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Review Article

Niosomes: A Promising Approach in Drug Delivery Systems

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ABSTRACT

Design of vesicles as a tool to enhance drug delivery has created a lot of interest among humans operating within drug delivery systems space over the past decade. Niosomes are formations of vesicles by a hydrating mixture of cholesterol and nonionic surfactants. Completely different novel approaches used to deliver these medicines include liposomes, microspheres, engineering science, small emulsions, antibody-loaded drug delivery, magnetic microcapsules, implantable pumps and niosomes. Design and development of novel drug delivery system (NDDS) has two prerequisites. First, it should distribute the drug in accordance with a predetermined rate and second it should release therapeutically effective amount of drug at the site of action. Conventional dosage forms are unable to meet these requisites. Niosomes are basically non-ionic surfactant based vesicles in which an aqueous solution of solute is completely sealed off by a membrane resulting from the group of surfactant macromolecules as bilayer. Niosomes remain in the bloodstream for a reasonable time, which is useful for targeted drug delivery. This review additionally presents an overview of the strategies of preparation of niosome, types of niosomes, characterization and their applications.

Keywords: Niosomes, Vesicles, NDDS, Conventional, Micromolecules.

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INTRODUCTION

Present investigation and development strategy focus on progress of drug delivery systems that make clinically established drugs do their therapeutic best rather than search for new drugs. The aim of any drug delivery system should always be to achieve maximum therapeutic response with minimum side effects. Like phospholipids, the nonionic surfactants are able to form vesicular delivery systems called "niosomes" when dispersed in water. This is a rather recent concept with a few but very important investigations which show that carrier system possesses great potential in delivery of drugs in biological system. They are known to be analogous to liposomes, and have been used in cosmetic formulations and experimentally as drug carriers ^{1, 2, 3}. Niosomal vesicles are able to encapsulate both lipophilic and hydrophilic drugs and protect them against acidic and enzymatic effects *in vivo*³. They deals with several advantages over liposomes such as higher chemical stability, intrinsic skin penetration enhancing the properties and lower costs ⁴. However, there may be problems of physical instability in niosome dispersions during storage like vesicles aggregation, fusion, leaking or hydrolysis of encapsulated drugs, which might affect the shelf life of the dispersion ⁵. 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. Above and beyond this, niosomes have been used to solve the problem of insolubility, instability and rapid degradation of drugs ⁶.

Advantages of Niosomes

1. Niosomes can offer control and sustained release system of drugs.
2. Improve oral bioavailability.
3. Niosomes can be designed according to the desired situation because of its flexibility in their structural characteristics (composition, fluidity and size).
4. Therapeutically can be increased if the drug is incorporate in Niosomes. Niosomes can accommodate variety of drug moieties such as hydrophilic,
5. Effective permeation of drugs into cells
6. Prolongation of existence of drugs in systemic circulation.
7. Delayed elimination of rapidly metabolized drugs.
8. Overcomes the problems of the drug insolubility, instability, and rapid degradations.

9. Performances can be improved by restricting effects to target cells and protecting drugs from biological environment⁷.
10. Niosomes are osmotically active and stability of entrapped drug can be increased by niosomal preparation.
11. Niosomes can enhance the skin penetration of drug through skin
12. They offer to reach the drug at the site of action by multiple routes such as oral, parenteral as well as topical routes.
13. Surfactants used in Niosomes are non-immunogenic, biodegradable and biocompatible.
14. No special conditions are not required for handling and storage of surfactants⁸.
15. As selective uptake is taken place so reduces toxicity.
16. Reduces the cost of therapy.
17. Niosomes are colloidal vesicular carriers and these vesicles can act as drug reservoirs and the rate of drug release can be modified by changing of their composition.
18. Niosomes can encapsulate both hydrophilic drugs (by loading in inner space) and hydrophobic drugs (in lipid area). That's why it is used in various drug delivery systems like drug targeting, controlled release and permeation enhancement of drugs⁹.

Disadvantages of Niosomes

Along with numbers of advantages of Niosomes, have some serious disadvantages which restrict their use. Drugs passively, which may lead to low drug loading efficiency and drug leakage in preparation, preservation and transport *in vivo*. Need of intensive sonication, lead to leakages of drug during storage. Thus the major problem of their stability acts as a barrier and thus limiting their use¹⁰⁻¹³.

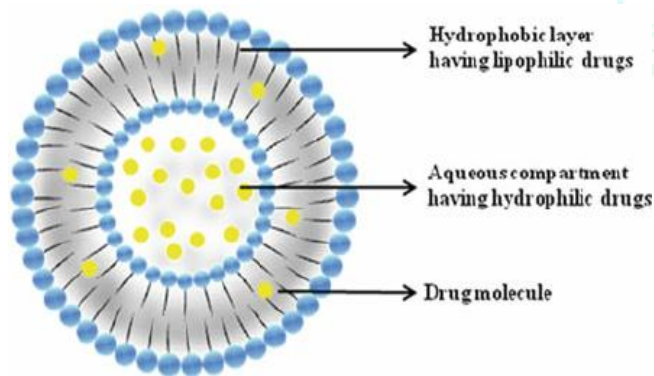


Figure1. Structure of Niosomes containing Hydrophilic and Hydrophobic layer of drug molecule

COMPONENTS USED IN THE PREPARATION OF NIOSOMES

Niosomes mainly contains following types of components:

Non-ionic Surfactants

The non-ionic surfactants orient themselves in bilayer lattices where the polar or hydrophobic heads align facing aqueous bulk (media) while the hydrophobic head or hydrocarbon segments align in such a way that the interaction with the aqueous media would be minimized. To attain thermodynamic stability, every bilayer folds over itself as continuous membrane *i.e.* forms vesicles so that hydrocarbon/water interface remains no more exposed¹⁴.

Mainly following types of non-ionic surfactants are used for the formation of niosomes:

Alkyl Ethers: L'Oreal described some surfactants¹⁴ for the preparation of niosomes containing drugs/ chemicals as

- i. Surfactant-I (molecular weight (MW 473)) is C₁₆ monoalkyl glycerol ether with average of three glycerol units.
- ii. Surfactant-II (MW 972) is diglycerol ether with average of the seven glycerol units.
- iii. Surfactant III (MW 393) is ester linked surfactant.

Other than alkyl glycerol, alkyl glycosides and alkyl ethers bearing polyhydroxyl head groups are also used in formulation of niosomes^{14, 15, 16}.

Alkyl Esters: Sorbitan esters are most preferred surfactant used for the preparation of niosomes amongst this category of surfactants^{17, 18}. Vesicles prepared by the polyoxyethylene sorbitan monolaurate are relatively soluble than other surfactant vesicles¹⁹. For example polyoxyethylene (polysorbate 60) has been utilized for encapsulation of diclofenac sodium¹¹. A mixture of polyoxyethylene-10-stearyl ether: glyceryl laurate: cholesterol (27: 15: 57) has been used in transdermal delivery of cyclosporine-A^{14, 21}.

Alkyl Amides: Alkyl amide (*e.g.* galactosides and glucosides) have been utilized to produce niosomal vesicles²².

Fatty Acid and Amino Acid Compounds: Long chain fatty acids and amino acid moieties have also been used in some niosomes preparation²³.

Cholesterol

Steroids are important components of the cell membrane and their presence in membrane affect the bilayer fluidity and permeability. 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 cannot be discarded. In general, incorporation of cholesterol affects properties of niosomes like membrane permeability, rigidity, encapsulation efficiency, ease of rehydration of freeze dried Niosomes and their toxicity. It prevents the vesicle aggregation by the inclusion of molecules that stabilize the system against the formation of aggregates by repulsive steric or electrostatic forces that leads to the transition from the gel to the liquid phase in niosome systems. As a result of this, the niosome becomes less leaky in nature²⁴.

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 phosphotidic 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 Niosomes²⁵. Only 2.5-5 mol percentage concentration of charged molecules is tolerable because high concentration can inhibit the niosome formation^{26, 27}.

TYPES OF NIOSOMES

Niosomes can be divided into following two types:-

On the basis of their vesicles size:

1. Small Uni-lamellar Vesicles (SUV, Size=0.025-0.05 μm)
2. Multi-lamellar Vesicles (MLV, Size=>0.05 μm)
3. Large Uni-lamellar Vesicles (LUV, Size=>0.10 μm).¹⁴

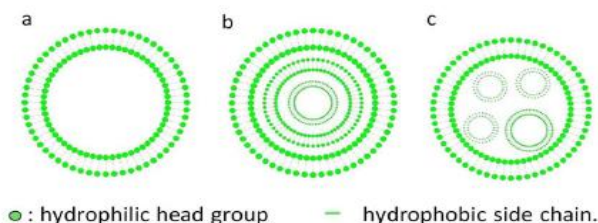


Figure 2. Schematic structures of non-ionic surfactant vesicle. (a) Uni-lamellar vesicle, (b,c). Multi-lamellar vesicle.

On the basis of material used:

- 1. Bola surfactant containing niosomes:** The surfactant use in Bola surfactant containing niosomes are made of omega hexadecylbis-(1-aza-18 crown-6) (bola surfactant): span- 80/cholesterol in 2:3:1 molar ratio ^{28, 29}.
 - 2. Proniosomes:** Proniosomes are the niosomal formulation containing carrier and surfactant, which requires to be hydrated before being used. The hydration results in the formation of aqueous niosome dispersion. Proniosomes decreases the aggregation, leaking and fusion problem associated with niosomal formulation ³⁰.
 - 3. Aspasomes:** Aspasomes is produced using the mix of acorbylpalmitate cholesterol and exceptionally charged lipid diacetyl phosphate prompts the arrangement of vesicles. Aspasomes are first hydrated with water/fluid arrangement and afterward it is subjected to sonication to get the niosomes. Aspasomes can be utilized to build the transdermal saturation of medications. Aspasomes have likewise been utilized to diminish scatter caused by responsive oxygen species as it has in cell reinforcement property.
 - 4. Niosomes in carbopolgel:** Niosomes were prepared from drug, spans and cholesterol then it is incorporated in carbopol-934 gel (1%w/w) base containing propylene glycol (10% w/w) and glycerol (30% w/w).
 - 5. Vesicles in water and oil system (v/w/o):** In this strategy, the aqueous niosomes into an oil stage frame vesicle in water in oil emulsion (v/w/o). This can be set up by expansion of niosomes suspension figured from blend of sorbitol monostearate, cholesterol and solulan C24 (Poly-24-Oxyethylene cholesteryl ether) to oil stage at 60 °C. This result in the formation of vesicle in water in oil (v/w/o) emulsion which by cooling to room temperature forms vesicle in water in oil gel (v/w/o gel). The v/w/o gel thus obtained can entrap proteins/ proteinous drugs and also protect it from enzymatic degradation after oral administration and controlled release.
 - 6. Niosomes of hydroxyl propyl methyl cellulose:** In this type, a base containing 10% glycerin of hydroxyl propyl methyl cellulose was first prepared and then niosomes were incorporated in it ^{31, 32}.
 - 7. Deformable niosomes:** The mixture of non-ionic surfactants, ethanol and water forms the deformable niosomes. These are smaller vesicles and easily pass through the pores of stratum corneum, which leads to increase penetration efficiency. It can be used in topical preparation ^{33, 34}.
- 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.
 - 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 Phase transition temperature (TC) of surfactant also effects entrapment efficiency i.e. Span 60 having higher TC, provides better entrapment.
 - 3. Cholesterol content and charge:** Inclusion of cholesterol in niosomes increased its hydrodynamic diameter and entrapment efficiency. In general, the action of cholesterol is two folds; on one hand, cholesterol increases the chain order of liquid-state bilayers and on the other, Cholesterol decreases the chain order of gel state bilayers. At a high cholesterol concentration, the gel state is transformed to a liquid ordered phase 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) ³⁵⁻³⁷.
 - 6. Nature of encapsulated drug:** The physico-synthetic properties of typified medicate impact charge and unbending nature of the niosome bilayer. The medication cooperates with surfactant head gatherings and builds up the charge that makes shared a version between surfactant bilayers and subsequently expands vesicle estimate. The aggregation of vesicles is prevented due to the charge development on bilayer.
 - 7. 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 ³⁸.

- 8. Structure of surfactants:** The geometry of vesicle to be shaped from surfactants is influenced by surfactant's structure, which can be characterized by basic pressing parameters. Geometry of vesicle to be shaped can be predicated on the premise of basic pressing parameters of surfactants. Critical packing parameters can be defined using following equation,

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

Where, V = hydrophobic group volume,

lc = the critical hydrophobic group length,

a_0 = the area of hydrophilic head group.

Critical packing parameter value type of micellar structure formed can be ascertained as given below, If $\text{CPP} < \frac{1}{2}$ formation of spherical micelles, If $\frac{1}{2} < \text{CPP} < 1$ formation of bilayer micelles, If $\text{CPP} > 1$ formation inverted micelles ³⁹.

METHOD OF PREPARATION OF NIOSOMES

The preparation method of niosomes affects the size, size distribution, number of bilayers, and entrapment efficiency of the aqueous phase and the membrane permeability of the vesicles. It also depends on the use of niosomes.

- 1. Ether injection method:** In this method a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C by slowly. Using a 14-gauge needle, the surfactant mixture in ether is injected into an aqueous solution of material. Single layered vesicles are formed after vaporization of ether ⁴⁰.
- 2. Sonication Method:** Sonication is a typical method for the production of vesicles. In this method a mixture is prepared by adding drug solution in buffer into the surfactant cholesterol which can be taken in 10-ml glass vial. Using a sonicator this mixture is sonicated at 60°C for 3 minutes with a titanium probe to yield niosomes ⁴¹.
- 3. Micro fluidization Method:** Recently, Micro fluidization method is used to prepare unilamellar vesicles of defined size distribution. This method works according to the submerged jet principle. According to this principle two fluidized streams interact at ultra-high velocities, in precisely defined micro channels within the interaction chamber. The energy supplied to the system remains within the area where niosomes is formed. The impingement of thin liquid sheet along a common front is arranged in such a way that the energy is supplied only the niosomes forming area. A greater uniformity, smaller size and better reproducibility of niosomes is formed by this method ⁴².
- 4. Multiple membrane extrusion method:** A thin film is made from the mixture of surfactant, cholesterol and dicetyl phosphate in chloroform by evaporation. The film is hydrated with aqueous drug polycarbonate membranes, solution and the resultant suspension extruded through which are placed in series for upto 8 passages. Niosome size is suitably controlled by this method ⁴³.
- 5. Reverse Phase Evaporation Technique (REV):** Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. Then aqueous phase which contain drug is added to the mixture. Final mixture contains two phases that are sonicated at 4-5 °C. The clear gel is formed where small amount of phosphate buffered saline (PBS) is added here then further sonicated. After sonication organic phase is removed at 40 °C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60 °C for 10 min to yield niosomes ⁴⁴.
- 6. Hand shaking method (thin film hydration technique):** Surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. A thin layer of solid mixture deposited on the wall of the flask after removing organic solvent at room temperature (20 °C) using rotary evaporator the dried The dried surfactant film can be rehydrated with aqueous phase at 0-60 °C with gentle agitation. Typical multilamellar niosomes is formed by this process ⁴⁵.
- 7. Transmembrane pH gradient Drug Uptake Process (Remote Loading):** A solution of surfactant and cholesterol is made in chloroform. A thin film on the wall of the round bottom flask is formed after evaporating the solvent under reduced pressure, similar to the hand shaking method. Hydration of this solution is done by using citric acid solution with help of vortex mixing. Multilamellar vesicles are formed then treated to three freeze thaw cycles and sonicated. Aqueous solution containing 10 mg/ml of drug is added to the niosomal suspension and vortexed. 1M disodium phosphate is used to raise the pH of the sample to 7.0-7.2 and mixture is later heated at 60 °C for 10 minutes to give niosomes ⁴⁶.
- 8. The "Bubble" Method:** Recently the "Bubble" method has been developed and this method allows the preparation of niosomes without the use of organic solvents. The bubbling unit consists of a round bottom flask with three necks which is placed in a water bath to control the temperature. Among the three necks, water cooled reflux and thermometer is positioned in the first and second neck and the third neck is used to supply nitrogen. Cholesterol and surfactant are dispersed together in a buffer (pH 7.4) at 70 °C and mixed for a period of 15 seconds with high shear homogenizer and immediately afterwards, it is bubbled at 70 °C using the nitrogen gas to yield niosomes ⁴⁷.
- 9. Formation of Niosomes from Proniosomes:** Proniosome is a dry formulation in which each water-soluble particle was covered with a thin film of dry surfactant. The niosomes were recognized by the adding aqueous phase at $T > T_m$ with brief agitation. T is the Temperature and T_m is the mean phase transition temperature ⁴⁸.
- 10. Method of Handjani:** The equivalent amounts of synthetic non-ionic lipids were mixed with the aqueous solution of active substance that was encapsulated. Homogenous lamellar film was formed through shaking. Using ultra-centrifugation and agitation, the resultant mixture was then homogenized at a controlled temperature ⁴⁹.
- 11. 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 ⁵⁰.

PHARMACEUTICAL APPLICATION OF NIOSOMES

The application of niosomal technology is widely varied and can be used to treat a number of diseases.

- 1. Niosomes as Drug Carriers:** Niosomes have also been used as carriers for iobitridol, a diagnostic agent used for X-ray imaging. Topical niosomes may serve as solubilization matrix, as a local depot for sustained release of dermally active compounds, as penetration enhancers, or as rate-limiting membrane barrier for the modulation of systemic absorption of drugs.
- 2. Drug Targeting:** One of the most useful aspects of niosomes is their ability to target drugs. Niosomes can be used to target drugs to the reticuloendothelial system. The reticulo-endothelial system (RES) preferentially takes up niosome vesicles. The uptake of niosomes is controlled by circulating serum factors called opsonins. These opsonins mark the niosome for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize to the liver and spleen. This localization of drugs can also be used for treating parasitic infections of the liver. Niosomes can also be utilized for targeting drugs to organs other than the RES. A carrier system (such as antibodies) can be attached to niosomes (as immunoglobulin's bind readily to the lipid surface of the niosome) to target them to specific organs.
- 3. Anti-neoplastic Treatment:** Most antineoplastic drugs cause severe side effects. Niosomes can alter the metabolism; prolong circulation and half-life of the drug, thus decreasing the side effects of the drugs. Niosomes are decreased rate of proliferation of tumor and higher plasma levels accompanied by slower elimination.
- 4. Leishmaniasis:** Leishmaniasis is a disease in which a parasite of the genus *Leishmania* invades the cells of the liver and spleen. Use of niosomes in tests conducted showed that it was possible to administer higher levels of the drug without the triggering of the side effects, and thus allowed greater efficacy in treatment.
- 5. Delivery of Peptide Drugs:** Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. In an in vitro study conducted by oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide.
- 6. Use in Studying Immune Response:** Due to their immunological selectivity, low toxicity and greater stability; niosomes are being used to study the nature of the immune response provoked by antigens. Nonionic surfactant vesicles have clearly demonstrated their ability to function as adjuvant following parenteral administration with a number of different antigens and peptides.
- 7. Niosomes as Carriers for Haemoglobin:** Niosomes can be used as carriers for haemoglobin within the blood. The niosomal vesicle is permeable to oxygen and hence can act as a carrier for haemoglobin in anaemic patients ⁵¹⁻⁵⁴.
- 8. Cancer therapy:** The drugs that are mostly used in the cancer therapy through Niosomal drug delivery are Doxorubicin HCL, Methotextrate, Bleomycin, Vincristine, Daunorubicin HCL. The side effect of Doxorubicin when administered as a free drug is cardiac toxicity, whereas when administered as a niosomal formulation the cardiac toxicity was reduced. By niosomal formulation, doxorubicin has increased level in tumor cells, serum and lungs. It also reduces the proliferation rate of tumor cells and increases the life span of tumor bearing mice. Methotrexate entrapped by niosomes gives higher plasma level and also increase the half-life of drug which gives prolonged action of the drug i.e, it will have slower elimination of drug.
- 9. As carrier:** Niosomes being the vesicles can easily permeate to oxygen and the hemoglobin dissociation curve is modified similarly to non-encapsulated hemoglobin. So they are used as the carrier for haemoglobin ⁵⁵.
- 10. Pre-oral delivery:** The drugs which are degraded by the proteolytic enzymes and gastric juices cannot be administered orally. This can be modified by a niosomal formulation. Eg: Insulin is a peptide hormone which balances the glucose level in the body. It cannot be administered orally because it gets degraded by the proteolytic enzymes in the stomach. Niosomes protects the insulin from degradation by its bilayer formation ⁵⁶.
- 11. Leishmaniasis:** Niosomes can be used in treatment of diseases of reticuloendothelial system. Leishmaniasis is one of the disease in which the protozoan parasites invades the liver and the spleen cells. It is treated using antimonials. These drugs as free drug cannot give increased plasma levels. Sodium stibogluconate niosomal formulation of antimonials can permeate through the cells and target the specific cells. Thus niosomes can be used in drug targeting ⁵⁷.
- 12. Transdermal drug delivery:** The delivery of drugs through skin indicates the transdermal drug delivery. The advantages of this delivery are it does not undergo first-pass metabolism. At the same time, the drawback of this delivery is the penetration of drugs is slow through skin. The skin acts as the barrier for the penetration of drugs this drawback can be overcome by the niosomal preparation. The mechanism followed by the niosomes for transdermal drug delivery is:
 - Diffusion through stratum corneum layer.
 - The amount of water present in the skin is important for this mechanism.
 - The lipophilic drugs cross the stratum corneum by aggregation, fusion and adhesion.
 - The niosomes loses the cells of stratum corneum which increases the permeation of drugs.
 - The non-ionic surfactant enhances the permeation and this leads to improved drug permeation through skin ^{58, 59}.
- 13. Niosomes as carrier in dermal drug delivery:** Niosomes were used for the dermatological purpose in 1975 in cosmetic industry. The first niosomal cosmetic product was launched by Lancome Niosome – an antiaging formulation. Topical formulations of niosomes which are developed recently are mentioned below.

- 14. Local anesthesia:** Absence of sensation is induced by local anesthetics through topical preparation. The penetration of drug is low through skin, so niosomes acts as a carrier to improve the penetration of drug by entrapping them in vesicles which moves through the skin easily. Lidocaine hydrochloride a local anesthetic prepared by niosomes i.e, lidocane entrapped with tween 20 and cholesterol showed better performance compared with liposomes⁶⁰.
- 15. Psoriasis:** Psoriasis is a dermal disorder, caused by a T-lympocytemediated autoimmune disease of dermis and epidermis. It is a chronic inflammatory condition of skin. It forms scaling erythematous plaques on skin. The patient suffers from itching, painful and disfiguring skin lesions. The drugs which are used topically for the treatment of Psoriasis are Anthralin, Methotrexate, Corticosteroids, VitD3, coal tar, Tacrolimus. Methotrexate is an anti-cancer drug used in the treatment of psoriasis, when administered systemically it leads to several adverse effects one which is hepatotoxicity. So, topical application can be selected as an alternate to reduce the adverse effects. The niosomal chitosin Methotrexate gel shows 3 times reduction in lesion after 12 weeks. Thus niosomal Methotrexate gel can be used in topical treatment of psoriasis⁶¹.

CHARACTERIZATION OF NIOSOMES

- 1. Size:** Shape of niosomal vesicles is assumed to be spherical, and their mean diameter can be determined by using laser light scattering method. Also, diameter of these vesicles can be determined by using electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation microscopy, optical microscopy and freeze fracture electron microscopy. Freeze thawing (keeping vesicles suspension at 20 °C for 24 hrs and then heating to ambient temperature) of Niosomes increases the vesicle diameter, which might be attributed to fusion of vesicles during the cycle⁶².
- 2. Stability study:** Stability studies are done by storing niosome at two different conditions, usually 4±1 0C and 25±2 0C. Formulation size, shape and number of vesicles per cubic mm can be assessed before and after storing for 30 days. After 15 and 30 days, residual drug can also be measured. Light microscope is used for determination of size of vesicles and the numbers of vesicles per cubic mm is measured by haemocytometer^{63,64}.

Number of niosomes per cubic mm = Total number of niosomes x dilution factor x 400/ Total number of small squares counted

- 3. Vesicular surface charge:** Niosomes are generally prepared by the inclusion of charged molecules in bilayer to prevent the aggregation of vesicles⁶⁵. A reduction in aggregate formation was observed when charged molecule like dicetyl phosphate was incorporated in vesicles. The charge on vesicles is expressed in terms of zeta potential and calculated using the Henry's equation^{66,67}.

$$\xi = \mu E \pi \eta / \Sigma$$

Where,

- ξ - Zeta potential
 μE - Electrophoretic mobility
 η - Viscosity of medium
 Σ - Dielectric constant

- 4. Bilayer Formation:** Assembly of non-ionic surfactants to form a bilayer vesicle is characterized by an X-cross formation under light polarization microscopy⁶⁸.
- 5. Number of Lamellae:** This is determined by using nuclear magnetic resonance (NMR) spectroscopy, small angle X-ray scattering and electron microscopy⁶⁹.
- 6. Membrane Rigidity:** The mobility of fluorescence probe as a function of temperature has been used for the determination of membrane rigidity of some niosomal formulations. Membrane rigidity can be measured by means of mobility of fluorescence probe as a function of temperature⁷⁰.
- 7. Entrapment Efficiency:** drug is separated 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 drug⁷¹.

Drug Entrapment efficiency = (Amount entrapped / total amount) x 100.

- a. In-Vitro Release Study:** A method of in vitro release rate study has been reported with the help of dialysis tubing. A dialysis sac is washed and soaked in distilled water. The vesicle suspension is pipetted into a bag made up of the tubing and sealed. The bag containing the vesicles is then placed in 200 ml buffer solution in a 250 ml beaker with constant shaking at 25 °C or 37 °C. At various time intervals, the buffer is analyzed for the drug content by an appropriate assay method. In another method, isoniazid-encapsulated niosomes are separated by gel filtration on Sephadex G-50 powder kept in double distilled water for 48 h for swelling. At first, 1 ml of prepared niosome suspension is placed on the top of the column and elution is carried out using normal saline. Niosomes encapsulated isoniazid elutes out first as a slightly dense, white opalescent suspension followed by free drug. Separated niosomes are filled in a dialysis tube to which a sigma dialysis sac is attached to one end. The dialysis tube is suspended in phosphate buffer of pH 7.4, stirred with a magnetic stirrer, and samples are withdrawn at specific time intervals and analyzed using high-performance liquid chromatography (HPLC) method^{71,72}.

- b. In Vivo Release Study:** Albino rats are used for this study. These rats are subdivided with groups. Niosomal suspension used for in vivo study is injected intravenously (through tail vein) using appropriate disposal syringe^{71,72}.

CONCLUSION

For decades, pharmaceutical sciences have been utilizing nanoparticles to reduce harmfulness and side impacts of drugs. Niosomal drug delivery systems to be favourable controlled drug delivery systems to the target area. Niosomes are composed mainly of non-ionic surfactants and cholesterol. Niosomes are relatively non-toxic and stable and offer successful drug localization in skin. Physical and chemical instability of active drug can be protected by vesicular carriers. The properties of Niosomes are affected by additives, methods of preparation, drug properties, amount, structure and type of surfactant used, cholesterol content and resistance to osmotic stress. In nutshell, as a drug delivery device, compared to liposomes, niosomes are osmotically active and are quite stable chemically by their own as well as improve the stability of the drug so entrapped and delivered. Among the all of these points of interest there

are still a few challenges in this range. The sort of surfactant is the most parameter since it influences the arrangement of the vesicles, their poisonous quality and soundness. So the specialists should be more alert within the choice of appropriate surfactant for niosome arrangement.

REFERENCES

- Yoshida A, Lehr CM, Kok W, Junginger HE, Verhoef JC, Bouwstra JA. Niosomes for oral delivery of peptide drugs. *J. Control Release*. 1992; 21:145-154.
- Rastogi V, Shukla SS, Singh R, Lal N, Yadav P. Microspheres: A Promising Drug Carrier, *JDDT*, 2016; 6(3):18-26.
- Manconi M., Sinico C, Donatella V, Loy G, Fadda AM. Niosomes as carriers for tritenion. I. Preparation and properties. *Int. J. Pharm.* 2002; 234:237-248.
- Hu C, Rhodes DG. Proniosomes: a novel drug carrier preparation. *Int. J. Pharm.* 2000; 206:110-122.
- Baillie AJ, Florence AT, Hume LR, Muirhead GT, Rogerson A. The preparation and properties of niosomes non-ionic surfactant vesicles. *J. Pharm. Pharmacol.* 1985; 37:863-868.
- Yoshioka T, Stermberg B, Florence AT. Vesicle (niosome)-in-water-in-oil (v/w/o) emulsions: an in vitro study. *Int J Pharm.* 1994; 105:1-6.
- Chandraprakash KS, Udupa N, Umadevi P, Pillai GK. Pharmacokinetic evaluation of surfactant vesicles containing methotrexate in tumor bearing mice. *Int J Pharm.* 1990; 61:R1-R3.
- Buckton G, Harwood. *Interfacial phenomena in drug delivery and targeting*. Switzerland Academic Publishers. 1995; 154-155.
- Akhilesh D, Hazel G, Kamath JV. Proniosomes - A propitious provesicular drug carrier. *International Journal of Pharmacy and Pharmaceutical Science Research*. 2011; 1(3):98-103.
- 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 NK. Niosomes as Drug Carriers. *Indian Drugs*, 1994; 31(3):81-866.
- Alsarra A, Bosela A, Ahmed SM, Mahrous GM. Proniosomes as a drug carrier for transdermal delivery of ketorolac. *Eur. J. Pharm. and Biopharm.* 2004; 2(1):1-6.
- Vyas SP, Khar RK. *Targeted and Control Drug Delivery*. 1st ed., CBS Publishers and Distributors, New Delhi; 2002. P. 249-276.
- Kiwada H, Niimura H, Fujisaki Y, Yamada S, Kato Y. Application of synthetic alkyl glycoside vesicles as drug carriers. I preparation and physical properties. *Chem. Pharm. Bull.* 1985; 33:753-759.
- Reddy DN, Udupa N. Formulation and Evaluation of Oral and Transdermal Preparations of Flurbiprofen and Piroxicam Incorporated with Different Carriers. *Drug Dev. Ind. Pharm.* 2008; 19(7):843-852.
- Carafa M, Santucci E, Alhaique F, Coviello T, Murtas E, Ricciari FM, Lucania G, Torrisi MR. Preparation and properties of new unilamellar non-ionic surfactant vesicles. *Int J Pharm* 1998; 160:51-59.
- Rajanaresh RA, Chandrashekhar G, Pillai G K, Udupa N. Antiinflammatory activity of Niosome encapsulated diclofenac sodium with Tween-85 in Arthitic rats. *Indian J. Pharmacol.* 1994; 26:46-48.
- Niemiec SM, Hu Z, Ramachandran C, Wallach DFH, Weiner N. The effect of dosing volume on the disposition of cyclosporin-A in hairless mouse skin after topical application of a nonionic liposomal formulation: An *in vitro* diffusion study. *STP Pharma Sci.* 1994; 4:145-149.
- Guedj C, Pucci B, Zarif L, Coulomb C, Riess JG, Pavia A. Vesicles and other supramolecular systems from biocompatible synthetic glycolipids with hydrocarbon and/or fluorocarbon chains. *Chem. Phys. Lipids.* 1994; 72:153-173.
- Gebicki JM, Hicks M. Preparation and properties of vesicles enclosed by fatty acid membranes. *Chem Phys Lipids* 1976; 16:142-160.
- Sahin NO. *Nanomaterials and Nanosystems for Biomedical Applications*. Edited by Mozafari M. R., Springer, The Netherlands; 2007.P. 67-81.
- Uchegbu IF, Vyas SP. Nonionic surfactant based vesicles (niosomes) in drug. *International journal of pharmaceutics*. 1998; 172(1-2):33-70.
- Hu C, Rhodes DG. Proniosomes: a novel drug carrier. *Int J Pharm.* 1999; 185: 23-35.
- Cosco D, Paolino D, Muzzalupo R, Celia C, Citraro R, Caponio D, Picci N, Fresta M. Novel PEG-coated niosomes based on bola-surfactant as drug carriers for 5-fluorouracil. *Biomed Microdevices*. 2009; 11:1115-1125.
- Junyaprasert VB, Teeranachaideekul V, Supapern T. Effect of Charged and Non-ionic Membrane Additives on Physicochemical Properties and Stability of Niosomes. *AAPS PharmSciTech*. 2008; 9:851-859.
- <http://pharmaxchange.info/articles/niosomes/niosomes.html>
- Jain CP, Vyas SP, Dixit VK. Niosomal system for delivery of rifampicin to lymphatics. *Indian J Pharm Sci.* 2006; 68(5):575.
- Cevc G. Transfersomes, liposomes and other lipid suspensions on the skin: permeation enhancement, vesicle penetration, and transdermal drug delivery. *Crit Rev Ther Drug Carrier Syst.* 1996; 13(3-4):257.
- Makeshwar K, Wasankar S. Niosomes: a novel drug delivery system. *Asian J. Pharm. Res.* 2013; 3:16-20.
- Verma A. A vital role of niosomes on Controlled and Novel Drug delivery. *Indian Journal of Novel Drug Delivery*. 2011; 3:238-246.
- Arul J, Shanmuganathan S, Nagalakshmi. An Overview on Niosome as Carrier in Dermal Drug Delivery. *Journal of pharmaceutical sciences and research*. 2015; 7:923-927.
- Moghassemi S, Hadjizadeh A. Nano-niosomes as Nanoscale Drug Delivery Systems: An illustrated review. *Journal of Controlled Release*. 2014; 2:22-36.
- Schreier H. Liposomes and niosomes as topical drug carriers: dermal and transdermal delivery. *J. Controlled Release*, 1985; 30:863-868.
- Desai TR, Finlay WH. Nebulization of niosomal all-trans-retinoic acid: An inexpensive alternative to conventional liposomes. *Int J Pharm.* 2002; 241(2):311-317.
- Hunter CA, Dolan TF, Coombs GH, Baillie AJ. Vesicular systems (niosomes and liposomes) for delivery of sodium stibogluconate in experimental murine visceral leishmaniasis. *J.Pharm. Pharmacol*, 1988; 40(3):161-165.
- Kaur H, Dhiman S, Arora S. Niosomes: A novel drug delivery system. *Int. J. Pharm. Sci. Rev. Res.* 2012; 15:113-120.
- Navya M. Niosomes As novel vesicular drug delivery system- A review. *Asian Journal of Research in Biological and Pharmaceutical Sciences*. 2014; 2:62-68.
- Kumar GP, Rao PR. Ultra deformable niosomes for improved transdermal drug delivery: The future scenario. *Asian Journal of Pharmaceutical Sciences*, 2012; 7(2):96-109.
- Satturwar PM, Fulzele SV, Nande VS, Khandare JN. Formulation and evaluation of ketoconazole Niosomes. *Indian J.Pharm*, 2002; 64(2):155-158.
- Vyas SP, Khar RK. *Targeted and Control Drug Delivery*. 1st ed., CBS Publishers and Distributors, New Delhi; 2002. P. 278-279.
- Gibaldi M, Perrier D. *Pharmacokinetics*, second edition, New York, Marcel Dekker, Inc., 1982. P. 127-134.
- Namdeo A, Jain NK, Niosomal delivery of 5-fluorouracil. *J. Microencapsul.* 1999; 16(6):731-740.
- Mayer LD, Bally MB, Hope MJ, Cullis PR, *Biochem Biophys. Acta.* 1985; 816:294-302.
- Pawar SD, Pawar RG, Kodag PP, Waghmare AS, Niosome: An Unique Drug Delivery System, *International Journal of Biology, Pharmacy and Allied Sciences*. 2012; 3:409-412.
- Weissman G, Bloomgarden D, Kaplan R, Cohen C, Hoffstein S, Collins T, Gotlieb A, Nagle D. A general method for the introduction of enzymes, by means of immunoglobulin-coated liposomes, into lysosomes of deficient cells. *Proc. Natl. Acad. Sci.* 1975; 72:88-92.
- Blazek-Walsh AI, Rhodes DG. SEM imaging predicts quality of niosomes from maltodextrin-based proniosomes, *Pharm. Res.*, 2001; 18:656-661.
- Devi G, Venkatesh P, Udupa, N. Niosomal sumatriptan succinate for nasal administration, *Int. J. Pharm. Sci.* 2000; 62(6): 479-481.
- Keservani RK, Sharma AK, Ayaz1 M. Novel drug delivery system for the vesicular delivery of drug by the niosomes.

- International Journal of Research in Controlled Release. 2011; 1:1-8.
50. Ruckmani K, Jayakar B and Ghosal SK. Non-ionic surfactant vesicles (Niosomes) of cytarabine hydrochloride for effective treatment of leukaemia: Encapsulation, Storage and In-vitro release Drug Development and Industrial Pharmacy. 2000; 26:217-222.
 51. Baillie AJ, Coombs GH and Dolan TF. Non-ionic surfactant vesicles, niosomes, as delivery system for the anti-leishmanial drug, sodium stibogluconate. J. Pharm. Pharmacol. 1986; 38:502-505
 52. Conacher M, Alexanderand J, Brewer JM, Conacher M, and Alexander J. Niosomes as Immunological Adjuvants. In "Synthetic Surfactant Vesicles. International Publishers Distributors Ltd. Singapore, 2000. P.185-205.
 53. Azmin MN, Florence AT, Handjani-Vila RM, Stuart JB, Vanlerberghe, G and Whittaker JS, J. Pharm. Pharmacol. 1985; 37:237.
 54. Mozafari MR. Nanomaterials and Nanosystems for Biomedical Applications, Springer, 2007. P. 67–81.
 55. Elbary AA, El-laithy HM, Tadros MI. Sucrose stearate-based proniosomederived niosomes for the nebulisable delivery of cromolyn sodium. Int J Pharm, 2008; 357:189-198.
 56. Perrett S, Golding M, Williams WP. A simple method for the preparation of liposomes for pharmaceutical application and characterization of liposomes. J Pharm Pharmacol. 1991; 43:154-161.
 57. Schreier H, Bouwstra J. Liposomes and niosomes as topical drug carriers: dermal and transdermal drug delivery. J. Control Release. 1994; 30:1-15.
 58. Carafa M, Santucci E, Alhaique F, Coviello T, Murtas E, Riccieri F, Lucania G, Torrisi MR. Lidocaine loaded non-ionic surfactant visicles: Characterization and invitro permeation studies. Int J Pharm. 2002; 231:21-32.
 59. Rastogi V, Pragya, Upadhyay P. A Brief View on Antihypertensive Drugs Delivery through Transdermal Patches. IJPSR. 2012; 3(7):1955-1970.
 60. Preeti K, Suresh, Singh P, Saraf S. Novel topical drug carriers as a tool for treatment of psoriasis: Progress and advances. African Journal of Pharmacy and Pharmacology, 2010; 7:138-147.
 61. Ansel HC, Popovich NG, Allen LV. Pharmaceutical dosage forms and drug delivery systems. Lippincott Williams & Wilkins; 1995.
 62. Erdogan S, Ozer AY, Bilgili H. Niosomes: A Controlled and Novel Drug delivery System, International Journal of Pharmaceutics. 2005; 295:1-6.
 63. Bayindir ZS, Yuksel N. Niosomes: A Controlled and Novel Drug delivery System, Journal of Pharmaceutical Sciences. 2010; 99:2049-2060.
 64. Reddy DN, Udupa N, Vesicles of Non-ionic Surfactants (Niosomes) and Drug Delivery Potential. Drug Dev. Ind. Pharm., 1993; 19:843.
 65. Desai AR, Raghuvveer I, Chitme HR, Chandra R. Niosomes: A Controlled and Novel Drug delivery System. Drug Invention Today. 2010; 2:325-327.
 66. Khacndare JN, Madhavi G, Tamhankar BM. Niosomes: Novel drug delivery system. The Eastern Pharmacist. 1994; 37:614.
 67. Manosroi A, Wongtrakul P, Manosroi J, Sakai H, Sugawara F, Yuasa M. Characterization of vesicles prepared with various non-ionic surfactants mixed with cholesterol. Colloids Surf B. 2003; 30:129-38.
 68. Biswal S, Murthy PN, Sahu J, Sahoo P, Amir F. Vesicles of non-ionic surfactants (niosomes) and drug delivery potential. Int J Pharm Sci Nanotech. 2008; 1:1-8.
 69. Rajera R, Nagpal K, Singh SK, Mishra DN. Niosomes: A controlled and novel drug delivery system. Bio Pharm Bull. 2011; 34(7):945-953
 70. Agarwal R, Katare OP, Vyas SP. Preparation and in vitro evaluation of liposomal/niosomal delivery systems for antipsoriatic drug dithranol. Int J Pharm. 2001; 228(1):43-52.
 71. Karki R, Mamatha GC, Subramanya G, Udupa N. Preparation, characterization and tissue disposition of niosomes containing isoniazid. Rasayan J Chem. 2008; 1:224-227.
 72. Uchegbu IF, Vyas SP. Non-ionic surfactant based vesicles (niosomes) in drug delivery. Int J Pharm. 1998; 172:33-70.



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