REVIEW ARTICLE

# Niosomal Drug Delivery - A Comprehensive Review

**Vrunal V. More[1], Ritu M. Gilhotra[2], Manoj M. Nitalikar[3], Prajakta K. Khule[1]**

*[1]Department of Pharmaceutics, Suresh Gyan Vihar University Jaipur, SVERI's College of Pharmacy, Pandharpur, Maharashtra, India, [2]Department of Pharmaceutics, Suresh Gyan Vihar University, Jaipur, Rajasthan, India, [3]Department of Pharmaceutics, Rajarambapu College of Pharmacy, Kasegaon, Sangli*

## Abstract

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. The basic process of preparation is the same, i.e., hydration by aqueous phase of the lipid phase which may be either a pure surfactant or a mixture of surfactant with cholesterol. After preparing niosomal dispersion, unentrapped drug is separated by dialysis centrifugation or gel filtration. A method of *in vitro* release rate study includes the use of dialysis tubing. Niosomes are promising vehicle for drug delivery, and being non-ionic, it is less toxic and improves the therapeutic index of the drug by restricting its action to target cells. Niosomes are unilamellar or multilamellar vesicles formed from synthetic non-ionic surfactants. They are very similar to the liposomes. Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Niosomes have numerous advantages so they are better option for drug delivery.

**Key words:** Niosomes, a non-ionic surfactant, evaluation of niosomes

## 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 the desired site of action with little or no interaction with non-target tissue.[1] At present, no available drug delivery system achieves the site-specific delivery with controlled release kinetics of drug in predictable manner. A number of carriers were utilized to carry the drug at the target organ/tissue, which includes immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, and niosomes.[2] Among different carriers, liposomes and niosomes are well-documented drug delivery. Drug targeting can be defined as the ability to direct a therapeutic agent specifically to the desired site of action with little or no interaction with non-target tissue.[3] 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.[4] In niosomes, the vesicle-forming amphiphile is a non-ionic surfactant such as Span-60 which is stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate.[5] Schematic representation of a drug targeting through its linkage to niosome through antibody is shown in Figure 1.[6]

### 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

**Address for correspondence:**
Vrunal V. More, Suresh Gyan Vihar University Jaipur, SVERI's College of Pharmacy, Pandharpur, Maharashtra, India. Tel.: +91-9665196666.
E-mail: vvmore@cop.sveri.ac.in

**Received:** 30-09-2018
**Revised:** 12-11-2018
**Accepted:** 24-11-2018

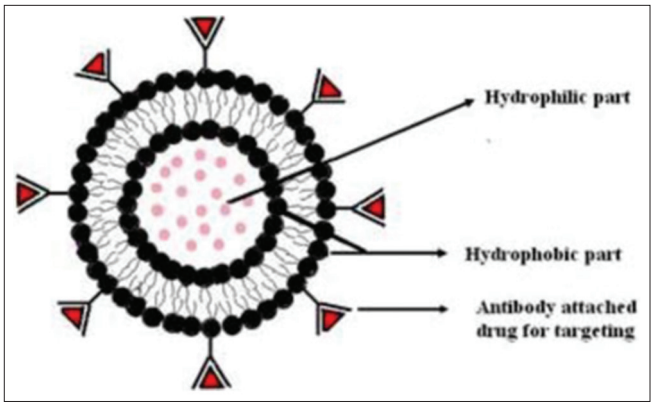



**Figure 1:** Structure of niosome

prepare niosomes make them more stable, and thus, niosomes offer many more advantages over liposomes.[1,6] The sizes of niosomes are microscopic and lie in nanometric scale. The particle size ranges from 10 to 100 nm.

## 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 vesicles.

## Advantages of Niosomes[7]

1. The vesicles may act as a depot, releasing the drug in a controlled manner.
2. They are osmotically active and stable, and also they increase the stability of entrapped drug.
3. 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.
4. The surfactants used are biodegradable, biocompatible, and non-immunogenic.
5. They improve the oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
6. They can be made to reach the site of action by oral, parenteral as well as topical routes
7. The vesicles may act as a depot, releasing the drug in a controlled manner.
8. Handling and storage of surfactants require no special conditions.
9. Due to the unique infrastructure consisting of hydrophilic, amphiphilic, and lipophilic moieties together, they, as a result, can accommodate drug molecules with a wide range of solubilities.
10. Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-aqueous phase.

## Challenges

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.

## Factors affecting the Formation of Niosomes

1. Type of surfactants: Type of the surfactants influences encapsulation efficiency, toxicity, and stability of niosomes. The first niosomes were formulated using cholesterol and single-chain surfactants such as alkyl oxyethylene. The alkyl group chain length is usually from C12–C18. The hydrophilic-lipophilic balance (HLB) is a good indicator of the vesicle-forming ability of any surfactant. Uchegbu *et al*. reported that the sorbitan monostearate (Span) surfactants with HLB values between 4 and 8 were found to be compatible with vesicle formation. Polyglycerol monoalkyl ethers and polyoxylate analogs are the most widely used single-chain surfactants. However, it must be noted that they possess less encapsulation efficiency in the presence of cholesterol. Etheric surfactants have also been used to form niosomes. These types of surfactants are composed of single-chain, monoalkyl, or dialkyl chain. The latest ones are similar to phospholipids and possess higher encapsulation efficiency. Esther type amphiphilic surfactants are also used for niosome formulation. They are degraded by esterases, triglycerides, and fatty acids. Although these types of surfactants are less stable than ether type ones, they possess less toxicity.
2. Surfactant: lipid and surfactant: water ratios: Other important parameters are the level of surfactant: lipid and surfactant: water ratio. The surfactant: lipid ratio is generally 10–30 mM (1–2.5% w/w). If the level of surfactant/lipid is too high, increasing the surfactant/lipid level increases the total amount of drug encapsulated. Change in the surfactant: water ratio during the hydration process may affect the system's microstructure and thus the system's properties.
3. Cholesterol: Steroids are important components of cell membranes, and their presence in membranes brings about significant changes with regard to bilayer stability, fluidity, and permeability. Cholesterol, a natural steroid, is the most commonly used membrane additive [Figure 2] and can be incorporated to bilayers at high molar ratios. Cholesterol by itself, however, does not form bilayer vesicles. It is usually included in a 1:1 molar ratio in most formulations to prevent vesicle aggregation by the inclusion of molecules that stabilize the system against the formation of aggregates by repulsive steric or electrostatic effects. It leads to the transition from the

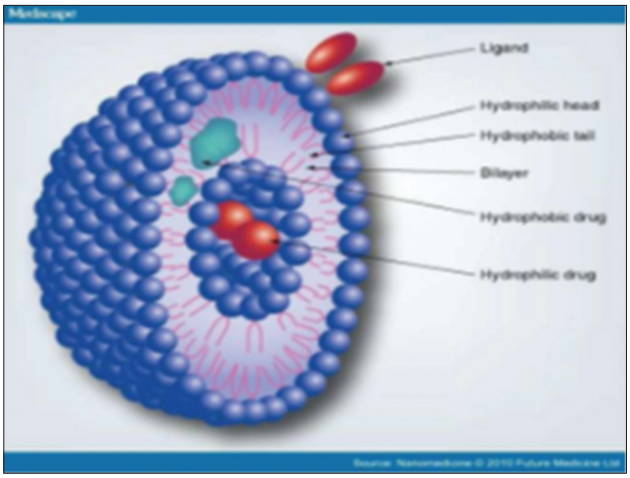
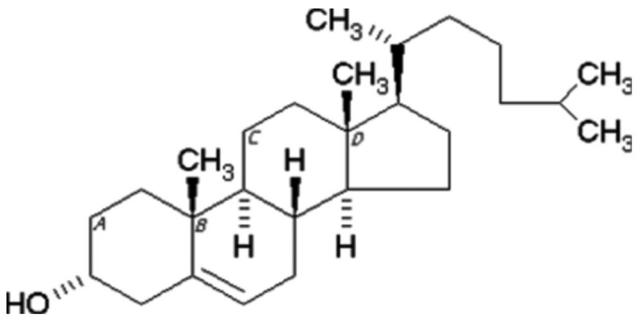



**Figure 2:** Niosomal drug delivery

gel state to liquid phase in niosome systems. As a result, niosomes become less leaky.




4. Other additives: As is the case with liposomes, charged phospholipids such as dicetyl phosphate and stearyl amine have been used to produce charge in niosome formulations. The former molecule provides negative charge to vesicles, whereas the later one is used in the preparation of positively charged (cationic) niosomes.
5. Nature of the drug: One of the overlooked factors is the influence of the nature of the encapsulated drug on vesicle formation [Figure 1]. The encapsulation of the amphipathic drug doxorubicin has been shown to alter the electrophoretic mobility of hexadecyl diglycerol ether (C16G2) niosomes in a pH-dependent manner, indicating that the amphipathic drug is incorporated in the vesicle membrane.

## Types of Niosomes[8]

The niosomes are classified as a function of the number of bilayer (e.g., multilamellar vesicle [MLV] and small unilamellar vesicle [SUV]) or as a function of size (e.g., large unilamellar vesicle [LUV] and SUV) or as a function of the method of preparation (e.g., REV and DRV). The various types of niosomes are described as follows:

i. MLVs (size ≥0.05 μm)
ii. LUVs (size ≥0.10 μm).
iii. SUVs (size =0.025–0.05 μm).

## Method of the Preparation of Niosomes

Niosomes are prepared by different methods based on the desired sizes of the vesicles and their distribution number of double layers, entrapment efficiency of the aqueous phase, and permeability of vesicle membrane.

i. Preparation of SUVs
   a. Sonication: The aqueous phase containing drug is added to the mixture of surfactant and cholesterol in a scintillation vial 13. The mixture is probe sonicated at 60°C for 3 min to produce small and uniform in size niosomes.[9]
   b. Microfluidization: Microfluidization is a recent technique 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 microchannels within high velocities and in precisely defined microchannels 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 niosome formation. The result is a greater uniformity, smaller size, and better reproducibility of niosomes formed.[1]
ii. Preparation of multilamellar vesicles
   a. Handshaking method (thin-film hydration technique): In the handshaking method, surfactant and cholesterol are dissolved in a volatile organic solvent (such as diethyl ether, 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 is hydrated with aqueous phase containing drug at 50–60°C with gentle agitation. This process forms typical multilamellar niosomes.[9]

   b. Transmembrane pH gradient (inside acidic) drug uptake process (remote loading):Surfactant and cholesterol are dissolved in chloroform.[10] The solvent is then evaporated under reduced pressure to obtain a thin film on the wall of the round-bottom flask. The film is hydrated with 300-mm citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0–7.2 with 1 M disodium phosphate. This mixture is later heated at 60°C for 10 min to produce the desired multilamellar vesicles.
iii. Preparation of LUVs
   c. Reverse phase evaporation technique: In this method, cholesterol and surfactant are dissolved in

a mixture of ether and chloroform.[11] 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. The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with phosphate-buffered saline and heated in a water bath at 60°C for 10 min to yield niosomes.

d. Ether injection method: The ether injection method is essentially based on slow injection of niosomal ingredients in diethyl ether through a 14-gauge needle at the rate of approximately 0.25 ml/min into a preheated aqueous phase maintained at 60°C.[9,12] The probable reason behind the formation of larger unilamellar vesicles is that the slow vaporization of solvent results in an ether gradient extending toward the interface of aqueous–non-aqueous interface. The former may be responsible for the formation of the bilayer structure. The disadvantages of this method are that a small amount of ether is frequently present in the vesicle suspension and is difficult to remove.

iv. Miscellaneous

e. Multiple membrane extrusion method: A mixture of surfactant, cholesterol, and diacetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug solution and the resultant suspension extruded through polycarbonate membranes, which are placed in a series for up to eight passages. This is a good method for controlling noisome size.[13]

f. Emulsion method: The oil in water (o/w) emulsion is prepared from an organic solution of surfactant, cholesterol, and an aqueous solution of the drug.[14,15] The organic solvent is then evaporated, leaving niosomes dispersed in the aqueous phase.

g. Lipid injection method: This method does not require expensive organic phase. Here, the mixture of lipids and surfactant is first melted and then injected into a highly agitated heated aqueous phase containing the dissolved drug. Here, the drug can be dissolved in molten lipid, and the mixture will be injected into agitated, heated aqueous phase containing surfactant.

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 are 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, and the dispersion mixed for 15 s with high shear homogenizer and immediately afterward "bubbled" at 70°C using niosomes.[10]

i. Formation of niosomes from proniosomes: Another method of producing niosomes is to coat 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.[15]

- T = Temperature
- Tm = Mean phase transition temperature.

## Separation of Unentrapped Drug

The removal of unentrapped solute from the vesicles can be accomplished by various techniques, which include:

i. Dialysis

The aqueous niosomal dispersion is dialyzed in dialysis tubing against phosphate buffer or normal saline or glucose solution.[10]

ii. 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.[16,17]

iii. Centrifugation

The 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.[3]

## Evaluation of Niosomes[18,19]

### *Measurement of the angle of repose*

The angle of repose of dry niosome powder was measured by a funnel method. The niosome powder was poured into a funnel which was fixed at a position so that the 13 mm outlet orifice of the funnel is 5 cm 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.

### *Scanning electron microscopy (SEM)*

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 SEM. Niosomes were sprinkled on the double sided tape that was affixed on aluminum stubs. The aluminum stub was placed in the vacuum chamber of a SEM (XL 30 ESEM with EDAX, Philips, Netherlands). The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 ton and acceleration voltage: 30.00 KV) XL 30, (Philips, Netherlands).

### *Optical microscopy*

The niosomes were mounted on glass slides and viewed under a microscope with a magnification of ×1200 for morphological observation after suitable dilution. The photomicrograph of the preparation was also obtained from the microscope using a digital SLR camera.

### *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 laser beam of 632.8 nm focused with a minimum power of 5 mW using a Fourier Lens (R85) 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 and Rhodes[20-22] in 1999 reported that the average particle size of niosomes derived niosomes is approximately 6 Um while that of conventional niosomes is about 14 Um.

### *Entrapment efficiency*

Entrapment efficiency of the niosomal dispersion 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% propanol or 0.1% Triton ×100 and analyzing the resultant solution by appropriate assay method for the drug. Where

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

### *Osmotic shock*

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

### *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 decrease in the percentage drug retained. The niosomes were sample at regular intervals of time (0, 1, 2, and 3 months), observed for color change and surface characteristics, tested for the percentage drug retained after being hydrated to form niosomes, and analyzed by suitable analytical methods (UV spectroscopy, HPLC methods, etc.,).

### *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 were 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.

## CONCLUSION

Niosomes are novel nanodrug carriers to design effective drug delivery systems. They offer a great opportunity for loading hydrophilic, lipophilic drugs, or both drugs together. Niosomes have great drug delivery potential for targeted delivery of anticancer and anti-infective agents. Drug delivery potential of niosome can enhance using novel concepts such as proniosomes. Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant. Niosomes are used for better targeting of the drug at appropriate tissue destination. Niosomes are made up of uncharged single chain surfactant molecules. Toxic drugs which needed higher doses can possibly be delivered safely using niosomal application. Niosomes are thought to be better candidate drug delivery as compared to liposomes due to various factors such as cost and stability. Various types of drug deliveries can be possible using niosomes such as targeting, ophthalmic, topical, and parental.

## REFERENCES


1. Khandare JN, Madhavi G, Tamhankar BM. Niosomes novel drug delivery system. East Pharm 1994;31:61-4.
2. Biswal S, Murthy PN, Sahu J, Sahoo P, Amir F. Vesicles of non-ionic surfactants (niosomes) and drug delivery potential. Int J Pharm Sci Nanotechnol 2008;1:1-8.
3. Bhaskaran S, Panigrahi L. Formulation and evaluation of niosomes using different nonionic surfactant. Indian J Pharm Sci 2002;63:186.
4. Malhotra M, Jain NK. Niosomes as drug carriers. Indian Drugs 1994;31:81-6.
5. Harwood BG. Interfacial Phenomena in Drug Delivery and Targeting. Switzerland: Academic Publishers; 1995. p. 154-5.
6. Baillie AJ, Florence AT, Hume LR, Muirhead GT, Rogerson A. The preparation and properties of niosomes non-ionic surfactant vesicles. J Pharm Pharmacol 1985;37:863-8.
7. Soumya S. Niosomes: A role in targeted drug delivery system. Int J Pharm Sci Res 2013;4:550-7.

8. Gadhiya P, Shukla S, Modi D, Bharadia P. A review-niosomes in targeted drug delivery. Int J Pharm Res Sch 2012;2:61.
9. Baillie AJ, Coombs GH, Dolan TF, Laurie J. Non-ionic surfactant vesicles, niosomes, as a delivery system for the anti-leishmanial drug, sodium stibogluconate. J Pharm Pharmacol 1986;38:502-5.
10. Chauhan S, Luorence MJ. The preparation of polyoxyethylene containing non-ionic surfactant vesicles. J Pharm Pharmacol 1989;4:6.
11. Naresh RA, Chandrashekhar G, Pillai GK, Udupa N. Anti-inflammatory activity of niosome encapsulated diclofenac sodium with Tween-85 in arthitic rats. Indian J Pharmacol 1994;26:46-8.
12. Rogerson A, Cummings J, Willmott N, Florence AT. The distribution of doxorubicin in mice following administration in niosomes. J Pharm Pharmacol 1988;40:337-42.
13. Uchegbu IF, Vyas SP. Non-ionic surfactant based vesicles (niosomes) in drug delivery. Int J Pharm 1998;172:33-70.
14. Hao Y, Zhao F, Li N, Yang Y, Li K. Studies on a high encapsulation of colchicine by a niosome system. Int J Pharm 2002;244:73-80.
15. Blazek-Walsh AI, Rhodes DG. SEM imaging predicts quality of niosomes from maltodextrin-based proniosomes. Pharm Res 2001;18:656-61.
16. Yoshioka T, Sternberg B, Florence AT. Preparation properties of vesicles (niosomes) of sobitan monoesters (Span 20, 40, 60, and 80) and a sorbitantriester (Span 85). Int J Pharm 1994;105:1-6.
17. Gayatri DS, Venkatesh P, Udupa N. Niosomal sumatriptan succinate for nasal administration. Int J Pharm Sci 2000;62:479-81.
18. Schreier H. Liposomes and niosomes as topical drug carriers: Dermal and transdermal delivery. J Controll Release 1985;30:863-8.
19. Suzuki K, Sokan K. The application of liposome's to cosmetics. Cosmet Toiletries 1990;105:658-78.
20. Available from: http//www.en.wikipedia.org/wiki/Niosomes,structures.
21. Hu C, Rhodes DG. Proniosomes: A novel drug carrier preparation. Int J Pharm 1999;185:23-35.
22. Silver BL. The Physical Chemistry of Membranes. New York: Alan/Unwin and Solomon Press; 1985. p. 209-30.

**Source of Support:** Nil. **Conflict of Interest:** None declared.