International Journal of Research in Pharmacy and Pharmaceutical Sciences
ISSN: 2455-698X; Impact Factor: RJIF 5.22
Received: 18-01-2019; Accepted: 23-02-2019
www.pharmacyjournal.in
Volume 4; Issue 2; March 2019; Page No. 73-78

Niosomes: As novel drug delivery system

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Abstract
Niosomes are formations of vesicles by hydrating mixture of cholesterol and non-ionic surfactants. Different novel approaches used for delivering these drugs include liposomes, microspheres, nanotechnology, micro emulsions, antibody-loaded drug delivery, magnetic microcapsules, implantable pumps and niosomes. Niosomes and liposomes are equiactive in drug delivery potential and both increase drug efficacy as compared with that of free drug. Niosomes are preferred over liposomes because the former exhibit high chemical stability and economy.
The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic purpose may offer several advantages. They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells. This article focuses on the recent advances in niosomal drug delivery, potential advantages over other delivery systems, formulation methods, methods of characterization and the current research in the field of niosomes. 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. Drug delivery potential of niosome can enhance by using novel concepts like proniosomes, discomes and aspasome. Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant. Thus these areas need further exploration and research so as to bring out commercially available niosomal preparation.

Keywords: niosomes, defination and structure, advantages, application, liposomes vs niosomes

Introduction [3, 4, 5]

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.
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.
In recent years, niosomes have been extensively studied for their potential to serve as a carrier for the delivery of drugs, antigens, hormones and other bioactive agents. Besides
this, niosome has been used to solve the problem of insolubility, instability and rapid degradation of drugs.

Defination [6, 7]

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. The sizes of niosomes are microscopic and lie in
nanometric scale. The particle size ranges from 10nm-100nm 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.

Advantages of Niosomes [8]

- The vesicles may act as a depot, releasing the drug in a controlled manner.
- They are osmotically active and stable, and also they increase the stability of entrapped drug.
- The surfactants used are biodegradable, biocompatible and non-immunogenic.
- They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
- They can be made to reach the site of action by oral, parenteral as well as topical routes.
- The vesicles may act as a depot, releasing the drug in a controlled manner.
- Due to the unique infrastructure consisting of hydrophilic,
- Niosomal dispersion in an aqueous phase can be

Components of Niosomes [9]

Niosomes mainly contains following types of components:

1. Non-ionic 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. – 1. Spans (span 60, 40, 20, 85, 80)
2. Tweens (tween 20, 40, 60, 80)
3. Brijs (brij 30, 35, 52, 58, 72, 76).
4. Alkyl amide (*e.g.* galactosidesand, glucosides)

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

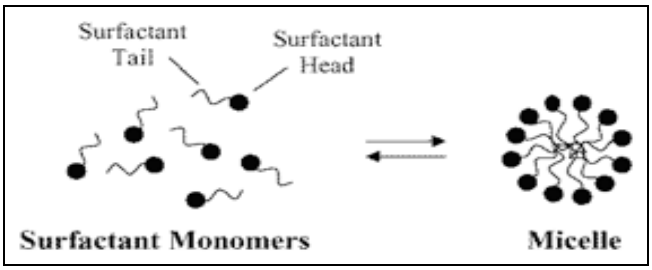

Fig 1: Non ionic surfactant

2. Cholesterol
Cholesterol is used to provide rigidity and proper shape, conformation to the niosomes preparations. Cholesterol is a steroid derivative, which is mainly used for the formulation of niosomes. Although it may not show any role in the formation of bilayer, its importance in formation of niosomes and manipulation of layer characteristics can not be discarded.

3. Charged Molecule
Some charged molecules are added to niosomes to increase stability of niosomes by electrostatic repulsion which prevents coalescence. The negatively charged molecules used are diacetyl phosphate (DCP) and phosphatidic acid. Similarly, stearylamine (STR) and stearyl pyridinium chloride are the well known positively charged molecules used in niosomal preparations. These charged molecules are used mainly to prevent aggregation of niosomes

Method of Preperation [11, 12, 13, 14, 15]
Some important methods that are used to formulate niosomes are as follows:

1. Ether Injection Method
In this method a solution containing a particular ratio of cholesterol and surfactant in ether is slowly injected into the preheated aqueous solution of the drugs maintained at 60°C through the specified gauze needle. The vaporization of ether leads to the formation of vesicles of the surfactants containing drug. Alternatively, fluorinated hydrocarbons have been used as a substitute for ether for thermolabile drugs, as they vaporize at a much lower temperature. The size of niosomes obtained by this method varies between 50 - 1000 mm.

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

Fig 2: Ether Injection Method

2. Hand Shaking Method (Thin film hydration technique)
Firstly cholesterol and surfactant are dissolved in some organic solvent (like ether, chloroform, benzene *etc*.). Thereafter, solvent is evaporated under reduced pressure in a vacuum evaporator in a round bottom flask which then leaves the mixture of solid surfactant and cholesterols on the walls of round bottom flask. This layer was then rehydrated with aqueous solution containing drug with continuous shaking which results in swelling of surfactant layer. Swelled amphiphiles eventually folds and form vesicles which entrap the drugs.

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

Fig 3: Hand Shaking Method

3. Sonication Method
In this method at first the surfactant-cholesterol mixture is dispersed in the aqueous phase.This dispersion is then probe sonicated for 10 min at 60°C, which leads to the formation of multilameller vesicles (MLV). These MLVs are further ultrasonicated either by probe sonicator or bath sonicator, which in turn leads to the formation of unilameller vesicles.

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.

Fig 4: Sonication Method

4. Micro fluidization Method
In this method two fluidized streams (one containing drug and the other surfactant) interact at ultra high velocity, in precisely defined micro channels within the interaction chamber in such a way that the energy supplied to the system remains in the area of niosomes formations. This is called submerged jet principle. It results in better uniformity, smaller size and reproducibility in the formulation of niosomes**.**

Preparation steps

Two ultra-high speed jets inside interaction chamber
↓
Impingement of thin layer of Liquid in micro channels
↓
Formation of uniform Niosomes.

Fig 5

5. Reverse Phase Evaporation Method
In this method the solution of cholesterol and surfactant is prepared in a mixture of ether and chloroform (1 : 1). To this, the aqueous solution of drug is added and sonicated at temperature 4 - 5°C. The solution thus obtained is further sonicated after addition of phosphate buffer saline (PBS) resulting in the formation of gel. Thereafter temperature is raised to 40 °C and pressure is reduced for the removal of solvent. The PBS is added again and heated on water bath at 60 °C for 10 min to yield niosomes.

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.

Fig 6

6. Extrusion Method

In this method, a mixture of cholesterol and diacetyl phosphate is prepared and then solvent is evaporated using rotary vacuum evaporator to leave a thin film. The film is then hydrated with aqueous drug solution and the suspension thus obtained is extruded through the polycarbonate membrane (mean pore size 0.1m m) and then placed in series up to eight passages to obtain uniform size niosomes.

7. The "Bubble" Method

It is one step technique by which liposomes and niosomes are prepared without the use of organic solvents. Round bottomed flask is used as bubbling unit with its 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. At 70°C Cholesterol and surfactant are dispersed together in the buffer (pH 7.4) and mixed with high shear homogenizer for 15 seconds and immediately afterwards "bubbled" at 70°C using nitrogen gas.

Separation of Unentrapped Drug [16, 17, 18, 19]

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.

Types of Niosomes [20]

The niosomes have been classified as a function of the number of bilayer or as a function of size. The various types of niosomes are follows.

1. **According to the nature of lamellarity**
   - Multilamellar vesicles (MLV) 1 - 5 μm in size.
   - Large unilamellar vesicles (LUV) 0.1 - 1 μm in size
   - Small unilamellar vesicles (SUV) 25 - 500 nm in size.
2. **According to the size**
   - Small niosomes (100 nm – 200 nm)
   - Large niosomes (800 nm – 900 nm)
   - Big niosomes (2 μm – 4 μm)

Various types of niosomes are as described below

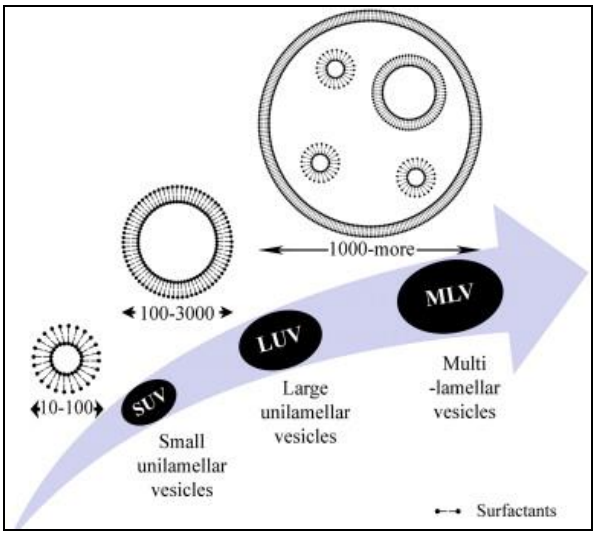

Fig 7: Types of Niosome

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. 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.

Characterisation of Niosomes [23, 24]

1. **Size-** Shape of niosomal vesicles is assumed to be spherical, and various techniques can be used for determination of their mean diameter like laser light scattering method, electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation microscopy and optical microscopy and freeze fracture electron microscopy.
2. **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.

3. **Bilayer formation, Membrane rigidity and Number of lamellae-** Bilayer vesicle formation by assembly of non-ionic surfactants is characterized by X-cross formation under light polarization microscopy and membrane rigidity can be measured by means of mobility of fluorescence probe as function of temperature. NMR spectroscopy, small angle X-ray scattering and electron microscopy are used to determine the no of lamellae.
4. **Entrapment efficiency -** As described above after preparing niosomal dispersion, unentrapped drug is separated by dialysis, centrifugation or gel filtration and/ or complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 is done for the estimation of the drug remained entrapped in niosomes and then analyzing the resultant solution by appropriate assay method for the drug.

   Where, Entrapment efficiency (EE) can be defined by

   Entrapment efficiency (EE) =

   (Amount entrapped/ total amount) x100.

***In vitro* release study [22, 23]**

1. **Dialysis:** With the help of dialysis tubing *in vitro* release rate study can be done. A dialysis sac was washed and soaked in distilled water. The suspension of vesicle was pipetted intoa bag made up of the tubing and then sealed and placed in 200 ml buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. The buffer was analysed at various time intervals, for the drug content by an appropriate assay method.
2. **Reverse dialysis:** In this technique, niosomes are placed in a number of small dialysis tubes containing 1 mL of dissolution medium and the niosomes are then displaced from the dissolution medium.
3. **Franz diffusion cell:** In a Franz diffusion cell, the cellophane membrane is used as the dialysis membrane. The niosomes are dialyzed through a cellophane membrane against suitable dissolution medium at room temperature. The samples are withdrawn at suitable time intervals and analyzed for drug content37.

***In vivo* release study [23]:** For *In vivo* study niosomal suspension was injected intravenously (through tail vein) to the albino rats using appropriate disposal syringe. These rats were subdivided into groups.

Applications [27, 28. 29]

Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Few of their therapeutic applications are as follows:

1. **Targeting of bioactive agents**
   a) **To reticulo-endothelial system (RES)-**The vesicles occupy preferentially to the cells of RES. It is due to circulating serum factors known as opsonins, which mark them for clearance. Such localized drug accumulation has, however, been exploited in treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of liver.
   b) **To organs other than reticulo-endothelial system (RES)-** By use of antibodies, carrier system can be directed to specific sites in the body. Immunoglobulins seem to have affection to the lipid surface, thus providing a convenient means for targeting of drug carrier. Many cells have the mintrinsic ability to recognize and bind particular carbohydrate determinants and this property can be used to direct carriers system to particular cells.
2. **Neoplasia-** The anthracyclic antibiotic Doxorubicin, with broad spectrum anti tumour activity, shows a dose dependant irreversible cardio toxic effect. The half-life of the drug increased by its niosomal entrapment of the drug and also prolonged its circulation and its metabolism altered. E.g. Methotrexate entrapped in niosomes if administered intravenously to S-180 tumour bearing mice results in totalregression of tumour and also higher plasma level and slower elimination.
3. **Delivery of peptide drugs-** Niosomal entrapped oral delivery of 9-desglycinamide, 8- arginine vasopressin was examined in an in-vitro intestinal loop model and reported that stability of peptide increased significantly.
4. **Immunological applications of niosomes**- For studying the nature of the immune response provoked by antigens niosomes have been used. Niosomes have been reported as potent adjuvant in terms of immunological selectivity, low toxicity and stability.
5. **Niosome as a carrier for Hemoglobin-** Niosomal suspension shows a visible spectrum superimposable onto that of free hemoglobin so can be used as a carrier for hemoglobin. Vesicles are also permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin.
6. **Transdermal delivery of drugs by niosomes-** An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes as slow penetration of drug through skin is the major drawback of transdermal route of delivery for other dosage forms.
7. **Diagnostic imaging with niosomes**- Niosomal system can be used as diagnostic agents. Conjugated niosomal formulation of gadobenate dimeglcemine with [N-palmitoylglucosamine(NPG)], PEG 4400, and both PEG and NPG exhibit significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging.
8. **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. Bioadhesive-coated niosomal formulation of acetazolamide prepared from span 60,cholesterol stearylamine or dicetyl phosphate exhibits more tendencies for reduction of intraocular pressure as compared to marketed formulation (Dorzolamide).
9. **Other Applications**
   a) **Sustained Release-** Drugs with low therapeutic index and low water solubility could be maintained in the circulation via niosomal encapsulation, through niosomes sustained release action can be obtained. Azmin *et al.* 30 suggested the role of liver as a depot for methotrexate after niosomes are taken

up by the liver cells.

b) Localized Drug Action- To achieve localized drug action, niosomal dosage form is one of the approaches because of the size of niosomes and their low penetrability through epithelium and connective tissue the drug localized at the site of administration. This results in enhancement of efficacy and potency of the drug and also reduces its systemic toxic effects e.g. Antimonials encapsulated within niosomes are taken up by mononuclear cells resulting in localization of drug, increase in potency and hence decrease both in dose and toxicity.

Routes of Drug Administration and Examples of Drugs [30]

1. **Intravenous route:** Doxorubicin, Methotrexate, Sodium Stibogluconate, Iopromide, Vincristine, Diclofenac Sodium, Flurbiprofen, Centchroman, Indomethacin, Colchicine, Rifampicin, Tretinoin, Transferrin and Glucose ligands, Zidovudine, Insulin, Cisplatin, Amarogentin, Amphotericin B, 5-Fluorouracil, Camptothecin, Adriamycin, Cytarabine Hydrochloride
2. **Peroral route:** DNA vaccines, Proteins, Peptides, Ergot, Alkaloids, Ciprofloxacin, Norfloxacin, Insulin
3. **Transdermal route:** Flurbiprofen, Piroxicam, Estradiol Levonorgestrol, Nimesulide, Dithranol, Ketoconazole, Enoxacin, Ketorolac
4. **Ocular route:** Timolol Maleate, Cyclopentolate
5. **Nasal route:** Sumatriptan, Influenza Viral Vaccine
6. **Inhalation:** All trans retinoic acids

Conclusion

Neosomal drug delivery system is one of the examples of great evolution in drug delivery technologies. Niosomes have great drug delivery potential for targeted
delivery of anti-cancer, anti-infective agents. Drug delivery potential of niosome can enhance by using novel concepts like proniosomes.

Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant. The concept of incorporating the drug into niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers. Niosomes represent a promising drug delivery module. They present a structure similar to liposome. Various type of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parenteral. They represent alternative vesicular systems with respect to liposomes also having various advantages over liposomes like cost, stability etc. Niosomes represent a promising drug delivery technology and much research has to be inspired in this to juice out all the potential in this novel drug delivery system

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