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REVIEW ON: MRNA DELIVERY VIA LIPID NANOPARTICALS

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ABSTRACT

Messenger RNA (mRNA) has emerged as a transformative tool in modern biomedical science, capable of directing cells to produce therapeutic proteins and vaccines. However, its clinical potential was long constrained by instability, rapid degradation by nucleases, and inefficient cellular uptake. The advent of lipid nanoparticle (LNP) delivery systems revolutionized this landscape, offering a biocompatible and efficient platform to encapsulate, protect, and deliver mRNA into target cells. This review outlines the fundamental principles, evolution, mechanisms, advantages, limitations, and future prospects of mRNA delivery via lipid nanoparticles. The discovery of mRNA in the early 1960s laid the foundation for molecular biology, yet decades of research were required to overcome the challenges of mRNA degradation and immunogenicity. In the 1990s, lipid-based carriers were proposed as potential delivery vehicles, and by the 2000s, major breakthroughs such as chemical modification of nucleosides and the development of ionizable lipids-enabled safe and effective delivery. These advances culminated in the unprecedented success of mRNA-LNP vaccines during the COVID-19 pandemic, proving the platform's clinical efficacy and scalability. Structurally, LNPs are composed of four major lipid components-ionizable, lipids, helper lipids (phospholipids), cholesterol, and polyethylene glycol (PEG)-lipids. Ionizable lipids play a key role in mRNA encapsulation and endosomal escape by altering their charge in response to pH changes. Helper lipids stabilize the bilayer structure, cholesterol enhances rigidity and strength, while PEG-lipids improve circulation time and prevent aggregation.

KEYWORDS: mRNA delivery, lipid nanoparticles (LNPs), ionizable lipids, nucleoside modification, endosomal escape, mRNA vaccines, drug delivery systems, therapeutic proteins.

1. INTRODUCTION

Messenger RNA (mRNA) is a molecule that has become very important in modern medicine especially after the success of mRNA vaccines during the COVID-19 pandemic. To understand why mRNA delivery is a challenge and how lipid nanoparticles (LNPs) have solved this problem, it is important to first know what mRNA is, why it needs delivery support, and how LNPs work.[1]

- **What is mRNA**

Messenger RNA, or mRNA, is a type of genetic material found in all living cells. Its main function is to carry information from DNA (the genetic blueprint) to the ribosomes, which are the protein-making machines of the cell.[2]

- **Why is Delivery Needed for mRNA?**

Even though mRNA has many advantages, it is also very unstable and fragile. In the human body, there are many enzymes called RNases that can quickly destroy mRNA within minutes.[2]

- **What are Lipid Nanoparticles?**

Lipid nanoparticles (LNPs) are tiny spherical particles made from lipids, which are molecules similar to fats. At the nanoscale (a billionth of a meter), these particles are small enough to travel easily in the body but large enough to carry and protect mRNA.[6]

2. History of mRNA Delivery via Lipid Nanoparticles

- **Discovery of mRNA (1960s–1970s)**

The concept of messenger RNA was first described in the early 1960s by François Jacob, Sydney Brenner, and Matthew Meselson.

This discovery was a breakthrough in molecular biology, as it explained how genetic information is expressed in living organisms.

By the 1970s, scientists attempted to introduce synthetic mRNA into cells.

They hoped it could be used to produce therapeutic proteins or vaccines. Unfortunately, early experiments faced major setbacks.[11]

- **Challenges with Early mRNA Therapeutics (1980s–1990s)**

By the 1990s, lipid-based carriers emerged as a possible solution.

Lipid nanoparticles—tiny fat-like spheres—were studied for their ability to encapsulate mRNA, protect it from degradation, and transport it into target cells.[12]

- **Breakthroughs in mRNA Technology (2000s)**

The real turning point came in the 2000s with two critical discoveries. First, Katalin Karikó and Drew Weissman demonstrated that chemically modifying mRNA nucleosides reduced its tendency to provoke harmful immune responses.

Second, improvements in lipid nanoparticle technology revolutionized delivery. Researchers developed ionizable lipids, which change their charge in acidic environments, helping mRNA escape cellular compartments and reach the cytoplasm where protein synthesis occurs.[12]

- **KPre-COVID Applications of mRNA-LNPs (2010s)**

In the 2010s, biotechnology companies such as Moderna and BioNTech began investing heavily in mRNA-based therapies. Clinical trials were launched for vaccines against infectious diseases including influenza, Zika virus, and rabies. Researchers also explored mRNA-LNPs in cancer immunotherapy and rare disease treatments.[5]

- **COVID-19 Pandemic and Global Breakthrough(2020)**

When the COVID-19 pandemic emerged in late 2019, mRNA-LNP technology proved its worth. The genetic sequence of SARS-CoV-2 was published in January 2020, and within weeks both BioNTech/Pfizer and Moderna had designed vaccine candidates.[27]

3. Challenges in mRNA Delivery via Lipid Nanoparticles (LNPs)

Messenger RNA (mRNA) has emerged as a powerful therapeutic tool, especially after the success of mRNA-based vaccines against COVID-19. Some of the major challenges are described below.

- **Instability of mRNA**

mRNA molecules are inherently unstable because of their chemical structure.

They are long, single-stranded nucleic acids that can easily fold into complex secondary structures.

For example, this is why most mRNA vaccines require strict cold-chain storage at very low temperatures.[22]

- **Degradation by Enzymes (RNases)**

One of the biggest challenges for mRNA delivery is enzymatic degradation.

The human body naturally contains ribonucleases (RNases), which are enzymes that break down RNA molecules. RNases are present almost everywhere—in blood, tissues, and even on the surface of the skin.[7]

- **Poor Cellular Uptake**

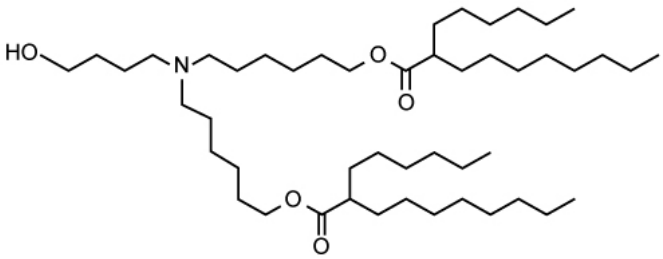
Another major challenge is ensuring that mRNA successfully enters target cells.

LNPs improve uptake by using ionizable lipids that can interact with the cell membrane and promote endocytosis (the process by which cells engulf external particles).[10]

4. Basic Structure of Lipid Nanoparticles (LNPs)

Lipid nanoparticles are tiny, spherical carriers made up of different types of lipids that work together to protect and deliver mRNA into cells. Each one has a unique structure and function that ensures stability and efficient delivery.[2]

- **Ionizable Lipids**

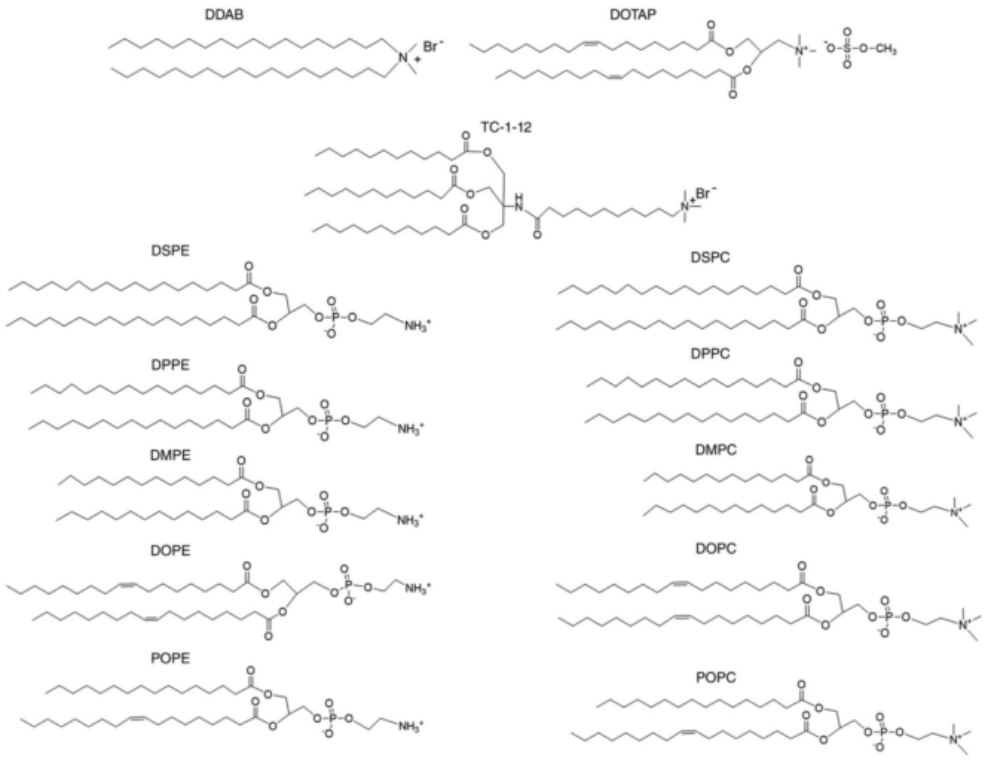


Structure No: 01.

Role

They are the key component for encapsulating and releasing mRNA inside the cell.

- **Helper Lipids (Phospholipids)**



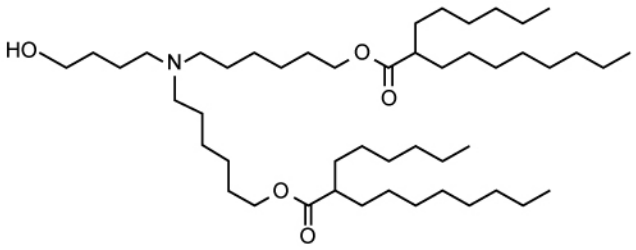
Structure No: 02.

Helper Lipids (Phospholipids)

Role

1. Help form the bilayer structure of the nanoparticle.
2. Provide structural stability to the LNP.

- **Cholesterol**



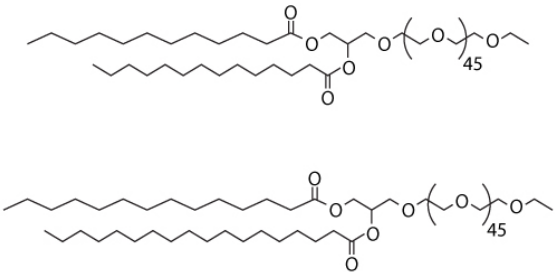
Structure No: 03.

Cholesterol

Role

1. Acts like a “glue” that fills gaps between lipids.
2. Provides rigidity and strength to the nanoparticle.

- **PEG-Lipids (Polyethylene Glycol-Lipids)**



Structure No: 04.

PEG-Lipids (Polyethylene Glycol-Lipids)

Role

1. Increase circulation time in the bloodstream by reducing clearance.
2. Control the particle size and prevent aggregation.

5. Mechanism of mRNA Delivery via Lipid Nanoparticles

- **Entry into the Body**

Route of administration

LNPs are usually administered via injection (intramuscular or intravenous). For vaccines, intramuscular injection is most common.[27]

- **Uptake by Cells**

Interaction with cell membrane

The LNPs approach target cells and interact with the lipid bilayer of the cell membrane.[30]

- **Release of mRNA Inside Cells**

Endosomal escape

Once inside the endosome, the acidic environment protonates the ionizable lipids, giving them a positive charge.[10]

- **Protein Synthesis**

Translation machinery: Once free in the cytoplasm, the mRNA is recognized by ribosomes, the cellular protein-making machinery.[37]

6. Applications of mRNA Delivery via Lipid Nanoparticles

The major applications include vaccines, gene therapy, and protein replacement therapy.

- **Vaccines**

Example: mRNA-LNP vaccines against COVID-19 (Pfizer-BioNTech and Moderna) successfully demonstrated rapid development, strong immune responses, and scalability.[27]

- **Gene Therapy**

Applications

Providing a safer and reversible alternative compared to permanent gene editing.[37]

- **Protein Replacement Therapy**

Applications

1. Replacement of blood-clotting factors in hemophilia.
2. Delivery of hormones or growth factors for metabolic regulation.[36]

7. Advantages of mRNA Delivery via Lipid Nanoparticles (LNPs)

- **Protection of mRNA**

Naked mRNA is highly unstable and prone to rapid degradation by nucleases in the body.[4]

- **Efficient Cellular Uptake**

This improves the delivery of mRNA into the cytoplasm where protein synthesis occurs, ensuring higher therapeutic effectiveness.[10]

- **Controlled Release**

LNPs are engineered to release mRNA inside the cell (after endosomal escape.[12]

- **Biocompatibility and Safety**

LNP components (ionizable lipids, cholesterol, phospholipids, and PEG-lipids) are generally safe and biodegradable.[16]

8. Limitations and Challenges of mRNA Delivery via Lipid Nanoparticles

- **Side Effects and Safety Concerns**

Immune Reactions: Some patients experience strong immune responses, such as inflammation, fever, or allergic reactions (e.g., to PEG-lipids).[9]

- **Storage and Stability Issues**

Cold Chain Requirement: mRNA-LNP formulations are highly sensitive to temperature. For example, some vaccines need storage at –20°C to –70°C.[9]

- **Cost and Large-Scale Manufacturing**

High Production Costs: Manufacturing high-purity mRNA and formulating stable LNPs requires advanced technology and expensive raw materials.[9]

- **Delivery Challenges**

Target Specificity: Current LNPs mainly accumulate in the liver, limiting delivery to other organs or tissues.[9]

9. Future Prospects of mRNA Delivery via Lipid Nanoparticles

Researchers are now exploring advanced applications that can transform treatment strategies. Some key future prospects include:

- **Personalized Medicine**

Role of mRNA-LNPs

LNPs can deliver customized mRNA sequences to produce therapeutic proteins specific to a patient's condition.

Example: In rare genetic disorders, LNPs could deliver mRNA designed uniquely for the patient's defective gene.(12)

- **Cancer Immunotherapy**

Role of mRNA-LNPs

1. Deliver mRNA encoding tumor-specific antigens into the body.
2. This enables patient's immune cells to recognize and destroy cancer cells.[18]

- **Next-Generation Vaccines**

Role of mRNA-LNPs

Enable rapid development of vaccines against emerging viral threats (influenza, Zika, HIV).[14]

10. CONCLUSION

mRNA delivery via lipid nanoparticles (LNPs) represents a groundbreaking advancement in modern medicine. LNPs solve the major challenges of mRNA instability, degradation, and poor cellular uptake by protecting and transporting mRNA safely into cells, where it can be translated into functional proteins. Ongoing research is working toward overcoming these hurdles, with future directions focusing on personalized medicine, cancer immunotherapy,

and next-generation vaccines. With continued innovation, mRNA-LNP technology has the potential to reshape the future of healthcare by offering safe, adaptable, and powerful treatment options for a wide range of diseases.

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