NIOSOMES: A REVIEW OF THEIR STRUCTURE, PROPERTIES, METHODS OF PREPARATION, AND MEDICAL APPLICATIONS

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Abstract:

Drug targeting is a type of phenomenon in which a drug is distributed in the body in such a way that the drug interacts with the target tissue at the cellular or subcellular level to achieve the desired therapeutic response at the desired site without unwanted interactions at other sites. This can be achieved by modern methods of drug delivery system targeting such as niosomes. Niosomes are a type of non-ionic surfactant vesicles that are biodegradable, non-toxic, more stable and cheaper, which is a new approach to liposomes. Their structure is similar to liposomes and therefore they may represent alternative vesicular systems to liposomes. Niosomes tend to load different types of drugs. This review article presents niosome structure, advantages, disadvantages, niosome preparation methods and characterization of pharmaceutical NSVs. The concept of a drug delivery system refers to the process of administering pharmaceutical compounds at a predetermined rate to achieve a therapeutic effect in humans or animals at the site of disease while simultaneously reducing the concentration of the drug in surrounding tissues. The localized action of the drug increases the effectiveness of the drug and reduces systemic toxic effects on tissues. Paul Ehrlich proposed the idea of targeted delivery directly to a diseased cell without harming healthy cells in 1909, and this strategy was known as the "magic bullet". Since then, a variety of drug carrier systems have emerged, including immunogolds, serum proteins, synthetic polymers, liposomes, microspheres, and niosomes. Among these systems, liposomes and niosomes are well-documented vesicular drug delivery systems. In general, a vesicular system is a drug delivery platform that enables efficient bioavailability of drugs through the controlled release of therapeutic drugs over extended periods of time. Vesicles consist of bilayered amphiphilic molecules that surround an aqueous compartment. Niosomes are vesicles of nonionic surfactant (for example, alkyl ester and alkyl ether) and cholesterol that act as a carrier for amphiphilic and lipophilic drugs. Niosomes improve the therapeutic efficacy of encapsulated drug molecules by protecting the drug from the harsh biological environment, resulting in their delayed clearance. New drug development is both time-consuming and expensive.

Keywords: Niosomes, Liposomes, Non-ionic surfactants, Drug delivery, Nanocarriers, Encapsulation technology

Introduction:

The concept of a drug delivery system refers to the process of administering pharmaceutical compounds at a predetermined rate to achieve a therapeutic effect in humans or animals at the site of disease while simultaneously reducing the concentration of the drug in surrounding tissues. The localized action of the drug increases the effectiveness of the drug and reduces systemic toxic effects on tissues. Paul Ehrlich proposed the idea of targeted delivery directly to a diseased cell without harming healthy cells in 1909, and this strategy was known as the "magic bullet". Since then, a variety of drug carrier systems have emerged, including immunogolds, serum proteins, synthetic polymers, liposomes, microspheres, and niosomes. Among these systems, liposomes and niosomes are well-documented vesicular drug delivery systems. In general, a vesicular system is a drug delivery platform that enables efficient bioavailability of drugs through the controlled release of therapeutic drugs over extended periods of time. Vesicles consist of bilayered amphiphilic molecules that surround an aqueous compartment. Niosomes are vesicles of nonionic surfactant (for example, alkyl ester and alkyl ether) and cholesterol that act as a carrier for amphiphilic and lipophilic drugs. Niosomes improve the therapeutic efficacy of encapsulated drug molecules by protecting the drug from the harsh biological environment, resulting in their delayed clearance. New drug development is both time-consuming and expensive. A new drug costs an estimated $120 million to develop and takes decades to go from discovery, clinical testing and development to regulatory approval. Specific drug delivery systems alleviate the urgency of bringing new drugs to market by increasing drug selectivity and therapeutic index while reducing the effective dose. This narrative review discusses the role of niosomes as a drug delivery system and details their structure, preparation, properties, and mutual applications to form a closed bilayer structure that encapsulates solutes in aqueous solution. As a result, the closed bilayer structure of niosomes has a hydrophilic inner and outer surface sandwiched between them by a lipophilic region. Energy, such as heat or physical mixing, is required to form a closed bilayer structure. Various forces inside the vesicles have been found to play an important role in maintaining the vesicular structure, such as van der Waals and repulsive forces that exist.
between surfactant molecules. Changing the vesicle components (including type, composition, and concentration), size, surface charge, or volume is likely to alter the properties of the resulting niosomes. Niosomes can be categorized into three groups based on their vesicle size, namely small unilamellar vesicles (0.025–0.05 mm), multilamellar vesicles (>0.05 mm), and large unilamellar vesicles (>0.10 mm).[1][2][3]

**Niosomes**

**Structure of niosomes:**
The main components of niosomes are nonionic surfactants, a hydration medium, and lipids such as cholesterol. Self-assembly of nonionic surfactants in aqueous media leads to closed bilayer structures (Figure 1). The high interfacial tension between water and the hydrophobic tails of the amphiphile causes their association. The steric and hydrophilic repulsion between the head groups of the nonionic surfactant ensures that the hydrophilic ends face outwards and are in contact with water. Assembly into closed bilayers usually requires some energy input, such as mechanical or thermal. Niosomes can be divided into three groups according to their size and bilayer. Small unilamellar vesicles (SUVs) (10–100 nm), large unilamellar vesicles (LUVs) (100–3000 nm) and multilamellar vesicles (MLVs) where more than one bilayer is present.

**Figure no.1: Structure of Niosomes**

**COMPOSITION OF NIOSOMES**
Two components use in niosome preparation are
- ✓ Cholesterol
- ✓ Non-ionic surfactants A.

A. Cholesterol is a steroid derivative, which is used to provide rigidity and proper shape, conformation to niosome form.

B. Non-ionic Surfactants are generally used for the preparation of niosomes. Examples: a. Tweens (20, 40, 60, 80) b. Spans (Span 60, 40, 20, 85, 80) c. Brij 30, 35, 52, 58, 72, 76.

**ADVANTAGES**
1. Niosome can accommodate a variety of drug moieties such as hydrophilic, lipophilic, as well as amphiphilic drugs.
2. Vesicle characteristics can be controlled by altering the composition of vesicle, size lamellarity, surface charge, tapped volume and concentration.
3. The drug can release in the sustained/controlled manner.
4. No special conditions required for handling and storage of surfactants.
5. Due to the depot formulation, it allows controlled release of the drug.
6. Poorly soluble drugs have increased oral bioavailability.
7. Surfactants possess following response biodegradable, biocompatible, non-toxic and nonimmunogenic.
DISADVANTAGES
1. Poor drug loading capacity.
2. Unpredictable gelation tendency.
3. High water content.
4. Low hydrophilic drugs loading capacity due to partitioning effects. [4]

METHOD OF PREPARATION
A. Ether Injection Method:
This method provides a means of producing niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warmwater maintained at 60°C. A mixture of surfactant in ether is injected with a 14 gauge needle into an aqueous solution of the material. Evaporation of the ether leads to the formation of single-layer vesicles. Depending on the conditions used, the vesicle diameter ranges from 50 to 1000 nm.

B. Hand Shaking Method (Thin Film Hydration Technique):
A mixture of vesicle-forming components such as surfactant and cholesterol is dissolved in a volatile organic solvent (diethyl ether, chloroform, or methanol) in a round-bottom flask. The organic solvent is removed at room temperature (20 ºC) using a rotary evaporator and a thinlayer of solid mixture is deposited on the wall of the flask. The dried surfactant film can be rehydrated with the aqueous phase at 0-60°C with gentle stirring. This process forms typical multilamellar niosomes. Thermosensitive niosomes were prepared by Raja Naresh et al. by evaporating the organic solvent at 60 ºC and leaving a thin film of lipid on the wall of a rotary flash evaporator. The aqueous phase containing the drug was slowly added with intermittent shaking of the flask at room temperature followed by sonication.

C. Sonication
In this method, an aliquot of the drug solution in buffer is added to the surfactant/cholesterol mixture in a 10 ml glass vial. The mixture is sonicated at 60°C for 3 minutes using a titanium probe sonicator to obtain niosomes.

D. Micro fluidization
Microfluidization is a recent technique used to prepare unilamellar vesicles with a defined size distribution. This method is based on the principle of an immersion jet, in which two fluidized streams interact at ultra-high speeds in precisely defined microchannels in an interaction chamber. The impact of the thin liquid sheet along the common front is arranged so that the energy supplied to the system remains in the region of niosome formation. The result is greater uniformity, smaller size and better reproducibility of the formed niosomes. [5]
E. Multiple membrane extrusion method:
A mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is evaporated to a thin film. The film is hydrated with an aqueous drug solution and the resulting suspension is extruded through polycarbonate membranes that are placed in series for up to 8 passes. It is a good method to control the size of niosomes.

F. Reverse Phase Evaporation Technique (REV)
Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. To this, the aqueous phase containing the drug is added and the resulting two phases are sonicated at 4-5°C. The resulting clear gel is further sonicated after adding a small amount of phosphate-buffered saline (PBS). The organic phase is removed at 40°C under reduced pressure. The resulting viscous suspension of niosomes was diluted with PBS and heated in a water bath at 60 °C for 10 min to obtain niosomes. Raja Naresh et al. reported the preparation of diclofenac sodium niosomes using Tween 85 by this method.

G. Trans membrane pH gradient (inside acidic) Drug Uptake Process(remote Loading)
The surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to form a thin film on the wall of the round bottom flask. The film is hydrated with 300 mM citric acid (pH4.0) by vortexing. Multilamellar vesicles are frozen and thawed three times and later sonicated. An aqueous solution containing 10 mg/ml drug was added to this niosomal suspension and mixed. The pH of the sample is then raised to 7.0-7.2 using 1M sodium phosphate. This mixture is later heated at 60°C for 10 minutes to obtain niosomes.[6]

H. The “Bubble” Method
It is a new technique for the one-step preparation of liposomes and niosomes without the use of organic solvents. The bopper unit consists of a round-bottom flask with three necks placed in a water bath for temperature control. A water-cooled reflux and thermometer are placed in the first and second ports of the homogenizer and immediately "bubbled" at 70°C using nitrogen and nitrogen through the third port. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70 °C, the dispersion is stirred for 15 seconds at high shear.[7]

Factors Influencing Niosomes Formulation
1. Nature of Surfactant:
Increase in the HLB value of surfactants leads to the increase in the mean size of niosomes due to the decrease in surface free energy with an increase in the surfactant hydrophobicity. The bilayers of the niosomes can exist either as a liquid state or in a gel state. Eg: span 60 with higher TC exhibits better entrapment

2. Nature of Encapsulated Drug:
The charge and the rigidity of the niosomal bilayer are greatly influenced by physical chemical properties of the encapsulated drug. Entrapment of drug occurs by interacting with the surfactant.

3. Hydration Temperature:
The size and shape of the niosome are affected by the temperature of hydration. Hydration temperature should be above the gel, liquid phase transition temperature. Change in temperature affects the assembly of surfactants into vesicles and vesicle shape modification.

4. Cholesterol Content:
Incorporation of cholesterol increases the entrapment efficiency and hydro-dynamic diameter of niosomes. Cholesterol acts in two ways:
- Increases the chain order of liquid state bilayers.
- Decreases the chain order of gel state bilayers. [8][9][10]

Figure no-3: Factors Influencing Niosomal Formulation
Applications of Niosomes:

- Niosomes have been introduced for use in the cosmetic industry. The first report of surfactant vesicles comes from cosmetic applications designed by L’Oreal. Phospholipids and nonionic surfactants have been reported to act as penetration enhancers that can overcome the transdermal drug delivery barrier. Since then, interest in the use of niosomes in the pharmaceutical, cosmetic and food industries has grown, leading to the publication of more than 1200 research articles, about 200 patents and six clinical studies since 1980. Most of these publications refer to the importance of nanovector characterization. Niosomal carriers are suitable for the delivery of a range of pharmacological and diagnostic agents, including antioxidant, anti-cancer, anti-inflammatory, anti-asthmatic, antimicrobial, anti-Alzheimer and antibacterial molecules, oligonucleotides and others.

- Depending on the type of drug, surfactant, disease and relevant anatomical site, there are various routes of administration of niosomal drugs: i.e. intravenous, intramuscular, oral, ocular, subcutaneous, pulmonary and transdermal. Administer niosomal drugs, including intraperitoneal and vaginal routes.

![Applications of Niosomes](image)

**Figure no-3: Applications of Niosomes**

- Niosomes have been used to successfully target drugs to various organs such as the liver and brain or to pathological areas such as tumor, enhancing the pharmacological activities of drugs while reducing side effects.

- Specifically, targeted niosomal systems with different mechanisms of action, including active, passive and magnetic targeting, have been designed, leading to more advanced and specific macromolecular drug carriers.

- Transdermal administration of drugs by niosomes: The main disadvantage of the transdermal method of administration is the slow penetration of the drug through the skin. An increase in the rate of penetration was achieved by transdermal administration of the drug incorporated into niosomes.

- Niosomal drug loading and encapsulation efficiency: To determine the drug loading and encapsulation efficiency, the niosomal aqueous suspension was ultracentrifuged, the supernatant was removed, and the sediment was washed twice with distilled water to remove the adsorbed drug.[11][12][13]

- Reverse dialysis: A series of small dialyses containing 1 ml of dissolution medium are placed into the proniosomes. The proniosomes are then displaced into the dissolution medium. Direct dilution of proniosomes is possible with this method and rapid release cannot be quantified using this method.[14]

**Conclusion:**

The concept of drug incorporation into liposomes or niosomes for better drug targeting to the appropriate tissue destination is widely accepted by researchers and academicians. Niosomes represent a promising module for drug delivery. They present a liposome-like structure and therefore may represent alternative vesicular systems with respect to liposomes, due to the ability of niosomes to encapsulate different types of drugs within their multi-environmental structure. Niosomes are considered better candidates for drug delivery compared to liposomes due to various factors such as cost, stability, etc. Various types of drug delivery such as targeted,ophthalmic, topical, parenteral, etc. can be possible using niosomes.

**References:**


