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REVIEW ARTICLE

NIOSOMES – A NOVEL DRUG DELIVERY DEVICE

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ABSTRACT

Niosomes are non-ionic surfactant based multilamellar or unilamellar vesicles in which an aqueous solution of solute is entirely enclosed by a membrane resulting from the organization of surfactant macromolecules as bilayer. Niosomes are formed on hydration of non-ionic surfactant film which eventually hydrates imbibing or encapsulating the hydrating aqueous solution. Niosomes proved to be a promising drug carrier and has potential to reduce the side effects of drugs and increased therapeutic effectiveness in various diseases. The main aim of development of niosomes is to control the release of drug in a sustained way, modification of distribution profile of drug and for targeting the drug to the specific body site. This paper deals with advantages, preparations, evaluation and pharmaceutical applications of niosomes.

Key words: Novel drug delivery system, Niosomes, Non-ionic surfactants, Ether injection method.

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INTRODUCTION

In recent years, niosomes have been extensively studied for their potential to serve as a carrier for the delivery of drugs, hormones, antigens and other biologically active drugs. It has also been used to solve the problem of insolubility, instability and rapid degradation of drugs [1]. Niosomes are non-ionic surfactants with multilameller vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of sterol such as cholesterol or other lipids [2]. The presence of the steroidal system in the niosomes, it improves the rigidity of the bilayer, to affect the bilayer fluidity and permeability and also to protect the drug molecules from the degradation due to some unwanted biological effects [3]. Niosomes and liposomes are equiactive in drug delivery potential and both increase drug efficacy as compared with that of free drug. Mainly, Niosomes are preferred over liposomes because the former exhibit high chemical stability and economy [4]. In general, niosomal drug delivery has been studied using various routes of administration including intramuscular [5], intravenous [6], peroral and transdermal [7].

Advantages of Niosomes [8, 9]

- To 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
- To increase the stability of entrapped drug since these are osmotically active and stable.
- To regulate the delivery rate of drug and administer normal vesicle in external non-aqueous phase.
- To improve the oral bioavailability of poorly absorbed drugs and to enhance skin penetration of drugs.
- To act as a depot, for releasing the drug in a controlled manner.
- They have better patient compliance and better therapeutic effect than conventional oily formulations.
- They can be made to reach the site of action by oral, parenteral as well as topical routes.
- They can show a greater bioavailability than conventional dosage forms.
- They are biodegradable, biocompatible and non immunogenic to the body.
- They are more stable than liposomes.
- No special conditions required for handling and storage of surfactants used in niosomal drug delivery.

METHODS OF PREPARARTION

Some of the important methods that are used to prepare niosomes are as follows:

Hand shaking method : The Cholesterol and surfactant are dissolved in some organic solvents such as ether, chloroform, benzene etc. Then, the solvent is evaporated under reduced pressure in a vacuum evaporator in a round bottom flask which then leaves the mixture of solid

surfactant and cholesterol on the walls of round bottom flask. This layer was then rehydrated with aqueous solution containing drug with continuous shaking which results in swelling of surfactant layer. Swelled amphiphiles eventually folds and form vesicles which entrap the drugs [10].

Ether injection method: A solution containing a particular ratio of cholesterol and surfactant in ether is slowly injected into the preheated aqueous solution of the drugs maintained at 60 °C through the specified gauze needle. The vaporization of ether leads to the formation of unilameller vesicles of the surfactants containing drug. Alter-natively, fluorinated hydrocarbons have been used as a substitute for ether for thermo labile drugs, as they vaporize at a much lower temperature. The size of niosomes obtained by this method varies between 50—1000 nm, which mainly depends on the formulation variables and experimental conditions [11].

Reverse phase evaporation method: The solution of cholesterol and surfactant is prepared in a mixture of ether and chloroform (1: 1). To this, the aqueous solution of drug is added and sonicated at temperature 4 - 5 °C. The solution thus obtained is further sonicated after addition of phosphate buffer saline (PBS) resulting in the formation of gel. Thereafter temperature is raised to 40 °C and pressure is reduced for the removal of solvent. The PBS is added again and heated on water bath at 60 °C for 10 min to yield niosomes [12].

Extrusion method: A mixture of cholesterol and diacetyl phosphate is prepared and then solvent is evaporated using rotary vacuum evaporator to leave a thin film. The film is then hydrated with aqueous drug solution and the suspension thus obtained is extruded through the polycarbonate membrane (mean pore size 0.1 nm) and then placed in series up to eight passages to obtain uniform size niosomes [13].

Sonication method: A mixture consists of surfactant and cholesterol, is dispersed primarily in the aqueous phase. This dispersion is then probe sonicated for 10 min at 60 °C, which leads to the formation of multilameller vesicles (MLV). These MLVs are further ultrasonicated either by probe sonicator or bath sonicator, which in turn leads to the formation of unilameller vesicles [14].

Trans membrane pH gradient (inside acidic) Drug uptake process: 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 citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to give niosomes [15].

Micro fluidization method: Two fluidized streams (one containing drug and the other surfactant) interact at ultra high velocity, in precisely defined micro channels within the interaction chamber in such a way that the energy supplied to the system remains in the area

of niosomes formations. This is called submerged jet principle. It results in better uniformity, smaller size and reproducibility in the formulation of niosomes [16].

The "Bubble" Method: It is novel technique for the one step preparation of 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 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 [17].

FACTORS INFLUENCING NIOSOMES FORMATION

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 niosomes [18].

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 [19].

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 (CPP) can be defined using following equation [20],

$$\mathbf{CPP = v / lc \times a_0}$$

Where, v = hydrophobic group volume, lc = the critical hydrophobic group length,

a_0= the area of hydrophilic head group.

from the CPP value, type of miceller structure formed can be ascertained as given below,

If CPP < ½ then formation of spherical micelles, If ½ < CPP < 1 formation of bilayer micelles and If CPP > 1 formation inverted micelles.

Temperature of hydration: Hydration temperature influences the shape and size of the noisome. 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 [21].

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 [22].

CHARACTERIZATION OF NIOSOMES

Vesicle diameter: Niosomes, similar to liposomes, assume spherical shape and so their diameter can be determined using light microscopy, photon correlation 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 cycle [23].

In-Vitro Release: A method of 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 pipetted into a bag made up of the 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°C or 37°C. At various time intervals, the buffer is analyzed for the drug content by an appropriate assay method [24].

Entrapment Efficiency (EE): It is defined as the percentage amount of drug which is entrapped by the niosomes. EE is calculated by using the formula:

EE = Amount of entrapped drug / Total amount added x 100

For the determination of entrapment efficiency, the unentrapped drug is first separated using centrifugation method. The resulting solution is then separated and supernatant liquid is collected. The collected supernatant is then diluted as specified and estimated using appropriate method as described in monograph of that particular drug. Both the entrapment efficiency (EE) and yield of niosome depend on the method of preparation as well as physico-chemical properties of drug. The number of double layers, vesicle size and its distribution, entrapment efficiency of the aqueous phase, and the permeability of vesicle membranes are influenced by the methodology used for formulation as well as the addition of cholesterol as they make the niosomes less leaky [25].

Bilayer formation: Assembly of non-ionic surfactants to form bilayer vesicle is characterized by X-cross formation under light polarization microscopy [26].

Membrane rigidity: Membrane rigidity can be measured by means of mobility of fluorescence probe as function of temperature [26].

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Number of lamellae: It is determined by using NMR spectroscopy, small angle X-ray scattering and electron microscopy [27].

Stability studies: Stability studies are done by storing niosome at two different conditions, usually 4 ± 1 °C and 25 ± 2 °C. Formulation size, shape and number of vesicles per cubic mm can be assessed before and after storing for 30 d. After 15 and 30 d, 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 [24].

$$\text{Number of niosomes per cubic mm} = \frac{\text{Total number of niosomes x dilution factor x 400}}{\text{Total number of small squares counted}}$$

PHARMACEUTICAL APPLICATIONS OF NIOSOMES

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

Targeting of bioactive agents

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 known to metastasize to the liver and spleen and in parasitic infestation of liver [28].

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 [29].

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 S-180 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 [30].

Leishmaniasis

Niosomes can be used for targeting of drug in the treatment of diseases in which the infecting organism resides in the organ of reticuloendothelial 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 they damage the heart, liver and kidney [31].

Immunological application of niosomes

Niosomes have been used for studying the nature of the immune response provoked by antigens. Brewer and Alexander [32] have reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability.

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 [30].

Ophthalmic drug delivery

Bioadhesive-coated niosomal formulation of acetazolamide prepared from span 60, cholesterol stearylamine or dicetyl phosphate exhibits more tendency for reduction of intraocular pressure as compared to marketed formulation (Dorzolamide). The chitosan coated niosomal formulation timolol maleate (0.25%) exhibits more effect for reduction intraocular pressure as compared to a marketed formulation with less chance of cardiovascular side effects [33].

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 [34] 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.

Diagnostic imaging with Niosomes

Niosomes are considered as a carrier of iobitridol, a diagnostic agent for X-ray imaging. The niosomes prepared using the film hydration method followed by sonication. Method allows the increasing encapsulation and the stability of vesicles were carried out [35].

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CONCLUSION

Niosomes, as a drug delivery device, compared to liposomes, are osmotically active and are quite stable chemically by their own as well as improve the stability of the drug so entrapped and delivered. Niosomes offer various advantages over other drug delivery devices and have found applicability in pharmaceutical fields. It was thus concluded that niosomes are very effective drug delivery tools for targeting of various therapeutically active moieties. 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 preparations.

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