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Comprehensive approaches towards niosomes: A review

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Abstract
Scientists have been interested in improving drug delivery systems including liposomes, niosomes, transferosomes, ethosomes, and pharmacosomes for decades. Niosomes serve a vital function in medication delivery systems. Niosomes are a unique drug delivery technology that can hold both hydrophilic and hydrophobic medicines. The niosomes are incredibly small and microscopic. Niosomes are classed according to the number of bilayers: small unilamellar vesicles (SUV), large unilamellar vesicles (LUV), and multi-lamellar vesicles (MLV). Niosomes are composed of cholesterol and a non-ionic surfactant. The current review covers all aspects of niosomes, including their introduction, composition, advantages and disadvantages, technique of preparation, factors influencing them, evaluation, and application.

Keywords: Niosomes, method of preparation, evaluation study, application of niosomes

Introduction

In 1909, Poul Ehrlich started working on targeted drug delivery. The intended or targeted site is immediately impacted by the targeted pharmaceutical delivery. Targeted drug delivery is the ability of a therapeutic material to work exclusively on a desired site with minimal to no interaction with any other non-targeting locations. Targeted drug administration employs a range of carriers, including the well-known drug delivery systems liposomes and niosomes. Additional carriers include of synthetic polymers, immunoglobulin, plasma protein, microspheres, and occasionally erythrocytes [1].

A carrier is a unique molecule or system that is utilised to move drugs efficiently from loaded locations to predetermined locations for targeted medication administration. Carriers are designed vectors that encapsulate, spacer moiety, and/or physically or chemically interact to retain pharmaceuticals on the surface of the cell or in a subcellular compartment [2]. Because of the following benefits, nanocarriers have been the subject of much research in recent years in an effort to overcome the shortcomings of conventional drug delivery systems: (a) they allow for targeted drug delivery to the diseased site; (b) they improve absorption as surface area increases, increasing bioavailability; (c) they enhance pharmacokinetics and biodistribution of therapeutic agents; and (d) they increase retention in biological systems and prolong the efficacy of drugs [3]. Because they can encapsulate water-soluble, lipid-soluble, and amphiphilic active substances without the need for chemical modification, niosomes are an efficient compound carrier [4].

One of the most promising drug delivery systems is the niosome, which is an aqueous phase containing cholesterol and nonionic surfactants that self-assemble to form a bilayer structure. Niosomes are immuneogenic, biocompatible, and biodegradable. They are highly stable, have a long shelf life, and allow for regulated and/or sustained drug delivery at the target site [5].

Both hydrophilic and hydrophobic medications can be included into niosomes because they are a unique drug delivery system that traps hydrophilic drugs in the core cavity and hydrophobic drugs in the non-polar region located inside the bilayer. Niosomes are named because they are ampiphillic in nature, meaning that the drug is encased in a vesicle comprised of nonionic surfactant. L'Oreal created and patented the first niosome formulations in 1975 [6].

Niosomes can be divided into three categories according to the size or quantity of their bilayers: Multi-Lamellar Vesicles (MLV), Large Unilamellar Vesicles (LUV), and Small Unilamellar Vesicles (SUV). These non-ionic vesicles have particles that are submicron in size. SUVs are estimated to be between 10 and 100 nm in size, LUVs to be between 100 and 3000 nm in length, and MLVs to be larger than 5 µm [7]. Niosomes are amphiphilic surfactants that are non-ionic that self-assemble to create vesicles. The addition of cholesterol and, on occasion, charged molecules stiffens the bilayers and improves system stability. Similar in structure to liposomes, niosomes were developed as a substitute to get around issues with liposome stability, sterilisation, and large-scale manufacture [8]. Due to niosomes' ability to outperform liposomes in certain areas, niosomal formulations have recently attracted more attention from researchers [9].

First reports of niosome production came from the cosmetics industry in the 1970s, but later on, niosomes' potential uses for pharmacological agents—including antioxidants, anti-inflammatory, anti-asthma, anticancer, antiviral, and antibacterial molecules—were expanded [10]. Niosomes have been the subject of much research recently due to their potential as a vehicle for the administration of medications, antigens, hormones, and other bioactive substances. In addition, niosomes have been employed to address the issues of drug instability, insolubility, and fast degradation [11].

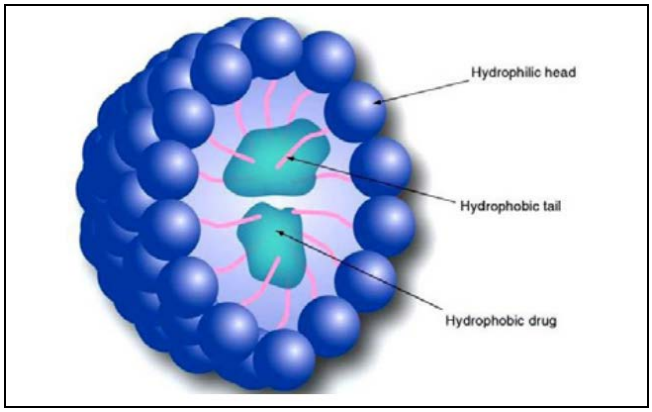

Fig 1: Structure of Niosome

Salient features of niosomes (6,12)

- Niosomes can trap solutes.
- Niosomes are stable and osmotically active.
- They promote medication solubility and oral bioavailability, as well as skin permeability when administered topically.
- Niosomes' structural features (composition, fluidity, and size) are adaptable and can be customised to meet specific needs.
- Niosomes can enhance the performance of medicinal compounds.
- Improved availability to a specific spot simply by shielding the medicine from the biological environment.
- Niosomes improve the stability of the entrapped medication.
- Structurally composed of hydrophobic and hydrophilic moieties, allowing medicinal molecules to entrap easily.
- Have the ability to boost the bioavailability and therapeutic index of medicinal compounds.
- Protects the medicine from the natural environment.
- Biodegradable, harmless, and non-immunogenic in nature.

Composition of Niosome (13)

Niosomes are made using two components

1. Cholesterol
2. Non-ionic surfactants.

a. Cholesterol's steroid-like structure offers stability, appropriate shape, and configuration to the niosome form.

b. Non-ionic surfactants are often employed to manufacture niosomes.

Examples include

a. Tween 40, Tween 20, Tween 60, and Tween 80

b. Span 80, Span 60, Span 40, Span 20, and Span 85

c. Brij 76, Brij 30, Brij 35, Brij 52, Brij 58, and Brij 72

Advantage of Niosome (1, 11, 14)

1. The niosome formulation is more cost-effective than other formulations. All of the ingredients required for niosome formulation are low-cost and readily available.
2. Niosomes can be administered by many ways, including oral, parenteral, and topical.
3. They enhance the therapeutic effectiveness of drugs by delaying their clearance from circulation.
4. Niosomes outperform conventional oily formulations in terms of patient compliance and therapeutic impact.
5. Niosomes provide controlled and prolonged drug release through depot formation.
6. Niosomes are biodegradable, biocompatible, and not immunogenic to the body.
7. Niosomes can be easily handled, stored, and transported. The drug's oral bioavailability can be increased by niosomes.
8. Vesicular systems have potential benefits for cosmetic and therapeutic applications.
9. Delaying medication clearance improves its therapeutic effectiveness.
10. Vesicles can release the medication in a regulated manner.
11. Niosome formulations are low in toxicity due to the ingredients used in manufacture. Furthermore, non-ionic surfactants are the primary constituents of niosomes, and their toxicity is quite low.

Disadvantage of niosomes (1,14)

1. The niosome formulation exhibits physical instability.
2. In niosome formulation, differing charges on the surface of vesicles can cause fusion by attracting opposing charges.
3. Non-standard preparation methods can lead to niosome aggregation.
4. Entrapped drugs may undergo hydrolysis on occasion
5. Some patients showed insufficient medication loading.
6. The formation of niosomes is time-consuming.
7. The shelf life of aqueous niosome solutions may be limited due to drug fusion, aggregation, leakage, and hydrolysis.
8. Preparing multilamellar vesicles through extrusion or sonication takes time and may require specialised equipment.

Types of Niosomes (6)

1. Multilamellar Vesicles (MLV) are the most often used niosomes. It consists of a number of bilayers. Vesicles are approximately 0.5-10 μm in diameter. It is simple to create and mechanically stable when stored for a long time.
2. Large Unilamellar Vesicles (LUV) can hold more bio-active materials due to their high aqueous/lipid compartment ratio.
3. Small Unilamellar Vesicles (SUV) are typically made from multilamellar vesicles using sonication, French press, or extrusion methods.

Methods of Preparation (11, 5, 3, 15, 7, 13, 12, 16)

1. Hand shaking method for hydrating thin films.

The thin film hydration method is straightforward, however it involves the use of organic solvents to dissolve surfactants and cholesterol. Surfactants and cholesterol are dissolved in a round-bottomed flask, followed by the evaporation of the organic solvent, which forms a thin film on the bottom. The addition of water medium causes the film to swell from the wall of the round bottom flask at a temperature above the surfactant's transition temperature for a set period of time with steady gentle agitation, producing multilamellar vesicles that are then treated to form unilamellar vesicles.

2. Sonication

Sonication is a commonly used process for preparing niosomes. This approach is simple to use; simply add the drug solution (in buffer) to the appropriate combination of non-ionic surfactant at the optimal ratio and sonicate at the chosen frequency, temperature, and time to create the required niosomes. This is also an appropriate method for controlling the particle sizes of niosomes. D. Pando *et al*. revealed that resveratrol niosomes were synthesised with a 43% encapsulation rate using two-stage technologies: mechanical agitation and sonication. Sonication can reduce the diameter of niosomes with a restricted size distribution. However, probe sonication uses a lot of energy, which can lead to a fast increase in temperature and titanium shedding.

3. Bubbling Method

This involves homogenising a surfactant/lipid mixture and bubbling nitrogen gas through it. This is a new process for manufacturing liposomes and niosomes in a single step that does not require the use of organic solvent. The bubbling unit consists of a round-bottomed flask. The mixture is blended for 15 seconds with a high shear homogenizer and then "bubbled" at 70ºC with nitrogen gas.

4. Reverse-Phase Evaporation (REV)

The REV technique to niosome production is preferred for encapsulating hydrophilic payloads because it ensures a more highly aqueous core than the film hydration method. The REV method involves combining cholesterol and surfactant in a combination of ether and chloroform. The payload is added to an aqueous solution and sonicated for 5 minutes at 4-5 ◦C to create two phases. The transparent gel is sonicated after adding 10 mL of aqueous phase. The organic phase is then extracted under low pressure at ~40 ◦C using a rotary evaporator. The resulting viscous solution is diluted with an aqueous phase and heated in a water bath at temperatures above Tc for 10 minutes to produce niosomes. The biggest disadvantage of this approach is the possibility of remaining solvent, which could cause unwanted biological effects.

5. The Ether Injection Method (EIM)

The ether injection method involves dissolving surfactants with additives in diethyl ether and slowly injecting them through a needle into an aqueous drug solution at a steady temperature that is higher than the boiling point of the organic solvent. The organic solvent is evaporated with a rotary evaporator. During vaporisation, single-layered vesicles are formed.

6. Supercritical Carbon Dioxide Fluid (scCO2) method

In recent years, Manosroi *et al*. proved the scCO2 approach as a novel niosome preparation method. Briefly, they placed surfactant, cholesterol, PBS with glucose, and ethanol in a glass view cell with two windows and a fixed volume. CO2 was delivered into the system's view cell while maintaining pressure and temperature at 200 bar and 60°C, respectively. Niosomes are formed after 30 minutes of magnetic stirring, and the pressure is then removed. This approach yields LUV niosomes in the size range of 100 to 440 nm. The scCO2 approach has the advantage of being a one-step process that does not require the use of any poisonous, flammable, or volatile organic solvents.

7. Multiple Membrane Extrusion Method

A thin film is created by evaporating a chloroform mixture containing surfactant, cholesterol, and dicetyl phosphate. The film is hydrous with an aqueous drug polycarbonate membrane solution, and the resulting suspension is extruded, allowing up to eight passageways to be placed sequentially. It's an effective approach to keep niosome size under control.

8. Microfluidization Method.

In this technology, two fluidized streams (one containing medication and the other surfactant) contact at ultra high velocity in carefully defined micro channels within the interaction chamber, ensuring that the energy given to the system remains in the area of niosome formation. This is the submerged jet principle. It improves homogeneity, size, and reproducibility in niosome formulation.

Factors Affecting Niosomes (6, 1, 11, 13, 14, 16)

1. Drug property

The molecular weight, chemical structure, lipophilicity, hydrophilicity, and HLB value of the drug all influence the size of the niosome. The HLB value influences drug entrapment efficiency. Drug trapping in niosomes increases with vesicle size.1 When a medicine is entrapped in a niosome, the solute charge interacts with the head group of a surfactant, causing repulsion and increasing the size of the vesicle. Some drugs are added to polyethylene glycol-coated vesicles, reducing the tendency for vesicle size to increase.

2. Membrane additives

The amount of additives used to niosomal formulations, in addition to surfactants and medicines, can boost their stability. The membrane stability, shape, and permeability of vesicles are modified by a variety of additions. For example, adding cholesterol to the niosomal system increases stiffness and decreases drug permeability across the membrane. Niosomes made from C16G2/cholesterol/M-polyethylene glycol (PEG)-Chol exhibit spherical vesicles with dimensions ranging from 20 to 200 nm.

3. Nature of the Encapsulated Drug

The charge and rigidity of the niosome bilayer are affected by the physicochemical parameters of the enclosed molecule. The medication interacts with surfactant head groups, resulting in mutual repulsion between surfactant bilayers and increasing vesicle size.

4. Surfactants

Niosome formulations require a surfactant with a hydrophilic head and hydrophobic tail. The hydrophobic tail can be made up of one or two alkyl or perfluoroalkyl groups, or even a single steroidal group. Ether type surfactants with a single chain alkyl hydrophobic tail are more hazardous than suitable dialkyl ether chains. Ester surfactants are chemically less stable than ether surfactants, and the former is less hazardous than the latter because ester-linked surfactants are destroyed *in vivo* by esterases to triglycerides and fatty acids. Niosomes can be prepared using surfactants with alkyl chain lengths ranging from C12 to C18. Surfactants such as span series, which have HLB values ranging from 4 to 8, can produce vesicles.

5. Surfactant amount and type

Niosome size increases proportionally with surfactant HLB, ranging from Span 85 (HLB 1.8) to Span 20 (HLB 8.6). This is due to a decrease in surface free energy with increasing hydrophobicity. The bilayers of the vesicles are either liquid or gel, depending on the temperature, type of lipid or surfactant, and presence of additional components such as cholesterol. In the gel state, alkyl chains have a well-ordered structure, whereas in the liquid state, the structure of the bilayers is more disordered.

6. Cholesterol Content.

The presence of cholesterol in niosomes boosts the hydrodynamic diameter and entrapment efficiency of the technique. In general, cholesterol promotes the ordered character of bilayers in the liquid state while decreasing order in the gel state. When significant amounts of cholesterol are employed, the gel state changes into an organised liquid phase. When the cholesterol content of the bilayers increases, the rate of release of encapsulated components decreases because the bilayers become more rigid. The presence of charges increases the interlamellar distance between successive MLV bilayers, resulting in a larger overall space for entrapment.

7. Temperature of Hydration

Hydration temperature controls the shape and size of the niosome, and temperature changes in the niosomal system affect surfactant assembly into vesicles, resulting in vesicle shape metamorphosis. Ideally, the hydration temperature for noisome production should be higher than the system's gel to liquid transition temperature.

8. Resistance to osmotic stress.

The addition of a hypertonic salt solution to a niosome suspension reduces its diameter. In hypotonic salt solution, there is an initial delayed release with slight enlargement of the vesicles, most likely due to inhibition of eluting fluid from the vesicles, followed by rapid release, which could be due to mechanical loosening of the vesicles' structure under osmotic pressure.

Evaluation of Niosomes (6, 11, 5, 3, 15,12, 16)

1. Efficient entrapment.

After creating the niosomal dispersion, the unentrapped medication is separated using dialysis centrifugation and gel filtering. The drug remaining encapsulated in niosomes is measured by full vesicle disruption with 50% n-propanol or 0.1% Triton X-100, and the resultant solution is analysed using the appropriate assay method using the equation below.

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

2. Number of Lamellae

NMR spectroscopy, small angle X-ray spectroscopy, and electron microscopy were used to determine the number of lamellae.

3. Membrane rigidity

The temperature-dependent mobility of a fluorescent probe has been utilised to determine the membrane stiffness of particular niosomal formulations.

4. Zeta Potential.

Niosomes' surface zeta potential can be evaluated using a zeta sizer and DLS equipment. Niosome behaviour is heavily influenced by their surface charge. In general, charged niosomes are more resistant to aggregation than uncharged vesicles. Bayindir and Yuksel developed paclitaxel-loaded

niosomes and examined their physicochemical features, including their zeta potential. Negative zeta potential values of −41.7 to −58.4 mV are sufficient for electrostatic stabilisation of niosomes.

5. Size and dispersion of niosome particles.

Particle size is an important characteristic in the characterisation of niosomes since it indicates the physical properties and stability of the formulation. S. Chen *et al*. European Journal of Pharmaceutics and Biopharmaceutics 144 (2019), 18-39. 26 approaches include dynamic light scattering (DLS) and microscopy. DLS is often referred to as photon correlation spectroscopy. This procedure is quick and non-destructive, and just a minimal amount of sample is needed. It can monitor particles ranging from 3 to 3000 nm.

6. Stability of Niosomes

The stability of niosomes is critical for their formulation development. It is influenced by the technique of preparation, the medications used, and the type of membrane forming material. The stability of their storage can be evaluated by measuring changes in particle size, zeta potential, morphology, and loaded drug leakage rate. To test the stability of niosomes in circulation, drug-loaded vesicles can be incubated at 37 ◦C in serum or severe circumstances, simulating real-life scenarios. The sizes, zeta potential, and leakiness of pharmaceuticals placed into niosomes are assessed as a proportion of time to assess the stability of these vesicles. Niosomes are more stable than liposomes and may have clinical applications.

7. Viscosity

Viscosity is measured using viscometers and rheometers. Viscosity is defined as the fluid's resistance to progressive deformation caused by shear or tensile stresses. The viscosity of niosomes is evaluated using an Ostwald viscometer. The temperature is maintained at 25 ± 0.5 ºC and 35 ± 0.5 ºC.

8. *In-vitro* Drug Release

In vitro payload release behaviour from niosomes is a critical parameter that can be altered, including drug concentration, hydration volume, stiffness, and bilayer state. The release of drug compounds from niosomes is typically investigated utilising dialysis membrane methods. To prepare purified niosomal suspension, place it in a dialysis bag, seal it at both ends, and place it in a vessel with simulated body fluids or phosphate buffered saline. Maintain the temperature at 37 ◦C with constant agitation. Samples are collected at predefined intervals and replaced with an equal amount of fresh medium. These samples are then analysed using appropriate quantification techniques to estimate the concentration of payload delivered over time. Other methods based on Franz diffusion cells have been published, and they follow similar general procedures.

Conclusion

Niosomes are a targeted drug delivery technique. They exhibit a liposome-like structure. Niosome formation is fully reliant on liposome preparation procedures. They do not require specific handling, protection, or storage conditions, as well as industrial manufacturing. Niosomes have several advantages over liposomes, including cost, improved purity, solubility, bioavailability, and sterility. Stability. Niosomes have some advantages over liposomes. It was so found that niosomes are an extremely effective medication delivery method.

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