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Review Article

Non-Ionic Surfactant Vesicle (Niosome): A Novel Drug Delivery System

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ABSTRACT

Niosomes are vesicles that are created by hydrating a mixture of lipids that are biodegradable, non-ionic surfactant, and cholesterol. In comparison to a drug's traditional dosing form, niosomes boost the drug's action. Drugs that are amphiphilic or lipophilic can be transported via niosomes. The problems associated with pharmaceutical instability, rapid disintegration, insolubility, and low bioavailability may be resolved by niosomes. The manner of formulation determines whether niosomes are multilamellar or unilamellar in structure. For the site-specific administration of anti-cancer, anti-infective drugs, etc., niosomes have a very effective drug delivery capability. In comparison to other drug formulations, niosomes are stable and inexpensive carriers. Niosomes are also used in innovative drug delivery systems, topical drug delivery systems, oral drug delivery systems, and parental drug delivery systems. This review provides an extensive summary of niosomal studies to date, as well as a detailed look at formulation aspects, niosome types, physical characterization methods, and recent pharmaceutical applications like transmucosal, oral, ocular, topical, and pulmonary drug delivery as well as cosmetic applications.

INTRODUCTION

"A good drug delivery system delivers drug to the T-site for use throughout treatment. Targeted delivery is a strategy for delivering drugs to tissues while reducing the concentration of the drug in surrounding tissue. Niosomes are thin lamellar vesicles that are not toxic to organisms. They are formed by mixing cholesterol with a non-toxic alkyl class surfactant or dialkylpolyglycerol ether, followed by hydration in water [1]. Niosomes are versatile and can be combined to deliver several forms of drugs to the intended site. A niosome is a vesicle that can be unilamellar or multilamellar and is formed of non-ionic surfactant, cholesterol, and ionic surfactant. Its purpose is to reduce structural bonds. Drugs that are hydrophilic, lipophilic, or amphiphilic can be incorporated into the niosome's bilayer structural vesicle. Niosome shows more stability than liposome because the liposome can be degraded and oxidized due to its particular lipophilic nature.

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Because niosomal formulations have a non-ionic surfactant, they remain in the bloodstream for a longer period of time, enhancing their target action [2, 3].

Structure of Niosomes

Niosomes are microscopic, spherical, lamellar (unilamellar or multilamellar) structures. The bilayer is produced by combining charge-inducing agent with nonionic surfactants, either with or without cholesterol. Niosomes are formed by combining various surfactant types in different combinations and molar ratios. Alkyl glyceryl ethers, Alkyl ethers, polyoxyethylene fatty acid esters and sorbitan fatty acid esters are a few examples of surfactants [2, 4]. Cholesterol addition keeps the bilayer firm, resulting in fewer leaky niosomes [5]. Charge inducers, but on the other hand, give the vesicles a charge and expand their size, improving drug entrapment effectiveness. The vesicles are stabilised by positive charge inducers such stearylamine and cetylpyridinium chloride as well as negative charge inducers like dihexadecyl phosphate, dicetyl phosphate, and lipoamino acid [6]. Nonionic surfactants in niosomes have a tendency to have hydrophobic ends that face

inward toward one another and hydrophilic ends that face outward (toward the aqueous phase), resulting in closed bilayer structures that contain solutes in aqueous solutions. Lipophilic regions are consequently sandwiched between the hydrophilic inner and outer sides of the closed bilayer structure of niosomes [4]. The formation of the closed bilayer structure requires energy, such as heat or physical agitation. It was discovered that a number of forces, including van der Waals and repulsive forces between surfactant molecules, play a significant role in maintaining the vesicular structure. The properties of the resulting niosomes will probably change if the vesicle's components (including type, content, and concentration), size, surface charge, or volume are changed.

Based on vesicle size, niosomes can be divided into three groups. Large unilamellar vesicles (LUV, size => 0.10 µm), multilamellar vesicles (MLV, size => 0.05 µm), and small unilamellar vesicles (SUV, size = 0.025-0.05 µm) are the three types of these.

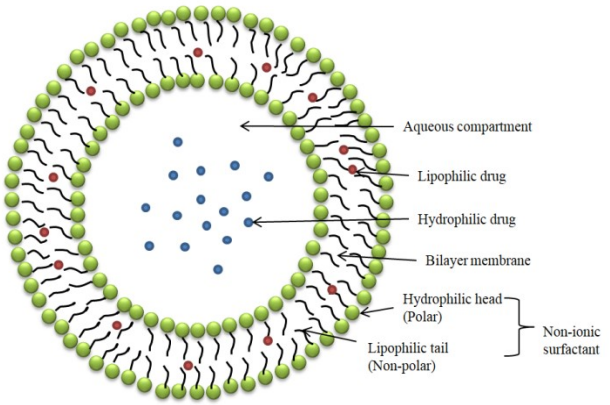

Figure 1: Structure of Niosomes

Advantages [7-9]

1. The niosome structure is relatively inexpensive in comparison to other structures. Niosome can be made from any inexpensive, easily available substance.
2. Also, non-ionic surfactant is a major component of the niosome and non-ionic surfactant toxicity is very low.
3. The structure of the niosome shows all nature such as hydrophilic, lipophilic and amphiphilic, so they can be used in a variety of drugs.
4. Many body components such as enzyme, pH and others affect the chemical and physical properties of the drug, to avoid this niosome formation is preferred.
5. Surfactants are often non-allergic since they are biodegradable, biocompatible, and non-immunogenic.
6. Because niosomes are nano particles, they can penetrate the skin more readily and increase drug absorption through the skin. Niosome formulations also have minimal harmful side effects, making them suitable for topical, oral, parenteral, and ophthalmic administration.
7. Niosome is osmotically stable and active.
8. The drug present in the niosome is protected in the biological environment because the degradation of the drug occurs very slowly and also avoids the first pass metabolism hence enhances bioavailability of drug.
9. The handling and maintenance of surfactant does not require special conditions and thus reduces the cost of preparation.
10. A niosome characteristic such as size, shape depends entirely on the ingredient and the amount used to make the niosome. For example, when cholesterol levels rise, vesicle stiffness also increases. Also, by increasing the concentration of the drug in the formulation affects the size of the vesicle.
11. Niosome is used in many preparations such as pharmaceutical preparations and cosmetics.
12. The formation of a liquid base of the niosome vesicle shows patient compliance much more than an oil-based system.

Preparation of Niosomes

The preparation of niosomes has been described using a variety of techniques in the literature. These include the microfluidization method, transmembrane pH gradient drug uptake process, ether injection method, thin-film hydration method, and reverse-phase evaporation method, bubble method, sonication [10, 11].

1. Ether Injection Method

The ether injection method works by injecting a surfactant slowly, injection of a cholesterol solution in ether (14-gauge needle). The aqueous solution/phase is heated to 60 degrees Celsius for this step. The production of single-layer vesicles is caused by the evaporation of ether, which causes an ether gradient at the ether-water interface. Between 50 nm and 1000 nm will be the diameter.

Table 1: Types of surfactant and their examples used in niosome formulation

Non-ionic surfactants	Examples
Alkyl esters:	
a. Sorbitan fatty acid esters(Spans)	Span 20, span 40, Span60, Span 65, Span 80, Span 85
b. Polyoxyethylene Sorbitan fatty acid esters (Tweens)	Tween 20 , Tween 80, Tween 60, Tween 65, Tween 40, Tween 85
Alkyl ethers:	
a. Alkyl glycerol ethers:	Hexadecyldiglycerol ether
b. Polyoxyethylene glycol alkyl ethers:	Brij 30, Brij 52, Brij 76, Brij 78, Brij 72
Alkyl amides:	
a. Glycosides	C-Glycosides derivative surfactants
b. Alkyl poly-glucosides	Octyl-decylpolyglucoside, Decylpolyglucoside
Fatty acids and Fatty alcohols:	
a. Fatty alcohol	Myristyl alcohols, acetyl alcohol, stearyl alcohol,
b. Fatty acids	Myristic acid, Palmitic acid, Stearic acid
Block copolymers:	
a. Pluronic	Pluronic P105, Poloxamer 188, Pluronic L64
Charge molecule:	
a. Negative charge	Diacetyl phosphate, Phosphotidis acid, Lipoamino acid, Dihexadecyl phosphate
b. Positive charge	Stearylamine, Cetylpyridinium chloride, Stearylpyridinium chloride
Lipidic components:	
Cholesterol	
l-α-Soya phosphatidyl choline	

2. Thin Hydration Techniques

Hand stirring is similar to thin film hydration in that it produces MLV. In this method, additives and surfactants are dissolved in organic solutions, which are then evaporated using a rotary evaporator to form a thin film, which is then mixed with an aqueous one hydrated solution. PBS pH = 7.4 containing medication; mechanically swirl this mixture for 1 hour to generate niosomes.

3. Bubble Method

For niosomal products, the Bubble process is a modern, new technology. The most significant advantage of this technology is that niosomes can be manufactured in a single step and in a short amount of time. For the preparation of niosomes, no organic solution is used in this process. The bubbling unit has a round bottom flask with three necks that are placed in a water bath to vary the temperature at which the water can be cooled. The thermometer is in the second neck, and the nitrogen is delivered through the third neck. Surfactant and cholesterol are dispersed simultaneously in a buffer pH 7.4 at 70°C, mixed for 15 seconds, and then immediately bubbled at 70°C using nitrogen gas.

4. Reverse Phase Evaporation Technique

This process involves dissolving surfactant and cholesterol (1:1) in a combination of ether and chloroform, adding an aqueous phase containing the medication, and mixing the two phases at 4-5. sonicated After adding a tiny amount of PBS (phosphate-buffered saline solution), the transparent gel is sonicated, and the organic phase is extracted at 40°C under low pressure. Phosphate buffer saline solution is used to dilute the toxic suspension that results. For loud formulation, heat for 10 minutes in a 60°C water bath. Furthermore, this approach is primarily utilised to create LUV.

5. Sonication Method

A medication solution and buffer are added to the cholesterol/surfactant mixture in a 10 ml glass vial using the sonication method. The mixture is sonicated for 3 minutes at 60°C using a sonicator. As a result, vesicles have niosomes of the unilamellar kind.

6. Transmembrane pH Gradient Drug Uptake Process

Chloroform is used to dissolve cholesterol and surfactants. In a round bottom flask at reduced

pressure, a mixture of cholesterol solvent, chloroform, and surfactant was evaporated into a thin layer. Shaking was used to hydrate the membrane with 300 mL of citric acid pH 4.0. The film was then thawed three times before being sonicated. To this dangerous suspension, an aqueous solution containing 10 mg/ml of medication is added. Then give the solution a good shake. The pH of the liquid should then be raised to 7.0-7 by adding 1 M disodium phosphate. Bring the mixture to 60°C and keep it there for 10 minutes, or until lumps appear.

7. Micro Fluidization Method

This approach is based on the notion of a submerged jet. Two fluidized streams, one containing medication and the other surfactant, interact at ultrahigh velocity in the micro fluidization process. That is within the interaction chamber, in a well defined micro channel, such that the energy provided to the system remains in the area of niosome formations. This is referred to as the submerged jet principle. In the formulation of niosomes, it resulted in higher uniformity, lower size, and reproducibility.

Characterization

1. Niosome Particle Size and Size Distribution

As it reveals physical characteristics and the stability of the formulation, particle size is a crucial metric in the characterisation of niosomes [12]. Dynamic light scattering (DLS) and microscopy are two methods that can be used to determine the size of niosomes. Photon correlation spectroscopy is another name for DLS. Only a minimal amount of sample is needed for this approach, which is quick and non-destructive. It may be used to measure particles between 3 and 3000 nm in size. This method is based on the idea of small particles scattered in a medium moving randomly, as described by Brownian motion. The niosome suspension is exposed to a laser produced by the apparatus, and the niosomes then scatter light. With the intensity of the variations in scattered light from the collision of particles resulting from random Brownian motion as a function of time, this is monitored at either a fixed or variable scattering angle. Due to their higher diffusion coefficient, smaller particles induce fluctuations with a higher intensity, whereas larger particles travel more slowly and produce oscillations with a lower intensity. A monodispersed sample is indicated by a polydispersity index (PDI) value less than 0.5, which measures the distribution of niosome size. The drawback of DLS is that it doesn't offer any details regarding the niosomes' shape [13]. The size of niosomes can also be determined using electronic microscopic methods, and DLS and microscopic methods are occasionally combined to create more reliable results.

2. Morphology

The morphology of niosomes is investigated using microscopic methods. While scanning electron microscopy (SEM) is used for solid samples, electronic microscopic techniques such as transmission electronic microscopy (TEM), negative-staining transmission electronic microscopy (NS-TEM), and freeze-fracture transmission electronic microscopy (FF-TEM) are used more frequently for liquid state samples. In 1982, Binnig's group employed scanning tunnelling microscopy (STM) and atomic force microscopy (AFM) to characterise structures at the micro- and nanoscale. Due to its analytical capabilities in the vertical axis, STM is helpful in evaluating the bilayer thickness of liposomes and niosomes [14].

3. Zeta Potential

Determining the physical stability of niosomes requires knowledge of the zeta potential, sometimes referred to as surface charge. Laser Doppler anemometry can be used to detect the surface potential, and the size of the zeta potential gives an indicator of the strength of the electrostatic attraction between two nearby particles. Niosomes are regarded as having acceptable stability if their zeta potential is greater than or equal to 30 mV [13, 15].

4. Niosome Stability

The vesicular system's stability is a problem that affects not only its physical and chemical stability but also its biological stability. The prospective in vivo and in vitro applications of the niosomes are determined using this essential characteristic. Particle size and zeta potential are typically monitored over time to determine stability, with changes in these two metrics indicative of potential instability. To evaluate the impact of temperature on stability, stability is frequently tested over a three-month period under various settings, such as 4°C, 25°C, and 40°C at 75% relative humidity [16].

5. Entrapment Efficiency

The amount of drug molecules successfully trapped inside vesicles, in this case niosomes, is known as EE and it can be stated by the following equation:

$$EE\% = \frac{\text{Amount of drug entrapped}}{\text{Total amount of drug added}} \times 100$$

The overall amount of drug refers to the entire amount of drug used in preparation, whereas the amount of drug entrapped refers to the actual amount of drug molecules successfully encased in the vesicles. By using techniques like dialysis, filtration, or centrifugation, the free drug molecules must be distinguished from the drug that is trapped. For genetic materials, spectrophotometry or gel electrophoresis followed by UV densitometry can be used to measure the EE. Additionally, a fluorescence metre can be used to determine this parameter [17, 18].

6. *In Vitro* Drug Release

Niosome *in vitro* release behaviour is a fundamental metric that is influenced by a variety of variables, including drug concentration, hydration volume, and membrane make-up. A dialysis membrane is typically used to study the release of medicinal compounds from niosomes. Here, a dialysis bag filled with a purified niosomal solution devoid of free medication is filled, tied at the ends, and placed in a beaker of phosphate buffered saline (PBS) at a constant temperature of 37°C while being stirred magnetically. At predefined intervals, samples are obtained, and the same volume of new medium is then substituted. The concentration of medication released over time is then calculated from these samples using the relevant assays . The releasing behaviour of niosomes has also been investigated using Franz diffusion cells. The donor compartment of the apparatus is filled with niosomal suspension, and the dialysis membrane is positioned here between the donor and receptor compartments. The entire system is kept at 37°C, and the receptor compartment contains PBS with a pH of 7.4. At predetermined intervals, samples are taken from the receptor [19, 20].

Applications:

1. Niosomes in Ocular Delivery

Because of the large and pharmacokinetically specialised environment that exists in the eye, developing ocular dosage forms is the most appealing and hardest task ever confronted by pharma scientists. The goal is to get through the eye's shielding barrier without causing irreversible tissue damage. The majority of current ocular medication delivery systems are still ineffective and crude. Because of the various mechanisms that exist in the eye, achieving effective medication concentration is a difficult endeavour.

In light of these considerations, the creation of a medication delivery system is critical in the treatment of a variety of ocular illnesses. The goals of ocular medication targeting are significant [21, 22].

1. Improved drug permeation
2. Enhance bioavailability
3. Controlling the drug's release
4. Targeting the drug at active site

Because of the eye's unique anatomy and physiology, ocular medication administration poses numerous obstacles. Many barriers exist in the eye, including distinct layers of cornea, sclera, and retina, as well as blood retinal barriers, lachrymal fluid-eye barriers, and drug loss from the ocular surface. Overcoming these obstacles is a major problem for the formulator. Due to limited absorption, topical administration is ineffective. Eye drops are the most convenient mode of administration. It drains out due to continual tear flow. Cornea is the eye's front layer, made up of epithelium, stroma, and endothelium. Due to their high lipid content, epithelium and endothelium hinder the passage of hydrophilic molecules. Because of its high water content, Stroma is impervious to lipophilic compounds.

Using traditional dose formulations, only 1-3% drug absorbed through cornea. Nanotechnology can be used to help solve these difficulties. Drugs encapsulated in lipid vesicles for use in vesicular systems. Non-ionic surfactant vesicles are referred to as niosomes. In several disorders, niosomes act as drug transporters, reducing adverse effects and increasing therapeutic effectiveness.

Niosomes provide a number of advantages over other vesicular systems, including low toxicity, chemical stability, and biocompatibility, as well as the capacity to increase medication availability at a specific location. It also has a regulated and long-lasting effect on the cornea. It

stops the medicine from being broken down by enzymes on the cornea/tear epithelium's surface [23].

2. Oral Delivery

The most accessible and practical method of drug administration, particularly when repeated administration is necessary, is often regarded as oral delivery. When developing oral drugs, there are a number of factors to consider, such as the stomach's acidic environment, the gastrointestinal tract's enzymatic degradation, first pass metabolism, limited absorption, and variable drug bioavailability. By enhancing absorption and bioavailability, niosomes have been investigated as a potential solution to these problems [24, 25].

3. Topical and Transdermal Delivery

A few benefits of topical drug delivery include localised drug release at the site of action and fewer side effects due to less systemic absorption [26]. When using transdermal drug delivery, the active substances are spread into the skin for systemic circulation, which provides a number of benefits over conventional methods of administration. Because first-pass hepatic metabolism may be avoided, transdermal distribution increases bioavailability, is non-invasive because no needle is needed, prevents enzymatic and acidic gastrointestinal tract degradation, and reduces the possibility of drug-food interactions. The stratum corneum serves as the main barrier to medication absorption across the skin, which limits the utilisation of the transdermal route due to the low penetration rate of drug molecules (SC).

The properties of the drugs that make them most suitable for transdermal delivery include their low molecular weight (500 ≤Da), lipophilicity, and efficacy at low dosage. Only a small percentage of drugs have been effectively formulated into transdermal formulations; many medications do not, however, have the required physicochemical properties [27]. Due to their capacity to improve cutaneous drug delivery to the epidermis and dermis layer, topical uses of niosomes have received extensive attention. To explain their penetration-enhancing properties, a number of processes have been put forth. First, drug-loaded vesicles adsorb to and fuse to the skin's surface, resulting in a high thermodynamic activity gradient of the drug at the SC and vesicle surfaces that functions as a catalyst for drug penetration.

Second, by altering the structural composition of the SC, disruption of the tightly packed lipids that line its extracellular gaps increases the permeability of drugs. Thirdly, by functioning as penetration enhancers, non-ionic surfactants are extremely important in increasing penetration. When vesicle bilayers enter the SC, the intercellular lipids are subsequently changed, increasing the overall fluidity of the membrane. Lastly, niosomes affect SC characteristics by reducing trans-epidermal water loss, which increases SC hydration and loosens the tightly packed cellular structure of the SC.

4. Pulmonary Delivery

When treating conditions like lung infections, respiratory tract inflammation, or lung cancer, pulmonary drug delivery is preferable over oral delivery because it delivers drug directly to the site of action for either local or systemic treatment. With a surface area of roughly 50 to 75 square metres, the lung is said to contain the equivalent of 2400 kilometres of airways and 700 million alveoli [28, 29]. The use of drug delivery systems like inhalers and nebulizers to treat a variety of lung disorders dates back decades because of the huge surface area that is optimal for drug absorption. The inhalation systems' low effectiveness and the inconsistent drug loading each inhalation from the inhaler are just two of their drawbacks, though.

The pulmonary route of niosomal drug administration has a number of benefits, including enhanced mucus permeability, sustained drug delivery, targeting, and enhanced therapeutic benefits.

5. Transmucosal Delivery

In order to enhance local and systemic absorption, bioadhesion has been extensively investigated in the development of pharmaceuticals. In the last decade, transmucosal medication administration has significantly increased, notably with the development of nano drug delivery technologies. Ocular, nasal, oromucosal (buccal, sublingual, and gingival), pulmonary, gastrointestinal, and vaginal sites are among the transmucosal drug delivery pathways. Each of these sites has unique qualities when taking their potential for medication administration into account. These characteristics must be taken into account while creating an effective drug delivery system. Because of their advantages, niosomes have been researched for transmucosal administration of

different substances through the oral, nasal, and vaginal mucosa [30].

6. Parenteral Delivery

The most popular and effective technique to provide drugs with low bioavailability and a narrow therapeutic range is via parenteral administration. Additional benefits of parenteral delivery include maximising drug use and minimising fluctuations in the steady-state plasma drug level. Conversely, disadvantages include limited scope for dosage modifications, difficulty in recovering the drug in cases of toxicity, and low patient compliance with injections because of needle anxiety. To address the issues with standard parenteral delivery formulations, some success has been achieved employing nanocarriers, which can achieve targeted drug delivery and sustained release [31].

7. Targeted Drug Delivery

There are two ways to use niosomal systems to deliver targeted drugs. First, passive targeting of the immune system's reticuloendothelial system (RES), which consists of phagocytic cells positioned in reticular connective tissue. The niosomes are identified for clearance by macrophages by the circulating serum factor opsonin. Niosomes can therefore be employed to treat infectious disorders where the causative agent is found in the RES. Second, to target certain organs or tissues, niosomes can be combined with functionalized ligands [32].

8. Cosmetic Applications

The first niosomes were developed and patented by the cosmetics business L'Oréal (Clichy, France) in 1975, and products were introduced under the trade name Lancôme (Paris, France) in 1987. Since then, numerous cosmetic products with varied uses, including anti-wrinkle, skin whitening, moisturising, and sunscreen, have been developed and marketed. Because of their benefits, such as better stability of entrapped active components, enhanced skin penetration, bioavailability, improved surface adherence, and prolonged release properties, niosomes have received a lot of attention as a carrier system for cosmetic actives. Niosomes' utility in cosmetic formulations has been assessed in comparison to more traditional formulations like emulsions. Niosomes demonstrated lesser toxicity, allowing for the controlled release of the active ingredients that were loaded and had qualities that are advantageous for skin moisturising and tanning treatments [32, 33].

CONCLUSION

Niosomes are a drug delivery system that can be used to deliver drugs in a controlled, sustained, and targeted manner. Due to their capacity to simultaneously encapsulate hydrophilic and hydrophobic medicines, niosomes are gaining more attention. They can be used to encapsulate almost all form of drug, including compounds with natural sources, enzymes, peptides, DNA, vaccines, and anti-cancer drugs. They can attain better EE than their analogue system, liposomes, and are cheap and simple to prepare. The domains of pharmaceutical and cosmetic sciences have a lot of potential for this adaptable drug delivery technique. They provide versatility in the mode of administration in addition to the drug.

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