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## Review Paper

# Niosomes in Modern Therapeutics: Engineering Smarter Vesicular Carriers for Targeted Drug Delivery

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## ABSTRACT

Niosomes, non-ionic surfactant-based vesicular systems, have emerged as promising nanocarriers for targeted and controlled drug delivery. Their unique structural features enable the encapsulation of both hydrophilic and lipophilic drugs, offering enhanced stability, biocompatibility, and cost-effectiveness compared to conventional systems such as liposomes. Recent advances have focused on the development of stimuli-responsive, surface-functionalized, and hybrid niosomal systems to improve therapeutic efficacy and site-specific delivery. This review provides a comprehensive overview of niosome composition, preparation methods, characterization techniques, drug loading and release mechanisms, and therapeutic applications. Particular emphasis is placed on recent innovations, including smart niosomes, transdermal delivery systems, and gene delivery applications. Despite significant progress, challenges related to scalability, stability, and clinical translation remain. Future perspectives highlight the integration of artificial intelligence and sustainable approaches in the design of next-generation niosomal systems.

## INTRODUCTION

Niosomes represent an advanced and promising approach in modern drug delivery. In this system, the therapeutic agent is enclosed within tiny vesicular structures formed by bilayers of non-ionic surfactants, which is why they are termed *niosomes*. These vesicles are microscopic in nature

and typically fall within the nanometer size range, making them suitable for nanoscale drug transport<sup>1</sup>.

Structurally, niosomes resemble liposomes; however, they possess distinct advantages such as improved stability, cost-effectiveness, and ease of storage. Their unique architecture enables them to

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encapsulate both hydrophilic and lipophilic drugs efficiently. Recent research has demonstrated that niosomes can significantly enhance transdermal drug permeation and are also capable of delivering drugs to specific target sites within the body. Because of these benefits, niosomal systems are gaining considerable attention as versatile and innovative carriers in the field of targeted and controlled drug delivery<sup>2,3</sup>.

Both traditional and advanced drug delivery systems have been developed to overcome major challenges associated with drug therapy, such as poor pharmacokinetics and unfavorable biodistribution that often cause serious side effects (as seen in chemotherapy), rapid drug degradation in the bloodstream by the reticuloendothelial system, and inadequate accumulation of drugs at the intended target site leading to reduced therapeutic efficacy. In this context, nanocarriers have emerged as a transformative strategy, offering protection of the drug cargo, improved stability in circulation, and enhanced delivery to specific tissues. Because many human diseases are complex and multifactorial, conventional *in vivo* treatments may fail to achieve optimal outcomes, highlighting the need for biologically functional nanocarriers capable of selectively binding to and acting on specific cells. Although extensive efforts have been made to design and functionalize nanocarriers to maximize their performance, only a limited number have demonstrated significant clinical success so far. Among the various nanoscale systems, vesicles formed from non-ionic surfactants have attracted growing interest due to their flexibility and therapeutic versatility. With the rapid advancement of nanotechnology, drug delivery research has undergone a remarkable evolution, enabling the engineering of nanomaterials into vesicular systems such as liposomes, micelles, and polymer-based nanoparticles, some of which have already progressed to advanced development stages or

gained regulatory approval. Over the past two decades, improvements in synthesis, characterization, and molecular-level manipulation have led to the creation of highly sophisticated nanocarriers that are increasingly multifunctional, integrating features such as controlled or on-demand drug release, tissue-specific targeting, real-time imaging, diagnostic capabilities, and even photothermal therapy<sup>4-7</sup>.

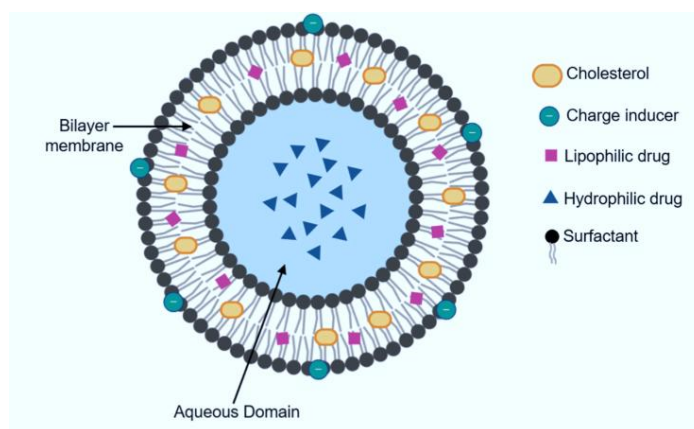
This review aims to provide a comprehensive and up-to-date overview of niosomes, focusing on their methods of preparation, key characterization techniques, and diverse pharmaceutical applications, with special emphasis on recent formulation advances. As research in this area is rapidly evolving, it is not possible to cover every emerging aspect of niosomal technology in a single article. However, this paper seeks to highlight the growing scientific and clinical interest in niosomes, particularly their expanding role in disease diagnosis, targeted therapy, and even cosmetic applications. By summarizing current developments and trends, the review intends to offer readers a clear understanding of the potential and versatility of niosomal systems in modern healthcare.

## **1. STRUCTURAL ARCHITECTURE OF NIOSOMES: MOLECULAR DESIGN AND SELF-ASSEMBLY PRINCIPLES**

The performance of any drug delivery system largely depends on the nature and quality of its individual components. For niosomal formulations, each ingredient must be carefully selected and evaluated based on its physicochemical properties, biological compatibility, and clinical suitability to ensure the formation of stable vesicles with desired characteristics. The fundamental constituents of niosomes include non-ionic surfactants, an aqueous hydration medium, and membrane



stabilizers such as cholesterol, all of which work together to create a functional vesicular structure.



**Figure 1: Bilayer structure of niosomes.**

### 1.1 Non-ionic surfactants

**Non-ionic surfactants** play a central role in the formation of niosomes. Similar to ionic surfactants, they are amphiphilic molecules, meaning they contain two distinct regions within the same structure: a hydrophilic (water-attracting) head and a hydrophobic (water-repelling) tail. These two segments may be connected through chemical linkages such as ether, ester, or amide bonds. Niosomal vesicles can be prepared using a variety of non-ionic surfactant molecules, including derivatives of amino acids, fatty acids, amides, alkyl esters, and particularly alkyl ether surfactants, which are among the most commonly used due to their favorable stability and vesicle-forming ability<sup>8-13</sup>.

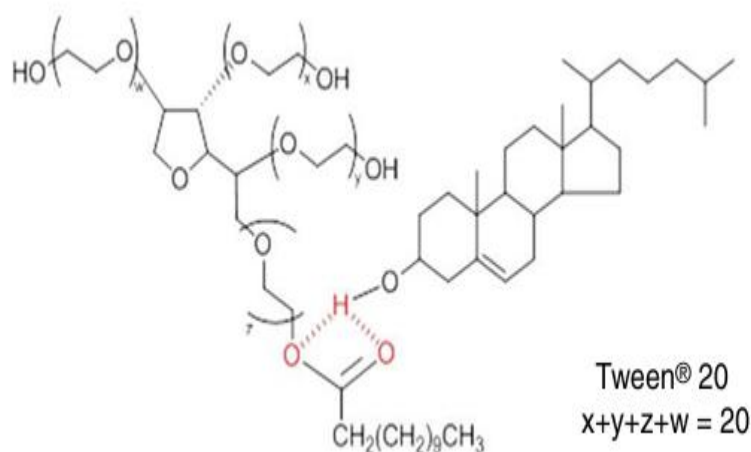
Alkyl ether surfactants used in niosome formulation are mainly grouped according to the type of hydrophilic head they possess. Some contain glycerol or sugar-based units, while others have repeating ethylene oxide chains. This structural difference influences vesicle formation and stability. Early niosomes were prepared using cholesterol along with single-chain surfactants such as alkyl oxyethylene derivatives (C12–C18). Polyglycerol monoalkyl ethers and polyoxyethylene analogues are commonly used due to their good vesicle-forming ability. Ether-type surfactants, especially those with dialkyl

chains resembling phospholipids, often provide better drug entrapment. Ester-type surfactants are also employed; although they are less stable because they can be broken down by esterases, they are generally less toxic. Additionally, glucoside derivatives of fatty alcohols can form stable niosomes. Continuous research is focused on designing new surfactants with tailored hydrophilic head groups to improve vesicle performance, and novel molecules such as bola-type surfactants have shown promising self-assembling and drug delivery potential<sup>14-16</sup>.

### 1.2 Cholesterol

Cholesterol is widely recognized as a key component in determining the structure and physical behavior of niosomes because of its interaction with non-ionic surfactants. In many cases, certain surfactants are unable to form stable vesicles unless cholesterol is added, typically in concentrations ranging from 30 to 50 mol%<sup>17</sup>. The required amount of cholesterol depends largely on the hydrophilic–lipophilic balance (HLB) of the surfactant. When the HLB value exceeds 10, higher cholesterol levels are generally needed. This is because surfactants with larger, more hydrophilic head groups tend to disrupt optimal molecular packing. Cholesterol helps counterbalance this effect by adjusting the critical

packing parameter (CPP), thereby promoting proper bilayer formation and improving vesicle stability<sup>18,19</sup>.



**Figure 2: A potential hydrogen bond may form between the hydroxyl (3-OH) group of cholesterol and the carbonyl oxygen atom of the neighboring molecule, along with a comparatively weaker interaction involving the oxygen atom present in the ester linkage.**

Tween 20 is a highly water-soluble non-ionic surfactant with an HLB value of 16.7, which means it has a strong affinity for water. Because of this high hydrophilicity, Tween 20 molecules tend to remain well hydrated and dispersed as individual monomers in aqueous solution. In fact, at 20 °C its critical micelle concentration (CMC) is about 60 mg/L, indicating that it prefers to exist freely in solution rather than spontaneously forming vesicular structures<sup>20</sup>.

However, when cholesterol is incorporated at an equimolar ratio, the behavior of Tween 20 changes significantly. Cholesterol reduces the excessive hydration of the surfactant head groups and promotes tighter molecular packing. This adjustment favors bilayer formation, enabling the system to assemble into stable non-ionic surfactant vesicles (niosomes). Without cholesterol, Tween 20 alone would not readily organize into such stable vesicular structures due to its strong water solubility<sup>21-23</sup>.

Research suggests that cholesterol (CHOL) interacts directly with amphiphilic molecules in vesicular systems. At an equimolar ratio (CHOL:amphiphile), the 3-OH group of

cholesterol is believed to associate with the hydrophobic region of the surfactant or phospholipid near the head group. This interaction may explain how cholesterol influences the formation and hydration behavior of Tween 20 (Tw20) niosomes, even in cases where cholesterol crystals remain partially undissolved<sup>24</sup>.

Further evidence of cholesterol's importance comes from studies showing that certain hydrophilic surfactants, such as decyl polyglucoside, can only form stable and spherical vesicles when large amounts of cholesterol are present. Cholesterol appears to strengthen interactions among the non-polar regions of the bilayer, thereby improving membrane cohesion and stability.

In general, cholesterol is known to regulate the mechanical strength and water permeability of amphiphile bilayers properties that are especially critical under physiological stress conditions. However, findings in the literature are not always consistent. Some studies report that increasing cholesterol enhances vesicle size and drug entrapment efficiency, while others show that

reducing cholesterol content can improve the encapsulation of certain hydrophilic drugs<sup>25</sup>.

Cholesterol also helps protect niosomes from destabilizing components in plasma and serum and reduces leakage of entrapped substances. Overall, its role remains somewhat controversial. The decision to include cholesterol and in what amount should be made carefully for each formulation, based on the specific physicochemical properties of the surfactant and the drug being delivered<sup>26</sup>.

### 2.3 Charged Molecules

One common strategy to improve the stability of niosomes is the incorporation of a small amount of charged molecules into the bilayer. Negatively charged additives such as dicetyl phosphate (DCP) and phosphatidic acid, as well as positively charged compounds like stearylamine (SA) and cetylpyridinium chloride, are frequently used to reduce vesicle aggregation. These charged components create electrostatic repulsion between vesicles, helping them remain dispersed rather than clumping together<sup>27,28</sup>.

Typically, charged molecules are included at low concentrations—around 2.5–5 mol%. Higher amounts may interfere with proper vesicle formation and destabilize the system. In colloidal systems, a zeta ( $\zeta$ ) potential greater than  $\pm 30$  mV is generally considered sufficient for strong electrostatic stabilization. Values between  $\pm 5$  and  $\pm 15$  mV indicate limited stability, while values closer to  $\pm 3$  to  $\pm 5$  mV are associated with a higher risk of aggregation. In simple terms, vesicles with higher absolute  $\zeta$ -potential values are less likely to aggregate due to stronger electrical repulsion.

However, this guideline does not always apply when steric stabilizers are present. These stabilizers can shift the shear plane of particles, reducing the measured  $\zeta$ -potential without necessarily compromising stability. Additionally,  $\zeta$ -potential is highly sensitive to the ionic

composition of the surrounding medium, which must be considered during formulation<sup>29</sup>.

Beyond preventing aggregation, charged molecules also serve additional purposes. They can enhance drug encapsulation efficiency, improve skin permeation, and facilitate the formation of hybrid niosomal complexes. Therefore, their inclusion in niosomal formulations can be tailored not only for stability but also for improved therapeutic performance<sup>30</sup>.

## 3. Advantages and Limitations of Niosomal Systems

### 3.1 Advantages over Liposomes and Other Nanocarriers

Niosomes have gained considerable attention as drug delivery carriers largely because they overcome several practical and stability-related drawbacks associated with conventional vesicular systems, particularly liposomes. One of the most notable advantages lies in their **enhanced chemical stability**. Unlike liposomes, which are primarily composed of phospholipids that are prone to oxidation and hydrolysis, niosomes are formed from non-ionic surfactants that exhibit greater resistance to degradation. This intrinsic stability contributes to a longer shelf life and reduces the need for stringent storage conditions, making niosomes more suitable for large-scale pharmaceutical applications<sup>31,32</sup>.

Another important benefit is **cost-effectiveness and ease of production**. The raw materials used in niosome preparation are generally less expensive and more readily available compared to phospholipids required for liposomes. In addition, niosomes can be prepared using relatively simple and scalable techniques, which supports their industrial feasibility<sup>33</sup>. This makes them particularly attractive for developing countries and for commercial drug formulation.

From a functional perspective, niosomes demonstrate **high drug encapsulation efficiency** for both hydrophilic and lipophilic drugs due to their amphiphilic bilayer structure. This versatility allows them to accommodate a wide range of therapeutic agents, including small molecules, peptides, and nucleic acids<sup>34</sup>. Furthermore, their bilayer composition can be easily modified to achieve **controlled and sustained drug release**, improving therapeutic efficacy and reducing dosing frequency<sup>35</sup>.

Niosomes also offer **enhanced bioavailability and targeted delivery potential**. Surface modification strategies, such as ligand attachment or PEGylation, enable site-specific drug delivery, minimizing systemic side effects and improving drug accumulation at the target site<sup>36</sup>. In comparison to other nanocarriers like solid lipid nanoparticles or polymeric nanoparticles, niosomes provide a balanced combination of **biocompatibility, flexibility, and tunable surface properties**.

Additionally, niosomes exhibit **improved penetration across biological barriers**, particularly in transdermal and mucosal delivery systems. Their ability to enhance drug permeation through the skin has made them highly promising in dermatological and cosmetic applications<sup>37</sup>. Overall, these advantages position niosomes as a versatile and practical alternative to traditional nanocarriers.

### 3.2 Challenges and Limitations

Despite their many advantages, niosomal systems are not without limitations, and several challenges must be addressed to ensure their successful clinical translation. One of the primary concerns is **physical instability**, particularly issues such as aggregation, fusion, and leakage of the encapsulated drug during storage. These problems can affect the consistency and reproducibility of the formulation over time<sup>34</sup>.

Another limitation is the **variability in drug entrapment efficiency**, which can be influenced by factors such as surfactant type, cholesterol content, and preparation method. This variability makes it difficult to achieve uniform formulations, especially when scaling up production<sup>31</sup>. Additionally, the **lack of standardized preparation protocols** further complicates reproducibility and regulatory approval.

Niosomes may also face challenges related to **sterilization and large-scale manufacturing**. Conventional sterilization methods, such as autoclaving or filtration, can disrupt vesicle integrity, leading to structural changes or drug leakage<sup>38</sup>. Similarly, scaling up laboratory methods to industrial production without compromising quality remains a significant hurdle.

From a biological standpoint, although niosomes are generally considered biocompatible, there are still concerns regarding **toxicity and immunogenicity**, particularly when using certain surfactants or surface modifiers. Long-term safety data are still limited, and further in vivo studies are required to fully understand their biological interactions<sup>36</sup>.

Another important issue is **limited in vivo and clinical data**. While numerous in vitro and preclinical studies have demonstrated promising results, only a few niosomal formulations have progressed to clinical trials. This gap highlights the need for more robust clinical validation and regulatory frameworks<sup>39</sup>.

Finally, niosomes may exhibit **batch-to-batch variability and stability issues under physiological conditions**, such as dilution in the bloodstream or interaction with plasma proteins. These factors can influence drug release behavior and targeting efficiency, potentially reducing therapeutic outcomes<sup>40</sup>.

## 4. METHODS OF PREPARATION OF NIOSOMES

The method used to prepare niosomes plays a crucial role in determining their **size, lamellarity, drug entrapment efficiency, and overall stability**. Over the years, both conventional and advanced techniques have been developed to optimize vesicle characteristics and improve scalability. The choice of method depends on the nature of the drug, desired vesicle properties, and intended application.

### 4.1 Conventional Techniques

Traditional preparation methods are widely used due to their simplicity and cost-effectiveness. However, they often face limitations in terms of reproducibility and large-scale production.

#### 4.1.1 Thin-Film Hydration Method (Hand Shaking Method)

This is one of the most commonly employed techniques for niosome preparation. In this method, non-ionic surfactants and cholesterol are dissolved in an organic solvent, which is then evaporated under reduced pressure to form a thin lipid film. Upon hydration with an aqueous phase containing the drug, the film swells and forms multilamellar vesicles.

This method is favored for its **simplicity and versatility**, but it may produce vesicles with **heterogeneous size distribution**, requiring further size reduction techniques such as sonication or extrusion<sup>31</sup>.

#### 4.1.2 Reverse Phase Evaporation Method (REV)

In this technique, a water-in-oil emulsion is first created by mixing an aqueous drug solution with surfactants dissolved in an organic solvent. The solvent is then removed under reduced pressure, resulting in the formation of large unilamellar vesicles.

REV is particularly useful for achieving **high encapsulation efficiency**, especially for hydrophilic drugs. However, the use of organic solvents raises concerns regarding **toxicity and residual solvent contamination**<sup>34</sup>.

#### 4.1.3 Ether Injection Method

Here, a solution of surfactant in diethyl ether is slowly injected into a warm aqueous phase. As the ether evaporates, niosomes are formed spontaneously.

Although this method allows for **controlled vesicle size**, it is less commonly used due to **safety concerns associated with organic solvents** and difficulties in scaling up<sup>33</sup>.

#### 4.1.4 Sonication Method

Sonication involves the application of ultrasonic energy to reduce vesicle size and produce small unilamellar vesicles. It is often used as a secondary step following thin-film hydration.

While effective in size reduction, prolonged sonication may lead to **drug degradation and structural instability**, limiting its application for sensitive molecules<sup>39</sup>.

### 4.2 Advanced and Novel Techniques

To overcome the limitations of conventional methods, several modern approaches have been developed, focusing on **reproducibility, scalability, and precise control over vesicle properties**.

#### 4.2.1 Microfluidization

Microfluidization is an advanced technique in which fluid streams are forced through narrow channels under high pressure, resulting in uniform and reproducible vesicles.

This method enables the production of niosomes with **narrow size distribution and high stability**, making it suitable for industrial applications. Additionally, it minimizes batch-to-batch variability<sup>31</sup>.



#### 4.2.2 Supercritical Fluid Technology

Supercritical fluids, particularly carbon dioxide, are used as an alternative to organic solvents in this eco-friendly method. The surfactants are solubilized in supercritical CO<sub>2</sub> and then rapidly expanded to form vesicles.

This approach offers **solvent-free preparation**, improved safety, and better control over particle characteristics. However, it requires specialized equipment and high operational costs<sup>32</sup>.

#### 4.2.3 Proniosome Technology

Proniosomes are dry, free-flowing formulations that can be hydrated to form niosomes just before use. This approach significantly enhances **stability during storage and transportation**.

Proniosomes also provide **improved dosing accuracy and convenience**, making them highly suitable for transdermal and oral delivery systems<sup>35</sup>.

#### 4.2.4 Bubble Method

The bubble method is a solvent-free technique where surfactants and cholesterol are dispersed in an aqueous phase and subjected to high shear mixing and nitrogen bubbling.

This method is advantageous because it **avoids the use of harmful organic solvents** and reduces processing steps. However, optimization is required to achieve consistent vesicle characteristics<sup>36</sup>.

#### 4.2.5 Microfluidic-Based Synthesis

Recent advancements have introduced microfluidic platforms for the controlled synthesis of niosomes. These systems allow precise manipulation of fluid flow, enabling the formation of vesicles with **uniform size and enhanced reproducibility**.

Microfluidics is emerging as a promising tool for **personalized medicine and on-demand drug formulation**, although its large-scale application is still under development<sup>34</sup>.

### 5. CHARACTERIZATION OF NIOSOMES

A thorough characterization of niosomes is essential to ensure their **quality, stability, and performance as drug delivery systems**. The physicochemical properties of niosomes directly influence their biological behavior, including drug release, biodistribution, and therapeutic efficacy. Therefore, multiple analytical techniques are employed to evaluate vesicle size, morphology, surface charge, encapsulation efficiency, and stability.

#### 5.1 Particle Size, Size Distribution, and Polydispersity Index (PDI)

Particle size is one of the most critical parameters affecting **drug release, cellular uptake, and circulation time**. Niosomes typically range from nanometer to micrometer scale, depending on the preparation method. Smaller vesicles tend to exhibit enhanced permeability and bioavailability, particularly in targeted and transdermal delivery. Dynamic Light Scattering (DLS) is commonly used to determine **average particle size and size distribution**, while the **polydispersity index (PDI)** indicates uniformity. A PDI value below 0.3 is generally considered acceptable for homogeneous formulations<sup>31,34,41</sup>.

#### 5.2 Zeta Potential (Surface Charge Analysis)

Zeta potential reflects the **surface charge of niosomes**, which plays a vital role in predicting their physical stability. High absolute zeta potential values (either positive or negative) help prevent vesicle aggregation due to electrostatic repulsion.

Typically, values greater than  $\pm 30$  mV indicate good stability. Additionally, surface charge can influence **interaction with biological membranes and cellular uptake**, making it a key parameter in targeted drug delivery<sup>36</sup>.

#### 5.3 Morphology and Vesicle Structure

The shape and structural characteristics of niosomes are analyzed using imaging techniques such as:

- Transmission Electron Microscopy (TEM)
- Scanning Electron Microscopy (SEM)
- Atomic Force Microscopy (AFM)

These methods provide detailed information about **vesicle shape (spherical or irregular), lamellarity (unilamellar or multilamellar), and surface characteristics**. Morphological evaluation is crucial to confirm successful vesicle formation<sup>39</sup>.

#### 5.4 Entrapment Efficiency (EE%)

Entrapment efficiency measures the **percentage of drug successfully encapsulated within the niosomes** relative to the total drug used. It is a key indicator of formulation effectiveness.

EE% is typically determined by separating untrapped drug using centrifugation, dialysis, or gel filtration, followed by drug quantification using spectroscopic or chromatographic methods.

Factors influencing EE% include:

- Type of surfactant
- Cholesterol concentration
- Drug solubility
- Preparation method

High entrapment efficiency is desirable for improving **drug loading capacity and therapeutic outcomes**<sup>33,34</sup>.

#### 5.5 In Vitro Drug Release Studies

Drug release studies evaluate the **release profile of the encapsulated drug over time**, which is critical for controlled and sustained delivery applications.

Common techniques include:

- Dialysis bag method
- Franz diffusion cell

Release data are often fitted into kinetic models such as:

- Zero-order

- First-order
- Higuchi model
- Korsmeyer–Peppas model

These studies help in understanding the **mechanism of drug release** and predicting in vivo performance<sup>35</sup>

#### 5.6 Stability Studies

Stability assessment ensures that niosomes maintain their **physicochemical integrity during storage**. Parameters monitored include:

- Particle size changes
- Drug leakage
- Zeta potential variation

Stability studies are typically conducted under different conditions of **temperature, humidity, and time**, following ICH guidelines. Proniosomal formulations are often preferred to enhance stability<sup>31</sup>.

#### 5.7 Bilayer Rigidity and Phase Behavior

The rigidity and fluidity of the niosomal bilayer influence drug retention and release. Techniques such as **Differential Scanning Calorimetry (DSC)** and **Fourier Transform Infrared Spectroscopy (FTIR)** are used to study:

- Phase transition temperature
- Interaction between drug and bilayer components

These analyses provide insights into **vesicle stability and compatibility of formulation components**<sup>36</sup>.

#### 5.8 Surface Chemistry and Functionalization Analysis

For targeted and modified niosomes, it is important to confirm **surface functionalization**. Techniques include:

- FTIR spectroscopy
- Nuclear Magnetic Resonance (NMR)
- X-ray Photoelectron Spectroscopy (XPS)

These methods help verify the presence of ligands, polymers, or other surface modifiers that enhance targeting efficiency<sup>34</sup>.

### 5.9 In Vitro and In Vivo Performance Evaluation

Beyond physicochemical characterization, biological evaluation is essential. This includes:

- Cell viability and cytotoxicity assays (MTT assay)
- Cellular uptake studies
- Pharmacokinetic and biodistribution studies

Such studies provide a better understanding of **therapeutic efficacy, safety, and targeting capability** of niosomal systems<sup>42</sup>.

## 6. DRUG LOADING AND RELEASE MECHANISMS

Understanding how drugs are incorporated into niosomes and subsequently released is fundamental to optimizing their performance as **controlled and targeted drug delivery systems**. Drug loading determines the therapeutic capacity of the vesicles, while release mechanisms govern the **rate, duration, and site of drug action**.

### 6.1 Drug Loading Mechanisms

Drug loading in niosomes can be broadly classified into **passive loading** and **active (remote) loading**, depending on the stage at which the drug is incorporated and the driving forces involved.

#### 6.1.1 Passive Loading

Passive loading is the most commonly used approach, where the drug is incorporated during vesicle formation. The distribution of the drug depends primarily on its **physicochemical properties**, particularly solubility.

- **Hydrophilic drugs** are encapsulated within the aqueous core

- **Lipophilic drugs** are incorporated into the hydrophobic bilayer
- **Amphiphilic drugs** may partition between both regions

This method is simple and widely applicable but may result in **lower encapsulation efficiency**, especially for highly water-soluble drugs due to leakage during formation<sup>31,34</sup>.

#### 6.1.2 Active (Remote) Loading

Active loading involves incorporating the drug into preformed niosomes using **transmembrane gradients** such as pH or ion gradients. This method enhances drug loading efficiency by driving the drug into the vesicle interior.

For example:

- **pH gradient method**: weakly basic drugs accumulate inside acidic vesicles
- **Ion gradient method**: uses electrochemical gradients to facilitate drug uptake

Active loading offers **higher encapsulation efficiency and better drug retention**, making it suitable for potent drugs and targeted therapies<sup>36</sup>.

#### 6.1.3 Factors Affecting Drug Loading

Several formulation and process variables influence drug loading capacity:

- Type and concentration of surfactant
- Cholesterol content (affects membrane rigidity)
- Drug solubility and partition coefficient
- Method of preparation
- Hydration conditions and temperature

Optimizing these parameters is essential to achieve **maximum drug entrapment and stability**<sup>33</sup>.

### 6.2 Drug Release Mechanisms

Drug release from niosomes is a complex process governed by **diffusion, vesicle degradation, and environmental triggers**. The release profile can be tailored to achieve **sustained, controlled, or site-specific delivery**.



### 6.2.1 Diffusion-Controlled Release

In this mechanism, the drug diffuses gradually from the vesicle core through the bilayer into the surrounding medium.

- Common in **stable niosomal systems**
- Provides **sustained and prolonged drug release**
- Influenced by bilayer composition and fluidity

Diffusion-controlled release is particularly useful for maintaining **therapeutic drug levels over extended periods**<sup>35</sup>.

### 6.2.2 Vesicle Erosion and Degradation

Drug release may also occur due to **structural disruption or degradation** of the niosomal bilayer. Factors such as enzymatic activity, oxidation, or hydrolysis can destabilize the vesicles.

This mechanism is more prominent in **biological environments**, where interaction with enzymes and biomolecules can accelerate release<sup>42</sup>.

### 6.2.3 Stimuli-Responsive Release

Recent advancements have introduced **smart niosomes** that release drugs in response to specific stimuli:

- **pH-sensitive niosomes**: release drug in acidic tumor or inflammatory environments
- **Temperature-sensitive systems**: release triggered by hyperthermia
- **Enzyme-responsive systems**: activated by disease-specific enzymes
- **Redox-sensitive niosomes**: respond to intracellular redox conditions

These systems enhance **target specificity and reduce systemic side effects**, representing a major advancement in precision medicine<sup>32</sup>.

### 6.2.4 Osmotic Shock and Dilution Effects

In physiological conditions, changes in osmotic pressure or dilution in body fluids can cause **vesicle swelling or rupture**, leading to drug

release. This is particularly relevant for intravenously administered niosomes<sup>39</sup>.

### 6.3 Kinetics of Drug Release

To better understand and predict drug release behavior, experimental data are fitted into mathematical models such as:

- **Zero-order kinetics** – constant drug release over time
- **First-order kinetics** – release dependent on drug concentration
- **Higuchi model** – diffusion-based release
- **Korsmeyer–Peppas model** – mechanism-based interpretation

These models help in designing formulations with **desired release profiles and therapeutic outcomes**<sup>31</sup>.

## 7. THERAPEUTIC APPLICATIONS OF NIOSOMES

Niosomes have emerged as versatile nanocarriers with broad therapeutic applicability due to their **biocompatibility, ability to encapsulate diverse drugs, and controlled release properties**. Recent research (2023–2026) highlights their growing importance in **cancer therapy and transdermal delivery**, while also demonstrating promising outcomes in antimicrobial, anti-inflammatory, gene delivery, and cosmetic applications. Their adaptability allows them to be engineered for **target-specific delivery, improved bioavailability, and reduced systemic toxicity**.

### 7.1 Cancer Therapy

Cancer treatment remains one of the most extensively explored areas for niosomal drug delivery. Conventional chemotherapy often suffers from **poor selectivity, systemic toxicity, and multidrug resistance**. Niosomes help address these challenges by enabling **targeted and controlled delivery of anticancer agents**.

Niosomal formulations have been successfully developed for drugs such as doxorubicin, paclitaxel, and cisplatin, showing improved **drug accumulation in tumor tissues via enhanced permeability and retention (EPR) effect**. Surface-functionalized niosomes, including ligand-targeted systems, further enhance **site-specific delivery to cancer cells**, minimizing damage to healthy tissues<sup>34,43</sup>.

Additionally, niosomes can co-deliver multiple therapeutic agents or combine chemotherapy with gene therapy, improving treatment outcomes. Their role in overcoming drug resistance and enhancing intracellular uptake makes them highly promising in **modern oncological nanomedicine**<sup>32</sup>.

### 7.2 Antimicrobial and Antiviral Delivery

The rise of antimicrobial resistance has created an urgent need for more effective drug delivery systems. Niosomes enhance the efficacy of antimicrobial and antiviral agents by improving **drug stability, penetration, and sustained release**.

Encapsulation of antibiotics such as ciprofloxacin and antifungal agents like amphotericin B in niosomes has demonstrated improved **therapeutic efficiency and reduced toxicity**. In antiviral therapy, niosomes facilitate better delivery of drugs across biological barriers, enhancing their bioavailability<sup>42</sup>.

Moreover, niosomes can improve drug retention at infection sites and enable **localized delivery**, which is particularly beneficial in treating skin and mucosal infections. Their ability to bypass resistance mechanisms makes them a promising tool in combating **drug-resistant pathogens**<sup>39</sup>.

### 7.3 Anti-inflammatory Applications

Niosomes are widely investigated for the delivery of anti-inflammatory drugs, especially in chronic conditions such as arthritis, psoriasis, and

inflammatory skin disorders. Traditional anti-inflammatory therapies often require frequent dosing and may cause systemic side effects.

Niosomal formulations of drugs like diclofenac and ibuprofen have shown **prolonged drug release and enhanced therapeutic efficacy**, reducing dosing frequency. In transdermal delivery, niosomes improve **skin penetration and localized drug action**, minimizing systemic exposure<sup>35</sup>.

Furthermore, their ability to encapsulate natural anti-inflammatory compounds, such as curcumin, enhances **bioavailability and stability**, making them suitable for both pharmaceutical and nutraceutical applications<sup>36</sup>.

### 7.4 Gene and Vaccine Delivery

Niosomes have recently gained attention as non-viral vectors for **gene and vaccine delivery**, offering a safer alternative to viral systems. They can encapsulate DNA, RNA, and proteins while protecting them from degradation.

In gene therapy, niosomes facilitate **efficient cellular uptake and intracellular delivery of genetic material**, enabling gene expression or silencing. Their surface can be modified to improve targeting and transfection efficiency<sup>34</sup>.

In vaccine delivery, niosomes act as **adjuvants and antigen carriers**, enhancing immune responses. They have been explored for delivering protein antigens and mRNA-based vaccines, showing potential in **infectious disease prevention and immunotherapy**<sup>44</sup>.

### 7.5 Cosmetic and Dermatological Applications

Niosomes are extensively used in the cosmetic and dermatological field due to their ability to enhance **skin penetration and controlled release of active ingredients**. They are particularly valuable in transdermal and topical formulations, which are among the fastest-growing application areas.

Niosomal systems are used to deliver:



- Anti-aging agents (e.g., retinoids, vitamins)
- Skin-whitening agents
- Moisturizers and antioxidants

These formulations improve **drug stability, reduce irritation, and prolong the action of cosmetic ingredients**. Additionally, niosomes enhance the delivery of drugs used in dermatological conditions such as acne, eczema, and psoriasis<sup>35</sup>.

Recent advances include the development of **elastic and deformable niosomes**, which further enhance penetration through the stratum corneum, making them highly effective for **transdermal drug delivery systems**.

## 8. RECENT ADVANCES AND EMERGING TRENDS IN NIOSOMAL DRUG DELIVERY

In recent years, niosomal systems have undergone significant transformation, evolving from simple vesicular carriers into **highly sophisticated, multifunctional nanoplatforms**. Current research (2023–2026) emphasizes innovations that improve **target specificity, responsiveness, scalability, and clinical translation**. These advances are largely driven by the integration of **nanotechnology, materials science, and computational tools**, positioning niosomes at the forefront of next-generation drug delivery systems

### 8.1 Stimuli-Responsive (Smart) Niosomes

One of the most important developments is the design of **stimuli-responsive or “smart” niosomes**, which release drugs in response to specific internal or external triggers.

- **pH-sensitive niosomes** target acidic tumor microenvironments or inflamed tissues
- **Thermo-responsive systems** release drugs under elevated temperatures (e.g., hyperthermia in cancer therapy)
- **Enzyme-responsive niosomes** are activated by disease-specific enzymes

- **Redox-sensitive systems** respond to intracellular oxidative conditions

These systems enable **site-specific drug release**, minimizing systemic toxicity and improving therapeutic precision<sup>36</sup>.

### 8.2 Surface-Engineered and Targeted Niosomes

Surface modification has significantly enhanced the **targeting capabilities** of niosomes. Modern approaches include:

- **Ligand-based targeting** (antibodies, peptides, aptamers)
- **PEGylation** for stealth properties and prolonged circulation
- **Receptor-mediated targeting** for cancer and brain delivery

These engineered systems improve **cellular uptake, biodistribution, and therapeutic efficacy**, particularly in oncology and neurological disorders<sup>34</sup>.

### 8.3 Hybrid and Multifunctional Niosomes

Recent studies focus on combining niosomes with other nanomaterials to create **hybrid systems** with enhanced functionality. Examples include:

- **Polymer–niosome hybrids** for improved stability
- **Niosome–nanoparticle composites** (e.g., gold, silica) for imaging and therapy
- **Magnetic niosomes** for guided drug delivery

These multifunctional platforms enable **simultaneous diagnosis and therapy (theranostics)**, representing a major step toward personalized medicine<sup>44</sup>.

### 8.4 Elastic and Deformable Niosomes

Elastic or ultra-deformable niosomes have been developed to enhance **transdermal and mucosal drug delivery**. These vesicles can penetrate through narrow pores in biological membranes, particularly the **stratum corneum**.

They are widely used in:

- Transdermal drug delivery systems

- Cosmetic formulations
- Localized therapy

This advancement has significantly improved **drug permeation and bioavailability**, making transdermal delivery one of the fastest-growing application areas<sup>35</sup>.

### 8.5 Green and Sustainable Formulation Approaches

There is a growing emphasis on **eco-friendly and sustainable synthesis methods**. Researchers are exploring:

- Use of **biodegradable and natural surfactants**
- **Solvent-free preparation techniques** (e.g., bubble method)
- Supercritical fluid technologies

These approaches aim to reduce environmental impact while maintaining **high efficiency and safety**, aligning with global sustainability goals<sup>31</sup>.

### 8.6 AI and Computational Modeling in Niosome Design

Artificial intelligence (AI) and computational tools are increasingly being used to **optimize formulation parameters and predict performance**.

Applications include:

- Predicting drug encapsulation efficiency
- Modeling release kinetics
- Designing targeted delivery systems

AI-driven approaches reduce experimental time and cost while improving **precision and reproducibility**, marking a shift toward **data-driven pharmaceutical development**<sup>33</sup>.

### 8.7 Advances in Gene and mRNA Delivery

With the success of mRNA-based therapeutics, niosomes are being explored as **non-viral vectors for nucleic acid delivery**. They offer:

- Protection of genetic material from degradation
- Enhanced cellular uptake

- Lower immunogenicity compared to viral vectors

This trend is particularly relevant in **vaccine development and gene therapy**, where safe and efficient delivery systems are crucial<sup>44</sup>.

### 8.8 Clinical Translation and Commercialization Efforts

Although many niosomal systems remain in the research stage, recent efforts are focused on overcoming barriers to **clinical translation**, including:

- Scale-up and manufacturing challenges
- Regulatory approval pathways
- Stability and reproducibility issues

Proniosomal formulations and advanced manufacturing techniques are helping bridge the gap between **laboratory research and industrial application**<sup>39</sup>.

## CONCLUSION

Niosomes have established themselves as a versatile and promising class of nanocarriers in the field of advanced drug delivery. Owing to their unique composition based on non-ionic surfactants, they offer significant advantages such as **improved stability, cost-effectiveness, biocompatibility, and the ability to encapsulate both hydrophilic and lipophilic therapeutic agents**. These properties make them a strong alternative to conventional vesicular systems, particularly liposomes.

This review demonstrates that niosomal systems have evolved considerably, with recent innovations focusing on **targeted delivery, controlled release, and functional surface modifications**. The development of **stimuli-responsive and hybrid niosomes** has further enhanced their ability to deliver drugs in a site-specific and efficient manner. Among various applications, **cancer therapy and transdermal drug delivery** have emerged as the most



prominent, while expanding research in **antimicrobial therapy, gene delivery, and cosmetic formulations** highlights their broad therapeutic potential.

Despite these advancements, certain limitations persist, including **physical instability, challenges in large-scale production, and limited clinical translation**. Addressing these issues requires the development of **standardized preparation methods, improved formulation strategies, and extensive in vivo and clinical studies** to ensure safety and efficacy.

Looking forward, the integration of **novel technologies such as artificial intelligence, green synthesis approaches, and multifunctional nanocarrier design** is expected to further refine niosomal systems. Continued interdisciplinary research will be essential to overcome current barriers and unlock their full potential in personalized and precision medicine.

#### AUTHORS CONTRIBUTION

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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#### CONFLICTS OF INTEREST

No Conflict of interest

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