INTERNATIONAL JOURNAL IN PHARMACEUTICAL SCIENCES

Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Advancements In Lipid Nanoparticles For Enhanced Drug Delivery: A Comprehensive Review

Nihar Ranjan Kar*

Centurion University of Technology and Management, Gopalpur, Balasore, Odisha, India-756044

ARTICLE INFO

Received: 28 Aug 2023
Accepted: 30 Aug 2023
Published: 08 Sept 2023

Keywords:
Lipid nanoparticles, Drug delivery, Biocompatible, Biodegradable, Safe, Targeted, Emerging, Novel Drug delivery System

DOI:
10.5281/zenodo.8328533

ABSTRACT

Lipid nanoparticles have emerged as promising carriers for drug delivery due to their biocompatibility, versatility, and ability to encapsulate a wide range of therapeutic agents. This review article explores the recent advancements in lipid nanoparticles and their applications in pharmaceutical formulations. The article discusses various types of lipid nanoparticles, including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid-drug conjugates, highlighting their unique characteristics and advantages. The focus is on their potential to overcome challenges associated with traditional drug delivery systems, such as poor bioavailability, limited stability, and off-target effects.

INTRODUCTION

Drug Delivery Systems and its Importance[1]

Drug delivery systems (DDS) are formulations designed to improve how drugs are delivered to the body. They can improve the efficacy, safety, and convenience of drug therapy.

There are many reasons why DDS are necessary. Some of the critical benefits of DDS include:

1. **Improved efficacy**: DDS can improve the efficacy of drugs by increasing their solubility, stability, and bioavailability. This can lead to better drug absorption and distribution, which can improve the drug's therapeutic effect.
2. **Reduced side effects**: DDS can reduce the side effects of drugs by targeting them to specific tissues or cells. This can help minimize the exposure of healthy tissues to the drug, reducing the risk of side effects.
3. **Increased convenience**: DDS can increase the convenience of drug therapy by making it easier to take drugs or by reducing the number of doses that need to be taken. This can

***Corresponding Author:** Nihar Ranjan Kar
Address: *Centurion University of Technology and Management, Gopalpur, Balasore, Odisha, India-756044*
Email : nihar_795@rediffmail.com

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.

improve patient compliance and adherence to treatment.

4. **New therapeutic possibilities**: DDS can enable the delivery of new drugs or the delivery of existing drugs to new sites of action. This can open up new therapeutic possibilities for the treatment of a variety of diseases.

Introduction to lipid nanoparticles and their relevance in enhancing drug delivery [2,3]

Lipid nanoparticles (LNP) are a type of nanomaterial made up of lipids, which are the building blocks of cell membranes. They can encapsulate various drugs, including hydrophobic, hydrophilic, and nucleic acids. LNPs have several advantages over traditional drug delivery methods. They are:

1. **Biocompatible and biodegradable**: LNPs are made of natural materials that are safe for the body. They are also easily broken down by the body's natural enzymes.
2. **Efficient**: LNPs can improve the solubility and stability of drugs, leading to better drug absorption and efficacy.
3. **Targeted**: LNPs can be designed to target specific tissues or cells, improving drug delivery to the intended site of action.
4. **Safe**: LNPs are safe in clinical trials.

LNP is being investigated for delivering a wide range of drugs, including cancer, gene therapy, and vaccines. They have the potential to revolutionize how drugs are delivered to the body and improve the treatment of various diseases.

Here are some of the ways that LNPs can enhance drug delivery:

1. **Improved solubility**: Lipid nanoparticles can improve the solubility of hydrophobic drugs, which do not dissolve well in water. This can make it easier to administer drugs orally or by injection.
2. **Improved stability**: Lipid nanoparticles can protect drugs from degradation in the body. This can help to improve the efficacy and safety of drugs.
3. **Targeted delivery**: Lipid nanoparticles can be designed to target specific tissues or cells. This can improve the delivery of drugs to the intended site of action and reduce the side effects of drugs.
4. **Sustained release**: Lipid nanoparticles can be designed to release drugs over a controlled period. This can improve the efficacy of drugs and reduce the doses that need to be taken.

History of Lipid Nanoparticles [4,5]

- **1965**: The first liposomes were created by Alec Bangham and colleagues at the University of Cambridge. Liposomes are spherical vesicles composed of lipid bilayers that can encapsulate drugs and other molecules.
- **1980**: Philip Felgner pioneered artificially-created cationic lipids (positively-charged lipids) to bind lipids to nucleic acids to transfect the latter into cells. This work laid the foundation for developing LNPs as a drug delivery vehicle for nucleic acids, such as mRNA and DNA.
- **1990**: A team of researchers at the University of California, San Francisco, invented the first lipid nanoparticles. LNPs are similar to liposomes but have a more solid lipid core. This makes them more stable and less likely to leak their contents.
- **1990s**: LNPs began to be investigated as potential drug delivery vehicles. They were shown to be able to improve the solubility, stability, and bioavailability of drugs.
- **2000s**: LNPs were further developed, and their potential for treating various diseases was explored. They effectively delivered drugs to the brain, eye, and other tissues.
- **2010s**: LNPs were used to develop several FDA-approved drugs, including Doxil (doxorubicin) and Inflexxa (etanercept).

- **2020s**: LNPs are being investigated for delivering various drugs, including vaccines, gene therapy, and cancer treatments.

Drugs Used in Lipid Nanoparticle Formulations [6,7]

Developing new lipid nanoparticle-based drug delivery systems is an active area of research, and there is great potential to improve the efficacy and safety of different drugs. Here are a few essential examples of drugs and biologicals used in lipid nanoparticle formulations.

- **Doxil (**Doxorubicin): Doxil is an LNP-based formulation of the chemotherapy drug doxorubicin. It is used to treat breast, ovarian, and lung cancer.
- **Paclitaxel:** Paclitaxel is another chemotherapy drug that is used to treat cancer. It is encapsulated in lipid nanoparticles to improve its delivery to cancer cells.
- **Fludarabine:** Fludarabine is a chemotherapy drug used to treat chronic lymphocytic leukaemia. It is encapsulated in lipid nanoparticles to improve solubility and stability and target cancer cells.
- **Infliximab:** Infliximab is another biological drug used to treat rheumatoid arthritis. It is encapsulated in lipid nanoparticles to improve its solubility and stability and to target it to the joints.
- **Inflexxa (etanercept):** Inflexxa is an LNP-based formulation of the rheumatoid arthritis drug etanercept. It is injected under the skin and provides sustained drug release over several weeks.
- **Vaxevria (COVID-19 vaccine):** Vaxevria is an LNP-based vaccine against COVID-19. It is administered intramuscularly and is safe and effective in clinical trials.
- **Glybera (alipogene tiparvovec):** Glybera is an LNP-based gene therapy for treating lipoprotein lipase deficiency. It is administered under the skin and is safe and effective in clinical trials.
- **Herceptin (trastuzumab)** is a monoclonal antibody used to treat breast cancer. It can be formulated in LNPs to improve its delivery to cancer cells.
- **Keytruda (pembrolizumab):** Keytruda is an immune checkpoint inhibitor used to treat cancer. It can be formulated in LNPs to improve its delivery to cancer cells.
- **Onpattro (patisiran):** Onpattro is an LNP-based gene therapy for treating hereditary transthyretin amyloidosis. It is administered intravenously and is safe and effective in clinical trials.
- **Zolgensma (onasemnogene abeparvovec):** Zolgensma is an LNP-based gene therapy for treating spinal muscular atrophy. It is administered intravenously and is safe and effective in clinical trials.
- **Insulin:** Insulin is a hormone that is used to treat diabetes. It is encapsulated in lipid nanoparticles to improve absorption and reduce side effects.

Here are some other biologicals that are being investigated for use in lipid nanoparticle formulations:

- **siRNA (small interfering RNA):** siRNA is used to silence genes. It can be encapsulated in lipid nanoparticles to improve its delivery to cells.
- **miRNA (microRNA):** miRNA is also used to silence genes. It can be encapsulated in lipid nanoparticles to improve its delivery to cells.
- **CRISPR/Cas9:** CRISPR/Cas9 is a gene editing tool. It can be encapsulated in lipid nanoparticles to improve its delivery to cells.
- **Peptides:** Peptides are short chains of amino acids. They can be encapsulated in lipid nanoparticles to improve their delivery to cells.

Types of Lipid Nanoparticles[8]

There are many different types of lipid nanoparticles (LNP) present; some of the most common types include:

i. **Liposomes:** Liposomes are spherical vesicles that are made up of a lipid bilayer. The inner leaflet of the bilayer can be loaded with drugs, while the outer leaflet can be modified to target specific cells or tissues.
ii. **Solid lipid nanoparticles (SLN):** SLN is made up of a solid lipid core that is surrounded by a lipid bilayer. The solid lipid core provides stability and prevents the drug from leaking out.
iii. **Nanostructured lipid carriers (NLC):** NLCs are similar to SLN but have a more heterogeneous structure. This allows them to encapsulate a broader range of drugs and to have a better-controlled release profile.
iv. **Polymer-lipid hybrid nanoparticles:** Polymer-lipid hybrid nanoparticles comprise a combination of lipids and polymers. The polymers provide stability, and the lipids provide biocompatibility.
v. **Polymer drug conjugates:** These are conjugation of lipids to drug molecules by covalent linkage. It can be used in a variety of drugs, i.e., hydrophilic and hydrophobic in nature.

Table-1: Types of LNPs with their Structure, advantages and disadvantages[9]

Type of LNP	Structure	Advantages	Disadvantages
Liposomes	Spherical vesicles made up of a lipid bilayer	Biocompatible, biodegradable, can encapsulate a wide range of drugs.	Sensitive to shear forces, producing at a large scale can be challenging.
Solid lipid nanoparticles (SLN)	Made up of a solid lipid core surrounded by a lipid bilayer	Stable, can be used to encapsulate a wide range of drugs	It can be challenging to target specific cells or tissues
Nanostructured lipid carriers (NLC)	Similar to SLN, but has a more heterogeneous structure	Stable, can be used to encapsulate a broader range of drugs, have a better-controlled release profile	It can be more challenging to produce than SLN
Polymer-lipid hybrid nanoparticles	Made up of a combination of lipids and polymers	Biocompatible, biodegradable, can be used to target specific cells or tissues.	It can be more challenging to produce than other types of LNP
Polymer Drug Conjugates	conjugation of lipids to drug molecules by covalent linkage	It can be used in a variety of drugs, i.e., hydrophilic and hydrophobic	methods require specialized equipment or reagents, which may be unavailable

LIPOSOMES

Liposomes are spherical vesicles (or capsules) composed of one or more phospholipid bilayers. They are similar in structure to cell membranes, and this makes them attractive for use as drug delivery vehicles. Liposomes can be used to encapsulate a variety of therapeutic agents, including drugs, genes, and vaccine[10].

Types of Liposomes [11,12,13]

There are many different types of liposomes, which can be classified based on their structure, composition, and applications.

Structural classification

I. **Unilamellar liposomes:** These liposomes have a single lipid bilayer. They can be further classified into:
   a. **Small unilamellar vesicles (SUVs)**: These are the most minor type of unilamellar liposomes, with a diameter of less than 100 nanometers.
   b. **Large unilamellar vesicles (LUVs):** These are larger than SUVs, with a 100-1000 nanometers diameter.

c. **Giant unilamellar vesicles (GUVs):** These are the most significant type of unilamellar liposomes, with a diameter of more than 1000 nanometers.

II. **Multilamellar liposomes:** These liposomes have multiple lipid bilayers. They can be further classified into:

a. **Multilamellar vesicles (MLVs)**: These are the most common type of multilamellar liposomes. They have an onion-like structure with concentric layers of lipid bilayers.

b. **Multivesicular vesicles (MVVs)**: These liposomes have internal, non-concentrically arranged smaller vesicles within them.

Compositional classification

a. **Conventional liposomes**: These liposomes are made from naturally occurring phospholipids.

b. **Charged liposomes**: These have a net charge, which can be positive or negative. Charged liposomes can be used to target specific cells or tissues.

c. **Stealth liposomes**: These liposomes are coated with a layer of polyethene glycol (PEG). PEG is a water-soluble polymer that makes liposomes less likely to be recognized and cleared by the immune system.

d. **Actively targeted liposomes**: These are coated with specific ligands that can bind to receptors on specific cells or tissues. This allows the liposomes to target the desired cells or tissues more specifically.

e. **Stimuli-responsive liposomes**: They can change their properties in response to certain stimuli, such as temperature, pH, or specific molecules. This can control the release of the encapsulated drug or other molecules.

Methods of Preparation of Liposomes [14,15]

There are many methods for preparing liposomes, each with advantages and disadvantages. Some of the most common methods include:

1. **Solvent Injection Method:** involves dissolving lipids in an organic solvent, such as chloroform or methanol. The solvent is then evaporated, leaving behind a thin film of lipids. This film is then hydrated with an aqueous solution, forming liposomes.
2. **Thin-film hydration Method**: This method is similar to solvent injection, but the lipids are dissolved in water instead of using an organic solvent. The lipid solution is then spread onto a glass surface and dried under a stream of nitrogen gas. The dried film is then hydrated with an aqueous solution, forming liposomes.
3. **Emulsion solvent diffusion Method**: This method involves creating an emulsion of lipids and an aqueous solution. The emulsion is then heated, causing the solvent to evaporate. This leaves behind liposomes in the aqueous solution.
4. **Extrusion Method**: This method involves forcing liposomes through filters with different pore sizes. This process helps reduce the liposome size and make them more uniform.
5. **Sonication Method**: This method involves using ultrasonic waves to disrupt lipid molecules. This process can be used to create liposomes of various sizes and morphologies.

The choice of liposome preparation method will depend on several factors, such as the desired size and morphology of the liposomes, the type of lipids used, and the availability of equipment.

Here is a table that summarizes the advantages and disadvantages of each method:

Table-2: Methods of Preparation of Liposomes with their advantages and disadvantages[16]

Method	Advantages	Disadvantages
Solvent injection	It can be used to prepare liposomes of various sizes and morphologies.	It requires organic solvents, which can harm some drugs and biological materials.
Thin-film hydration	It does not require the use of organic solvents.	It cannot be easy to control the size and morphology of the liposomes.
Emulsion solvent diffusion	It does not require the use of organic solvents.	It can be challenging to control the size and morphology of the liposomes.
Extrusion	It can be used to prepare liposomes of uniform size.	It can be time-consuming and expensive.
Sonication	It can be used to prepare liposomes of various sizes and morphologies.	It can damage sensitive drugs and biological materials.

Solid Lipid Nanoparticles

SLN comprises a solid lipid core, a liquid lipid shell, and a surfactant. The solid lipid core typically comprises a wax or fatty acid. The liquid lipid shell typically comprises a phospholipid or other amphiphilic molecule. The surfactant is used to stabilize the SLN and prevent them from aggregating. SLNs are typically spherical. The size of the SLN can vary from a few nanometres to a few micrometres. The structure of the SLN is affected by the composition of the lipids, the type of surfactant used, and the preparation method.SLN are biocompatible and biodegradable. They are also relatively stable in the body. SLN can deliver various drugs, including hydrophilic and hydrophobic drugs. They can also be used to deliver drugs to specific tissues or cells [17,18].

Method of Preparation of SLNPs

1. **High-pressure homogenization (HPH):** HPH breaks down the solid lipid into small particles. The solid lipid is mixed with a liquid lipid and a surfactant and then passed through a high-pressure homogenizer. The homogenizer's high pressure and shear force break down the solid lipid into small particles[19].

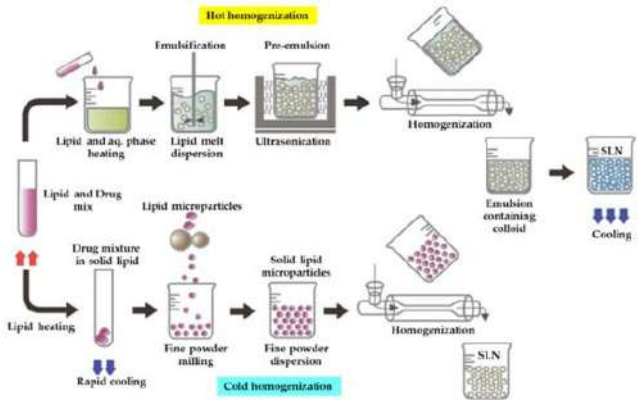

Figure-1: Schematic Diagram of Hot/Cold Homogenization Process involved in Preparation of SLNPs[20]

2. **Microemulsion:** Microemulsions are thermodynamically stable dispersions of oil, water, and surfactant. SLN can be prepared by forming a microemulsion of the solid, liquid, and surfactant. The microemulsion is then subjected to solvent evaporation or exchange to remove the solvent and leave behind the SLN[21].

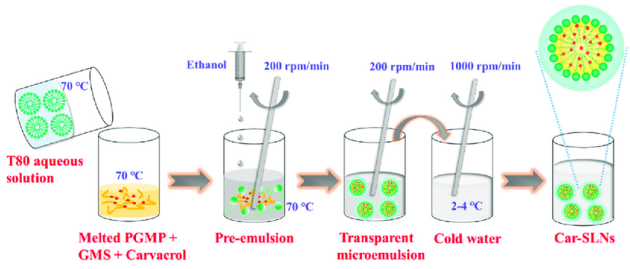

Figure-2: Schematic Diagram of Microemulsion Process involved in Preparation of SLNPs[22]

3. **Solvent emulsification-evaporation:** Solvent emulsification-

evaporation prepares SLN by dispersing the solid lipid in a solvent, such as ethanol or acetone. The solvent is then evaporated, leaving behind the SLN[23].

Figure-3: Schematic Diagram of Solvent Emulsification/Evaporation Process involved in Preparation of SLNPs[24]

4. **Supercritical fluid technology** is a method of preparing SLN by using a supercritical fluid, such as carbon dioxide, to dissolve the solid lipid. The supercritical fluid is then depressurized, which causes the solid lipid to precipitate as SLN [25].

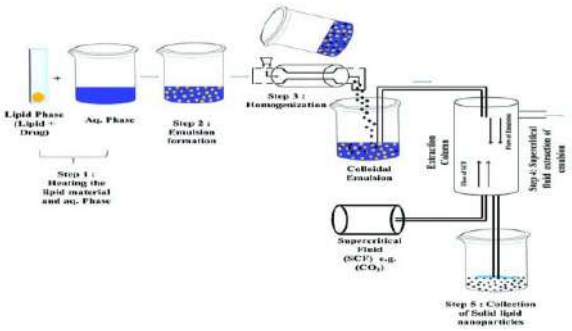

Figure-4: Schematic Diagram of Supercritical fluid technological Process involved in Preparation of SLNPs[26]

5. **Sonoporation:** Sonoporation is a method of preparing SLN using ultrasound waves to disrupt the cell membrane. The solid lipid is then encapsulated in the cells and broken down to release the SLN[27].

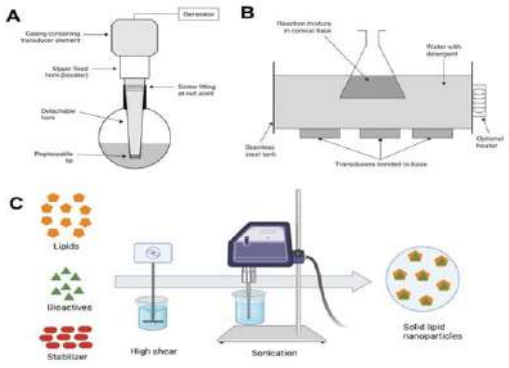

Figure-5: Schematic Diagram of Sonoporation Process involved in Preparation of SLNPs[28]

6. **In situ gelation:** In situ, gelation is a method of preparing SLN by mixing the drug and lipids in a solvent. The solvent is removed, leaving behind a gel containing the SLN. In situ gelation can be used to prepare SLNs that are targeted to specific tissues or cells[29].

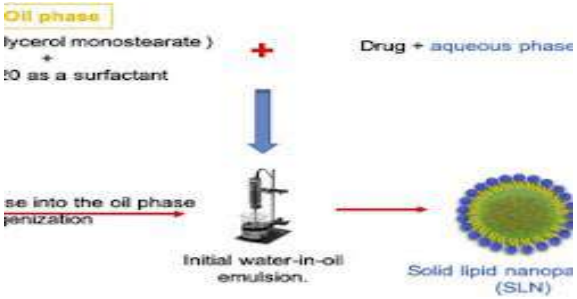

Figure-6: Schematic Diagram of *In-situ* gelation Process involved in Preparation of SLNPs[30]

Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers (NLCs) are a type of lipid nanoparticle similar to solid lipid nanoparticles (SLN) but have a more uniform structure. This is because NLCs contain a mixture of solid and liquid lipids, whereas SLN only contains solid lipids. The liquid lipids in NLCs help to make the particles more flexible and less likely to aggregate[31].

There are some specific improvements that NLCs have over SLN:

- NLCs have a more uniform size distribution than SLNs. This is important because it can improve the stability and efficacy of the NLCs.

- NLCs have a higher drug-loading capacity than SLNs. This means more drugs can be encapsulated in the NLCs, improving their therapeutic potential.
- NLCs are more resistant to aggregation than SLN. This means that they are less likely to clump together, which can improve their stability and efficacy.
- NLCs can be targeted to specific tissues or cells. This can improve the delivery of drugs to the intended site of action and reduce side effects[32].

Formulation strategies of Nanostructured lipid carriers (NLCs)

1. Blend approach: This is the most common approach for preparing NLCs. It involves blending a mixture of solid and liquid lipids with a surfactant. The surfactant is used to stabilize the NLCs and prevent them from aggregating[33].
2. The matrix approach involves forming a solid lipid matrix and then incorporating the drug into the matrix. The matrix can be formed by melting the solid lipid and cooling it down. The drug can be incorporated into the matrix by dissolving it in the molten lipid or by encapsulating it in the matrix using a technique such as solvent evaporation[34].

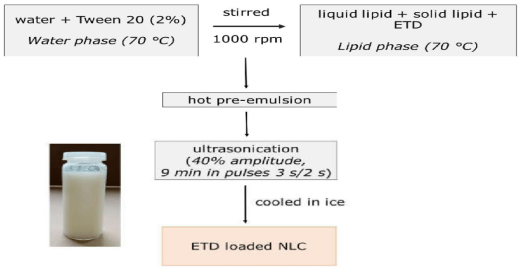

Figure-7: Schematic Diagram of *the Matrix Approach* involved in Preparation of NLCs[35]

3. **Coacervation approach:** This approach involves forming a coacervate, which is a complex of oppositely charged molecules. The coacervate can be formed by mixing a solution of the drug with a solution of the lipid and surfactant. The drug and lipid will form a coacervate, which can then be stabilized by adding a third component, such as a polymer[36].

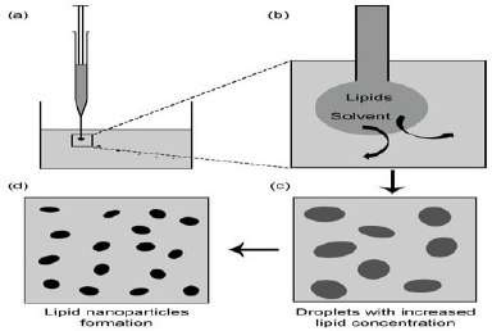

Figure-8: Schematic Diagram of *Coacervation Approach* involved in Preparation of NLCs[37]

4. **Emulsification-solvent evaporation approach:** This approach is similar to the matrix approach but uses a solvent to dissolve the drug. The drug is dissolved in a miscible solvent with a solid lipid. The mixture is then emulsified in water, and the solvent is evaporated. This leaves behind the NLCs with the drug encapsulated in the solid lipid matrix[38].

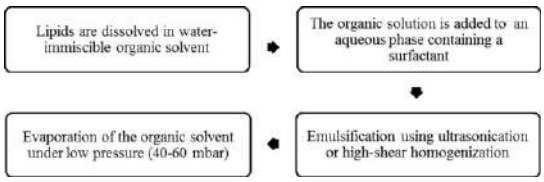

Figure-9: Schematic Diagram of *Emulsification-solvent evaporation Approach* involved in Preparation of NLCs[39]

Lipid-Drug Conjugates

Lipid-drug conjugates (LDCs) are drug molecules covalently modified with lipids. The conjugation of lipids to drug molecules increases lipophilicity and changes other drug properties, such as their solubility, stability, and pharmacokinetics[40].

Synthesis Methods of Lipid-Drug Conjugates [41,42.43]

There are several methods for synthesizing lipid-drug conjugates (LDCs). The choice of method depends on the chemical nature of the drug and the lipid, as well as the desired properties of the conjugate.

I. **Coupling reactions:** This is a standard method for synthesizing LDCs. In this method, a functional group on the drug is reacted with a functionalised lipid to form a covalent bond. The functionalized lipid can be prepared by reacting with a chemical reagent that introduces a reactive functional group. The most common functional groups used for functionalizing lipids are:
   - **-COOH:** This functional group can be introduced by reacting a lipid with succinic anhydride or 1,2-dicyclohexylcarbodiimide.
   - **-NH2:** This functional group can be introduced by reacting a lipid with ethylenediamine or benzylamine.
   - **-OH:** This functional group can be introduced by reacting a lipid with 3-aminopropyltriethoxysilane.

The most common coupling reactions occurs between functionalised lipid with a functional group of drugs are:

- **Carbodiimide coupling:** This reaction forms amide bonds between carboxylic acids and amines.
- **Esterification:** This reaction forms ester bonds between carboxylic acids and alcohols.
- **Michael addition:** This reaction forms carbon-carbon bonds between alkenes and carbonyl compounds.

II. **Copolymerization:** In this method, a drug is copolymerized with a lipid. This can be done by reacting the drug and lipid with a comonomer and a radical initiator. The comonomer can be a small molecule, such as styrene, divinylbenzene, or another lipid.

III. **Self-assembly:** In this method, a drug is self-assembled with a lipid to form a conjugate. This can be done by mixing the drug and lipid in a solvent and allowing the mixture to form aggregates spontaneously. The aggregates can be nanoparticles, micelles, or liposomes.

The choice of synthesis method for LDCs depends on several factors, including:

- The chemical nature of the drug and the lipid: Some methods are more suitable for specific drugs or lipids. For example, carbodiimide coupling is unsuitable for drugs containing primary amines.
- The desired properties of the conjugate: Some methods can synthesize conjugates with specific properties, such as controlled release or targeting specific tissues.
- The availability of equipment and reagents: Some methods require specialized equipment or reagents that may be limited.

Examples of Successful Lipid Drug Conjugates [44,45]

1. **Dostarlimab** is an LDC that is used to treat endometrial cancer. It comprises the monoclonal antibody dostarlimab conjugated to a lipid called polyethene glycol (PEG). Dostarlimab targets the PD-1 receptor on cancer cells, which helps to prevent the immune system from attacking them. PEG helps to prolong the circulation time of dostarlimab in the body.
2. **Pegylated liposomal doxorubicin** (PLD) is an LDC used to treat cancer. It is made up of the chemotherapy drug doxorubicin conjugated to PEG-coated liposomes. The liposomes protect the doxorubicin from being broken down by enzymes in the body, which allows it to reach cancer cells more effectively. PEG also helps to prolong the circulation time of PLD in the body.
3. **Fuzeon** is an LDC that is used to treat HIV. It comprises the HIV protease inhibitor enfuvirtide conjugated to a lipid called distearoylphosphatidylethanolamine (DSPE). The DSPE helps to improve the solubility and stability of enfuvirtide in the body. Fuzeon is a

long-acting injectable medication that is given every two weeks.

4. **Inflexiva** is an LDC that is used to treat rheumatoid arthritis. It comprises the tumour necrosis factor (TNF)-α inhibitor infliximab conjugated to a lipid called DSPE-PEG. The DSPE-PEG helps to prolong the circulation time of infliximab in the body. Inflexiva is given by intravenous infusion every eight weeks.
5. **Doxil:** Doxil is an LDC of doxorubicin, a chemotherapy drug. It is used to treat cancer of the breast, ovary, lung, and other solid tumours. Doxil is more effective than doxorubicin alone and has fewer side effects.
6. **Oncaspar:** Oncaspar is an LDC of asparaginase, a chemotherapy drug. It is used to treat acute lymphoblastic leukaemia (ALL). Oncaspar is more effective than asparaginase alone and has fewer side effects.
7. **Vismodegib:** Vismodegib is an LDC of a hedgehog signalling pathway inhibitor. It is used to treat basal cell carcinoma, a type of skin cancer. Vismodegib is more effective than other treatments for basal cell carcinoma and has fewer side effects.
8. **Eculizumab:** Eculizumab is an LDC of a complement factor C5 inhibitor. It treats paroxysmal nocturnal hemoglobinuria (PNH), a rare blood disorder. Eculizumab is the only treatment that can cure PNH.
9. **Glybera:** Glybera is an LDC of a lipoprotein lipase (LPL) activator. It is used to treat lipoprotein lipase deficiency, a rare genetic disorder that causes high levels of triglycerides in the blood. Glybera is the first and only approved LDC in Europe.
10. **Praluent:** This LDC is used to treat high cholesterol. It is made up of a lipid nanoparticle that carries the drug evolocumab. Praluent has been shown to lower LDL cholesterol by up to 60%.
11. **Inflamyx:** This LDC is in clinical development for treating rheumatoid arthritis. It is made up of a lipid nanoparticle that carries the drug infliximab. Inflamyx is effective in reducing inflammation and pain in patients with rheumatoid arthritis.
12. **Abraxane:** This LDC is used to treat breast cancer. It is made up of a lipid nanoparticle that carries the chemotherapy drug paclitaxel. Abraxane effectively shrinks tumours and improves survival rates in breast cancer patients.
13. **Onivyde:** This LDC is used to treat advanced pancreatic cancer. It comprises a lipid nanoparticle that carries the chemotherapy drug irinotecan. Onivyde has been shown to prolong survival in patients with advanced pancreatic cancer.

Polymer lipid hybrid nanoparticles [46,47,48]

Polymer lipid hybrid nanoparticles (PLNs) are a type of nanocarrier that combines the advantages of polymeric nanoparticles and liposomes. PLNs consist of a polymeric core and a lipid shell, which provides them with the physical stability and biocompatibility of both types of nanocarriers.

Synthesis methods of Polymer lipid Hybrid nanoparticle

There are two main methods for synthesizing polymer lipid hybrid nanoparticles (PLHNs):

1. **Single-step method:** The polymer and lipid components are dissolved in a common organic solvent and then emulsified in an aqueous phase. The solvent is then evaporated, leaving behind the PLHNs.
2. **Two-step method:** In this method, the polymer nanoparticles are synthesized first, followed by the synthesis of the lipid shell. The two components are then mixed to form the PLHNs.

The single-step method is more straightforward and efficient, but it can be challenging to control the size and morphology of the PLHNs. The two-

step method is more complex, but it offers greater control over the properties of the PLHNs.

Here are some of the specific techniques that can be used to synthesize PLHNs:

1. **Solvent evaporation:** This is the simplest and most common method for synthesizing polymer nanoparticles. The polymer is dissolved in an immiscible solvent with water, and then the solvent is evaporated. This leaves behind a dispersion of polymer nanoparticles in water.
2. **Emulsification/solvent diffusion:** This method synthesises polymer nanoparticles with a narrow size distribution. The polymer is dissolved in an organic solvent, and then the solvent is emulsified in an aqueous phase. The organic solvent then diffuses out of the emulsion, leaving behind the polymer nanoparticles.
3. **Emulsification/reverse salting-out:** This method synthesises polymer nanoparticles with a high drug-loading capacity. The polymer is dissolved in an organic solvent, and then the solvent is emulsified in an aqueous phase containing a salt solution. The salt solution causes the polymer to precipitate out of the emulsion, forming polymer nanoparticles.
4. **Nanoprecipitation:** This method synthesises polymer nanoparticles with controlled size and morphology. The polymer is dissolved in a miscible solvent with water, and then the solution is added dropwise to an aqueous phase under vigorous stirring. The solvent then precipitates out of the solution, forming polymer nanoparticles.

Polymeric Micelles [49,50]

Polymeric micelles are nanoscale drug delivery systems formed by the self-assembly of amphiphilic block copolymers in aqueous solution. Amphiphilic block copolymers are molecules that have two or more different chemically bonded polymer chains. One chain is typically hydrophobic (water-fearing), while the other is hydrophilic (water-loving).

There are three main methods for preparing polymeric micelles:

1. **Direct dissolution:** This method is the simplest and most common for preparing polymeric micelles. It involves dissolving the amphiphilic block copolymer in an aqueous solution at a temperature above the critical micelle concentration (CMC). The micelles will then form spontaneously as the temperature is decreased.
2. **Solvent evaporation:** This method involves dissolving the amphiphilic block copolymer in a water-immiscible solvent, such as chloroform or methanol. The solution is then added to an aqueous solution under stirring. The solvent will evaporate, leaving behind the polymeric micelles.
3. **Dialysis:** This method involves dissolving the amphiphilic block copolymer in a water-immiscible solvent, such as chloroform or methanol. The solution is then dialyzed against an aqueous solution to remove the solvent. The micelles will form spontaneously as the solvent is removed.

Formulation Strategies and Characterization of Lipid Nanoparticles

Lipid Selection and Compatibility with Drugs [51,52,53]

The selection of lipids for formulating lipid nanoparticles (LNP) is an important consideration that can affect the final product's stability, efficacy, and safety. There are several factors to consider when selecting lipids, including:

- The solubility of the drug in the lipid: The lipid should be able to solubilize the drug without forming precipitates or crystals.
- The stability of the drug in the lipid: The lipid should not degrade the drug or its efficacy.

- The compatibility of the drug with the lipid: The drug and lipid should not interact in a way that produces toxic or harmful byproducts.
- The physicochemical properties of the lipid: The lipid should have the desired properties for the intended application, such as size, shape, and surface charge.
- The cost of the lipid: The lipid should be cost-effective to produce and use.

Several different lipids can be used to formulate LNPs, each with advantages and disadvantages. Some of the most common lipids used for LNPs include:

- Cholesterol: Cholesterol is a nonpolar lipid that helps to stabilize the LNP structure. It is also relatively inexpensive.
- Phospholipids: Phospholipids are polar lipids that help to solubilize the drug and improve the stability of the LNP. They are also relatively inexpensive.
- PEGylated lipids: PEGylated lipids are coated with polyethene glycol (PEG). This coating helps to prolong the circulation time of the LNP and protect it from degradation. PEGylated lipids can be more expensive than other types of lipids.
- Solid lipids: Solid lipids are used to form the core of the LNP. They help to control the size and shape of the LNP and improve its stability. Solid lipids can be more expensive than other types of lipids.
- Triglycerides: Triglycerides are a type of lipid that is composed of three fatty acids attached to a glycerol backbone. They are lipophilic and can help to solubilize drugs that are not soluble in water.

The selection of lipids for formulating LNPs is a complex process that requires careful consideration of the drug, the intended application, and the desired properties of the LNP. By carefully selecting the lipids, it is possible to produce LNPs that are safe, effective, and cost-effective.

Here are some additional considerations for lipid selection and compatibility with drugs:

- The lipid should be compatible with the drug's degradation products. If the lipid reacts with the drug's degradation products, it can produce toxic or harmful byproducts.
- The lipid should not interfere with the drug's absorption, distribution, metabolism, or excretion.
- The lipid should not have any adverse effects on the patient.

Techniques to Evaluate Drug Loading Efficiency [54,55]

Two main tests are used to evaluate direct and indirect drug loading efficiency in lipid nanoparticles.

Direct Tests

Direct tests measure the amount of drug that is encapsulated in the nanoparticles. This can be done by:

- **Chromatography:** This technique separates the drug from the nanoparticles and measures the amount of the present drug.
- **Spectroscopy:** This technique measures the absorption or emission of light by the drug and the nanoparticles. The amount of encapsulated drugs can be calculated from the difference in the spectra of the free and encapsulated drugs.

Indirect Tests

Indirect tests measure the amount of drug not encapsulated in the nanoparticles. This can be done by:

- **Supernatant assay:** This technique measures the amount of drug present in the supernatant after centrifuging the nanoparticles.
- **Desorption assay:** This technique removes the drug from the nanoparticles and measures the drug released.

Controlling Particle Size and its impact on Drug Release

The particle size of lipid nanoparticles (LNPs) significantly impacts their drug release profile, stability, and biodistribution. Smaller LNPs have faster drug release rates due to their larger surface area-to-volume ratio, allowing for more rapid drug diffusion. Controlling particle size involves high-pressure homogenizers or solvent/non-solvent methods, which break down the LNP solution into smaller particles[56]. Smaller LNPs are also more stable due to their lower hydrodynamic volume, making them less likely to aggregate. Additionally, smaller LNPs are more easily taken up by cells, making them more effective for delivering drugs to specific tissues or cells. By controlling the particle size of LNPs, optimizing their performance for specific applications is possible[57].

Methods of Characterisation of Lipid Nanoparticles[57,58]

Lipid nanoparticles (LNP) are colloidal carriers composed of lipids used in drug delivery. They have a wide range of potential applications, including the delivery of vaccines, nucleic acids, and small molecules.

The characterization of LNPs is essential to ensure their quality and safety. Several methods are available for the characterization of LNPs, including:

- Size and size distribution: LNPs can be determined using dynamic light scattering (DLS) or nanoparticle tracking analysis (NTA).
- Morphology: The morphology of LNPs can be visualized using electron microscopy (EM) or atomic force microscopy (AFM).
- Surface properties: The surface properties of LNPs can be characterized using techniques such as zeta potential, surface tension, and surface hydrophobicity.
- Composition: The composition of LNPs can be determined using a variety of methods, including high-performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR), and Fourier transform infrared spectroscopy (FTIR).
- Drug loading and encapsulation efficiency: The drug loading and encapsulation efficiency of LNPs can be determined using various methods, including high-performance liquid chromatography (HPLC) and radiolabeling.
- In vitro stability: The in vitro stability of LNPs can be assessed by measuring their size, morphology, surface properties, composition, drug loading, and encapsulation efficiency over time.
- In vivo stability: The in vivo stability of LNPs can be assessed by measuring their distribution, biodistribution, and clearance in animal models.

Importance of Physiochemical properties on drug delivery [59,60,61]

The physicochemical properties of lipid nanoparticles (LNs) are essential for their performance as drug-delivery vehicles. These properties include:

- Size: The size of LNs is essential for their ability to target specific tissues or cells. Smaller LNs can be taken up by cells more efficiently, while larger LNs can be readily cleared from the body.
- Charge: The charge of LNs can affect their interactions with cells and tissues. For example, positively charged LNs can be attracted to negatively charged cells, such as cancer cells.
- Surface properties: The surface properties of LNs can affect their body stability and ability to interact with cells and tissues. For example, LNs with a hydrophilic surface are more likely to be taken up by cells, while LNs with a hydrophobic surface are more likely to be cleared from the body.
- Composition: The composition of LNs can affect their stability, solubility, and

biocompatibility. For example, LNs made of naturally occurring lipids in the body are more likely to be biocompatible.

The ideal physicochemical properties of LNs for drug delivery will vary depending on the specific drug and the desired therapeutic outcome. However, in general, LNs with the following properties are likely to be more effective drug-delivery vehicles:

- Small size (<100 nm)
- Positive charge
- Hydrophilic surface
- Composition of naturally occurring lipids

By carefully controlling the physicochemical properties of LNs, it is possible to develop targeted, efficient, and safe drug delivery systems. Here are some specific examples of how the physicochemical properties of LNs can be used to improve drug delivery:

- LNs can be used to deliver drugs to specific tissues or cells by targeting the LNs to the desired tissue or cell type. For example, LNs with a positive charge can be targeted to cancer cells, which often have a negative charge.
- LNs can be used to increase the solubility of poorly water-soluble drugs. This can improve the bioavailability of the drug and make it more effective.
- LNs can be used to control the release of drugs. This can ensure that the drug is released at the desired rate and location.
- LNs can be used to protect drugs from degradation in the body. This can improve the stability of the drug and make it more effective.

Enhanced Drug Delivery Applications [62,63]

Lipid nanoparticles are a promising new drug delivery system with many potential applications. Some of the most promising applications of lipid nanoparticles include:

a) **Overcoming the blood-brain barrier:** The blood-brain barrier is a protective layer that prevents most drugs from entering the brain. Lipid nanoparticles can be designed to specifically target the blood-brain barrier, allowing them to deliver drugs that would otherwise be unable to cross. This has the potential to revolutionize the treatment of neurological diseases, such as Alzheimer's disease and Parkinson's disease.

b) **Targeted delivery of anticancer agents:** Lipid nanoparticles can be loaded with anticancer drugs and targeted to specific cancer cells. This can improve chemotherapy's efficacy and reduce the treatment's side effects.

c) **Lipid-based delivery of nucleic acids in gene therapy:** Lipid nanoparticles can deliver nucleic acids, such as DNA and RNA, to cells. This can potentially treat various genetic diseases, including cancer, cystic fibrosis, and sickle cell disease.

d) **Applications in infectious disease treatment:** Lipid nanoparticles can deliver antibiotics and other drugs to cells infected with bacteria, viruses, and other pathogens. This can improve the treatment of infectious diseases, such as HIV/AIDS, malaria, and tuberculosis.

e) **Potential for personalized medicine through tailored lipid nanoparticle formulations:** Lipid nanoparticles can be tailored to the specific needs of individual patients. This can revolutionize how drugs are developed and delivered, leading to more effective and safer treatments for various diseases.

Overcoming Challenges in Drug Delivery [64,65,66,67]

Here are some strategies to overcome the challenges in drug delivery relevant to:

Strategies to enhance lipid nanoparticle stability during storage:

- One strategy is to use stabilizers, such as polyethene glycol (PEG), to coat the lipid nanoparticles. PEG can help to prevent the nanoparticles from aggregating and degrading.
- Another strategy is to use cryoprotectants, such as trehalose, to protect the nanoparticles from freezing damage.
- Finally, storing the lipid nanoparticles under controlled conditions, such as at a cool temperature and in a dark environment, is essential.

Approaches to control drug release profiles:

- One approach is to use polymers with different degradation rates. For example, a polymer with a fast degradation rate can deliver a drug quickly, while a polymer with a slow degradation rate can deliver a drug slowly.
- Another approach is to use stimuli-responsive polymers. These polymers can degrade in response to a specific stimulus, such as pH, temperature, or light. This can be used to control the release of the drug in a specific location or at a specific time.

Mitigating potential toxicity concerns:

- One way to mitigate potential toxicity concerns is to use biocompatible and biodegradable materials. These materials are less likely to cause adverse reactions in the body.
- Another way to mitigate potential toxicity concerns is to use low **drug doses. This can help to reduce the risk of side effects.**

Challenges associated with large-scale production:

- One challenge associated with large-scale production is the cost of materials. Lipid nanoparticles are often made from expensive materials like PEG and polymers.
- Another challenge associated with large-scale production is the complexity of the manufacturing process. Lipid nanoparticle production is a multi-step process that can be difficult to scale.
- Finally, ensuring that the lipid nanoparticles are produced under sterile conditions is essential to prevent contamination.

Clinical Translation and Regulatory Considerations[68]

Several lipid nanoparticle-based formulations have been tested in clinical trials. Some of the most notable examples include:

- Doxil® (pegylated liposomal doxorubicin): This formulation of doxorubicin is used to treat cancer. It effectively delivers the drug to cancer cells while minimizing systemic toxicity.
- Onpattro® (patisiran): This formulation of patisiran is used to treat hereditary transthyretin amyloidosis. It is effective in reducing amyloid deposits in the heart and liver.
- COVID-19 vaccines: Several COVID-19 vaccines are based on lipid nanoparticles. These vaccines are safe and effective in preventing COVID-19.

Regulatory pathways for lipid nanoparticle-based drugs [69]

The regulatory pathway for lipid nanoparticle-based drugs can vary depending on the drug and the intended use. However, these drugs must undergo a rigorous safety and efficacy testing process before they can be approved for marketing.

The first step in the regulatory process is typically preclinical testing. This involves testing the drug in animals to assess its safety and efficacy. If the drug shows promise in preclinical testing, it moves to clinical trials.

Clinical trials are conducted in three phases:

- Phase 1 trials are conducted with a few healthy volunteers to assess the drug's safety.
- Phase 2 trials: These trials are conducted in more patients to assess the drug's efficacy.
- Phase 3 trials: These trials are conducted on many patients to confirm the efficacy and safety of the drug.

If the drug succeeds in clinical trials, it can be submitted to the regulatory agency for approval. The regulatory agency will review the data from the clinical trials and decide whether to approve the drug for marketing.

Safety and toxicology considerations[70]

Lipid nanoparticle-based drugs are generally considered to be safe. However, some potential safety concerns need to be considered, such as:

- The potential for the nanoparticles to be toxic to cells.
- The potential for the nanoparticles to accumulate in tissues.
- The potential for the nanoparticles to interact with other drugs or medical devices.

These safety concerns must be carefully evaluated during preclinical testing and clinical trials.

Intellectual property and commercialization challenges[71]

Lipid nanoparticle-based drugs are often protected by intellectual property (IP). This IP can include patents, trademarks, and trade secrets. IP can be valuable for companies that develop and commercialize these drugs.

However, IP can also be a challenge for companies wanting to enter the lipid nanoparticle-based drug market. This is because other companies may already have patents on specific aspects of these drugs. This can make it difficult for new companies to compete in the market.

Future Perspectives[72]

Lipid nanoparticle (LNP) technology is a rapidly developing field with the potential to revolutionize drug delivery. LNPs have several advantages over traditional delivery methods, including protecting drugs from degradation, improving drug solubility, and targeting drugs to specific tissues or cells.

Current trends and emerging research directions in lipid nanoparticle technology[73]

Current research in LNP technology is focused on several areas, including:

- Developing new LNP formulations that are more efficient at delivering drugs to target tissues or cells
- Improving the stability of LNPs under physiological conditions
- Developing LNPs that can be administered by different routes, such as orally or through the skin
- Investigating the potential of LNPs to deliver gene therapy and other novel therapies

The potential for combination therapy using lipid nanoparticles[74]

Combination therapy using LNPs has the potential to overcome some of the limitations of traditional drug delivery methods. For example, LNPs can be used to deliver two or more drugs that are incompatible when delivered separately. Additionally, LNPs can be used to deliver drugs that target different cells or tissues, improving treatment efficacy.

Contributions to patient care and drug development[75]

LNP technology has already made a significant contribution to patient care. For example, LNPs are used in the commercial COVID-19 vaccine developed by Pfizer and BioNTech. LNPs are also being investigated to treat various diseases, including cancer, Alzheimer's, and HIV/AIDS.

CONCLUSION

Lipid nanoparticle technology is a rapidly developing field with the potential to transform how drugs are delivered. The future of LNP research is bright, and there is no doubt that this technology will continue to play an increasingly important role in patient care and drug

development. In conclusion, lipid nanoparticle technology is a promising new approach to drug delivery with the potential to improve the efficacy and safety of treatment for a wide range of diseases. Recent advances in LNP design and manufacturing have paved the way for the clinical translation of LNP-based therapies, and future research is likely to expand the potential of this technology further.

REFERENCES

1. Swetha, K., Kotla, N. G., Tunki, L., Jayaraj, A., Bhargava, S. K., Hu, H., ... & Kurapati, R. (2023). Recent advances in the lipid nanoparticle-mediated delivery of mRNA vaccines. Vaccines, 11(3), 658.
2. Atabakhshi-Kashi, M., Geranpayehvaghei, M., Wang, Y., Akhbariyoon, H., Taleb, M., Zhang, Y., ... & Nie, G. (2020). Recent Advances of Nanocarriers for Effective Delivery of Therapeutic Peptides. Precision Nanomedicine, 3(2), 549-576.
3. Hou, X., Zaks, T., Langer, R., & Dong, Y. (2021). Lipid nanoparticles for mRNA delivery. Nature Reviews Materials, 6(12), 1078-1094.
4. Zhao, Y. Q., Li, L. J., Zhou, E. F., Wang, J. Y., Wang, Y., Guo, L. M., & Zhang, X. X. (2022). Lipid-Based Nanocarrier Systems for Drug Delivery: Advances and Applications. Pharmaceutical Fronts, 4(02), e43-e60.
5. Mahmoud, K., Swidan, S., El-Nabarawi, M., & Teaima, M. (2022). Lipid based nanoparticles as a novel treatment modality for hepatocellular carcinoma: A comprehensive review on targeting and recent advances. Journal of Nanobiotechnology, 20(1), 109.
6. Akombaetwa, N., Ilangala, A. B., Thom, L., Memvanga, P. B., Witika, B. A., & Buya, A. B. (2023). Current Advances in Lipid Nanosystems Intended for Topical and Transdermal Drug Delivery Applications. Pharmaceutics, 15(2), 656.
7. Tenchov, R., Bird, R., Curtze, A. E., & Zhou, Q. (2021). Lipid nanoparticles─ from liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement. ACS nano, 15(11), 16982-17015.
8. Ezike TC, Okpala US, Onoja UL, Nwike CP, Ezeako EC, Okpara OJ, Okoroafor CC, Eze SC, Kalu OL, Odoh EC, Nwadike UG, Ogbodo JO, Umeh BU, Ossai EC, Nwanguma BC. (2023). Advances in drug delivery systems, challenges and future directions. Heliyon. Jun;9(6): e17488.
9. Abdellatif, A. A., Mohammed, H. A., Khan, R. A., Singh, V., Bouazzaoui, A., Yusuf, M., ... & Al-Omar, M. S. (2021). Nano-scale delivery: A comprehensive review of nano-structured devices, preparative techniques, site-specificity designs, biomedical applications, commercial products, and references to safety, cellular uptake, and organ toxicity. Nanotechnology Reviews, 10(1), 1493-1559.
10. Duan, Y., Dhar, A., Patel, C., Khimani, M., Neogi, S., Sharma, P., ... & Vekariya, R. L. (2020). A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems. RSC advances, 10(45), 26777-26791.
11. Guevara, M. L., Persano, F., & Persano, S. (2020). Advances in lipid nanoparticles for mRNA-based cancer immunotherapy. Frontiers in chemistry, 8, 589959.
12. Yousry, A., Hassan, T., Elaidy, S. M., & Gad, S. (2022). Nanocarriers as pulmonary drug delivery systems. Records of Pharmaceutical and Biomedical Sciences, 6(3), 113-119.
13. Saez, V., Souza, I. D. L., & Mansur, C. R. E. (2018). Lipid nanoparticles (SLN & NLC) for delivery of vitamin E: a comprehensive review. In International Journal of Cosmetic Science, 40(2), 03–116.

14. Stefanov, S. R., & Andonova, V. Y. (2021). Lipid nanoparticulate drug delivery systems: recent advances in the treatment of skin disorders. Pharmaceuticals, 14(11), 1083.
15. Pandey, S., Shaikh, F., Gupta, A., Tripathi, P., & Yadav, J. S. (2022). A Recent Update: Solid Lipid Nanoparticles for Effective Drug Delivery. In Advanced Pharmaceutical Bulletin, 12(1),17–33.
16. Dhankhar, R., Vyas, S. P., Jain, A. K., Arora, S., Rath, G., & Goyal, A. K. (2010). Advances in novel drug delivery strategies for breast cancer therapy. In Artificial Cells, Blood Substitutes, and Biotechnology, 38(5),230–249.
17. Sivadasan, D., Sultan, M. H., Madkhali, O., Almoshari, Y., & Thangavel, N. (2021). Polymeric lipid hybrid nanoparticles (plns) as emerging drug delivery platform—A comprehensive review of their properties, preparation methods, and therapeutic applications. Pharmaceutics, 13(8), 1291.
18. Mahmoud, K., Swidan, S., El-Nabarawi, M., & Teaima, M. (2022). Lipid based nanoparticles as a novel treatment modality for hepatocellular carcinoma: A comprehensive review on targeting and recent advances. Journal of Nanobiotechnology, 20(1), 109.
19. Sokkula, S. R., & Gande, S. (2020). A comprehensive review on self-nano emulsifying drug delivery systems: advancements & applications. Int. J. Pharm. Sci. Drug Res, 12(5), 576-583.
20. Doktorovova, S., & Souto, E. B. (2009). Nanostructured lipid carrier-based hydrogel formulations for drug delivery: a comprehensive review. Expert opinion on drug delivery, 6(2), 165-176.
21. Yoon, G., Park, J. W., & Yoon, I. S. (2013). Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs): recent advances in drug delivery. Journal of Pharmaceutical Investigation, 43, 353-362.
22. Singh, M., & Mazumder, B. (2022). Recent Advancements in Nanodiamond Mediated Brain Targeted Drug Delivery and Bioimaging of Brain Ailments: A Holistic Review. Pharmaceutical Nanotechnology, 10(1), 42-55.
23. Narayan, R., Nayak, U. Y., Raichur, A. M., & Garg, S. (2018). Mesoporous silica nanoparticles: A comprehensive review on synthesis and recent advances. Pharmaceutics, 10(3), 118.
24. Das, S., & Chaudhury, A. (2011). Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. Aaps Pharmscitech, 12, 62-76.
25. Tenchov, R., Bird, R., Curtze, A. E., & Zhou, Q. (2021). Lipid nanoparticles─ from liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement. ACS nano, 15(11), 16982-17015.
26. Severino, P., Andreani, T., Macedo, A. S., Fangueiro, J. F., Santana, M. H. A., Silva, A. M., & Souto, E. B. (2012). Current state-of-art and new trends on lipid nanoparticles (SLN and NLC) for oral drug delivery. Journal of drug delivery, 2012.
27. Puglia, C., & Bonina, F. (2012). Lipid nanoparticles as novel delivery systems for cosmetics and dermal pharmaceuticals. Expert Opinion on Drug Delivery, 9(4), 429-441.
28. Fathi-Karkan, S., Arshad, R., Rahdar, A., Ramezani, A., Behzadmehr, R., Ghotekar, S., & Pandey, S. (2023). Recent advancements in the targeted delivery of etoposide nanomedicine for cancer therapy: A comprehensive review. European Journal of Medicinal Chemistry, 115676.
29. Narayana, S., Ahmed, M. G., Gowda, B. H., Shetty, P. K., Nasrine, A., Thriveni, M., ... &

Sanjana, A. (2021). Recent advances in ocular drug delivery systems and targeting VEGF receptors for management of ocular angiogenesis: A comprehensive review. Future Journal of Pharmaceutical Sciences, 7(1), 1-21.

30. Jacob, S., Nair, A.B., Shah, J., Gupta, S., Boddu, S.H., Sreeharsha, N., Joseph, A., Shinu, P. and Morsy, M.A. (2022). Lipid Nanoparticles as a Promising Drug Delivery Carrier for Topical Ocular Therapy—An Overview on Recent Advances. Pharmaceutics, 14(3), p.533.
31. Kamble, P., & Singh, P. (2020). A critical review on potential advancements of nanostructured lipid carriers in drug delivery. Current Nanomedicine (Formerly: Recent Patents on Nanomedicine), 10(4), 298-325.
32. Bai, X., Smith, Z. L., Wang, Y., Butterworth, S., & Tirella, A. (2022). Sustained drug release from smart nanoparticles in cancer therapy: A Comprehensive review. Micromachines, 13(10), 1623.
33. Al-Sayadi, G. M., Verma, A., Choudhary, Y., Sandal, P., Patel, P., Singh, D., ... & Das Kurmi, B. (2023). Solid Lipid Nanoparticles (SLNs): Advancements in Modification Strategies Toward Drug Delivery Vehicle. Pharmaceutical Nanotechnology, 11(2), 138-154.
34. Dolatabadi, J. E. N., Valizadeh, H., & Hamishehkar, H. (2015). Solid lipid nanoparticles as efficient drug and gene delivery systems: recent breakthroughs. Advanced pharmaceutical bulletin, 5(2), 151.
35. Amoabediny, G., Haghiralsadat, F., Naderinezhad, S., Helder, M. N., Akhoundi Kharanaghi, E., Mohammadnejad Arough, J., & Zandieh-Doulabi, B. (2018). Overview of preparation methods of polymeric and lipid-based (niosome, solid lipid, liposome) nanoparticles: A comprehensive review. International Journal of Polymeric Materials and Polymeric Biomaterials, 67(6), 383-400.
36. Jacob, S., Nair, A. B., Shah, J., Gupta, S., Boddu, S. H. S., Sreeharsha, N., ... & Morsy, M. A. (2022). Lipid nanoparticles as a promising drug delivery carrier for topical ocular therapy—an overview on recent advances. Pharmaceutics 2022; 14 (3): 533.
37. Schäfer-Korting, M., Mehnert, W., & Korting, H. C. (2007). Lipid nanoparticles for improved topical application of drugs for skin diseases. Advanced drug delivery reviews, 59(6), 427-443.
38. Gupta, P., Neupane, Y. R., Aqil, M., Kohli, K., & Sultana, Y. (2023). Lipid-based nanoparticle-mediated combination therapy for breast cancer management: a comprehensive review. Drug Delivery and Translational Research, 1-28.
39. Wong, H. L., Bendayan, R., Rauth, A. M., Li, Y., & Wu, X. Y. (2007). Chemotherapy with anticancer drugs encapsulated in solid lipid nanoparticles. Advanced drug delivery reviews, 59(6), 491-504.
40. Naziris, N., & Demetzos, C. (2022). Lipid nanoparticles as platforms for theranostic purposes: recent advances in the field. Journal of Nanotheranostics, 3(2), 86-101.
41. Andra, V. V. S. N. L., Pammi, S. V. N., Bhatraju, L. V. K. P., & Ruddaraju, L. K. (2022). A comprehensive review on novel liposomal methodologies, commercial formulations, clinical trials and patents. BioNanoScience, 12(1), 274-291.
42. Almeida, A. J., & Souto, E. (2007). Solid lipid nanoparticles as a drug delivery system for peptides and proteins. Advanced drug delivery reviews, 59(6), 478-490.
43. Böttger, R., Pauli, G., Chao, P. H., Fayez, N. A., Hohenwarter, L., & Li, S. D. (2020). Lipid-based nanoparticle technologies for liver

targeting. Advanced drug delivery reviews, 154, 79-101.
44. Charron, D. M., Chen, J., & Zheng, G. (2015). Theranostic lipid nanoparticles for cancer medicine. Nanotechnology-based precision tools for the detection and treatment of cancer, 103-127.
45. Geszke-Moritz, M., & Moritz, M. (2016). Solid lipid nanoparticles as attractive drug vehicles: Composition, properties and therapeutic strategies. Materials Science and Engineering: C, 68, 982-994.
46. Fan, Y., Marioli, M., & Zhang, K. (2021). Analytical characterization of liposomes and other lipid nanoparticles for drug delivery. Journal of pharmaceutical and biomedical analysis, 192, 113642.
47. Harde, H., Das, M., & Jain, S. (2011). Solid lipid nanoparticles: an oral bioavailability enhancer vehicle. Expert opinion on drug delivery, 8(11), 1407-1424.
48. Iqbal, M. A., Md, S., Sahni, J. K., Baboota, S., Dang, S., & Ali, J. (2012). Nanostructured lipid carriers system: recent advances in drug delivery. Journal of drug targeting, 20(10), 813-830.
49. Patra, J. K., Das, G., Fraceto, L. F., Campos, E. V. R., Rodriguez-Torres, M. D. P., Acosta-Torres, L. S., ... & Shin, H. S. (2018). Nano based drug delivery systems: recent developments and future prospects. Journal of nanobiotechnology, 16(1), 1-33.
50. Handa, M., Beg, S., Shukla, R., Barkat, M. A., Choudhry, H., & Singh, K. K. (2021). Recent advances in lipid-engineered multifunctional nanophytomedicines for cancer targeting. Journal of Controlled Release, 340, 48-59.
51. Müller, R. H., Mäder, K., & Gohla, S. (2000). Solid lipid nanoparticles (SLN) for controlled drug delivery–a review of the state of the art. European journal of pharmaceutics and biopharmaceutics, 50(1), 161-177.
52. Scioli Montoto, S., Muraca, G., & Ruiz, M. E. (2020). Solid lipid nanoparticles for drug delivery: pharmacological and biopharmaceutical aspects. Frontiers in molecular biosciences, 7, 319.
53. Has, C., & Sunthar, P. (2020). A comprehensive review on recent preparation techniques of liposomes. Journal of liposome research, 30(4), 336-365.
54. Tom, S., Gowda, D. V., Manjunath, M., Koshy, T. M., Karunakar, G., & Srivastava, A. (2016). Solid Lipid Nanoparticles-A Breakthrough In Novel Drug Delivery System. Amer J Pharm Res, 6, 131-146.
55. Ghan, R. C. (2020). Nanoparticulate treatments for oral delivery. Drug Delivery Trends, 103-122.
56. Seyfoddin, A., Shaw, J., & Al-Kassas, R. (2010). Solid lipid nanoparticles for ocular drug delivery. Drug delivery, 17(7), 467-489.
57. Blasi, P., Giovagnoli, S., Schoubben, A., Ricci, M., & Rossi, C. (2007). Solid lipid nanoparticles for targeted brain drug delivery. Advanced drug delivery reviews, 59(6), 454-477.
58. Allen, T. M., & Cullis, P. R. (2013). Liposomal drug delivery systems: from concept to clinical applications. Advanced drug delivery reviews, 65(1), 36-48.
59. Beloqui, A., Solinís, M. Á., Rodríguez-Gascón, A., Almeida, A. J., & Préat, V. (2016). Nanostructured lipid carriers: Promising drug delivery systems for future clinics. Nanomedicine: Nanotechnology, biology and medicine, 12(1), 143-161.
60. Sujeevan, O. (2023). Comprehensive review on nano drug delivery systems bioanalysis. GSC Advanced Research and Reviews, 14(1), 127-140.
61. Birajdar, G. O., Kadam, V. S., Chintale, A. G., Halle, P. D., Nabde, M. K., & Maske, K. S. (2013). A Comprehensive review on

nanotechnology. Research Journal of Pharmacy and Technology, 6(5), 486-495.
62. Fang, C. L., A Al-Suwayeh, S., & Fang, J. Y. (2013). Nanostructured lipid carriers (NLCs) for drug delivery and targeting. Recent patents on nanotechnology, 7(1), 41-55.
63. Muchow, M., Maincent, P., & Müller, R. H. (2008). Lipid nanoparticles with a solid matrix (SLN®, NLC®, LDC®) for oral drug delivery. Drug development and industrial pharmacy, 34(12), 1394-1405.
64. Filipczak, N., Pan, J., Yalamarty, S. S. K., & Torchilin, V. P. (2020). Recent advancements in liposome technology. Advanced drug delivery reviews, 156, 4-22.
65. Yeh, Y. C., Huang, T. H., Yang, S. C., Chen, C. C., & Fang, J. Y. (2020). Nano-based drug delivery or targeting to eradicate bacteria for infection mitigation: a review of recent advances. Frontiers in chemistry, 8, 286.
66. Kalhapure, R. S., Suleman, N., Mocktar, C., Seedat, N., & Govender, T. (2015). Nanoengineered drug delivery systems for enhancing antibiotic therapy. Journal of pharmaceutical sciences, 104(3), 872-905.
67. Poonia, M., Ramalingam, K., Goyal, S., & Sidhu, S. K. (2017). Nanotechnology in oral cancer: A comprehensive review. Journal of oral and maxillofacial pathology: JOMFP, 21(3), 407.
68. Namiki, Y., Fuchigami, T., Tada, N., Kawamura, R., Matsunuma, S., Kitamoto, Y., & Nakagawa, M. (2011). Nanomedicine for cancer: lipid-based nanostructures for drug delivery and monitoring. Accounts of chemical research, 44(10), 1080-1093.
69. Paliwal, R., Paliwal, S. R., Kenwat, R., Kurmi, B. D., & Sahu, M. K. (2020). Solid lipid nanoparticles: A review on recent perspectives and patents. Expert opinion on therapeutic patents, 30(3), 179-194.
70. Pearce, T. R., Shroff, K., & Kokkoli, E. (2012). Peptide targeted lipid nanoparticles for anticancer drug delivery. Advanced materials, 24(28), 3803-3822.
71. Ensign, L. M., Cone, R., & Hanes, J. (2012). Oral drug delivery with polymeric nanoparticles: the gastrointestinal mucus barriers. Advanced drug delivery reviews, 64(6), 557-570.
72. Agrawal, S., Garg, A., & Varshney, V. (2022). Recent updates on applications of Lipid-based nanoparticles for site-specific drug delivery. Pharmaceutical Nanotechnology, 10(1), 24-41.
73. Müller, R. H., Petersen, R. D., Hommoss, A., & Pardeike, J. (2007). Nanostructured lipid carriers (NLC) in cosmetic dermal products. Advanced drug delivery reviews, 59(6), 522-530.
74. Gordillo-Galeano, A., & Mora-Huertas, C. E. (2018). Solid lipid nanoparticles and nanostructured lipid carriers: A review emphasizing on particle structure and drug release. European Journal of Pharmaceutics and Biopharmaceutics, 133, 285-308.
75. Ghasemiyeh, P., & Mohammadi-Samani, S. (2018). Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems: Applications, advantages and disadvantages. Research in pharmaceutical sciences, 13(4), 288.

HOW TO CITE: Nihar Ranjan Kar, Advancements In Lipid Nanoparticles For Enhanced Drug Delivery: A Comprehensive Review, Int. J. in Pharm. Sci., 2023, Vol 1, Issue 9, 95-115. https://doi.org/10.5281/zenodo.8328533