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Original Article

"Lipid Nanoparticles for Drug Delivery: Recent Advances, Formulation Strategies and Clinical Application"

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ABSTRACT

Lipid nanoparticles (LNPs) have become a promising drug delivery method because they can increase drug stability, bioavailability, and therapeutic efficacy. The newest developments, formulation techniques, and clinical uses of lipid nanoparticles are the main topics of this review. Liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) are the main categories of lipid-based nanocarriers. Ionisable lipids, phospholipids, cholesterol, and polyethylene glycol (PEG)-lipids are the primary constituents that support drug encapsulation, delivery efficiency, and particle stability. A number of formulation methods are covered, including solvent diffusion, ultrasonication, microemulsion, and high-pressure homogenisation. Additionally highlighted are crucial characterisation factors such as drug loading capacity, zeta potential, particle size, polydispersity index, and physical stability. LNPs help deliver therapeutic drugs, such as small interfering RNA (siRNA) and messenger RNA (mRNA). Cancer treatment, gene therapy, and mRNA vaccines are some of their clinical uses. Onpattro, Comirnaty, and Spikevax are examples of approved medications that show the clinical value of LNP technology. Recent developments in stimuli-responsive formulations, targeted nanoparticles, and AI-assisted design present fresh chances to enhance medication delivery. Nevertheless, there are still issues with endosomal escape, limited tissue targeting, toxicity, storage stability, and formulation complexity. All things considered, lipid nanoparticles are a potential platform for sophisticated drug administration; however, more investigation is needed to improve their stability, safety, and therapeutic efficacy.

Keywords: Lipid Nanoparticles, Drug Delivery, Recent Advances, Formulation Strategies, Clinical Application

INTRODUCTION:

1.1 Overview of Nanotechnology in Drug Delivery System:

Nanotechnology is a promising and fast developing area of the 21st century, which affects various fields of science: physics, chemistry, biology, engineering, microelectronics, medicine. Nanotechnology is based on the use of materials that when reduced to the nanoscale acquire unique structural, optical, mechanical, magnetic, electrical, and biological properties. Within medical nanotechnology, various nanoscale structures have been developed on the basis of such materials. They can be used as carriers of drugs to improve their bioavailability, reduce systemic side effects, and increase therapeutic efficacy. Such carriers should possess several properties like bio inertness, biocompatibility, biodegradability, non-toxicity to the organism, and protection of the drug against degradation and inactivation during transportation to the specific site, thus enabling its prolonged release in the target area. Drug delivery mechanisms are classified according to their origin into polymeric systems, cellular carriers and viruses, and inorganic carriers. Polymer carriers include micelles, liposomes, dendrimer aggregates, hydrogels etc. The body's immune cells (macrophages and T-cells), blood cells (erythrocytes and platelets), stem cells, exosomes and adipocytes can serve as cellular drug carriers. The immobilization is carried out using different types of carriers depending upon the physicochemical properties of the drug molecules. [1,2]

- **Definition And Types of Nanotechnology**:

Nanotechnology drug delivery involves the use of nanoscale technologies to create drug delivery systems that convey the drug substance to its target site within the body. The systems are capable of improving the drug's solubility, bioavailability, stability, sustained delivery, and efficacy among others. [3]

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

1. **Lipid-Based Nanocarriers**: Nanoscale systems made up mainly of lipids that spontaneously form core-shell or matrix type structures. {example: mRNA delivery} [4,5,6]
2. **Polymeric Nanocarriers**: Nanoscale structures formed using natural or synthetic polymers that are designed for entrapment, encapsulation, or covalent attachment of drugs. {example: Chitosan nanoparticles} [3]
3. **Inorganic Nanocarriers**: Designed nanoscale systems with the core made up of inorganic compounds such as gold, silica, or iron oxides. {example: gold nanoparticles} [3]
4. **Biological Nanocarriers**: Nanoscale systems made up of biological sources or biomimetic systems taken from live cells or engineered viruses. {example: exosomes} [3]
5. **Other Nanoscale Drug Delivery Systems**: Nanoscale systems focused on altering the physical state or phase of the substance rather than employing the complex hollow carrier system.[3]

1.2 Need for Advanced Drug Delivery System:

To get beyond the drawbacks of traditional dose forms and enhance the therapeutic efficacy of medications, sophisticated drug delivery methods have been created. Poor bioavailability, variations in plasma drug concentrations, quick drug clearance, and challenges in precisely delivering medications to the intended site are all possible drawbacks of conventional drug administration methods such tablets, capsules, and injections. These systems may offer targeted delivery, enhanced drug stability, decreased dosing frequency, and sustained or controlled drug release, depending on how they are designed. To enhance the delivery of medications with difficult physicochemical characteristics, nanotechnology-based carriers such as liposomes, lipid nanoparticles, polymeric nanoparticles, and micelles are being researched. Therefore, the development of safer, more efficient, and patient-focused pharmaceutical formulations is greatly aided by advanced drug delivery systems. [3]

1.3 Introduction to Lipid Nanoparticles:

To conserve active components, enhance drug efficacy, and guide site-specific drug administration, a variety of drug delivery methods have been created. For many years, drug delivery via nanoparticles has been the subject of intense research. Liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLSs) are examples of lipid-based nanoparticles that have shown remarkable clinical efficacy in delivering both hydrophobic and hydrophilic medicines. Doxil, the first FDA-approved nanodrug, is a PEGylated liposome loaded with doxorubicin (DOX) that is used to treat solid lipid tumours, ovarian cancer, and breast cancer. A significant turning point for lipid-based drug delivery systems and cancer nanomedicine was the clinical approval of Doxil in 1995. However, because of their exceptional biocompatibility, biodegradability, and entrapment effectiveness, lipid nanoparticles (LNPs) have also been identified as an appropriate carrier for nucleic acids such as DNA, mRNA, and siRNA. [4,5,7,8]

1.4 Need for Lipid Nanoparticles in the Pharmaceutical Industry:

A very versatile family of nanocarriers, lipid-based nanoparticles (LNPs) are widely used in pharmacology and medical research. For a variety of uses, they can encapsulate different medicinal substances, such as tiny compounds, nucleic acids, and monoclonal antibodies. LNPs provide a number of advantages, including protecting medications from in vivo degradation, increasing their solubility and effectiveness, facilitating targeted drug delivery to the illness site, controlling drug release, and modifying drug biodistribution. LNP-based medications have seen tremendous growth in both the academic and industrial sectors in recent years as their promise has become more widely acknowledged. The market for LNP-based gene therapy was estimated to be worth $3.5 billion in 2021 and is expected to increase at a compound annual growth rate of roughly 18.5% between 2021 and 2026. The market value of liposomal therapies used to treat cancer, such as Doxil, DaunoXome, Myocet, DepoCyt, Marqibo, and Onivyde, was over $3.72 billion in 2021 and is projected to grow to nearly $7 billion by 2027. The FDA has approved LNP-based medicines for the treatment of cancer as well as other illnesses, such as amyloidosis (Onpattro) and COVID-19 vaccination (Spikevax, Comirnaty), by delivering siRNA and mRNA, respectively. However, LNP-based treatments must be manufactured using methods that guarantee stability during storage, compatibility with sterilisation, quality control, and regulatory compliance in order to be therapeutically meaningful. [3,5,9,10]

2. Lipid Nanoparticles: An Overview

2.1 Definition And Components of Lipid Nanoparticles (LNPs):

Small-molecule medications, proteins, peptides, mRNA, siRNA, and other nucleic acids can all be encapsulated, protected, and delivered to target cells or tissues using lipid nanoparticles (LNPs), which are nanoscale lipid-based drug delivery systems. Phospholipids and cholesterol, which are essential for particle formation and stability; cationic or ionisable lipids, which allow binding with negatively charged nucleic acids and increase drug loading; and PEGylated lipids, which contribute to improved particle stability and circulation time within the biological system, are the four main lipid components of LNPs. LNPs can readily pass through cell membranes to transport nanoparticle contents to the intended intracellular locations because of their biomimetic architecture and lipid components' resemblance to those of cell membranes. [4,5,6]

2.2 Historical Development:

Controlled-release formulations and drug delivery systems based on nanotechnology have gradually replaced traditional dosage forms in the history of sophisticated drug delivery systems. Sustained-release formulations were developed in the 1950s to extend the duration of medication activity and lower the frequency of administration. Alec Bangham's observations of lipid bilayer structures during the 1960s helped develop liposomes as possible medication carriers. In order to limit drug release and sustain therapeutic benefits for extended periods of time, research concentrated on controlled-release technologies during the 1970s and 1980s. The prospects for pharmaceutical treatment were enhanced in the 1990s by developments in liposomal drug delivery and long-acting formulations. The 1995 approval of Doxil, a doxorubicin PEGylated liposomal formulation, was a significant turning point in the development of nanotechnology-based drug delivery. Research on various nanocarriers, including liposomes, albumin-based nanoparticles, and polymeric nanoparticles, grew in the 2000s. Onpattro (patisiran), a siRNA medication administered using lipid nanoparticles (LNPs), was approved in 2018, marking a significant development in RNA-based treatment. The use of lipid nanoparticles in mRNA-based COVID-19 vaccines began to garner additional attention in 2020. [5,7,11]

2.3 Types of Lipid Nanoparticles:

Three common kinds of lipid-based drug delivery nanoparticles include liposomes, SLNs, and NLCs. [8,12,13]

Types	Structure and Composition	Advantages	Application
Liposomes	The aqueous core may include hydrophilic medications, while the lipid bilayer may contain hydrophobic drugs.	Adaptable carriers that can deliver various medicinal substances.	Delivery of proteins, nucleic acids, and anticancer medications.

Types	Structure and Composition	Advantages	Application
Solid Lipid Nanoparticles	A surfactant-stabilized solid lipid core.	Can enhance formulation stability and safeguard integrated medications.	Administration of antibiotics, antioxidants, and anticancer medications.
Nanostructured Lipid Carriers (NLCs)	A less-ordered lipid matrix made up of a combination of liquid and solid lipids	Can decrease drug ejection during storage and enhance drug loading.	Delivery of medications that are hydrophilic or hydrophobic.

• Liposomes:

Originally identified by Bangham and associates in 1965, liposomes are self-assembling, nanoscale lipid vesicles made up of one or more concentric phospholipid bilayers that enclose distinct aqueous regions. Because liposomes may transport a wide variety of therapeutic medications, with hydrophilic drugs confined inside their aqueous core and hydrophobic drugs integrated into the lipid bilayer, their potential as drug delivery devices was immediately recognised. Liposomes are a very flexible drug delivery system because they can also carry other macromolecules like proteins, nucleic acids, and various imaging agents. Depending on the particular formulations and synthesis techniques, liposomes can be produced into unilamellar or multilamellar vesicles that range in size from 20 to 1000 nm. Higher encapsulation efficiency, better drug half-life, and immune system evasion are all demonstrated by small unilamellar liposomes (≤100 nm). [7,8,11,14]

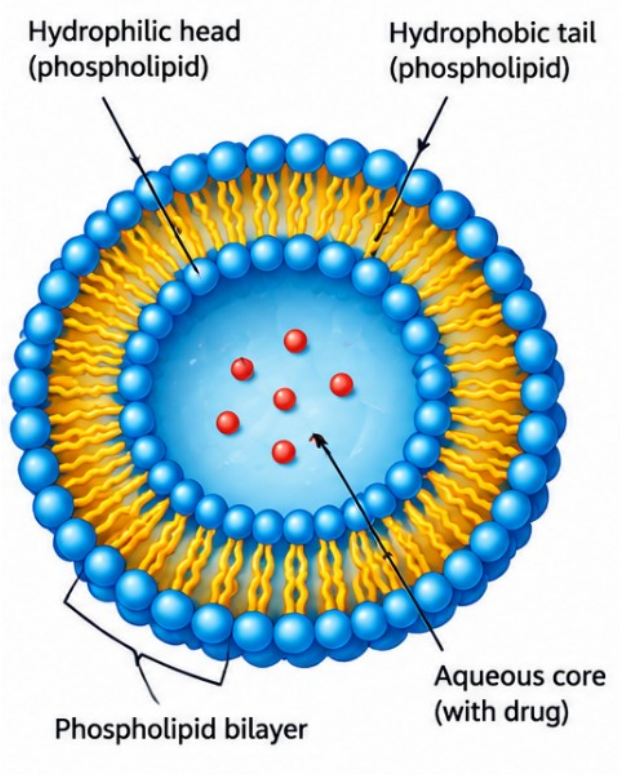

Figure 1.1: Structure of Liposome

• SLCs:

Originally designed as tiny spherical particles with a solid lipid core at room temperature, solid lipid nanoparticles (SLNs) have evolved into flat ellipsoidal or disc-like geometries with sizes ranging from 50 to 100 nm. The active ingredient in SLNs can be distributed across the entire lipid matrix or added to the lipid core or lipid shell. Compared to liposomes, SLNs' solid lipid core offers a novel way to increase particle stability. Cationic lipids can improve the particles' cellular internalisation when added to SLN shell compositions. To improve SLNs' specificity at targeted treatment areas, macromolecules like oligosaccharides, proteins, particular ligands, and antibodies can be added to their outer shell. [12,15,16,17]

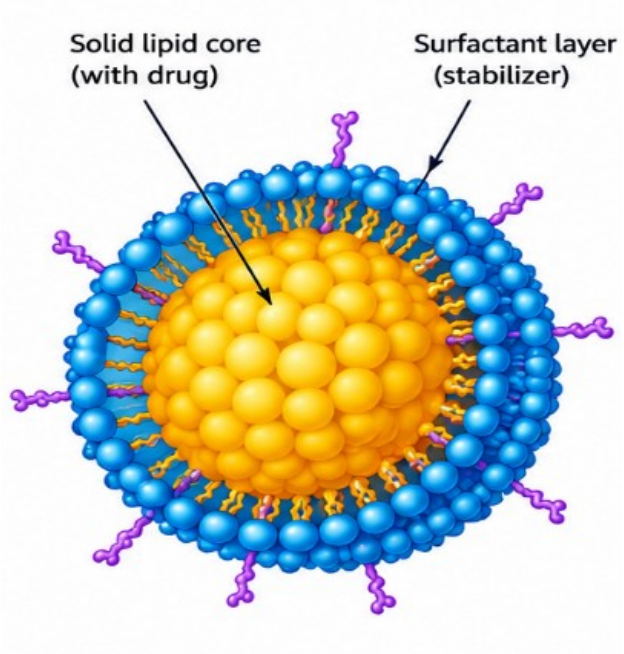

Figure 1.2: Structure of SLNs

• NLCs:

As was previously indicated, a major flaw of solid lipid nanoparticles (SLNs) is their restricted ability to carry drugs. In order to overcome this difficulty, scientists have developed a second generation of SLNs called nanostructured lipid carriers (NLCs), which

have a more disordered lipid structure because they contain both liquid and solid lipids in their cores. Compared to SLNs, this structural feature enables greater drug loading capacity and better drug release kinetics. Hydrophilic and hydrophobic medications can be delivered specifically by modifying NLCs with ligands or polymers. RNA- and pDNA-loaded NLCs are effective carriers that allow for the delivery of therapeutic proteins, gene therapy, and personalised medicine. These lipid-based nanoparticles provide flexible platforms based treatment for cancer and hereditary disorders. [12,13,16,17]

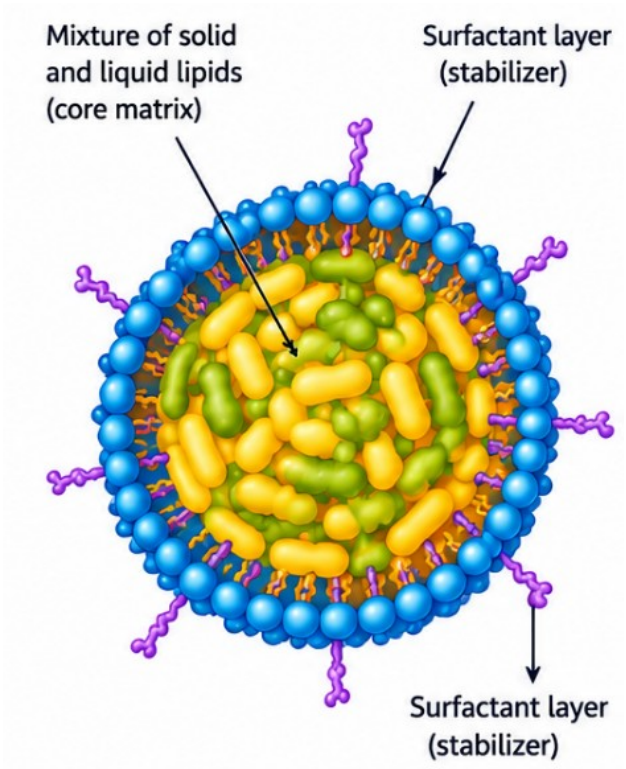

Figure 1.3: Structure of NLCs

3. Composition of Lipid Nanoparticles:

The four main components of LNPs are: (1) ionisable lipids, which are crucial for encapsulating and delivering nucleic acids; (2) polyethylene glycol (PEG)-lipids, which control LNP size and stability; (3) phospholipids, which influence LNP fusogenicity; and (4) cholesterol, which enhances LNP stability and fluidity. [4,5,6,19]

• Ionizable Lipid:

LNPs were initially created using permanently charged cationic lipids, which have the ability to electrostatically bind to the negatively charged phosphate backbones of nucleic acids. Strong electrostatic interactions help nucleic acids condense into stable nanoparticles. Cationic lipids, on the other hand, are highly immunogenic and poisonous. More sophisticated ionisable lipids have been created to solve these problems. The ionisable polar head group, the linker, and two or more hydrophobic hydrocarbon tails are the three components of ionisable lipids. Ionisable lipids can be protonated and positively charged in low pH environments while remaining neutral at physiological pH because they usually have a pKa value between 6.2 and 6.5. [6,19,20,21]

• Phospholipid:

Also referred to as helper lipids, phospholipids are crucial for the formulation of LNP. By maintaining structural integrity and adjusting the lipid bilayer's fluidity, they can promote the stability of LNPs. The stiff structure of the two saturated fatty acid chains in DSPC allows for the creation of a lamellar phase and improves the stability of LNPs. Notably, BNT162b2 and mRNA-1273, two commercially available COVID-19 vaccines, contain it. Due to its fusogenic characteristics, DOPE with two unsaturated fatty acid chains has the potential to destabilise the endosomal membrane by forming an inverted hexagonal H (II) phase. Consequently, DOPE can enhance delivery efficacy and help LNPs escape the endosome. Phosphocholin is present in DOPC. [4,5,6]

• Cholesterol:

An essential part of LNPs is cholesterol. It improves particle stability, modifies membrane integrity, and controls stiffness, among other things. By enhancing the compactness of LNPs and integrating into the lipid bilayer, cholesterol can stop premature disintegration and boost the effectiveness of nucleic acid delivery. In LNPs, the molar ratio of cholesterol is usually 50%. LNP formation and function can be impacted by cholesterol levels. Kawaguchi et al. found that cellular internalisation and protein expression dramatically dropped when the proportion of cholesterol in LNPs was lowered from 40% to 10%. [5,6,22]

• PEG-lipids:

PEG is a hydrophilic polymer that, when coupled to lipids, creates an anti-fouling PEG shell around the LNP, increasing its stability, decreasing immune system identification and clearance, and extending its circulation time in-vivo.1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N [methoxy](polyethylene glycol-2000)] and 1,2-dimyristoyl-rac-glycero-3-

methoxypolyethylene glycol-2000 (DMG-PEG2000) are two frequently utilised PEG-lipids. (PEG2000, DSPE). The physicochemical characteristics and functions of LNPs, including polydispersity, size, encapsulation efficiency, transfection efficiency, and immunological responses, can be influenced by PEG-lipids. [4,5,10]

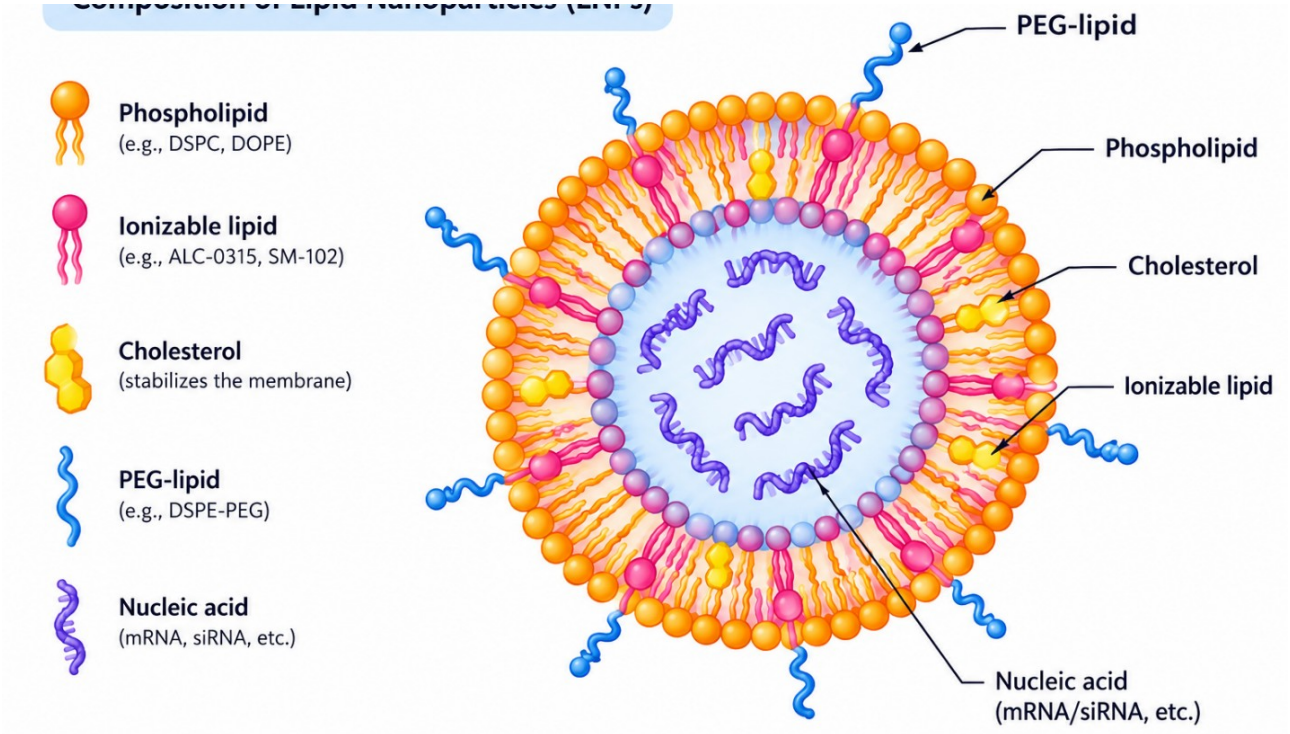

Figure 2: Composition of Nanoparticles

4. Formulation Strategies:

The two primary groups of methods used to produce LNPs are categorised based on the energy required: (i) using high energy, which is supplied by devices like ultrasound, high-speed homogenisation, and hot or cold high-pressure homogenisers; (ii) using low energy, which includes the use of mixing processes under low agitation with microemulsions and solvent diffusion. [12,13,23,24]

4.1 High Energy Level:

• Hot High-Pressure Homogenisation:

High-Pressure Homogenisation one of the most promising methods for making lipid nanoparticles (LNs) is high-pressure homogenisation (HPH). At pressures ranging from 100 to 2000 bar, it uses cavitation and shear forces to reduce particle size to the nanometre level. Every sample must have the same energy intensity in order to achieve a homogeneous particle size distribution. The homogenizer's tiny aperture (less than 30 µm) guarantees consistent shear stress across the sample. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are frequently made using hot and cold homogenisation. The medication is dissolved or distributed in the lipid phase prior to the homogenisation procedure in both approaches. [12,13,25]

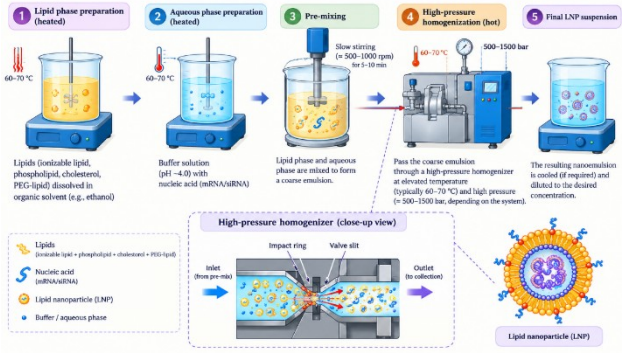

Figure 3.1: Hot High-Pressure Homogenisation

• Cold High-Pressure Homogenisation:

Heat-sensitive and bioactive materials are subjected to cold high-pressure homogenisation (HPH). The bioactive component is distributed throughout the molten lipid phase, which is quickly chilled with liquid nitrogen or dry ice to create a solid combination. This mixture is disseminated in a cold surfactant solution after being pulverised into 50–100 µm particles. To create nanoparticles, the suspension is subsequently homogenised under high pressure. This

technique offers control over lipid crystallisation, enhances medication distribution and retention within the lipid matrix, and lessens heat degradation. [12,13,25]



Figure 3.2: Cold High-Pressure Homogenisation

• Ultrasonic Homogenization:

The lipid phase is heated to 5–10°C above its melting point during ultrasonic homogenisation. After that, it is quickly stirred and distributed in a hot aqueous phase that contains surfactant to create a pre-emulsion. Through turbulence and cavitation, sonication decreases the size of the droplets. Cooling the emulsion below the lipid crystallisation temperature results in the formation of lipid nanoparticles. This process increases stability and yields nanoparticles between 30 and 180 nm. However, its main drawbacks include excessive energy consumption, decreased encapsulation efficiency, and potential metal contamination. [12,13,25]

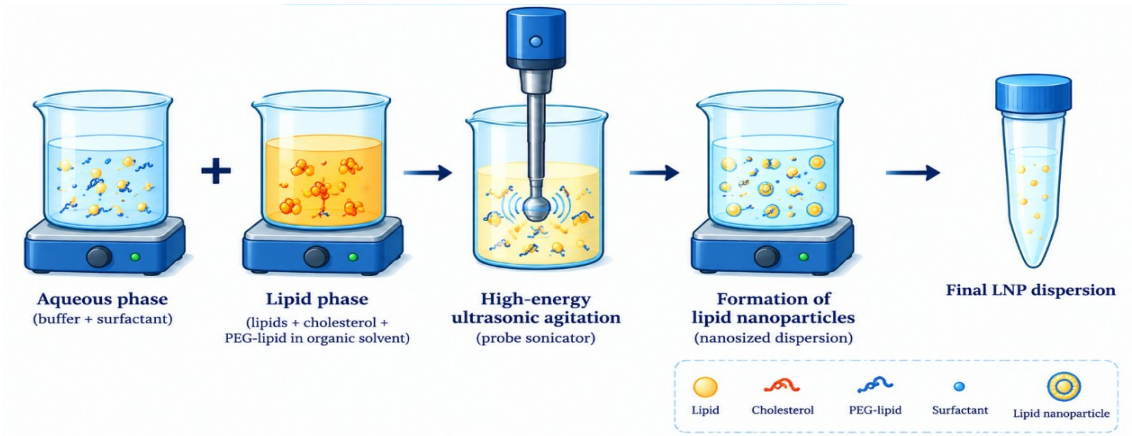

Figure 3.3: Ultrasonic Homogenization

4.2. Low Energy Level:

• Microemulsion:

The bioactive ingredient is combined with the melting lipid phase. To create a microemulsion, a surfactant and co-surfactant are introduced at the same temperature as the aqueous phase. Following their dispersion in cold water (2–10°C), lipid droplets quickly recrystallise and produce lipid nanoparticles (LNs). The range of the dilution ratio is 1:25 to 1:50. Surfactants induce self-assembly, generating micelles and bilayer structures. The key advantages are quick production and enhanced solubilisation of lipophilic substances. However, this approach demands high quantities of surfactant and co-surfactant. [12,13,25]

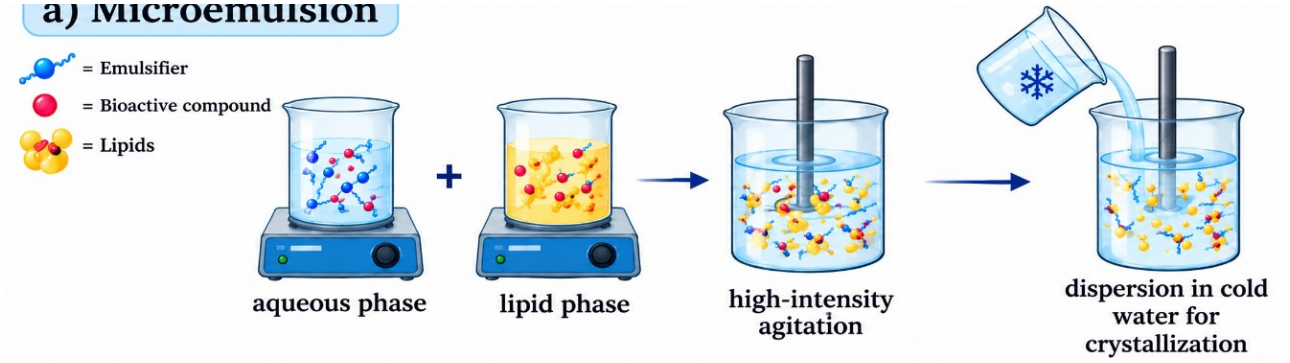

Figure 3.4: Microemulsion

• Solvent Diffusion:

To guarantee initial thermodynamic equilibrium, somewhat water-miscible organic solvents (benzyl alcohol, butyl lactate, isobutyric acid, isovaleric acid, and tetrahydrofuran) are first saturated with water. The water-saturated solvent then dissolves the lipids and the bioactive ingredient. An oil-in-water (O/W) emulsion is created by emulsifying this combination in an aqueous emulsifier solution that has been saturated with solvent using a mixer.[12,13,25]

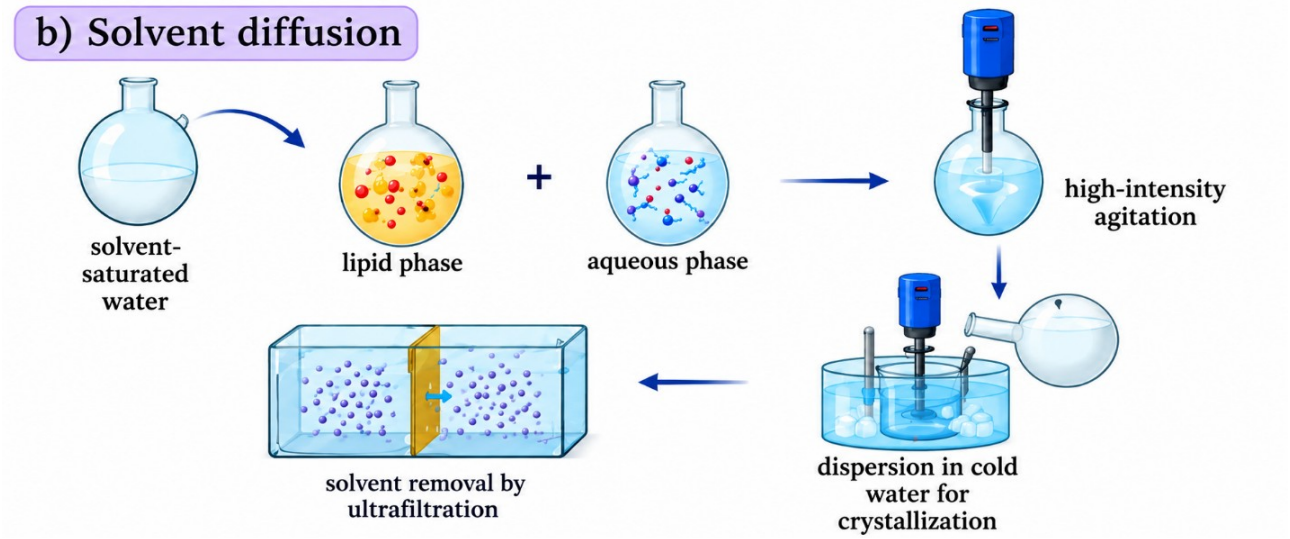

Figure 3.5: Solvent Diffusion

5. Characterization of Lipid Nanoparticles:

LNs' intrinsic qualities (size, formulation, and thermal properties, among others) affect their physicochemical features and functional performance, including stability, optical properties, delivery rate, and metabolic fate. The complexity of the systems involved and the small size of LNs make characterising them extremely difficult. This section presents the most popular techniques for characterising LNs. [12,13,25,26]

5.1 Particle Size (PS) and Polydispersity Index (PDI):

One of the most crucial characteristics for LNs is PS. This decision can verify if particular formulas and procedures were used to achieve the desired dimensions and, more crucially, whether these dimensions are maintained during storage or further processing. Since LNs' dimensions affect their physicochemical characteristics, functionality, and possible applications, controlling them is crucial. In order to guarantee long-term stability, this index should be reduced since it has a major influence on the physical stability of LNs. A tight size range is shown by PDI values between 0.1 and 0.25, which suggests that LNs have comparable PS. On the other hand, PDI values higher than 0.5 indicate a wide dispersion and possible system instability, which could result in LN aggregation. LN dispersions must be diluted with ultrapure water (between 1:10 and 1:100) to achieve a sufficient dispersion intensity (particle count between 100 and

1000 s−1) before PS and PDI are determined. [12,13,25]

5.2 Zeta Potential (ZP):

The ZP is commonly employed as a characteristic parameter to indicate the charge of LNs because the surface potential of particles cannot be measured directly. ZP is primarily utilised to provide data on formulation stability during storage, enabling significant formulation modifications. The electric potential at the hydrodynamic shear surface around colloidal particles is indirectly measured by the ZP. It shows how far away from the particle surface counterions stay firmly bonded when the particles are moving in the presence of an electric field. Due to electrical repulsion, ZP values around ±30 mV are thought to be a good indicator of system stability, indicating a lesser tendency to flocculate or coalesce. Because of electrostatic attraction, positively charged particles usually stick to negatively charged surfaces or components, and vice versa. Analytical tools that detect electrophoretic or electroacoustic mobility can be used to calculate ZP. [12,13,25]

5.3. Morphology:

LNs can differ greatly in their morphology. Because they provide longer diffusion paths and less interaction with the aqueous media, spherical particles are especially useful for the prolonged release and trapping of bioactive chemicals. Additionally, because spherical LNs have a smaller specific surface area, they usually require less emulsifier for stabilisation. Anisometric particles, on the other hand, can be advantageous for encasing substances in the emulsifier layer. The most popular microscopy methods for describing the structure and morphology of LNs are optical, electron, and scanning microscopy. [12,13,25]

5.4. Drug Loading Capacity:

For an LN delivery system to be deemed appropriate for the entrapment of bioactive compounds, a number of characteristics must be present, with high LC being one of the most crucial. The LC parameter is the ratio of the amount of encapsulated compound to the total amount of lipid phase; factors that affect this ratio include the physical structure of LNs, their polymorphic form, and the solubility of the bioactive compound in the lipid phase. LC represents the lipid matrix's capacity to transport the desired bioactive compound to the target site for adsorption. [12,13,25]

5.5. Physical Stability:

The ability of an emulsion to maintain its characteristics over time is referred to as the stability of colloidal systems. Put otherwise, the emulsion's properties will change more slowly if it is more stable. There are two main elements that affect LNs' physical stability. First, destabilisation processes including flocculation, creaming, sedimentation, and coalescence affect the LNs' dispersion's capacity to stay homogeneous, or in a single phase. Second, the solid lipid matrix's durability, which establishes how resistant it is to recrystallisation over time. [12,13,25]

6. Mechanism of Drug Delivery:

The drug delivery mechanism of lipid nanoparticles (LNPs), which are nanoscale drug delivery systems, includes encapsulation, cellular uptake, intracellular release, and the delivery of therapeutic nucleic acids like messenger RNA (mRNA) and small interfering RNA (siRNA).

6.1 Drug Encapsulation and Protection:

Depending on the formulation and type of drug, lipid nanoparticles encapsulate therapeutic agents within their lipid matrix or internal structure. Ionisable lipids interact with negatively charged nucleic acids to facilitate their incorporation into LNPs. The encapsulated drug is protected from environmental conditions and enzymatic degradation by the lipid components, which can enhance drug stability and facilitate intracellular delivery. The efficiency and stability of the lipid composition, the preparation technique, and the physicochemical characteristics of the therapeutic agent. [4,5,6]

6.2 Cellular Uptake of Lipid Nanoparticles:

After being administered, lipid nanoparticles interact with biological membranes to reach target cells. Cellular uptake typically takes place through endocytosis, in which the cell membrane encircles the nanoparticles and forms intracellular vesicles called endosomes. The effectiveness of cellular uptake depends on the biological characteristics of the target cells, particle size, surface characteristics, and lipid composition. Nevertheless, cellular uptake by itself does

not ensure that the encapsulated cargo must also escape the endosome to reach its intracellular site of action. [2,4,5]

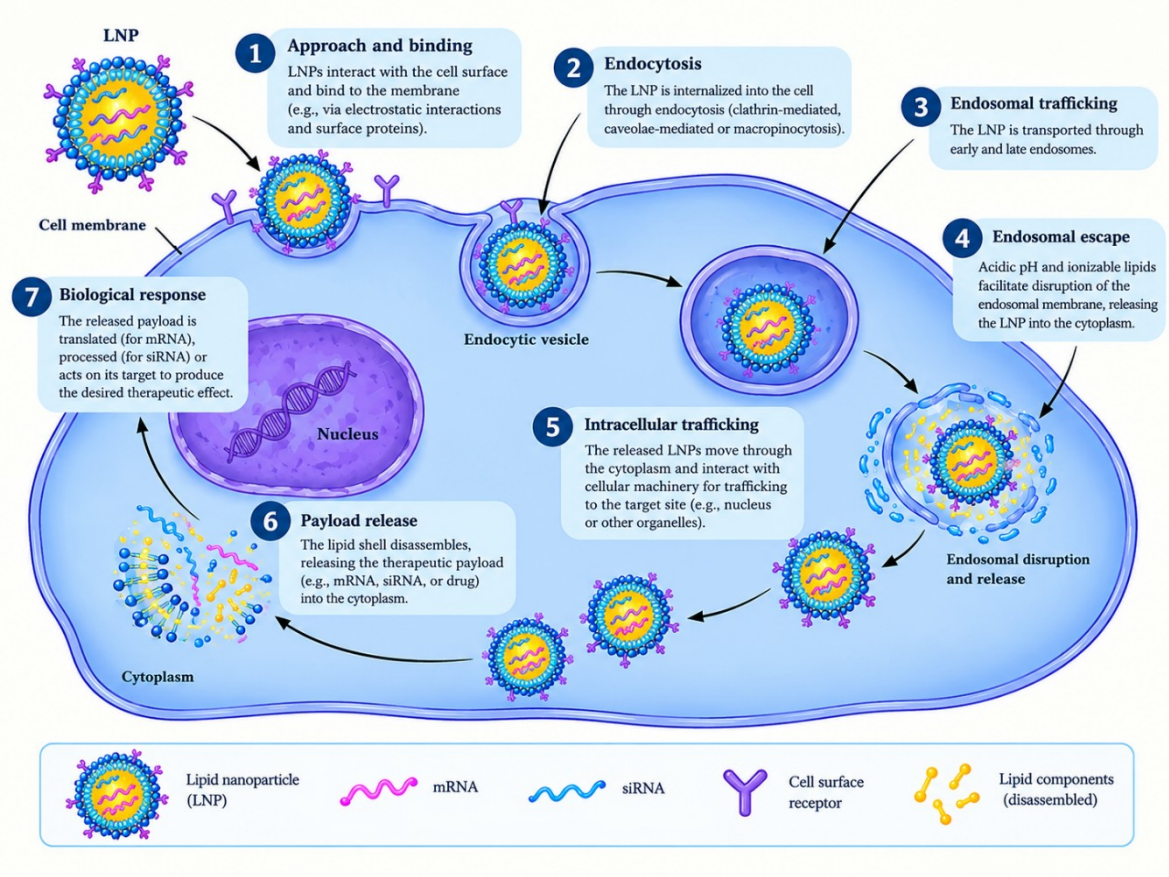

Figure 4: Mechanism of Cellular Uptake

6.3 Intracellular Drug Release:

Following cellular uptake, LNPs enter endosomes, where the acidic environment encourages the protonation of ionisable lipids. These lipids interact with the endosomal membrane and may cause membrane destabilisation and rearrangement, which can facilitate endosomal escape and allow the therapeutic cargo to enter the cytoplasm. Pei (2025) discusses the vesicle budding-and-collapse (VBC) mechanism as a possible explanation for endosomal escape. The effectiveness of LNP formulations is crucial. [4,5,27]

7. Lipid Nanoparticles (LNPs) Clinical Uses:

Advanced drug delivery devices called lipid nanoparticles (LNPs) shield therapeutic compounds from deterioration and make it easier for them to enter cells. They have significant uses in gene silencing, immunisation, RNA-based medications, and the creation of novel therapies. Approved medications like Onpattro and LNP-based mRNA vaccines indicate their clinical significance. [3,5,9,28,29]

7.1 Lipid Nanoparticle Products Approved by the FDA: Nucleic acid-delivering medications have been made possible using LNP technology. Notable instances consist of:

- Onpattro (patisiran): An LNP-formulated siRNA medication authorised for the management of adult polyneuropathy linked to inherited transthyretin-mediated amyloidosis. It lowers the liver's synthesis of transthyretin. [3]
- Comirnaty: A COVID-19 preventive mRNA vaccine made with LNP. [28]
- Spikevax: A COVID-19 preventive mRNA vaccine made with LNP. [29]]

These goods show how useful LNPs are in the clinical setting for delivering therapeutic RNA. [3,28,29]

7.2. Vaccines with mRNA:

Because LNPs shield mRNA from deterioration and make it easier for it to enter cells, they are crucial to the creation of mRNA vaccines. The mRNA instructs

the production of a particular antigen following cellular absorption and release into the cytoplasm. When the immune system detects this antigen, it launches an attack. [4,5,28,29]

7.3. Clinical Trials:

Clinical research is being done on LNPs for uses other than those of existing approved medications. The goal of these studies is to enhance nucleic acid delivery, stability, and therapeutic efficacy. Cancer immunotherapy: LNPs are being studied for the delivery of mRNA encoding immune-modulating proteins or tumor-associated antigens. [2,9,10,19,30]]

7.4. Business-Related Items:

There are a number of commercially marketed medications and vaccines based on lipid nanoparticles (LNPs) for use in therapeutic settings.

- Onpattro (Patisiran): Onpattro is a small interfering RNA (siRNA) medication based on LNP that is used to treat polyneuropathy in adults with inherited transthyretin-mediated amyloidosis. Transthyretin protein synthesis is decreased by delivering siRNA to liver cells. [3]
- Comirnaty (Pfizer-BioNTech): Comirnaty is a COVID-19 preventive mRNA vaccine made with LNPs. The mRNA is shielded by the LNPs and made easier to enter cells, where it controls the synthesis of a viral antigen that triggers an immunological reaction. [28]

8. Therapeutic Applications of Lipid Nanoparticles (LNPs):

Advanced drug delivery devices called lipid nanoparticles (LNPs) help transfer therapeutic chemicals into cells while preventing their breakdown. Vaccines, gene therapy, ophthalmic medication delivery, neurological disorders, cardiovascular diseases, pulmonary drug delivery, oral drug delivery, and cancer therapy are all under investigation. [3,9,10]

- **Cancer Therapy:** Anticancer medications and nucleic acids, such as mRNA and siRNA, are being studied for delivery via LNPs. They can aid in intracellular transport and safeguard medicinal compounds. To boost immune responses to tumor-associated antigens, LNP-based mRNA strategies are also being researched. [2,9,10]
- **Ocular Drug Delivery:** Lipid nanoparticles are being used to investigate the delivery of therapeutic medicines to ocular tissues. They may improve the stability and retention of drugs and facilitate their delivery to certain eye tissues. One potential application is the treatment of retinal disorders and other eye conditions. [1,2]
- **Neurological Disorders:** LNPs are being investigated as carriers of nucleic acids for neurological illnesses and medicinal medicines. The blood –brain barrier, which prevents many medicinal compounds from entering the brain, is a significant obstacle. [2,30]

9. Recent Advances in Lipid Nanoparticles (LNPs):

Advanced drug delivery systems called lipid nanoparticles (LNPs) are utilised to carry therapeutic molecules into cells, including mRNA, siRNA, and other nucleic acids. Enhancing their stability, intracellular delivery, targeting capability, and safety are the main goals of recent research. PEGylated LNPs, ligand-targeted LNPs, stimuli-responsive LNPs, mRNA delivery methods, and AI-assisted formulation design are all significant advancements. These strategies seek to improve the effectiveness and suitability of LNP-based medications for a greater variety of illnesses. [5,9,10,19]

- Excessive PEGylation can hinder intracellular delivery and decrease cellular absorption. Additionally, some people may experience immunological reactions to PEG, which may compromise the safety and long-term use of some formulations. In order to balance stability with efficient drug delivery, current research examines PEG content, lipid-anchor structure, and PEG shedding. [4,5,10]
- The nanoparticles may enter the target cells by receptor-mediated endocytosis after attaching to the appropriate receptor. This approach may increase treatment efficacy, decrease exposure to non-target tissues, and improve delivery to specific areas. Applications for ligand-targeted LNPs include immune-cell targeting, cancer treatment, and the administration of genetic medications outside of the liver. [2,19,30]

- Messenger RNA (mRNA) treatments now heavily rely on lipid nanoparticles as carriers. Encapsulation in LNPs promotes mRNA distribution into cells and aids in its protection. Improved ionisable lipids, more efficient intracellular transport, tissue-selective formulations, and strategies that can lessen undesirable immunological reactions are currently being studied. [4,5,28,29]
- Researchers may be able to create LNPs with enhanced potency, stability, and tissue selectivity by combining AI with experimental testing. Predictions, however, rely on the calibre and variety of the data at hand. The safety and repeatability of the resulting formulations must be determined, and AI-generated predictions must be verified empirically. [9,10]

10. Advantages and Limitations:

Because they can encapsulate therapeutic compounds, shield delicate molecules from degradation, and make distribution into cells easier, lipid nanoparticles (LNPs) are being studied extensively as drug-delivery systems. However, manufacturing complexity, stability, toxicity, and regulatory constraints may have an impact on their clinical use. [3,5,9,10]

- **Better medication delivery:** LNPs can help transfer therapeutic molecules into cells, such as mRNA and short interfering RNA (siRNA). [1,4,5]
- **Degradation protection:** Encapsulation shields delicate medicinal compounds from environmental and enzymatic deterioration. [1,4,5]
- **Increased bioavailability:** Lipid-based carriers can enhance the absorption and delivery of some medications, especially those with low water solubility. [1,9,10]
- **Biocompatibility:** Lipids that are compatible with biological systems are used in many LNP formulations. Nevertheless, the lipid content, dosage, and mode of administration all affect biocompatibility. [5,9,10]

10.1. Current Challenges:

- **Formulation complexity:** Particle size, encapsulation effectiveness, stability, and delivery performance are all impacted by the choice and ratio of lipids. Extensive experimentation may be necessary to optimise these factors. [4,5,9]
- **Limited tissue targeting:** Because conventional LNPs frequently build up in the liver, it can be challenging to effectively distribute them to certain other organs and cell types. [2,30]
- **Low endosomal escape:** Some LNPs are stuck in endosomes after being taken up by cells. As a result, the cytoplasm may only receive a part of the encapsulated medicinal substance. [4,5,27]
- **Storage instability:** Product quality may be impacted by variations in particle size, aggregation, lipid breakdown, or encapsulated material leakage. [10,12,13]

11. Regulatory and Safety Considerations of Lipid Nanoparticles (LNPs):

The development of safe and repeatable LNP-based medications depends on a thorough evaluation of lipid nanoparticles (LNPs) to guarantee their quality, safety, and therapeutic efficacy. Regulatory assessment encompasses the characterisation of lipid components, manufacturing processes, product stability, toxicological properties, and quality-control procedures. [1,9,10]

11.1 Regulatory Guidelines:

Because the lipid composition, encapsulated drug, and manufacturing process can affect product quality and safety, regulatory evaluation is a crucial component of LNP development. Developers must give the appropriate proof of identity, purity, quality, safety, and efficacy to the appropriate regulatory authorities. [1,9,10]

Important factors include:

- Characterisation of lipid components and other excipients. [9,10]
- Evaluation of particle size, size distribution, and encapsulation efficiency. [9,12,13]
- Assessment of impurities and residual solvents. [9,10]
- Proof of product stability under the suggested storage conditions. [10,12,13]

11.2 Quality Control:

Lipid nanoparticle (LNP) formulations are guaranteed to satisfy predetermined quality criteria through

quality control. Drug distribution, stability, and therapeutic efficacy may be impacted by variations in particle properties. [9,12,13]

Crucial quality-control examinations consist of:

- The Polydispersity Index (PDI) quantifies the distribution of particle sizes. [12,13,25]
- Particle surface charge is revealed by the zeta potential. [12,13,25]
- Encapsulation Efficiency: Quantifies the drug or nucleic acid content of LNPs. [12,13,25]
- Particle form and structure are examined by morphological analysis. [12,13,25]
- Particle changes during storage are assessed using stability testing. [10,12,13]
- Purity testing finds pollutants, impurities, and leftover solvents. [9,10]

12. Future Perspective of Lipid Nanoparticles:

Particularly for nucleic acid treatments, lipid nanoparticles (LNPs) are potential drug delivery methods. Future studies will concentrate on enhancing production, targeting, safety, and stability. Lipid chemistry and nanotechnology developments may increase their use in targeted therapy and personalised medicine. [1,9,10,19]

12.1 Personalized Medicine:

By enabling researchers to alter lipid composition and surface characteristics to meet various treatment requirements, LNPs may help personalised medicine. While more safety and clinical research is needed, combining LNP technology with genomic data may aid in the development of patient-specific medicines. [9,10,19]

12.2 Smart Lipid Nanoparticles:

Smart LNPs are designed to respond to specific biological conditions, such as changes in pH, and release their therapeutic cargo under particular conditions. Ligand-functionalized LNPs may also improve delivery to selected cells or tissues. [9,10,19]

12.3 Theranostics:

Theranostics is a platform that unifies diagnosis and treatment. Therapeutic and imaging chemicals are being carried by lipid-based nanoparticles, which could aid in the diagnosis and treatment of disease. Research is still needed on several of these strategies. [3,9,10]

12.4 Sustainable Manufacturing:

Reducing waste output, resource consumption, and the environmental impact of pharmaceutical manufacture are the goals of sustainable manufacturing. Reducing solvent use, increasing production efficiency, and optimising raw resources could be the main goals of future LNP development. Continuous production and microfluidic mixing may enhance product consistency and process control. But product quality and environmental benefits need to be properly assessed. [9,10,23,24]

12.5 Emerging Technologies:

New technologies could enhance LNP design, targeting, and production.

Among the crucial research topics are:

- Machine learning (ML) and artificial intelligence (AI) can be used to find potential formulations and forecast the impacts of lipid composition. [9,10]
- Advanced Targeting Strategies: To enhance distribution to certain tissues, targeting ligands and modified lipids are being investigated. [1,19,30]
- Gene-Editing Delivery: LNPs are being studied as non-viral carriers for several gene-editing systems, including CRISPR/Cas9 components. [2,30]
- Hybrid Nanocarriers: By combining LNPs with different delivery systems, drug loading, stability, and release may be better controlled. [1,9,10]
- Better Manufacturing Technologies: Continuous processing, automation, and microfluidics may enhance repeatability and enable large-scale. [23,24]

CONCLUSION:

Lipid nanoparticles (LNPs) have become a promising drug delivery technology in the pharmaceutical industry because they can enhance medication stability, bioavailability, and therapeutic efficacy. They aid in the delivery of a variety of molecules, including proteins, peptides, nucleic acids like siRNA and mRNA, and small-molecule medications. They also shield therapeutic materials from deterioration. A variety of

lipid-based nanocarriers, such as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), provide flexible methods for drug transport and encapsulation. The creation of stable and efficient lipid nanoparticle formulations has been further aided by developments in formulation methodologies and characterisation methods. Their important significance in contemporary drug delivery is demonstrated by their successful clinical uses, especially in siRNA-based therapies and mRNA vaccines. But there are still significant issues with formulation stability, targeted distribution, endosomal escape, safety, and large-scale manufacturing. These restrictions might be addressed by future studies concentrating on sophisticated lipid compositions, targeted delivery strategies, personalised medication, and enhanced manufacturing technology. All things considered, lipid nanoparticles offer a useful platform for the creation of novel drug delivery methods, with significant potential to enhance therapeutic results and broaden pharmaceutical applications. Their continuing development and clinical application will require more investigation and a thorough assessment of their efficacy, safety, and quality. [2,3,5,910,27,28,29]

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