NIOSOMES: A UNIQUE DRUG DELIVERY TOOL

Umar Farroq, Irfan Bashir*, Muhammad Jamshaid, Imtiaz Majeed, Muhammad Nadeem Alvi, Faheem Ahmed Siddiqui, Khalid Idrees Khan, Yasir Mehmood

Faculty of Pharmacy, University of Central Punjab, Lahore, Pakistan.

ABSTRACT
Synthetic nonionic surfactants such as alkyl or dialkyl poly glycerol ether class when hydrated give niosomes. Niosomes are the drug carriers which provide substitute to liposomes and encapsulate the solutes in a way similar to liposomes. These may be unilamellar or multilamellar vesicles, present more in vitro stability and improved stability of drugs entrapped in comparison with the dosage forms which are conventional. [1] Niosomes can hold amphiphillic as well as lipophilic drugs and have the advantage of being biocompatible, biodegradable and non immunogenic over liposomes. Niosomes are used for targeted as well as controlled release for the treatment of many diseases including cancer, viral and other microbial diseases. Encapsulation of drugs in niosomes results in prolonged existence of drugs in circulation and improved penetration into the tissues targeted. [2] The purpose of this review is to have an overview of preparation, composition, structure and applications of niosomes in pharmacy. The main purpose of development of niosomal preparations is to control the release profile of the drugs by making their release sustained and targeting drugs to the sites desired.

KEYWORDS: Synthetic nonionic, Unique drug, composition, structure and applications of niosomes in pharmacy.

INTRODUCTION
L’Oreal for the 1st time used nisomes in cosmetics. [3] Niosomes being non ionic surfactants in nature have provided an alternative to liposomes. [4] Delivery of different kinds of drugs can be made targeted by incorporating them in niosomes such as parenterals, ophthalmics and topical, etc.
Structure of the Niosomes \[^5\]

Niosomes are just like liposomes as per structure is concerned but the difference lies in the bilayer creation which is made up of non ionic surfactants in case of niosomes and phospholipids in case of liposomes. When water is added in some of the surfactants they form a bilayer resulting in niosomes having their hydrophilic ends outside and hydrophobic ends inside. As a result drugs which are hydrophobic are captured in the bilayer whereas hydrophillic drugs are present in the space of vesicles. Following figure shows targeting of drugs through niosomes.

![Figure: Structure of Niosome. \[^3\]](image)

Types of Niosomes \[^6\]

Depending upon vesicle size, niosomes are classified as:

i. Small Unilamellar Vesicles (SUV, Size=0.025-0.05 μm)

ii. Multilamellar Vesicles (MLV, Size≥0.05 μm)

iii. Large Unilamellar Vesicles (LUV, Size≥0.10 μm).

Advantages Associated with Niosomes

1. Being water–based vehicle niosomes offer better patient compliance as compared to other oily dosage forms.

2. Drugs of different solubilities can be accommodated as niosomes consisting of amphiphilic, hydrophilic and lipophilic moieties together.

3. Alternating the composition of vesicles provides control over different varying characteristics of niosomes such as concentration, tapped volume, lamellarity, size and surface charge.
4. Different routes can be opted to deliver niosomes at targeted site of action, such as oral, parenteral and topical.

5. Surfactants do not need any special or essential conditions for handling and storage.

6. Niosomes can enhance the bioavailability and penetration of drugs which are poorly absorbed form skin.

7. Niosomes entrap the drugs with greater efficiency.

8. By using niosomes systemic clearance of the drug is delayed thus increasing the therapeutic effect.

9. Niosomes are stable, osmotically active and increase the stability of entrapped drug.

10. Niosomes can act as depot and discharge the drug in a controlled mode.

11. Niosomes can protect the drug from biological environmental conditions and restrict the effect only at the specific targeted site.

Compositions of Niosomes \([7,8,9]\)

Following are the major components used in the formation of niosomes.

A. **Cholestrol**: Cholesterol provides firmness, structure, shape and conformation for the proper formation of niosomal preparations.

B. **Non ionic surfactant**: Surfactants have a prominent role in the formation of niosomal preparation. Non ionic surfactants contain hydrophobic tail and a hydrophilic head. The hydrophobic tail consists of one or two alkyl or perfluoro alkyl and in some conditions single group which is steroidal in nature. \([4]\)

Generally used non ionic surfactants in the preparation of niosomes are: Span (span 60, 40, 20, 85, 80), Tweens (tween 20, 40, 60, 80), Brij (brij 30, 35, 52, 58, 72, 76). Sorbitan monopalmitate, Sorbitan monolaurate, Sorbitan monostearate, Polyoxyethylene (20) sorbitan monolaurate, Polyoxyethylene (20) sorbitan monostearate, Polyoxyethylene (10) stearyl ether, Polyoxyethylene (20) stearyl ether and Polyoxyethylene (2) stearyl ether, etc.

C. **Other additives**: Niosomes are often included with membrane additives which are charge inducers because they deprive the formation of vesicles, flocculation, fusion and aggregation. Stearyl amine (SA) and Dicetyl phosphate (DCP) can induce positive and negative charges and are examples of these kinds of membrane additives.
Niosomes vs. Liposomes

1. Ingredients in liposomes like phospholipids are expensive as well as predisposed to oxidative degradation and need unusual conditions for storage and handling while in case of niosomes we do not have to face these problems.

2. Behavior of niosomes invivo is just like liposomes. Niosomes enhance the existence of entrapped drug in systemic circulation and can alter metabolic stability and supply of drugs to the targeted organs. \[^{10}\]

3. Characteristics of both the liposomes and niosomes depend on method of preparation and composition of their bilayer. \[^{11}\] Different types of surfactants used can alter and control the tissue distribution, cellular interaction and metabolism of entrapped drugs as well as targeting and control release of drug to the desired sites. \[^{12,13}\]

4. Entrapment efficiency of niosomes is increased when surfactants in high concentration and lipophilicity are used. \[^{14}\]

5. Niosomes are formed by uncharged, single chain surfactant and cholesterol whereas liposomes are made from neutral or charged double-chain phospholipids.

Methods of Preparation of Niosomes

Niosomes can be prepared by different methods. Any method for the preparation of niosomes is opted out according to desired entrapment efficiency, vesicle membrane permeability, number of double layers in aqueous phase, size and distribution.

(i) Preparation of Small Unilamellar Vesicles

(a) Sonication

In this typical method an aliquot of solution containing drug and buffer is added to the mixture of surfactant/cholesterol in glass vial of 10 ml. At 60°C the mixture is probe sonicated, to give up niosomes, with a titanium probe by using a sonicator. \[^{15}\]

![Fig 2: Niosomes after sonication][15]
(b) Micro Fluidization
Usually unilamellar vesicals are prepared by this technique by interacting two high velocity streams in an interaction chamber containing defined micro channels. Energy of the system remains restricted to area of niosomes formation along a common front. In this technique niosomes formed are of smaller size, greater reproducibility and uniformity. [16]

(ii) Preparation of Multilamellar Vesicles
(a) Hand Shaking Method (Thin Film Hydration Technique)
A mixture of vesicle forming agents and cholesterol is dissolved in diethyl ether, chloroform or any other organic volatile solvent in a round bottom flask. At room temperature organic solvent is removed by using rotary evaporator and a thin layer is formed on the walls of flask. Multilamellar niosomes are produced when dried film is rehydrated with an aqueous phase by gentle shaking.[15]

(b) Transmembrane pH Gradient Drug Uptake Process (Remote Loading)
Solution of surfactant and cholesterol is formed in chloroform. Pressure is kept low to evaporate the solvent and form a thin layer on the walls of round bottom flask which is hydrated with citric acid by using vortex mixing to get multilamellar vesicles. These vesicles are then treated with three freeze thaw cycles and sonicated. Solution of the drug is added and PH is increased to 7.0-7.2 using 1 molar disodium phosphate. Mixture is heated for 10 minutes at 60°C to obtain niosomes.

(iii) Preparation of Large Unilamellar Vesicles
(a) Reverse Phase Evaporation Technique (REV)
Solution of surfactant and cholesterol is formed. Aqueous phase containing drug is added to this mixture and sonicated at 4-5°C to form a clear gel. Phosphate buffer solution (PBS) is added and more sonication is done. Temperature is raised to 40°C and pressure is decreased for removing organic phase. A thick suspension is formed which is further diluted with PBS. Additional heating is done in the water bath at 60°C for 10 minutes to obtain niosomes.

(b) Ether Injection Technique
A solution of surfactant and diethyl ether is formed. An injection needle (14 gauge) is used to add the solution in aqueous medium containing the drug. Vesicle formation takes place after the evaporation of organic solvent. Size of the niosomes formed by this technique varies in between 50-1000 μm. [17]
(iv) Miscellaneous

(a) The “Bubble” Technique
The equipment used in this method is a round bottom flask containing three necks which are cited in the water bath to maintain the temperature. One neck is used to supply nitrogen while the other two are positioned with thermometer and water reflux. Surfactants and cholesterol are mixed mutually for 15 seconds in a buffer having PH 7.4 at 70°C and homogenized in a high shear homogenizer and it is bubbled with nitrogen gas at 70°C to obtain niosomes. [18]

(b) Multiple Membrane Extrusion Technique
This technique is a good way to control the size of niosomes. [16] A solution of dicetyl phosphate, surfactant and cholesterol is made in chloroform. Organic solvent is evaporated to make a thin film which is further hydrated with the aqueous solution of drug and resultant suspension is extruded through which are placed in series for up to 8 passages.

Characterization of Niosomes
1. Size, Shape and Morphology
Structure of the vesicles formed by surfactant is examined by freeze fractured microscopy. Mean diameter of the surfactant is determined by photon correlation spectroscopy. [19,20] Morphology of vesicles is studied by electron microscopy. Size distribution and mean surface diameter can be determined by laser beam.

2. Entrapment Efficiency
After the formation of niosomes unentrapped drug can be separated by using any of the technique from gel filtration, dialysis and centrifugation. Measurement of drug entrapped in niosomes is determined by complete disruption of vesicles by the use of 50% n-propanol or 0.1% Triton X-100 and performing the assay of final solution. [21] Percentage efficiency is calculated by the formula.

% Entrapment efficiency (% EF) = (Amount entrapped/ total amount of drug) x 100

3. Bilayer Formation
Bilayer vesicles formed by nonionic surfactant can be examined under light polarization microscopy by an X cross formation. [22]
4. **Number of Lamellae**
Small angle X-ray scattering, nuclear magnetic resonance (NMR) spectroscopy and electron microscopy is used to determine number of lamellae. [20]

5. **Membrane Rigidity**
Technique of means of mobility of fluorescence probe as a function of temperature can be used to determine membrane rigidity. [22] Distribution and degradation of the niosomes is influenced by the bilayer.

6. **pH Measurement**
pH measurement is done at 25°C by a Ph meter (Accumet® basic model AB15, Fisher Scientific, Pennsylvania, USA).

7. **In vitro Release**
Dialysis tube is used for this purpose. After drenching the tube in distilled water the niosomal preparation containing the drug is added to the tube containing buffer at 37°C, from time to time in a known amount and sealed. An assay of the buffer containing niosomal preparation is done to analyze the drug present in it.

8. **Vesicle Charge**
Any of the following techniques including zeta potential analyzer, pH Sensitive fluorophores and dynamic light scattering can be used to find out the zeta potential of niosomal preparation. *Invivo* and *invitro* behavior of niosomes is determined by surface charge. If vesicles are uncharged aggregation may result sometimes.

9. **Homogeneity**
Any of the differential scanning calorimetry(DSC), fourier transform-infra red spectroscopy (FT-IR), nuclear magnetic resonance (NMR) and fluorescence resonance energy transfer (FRET) can be used to study deeply the structure, size and shape of the prepared niosomes.

10. **Measurement of Angle of Repose**
Angle of repose can be determined by a simple funnel method. Funnel containing dry powdered niosomal preparation is fixed at a position in such a way that it is 5cm above the surface level and its outlet orifice is 13mm. The powder starts to flow down after the funnel is removed and a cone is formed on the surface. The angle of repose can be simply calculated by measuring the height and diameter at the base.
11. Osmotic Shock
To have an idea about the change in vesicle size of the niosomal preparation, the niosomes are studied under optical microscope after incubation of niosomal preparation with hypo, hyper and isotonic solutions for at least 3 hours.

Applications of Niosomes
Niosomes can be used as drug delivery system to deliver drug in a number of diseases.

1. Niosomes as Drug Carriers
Niosomes can be used to carry hemoglobin and iobitridol. Iobitridol has its role in diagnosis and is used in X ray imaging technique. Topically niosomes are used as penetration enhancer and a local reservoir for the release of compounds having activity for skin.

2. Drug Targetting
Drugs to be targeted to reticuloendothelial system are delivered through niosomes. Opsonins (serum factor) are responsible for the niosomal uptake. This localization is exploited to treat liver parasitic infection and tumors. Drug targeting to other organs except reticuloendothelial system can also be done through niosomes. Niosomes can also attach other carrier systems including antibodies for specific organ targeting because lipid surfaces can attach immunoglobulins quickly.

3. Anti-neoplastic Treatment
Some drugs having broad spectrum anti tumor activity also show irreversible side effects. For example doxorubicin can cause irreversible cardiac toxicity which can be avoided by administering the drug through niosomal delivery. Administering the drug through niosomes also show the benefit of less proliferation rate of sarcoma. Drugs, like methotrexate entrapped in niosomes, shows greater half life, slower elimination and altered metabolism. Some of the anti cancer agents which have been studied to deliver through niosomes include daunorubicin hydrochloride, doxorubicin, Methotrexate, Bleomycin and Vincristine, etc.

4. Leishmaniasis
Leishmaniasis is caused by the invasion of a parasite in the liver. Experiments conducted to study the delivery of drug through niosomes have shown greater efficacy without triggering side effects.
5. **Delivery of Peptide Drugs**

Entrapment in the niosomes can increase the stability of peptides as studied by Yoshida et al in investigating oral niosomal delivery of vasopressin and arginine in an invitro intestinal loop design.\(^ {33}\)

6. **Use in Studying Immune Response**

As reported by Brewer and Alexander niosomes are potent immunological adjuvant which are suitable to study antigen induced immune response because niosomes have low toxicity and better stability.\(^ {34, 35}\)

7. **Transdermal Delivery of Drugs through Niosomes**

Drawback of lesser penetration of drugs in skin trough transdermal route can be overcome by incorporating the drugs in niosomes. Toxicity studies of nonionic surfactant vesicles revealed that if chain length of alkyl group is increased it results in decreased toxicity for topical administration.\(^ {36}\)

8. **Sustained Release**

Niosomal entrapment of the drugs having low therapeutic index and water solubility is helpful in maintaining bioavailability in systemic circulation. Sustained release of paclitaxel (PCT) encapsulated with niosomes was observed after its oral administration in Wister rats.\(^ {37}\)

9. **Localized Drug Action**

Localized action of drug has the benefit of greater efficacy, lower systemic toxicity and decreased dose. Antimonials show localized action when delivered after incorporation with niosomes.\(^ {32}\)

Recent studies have reported niosomal preparation based hydrogels as promising tool for localized action of atenolol in the eye for treatment of glaucoma.\(^ {38}\)

10. **Use in Diagnosis**

Niosomes are helpful in diagnostic imaging. Niosomal preparations conjugated with [N-palmitoyl-glucosamine (NPG)] and PEG 4400 improve the assessment of magnetic resonance imaging. Radioactive iopromide encapsulated in niosomes was investigated for the diagnostic purposes in kidney but encapsulating efficiency of the agent was very low to practice it on clinical bases.\(^ {39}\)
11. Delivery of Vaccines
Niosomes are gaining significance as carrier systems for peroral and topical immunization. Systems based on non-ionic surfactants to carry vaccines are themselves weekly immunogenic. Studies on nasal mucosal delivery of influenza antigen and topical delivery of Hepatitis B surface antigen encapsulated in niosomes have shown comparable results with other delivery systems of vaccines.[40,41]

Future Prospects
A lot of research is required to encapsulate anti-viral, anti-infective, anti-AIDS, toxic anti-cancer and anti-inflammatory drugs. Use of niosomes in drug delivery is a promising tool to achieve better targeting as well as bioavailability and reduce the toxicity and undesired side effects of different drugs.

CONCLUSION
As niosomes are made of non-ionic surfactants so these are more stable, safe and convenient to handle than other ionic drug carriers. Concept of incorporating drugs with noisome to deliver the drugs for localized as well as systemic action has gained wide acceptance and provided alternative to liposomal delivery system being less costly and more stable than liposomes. Niosomal drug delivery systems can be designed to deliver drug through various routes including topical, parenteral, oral and ophthalamic, etc.

REFERENCES


42. Mehmood, Y., et al., *Preparation and characterization of solid dispersion tablet of simvastatin employing starch phosphate as carrier.*


44. Mehmood, Y., *Combination of Allopurinol’and Sustained Release Diclofenac Sodium for Treatment of Gout.*