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NIOSOMES: A NEW TECHNIQUE FOR DRUG TARGETING

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ABSTRACT

This is a review of the niosome as a drug carrier that increase drug bioavailability, improve skin penetration, releases the drug in a prolonged manner and is considered as drug targeting technique to specific organs in the body. The niosomal drug delivery system is a new drug delivery system composed of nano scale non-ionic vesicles made of non-ionic surfactants. Niosomes have the potential to decrease drug side effects and improve therapeutic efficacy in a variety of diseases, it can also serve as a carrier for drugs to be applied transdermally. This review provides an overview of various kinds of formulation, characterization and applications of niosomes.

KEYWORDS: Niosome, new drug delivery system, non-ionic surfactant, drug entrapment efficiency.

INTRODUCTION

For many years, researchers have been looking for novel and improved drug delivery system alternatives, and this will continue until the drug delivery system has no adverse effects while providing optimal therapeutic action. Despite the fact that they have side effects, conventional dosage forms are still in use due to high patient compliance. Recently, vesicular systems, which have numerous benefits over other drug delivery systems, have received a lot of attention. The vesicular system includes niosome, liposome, transferosomes.[1]

Niosomes, also known as nonionic surfactant vesicles, are drug carriers that transport drugs to the organ site of action. Niosomes are vesicular carriers of non-ionic surfactants with sizes ranging from 10 to 1000 nm, in which the aqueous phase is surrounded by a highly ordered bilayer of non-ionic surfactants containing or not containing cholesterol and dicetyl phosphate. Niosomes have the capability to entrap both aqueous and non-aqueous drugs, as shown in Figure 1.

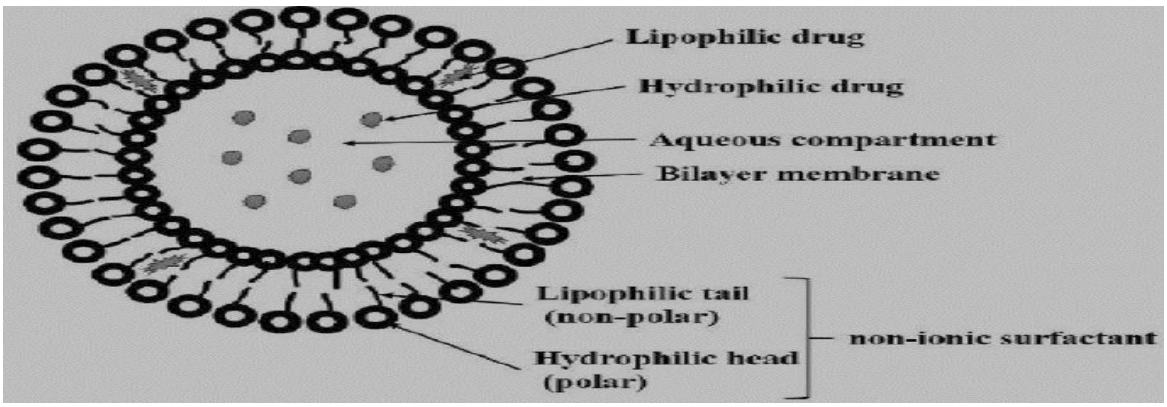

Figure 1: Schematic structure of Niosomes.

Niosomes are novel drug delivery system, preferred over another vesicular system because of its low toxicity, nonionic nature, bio-degradable, better availability of the drug at the site, and good intrinsic skin penetration.

Encapsulating the drug in the noisome can protect the drug from acidic and enzymatic degradation after administration.[1]

Many attempts have been made in the research of niosomes to encapsulate various NSAIDs for better bioavailability, and better permeation through the skin. Novel drug delivery system has limitations such as high cost, which makes it difficult for production and have problem with dose adjustments. So this problem can be overcome by using vesicular drug delivery system like niosomes, which may sustain the drug's presence in the systemic circulation, increase permeation through the skin and reduce toxicity.[2]

Advantages of Niosomes

- Because it contains both aqueous and non-aqueous components, niosomes can serve as a carrier for drugs with a wide range of solubility.
- Niosome surfactants are biodegradable, non-immunogenic, and biocompatible.
- Niosomes with desired properties can be created by modifying vesicle properties such as lamellarity, size, composition, surface charge, and tapped volume.
- Niosomes may also be used as a prolonged release formulation.
- Because ribosomal suspension has a hydrophilic tail, It may improve patient compliance over oil-based formulations.
- Niosomes not only have good stability but also have an osmotic property which makes it superior to oil-based formulations and also increases the entrapment efficiency.
- Niosomes are considered versatile because they can be administered orally, parenterally, or topically.
- Niosomes have been proposed to penetrate the cornea, allowing them to be used for ocular drug delivery.[3,4]

Disadvantages of Niosomes

- Niosomal hydrophilic suspensions have a short shelf life because of drug fusion, aggregation, leakage, and hydrolysis.
- Niosomal formulation techniques as sonication and extrusion are time-consuming and necessitate specialized processing equipment.[5]

various types of niosomes

Niosomes are classified into three types based on vesicle. These are unilamellar vesicles that are small in size, which ranged from 0.025 to 0.05 μm, multilamellar vesicles (more than 0.05 μm) and bigger unilamellar vesicles (more than 0.10 μm).

Formulation Methods

Niosomes are formulated by various methods and they are:

Formulation of Small Unilamellar Vesicles

Sonication

This technique usually includes the addition of surfactant/cholesterol in organic solvent and drug in aqueous solution. The drug's aqueous solution is combined with a surfactant solution and further homogenized for 3 minutes at a temperature of 60°C.[6]

Micro fluidization

For niosome formulation, the submerged jet principle is used. A fluidized stream of drug and surfactant interacts at ultra-high speeds through a micro channel located in the chamber. The entanglement of a thin liquid sheet along a common front is designed to keep the system's energy within the niosome formation region. The method yields niosomes that are smaller in size, more uniform, and more reproducible.[5]

Preparation of Multilamellar Vesicles

Handshaking method (Thin film hydration method)

This method involves the formation of the thin dried layer on the inner wall of the flask. In this method, surfactant and cholesterol are solubilized in an organic solvent. Both the solutions are mixed and the mixture is vanished at a low pressure at a definite temperature to form a thin layer on the inner side of the flask. After evaporation, hydration is carried out with sonication to form niosomes.[6]

Trans-membrane pH gradient drug uptake process

This technique employs a thin film hydration method. In this technique, a specific ratio of cholesterol and surfactant is solubilized in organic solvents like ether or chloroform and evaporated under negative pressure to form a thin dried film.

The resulting film is hydrated with 300 mM citric acid via vortex mixing (pH 4.0). The formed vesicles are repeatedly thawed and frozen before being sonicated to obtain niosomes. The niosomal suspension described before is vortexed with an aqueous solution of the drug. The pH of the niosomal suspension is adjusted to 7.0-7.2 with 1 M disodium phosphate and heated to 60°C for 10 minutes to form the multilamellar vesicles.[7]

Formulation of Large Unilamellar Vesicles

Reverse phase evaporation technique (REV)

A specific ratio of cholesterol and surfactant are solubilized in organic solvents such as ether or chloroform and evaporated under negative pressure to form a thin dried film in this technique. By vortex mixing, the resulting film is hydrated with 300 mM citric acid (pH 4.0). The gel is sonicated again after a minute amount of phosphate buffer solution is added, and the organic phase present is removed at 40°C, yielding high viscosity niosomes. This resulted niosome is diluted with phosphate buffer saline which is maintained at 60°C for 10-15 minutes.[8]

Ether injection method
This technique is used to make large unilamellar vesicles by dissolving the density ratio of surfactant and cholesterol in an organic solvent. To the above mixture, the organic mixthure of the drug is added and injected to the aqueous solution positioned at magnetic stirrer maintained at 60ºC with continuous stirring forming a niosomal suspension.[6]

Miscellaneous
Multiple membrane extrusion methods
Surfactant and cholesterol are dissolved in a non-aqueous solvent, chloroform, in this technique. The non-aqueous surfactant/cholesterol solution is then treated with dicetyl phosphate, and the resulting solution is evaporated under reduced pressure to form a thin film. An aqueous drug solution is used to rehydrate the formed film.

The resulting suspension is pushed through up to eight passages of polycarbonate membranes. This technique can be used to regulate the size of the liposomal formulation.[8]

Emulsion method
Two solutions are prepared. One contains the drug, the other a surfactant and cholesterol dissolved in an organic solvent. These are mixed together to form an oil in water emulsion. After being extracted with an organic solvent, the niosomes are left in the aqueous phase to disperse.[9]

Lipid injection method
Lipids and surfactants are used in this method. Lipids and surfactants are melted, and the resulting mixture is injected into a heated aqueous drug solution. Another method entails putting the drug in lipids and melting it. The molten solution is injected into an aqueous surfactant solution, which is then heated to form niosomes. [3]

The bubble method
This is a one-step method for making noisome that does not require the use of an organic solvent. The bubbling unit consists of a round-bottomed flask with three necks that is placed in a water bath to maintain temperature. The first neck contains water-cooled reflux, the second a thermometer, and the third a nitrogen supply. Niosome dispersion is made by dissolving surfactant and cholesterol in phosphate buffer pH 7.4 at 70°C and mixing for 15 seconds with a high shear homogenizer. At 70°C, it is then bubbled with nitrogen gas.[10]

Separation of Un-entrapped Drug
The un-entrapped drug can be separated by different techniques.

Dialysis
The free drug is separated from niosomal dispersion by using a dialysis bag in phosphate buffer as media.

Gel filtration
The un-entrapped drug in niosomal dispersion is removed using gel filtration, which involves passing the drug through a Sephadex G-50 column and eluting it with phosphate buffer or normal saline.

Centrifugation
Here the separation of the free drug is achieved by centrifugation of the niosomal suspension for 30 minutes. The supernatant solution is decanted, and the precipitate is washed and re-suspended in phosphate buffer to obtain a liposomal suspension free from the un-entrapped drug.[11]

Characterization of Niosomes
Vesicle diameter
The shape of niosomes is spherical in nature and the size ranges from 20 nm to 50 nm. Vesicular form and size distribution can be determined by light microscopy. Another method used for determination of diameter and size of niosome is freeze-fracture electron microscopy.[3]

Vesicle charge
Vesicle charge is determined by measuring zeta potential. Charged niosomes are more stable than uncharged liposomal dispersion. As a result, charged vehicles such as diacetyl phosphate are added to the cholesterol/surfactant mixture during the preparation.[3]

Bilayer formation and number of lamellae
Niosome bilayer formation is characterized by X-cross formation. NMR spectroscopy, electron microscopy, and small angle X-ray scattering are used to determine the number of lamellae.[3]

Membrane rigidity and homogeneity
The rigidity of membrane affects bio-degradation and bio-distribution of niosomes. Determination of rigidity of niosomal suspension is done by fluorescence probe as a function of temperature. Differential scanning calorimetry (DSC), P-NMR, Fourier transform-infra red spectroscopy (FTIR) and fluorescence resonance energy transfer (FRET) are employed to detect the membrane homogeneity.[3]

Encapsulation efficiency (EE%)
It can be done by separating the un-entrapped drug in the niosomal dispersion by using various methods like centrifugation, gel filtration and dialysis. Another method of separation includes complete disruption of vesicle using 0.1% Triton X-100 or 50% n-propanol and then the required disrupted vesicle is analyzed for the drug content and hence EE% can be determined according to the following equation.[12]

$$EE\ (\%) = (C_{total} - C_{free\ drug}/C_{total}) \times 100$$

In vitro drug permeability
In vitro drug permeability of niosomes can be characterized by the following methods

Dialysis
Dialysis is carried out by placing niosomal dispersion in dialysis bag which is pre-washed and presoaked and are tied at both the ends. The dialysis bag is suspended into a dissolution media maintained at 37°C with continuous stirring. Samples are withdrawn at a regular time interval and replaced with a fresh sample. The withdrawn samples are analyzed for the drug content.[6]

Franz diffusion cell
This cell assembly is made up of the donor and receptor compartments, which are separated by a cellophane or dialysis membrane. Niosomal dispersion is placed in the donor compartment, and dissolution media, such as phosphate buffer, is placed in the receptor compartment, which is kept at 37°C and constantly stirred by the aid of a magnetic stirrer. The samples are removed at regular intervals, replaced with fresh media, and analyzed for drug content.[13]

In vivo experiment
The in vivo research is being conducted on albino wistar male rats weighing 150-200 gm. The animals are divided into three groups, each with six animals. Group I receives no treatment, Group II receives a pure drug solution, and Group III receives a liposomal formulation of the drug (dose to be determined). Blood samples are taken from the rats at 0.5h, 2h, 4h, 8h, 12h, and 16h intervals via a catheter implanted in the femoral artery. The catheter is filled with physiological saline on a continuous basis. The collected blood samples are centrifuged in a cooling centrifuge at 12,000 rpm for 3 minutes to separate the blood plasma.

The separated blood plasma is kept in a freezer at -4 degrees Celsius until it is analyzed using HPLC or another precise method.[14]

Stability of niosomes
Niosomes are stored under two distinct conditions, usually 4±1 ºC and 25±2 ºC. The constant particle size and concentration of entrapped drug indicate that niosomes are stable. The concentration and type of surfactant, cholesterol also affects niosome stability. The light microscope is used to detect the vesicle size and the number of vesicles per cubic mm.[15]

Factors Affecting Niosomes Formation
Selection of surfactants and additives
For the formation of niosome vesicles, non-ionic surfactants are used. Surfactants with a hydrophobic tail may contain one or two alkyl groups, one or two fluoro alkyl groups, or, in some cases, a single steroidal group. The toxicity of ether-type surfactants with a single alkyl chain is higher than that of ester-type surfactants. When it comes to stability, ester-linked surfactants are less stable than ether-linked surfactants. This is because ester-linked surfactants are degraded in vivo by esterase into triglycerides and fatty acids.

Surfactants with an alkyl chain length ranging from C to C are appropriate for the formulation of 12-18 niosomes. Suitability of niosome vesicle formation in surfactants with HLB values ranging from 4 to 8.[16,17]

Surfactant and lipid level
Surfactant/lipid levels, which are required for niosomal formulation, are typically kept between 10-30 mM (1-2.5 percent w/w). During the hydration step, changes in surfactant and water ratio affect niosomal dispersion. The total quantity of drug entrapped increases as the surfactant/lipid level rises.[18]

Composition of the membrane
Stabilization of niosomes can be achieved by adding different additives to the surfactant mixture. One main disadvantage of niosome formulation is the leakage of drug from the vesicles which can be controlled by the addition of cholesterol. Cholesterol confers better rigidity to the membrane and therefore leakage of the drug is reduced.[18]

Nature of encapsulated drug
Niosomal formulation is influenced by the nature of the drug being encapsulated. The interaction of the surfactant head groups lead to entrapment of drug in vesicles and cause an increase in charge. The formation of charge causes mutual repulsion of the surfactant bilayer, resulting in an increase in vesicle size. The drug's HLB also improves the degree of entrapment.[19]

The temperature of hydration
The shape and size of noisome are influenced by hydration temperature. Variation in temperature affects surfactants to assemble into vesicles and therefore, affects niosomal vesicle formation. To enable niosome formation, the hydration temperature for the system's gel to liquid phase transition temperature should be higher than the system's gel to liquid phase transition temperature.[6]

Cholesterol content
Addition of cholesterol in niosomal formulation improves entrapment efficiency and thereby provides rigidity to the vesicles. It also increases the hydrodynamic diameter of the niosomal vesicles. Cholesterol also alters the chain order of liquid state bilayers while decreasing the chain order of gel state bilayers. By increasing the concentration of cholesterol, gel-state bilayers can be converted to liquids.[20]

Charge
In a multi-lamellar vesicle structure, the inter-lamellar distance between successive bilayers increases due to the presence of charge. This results in greater overall entrapped volume.[6]

Applications
Generally, peptide drugs have stability problem so it is difficult to formulate in the form of tablets, parenteral.

Therefore, using niosome as a drug carrier can improve the stability of peptide drugs.[3]
Nowadays due to various disadvantages of oral drug delivery system, research is going on for transdermal drug delivery and this has achieved a good response. Niosome as a drug carrier has good penetration capacity. Therefore, niosome can be used as transdermal drug delivery for various drugs. Niosomes have the potential to be an effective drug delivery system for the administration of anticancer drugs such as 5-FU cancer therapy. It is also used for increasing the efficacy of the drug by incorporating it into niosome.[21]

Because the visible spectrum of niosomal suspension can be superimposed on that of free hemoglobin, it can be used as a hemoglobin carrier. Niosomal system can encapsulate drugs which have a low water solubility and low therapeutic index and this can be maintained in the circulation showing sustained release action. The treatment of leishmaniasis is mostly achieved by antimony derivatives.

It has side effects at higher concentrations which may cause liver, cardiac and kidney damage. These side effects at higher concentration can be overcome by niosomes as a drug carrier.[3]

Niosomal system also finds use in diagnostic agents. It can also act as a carrier for radio-pharmaceuticals. The anti-inflammatory effect of diclofenac sodium niosomal formulation prepared with 70% cholesterol was greater than that of the free drug. Likewise, nimesulide and ibuprofen were discovered to be more active than the free drug.[22]

Recent Developments
Various studies have been carried out in the field of niosomes. Attempts were made to improve the oral bioavailability of Cefdinir by incorporating into niosomes and study revealed that formulated niosome showed higher release and improved permeability across animal intestinal membrane than plain drug formulation and marketed formulation.[23]

Research carried out to increase the solubility of BCS class II drug valproic acid by incorporating into a niosomal gel concluded that niosomal entrapped gel had better in vitro release across the animal nasal membrane and hence it can be used as an efficient carrier for valproic acid.[24] Oxcarbazepine niosomes were created and tested to see if they had any advantages over traditional dosage forms. Pharmacokinetic studies have revealed that oxcarbazepine niosomes have a longer elimination half-life and a higher area under the curve when compared to pure oxcarbazepine, indicating their potential to improve the drug's efficacy and safety profile.[25]

CONCLUSION

The field of vesicular drug delivery system is still in its infancy and increasing gradually during the past few decades. It is expected that this trend will continue to increase further. When compared to liposomes, niosomes are a promising vesicular delivery system due to their low cost, stability, and ability to encapsulate a wide range of drugs.

It has been shown in studies to be useful in the delivery of anti-cancer, antiepileptic, and anti-inflammatory agents. It also targets specific areas of mammalian anatomy and is thus used as a diagnostic imaging agent.

Its applications have broadened to include vaccine delivery systems, tumor targeting agents, ophthalmic, and transdermal delivery systems. As a result, more research is needed to unlock the full potential of niosomes.

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