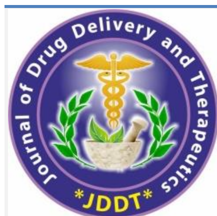

Available online on 15.03.2024 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Review Article

An Overview of Niosomes

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Article Info:

Article History:

Received 22 Dec 2023
Reviewed 08 Feb 2024
Accepted 25 Feb 2024
Published 15 March 2024

Cite this article as:

Kaur P, Rani R, Singh AP, Singh AP, An Overview of Niosomes, Journal of Drug Delivery and Therapeutics. 2024; 14(3):137-146

DOI: http://dx.doi.org/10.22270/jddt.v14i3.6450

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Abstract

In recent times, there has been a significant shift towards developing targeted biological substances for the treatment of infectious diseases and vaccination. Non-ionic surfactant vesicles, known as niosomes, have emerged as a distinctive vesicular structure in contemporary drug delivery methods due to their biological breakdown, compatibility, chemical resistance, cost-effectiveness, ease of manufacturing and preservation, and low toxicity. The progress in nanocarrier technology has garnered attention for its safety and associated advantages, including enhanced therapeutic administration with diverse pharmacological effects, improved targeting capabilities, and reduced side effects. Niosomes serve as vesicular carriers for drugs, composed of non-ionized surfactants, cholesterol or analogs, and charged molecules that enable controlled and targeted drug delivery. They are categorized as unilamellar, oligolamellar, or multilamellar structures. This comprehensive review article provides an overview of niosomes, covering their structure, types, formulation methods, characterization, advantages and disadvantages, preparation techniques, influencing factors, evaluation criteria, applications, and currently available formulations in the market.

Keywords: Niosomes, drug delivery system, methods of Preparation, Applications.

INTRODUCTION

Niosomes are a new drug delivery system (NDDS) with the goal of delivering the medication at a regulated pace dictated by the demands of the body during the course of treatment of an illness to improve absorption and distribute the active substance to the target location.[1] The capacity to focus a therapeutic substance at the targeted location of action with minimal or no contact with adjacent tissue is referred to as drug targeting. The controlled medication delivery system is intended to provide the proper medicine release profile over an extended period of time. Niosomes are one approach for implementing the controlled release mechanism notion.[2] Cosmetic researchers were the first to discover that non-ionized surfactants might assemble themselves into vesicles in the 1970s. When nonionic surfactants from the alkyl or dialkyl polyglycerol ether family are combined with cholesterol levels, tiny spherical structures known as niosomes (non-ionic surfactant vesicles) emerge.[3]. The niosomal drug delivery technique encases medication in a vesicle. The vesicle is generated by the mixing of a surfactant that is not ionic of the alkyl or dialkyl poly glycerol ether type ofa bilayer (thus the term niosomes) with cholesterol in aqueous environments, followed by hydration. Niosomes are remarkably tiny and microscopic by dimension. The dimensions of these particles are on the nanometric range. Niosomes are more stable than liposomes, which can be damaged and oxidized due to the lipophilic characteristics. Because of their non-ionizing surfactants, niosomal formulations last longer in the circulation and so have a greater focused impact.[4,5] Because of the drawbacks of liposomes, attention has switched to niosomes. Niosomes as well as liposomes both act as medication vehicles for amphiphilic along with lipophilic medicines.[6] Niosomes are tiny, microscopic particles. The niosome measures from 20 to 100 nanometers in size. Niosomes are essentially equivalent with liposomes but provide several benefits Because of their tiny size (in nanometers), they can readily pass through all routes of action via the skin. The niosome undergoes less metabolism and removal by the reticular endothelial system due to its nanoscale size.[7] Niosomes are thought to be the ideal drug delivery vehicles since they are non-ionic in nature, have low toxicity, and improve a medicine's therapeutic efficiency by targeting certain cells.[8] One among the reasons for producing niosomes is that detergents are thought to have superior chemical stability over phospholipids, which are employed in the manufacture of liposomes. Phospholipids are quickly degraded because of the existence of an ester bond.[6] Niosome medicines minimize the not specific systemic adverse effects of anticancer treatments. The liver demonstrates the enzyme lipase in breaking down the niosome, and the medication is collected by the niosome then released into the blood. Cholesterol is vital in the construction of niosomes, hardening the vesicles, however increasing the amount of cholesterol levels in the vessels impacts fluidity as well as drug penetration and permeability. Niosome medicines are supplied through a variety of methods, including transdermal, intravenous, oral,

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ophthalmic, and subcutaneous.[7] Because niosomes have an amphiphillic membrane structure, it might be utilized for delivering hydrophilic medications in the aqueous core and lipophilic pharmaceuticals in the surfactant-based bilayer. Nonionic surfactant was used as a film forming agent in niosomes, cholesterol was used as a bilayer stabilizing and rigidizing agent, and various charge inducers were used to generate a charge on the outer layer of niosomes and stabilize the formulation that was created by the resulting repulsive forces.[9] Niosomal medication delivery has been explored utilizing a variety of ways, including intramuscular, intravenous, per oral, and transdermal injection. Furthermore, as drug-transporting vesicles, niosomes have been found to improve the absorption of drugs across cell membranes, localize in specific organs and tissues, and evade the reticuloendothelial system.[10]

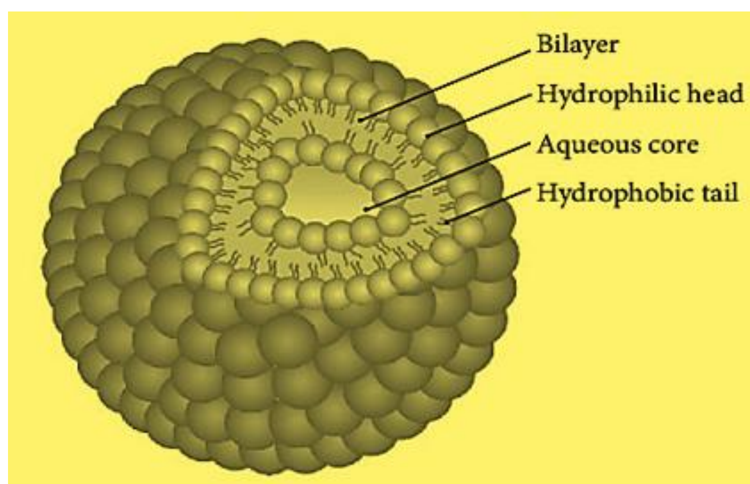

Figure 1: Structure of Niosome[8]

COMPOSITION OF NIOSOMES

Niosomes get thermodynamically stable, with a bilayered structure made up of non-ionic surface-active substances that can only be created when surfactants and cholesterol are combined in the appropriate ratio at temperatures above the gel liquid transition point. Its - has a hollow region in the center where hydrophilic and hydrophobic medicines are enclosed.[8] Conventional niosomal vesicles can be made up of vesicles that create an amphiphilic, i.e., nonionic, surfactant like Span60, which is normally maintained by a combination of cholesterol and a tiny quantity of anions such dicetyl phosphate for use in vesicle stability surfactant.[7] The following three components are used in the production of niosomes:

- Cholesterol
- Non-ionic surfactants
- Charged molecule

Cholesterol is a steroids precursor utilized for imparting stiffness and appropriate shape to niosomes, as well as to strengthen and produce niosome preparations. Steroids influence the fluidity and permeability of the bilayer and are thus essential components. To give stiffness and orientational order, a cholesterol a waxy steroid metabolite is often included in surfactants that are nonionic. It has no effect on the bilayer and can be assimilated in high molar ratios. Cholesterol is an amphiphilic molecule, with its OH group facing the aqueous phase and its aliphatic chain facing the surfactant's hydrocarbon chain. Rigidity is supplied by constraining the mobility of hydrocarbon carbons by alternately placing a stiff steroidal backbone alongside the molecules of surfactant inside the bilayer. Cholesterol has additionally been shown to inhibit leaks by preventing the gel to liquid form conversion.[11]

Non-ionic Surfactants are commonly employed in the synthesis for niosomes. For instance: Tween (20, 40, 60, 80).[2,7] Nonionic surfactants comprise surfactants that lack charged groups within their hydrophilic heads. When contrasted with anionic, amphoteric, or cationic equivalents, they are more stable, biocompatible, and less poisonous. As a result, they are favored for the creation of stable niosomes in vitro and in vivo. Nonionic surfactants comprise amphiphilic compounds with two distinct regions: one hydrophilic (water-soluble) as well as one hydrophobic (organic soluble). The primary nonionic surfactant classes employed in niosome synthesis include alkyl ethers, alkyl esters, alkyl amides, and fatty acids.The hydrophilic-lipophilic balance (HLB) and critical packing parameter (CPP) values are important in determining which surfactant molecules to use over niosome synthesis.[12]

Charged molecule: The insertion of charged groups to the vesicle bilayer increases the stability for the vesicles. They reduce vesicle aggregation through increased its surface charge density. They inhibit vesicle fusion due to repulsive forces of the same charge resulting in larger zeta values for potential. Dicetyl phosphate as well as phosphatidic acid are the most often employed negatively charged molecules during niosome synthesis, whereas stearylamine and stearyl pyridinium chloride are well-known positively charged compounds.[13] Normally, 2.5-5% of the charged molecule is incorporated to the niosomal formulation. Nevertheless, enhancing the number of molecules with charges can impede the production of niosomes.[12]

ADVANTAGES OF NIOSOMES

When compared to oily dose forms, a vesicle suspension's based on water carrier provides good patient compliance.

Controlled and precise medication administration.

Drug compounds with a wide variety of solubilities may be supported in the infrastructure supplied via hydrophilic, lipophilic, and amphiphilic in moieties in niosomes.

Changes within vesicle composition, size lamellarity, surface charge, tapped volume, and concentration may all be used to influence vesicle properties.

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They have the ability to release the medicine in a regulated and continuous manner.

Niosomes are immune-inhibiting, safe, environmentally friendly, and disposable.

Surfactants require no particular conditions enable storing or transportation, such as low temperature or an inert environment, and can act as a depot formulation, allowing for regulated drug release.

They improve the oral bioavailability of medicines that are poorly soluble.

Even though they are in emulsion form, they have a stable structure.

Oral, parenteral, and topical methods can all be used to aggressively achieve the location of action.

They are cost effective for large-scale manufacture.

They have the ability to shield the medication through enzyme metabolism.

They can improve drug penetration through the skin.

Niosomes appear in a variety of medications, including pharmaceuticals as well as cosmetics.

Late elimination into bloodstream can increase the beneficial effects of medicinal compounds.

They have the ability to shield the active component from physiological circulation.

Niosomes can be delivered to the site that acts by oral, topical, or parenteral methods.[14-17,7,8]

DISADVANTAGES OF NIOSOMES

Physical insecurity

Inadequate drug loading capacity. Aggregation

Fusion Manufacturing requires specialized equipment.

It is costly.

Entrapped medication leakage

Techniques that take a long time

The hydrolysis of encapsulated medicines reduces the shelf-life of the dispersion.

Because opposing charges approach and niosomal vesicles merge, various charges can exist on the surface of niosome vesicles during niosome synthesis.

Preparing niosomes is a time-consuming operation. [2,7,8,14,16,17]

TYPES OF NIOSOMES

The niosomes are categorized based on the quantity of bilayers (e.g. SUV, MUV), their size (e.g. LUV, SUV), or their manufacturing process (e.g. REV, DRV). Niosomes are classified into three categories. The following are descriptions of the many forms of niosomes: Multi lamellar vesicles (MLV), Large unilamellar vesicles (LUV), and Small unilamellar vesicles (SUV) are the three types of vesicles.[1,14,15]

Multilamellar Vesicles(MLV)

It is made up of many bilayers that enclose the aqueous lipid compartment individually. The diameter of such a vesicle is around 0.5 to 10 m. MLV are the most often utilized niosomes. These generally quick to build and mechanically stable over lengthy periods of storage. These kinds of vesicles have the greatest potential for medication delivery of lipophilic substances. The hand shaking technique is used to prepare niosomes.[7,14,15]

Large Unilamellar Vesicles (LUV)

These Niosomes have a higher aqueous for lipid compartment ratio, allowing a significant amount of bioactive compounds to be captured while using little membrane lipids. Large unilamellar vesicles have a diameter larger than 0.10m.[7,14,15,18]

Small UnilamellarVesicles(SUV)

The most common methods used to create these kinds of niosomes include solvent dilution, homogenization, French press extrusion, and sonication of multilamellar vesicles. Small unilamellar vesicles, with a diameter of 0.025-0.05 µm, are prone to aggregation and fusion due to their thermodynamic instability. Their proportion of an aqueous solute entrapped is modest, and their entrapped volume is minimal.[15,19] The reverse phase evaporation process is used to create niosomes.[7]

Some Other Types of Niosomes

Bolasurfactant containing niosomes

The surfactants composed of omegahexadecylbis-(1-aza-18 crown-6) (bola surfactant) are those that include niosomes: span-80/cholesterol in a ratio of 2:3:1.[20]

Aspasomes: Aspasomes are formed when acorbylpalmitate, cholesterol, and highly charged lipid diacetyl phosphate are combined. To obtain niosomes, aspasomes are first hydrated with water/aqueous solution and then sonicated. Aspasomes can be utilized to improve medication transdermal permeability. Because of their natural antioxidant properties, aspasomes have also been employed to reduce disorder produced by reactive oxygen species.[21]

MECHANISMS OF NIOSOMES PENETRATION THROUGH SKIN DELIVERY

Niosomes are a difficult device for dermatological problems. Niosomes have also been employed in cosmetics and peptide medication delivery. The ability of niosomes to increase drug transfer through the skin has been attributed to a variety of mechanisms, including alteration of the stratum corneum's barrier function as a result of reversible lipid organization, reduction of transepidermal water loss, which increases hydration and loosens the stratum corneum's tightly packed cellular structure, and adsorption and/or fusion of niosomes. Topically applied niosomes can improve medication residence duration in the SC and epidermis while decreasing systemic absorption. Drug transport across the stratum corneum can be accomplished via three routes: intercellular, transcellular (paracellular), and transappendageal. After passing through the epidermis, a material may be removed by deeper tissues via the dermal circulation. They are considered to improve horny layer qualities by lowering transepidermal water loss and smoothness by replenishing depleted skin lipid. As a result, niosomes work as penetration enhancers. Adsorption and fusing of niosomes onto the skin's surface results in a significant thermodynamic activity gradient at the interface, which is the driving force for lipophilic drug penetration.

The action of vesicles as penetration enhancers lowers stratum corneum barrier characteristics. Surfactants, which are components of niosomes, boost transdermal penetration and percutaneous absorption by lowering surface tension, promoting skin wetting, and enhancing drug dispersion.

Niosome lipid bilayers serve as a rate-limiting barrier for medicines. [21,22,23]

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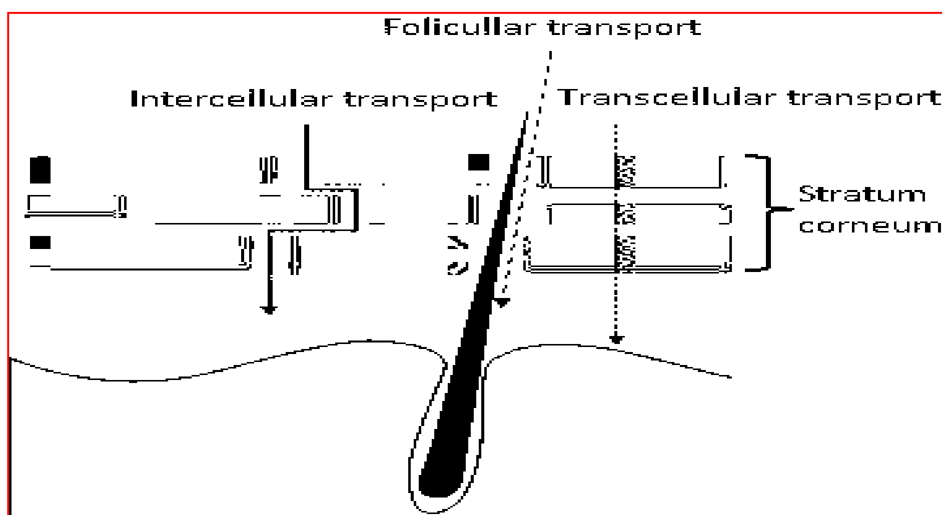

Figure 2: Skin transport pathways[24]

NIOSOME PREPARATION METHODS

There are several techniques for creating lipid-based vesicles, known as niosomes, which are employed as medication delivery systems. It contains therapeutically active ingredients, non-ionic surfactants with a hydrophilic head and a hydrophobic tail [e.g. - Spans (Span 20, 40, 60, 80, 85), Tweens (tween 20, 40, 60, 80)], cholesterol, which acts as a derived steroids employed for its flexibility, stiffness, alongside shape, phospholipids (e.g., phosphatidylcholine), and organic solvent.[8,10]

Several techniques for preparing niosomes have been documented, including:

Ether injection method: The ether injection method is mainly based upon the gradual injection of niosomal components solution of the surfactant and other additives in diethyl ether through a 14-gauge needle into warm water (60°C) containing the medication at a rate of about 0.25 ml/min. The creation of bigger unilamellar vesicles is most likely due to the sluggish vaporization of the solvent, which results in an ether gradient extending towards the aqueous non-aqueous boundary. The former might be in charge of the creation of the bilayer structure. The diameter of the vesicle might range from 50 to 1000 nm based on the circumstances. The downside of this approach is that a little quantity of ether is usually present that's hard to eliminate from the vesicle solution.[16,25,26,27] Surfactants as well as additives are dispersed in diethyl ether and gently administered using a needle into constant-temperature aqueous medicine solution which lies beyond its boiling point for an organic solvent used in the ether injecting technique. To extract the organic solvent, a rotary evaporator is used. Following the vaporisation process, single-layered vesicles are generated.[23]

Hand shaking method (Thin film hydration technique):

Ingredients such as surfactant and cholesterol are dissolved in a volatile organic solvent before being removed with a rotary evaporator. At 0-60°C, the dried surfactant film is rehydrated with aqueous phase to create multilamellar niosomes. The type of the medicine determines how it is added, with hydrophilic pharmaceuticals being added to the aqueous phase and hydrophobic drugs being dissolved in an inorganic solvent with other components. The addition of a medication is determined by the type of the substance.[8,28] Thin-film hydration is a typical preparation process that uses a flask to dissolve surfactants, cholesterol, and additives. A rotating vacuum evaporator is used to remove the solvent, leaving a thin coating on the inside wall of the flask. The dry film is hydrated for a set period above the surfactant's transition temperature while being constantly shaken, resulting in the formation of multilamellarniosomes.[23]

Sonication:

Sonicating the solution is a typical way to create air bubbles. In this approach, an aliquot of drug solution in buffer is introduced to a 10-ml glass vial containing a surfactant/cholesterol combination. To get niosomes, the mixture gets probe sonicated at 60°C approximately 3 minutes utilizing the sonicator equipped with a titanium probe.[7,16,27]

Reverse phase evaporation technique (REV):

A combination of ether and chloroform was used to dissolve cholesterol and surfactant (1:1). The drug-containing aqueous phase was subsequently added, and the resultant two phases were sonicated at 4-5°C. The transparent gel generated had been sonicated again, and then a little quantity of phosphate buffered saline (PBS) was added. The organic phase was extracted under low pressure at 40°C. To improve niosome yield, the viscous niosome solution was mixed using PBS and heated over a water bath at 60°C for 10 minutes.[9,16]

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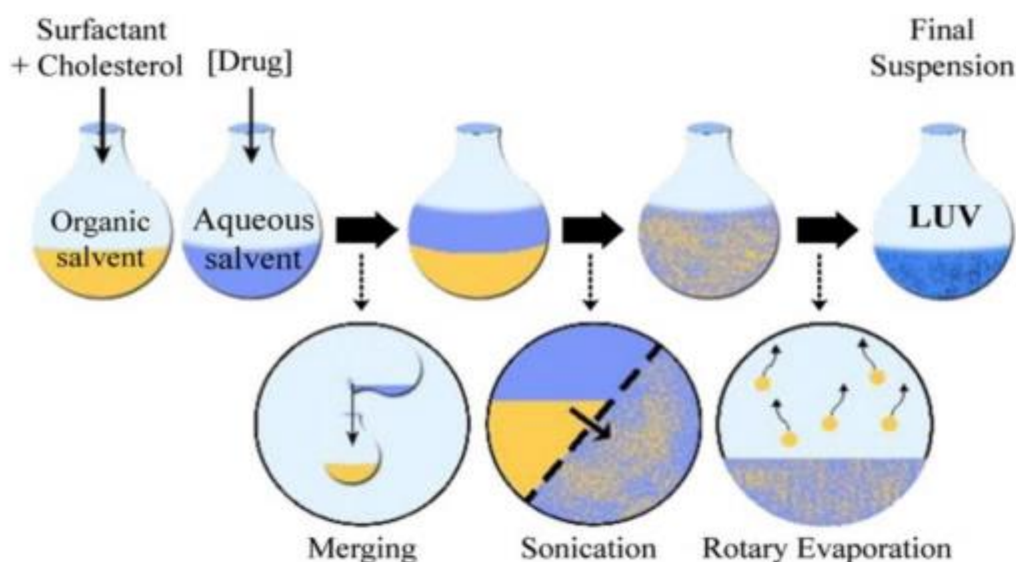

Figure 3: Niosome preparation by reverse phase evaporation method[7]

Microfluidization: A modern approach creates unilamellar vesicles with a specified size distribution using the submerged jet concept. In the interaction chamber, two fluidized streams interact at high speeds in tiny channels. Thin liquid sheets impinge on a shared front, ensuring that energy stays inside the niosome formation region. As a result, niosomes have smaller diameters, more homogeneity, and improved repeatability.[9,27] The immersed jet concept lies at the heart of the microfluidization process. Fluidized streams of medication and surfactant interact at extremely high speeds in narrowly defined microchannels within the interaction chamber using this method. Niosomes develop as a result of the high-energy, high-speed collision. This method produces more homogenous niosomes with smaller sizes, unilamellar vesicles, and high repeatability.[23]

Multiple membrane extrusion method: Evaporation transforms a surfactant, cholesterol, plus dicetyl phosphate mixture in chloroform creating a thin film. The film is hydrated with aqueous medication polycarbonate membranes, solution, and extruded suspension, which are inserted in succession for up to 8 passes. The multiple membrane extrusion approach is superior for managing niosome size.[9,27]

Trans membrane pH gradient (inside acidic) drug uptake process (remote loading): Chloroform is used to dissolve surfactant plus cholesterol. The solvent is then evaporated at decreased pressure to form a thin layer over the round bottom flask's wall. Vortex mixing hydrates the film with 300 mM citric acid (pH 4.0). The frozen as well as thawed multilamellar vesicles are then sonicated three times. An aqueous solution containing 10 mg/ml of medication is added to this niosomal suspension and vortexed. After that, 1M disodium phosphate is used to elevate the pH of the sample to 7.0-7.2. The resulting mixture is then heated for 10 minutes at 60°C to produce niosomes.[9,16,27]

Bubble method: Surfactants, additives, and the buffer are mixed in a glass flask with three necks in this procedure. Niosome components are disseminated at 70°C and combined using a homogenizer. The flask is then immediately put in a water bath, followed by the bubbling of nitrogen gas at 70°C. When nitrogen gas is fed over a sample of homogenized surfactants, huge unilamellar vesicles develop.[12,27]

Formation of niosomes from proniosomes: Proniosome approach entails covering a water-soluble carrier with surfactant, such as sorbitol or mannitol. A dry formulation is formed as a result of the coating process. This preparation is known as "Proniosomes" and must be hydrated before use. The inclusion of the aqueous phase results in the formation of niosomes. This approach reduces physical stability issues such as aggregation, leakage, and fusing while also providing simplicity in dosing and preservation with enhanced outcomes when compared to traditional niosomes.[27] A surfactant-coated soluble in water transporter, including sorbitol as well as mannitol, is utilized. The coating technique produces a dry formulation. This chemical is known as "Proniosomes," so it have to be moistened prior use. The presence of the water phase leads in the production of niosomes. This method provides convenience in dosing, distribution, transportation, and storage while reducing physical stability difficulties such as accumulation, water loss, and fusion with delivering superior results than standard niosomes.[23]

SEPARATION OF UN-ENTRAPPED DRUG

Various approaches may be used to remove unentrapped solute from the vesicles, including[16,29]:

- Dialysis;
- Gelfiltration(e.g. SephadexG50);
- Centrifugation (e.g. 7000 rpm for 30 min for the niosomes prepared by shaking the hands and ether injection methods);
- Ultracentrifugation(150000rpmfor1.5hours).

Dialysis: With room temperature, the aqueous niosomal dispersion is dialyzed in dialysis tubing against a suitable dissolving media. At appropriate time intervals, the samples are removed from the medium, centrifuged, and evaluated for drug content using appropriate methods (U.V. spectroscopy, HPLC, etc.

Gel filtration: The unentrapped medication is extracted by gel filtration of niosomal dispersion through a Sephadex-G-50 column, rinsed through a suitable mobile phase, and evaluated using appropriate analytical methods.[14,16]

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Centrifugation: In water or saline, the niosomal dispersion is centrifuged. Niosomes settle as a pellet, which is washed and resuspended to produce a niosomal suspension devoid of unentrapped medication. The unentrapped medication is extracted from the supernatant.[14,30]

Heating Method: Mozafari et al. devised a novel method for niosome production. In a buffer, they hydrated surfactants and cholesterol before heating to 120°C and stirring to dissolve the cholesterol. The dissolved cholesterol was then treated using surfactants and other agents. Niosomes generated at room temperature were held under nitrogen at 4-5°C until required.[23] This approach is a single-step, adaptable, as well as non-hazardous and it is also patent-protected. A appropriate aqueous media, such as buffered distilled water, into which mixes of nonionic surfactants, cholesterol, and/or charge inducing molecules are introduced with the addition of a polyol, such as glycerol. The mixture is heated (at modest shear pressures) until vesicles formed.[2]

The "Bubble" Method:-A flask of glass containing all three necks is full containing surfactants as well additives, plus the buffer in this approach. After being distributed at 70°C, niosome components are mixed using a homogenizer. The flask is subsequently submerged in water being bubbled with nitrogen gas at a temperature of 70 °C. When a sample of homogenized surfactants is exposed to nitrogen gas, huge unilamellar vesicles form.[23] A glass flask with three necks is used to distribute cholesterol and surfactant in a buffer at 70°C. This dispersion is blended for 15 seconds with a high shear homogenizer before nitrogen gas is fed into the homogenizer to create big unilamellarniosomes.[8]

FACTORS AFFECTING FORMULATIONOF NIOSOME

Drug:

The physicochemical parameters of the encapsulated medication impact the niosome bilayer's charge and stiffness.[31] Entrapment of a substance inside niosomes increases vesicle size, most likely because of substance interaction with surfactant head groups, which increases the electrical charge and mutual repulsion between the surfactant bilayers, leading to larger vesicle size; the hydrophilic lipophilic balance of the drug influences the degree of entrapment.[32] The drug's adherence to the niosome expands the quantity of its fluid vesicles.[7]

Type of surfactant:

Hydrophilic-Lipophilic Balance (HLB): HLB is a parameter with no dimension that indicates the solubility of a surfactant molecule. The HLB value describes the balance of the nonionic surfactant's hydrophilic and lipophilic parts. Fornonionic surfactants in the HLB range vary from 0 to 20. Lower HLB denotes an increased lipophilic surfactant, while greater HLB denotes a more hydrophilic surfactant. Surfactants having an HLB of 4 to 8 can be employed to produce vesicles. Because of their high water solubility, hydrophilic surfactants with HLB values ranging from 14 to 17 are unsuitable for the formation of a bilayer membranes.[12] However, when a suitable dose of cholesterol is added, niosomes are generated from polysorbate 80 (HLB value = 15) and tween 20 (HLB value = 16.7).In the presence of equimolar cholesterol concentration, tween 20 generates stable niosomes. The contact takes place at an equimolar ratio between the hydrophobic region of the amphiphile close to the head group and the 3-OH group of cholesterol, and this interaction might explain the influence of cholesterol on the formation and hydration behavior of Tween 20 niosomal membranes. The drug entrapment effectiveness of niosomes is similarly regulated by the surfactant's HLB value. Shahiwala et al. used the lipid film hydration approach to introduce nimesulide into niosomes by altering the HLB. Entrapment efficiency diminishes when the HLB value of the surfactant decreases from 8.6 to 1.7.[24]

Critical Packing Parameter (CPP): The critical packing parameter (CPP) of a surfactant determines the morphology of vesicles during niosomal production. The mean size of niosomes grows proportionately to surfactant hydrophobicity, since surface free energy decreases with surfactant hydrophobicity. Vesicle bilayers are either liquid or gel depending on temperature, lipid type, surfactant, and other components such as cholesterol. Alkyl chains create a well-ordered structure in the gel state, but the bilayer structure is more disordered in the liquid state. Surfactant and lipid gel-liquid phase transition temperatures (TC) also influence entrapment effectiveness, with greater TC resulting in better entrapment. As the quantity of HLB surfactant rises, the average size of niosomes increases, from Span 85 (HLB 1.8) to Span 20 (HLB 8.6). Surfactant plus lipid liquid-gel transition temperatures (Tc) also influence capturing effectiveness, with greater Tc leading with improved shooting.[7, 17,29]

Membrane composition:

The stable niosomes are created by combining various chemicals, surfactants, and medicines. Niosomes generated have a variety of morphologies, and their permeability and stability features may be varied by modifying membrane properties with various additions. Polyhedral niosomes created by C16G2: solulan C24 in ratio (91:9) have larger size (8.0 0.03mm) compared to spherical/tubular niosomes made by C16G2: cholesterol: solulan C24 in ratio (49:49:2) (6.60.2mm). The addition of the cholesterol molecule into the niosomal system stiffens the membrane along with minimizes drug leakage through the niosome.[31]

Cholesterol content and load:

The presence of cholesterol in niosomes improves their hydrodynamic diameter and capture effectiveness. In overall, cholesterol has two effects. On the other the same direction, cholesterol promotes chain order throughout the liquid bilayer, whereas on the opposite end, cholesterol reduces chain order in the gel double layer. The gel state transforms into a neat liquid with high cholesterol concentrations. A rise of cholesterol concentration inside the bilayer slows the release of the encapsulated material, increasing the stiffness of the layer that forms the bilayer. In a multilayered lenticular structure, the presence of an electric charge tends to increase the interlayer distance between consecutive bilayers, resulting in a rise overall trapping mass.[7]

Resistance to osmotic pressure: When hypertonic saline had been included to the niosome solution, the diameter shrank. In hypotonic saline, an extended release involving minor enlargement within the vesicles is noted at first, possibly due to inhibition of vesicle eluate, followed by a more fast release because to muscular relaxation. The investigation of vesicle structure under the impact of the osmotic pressure.[7]

Hydration Temperature: The temperature of hydration influences the size and form of the niosome. The temperature of hydration should be higher than the gel-liquid phase transition temperature. The assembling of surfactants into vesicles and the modulation of vesicle shape are both affected by temperature changes. The alteration is also accounted for by the hydration duration and volume of the hydration medium. Improper hydration temperature, duration, and medium

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volume selection results in brittle niosomes/drug leakage issues.[2]

Charge: A presence of charge increases the interlamellar spacing amongst consecutive dual layers within a multilamellar vesicles arrangement therefore increases the total entrapped volume.[2]

CHARACTERIZATION OF NIOSOMES

FTIR: The FTIR analysis is performed to determine whether there are any interactions among the medicine and the excipients included within the formulation.[1]

Vesicle diameter: Because niosomes appear spherical, the diameter may be measured with light microscopy, freeze fracture electron microscopy, and photon correlation microscopy. Freeze thawing can also be used for this purpose.[10,15]

Vesicle size & Morphology: The niosomes were observed under a scanning electron microscopy(SEM) (JSM 6100 JEOL, Tokyo, Japan). They were mounted directly onto the SEM sample stub using double sided sticking tape and coated with gold film of thickness of 200 nm under reduced pressure of 0.001mmHg. Photographs were taken at suitable magnification[22] -scanning electron microscopy (SEM), dynamic light scattering (DLS), and transmission The most popular techniques for determining niosome sizes and morphology are electron microscopy (TEM), freeze fracture replication electron microscopy (FF-TEM), and cryotransmission electron microscopy (cryo-TEM). DLS concurrently gives useful data on the homogeneity of the solution and cumulative information on particle size. A single population of scatterers is implied by a single sharp peak in the DLS profile. In this regard, the PI is beneficial. The morphology of the niosomes is typically studied using microscopic methods.[23]

Vesicle charge: Vesicle charge can play important role in the behavior of niosomes *in vitro* and *in vivo*. Charged niosomes are more stable against aggregation and fusion than uncharged vesicle.In order to obtain an estimate of the surface potential, the zeta potential of individual niosomes canbe measured by micro electrophoresis. Another approach is the use of p^{H}-sensitive fluorophores. Dynamic light scattering have been used to measure the zeta potential used nowadays.[2,15]

Bilayer formation: Bilayer vesicle formation can be characterized by x-cross formation due to the assembly of non-ionic surfactants under light polarization microscopy.[29]

Number of lamellae: NMR spectroscopy, electron microscopy, and small angle X-ray scattering are used to determine the number of lamellae in vesicles.[29]

Membrane rigidity and homogeneity: The distribution in the body and breakdown of niosomes is affected by the rigidity of their membrane. Examining the movement of a fluorescent probe at various temperatures allows the determination of vesicle bilayer stiffness. Techniques such as P-NMR, differential scanning calorimetry (DSC), Fourier transform-infrared spectroscopy (FT-IR), and fluorescence resonance energy transfer (FRET) can be employed to assess the uniformity of the membrane.[29]

Drug loading and encapsulation efficiency: The assessment of drug loading and encapsulation efficiency in niosomal dispersion involves the separation of un-entrapped drug. Following the preparation of the niosomal dispersion, un-entrapped drug is isolated through methods such as dialysis, centrifugation, or gel filtration, as detailed earlier. The determination of the drug retained within the niosomes is achieved by completely disrupting the vesicles using 50% n-propanol or 0.1% Triton X-100. The resulting solution is then analyzed using an appropriate drug assay method. Entrapment efficiency, expressed as a percentage, represents the proportion of the drug captured and retained by the niosomes. Techniques like centrifugation, dialysis, or gel chromatography are employed to eliminate unencapsulated free medication from the niosomal solution. Subsequent to this phase, the loaded drug can be released from the niosomes by disrupting the vesicles.[23,28,29]

Entrapment efficiency= (Amount entrapped/total amount)x 100.

***In-vitro* drug release:** The drug's release can be tracked by subjecting the niosomal suspension to dialysis against a specific temperature buffer and assessing the drug content in the dialysate.[33]

Zeta Potential:- The surface zeta potential of niosomes can be determined using Zetasizer and DLS equipment. The characteristics of niosomes are notably affected by their surface charge, with charged niosomes demonstrating greater resistance to aggregation compared to uncharged vesicles. Researchers Bayindir and Yuksel, who focused on the physicochemical attributes of paclitaxel-loaded niosomes, utilized this approach to examine the zeta potential of the niosomes.[23]

Stability studies: Stability assessments involve placing niosomes under two distinct conditions, typically at 4 ± 1 °C and 25 ± 2 °C. The evaluation includes examining the formulation's size, shape, and the number of vesicles per cubic mm both before and after a 30-day storage period. Residual drug content is measured at intervals of 15 and 30 days. A light microscope is employed to determine the vesicle size, while the count of vesicles per cubic mm is measured using a haemocytometer.[34]

Evaluating the stability of niosomes involves measuring the average vesicle size, size distribution, and entrapment efficiency during extended storage at different temperatures over several months. Regular sampling of niosomes throughout storage helps determine the retained drug amount within them. The percentage of drug retention is subsequently analyzed using UV spectroscopy or HPLC techniques.[23]

APPLICATION OF NIOSOMES

Niosomal drug delivery holds potential for the effective administration of various pharmacological agents targeting diverse diseases. Several therapeutic applications are discussed below.

Niosomesas Drug Carriers: Utilizing niosomes as carriers has been explored, including their application in transporting iobitridol, a diagnostic agent employed in X-ray imaging. Topical niosomes can function as a solubilization matrix, provide a local depot for sustained release of dermally active compounds, enhance penetration, or act as a membrane barrier influencing the systemic absorption of drugs. Additionally, niosomes have been employed for the transportation of iobitridol, a diagnostic substance used in X-ray imaging.[23,24]

Drug Targeting: One of the key advantages of niosomes is their capacity for targeted drug delivery. Niosomes can be employed to direct drugs specifically to the reticuloendothelial system (RES), which exhibits a preference for the uptake of niosome vesicles. The uptake of niosomes is regulated by circulating serum factors known as opsonins, which label the niosomes for clearance. This targeted drug localization has been utilized in the treatment of tumors prone to metastasize to the liver and spleen in animals. It is also applicable in addressing parasitic

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infections affecting the liver. Beyond the RES, niosomes can be employed to target drugs to other organs. Attaching a carrier system, such as antibodies, to niosomes is one approach, given that immunoglobulins readily bind to the lipid surface of niosomes, facilitating specific organ targeting.[23,24]

Anti-neoplastic Treatment: The majority of antineoplastic drugs are associated with severe side effects. Niosomes offer a potential solution by modifying drug metabolism, extending drug circulation and half-life, thereby reducing the adverse effects associated with these drugs. Niosomes contribute to a decrease in the rate of tumor proliferation, leading to higher plasma levels of the drug accompanied by a slower elimination process.[24]

Delivery of Peptide Drugs: The challenge of oral peptide drug delivery lies in overcoming enzymatic breakdown in the gastrointestinal tract. Current research is exploring the use of niosomes to protect peptides effectively from gastrointestinal degradation. In an in-vitro study focusing on the oral delivery of a vasopressin derivative encapsulated in niosomes, it was observed that the entrapment of the drug significantly enhanced the stability of the peptide. Overcoming the issue of enzymatic breakdown of peptides in oral medication administration is a longstanding challenge, and investigations are underway to determine if niosomes can serve as an effective shield against gastrointestinal peptide degradation.[23,24]

Study of Immune Response: Niosomes are currently employed in the investigation of immune responses due to their immunological selectivity, low toxicity, and enhanced stability. These non-ionic surfactant vesicles have proven their ability to serve as adjuvants when administered parenterally with various antigens and peptides, contributing to a better understanding of the nature of immune responses.[24]

Diagnostic Imaging with Niosomes: Niosomes function as carriers for radiopharmaceuticals, exhibiting site specificity for the spleen and liver in imaging studies through the use of 99mTc-labeled DTPA-containing niosomes. Enhanced tumor targeting of a paramagnetic agent has been achieved through the formulation of gadobenate with conjugated niosomes, incorporating (N-palmitoyl glucosamine, NPG), PEG 4400, and a combination of both PEG and NPG.[7]

Niosomes as Hemoglobin Carriers: Niosomes can be utilized as carriers for hemoglobin within the bloodstream, providing a permeable vesicle for oxygen transport. This property makes niosomes suitable as carriers for hemoglobin in patients suffering from anemia[24]

Magnetic Targeting in Drug Delivery: Niosomes demonstrate effective magnetic targeting in drug delivery, particularly in cancer therapy applications. The encapsulation of both a model anti-tumor and EMG 707 magnetic ferrofluids within the water core of niosomes has led to the development of doxorubicin-loaded atom-loaded formulations without additional toxicity.[23,24]

Ophthalmic Applications: In experimental studies with eye drops, gentamicin sulfate, a water-soluble antibiotic, exhibited a notable variation in release rates. The niosomal formulation, unlike conventional drug samples, demonstrated delayed release. Additionally, timolol maleate niosomes (0.25%), prepared with chitosan coating, have demonstrated a more significant impact on intraocular pressure with fewer side effects compared to commercially available products.[23,24]

Treatment of Leishmaniasis: Niosomes have potential applications in targeting drugs for diseases such as leishmaniasis, where the infecting organism resides in the reticuloendothelial system (RES). Niosomal formulations have shown increased efficacy and reduced side effects, particularly in the case of sodium stibogluconate, a commonly prescribed drug related to arsenic.[23,24]

Anticancer Drug Delivery: Niosomes, composed of non-ionic surfactants, cholesterol, and diketyl phosphate, have encapsulated anticancer drugs like methotrexate, vincristine, bleomycin, and paclitaxel. This encapsulation has led to increased absorption from the gastrointestinal tract upon oral administration, reduced toxicity, and improved antitumor activity.[23,24]

Transdermal Drug Delivery: Niosomes have been employed to address the slow penetration of drugs through the skin in transdermal drug delivery. Incorporating drugs into niosomes has enhanced the penetration rate, overcoming a major drawback of the transdermal route.[24]

Cosmetic Applications: L'Oreal pioneered the use of non-ionic surfactant vesicles (niosomes) for cosmetic applications, leading to the introduction of the first product, 'Niosome,' in 1987 by Lancôme. Niosomes in cosmetics offer advantages such as increased stability of entrapped drugs, improved bioavailability of poorly absorbed ingredients, and enhanced skin penetration.[23,24]

Hormone Delivery: Niosomes composed of non-ionic n-alkyl polyoxyethylene ether surfactants have been studied for the in-vitro permeation of estradiol through human stratum corneum. The mechanisms involved include the penetration-enhancing effect of surfactant molecules and the impact of vesicular structures at the stratum corneum suspension interface.[23,24]

Neoplasia Treatment: Niosomal delivery of anthracyclic antibiotic doxorubicin to mice bearing S-180 tumors increased their lifespan and decreased sarcoma proliferation. Niosomal entrapment enhanced the half-life of the drug, prolonged circulation, and altered its metabolism. Intravenous administration of methotrexate entrapped in niosomes to S-180 tumor-bearing mice resulted in total regression of the tumor, higher plasma levels, and slower elimination.[23,24]

Vaccine Delivery: Niosomes, weakly immunogenic on their own, are being explored as carriers for vaccines, particularly for oral and topical immunization. Varying proportions of surfactant, cholesterol, and dicetyl phosphate in niosomes were investigated for their impact on morphology, particle size, entrapment efficiency, and in-vitro antigen release. Topical niosomes demonstrated comparable immune-stimulating activity to intramuscular recombinant HBsAg and topical liposomes.[23,24]

Diagnostic Imaging with Niosomes: Niosomes are considered effective carriers for iobitridol, a diagnostic agent for X-ray imaging. The preparation of niosomes using the film hydration method followed by sonication allows increased encapsulation and stability of vesicles in diagnostic imaging studies.[7]

Prolonged Release Capability of Niosomes:The sustained release property of niosomes finds practical application for drugs characterized by a low therapeutic index and poor water solubility. This is because niosomal encapsulation enables the maintenance of such drugs in the circulation. [30,31,33,34]

Targeted Drug Action at Specific Sites: Utilizing niosomes for drug delivery presents an avenue to achieve localized drug action. The inherent characteristics of niosomes, including their size and limited penetrability through epithelium and connective tissue, contribute to keeping the drug localized at the specific site of administration.[30,31,33,34]

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Table 1: Marketed Formulations of Niosomes[2,7]

Sr. no.	Brand	Name of Products
1.	Britney Spears – Curious	Curious Coffret: Edp Spray 100ml +Dual ended Parfume& Pink Lipgloss + Body soufflé 100 ml
2.	Orlane – Lipcolor and Lipstick	Lip Gloss
3.	Loris Azzaro – Chrome	Chrome Eau De Toilette Spray 200 ml

CONCLUSION

Niosomes, a recent technological advancement, exhibit potential in the realms of cancer and infectious disease treatments. Serving as an alternative to liposomes, they offer advantages such as increased chemical stability, enhanced purity, and reduced cost. Niosomes, which are non-ionic surfactant vesicles, influence drug plasma clearance, tissue distribution, metabolism, and cellular interaction. Already employed in cosmetic products, they hold promise for diverse drug delivery applications, such as targeting, ophthalmic, topical, and parenteral. Advanced targeted niosomal systems utilizing active, passive, and magnetic mechanisms have been devised for precise macromolecular drug delivery. Niosomes are deemed safer and more practical than ionic drug carriers, without requiring special handling or storage conditions. The potential of efficiently delivering drugs to tumor sites is highlighted, particularly with the assistance of activated macrophages. While current findings are limited to animal experiments, further clinical investigations are imperative to fully leverage niosomes as effective drug carriers for cancer, infections, and other ailments. There exists considerable potential for encapsulating various drugs, including toxic anti-cancer, anti-infective, anti-inflammatory, and anti-viral agents, within niosomes.

Acknowledgment

It's our privilege to express the profound sense of gratitude and cordial thanks to our respected chairman Mr. Anil Chopra and Vice Chairperson Ms. Sangeeta Chopra, St. Soldier Educational Society, Jalandhar for providing the necessary facilities to complete this review/research work.

Conflicts of Interests

There are no conflicts of interest.

Funding

Nil

Authors Contributions

All the authors have contributed equally.

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