

NIOSOMAL DRUG DELIVERY SYSTEM: FORMULATION AND APPLICATIONS

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ABSTRACT

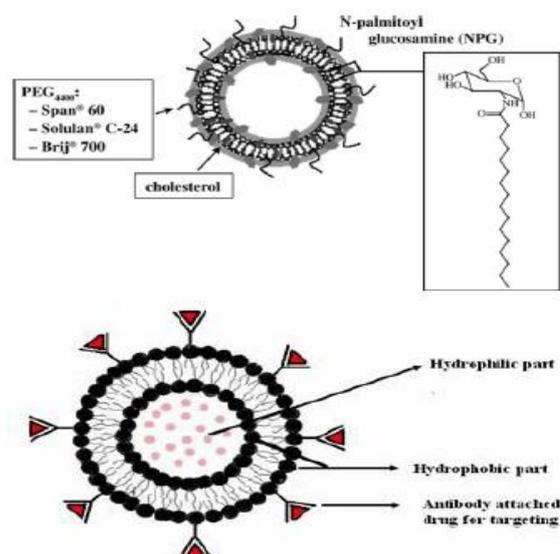
Nonionic surfactant vesicles (niosome) have drawn a lot of attention in the area of modern drug delivery systems due to their salient features such as biodegradability, biocompatibility, chemical stability, low production cost, easy storage and handling and low toxicity. Niosomes are hydrated vesicular systems having a lamellar bilayer structure formed from nonionic surfactants with or without cholesterol and they are capable of encapsulating bioactive compounds with a wide range of solubility. Niosomal systems offer advantages over conventional delivery systems via delivering the bioactives in a controlled/sustained manner and delivering the actives to the target site. Niosomes tackle the problem of insolubility, instability, low bioavailability and rapid degradation of drugs. This paper overviews the general advantages of niosomal systems along with their potential applications in pharmaceutical areas. This article also highlights the effect of niosomal formulation on the physicochemical properties of niosomal systems. Various techniques of preparation are detailed and some down-sizing approaches have been identified.

KEYWORDS: Niosomes, controlled release kinetics, Bioavailability, preparation, applications.

INTRODUCTION

Niosomes are colloidal particles formed from the self-assembly of non-ionic surfactants in aqueous medium resulting in closed bilayer structures. The assembly into closed bilayers is not always spontaneous and requires input of external energy such as heat or shearing forces. Niosomes were first reported as a feature of cosmetic industry in the seventies and have been used in cosmetic formulations devised by L'Oreal and since then niosomes were extensively studied as an alternative drug delivery system to liposomes. Niosomes and liposomes are both similar in structure, as well as the manner of entrapping drugs. Niosomes structurally consist of a non-ionic surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicle to the aqueous phase, while hydrophobic chains face each other within the bilayer. Like liposomes, niosomes are also capable of entrapping both hydrophilic and hydrophobic drugs. In contrast to liposomes, the bilayer system in niosomes is made up of uncharged single-chain nonionic surface-active agents, while double-liposomal structures. Niosomes as drug carriers offer remarkable advantages that make them preferable over other conventional and vesicular delivery systems. Biodegradability, biocompatibility, chemical stability, low production cost, easy storage and handling and low toxicity are the main benefits for developing niosomal systems. Niosomes can be administered through various routes such as oral, parenteral, topical, ocular, etc. In recent years niosomal formulations have been extensively used as a carrier to

deliver different types of drugs (synthetic and herbal), antigens, hormones and other bioactive compounds. This article presents some advantages of niosomes along with an overview of the preparation techniques and the current applications of niosomes in encapsulation and chain phospholipids (neutral or charged) seen in the delivery of bioactive compounds. This review also addresses the influence of formulation such as the nature of the surfactant, cholesterol and the encapsulated drug on the characteristics of niosomes.

Fig 1: Structure of Niosomes

Advantages of Niosomes

- The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic purpose may offer several advantages.
- They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.
- Niosomal dispersion in an aqueous phase can be emulsified in a nonaqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-aqueous phase.
- They are osmotically active and stable, as well as they increase the stability of entrapped drug.
- Handling and storage of surfactants requires no special conditions.
- They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
- They can be made to reach the site of action by oral, parenteral as well as topical routes.
- They possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties

together and as a result can accommodate drug molecules with a wide range of solubilities.

- The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics.
- The vesicles may act as a depot, releasing the drug in a controlled manner.

METHODS OF PREPARATION

A. 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.

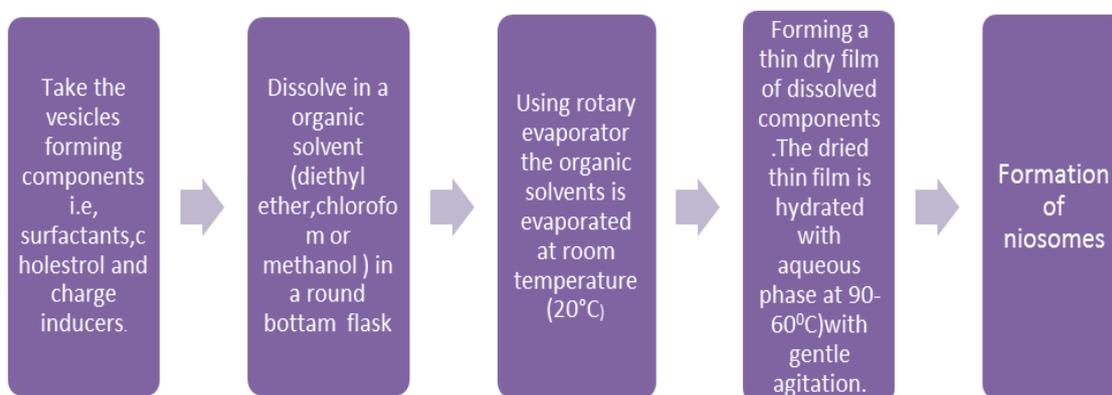


Fig 2: Steps in formulation of niosomes by thin film hydration Technique.

B. Reverse Phase Evaporation Technique (REV)

Novelty in this system is the removal of volatile organic solvent by the process of evaporation. Mixture of ether and chloroform is taken; disperse cholesterol and surfactant in equal ratio i.e (1:1) to the above solvent. Aqueous phase containing drug is added to the above solution and the resulting two phases are sonicated for

few minutes. Clear gel is formed which is further sonicated for few minutes by the addition of small amount of phosphate buffer saline. Underneath at low pressure, the organic phase is removed by evaporation. The resulting suspension is further diluted with PBS solution and heated on water bath at optimum temperature (45°C) for 10 min to yield niosomes.

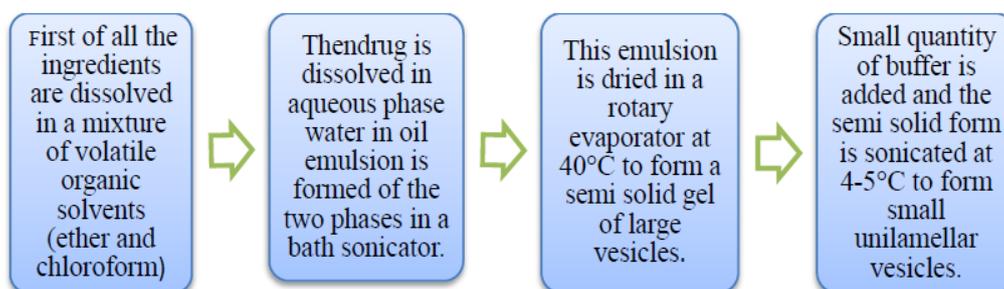


Fig 3: Steps in formulation of niosomes by Reverse Phase Evaporation Technique.

C. 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 1000nm.

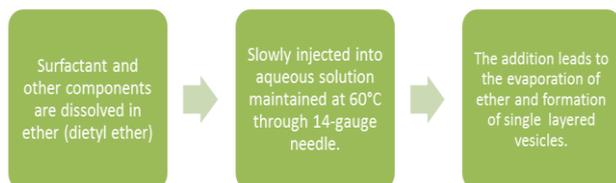


Fig 4: Steps in formulation of niosomes by Ether injection method.

D. Trans membrane pH gradient (inside acidic) Drug Uptake Process (remote Loading)

The organic solvent chloroform is taken in round bottom flask to which the surfactant and cholesterol is added. Organic solvent on evaporation leads to production of lipid film on the side walls of the flask. Furthermore, the formulated thin film is undergone to hydration process by vortex mixing with 300 mM citric acid (pH 4.0). The formed multi lamellar niosomes are frozen and thawed three times followed by the sonication process for few minutes. To this niosomal suspension aqueous solution containing 10 mg/ml of drug is added and later vortexed. Adding up of the disodium phosphate (1M) gradually raises pH from 7.0-7.2. At last, the solution should be mixed properly and heated at 60°C for 10 minutes to produce the desired multi lamellar vesicles.

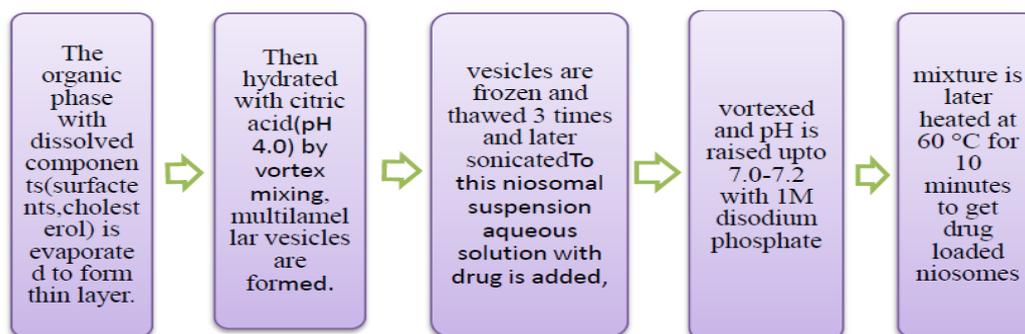


Fig 5: Steps in formulation of niosomes by Trans membrane pH gradient (inside acidic) Drug Uptake Process.

E. The “Bubble” Method

This method is suitable for preparation of niosomes and liposomes without the use of volatile organic solvents. Bubbling unit comprises of 3 necked round bottomed flasks which is kept in water bath for controlling the temperature. To the 1st neck of the flask water cooled reflux and 2nd neck thermometer is placed, and nitrogen

supply through the 3rd neck. By the side heat the flask to 70°C temperature. Membrane additives like cholesterol and surfactant are added together in the buffer (pH 7.4) and miscellaneous with elevated shear homogenizer for 15 seconds and immediately afterwards “bubbled” at 70°C using nitrogen gas.

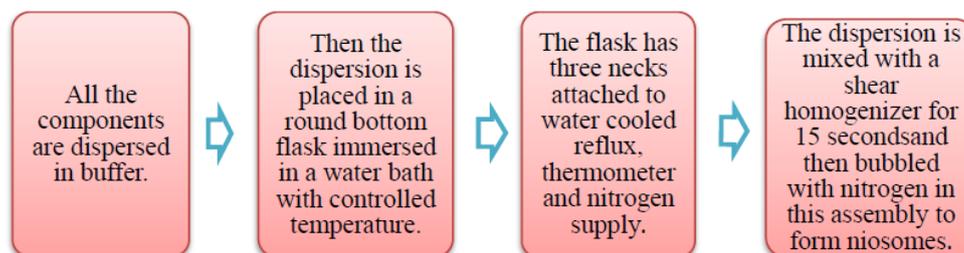


Fig 6: Steps in formulation of niosomes by Bubble Method.

F. Sonication

Sonication is a usual technique for the preparation of niosome vesicles. 10-ml glass vial containing drug, surfactants and cholesterol is taken and is mixed with buffer. After that the mixture is probe sonicated for about 3 minutes by a sonicator with titanium probe to produce niosomes. The resulting product contains small and unilamellar vesicles. This technique is most widely used in preparation of small vesicles. Sonication process

comprises of two types and they are of probe and bath type sonicators, depending upon the requirement either of which can be used.

Separation of Unentrapped Drug

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

1. Dialysis: The aqueous niosomal dispersion is dialyzed in a dialysis tubing against phosphate buffer or normal saline or glucose solution. organic solvents. The bubbling unit consists of round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer 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.

2. Gel Filtration: The untrapped drug is removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution with phosphate buffered saline or normal saline.

3. Centrifugation: The niosomal suspension is centrifuged and the supernatant is separated. The pellet is washed and then resuspended to obtain a niosomal suspension free from untrapped drug.

Formation of niosomes from proniosomes

Another method of producing niosomes is to coat a water-soluble carrier such as sorbitol with surfactant. The result of the coating process is a dry formulation. In which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed “Proniosomes”. The niosomes are recognized by the addition of aqueous phase at $T > T_m$ and brief agitation. T =Temperature. T_m = mean phase transition temperature have 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.

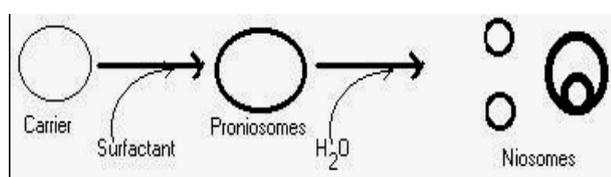


Fig.7: Formation of niosomes from proniosomes.

Comparison of Niosomes and Liposomes

Niosomes are now widely studied as an alternative to liposomes, which exhibit certain disadvantages such as – they are expensive, their ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they require special storage and handling and purity of natural phospholipids is variable. Niosomes are prepared from uncharged single-chain surfactant and cholesterol whereas liposomes are prepared from doublechain phospholipids (neutral or charged).

Niosome behave *in-vivo* like liposomes, prolonging the circulation of entrapped drug and altering its organ

distribution and metabolic stability. Encapsulation of various anti neoplastic agents in these carrier vesicles has been shown to decrease drug induced toxic side effects, while maintaining, or in some instances, increasing the anti-tumor efficacy. Such vesicular drug carrier systems alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug. They can be expected to target the drug to its desired site of action and/or to control its release.

Characterization and Factors Affecting Formation of Niosomes Size

The formulated niosomes are assumed to be sphere-shaped and also different techniques can be utilized to resolve their mean diameter. Laser light scattering method, electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation microscopy, optical microscopy and freeze fracture electron microscopy. Bilayer vesicle formation by combination 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 number of lamellae.

Nature of surfactants

A surfactant used for preparation of niosomes must have a hydrophilic head and hydrophobic tail. The hydrophobic tail may consist of one or two alkyl or perfluoroalkyl groups or in some cases a single steroidal Group. The ether type surfactants with single chain alkyl as hydrophobic tail is more toxic than corresponding dialkylether chain. The ester type surfactants are chemically less stable than ether type surfactants and the former is less toxic than the latter due to ester-linked surfactant degraded by esterases to triglycerides and fatty acid *in vivo*. The surfactants with alkyl chain length from C12-C18 are suitable for preparation of niosome.

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.

Membrane 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 (cholesteryl poly-24-oxyethylene ether), which prevents aggregation due to development of steric hindrance.

Nature of encapsulated drug

The physico-chemical properties of encapsulated drug influence charge and rigidity of the niosome bilayer. The drug interacts with surfactant head groups and develops the charge that creates mutual repulsion between surfactant bilayers and hence increases vesicle size.

Temperature of hydration

Hydration temperature influences the shape and size of the niosome. For ideal condition it should be above the gel to liquid phase transition temperature of system. Temperature change of niosomal system affects assembly of surfactants into vesicles and also induces vesicle shape transformation.

Bilayer formation

Assembly of non-ionic surfactants to form bilayer vesicle is characterized by X-cross formation under light polarization microscopy.

Entrapment efficiency (EE)

The entrapment efficiency (EE) is expressed as $EE = \frac{\text{amount entrapped}}{\text{total amount added}} \times 100$. It is determined after separation of untrapped drug, on complete vesicle disruption by using about 1ml of 2.5% sodium lauryl sulfate, briefly homogenized and centrifuged and supernatant assayed for drug after suitable dilution. Entrapment efficiency is affected by following factors.

a. Surfactants

The chain length and hydrophilic head of nonionic surfactants affect entrapment efficiency, such as stearyl chain C18 non-ionic surfactant vesicles show higher entrapment efficiency than lauryl chain C12 non-ionic surfactant vesicles. The tween series surfactants bearing a long alkyl chain and a large hydrophilic moiety in the combination with cholesterol at 1:1 ratio have highest entrapment efficiency for water soluble drugs. HLB value of surfactants affects entrapment efficiency, such as HLB value of 14 to 17 is not suitable for niosomes but HLB value of 8.6 has highest entrapment efficiency and entrapment efficiency decreases with decrease in HLB value from 8.6 to 1.7.

b. Cholesterol contents

The incorporation of cholesterol into bilayer composition of niosome induces membrane stabilizing activity and

decreases the leakiness of membrane. Hence, incorporation of cholesterol into bilayer increases entrapment efficiency. The permeability of vesicle bilayer to 5, 6-carboxy fluorescein (CF) is reduced by 10 times due to incorporation of cholesterol

Evaluation of Formulations

A. Scanning electron microscopy: The shape and surface characteristics of niosomes can be evaluated by scanning electron microscopy. The lyophilised sample is mounted directly on to the sample holder using double-sided sticking tape and after gold coating images were recorded at the required magnification. 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 are sprinkled on to the double-sided tape that was affixed on aluminum stubs. The aluminum stub is placed in the vacuum chamber of a scanning electron microscope (XL 30 ESEM with EDAX, Philips, Netherlands). The samples are observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 torr, acceleration voltage: 30.00 KV) XL 30, (Philips, Netherlands).

B. Particle size: Vesicle size determination can be carried out using an optical microscopy with a calibrated eyepiece micrometer. About 200 niosomes were measured individually, average was taken, and their size range, mean diameter were calculated.

C. Entrapment efficiency: The percentage entrapment efficiency of the vesicles can be determined by freeze thawing centrifugation technique. Niosomal suspension was filled in drop tubes and stored at -20°C in a refrigerator for 24 hours. After 24 hours niosomal suspension was taken from refrigerator and stored at room temperature. The niosomal suspension was centrifuged at 1500 X G rpm for 30 minute. Supernatant containing untrapped drug was withdrawn and diluted with water methanol mixture (80:20), then measured UV spectrophotometrically at 244 nm against water methanol mixture as standard.

Entrapment efficiency (EE) can be calculated by using following equation:

$$\text{Percentage EE} = \frac{\text{Total amount of drug in suspension} - \text{drug in suspension}}{\text{Total amount of drug present in suspension}} \times 100$$

D. Stability study

Stability studies are performed by storing niosome at two different conditions, usually $4 \pm 1^{\circ}\text{C}$ and $25 \pm 2^{\circ}\text{C}$. Formulation size, shape and number of vesicles per cubic mm can be measured before and after storing for 30 days. After 15 and 30 days, residual drug can also be

measured. Light microscope can be used for determination of size of vesicles and the numbers of vesicles per cubic mm is measured by haemocytometer. Number of niosomes per cubic mm = Total number of niosomes x dilution factor x 400/Total number of small squares counted. 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. In the percentage drug retained. The niosomes were sampled 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).

E. In vitro release study

Dialysis: A method of in vitro release rate study is reported with the help of dialysis tubing. A dialysis bag was 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 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.

Reverse dialysis: In this technique, niosomes are placed in a number of small dialysis tubes containing 1 ml of dissolution medium and the niosome are then displaced from the dissolution medium.

Franz diffusion cell: In the Franz diffusion cell, the cellophane membrane is used as the dialysis membrane. Niosomes are dialyzed through a cellophane membrane against a suitable dissolution medium at room temperature. The samples are withdrawn at suitable time interval and analyzed for drug content using suitable method (U.V spectroscopy, HPLC, etc). The maintenance of sink condition is essential.

Applications

The application of niosomes technology is widely varied and can be used to treat a number of diseases. The following are a few uses of niosomes which are either proven or under research.

Niosomes can also be utilized for sustained drug release and localized drug action to greatly increase the safety and efficacy of many drugs. Toxic drugs which need higher doses can possibly be delivered safely using niosomal encapsulation. Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Some of their therapeutic applications are discussed below:

1. Targeting of bioactive agents

a) To reticulo-endothelial system (RES): The niosomal vesicles are taken up by the cells RES normally e.g. circulating serum factor known as opsonin, which mark them for clearance. Such localized drug accumulation has been exploited in treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of liver.

b) To organs other than RES: It has been suggested that carrier system can be directed to specific sites in the body by use of antibodies. Immunoglobulins seem to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier. Many cells possess the intrinsic ability to recognize and bind particular carbohydrate determinants and this can be exploited to direct carriers system to particular cells. There are proved examples for success of such delivery.

(1). Neoplasia: Doxorubicin, the anthracyclic antibiotic with broad spectrum anti tumor activity, shows a dose dependant irreversible cardio toxic effect. Niosomal delivery of this drug to mice bearing S180 tumor increased their life span and decreased the rate of proliferation of sarcoma. Niosomal entrapment increased the half-life of the drug, prolonged its circulation and altered its metabolism. Intravenous administration of methotrexate entrapped in niosomes to S-180 tumor bearing mice resulted in total regression of tumor and also higher plasma level and slower elimination.

(2). Leishmaniasis: Niosomes can be used for targeting of drug in the treatment of diseases in which the infecting organism resides in the organ of reticulo-endothelial system. Leishmaniasis is such a disease in which parasite invades cells of liver and spleen. The commonly prescribed drugs are antimonials at high concentration they damage the heart, liver and kidney. The study of antimony distribution in mice, performed by Hunter et al showed high liver level after intravenous administration of the carrier forms of the drug. Ovulation and that the effect of two doses given on successive days was additive.

(3). Delivery of peptide drugs: Yoshida et al investigated oral delivery of 9- desglycinamide, 8- arginine vasopressin entrapped in niosomes in an in-vitro intestinal loop model and reported that stability of peptide increased significantly.

(4). Immunological application of niosomes: Niosomes have been used for studying the nature of the immune response provoked by antigens. Brewer and Alexander have reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability.

(5). Niosomes as carriers for hemoglobin: Niosomes can be used as a carrier for hemoglobin. Niosomal suspension shows a visible spectrum super imposable onto that of free hemoglobin. Vesicles are permeable to

oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin.

(6). Transdermal delivery of drugs by niosomes: Slow penetration of drug through skin is the major drawback of transdermal route of delivery. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes. Jayraman et al has studied the topical delivery of erythromycin from various formulations including niosomes or hairless mouse. From the studies, and confocal microscopy, it was seen that nonionic vesicles could be formulated to target pilosebaceous glands.

(7). Diagnostic imaging: Niosomal system can be used as diagnostic agents. Conjugated niosomal formulation of gadobenate dimeglumine with [N-palmitoyl glucosamine (NPG)], PEG 4400, and both PEG and NPG exhibit significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging.

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

(9). Brain targeting for the vasoactive intestinal peptide (VIP): Radioactive (I125) VIP loaded glucose bearing niosomes were injected intravenously to mice. Encapsulated VIP within glucose bearing ribosomes exhibits higher VIP brain uptake as compared to control.

2. Other applications

- **Sustained Release Action:** Azmin et al suggested the role of liver as a depot for methotrexate after niosomes are taken up by the liver cells. Sustained release action of niosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via niosomal encapsulation.
- **Localized drug action:** Niosomal Drug delivery can be used to achieve localized drug action, since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration. Localized drug action results in enhancement of efficacy of potency of the drug and at the same time reduces its systemic toxicity. For example antimonials encapsulated within niosomes are taken up by mononuclear cells resulting in localization of drug, increase in potency and decrease both dose and toxicity.

CONCLUSION

It is obvious that niosome appears to be a well preferred drug delivery system over liposome as niosome being stable and economic. Also niosomes have great drug delivery potential for targeted delivery of anti-cancer, antiinfective agents. Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant. Thus these areas need further exploration and research so as to bring out commercially available niosomal preparation. The concept of incorporating the drug into liposomes or niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. Niosomes represent a promising drug delivery module. They presents a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multienvironmental structure. Niosomes are thoughts to be better candidates drug delivery as compared to liposomes due to various factors like cost, stability etc. Various type of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical and parenteral.

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