A Comprehensive Review on Niosomes in Drug Delivery and Recent Advancement

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Abstract

Niosomes are non-ionic surfactant-based vesicles that have gained significant attention in the field of drug delivery due to their ability to encapsulate a wide variety of therapeutic agents, including hydrophilic and hydrophobic drugs, proteins, and nucleic acids. These vesicles offer several advantages over traditional drug delivery systems, such as improved drug stability, controlled release profiles, biocompatibility, and reduced toxicity. This review provides a comprehensive overview of the structure, composition, and preparation techniques of niosomes, as well as their diverse applications in drug delivery, including cancer therapy, transdermal delivery, gene therapy, and vaccine development. Recent advancements in niosome-based drug delivery are also discussed, highlighting innovations such as surface modification for targeted drug delivery, stimuli-responsive niosomes, hybrid systems, and multifunctional platforms for combined therapy and diagnostics (theranostics). Additionally, the review addresses the challenges associated with niosome-based formulations, including stability, scalability, and regulatory concerns, and explores future directions in the development of niosomes for advanced therapeutic applications. Overall, niosomes represent a promising and versatile approach in drug delivery, with the potential for significant clinical impact in the treatment of various diseases.

Keywords: *Niosomes, Targeted drug delivery, Nanomedicine, Multifunctional niosomes, Drug encapsulation, Cancer therapy.*

1. INTRODUCTION

Niosomes are a new drug delivery system, which entangled the hydrophilic drug in the core depression and hydrophobic drugs in the non-polar region present within the bilayer hence both hydrophilic and hydrophobic drugs can be incorporated into niosomes [1]. The first niosome phrasings were developed and patented by L'Oreal in 1975. In the presence of proper fusions of surfactants and charge converting agents from the thermodynamically stable vesicles

[2]. Niosomes can be conducted through various routes similar as oral, parenteral, topical. Niosomes are used as a carrier to deliver different types of drugs similar as synthetic and herbal, antigens, hormones and other bioactive composites[3,4]. Niosomes are concentric bilayered vesicles in which an waterless volume is entirely enclosed by a membranous lipid bilayer substantially composed ofnon-ionic surfactants and cholesterol. Niosomes can be used to deliver both hydrophobic and hydrophilic drugs via transdermal route. Although niosomes were tried for various routes, it's used in the request for transdermal route (Novasome Products similar as 30 Petrolatum Novasomes and 10 salicyclic acid novasomes). Niosomes increase skin penetration of drugs and it can act as original depot for sustained release of dermally active composites [5]. Niosomes are bitsy lamellar structures of size range between 10 to 1000 nm and consists of biodegradable,non-immunogenic and biocompatible surfactsnts. The niosomes are ampiphillic in nature Niosomes can ameliorate the performance of the drug motes [4].

Advantages of Niosomes:

- Niosomes can entrap solutes.
- Niosomes are osmotically active and stable.
- Niosomes have an infra- structure comprising of hydrophobic and hydrophilic for the utmost part together therefore likewise oblige the drug tittles with an expansive variety of dissolvability.
- Niosome discharge the drug in a controlled way by means of its bilayer which give supported appearance of the boxed drug, so niosomes fill in as drug storehouse in the body.
- Iosomes exhibits inflexibility in their structural characteristics(composition, fluidity and size) and can be designed according to the asked situation.[4 5 6]

STRUCTURE OF NIOSOME

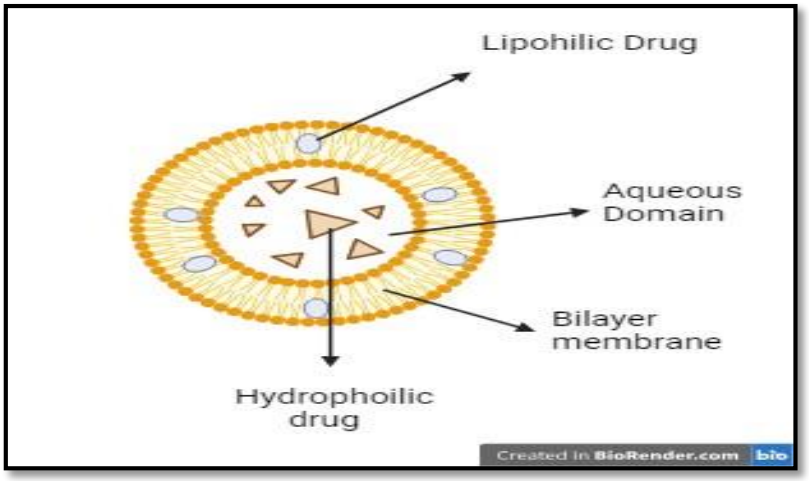

Figure 1 Structure Of Niosome

2. METHODS OF PRPERTION OF NIOSOME

- **Ether injection** [7]
  Using a 14-gauze needle and a gradual injection technique, cholesterol (150 micromoles) in 20 milliliters of ether (25 milliliters/min.) In a 4 ml heated aqueous phase kept at 60°c. Using a rotary evaporator, the ether solution was evaporated. Single-layered vesicles were formed as a result of the organic solvent evaporating or in this method, a mixture of vesicle-forming agents like surfactant and cholesterol is dissolved in a volatile organic solvent such as diethyl ether or chloroform within a round-bottom flask. The organic solvent is evaporated at room temperature using a rotary evaporator, leaving behind a thin film of the solid mixture deposited on the flask walls. This dried surfactant film can subsequently be rehydrated with an aqueous phase under gentle agitation, resulting in the formation of multilamellar niosomes [8].
- **Hand Shaking Method (Thin Film Hydration Technique)**
  This approach involves dissolving a combination of vesicle-forming ingredients, such as cholesterol and surfactant, in a volatile organic solvent, such as diethyl ether or chloroform.circular-bottom flask. A rotary evaporator is used to evaporate the organic solvent at room temperature, leaving behind a thin layer of solid mixture that is deposited on the flask walls. Multilamellar niosomes can then be produced by gently agitating the aqueous phase while rehydrating the dried surfactant film [8].
- **Extrusion method** [9]
  By extruding C16g2, a chemically specified non-ionic surfactant, across a polycarbonate membrane, niosomes were created utilizing this technique. These studies show how size affects drug encapsulation in addition to the number of extrusions' effect on vesicle size.
- **Sonication**
  by employing the sonication process, baillie et al. (1986) created niosomes. in this approach, a mixture of surfactant and cholesterol (150 micromoles) was dissolved in 2 milliliters of aqueous phase inside a vial. the dispersion is probe-sonicated at 60 degrees celsius for three minutes.using this technique, mlvs that are vibrated at ultrasonic frequencies are formed. there are two types of sonicators: bath and probe. The bath sonicator is used for large sample volumes, whereas a probe sonicator is used for small sample volumes [9].
- **Reverse phase evaporation technique (REV):**
  His procedure involves mixing a combination of ether and chloroform with surfactant (1:1) and Cholesterol. A phase of water adding medication to this, and then sonicating the two resultant Phases at 4-5°C. The transparent gel that has formed above is then further sonicated when a small Amount of phosphate buffer saline is added. The organic phase is eliminated at 40°C and low Pressure. To produce niosomes23, phosphate-buffer saline is added to the resultant viscous Niosome suspension and cooked in a water bath at 60°C for 10 minutes [10].
- **The "Bubble" Method**
  This technology, which was very recently invented, makes it possible to create niosomes without the application of organic solvents. A round-bottom flask with three necks makes up the bubbling unit, which is submerged in a water bath to regulate temperature. The first and second necks contain a thermometer and a water-cooled reflux, while the third neck is where

nitrogen is supplied. At 70°c, cholesterol and surfactant are distributed in a ph 7.4 buffer. After mixing this dispersion for 15 seconds with a high shear homogenizer, it is immediately bubbled at 70°c with nitrogen gas to produce niosomes [11].

- **Micro fluidization** [12]
  Micro fluidization is a relatively new method that works on the submerged jet principle. Two fluidized streams interact in this situation at extremely high velocities. And proceed through the interaction chamber's perfectly designed micro channel. Greater homogeneity, smaller size, and improved reproducibility of the formed niosomes are the outcome of the thin liquid sheet impingement along a common front organized so that the energy provided to the system stays inside the area of niosome formation [20].
- **Separation of unentrapped drug** [13-19]
  There are several methods for removing the unentrapped solute from the vesicles, including gel
  Filtration, dialysis, and centrifugation.

(i) Dialysis: One of the most crucial methods for extracting unentrapped medication from vesicles is dialysis. This method dialyzes the aqueous niosomal dispersion against phosphate buffer, regular Saline, or glucose solution in dialysis tubing.

(ii) Gel Filtration: This method involves eluting niosomal dispersion using phosphate buffered Saline or regular saline after gel filtration of the drug's unentrapped form through a Sephadex-G-50 column.

(iii) Centrifugation: After centrifuging the niosomal suspension, the supernatant is extracted. To create a niosomal suspension free of medication that is not entrapped, the pellet is first rinsed and then resuspended [20].

3. PHYSICO-CHEMICAL EVALUATION OF NIOSOME

3.1. Morphological Characterization

- **Transmission Electron Microscopy (TEM)**: Provides high-resolution images to observe the size, shape, and vesicular structure of niosomes.
- **Scanning Electron Microscopy (SEM)**: Used to analyze the surface morphology and shape of niosomes, providing insights into their surface texture.
- **Atomic Force Microscopy (AFM)**: Offers detailed surface topography at the nanoscale, revealing vesicle shape, surface roughness, and size.
- **Dynamic Light Scattering (DLS)**: Measures the hydrodynamic size and size distribution of niosomes in suspension, providing information about particle uniformity [20].

3.2. Size and Size Distribution

- **Dynamic Light Scattering (DLS)**: As mentioned, DLS is a widely used technique to assess the average size, size distribution, and polydispersity index (PDI) of niosomes.
- **Laser Diffraction**: Another method for determining the size distribution of niosomes.
- **Nanoparticle Tracking Analysis (NTA)**: Provides real-time tracking of individual particle movement to measure size and distribution [20].

3.3. Encapsulation Efficiency (EE) and Drug Loading

- **Ultrafiltration**: The unencapsulated drug is separated from niosomes, and the concentration of free drug is measured to calculate encapsulation efficiency.

- **Dialysis Method**: Similar to ultrafiltration, this technique involves separating free drug molecules using a dialysis membrane and quantifying the encapsulated drug.
- **Centrifugation**: The niosomes are centrifuged to separate them from the free drug, and the amount of drug in the supernatant is quantified to determine the drug loading capacity[21].

3.4. Surface Charge (Zeta Potential)

- **Zeta Potential Measurement**: This technique determines the surface charge of niosomes. A high zeta potential (positive or negative) generally indicates good colloidal stability, as it prevents aggregation of niosomes [22].

3.5. In Vitro Drug Release Studies

- **Dialysis Technique**: This method uses a dialysis bag to separate the niosome-containing solution from a release medium. Samples are taken at various time points to measure the amount of drug released.
- **Franz Diffusion Cell**: A model for studying the release of drugs from niosomes across a membrane, simulating biological barriers.
- **UV-Vis Spectrophotometry or HPLC**: Used to quantify the amount of drug released over time by measuring absorbance or by analyzing the concentration through chromatographic methods [23].

3.6. Stability Studies

- **Physical Stability**: Niosomes are stored under different conditions (temperature, humidity, light) to assess physical changes, such as vesicle aggregation, leakage, and sedimentation over time.
- **Chemical Stability**: The chemical stability of the encapsulated drug is assessed by measuring the drug concentration over time, often using methods like UV spectrophotometry or HPLC.
- **Accelerated Stability Testing**: To predict the shelf life of niosomes, samples are subjected to elevated temperatures and humidity to observe changes in size, morphology, and drug release properties [24].

3.7. In Vitro Cytotoxicity and Biocompatibility

- **MTT Assay**: A common assay to assess cell viability and cytotoxicity of niosomes on cultured cells (e.g., fibroblasts, tumor cells).
- **Cellular Uptake Studies**: Techniques like flow cytometry or fluorescence microscopy are used to study how efficiently niosomes are internalized by target cells.
- **Hemolysis Test**: Used to evaluate the biocompatibility of niosomes with blood cells by assessing their ability to lyse red blood cells upon contact [25].

3.8. In Vivo Evaluation

- **Biodistribution Studies**: Niosomes labeled with fluorescent or radiolabeled tracers are injected into animal models to study their distribution, accumulation, and clearance in different tissues.
- **Pharmacokinetic Studies**: Measurement of drug concentrations in plasma and tissues over time to determine the release profile and circulation time of drug-loaded niosomes.
- **Therapeutic Efficacy Studies**: Evaluation of the therapeutic effect of drug-loaded niosomes in animal disease models (e.g., tumor-bearing rats for cancer therapy) [22].

3.9. Thermal Analysis

- **Differential Scanning Calorimetry (DSC)**: Used to study the thermal behavior of niosomes, such as phase transitions of the surfactant and drug, as well as the stability of the vesicular structure.
- **Thermogravimetric Analysis (TGA)**: Measures changes in the weight of niosome samples as a function of temperature, which helps in assessing their stability and composition[21].

3.10. Release Kinetics and Mathematical Modeling

- **Modeling Release Patterns**: The release of the encapsulated drug is often modeled using kinetic models (e.g., zero-order, first-order, Higuchi, Korsmeyer-Peppas) to better understand the mechanism of drug release and its potential for controlled release applications.
- **Release Mechanism Studies**: These studies examine whether drug release from niosomes occurs via diffusion, degradation, or swelling mechanisms.

APPLICATIONS OF NOISOME

1. **Niosomes Drug Transporters**
   Niosomes have also been employed as delivery systems for the individual drug iobitridol, which is used inX-ray imaging. Topical niosomes can work as a solubilization matrix, a original point for the dragged release of substances that are dermally active, penetration enhancers, or a membrane hedge that limits the rate at which specifics are absorbed systemically [23].
2. **Treatment for leishmaniasis**
   The most often given medications for leishmaniasis are derivatives of antimony. These medications in increased concentrations – can harm the kidneys, liver, and heart. By demonstrating that negative effects may be overcome at higher concentrations as well, the use of niosomes as a medication carrier has demonstrated increased efficacy in treatment [24].
3. **Focusing on bioactive substances** [25, 26].
   a) To the endothelium-reticulum system (RES)
   The vesicles are selectively absorbed by the res cells. Niosome absorption by the additionally, cells are marked for clearance by circulating serum substances called opsonins, which increase the vesicle mark of niosomes at 20°c for 24 hours before heating to room temperature. However, such localized medication accumulation has been used to treat liver parasite infestation and animal tumours that have been known to spread to the liver and spleen.
   (b) To organs apart from RES.
   It has been proposed that the carrier system can be targeted to particular bodily locations by the use of immunoglobulins, which attach to lipid surfaces fairly easily. Providing a practical way to target drug carriers. It is possible to use the innate ability of many cells to identify and bind specific carbohydrate determinants to guide transport systems to specific cells.
4. In an in vitro intestinal model, niosomal ruse oral administration **Transport of peptide specifics**
   of 9- desglycinamide, 8- arginine vasopressin was delved . circle model and set up that there was a notable enhancement in peptide stability41.Applications of niosomes in immunology niosomes have been employed to explore the nature of the vulnerable response touched off by

antigens. According to reports, niosomes are a important adjuvant with strong immunological particularity, minimum toxin, and stability [27].

5. **Anti Neoplastic**

Niosomes can modify drug metabolism, extend circulation times, and prolong the half-life of Antineoplastic drugs, thereby reducing their side effects. They also contribute to lower tumor Proliferation rates and result in higher drug concentrations in the bloodstream with slower elimination [23].

6. Treatment of Cancer

Niosomal phrasings can deliver various anticancer drugs with low side goods. Conventional chemotherapy cannot widely target the cancerous cells and is associated with low remedial efficacity and a high prevalence of side goods and toxin to normal cells. Colloidal niosomal phrasings are promising systems for drug delivery to cancerous apkins, passively and laboriously. Delivery of anticancer drugs by niosomal phrasings can overcome low bioavailability and stability, significant threat of side goods, and shy access to the drug because of low saturation of the blood- brain hedge. The niosomal phrasings have been reported to drop the toxin of Withaferin – A (WA) as an active element of Withania somnifera(173), tamoxifen(TMX)/ curcumin.(174)

6.1 Type of cancer [30]

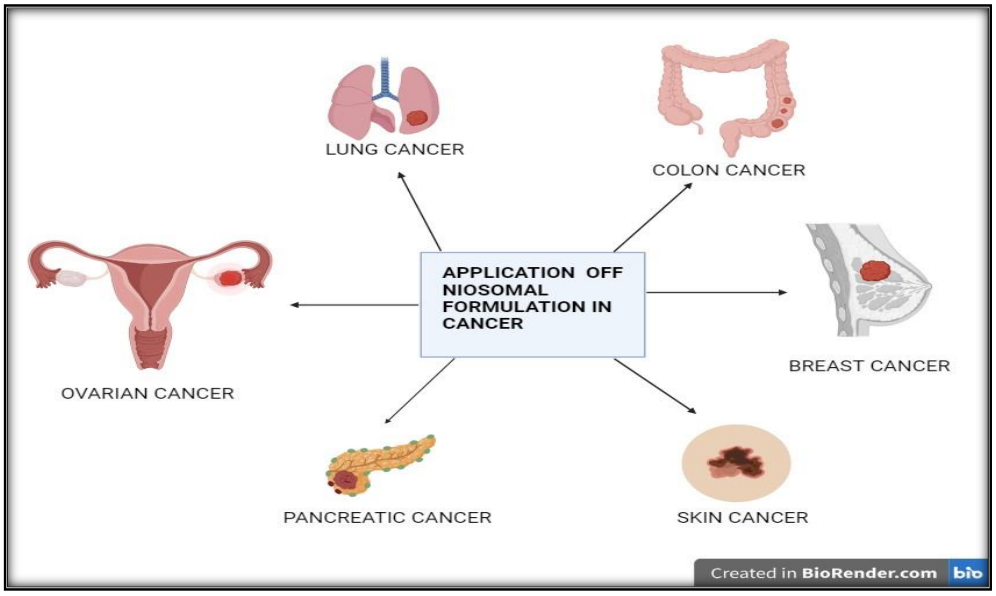

Figure 2 Application of Niosome in various types of cancer treatment

1. **Breast cancer**

Drug used in the treatment of breast cancer are Tamoxifen, Docetaxel, Metformin, Celecoxib, Gemcitabine , Ascorbic acid, Geranium oil , Curcumin , Cisplatin, Epirubicin , Curcumin, Folic acid ,

Letrozole, Cyclophosphamide, Folic Acid , Farnesol, Gingerol , Doxorubici cisplatin, Doxorubicin , Epirubicin, Hyaluronic acid , Morusin , Melittin , Paclitaxel Paclitaxel , Curcumin , 2,5-DiketopiperazineCarnosine, Melittin , Ascorbic acid, Curcumin , Doxorubicin, Curcumin , Trastuzumab, Mcl-1 Nioplex. They are all prepared by Thin-film hydration formulation methods.

2. **Lung cancer**
   Drug used in the treatment of Lung cancer Nintedanib , Artemisin, Metformin , Metformin, Silibinin, Sunitinib, They are all prepared by Thin-film hydration formulation. 5-fluorouracil is also used and it is Prepared by Various techniques formulation (thin-film hydration, reverse-phase evaporation, sonication, Ethanol injection)Drug used in the treatment Colorectal cancer Oxaliplatin, Paclitaxel, Curcumin, Saccharomyces cerevisiae Silibinin They are all prepared by Thin-film hydration.
3. **Skin cancer**
   Drug used in the treatment of Skin cancer Hippadine it is prepared by Microfluidic mixing ,Gammaoryzanol it is prepared by Solvent injection method, Amygdalin and Ozonated olive oil it is Prepared by Thin-film hydration
4. **Ovarian cancer**
   Ovarian cancer is a general gynecological cancer that contributes to mortality. Despite this, an effective remedy for this complaint remains fugitive owing to several obstacles, including the fact that previous discovery is nearly insolvable as the symptoms in the early stage are minimum. In addition, ovarian cancer has a high chance of relapse and is noticeably resistant to chemotherapy treatments. Current cancer remedy exploration is concentrated on developing restorative mending agents to target ovarian cancer. Current cancer remedy exploration is concentrated on developing restorative mending agents to target ovarian cancer

7. Niosome used in treatment of various Diseases [28 29]

Niosome are used in different types of disease

Table 1 Niosome are used in different types of disease

Diseases	Surfactant (s)	Additive(s)	Drug	product system of drug	Results
Glaucoma	Span 20, 40, 60, Tween 20, 40	Cholestero	Timolol maleate	TFH [Targeted-Fusion Hybrid system]	Loftiest EE set up in niosomes prepared with span60 and Tween 40(> 90), and niosomes dragged drug release and IOP- lowering exertion up to 24 h
Conjunctivitis	Span 60	Cholestero	Azithro mycin-β-CD	SI, TFH, Hand shaking [Self-Injectable]	Shaking EE% of prepared niosomes (>30%) and niosomal in situ gel formulations (>63%) Were high, and niosomes prolonged drug release up to 12 h with increased corneal permeation

Fungal keratitis	Span 60	Cholesterol Dicetyl phospate N-Trimethyl chitosan	Natamy -cin	TFH	Both uncoated and TMC coated niosomes extended drug release up to 12 h., and TMC Coated niosomes are higher mucoadhesion and corneal permeability than uncoated niosomes

Diseases	**Surfactant (s)**	**Additive(s)**	**Drug**	**product system of drug**	**Results**
Genetic retinal disorders	Tween 80 Poloxamer 188	chloroquine(CQ) Cationic lipid 2,3- di(tetra decyloxy) propan-1- amine	pCMS-EGFP plasmid	REV **[**Reverse-Phase Evaporation]	Transfection effectiveness of pristine nioplexes was advanced than CQ- nioplexes but effectiveness of both nioplexes were lower compared to Lipofectamine 2000, and CQ- nioplexes transfected cells in inner layers of retina
Corneal graft rejection	Span 60 Tween 80	Hyaluronic acid	Cyclosp orine A	SI	HA- carpeted elastic niosomes had EE of> 92, and HA- carpeted phrasings were advanced corneal permeability than drug conflation and Span60 niosomes
Diabetic keratopathy	Span 60 Solulan C24 Sodium cholate	Cholesterol Dicetyl phospate	Naltrex one	REV	All of the niosomal formulations showed no irritation and have good corneal tolerability

CONCLUSION:

Recent advancements in niosome-based drug delivery have focused on enhancing their stability, targeting ability, and functionality. Surface modifications, such as PEGylation and ligand targeting, have improved their pharmacokinetic profiles and enabled site-specific drug delivery. Moreover, stimuli-responsive niosomes and hybrid systems that combine niosomes with other drug delivery technologies (e.g., liposomes, nanoparticles) are paving the way for more sophisticated, multifunctional platforms. These innovations hold great promise for the development of "smart" drug delivery systems capable of achieving higher therapeutic efficacy with minimal side effects. Despite these advances, challenges remain in the commercialization of niosomes, particularly in the areas of long-term stability, large-scale production, and regulatory hurdles. However, ongoing research is actively addressing these issues, with new techniques being developed to optimize niosome formulations for clinical use.

In conclusion, niosomes represent a highly adaptable and effective platform for drug delivery, with substantial potential for improving therapeutic outcomes in various diseases. Continued research and development, along with advancements in nanotechnology and surface engineering, are expected to drive the future success of niosome-based systems in clinical applications, making them a key component in the next generation of drug delivery technologies.

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