



**International Journal of Biology, Pharmacy
and Allied Sciences (IJBPAS)**

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

NIOSOME: AN UNIQUE DRUG DELIVERY SYSTEM

**PAWAR SD *, PAWAR RG, KODAG PP, WAGHMARE AS, GADHAVE MV,
JADHAV SL AND GAIKWAD DD**

Department of Pharmaceutics, Vishal Institute of Pharmaceutical Education & Research, Ale,
Pune – 412411 (Maharashtra)

***Corresponding Author: Email: sagar24188@gmail.com**

ABSTRACT

Niosomes 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. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and Lipophilic drugs. Their size lies in the nanometric scale. Niosomes represent a promising drug delivery technology various type of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parenteral, This systemic review article deals with preparation methods, characterizations, advantages, and applications of niosomes.

Keywords: Niosomes, Surfactants, Targeting, Ophthalmic, Parenteral.

INTRODUCTION

In the past few decades, considerable attention has been focused on the development of new drug delivery system (NDDS). The NDDS should ideally fulfill two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity

to the site of action. At present, no available drug delivery system behaves ideally, but sincere attempts have been made to achieve them through various novel approaches in drug delivery [1].

Lipid vesicles were first described by **Dr. Alec Bangham in 1965**. He had observed that handshake phospholipids dispersions in

water form multilamellar spherical structures. These vesicles, soon named leptosomes, consist of an aqueous cavity encapsulated by one or more lipid bilayer membranes. 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 [2].

Structure of 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 unilamellar or 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 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 [3].

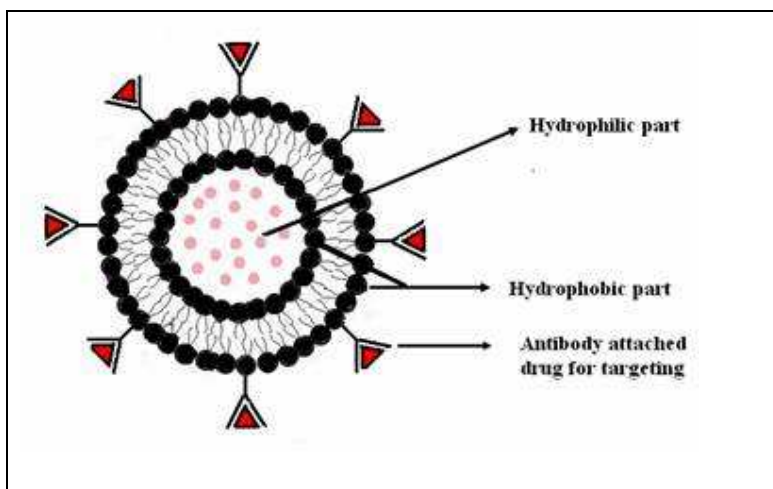


Figure 1: Structure of Niosomes [4]

A typical niosome vesicle would consist of a vesicle forming amphiphile 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 [5].

Niosomes or Non-Ionic Surfactant Vesicles

Alkyl Ethers

An alkyl glycerol ethers compound is used to form niosomal vesicular dispersions. Notable application of these compounds has been as vesicle dispersions in the field of experimental cancer chemotherapy where both methotrexate and doxorubicin have been encapsulated and the effect of delivery in niosomes studied. Alkyl glycerol ethers have also been used to prepare non-ionic surfactant vesicles for cosmetic application.

Alkyl Esters

Alkyl esters, such as the sorbitan esters widely used in foodstuffs, have been studied as the basis of non-ionic surfactant vesicles. A non-ionic surfactant vesicle formulation consisting of a mixture of alkyl ether and alkyl ester surfactants, namely polyoxyethylene-10-stearyl ether (C₁₈EO10): glyceryl laurate (C₁₂G1): cholesterol (27:15:57) has been used in the transdermal delivery of cyclosporin A.

Alkyl Amides

Alkyl galactosides and glucosides incorporating amino acid spacers have also been found to produce vesicles. While, as a general rule, the alkyl groups in all vesicles forming amphiphiles consist of fully or partially saturated C₁₂ to C₂₂ hydrocarbons,

certain novel amide compounds bearing fluorocarbon chains.

Fatty Acid and Amino Acid Compounds

In addition to alkyl glycosides, amino acid moieties, when made suitably amphiphilic by the addition of hydrophobic alkyl side chains, are vesicle formers. Long chain fatty acids also form 'ufasomes', closed vesicles formed from fatty acid bilayers. The latter vesicles were prepared at pH 8 resulting in a degree of ionization and subsequent increase in the effective volume of the hydrophilic head group and a series of spans and tweens [6, 7].

Similar to liposomes, there are 3 major types of niosomes multilamellar vesicles (MLV, size >0.05 µm), small unilamellar vesicles (SUV, size -0.025-0.05 µm), large unilamellar vesicles (LUV, size >0.10 µm). In lipid compositions. SUVs are commonly produced by sonication, and French Press procedures. Ultrasonic electrocapillary emulsification or solvent dilution techniques can be used to prepare SUVs. The injections of lipids solubilised in an organic solvent into an aqueous buffer, can result in spontaneous formation of LUV. But the better method of preparation of LUV is reverse phase evaporation, or by detergent solubilisation method [8].

Advantages of Niosomes

- Greater patient compliance. The vesicles can act as a depot to release the drug slowly and offer a controlled release.
- They are osmotically active and stable.
- They increase the stability of the entrapped drugs.
- Handling and storage of surfactants do not require any special conditions.
- Can increase the oral bioavailability of drugs.
- Can enhance the skin penetration of drugs.
- They can be used for oral, parenteral as well topical use.
- The surfactants are biodegradable, biocompatible, and non-immunogenic.
- Improve the therapeutic performance of the drug by protecting it from the biological environment and restricting effects to target cells, thereby reducing the clearance of the drugs.

Method of Preparation of Niosomes

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 (300mM, pH 4.0) 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 (this causes the drug which is outside the vesicle to become non-ionic and can then cross the niosomal membrane, and once inside it is again ionized thus not allowing it to exit the vesicle). The 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.

Formation of Niosomes from Proniosomes

To create proniosomes, a water soluble carrier such as sorbitol is first coated with the surfactant. The coating is done by preparing a solution of the surfactant with cholesterol in a volatile organic solvent, which is sprayed onto the powder of sorbitol kept in a rotary evaporator. The evaporation of the organic solvent yields a thin coat on the sorbitol particles. The resulting coating is a dry formulation in which a water

soluble particle is coated with a thin film of dry surfactant. This preparation is termed Proniosome. The niosomes can be prepared from the proniosomes by adding the

aqueous phase with the drug to the proniosomes with brief agitation at a temperature greater than the mean transition phase temperature of the surfactant [9].

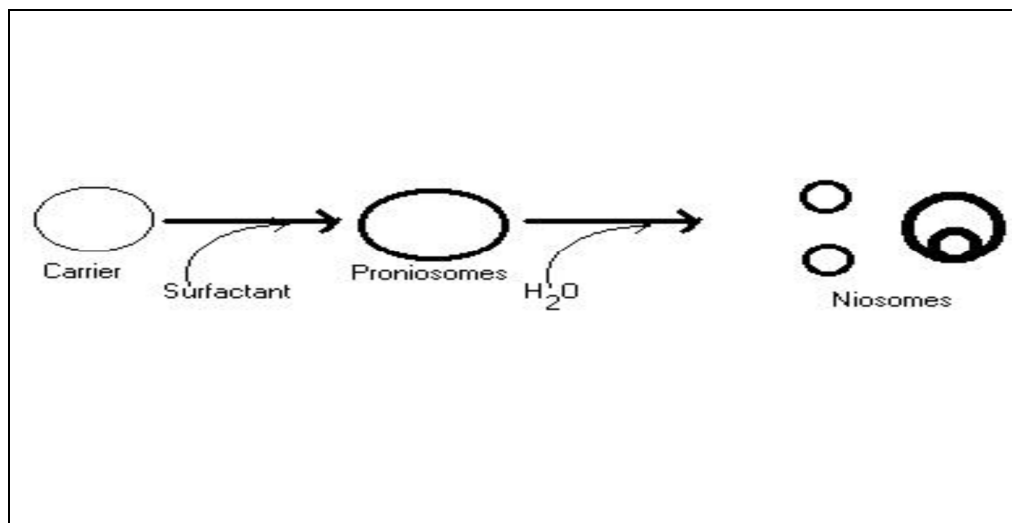


Figure 2: Formation of Niosomes from Proniosomes [9]

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 niosomes formed [10].

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 [11].

Sonication

A typical method of production of the vesicles is by sonication of solution as described by Cable [11]. 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.

Characterization of Niosomes

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.

Freeze Fractured Microscopy

Vesicles are freeze thawed and visualized using freeze fracture electron microscopy. The vesicular suspension is cryofixed in liquid propane. Some cryoprotectant like glycerol can be used. The cryofixed vesicles are fractured at an angle between 90-150° while low pressure is maintain (10^{-2} pa). The surface obtained following fracturing is then shadowed using platinum or carbon vapours at an angel of 45°C. Coating with carbon further strengthens to form replica and examine using transmission electron microscope. The niosomes have been observed 80 nm to 800 nm as larger ULVs and they can be more 1 µm in size as MLVs.

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.

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.

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 analyzing the resultant solution by appropriate assay method for the drug. Where,

$$\text{Entrapment efficiency (EF)} = (\text{Total amount entrapped}) \times 100$$

Encapsulation Efficiency

Encapsulation efficiency can be said as a product of the stability of the dispersion. That is, the encapsulated solute and the solute retention capability of encapsulating membrane, together with the stability of

both surfactant and the vesicle structure, all contribute to the stability of formulation. Encapsulation efficiency is governed by the method of loading, nature of solute and hydration temperature. Vesicles loaded by transmembrane ion gradient show higher entrapment efficiency than those loaded during the hydration steps. As a rule, larger niosomes show higher entrapment efficiencies than smaller vesicles. Encapsulation of water soluble solutes results in increased vesicles size [12].

Applications of Niosomes

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 X-ray 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 [13].

Drug Targeting

One of the most useful aspects of niosomes is their ability to target drugs. Niosomes can be used to target drugs to the reticulo-

endothelial 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 [13].

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 [14].

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 invitro 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 [15].

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 adjuvants 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 anemic patients.

Other Applications

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 [15].

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 [16, 17].

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 multienviromental 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. Much research has to be inspired in these delivery systems to juice out all the potential in this novel drug delivery system.

REFERENCES

- [1] Namdeo A and Jain NK, Indian J. Pharm. Sci., 1996, 58, 41.
- [2] Baille AJ, Florence AT, Hume LR, Muihead G, and Rogerson AJ, J. Pharm. Pharmacol., 37, 1985, 863.
- [3] Chandraprakash KS, Udupa N, Umadevi P and Pillai GK, Indian J. Pharm. Sci., 54, 1992, 197.
- [4] www.pharmainfo.net/reviews/niosome-unique-drug-delivery-system.
- [5] Duijad RC, Manvi FC, Swati S and Rony M, Indian Drugs, 2008, 713.
- [6] Barenholz Y, Crommelin D, Liposomes as Pharmaceutical Dosage Forms, Marcel Dekker Inc, New York, 1994.
- [7] Parthasarathi G, Udupa N and Pillai GK, Indian J. Pharm. Sci., 56, 1994, 90.
- [8] Chandraprakash KS, Udupa N, Umadevi P and Pillai GK, Int. J. Pharm., 1990, 61.
- [9] Yoshioka T and Florence AT, Int. J. Pharm., 168, 1994, 117-137.
- [10] Hu C and Rhodes DG, Proniosomes: a novel drug carrier preparation, Int J Pharm., 185(1), 1999, 23-35.
- [11] Vyas SP and Khar RK, Targeted and controlled drug delivery, 1st edn, CBS publisher, Delhi, 2002, 249-27.
- [12] Ramana MV and Anil Kumar N, Scientific Abstract, 1999, 371.
- [13] Akul Mehta, PharmaXChange_info - Articles – Niosomes.
- [14] Ruckmani K, Jayakar B and Ghosal SK, Drug Development and Industrial Pharmacy, 26(2), 2000, 217-222.
- [15] Baillie AJ, Coombs GH and Dolan TF, Non-ionic surfactant vesicles, niosomes, as delivery system for the anti-leishmanial drug, sodium stibogluconate, J. Pharm. Pharmacol., 38, 1986, 502-505.
- [16] 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, 185-205.
- [17] Azmin MN, Florence AT, Handjani-Vila RM, Stuart JFB,

Vanlerberghe, G and Whittaker JS,
J. Pharm. Pharmacol., 37, 1985,
237.

[18] Rogerson A, Cummings J, Floren
AT, J. Microencapsulation, 4(4),
1987, 321 -328.