REVIEW ARTICLE

A NOVEL DRUG DELIVERY SYSTEM: NIOSOMES REVIEW

***Lohumi Ashutosh, Rawat Suman, Sarkar Sidhyartha, Sipai Altaf bhai., Yadav M. Vandana**

Department of Pharmaceutics, Gautham College of Pharmacy, Sultanpalya, R.T.Nagar, Bangalore- 560032, Karnataka, India

**Corresponding author's: Mobile: +917795075933, E-mail: ashuford.lohumi00@gmail.com*

Received 01 August 2012; Review Completed 14 Aug 2012; Accepted 14 Aug 2012, Available online 15 Sep 2012

ABSTRACT:

Treatment of infectious diseases and immunisation has undergone a revolutionary shift in recent years. Not only a large number of disease-specific biological have been developed, but also emphasis has been made to effectively deliver these biological. Niosomes represent an emerging class of novel vesicular systems. Niosomes are self assembled vesicles composed primarily of synthetic surfactants and cholesterol. A comprehensive research carried over niosome as a drug carrier. Various drugs are enlisted and tried in niosome surfactant vesicles. Niosomes proved to be a promising drug carrier and has potential to reduce the side effects of drugs and increased therapeutic effectiveness in various diseases. This article presents an overview of the techniques of preparation of niosome, types of niosomes, characterisation and their applications.
Key words: Niosomes, surfactant, proniosomes, drug entrapment, bilayer.

INTRODUCTION:

For many decades, medication of an acute disease or a chronic illness has been accomplished by delivering drugs to the patients via various pharmaceutical dosage forms like tablets, capsules, pills, creams, ointments, liquids, aerosols, injectables and suppositories as carriers. To achieve and then to maintain the concentration of drug administered within the therapeutically effective range needed for medication, it is often necessary to take this type of drug delivery systems several times in a day. This results in a fluctuated drug level and consequently undesirable toxicity and poor efficiency. To minimize this fluctuation, novel drug delivery systems have been developed, which include niosomes, liposomes, nanoparticles, microspheres, micro-emulsions, impalatable pumps and magnetic microcapsules.[1-2]

The concept of targeted drug delivery is designed for attempting to concentrate the drug in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. As a result, drug is localised on the targeted site. Hence, surrounding tissues are not affected by the drug. In addition, loss of drug does not happen due to localisation of drug, leading to get maximum efficacy of the medication. Different carriers have been used for targeting of drug, such as immunoglobulin, serum proteins, synthetic polymers, liposome, microspheres, erythrocytes and niosomes.[3]

Niosomes are one of the best among these carriers. Structurally, niosomes are similar to liposomes and also are equiactive in drug delivery potential but high chemical stability and economy makes niosomes superior than liposomes. Both consist of bilayer, which is made up of non-ionic surfactant in the case of niosomes and phospholipids in case of liposomes. Niosomes are microscopic lamellar structures of size range between 10 to 1000 nm and consists of biodegradable, non-immunogenic and biocompatible surfactsnts[4]. The niosomes are ampiphillic in nature, which allows entrapment of hydrophilic drug in the core cavity and hydrophobic drugs in the non-polar region present within the bilayer hence both hydrophilic and hydrophobic drugs can be incorporated into niosomes. The structure of niosomes is given below in Fig.No.1.[5]

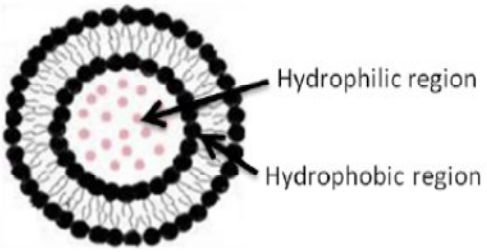

Figure 1: Structure of niosomes.

MERITS AND DEMERITS OF NIOSOMES

Merits of niosomes are following[6, 7, 8]:

- Niosomes can be novel drug dosage form for drug molecules having a wide range of solubility as their infrastructure consists of hydrophilic and hydrophobic part
- Vesicles had flexible characteristic properties; by altering vesicle's characteristics like vesicle composition, size, lamellarity, tapped volume, surface charge and concentration the niosomes of desired property can be obtained
- As vesicle suspension is water based vehicle hence provide better patient compliancy than oil based dosage forms
- By improving oral bioavailability of poorly absorbed drugs, by delaying clearance from the circulation and by protecting the drug from biological environment they improve the therapeutic performance of the drug molecules
- They are osmotically active, stable and also increase the stability of entrapped drug. Oral, parenteral as well as topical routes can be adopted for their administration

- The biodegradable, biocompatible and non-immunogenic surfactants are used in preparation of niosomes and also handling and storage of surfactants requires no special conditions

The niosomes suffer certain demerits, which include the following[9]:

- The aqueous suspensions of niosomes may have limited shelf life due to fusion, aggregation, leaking of entrapped drugs, and hydrolysis of encapsulated drugs
- The methods of preparation of multilamellar vesicles such as extrusion, sonication, are time consuming and may require specialized equipments for processing

FACTORS GOVERNING NIOSOME FORMATION:

Composition of niosome: Theoretically for the niosome formation the presence of a particular class of amphiphile and aqueous solvent is needed but in certain cases cholesterol is required in the formulation to provide rigidity, proper shape and conformation to the niosomes. Cholesterol also stabilizes the system by prohibiting the formation of aggregates by repulsive steric or electrostatic effects. An example of steric stabilisation is the inclusion of Solulan C24 (a cholesteryl poly-24-oxyethylene ether) in doxorubicin (DOX) sorbitan monostearate (Span 60) niosome formulations**.** An example of electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes[10].

Surfactant and lipid level: To make niosomal dispersions the surfactant/lipid level is generally kept 10-30 mM (1-2.5% w/w). If the surfactant, water ratio is altered during the hydration step may affect the microstructure of the system and it's properties. If we increasing the surfactant/lipid level the total amount of drug encapsulated also increases, but the viscosity level of system also increase[11].

Nature of the encapsulated drug:

The nature of encapsulated drug influences the niosomal formation, generally the physico chemical properties of encapsulated drug influence charge and rigidity of the niosome bilayer. The encapsulated drug interacts with surfactant head groups and develops the charge that creates mutual repulsion between surfactant bilayers and hence vesicle size increases and also cause the aggregation of vesicles, which is prevented by using electrostatic stabilizers like dicetyl phosphate in 5(6)-carboxyfluorescein (CF)[12].

Structure of surfactants:

The geometry of vesicle to be formed from surfactants is affected by surfactant's structure, which can be defined by critical packing parameters. Geometry of vesicle to be formed can be predicated on the basis of critical packing parameters of surfactants .Critical packing parameters can be defined using following equation,

$$CPP \text{ (Critical Packing Parameters)} = V/ lc \times a_0$$

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 miceller structure formed can be ascertained as given below,

If CPP < ½ formation of spherical micelles,

If ½ < CPP < 1 formation of bilayer micelles,

If CPP > 1 formation inverted micelles[11,13]

Temperature of hydration:

Hydration temperature influences the shape and size of the niosome, temperature change of niosomal system affects assembly of surfactants into vesicles by which induces vesicle shape transformation. Ideally the hydration temperature for niosome formation should be above the gel to liquid phase transition temperature of system[14,15].

COMPOSITION OF NIOSOMES

Cholesterol and Non ionic surfactants are the two major components used for the preparation of niosomes. Cholesterol provides rigidity and proper shape. The surfactants play a major role in the formation of niosomes. non-ionic surfactants like spans(span 20,40,60,85,80), tweens (tween 20,40,60,80) and brij (brij 30,35,52,58,72,76) are generally used for the preparation of niosomes[16]. Few other surfactants that are reported to form niosomes are as follows[17,18]:

- Ether linked surfactant
- Di-alkyl chain surfactant
- Ester linked
- Sorbitan Esters
- Poly-sorbates

METHOD OF PREPARATION:

Preparation of small unilamellar vesicles

Sonication:

It is a typical method of production of the vesicles in which a 10-ml glass vial drug solution in buffer is added to the surfactant/cholesterol mixture. Then the mixture is probe sonicated at 60°C for 3 minutes using a sonicator with titanium probe to yield niosomes. The resulting vesicles are small and unilamellar[19]**.**

Micro fluidization:

It is a recent technique based on submerged jet principle. In this two fluidized streams interact at ultra high velocities and move forward through precisely defined micro channel within the interaction chamber. The impingement of thin liquid she*et al*ong a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation which results in a greater uniformity, smaller size and better reproducibility of niosomes formed[20].

Preparation of multilamellar vesicles

Hand shaking method (Thin film hydration technique):

Surfactant and the other vesicles forming ingredients like cholesterol are blended and mixture is dissolved in a volatile organic solvent like diethyl ether, chloroform or methanol in a round bottom flask. Using rotary evaporator the organic solvent is removed at room temperature (20°C), by this a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with

 ISSN: 2250-1177 CODEN (USA): JDDTAO

aqueous phase at 60°C with gentle agitation results in formation of multilamellar niosomes[19].

Trans-membrane pH gradient (inside acidic) drug uptake process

(Remote Loading):

In a round-bottom flask blend of Surfactant and cholesterol are dissolved in chloroform and the chloroform is then evaporated under reduced pressure to obtain a thin film on the wall of the flask. The film is hydrated by vortex mixing with 300 mM citric acid (pH 4.0). The multilamellar vesicles are frozen and thawed three times and then sonicated. Aqueous solution containing 10 mg/ml of drug is added to this niosomal suspension and vortexed. With 1M disodium phosphate the pH of the sample is raised to 7.0-7.2 and the mixture is then heated at 60°C for 10 minutes to produce the desired multilamellar vesicles[21, 22].

Preparation of large Unilamellar Vesicles

Reverse phase evaporation technique (REV):

In this method, cholesterol and surfactant (1:1) is added 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. A small amount of phosphate buffer saline is then added to the clear gel formed above and is further sonicated. Under low pressure and at 40°C the organic phase is removed. Phosphate-buffer saline is added to dilute the resulting viscous niosome suspension and heated in a water bath at 60°C for 10 min to yield niosomes[23].

Ether injection method:

A solution of surfactant mixture is prepared first and then slowly introduced into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material. Single layered vesicles are formed by the vaporization of ether. The vesicles of diameter range from 50 to 1000 nm are obtained depending upon the conditions used. The small amount of ether is often still present in the vesicle suspension and is often difficult to remove that is the major disadvantage of this method[24].

Miscellaneous

Multiple membrane extrusion method:

A blend of surfactant, cholesterol, and di acetyl phosphate is dissolved in chloroform and the solvent is evaporated leading to formation of thin film. Using aqueous drug solution the film is hydrated and the resultant suspension extruded through polycarbonate membranes, which are placed in a series for up to eight passages. This is a best method for controlling niosome size[24].

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[10].

Formation of niosomes from proniosomes:

In this method of producing niosomes a water-soluble carrier such as sorbitol is coated with surfactant resulting in the formulation of dry formulation in which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed "Proniosomes". Then proniosome powder is filled in a screw capped vial, and mixed with water or saline at 80 °C by vortexing, followed by agitation for 2 min results in the formation of niosomal suspension[25].

Emulsion method:

From an organic solution of surfactant, cholesterol, and aqueous solution of drug, oil in water (o/w) emulsion is prepared. The organic solvent is then evaporated, leaving niosomes dispersed in the aqueous phase[26,14].

Lipid injection method:

In this process, either mixture of lipids and surfactant is first melted and then injected into a highly agitated heated aqueous phase containing dissolved drug, or the drug can be dissolved in molten lipid and the mixture will be injected into agitated, heated aqueous phase containing surfactant. This method does not require expensive organic phase[22].

Niosome preparation using Micelle:

Niosomes may also be formed by the use of enzymes in a mixed micellar solution. A mixed micellar solution of C16 G2, dicalcium hydrogen phosphate (DCP), polyoxyethylene cholesteryl sebacetate di ester (PCSD) when incubated with esterases converts to a noisome dispersion. PCSD is cleaved by the esterases action to yield polyoxyethylene, sebacic acid and cholesterol and then cholesterol in combination with C16 G2 and DCP then yields C16 G2 niosomes[22].

Niosome preparation using polyoxyethylene alkyl ether:

Charactersitics like the size and number of bilayers of polyoxyethylene alkyl ethers and cholestrol consisting vesicles can be changed in alternative way. Small unilamellar vesciles transforms to large multilamellar vesicles by temperature rise above 600° C, while multilamellar vesicles can be transformed into unilamellar ones by vigorous shaking at room temperature. It is the characteristics for the polyoxythelene alkyl ether surfactants to transfromation from unilamellar to multilamellar vesicles at higher temperature since it is known that polyethyleneglycol (PEG) and water at higher temperature demixes due to a breakdown of hydrogen bonding between water and PEG moieties[27].

Separation of Unentrapped Drug

Various techniques can be accomplished for the removal of unentrapped solute from the vesicles which include[25]:

- Dialysis
- Gel Filtration
- Centrifugation

CHARACTERISATION OF NIOSOMES

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[13,28,29].

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[30,31].

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 (EF) can be defined by[11]:

Entrapment efficiency (EF) = (Amount entrapped/ total amount) x100.

***In vitro* Release Study**

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 into a 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 [32].

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[35].

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 content[37].

***In vivo* Release Study**

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[35].

FACTORS AFFECTING VESICLES SIZE, ENTRAPMENT EFFICIENCY, AND RELEASE CHARACTERISTICS:

Drug:

Vesicle size increases by entrapment of drug in niosomes, probably by increasing the charge and mutual repulsion of the surfactant bilayers or interaction of solute with surfactant head groups. But some drug is entrapped in the long PEG chains In case of polyoxyethylene glycol (PEG)-coated vesicles, thus tendency to increase the size reduces. The degree of entrapment is affected by hydrophilic lipophilic balance of the drug[23].

Amount and type of surfactant:

With increase in the hydrophilic-lipophilic balance (HLB) of surfactants such as Span 85 (HLB 1.8) to Span 20 (HLB 8.6) the mean size of niosomes increases proportionally, because with an increase in hydrophobicity of surfactants the surface free energy decreases.

Depending on the temperature, the type of lipid or surfactant and the presence of other components such as cholesterol the bilayers of the vesicles are either in the so called liquid state or in gel state. When the structure of the bilayers is disordered it will be in liquid state and if alkyl chains are present in a well ordered structure it will be in the gel state.

Entrapment efficiency is also affected by phase transition temperature of surfactants, for example Span 60 having higher phase transition temperature provides better entrapment[20].

Cholesterol content and charge:

Cholesterol increases the chain order of liquid state bilayers and also it decreases the chain order of gel state bilayers. The gel state is transformed to a liquid-ordered phase at a high cholesterol concentration. An increase in cholesterol content of the bilayers resulted in a decrease in the release rate of encapsulated material, and therefore an increase in the rigidity of the resulting bilayers. The interlamellar distance between successive bilayers in multilamellar vesicle tends to increase due to presence of charge and leads to greater overall entrapped volume[34].

Methods of Preparation:

Ether injection method (50-1,000 nm) forms vesicles with small diameter than vesicles formed by Hand shaking method (0.35-13 nm). By Reverse Phase Evaporation (REV) method small-sized niosomes can be produced while by microfluidisation greater uniformity and small-sized vesicles are obtained[20].

Resistance to osmotic stress:

If in a suspension of niosomes hypertonic salt solution is added, reduction in diameter occurs. In hypotonic salt solution, probably due to inhibition of eluting fluid from vesicles, there is initial slow release with slight swelling of vesicles, followed by faster release, which may be due to mechanical loosening of vesicles structure under osmotic stress[35].

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Applications

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

Targeting of bioactive agents

1. 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[35].

2. 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 intrinsic ability to recognize and bind particular carbohydrate determinants and this property can be used to direct carriers system to particular cells[36, 37].

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. If the mice bearing S-180 tumour is treated with niosomal delivery of this drug it was observed that their life span increased and the rate of proliferation of sarcoma decreased[38].

Methotrexate entrapped in niosomes if administered intravenously to S-180 tumour bearing mice results in total regression of tumour and also higher plasma level and slower elimination[39, 40].

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[41]. **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[42].

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[43].

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. The topical delivery of erythromycin from various formulations including niosomes has studied on hairless mouse and from the studies, and confocal microscopy, it was found that non-ionic vesicles could be formulated to target pilosebaceous glands[24].

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[44].

Leishmaniasis therapy

Derivatives of antimony are most commonly prescribed drugs for the treatment of leishmaniasis. These drugs in higher concentrations – can cause liver, cardiac and kidney damage. Use of niosomes as a drug carrier showed that it is possible to overcome the side effects at higher concentration also and thus showed greater efficacy in treatment[34].

Niosome formulation as a brain targeted delivery system for the vasoactive intestinal peptide (VIP)

Radiolabelled (I125) VIP-loaded glucose-bearing niosomes were injected intravenously to mice. Encapsulated VIP within glucose-bearing niosomes exhibits higher VIP brain uptake as compared to control[45].

Ophthalmic drug delivery

From ocular dosage form like ophthalmic solution, suspension and ointment it is difficult to achieve excellent bioavailability of drug due to the tear production, impermeability of corneal epithelium, non-productive absorption and transient residence time. But niosomal and liposomal delivery systems can be used to achieve good bioavailability of drug. Bioadhesive-coated niosomal formulation of acetazolamide prepared from span 60, cholesterol stearylamine or dicetyl phosphate exhibits more tendencies for reduction of intraocular pressure as compared to marketed formulation (Dorzolamide) [46].

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[10,34].

Table 1: List of Drugs formulated as Niosomes

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

CONCLUSION:

Neosomal drug delivery system is one of the examples of great evolution in drug delivery technologies. The concept of drug incorporation in the niosomes and to target the niosomes to the specific site is widely accepted by researchers and academicians. 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.

REFERENCES:

1. Yie W Chien: Concepts and System Design for Rate-Controlled Drug Delivery. Chapter 1 in Novel Drug Delivery System, Marcel Dekker, Inc, New York, 2nd Edition 1992.P. l-42.
2. Yie W Chien: Rate-controlled Drug Delivery Systems. Ind J Pharm Sci 1988.P. 63-65.
3. Allen TM: Liposomal drug formulations: Rationale for development and what we can expect for the future. Drugs, 1998, (56), 747-756.
4. Handjani-vila RM: Dispersion of lamellar phases of nonionic lipids in cosmetic products. Int J Cosmetic Sci, 1979; 1**:** 303.
5. Mehta A: Niosomes. www.pharmainfo.net. 2009.
6. Biju SS, Telegaonar S, Mishra PR, Khar RK: Vesicular system: an overview, Indian J Pharm Sci, 2006, (68) 141-153.
7. Vyas SP, Khar RK: Controlled drug delivery system: concept and advances.CBS Publishers and Distributors New Delhi, 2002.
8. Indhu PK, Garg A, Anil KS, Aggarwal D: Vesicular system in ocular drug delivery. Indian J Pharm Sci, 2004, (269), 1-14.
9. Verma S, Singh SK, Navneet S, Mathur P, Valecha V: Nanoparticle vesicular systems: a versatile tool for drug delivery. J Chem Pharm Res, 2010.P.496-509.
10. Chauhan S, Luorence MJ, The preparation of polyoxyethylene containing non-ionic surfactant vesicles. J Pharm Pharmacol, 1989, (41), 6.
11. Alemayehu Tarekegn, Nisha M Joseph, S Palani, Anish Zacharia, Zelalem Ayenew: niosomes in targeted drug delivery: some recent advances. IJPSR, 2010, (9), 1-8.
12. Stafford S, Ballie AJ, Florence AT: Drug effect on the size of chemically defined nonionic surfactant vesicles. J Pharm Pharmacol, 1988, (26), 40.
13. Biswal S, Murthy PN, Sahu J, Sahoo P, Amir F: Vesicles of Non-ionic Surfactants (Niosomes) and Drug Delivery Potential. International Journal of Pharmaceutical Sciences and Nanotechnology, 2008, (1), 1-8.
14. Uchegbu FI, Vyas PS, Non-ionic surfactant based vesicles (niosomes) in drug delivery. Int J Pharm, 1998, (33), 172.
15. Arunothayanun P *et al*: The effect of processing variables on the physical characteristics of nonionic surfactant vesicles (niosomes) formed from hexadecyl diglycerol ether. Int J Pharm, 2000, (7), 201.
16. Parthasarathi G, Udupa N, Umadevi P, Pillai GK: Niosome encapsulated of vincristine sulfate: improved anticancer activity with reduced toxicity in mice. J Drug Target,1994, (2), 173-182.
17. Rogerson A, Cummings J, Willmott N and Florence AT: The distribution of doxorubicin in mice following administration in niosomes. J Pharm Pharmacol, 1988, (40), 337-342.
18. Pranshu Tangri, Shaffi Khurana; Niosomes: formulation and evaluation. International Journal of Biopharmaceutics, 2011, (2), 47-53.
19. Baillie AJ, Coombs GH, Dolan TF: Non-ionic surfactant vesicles, niosomes, as delivery system for the anti-leishmanial drug, sodium stribogluconate. J Pharm Pharmacol, 1986, (38), 502-505.
20. Khandare JN, Madhavi G, Tamhankar BM: Niosomes Novel Drug Delivery System. The Eastern Pharmacist, 1994, (37), 61-64.
21. Mayer LD, Bally MB, Hope MJ, Cullis PR: Uptake of antineoplastic agents into large unilamellar vesicles in response to a membrane potential. Biochem Biophys Acta, 1985, (816), 294-302.
22. Kazi Masud Karim, Asim Sattwa Mandal, Nikhil Biswas, Arijit Guha, Sugata Chatterjee, Mamata Behera: Niosome: A future of targeted drug delivery systems. J Adv Pharm Tech Res, 2011, (62), 122.
23. Raja Naresh RA, Chandrashekhar G, Pillai GK, Udupa N: Antiinflammatory activity of Niosome encapsulated diclofenac sodium with Tween -85 in Arthitic rats. Ind J Pharmacol, 1994, (26), 46-48.
24. Jayaraman SC, Ramachandran C, Weiner N: Topical delivery of erythromycin from various formulations: An *in vivo* hairless mouse study. J Pharm Sci, 1996, (85), 1082-1084.
25. Blazek Welsh AI, Rhodes DG: SEM Imaging Predicts Quality of Niosomes from Maltodextrin-Based Proniosomes. Pharm Res, 2001, (18), 656-661.
26. Hao Y, Zhao F, Li N, Yang Y, Li K: Studies on a high encapsulation of colchicines by a noisome system. Int J Pharm, 2002, (244), 73-80.
27. Kaneshina S, Shibata O, Nakamura M: The effect of pressure on the mutual solubility of anonionic surfactant water system. Bull Chem Soc Japan, 1982, (55), 951-952.
28. Almira I, Blazek-welsh IA, Rhodes GD: Maltodextrin – Based proniosomes. AAPS Pharm Sci Tech, 2001, (3), 1-8.

29. Manosroi A: Characterization of Vesicles Prepared with Various Nonionic Surfactants mixed with Cholesterol. Colloids and surfaces Biointerfaces, 2003.P.129.
30. Azmin MN, Florence AT, Handjani-Vila RM, Stuart JF, Vanlerberghe G, Whittaker JS: The effect of non-ionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice. J Pharm Pharmacol, 1985, (37), 237-242.
31. Kreuter J: Colloidal Drug Delivery System of Niosome, Dekker series, Dekker publication .P.66-73.
32. Yoshioka T, Stermberg B, Florence AT: Preparation and properties of vesicles (niosomes) of sobitan monoesters (Span 20, 40, 60, and 80) and a sorbitan triester (Span 85). Int J Pharm, 1994, (105),1-6.
33. Attaullah Khan, Pramod Kumar Sharma, Sharad Visht, Rishabha Malviya: Niosomes as colloidal drug delivery system: a review. Journal of Chronotherapy and Drug Delivery, 2011, (40), 15-21.
34. Hunter CA, Dolan TF, Coombs GH and Baillie AJ: Vesicular systems (niosomes and liposomes) for delivery of sodium stibogluconate in experimental murine visceral leishmaniasis. J Pharm Pharmacol, 1988, (40), 161-165.
35. Malhotra M, Jain NK: Niosomes as Drug Carriers. Indian Drugs, 1994, (31), 81-86.
36. Gregoriadis G: Targeting of drugs: implications in medicine. Lancet, 1981, (2), 241-246.
37. Weissman G *et al*: General method for the introduction of enzymes, by means of immunoglobulincoated liposomes, into lysosomes of deficient cells. Proc Natl Acad Sci, 1975, (72), 88-92.
38. Cummings J, Staurt JF, Calman KC: Determination of adriamycin, adriamycinol and their 7-deoxyaglycones in human serum by high performance liquid chromatography. J Chromatogr, 1984, (311), 125- 133.
39. Chandraprakash KS *et al*: Formulation and evaluation of Methotrexate niosomes. Ind J Pharm Sci, 1992, (54), 197.
40. Suzuki K, Sokan K: The Application of Liposomes to Cosmetics. Cosmetic and Toiletries, 1990,(105), 65-78.
41. Yoshida H *et al*: Niosomes for oral de-livery of peptide drugs. J Control Rel, 1992, (21), 145–153.
42. Brewer JM and Alexander JA: The adjuvant activity of non-ionic surfactant vesicles (niosomes) on the BALB/c humoral response to bovine serum albumin. Immunology, 1992, (75), 570-575.
43. Moser P *et al*: Niosomes d'hémoglobine, Preparation, proprietes physicochimiques oxyphoriques, stabilite. Pharma Acta Helv, 1989, (64), 192-202.
44. Luciani A: Glucose Receptor MR Imaging of Tumors: Study in Mice with PEGylated Paramagnetic Niosomes. J Radiology, 2004, (2), 135.
45. Dufes C *et al*: Glucose-targeted niosomes deliver vasoactive intestinal peptide (VIP) to brain. Int J of Pharm, 2004, (285), 77.
46. Aggarwal D *et al*: Development of topical niosomal preparation of acetazolamide: preparation and evaluation. J Pharm Pharmacol, (2004), 56: 1509.

 ISSN: 2250-1177 CODEN (USA): JDDTAO