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NIOSOMES: AN EXTENSIVE ANALYSIS OF ITS STRUCTURE, PREPARATION, AND USES IN DRUG DELIVERY

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ABSTRACT

Background: Niosomes are sophisticated drug delivery vehicles composed of non-ionic surfactants that have a lot of potential for delivering drugs. Their unique bilayer structure enables the targeted and regulated release of both fat-soluble and water-soluble medications, enhancing their stability and absorption. This review discusses the components, production processes, benefits, drawbacks, and potential uses of niosomes in various medical fields, including cutaneous medication delivery and cancer treatment. **Objective:** This article provides an in-depth overview of niosomes as novel drug delivery vehicles, highlighting their benefits, preparation techniques, applications, and assessment criteria. It aims to highlight how they can improve therapeutic efficacy and bioavailability across various medicinal domains. **Methodology:** This article outlines multiple techniques employed in the preparation of niosomes, including the ether injection method, sonication method, hand-shaking method, extrusion method, thin film hydration, microfluidization method, and Transmembrane pH gradient drug uptake process. It also examines elements that impact niosome synthesis, such as the kind of surfactant utilized, the drug's characteristics, and environmental conditions. **Conclusion:** Ongoing research is focused on enhancing niosomal formulations and expanding their use in clinical settings, despite challenges such as instability and a short shelf life. Overall, niosomes are a significant development in drug delivery technology, with the potential to enhance treatment effectiveness and improve patient care.

INTRODUCTION

In the 21st century, bioengineering, medicinal chemistry, pharmaceutical and cosmetic sciences, medicine, heredity engineering, and food innovation are just a few of the scientific domains where nanotechnology has demonstrated significant promise [1]. Engineering, biological sciences, and the creative design, manufacture, and use of frameworks at the nanoscale (range between 1 and 100 nm), or nanotechnology, are emerging issues in this multidisciplinary research on a global scale [3]. Nanoparticles, known as vesicular delivery systems, function similarly to niosomes in enhancing the therapeutic efficacy of drugs by modifying their surface and targeting specific cells, thereby reducing the drug's clearance [4]. The last 30 years have seen considerable interest in the potential application of niosomes, microscopic bubble-like carriers, in the delivery of pharmaceuticals [2]. An aqueous compartment encloses the

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lamellar (bilayer) structures in which their amphiphilic molecules are organized [5]. Niosomes are made up of non-ionic surfactants instead of the phospholipids that make up liposomes, and they share similarities with liposomes in their multilamellar vesicular structure [6].

Consequently, niosomes, also referred to as non-ionic surfactant vesicles, are presently the subject of intensive investigation as an alternative to liposomes (Figure 1). Vesicles, which are tiny bubbles that may retain both water-loving (hydrophilic) and water-repelling (hydrophobic) molecules, can be produced by a variety of surfactants [7]. Non-ionic surfactants and additives are the two primary component types found in niosomes. Liposomes can degrade and become damaged due to their fatty nature, but niosomes are more resilient. It is possible to increase the oral bioavailability of medications. Additionally, the unique groups on their water-loving ends make it simple to alter their surface [8]. There are three distinct groups of niosomes. These comprise three different kinds of vesicles: multilamellar (MLV size = 0.05 μm), big (LUV size = 0.10 μm), and small (SUV size = 0.025-0.05 μm). Because niosomal formulations contain a non-ionic surfactant that improves their target effect, & their half-life in the blood is prolonged [9]. Niosomes are small, minuscule creatures. On the nanometric scale, niosomes are between 20 and 100 nm in size. Although they have structural similarities with liposomes, niosomes are superior. Their modest size (measured in nanometers) allows for easy administration by any transdermal route. The reticular-endothelial system is less likely to break down and eliminate niosomes because they are so small [10]. The advantages/disadvantages of niosomes & ideal properties of niosomes are given in Table 1 and Figure 2, respectively.

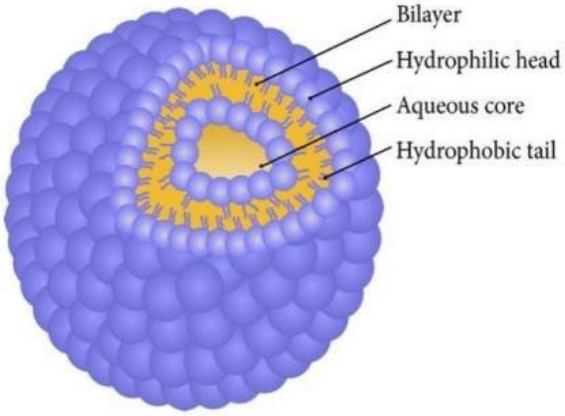

Figure 1. Structure of liposomes

Table 1: Advantages/Disadvantages of niosomes

SN	Advantages	Disadvantages
1.	Non-immunogenic, biodegradable, and biocompatible	Instability in physicochemistry.
2.	Improved & greater bioavailability	A short shelf life.
3.	Controlled shape, size, & composition & more stable than liposomes.	The potential for vesicle fusion & aggregation
4.	They are active, osmotically stable, and improve the stability of the medication that is entrapped.	A lengthy procedure [13].
5.	Surfactant can be handled & store without any special requirements[11]	When trapped, the drug seeps.
6.	Drugs can be released in a controlled and sustained manner.	Hydrolysis of the natural chemical or medication that is encapsulated [14].
7.	Condense the enormous drug amount into a tiny vesicular volume[12].	It takes a long time to formulate.
8.	Capable of targeted medication delivery.	----------

COMPONENTS OF NIOSOMES

Non-ionized surfactant: Niosomes are bilayer structures of surfactants that face each other with a non-polar tail and a polar head toward the fluid stage. A range of non-ionic surfactant types is used in niosome formulation. Alkyl esters, alkyl ethers, alkyl amides, alcohols, or fatty acids [52].

Cholesterol: Cell membranes include cholesterol, a steroid that is essential for their stiffness, fluidity, and permeability. As a steroid, cholesterol is necessary for the formation of niosomes. Although it is present in niosomes, cholesterol is present in minimal amounts, as high cholesterol levels affect the niosomal vesicle's ability to penetrate or be porous.

It improves permeability, stiffness, and encapsulation effectiveness. It also demonstrates the toxicity of freeze-dried niosomes and their easy rehydration [15].

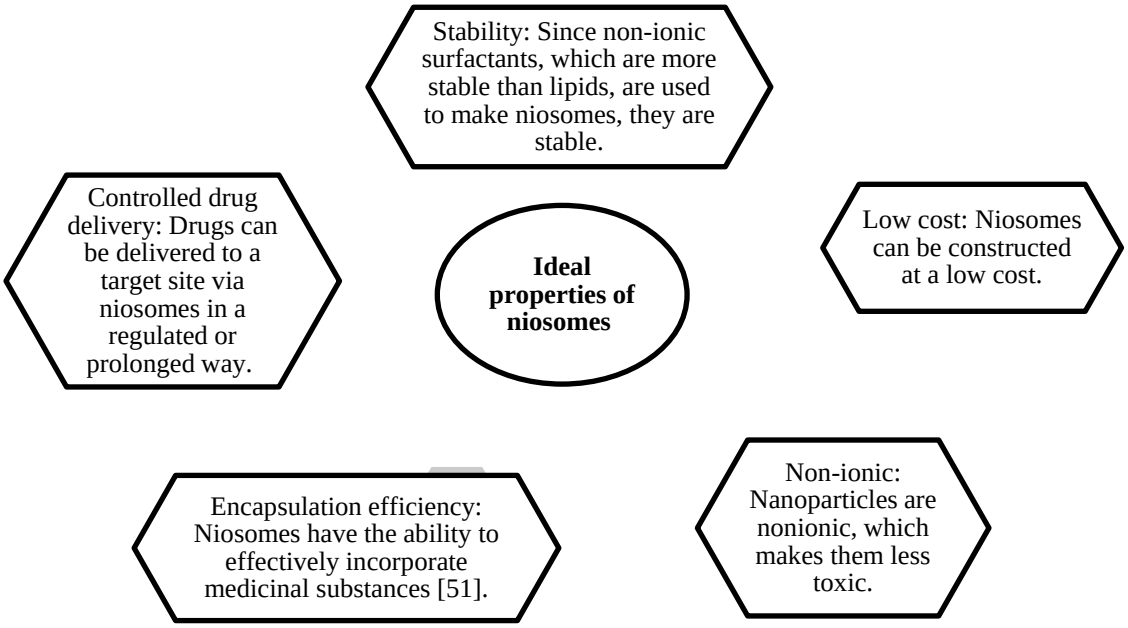

Figure 2: Properties of Niosomes

NIOSOME PREPARATION TECHNIQUES

The preparation techniques should be chosen based on the utilization of niosomes, as the organization strategies have an impact on the number of bilayers, size, delivery, and entrapped productivity of the aqueous phase, as well as the layer permeability of the vesicles.

Ether Injection Method: Using a specific gauze needle, a solution with an accurate proportion of cholesterol to surfactant in ether is gradually injected into the drug's heated water-based solution, which is kept at 60°C. Ether evaporates to form drug-containing single-layer vesicles composed of surfactants [16]. However, because they evaporate at a far lower temperature, fluorinated hydrocarbons have been used in place of ether for thermolabile medications. Niosomes produced with this method range in size from 50 to 1000 nm, primarily depending on the formulation parameters and experimental setup [17].

Sonication Method: Sonication is a commonly used method for creating niosome vesicles. In a 10-ml glass vial, the drug, cholesterol, and surfactants are removed and mixed with buffer. A titanium probe is then used to sonicate the liquid for approximately three minutes to produce niosomes. There are tiny, unilamellar vesicles in the finished product. Tiny vesicles are the most prevalent application for this method. Probe and bath sonicators are the two primary types of sonicators used in the sonication process. Any kind can be used, depending on the circumstances [18].

Hand Shaking Method: Firstly, dissolve the cholesterol and surfactant in an organic solvent (such as ether, chloroform, or benzene). A vacuum evaporator is then used to evaporate the contents of the flask, removing the solid cholesterol and surfactant mixture from the flask walls. After this layer was continuously shaken and rehydrated with a drug-containing water solution, the surfactant layer inflated. Amphiphilic molecules finally fold themselves to form drug-holding vesicles after swelling and absorbing water. Only 5–10% of the liquid volume was discovered to be trapped in vesicles [19].

Reverse-Phase Evaporation Method: This method utilizes a 1:1 mixture of ether and chloroform to dissolve cholesterol and surfactant. After that, the drug is placed in a water-based solution at a temperature between 4 and 5°C and agitated using sound waves. After adding phosphate buffer saline (PBS), the mixture is further sonicated to create a gel. The solvent is then evacuated by increasing the temperature to 40°C and lowering the pressure. To produce niosomes, the PBS is added once again and cooked in a water bath at 60°C for ten minutes [20].

Extrusion Method: To form a thin layer, a mixture of diacetyl phosphate and cholesterol is prepared, and the solvent is then evaporated using a rotating vacuum evaporator [21]. To create uniformly sized niosomes, the film is soaked in an aqueous drug solution and then extruded using a polycarbonate membrane with a mean pore size of 0.1 mm. Up to eight repetitions of this procedure are possible [22].

Micro-Fluidization method: The micro-fluidization process involves dissolving drugs and surfactants in a solvent and then pumping them under pressure from a reservoir to an interaction chamber filled with ice. To absorb the heat produced during the process, the solution is sent through a cooling loop. With this method, niosomes with greater homogeneity and reduced size can be produced [23].

Thin film hydration method: The micro-fluidization procedure involves dissolving drugs and surfactants in a solvent, then pumping the mixture via pressure from a reservoir to an interaction chamber filled with ice [24]. The resulting product will pass through a cooling loop to absorb the heat generated during the procedure. This technique can be used to create niosomes that are smaller and more uniform [25].

Transmembrane pH Gradient (Inside Acidic) Drug Uptake Process (Remote Loading): According to this theory, the pH of the niosome's inside is lower than that of its outside, and it is acidic. The extra noncharged basic drug can pass through the niosome membrane. However, it becomes charged in the niosome's acidic environment and cannot escape. The trapping of these drugs within the niosomes is much more effective by this process. The acidic pH of the niosomes traps the medications inside the vesicles [26].

FACTORS INFLUENCING NIOSOME FORMATION

Numerous factors influence the niosome's chemical and physical characteristics.

Drug: The size of the vesicle increases when a medication becomes trapped in niosomes. This is likely due to the interaction between the surfactant's head groups and the solute, which intensifies the mutual repulsion and charge of the surfactant bilayers [27]. A portion of the medication becomes lodged in the lengthy PEG chains in vesicles coated with polyoxyethylene glycol (PEG). As a result, the vesicles are kept from expanding. The degree of entrapment is influenced by the drug's hydrophilic-lipophilic equilibrium [28].

Surfactant nature: Ester-type non-ionic surfactants are less dangerous than ether-type non-ionic surfactants, despite the latter being more stable. For the generation of niosomes, the surfactant's HLB value is particularly crucial. This equation is used to calculate it. The formula for CPP is v/Ic times 0. The volume of the hydrophobic sections (Vlc), which is equivalent to the critical length of these hydrophobic areas (a0), and the area of the hydrophilic head group are used to compute the critical packing parameter (CPP). The longer hydrophobic chain of the surfactant enhances the stability of the niosome suspension, improves drug encapsulation, reduces leakage of low molecular weight drugs from the aqueous compartment, and increases the melting temperature [29].

The temperature of hydration: The temperature at which pro-niosomes are hydrated affects their size and structure. Solulan C_{24} (91:9) $C_{16}G_2$ is a polyhedral vesicle that is based at 25°C. It changes into a spherical vesicle at 45°C, and upon cooling, it forms a cluster of smaller spherical niosomes at 55–49°C [30].

Cholesterol charge and content: The hydrodynamic diameter and trapping effectiveness of niosomes are increased when cholesterol is present. Cholesterol has two main effects: it makes liquid-like layer structures more organized, and it makes solid-like layer structures less organized [31]. The gel state changes into a liquid-organized stage at high cholesterol concentrations. The rigidity of the resultant bilayers increased with a larger cholesterol content, which also decreased the rate of encapsulated material release [32]. In a multilamellar vesicle structure, charge tends to increase the interlamellar distance between subsequent bilayers, hence increasing the total entrapped volume [33].

Osmotic stress tolerance: Upon the addition of a hypertonic salt solution, the diameter of a niosome suspension shrinks, indicating resistance to osmotic stress. In a hypotonic salt solution, the vesicles first discharge moderately and then gradually swell, most likely due to the reduction of the eluting fluid. A quicker discharge occurs next, which may be a consequence of the vesicles' physical structure relaxing under osmotic stress [34].

Membrane Additives: In addition to medicines and surfactants, the quantity of additives used in niosomal formulation can boost niosome stability. Many additives have an impact on the permeability, shape, and membrane stability of vesicles [35]. For example, adding cholesterol to the niosome system stiffens it, decreasing the ease with which pharmaceuticals can flow through the membrane. The spherical vesicles that are produced by 1 $C_{16}G_2$/cholesterol/M-polyethylene glycol (PEG)-chol have dimensions that range from 20 to 200 nm [36] [37].

APPLICATIONS

Several applications for niosomes are listed with some examples.

Ocular Drug Delivery: Research on using niosomes to transport drugs straight to the eye is ongoing to increase drug retention and absorption. For instance, timolol maleate niosomal formulations have been developed and, when compared to conventional eye drops, have demonstrated an improved decrease in intraocular pressure in glaucoma patients.

Targeted Drug Delivery: Niosomes are being utilized to target specific cells or tissues, thereby increasing treatment efficacy while minimizing adverse effects. For example, doxorubicin-loaded niosomes have been developed for targeted cancer treatment and have demonstrated improved tumor targeting and reduced systemic toxicity in preclinical studies.

Diagnosis: For diagnostic purposes, niosomal targeting technology is being investigated, especially in imaging and biomarker detection. For instance, niosomes have been utilized to transport imaging agents for enhanced MRI contrast, which makes tumors and other anomalies more visible.

Immunological Studies: To better understand immune mechanisms and develop vaccines, niosomes are being utilized to investigate how the immune system responds to antigens. As an illustration, niosomal formulations carrying particular antigens have demonstrated improved immune responses in vaccine tests as compared to free antigens, suggesting their potential as vaccine carriers.

Transdermal Drug Delivery: Niosomes are being developed for transdermal applications to increase drug absorption via the skin. For instance, niosomal gels containing diclofenac have been developed for transdermal administration and have demonstrated improved skin penetration and analgesic effects compared to traditional formulations.

Peptide Drug Delivery: Peptide medications, which frequently have issues with stability and bioavailability, are delivered using niosomes. For instance, niosomal insulin formulations have been developed to improve oral bioavailability and have shown promise in preclinical research for the treatment of diabetes.

Cancer Treatment: Niosomes are being explored as carriers for anti-cancer medications, enabling for targeted and selective treatment of malignancies. For instance, paclitaxel-encapsulated niosomes have demonstrated increased cytotoxicity against a range of cancer cell types, suggesting the possibility of more potent cancer treatments [40].

***EVALUATION PARAMETER OF NIOSOMES* (given in Table 2)**

Actual Drug Content and Entrapment Efficiency: Niosome centrifugation is used to determine the actual drug content and efficiency. The free drug is then separated using a centrifugation technique, and its confirmation is obtained using spectroscopy [41].

Production Yield Calculation: The following formula is used to calculate production yield to determine efficiency: Production yield is calculated as follows:

$$\boldsymbol{Yield} = \frac{\boldsymbol{Practical\ yield}}{\boldsymbol{Theoretical\ yield}} \times \mathbf{100}$$

Infrared Spectroscopy: This technique utilizes a spectrogram to examine the interactions between the drug and additives, thereby determining the functional groups of the drugs.

Differential Scanning Colorimetry: A differential scanning calorimeter is used to perform thermal examinations of drug-loaded niosomes, Span 60, cholesterol, and the pure drug. We can learn about drug excipients using thermograms [42].

Scanning Electron Microscopy: This technique provides us with all the information regarding the surface morphology as well as the physical morphology of individual particles.

Transmission Electron Microscopy: Transmission electron microscopy is used to examine the internal structure and properties of niosomes. Transmission microscopy provides insight into the intrinsic properties of our compositions [43].

Zeta Potential: The zeta potential apparatus, operated at 25°C, measures the charges on the vesicular surface by combining phase analysis light scattering with laser Doppler velocimetry. Bi-distilled water can be used to tenfold dilute GLM niosome dispersions. After being transferred to a quartz cuvette, the samples will be weighed at room temperature. Every measurement will be made three times, and the standard deviations and mean values will be noted [44].

Particle Size Analysis: To determine the actual average particle size of our formulation, a total average particle size analysis will be performed utilizing particle size analyzers.

In Vitro Permeation: To test drug absorption, various animal skins, including the skin of a male albino rat, a shed snake, the ear of an albino pig, and a male guinea pig, can be used to assess the transdermal niosomal drug release pattern [45].

In vitro skin penetration: The in vitro skin penetration experiments also utilize the Franz diffusion cell. Throughout the experiment, the receptor phase temperature was kept at 37 ± 1 °C. The amount of medication that leaked through the previously mentioned different animal skins was measured by taking samples from the receptor compartment at predetermined intervals. Analysis was done on the extracted samples. Spectrophotometric analysis was performed on the extracted materials [46] [53].

Stability Study: To perform stability tests, all niosomal formulations were maintained in a thermostatic oven at 4°C, 25°C, and 37°C for three months. After a month, the drug content of each formulation was examined using an appropriate technique. To determine the medication release pattern, in vitro release studies of specific formulations can also be conducted [47].

Osmotic Shrinkage: The decrease in vesicle width that happens when a hypertonic salt solution is added to the niosomal suspension can be used to track the osmotic shrinking of vesicles. The ability of the lipid to maintain membranes is demonstrated by the fact that niosomes composed of pure surfactant are osmotically more sensitive than vesicles containing cholesterol [48].

Number of Lamellae: The number of lamellae has been ascertained using electron microscopy, small-angle X-ray spectroscopy, and NMR spectroscopy [49].

Membrane Rigidity: The membrane stiffness of particular niosomal formulations has been evaluated by measuring the mobility of a fluorescent probe as a function of temperature [50].

Table 2: Evaluation parameters and methods

Evaluation Parameter	Method
Production Yield	Practical yield / Theoretical yield x 100
Actual Drug Content	Niosome centrifugation followed by spectroscopy
Entrapment Efficiency	Niosome centrifugation and spectroscopy
Infrared Spectroscopy	Spectrogram analysis to examine drug-additive interactions
Differential Scanning Calorimetry	Thermal examination using a differential scanning calorimeter
Scanning Electron Microscopy	Surface and physical morphology analysis
Transmission Electron Microscopy	Internal structure examination
Zeta Potential	Phase analysis light scattering and laser Doppler velocimetry
Particle Size Analysis	Particle size analyzers
In Vitro Permeation	Assessment using various animal skins for transdermal drug release
In Vitro Skin Penetration	Franz diffusion cell method
Stability Study	Storage at 4°C, 25°C, and 37°C for three months; drug content analysis
Osmotic Shrinkage	Observation of vesicle width changes in hypertonic solutions
Number of Lamellae	Electron microscopy, small-angle X-ray spectroscopy, NMR spectroscopy
Membrane Rigidity	Fluorescent probe mobility measurement at varying temperatures

CONCLUSION

In conclusion, niosomes are a significant development in drug delivery systems, utilizing their special qualities to improve bio-availability and therapeutic efficacy. In comparison with conventional liposomes, their structure, which is composed of cholesterol and non-ionic surfactants, enables greater stability

and adaptability. Numerous hydrophilic and hydrophobic medications can be encapsulated by niosomes, allowing for targeted distribution and regulated release. This is very advantageous when treating infectious diseases and cancer, among other medical disorders. Although their benefits are evident, issues such as physicochemical instability, short shelf life, and possible drug leakage need to be resolved in order to maximize their application and formulation. The potential of niosomes for use in pharmaceutical applications will be further enhanced by an ongoing study into their preparation, characterization, and assessment techniques. As nanotechnology advances, niosomes are likely to play a significant role in future medication delivery, offering innovative approaches to enhance patient outcomes and therapeutic efficacy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTION

Vaishali Sharma, Chinkey Mittal, and Shweta Shekhedwal contributed to the literature collection, conceptualization, drafting, and organization of the manuscript. Vasu Chaudhary and Sachin Kumar assisted with manuscript review, editing, and content validation. All authors have read and approved the final version of the manuscript.

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