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A Mini Review on Niosome

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Arun Kumar*, D. M. Tripathi, Swarnim Srivastava

Aryakul College of Pharmacy and Research, Lucknow, U.P., India

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ABSTRACT

The solution is contained in a vesicle made of a non-ionic surfactant in a unique drug delivery device called a "vesicular medication delivery system," such as the Niosome. When compared to traditional medication therapy, niosomes offer a number of significant benefits. In terms of structure, niosomes resemble liposomes in that they both consist of a bilayer. However, unlike liposomes, which have phospholipids as part of the bilayer, niosomes have non-ionic surface-active molecules as part of the bilayer. Niosomes addressed the problems of drug insolubility, instability, low bioavailability, and rapid degradation. This study provides an overview of niosome preparation techniques and their uses in the pharmaceutical industry.

INTRODUCTION

The microscopic lamellar structures known as niosomes or non-ionic surfactant vesicles are created when non-ionic surfactant of the alkyl or dialkyl polyglycerol ether and cholesterol are mixed together and then hydrated in aqueous environments [1]. The non-ionic surfactant span-60, which forms vesicles in niosomes, is stabilised in most cases by adding cholesterol and a little amount of an anionic surfactant like dicetyl phosphate [2].

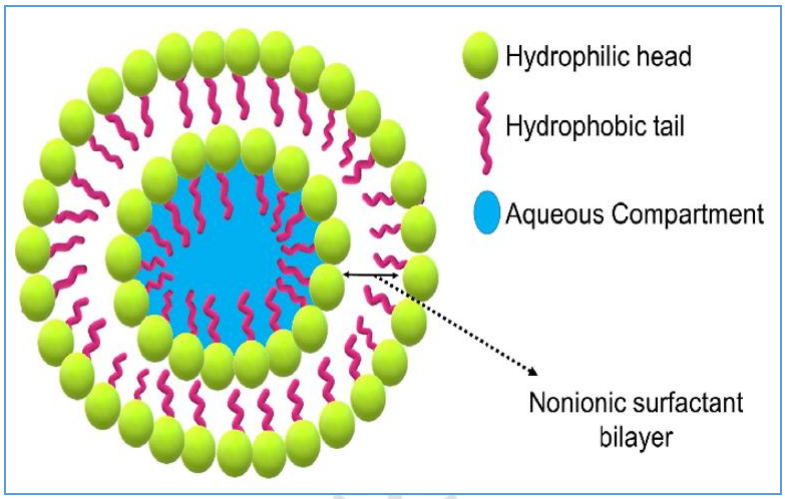

Fig. No.1: Structure of niosomes

ADVANTAGES OF NIOSOMES

- Niosomes offer high patient compliance in comparison with oily dosage from. They possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as result can accommodate drug molecules with a wide range as a result can accommodate drug molecules with a wide range of solubility.
- The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, taped volume, surface charge and concentration can control the vesicle characteristics.
- The vesicles may act as a depot, releasing the drug in a controlled manner.
- 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.

PREPARATION METHODS OF NIOSOMES

A. Ether Injection Method [3, 4]: This method provides a means of making Niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60oc. The surfactant mixture in ether is injected through 14-guage needle into an aqueous solution of material. Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used the diameter vesicle range from 50 to 1000nm.

B. Hand Shaking Method (Thin Film Hydration Technique) [4]: The mixture of vesicle 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 (20oc) using rotator 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 0-60oc with gentle agitation. This process forms typical multilamellar Niosomes.

Thermosensitive niosomes can be prepared by evaporating the organic solvents at 60oc and leaving a thin film of lipid on the wall of rotary flash evaporator [5]. The aqueous phase containing drug is then slowly added with intermittent shaking of flask at room temperature followed by sonication.

C. Sonication [4]: In this method an aliquot of drug solution in buffer is added to the surfactant /cholesterol mixture in a 10-ml glass vial. The mixture is probe sonicated at 60o c for three minutes using a sonicator with a titanium probe to yield niosomes.

D. Micro Fluidization [6]: Micro fluidisation is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which to fluidize streams interact at ultra-high velocity, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet long 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.

E. Multiple Membrane Extrusion Method [6]: Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug solution and the resultant suspension extruded through polycarbonate

membranes, which are placed in series for up to 8 passages. It is a good method for controlling niosomes size.

F. Reverse Phase Evaporation Technique (REV) [5]: In this method the cholesterol and surfactant in 1:1 ratio are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5oc. The clear gel is formed is further sonicated after the addition of small amount of phosphate buffered saline (PBS). The organic phase is removed at 40oc under low pressure. The resulting viscous Niosomes suspension is diluted with PBS and heated on water bath at 60 c for 10 min to yield Niosomes.

G. Trans membrane pH gradient (inside acidic) Drug Uptake Process (remote Loading) [7]: Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydrated with 300 mM citric acid (pH4) by vortex mixing. The multi lamellar vesicle are frozen and thawed three times and sonicated. To this niosomal suspension aqueous solution containing 10 mg /ml of drug is added and vortexed. The pH of sample is then raised to 7-7.2 with 1M disodium phosphate. The mixture is later heated at 60oc for 10 minutes to give niosomes.

H. The "Bubble" Method [8]: It is noval technique for the one step preparation of liposomes and Niosomes without the use of organic solvents. The bubbling unit consists of round bottomed flask with three necks positioned in water bath to control the temperature. Water cooled reflex 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 70oc, the dispersion mixed for 15 seconds with high shear homogenizer Are immediately afterwards "bubbled" at 70 °C using nitrogen gas.

I. Formation of Niosomes from proniosomes [9]: 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 recognised by the addition of aqueous phase at T>Tm and brief agitation.

T= Temperature.

Tm= mean phase transition temperature.

Table No. 1: Brief example of some drugs incorporated into niosomes using different methods

Method of preparation	Drug incorporated
Ether injection	Sodium stibogluconate Doxorubicin
Hand shaking	Methotrexate Doxorubicin
Sonication	9-desglycinamide 8-arginine Vasopressin Oestradiol

SEPERATION OF UNENTRAPPED DRUG

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

1. Dialysis [8]: The aqueous nisomal dispersion is dialyzed in a dialysis tubing against phosphate buffer or normal saline or glucose solution.

2. Gel Filtration [9, 10]: The unentrapped drug is removed by gel filtration of niosomal dispersion through a cephadex-G-50 column and elution with phosphate buffered saline or normal saline.

3. Centrifugation [11, 12]: The niosomal suspension is centrifuged and the supernatant is separated. The pellet is washed and then resuspended to obtain a niosomal suspension from unentrapped drug.

CHARECTERISATION OF NIOSOMES

a. Entrapment efficiency: After preparing niosomal dispersion, unentrapped drug is separated by dialysis, centrifugation, or gel filtration as described above the drug remind entrapped in Niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% triton x-100 and analysing the resultant solution by appropriate assay method for the drug.

Entrapment efficiency (EF) = (Amount entrapped total amount) x 100

b. Vesicular diameter: Niosomes, similar to liposomes, assumes spherical shape and so their diameter can be determined using light microscopy, photon-correlation microscopy and freeze fracture electron microscopy.

Freeze thawing [6] (keeping vesicles suspension at-20 °C for 24 hours and then heating to ambient temperature) of Niosomes increase the vesicle diameter, which might be attributed to fusion of vesicles during the cycle.

c. *In vitro* release: A method in vitro release rate study includes the use of dialysis tubing. A dialysis sac is washed and soaked in distilled water. The vesicle suspension is pippeted into a bag made up of tubing and sealed. The bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25 or 37 °C. At various time intervals, the buffer is analysed for the drug content by an appropriate essay method [9].

Factors affecting vesicles size, entrapment efficiency and release characteristics:

a. Drug: Entrapment of drug in Niosomes increases vesicle size, probably by intraction of solute with surfactant head groups, increase in the charge and mutual repulsion of the surfactant bilayers, thereby increasing vesicle size [9,12]. In polyoxyethylene glycol (PEG) coated vesicles, some drug is entrapped in the long peg chains, thus reducing the tendency to increase the size [11]. The hydrophilic lypophylic balance of the drug effects degree of entrapment.

b. Amount and Type of Surfactant: The mean size of niosomes increases proportionally with increase in the HLB of 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 [9].

The bilayers of the vesicles are either in the so-called liquid state or in gel state, depending on the temperature, the type of lipid or surfactant and the presence of other components such as cholesterol. In the gel state, alkyl chains are present in a well-ordered structure, and in the liquid state, the structure of the bilayers is more disordered. The surfactants and lipids are characterized by the gel-liquid base transition temperature (TC) [9]. Phase transition temperature (TC) of surfactant also affects entrapment efficiency i.e. Span 60 having higher TC, provides better entrapment.

c. Cholesterol Content and Charge: inclusion of cholesterol in niosomes increases its hydrodynamic diameter and entrapment efficiency [9]. In general, the action of cholesterol is two folds; on one hand, cholesterol increases the chain order of liquids-state bilayers and on the other, cholesterol decreases the chain orders by gel state bilayers. At a high cholesterol concentration, the gel state is transformed to a liquid-ordered phase.

An increase in cholesterol content of the bilayers resulted in a decrease in the release rate of encapsulated material and therefore an increase of rigidity of the bilayers obtained [12, 13, 14]. Presence of charge tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle structure and leads to greater overall entrapped volume.

d. Methods of Preparations: Hand shaking method forms vesicles with greater diameter (0.35-13 nm) compared to the ether injection method (50-1000 nm) [6]. Small sized niosomes can be produced by reverse phase evaporation (REV) method [5, 15]. Microfluidization [6] method gives greater uniformity and small size vesicles.

e. 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 slight swelling of vesicle probably due to inhibition eluting fluid from vesicles, followed by faster released, which may be due to mechanical loosening of vesicles structure under osmotic stress [1,16].

APPLICATIONS OF NIOSOMES

Niosomal drug delivery is potentially applicable to many pharmacological agents for their actions against various diseases. Some of their therapeutic applications are discussed below.

1) Targeting on bioactive agents

b. To organs other than RES: It has been suggested that carrier system can be directed to specific site in the body by use of antibodies [17]. Immunoglobulins seem to bind quite readily to the lipids surface, thus offering a convenient means for targeting drug carrier [18]. Many cells possess the intrinsic abilities to recognise and bind particular carbohydrates determinants and these can be exploited to direct carrier system to particular cell.

a. To reticulo-endothelial system (RES): The cells of RES preferentially take up the vesicles. The uptake of niosomes by the cells is also by circulating serum factors known as opsonins, which mark them for clearance such localized drug accumulation has however, been

exploited in treatment of animal tumors to metastasize to the liver and the spleen and in parasitic infestation of liver [1].

2. Neoplasia:

Doxorubicin, the anthracyclic antibiotic with broad spectrum antitumor activity, shows a dose – dependent irreversible cardiotoxic effect. Niosomal delivery of this drug to mice bearing S-180 tumor increased their life span and decreased the rate of proliferation of sarcoma [19]. Niosomal entrapment increased the half-life of the drug, prolonged its circulation and altered its metabolism. Intra venous 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 [21,20].

3. 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, which are related to arsenic, and at high concentration the damage the heart, liver and kidney.

4. Delivery of peptide drugs:

Yoshida et al [14] 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

5. Immunological applications of niosomes:

Niosomes have been used for studying the nature of the immune response provoked by antigens. Brewer and Alexander [22] have reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability.

6. Niosomes as carriers for Hemoglobin:

Niosomes can be used as carrier for haemoglobin. Niosomal suspension shows a visible spectrum of superimposable on to that of free haemoglobin. Vesicles are permeable to oxygen and haemoglobin dissociation curve can be modified similarly to non-encapsulated haemoglobin [23,24].

7. 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 [25] 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 non-ionic vesicles could be formulated to target pilosebaceous glands.

8. Sustained release:

Azmin et al [26, 27] suggested the role of liver as a depot for methotrexate after niosomes are taken up by a liver cell. 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.

9. Localized drug action:

Drug delivery through niosomes is one of the approaches to achieve localized drug action, since their size and low penetrability through epithelium and connective tissue keeps the drug localised at the site of administration.

Localized drug action results in enhancements of efficacy of potency of the drug and at the same time reduces its systemic toxic effects. (Eg.) 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 [8,27, 28-30].

CONCLUSION:

A novel drug delivery technique involves drug consolidation in the niosomes to concentrate around the niosomes to the target region. Due to the ability of niosomes to demonstrate various types of medications inside their multi-environmental structure and furthermore because of different factors like cost, stability, and so on, they exhibit a structure similar to a liposome and can therefore be compared to elective vesicular frameworks as for liposomes. It is a more effective targeting agent because of these advantages over liposomes. For greater efficacy, the medication is administered by ophthalmic, topical, parenteral, and other routes to the site of action.

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