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Review Article

NIOSOMES AS A TARGETTED DRUG DELIVERY SYSTEM-AN OVERVIEW

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ABSTRACT
Over several years, treatment of infectious diseases has undergone a big revolution shift. Niosomes are composed of non-ionic surfactants that are biodegradable, comparatively non-toxic, more stable & inexpensive as compared to liposomes. This article reviews the widest interest on niosomes and also overview the preparation methods of niosomes, types and composition of niosomes, its salient features and evaluation parameters of niosomes with their applications.

Keywords: Drug entrapment, Niosomes, Surfactants, Preparation and Evaluation.

INTRODUCTION

Pharmaceutical compounds are administered at a predefined rate to people or animals to create therapeutic effects while lowering their concentration in surrounding tissues. Vesicles are colloidal particles that contain an aqueous compartment surrounded by a concentric bilayer of amphiphilic molecules [1]. The use of vesicular systems for drug delivery is among the most cutting-edge approaches, as they can direct, release, and manage the distribution of medicinal substances. Nanomedicine has been credited with stimulating the development of nanocarriers as a result of its use in clinical treatments. The pharmacokinetics and distribution of conventional drugs are not ideal, which can lead to unwanted side effects that can negatively affect the effectiveness of traditional drugs. Various factors can lead to the reduction in the effectiveness of drugs, including the degradation of drugs by the reticuloendothelial system and an insufficient uptake of drugs at the target site. This challenge has been addressed in part by the use of nanocarriers [2]. A niosome is a novel drug delivery system that entraps hydrophilic drugs within the core cavity of the molecule, while hydrophobic drugs are entrapped within the non-polar region present within the bilayer. Thus, both hydrophobic and hydrophilic drugs may be incorporated into niosomes [3]. Because Niosomes contain a non-ionic surfactant, their name comes from their ampiphillic nature. It is important to note that niosomes are extremely small and microscopic [4].

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A Salient Feature of Niosomes

- A niosome is capable of entrapping solutes.
- It is important to note that niosomes are stable and osmotically active.
- When administered topically, they increase the permeability of the skin and improve the oral bioavailability and solubility of poorly soluble medications.
- Stability of the medicine is more when it is entrapped in niosomes.

Advantages of Niosomes

- Drugs can be released in a sustained/controlled manner through these devices.
- They improve the oral bioavailability and skin penetration of poorly soluble drugs.
- Surfactants are biodegradable, biocompatible, non-toxic and non-immunogenic.
- They can protect the drug from enzyme metabolism.
- They are not only osmotically stable and active but also improve the stability of entrapped drug [5].

Disadvantages of Niosomes

- Time consuming.
- Requires specialized equipment.

Types and Composition of Niosomes [6]

The niosomes are classified into following types based on their size:

- **Small unilamellar vesicles**: These have a size of 0.025 - 0.05µm. These small unilamellar vesicles are mostly prepared from multi lamellar vesicles by sonication method and extrusion method.
- **Multi lamellar vesicles**: These have a size of 0.05µm or more. They are easy to make and maintain their mechanical stability over extended storage.
- **Large unilamellar vesicles**: There is a size limit of 0.10µm or more for these. These are unilamellar vesicles with a high ratio of aqueous to lipid compartments, allowing larger volumes of bioactive substances to be entrapped.

- **Cholesterol**

A cholesterol molecule aligns its aliphatic chain with the hydrocarbon chain of a surfactant and its OH group with the aqueous phase.

- **Non-ionic surface acting agent**

It has hydrophilic head group and hydrophobic tail. HLB values 8 have highest entrapment efficiency. Non-ionic surfactants are as follows

- **Ether linked surfactant:**

Surfactants such as these contain hydrophilic and hydrophobic moieties that are linked by ether, polyoxyethylene alkyl ethers.

- **Di-alkyl chain surfactant:**

There has been an investigation of the potential effectiveness of surfactant as a principle component of niosomal preparations of sodium stibogluconate for antileishmanial treatment in experimental marine visceral leishmaniasis.

- **Ester linked surfactant:**

These surfactants are also known as ester-linked surfactants because of the ester linkage that exists between their hydrophilic and hydrophobic groups.

- **Sorbitan esters:**

These are the ester linked surfactants. The commercial sorbitan esters are mixtures of the partial esters of sorbital and its mono and di-anhydrides with oleic acid.

- **Fatty acid and amino acid compounds:**

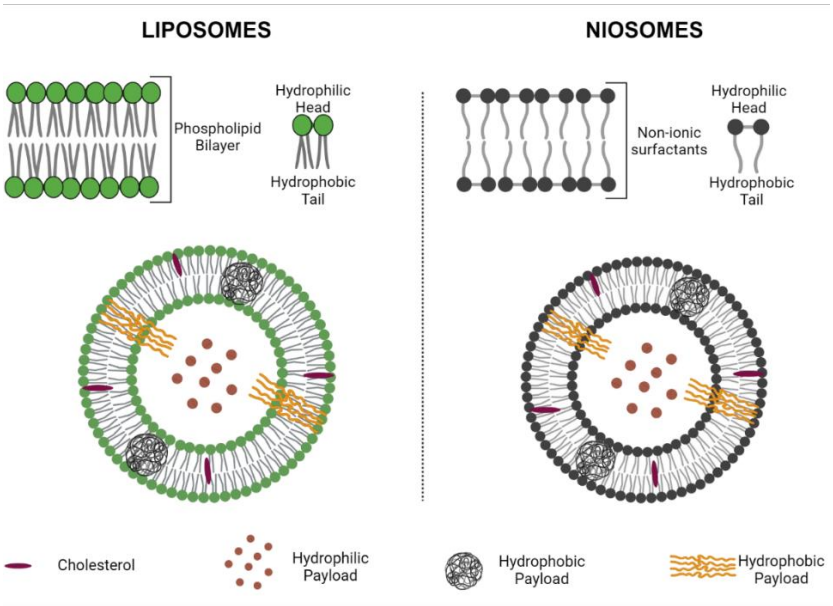
Long chain fatty acids and amino acid moieties have also been used in some niosomes preparation which form “Ufasomes” vesicles.

- **Charge inducers**

Two types of charge inducers exist, namely positive and negative charge inducers. By inducing a charge on the surface of the prepared vesicles, it increases the stability of the vesicles. Among the most commonly used positive charge inducers are sterylamine and cetylpyridinium chloride, while the most commonly used negative charge inducers are dicetyl phosphate, dihexadecyl phosphate, and lipoamine acid.

Niosomes: A Better Medication Delivery System Than Liposomes

Similar to liposomes, niosomes have a bilayer structure [7]. Uncharged single-chain surfactants and cholesterols are used to make niosomes. Double chain phospholipids, either neutral or charged, are used to make liposomes. Liposomes have a lower drug entrapment efficiency than niosomes. Niosomes are reasonably priced. Due to the unstable chemical components (phospholipids), which degrade oxidatively, liposome preparation is expensive [8]. Compared to liposomes, niosomes have a longer shelf life. While liposomes have a short shelf life due to the rancidification of their lipid components, they increase metabolic stability in an emulsified form and prolong the circulation of encapsulated drugs [9-11].



Niosome Preparation Methods

Niosomes can be synthesized using a variety of techniques depending on their clinical uses, lamellarity, and particle size.

➢ **Bubble technique**

This method involves combining all the ingredients at a specific temperature in three neck flasks. In an organized system, one neck is attached to a water-cooled reflux, another is used to purge nitrogen, and the third is situated on a thermometer. At 70 °C, all ingredients are distributed and homogenized for roughly 15 seconds. A stream of nitrogen gas is immediately introduced to the mixture. Large monolayer vesicles are produced by this technique [12].

➢ **Ether Injection**

A surfactant solution dissolved in diethyl ether is slowly added to warm water kept at 60°C in order to form niosomes. The surfactant mixture in ether is injected into an aqueous solution using a needle of 14 gauge. Vesicles are formed when ether is vaporized and result in a single layer of vesicles. Depending on the circumstances, the vesicle's diameter can vary from 50 to 1000 nm. This method's drawback is that a tiny quantity of ether is frequently still in the vesicle suspension and is challenging to eliminate [13].

➢ **Hand Shaking Method**

This technique is comparable to the thin-layer hydration technique that is discussed below. Here, an organic solvent is used to dissolve surfactants, cholesterol, and other lipophilic additives. The organic solvent then evaporates, forming a thin layer. Following hydration of the thin layer and mild mechanical shaking, the milky mixture containing the niosomes is created[14].

➢ **Heating Method**

Surfactants, cholesterol, and other additives are individually hydrated in a buffer solution under a nitrogen atmosphere. The glass containing cholesterol is cooled to 60 °C after being heated to 120 °C for 15 to 20 minutes. The remaining ingredients are added to the stirring cholesterol container after 15 minutes. A refrigerator at 4 to 5 degrees Celsius with an N2 atmosphere is used to stabilize the prepared niosomes after 30 minutes at room temperature [15].

➢ **Microfluidization method**

This process involves dissolving medications and surfactants in a solvent and then pumping the mixture under pressure from a reservoir to an ice-filled interaction chamber. To absorb the heat produced during the procedure, the solution is run through a cooling loop. Smaller niosomes with superior homogeneity can be produced using this technique [16].

➢ **Multiple membrane extrusion technique**

This technique works well for regulating a niosomal formulation's size. Evaporation transforms a mixture of diacetyl phosphate, cholesterol, and surfactant in chloroform into a thin film. An aqueous drug solution is added to the resultant film, and the suspension is then extruded through polycarbonate membranes [17].

➢ **Reverse evaporation method**

After combining cholesterol and surfactants in an organic solvent, the organic phase is supplemented with an aqueous solution. Under negative pressure, the organic

phase is eliminated and the two-phase system is homogenized. Large monolayer vesicles can then be produced [17].

➢ **The sonication method**

In the first step, a glass vial containing cholesterol and surfactants (such as Pluronic L121, Dicetylphosphate, and Span 60) is filled with a drug-containing buffer solution (such as rifampicin and ceftriaxone sodium). Using a titanium probe, the mixture is probe-sonicated at 60 °C for three minutes to produce niosomes. Various types of vesicles can be created, including unilamellar vesicles and multilamellar vesicles [18].

➢ **Transmembrane pH gradient technique**

By changing the pH between the outer membrane and the core, niosomes can form. An organic solvent is used to dissolve cholesterol and surfactants. After the solvent evaporates, a thin film is formed, which is then hydrated by the acidic solution before the final product is frozen. To maintain the pH, niosomes are mixed with a buffer that has a neutral pH of 7.0, which includes an aqueous drug solution. By shifting the pH from the outer membrane to the core, weakly acidic medications (typically having a pKa <5) can be ionized [20].

➢ **Thin film hydration method**

Lipidophilic additives such as surfactants and cholesterol are dissolved in an organic solvent in a round bottom flask. The organic solvent is removed using a rotary vacuum evaporator. On the inner surface of the flask, organic solvent-soluble materials form a thin, dry layer. A solution containing the drug is added to the flask at a temperature above the thin layer's hydration temperature. Hydration results in the formation of multilayer vesicles. It is possible to produce niosomes of small size using membranes or high-pressure homogenizers that are cut off to the right size [19].

Evaluation of Niosomes [21]

The niosomal preparation should be evaluated by the following characteristics

1.Vesicle diameter :
Size : 20nm - 50µm
Shape : spherical

Techniques used :
- Light microscopy
- Coulter counter
- Photon correlation microscopy,
- Freeze fracture electron microscopy,
- Scanning electron microscopy
- Atomic force microscopy

2. Vesicle charge:

The stability of charged niosomes against aggregation and fusion is greater than that of uncharged niosomes.

Techniques used:
- Dynamic light scattering
- Microelectrophoresis
- pH sensitive fluorophores

3. Bilayer formation:

X-cross formation occurs when non-ionic surfactants are assembled into bilayer vesicles under light colonization microscopy.

4. Number of lamellae:

NMR spectroscopy, electron microscopy, and small angle x-ray scattering are used to determine the number of lamellae in vesicles.

5. Entrapment efficiency:

It is determined after the separation of unentrapped drug

Separation of unentrapped drug:
- Dialysis
- Centrifugation
- Gel Filtration

Entrapped efficiency can be calculated as

$$\text{Entrapment Efficiency (\%)} = \frac{\text{amount of drug in niosomes}}{\text{amount of drug used}} \times 100$$

Drug loading percentage can be calculated as

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

6. *In-Vitro* drug release:
Methods used:
- Dialysis
- Reverse dialysis
- Franz diffusion cell.

Table 1: Current Applications of Niosomes[1]

Leishmaniasis	Amarogentin
Acquired Immune Deficiency Syndrome	AZT
Neoplasia	Daunorubicin, Methotrexate, Curcumin
Lung Disease	Gentamycin
Inflammation	Diclofenac, Flubiprofen, Nimesulide

CONCLUSION

Niosomes have been studied as an alternative to liposomes. Some advantages over liposomes, such as their relatively higher chemical stability, improved purity and relatively lower cost in comparison with liposomes. Non-ionic surfactant vesicles alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug. Niosomes represent a promising drug delivery molecule. There is a lot of scope to encapsulate toxic anti-cancer drugs, anti-infective drugs, anti-AIDS drugs, anti-inflammatory drugs, anti-viral drugs, etc. niosomes are to use them as promising drug carriers to achieve better bioavailability and targeting properties and for reducing the toxicity and side-effects of the drugs. The ionic drug carriers are relatively toxic and unsuitable whereas niosomal carriers are safer. Handling and storage of niosomes require no special conditions**.**

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