

# A Review on Liposome and Niosome as Novel Drug Delivery Carrier

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**Abstract:** *Rapid advancements in drug delivery technologies have increased medication safety, therapeutic efficacy, and patient compliance. Liposomes and niosomes are two types of nanocarriers that have garnered a lot of interest because of their special capacity to encapsulate hydrophilic and lipophilic medications, shield them from deterioration, and allow for regulated and targeted release. Liposomes are phospholipid-based vesicles that are very biocompatible and adaptable in pharmacological applications because they closely mimic biological membranes. In contrast to liposomes, niosomes are vesicular systems made of cholesterol and nonionic surfactants that have superior chemical stability, lower production costs, and easier storage. Both carriers have been investigated in a variety of therapeutic domains, such as transdermal applications, infectious disease treatment, cancer treatment, and vaccine delivery. Their extensive clinical usage is nevertheless restricted by obstacles including large-scale manufacture, stability concerns, and regulatory approval, despite their encouraging promise. To get over these obstacles, current research is concentrating on hybrid vesicles, stimuli-responsive formulations, and surface changes. The structural characteristics, methods of synthesis, relative benefits, and uses of liposomes and niosomes are highlighted in this study. Recent developments and prospects for the development of these nanocarriers as efficient instruments for contemporary drug administration are also covered.*

**Keywords:** Liposomes, Niosomes, Nanocarriers, Drug delivery systems, Targeted drug delivery, Controlled release, Biocompatibility, Encapsulation efficiency, Surfactant-based vesicles, Therapeutic application

## I. INTRODUCTION

### Overview of drug delivery systems:

Over the past few decades, the field of pharmaceuticals has undergone a remarkable transformation, with drug delivery systems emerging as one of the most dynamic areas of research and development. Drug delivery refers to the technique of administering therapeutic agents in a manner that maximizes efficacy while minimizing adverse effects. Conventional delivery methods such as tablets, capsules, and injections, although widely used, often suffer from several limitations, including systemic toxicity, nonspecific drug distribution, rapid metabolism, low bioavailability, and the need for frequent dosing. Many drugs also undergo first-pass metabolism extensive hepatic or gastrointestinal degradation before reaching systemic circulation which reduces therapeutic efficiency and necessitates higher doses that may cause side effects. These challenges have prompted researchers to develop novel drug delivery systems (NDDS) that improve stability, solubility, selectivity, and bioavailability [1].

Traditional delivery systems such as oral, parenteral, and topical formulations remain the cornerstone of therapy but often fail to provide site-specific or sustained drug release. In contrast, NDDS aim to optimize pharmacokinetics and pharmacodynamics by controlling the rate, duration, and target site of drug release. Systems such as nanoparticles, liposomes, niosomes, dendrimers, polymeric micelles, and nanogels have been developed to achieve sustained release, reduced toxicity, and improved therapeutic outcomes [2]. These advanced systems are especially valuable given that about 40% of newly developed drugs suffer from poor solubility, which limits absorption and bioavailability.



Furthermore, macromolecular drugs like peptides, proteins, and nucleic acids are prone to enzymatic degradation, making conventional delivery ineffective. Liposomes and niosomes, in particular, have gained attention for their ability to enhance bioavailability and protect sensitive drugs from degradation [3].

Vesicular systems, including liposomes (phospholipid-based vesicles) and niosomes (cholesterol and nonionic surfactant-based vesicles), are among the most promising NDDS due to their biocompatibility and ability to encapsulate both hydrophilic and lipophilic drugs. While liposomes offer excellent biocompatibility, niosomes are comparatively more stable, economical, and suitable for large-scale production [4]. Targeted drug delivery either through passive mechanisms such as the enhanced permeability and retention (EPR) effect or active targeting using ligands like peptides or antibodies further improves site-specific delivery and minimizes systemic side effects [5].

Innovative drug delivery systems have demonstrated significant success across multiple therapeutic areas. Liposomal formulations of anticancer drugs like (doxorubicin) and (daunorubicin) have achieved superior safety and efficacy compared to conventional drugs. Similarly, liposomes and niosomes serve as effective carriers in vaccines, dermatological preparations, and even in targeting neurological disorders by enhancing blood–brain barrier penetration [6].

#### Rationale for using nanocarriers in modern pharmaceuticals:

The development of novel drug delivery systems (NDDS) has transformed pharmaceutical sciences by addressing the limitations of traditional dosage forms such as tablets, capsules, and injections. Conventional systems, though effective, often suffer from low bioavailability, rapid clearance, non-specific distribution, and dose-related toxicity. To overcome these issues, researchers have developed nanocarrier-based drug delivery systems, which employ nanoscale materials (1–1000 nm) possessing a high surface area, adjustable surface properties, and the ability to encapsulate various drugs, thereby enhancing therapeutic performance [7]. Nanocarriers significantly improve the solubility and bioavailability of poorly water-soluble drugs an issue affecting nearly 40–60% of new compounds. Systems such as liposomes, polymeric micelles, and solid lipid nanoparticles enhance dissolution and absorption of drugs like amphotericin B and paclitaxel, improving efficacy [8]. They also protect labile drugs (proteins, peptides, nucleic acids) from enzymatic degradation, as seen with liposomal amphotericin B, which enhances stability and reduces toxicity, and niosomal insulin formulations offering sustained release. Furthermore, nanocarriers enable targeted and controlled drug delivery through passive and active targeting, improving drug accumulation at specific sites and reducing systemic toxicity. Stimuli-responsive nanocarriers, which release drugs in response to environmental triggers such as pH or temperature, represent a promising step toward intelligent, site-specific therapies [9].

#### Importance of liposomes and niosomes:

Liposomes and niosomes are among the most studied nanocarrier systems due to their vesicular structure and ability to encapsulate diverse therapeutic agents. Liposomes, composed of phospholipid bilayers, are biocompatible and biodegradable, with clinically approved formulations like Doxil®, AmBisome®, and DepoCyt® used in cancer, infection control, and vaccine delivery, though they face stability and cost challenges. Niosomes, formed from cholesterol and nonionic surfactants, offer greater chemical stability, lower production costs, and enhanced transdermal and mucosal penetration. Both systems improve bioavailability, reduce toxicity, and enable targeted, controlled drug release, forming the foundation for next-generation smart delivery systems [10].

Table 1: Key Features and Importance of Liposomes vs. Niosomes [11]

Feature/Aspect	Liposomes	Niosomes
Basic Structure	Vesicles of phospholipid bilayers	Vesicles of nonionic surfactants + cholesterol
Biological Similarity	High mimic natural cell membranes	Moderate do not fully resemble membranes
Stability	Relatively unstable (prone to oxidation,	More stable chemically and physically



	leakage)	
Cost of Production	Expensive (phospholipids are costly, need special handling)	Cost-effective (nonionic surfactants are cheaper & stable)
Encapsulation Ability	Both hydrophilic and lipophilic drugs	Both hydrophilic and lipophilic drugs
Clinical Use	Several FDA-approved formulations available	Mostly in preclinical/clinical research stage
Applications	Cancer therapy, antifungals, vaccines, CNS drug delivery	Transdermal, ocular, oral, parenteral, vaccine delivery
Commercial Examples	Doxil®, AmBisome®, DepoCyt®	No major FDA-approved marketed product yet

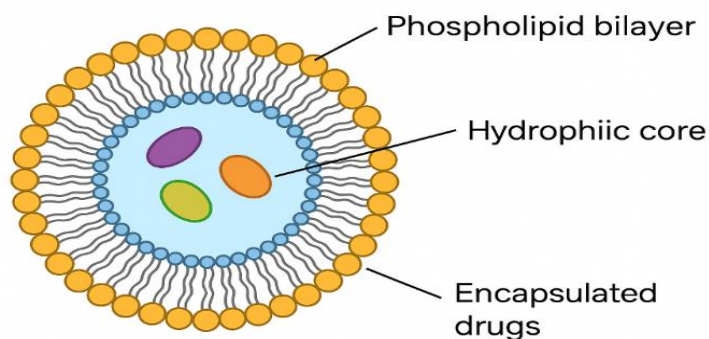
### 1. Liposomes: Structure and Applications:

#### Historical background and development:

Liposomes are among the most extensively studied and therapeutically effective drug delivery systems in modern pharmaceuticals. Discovered in the early 1960s by Alec D. Bangham and colleagues at the Babraham Institute (UK), liposomes were found to form spontaneously from phospholipids in water, creating bilayer vesicles capable of encapsulating aqueous solutions—mimicking biological membranes. Initially used to study membrane behavior, liposomes soon gained recognition for their ability to encapsulate both hydrophilic and lipophilic drugs, enhancing pharmacokinetics and reducing systemic toxicity. The 1970s–1980s saw rapid advances in lipid chemistry and formulation, leading to the development of multilamellar (MLVs), large unilamellar (LUVs), and small unilamellar vesicles (SUVs), which improved control over drug loading and release. In the 1990s, the introduction of PEGylated “stealth liposomes” marked a major breakthrough, extending circulation time and enabling enhanced permeability and retention (EPR)–based targeting in tumors. The FDA approval of Doxil® (liposomal doxorubicin) in 1995 demonstrated their clinical success in cancer therapy. Subsequent decades brought innovations such as ligand-targeted and stimuli-responsive (“smart”) liposomes, which improve site-specific delivery and controlled release. Recently, liposomes have become vital in vaccine and mRNA delivery, including during the COVID-19 pandemic, showcasing their versatility and growing importance in precision medicine [12].

Composition and structural organization:

Fig.1: Schematic of a unilamellar liposome showing the phospholipid bilayer, hydrophilic core, and encapsulated drugs [14].



Liposomes are spherical vesicles primarily composed of phospholipids, which possess both hydrophilic heads and hydrophobic tails. In aqueous media, these amphiphilic molecules self-assemble into bilayer structures, forming vesicles with an aqueous core enclosed by one or more lipid bilayers. This unique structure allows liposomes to



encapsulate both hydrophilic drugs (in the core) and lipophilic drugs (in the bilayer), making them highly versatile delivery systems [13].

Cholesterol is commonly incorporated into liposomal bilayers to enhance stability, rigidity, and drug retention. It fills gaps between phospholipids, reducing membrane permeability, preventing vesicle aggregation, and minimizing premature drug leakage. The cholesterol-to-phospholipid ratio is a key factor influencing membrane fluidity and controlled release. Liposomes are also categorized by size and bilayer number: multilamellar vesicles (MLVs) contain multiple layers (0.1–10  $\mu\text{m}$ ), while small unilamellar vesicles (SUVs) (20–100 nm) and large unilamellar vesicles (LUVs) (>100 nm) have single bilayers. The vesicle type selected depends on the drug properties and therapeutic application [15].

Table 2: Common Components of Liposomes and Their Functions [16]:

Component	Function	Examples
Phospholipids	Form bilayer structure, encapsulate drugs	Phosphatidylcholine, phosphatidylethanolamine
Cholesterol	Stabilizes bilayer, reduces drug leakage	Cholesterol
Hydrophilic polymer	Evade immune system, prolong circulation	Polyethylene glycol (PEG)
Targeting ligands	Enable active targeting to specific cells/tissues	Antibodies, peptides, folic acid
Charge modifiers	Adjust surface charge, improve stability	Stearylamine (positive), phosphatidylserine (negative)

#### Methods of preparation:

**Thin-Film Hydration Method:** The thin-film hydration approach is among the most popular ways to produce liposomes. This method creates a thin, homogeneous lipid layer on the inside of a round-bottom flask by first dissolving lipids in an organic solvent and then evaporating the solvent, usually at lower pressure. Liposomes are created spontaneously when this dried lipid film is then moistened with an aqueous solution. Depending on the intended use, methods like sonication or extrusion can be used to further alter the size and lamellarity of the resultant vesicles.

**Reverse-Phase Evaporation Method:** The reverse-phase evaporation process is another way to manufacture liposomes. This technique creates a water-in-oil emulsion by dissolving lipids in an organic solvent first, then adding an aqueous phase that contains the medication. The production of liposomes with a comparatively high internal aqueous volume follows the progressive removal of the organic solvent under decreased pressure. Because it gives a better encapsulation efficiency than certain other approaches, this technology is especially helpful for encapsulating hydrophilic medicines.

**Ethanol Injection Method:** The ethanol injection approach is another popular way for making liposomes. A lipid-alcohol solution typically ethanol is quickly injected into an aqueous phase while being continuously stirred in this procedure. Liposome production results from the spontaneous self-assembly of lipids into bilayer vesicles caused by the abrupt dilution of ethanol in water. For thermolabile medications, this approach is appropriate since it is straightforward, repeatable, and does not require high temperatures. The partial elimination of leftover ethanol, which might compromise medication safety and liposome stability, is one drawback.

**Supercritical Fluid Method:** A more recent method for creating liposomes is the supercritical fluid method, which uses supercritical carbon dioxide ( $\text{CO}_2$ ) as a lipid solvent. This method creates liposomes on their own by dissolving lipids in supercritical  $\text{CO}_2$  and then quickly expanding them into an aqueous phase. Since it does not need the use of hazardous organic solvents and makes it simple to remove  $\text{CO}_2$  following liposome synthesis, this technique is regarded as ecologically benign. It is a potential method for large-scale manufacturing since it also provides high control over particle size and scalability.



**Sonication:** One of the oldest and most basic methods for creating tiny liposomes is the sonication method. This technique breaks apart bigger vesicles and breaks them down into tiny liposomes by applying high-frequency sound waves to lipid solutions. This procedure can increase the encapsulation efficiency of some medications and assist produce more consistent vesicle sizes. The technique does have several drawbacks, though, including the possibility of sensitive bioactive chemicals degrading as a result of the heat and shear stress produced during sonication and the possibility of contamination from the probe tip when utilizing probe-type sonicators.[17].

**Extrusion:** One popular approach for creating liposomes with a consistent size distribution is extrusion. This method uses pressure to repeatedly push liposome solutions through polycarbonate membranes with predetermined pore diameters. Larger vesicles are broken down mechanically, producing liposomes with a regulated and repeatable size, usually in the nanometer range. After liposomes are formed using conventional techniques (such thin-film hydration), extrusion is frequently used to increase uniformity and refine particle size, two important aspects for drug delivery applications. However, due to equipment and time restrictions, it might not be appropriate for large-scale manufacturing.

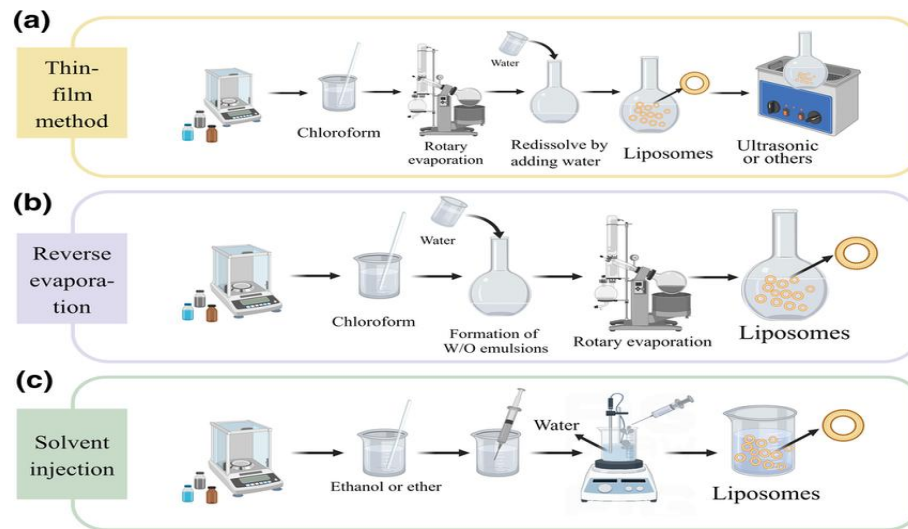


Fig. 2: Method of Preparation of Liposome [18].

#### Mechanism of drug encapsulation and release:

Liposomes and niosomes encapsulate both hydrophilic and hydrophobic drugs, enhancing bioavailability, stability, and therapeutic efficacy. Hydrophobic drugs integrate into the bilayer, while hydrophilic ones reside in the aqueous core. Vesicle structure and drug properties including size, lamellarity, solubility, and polarity significantly influence encapsulation efficiency and release behavior.

#### Encapsulation Mechanisms:

Liposomes, spherical using ion or pH gradients to drive drug loading. Similarly, niosomes, composed of cholesterol and nonionic surfactants, encapsulate drugs based on their amphiphilic nature. The type and concentration of surfactants, cholesterol ratio, and preparation method influence encapsulation efficiency. Optimizing these parameters is essential to achieve high drug loading, controlled release, and enhanced therapeutic performance [19].



## MECHANISM OF DRUG ENCAPSULATION AND RELEASE

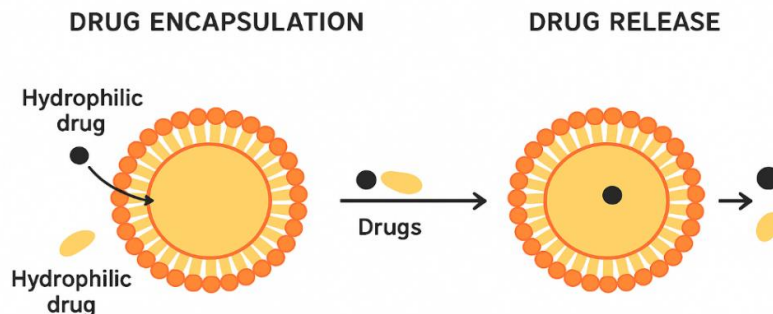


Fig.3: Mechanism of drug encapsulation and release [20].

### Release Mechanisms:

Drug release from liposomes and niosomes occurs either passively through diffusion or in response to external stimuli. Passive release depends on drug properties, vesicle size, and membrane composition. Stimuli-responsive vesicles can release drugs under specific conditions like pH, temperature, light, or enzymatic activity. For example, pH-sensitive liposomes effectively target tumors or inflamed tissues, while light-sensitive vesicles allow spatial and temporal control of delivery. In niosomes, surfactant type and additives affecting bilayer permeability influence release rates. Incorporating specific polymers or surfactants can modulate bilayer stability, enabling controlled and sustained drug release tailored to therapeutic requirements [21].

### Applications in drug delivery and therapeutics:

Vesicular nanocarriers like liposomes and niosomes have revolutionized drug delivery by improving bioavailability, stability, and controlled release of therapeutics. Their amphiphilic nature enables encapsulation of both hydrophilic and hydrophobic drugs. These systems find broad applications in transdermal delivery, gene therapy, cancer treatment, and vaccine development, demonstrating significant clinical potential.

### Cancer Therapy:

Liposomes enable targeted cancer therapy by encapsulating chemotherapeutic drugs and delivering them selectively to tumor tissues through ligand-based active targeting, reducing systemic toxicity. Doxorubicin-loaded liposomes show enhanced efficacy and fewer side effects. Niosomes, composed of cholesterol and nonionic surfactants, offer cost-effective, stable, and efficient alternatives for safe cancer drug delivery [22].

### Gene Delivery:

Liposomes and niosomes serve as efficient non-viral gene delivery systems by encapsulating DNA or RNA. Cationic liposomes electrostatically bind negatively charged nucleic acids, enhancing encapsulation and uptake. Their bilayer fusion with cell membranes enables cytoplasmic release, facilitating gene therapy for cancer, genetic disorders, and other diseases [23].

### Vaccine Development:

Liposomes and niosomes act as effective vaccine adjuvants and delivery systems by encapsulating antigens and mimicking natural infections to enhance humoral and cellular immunity. Liposomal hepatitis B vaccines show strong immune responses, while niosomes offer stable, low-cost alternatives for antigen delivery and immunostimulant in vaccine development [24].



### **Transdermal Drug Delivery:**

Liposomes and niosomes enhance transdermal drug delivery by improving penetration through the stratum corneum. Niosomes, in particular, increase drug solubility, stability, and skin permeation. Studies demonstrate effective niosomal delivery of drugs like diclofenac and ketoconazole, providing a non-invasive, patient-friendly alternative for systemic therapy via the skin .

Ocular Drug Delivery: Liposomes and niosomes overcome ocular barriers by enhancing drug absorption and retention in eye tissues. They encapsulate both hydrophilic and lipophilic drugs for sustained release, reducing dosing frequency. Their stability, biocompatibility, and cost-effectiveness make them promising for treating glaucoma, macular degeneration, and other ocular diseases.

### **Pulmonary Drug Delivery:**

Liposomes and niosomes enable efficient pulmonary drug delivery by targeting lung tissues directly through inhalation. Liposomal antibiotics enhance drug retention and reduce systemic toxicity, while niosomal formulations deliver anti-inflammatory drugs for asthma and COPD, offering localized effects, improved stability, and better therapeutic outcomes in respiratory disease management.

### **iv) Limitations and challenges:**

Despite their significant therapeutic potential, liposomes and niosomes face several challenges that limit their broad clinical application. One major issue is stability. Liposomes, composed of phospholipid bilayers, are prone to oxidative and hydrolytic degradation, leading to vesicle instability and drug leakage over time. Although niosomes exhibit greater chemical stability due to non-ionic surfactants, they can still experience aggregation, fusion, or drug leakage during storage. Both systems often suffer from low encapsulation efficiency, particularly for hydrophilic drugs, which can reduce therapeutic efficacy during preparation or prolonged storage .

Another limitation is scalability and reproducibility. Laboratory-scale techniques such as thin-film hydration or reverse-phase evaporation are difficult to replicate on an industrial scale while maintaining consistent vesicle characteristics. The high production cost especially for liposomes requiring sterile environments and high-purity phospholipids further restricts commercialization. Moreover, conventional liposomes are rapidly cleared by the reticuloendothelial system (RES), reducing circulation time and drug bioavailability. While PEGylation can extend their half-life, it adds complexity and cost. Similarly, poorly formulated niosomes may also be cleared quickly. Finally, toxicity and immunogenicity must be considered. Repeated liposome administration may provoke immune responses, while certain surfactants used in niosomes can exhibit cytotoxic effects depending on concentration and formulation conditions [25].

## **2.Niosomes: Structure and Applications:**

### **Origin and concept of niosomes:**

Niosomes, introduced in the late 1970s and early 1980s, are non-ionic surfactant-based vesicular systems developed as stable, cost-effective alternatives to liposomes for drug delivery. Composed of non-ionic surfactants and cholesterol, they form bilayer vesicles capable of encapsulating both hydrophilic and lipophilic drugs . Their development aimed to overcome liposomal limitations such as high production cost, oxidative degradation, and chemical instability. Initially studied by L'Oréal for cosmetic applications, niosomes were later adapted for pharmaceutical use due to their ability to enhance drug stability, bioavailability, and targeted release. Their amphiphilic nature allows self-assembly into bilayers in aqueous environments, while parameters like surfactant type, cholesterol ratio, and preparation method enable customization of vesicle size, encapsulation efficiency, and release characteristics. This adaptability makes niosomes highly suitable for diverse routes of administration oral, ophthalmic, transdermal, and parenteral and valuable in controlled and site-specific drug delivery systems [26].

### **Composition and types of nonionic surfactants:**

Niosomes are vesicular systems composed mainly of non-ionic surfactants and cholesterol, forming bilayers that encapsulate both hydrophilic and hydrophobic drugs. Their composition critically influences stability, encapsulation efficiency, vesicle size, and drug release, allowing optimization for specific therapeutic applications through precise selection of surfactant type and cholesterol ratio.[27].



The primary components of niosomes are:

Non-ionic surfactants are amphiphilic molecules that self-assemble into bilayer structures in aqueous environments. They are preferred for niosomes due to their low toxicity, biodegradability, and chemical stability. The choice of surfactant significantly affects vesicle size, stability, encapsulation efficiency, and drug release behavior, making it crucial for optimized formulations.

Spans (sorbitan esters), such as Span 20, 40, 60, and 80, are widely used non-ionic surfactants in niosome preparation, derived from sorbitol and fatty acids. Span 60 is favored for its high phase transition temperature, forming stable, low-permeability vesicles with enhanced encapsulation efficiency, sustained release, and improved drug retention.

Tweens (Polysorbates): Commonly used in niosome formulations, Tweens (polysorbates) are hydrophilic derivatives of Spans and include Tween 20, Tween 40, Tween 60, and Tween 80. They have polyoxyethylene chains that make the surfactant more hydrophilic, which affects the stability, size, and effectiveness of drug encapsulation. The niosomal formulation's Tween type and ratio may be changed to customize the vesicles' characteristics for certain drug delivery uses.

Brij series surfactants: (polyoxyethylene alkyl ethers), including Brij 30, 58, and 72, are used in niosomal formulations to adjust vesicle size, stability, and drug encapsulation efficiency. Their variable alkyl chain length and ethylene oxide content allow precise optimization for specific therapeutic applications [28].

#### **Cholesterol:**

Cholesterol is an essential component of niosomes, enhancing bilayer rigidity, stability, and drug retention while reducing membrane permeability. The cholesterol-to-surfactant ratio is critical; excess causes bilayer disruption, whereas deficiency leads to leaky vesicles. Optimizing this ratio ensures high encapsulation efficiency, controlled release, and improved vesicle stability[29].

Types of Non-Ionic Surfactants in Niosomes:

Non-ionic surfactants used in niosome formulations are classified by ethoxylation degree, HLB value, and hydrophobic chain properties, influencing niosome stability, self-assembly, encapsulation efficiency, vesicle size, and drug release.

Sorbitan esters (Spans) with low HLB values (4–8) form rigid, stable niosomes ideal for encapsulating and controlled release of hydrophobic drugs.

Polysorbates (Tweens) with high HLB values (14–16) are mixed with Spans to enhance hydrophilic drug encapsulation, increase aqueous core capacity, and improve vesicle flexibility and stability in niosomal formulations.

Polyoxymethylene alkyl ethers (Brij) with medium HLB values (8–18) allow fine-tuning of niosomal properties, enabling balanced encapsulation of hydrophilic and hydrophobic drugs by adjusting vesicle size, membrane fluidity, and release behavior.

Other non-ionic surfactants like Pluronic block copolymers and PEG derivatives enhance niosome stability, provide stealth properties, extend circulation time, and allow precise control over vesicle size, encapsulation efficiency, and drug release.

#### **Methods of preparation:**

**Thin-Film Hydration Method (Hand-Shaking Method):** The thin-film hydration method forms niosomes by dissolving surfactants and cholesterol in an organic solvent, evaporating it to form a thin film, and hydrating it with a drug-containing aqueous solution.

Because of its ease of use, repeatability, and capacity to encapsulate both hydrophilic and lipophilic medications, this technique is often employed and provides efficient control over vesicle size by subsequent sonication or extrusion [30].

**Reverse-Phase Evaporation Method:**

The reverse-phase evaporation method forms niosomes by dissolving cholesterol and surfactants in an organic solvent and emulsifying with an aqueous drug solution. After solvent removal under reduced pressure, unilamellar vesicles with high encapsulation efficiency are obtained, ideal for hydrophilic drugs requiring substantial loading despite being more labor-intensive.



**Ether Injection Method:**

In the ether injection method, cholesterol and surfactants dissolved in diethyl ether are slowly injected into a heated aqueous drug solution. Vesicles form as ether evaporates, yielding small unilamellar vesicles suitable for injectables, though residual solvent may cause toxicity concerns.

**Sonication Method:**

Small unilamellar vesicles (SUVs) are created by sonication from multilamellar vesicles (MLVs), which are usually made via thin-film hydration. By using either probe or bath sonication, this method creates homogenous preparations with a narrow size distribution and decreases vesicle size. However, if the encapsulated chemical is susceptible to heat or shear stress, sonication may cause drug degradation.

**Heating Method:**

To create niosomes, the heating process entails hydrating cholesterol and surfactant with an aqueous drug solution at high temperatures while stirring constantly. Bilayer vesicles develop on their own when the mixture cools. This method is especially appropriate for medications that are thermally stable, is rather easy to use, and does not require organic solvents.

**Ethanol Injection Method:**

By dissolving cholesterol and surfactant in ethanol, the medication is quickly delivered into an aqueous phase using the ethanol injection technique. Niosomal vesicles spontaneously develop when the ethanol rapidly diffuses into the water. This process creates tiny, uniformly sized vesicles quickly and scalable. To prevent toxicity, leftover ethanol must be carefully removed.

**Mechanism of drug encapsulation and release:**

Niosomes, like liposomes, are vesicular systems of cholesterol and non-ionic surfactants encapsulating hydrophilic and hydrophobic drugs. Drug encapsulation and release depend on bilayer structure, composition, and physicochemical drug properties such as solubility and charge

**Mechanism of Drug Encapsulation:**

Niosomes encapsulate drugs through self-assembly of surfactant molecules into bilayer vesicles, entrapping hydrophilic drugs in the aqueous core and hydrophobic drugs in the bilayer, enabling versatile drug delivery applications.

**Passive Loading:** In passive encapsulation, drugs present during vesicle formation become trapped within niosomes. Though simple, this method often shows low encapsulation efficiency for hydrophilic drugs, leaving much untrapped in the surrounding medium.

**Active Loading:** Active loading uses transmembrane ion gradients (pH or ammonium sulfate) to load weak acids or bases into niosomes, enhancing encapsulation efficiency. Drug trapping occurs via ionization. Encapsulation depends on surfactant type, cholesterol content, solubility, and vesicle size cholesterol stabilizes the bilayer and reduces leakage [31].

**Mechanism of Drug Release:**

Drugs that are contained within niosomes may be released by stimuli-triggered processes, diffusion, or bilayer destabilization:

**Passive Diffusion:** Drugs are released from niosomes mainly by passive diffusion, influenced by solubility, vesicle size, membrane rigidity, and cholesterol content higher cholesterol improves bilayer stability, slowing diffusion and reducing drug release.

**Bilayer Destabilization:** Drugs can also be released from niosomes through bilayer instability caused by interactions with biological membranes, surfactant exchange, or enzymatic degradation. Factors like surfactant type, vesicle composition, and biological environment influence the extent of destabilization and subsequent drug leakage.[32].

Applications in drug delivery and therapeutics:

Liposomes and niosomes, with their amphiphilic bilayer structures, encapsulate both hydrophilic and hydrophobic drugs, offering biocompatible, customizable, and versatile platforms for targeted and controlled drug delivery applications.



**Cancer Therapy:**

Liposomes and niosomes enhance cancer therapy by improving drug targeting and minimizing systemic toxicity. Through the EPR effect and ligand-based active targeting, drugs like doxorubicin, cisplatin, and paclitaxel show increased efficacy, stability, and controlled release with reduced side effects, offering safer, more efficient cancer treatment strategies.

**Gene and Nucleic Acid Delivery:**

Liposomes and niosomes efficiently deliver genetic material by encapsulating negatively charged DNA or RNA, protecting it from enzymatic degradation, enhancing cellular uptake, and promoting gene expression, offering safer, less immunogenic, and effective non-viral gene therapy alternatives to viral vectors.

**Vaccine Delivery:**

Liposomes and niosomes act as efficient adjuvants in vaccine delivery by encapsulating antigens, mimicking natural infections, and enhancing immune responses. Niosomes offer stable, affordable alternatives, especially for influenza and hepatitis B vaccines, while improving humoral and cellular immunity when combined with immunostimulatory agents [33].

**Transdermal and Topical Drug Delivery:**

Liposomes and niosomes enhance transdermal drug delivery by improving penetration through the stratum corneum. Niosomes, in particular, enable controlled release, greater stability, and reduced irritation, making them ideal for non-invasive delivery of analgesic, antifungal, and anti-inflammatory drugs with improved therapeutic effectiveness.

**Ocular Drug Delivery:**

Ocular drug delivery is enhanced by liposomes and niosomes, which improve corneal penetration and provide sustained release. Their ability to encapsulate hydrophilic and lipophilic drugs aids in treating glaucoma and macular degeneration, while niosomes offer superior stability and prolonged retention for better patient compliance.

**Pulmonary Drug Delivery:**

Inhalable liposomes and niosomes enable direct pulmonary drug delivery, enhancing treatment for asthma, COPD, and lung infections. Their encapsulation offers controlled release, protection from enzymatic degradation, and reduced systemic toxicity, improving therapeutic efficacy and safety in respiratory disease management.

**Other Applications:**

Beyond common uses, liposomes and niosomes enable targeted delivery of hormones, peptides, and antimicrobial drugs. Their stimuli-responsive systems release drugs under specific physiological conditions, enhancing therapeutic precision and effectiveness[34].

**iv) Limitations and challenges:**

Although niosomes and liposomes have several benefits as drug delivery vehicles, a number of drawbacks and difficulties may limit their use in clinical settings.

**Stability:**

Because liposomes are made of phospholipid bilayers, they are susceptible to hydrolysis and oxidative deterioration, which can result in medication leakage and a shorter shelf life. Despite having non-ionic surfactants that make them chemically more stable, niosomes can nevertheless aggregate, fuse, or leak, especially when stored under different circumstances.

**Encapsulation Efficiency and Drug Leakage:**

Drugs that are hydrophilic and confined in the aqueous core may diffuse out during delivery or storage, decreasing the effectiveness of treatment. The kind of surfactant, the amount of cholesterol, and the manner of production all affect how well niosomes encapsulate [35].



**Toxicity and Immunogenicity:**

Despite being typically biocompatible, liposomes or niosomes might cause immunological reactions, such as hypersensitivity reactions and rapid blood clearance, when administered repeatedly. At greater quantities, some surfactants that are used in niosomes may potentially be harmful.

**Targeting and Controlled Release:**

While smart liposomes and niosomes show promise, regulatory approval and clinical translation remain difficult due to formulation complexity and reproducibility issues. Careful surface modification, ligand attachment, or stimuli-responsive designs are necessary to achieve precise drug targeting without affecting healthy tissues.

Comparative Analysis: Liposomes vs. Niosomes:

**Structural and compositional differences:**

Liposomes and niosomes, both vesicular nanocarriers, encapsulate hydrophilic and hydrophobic drugs but differ in composition, stability, and functionality. Understanding these differences is essential for selecting optimal drug delivery systems.

**Composition:**

**Liposomes:**

Liposomes are spherical vesicles composed mainly of phospholipids that self-assemble into bilayers upon hydration. Incorporating cholesterol enhances membrane stability and fluidity, allowing liposomes to encapsulate both hydrophilic and hydrophobic drugs for versatile therapeutic delivery.

**Niosomes:**

Niosomes are vesicular structures composed of non-ionic surfactants, cholesterol, and optional additives. Forming bilayer structures like liposomes, they encapsulate both hydrophilic and hydrophobic drugs, with cholesterol enhancing membrane stability and reducing permeability[36].

**Structural Characteristics:**

**Liposomes:**

**Bilayer Structure:** There are two types of lipid bilayer structures seen in liposomes: unilamellar, which has a single bilayer encircling the aqueous core, and multilamellar, which has many concentric bilayers divided by aqueous layers. Drug loading capacity, release profile, and stability are all impacted by the choice between unilamellar and multilamellar vesicles, enabling customization for particular therapeutic uses.

**Size Range:** Depending on how they are prepared, liposomes can be anywhere from 50 and 1000 nanometers in size. Large unilamellar vesicles (LUVs) and multilamellar vesicles (MLVs) can grow to sizes of several hundred nanometers to more than a micron, whereas smaller vesicles, including small unilamellar vesicles (SUVs), are usually between 20 and 100 nm. Liposomes' drug loading, circulation duration, biodistribution, and cellular absorption are all strongly impacted by their size.

**Surface Charge:** By adding charged lipids, liposomes' surface charge may be adjusted, affecting how they interact with biological membranes, how they circulate, and how well they are absorbed by cells. While anionic or neutral liposomes may show decreased clearance by the reticuloendothelial system (RES), extending circulation duration, cationic liposomes can effectively adhere to negatively charged cell membranes, improving uptake. Therefore, adjusting surface charge is a crucial tactic for maximizing liposomal drug delivery.

**Niosomes:**

**Bilayer Structure:** Like liposomes, niosomes have a bilayer structure made up of non-ionic surfactants on both sides. The aqueous center of the bilayer can hold hydrophilic medications, whereas the surfactant tails can hold hydrophobic medications. By adjusting the cholesterol level and surfactant type, the bilayer's characteristics such as its stiffness, permeability, and stability can be tailored to meet certain drug delivery needs.

**Size Range:** Like liposomes, niosomes usually have a size range of 50 to 1000 nanometers, and their size may be regulated by the manufacturing process, cholesterol content, and surfactant selection. These factors further affect the release profile, cellular absorption, and the effectiveness of drug encapsulation.



**Surface Charge:** The kind of surfactant and the addition of charged additives can alter the surface charge of niosomes, influencing their stability, aggregation, and cell-interaction behavior. Niosomes can attain improved cellular uptake and dispersion stability by modifying these factors, which qualifies them for tailored drug delivery applications[37].

**Stability and Storage:**

**Liposomes:**

**Physical Stability:** Physical instability in liposomes might show up as encapsulated drug aggregation, fusion, or leakage, especially when stored in unfavorable settings like high temperatures, light exposure, or frequent freeze-thaw cycles. Drug effectiveness and shelf life may be lowered by these stability problems, requiring cautious formulation and storage techniques.

**Chemical Stability:** Liposomes are also subject to chemical instability, since their phospholipids can undergo hydrolysis, leading in deterioration of the vesicle structure and loss of encapsulated medicines. This emphasizes that in order to preserve liposome integrity over time, stabilizing agents, appropriate storage conditions, and antioxidant inclusion are required.

**Storage Conditions:** For liposomes to retain their structural integrity, proper formulation and storage conditions are necessary. For encapsulated medications to remain effective and have a long shelf life, they frequently require refrigeration and the addition of stabilizers or antioxidants to stop deterioration, aggregation, or leaking.

**Niosomes:**

**Physical Stability:** When compared to liposomes, niosomes often exhibit greater physical stability and a decreased propensity for drug encapsulation aggregation, fusion, and leakage. The ability to adjust bilayer composition with cholesterol and additives, as well as the chemical resilience of non-ionic surfactants, are responsible for this enhanced stability.

**Chemical Stability:** Because the non-ionic surfactants that make up their bilayers are less prone to hydrolysis than the phospholipids found in liposomes, niosomes have better chemical stability. This characteristic makes niosomes more resilient for long-term preservation and real-world pharmaceutical applications by preserving the integrity of the vesicle and preventing the early leaking of encapsulated medications.

**Storage Conditions:** The requirement for rigorous refrigeration is lessened since niosomes are often more resilient to a variety of storage settings, including room temperature. They are therefore beneficial for pharmaceutical applications where cost-effectiveness, convenience of handling, and long-term stability are crucial factors.[38].

**Toxicity and Biocompatibility:**

**Liposomes:**

**Biocompatibility:** In general, liposomes are biocompatible and exhibit minimal toxicity, particularly those derived from natural phospholipids. Because of their resemblance to biological membranes, they are well-tolerated by the body and may be administered by a variety of methods, such as topical, oral, and intravenous.

**Immunogenicity:** The selection of lipids and included additives might affect the immunogenicity of liposomes, which in some situations may elicit immunological reactions. Certain liposomal formulations, for example, might cause accelerated blood clearance (ABC) with repeated administration, underscoring the necessity of component selection to reduce immunological side effects.

**Niosomes:**

**Biocompatibility:** Non-ionic surfactants, which are used to make niosomes, are often less immunogenic and hazardous than the phospholipids used to make liposomes. Because of this property, niosomes are safer to administer repeatedly and may be used for a variety of pharmaceutical applications, such as parenteral, topical, and oral drug delivery.

**Toxicity:** The kind and quantity of surfactants employed in the formulation of niosomes might affect their toxicity. However, because non-ionic surfactants are suited for repeated or long-term administration and have minimal toxicity and biocompatibility, they are widely regarded as safer alternatives to liposomes in many settings[39].

**Drug Encapsulation Efficiency:**



**Liposomes:**

**Hydrophilic Drugs:** Hydrophilic medications can be effectively encapsulated by liposomes in their aqueous core, which prevents degradation and permits regulated or prolonged drug release. This characteristic improves the therapeutic effectiveness, bioavailability, and stability of the medicine.

**Hydrophobic Drugs:** Drugs that are hydrophobic can be integrated into the lipid bilayer of liposomes to provide regulated or prolonged release while being shielded from degradation. Liposomes are flexible carriers for a variety of therapeutic agents due to their dual encapsulation capabilities, which allows them to include hydrophilic medications in the aqueous core and hydrophobic pharmaceuticals in the bilayer.

**Niosomes:**

**Hydrophilic Drugs:** Like liposomes, niosomes may efficiently encapsulate hydrophilic medications within their watery core. This improves stability and therapeutic efficacy by preventing enzymatic breakdown and permitting regulated or prolonged drug release.

**Hydrophobic Drugs:** It is possible to integrate hydrophobic medications into the niosome bilayer, which protects them from degradation and allows for regulated or prolonged release. Niosomes are a flexible platform for delivering a variety of therapeutic agents because of their dual encapsulation capabilities, which allows them to contain hydrophilic medications in the aqueous core and hydrophobic pharmaceuticals in the bilayer [40].

Advances in Liposomal and Niosomal Technology:

Surface modification and ligand-targeted systems:

Liposomes and niosomes serve as versatile nanocarriers in drug delivery due to their biocompatibility and ability to encapsulate diverse drugs. Advances focus on enhancing targeting through surface modifications like PEGylation and ligand, antibody, or peptide conjugation, enabling site-specific delivery and improved therapeutic efficacy .

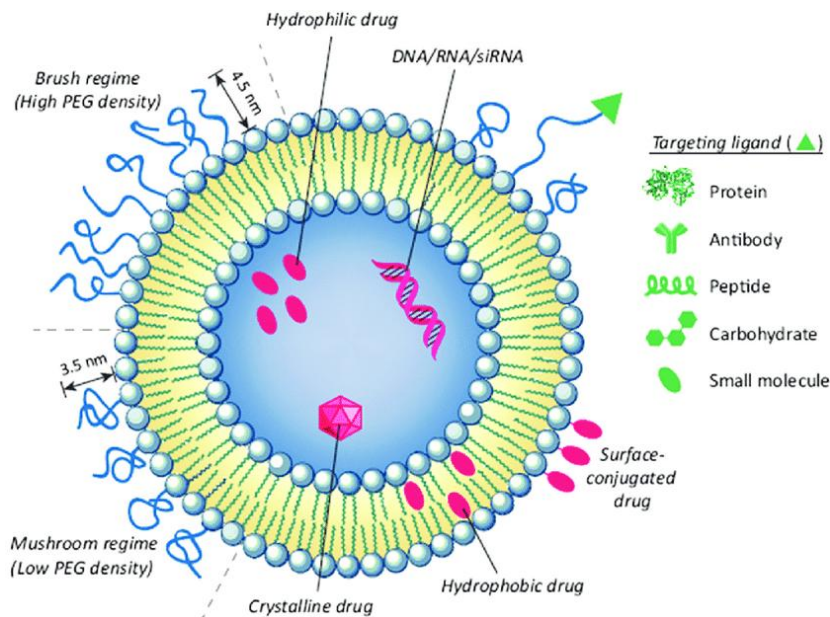


Fig. 4: Surface modification and ligand-targeted systems [41].

**Surface Modification Techniques:**

**Polyethylene Glycol (PEG)ylation:**

PEGylation, the covalent attachment of polyethylene glycol (PEG) chains to vesicle surfaces, enhances circulation time, reduces immune clearance, and improves pharmacokinetics and therapeutic efficacy of liposomes and niosome .



**Charge Modification:**

**Incorporation of Stimuli-Responsive Materials:**

Surface modification with stimuli-responsive materials like pH-sensitive polymers enables controlled drug release at target sites, such as acidic tumors or inflamed tissues, enhancing selectivity and minimizing systemic side effects.

**Receptor-Mediated Targeting:**

Ligand-targeted liposomes and niosomes use surface-bound ligands like peptides or antibodies to recognize receptors on target cells. For example, transferrin-conjugated niosomes enhance brain-targeted delivery by exploiting transferrin receptors, increasing CNS accumulation and reducing off-target effects.

**Dual-Ligand Targeting:**

Dual-ligand systems enhance targeting precision by combining two ligands recognizing different cell receptors, improving uptake, therapeutic efficacy, and selectivity while minimizing systemic toxicity in chemotherapeutic drug delivery.

**Multivalent Ligand Systems:**

By displaying many ligands on a nanocarrier's surface, multivalent interactions increase the binding affinity to target receptors. This approach improves cellular absorption, increases drug accumulation at the target region, and boosts therapeutic effectiveness by increasing the avidity of nanocarrier-receptor interactions[42].

Applications in Drug Delivery:

**Cancer Therapy:**

Ligand-targeted liposomes and niosomes enable precise chemotherapeutic delivery to tumor cells, minimizing toxicity. Folate-conjugated niosomes effectively target folate receptor-overexpressing cancers, enhancing drug accumulation and treatment efficacy while reducing systemic side effects.

**Gene Delivery:**

Niosomes and liposomes with surface modifications are efficient delivery systems for genetic material, such as DNA or RNA, to certain cells. These nanocarriers are especially well-suited for gene therapy applications, such as the treatment of genetic diseases and some types of cancer, since PEGylation and receptor-targeting techniques improve their stability, circulation time, and cellular absorption.

**Vaccine Delivery**

By delivering antigens straight to immune cells, ligand-targeted vesicles can boost the immunological response. By directing antigens to certain immune cell populations, surface changes with adjuvants or targeting ligands enhance vaccination effectiveness even further, fostering more robust and focused humoral and cellular protection [43].

Stealth liposomes and long-circulating vesicles:

Conventional liposomes are swiftly cleared by the mononuclear phagocyte system (MPS). Stealth or long-circulating liposomes overcome this by evading immune detection, extending circulation, and enhancing drug accumulation at tumor sites via the enhanced permeability and retention (EPR) effect.

Structural Features:

**Polyethylene Glycol (PEG) Coating:**

PEGylation is the process by which hydrophilic polymers, most frequently polyethylene glycol (PEG), are applied to stealth liposomes. On the liposome surface, the PEG chains provide a protective steric barrier that inhibits phagocytic uptake and decreases opsonization by plasma proteins. PEGylation also raises the vesicles' hydrodynamic radius, giving them a "stealth" effect that boosts drug concentration at target areas and extends circulation duration.

**Lipid Composition:**

Long-circulating vesicles use high-transition-temperature lipids like DSPC or HSPC with cholesterol to enhance bilayer rigidity, reduce drug leakage, and improve vesicle stability and circulation longevity in systemic drug delivery.



Table. 3: Stealth liposomes and long-circulating vesicles

Feature	Conventional Liposomes	Stealth/Long-Circulating Liposomes
Circulation Time	Short (minutes–hours)	Extended (hours–days)
Surface Modification	None	PEGylation / Polymer Coating
MPS Uptake	High	Low
Drug Accumulation at Target	Moderate	Enhanced via EPR effect
Stability	Moderate	High
Clinical Examples	Various	Doxil®, DaunoXome®

**Stimuli-responsive systems (pH, temperature, enzymatic):**

Advanced delivery systems aim for precise, safe drug release at target sites. Modern research develops stimuli-responsive liposomes and niosomes that exploit triggers like pH or temperature for controlled, targeted therapeutic delivery.

**Applications:**

Thermosensitive liposomal doxorubicin releases the drug under mild heat, enabling targeted delivery to liver tumors. These hyperthermia-assisted vesicles enhance therapeutic efficacy and minimize systemic toxicity in combined chemothermal therapy .

**Applications in Disease Management:**

**Cancer therapy:**

Liposomes and niosomes are promising nanocarriers in cancer therapy due to their ability to encapsulate both hydrophilic and hydrophobic drugs, improving pharmacokinetics and reducing systemic toxicity. Conventional chemotherapeutics such as doxorubicin, paclitaxel, and cisplatin often face limitations like poor solubility, rapid clearance, and non-specific distribution. Liposomal formulations, including Doxil® (liposomal doxorubicin), enhance therapeutic efficacy by prolonging circulation time, utilizing the enhanced permeability and retention (EPR) effect, and minimizing cardiotoxicity. Niosomes, composed of cholesterol and nonionic surfactants, offer cost-effective and stable alternatives. Surface modifications like PEGylation and ligand conjugation enhance tumor targeting, while stimuli-responsive vesicles enable controlled, localized drug release under tumor-specific conditions [44].

**Infectious diseases:**

Liposomes and niosomes have been extensively explored as nanocarriers to enhance the delivery, stability, and bioavailability of antimicrobial drugs for infectious disease treatment. Conventional antibiotics and antifungals often face challenges like poor solubility, rapid clearance, and inadequate drug concentrations at infection sites, promoting resistance. Liposomal amphotericin B (AmBisome®) is clinically approved for systemic fungal infections, reducing nephrotoxicity while maintaining efficacy. Niosomal formulations of antibiotics such as ciprofloxacin and gentamicin improve biofilm penetration and sustain drug release. Moreover, liposomal and niosomal carriers enhance antiviral delivery (e.g., tenofovir, acyclovir) and protect biologics from degradation, supporting advanced vaccine platforms for diseases like COVID-19, influenza, and malaria [45].

**Neurological disorders:**

The blood–brain barrier (BBB) poses a major challenge in delivering therapeutic agents to the central nervous system (CNS). Liposomes and niosomes have emerged as effective strategies to overcome this limitation. Neurological disorders such as epilepsy, Parkinson’s, Alzheimer’s, and brain tumors often suffer from poor drug permeability, systemic clearance, and off-target toxicity. Liposomes can encapsulate both hydrophilic and lipophilic neurotherapeutics, while ligand modification with transferrin, lactoferrin, or apolipoproteins enhances receptor-mediated BBB transport. PEGylated and ligand-functionalized liposomes improve brain accumulation and prolong circulation for drugs like donepezil and rivastigmine. Similarly, stable and cost-effective niosomes offer tunable surfaces for scalable CNS-targeted neurotherapeutic delivery [46].

Future Perspectives:



Future advancements in liposomal and niosomal drug delivery systems aim to overcome current limitations while advancing precision and personalized medicine. Despite successes such as liposomal doxorubicin and amphotericin B, scalability, stability, and reproducibility challenges persist. Emerging research focuses on multifunctional vesicles combining targeting ligands, imaging agents, and therapeutics for real-time monitoring. Incorporating stimuli-responsive elements like pH-, thermo-, or enzyme-sensitive materials enables spatiotemporally controlled drug release. Integration with biopolymers, peptides, and biomimetic coatings enhances biocompatibility and barrier permeability. Personalized vesicles tailored through omics-driven approaches will optimize efficacy and safety. Scalable microfluidic manufacturing and regulatory standardization will further accelerate clinical translation of next-generation, intelligent nanocarriers [47].

## II. CONCLUSION

Liposomes and niosomes are among the most promising and adaptable nanocarriers in modern drug delivery. Despite sharing a bilayer vesicular structure, they are complementary technologies differing in composition, stability, and cost. Liposomes, composed mainly of phospholipids, demonstrate excellent biocompatibility and have numerous FDA-approved formulations for hydrophilic and hydrophobic drugs. Niosomes, made of cholesterol and nonionic surfactants, offer superior chemical stability, cost-effectiveness, and therapeutic performance for large-scale use. Advances such as surface modification, ligand-mediated targeting, and stimuli-responsive systems have expanded their therapeutic applications. However, challenges in scalable manufacturing, reproducibility, and regulatory approval remain key barriers to their full clinical and commercial potential.

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