

NIOSOMES: A NOVEL TREND OF DRUG DELIVERY

Md. Rageeb Md. Usman*, Prasanna R. Ghuge and Bharat V. Jain

Smt. S. S. Patil College of Pharmacy, Chopda, Maharashtra, India.

***Corresponding Author: Md. Rageeb Md. Usman**

Smt. S. S. Patil College of Pharmacy, Chopda, Maharashtra, India.

Article Received on 06/05/2017

Article Revised on 27/05/2017

Article Accepted on 17/06/2017

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. Niosome 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, in vitro methods, drug release kinetics, and applications of niosome.

KEYWORDS: Niosomes, Compositions, Preparation Methods, Factors affecting, Characterizations, Invitro methods and Applications.

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 tissue¹. In niosome, 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 niosome 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.

ORIGIN OF NIOSOMES

The first niosome formulations were developed and patented by L'Oreal in 1975. Niosomes were first utilized in drug delivery for anticancer drugs. The developed niosome formulations were capable of altering the pharmacokinetic profile, organ distribution and metabolism of methotrexate in mice. Niosomes are versatile in structure, morphology and size; they can entrap hydrophilic drugs in aqueous compartments or

lipophilic drugs by partitioning of these molecules into bilayer domain. Furthermore, they can be formulated as unilamellar, oligolamellar or multilamellar vesicle. Niosomes also possess good physical stability, are cost-effective, and are relatively straight forward for routine and large-scale production.

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 The sizes of niosomes are microscopic and lie in nonometric scale. The particle size ranges from 10nm-100nm.^[1,2]

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]

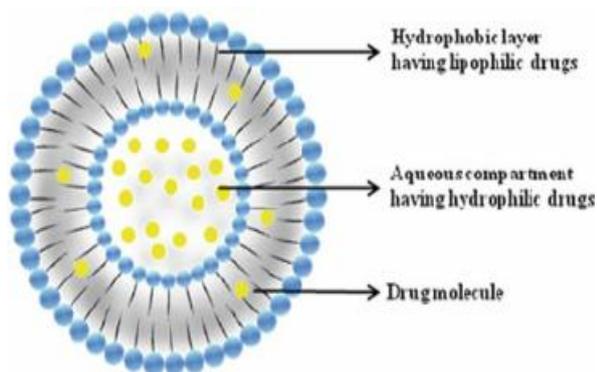


Fig. No 1: Structure of Niosome

ADVANTAGES OF NIOSOMES

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.
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 dispersion⁵⁻⁸.

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.

- Egs. 1. Spans (span 60, 40, 20, 85, 80)
 2. Tweens (tween 20, 40, 60,80).
 3. Brijis (brij 30, 35, 52, 58, 72, 76).

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

Structure of surfactants

The geometry of vesicle to be formed from surfactants is affected by its structure, which is related to critical packing parameters. On the basis of critical packing parameters of surfactants can predicate geometry of vesicle to be formed. Critical packing parameters can be defined using following equation,

CPP (Critical Packing Parameters) = $v / lc \cdot a_0$ where v = hydrophobic group volume,
 lc = the critical hydrophobic group length, a_0 = the area of hydrophilic head group.

From the critical packing parameter value type of micellar structure formed can be ascertained as given below,

If $CPP < 1/2$ then formation of spherical micelles,
 If $1/2 < CPP < 1$ formation of bilayer micelles, If $CPP > 1$ formation inverted micelles.

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.

$$T > T_m$$

Where,

T = Temperature

T_m = 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.

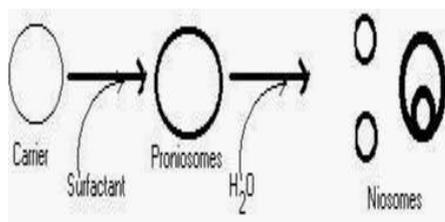


Fig.No.2: Formation of Niosomes from Proniosomes

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 gauge needle

Ether is vaporized to form single layered niosomes.^[2]

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 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 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.^[22]

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.

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.

F. Trans membranes PH gradient (inside acidic) Drug Uptake 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 film 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 vortexed. 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

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.^[24]

Separation of Untrapped Drug

The removal of untrapped 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 untrapped 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 untrapped drug.

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 vortexing
 ↓
 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 7

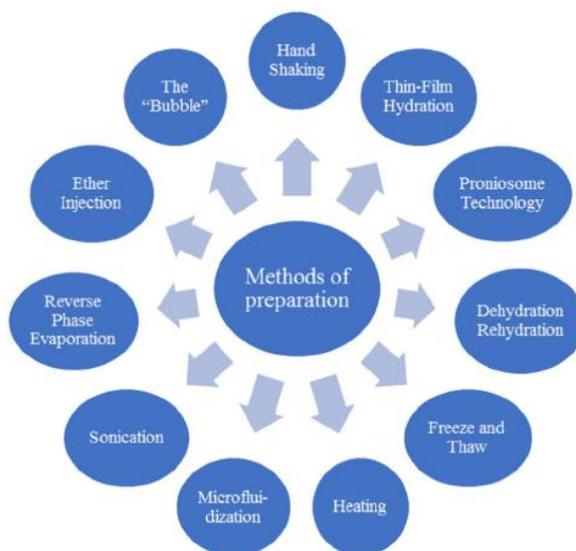


Fig: No.3: Methods of Preparation of Niosomes

Factors affecting niosomes formulation^[24-26]

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 affects 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 niosome 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).

CHARACTERIZATION OF NIOSOMES^[27-28]

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.

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 6 μ m while that of conventional niosomes is about 14 μ m.

e. Entrapment efficiency

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

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. The niosomes were sample at regular intervals of time (0,1,2, and 3 months), 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).

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:

1. Dialysis Tubing
2. Reverse Dialysis
3. 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^{29-30]}

Applications of niosomes

1. The application of niosomes technology is widely varied and can be used to treat a number of diseases.
2. The following are a few uses of niosomes which are either proven or under research.
3. It is used as Drug Targeting.
4. It is used as Anti-neoplastic Treatment i.e. Cancer Disease.

5. It is used as Leishmaniasis i.e. Dermal and Mucocutaneous infections e.g. Sodium stibogluconate.
6. It is used act as Delivery of Peptide Drugs.
7. It is used in Studying Immune Response.
8. Niosomes as Carriers for Hemoglobin.
9. Transdermal Drug Delivery Systems Utilizing Niosomes It is used in Ophthalmic drug delivery.

Formulation: Basic components used in Niosomes are;

1. Targeting molecule: It is active agent or drug substance.
2. Charge producing agent: these agent help to produce opposite charge in different environment. E.g. Alkylbenzene sulfonate quaternary ammonium compounds, tween.^[31-33]

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 – **Lancome**.

RESULTS

From various studies it was concluded that niosome technology proved to have more product stability, extend shelf life from weeks to sometimes years, prevent oxidation and emulsification, and also permits isolating antagonistic ingredient within the formulation until use. Some patented information shows its wide range of application in the field of pharmaceutical, foods, agrochemical, etc. many dermatological preparation have marked a new improvement in their efficacy by utilizing niosometechnology.

CONCLUSION

As niosomes are made of non ionic surfactants so these are more stable, safe and convenient to handle than other ionic drug carriers. The concept of drug targeting at specific tissue site by incorporating drug into niosomes is widely accepted by researchers and academicians. Niosomes is a well preferred drug delivery system and

present a structure similar to liposomes, so it can be used as alternative drug delivery system and also having various advantages over liposomes like cost, stability etc. Niosomes have ability to encapsulate different type of drugs within their multi environmental structure like anti infective, anticancer drug. And various types of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parenteral, etc.

ACKNOWLEDGEMENT

Smt. S. S. Patil College of Pharmacy, Chopda Support for the Collection of literature survey & facilities.

REFERENCES

- Khandare JN., Madhavi G., Tamhankar BM., Niosomes Novel Drug Delivery System. The Eastern Pharmacist, 1994, 37: 61-64.
- Baillie AJ., Florence AT., Hume LR., Muirhead GT., Rogerson A., The preparation and properties of niosomes non-ionic surfactant vesicles. J. Pharm. Pharmacology, 1985; 37: 863- 868.
- <http://en.wikipedia.org/wiki/Niosomes>, structure of niosomes.
- Rogerson A., Cummings J., Willmott N., Florence AT., The distribution of doxorubicin in mice following administration in niosomes. J. Pharm. Pharmacol, 1988, 40: 337-342.
- Biju SS., Talegaonkar S., Misra PR., Khar RK., Vesicular systems: An overview. Indian J. Pharm. Sci., 2006, 68: 141-153.
- Ijeoma F., Uchegbu., Suresh P., Vyas., Non-ionic surfactant based vesicles (niosomes) in drug delivery. Int. J. Pharm., 1998; 172: 33-70.
- Malhotra M., Jain N.K., Niosomes as Drug Carriers. Indian Drugs, 1994; 31(3): 81-866.
- Alsarra A., Bosela A., Ahmed S.M., Mahrous G.M., Proniosomes as a drug carrier for transdermal delivery of ketorolac. Eur. J. Pharm. and Biopharm, 2004; 2(1): 1-6.
- Hu C., Rhodes D.G., Proniosomes: a novel drug carrier preparation. Int. J. Pharm. 1999, 185: 23-35.
- Blazek-Walsh A.I., and Rhodes D.G., Pharm. Res. SEM imaging predicts quality of niosomes from maltodextrin-based proniosomes, 2001, 18: 656-661.
- Yoshioka T., Stemberg B., Florence A.T., Preparation and properties of vesicles (niosomes) of sorbitan monoesters (Span 20, 40, 60, and 80) and a sorbitan triester (Span 85). Int. J Pharm., 1994; 105: 1-6.
- Parthasarathi, G, Udupa, N., Umadevi P., Pillai G.K., Formulation and *in vitro* evaluation of vincristine encapsulated Niosomes. Journal of Drug Targeting, 1994; 2: 173-82.
- Sudhamani. T., Priyadarisini.N., Radhakrishnan. M., Proniosomes – A Promising Drug Carrier, IJ. Pharm Tech Research, 2010; 2(2): 1446-1454.
- Yoshida H., Lehr, C.M., Kok W., Junginger H.E., Verhoef J.C., Bouwistra J.A., Niosomes for oral delivery of peptide drugs. J.Control Rel., 1992; 21: 145-153.
- Satturwar, P.M., Fulzele, S.V., Nande, V.S., Khandare, J.N., Formulation and evaluation of ketoconazole Niosomes. Indian J.Pharm, 2002; 64(2): 155-158.
- Vyas S.P., Khar R, K., Niosomes Targeted and Controlled Drug delivery, 2008; 249 – 279.
- Gibaldi .M and Perrier D; Pharmacokinetics, second edition, New York, Marcel Dekker, Inc., 1982; 127-134.
- Namdeo, A., Jain, N.K., Niosomal delivery of 5-fluorouracil. J. Microencapsul, 1999; 16 (6): 731 – 740.
- Bhaskaran S., Panigrahi L., Formulation and Evaluation of Niosomes using Different Nonionic Surfactant. Ind J Pharm Sci., 2002, 63: 1-6.
- Balasubramanian A., Formulation and In-Vivo Evaluation of Niosome Encapsulated Daunorubicin Hydrochloride. Drug Dev and Ind.Pharm, 2002, 3(2): 1181-84.
- Mayer L.D., Bally M.B., Hope M.J., Cullis P.R., Biochem Biophys. Acta, 1985, 816: 294-302.
- Raja Naresh R.A., Chandrashekhar G., Pillai G.K., Udupa N., Antiinflammatory activity of Niosome encapsulated diclofenac sodium with Tween-85 in Arthitic rats. Ind.J. Pharmacol., 1994, 26: 46-48.
- Chauhan S., Luorence M.J., The preparation of polyoxyethylene containing non-ionic surfactant. Vesicles. J. Pharm. Pharmacol, 1989; 41: 1-6.
- Schreier H., Liposomes and niosomes as topical drug carriers: dermal and transdermal delivery. J. Controlled Release, 1985; 30: 863-868.
- Buckton G., Harwood, Interfacial phenomena in Drug Delivery and Targeting Academic Publishers, Switzerland, 1995; 154-155.
- Hunter C.A., Dolan T.F., Coombs G.H., Baillie A.J, Vesicular systems (niosomes and liposomes) for delivery of sodium stibogluconate in experimental murine visceral leishmaniasis. J.Pharm. Pharmacol, 1988; 40(3): 161-165.
- Bairwa N. K., Choudhary Deepika., Proniosome: A review, Asian Journal of Biochemical and Pharmaceutical Research, 2011; 2(1): 690-694.
- Suzuki K., Soka K., The Application of Liposome's to Cosmetics. Cosmetic and Toiletries, 1990; 105: 65-78.
- Chandraprakash KS, Udupa N., Umadevi P., Pillai GK., Formulation and Evaluation of Methotrexate Niosomes. Ind J Pharm. Sci., 1992, 54(5): 197.
- Agarwal S., Vasudha Bakshi., Villa P., Raghuram AP., Pandey S., Udupa N., Effect of cholesterol content and surfactant HLB on vesicle properties of niosomes. IJPS, 2004, 66(1): 121-123.
- Madhav. NVS and saini. A, niosomes: a novel drug delivery system. Int. J.rpck 2011, 1(3): 498-511.
- Mark chasin, Biodegradable polymers as drug delivery systems, 2008, 261-338.