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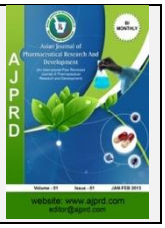

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Review Article

Unlocking the Potential of Niosomes: A Comprehensive Review

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A B S T R A C T

Niosomes are vesicular systems that are similar to liposomes and are obtained by hydrating synthetic nonionic surfactants, with or without incorporating cholesterol or their lipids. They can be used as carriers for amphiphilic and lipophilic drugs and are biodegradable, biocompatible, non-immunogenic, and flexible in their structural characterization. Niosomes have been widely evaluated for controlled release and targeted delivery for the treatment of cancer, viral infections, and other microbial diseases. They can entrap both hydrophilic and lipophilic drugs and prolong the circulation of the entrapped drug in the body. By encapsulating drugs in a vesicular system, the existence of the drug in the systemic circulation can be extended, and penetration into target tissue can be enhanced, reducing toxicity if selective uptake can be achieved. This review article focuses on the advantages, disadvantages, types, preparation methods, factors affecting, characterizations and applications of niosomes.

Keywords: Niosomes, Surfactant, Nano-carrier, Drug delivery, Method of preparation.

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INTRODUCTION

Niosomes are a type of novel drug delivery system (NDDS) that aim to deliver medication at a controlled rate, as required by the body, during the course of treatment for a disease. This system enhances bioavailability and ensures that the active ingredient reaches the targeted site [1]. In niosomal drug delivery, medication is encapsulated in a vesicle formed by mixing non-ionic surfactants from the alkyl or dialkyl polyglycerol ether class with cholesterol. The mixture is then hydrated in an aqueous medium, resulting in the formation of microscopic vesicles called niosomes [2,3].

Niosomes are typically very small, with a size that falls into the nanometric scale. They are prepared for several reasons, including the higher chemical stability of the surfactants used, which is superior to that of phospholipids used in liposome preparation. Phospholipids are easily hydrolyzed due to the presence of an ester bond [4]. Niosomes bilayer structure is amphiphilic, making it possible to deliver hydrophilic drugs in its aqueous core, and lipophilic drugs in the bilayer made up of surfactants.

Niosomes include various additives, such as nonionic surfactants as film-forming agents, cholesterol as a stabilizing and rigidizing agent for the bilayer, and various charge inducers which develop a charge on the surface of niosomes and stabilize the formulation by creating repulsive forces [5]. Niosomal drug delivery has been studied using severa techniques of administration, which incorporates intramuscular, intravenous, peroral, and transdermal. In addition, niosomes have been shown to enhance the absorption of some drugs across cell membranes, localize in targeted organs and tissues, and elude the reticuloendothelial system [6].

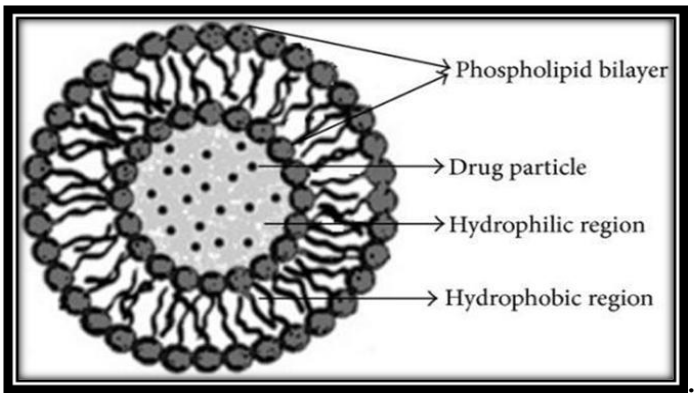

Figure 1: Structure of Niosome

FUNCTIONS OF NIOSOMES: -

The two main ingredients used in the preparation of niosomes are:

- Non-ionic surfactants
- Cholesterol

Non-ionic materials: Non-ionic surfactants are used in the synthesis of niosomes due to their stability, biocompatibility and low toxicity compared to anionic and cationic surfactants[7].

Ethers: Brij, Lauryl glycoside, Decyl glycoside, Nonoxynol-9 Block polymers:

PoloxamersEsters: Glyceryl laurate, Spanes, Polysorbates Fatty alcohols: Stearyl alcohol, Cetyl alcohol, Oleyl alcohol

Cholesterol: Cholesterol is used to provide niosome preparations for hardness, good structure and flexibility[8]. Cholesterol-based niosomes are also less susceptible to adverse effects in plasma and serum fractions and reduce partial degradation[9]

TYPES OF NIOSOME

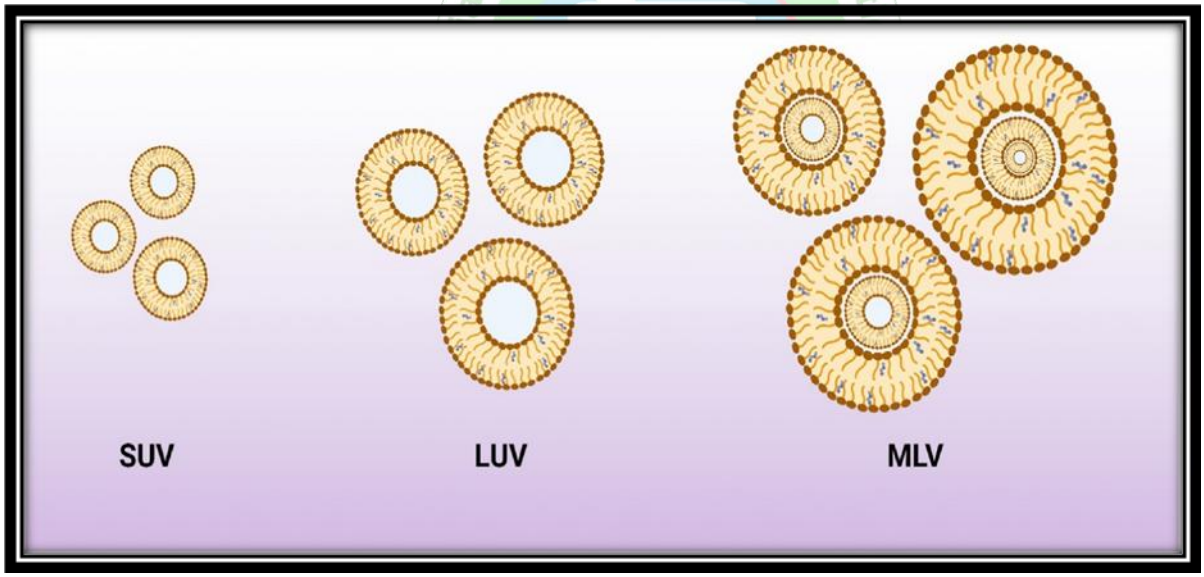

Figure 2: Types of noisome based on the size and number of lamellar

1. Multi lamellar Vesicles (MLV):
The lipid compartment is enclosed by a bilayer and can carry lipophilic compounds. The vesicles are between 0.5 and 10 µm in diameter, making them ideal for drug delivery..

2. Large Unilamellar Vesicles (LUV): -

Niosomes of this type have a high aqueous-to-lipid compartment ratio, which enables the entrapment of larger volumes of bioactive materials, while using membrane lipids very efficiently.

3. Small Unilamellar Vesicles (SUV):-

Small unilamellar vesicles are usually created by using techniques like sonication, French press extrusion, or homogenization on multilamellar vesicles. They have an approximate diameter of 0.025-0.05 µm and are thermodynamically unstable, which means they tend to aggregate and fuse. Their small size results in a low percentage of entrapped aqueous solute and a small entrapped volume[10,11,12].

Advantages of Niosomes [13,14,15,16]

1. The vesicle suspension being water-based vehicle offers high patient compliance when compared to oily dosage forms.
2. Drug molecules of wide range of solubilities can be accommodated in the niosomes provided by the infrastructure consisting of hydrophilic, lipophilic and amphiphilic moieties.
3. Vesicle characteristics can be controlled by altering the composition of vesicle, size lamellarity, surface charge, tapped volume and concentration.
4. They can release the drug in sustained/controlled manner.
5. Storage and handling of surfactants oblige no special conditions like low temperature and inert atmosphere.
6. They can act as a depot formulation, thus allowing the drug release in a controlled manner.
7. They enhance the oral bioavailability of poorly soluble drugs.
8. They possess stable structure even in emulsion form.
9. They are economical for large scale production.
10. They can protect the drug from enzyme metabolism.
11. They can enhance the permeation of drugs through skin.
12. Therapeutic concert of the drug molecules can be improved by tardy clearance from circulation.
13. They can protect the active moiety from biological circulation.

Disadvantages Of Niosomes [13,15,16]

1. Physical instability
2. Aggregation
3. Fusion
4. Leaking of entrapped drug
5. Hydrolysis of encapsulated drugs which limiting the shelf-life of the dispersion

Salient features of Niosomes [17,18,19]

1. Niosomes can entrap solutes.
2. Niosomes are osmotically active and stable.
3. Niosomes have a structure consisting of hydrophobic and hydrophilic parts, which allows for a wide range of drug solubility.
4. Niosomes release the drug in a controlled manner through its bilayer, providing sustained release and acting as a drug depot in the body.
5. Targeted drug delivery can be achieved using Niosomes, as the drug is delivered specifically to the body part where the therapeutic effect is required, reducing the required dosage to achieve the desired effect.
6. Niosomes can improve the solubility and oral bioavailability of poorly soluble drugs and also enhance the skin permeability of drugs when applied topically.
7. Niosomes exhibit flexibility in their structural characteristics (composition, fluidity, and size) and can be designed according to the desired situation.
8. Niosomes can improve the performance of drug molecules.
9. Better availability to the particular site, just by protecting the drug from biological environment.
10. Niosomes increase the stability of the entrapped drug.

Factors affecting formulation of Niosome –

1. Drug

When a drug is trapped inside niosomes, it can improve the vesicle's size. This may happen because the solute interacts with the surfactant head groups, which increases the charge and mutual repulsion of the surfactant bilayers, ultimately leading to an increase in vesicle size. It's worth noting that the degree of entrapment is influenced by the drug's hydrophilic lipophilic balance[20,21]

2. Amount and Type of Surfactant:

When we increase the Hydrophilic-Lipophilic Balance (HLB) of surfactants, such as Span 85 (HLB 1.8) to Span 20 (HLB 8.6), the size of the particles also increases proportionally. This phenomenon occurs because the surface free energy reduces when the surfactant's hydrophobicity increases. The bilayers of the vesicles can exist in either a liquid state or a gel state, depending on various factors such as the temperature, type of lipid or surfactant, and the presence of other components like cholesterol [22].

3. Membrane Composition:

Niosomes are stable vesicles formed by adding different additives to surfactants and drugs. By manipulating the membrane characteristics with different additives, the resulting niosomes can have varied shapes, permeability, and stability properties. The size of the niosomes is influenced by the membrane composition. For instance, polyhedral niosomes formed by a C16G2:solulan C24 (91:9) ratio are larger (8.0 ± 0.03 mm) than spherical/tubular niosomes formed by a C16G2:cholesterol:solulan C24 (49:49:2) ratio (6.6±0.2 mm). The addition of cholesterol to the niosomal system provides rigidity to the membrane and reduces drug leakage from the niosome[23].

4. Methods of Preparation:

Numerous methods have been studied by scientists to produce niosomes, such as hand shaking, ether injection, and sonication. Hand shaking creates larger vesicles (ranging from 0.35-13nm) associated to the ether injection method (50-1000nm). The reverse phase evaporation (REV) technique produces smaller niosomes, while the microfluidization method results in more uniform and smaller vesicles. Parthasarthi et al. used the

transmembrane pH gradient (inside acidic) drug uptake process to prepare niosomes, which showed higher entrapment efficiency and better drug retention[24,25].

5. Resistance to Osmotic Stress:

When a hypertonic salt solution is added to a suspension of niosomes, the size of the vesicles decreases. On the other hand, in a hypotonic salt solution, there is a slow initial release with a slight swelling of the vesicles. This is probably due to the inhibition of eluting fluid from the vesicles. As time passes, there is a faster release, which might be due to the mechanical loosening of the vesicle's structure under osmotic stress[26].

6. Temperature of Hydration:

Hydration temperature affects the shape and size of the niosome. Temperature change of niosomal system affects assembly of surfactants into vesicles and also induces vesicle shape transformation[27]. According to a recent report by scientists, a polyhedral vesicle was formed by C16G2: solulan C24 (91:9) at a temperature of 25°C. Upon heating, the vesicle transformed into a spherical vesicle at 48°C. However, upon cooling from 55°C, the vesicle produced a cluster of smaller spherical niosomes at a temperature of 49°C before changing back to polyhedral structures at 35°C. In contrast vesicle formed by C16G2:cholesterol: solulanC24 (49:49:2) shows no shape transformation on heating or cooling[27.] Along with the above mentioned factors, volume of hydration medium and time of hydration of niosomes are also critical factors. Improper selection of these factors may result in formation of fragile niosomes or creation of drug leakage problems[21,22,28,29].

Preparation methods of niosomes[30-36]

A. Ether injection method:

This method describes a process for creating niosomes. First, a solution of surfactant dissolved in diethyl ether is introduced slowly into warm water that is kept at a temperature of 60°C. This solution is injected through a 14-gauge needle into an aqueous solution of the desired material. The ether vaporizes, which leads to the formation of single-layered vesicles. Depending on the conditions used, the diameter of the vesicles can range from 50 to 1000 nm.

Preparation step

Surfactant is dissolved in diethyl ether

↓

Then injected in warm water maintained at 60oC through a 14 gauge needle

↓

Ether is vaporized to form single layered niosomes

B. Hand shaking method (thin film hydration technique):

A mixture of ingredients, including surfactant and cholesterol, is combined to form vesicles. These vesicles are then dissolved in a volatile organic solvent, such as diethyleither, chloroform, or methanol, in a round bottom flask. The mixture is left to dry at room temperature (20°C) using a rotary evaporator, which results in a thin layer of solid mixture deposited on the wall of the flask. To rehydrate the dried surfactant film, it can be mixed with an aqueous phase at 60°C with gentle agitation. This process typically forms multilamellar niosomes.

Preparation step:

Surfactant + cholesterol + solvent

↓

Remove organic solvent at Room temperature

↓

Thin layer formed on the Walls of flask

↓

Film can be rehydrated to form multilamellar Niosomes.

C. **Sonication method**

One common way to produce vesicles is through the process of sonication, as described by Cable. To achieve this, a portion of a drug solution in buffer is added to a mixture of surfactant and cholesterol in a 108ml glass vial. The mixture is then sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to generate niosomes.

Preparation step:

Drug in buffer + surfactant/cholesterol in 10 ml

↓

Above mixture is sonicated for 3 mints at 60oC using titanium probe yielding noisome

D. Micro fluidization method

Microfluidization is a modern technique used to create unilamellar vesicles of specific sizes. The method involves the interaction of two fluid streams at ultra-high velocities within precisely defined microchannels in the interaction chamber. The impingement of a thin liquid sheet is arranged in such a way that the energy supplied to the system remains within the area of niosome formation. This results in greater uniformity, smaller size, and better reproducibility of the niosomes formed[37].

Preparation step

Two ultra high speed jets inside interaction chamber

↓

Impingement of thin layer of liquid in micro channels

↓

Formation of uniform niosomes.

E. Multiple membrane extrusion method

To create a uniform size of particles, a combination of surfactant, cholesterol, and dicetyl phosphate in chloroform is evaporated to form a thin film. The film is then hydrated with a solution of aqueous drug polycarbonate membranes, and the resulting suspension is extruded through a series of filters for up to 8 passages. This is an effective method for controlling particle size distribution[37]

F. Reverse phase evaporation technique

Cholesterol and surfactant are dissolved in a mixture of ether and chloroform in a 1:1 ratio. An aqueous phase containing drug is then added to this mixture. The resulting two phases are sonicated at a temperature of 48°C. The clear gel formed is sonicated after adding a small amount of phosphate buffered saline (PBS). The organic phase is then removed under low pressure at a temperature of 40°C. The resulting viscous suspension is diluted with PBS and heated on a water bath at 60°C for 10 minutes to yield niosomes[38].

Preparation step

Cholesterol + surfactant dissolved in ether + chloroform

↓

Sonicated at 5oc and again sonicated after adding PBS

↓

Drug in aqueous phase is added to above mixture

↓

Viscous niosomes suspension is diluted with PBS

↓

Organic phase is removed at 40oC at low pressure

↓

Heated on a water bath for 60oC for 10 mints to yield niosomes.

G. Bubble method

A novel technique has been developed for the one step preparation of liposomes and niosomes without the use of organic solvents. The process involves a round-bottomed flask with three necks, which is positioned in a water bath to regulate the temperature. A water-cooled reflux and thermometer are positioned in the first and second neck, respectively, while the third neck is used for nitrogen supply. Cholesterol and surfactant are dispersed together in a buffer with a pH of 7.4 at a temperature of 70°C. The resulting dispersion is mixed for 15 seconds with a high shear homogenizer and then immediately bubbled at 70°C using nitrogen gas[39].

Separation of Un-Entrapped Drug

The removal of un-entrapped solute from the vesicles can be accomplished by various techniques, which include

1. Dialysis;
2. Gel filtration (e.g. Sephadex G50)

3. Centrifugation (e.g. 7000 rpm for 30 min for the niosomes prepared by hand shaking and ether injection methods)
4. Ultracentrifugation (150000 rpm for 1.5 h).

1. **Dialysis:** The process of dialysis involves placing the aqueous niosomal dispersion into dialysis tubing and immersing it into a suitable dissolution medium at room temperature. Samples are periodically taken from the medium, followed by centrifugation and analysis for drug content using methods such as U.V. spectroscopy or HPLC[40].
2. **Gel filtration:**The drug that is not entrapped is separated from the niosomal dispersion through a Sephadex-G-50 column using a suitable mobile phase and examined with various analytical methods[41].
3. **Centrifugation:**The niosomal dispersion is centrifuged in either water or saline. The niosomes are sedimented down as pellets which are washed and resuspended to obtain a niosomal suspension that is free from un-entrapped drugs. The supernatant containing the un-entrapped drug is separated [42].

Characteristics of Niosomes:

1. Vesicle diameter and morphology
2. Vesicle charge
3. Bilayer formation
4. Number of lamella
5. Membrane rigidity and homogeneity
6. Drug loading and encapsulation efficiency
7. *In-vitro* drug release
8. Stability studies

Vesicle diameter: Niosomes are small spherical structures that range in size from 20 nm to 50 nm. Different techniques are used to determine the size and size distribution of these vesicles, including light microscopy, Coulter counter, photon correlation microscopy, and freeze-fracture electron microscopy. Additionally, scanning electron microscopy, atomic force microscopy, and cyto transmission electron microscopy are used to determine the shape and surface characteristics of niosomes[43].

Vesicle charge:

The surface charge of vesicles is an important factor that affects the behavior and stability of niosomes. Charged niosomes tend to be more stable than uncharged ones, as they are less likely to fuse or aggregate. The surface potential of niosomes can be determined by measuring the zeta potential using microelectrophoresis or dynamic light scattering techniques. Alternatively, PH-sensitive fluorophores can be used as a substitute method[44].

Bilayer formation:

Bilayer vesicle formation can be characterized by X-shaped formations due to the assembly of non-ionic surfactants under light polarization microscopy[45].

Number of lamellae:

Characterization of the number of lamellae in vesicles by NMR spectroscopy, electron microscopy, and small-angle X-ray scattering[46].

Membrane rigidity and homogeneity:

The rigidity of the membrane affects how niosomes are distributed and degraded in the body. The stiffness of the vesicle's bilayer can be measured by observing the movement of a fluorescence probe at different temperatures. The uniformity of the membrane can be determined using techniques such as P-NMR, differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FT-IR), and fluorescence resonance energy transfer (FRET)[47].

Drug loading and encapsulation efficiency:

Drug loading and encapsulation efficiency of niosomal dispersion are determined by separating unentrapped drug through dialysis, centrifugation, or gel filtration. Niosomal recoveries can be calculated later

.

$$\text{Niosomal recovered (\%)} = \frac{\text{Amount of niosomes}}{\text{Amount of polymer + drug + excipient}} \times 100 \text{ recovery}$$

To determine the drug entrapped in the niosomes, complete vesicular disruption can be achieved using either 0.1% Triton X-100 or 10% n-propanol. The resulting solution can then be assayed using an appropriate method. The entrapment efficiency can be calculated using the following formula:

$$\text{Entrapment efficiency (\%)} = \frac{\text{Amount of drug in Drug niosomes}}{\text{Amount of drug used}} \times 100$$

Drug loading percentage can be calculated as

$$\text{Drug loading (\%)} = \frac{\text{Amount of drug in niosomes}}{\text{Amount of niosomes recovered}} * 100$$

vii. *In-vitro* drug release:-

In-vitro drug release of niosomes can be characterized by the following methods[48].

1. Dialysis
2. Reverse dialysis
3. Franz diffusion cell

1. Dialysis: One of the simplest way to determine the invitro release kinetics of niosomal loaded drug is by using dialysis tubing. The process involve placing the niosomal suspension in a hermetically sealed dialysis sack. The sack is then placed in 200ml of buffer solution with constant stirring at a temperature of 25ºC or 27ºC. At regular intervials, samples are withdrawn and drug content analysis is carried out using suitable method.

2. Reverse dialysis: Small dialysis tubes are filled with niosomes and added to 1 ml of dissolution medium before being displaced from it.

3. Franz diffusion: Niosomes are put into a Franz diffusion cell and dialyzed with a suitable dissolution media at room temperature. Samples are taken out at regular intervals, and drug content is analyzed. Nowadays, FRET is utilized to keep track of the release of encapsulated substances in niosomes.

4. Stability of niosomes

The stability of niosomes can be determined by observing the consistent particle size and drug concentration within them. The concentration and type of surfactant, as well as cholesterol play a crucial role in maintaining the stability of niosomes. For instance, sonicated spherical niosomes are stable at room temperature, while sonicated polyhedral niosomes may be unstable at room temperature but can remain stable at temperatures above the phase transition temperature[49,50].

Application of niosomes

1. Niosomes as drug carriers

Niosomes are used as carriers for iobitridol, a diagnostic agent used in X-ray imaging. Topical niosomes can serve as solubilization platforms, as a local depot for sustained release of dermally active compounds, as penetration enhancers, or as rate-limiting membrane barriers to modify systemic absorption of drugs [51].

2. Ophthalmic drug delivery

It can be challenging to achieve efficient bioavailability of drugs from ocular dosage forms such as ophthalmic solutions, suspensions, and ointments due to various factors like tear production, impermeability of corneal epithelium, non-productive absorption, and short residence time. However, to enhance bioavailability, niosomal vesicular systems have been proposed. According to a study by Carter et al., multiple dosing with sodium stibogluconate loaded niosomes was found to be more effective against parasites in the liver, spleen, and bone marrow as compared to simple solutions of sodium stibogluconate[52,53].

3. Transdermal delivery of drugs by niosomes

Incorporating drugs in niosomes enhances skin penetration in transdermal delivery[54].

4. Leishmaniasis

Niosomes can be used to target medication in the treatment of diseases where the infecting organism resides in the reticulo-endothelial system. Leishmaniasis is an example of such a disease where the parasite invades liver and spleen cells[55,56,57,58].

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