



A GUIDE TO

LIPID NANOPARTICLE FORMULATION:

BASIC CONCEPTS &

PREPARATION PROCEDURES

The success of mRNA-based COVID-19 vaccines could not have been possible without decades of research on lipid-based drug delivery (LBDD). LBDD systems are highly versatile and have been used to deliver various bioactive molecules to targeted cells and tissues. LBDD has several advantages over conventional drug delivery methods, including increased drug stability, bioavailability, and distribution.

Lipid nanoparticles (LNPs) are a significant advancement for the delivery of oligonucleotide-based therapeutics. Oligonucleotides encapsulated within LNPs are protected from enzymatic degradation during the delivery process and are efficiently delivered to cells, where the therapeutic cargo is released.

Use this guide to learn about LBDD systems, the cargoes they deliver, and to explore basic concepts and procedures for the preparation of LNPs.

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LNP FORMULATION

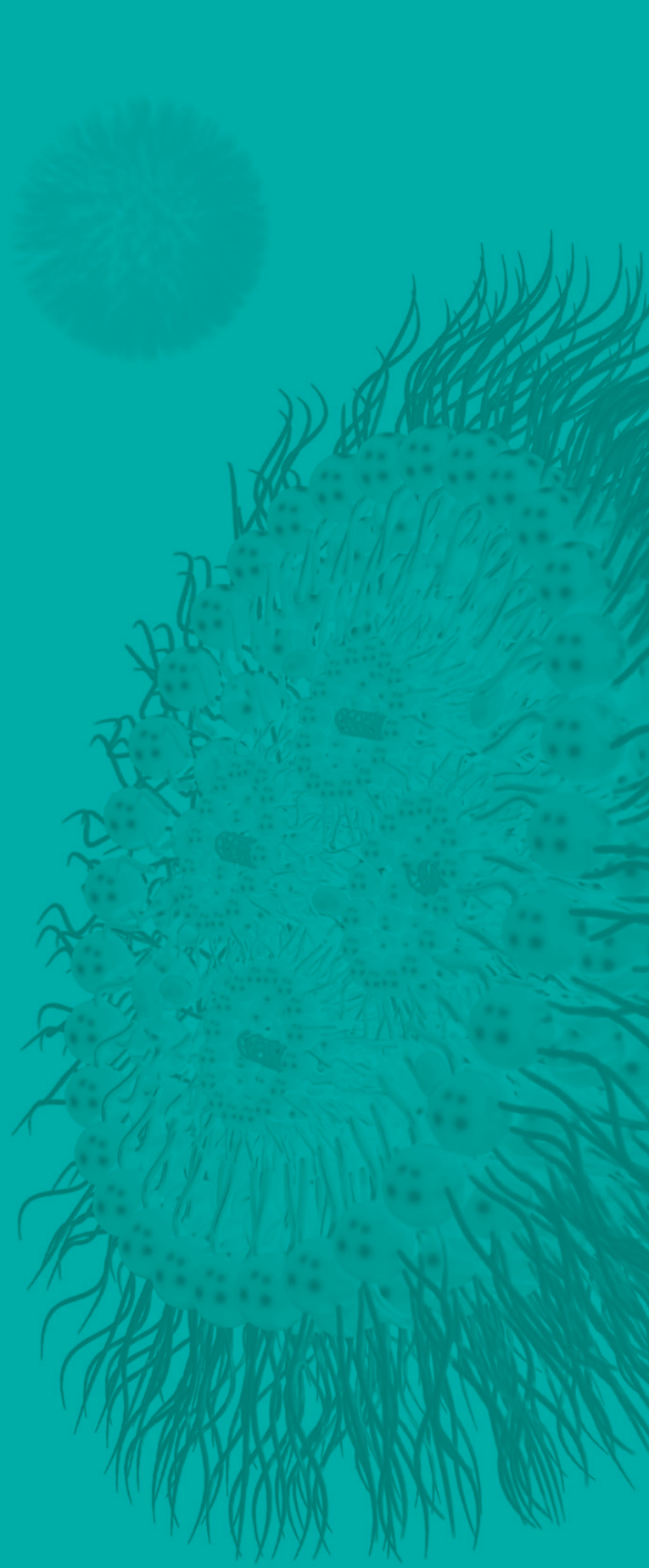
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TYPES OF LBDD SYSTEMS

This glossary introduces terms commonly used to describe LBDD systems and includes the structure and type of cargo encapsulated in these different systems.

Lipid nanoparticles (LNPs): a lipid shell surrounding an internal core composed of reverse micelles that encapsulate and deliver oligonucleotides, like siRNA, mRNA, and plasmid DNA (pDNA).

Liposomes: contain one or more lipid bilayers and an aqueous core. They are further classified by lamellarity and size. Liposomes can be used for the delivery of hydrophobic and/or hydrophilic small molecules.

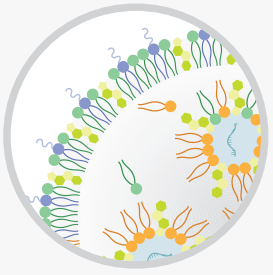
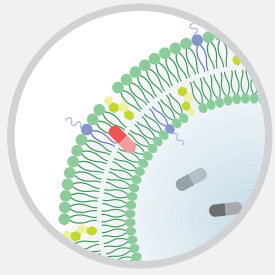
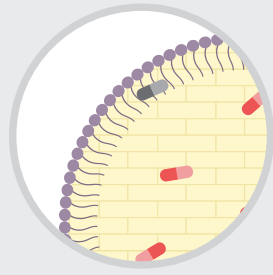
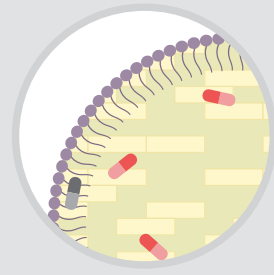
Solid lipid nanoparticles (SLNs): a surfactant shell surrounding a core matrix composed of solid lipids. They are used for the encapsulation of hydrophobic and/or hydrophilic cargo.












Nanostructured lipid carriers (NLCs): a surfactant shell surrounding a core matrix composed of solid and liquid lipids. They are used for the encapsulation of hydrophobic and/or hydrophilic cargo.

Micelles: self-assemblies of lipid monolayers in aqueous solutions. They have a hydrophobic core, where the phospholipid tails are oriented towards the interior, and can be used for the encapsulation of small hydrophobic cargo.

Reverse micelles: an inverted structure compared with traditional micelles. They form a hydrophilic core, with the phospholipid tails oriented towards the exterior, and can be used for the encapsulation of small hydrophilic cargo, like oligonucleotides in LNPs.

LNPs compared to other LBDD systems

				
	Lipid Nanoparticle	Liposome	Solid Lipid Nanoparticle	Nanostructured Lipid Carrier
Lipid Shell	Monolayer	Bilayer	Surfactant	Surfactant
Internal Core	Reverse micelles	Aqueous	Solid lipids	Solid and liquid lipids
Cargo	Oligonucleotides	Hydrophobic and/or hydrophilic small molecules	Hydrophobic and/or hydrophilic small molecules	Hydrophobic and/or hydrophilic small molecules
Size	~20-100 nm	~50-1,000 nm	~40-1,000 nm	~40-1,000 nm

 Cationic Lipid	 PEGylated Lipid	 Phospholipid	 Surfactant	 Oligonucleotide	 Sterol Lipid
 Solid Lipid	 Liquid Lipid	 Aqueous Phase	 Hydrophilic Drug	 Hydrophobic Drug	

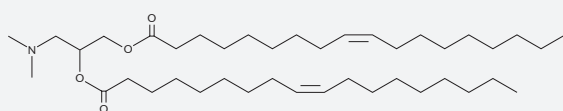
STRUCTURAL COMPONENTS

LNPs are typically composed of glycerophospholipids, cationic lipids, sterol lipids, and PEGylated lipids that encapsulate oligonucleotides, which are contained within an aqueous phase. Many of the same structural components used in LNPs are components of other LBDD particles. Lipids and molecules that contain them, like surfactants, can be used to tailor the behavior and properties of LBDD particles. Examples of lipid components used in clinically approved therapeutics are listed below for each class.



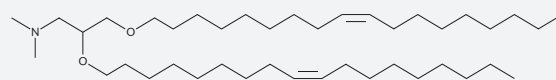
Ionizable cationic lipids circumvent the untoward cytotoxicity associated with **cationic lipids**.

These lipids possess a transient cationic charge that is acquired at low pH (typically <7), forming reverse micelles that encapsulate oligonucleotides in the LNP core. As these lipids have near-neutral charge at physiological pH, they deliver oligonucleotide cargo without cytotoxicity.



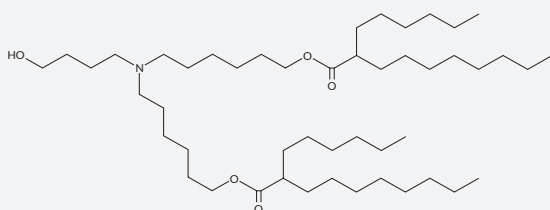
DODAP

pK_a Value of Tertiary Amine: 5.59



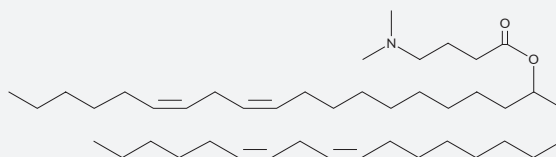
DODMA

pK_a Value of Tertiary Amine: 6.59



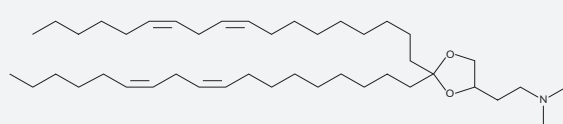
ALC-0315

pK_a Value of Tertiary Amine: 6.09



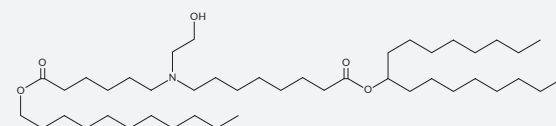
DLin-MC3-DMA

pK_a Value of Tertiary Amine: 6.44



DLin-KC2-DMA

pK_a Value of Tertiary Amine: 6.68

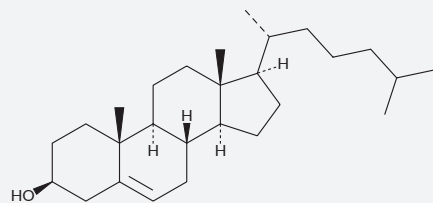


SM-102

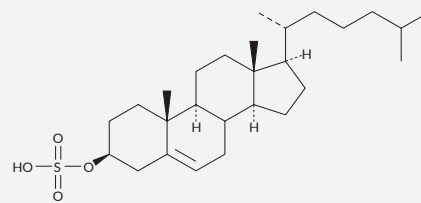
pK_a Value of Tertiary Amine: 6.68



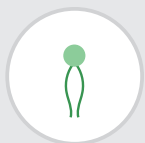
Sterol lipids, such as **cholesterol**, are used to fill lipid membrane packing defects and provide structural integrity. They also aid in membrane fusion of the LNP and target cell, and some cholesterol derivatives, like **7 α -hydroxy cholesterol**, have been used to improve the delivery of oligonucleotide cargo. Cholesterol is typically 20-50% of LBDD formulations.



Cholesterol



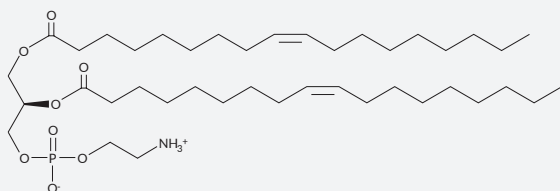
Cholesteryl sulfate



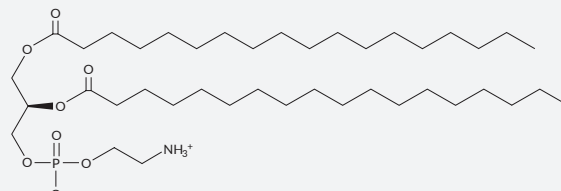
Glycerophospholipids are a class of phospholipid that contains a hydrophilic head group and two hydrophobic fatty acyl tails attached to a glycerol backbone. The hydrophilic head determines the charge of the LBDD particle, which can be neutral, anionic (negative), or cationic (positive).

Neutral phospholipids improve the efficacy of membrane fusion and can also be used to distribute or modify the net surface charge of the lipid particle. The phospholipid head groups with an overall neutral charge are **phosphatidylcholine (PC)** and **phosphatidylethanolamine (PE)**.

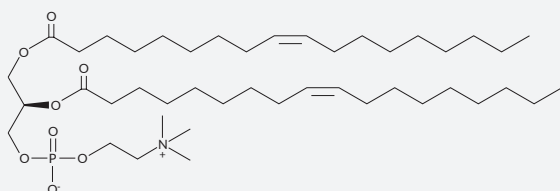
Anionic lipids are typically used for the delivery of small molecules and are incorporated into neutral LBDD systems to prevent aggregation during storage. They can also be used to modify the net surface charge of the lipid particle. **Phosphatidylglycerol (PG)**, **phosphatidylinositol (PI)**, **phosphatidylserine (PS)**, and **phosphatidic acid (PA)** are phospholipids that contain anionic head groups.



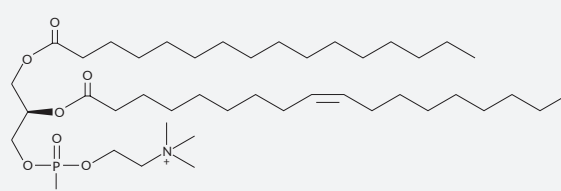
1,2-DOPE



1,2-DSPE



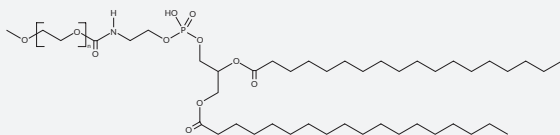
1,2-DOPC



1,2-POPC



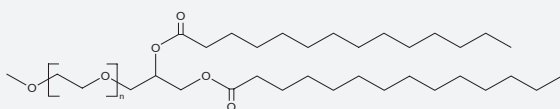
PEGylated lipids prevent serum protein adsorption, inhibiting uptake by the mononuclear phagocyte system (MPS), a major obstacle in the delivery of LBDD systems. Some PEGylated lipids also contain terminal functional groups, such as **amine** or **maleimide**, which can be used to conjugate other molecules that improve cellular targeting and uptake.



DSPE-MPEG(2000)



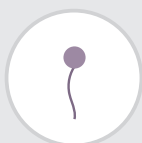
ALC-0159



DMG-PEG(2000)



The **aqueous phase** solubilizes hydrophilic molecules, like oligonucleotides in LNPs and hydrophilic drugs in liposomes, whereas lipid components solubilize hydrophobic cargo.



Surfactants are a major component of the lipid shell of SLNs and NLCs. They reduce the interfacial tension between the lipophilic core and aqueous phase due to their amphipathic nature and improve stability during storage. Lecithin, which contains **phosphatidylcholines**, is one surfactant that has been used in SLNs and NLCs.



Solid lipids, colloquially known as fats, are solid at ambient temperature and used in the preparation of both SLNs and NLCs. Solid lipids used to prepare SLNs or NLCs are typically saturated and include **glycerolipids**, as well as **stearic acid**.



Liquid lipids, also referred to as oils, are fluid at ambient temperature. NLCs are formulated with a mixture of solid and liquid lipids, which increases drug loading capacity and prevents drug leakage. Liquid lipids used in NLCs are typically unsaturated and include **oleic acid**, **α -tocopherol**, and **squalene**.

Read our article **The Heads and Tails of Lipid-Based Drug Delivery** to dive deeper into the biophysical properties of lipids used in LBDD systems.

CUSTOM LIPID SYNTHESIS & BULK QUANTITIES AVAILABLE

Partner with our team of synthetic organic and medicinal chemists to design and synthesize your custom nanoparticle components. Bulk quantities of the lipid components in our catalog are also available for your R&D needs:

- Neutral Phospholipids
- Anionic Lipids
- Ionizable & Cationic Lipids
- Sterol Lipids & Cholesterol Derivatives
- Sphingolipids
- PEGylated Lipids
- Glycerolipids

Contact us to inquire about custom synthesis

CARGO

LNPs are superior for the encapsulation of oligonucleotides, whereas other LBDD systems are preferable for the delivery of small molecule inhibitors or lipids. The requisite LBDD system for your application depends on the cargo, and the localization of the cargo within the LBDD particle depends on its physicochemical properties.

Oligonucleotides



mRNA, siRNA, and pDNA are common oligonucleotide cargo. Oligonucleotides are negatively charged and best encapsulated within LNPs using ionizable cationic lipids. mRNA-containing LNPs are the basis for most COVID-19 vaccines, and LNPs containing transthyretin-targeting siRNA are used to treat hereditary amyloidogenic transthyretin (ATTRv) amyloidosis.

Small Molecules

Hydrophobic and/or hydrophilic small molecules can be solubilized in the lipophilic or aqueous compartments, respectively, of liposomes, SLNs, and NLCs.

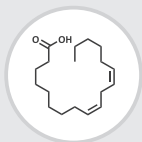


Hydrophobic drugs are dispersed in the lipophilic compartments of LBDD systems. [Amphotericin B](#), an antifungal agent, and [verteporfin](#), a photosensitizing agent, are examples of FDA-approved hydrophobic drugs that have been formulated in liposomes.



Hydrophilic drugs are solubilized in the aqueous compartments of LBDD systems. [Doxorubicin](#), an antitumor antibiotic, is a hydrophilic drug. Doxil® is a form of doxorubicin encapsulated in liposomes and was the first LBDD formulation to be approved by the FDA.

Bioactive Lipids



Fatty acids, monoglycerides, and other bioactive lipids may also be incorporated into LBDD systems. [Lauric acid](#), [linoleic acid](#), and [oleic acid](#) have been incorporated into liposomes with bactericidal activity. [C6 ceramide](#), a sphingolipid, has been delivered to cancer cells, where it has pro-apoptotic activity.

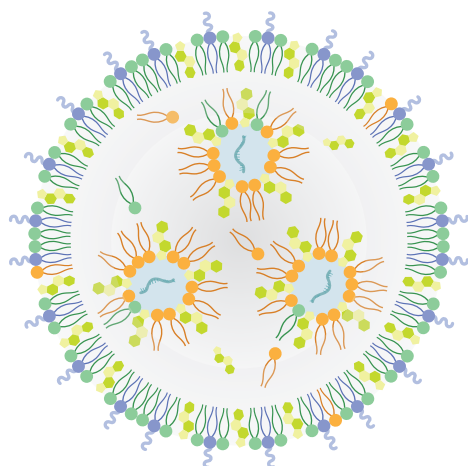
Expanded opportunities for small molecule delivery

Our collection of research tools offers a comprehensive source for LBDD system components:

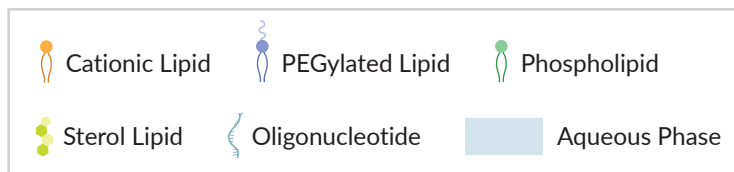
- More than 4,800 **small molecule inhibitors**
- More than 3,400 **lipid compounds**

DESIGN

Several factors should be considered when selecting lipids and how they are formulated into LNPs. Below, we outline these factors and how each of them influences the physiological behavior of LNP particles.



Lipid Nanoparticle



The **lipid molar ratio** determines the lipid composition of the particles and influences their size, polydispersity, and efficacy. We recommend starting with a literature review to identify lipid molar ratios that have been previously developed for similar applications.

Lipid molar ratios for LNPs in FDA-approved agents

	Patisiran	BNT162b2	mRNA-1273
Cargo	siRNA	mRNA	mRNA
Ionizable Cationic Lipid	DLin-MC3-DMA	ALC-0315	SM-102
Neutral Phospholipid	1,2-DSPC	1,2-DSPC	1,2-DSPC
Sterol Lipid	Cholesterol	Cholesterol	Cholesterol
PEGylated Lipid	C-DMG-PEG(2000)	ALC-0159	DMG-PEG(2000)
Lipid Molar Ratio ^a	50:10:38.5:1.5	46.3:9.4:42.7:1.6	50:10:38.5:1.5

^aionizable cationic lipid:neutral phospholipid:cholesterol:PEGylated lipid



The **lipid:oligonucleotide weight ratio** influences the encapsulation efficiency. Most LNPs are formulated with a lipid:oligonucleotide weight ratio of 10:1.



The ionizable lipid **nitrogen:oligonucleotide phosphate (N:P) molar ratio** represents the charge balance between the cationic tertiary amine of the ionizable cationic lipid and the anionic phosphate group in the oligonucleotide backbone. This property is the basis for the complexation of ionizable cationic lipids with oligonucleotides. LNPs commonly have an N:P ratio around six.



The **lipid acid dissociation constant (lipid pK_a)** is the pH at which the ionized and nonionized forms of a lipid exist in equal concentrations. Lipid pK_a impacts the LNP encapsulation efficiency, efficacy, delivery, and toxicity. For RNA delivery, the lipid pK_a generally ranges from 6-7.



Three important parameters for an **aqueous buffer** are its composition, ionic strength, and pH. Buffers stabilize the oligonucleotides in solution, and ionizable cationic lipids become protonated and positively charged in the acidic aqueous buffer upon mixing. Commonly used buffers in LNP preparations are 25-50 mM sodium acetate or sodium citrate, pH 4-5. LNPs are dialyzed into a neutral buffer, such as PBS, pH 7.4, for storage and use.



The **particle size** alters the pharmacokinetics of the administered particle. Smaller particles typically have longer circulation half-lives, as they evade elimination by the MPS. Particles less than 100 nm can easily pass through fenestrated endothelium to penetrate target tissues. The particle size is dependent on the preparation method. Depending on the LNP preparation method, extrusion can be used to achieve smaller, more uniform particle sizes.



The two most commonly used **routes of administration** for LNPs are intravenous and intramuscular injection. Of note, formulations optimized for a given route of administration are generally not applicable for other routes of administration.

Intravenously administered LNPs with net positive, neutral, and negative charges can be targeted to the lungs, liver, and spleen, respectively. The inclusion of **cholesterol** or **PEGylated lipids** in the formulation, as well as increasing the LNP size, increases distribution to the spleen.

Intramuscular administration is commonly used for vaccines, as it facilitates lymph node targeting and activation of the immune response. When a vaccine is administered, antigen-presenting cells (APCs), like macrophages and dendritic cells, are recruited to the delivery site, where they can encounter vaccine antigens. They then migrate to lymph nodes where they stimulate T cell responses.



The **preparation method** determines the properties of LNPs, including size, homogeneity, and encapsulation efficiency. When selecting a preparation method, cost, scalability, reproducibility, and time commitment should also be considered.

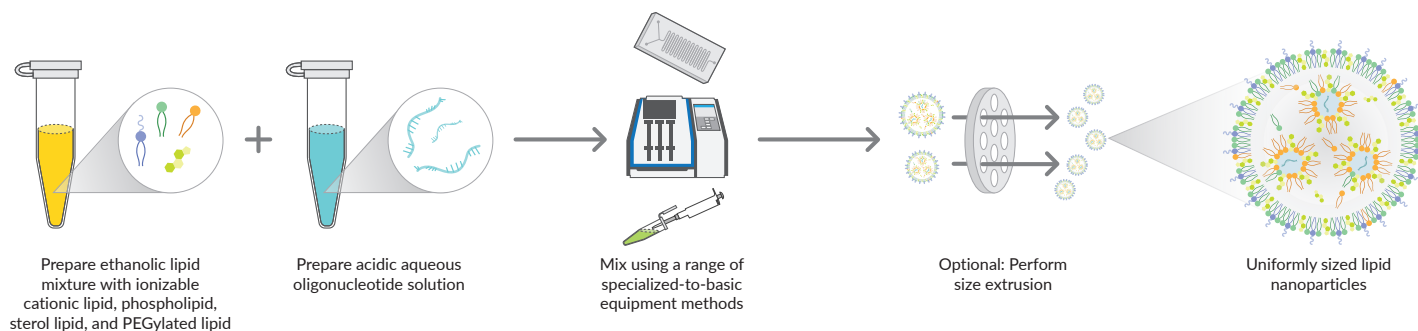
PROCEDURES

In the next sections, we give a series of a simple procedures to follow for producing LNPs. The entire range of the LNP life cycle is covered, starting with LNP preparation at the bench and ending with how to use and what to expect when testing LNPs in your *in vitro* or *in vivo* experiments.

LNP Preparation

Before beginning, ensure that all supplies, reagents, and working environments are RNase-free. siRNA and mRNA are chemically labile to RNases, which are enzymes that degrade RNA-based oligonucleotides. The steps in LNP formation are summarized below.

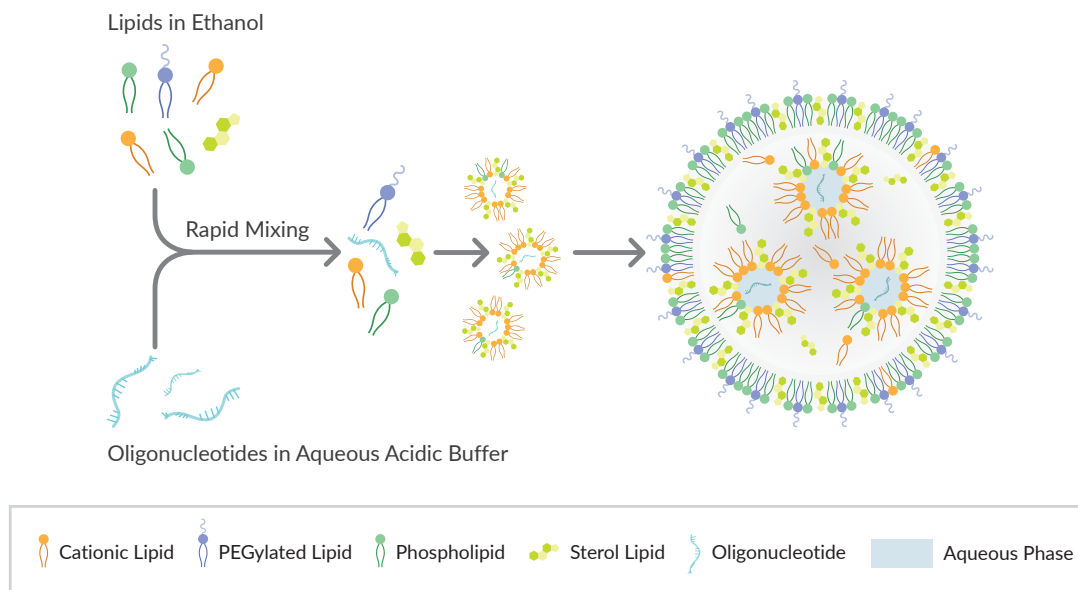
LNP preparation workflow



Mixing

LNPs are prepared by mixing an ethanolic lipid mixture with an acidic aqueous solution containing oligonucleotides. A 1:3 ratio of ethanolic lipid mixture to aqueous buffer is generally used. Several methods are suitable for laboratory-scale, small-volume LNP production. Four of these methods, applicable for a range of specialized-to-basic equipment, are compared briefly on page 11.

Schematic of oligonucleotide-containing LNP formation





Microfluidic Mixing Devices: Automated microfluidic devices or microfluidic chips are fast and efficient methods to prepare LNPs. These devices enable rapid mixing in a highly controllable, reproducible manner that achieves homogeneous LNPs and high encapsulation efficiency. In these devices, individual streams of the ethanolic lipid mixture and aqueous oligonucleotide solution are rapidly combined. LNPs form as the two streams mix and are collected into a single collection tube. Parameters such as the flow rate ratio and total flow rate can be altered to fine-tune LNPs.



T- or Y-junction Mixers: These mixers can be assembled with common and inexpensive laboratory materials. A T- or Y-connector can be fitted with two inlets coupled to individual syringes containing the lipid mixture or oligonucleotide solution and one outlet to direct the LNPs into a collection tube. Optionally, the inlet flow rates can be controlled with syringe pumps.



Ethanol-injection: This method is accessible to all laboratories. Mixing of the ethanolic lipid mixture and aqueous oligonucleotide solution is performed with the aid of a magnetic stir plate. Inject the ethanolic lipid mixture into the aqueous acidic oligonucleotide solution with constant stirring and continue to mix for 30 minutes. This method may yield more heterogeneous LNPs with lower encapsulation efficiencies and is prone to variability.



Hand-mixing: This is a simpler alternative method to ethanol-injection. Transfer the ethanolic lipid mixture into the aqueous acidic oligonucleotide solution and mix for 15 seconds by rapid pipetting. Leave the mixture undisturbed for 10 minutes. As with the ethanol-injection method, hand-mixing of LNPs results in heterogeneous LNPs with low encapsulation efficiency and can yield variable results.

Explore LNPs in a simple and cost-effective way

With our Lipid Nanoparticle Exploration Kits, you can deliver your oligonucleotide cargo with adaptable protocols suited for a range of specialized-to-basic equipment. Our kits are supplied as conveniently packaged reagents for preparing LNPs used in existing therapeutics.

Lipid Nanoparticle (LNP-102) Exploration Kit

Item No. 35425

Lipid Nanoparticle (LNP-0315) Exploration Kit

Item No. 35426

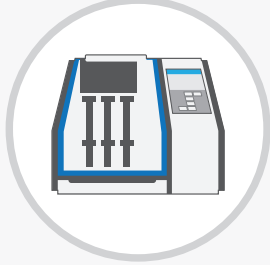


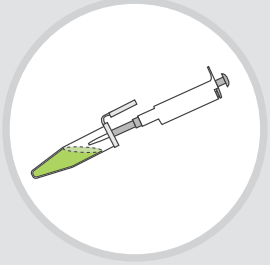
Lipid Nanoparticle (LNP-MC3) Exploration Kit

Item No. 36970

FEATURES

- Prepare SM-102-, ALC-0315-, or DLin-MC3-DMA-containing LNPs
- Encapsulate mRNA or siRNA cargo
- Eliminate the need for specialized equipment

Feature comparison of LNP preparation methods

	 Microfluidic Mixing Devices	 T- or Y-junction Mixers	 Ethanol-injection	 Hand-mixing
Cost	High	Low	Low	Low
Scalability	High	High	Medium	Low
Encapsulation Efficiency	High	High	Medium	Low
Reproducibility	High	High	Medium	Low
Polydispersity Index	Low	Medium	High	High

Final Preparation

The final preparation of LNPs is performed after they have been formed during the mixing step. The steps that follow help ensure that the LNPs are homogeneous, stable during storage and use, and free of any residual chemical or biological contaminants.



Extrusion: Extrusion reduces particle size and generates uniform particle size distributions. This step is generally performed with ethanol-injection or hand-mixing methods.



Dialysis: Dialyze the LNPs in storage buffer using appropriate molecular weight cut-off (MWCO) tubing. This step removes unencapsulated cargo, excess lipid components, and ethanol from the final preparation. Dialysis also adjusts the pH of the LNPs from the acidic preparation buffer to the neutral storage solution.



Filter-sterilize: Filtration is the recommended method for sterilization of LNPs. Filter-sterilize LNPs with a 0.22 μm filter before storage to remove bacteria or other contaminants. For larger particles or highly viscous solutions, other sterilization methods, such as autoclaving or irradiation, may be used, but these methods may impact the LNP integrity.

STABILITY & STORAGE

After LNPs have been prepared, they may either be used immediately or stored for later use. Below, we discuss factors that can compromise LNP integrity during storage and provide tips to limit storage instability.



Physical stability describes the structural integrity of LNPs during storage. Particle fusion or aggregation, as well as leakage of encapsulated cargo are examples of physical instability.

- ✓ Ensure size distribution remains small and homogeneous:
 - Use anionic or PEGylated lipids to prevent particle fusion/aggregation
- ✓ Prevent cargo leakage:
 - Include cholesterol
- ✓ Follow storage requirements:
 - Adjust temperature, buffers, and pH
 - Avoid freeze-thaw cycles



Chemical stability defines the resistance of LNP lipid and cargo components to modifications in their molecular structure. Hydrolysis, oxidation, and transesterification can lead to oligonucleotide and lipid degradation or the formation of lipid-oligonucleotide adducts and loss of efficacy.

- ✓ Limit cargo degradation:
 - Use RNase-free reagents and supplies
 - Consider oligonucleotide cargo with backbone modifications
- ✓ Prevent lipid oxidation:
 - Include [antioxidants](#) or cryoprotectants during storage
- ✓ Follow storage requirements:
 - Adjust temperature, buffers, and pH
 - Avoid freeze-thaw cycles



Biological stability relates to the capacity of LNPs to avoid early degradation. Factors that contribute to biological stability include lipid composition, particle size, and surface charge.

- ✓ Reduce serum protein opsonization:
 - Include PEGylated lipids
 - Decrease particle size
 - Achieve near-neutral zeta potential
 - Increase LNP hydrophilicity
- ✓ Prevent cargo leakage:
 - Follow storage requirements
 - Incorporate long and/or unsaturated lipids
 - Include cholesterol



Storage is a critical parameter in the stability of LNP formulations. Generally, LNPs may be stored at 4°C for up to one week or, for long-term storage, lyophilized and held at -80°C. Storage temperature, buffers, and pH may need to be optimized. The inclusion of cryoprotectants is recommended when freezing with or without lyophilization.

CHARACTERIZATION

Characterization of LNP attributes prior to *in vitro* or *in vivo* use is critical for reproducibility.



The **LNP size** describes the average diameter of LNPs and influences their biodistribution and cellular uptake. The **polydispersity index (PDI)** is a measure of the LNP size distribution. Homogeneous, uniformly sized samples have small PDIs, and samples with heterogeneous size distributions have large PDIs. The LNP size and PDI of an LNP preparation can be reduced by optimizing lipid components, increasing the mixing rate, selecting a different preparation method, or by adding an extrusion step.



The **zeta potential** is the electrostatic potential surrounding the LNP. In general, a near-neutral zeta potential is desirable. Anionic LNPs may be electrostatically repelled from negatively charged plasma membranes, and cationic LNPs can be cytotoxic. The zeta potential can be adjusted by altering the N:P ratio.



Encapsulation efficiency is the final amount of oligonucleotide contained within the LNP compared to the starting amount. Microfluidic mixing yields the highest encapsulation efficiencies.



Quantification of the **particle concentration** is necessary to ensure comparable results between experiments. LNPs may be concentrated by ultracentrifugation or diluted as desired.



Lipid and cargo integrity are essential for the efficacy and stability of LNPs. Refer to the stability and storage section on page 12 for more information. Our [Chemical Synthesis](#) team offers lipid characterization services.

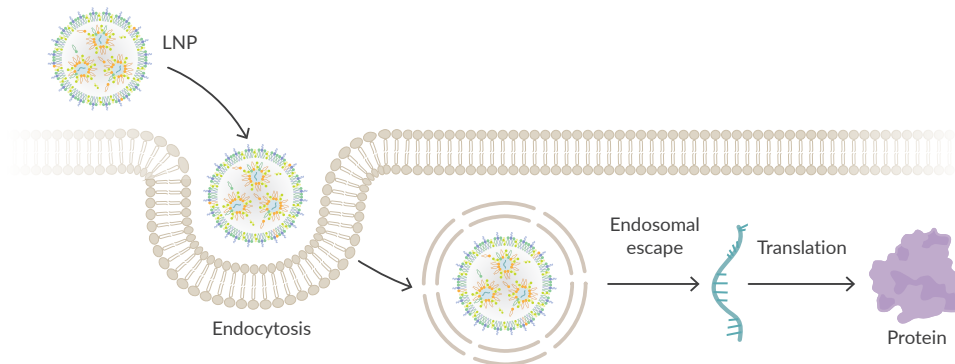
Analytical methods for LNP characterization

Attribute	Assay(s)
LNP size	Dynamic light scattering (DLS)
PDI	DLS
Zeta potential	Laser Doppler electrophoresis
Encapsulation efficiency	Fluorescent dyes; UV spectroscopy with Triton-X
Particle concentration	DLS; fluorescence correlation spectroscopy; UV-vis spectroscopy; UPLC
Lipid and cargo integrity	RP-HPLC; SE-HPLC; IP-HPLC; LC-MS/MS

Adapted from Schoenmaker, L., *et al.* 2021 and Lin *et al.* 2014

ASSESSMENT

LNPs are internalized by target cells *via* endocytosis. Endosomal escape is the process by which the LNP cargo is delivered to the cytosol. Ionizable cationic lipids become positively charged in the acidic environment of the endosomal lumen, which disrupts the negatively charged endosomal membrane and promotes release of the encapsulated oligonucleotide cargo into the cytosol, where translation occurs.



Cellular models and simple molecular biology techniques can be used to test the efficacy of LNPs *in vitro*. Measurement of knockdown or expression of the gene or protein of interest can be accomplished *via* qPCR or [Western blot](#), respectively. Cell-based reporter or luciferase assays are also used to determine LNP efficacy.



Animal models provide valuable insight into the efficacy of LNP-based therapeutics *in vivo*. Protein expression of oligonucleotide products *in vivo* follows a target-dependent time course. Oligonucleotides encoding functional proteins produce changes in protein concentrations within hours, whereas those designed to elicit an antibody response can occur between several days to a couple of weeks. It is often necessary to use repeated dosing regimens to achieve sustained protein expression. ELISAs and multiplexed assays can be used to measure target protein responses, and flow cytometry can determine changes in cellular phenotype.



The **fate of LNPs** after administration depends on the lipid composition, LNP design, and the route of administration. Lipids used in LNPs are detectable in the tissues that LNPs are distributed to after administration. These lipids are biocompatible and rapidly degraded, and they are generally eliminated within 24 to 48 hours after administration. To determine lipid tissue concentrations, mass spectrometry-based approaches can be used. Our [Analytical Chemistry](#) team can assist you in the detection of lipids in various tissues and sample matrices.

Technical Support at any step of your research

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