NIOSOME DRUG DELIVERY SYSTEM: BASICS, ADVANTAGE, DISADVANTAGE, APPLICATIONS

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INTRODUCTION
Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. In Niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as Span – 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs.

ADVANTAGES OF NIOSOMES

• Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-aq media.
• The vesicle suspension is water–based vehicle. This offers high patient compliance in comparison with oily dosage forms.
• Niosomes possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities. The characteristics of the vesicle formulation are variable and controllable.
• The vesicles may act as a depot, releasing the drug in a controlled manner.
• They are osmotically active and stable, as well as they increase the stability of entrapped drug.
• They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
• They can be made to reach the site of action by oral, parenteral as well as topical routes.
• The surfactants are biodegradable, biocompatible and non-immunogenic hence can be used safely in preparation of Niosomes.
Disadvantages of Niosomes

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

METHODS OF PREPARATION

A. Ether injection method

This method provides a means of making Niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material. Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used the diameter of the vesicle range from 50 to 1000 nm.
B. Hand shaking method (Thin film hydration technique)$^3$

The mixture of vesicles forming ingredients like surfactant and cholesterol are 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°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar Niosomes.
C. Sonication
A typical method of production of the vesicles is by Sonication of solution was introduced. In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10-ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield Niosomes.

D. Micro fluidization
Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of Niosomes formation.

E. Multiple membrane extrusion method
Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug solution and the resultant suspension extruded through polycarbonate membranes, which are placed in series for up to 8 passages. It is a good method for controlling niosome size.
F. Reverse Phase Evaporation Technique

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension.

G. Drug Uptake Process (remote Loading)

Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydrated with 300 mM citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to give Niosomes.

H. The “Bubble” Method

It is novel technique for the one step preparation of liposomes and Niosomes without the use of organic solvents. The bubbling unit consists of roundbottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards “bubbled” at 70°C using nitrogen gas.

I. Formation of Niosomes from proniosomes

Another method of producing Niosomes is to coat a water-soluble carrier such as sorbitol with surfactant. The result of the coating process is a dry formulation. In which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed “Proniosomes”. The Niosomes are recognized by the addition of aqueous phase at T > Tm and brief agitation.

T=Temperature.
Tm = mean phase transition temperature.

It was reported that the formulation of Niosomes from maltodextrin based proniosomes. This provides rapid reconstitution of Niosomes with minimal residual
carrier. Slurry of maltodextrin and surfactant was dried to form a free flowing powder, which could be rehydrated by addition of warm water.

![Diagram showing the preparation of niosomes from Proniosomes.](image)

**Fig 4: Preparation of niosomes from Proniosomes**

**Separation of Unentrapped Drug**

1. **Dialysis**
The aqueous niosomal dispersion is dialyzed in dialysis tubing against phosphate buffer or normal saline or glucose solution.

2. **Gel Filtration**
The unentrapped drug is removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution with phosphate buffered saline or normal saline.

3. **Centrifugation**
The niosomal suspension is centrifuged and the supernatant is separated. The pellet is washed and then re suspended to obtain a niosomal suspension free from unentrapped drug.

**Table 1: Drugs incorporated into niosomes by various methods**

<table>
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<tr>
<th>Method of preparation</th>
<th>Drug incorporated</th>
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<tr>
<td>Ether Injection</td>
<td>Sodium stibogluconate</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>Hand Shaking</td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>Sonication</td>
<td>9-desglycinamide</td>
</tr>
<tr>
<td></td>
<td>8-arginine</td>
</tr>
<tr>
<td></td>
<td>Vasopressin</td>
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<td>Oestradiol</td>
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Table 2: Different types of non-ionic surfactants used in noisome preparation

<table>
<thead>
<tr>
<th>Type of non ionic surfactant</th>
<th>Examples</th>
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<tr>
<td>Fatty alcohol</td>
<td>Cetyl alcohol, stearly alcohol, cetostearyl alcohol, oleyl alcohol</td>
</tr>
<tr>
<td>Ethers</td>
<td>Lauryl glucoside</td>
</tr>
<tr>
<td>Esters</td>
<td>Spans, polysorbate</td>
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Comparison of niosomes Vs liposomes:¹¹,¹²

- Niosomes are now widely studied as an alternative to liposomes, which exhibit certain disadvantages such as—they are expensive, their ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they require special storage and handling and purity of natural phospholipids is variable.

- Differences in characteristics exist between liposomes and niosomes, especially since niosomes are prepared from uncharged single-chain surfactant and cholesterol whereas liposomes are prepared from double-chain phospholipids (neutral or charged).

- Niosomes behave *in-vivo* like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability. Encapsulation of various anti-neoplastic agents in these carrier vesicles has been shown to decrease drug induced toxic side effects, while maintaining, or in some instances, increasing the anti-tumor efficacy. Such vesicular drug carrier systems alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug. They can be expected to target the drug to its desired site of action and/or to control its release.

- As with liposomes, the properties of niosomes depends both on the composition of the bilayer and on method of their production. It was observed by Baillie et al that the intercalation of cholesterol in the bilayers decreases the entrapment volume during formulation and thus entrapment efficiency. As the concentration of cholesterol increases, entrapment efficiency decreases.

- The entrapment efficiency increases with increase in the concentration and lipophilicity of surfactant Chandraprakash et al made Methotrexate loaded non-ionic surfactant vesicles using lipophilic surfactants like Span 40, Span 60.
and Span 80 and found that Span 60 (HLB = 4.7) gave highest percent entrapment while Span 85 (HLB = 9.8) gave least entrapment. They also observed that as HLB value of surfactant decreased, the mean size was reduced.

CHARACTERIZATION OF NIOSOMES

a) Entrapment efficiency
After preparing niosomal dispersion, unentrapped drug is separated by dialysis, centrifugation, or gel filtration as described above and the drug remained entrapped in Niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analysing the resultant solution by appropriate assay method for the drug. Where,

Entrapment efficiency (EF) = (Amount entrapped / Total amount) x 100

b) Vesicle diameter
Niosomes, similar to liposomes, assume spherical shape and so their diameter can be determined using light microscopy, photon correlation microscopy and freeze fracture electron microscopy.

c) In-vitro release
A method of in-vitro release rate study includes the use of dialysis tubing. A dialysis sac is washed and soaked in distilled water. The vesicle suspension is pipetted into a bag made up of the tubing and sealed. The bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. At various time intervals, the buffer is analyzed for the drug content by an appropriate assay method.

APPLICATIONS

1) Targeting of bioactive agents

a) To reticulo-endothelial system (RES)
The cells of RES preferentially take up the vesicles. The uptake of Niosomes by the cells is also by circulating serum factors known as opsonins, which 20°C for 24 hrs and then heating to ambient temperature) of Niosomes increases the vesicle mark them for clearance. Such localized drug accumulation has, however, been exploited in treatment of animal tumours known to metastasize to the liver and spleen and in parasitic infestation of liver.
b) To organs other than RES

It has been suggested that carrier system can be directed to specific sites in the body by use of Immunoglobulins seem to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier. Many cells possess the intrinsic ability to recognize and bind particular carbohydrate determinants and this can be exploited to direct carriers system to particular cells.

2) Neoplasia

Doxorubicin, the anthracyclic antibiotic with broad spectrum anti tumor activity, shows a dose dependant irreversible cardio toxic effect. Niosomal delivery of this drug to mice bearing S-180 tumor increased their life span and decreased the rate of proliferation of sarcoma. Niosomal entrapment increased the half-life of the drug, prolonged its circulation and altered its metabolism. Intravenous administration of methotrexate entrapped in niosomes to S-180 tumor bearing mice resulted in total regression of tumor and also higher plasma level and slower elimination.

3) Leishmaniasis

Niosomes can be used for targeting of drug in the treatment of diseases in which the infecting organism resides in the organ of reticuloendothelial system. Leishmaniasis is such a disease in which parasite invades cells of liver and spleen. The commonly prescribed drugs are antimonials, which are related to arsenic, and at high concentration they damage the heart, liver and kidney. The study of antimony distribution in mice performed which showed high liver level after intravenous administration of the carriers forms of the drug. It was reported that increased sodium stibogluconate efficacy of niosomal formulation and that the effect of two doses given on successive days was additive.

4) Delivery of peptide drugs

The oral delivery of 9-desglycinamide, 8-arginine vasopressin entrapped in Niosomes in an in-vitro intestinal loop model and reported that stability of peptide increased significantly.

5) Immunological application of Niosomes

Niosomes have been used for studying the nature of the immune response provoked by antigens. It was reported that Niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability.
6) Transdermal delivery of drugs by Niosomes
Slow penetration of drug through skin is the major drawback of transdermal route of delivery. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes. It was studied the topical delivery of erythromycin from various formulations including niosomes or hairless mouse. From the studies.

7) Other Applications
   a) Sustained Release
   It was suggested that role of liver as a depot for Methotrexate after Niosomes are taken up by the liver cells. Sustained release action of Niosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via niosomal encapsulation.

   b) Localized Drug Action
   Drug delivery through Niosomes is one of the approaches to achieve localized drug action, since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration. Localized drug action results in enhancement of efficacy of potency of the drug and at the same time reduces its systemic toxic effects.
REFERENCES
