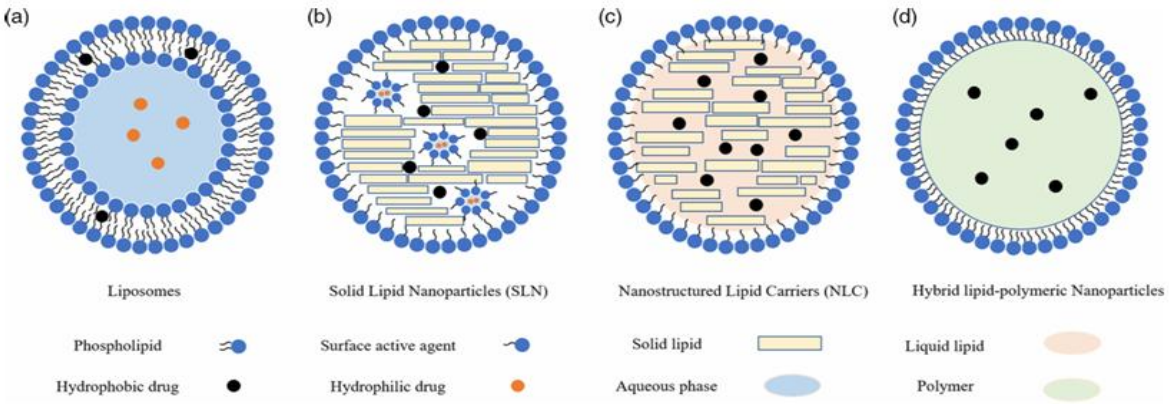


Figure 1. A schematic of three different classes of lipid-based nanoparticle:
a) Liposome, b) SLNs, c) NLCs d) Hybrid LNPs [4,5]

IV. Core Components of LNPs for Gene Delivery

4.1 Ionizable Lipids

Ionizable lipids represent the essential element in contemporary lipid nanoparticle compositions. By utilizing electrostatic force, they promote the packaging of genetic material and support its release from the endosome after internalization. The wide variety of ionizable lipid structures has led to ongoing enhancement in the effectiveness and safety profile of LNPs.[4,5] [5.5] [7.5]

Clinically approved ionizable lipids include:

- MC3 (DLin-MC3-DMA): Used in Onpattro (Patisiran)
- SM-102: Used in Moderna's COVID-19 vaccine
- ALC-0315: Used in Pfizer/BioNTech's COVID-19 vaccine
- The pKa of ionizable lipids is carefully tuned to remain neutral at physiological pH (~7.4) while becoming protonated in acidic endosomal compartments, triggering membrane destabilization and cargo release.

4.2 Helper Phospholipids

Helper phospholipids such as DSPC (distearoylphosphatidylcholine) and DOPE (dioleoylphosphatidylethanolamine) these lipids are often called fusogenic lipid because they facilitate the merging or coalescence of the LNP with the cell membrane. DSPC contributes to bilayer rigidity, while DOPE adopts a hexagonal phase that facilitates endosomal membrane disruption.[4,6] [5,6] [7,6]

4.3 Cholesterol

Cholesterol acts as a structural stabilizer or stiffening agent that modulates membrane rigidity. It also assists in the recruitment of proteins like Apolipoprotein E (ApoE), which mediates liver-specific delivery through LDL receptor interactions.

4.4 PEGylated Lipids

By creating a water-attracting physical shield around the LNP, PEG-lipids stop particles from clumping, minimize protein binding (opsonization), and grant stealth characteristics that allow the particles to remain in the bloodstream longer.

V. Mechanism of Drug and Gene Delivery

LNP-mediated delivery involves a series of coordinated biological processes:

- **Encapsulation:** During the formulation stage, therapeutics or genetic payloads are integrated into the LNP through electric charge interactions (for nucleic acids) or via distribution into lipid layers (for small molecules)
- **Systemic Circulation:** The PEG-modified exterior shields the LNPs from quick removal by the reticuloendothelial system (RES), thereby prolonging their presence in systemic circulation
- **Protein Corona Formation:** Upon intravenous administration, serum proteins adsorb onto the LNP surface, forming a "corona" that dictates subsequent receptor interactions and biodistribution.
- **Cellular Uptake:** Cells primarily take up LNPs through receptor-driven endocytosis, a process frequently aided by the binding of ApoE to LDL receptors on liver cells.

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- **Endosomal Escape:** As the environment inside the endosome becomes more acidic (dropping from pH 7.4 to 5.5) ionizable lipids gain a positive charge, which leads them to bind with negatively charged lipids in the endosomal wall, causing the membrane to break down and release the cargo.
- **Cargo Release:** The therapeutic payload is released into the cytoplasm, where mRNA can be translated into protein or siRNA can engage the RISC complex for gene silencing.[8][4.7][5,6]

VI. Methods of Preparation

The manufacturing of LNPs has evolved from traditional bulk methods to more precise technologies that ensure reproducibility and scalability:

6.1 High-Pressure Homogenization (HPH)

HPH is widely used for the large-scale production of solid lipid nanoparticles. Two approaches exist:

- Hot Homogenization: The lipid is melted and mixed with the drug before being dispersed in a hot surfactant solution. [8,1] [1,4]
- Cold Homogenization: Designed for heat-sensitive (thermolabile) or highly hydrophilic drugs. The drug-lipid mix is solidified using liquid nitrogen or dry ice before being homogenized in a cold medium.[8,2] [1,5]

6.2 Microfluidic Mixing

Microfluidics has become the gold standard for gene delivery LNPs, utilizing designs like hydrodynamic flow focusing (HFF) or staggered herringbone micromixers (SHMs). This approach ensures: [8,3] [1,5]

- Small, uniform particle size (typically 50–100 nm) [9]
- Narrow size distribution (low polydispersity) [9,1]
- High reproducibility
- Excellent encapsulation efficiency[9,2]
- The rapid mixing achievable with microfluidics allows precise control over self-assembly kinetics, producing consistent LNP formulations suitable for clinical applications. [9,3]

6.3 Other Methods

Supplementary formulation strategies consist of:

- Solvent emulsification-evaporation
- Nanoprecipitation
- Supercritical fluid (SCF) technology
- Thin-film hydration (for liposomes)

6.4 Characterization Parameters

Regulatory monitoring of LNP composition necessitates the evaluation of various essential metrics:

Parameter Target Range Method : [8,4] [1,4]

- Particle size 50–150 nm (for IV injection) Dynamic light scattering [8,5] [1,5]
- Polydispersity index (PDI) < 0.2 Dynamic light scattering [8,6] [1,6]
- Zeta potential Dependent on application Electrophoretic mobility [8,7] [1,7]
- Encapsulation efficiency > 70–95% Fluorescence assays [8,8] [1,8]

6.5 Purification and Sterilization

For clinical use, LNPs undergo rigorous processing:

- Purification: Cross-flow filtration or tangential flow filtration removes impurities and unencapsulated material [1,9] [8,9]
- Sterilization: Autoclaving or gamma irradiation, though these processes must be carefully monitored as they can impact particle size and drug release characteristics [1,10] [8,10]

VII. Therapeutic Applications

LNPs are being explored across a broad spectrum of clinical conditions:

7.1 Drug Delivery Applications [4,8] [9,3]

- **Cancer Therapy:** LNPs enable targeted delivery of anticancer drugs such as doxorubicin, improving pharmacokinetics and reducing systemic toxicity. The Enhanced Permeability and Retention (EPR) effect allows passive accumulation in tumor tissue due to leaky vasculature. [4,9] [9,4]
- **Ocular Diseases:** Lipid-based formulations are being developed for retinal drug delivery, addressing conditions like age-related macular degeneration. [4,10] [9,5]

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- **Cardiovascular Diseases:** LNPs can deliver therapeutic agents to the vasculature for treating atherosclerosis and other cardiovascular conditions . [4,11] [9,6]

7.2 Gene Delivery Applications

- **mRNA Vaccines:** The COVID-19 pandemic validated mRNA-LNP vaccines as a transformative platform for infectious disease prevention. This technology is now being applied to vaccines against HIV, influenza, and other pathogens. [4,12] [9,7] [10]
- **Gene Silencing (siRNA):** Onpattro demonstrated that LNPs can effectively deliver siRNA therapeutics for treating genetic disorders. Additional siRNA-LNP therapies are in clinical development. [4,13] [9,8] [10,1]
- **Cancer Immunotherapy:** LNPs can deliver mRNA encoding tumor-associated antigens (cancer vaccines) or facilitate in vivo reprogramming of immune cells for CAR T-cell therapy. [4,14] [9,9] [10,2]
- **Genome Editing:** LNPs are being developed to deliver CRISPR-Cas9 components—as mRNA, plasmid DNA, or ribonucleoproteins (RNPs)—for permanent genetic correction of hereditary diseases. [4,15] [9,10] [10,3]
- **Protein Replacement:** mRNA-LNPs can direct the production of therapeutic proteins in patients with deficiency disorders, offering an alternative to recombinant protein infusions.

VIII. Current Challenges and Future Directions

8.1 Remaining Challenges

Several obstacles must be overcome for broader clinical adoption of LNP therapeutics:

- Accessing hard-to-reach tissues (brain, muscle, bone) [11]
- Controlling protein corona interactions for predictable in vivo behavior [11,1]
- Minimizing immune responses including anti-PEG antibodies and inflammatory reactions [11,2]
- Improving formulation stability for storage and global distribution [11,3]
- Ensuring repeated-dose efficacy without accelerated clearance [11,4]
- Achieving tissue-specific gene delivery with high precision [11,5]

8.2 Emerging Solutions and Future Perspectives

Research is advancing on multiple fronts:

- **PEG Alternatives:** Polysarcosine and other polymers are being investigated as substitutes for PEG to avoid immunogenicity issues.
- **Biodegradable Lipids:** Novel ionizable lipids designed for rapid metabolism may improve safety profiles for repeated dosing.
- **Machine Learning:** Computational tools are being developed to optimize formulations and predict in vivo behavior, accelerating the design of next-generation LNPs.
- **Stimuli-Responsive Systems:** LNPs that respond to specific biological triggers (pH, enzymes, temperature) may enable more precise spatial and temporal control of drug release.
- **Personalized Nanomedicine:** Patient-specific formulations tailored to individual genetic profiles represent a frontier for precision medicine.
- **Expanded Applications:** Beyond current uses, LNPs hold promise for delivering gene editing tools (CRISPR) for permanent correction of genetic diseases, opening new therapeutic possibilities.

IX. Conclusion

Lipid nanoparticles have surfaced as a groundbreaking system for delivery, closing the divide between potential genetic therapies and practical clinical applications. From the early development of liposomes to the sophisticated ionizable LNPs used in COVID-19 vaccines, this technology has undergone remarkable evolution. The primary constituents are ionizable lipids, auxiliary phospholipids, cholesterol, and PEGylated lipid-act in unison to shield the nucleic acid payload, promote cellular ingestion and permit escape from endosomes. The clinical validation of mRNA-LNP vaccines has demonstrated the safety, efficacy, and scalability of this platform on a global scale. Ongoing research continues to address remaining challenges, including extrahepatic targeting, immunogenicity, and long-term stability. With advances in lipid chemistry, manufacturing technology, and computational design tools, LNPs are poised to expand their therapeutic reach into cancer immunotherapy, gene editing, and protein replacement therapies.

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As our understanding of structure–function relationships deepens and new targeting strategies emerge, lipid nanoparticles will continue to serve as indispensable tools in the advancement of modern medicine, enabling the clinical translation of nucleic acid therapeutics that were once considered impossible to deliver.

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