

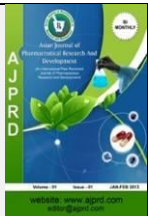


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Review Article

## Lipid Nanoparticles for Drug and Gene Delivery: Advances, Limitations and Future Perspectives

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### ABSTRACT

Lipid nanoparticles (LNPs) have emerged as one of the most promising nanocarrier systems for the delivery of therapeutic agents, including conventional small-molecule drugs, proteins, messenger RNA (mRNA), small interfering RNA (siRNA), DNA, and gene-editing components. Their growing importance is attributed to their biocompatibility, versatility, ability to encapsulate and protect sensitive therapeutic molecules, and potential to facilitate intracellular delivery. LNPs generally consist of ionizable lipids, phospholipids, cholesterol, and polyethylene glycol (PEG)-lipids, with each component contributing to particle formation, stability, biodistribution, cellular uptake, and therapeutic performance. The development of ionizable lipids has been particularly important because these lipids facilitate nucleic-acid encapsulation under acidic conditions while remaining relatively neutral at physiological pH, thereby reducing nonspecific interactions and toxicity. The clinical success of mRNA-LNP vaccines has provided strong evidence for the translational potential of this technology and has accelerated research into LNP-based therapeutics for cancer, infectious diseases, inherited disorders, and other conditions. Despite these advances, several challenges remain, including limited tissue-specific delivery, instability, immunogenicity, toxicity, endosomal entrapment, PEG-related limitations, manufacturing complexity, and regulatory requirements. This review discusses the principles, composition, preparation methods, mechanisms, therapeutic applications, recent advances, limitations, and future perspectives of lipid nanoparticles for drug and gene delivery, with particular emphasis on nucleic-acid therapeutics, targeted delivery, organ-selective LNPs, and emerging technologies.

**Keywords:** Lipid nanoparticles, gene delivery, mRNA, siRNA, nucleic acids.

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### INTRODUCTION

The development of efficient drug delivery systems remains an important objective in pharmaceutical and biomedical research because conventional drug administration is frequently associated with limitations such as poor aqueous solubility, low bioavailability, rapid degradation, nonspecific distribution, systemic toxicity, and inadequate accumulation at the intended site of action<sup>1</sup>. These limitations have encouraged the development of nanotechnology-based delivery systems capable of improving the physicochemical, pharmacokinetic, and pharmacodynamic characteristics of therapeutic agents. Among the different nanocarrier systems investigated to date, lipid nanoparticles (LNPs) have attracted

considerable attention because of their ability to accommodate a broad range of therapeutic molecules and facilitate their delivery to specific biological compartments. LNPs have become particularly important for the delivery of nucleic acids, which are otherwise difficult to administer because of their large molecular size, hydrophilicity, negative charge, poor membrane permeability, and susceptibility to enzymatic degradation<sup>2</sup>.

LNPs are nanoscale lipid-based delivery systems whose properties can be modified by changing their lipid composition, particle size, surface characteristics, and manufacturing conditions. Modern LNP formulations commonly contain an ionizable lipid, phospholipid, cholesterol, and a PEG-lipid. The combination of these components provides a balance between payload

encapsulation, nanoparticle stability, cellular uptake, and intracellular release. The development of ionizable lipid chemistry has substantially improved the efficiency of nucleic-acid delivery. These lipids can interact with negatively charged nucleic acids during formulation under acidic conditions and subsequently facilitate endosomal escape following cellular uptake. At physiological pH, many ionizable lipids remain predominantly uncharged, which can reduce nonspecific interactions with cellular membranes and plasma proteins<sup>3</sup>.

The importance of LNP technology increased significantly following the development of clinically successful mRNA-based vaccines. The ability of LNPs to protect mRNA from degradation and promote its delivery into the cytoplasm demonstrated the practical potential of this platform on a large scale. This success has expanded research beyond vaccines toward therapeutic applications involving siRNA, mRNA-based protein replacement, gene editing, cancer immunotherapy, and treatment of inherited diseases. Nevertheless, the biological behavior of LNPs is highly dependent on their composition and physicochemical properties, and achieving precise delivery to tissues other than the liver remains a major research challenge. Therefore, continued development of lipid chemistry, formulation strategies, targeting technologies, and manufacturing processes is required to realize the full potential of LNP-based therapeutics<sup>4</sup>.

### Structure and Composition of Lipid Nanoparticles

Lipid nanoparticles possess a complex internal organization that differs from the classical structure of conventional liposomes. Although the precise morphology of LNPs can vary depending on their composition and

manufacturing conditions, nucleic-acid LNPs generally contain an ionizable lipid associated with the therapeutic nucleic acid, together with structural phospholipids, cholesterol, and PEG-lipids. The organization of these components determines important characteristics such as particle size, polydispersity, encapsulation efficiency, surface properties, stability, biodistribution, cellular uptake, and intracellular release. Consequently, formulation development requires careful optimization of lipid identity and concentration rather than simply increasing the amount of lipid to improve encapsulation<sup>5</sup>.

Ionizable lipids are considered one of the most critical components of modern LNP systems, particularly for nucleic-acid delivery. These molecules contain functional groups capable of changing their ionization state depending on the surrounding pH. During formulation, the acidic environment promotes protonation of the ionizable lipid, allowing strong electrostatic interactions with negatively charged nucleic acids and facilitating efficient encapsulation. Following administration into the physiological environment, the ionizable lipid becomes substantially less charged, which can reduce nonspecific interactions and improve tolerability. After cellular uptake through endocytosis, the acidic environment of the endosome promotes protonation again<sup>6</sup>. The resulting interaction between the protonated lipid and negatively charged components of the endosomal membrane can destabilize the membrane and facilitate release of the therapeutic payload into the cytoplasm. Therefore, the pKa, molecular structure, biodegradability, and hydrophobic domains of ionizable lipids are important determinants of LNP performance<sup>7</sup>.

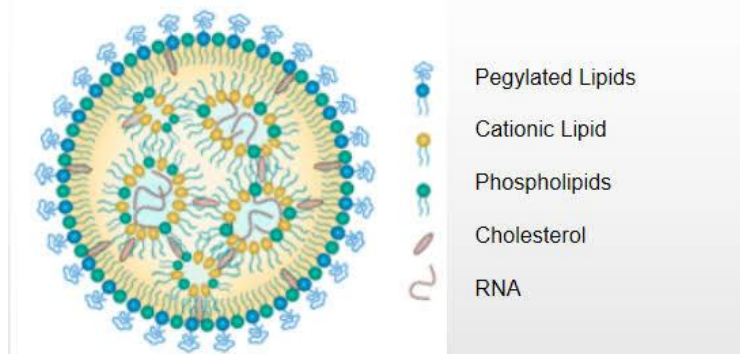


**Figure 1:** Overview of Lipid Nanoparticle

Phospholipids contribute to the structural organization and physical stability of LNPs. Commonly investigated phospholipids include distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylethanolamine (DOPE), and related phospholipid derivatives. Their molecular structure can influence lipid packing, membrane organization, particle morphology, and interactions with biological membranes. Cholesterol is another important structural component that contributes to particle stability and influences membrane fluidity and lipid packing. Modifications of cholesterol or the use of cholesterol derivatives have also been investigated as strategies for altering LNP morphology, stability, and biodistribution.

PEG-lipids consist of a polyethylene glycol chain attached to a lipid anchor and are primarily used to control particle size, reduce aggregation, and improve colloidal stability. However, excessive PEG-lipid content may reduce cellular uptake and endosomal escape, creating a formulation trade-off between stability and biological activity<sup>8</sup>.

### Types of Lipid-Based Nanocarriers

Several types of lipid-based nanocarriers have been developed for pharmaceutical applications, including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and modern lipid nanoparticles designed specifically for nucleic-acid delivery. Liposomes generally

consist of one or more phospholipid bilayers surrounding an aqueous compartment and are capable of incorporating both hydrophilic and hydrophobic therapeutic agents. Solid lipid nanoparticles contain lipids that remain in a solid state at physiological temperature and have been investigated for controlled delivery and enhancement of the bioavailability of poorly soluble compounds. Nanostructured lipid carriers combine solid and liquid lipids to create a less ordered lipid matrix that can provide improved drug-loading capacity compared with conventional solid lipid nanoparticles<sup>9</sup>.

LNPs developed for nucleic-acid delivery differ from traditional lipid-based systems because their composition is specifically optimized for efficient encapsulation, protection, cellular uptake, and intracellular release of genetic material. Their performance can be adjusted through modification of ionizable lipid structure, lipid ratios, PEG-lipid content, particle size, and manufacturing conditions. This flexibility has allowed LNPs to become an important platform for mRNA, siRNA, gene-editing components, and other nucleic-acid therapeutics<sup>10</sup>.

### Preparation of Lipid Nanoparticles

The preparation method used for LNP production has a significant influence on particle size, size distribution, encapsulation efficiency, morphology, stability, and biological activity. Conventional methods include thin-film hydration, ethanol injection, solvent evaporation, and high-pressure homogenization, while more advanced approaches include microfluidic mixing and other controlled mixing technologies. Thin-film hydration involves dissolving lipid components in an organic solvent followed by evaporation of the solvent to form a thin lipid film. The resulting film is hydrated using an aqueous phase to generate lipid vesicles or nanoparticles. Although this method is relatively simple and useful for laboratory-scale investigations, it may produce heterogeneous particle populations and frequently requires additional size-reduction procedures<sup>11</sup>.

Ethanol injection involves mixing an ethanolic lipid solution with an aqueous phase under controlled conditions. Rapid dilution of the organic solvent promotes lipid self-assembly and nanoparticle formation. The method is comparatively simple but may provide less precise control over particle properties when compared with advanced mixing systems. High-pressure homogenization uses high shear forces and pressure to reduce particle size and improve formulation uniformity and has been widely investigated for lipid-based drug delivery systems<sup>12</sup>.

Microfluidic mixing has become particularly important in the preparation of LNPs for nucleic-acid delivery. In this approach, an organic phase containing dissolved lipids is rapidly mixed with an aqueous phase containing the nucleic-acid payload under precisely controlled conditions. Rapid changes in solvent composition promote lipid self-assembly and association with the nucleic acid. Microfluidic methods can provide relatively narrow particle-size distributions, high encapsulation efficiencies, and improved reproducibility<sup>13</sup>. The process can also be

adapted to larger-scale production through parallelization and process optimization, making it attractive for the manufacture of advanced LNP therapeutics<sup>14</sup>.

### Mechanism of Drug Delivery

LNPs can improve drug delivery through several sequential processes, beginning with encapsulation of the therapeutic molecule within the lipid matrix. Encapsulation can protect sensitive therapeutic agents from chemical and enzymatic degradation and can improve their apparent stability in biological environments. Following administration, LNPs interact with proteins and other components of biological fluids, which can influence their circulation, biodistribution, cellular uptake, and clearance. The adsorption of plasma proteins onto nanoparticle surfaces, often described as formation of a protein corona, can substantially modify the biological identity of the nanoparticle<sup>15</sup>.

After reaching target tissues, LNPs can be internalized by cells through endocytic mechanisms. The particles are subsequently transported through intracellular vesicular compartments, where changes in pH and membrane composition can influence the interaction between the LNP and endosomal membrane. For many nucleic-acid LNP systems, protonation of the ionizable lipid under acidic endosomal conditions promotes membrane destabilization and facilitates endosomal escape. The therapeutic payload can then become available within the cytoplasm, where it can exert its intended biological activity. The efficiency of each stage, including tissue distribution, cellular uptake, endosomal escape, and intracellular release, ultimately determines the therapeutic performance of the LNP formulation<sup>16</sup>.

### Lipid Nanoparticles for Gene Delivery

Gene delivery represents one of the most important applications of LNP technology. Nucleic acids are highly attractive therapeutic molecules because they can regulate or modify biological processes at the genetic level. However, their clinical application is restricted by several delivery barriers. Most nucleic acids are negatively charged and hydrophilic, which limits their ability to cross cellular membranes. They can also be rapidly degraded by nucleases and eliminated from the body through biological clearance mechanisms. LNPs can overcome several of these limitations by encapsulating nucleic acids, protecting them from degradation, facilitating cellular uptake, and promoting intracellular release<sup>17</sup>.

LNP systems have been investigated for the delivery of mRNA, siRNA, microRNA, DNA, antisense oligonucleotides, and gene-editing components. The choice of nucleic-acid payload determines the desired intracellular destination and mechanism of action. For example, mRNA generally needs to reach the cytoplasm, where it is translated into a functional protein, whereas some gene-editing strategies require delivery of multiple components that act together within the cell. Therefore, the design of LNPs must be adapted to the biological requirements of the selected therapeutic strategy<sup>18</sup>.

### mRNA Delivery

Messenger RNA has become an important class of therapeutic molecules because it can provide temporary expression of functional proteins without requiring permanent modification of the genome. However, free mRNA is highly susceptible to enzymatic degradation and has limited ability to cross cellular membranes. LNP encapsulation protects mRNA from extracellular degradation and facilitates cellular uptake and cytoplasmic delivery. Once released into the cytoplasm, mRNA can undergo translation by the cellular protein-synthesis machinery, producing the desired therapeutic protein<sup>19</sup>.

The successful application of mRNA-LNP technology in vaccines has demonstrated the feasibility of this approach at both clinical and manufacturing scales. Beyond infectious-disease vaccination, mRNA-LNP systems are being investigated for protein replacement, cancer immunotherapy, regenerative medicine, and treatment of genetic disorders. The transient nature of mRNA expression can be advantageous for therapeutic applications where prolonged protein expression is unnecessary or undesirable. However, mRNA integrity, formulation stability, storage conditions, innate immune activation, and efficient cytoplasmic delivery remain important considerations<sup>20</sup>.

### siRNA Delivery

Small interfering RNA is capable of selectively reducing the expression of target genes through the RNA interference pathway. This provides an opportunity to suppress disease-associated genes that may be difficult to target using conventional small-molecule drugs.

Nevertheless, siRNA possesses physicochemical characteristics that limit its direct administration, including a relatively large molecular size, negative charge, poor membrane permeability, and susceptibility to degradation<sup>21</sup>.

LNPs can improve siRNA delivery by protecting the nucleic acid from degradation and facilitating its uptake into target cells. Following intracellular release, siRNA can participate in the RNA-induced silencing complex and promote sequence-specific degradation of complementary messenger RNA. LNP-based siRNA delivery has therefore attracted considerable interest in the treatment of genetic, metabolic, infectious, and malignant diseases. The clinical development of nucleic-acid therapeutics has demonstrated the feasibility of this approach, although efficient tissue targeting and safe repeat administration remain important areas of research<sup>22</sup>.

### LNPs for CRISPR and Gene Editing

The combination of LNPs with CRISPR-based gene-editing technologies represents an emerging area of pharmaceutical and genetic medicine research. CRISPR systems can potentially correct disease-causing genetic abnormalities by making targeted modifications to DNA. LNPs can be used to deliver different components of gene-editing systems, including messenger RNA encoding the nuclease and guide RNA responsible for target recognition. In some strategies, multiple components are encapsulated within the same nanoparticle to facilitate coordinated intracellular delivery<sup>23</sup>.

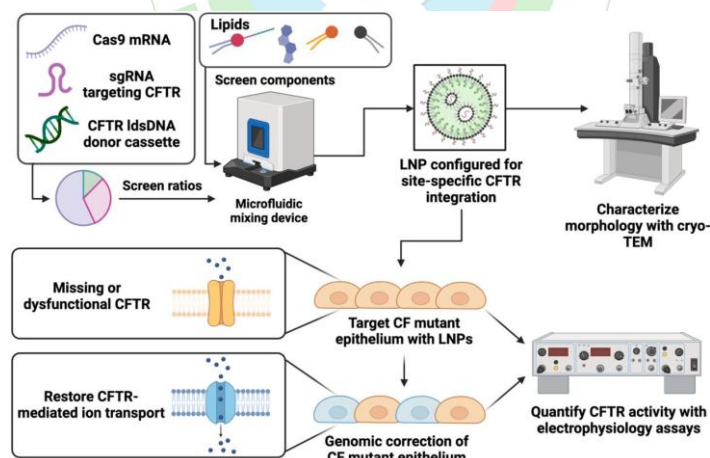


**Figure 2:** Lipid Nanoparticles for the Delivery of CRISPR

One potential advantage of LNP-mediated gene editing is the transient nature of the delivered components. Rather than requiring long-term expression of gene-editing proteins, delivery of mRNA can provide temporary production of the required protein, after which the therapeutic components can be degraded. However, achieving efficient and selective delivery to the appropriate tissue remains a major challenge. Off-target effects, immune responses, editing efficiency, and long-term safety must also be carefully evaluated before widespread clinical application<sup>24</sup>.

### Targeted Lipid Nanoparticles

Although conventional LNPs can achieve efficient delivery to certain organs, particularly the liver, nonspecific biodistribution remains a major limitation for many therapeutic applications. Targeted LNPs are therefore being developed to increase delivery to specific tissues or cell populations. Targeting can be achieved through surface modification with antibodies, peptides, aptamers, carbohydrates, receptor-binding ligands, or other targeting molecules. These ligands may recognize receptors that are

preferentially expressed on particular cell types, thereby increasing cellular uptake in the desired tissue<sup>25</sup>.

In addition to conventional ligand-based targeting, researchers have demonstrated that changes in lipid composition can substantially alter the organ distribution of LNPs. This has led to the development of organ-selective nanoparticles designed to deliver therapeutic molecules beyond the liver. Such approaches are particularly important for diseases affecting tissues such as the lung, heart, skeletal muscle, immune system, and central nervous system. However, achieving highly selective delivery while maintaining acceptable safety and manufacturing characteristics remains a major challenge<sup>26</sup>.

### Applications in Cancer Therapy

LNPs have considerable potential in cancer treatment because they can be used to deliver both conventional pharmaceutical agents and genetic therapeutics. LNP-mediated delivery of anticancer drugs may improve drug solubility, stability, pharmacokinetics, and tissue exposure while potentially reducing nonspecific systemic toxicity. In addition, LNPs can deliver siRNA or mRNA to regulate molecular pathways involved in tumor development and progression<sup>27</sup>.

mRNA-LNP systems have attracted particular interest in cancer immunotherapy because they can encode tumor-associated or patient-specific antigens and stimulate immune responses against malignant cells. LNPs are also being investigated for delivery of immune-modulating molecules, tumor suppressor genes, and gene-editing components. Personalized cancer vaccines represent an important future application in which tumor-specific molecular information could be used to design an individualized mRNA payload. Nevertheless, tumor heterogeneity, inefficient penetration

into solid tumors, immunosuppressive tumor microenvironments, and nonspecific biodistribution remain significant obstacles<sup>28</sup>.

### Applications in Infectious Diseases

The clinical success of LNP-based mRNA vaccines has established lipid nanoparticles as an important platform for infectious-disease prevention. LNPs protect mRNA and facilitate its delivery into cells, where the encoded antigen can be produced and presented to the immune system. This approach can enable relatively rapid development and modification of vaccines because the therapeutic sequence can be changed while maintaining much of the underlying delivery platform<sup>29</sup>.

Research is now extending LNP-based vaccine technology toward a broad range of infectious diseases, including respiratory viral infections and emerging pathogens. LNPs may also be useful for therapeutic applications involving infectious diseases by delivering nucleic acids capable of modifying host or pathogen-associated biological pathways. However, vaccine stability, storage requirements, immune responses, repeat dosing, and large-scale manufacturing remain important considerations<sup>30</sup>.

### Applications in Genetic Disorders

Genetic disorders represent an important therapeutic area for LNP-based delivery systems because nucleic-acid therapeutics can potentially address the underlying molecular mechanisms of disease. LNPs can deliver mRNA encoding functional proteins in situations where a patient's cells lack sufficient expression of a specific protein. Similarly, siRNA can be used to reduce expression of harmful proteins, while gene-editing systems may potentially correct disease-associated mutations<sup>31</sup>.

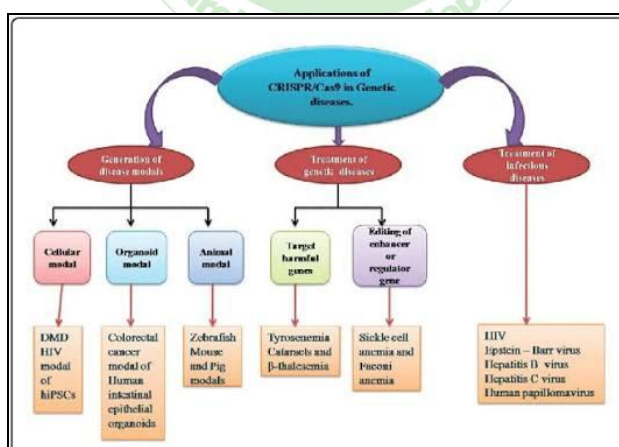


Figure 3: Applications of CRISPR in genetic disorders.

One important advantage of mRNA-based protein replacement is that it does not necessarily require permanent genomic modification. The temporary expression of therapeutic proteins can provide a potentially controllable treatment approach. However, repeated administration may be required for some diseases, and repeated exposure to the nanoparticle formulation may introduce additional immunological and safety considerations. Therefore, the

development of LNPs suitable for repeated dosing is an important area of current research<sup>32</sup>.

### Applications in Neurological Disorders

The delivery of therapeutic molecules to the central nervous system remains challenging because the blood-brain barrier restricts the passage of many pharmaceutical agents from the systemic circulation into brain tissue. Consequently, considerable research has focused on developing LNPs

capable of crossing or circumventing this biological barrier. Potential applications include delivery of mRNA, siRNA, gene-editing components, and other therapeutic molecules to neuronal or glial cells<sup>33</sup>.

Strategies under investigation include modification of lipid composition, surface targeting, receptor-mediated transport, and alternative administration routes. Despite promising experimental findings, efficient, selective, and safe delivery to the brain remains considerably more difficult than hepatic delivery. Future development will require a detailed understanding of nanoparticle transport across biological barriers, cellular uptake mechanisms, neurotoxicity, and long-term safety<sup>34</sup>.

### Advantages of Lipid Nanoparticles

LNPs possess several characteristics that make them attractive for modern drug and gene delivery. Their lipid-based composition can provide good compatibility with biological systems, while their formulation can be modified to accommodate different therapeutic payloads. They can protect fragile molecules from degradation, improve intracellular delivery, and facilitate the administration of nucleic acids that would otherwise exhibit poor cellular permeability. Their composition can also be systematically modified to control particle size, surface characteristics, stability, biodistribution, and payload release. Furthermore, advances in microfluidic manufacturing have improved the reproducibility and scalability of LNP production. The success of LNP-based nucleic-acid therapeutics has further demonstrated the potential of this platform for translation from laboratory research to clinical applications<sup>35</sup>.

### Limitations and Challenges

Despite substantial progress, several limitations continue to restrict the broader application of LNP technology. Physical and chemical instability can occur because of lipid oxidation, hydrolysis, aggregation, changes in particle structure, or degradation of the therapeutic payload. These processes can reduce product quality during storage and may affect therapeutic performance. Consequently, formulation composition, manufacturing conditions, packaging, storage temperature, and handling procedures must be carefully optimized<sup>36</sup>.

Immunogenicity and toxicity are also important considerations. Certain lipid components may activate innate immune pathways or cause inflammatory responses depending on their chemical structure and dose. PEG-lipids can improve colloidal stability and reduce aggregation, but excessive PEG content may decrease cellular uptake and endosomal escape. In addition, immune responses against PEG have stimulated interest in alternative surface-stabilizing approaches. The selection of biodegradable lipids is another strategy being investigated to reduce long-term accumulation and improve the safety profile of LNP formulations<sup>37</sup>.

Another major challenge is tissue specificity. Many systemically administered LNP formulations show preferential accumulation in the liver, which can be advantageous for hepatic diseases but limits applications requiring delivery to other organs. Although targeted and

organ-selective LNP technologies are advancing, achieving highly specific delivery without compromising safety or manufacturing feasibility remains difficult. Endosomal escape also remains a major biological bottleneck because cellular uptake does not necessarily result in efficient cytoplasmic release of the therapeutic payload. Improving the fraction of payload that escapes the endosomal compartment is therefore an important objective in LNP research<sup>38</sup>.

### Pharmacokinetic and Biodistribution Considerations

The pharmacokinetic behavior of LNPs depends on several interconnected factors, including particle size, surface charge, lipid composition, PEG density, administration route, payload characteristics, and interactions with plasma proteins. Following systemic administration, nanoparticles rapidly encounter proteins and other biomolecules in the bloodstream. These interactions can modify the surface properties of the nanoparticles and influence their uptake by different cell types. The resulting biological identity of the nanoparticle can therefore differ from its original physicochemical identity<sup>39</sup>.

LNP biodistribution is also influenced by organ-specific physiological characteristics and interactions with the mononuclear phagocyte system. The liver is a major site of accumulation for many intravenously administered LNP formulations. This phenomenon has been successfully exploited for hepatic delivery but creates challenges for extrahepatic applications. Understanding the relationship between lipid structure, protein adsorption, particle properties, and organ distribution is therefore essential for designing next-generation LNP systems with predictable pharmacokinetic behavior<sup>40</sup>.

### Recent Advances in LNP Technology

Recent research has focused heavily on the development of next-generation ionizable lipids with improved potency, biodegradability, and safety. Structural modification of ionizable lipids can influence pKa, lipid packing, membrane interaction, endosomal escape, and tissue distribution. Biodegradable ionizable lipids are particularly attractive because they may provide efficient delivery while subsequently undergoing metabolic degradation, potentially reducing long-term accumulation<sup>41</sup>.

Another important area of development is organ-selective delivery. Researchers are using combinatorial lipid libraries, high-throughput screening, and systematic formulation optimization to identify lipid structures capable of directing therapeutic molecules toward tissues beyond the liver. Surface engineering and ligand-based targeting are being combined with changes in lipid composition to achieve improved cellular specificity. These approaches could significantly expand the therapeutic applications of LNPs<sup>42</sup>.

Artificial intelligence and machine-learning methods are also beginning to influence nanoparticle formulation development. By analyzing relationships between lipid chemical structures, formulation parameters, physicochemical properties, and biological outcomes, computational approaches may help identify promising LNP formulations more efficiently than conventional trial-and-

error methods. Such approaches could reduce development time and accelerate discovery of optimized lipid structures<sup>43</sup>.

Stimuli-responsive LNPs represent another emerging strategy. These systems are designed to respond to biological conditions such as acidic pH, enzymes, redox potential, or other intracellular signals. Such responsiveness may enable controlled release of therapeutic payloads at specific locations and could improve therapeutic efficiency while reducing unwanted exposure<sup>44</sup>.

### Manufacturing and Regulatory Considerations

The successful translation of LNP therapeutics from research laboratories to clinical products requires highly controlled and reproducible manufacturing processes. Important quality attributes include particle size, polydispersity, encapsulation efficiency, lipid composition, lipid purity, payload integrity, surface characteristics, residual solvents, sterility, endotoxin levels, and stability. Small changes in manufacturing conditions can alter the physicochemical properties of LNPs and subsequently affect their biological performance<sup>45</sup>.

For nucleic-acid therapeutics, additional attention must be given to the purity and structural integrity of the genetic payload. Manufacturing processes must preserve the biological activity of the nucleic acid while maintaining consistent encapsulation and particle characteristics. Scale-up can introduce challenges because mixing conditions that work effectively at laboratory scale may not directly translate to commercial production. Therefore, scalable manufacturing technologies, process analytical tools, validated quality-control procedures, and appropriate regulatory frameworks are essential for successful commercialization of LNP-based therapeutics<sup>46</sup>.

### Future Perspectives

The future of LNP technology is expected to focus increasingly on improving tissue specificity, safety, biodegradability, repeat-dose capability, and manufacturing efficiency. One of the most important objectives is the development of extrahepatic delivery systems capable of selectively transporting therapeutic molecules to organs such as the brain, lung, heart, skeletal muscle, and immune system. Achieving this objective would substantially expand the range of diseases that could potentially be treated using LNP-based therapeutics<sup>47</sup>.

The development of biodegradable ionizable lipids is likely to remain a major research priority because these materials may improve both safety and therapeutic performance. High-throughput screening and artificial intelligence-assisted formulation design could accelerate the identification of novel lipid structures and optimized compositions. At the same time, targeted and stimuli-responsive LNPs may improve spatial and temporal control over therapeutic delivery<sup>48</sup>.

The combination of LNPs with gene-editing technologies is another particularly promising direction. Delivery of CRISPR-associated mRNA and guide RNA through LNPs could enable transient gene-editing activity and may provide new approaches for treating inherited diseases. Similarly,

mRNA-LNP platforms may expand beyond vaccines into protein replacement, cancer immunotherapy, regenerative medicine, and other therapeutic areas. However, long-term safety, immune responses, repeat administration, tissue specificity, manufacturing consistency, and regulatory standardization must be addressed before these applications can achieve widespread clinical use<sup>49</sup>.

### CONCLUSION

Lipid nanoparticles have evolved into one of the most important delivery platforms in modern nanomedicine. Their ability to encapsulate, protect, and intracellularly deliver conventional drugs and nucleic-acid therapeutics has created significant opportunities in drug delivery, vaccination, gene therapy, gene silencing, and gene editing. The clinical success of mRNA-LNP vaccines has demonstrated the feasibility of this technology and has accelerated research into a wide range of therapeutic applications.

Despite these achievements, limitations involving stability, toxicity, immunogenicity, endosomal escape, tissue specificity, manufacturing, and regulatory requirements remain significant. Future research should therefore focus on biodegradable ionizable lipids, organ-selective delivery, advanced targeting strategies, stimuli-responsive systems, AI-assisted formulation development, and scalable manufacturing technologies. Continued progress in lipid chemistry, nanotechnology, molecular biology, and pharmaceutical manufacturing is expected to further establish LNPs as a versatile platform for next-generation drug and genetic medicine.

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