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NIOSOMES AS ADVANCED VESICULAR DRUG DELIVERY SYSTEMS: A COMPREHENSIVE REVIEW

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Abstract:
Niosomes have been recognised as one of the most promising vesicular drug delivery systems due to their capacity to enhance the efficacy of several drugs. These small vesicles are composed of non-ionic surfactants and cholesterol. They can entrap hydrophilic and lipophilic drugs, protecting them from degradation and increasing their stability, bioavailability, and controlled release. Due to their biocompatibility, low toxicity, easy preparation, and cost-effectiveness, these vesicles offer promising prospects compared to traditional drug delivery systems as well as other vesicular systems. The pharmaceutical applications of niosomes include oral, topical, transdermal, ocular, pulmonary, and parenteral drug delivery for treating cancer, infections, inflammatory, neurological and other chronic diseases. Further advances in formulation approaches, surface modifications, targeted and stimuli-responsive systems have contributed towards widening their applications in the pharmaceutical industry. Future efforts are anticipated to help address all the present limitations, thus leading to the successful development of niosomal drug delivery systems.

Keywords: *Bioavailability; Controlled drug release; Drug delivery systems; Niosomes; Non-ionic surfactants; Nanocarriers; Targeted drug delivery ;.Vesicular drug delivery;*

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INTRODUCTION:

Drug delivery is an essential factor that determines the efficacy of medications for prevention, treatment, or management of diseases. Even though many medications exhibit very good therapeutic characteristics, they fail to provide good results because they do not reach the target site at effective concentrations. Traditional drug delivery systems, including tablets, capsules, injections, and topical formulations, experience problems related to low bioavailability, fast metabolism, short biological half-life, and side effects as a result of non-specific delivery into the body. To overcome these shortcomings and make sure that patients receive sufficient medication doses, researchers work on innovative drug delivery systems that allow increasing the stability and efficacy of medicines, prolonging their release, reducing toxicity, and improving outcomes.[1]

There exist many different types of advanced drug delivery techniques, but the ones that involve vesicular drug delivery systems have gained more prominence due to their capability of encapsulating both water-soluble and lipid-soluble drugs. Such vesicular drug delivery systems act as protective agents that protect the drug from degradation, help in increasing the absorption rate of the drug and help in releasing the drug in a controlled manner. Some of the vesicular carriers such as liposomes, transfersomes, ethosomes and niosomes have been created in the past few decades to counter the disadvantages of the traditional systems. Of all these systems, niosomes stand out as one of the most successful vesicular systems due to their simple nature, easy to prepare and cheap to produce.[2]

The niosomes are micro-vesicles that are made of non-ionic surfactants and cholesterol, and when these substances assemble, they form bilayers that trap various types of drugs. The formation of niosomes is special because they can trap hydrophilic drugs in the aqueous phase, while lipophilic drugs will be trapped in the lipid bilayer. They can alter the pharmacokinetics of drugs, including increasing the stability of drugs, extending the life span of drugs, and enhancing the controlled release of drugs. They are also capable of facilitating the drug entrapment in the target sites of action. Consequently, they have been studied for oral, transdermal, topical, ophthalmic, pulmonary, intravenous, and targeted delivery of drugs.[3]

During the past few years, there have been rapid advancements in niosomal drug delivery systems as a result of the development of novel formulation approaches, enhanced methods of production, and surface-engineered vesicles that enhance their targeting and therapeutic effects. There have been numerous studies into multifunctional niosomes that respond to environmental cues, can deliver more than one type of drug at the same time, and can deliver highly delicate biological molecules including proteins, peptides, and nucleic acids. This has increased the applications of niosomes in treating various diseases including cancers and infections.[4]

EVOLUTION OF VESICULAR DRUG DELIVERY SYSTEMS

The traditional drug delivery systems such as tablets, capsules, injections, syrup, and ointment have been in use for a long time now due to their simplicity in preparation and convenience to the patients. Nonetheless, these preparations have not succeeded in delivering the drug to the targeted site of action effectively. Drugs are subject to breakdown in the GI tract, metabolism in the liver, and excretion before they produce the anticipated pharmacological effect. This leads to an increase in dose requirements and the frequency of drug administration to achieve the desired result. Consequently, adverse effects may arise, and patient compliance decreases.

The invention of vesicular drug delivery systems was a major step forward in pharmaceutics. Vesicles are small spherical bodies that consist of one or more layers of lipids or surfactants, which make it possible to enclose both hydrophilic and lipophilic drugs in them. In addition to ensuring drug protection against chemical and enzymatic decomposition, their structure makes them stable and increases their bioavailability. The appearance of liposomes in the 1960s proved that vesicles were capable of targeting therapeutic drugs and releasing them in a controlled manner. This invention has led to the creation of other vesicles with better characteristics.[5]

After the success of liposomes, various sophisticated vesicular systems were developed to address the limitations that existed with the earlier delivery systems. Such vesicular systems include niosomes, transfersomes, ethosomes, pharmacosomes, and novasomes, all having certain structural and functional features. Niosomes are very important because their preparation through the use of non-ionic surfactants, which make them more stable and affordable to synthesise compared to traditional liposomes. Other vesicular systems were introduced to increase the skin permeation rate, flexibility, and drug-carrying capacity.

Currently, advances in vesicle-based drug delivery systems are seen in their combination with nanotechnology, biotechnology, and pharmaceutical science. Vesicles have been

developed to provide targeted drug delivery, controlled drug release, increased efficacy of therapy, and reduced toxicity to the body. Vesicle surface decoration with such compounds as polymers, antibodies, peptides, and other targeting agents makes it possible for vesicles to target specifically diseased tissues. Moreover, scientists are developing such vesicles that are capable of responding to various environmental stimuli (pH, temperature, enzymes, or light), releasing the cargo when necessary. Besides, artificial intelligence, Quality by Design, and continuous manufacturing technologies are increasingly used for the development of such systems.[6]

NIOSOMES

Niosomes are nano-vesicles that are prepared using the process of self-aggregation of non-ionic surfactants in the presence of cholesterol and other substances in the aqueous medium. In such a way, the surfactant molecules form one or several bilayers, giving rise to the formation of vesicles consisting of an aqueous core surrounded by the lipid-like membrane. Such a structure makes it possible for the niosomes to incorporate drugs of either hydrophilic type, incorporated into the aqueous core, or lipophilic type, incorporated into the bilayer membrane of the vesicle. Due to the amphiphilic properties of niosomes, they are capable of transporting various medicinal substances while protecting against their degradation.

Niosomes were discovered during the late 1970s and early 1980s when efforts to find an alternative to liposomes became a priority since liposomes were associated with high cost and problems related to instability. Non-ionic surfactants were observed to have the potential of forming stable bilayers, just like phospholipids; however, they were more chemically stable and inexpensive to manufacture. At first, niosomes were researched in the field of cosmetics to aid in the passage of substances across the skin. Motivated by their excellent results, the pharmaceutical sector was eventually drawn to the research of using niosomes as drug delivery agents. With the passage of time, advances in formulation and analysis have made niosomes one of the most widely studied vesicular drug delivery systems.[7]

The structure of niosomes involves one or more layers of bilayers comprising non-ionic surfactant molecules oriented such that the hydrophilic heads face the aqueous environment and the hydrophobic tails face the interior of the vesicles. The cholesterol molecules are included within the bilayer layer to make the membranes rigid, impermeable and increase stability. Hydrophilic drugs are entrapped within the aqueous core, whereas lipophilic drugs become trapped within the hydrophobic portion of the bilayers. Amphiphilic drugs can be entrapped in either portion of the vesicles. This ability of entrapment of drugs in two compartments makes the niosomes very versatile vehicles for delivery of a variety of drugs.

Niosomes are prepared by the spontaneous formation of a bilayer system using non-ionic surfactants when these are hydrated beyond their phase transition temperatures. On hydration, the hydrophobic end of the surfactant molecules avoids contact with water and orients towards the centre of the system, whereas the hydrophilic ends face the aqueous environment. This reduces free energy, resulting in the formation of a closed bilayer vesicle structure. The role of cholesterol is significant in filling the gaps between the surfactant molecules to stabilise the membranes and prevent leakage of the entrapped drug from within. The size, lamellarity, entrapment efficiency, and stability of the niosomes vary according to certain criteria.

The use of niosomes has become very significant in advanced drug delivery owing to their ability to overcome various drawbacks of conventional drug delivery systems. Niosomes can provide protection against chemical and enzymatic degradation of drugs, increase drug bioavailability, increase drug residence time, and provide controlled or sustained drug release. The accumulation of drugs at target sites by niosomes is possible, which may help in reducing the amount of drug used and thus reduce the toxic effects of the drug on the body system. The inclusion capability of niosomes allows them to deliver various types of drugs such as small molecules, proteins, peptides, vaccines, and nucleic acids, and they can be used for the treatment of different diseases.[8]

COMPOSITION OF NIOSOMES

Non-Ionic Surfactants

Non-ionic surfactants are the major constituents of niosomes that facilitate vesicle formation. They possess both hydrophilic and hydrophobic parts that allow them to form closed vesicles when hydrated in aqueous media. Typical examples of surfactants used in preparing niosomes include the Span, Brij, and Tween series, each with varying hydrophilic-lipophilic balance (HLB), chain length, and phase transition temperature. Choosing the right surfactant plays a crucial role in determining vesicle size, encapsulation capacity, membrane permeability, and stability of niosomes. Niosomes with the right HLB values usually have improved stability and drug release properties; hence, surfactants are the most essential ingredient in niosomal formulations.[9]

Cholesterol
Cholesterol is a vital compound that is introduced in niosome preparations to increase the stability and structural integrity of the bilayer structure. Cholesterol is known to act as a filler in the bilayer of niosomes and reduces fluidity to prevent the leakage of the drug from inside the niosomes. Another advantage of including cholesterol in niosomes is the ability of cholesterol to increase the strength of vesicles to protect them from aggregating, fusing, and degrading during storage. Nevertheless, the concentration of cholesterol should be carefully chosen since insufficient concentrations of cholesterol lead to instability of vesicles while high concentrations decrease the entrapment efficiency of drugs.

Charge-Inducing Agents
The role of charge-inducing agents is to increase the physical stability of vesicles through induction of electrostatic repulsion between individual particles. This ensures that there is no aggregation and fusion of the particles, thus ensuring that a good dispersion is maintained. Negatively charged agents like dicetyl phosphate and positively charged agents such as stearylamine are the common types used, depending on the surface characteristics desired. Charge-inducing agents also play the role of influencing the zeta potential of the niosomes, which is an important factor in evaluating the colloidal stability of the vesicles.[10]

Hydration Medium
Hydration medium acts as the aqueous medium needed for the formation of the niosomes. The process of hydration involves absorption of water by the dried surfactant film, which automatically rearranges into a bilayer structure. There may be many factors like the composition, pH, ionic strength, and temperature of the hydration medium that can influence the vesicle formation, particle size, entrapment efficiency and drug release mechanism. Distilled water and phosphate buffer saline are some of the frequently used hydration media. Drugs, which are sensitive to variation in the pH and ionic condition, require proper selection of the hydration medium to preserve the stability of the drug.

Drug Molecules
The ability of niosomes to carry a diverse range of drugs is attributable to the characteristic nature of its bilayer structure. Drugs that are hydrophilic in nature are entrapped within the core, whereas those that are lipophilic are entrapped in the hydrophobic layer of the bilayer structure. Those that have an amphiphilic nature can be entrapped in both layers of the bilayer structure depending on their physicochemical properties. Factors that affect the loading efficiency include molecular weight, solubility, ionisation, and affinity for the surfactant bilayer. Various categories of drugs that have been entrapped in niosomes include anti-cancer drugs, antibiotics, anti-fungal drugs, anti-inflammatory drugs, proteins, peptides, vaccines, herbs, and genetic material.[11]

Surface Modifiers
The surface modifiers are added to the structure of niosomes to enhance their biological performance as well as circulation properties. Hydrophilic polymers like polyethene glycol (PEG) have been used as coating material for niosomes and create stealth niosomes that do not get recognised by the reticuloendothelial systems. This results in increased circulation time of the niosomes in the body and an increase in the drug concentration at the target site. Different types of polymers like chitosan and polyethyleneimine can also be used to increase mucoadhesiveness, cellular uptake or stability of niosomes.

Targeting Ligands
Target ligands are bound to the surface of the niosome to obtain selective delivery of drugs to particular cells or tissues. Target ligands interact with and bind to the receptors that are present in higher amounts on the surface of diseased cells. Thus, the drug delivery is made more effective by accumulating the drug at its target location without affecting normal cells. Commonly used ligands include antibodies, peptides, folic acid, transferrin, aptamers, carbohydrates, and many others. Receptor-mediated uptake of the drug through endocytosis results in increased therapeutic action of the drug as well as decreased systemic toxicity. Targeted niosomes have become a field of great interest for the treatment of cancer, inflammation, infections, and neurodegenerative diseases.[12]

CLASSIFICATION

Basis of Classification	Type	Characteristics
Based on Size and Lamellarity	Small Unilamellar Vesicles (SUVs)	Single phospholipid/surfactant bilayer; size approximately 10–100 nm
	Large Unilamellar Vesicles (LUVs)	Single bilayer with large aqueous core; size >100 nm

	Multilamellar Vesicles (MLVs)	Multiple concentric bilayers; onion-like structure; size 0.5–10 µm
Based on Method of Preparation[13]	Thin-Film Hydration Niosomes	Prepared by hydration of a dried surfactant film
	Reverse Phase Evaporation Niosomes	Formed from water-in-oil emulsion
	Ether Injection Niosomes	Produced by injecting surfactant solution into a heated aqueous phase
	Sonicated Niosomes	Vesicles reduced in size using ultrasonic energy.
	Proniosome-Derived Niosomes	Hydrated from dry proniosomal formulations
Based on Route of Administration	Oral Niosomes	Designed for gastrointestinal drug delivery
	Topical Niosomes	Applied directly to the skin
	Transdermal Niosomes	Enhance drug permeation through skin.
	Ocular Niosomes	Designed for ophthalmic administration
	Pulmonary Niosomes	Administered through inhalation
	Parenteral Niosomes	Injectable formulations
	Intranasal Niosomes	Delivered through the nasal cavity
Based on Surface Modification	Conventional Niosomes	Unmodified vesicles
	PEGylated (Stealth) Niosomes	Surface coated with polyethene glycol (PEG)
	Ligand-Targeted Niosomes	Surface attached with antibodies, peptides, folic acid, etc.
	Polymer-Coated Niosomes	Coated with polymers such as chitosan
	Magnetic Niosomes	Contain magnetic nanoparticles
Based on Stimuli Responsiveness[14]	pH-Sensitive Niosomes	Release drug in acidic environments
	Thermosensitive Niosomes	Drug release triggered by temperature
	Redox-Responsive Niosomes	Respond to intracellular redox conditions.
	Enzyme-Responsive Niosomes	Activated by disease-specific enzymes
	Light/Ultrasound-Responsive Niosomes	Triggered by external stimuli

PHYSICOCHEMICAL PROPERTIES OF NIOSOMES

Bilayer Structure

The presence of bilayers is the basic property that differentiates niosomes from other traditional drug delivery systems. It comprises self-assembly of the non-ionic surfactants in an aqueous medium whereby the hydrophilic heads are directed towards water and hydrophobic heads towards the centre to create a bilayer membrane. Cholesterol is also added into the bilayer structure to increase its stiffness and decrease the permeability of the membrane. Such a structural arrangement not only gives mechanical strength to niosomes but also makes it possible for niosomes to carry various types of drugs.

Amphiphilic Nature

Niosomes have amphiphilic properties since they consist of molecules with hydrophilic and hydrophobic parts. Such an attribute allows the niosomes to load drugs with varied solubility. Drugs that are hydrophilic can be loaded in the aqueous core, while lipophilic drugs can be loaded in the hydrophobic bilayer. Amphiphilic drugs can be loaded in both regions depending on their physicochemical characteristics. Niosomes have a broad range of applications owing to this ability. It is also easy for niosomes to interact with cell membranes due to this attribute.[15]

Drug Encapsulation Efficiency

Drug loading efficiency is defined as the proportion of drug that is effectively loaded inside the niosomal vesicles as compared to the total quantity of drug used during preparation. This is one of the most important physicochemical characteristics because it affects the efficacy of the delivery system in terms of therapy. Drug loading efficiency is dependent upon various parameters such as type of surfactant, concentration of cholesterol, solubility of drug, size of vesicles, mode of preparation, and hydration of the vesicles. Niosomes can be considered highly efficient in loading both hydrophilic and lipophilic drugs into their vesicles.

Stability

Stability is one of the crucial attributes that determines the shelf life and efficiency of niosomal systems. Unlike liposomes, niosomes are more stable chemically due to the fact that non-ionic surfactants are not vulnerable to oxidation or hydrolysis. Cholesterol adds to membrane stability as it decreases bilayer mobility and prevents the leaking out of the entrapped substance. Still, there are factors like temperature, pH, and illumination that might affect the stability of vesicles. The right composition and storage of the system contribute to the maintenance of the appropriate particle size, drug entrapment, and membrane stability.[16]

Biocompatibility

Niosomes are usually regarded as biocompatible owing to their formation from non-toxic, biodegradable, and non-immunogenic non-ionic surfactants. Niosome formulation prevents irritation and makes the development of unwanted immune reactions less probable upon drug administration. Niosomal vesicles react harmlessly with biomembranes and slowly release the loaded drug without causing any tissue injury. Biocompatibility is another factor that facilitates better patient tolerance of the drugs and enables repeated administrations in case the therapy needs to be prolonged. However, biocompatibility is highly dependent on the type and amount of surfactants, surface-modifying agents, and other additives used for niosomal formulation.

Controlled and Sustained Drug Release

Controlled and sustained drug release is among the physicochemical advantages of niosomes. The bilayer membrane acts as a diffusion barrier controlling the entry of the loaded drug into the surrounding biological medium. The drug release rate can be modulated using parameters such as the composition of the surfactant, amount of cholesterol, vesicle size, surface coating, and the preparation method. Controlled drug release ensures that there are therapeutic levels of drugs for longer durations of time while avoiding variations in the concentration of drugs in the blood plasma. Consequently, this attribute makes niosomes very appropriate for treating chronic conditions.[17]

MECHANISM OF DRUG LOADING

Hydrophilic Drug Entrapment

During the formation of niosomes, the hydrophilic drugs get entrapped inside the aqueous core of the niosomes. When the surfactant bilayer is assembled in the aqueous phase, the soluble drugs get trapped in the inner aqueous layer. In this way, the drug gets protected from degradation, which increases its stability and bioavailability.

Lipophilic Drug Entrapment

The lipophilic drugs get entrapped in the hydrophobic part of the bilayer because of the nature of their attraction to the surfactant chains. During the formation of vesicles, the lipophilic drugs get entrapped in the lipid bilayer. It helps increase their solubility, release time, and membrane permeability.

Amphiphilic Drug Encapsulation

Amphiphilic medicines have hydrophilic and lipophilic properties and can partition into the aqueous core and bilayer membranes. The location of such drugs depends on polarity and the partition

coefficient. Dual compartmentalisation helps in increasing drug loading, sustaining its release, and improving stability and efficiency.[18]

MECHANISM OF DRUG RELEASE

Diffusion

The drug release via diffusion process involves the slow passage of the drug through the bilayer membranes of the niosomal vesicles and into the surrounding biological fluids. This release depends on the permeability of the membranes, solubility of the drug, vesicle size and concentration gradient.

Bilayer Erosion

This is the process that involves degradation of the surfactant bilayer leading to drug release. Factors such as enzymatic activity and pH may lead to the destabilisation of the bilayers, allowing the drug to be released.

Osmotic Swelling

Osmotic swelling takes place because of the flow of water into the vesicles through a difference in osmotic pressures inside and outside the vesicles. This leads to membrane swelling, releasing the entrapped drug.[19]

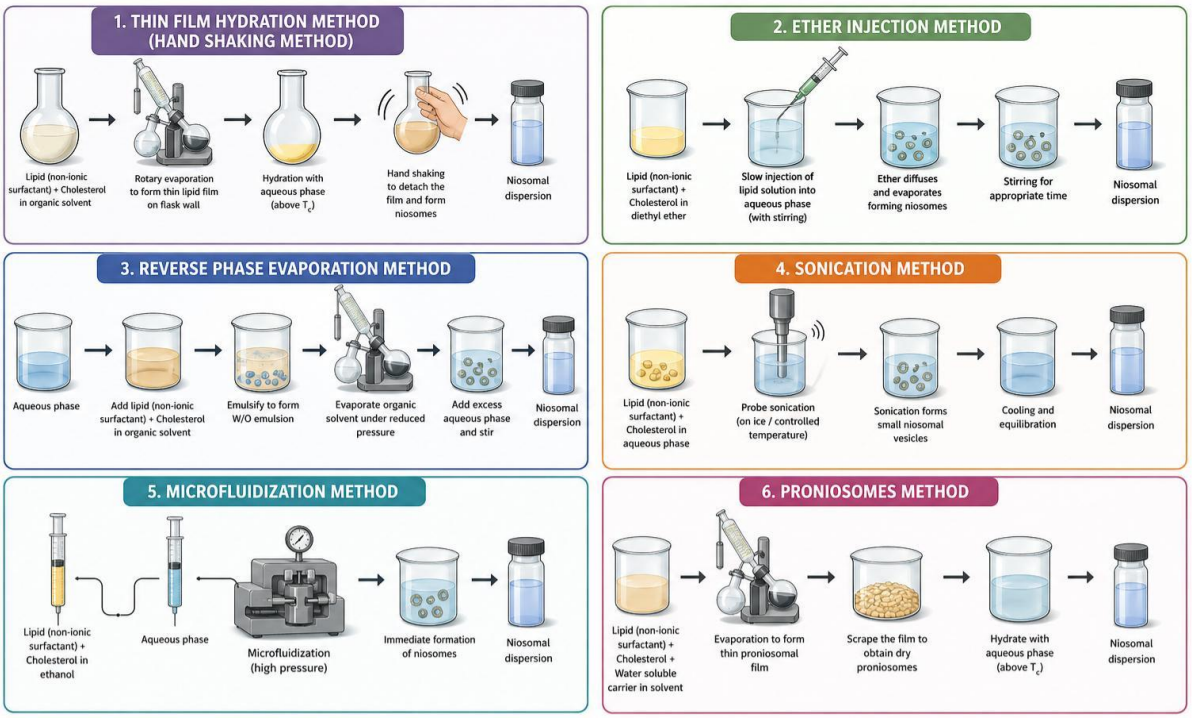
Stimuli-Responsive Release

The drug release from stimulus-responsive niosomes occurs after stimulation by some internal or external stimuli such as pH alteration, heat, enzymes, ultrasound waves, light, and magnetism. This release will prevent early drug release, maximise the drug concentration at the disease site and minimise adverse effects in the body.

Cellular Uptake Mechanisms

There are several pathways for cellular uptake of the niosome, including endocytosis, membrane fusion, and attachment to the cell surface. The released drug from inside these vesicles is localised in cellular compartments where drug uptake is maximised.

METHODS OF PREPARATION OF NIOSOMES



CHARACTERIZATION OF NIOSOMES

Vesicle Size

The size of the vesicles is a significant factor affecting drug entrapment, internalisation by cells, duration of circulation, and release of the drug. Small vesicles show greater tissue permeation and cell internalisation properties, while large vesicles have greater drug entrapment capabilities. Particles are usually measured using the methods of dynamic light scattering (DLS), laser diffraction, or electron microscopy.

Polydispersity Index (PDI)

The polydispersity index describes the homogeneity of vesicle sizes present in the formulation of the niosome preparation. Low values of PDI (<0.3) denote a homogeneous and stable formulation, whereas higher values of PDI show a wide range of particle sizes present in the formulation. Polydispersity index can be estimated by the technique of dynamic light scattering.

Zeta Potential

Zeta potential gives information about the surface charge of the niosomes and physical stability of the vesicles. Niosomes with high positive/negative zeta potentials have a repulsive interaction between themselves, which avoids any aggregation in the vesicles and makes them stable for storage. It can be determined by electrophoretic light scattering.[26]

Morphology
The assessment of morphology evaluates the morphological parameters, such as shape, surface properties, and lamellar nature of the niosomes. Generally, most niosomes have spherical or near-spherical shapes with smooth surfaces. TEM, SEM, AFM, and cryo-EM techniques give valuable insights into the structure of the vesicles.

Entrapment Efficiency
The entrapment efficiency gives the ratio between the quantity of drug that was entrapped inside the vesicles and the total quantity of the drug utilised for preparation of the niosomes. It shows the loading capability of the drug in the niosomes. The drug content is normally measured after separation of free drug using techniques like centrifugation, dialysis, or ultrafiltration.

Drug Loading Capacity
The drug loading capacity is defined as the quantity of drug loaded in the system per unit mass of the niosomal drug delivery system. The higher the drug loading capacity, the lower the requirement of the vehicle for the delivery of the desired drug concentration.

In Vitro Drug Release
In vitro drug release tests determine the release profile of the entrapped drug in an environment similar to physiological conditions. In vitro drug release tests help to determine whether the system can release the drug instantaneously, slowly, or in a controlled manner.[27]

Stability Studies
Stability studies are conducted to evaluate the capability of niosomes to maintain their physicochemical characteristics upon storage. The parameters analysed include vesicular size, zeta potential, drug loading, entrapment efficiency, and leakage of drugs. Stability studies play an important role in determining the shelf life of the formulations.

Differential Scanning Calorimetry (DSC)
Differential scanning calorimetry can be utilised for examining the thermodynamic properties of niosomes and for studying interactions between the drug and excipients. It provides information on melting points, phase transition points, and changes in the crystallinity state of a substance.

Fourier Transform Infrared Spectroscopy (FTIR)
FTIR is conducted to determine the functional groups and to investigate any possible interactions between the drug, surfactants, cholesterol, and other components of the formulation. It determines drug compatibility and ensures that there are no chemical modifications taking place during the formation of niosomes.[28]

X-ray Diffraction (XRD)
XRD technique is employed for the determination of crystallinity or amorphy of the drug in the niosomal formulation. Usually, encapsulation causes a lowering in the crystallinity of the drug, which indicates successful encapsulation in the vesicles.

Nuclear Magnetic Resonance (NMR) Spectroscopy
NMR spectroscopy is an analytical technique that gives details about the structure, environment, and interaction of the drug molecule with the niosomal bilayer. This technique is valuable in determining the presence of the drug molecules within the niosomes and other factors.

Rheological Evaluation
Rheology evaluates the viscosity and flow behaviour of niosomal dispersion, gel or cream. It affects the stability, spreadability and syringeability of the formulation. This technique is especially valuable for topical, transdermal and ophthalmic niosomal preparations.

Sterility Testing
Sterility testing is important in niosomes that are prepared for parenteral, ocular, and other sterile uses. This testing ensures that there are no viable microorganisms that may pose risks to patient safety. The sterility test is carried out in accordance with the pharmacopoeia guidelines through membrane filtration or direct inoculation procedures.[29]

EVALUATION OF NIOSOMES

Evaluation Parameter	Purpose	Common Methods/Instrument
Particle Size (Vesicle Size)	Determines drug delivery efficiency, cellular uptake, and biodistribution	Dynamic Light Scattering (DLS), Laser Diffraction, TEM, SEM
Polydispersity Index (PDI)	Evaluates uniformity of vesicle size distribution	Dynamic Light Scattering (DLS)
Zeta Potential	Measures surface charge and predicts physical stability	Zeta Potential Analyser (Electrophoretic Light Scattering)
Morphology and Shape	Examines vesicle shape, surface characteristics, and lamellarity	Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), Atomic Force Microscopy (AFM), Cryo-TEM
Entrapment Efficiency (EE%)	Determines the percentage of drug encapsulated within niosomes	Centrifugation, Dialysis, Ultrafiltration followed by UV-Visible Spectroscopy or HPLC
Drug Loading Capacity (DL%)	Measures the amount of drug loaded per unit weight of niosomes[30]	UV-Visible Spectroscopy, HPLC
In Vitro Drug Release	Evaluates the drug release profile over time	Dialysis Bag Method, Franz Diffusion Cell, USP Dissolution Apparatus
Drug Release Kinetics	Determines the mechanism of drug release	Zero-order, First-order, Higuchi, Korsmeyer–Peppas kinetic models
Surface Composition	Identifies elemental composition and surface chemistry	X-ray Photoelectron Spectroscopy (XPS), FTIR
Bilayer Fluidity	Evaluates membrane flexibility and rigidity	Fluorescence Polarisation, Electron Spin Resonance (ESR)
Thermal Behavior	Determines melting point, phase transition, and compatibility	Differential Scanning Calorimetry (DSC)
Chemical Compatibility	Detects interactions between drug and excipients	Fourier Transform Infrared Spectroscopy (FTIR), Raman Spectroscopy
Crystallinity	Determines crystalline or amorphous nature of the encapsulated drug	X-ray Diffraction (XRD)
Molecular Structure Analysis	Confirms drug incorporation and molecular interactions	Nuclear Magnetic Resonance (NMR) Spectroscopy
Surface Topography	Examines surface roughness and vesicle architecture	Atomic Force Microscopy (AFM)
Stability Studies	Evaluates long-term physical and chemical stability	ICH Stability Studies, Particle Size Analysis, Drug Leakage Studies
Leakage Study	Measures drug leakage during storage	UV-Visible Spectroscopy, HPLC

Osmotic Shock Test	Assesses membrane integrity under osmotic stress	Osmotic Stress Evaluation
Viscosity/Rheology	Determines flow characteristics of formulations	Brookfield Viscometer, Rheometer
Sterility Test	Confirms absence of microbial contamination	Membrane Filtration Method, Direct Inoculation Method
Pyrogen Test	Detects endotoxin contamination in injectable formulations	Limulus Amebocyte Lysate (LAL) Test
In Vitro Cytotoxicity	Evaluates cellular safety of the formulation	MTT Assay, Alamar Blue Assay
Hemocompatibility	Assesses compatibility with blood components	Hemolysis Assay, Coagulation Tests
Cellular Uptake Study	Determines uptake of niosomes by target cells	Confocal Laser Scanning Microscopy (CLSM), Flow Cytometry
In Vivo Pharmacokinetic Studies	Evaluates absorption, distribution, metabolism, and elimination	LC-MS/MS, HPLC[31]
Biodistribution Study	Determines organ-specific accumulation of niosomes	Fluorescence Imaging, Gamma Scintigraphy, PET/SPECT Imaging
In Vivo Pharmacodynamic Study	Assesses therapeutic efficacy	Disease-specific animal models
Toxicity Evaluation	Evaluates acute and chronic toxicity	OECD Toxicity Guidelines, Histopathological Examination

ADVANTAGES OF NIOSOMES

- Enhanced Drug Stability
- Improved Bioavailability
- Controlled and Sustained Drug Release[32]
- Targeted Drug Delivery
- Ability to Encapsulate Diverse Drugs[33]
- High Biocompatibility and Low Toxicity
- Cost-Effective and Easy to Prepare[34]

LIMITATIONS OF NIOSOMES

- Physical Instability
- Drug Leakage[35]
- Limited Shelf Life
- Low Encapsulation of Some Drugs
- Scale-Up and Manufacturing Challenges[36]
- Sterilisation difficulties for parenteral or ocular use can be difficult since typical sterilisation processes like heating or autoclaving might destroy the vesicle bilayer or cause drug leakage. The appropriate sterilisation process should be chosen carefully.
- Regulatory and Clinical Limitations, Lack of specific regulations, absence of adequate safety information, and lack of sufficient clinical trials are the main factors that restrict the clinical application of niosomes.[37]

APPLICATIONS OF NIOSOMES

Application	Route of Administration	Drug Example(s)	Therapeutic Benefits
Cancer Drug Delivery	Intravenous / Targeted	Doxorubicin, Paclitaxel, Methotrexate	Targeted tumour delivery, reduced systemic toxicity, enhanced solubility, prolonged circulation, controlled release
Oral Drug Delivery	Oral	Curcumin, Cyclosporine A, Ibuprofen	Improved bioavailability, gastric protection, enhanced absorption, sustained release
Topical Drug Delivery	Topical	Diclofenac, Ketoconazole, Clotrimazole	Enhanced skin permeation, prolonged residence, localised action, reduced systemic absorption.
Transdermal Drug Delivery	Transdermal	Diclofenac, Meloxicam, Ketoprofen	Improved permeation, sustained release, avoids first-pass metabolism
Ocular Drug Delivery	Ophthalmic	Timolol Maleate, Acetazolamide, Ciprofloxacin	Increased corneal penetration, prolonged residence, improved bioavailability
Pulmonary Drug Delivery	Inhalation	Salbutamol, Budesonide	Targeted lung delivery, prolonged retention, reduced side effects
Intranasal Drug Delivery	Intranasal	Rivastigmine, Donepezil, Sumatriptan	Rapid absorption, nose-to-brain delivery, BBB bypass
Vaccine Delivery	Injectable / Intranasal	Hepatitis B Antigen, Influenza Vaccine	Antigen protection, enhanced immune response
Gene & Nucleic Acid Delivery	IV / Local Injection	DNA, mRNA, siRNA, Plasmid DNA	Protection from degradation, enhanced cellular uptake
Protein & Peptide Delivery	Injectable / Nasal / Oral	Insulin, Calcitonin, BSA	Improved stability, sustained release
Herbal & Phytopharmaceutical Delivery	Oral / Topical	Curcumin, Quercetin, Resveratrol, Berberine	Improved solubility, bioavailability, controlled release
Antimicrobial Drug Delivery	Oral / Topical / Injectable	Amphotericin B, Ciprofloxacin, Vancomycin	Enhanced penetration, prolonged circulation, reduced dosing
Neurological Drug Delivery	Intranasal / IV	Rivastigmine, Donepezil, Levodopa	Improved BBB penetration, targeted brain delivery
Cosmetic & Cosmeceutical Applications	Topical	Vitamin C, Vitamin E, Coenzyme Q10, Retinol	Enhanced skin penetration, prolonged retention, reduced irritation

FUTURE PERSPECTIVES

Niosomes have significant potential as future drug carriers due to their advantages over conventional dosage forms. Current research focuses on developing targeted and stimulus-responsive niosomes that release drugs in response to pH, temperature, or enzymes, while surface modification with specific ligands enhances disease-specific targeting. Niosomes are also promising for the delivery of proteins, peptides, nucleic acids, vaccines, and gene therapies, with artificial intelligence aiding formulation optimisation. However, challenges such as large-scale clinical validation, standardised manufacturing, quality control, stability, shelf life, and production cost must be addressed. Collaboration among researchers, clinicians, regulatory authorities, and the pharmaceutical industry will be essential for successful clinical translation and commercialisation.[42]

CONCLUSION:

Niosomes are promising vesicular drug delivery systems that improve drug stability, bioavailability, controlled release, and targeted delivery of both hydrophilic and lipophilic drugs. Their advantages, including low cost, biocompatibility, ease of preparation, and chemical stability, make them suitable for oral, topical, transdermal, ophthalmic, pulmonary, parenteral, and targeted drug delivery. Recent advances such as ligand targeting, PEGylation, and stimulus-responsive niosomes have further enhanced their therapeutic potential. However, challenges related to large-scale production, stability, and clinical translation remain. Continued research and technological advancements are expected to establish niosomes as an important platform for future drug delivery systems.

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