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# Niosomes: Novel Drug Delivery System

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## ABSTRACT

*Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs.*

*Niosomes are promising vehicle for drug delivery and being non-ionic; it is less toxic and improves the therapeutic index of drug by restricting its action to target cells. This systemic review article deals with preparation methods, characterizations, rationale, advantages, disadvantages, and applications of niosomes. Niosomes are microscopic lamellar structures ranging between 10 to 1000 nm constitute of non-ionic surfactant and cholesterol. Niosomes are preferred over liposome due to chemicals stability and economy.*

***Keywords:*** *Niosomes, non-ionic surfactants, liposomes.*

## INTRODUCTION

Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include immunoglobulin's, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes etc. Among different carriers liposomes and niosomes are well documented drug delivery[1]. 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. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs[2]. Niosomes are very small, and microscopic in size. Their size lies in Nanomteric scale[3]. Niosomes are formed by hydration of non-ionic surfactant dried film resulting in imbibing or encapsulating the hydrating solution. Major component of niosomes is non-ionic surfactant which give it an advantage of being more stable when compared to liposomes thus overcoming the problems associated with liposomes i.e. susceptibility to oxidation, high price and the difficulty in procuring high purity levels which influence size, shape and stability. Niosomes can entrap both hydrophilic and lipophilic drugs in aqueous layer and vesicular membrane respectively[4].

## SALIENT FEATURES OF NIOSOME

1. Niosomes are osmotically active and stable.
2. Niosomes surfactants are biodegradable, biocompatible and non-immunogenic.
3. Niosomes possess infrastructure consisting of hydrophilic and hydrophobic mostly together and so accommodate the drug molecules with a wide range of solubility.
4. The bilayers of the niosomes protect the enclosed active pharmaceutical ingredient from the heterogeneous factors present both inside and outside the body. So niosomes can be used for the delivery of labile and sensitive drugs.

5. Niosomes exhibit flexibility in their structural characteristics and can be designed according to the desired situation.
6. Better availability at the particular site, just by protecting the drug from biological environment.
7. The formulation is in the form of aqueous vehicle based suspension having greater patient compliance when compared to oily dosage forms.
8. Niosomal dispersion being aqueous can be emulsified in anon aqueous phase to regulate the drug release rate and to administer the vesicles in non-aqueous phase[5].

**A. ADVANTAGES OF NIOSOMES:**

1. The vesicle suspension being water-based vehicle offers high patient compliance when compared to oily dosage forms.
2. Drug molecules of wide range of solubilities can be accommodated in the niosomes provided by the infrastructure consisting of hydrophilic, lipophilic and amphiphilic moieties.
3. Vesicle characteristics can be controlled by altering the composition of vesicle, size lamellarity, surface charge, tapped volume and concentration.
4. They can release the drug in sustained/controlled manner.
5. Storage and handling of surfactants oblige no special conditions like low temperature and inert atmosphere.
6. They can act as a depot formulation, thus allowing the drug release in a controlled manner.
7. They enhance the oral bioavailability of poorly soluble drugs.
8. They possess stable structure even in emulsion form.
9. Surfactants are biodegradable, biocompatible, non-toxic and non-immunogenic.
10. They are economical for large scale production.
11. They can protect the drug from enzyme metabolism.
12. They are not only osmotically stable and active but also improve the stability of entrapped drug.
13. They can enhance the permeation of drugs through skin.
14. Therapeutic concert of the drug molecules can be improved by tardy clearance from circulation.
15. They can protect the active moiety from biological circulation.
16. They can restrict the drug delivery rate as aqueous phase niosomal dispersion can be emulsified in the non-aqueous phase and thus normal vesicle can be administered in an external non-aqueous phase[6].

**DISADVANTAGES OF NIOSOMES**

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

**COMPOSITIONS OF NIOSOMES:**

The two major ingredients or components are used for the preparation of niosomes:

1. **Cholesterol: -** It provides rigidity and proper shape, conformation to the niosomes preparations.

**2. Non-ionic surfactants:-**Surfactants play an important role in the preparation of niosomes The following non-ionic surfactants are generally used for the preparation of niosomes.

e.g.

1. Spans (span 60, 40, 20, 85, 80)
2. Tweens (tween 20, 40, 60, 80) and
3. Brijs (brij 30, 35, 52, 58, 72, 76) [15, 19].

**RATIONALE FOR SITE SPECIFIC DRUG DELIVERY:**

**1)** To reach previously inaccessible domains e.g. intracellular site, bacteria, viruses,Parasites etc.
**2)** Exclusive drug delivery to the specific cells or diseased site in the body.
**3)** Reduction in the drug dose and side effects.
**4)** To control the rate and frequency of drug delivery at the pharmacological receptor.
**5)** To protect the drug and the body from one another until it reaches at the desired site of Action[8].

**TYPES OF NIOSOMES:**

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
(eg. 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 aqueouslipid 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. Thesevesicles 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.

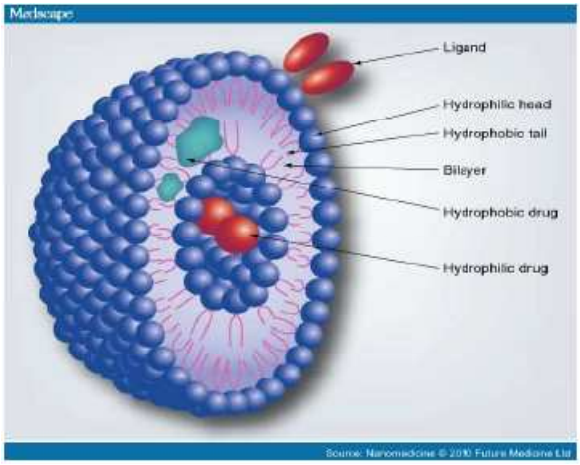
**3. Small unilamellar vesicles (suv):**

These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion electrostatic stabilization is the inclusion of
diacetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes[9].

**STRUCTURE OF NIOSOMES:**

A typical Niosomal 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 anionic surfactant such as dicetyl phosphate, which also helps in stabilizing the vesicle. Niosomes are microscopic lamellar structures, which are formed on the admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media[11].

**Fig. 1: Structure of Niosome**




**PREPARATION OF NIOSOMES:**

Vesicles of niosomes are prepared using surfactants. The surfactants used in the preparation of niosomes include alkyl and dialkyl polyglycerol ethers, PEG–polyglycerol and dialkylpolyethylene ethers, dialkylpolyglycerol and polyoxyethylene ethers. Other bilayer forming amphiphilic substances are steroidal oxyethylene ethers, laurate ethers, alkyl galactosides, sorbitan monooleate and polyoxyethylated hydrogenated castor oil.

Different methods used for the preparation of niosomes are described below:

**Ether injection**

This method is essentially based slow injection of surfactant: cholestrol solution in ether through a suitable needle at approximately 0.25 mL/min into preheated aqueous phase maintained at 60 $^0$C, where vaporization leads to formation of unilamellar vesicles.

**Hand shaking**

This is also known as thin film hydration technique. In this method, a mixture of surfactant and cholesterol are dissolved in volatile organic solvent such as diethyl ether, chloroform, methyl alcohol, in a round bottom flask. The organic solvent is removed by using rotary evaporator at room temperature, which leaves behind a thin layer of solid deposited on wall of the flask. After gentle agitation, the surfactant is rehydrated with aqueous phase at 0-60 $^0$C. This method forms multilamellar noisomes.

Thermo sensitive noisomes are prepared at 60 $^0$C by evaporating organic solvent and leaving a thin film of lipid of on the wall of rotary flask evaporator. The aqueous phase containing drug is added slowly by shaking at room temperature followed by sonication.

**Reverse phase evaporation**

The surfactant is dissolved in choloroform and phosphate buffer is added, followed by emulsification and sonication under reduced pressure.

**Bubbling of inert gas**

It is a novel technique for the preparation of niosomes and liposomes without use of organic solvents. The bubbling units consist of round bottom flask with three necks. The first neck is meant for water cooled reflux, the second neck is for thermometer, and the third neck is for nitrogen gas supply. Surfactant and cholesterol are dispersed together in buffer (pH 7.4) at 70 $^0$C for 15 sec with high shearing homogenizer and immediately nitrogen gas at 70 $^0$C is bubbled, which forms vesicles.

**Sonication**

Niosomes are prepared by using sonication method, in which mixture of surfactant and cholesterol is dispersed in aqueous phase in a vial. Then this dispersion is subjected to ultrasonic vibration for 30 min at 60$^0$C, which leads to formation of multilamellar vesicles.

**Micro fluidization**

It technique is based on submerged jet containing micro channels with interaction chamber in which two fluidized streams interact with each other at ultra velocities. The impingement of thin liquid sheet along with common front are arranged in such a way that the energy supplied for the formation of niosomes remains same. This forms unilamellar niosomes with better reproducibility and size uniformity.

**Multiple membrane extrusion**

Niosomes can be chemically prepared by extrusion through polycarbonate membrane (0.1µm nucleophore) by using C16 G12. By this method, a desired size of the vesicles can be obtained.

**Transmembrane pH gradient drug uptake**

Surfactant and cholesterol are dispersed into chloroform in a round bottom flask followed by solvent evaporation under reduced pressure leading to the formation of thin film on the wall of the flask. This film is hydrated with 300 mM citric acid by using vortex mixing. This forms multilamellar vesicles, which are frozen and sonicated to get niosomes. To this niosomal suspension, aqueous solution of drug containing is added and mixed by vortexing, after which, phosphate buffer treatment is done to maintain pH between 7.0 and 7.2 and the mixture is heated at 60$^0$C for 10 minutes to produce vesicles[10].

**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 is 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[11].

**SEPARATION OF UNENTRAPPED DRUG**

- **Dialysis**

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

- **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.

- **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[12].

**CHARACTERIZATIONS OF NIOSOMES:**

**1. 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.

**2. 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.

**3. 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.

**4. Number of lamellae**

It is determined by using NMR spectroscopy, small angle X-ray scattering and electron microscopy.

**5. Membrane rigidity**

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

**6. Bilayer formation**

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

**7. Stability study**

Stability studies are done by storing niosome at two different conditions, usually $4\pm1^0$C and 25±2 0C. Formulation Size, shape and number of vesicles per cubic mm can be assessed before and after storing for 30 days. After 15 and 30 days, residual drug can also be measured. Light microscope is used for determination of size of vesicles and the numbers of vesicles per cubic mm is measured by haemocytometer. Number of niosomes per cubic mm = Total number of niosomes x dilution factor x 400.Total number of small squares counted[13].

**Table 1: List of Drugs formulated as Niosomes[14]**

| Routes of drug administration | Examples of Drugs |
|---|---|
| **Intravenous route** | Doxorubicin, Methotrexate, Sodium Stibogluconate, Iopromide, Vincristine, Diclofenac Sodium, Flurbiprofen, Centchroman, Indomethacin, Colchicine,Rifampicin, Tretinoin,Transferrin and Glucose ligands, Zidovudine, Insulin,Cisplatin, Amarogentin, Daunorubicin, Amphotericin B, 5-Fluorouracil, Camptothecin, Adriamycin, CytarabineHydrochloride |
| **Peroral route** | DNA vaccines, Proteins, Peptides, Ergot, Alkaloids, Ciprofloxacin, Norfloxacin, Insulin |
| **Transdermal route** | Flburiprofen, Piroxicam, Estradiol Levonorgestrol,Nimesulide,Dithranol, Ketoconazole, Enoxacin, Ketorolac |
| **Ocular route** | Timolol Maleate, Cyclopentolate |
| **Nasal route** | Sumatriptan, Influenza Viral Vaccine |
| **Inhalation** | A l l - t r ans retinoic acids |

**Table2: Differences between Liposomes and Niosomes**[13]

| S. No | Liposomes | Niosomes |
|---|---|---|
| 1 | More expensive. | Less expensive. |
| 2 | Phospholipids are prone to oxidative degradation | But non-ionic surfactants are stable toward this. |
| 3 | Required special method for storage, handling and purification of phospholipids. | No special methods are required for such formulations comparatively. |
| 4 | Phospholipids may be neutral or charged. | Non-ionic surfactants are uncharged. |

## APPLICATIONS OF NIOSOMES

- **Leishmaniasis therapy**
  Leishmaniasis is a disease caused by parasite genus Leishmania which invades the cells of the liver and spleen. Most Commonly prescribed drugs for the treatment are the derivatives of antimony – which, in higher concentrations – can cause liver, cardiac and kidney damage. Use of niosomes as a drug carrier showed that it is possible to administer the drug at high levels without the triggering the side effects, and thus showed greater efficacy in treatment[10].
- **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[15].
- **Niosome as a carrier for Haemoglobin**
  Niosomal suspension shows a visible spectrum super imposable onto that of free haemoglobin so can be used as a carrier for haemoglobin. Vesicles are also permeable to oxygen and haemoglobin dissociation curve can be modified similarly to non-encapsulated Hemoglobin[12].
- 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 tumours known to metastasize to the liver and spleen and in parasitic infestation of liver[1].
- **Neoplasia**
  Doxorubicin, the anthracyclic antibiotic with broad spectrum antitumor activity, shows a dose dependant irreversible cardio toxic effect. Niosomal delivery of this drug to mice bearing S-180 tumour 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 tumour bearing mice resulted in total regression of tumour and also higher plasma level and slower elimination[12].
- **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[15].
- **Antibiotics**
  The feasibility of using non-ionic surfactant vesicles (niosomes) as carriers for the ophthalmic controlled delivery of a water soluble local antibiotic, gentamicin sulphate was investigated and the results demonstrated niosomes to be promising ophthalmic Carriers for the topical application of gentamicin sulphate. Preparation and evaluation of Cefpodoxime proxetil niosomes showed controlled release of 65.25% for 24 hours with zero order kinetics, thus reducing the chances of dose dumping during usage. The bioavailability of Cefuroxime axetil which is just 25% was improved by preparing niosomes. The prepared niosomes showed good entrapment efficiency and in vitro release and also were stable in bile salts[4].

- **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 pilo sebaceous glands[16].

- **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. 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[1].

- **Ophthalmic drug delivery**

  From ocular dosage form like ophthalmic solution, suspension and ointment it is difficult to achieve excellent bioavailability of drug due to the tear production, impermeability of corneal epithelium, non-productive absorption and transient residence time. But niosomal and liposomal delivery systems can be used to achieve good bioavailability of drug. Bioadhesive-coated niosomal formulation of acetazolamide prepared from span 60, cholesterolstearylamine or dicetyl phosphate exhibits more tendencies for reduction of intraocular pressure as Compared to marketed formulation (Dorzolamide)[1].

## CONCLUSION

It is obvious that niosome appears to be a well preferred drug delivery system over liposome as niosome being stable and economic. Also niosomes have great drug delivery potential for targeted delivery of anti-cancer, anti-infective agents. They 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 multi-environmental structure. Niosomes are considered to be better candidates for drug delivery as compared to liposomes due to various factors like cost, stability etc.

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