

RESEARCH ARTICLE

Niosome as an Effective Drug Delivery: A Review

Patel SM^{*1}, Rathod DR¹, Patel KN¹, Patel BA¹, Patel PA¹

¹Department of Pharmaceutics, Shree Swaminarayan Sanskar Pharmacy College, Zundal, Gandhinagar, Gujarat, India

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ABSTRACT

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name given as “Niosomes”. The niosomes are very small ranging usually in micron size. Their size lies in the nanometric scale. Although structurally similar to liposomes, they offer several advantages over them. Niosomes have recently been shown to greatly increase transdermal drug delivery and also can be used in targeted drug delivery, and thus increased study in these structures can provide new methods for drug delivery.

KEYWORDS

Niosome, Methotrexate, Cholesterol, Dicetyl phosphate, Maltodextrin, Doxorubicin, Indomethacin, Diclofenac sodium

INTRODUCTION

Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids. They are similar to liposomes. That can be used as carriers of amphiphilic and lipophilic drugs. It is less toxic and improves the therapeutic index of drug by restricting its action to target cells. Niosomes are microscopic lamellar structures obtained on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media.¹

The properties of the vesicles can be changed by varying the composition of the vesicles, size, lamellarity, tapped volume, surface charge and concentration.

Various forces act inside the vesicle, e.g., van der Waals forces among surfactant molecules, repulsive forces emerging from the electrostatic interactions among charged groups of surfactant molecules, entropic repulsive forces of the head groups of surfactants, short-acting repulsive forces, etc. These forces are responsible for maintaining the vesicular structure of niosomes. But, the stability of niosomes are affected by type of surfactant, nature of encapsulated drug, storage temperature, detergents, use of membrane spanning lipids, the interfacial polymerization of surfactant monomers in situ, inclusion of charged molecule.²

***Address for Correspondence:**

Shraddha M. Patel

Department of Pharmaceutics,

Shree Swaminarayan Sanskar Pharmacy College,

Zundal, Gandhinagar, Gujarat, India.

Email ID: shraddhu041@gmail.com

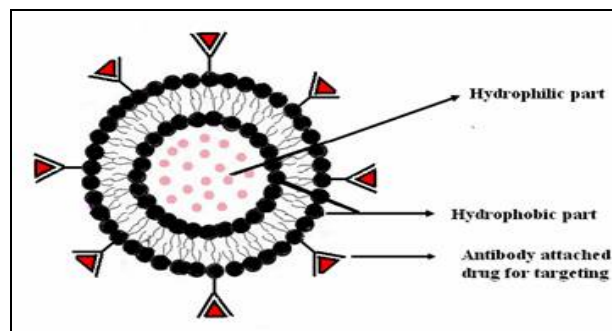


Figure: 1 Structure of Niosome

Niosomes may act as a depot, releasing the drug in a controlled manner. The therapeutic performance of the drug molecules can also be improved by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.³

Niosomes entrap solute in a manner analogous to liposomes. They are osmotically active, and are stable on their own, as well as increase the stability of the entrapped drugs^{4,5}. Handling and storage of surfactants require no special conditions. Niosomes possess an infrastructure consisting of hydrophilic and hydrophobic moieties together, and as a result, can accommodate drug molecules with a wide range of solubilities⁶. They exhibit flexibility in structural characteristics (composition, fluidity, size, etc.), and can be designed according to the desired situation⁷. Niosomes improve the oral bioavailability of poorly absorbed drugs⁸, and enhance skin penetration of drugs. They can be made to reach the site of action by oral [oral absorption of niosomes is better as compared to liposomes as replacement of phospholipids by nonionic surfactants has made niosomes less susceptible to the action of bile salts], parenteral⁹, as well as topical routes. They allow their surface for attachment of hydrophilic moieties in the bilayer, to bring about changes in-vivo, by incorporation of hydrophilic groups such as poly (ethylene glycol), concanavalin A, and polysaccharide to the non-ionic surfactant, thus acting as stealth or long circulating niosomes. Niosomal dispersion in the aqueous phase can be emulsified in non-aqueous phase to regulate delivery rate of drug, and administer to normal vesicles in extended non-aqueous phase.¹⁰

ADVANTAGES OF NIOSOMES

The first report of non-ionic surfactant vesicles came from the cosmetic applications devised by L'Oreal.¹¹

The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in

cosmetics and for therapeutic purpose may offer several advantages: -

- The vesicle suspension is water-based vehicle. This offers high patient compliance in comparison with oily dosage forms.
- They 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. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics.
- The vesicles may act as a depot, releasing the drug in a controlled manner.

Other advantages of niosomes include:

- They are osmotically active and stable, as well as they increase the stability of entrapped drug.
- Handling and storage of surfactants requires no special conditions.
- 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.
- They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.
- 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-aqueous phase.

NIOSOMES Vs. LIPOSOMES

a) 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.

b) 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)¹². Handjani-Vila *et al* were first to report the formation of vesicular system on hydration of mixture of cholesterol and a single-alkyl chain non-ionic surfactant.¹³

c) 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.¹⁴

d) 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.¹⁵

e) 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.¹⁶

METHOD OF PREPARATION

A. Ether injection method^{17, 18}

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)¹⁸

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.

Thermosensitive niosomes were prepared by evaporating the organic solvent at 60°C and leaving a thin film of lipid on the wall of rotary flash evaporator.¹⁹ The aqueous phase containing drug was added slowly with intermittent shaking of flask at room temperature followed by sonication.

C. Sonication¹⁸

A typical method of production of the vesicles is by sonication of solution as described by Cable. 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 fluidization²⁰

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. The result is a greater uniformity, smaller size and better reproducibility of niosomes formed.

E. Multiple membrane extrusion method²⁰

Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug polycarbonate membranes, solution and the resultant suspension extruded through which are placed in series for upto 8 passages. It is a good method for controlling niosome size.

F. Reverse Phase Evaporation Technique (REV)¹⁹

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 is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes.

Raja Naresh *et al*¹⁹ have 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)²¹

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” Method²²

It is novel technique for the one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round-bottomed 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 proniosomes²³

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 $T > T_m$ and brief agitation where T = Temperature and T_m = mean phase transition temperature.

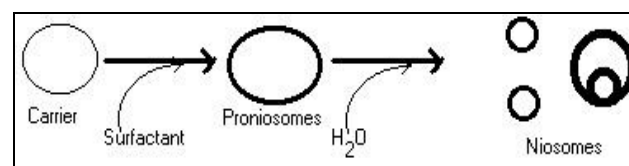


Figure: 2 Formation of Niosomes from Proniosomes

Blazek-Walsh A.I. *et al*²³ have reported 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.

CHARACTERIZATION OF NIOSOMES

(i) Size

Shape of niosomal vesicles is assumed to be spherical, and their mean diameter can be determined by using laser light scattering method. Also, diameter of these vesicles can be determined by using electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation microscopy, optical microscopy and freeze fracture electron microscopy.²⁴

(ii) Number of Lamellae

This is determined by using nuclear magnetic resonance (NMR) spectroscopy, small angle X-ray scattering and electron microscopy.²⁴

(iii) Bilayer Formation

Assembly of non-ionic surfactants to form a bilayer vesicle is characterized by an X-cross formation under light polarization microscopy.²⁵

(iv) Membrane Rigidity

Membrane rigidity can be measured by means of mobility of fluorescence probe as a function of temperature.²⁵

(v) Entrapment Efficiency

After preparing niosomal dispersion, untrapped 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 analyzing the resultant solution by appropriate assay method for the drug.²⁶

$$\text{Entrapment efficiency} = \left(\frac{\text{Amount entrapped}}{\text{total amount}} \right) \times 100$$

(vi) *In Vitro* Release Study

- One method of *in vitro* release rate study was reported with the help of dialysis tubing²⁷. A dialysis sac was washed and

soaked in distilled water. The vesicle suspension was pipetted into a bag made up of the tubing and sealed. The bag containing the vesicles was then placed in 200 ml buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. At various time intervals, the buffer was analyzed for the drug content by an appropriate assay method.

- Another method, isoniazid-encapsulated niosomes were separated by gel filtration on Sephadex G- 50 powder kept in double distilled water for 48 h for swelling.²⁸ At first, 1 ml of prepared niosome suspension was placed on the top of the column and elution was carried out using normal saline. Niosomes encapsulated isoniazid elutes out first as a slightly dense, white opalescent suspension followed by free drug. Separated niosomes were filled in a dialysis tube to which a sigma dialysis sac was attached to one end. The dialysis tube was suspended in phosphate buffer of pH (7.4), stirred with a magnetic stirrer, and samples were withdrawn at specific time intervals and analyzed using high-performance liquid chromatography (HPLC) method.

(vii) *In Vivo* Release Study

Albino rats were used for this study. These rats were subdivided with groups. Niosomal suspension used for *in vivo* study was injected intravenously (through tail vein) using appropriate disposal syringe.

APPLICATIONS

1) 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 elimination²⁹.

2) 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 mark them for clearance. Such localized drug accumulation has, however, been exploited in treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of liver³⁰.

(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 antibodies. Immunoglobulins seem to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier.³¹ 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.

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 reticulo-endothelial 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.³²

4) Niosomes as carriers for Hemoglobin.

Niosomes can be used as a carrier for hemoglobin. Niosomal suspension shows a visible spectrum superimposable onto that of free hemoglobin. Vesicles are permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin³³.

5) 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. Jayraman *et al* has studied the topical delivery of erythromycin from various formulations including niosomes or hairless mouse. From the studies, and confocal microscopy, it was seen that non-ionic vesicles could be formulated to target pilosebaceous glands.³³

6) Localized Drug Action

Localized drug action results in enhancement of efficacy of potency of the drug and at the same time reduces its systemic toxic effects e.g. Antimonials encapsulated within niosomes are taken up by mononuclear cells resulting in localization of drug, increase in potency and hence decrease both in dose and toxicity.³⁴

7) Sustained Release

The 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.⁸

NIOSOMES AS DRUG CARRIERS

Doxorubicin niosomes possessing muramic acid and triglycerol surfaces were not taken up significantly by liver. The triglycerol niosomes accumulated in the tumor and muramic acid vesicles accumulated in the spleen. Those vesicles with polyoxyethylene surface were rapidly taken up by the liver and accumulated to a lesser extent in tumor.¹⁸

Azmin *et al*⁸ reported the preparation and oral as well as intravenous administration of Methotrexate loaded niosomes in mice. They observed significant prolongation of plasma levels and high uptake of Methotrexate in liver from niosomes as compared to free drug solution.

Cable *et al*³⁵ modified the surface of niosomes by incorporating polyethylene alkyl ether in the bilayered structure. They compared the release pattern and plasma level of Doxorubicin in

niosomes and Doxorubicin mixed with empty niosomes and observed a sustained and higher plasma level of doxorubicin from niosomes in mice.

Raja Naresh *et al*¹⁹ reported the anti-inflammatory activity of niosome encapsulated Diclofenac sodium in arthritic rats. It was found that the niosomal formulation prepared by employing a 1:1 combination of Tween 85 elicited a better consistent anti-inflammatory activity for more than 72 hrs after administration of single dose.

Namdeo *et al*³⁶ reported the formulation and evaluation of Indomethacin loaded niosomes and showed that therapeutic effectiveness increased and simultaneously toxic side effect reduced as compared with free Indomethacin in paw oedema bearing rats.

Chandraprakash *et al*¹⁶ reported the formation and pharmacokinetic evaluation of Methotrexate niosomes in tumor bearing mice.

CONCLUSION

Liposomes or niosomes use for a better targeting of the drug at appropriate tissue. Niosomes represent a magical drug delivery module. They have a similar structure to liposome and hence they can represent alternative vesicular systems with respect to liposomes, Niosomes are thought to be better candidates drug delivery as compared to liposomes due to various factors like cost, stability etc. Various types of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parenteral, etc. Hence, researches are going on to develop a suitable technology for large production because it is a promising targeted drug delivery system. Niosomes are biodegradable, relatively nontoxic, more stable and an alternative to liposomes.

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