ISSN- 2231–5683 (Print) **www.asianpharmaonline.org**
ISSN- 2231–5691 (Online)

REVIEW ARTICLE

Niosome: a Novel Drug Delivery System

Kshitij B. Makeshwar*, Suraj R. Wasankar
Department of Pharmaceutics, Vidyabharti College of Pharmacy, Camp Road, Amravati, Maharashtra 444602.
*Corresponding Author E-mail: **kshitij.makeshwar87@gmail.com, wasankar@gmail.com**

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 niosomes. Structurally, niosomes are similar to liposomes, in that they are also made up of a bilayer. However, the bilayer in the case of niosomes is made up of non-ionic surface active agents rather than phospholipids as seen in the case of liposomes. Most surface active agents when immersed in water yield micellar structures however some surfactants can yield bilayer vesicles which are niosomes. Niosomes may be unilamellaror multilamellar depending on the method used to prepare them. The niosomes are classified as a function of the number of bilayer (e.g. MLV, SUV) or as a function of size. (e.g. LUV, SUV) or as a function of the method of preparation (e.g.REV, DRV). Niosomes present a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multienvironmental structure. The technology utilized in niosomes is still greatly in its infancy, and already it is showing promise in the fields of cancer and infectious disease treatments.

KEYWORDS: Unilamellar, Multilamellar, Niosomes, Phospholipids, Multienvironmental.

1. INTRODUCTION:
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 niosomes. The niosomes are very small, and microscopic in 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.

2] Salient features of niosomes[16].
1. Niosomes can entrap solutes in a manner analogous to liposomes.
2. Niosomes are osmotically active and stable.
3. Niosomes possess an infra structure consisting of hydrophobic and hydrophilic mostly together and so also accommodate the drug molecules with a wide range of solubility.
4. Niosomes exhibits flexibility in their structural characteristics (composition, fluidity and size) and can be designed according to the desired situation.
5. Niosomes can improve the performance of the drug molecules.
6. Better availability to the particular site, just by protecting the drug from biological environment.
7. Niosomes surfactants are biodegradable, biocompatible and non-immunogenic.

3] Structure of Niosomes(2-4).
Structurally, niosomes are similar to liposomes, in that they are also made up of a bilayer. However, the bilayer in the case of niosomes is made up of non-ionic surface active agents rather than phospholipids as seen in the case of liposomes. Most surface active agents when immersed in water yield micellar structures however some surfactants can yield bilayer vesicles which are niosomes. Niosomes may be unilamellaror multilamellar depending on the method used to prepare them.The niosome is made of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicle, while the hydrophobic chains face each other within the bilayer. Hence, the vesicle holds hydrophilic drugs within the space enclosed in the vesicle, while hydrophobic drugs are embedded within the

Received on 16.12.2012 Accepted on 30.01.2013

bilayer itself. The figure below will give a better idea of what a niosome looks like and where the drug is located within the vesicle. Shown in figure 1.

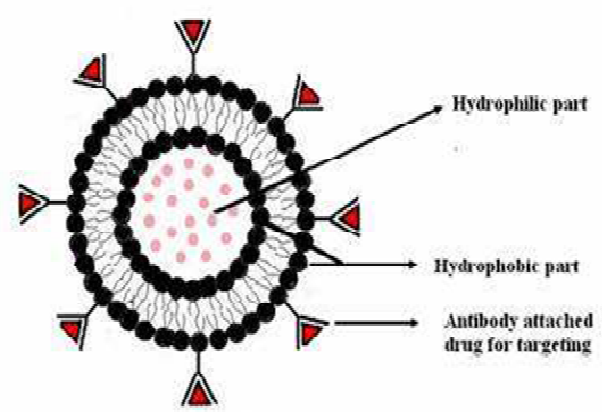

Figure 1: Structure of Niosomes

A typical niosome vesicle would consist of a vesicle forming ampiphile i.e. a non-ionic surfactant such as Span-60, which is usually stabilized by the addition of cholesterol and a small amount of non ionic surfactant such as diacetyl phosphate, which also helps in stabilizing the vesicle.

4] Advantages of niosomes[5].

A. The vesicle suspension is water- based vehicle. This offers high patient compliance in comparison with oily dosage forms.

B. 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.

C. 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.

D. The vesicles may act as a depot, releasing the drug in a controlled manner.

E. They can reduce drug toxicity because of their non-ionic nature.

5]Types of niosomes[5].

The niosomes are classified as a function of the number of bilayer (e.g. MLV, SUV) or as a function of size. (e.g. LUV, SUV) or as a function of the method of preparation (e.g.REV, DRV). The various types of niosomes are described below:

i) Multi lamellar vesicles (MLV),
ii) Large unilamellar vesicles (LUV),
iii) Small unilamellar vesicles (SUV).

1. Multilamellar vesicles (mlv):

It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 μm diameter. Multilamellar vesicles are the most widely used niosomes. It is simple to make and are mechanically stable upon storage for long periods. These vesicles are highly suited as drug carrier for lipophilic compounds.

2. Large unilamellar vesicles (luv):

Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids.

3. Small unilamellar vesicles (suv):

These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes.

6] Method of preparation of niosomes[6].

Niosomes can be prepared by a number of methods which are as follows:

Ether Injection Method

In this method, a solution of the surfactant is made by dissolving it in diethyl ether. This solution is then introduced using an injection (14 gauge needle) into warm water or aqueous media containing the drug maintained at 60°C. Vaporization of the ether leads to the formation of single layered vesicles. The particle size of the niosomes formed depend on the conditions used, and can range anywhere between 50-1000 μm.

Hand Shaking Method (Thin Film Hydration Technique)

In this method a mixture of the vesicle forming agents such as the surfactant and cholesterol are dissolved in a volatile organic solvent such as diethyl ether or chloroform in a round bottom flask. The organic solvent is removed at room temperature using a rotary evaporator, which leaves a thin film of solid mixture deposited on the walls of the flask. This dried surfactant film can then be rehydrated with the aqueous phase, with gentle agitation to yield multilamellar niosomes.

Reverse Phase Evaporation Technique (REV)

This method involves the creation of a solution of cholesterol and surfactant (1:1 ratio) in a mixture of ether and chloroform. An aqueous phase containing the drug to be loaded is added to this, and the resulting two phases are sonicated at 4-5°C. A clear gel is formed which is further sonicated after the addition of phosphate buffered saline (PBS). After this the temperature is raised to 40°C and pressure is reduced to remove the organic phase. This results in a viscous niosome suspension which can be diluted with PBS and heated on a water bath at 60°C for 10 mins to yield niosomes.

Transmembrane pH gradient Drug Uptake Process (Remote Loading)

In this method, a solution of surfactant and cholesterol is made in chloroform. The solvent is then evaporated under

reduced pressure to get a thin film on the wall of the round bottom flask, similar to the hand shaking method. This film is then hydrated using citric acid solution by vortex mixing. The resulting multilamellar vesicles are then treated to three freeze thaw cycles and sonicated. To the niosomal suspension, aqueous solution containing 10mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 using 1M disodium phosphate and mixture is later heated at 60°C for 10 minutes to give niosomes.

The "Bubble" Method

It is a technique which has only recently been developed and which allows the preparation of niosomes without the use of organic solvents. The bubbling unit consists of a round bottom flask with three necks, and this is positioned in a water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck, while the third neck is used to supply nitrogen. Cholesterol and surfactant are dispersed together in a buffer (pH 7.4) at 70°C. This dispersion is mixed for a period of 15 seconds with high shear homogenizer and immediately afterwards, it is bubbled at 70°C using the nitrogen gas to yield niosomes.

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

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 polycarbonate membranes solution and the resultant suspension extruded through which are placed in series for up to 8 passages. It is a good method for controlling niosome size.

Sonication

A typical method of production of the vesicles is by sonication of solution. 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.

7] 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. shown in figure 2.

T=Temperature.

Tm = mean phase transition temperature.

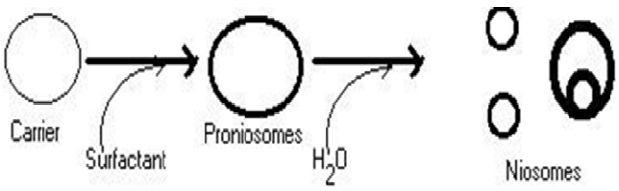

Figure 2 : Formulation of Niosomes from Proniosome

8] Separation of Unentrapped Drug[7-9].

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

1) Dialysis:

The aqueous niosomal dispersion is dialyzed in a 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 resuspended to obtain a niosomal suspension free from unentrapped drug.

9] Characterization of niosomes[10,17].

1. Size, Shape and Morphology

Structure of surfactant based vesicles has been visualized and established using freeze fracture microscopy while photon correlation spectroscopy used to determine mean diameter of the vesicles. Electron microscopy used for morphological studies of vesicles while laser beam is generally used to determine size distribution, mean surface diameter and mass distribution of niosomes.

2. 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 of drug entrapped/ total amount of drug) x 100

3. Vesicle diameter

Niosomes diameter can be determined using light microscopy, photon correlation microscopy and freeze fracture electron microscopy. Freeze thawing (keeping vesicles suspension at 20°C for 24 hrs and then heating to ambient temperature) of niosomes increases the vesicle

diameter, which might be attributed to fusion of vesicles during the cycle.

4. 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.

5. Vesicle charge

The vesicle surface charge can play an important role in the behavior of niosomes in vivo and in vivo. In general, charged niosomes are more stable against aggregation and fusion than uncharged vesicles. In order to obtain an estimate of the surface potential, the zeta potential of individual niosomes can be measured by microelectrophoresis. An alternative approach is the use of pH sensitive fluorophores. More recently, dynamic light scattering have been used to measure the zeta potential of niosomes.

6. Bilayer Rigidity and Homogeneity

The biodistribution and biodegradation of niosomes are influenced by rigidity of the bilayer. In omogeneity can occur both within niosome structures themselves and between niosomes in dispersion and could be identified via. NMR, differential scanning calorimetry (DSC) and fourier transform-infra red spectroscopy (FT-IR) techniques. Recently, fluorescence resonance energy transfer (FRET) was used to obtain deeper insight about the shape, size and structure of the niosomes.

7. Niosomal drug loading and encapsulation efficiency

To determine drug loading and encapsulation efficiency, the niosomal aqueous suspension was ultracentrifuged, supernatant was removed and sediment was washed twice with distilled water in order to remove the adsorbed drug.

The niosomal recovery was calculated as:

$$\text{Niosome recovery (\%)} = \frac{\text{Amount of niosomes recovered}}{\text{Amount of polymer + Drug + Excipient}} \times 100$$

The entrapment efficiency (EE) was then calculated using formula:

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

The drug loading was calculated as:

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

10] Niosomal drug release

Recently, FRET was used to monitor release of encapsulated matters in niosomes by using separate niosomal suspensions incorporating donor and acceptor. The simplest method to determine in vitro release kinetics of the loaded drug is by incubating a known quantity of drug loaded niosomes in a buffer of suitable pH at 37^0C with continuous stirring, withdrawing samples periodically and analyzed the amount of drug by suitable analytical technique. Dialysis bags or dialysis membranes are commonly used to minimize interference.

11] Applications of niosomes[11-15].

The application of niosomal technology is widely varied and can be used to treat a number of diseases.

Niosomes as Drug Carriers

Niosomes have also been used as carriers for iobitridol, a diagnostic agent used for Xray imaging. Topical niosomes may serve as solubilization matrix, as a local depot for sustained release of dermally active compounds, as penetration enhancers, or as rate-limiting membrane barrier for the modulation of systemic absorption of drugs.

Drug Targetting

One of the most useful aspects of niosomes is their ability to target drugs. Niosomes can be used to target drugs to the reticuloendothelial system. The reticulo-endothelial system (RES) preferentially takes up niosome vesicles. The uptake of niosomes is controlled by circulating serum factors called opsonins. These opsonins mark the niosome for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize to the liver and spleen. This localization of drugs can also be used for treating parasitic infections of the liver. Niosomes can also be utilized for targeting drugs to organs other than the RES. A carrier system (such as antibodies) can be attached to niosomes (as immunoglobulin's bind readily to the lipid surface of the niosome) to target them to specific organs.

Anti-neoplastic Treatment

Most antineoplastic drugs cause severe side effects. Niosomes can alter the metabolism; prolong circulation and half life of the drug, thus decreasing the side effects of the drugs. Niosomes, is decreased rate of proliferation of tumor and higher plasma levels accompanied by slower elimination.

Leishmaniasis

Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells of the liver and spleen. Use of niosomes in tests conducted showed that it was possible to administer higher levels of the drug without the triggering of the side effects, and thus allowed greater efficacy in treatment.

Delivery of Peptide Drugs

Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. In an in vitro study conducted by oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide.

Use in Studying Immune Response

Due to their immunological selectivity, low toxicity and greater stability; niosomes are being used to study the nature of the immune response provoked by antigens. Non-ionic surfactant vesicles have clearly demonstrated their ability to function as adjuvant following parenteral administration with a number of different antigens and peptides.

Niosomes as Carriers for Haemoglobin

Niosomes can be used as carriers for haemoglobin within the blood. The niosomal vesicle is permeable to oxygen and hence can act as a carrier for haemoglobin in anaemic patients.

Other Applications[13-15].

a) **Sustained Release**

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.

12] CONCLUSION:

Niosomes present a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multienvironmental structure. The technology utilized in niosomes is still greatly in its infancy, and already it is showing promise in the fields of cancer and infectious disease treatments. The system is already in use for various cosmetic products. Niosomes represent a promising drug delivery technology various type of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parenteral, etc.

13] REFERENCES:

1. Baillie AJ, Florence AT, Hume IR, Murihead GT, Rogerson A, The preparation and properties of niosomes-Nonionic surfactant vesicles,.J. Pharm. Pharmacol, 37, 2003, pp. 863-868.
2. Chandraprakash KS, Udupa N, Umadevi P and Pillai GK, Indian J. Pharm. Sci., 54, 1992, pp. 197.
3. www.pharmainfo.net/reviews/niosome-unique-drug delivery system
4. Duijad RC, Manvi FC, Swati S and Rony M, Indian Drugs, 2008, pp. 713.
5. Gadhiya P, Shukla S, Modi D, Bharadia P, A Review- Niosomes in Targeted Drug Delivery, International Journal for Pharmaceutical Research Scholars, 2, 2012, pp. 61.
6. Pawar SD, Pawar RG, Kodag PP, Waghmare AS, Niosome: An Unique Drug Delivery System, International Journal of Biology, Pharmacy and Allied Sciences,3, 2012, pp 409-412.
7. Khandare JN, Madhavi G, Tamhankar BM, Niosomes novel drug delivery system. The East Pharmacist. 37, 1994, pp. 61-64.
8. Maver LD, Bally MB, Hope MJ, Cullis PR, Biochem. Biophys. Acta. 816, 1985, pp. 294-302.
9. Blazek-Walsh AI, Rhodes DG, SEM imaging predicts quality of niosomes from maltodextrin-based proniosomes, Pharm. Res. 18, 2001, pp. 656-661
10. Gadhiya P, Shukla S, Modi D, Bharadia P, A Review- Niosomes in Targeted Drug Delivery, International Journal for Pharmaceutical Research Scholars, 2, 2012.
11. Akul Mehta, PharmaXChange_info - Articles – Niosomes
12. Ruckmani K, Jayakar B and Ghosal SK, Drug Development and Industrial Pharmacy, 26, 2000, pp. 217-222.
13. Baillie AJ, Coombs GH and Dolan TF, Non-ionic surfactant vesicles, niosomes, as delivery system for the anti-leishmanial drug, sodium stribogluconate, J. Pharm. Pharmacol., 38, 1986, pp. 502-505
14. Conacher M, Alexanderand J, Brewer JM, Conacher M, and Alexander J, Niosomes as Immunological Adjuvants. In "Synthetic Surfactant Vesicles" (Ed. I.F. Uchegbu) International Publishers Distributors Ltd. Singapore, 2000, pp. 185-205.
15. Azmin MN, Florence AT, Handjani-Vila RM, Stuart JB, Vanlerberghe, G and Whittaker JS, J. Pharm. Pharmacol., 37, 1985, pp, 237.
16. Gadhiya P, Shukla S, Modi D, Bharadia P, A Review- Niosomes in Targeted Drug Delivery, International Journal for Pharmaceutical Research Scholars, 2, 2012, pp. 60.
17. Pawar SD, Pawar RG, Kodag PP, Waghmare AS, Niosome: An Unique Drug Delivery System, International Journal of Biology, Pharmacy and Allied Sciences,3, 2012, pp. 412.