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REVIEW ARTICLE

Niosomes: A Novel Drug Delivery System

V. Pola Chandu[1*], A.Arunachalam[1], S.Jeganath[2], K.Yamini[1], K.Tharangini[1], G.Chaitanya[1]

[1]*Department of Pharmaceutics, A.M.Reddy Memorial College of Pharmacy, Narasaraopet, Guntur, A.P, India.*
[2]*Department of Pharmaceutics, K.K. College of Pharmacy, Chennai, Tamilnadu, India.*

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Abstract

Niosome are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or their lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Noisome are promising vehicle for drug delivery and being non-ionic; and Niosomes are biodegradable, biocompatible non-immunogenic and exhibit flexibility in their structural characterization. Niosomes have been widely evaluated for controlled release and targeted delivery for the treatment of cancer, viral infections and other microbial diseases. Niosomes can entrap both hydrophilic and lipophilic drugs and can prolong the circulation of the entrapped drug in body. Encapsulation of drug in vesicular system can be predicted to prolong the existence of drug in the systemic circulation and enhance penetration into target tissue, perhaps reduce toxicity if selective uptake can be achieved. This review article focuses on the advantages, Disadvantages, preparation methods, factors affecting, characterizations, invitro methods, drug release kinetics, and applications of noisome.

INTRODUCTION

Paul Ehrlich, in 1909, initiated the development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Drug targeting can be defined as the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with non target tissue[1]. In noisome, the vesicles forming amphiphile is a non-ionic surfactant such as Span-60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate. The first report of non-ionic surfactant vesicles came from the cosmetic applications devised by L'Oreal. The concept of incorporating the drug into noisome for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. Various types of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parental, etc.

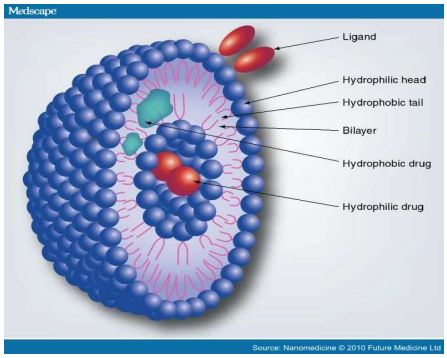
DEFINITIONS

A niosome is a non-ionic surfactant-based liposome. Niosomes are formed mostly by cholesterol incorporation as an excipient. Other excipients can also be used. Niosomes have more penetrating capability than the previous preparations of emulsions. They are structurally similar to liposomes in having a bilayer, however, the materials used to prepare niosomes make them more stable and thus niosomes offer many more advantages over liposomes[1, 2].The sizes of niosomes are microscopic and lie in nanometric scale. The particle size ranges from 10nm-100nm.

STRUCTURE OF NIOSOME

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 anionic surfactant such as dicetyl phosphate, which also helps in stabilizing the vesicle.[3, 4]

Figure 1. Structure of Niosome



ADVANTAGES OF NIOSOMES [5- 8]

1. Use of niosomes in cosmetics was first done by L'Oreal as they offered the following advantages
2. The vesicle suspension being water based offers greater patient compliance over oil based systems

▼ To whom correspondence should be addressed:
V.Pola chandu,
E-Mail address: chinni.chandu91@gmail.com
Tel.: +919030287109

3. Since the structure of the niosome offers place to accommodate hydrophilic, lipophilic as well as amphiphilic drug moieties, they can be used for a variety of drugs.
4. The characteristics such as size, lamellarity etc. of the vesicle can be varied depending on the requirement.
5. The vesicles can act as a depot to release the drug slowly and offer a controlled release.

Other advantages of Niosomes are

1. They are osmotically active and stable.
2. They increase the stability of the entrapped drug
3. Handling and storage of surfactants do not require any special conditions
4. Can increase the oral bioavailability of drugs
5. Can enhance the skin penetration of drugs
6. They can be used for oral, parenteral as well topical.
7. The surfactants are biodegradable, biocompatible, and non-immunogenic.
8. 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 drug.
9. The niosomal dispersions in an aqueous phase can be emulsified in a non-aqueous phase to control the release rate of the drug and administer normal vesicles in external non-aqueous phase.

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:[9-11]

The two major components used for the preparation of niosomes are,

1. Cholesterol
2. Nonionic surfactants

1. Cholesterol

Cholesterol is used to provide rigidity and proper shape, conformation to the niosomes preparations.

2. Nonionic surfactants

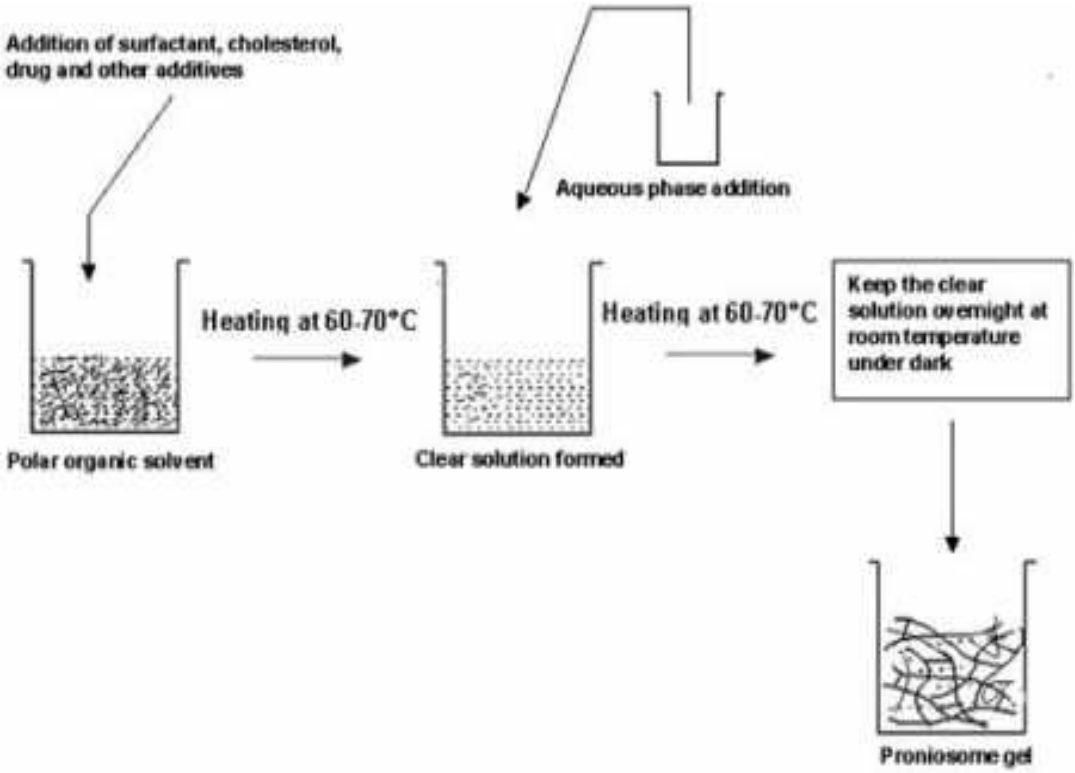
The role surfactants play a major role in the formation of niosomes. The following non-ionic surfactants are generally used for the preparation of niosomes.

E.g.

- Spans (span 60, 40, 20, 85, 80)
- Tweens (tween 20, 40, 60, 80) and
- Brijs (brij 30, 35, 52, 58, 72, 76).

The non ionic surfactants possess a hydrophilic head and a hydrophobic tail.[12]

Figure 2. Formation of Proniosomes



FORMATION OF NIOSOMES FROM PRONIOSOMES [13]

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.

$$T > Tm$$

Where,

T = Temperature

Tm = mean phase transition temperature

Blazek-Walsh A.I. et al has 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.

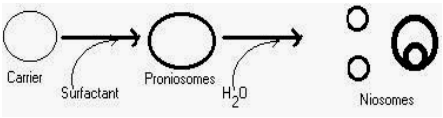


Figure 3. Formation of Niosomes from Proniosomes

PREPARATION METHODS OF NIOSOMES [14-20]

The preparation methods should be chosen according to the use of the niosomes, since the preparation methods influence the number of bilayers, size, size distribution, and entrapment efficiency of the aqueous phase and the membrane permeability of the vesicles.

A. Ether injection method

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.

Preparation steps

Surfactant is dissolved in diethyl ether

↓

Then injected in warm water maintained at 60°C through a 14 gauze needle

↓

Ether is vaporized to form single layered niosomes.

B. Hand shaking method (thin film hydration technique):

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl either, 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.

Preparation steps:

Surfactant + cholesterol + solvent

↓

Remove organic solvent at Room temperature

↓

Thin layer formed on the Walls of flask

↓

Film can be rehydrated to form multilamellar Niosomes.

C. Sonication Method

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.

Preparation steps

Drug in buffer + surfactant/cholesterol in 10 ml

↓

Above mixture is sonicated for 3 mints at 60°C using titanium probe yielding niosomes.

D. Micro fluidization Method

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.[21]

Preparation steps

Two ultra high speed jets inside interaction chamber

↓

Impingement of thin layer of Liquid in micro channels

↓

Formation of uniform Niosomes.

E. 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 upto 8 passages. It is a good method for controlling noisome size. [21]

F. Reverse Phase Evaporation Technique (REV)

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 noisome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes. [22]

Raja Naresh et al. have reported the preparation of Diclofenac Sodium niosomes using Tween 85 by this method.

Preparation steps

Cholesterol + surfactant dissolved in ether + chloroform
↓
Sonicated at 5°c and again sonicated after adding PBS
↓
Drug in aqueous phase is added to above mixture
↓
Viscous niosomes suspension is diluted with PBS
↓
Organic phase is removed at 40°C at low pressure
↓
Heated on a water bath for 60°C for 10 mints to yield niosomes.

G.Trans membranes PH gradient (inside acidic) Drug Upake Process: or Remote Loading Technique

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 firm is hydrated with 300mM citric acid (PH 4.00 by vertex mixing. The multilamellar vesicles are frozen and shared 3 times and later sonicated. To this niosomal suspension. Aqueous solution containing 10 mg ml of drug is added and vortexes. 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 so give niosomes.[23]

Preparation steps

Surfactant + cholesterol in chloroform
↓
Solvent is evaporated under reduced pressure
↓
Thin film is deposited on the walls of RBF
↓
Hydrated with citric acid by vortex mixing
↓
3 cycles of freezing and thawing then sonication
↓
Addition of aqueous drug solution and vortoxing
↓
pH raised to 7.0-7.2 by 1M disodium phosphate
↓
RBF as bubbling unit with three necks in water bath
↓
Reflux, thermometer and nitrogen supply by three necks
↓
Cholesterol + surfactant dispersed in buffer pH 7.4 at 70°C
↓
Above dispersion is homogenized for 15 sec and then bubbled with nitrogen gas at 70°c
↓
To get niosomes.

H. The Bubble Method

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.

Separation of Unentrapped Drug

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 dialysis tubing against suitable dissolution medium at room temperature. The samples are withdrawn from the medium at suitable time intervals, centrifuged and analyzed for drug content using suitable method (U.V. spectroscopy, HPLC etc).

2. **Gel Filtration**

The unentrapped drug is removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and eluted with suitable mobile phase and analyzed with suitable analytical techniques.

3. **CENTRIFUGATION:**

The proniosome derived 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.

Factors affecting niosomes formulation

1. Drug

Entrapment of drug in niosomes increases vesicle size, probably by interaction of solute with surfactant head groups, increasing the charge and mutual repulsion of the surfactant bilayers, thereby increasing vesicle size. In polyoxyethylene glycol (PEG) coated vesicles; some drug is entrapped in the long PEG chains, thus reducing the tendency to increase the size. The hydrophilic lipophilic balance of the drug affects degree of entrapment.

2. Amount and type of surfactant

The mean size of niosomes increases proportionally with increase in the HLB surfactants like Span 85 (HLB 1.8) to Span 20 (HLB 8.6) because the surface free energy decreases with an increase in hydrophobicity of surfactant.

The bilayers of the vesicles are either in the so-called liquid state or in gel state, depending on the temperature, the type of lipid or surfactant and the presence of other components such as cholesterol. In the gel state, alkyl chains are present in a well-ordered structure, and in the liquid state, the structure of the bilayers is more disordered. The surfactants and lipids are characterized by the gel-liquid phase transition temperature (TC). Phase transition temperature (TC) of surfactant also effects entrapment efficiency i.e. Span 60 having higher TC, provides better entrapment.

3. Cholesterol content and charge

Inclusion of cholesterol in niosomes increased its hydrodynamic diameter and entrapment efficiency. In general, the action of cholesterol is two folds; on one hand, cholesterol increases the chain order of liquid-state bilayers and on the other, cholesterol decreases the chain order of gel state bilayers. At a high cholesterol concentration, the gel state is transformed to a liquid-ordered phase.

An increase in cholesterol content of the bilayers resulted in a decrease in the release rate of encapsulated material and therefore an increase of the rigidity of the bilayers obtained. Presence of charge tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle structure and leads to greater overall entrapped volume.

4. Resistance to osmotic stress

Addition of a hypertonic salt solution to a suspension of niosomes brings about reduction in diameter. In hypotonic salt solution, there is initial slow release with slight swelling of vesicles probably due to inhibition of eluting fluid from vesicles, followed by faster release, which may be due to mechanical loosening of vesicles structure under osmotic stress.

5. Membranes Composition

The stable niosomes can be prepared with addition of different additives along with surfactants and drugs. Niosomes formed have a number of morphologies and their permeability and stability properties can be altered by manipulating membrane characteristics by different additives. In case of polyhedral niosomes formed from C16G2, the shape of these polyhedral noisome remains unaffected by adding low amount of solulan C24 (cholesterol poly-24- oxyethylene ether), which prevents aggregation due to development of stearic unhydrance. In contrast spherical Niosomes are formed by C16G2: cholesterol: solution (49:49:2). The mean size of niosomes is influenced by membrane composition such as Polyhedral niosomes formed by C16G2: solution C24 in ration (91:9) having bigger size (8.0 ± 0.03 mm) than spherical/tubular niosomes formed by C16G2: cholesterol: solution C24 in ratio (49:49:2) (6.6± 0.2 mm). Addition of cholesterol molecule to niosomal system provides rigidity to the membrane and reduces the leakage of drug from noisome.

CHARACTERIZATION OF NIOSOMES [24-28]

a. Measurement of Angle of repose

The angle of repose of dry niosomes powder was measured by a funnel method. The niosomes powder was poured into a funnel which was fixed at a position so that the 13mm outlet orifice of the funnel is 5cm above a level black surface. The powder flows down from the funnel to form a cone on the surface and the angle of repose was then calculated by measuring the height of the cone and the diameter of its base.

b. Scanning electron microscopy

Particle size of niosomes is very important characteristic. The surface morphology (roundness, smoothness, and formation of aggregates) and the size distribution of niosomes were studied by Scanning Electron Microscopy (SEM). Niosomes were sprinkled on to the double- sided tape that was affixed on aluminum stubs. The aluminum stub was placed in the vacuum chamber of a scanning electron microscope (XL 30 ESEM with EDAX, Philips, Netherlands). The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 torr, acceleration voltage: 30.00 KV) XL 30, (Philips, Netherlands).

c. Optical Microscopy

The niosomes were mounted on glass slides and viewed under a microscope (Medilux-207RII, Kyowa-Getner, Ambala, India) with a magnification of 1200X for morphological observation after suitable dilution. The photomicrograph of the preparation also obtained from the microscope by using a digital SLR camera.

d. Measurement of vesicle size

The vesicle dispersions were diluted about 100 times in the same medium used for their preparation. Vesicle size was measured on a particle size analyzer (Laser diffraction particle size analyzer, Sympatec, Germany). The apparatus consists of a He-Ne laser beam of 632.8 nm focused with a minimum power of 5 mW using a Fourier lens [R-5] to a point at the center of multielement detector and a small volume sample holding cell (Su cell). The sample was stirred using a stirrer before determining the vesicle size. Hu C. and Rhodes 7 in 1999 reported that the average particle size of niosomes derived niosomes is approximately 6µm while that of conventional niosomes is about 14µm.

e. Entrapment efficiency

Entrapment efficiency of the niosomal dispersion in can be done by separating the unentrapped drug 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,

$$\text{Percentage entrapment} = \frac{\text{Total drug} - \text{Diffused drug}}{\text{Total drug}} \times 100$$

f. Osmotic shock

The change in the vesicle size can be determined by osmotic studies. Niosomes formulations are incubated with hypotonic, isotonic, hypertonic solutions for 3 hours. Then the changes in the size of vesicles in the formulations are viewed under optical microscopy.

g. Stability studies

To determine the stability of niosomes, the optimized batch was stored in airtight sealed vials at different temperatures. Surface characteristics and percentage drug retained in niosomes and niosomes derived from proniosomes were selected as parameters for evaluation of the stability, since instability of the formulation would reflect in drug leakage and a decrease. In the percentage drug retained. The niosomes were sample at regular intervals of time (0,1,2,and 3months),observed for color change, surface characteristics and tested for the percentage drug retained

after being hydrated to form niosomes and analyzed by suitable analytical methods(UV spectroscopy, HPLC methods etc).

h. Zeta potential analysis

Zeta potential analysis is done for determining the colloidal properties of the prepared formulations. The suitably diluted niosomes derived from pronoisome dispersion was determined using zeta potential analyzer based on electrophoretic light scattering and laser Doppler velocimetry method (Zeta plus™, Brookhaven Instrument Corporation, New York, USA). The temperature was set at 25°C. Charge on vesicles and their mean zeta potential values with standard deviation of measurements were obtained directly from the measurement.

Table 1. Method for evaluation of niosomes

EVALUATION PARAMETER	METHOD
Morphology	SEM, TEM, freeze fracture technique
Size distribution, polydispersity index	Dynamic light scattering particle size analyzer
Viscosity	Ostwald viscometer
Membrane thickness	X-ray scattering analysis
Thermal analysis	DSC
Turbidity	UV-Visible diode array spectrophotometer
Entrapment efficacy	Centrifugation, dialysis, gel chromatography
In-vitro release study	Dialysis membrane
Permeation study	Franz diffusion cell

In-vitro methods for niosomes

In vitro drug release can be done by

- Dialysis tubing
- Reverse dialysis
- Franz diffusion cell

Dialysis tubing

Muller et al, in 2002 studied in vitro drug release could be achieved by using dialysis tubing. The niosomes is placed in prewashed dialysis tubing which can be hermetically sealed. The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, centrifuged and analyzed for drug content using suitable method (U.V. spectroscopy, HPLC etc). The maintenance of sink condition is essential.

Reverse dialysis

In this technique a number of small dialysis as containing 1ml of dissolution medium are placed in proniosomes. The proniosomes are then displaced into the dissolution medium. The direct dilution of the proniosomes is possible with this method; however the rapid release cannot be quantified using this method.

Franz diffusion cell

The in vitro diffusion studies can be performed by using Franz diffusion cell. Proniosomes is placed in the donor chamber of a Franz diffusion cell fitted with a cellophane membrane. The proniosomes is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, and analyzed for drug content using suitable method (U.V spectroscopy, HPLC, etc) .the maintenance of sink condition is essential.

Applications of niosomes [29-32]

The application of niosomes technology is widely varied and can be used to treat a number of diseases. The following are a few uses of niosomes which are either proven or under research.

- It is used as Drug Targeting.
- It is used as Anti-neoplastic Treatment i.e. Cancer Disease.
- It is used as Leishmaniasis i.e. Dermal and Mucocutaneous infections e.g. Sodium stibogluconate.
- It is used act as Delivery of Peptide Drugs.
- It is used in Studying Immune Response.
- Niosomes as Carriers for Hemoglobin.
- Transdermal Drug Delivery Systems Utilizing Niosomes
- It is used in Ophthalmic drug delivery

Other Applications: Niosomes can also be utilized for sustained drug release and localized drug action to greatly increase the safety and efficacy of many drugs. Toxic drugs which need higher doses can possibly be delivered safely using niosomal encapsulation.

Table 2. Route of application of niosomes drugs

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, cytarabine hydrochloride
Peroral route	DNA vaccines, proteins, peptides, ergot alkaloids, ciprofloxacin, norfloxacin, insulin
Transdermal route	Flurbiprofen, piroxicam, estradiol, levonorgestrol, nimesulide, dithranol, ketoconazole, enoxacin, ketorolac
Ocular route	Timolol maleate, cyclopentolate
Nasal route	Sumatriptan, influenza viral vaccine
Inhalation	All-trans retinoic acids

MARKETED PRODUCTS

Lancôme has come out with a variety of anti-ageing products which are based on niosomes Formulations. L'Oreal is also conducting research on anti-ageing cosmetic products. Niosomes Preparation in the Market is – **Lancôme** (www.lancome.com)

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