NIOSOMES: Future Medicament

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Abstract- When synthetic non-ionic surfactants are hydrated, either with or without the consolidation of cholesterol or other lipids, niosomes—non-ionic surfactant vesicles—form. They are vesicular structures, similar to liposomes, that can be used to transport both lipophilic and amphiphilic drugs. Being non-ionic, niosomes are a promising drug delivery system. These are biodegradable, biocompatible, and not immunogenic, thus show adaptability and flexibility in their structural characterization. For the treatment of tumors, viral infections, and other microbial illnesses, niosomes have generally been evaluated for controlled discharge and targeted delivery. Both hydrophilic and lipophilic drugs can become entangled by niosomes, which increases the drug residence time in the blood circulation. Medication encapsulation in vesicles is expected to prolong the presence of the medication in the systemic circulation, improve penetration into target tissue, and possibly reduce toxicity if targeted take-up is successful. This review focuses on the various components of niosomes, their different types, their advantages, methods of preparation, factors affecting, characterizations, and applications.

Keywords: Niosomes, Cholesterol, Composition, Application.

INTRODUCTION

Niosomes are vesicular, innovative drug delivery systems that can be utilised to deliver medications in a sustained, controlled, and targeted manner [1]. The niosomes are amphiphilic in nature, and their name derives from the fact that medicine is contained within a vesicle comprised of a non-ionic surfactant [2]. The size range of niosomes, which are microscopic lamellar structures, is between 10 and 1000 nm. Surfactants that are non-immunogenic, biodegradable, and biocompatible constitute the niosome. Niosomes are superior to liposomes and have greater surfactant chemical stability due to the ester bond than phospholipids, which are more easily hydrolysed and less expensive [3]. As niosomes alleviate the disadvantages of liposomes, they are mainly studied as alternatives to liposomes. The limitations of liposomes, such as chemical instability, are overcome by niosomes. Niosomes are an improvement over liposomes in categories like chemical instability. The variable phospholipid purity and sensitivity for oxidative degradation in liposomes cause their chemical instability.

There are several ways to administer niosomes, including orally, parenterally, and topically. The delivery of various drugs, including synthetic and natural ones, antigens, hormones, and other bioactive substances is carried out by niosomes [2]. Niosomes have received a positive deal of attention in recent years because of their potential to deliver drugs, antigens, hormones, and other bioactive agents. In addition to this, the insolubility, instability, and quick degradation of drugs have all been discussed using niosomes [4].

In 1975, L'Oréal created and received a patent for the first niosome formulations. Niosomes were initially used in the drug delivery of anticancer medications. The pharmacokinetic profile, organ distribution, and metabolism of methotrexate in mice were able to be altered as a result of the developed niosome formulations. Niosomes can entrap lipophilic drugs by partitioning these molecules into bilayer domains or hydrophilic drugs in aqueous compartments due to their versatility in structure, morphology, and size. They can also be designed as a unilamellar, oligo lamellar, or multilamellar vesicle [5]. Niosomes were first introduced to the market in 1987 by Lancôme primarily for the cosmetic industry, but they have since received thorough research as drug delivery and targeting agents. Niosomes have since been widely

studied in a variety of fields, including medicine, food science, and cosmetics, leading to a huge number of publications and patents. By using this system, the drug can be administered topically, parenterally, or orally, increasing the amount of the drug at the targeted site [6].

The main objective of this review is to summarise the fundamentals of niosome preparation, characterization, and drug delivery with a special emphasis on more recent studies. The growing interest in niosomes for drug delivery will be discussed in this review [7].

MAIN TEXT

1. STRUCTURE AND COMPOPNENTS OF NIOSOMES:

The main components of niosomes are lipids such as cholesterol, non-ionic surfactants and hydration medium. Non-ionic surfactants form closed bilayer structures when they self-assemble in aqueous media (Fig: 1). the hydrophobic tails of the amphiphile associate with water due to a high interfacial tension. Non-ionic surfactant hydrophilic termini point outward and come into contact with water due to the steric and hydrophilic attachment between the head groups. The formation of closed bilayers typically requires an energy input, such as mechanical or thermal energy [7].

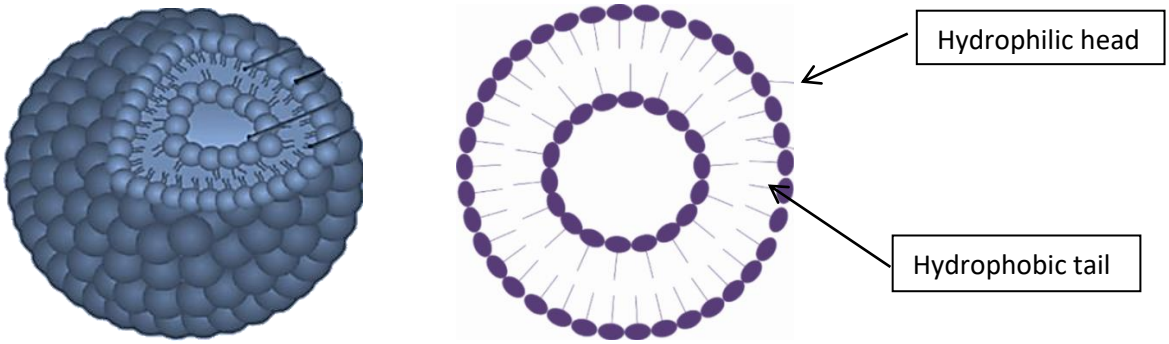

Fig.1: Structure of Niosome .

2. COMPONENTS OF NIOSOMES:

These following components used for the preparation of niosomes are,

1. Cholesterol.
2. Non-ionic surfactants.
3. Charged Molecules. [7]

2.1 Cholesterol:

Steroids are essential components of the cell film and their presence affects the fluidity and permeability of the bilayer. A steroid derivative, cholesterol is primarily used in the formation of niosomes. Despite the possibility that it plays no role in the formation of the bilayer, its importance in the development of niosomes and the control of layer characteristics cannot be discounted. Cholesterol inclusion affects the harmfulness of niosomes as well as their properties such as membrane permeability, rigidity, encapsulation effectiveness, and ease of rehydrating freeze-dried niosomes. It prevents the accumulation of vesicles by considering the atoms in the system to counteract the formation of aggregates by repellent steric or electrostatic forces, which cause the transition of niosome systems from the gel phase to the liquid phase. As a result, the niosomes nature is discovered to be less leaky. Cholesterol and non-ionic surfactants are generally used in a 1:1 M ratio [8].

2.2 Non-ionic surfactants:

Surfactants that have no charged groups in their hydrophilic heads are known as non-ionic surfactants. Compared to their anionic, amphoteric, or cationic counterparts, they are more stable, biocompatible, and less harmful. They are also preferred for the in vitro and in vivo manufacturing of stable niosomes. Non-ionic surfactants are amphiphilic molecules that have separate hydrophilic and hydrophobic (water-soluble and water-insoluble) regions (organic-soluble). The most common non-ionic surfactant classes utilised in the production of niosomes are alkyl ethers, alkyl esters, alkyl amides, and fatty acids. [9]

The following non-ionic surfactants are commonly used in the manufacture of niosomes:

a. Span 80, Span 60, Span 40, Span 20, and Span 85.
b. Tween 80, Tween 60, Tween 40, Tween 20.
c. Brij 76, Brij 35, Brij 52, Brij 58, Brij 72. [10]

2.3 Charged Molecules:

Niosomes are given some charged molecules to increase stability by supplying electric repulsion to prevent collision. Dicetyl phosphate (DCP) and phosphotidic acid are examples of molecules that are negatively charged. Similarly, well-known charged molecules used in niosomal preparations include stearyl amine and stearyl pyridinium chloride. [11]

3. TYPES OF NIOSOMES:

- According to their size, niosomes can be divided into three categories:
  1. Multi lamellar vesicles (MLV, size=>0.05 µm).
  2. Large unilamellar vesicles (LUV, size=>0.10 µm).
  3. Small unilamellar vesicles (SUV, size=0.025-0.05µm). [8]

- In addition, niosomes are classified according to the kind of non-ionic surfactant and other components used in manufacturing and the various clinical applications they have:

- Proniosomes:
  Niosomes composed of water-soluble carriers and surfactants can aggregate to form prosoniosomes. The proniosomes are niosomes that have been dehydrated but are later hydrated for use. For a while, prosoniosomes can reduce niosome problems like drug leakage, fusion, and aggregation. [12]

- Apsasome:
  Ascorbyl palmitate, cholesterol, and dihexadecyl phosphate, a highly charged lipid-like substance, are all components of the apsasome. It needs to be hydrated and sonicated by a water solvent to produce the final product. Apsasome may improve transdermal drug delivery systems and lessen disorders brought on by reactive oxygen species. [12]

- Discomes:
  Cholesteryl poly-24-oxyethylene ether (Soulan C24) and a small amount of cholesterol are used to manufacture these MLVs. Their sizes range from 11 to 60µm, and they are used to develop a sustained-release formulation for ocular delivery. [13]

- Niosomes in carbopol gel:
  In carbopol-934 gel (1% w/w), a base containing propanediol (10% w/w) and glycerine (30% w/w), niosomes are added. [11]

- Deformable niosomes:
  The deformable niosomes are formed from a mixture of non-ionic surfactants, ethanol, and water. The efficiency of penetration is increased because these are smaller vesicles that can easily pass through the pores of the stratum corneum. It is applicable for topical preparation. [14]

- Bola-niosomes:
  Bola-surfactant compounds are required in these kinds of niosomes, and they can be linked by one or two long lipophilic spacers, two hydrophilic heads, or both. The surfactant used in bola surfactant containing niosomes is omega hexadecyl-bis-(1-aza-18 crown-6): span-80/cholesterol in a 2:1:1 molar ratio.

- Elastic niosomes:
  This kind of niosome can be flexible without destroying its structure, which enables it to allow side-to-side pores while also reducing its size. Non-ionic surfactants, water, and ethanol are present in these vesicles. The penetration through intact skin layers can be increased by using this flexible structure. [15]

- Vesicles in water and oil system (v/w/o):
  According to this method, aqueous niosomes are incorporated into an oil-stage frame vesicle in a water-in-oil emulsion (v/w/o). To achieve this, a niosome suspension made of sorbitol monostearate, cholesterol, and solulan C24 (Poly-24-Oxyethylene Cholesteryl Ether) can be expanded to the oil stage at 60°C. As a result, a vesicle in water in oil (v/w/o) emulsion is formed, which can then be cooled to room temperature to form a vesicle in water in oil gel (v/w/o gel). After oral administration and controlled release, the v/w/o gel can entrap proteins and proteinous drugs while also protecting them from enzymatic degradation.

- Niosomes of hydroxyl propyl methylcellulose: This type required the preparation of a base containing 10% glycerine of hydroxypropyl methylcellulose before the incorporation of niosomes. [14]

4. Comparison of liposomes and niosomes:

There are many similarities between niosomes and liposomes. Liposomes contain phospholipids that are not stable in nature, whereas niosomes are composed of stable non-ionic surfactants. An unchanged single-chain non-ionic surfactant is used to make niosome, whereas Phospholipids with a double chain are used to make liposomes. Niosome sizes range from 10 to 100 nm, while liposome sizes range from 10 to 300 nm. In terms of price, niosomes are less expensive than liposomes. [16]

In the body, niosomes behave similarly to liposomes in that they prolong the circulation of the drug that is entrapped and change its metabolic stability and distribution to the organs. The distribution of tissues, cellular interactions with drugs, plasma clearance kinetics, and drug metabolism are all altered by these types of drug carrier vesicular systems. For controlled release and targeted drug delivery systems, it becomes the best option. [17]

5. SIGNIFICANCE OF NIOSOMES:

1. They increase the oral bioavailability of poorly absorbed medications and increase drug penetration through the skin.
2. To regulate the delivery, an aqueous phase of niosomal dispersion can be emulsified in a non-aqueous phase.
3. Surfactants don't require any special handling or storage procedures. [1]
4. Drugs that are hydrophilic, lipophilic or amphiphilic can all be accommodated by niosomes.
5. Protection against enzyme metabolism for drugs.
6. Low-cost colloidal vesicle carrier. [18]
7. It provides targeted and controlled drug delivery.
8. Good patient compliance is stated.

6. DRAWBACK OF NIOSOMES:

1. Aggregation.
2. Time consuming.
3. Fusion.
4. Entrapped drug leakage.
5. Physical instability.
6. Limiting the shelf life of the dispersion is the hydrolysis of drugs that are encapsulated. [19]

7. LIMITATIONS OF NIOSOMES:

1. Drug degradation results from the hydrolysis of drugs that are encapsulated, which reduces the stability of niosomal dispersion.
2. Drug loading or entrapment is made more difficult by niosomal vesicle fusion.
3. Niosomes collect and form a mass, which leads to drug leakage.
4. Drug leakage leads to physical instability and dosage issues. [20]

8. METHOD OF PREPARATION:

There are various methods for formulation of niosomes some of them are explained below:

8.1Thin film hydration technique/ Hand shaking method:

In this method, the surfactant and cholesterol were dissolved in a round-bottomed flask with a volatile organic solvent (diethyl ether, chloroform, or methanol). Using a rotary evaporator, the organic solvent is removed at room temperature (20°C), leaving a thin coating of the solid mixture deposited on the flask wall. Aqueous-phase phosphate buffer saline (PBS) with a pH of 7.4 is used to rehydrate the dried surfactant film while gently stirring it under normal pressure. This produces typical multilamellar niosomes. [20]

8.2 Ether injection method:

Using this method, niosomes are prepared by gradually adding a surfactant solution dissolved in diethyl ether to warm water maintained at 60°C. Through a 14-gauge needle, the surfactant mixture in ether is injected into the material's aqueous solution. The formation of single-layered vesicles is caused by ether vapourization. Such conditions produce vesicles that range in width from 50 to 1000 nm. [8]

8.3 Reverse phase evaporation technique:

To remove the aqueous product solution and keep water in the oil emulsion, cholesterol and surfactant (ratio 1:1) dissolve in an organic solvent mixture (ether and chloroform); two stages are acoustic at 4-5ºC. To produce a semi-solid gel of large vesicles, the emulsion is dried at 40°C in a rotary evaporator. The clear gel is covered with small amounts of phosphate-buffered saline (PBS), which is then sonicated once

more. Niosomes are created by further diluting a viscous niosomal suspension with phosphate-buffered saline and placing it in a water bath for 10 minutes. [21]

8.4 Sonication:

Sonication is one of the common techniques for the preparation of niosomes. In this method, drugs and buffer are dissolved to create the drug solution. The mixture of non-ionic surfactant is then added to this buffered drug solution in an ideal ratio. When the mixture is sonicated at a particular frequency, temperature, and duration, the desired niosomes are produced. It is one of the simple ways to control the particle size of the niosomes. The diameters of niosomes with a narrow size distribution can be reduced using this technique. It is also possible to use probe sonicators, but they use a lot of energy. This causes a sudden rise in temperature and the release of titanium. [16]

8.5 The Bubble method:

It is a novel method for making liposomes and niosomes in a single step without the use of organic solvents. It consists of the round-bottomed flask with three necks placed in a water bath to regulating the temperature. The first and second necks of the reflux are used to position the thermometer and water-cool the reflux, while the third neck is used to supply nitrogen. In this buffer (pH 7.4), surfactant and cholesterol are mixed at 70 °C. Niosomes are created by the dispersion process, which also generates and introduces a continuous stream of nitrogen gas bubbles.

8.6 Micro fluidization method:

Micro fluidization is a modern technique for arranging unilamellar vesicles with known estimated circulation. The submerged jet principle is the basis of this strategy, which connects two fluidized streams at extremely high speeds while mischaracterizing smaller-scale channels inside the interaction chamber. Thin liquid sheets are impinged along a common front in such a way that the energy supplied to the system stays in the area of niosome formation. As a result, the niosome shape is more consistent, smaller, and easily reproducible. [14]

8.7 Multiple membrane extrusion method:

A mixture of surfactant, cholesterol, and diacetyl phosphate is produced, and the solvent is then evaporated using a rotary vacuum evaporator to leave a thin film. The film is then hydrated with an aqueous drug solution, and the resulting suspension is extruded through the polycarbonate layer (mean pore size 0.1mm) and then placed in a series of up to eight passages to obtain uniform-sized niosomes. [8]

8.8 Emulsion method:

This is a simple technique to form niosomes in which an oil-in-water (o/w) emulsion is prepared from an organic solution of surfactant, cholesterol, and an aqueous solution of the drug. The organic solvent is finally evaporated, leaving the niosomes dispersed in the aqueous phase. [21]

8.9 Formation of niosomes from Proniosomes:

Another method of producing niosomes involves coating a water-soluble carrier, such as sorbitol, with a surfactant. A dry formulation is produced during the coating process. Each water-soluble particle is covered with a thin layer of dry surfactant. This preparation is known as "proniosomes." The niosomes are identified by adding the aqueous phase at Temperature Gretter, then heating to the mean phase transition temperature and briefly stirring. Niosomes are formulated from proniosomes. [10]

8.10 Transmembrane pH Gradient (Inside Acidic) Drug Uptake Process (Remote Loading):

In this step, a surfactant and cholesterol solution is produced in chloroform. The solvent is then evaporated under reduced pressure to create a narrow film on the wall of the round bottom flask, which is similar to the hand shaking process. The film is then vortex-mixed with a citric acid solution to hydrate it. After three freeze-thaw cycles, the resulting multilamellar vesicles are sonicated. The niosomal suspension and vortex are mixed with an aqueous solution containing a medication concentration of 10 mg/ml. The sample's pH is raised to 7.0-7.2 by adding 1M disodium phosphate, and then the mixture is heated to 140°C for 600 seconds to obtain the niosomes. [10]

8.11 Heating method:

The cholesterol is dissolved by heating to 120°C while stirring after the surfactants and cholesterol have been separately hydrated in a separate buffer. The temperature is lowered while stirring, and surfactants and other chemicals are added to the buffer in which the cholesterol is dissolved. Niosomes are created as a result of this process, which is followed by allowing them to cool to room temperature before being stored in a nitrogen atmosphere at 4-5°C until required. [9]

8.12 Lipid layer hydration method:

Chloroform was used to dissolve Span 60 and cholesterol (1:1), and a rotary flash evaporator was used to evaporate the solvent. With gentle agitation, drug-containing phosphate buffer saline with a pH of 7.4 is added to the dried thin film. On a vortex mixer, the mixture is blended irregularly. At 25°C, the mixture is sonicated for 1 minute with a probe sonicator set to 200 watts. [8]

8.13Extrusion method:

In this method, prepare the cholesterol and dicetyl phosphate mixture and using a rotary vacuum evaporator, the solvent of the mixture is evaporated to create a thin film. The drug solution is then used to hydrate the film and the resulting suspension is extruded through the polycarbonate membrane and then placed in order for up to eight passages to produce niosomes of the same size. [11]

8.14Single pass technique:

It is also mentioned as multiple membrane extrusion. In this technique, a suspension of a lipid-containing drug is passed from a porous device and then through a nozzle. It generates niosomes of uniform size, typically between 50-500 nm. [1]

9. Comparative assessment of niosomes produced by different methods:

Baillie et al. compared the niosomes produced by ether injection, hand shaking, and sonication. In comparison to hand-shaken and sonicated vesicles, the ether-injected niosomes' entrapment efficiency was noticeably higher. Niosomes made by sonication had the smallest mean size (152.5 ± 81.6 nm), whereas ether injection and hand shaking produced larger niosome particles (306.0 ±178.0 nm and 490.0 ±378.0 nm, respectively). Guinedi and Mortada et al. compared the acetazolamide-loaded niosomes produced using the TFH and RPE methods. The MLVs created using the TFH method showed higher entrapment efficiency than those created using the RPE after 8 hours of niosome storage. Multilamellar niosomes obtained particle sizes greater than those of REV. The IOP was consistently decreased by multilamellar acetazolamide niosomes, which were thought to be more effective. Key Yeo et al. created Cinnarizine-loaded niosomes using the TFH and micro fluidization methods. Thin-film hydration produced MLVs with a larger particle size distribution ranging from 827 to 7320 nm and a higher polydispersity index (PDI) of 0.3 to 0.9, whereas microfluidic hydration produced smaller vesicles (ranging from 155 to 355 nm) and a lower PDI value (0.011 to 0.209). The entrapment efficiency of niosomes manufactured by micro fluidization and the TFH technique was noticeably low (≥9% and ≥20, respectively). Bhaskaran et al. formed salbutamol sulphate-containing niosomes using Span 60 as a surfactant using various techniques such as TFH, ether injection, lipid layer hydration, and the membrane pH gradient method. Encapsulation efficiency varies between 62% - 82%. The membrane pH gradient method was the most satisfying method that showed a 78.4% drug release in a day and an 87.51 ± 0.239% entrapment efficiency.

These niosomes were assayed by extrusion, ultrasound, and freeze-thaw sonication (FTS), ultrasound, and nano synthesis. Among the techniques, the extrusion method was more efficient, reducing its size to 67.9. FTS, ultrasound, and sonication followed, with reductions of 61.2%, 26.7%, and 15.0%, respectively. The homogenization technique was found to be less efficient. [22]

10. FACTORS INFLUENCING NIOSOMAL FORMULATIONS:

10.1 Nature of Surfactants:

Since the surface free energy decreases as the surfactant hydrophobicity increases, an increase in the HLB value of the surfactants causes an increase in the mean size of niosomes. The temperature, sort surfactant, and cholesterol all are involved. In the gel state, alkyl chains are well ordered; in the liquid state, they are chaotic. The surfactant's gel-to-liquid phase change temperature (TC) has an impact on entrapment efficiency. [23]

10.2 Nature of Encapsulated Drug:

The physical and chemical characteristics of the drug contained have a significant impact on the charge and rigidity of the niosomal bilayer. Drugs are captured by interacting with the surfactant head groups, which increases charge and causes the surfactant bilayer to repel each other, increasing the vesicle. The level of trapping is determined by the drug's HLB. [21]

10.3 Osmatic Stress:

A suspension of niosomes is reduced in diameter by the addition of a hypertonic salt solution. In a hypotonic salt solution, there is an initial slow release

with slight swelling of the vesicles that may be caused by the inhibition of fluid elution from the vesicles, followed by a faster release that may be caused by mechanical loosening of the vesicles' structure under osmotic stress. [24]

10.4 Temperature of Hydration:

Hydration temperature controls the Niosome's size and shape. A change in the temperature of the niosomal system affects how surfactants are organised inside vesicles, which may result in a change in vesicle shape. It is ideal for the system's hydration temperature to be higher than the temperature at which the system transitions from the gel to the liquid phase. [25]

10.5 Properties of Drugs:

The drug entrapment is affected by the molecular weight, chemical structure, hydrophilicity, and lipophilicity balance (HLB) values of the drug. Vesicle size may increase due to the drug entrapment. Drug particles interact with the surfactant head groups, which may increase the charge on the polymer and thus cause repulsion of the surfactant bilayer, which leads to an increase in vesicle size. [26]

10.6 Membrane Composition:

Different additives, as well as surfactants and medications, may be used to make stable niosomes. Niosomes can have a variety of morphologies, and their permeability and stability properties can be changed by adjusting membrane properties with various additives. When a small amount of solulan C24 (cholesteryl poly24-oxyethylene ether) is added to polyhedral niosomes made from C16G2, the shape of the polyhedral niosomes is not affected, preventing aggregation due to the formation of steric hindrance. [10]

10.7 Zeta Potential:

The hydrophilicity of the surfactant increases the zeta potential value of the solvent formulation. This is due to the fact that the surface free energy of the span surfactant increases as the HLB value rises. [10]

10.8 Effect of Drug Concentration:

The drug entrapment efficiency of the niosome decreases as the drug concentration exceeds 50 mg. [10]

10.9 Cholesterol Contents:

The addition of cholesterol to the niosome's bilayer composition causes membrane stabilisation and reduces membrane leakiness. As a result, adding cholesterol to a bilayer improves entrapment effectiveness. The addition of cholesterol reduces the permeability of the vesicle bilayer to 5, 6-carboxyfluorescein (CF) by a factor of ten. [10]

10.10 Surfactant / lipid volume:

The surfactant/lipid level that is necessary for niosomal formulation is usually maintained between 10-30 mm (1-2.5 percent w/w). Variation of the surfactant, water ratio during the hydration process affects the niosomal dispersion. The total amount of the encapsulated drug also rises by raising the surfactant/lipid amounts. [25]

10.11 pH of the hydration medium:

Another factor that can affect a drug's entrapment efficiency is the pH of the hydration medium. Flurbiprofen, for example, has higher entrapment at acidic pH levels (maximum 94.6 percent at pH 5.5). [25]

10.12 Hydration time:

Yeo et al. prepared methylene blue niosomes by thin film hydration and probe-sonication to achieve uniform-sized vesicles. The impact of hydration time and hydration volume on entrapment efficiency and vesicular size was studied. The longer the hydration time and the less drug entrapment, the smaller the vesicles. According to them, 60 minutes of hydration time and 5 ml of hydration volume are ideal for complete hydration of span 60 and vesicular formation. Longer hydration times produce vesicles of smaller sizes. [25]

11 CHARACTERIZATION OF NIOSOMES:

11.1 Surface morphology: The noisome vesicles characterized for their shape and surface morphology using transmission electron microscope (TEM) and scanning electron microscopy (SEM).

Procedure:

- TEM: A drop of niosomal dispersion was smeared to a carbon film-covered copper grid and was stained with a 1% phospho-tungstic acid. Then,

samples were examined and photograph with TEM at an accelerating voltage of 100 kV.

- SEM: The samples are dried thoroughly in vacuum desiccators before mounting on brass specimen studies, using double sided adhesive tape. Gold palladium alloy of 120 °A Knees was coated on the sample sputter coating unit in Argon at ambient of 8-10 °C with plasma voltage about 20mA. The sputtering was done for nearly 5 minutes to obtain uniform coating on the sample to enable good quality SEM images. [27]

11.2 Zeta potential: Zeta potential is deeply crucial in the behaviour and properties of niosomes vesicles. The HLB value of surfactants are effective on zeta potential; if HLB value is high, there is more negative value of zeta potential. [28]

11.3 Entrapment efficiency: The unentrapped medication is separated by dialysis, centrifugation, or gel filtration as described above and the medication which remained entrapped in niosomes is determined by complete vesicle disruption utilizing 50% n-propanol or 0.1% Triton X-100 and analysing the resultant solution by appropriate assay technique for the medication. [8]

$$\text{Entrapment efficiency} = \frac{\text{Amount entrapped}}{\text{Total amount}} \times 100$$

11.4 Bilayer formation and number of lamellae: The formation of bilayers of niosomes is characterized by X-cross formation under the light polarization microscopy. Different methods, such as AFM, NMR, small-angle X-ray spectroscopy and electron microscopy are preferred for estimation of the number of lamellae. [25]

11.5 Membrane rigidity and homogeneity: Membrane rigidity affects bio-degradation and bio-distribution of niosomes. The determination of niosomal suspension rigidity is carried out as a function of temperature by using fluorescence probe. For assessing membrane homogeneity, P-NMR, Differential Scanning Calorimetry (DSC), Fourier Transform-infra red spectroscopy (FTIR) and Fluorescence Resonance Energy Transfer (FRET) are used. [25]

11.6 Measurement of vesicle size: Vesicles dispersions are diluted about 100 times in the same medium used for their preparation. Vesicle size can be measured by using a particle size analyzer. The apparatus consists of a 632.8 nm He-Ne laser beam centered using a Fourier lens [R-5] to a point at the middle of the multi-element detector and a small volume sample keeping cell with a minimum power of 5 mW. Until deciding the vesicle scale, the sample is stirred using a stirrer. [25]

11.7 pH measurement: The pH of niosomes can be measured by a pH meter. The pH estimation is performed at 25°C. [8]

11.8 In-vitro drug release: In vitro drug release can be done by Dialysis tubing, Reverse dialysis and Franz diffusion cell method.

a) Dialysis tubing: The niosomes are inserted in prewashed dialysis tubing in this process, which can be hermetically sealed. The dialysis sac is then dialyzed against an appropriate dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, centrifuged and tested for drug content using suitable procedure (U.V. spectroscopy, HPLC etc.). It is important to maintain the sink condition.

b) Reverse dialysis: A number of tiny dialysis containing 1 ml of dissolution medium is inserted in proniosomes in this process. Then the proniosomes are displaced into the medium of dissolution. With this approach, immediate dilution of the proniosomes is feasible; however, it is not possible to measure rapid release using this process.

c) Franz diffusion cell: Using the Franz diffusion cell, in vitro diffusion experiments may be carried out. Proniosomes are mounted in a Franz diffusion cell equipped with a cellophane membrane in the donor chamber. The proniosomes are then dialyzed at room temperature against an acceptable dissolution medium; the samples are collected at reasonable intervals from the medium and tested for drug content using the appropriate procedure (U.V spectroscopy, HPLC, etc.). [25]

11.9 Tissue distribution / in-vivo study: In-vivo tests for niosomes rely on the delivery route, drug dosage, drug impact and duration of presence in tissues such as liver, lung, spleen and bone marrow. Using animal models, tissue dissemination of a drug can be studied. Animals are slaughtered and separate tissues such as liver, kidney, breast, lungs, spleen should be separated, washed with buffer, homogenized and centrifuged to research the delivery pattern. For the drug material, the supernatant is analysed. [25]

11.10 Stability studies: In storage, because of aggregation and fusion, the drug can leak from the niosomes. Various humidity and light (UV) conditions are also exposed to niosomes. Parameters such as size, shape and entrapment performance are routinely tested during stability studies. [25]

12 PURIFICATION OF NIOSOMES:

12.1 Dialysis: The aqueous niosomal suspension is dialyzed in dialysis tubing by using phosphate buffer or glucose solution or normal saline. [16]

- Advantages:
  1) Suitable for large vesicles >10 μm.
  2) Suitable for highly viscous systems.

- Disadvantages:
  1) Extremely slow (5–24 h).
  2) Large volumes of dialysate required. [29]

12.2 Gel Filtration: The unentrapped drug in the niosomal suspension is removed by gel filtration using Sephadex-G-50 column and elution is done with phosphate buffered saline or normal saline. [16]

- Advantages:
  1) Quick (4–5 min with Sephadex G50).
- Disadvantages:
  1) Dilutes the niosome dispersion.
  2) Slow (1–2 h when using Sepharose 2B/4B for macromolecule separation).
  3) Not suitable for formulations with a large particle size (>10–20 μm). [29]

12.3 Centrifugation: In centrifugation, the niosomal suspension is centrifuged and the supernatant liquid is separated. Niosomal suspension free from unentrapped drug is obtained by washing the pellet and the resuspended solution. [16]

- Advantages:
  1) Concentrates the niosome dispersion Quick (~30 min).

- Disadvantages:
  1) May lead to the formation of aggregates.
  2) May lead to the destruction of fragile systems. [29]

13 APPLICATIONS OF NIOSOMES:

- Niosomes have been used to study the nature of the immune response induced by antigens.
- It provides drug targeting.
- Niosomes as Hemoglobin Carriers.
- Niosome-based transdermal drug delivery strategies.
- Niosomal systems can be used as diagnostic tools.
- It is used to treat leishmaniasis, which includes dermal and mucocutaneous infections like sodium stibogluconate.
- It is used as a method of delivering peptide drugs.
- It is used in the administration of ophthalmic drugs. [30]

14 APPLICATIONS OF NIOSOMAL DRUG DELIVERY SYSTEM:

1) Niosomal drug delivery for cancer therapy:

To increase drug bioavailability and decrease drug degradation and negative side effects, new drug delivery systems are being developed. A promising messenger has been discovered in niosomes. Anticancer drugs generally have significant side effects. By enhancing metabolism, niosomes can reduce adverse drug effects (longer circulation and half-life). If constructed correctly, anti-cancer medication-containing niosomes should be able to build up well inside tumours. The anticancer drug paclitaxel (PCT) has been successfully entrapped in a variety of niosome formulations. [10]

2) Drug targeting:

One of the most useful properties of niosomes is their ability to target medications. Drugs can be targeted at

the reticuloendothelial system using niosomes. The reticuloendothelial system (RES) takes up niosome vesicles preferentially. A carrier system (such as antibodies) can be connected to niosomes to direct them to particular organs (since immunoglobulins bind readily to the lipid surface of the niosome). [24]

3) Leishmaniasis:

Niosomes can be used to treat diseases that are based on the reticulo-endothelial system. One disease where the liver and spleen cells are taken over by protozoan parasites is leishmaniasis. Utilizing antimonial, it is treated. The sodium stibogluconate niosomal formulation of antimonial can easily penetrate and specifically target those cells. [23]

4) Ophthalmic drug delivery:

In ocular dosage forms like ophthalmic solution, suspension, and ointment, it is difficult to achieve excellent drug bioavailability due to tear production, corneal epithelial impermeability, non-productive absorption, and transient residence time. However, it has been suggested that niosomal vesicular systems can increase drug bioavailability. According to Carter et al., multiple doses of sodium stibogluconate-loaded niosomes were found to be more effective than a simple solution of sodium stibogluconate in treating parasites in the liver, spleen, and bone marrow. [31]

5) Niosomes as Carriers for Haemoglobin:

It is possible to use niosomes as haemoglobin carriers. The superimposable visible spectrum of niosomal suspension is known to be on the free haemoglobin range. The dissociation curve of haemoglobin can be altered similarly to that of unencapsulated haemoglobin because vesicles are oxygen-permeable. The majority of antineoplastic treatments have serious side effects. Niosomes enhance the drug's metabolism, lengthen its half-life, and increase its release, all of which help to reduce its side effects. Niosomes have higher plasma volumes and a lower tumour proliferation frequency, but their elimination is slower. [12]

6) Gene Delivery:

In recent years, gene therapy has been a powerful resource for the treatment of illnesses, but clinical applications still face delivery issues. Two strategies for delivering genetic material are non-viral gene carriers based on lipids and polymers. In published studies, niosomes were frequently used as oligonucleotide carriers to treat a number of diseases. Due to some advantages, including their relatively small sizes, strong chemical and physical properties, etc., these can be used for the transfer of genetic materials. [12]

7) Neoplasia:

Doxorubicin, an anthracycline antibiotic that shows broad-spectrum antitumor activity, causes an irreversible cardiotoxic effect that depends on the dose. When this medication was given to mice containing the S-180 tumour via niosomal delivery, the mice's lifespan was prolonged, and the rate of sarcoma proliferation was decreased. [14]

8) Anti-inflammatory agents**:**

When compared to the free drug, the niosomal formulation of diclofenac sodium with 70% cholesterol had a higher anti-inflammatory action. In comparison to the free drug, the niosomal formulation of Nimesulide and Flurbiprofen has higher anti-inflammatory activity. Fluconazole oral suspension in span-60 niosomal form was created by Sharma et al. (2009) for the treatment of a fungus infection. As compared to capsules and pills, it is more effective. [14]

9) Acne:

Skin problems like acne affect 70 to 80 percent of adolescents. Topical treatments are an option for treatment. Because topical treatments require effective skin medication delivery, niosomes are frequently used. Herbal and synthetic extracts can both be used to treat acne. When compared to synthetic alternatives, herbal extracts have fewer adverse effects. Along with other anti-acne medications, the synthetic antibiotic medicine benzyl peroxide was used to treat acne. Itching, skin redness, and irritation are side effects of benzyl peroxide when used as dermal administration. The effectiveness of niosomal benzyl peroxide in treating acne was examined in HPMC gel. The outcomes demonstrated good drug skin retention, prolonged release, and decreased drug toxicity with better drug permeability. [23]

10) Cosmetics:

L'Oréal's cosmetic uses are where non-ionic surfactant vesicles were first reported. In the 1970s and 1980s, L'Oréal created and patented niosomes. Niosome's first product was launched by Lancôme in 1987. The

advantage of niosomes in cosmetic and skincare applications is their capacity to improve the bioavailability of substances that are difficult to absorb as well as skin penetration. [32]

15 Route of Application of Niosomes Drugs:

Sr. No.	Route of Administration	Examples of Drugs
1.	Inhalation	All trans-retonic acids.
2.	Transdermal route	Piroxicam, Estradiol, Nimesulide.
3.	Ocular route	Timolol maleate, cyclopentol.
4.	Intravenous route	Doxorubicin, comptothecin, insulin, zidovudine, cisplatin, rifampicin.
5.	Nasal route	Sumatriptan, influenzavral vaccines.

Table 1: Drug used in niosomal delivery. [33]

16 Patents:

The number of patents for niosomal formulations is rising rapidly as niosomes are used more frequently in clinical settings. Table-2 provides a brief summary of important patents related to drug encapsulation in niosomes.

Patent publication number	Inventors	Title	Patent description in brief
US2007/0172520 AI	Michael Van Aukar, Anna Plaas and Elizabeth Hood	Immuno targeting of nonionic surfactant vesicles	The bioactive agent is retained in the cytoplasm of the target cells by niosomes, which deliver antigens to the host in a targeted manner.
US2010/0068264 Al	Norma Alclantar, Eva C Williams and Ryan Toomey	Niosome hydro gel drug delivery	A biodegradable polymer called cross-linked chitosan, used to make the drug-encapsulating niosomes, allows for the controlled release of the drug at specific temperatures and pH levels.
US2008/0050445 AI	Norma Alclantar, Kristina Dearborn, Michael Van Aukar, Ryan Toomey and Elizabeth Hood	Niosome hydro gel drug delivery	Niosomes made of a biodegradable polymer hydrogel network that are encapsulated with a drug have a two-fold increase in controlled release rate.
US2005/0239747 AI	Chih-Chiyang Yang, Yuan-Chih le and Chao-Cheng Liu	Compositions and methods of enhanced transdermal delivery of steroidal compounds and preparation methods	Niosomes are a method of administration that facilitates increased steroidal drug penetration across dermal tissue.
US2010/0226932 Al	Gail Smith, Dinesh B. Shenoy and Robert W. Lee	Adjuvant and vaccine compositions	Antigens in vaccines are more stable when they are encapsulated in niosomes for a specific immune response.
US2006/0292211 Al	Elizabeth Hood, Joel A. Strom and Michael Van Aukar	Ultrasound enhancement of drug release across nonionic surfactant membranes	By altering the niosome membrane structure when administered non-invasively, ultrasound improves the delivery of drugs encapsulated in niosomes.

Table 2: Important patents related to niosomes. [34]

17 Marketed Formulations:

Sr. No.	Brand	Name of the Product
1.	Lancôme-Foundation & complexation	Flash Retouch Brush on Concealer.
2.	Britney Spears- Curious	Curious Coffret: Edp Spray 100ml+Dualended Perfume & Pink Lipgloss+Body souffle 100ml.
3.	Loris Azzaro- Chrome	Chrome Eau De Toilette Spray 200ml.
4.	Orlane- Lipcolor & Lipstick	Lip Gloss

Table 3: Marketed Formulations of Niosomes. [3]

A variety of niosome-based anti-aging products from Lancôme have been released on the market. Research on a variety of cosmetic items is also being done by L'Oréal. Niosome Preparation is offered for sale by Lancôme.

Fig: 2 [35]

ABBREVIATIONS:

DCP: - Dicetyl Phosphate.
MLV: - Multi lamellar vesicles.
LUV: - Large unilamellar vesicles.
SLV: - Small unilamellar vesicles.
PBS: - phosphate buffer saline.
nm: - Nanometre.
µm: - Micrometre.
TFH: - Thin film hydration method.
RPE: - Reverse phase evaporation technique.
PDI: - Polydispersity index.
FTS: - Freeze-thaw sonication method.
HLB: - Hydrophilic-Lipophilic Balance.
TEM: - Transmission electron microscope.
SEM: - Scanning electron microscopy.
DSC: - Differential Scanning Calorimetry.
FTIR: - Fourier Transform-infra red spectroscopy.
FRET: - Fluorescence Resonance Energy Transfer.
P-NMR: - Proton nuclear magnetic resonance.
U.V. Spectroscopy: - Ultraviolet Spectroscopy.
HPLC: - High-performance liquid chromatography.

CONCLUSION

A drug delivery method called niosomes can be used to deliver medications in a regulated, sustained, and targeted manner. Niosomes are becoming more popular as they can simultaneously encapsulate drugs that are hydrophilic and hydrophobic. They can be used to encapsulate drugs from natural sources, such as enzymes, peptides, genes, vaccines, anti-cancer medications, and almost all varieties of drugs. In addition to the drug, they also provide flexibility in the route of administration. They are better suited for drug delivery due to their advantage over liposomes in that they are non-toxic. So it appears that niosome research will keep growing and could result in effective market formulations in the pharmaceutical industry.

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