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REVIEW ARTICLE

ROLE OF NIOSOMES AND PRONIOSOMES FOR ENHANCING BIOAVAILABILITY OF DRUGS

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ABSTRACT

Niosome are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or their lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Niosomes are promising vehicle for drug delivery and being non-ionic; and Niosomes are biodegradable, biocompatible nonimmunogenic and exhibit flexibility in their structural characterization. Niosomes can entrap both hydrophilic and lipophilic drugs and can prolong the circulation of the entrapped drug in body. Proniosomes are dry formulation of water soluble carrier particles that are coated with surfactant. They are rehydrated to form niosomal dispersion immediately before use on agitation in hot aqueous media within minutes. Proniosomes and niosomes are physically stable during the storage and transport. Drug encapsulated in the vesicular structure of proniosomes prolong the existence of drug in the systematic circulation and enhances the penetration into target tissue and reduce toxicity. From a technical point of view, niosomes and proniosomes are promising drug carriers as they possess greater chemical stability and lack of many disadvantages associated with liposomes, such as high- cost and variable purity problems of phospholipids. The present review emphasizes on overall methods of preparation characterization and applicability of niosomes and proniosomes in targeted drug delivery.

Keywords: proniosomes, targeted, Niosome,**INTRODUCTION**

The NDDS should ideally fulfill two prerequisites which are; firstly, it should deliver the drug at a rate directed by the needs of the body, till the period of treatment; Secondly, it should channel the active ingredient of the formulation to the site of action^{1,2,3}. In the past, the delivery of the drugs has been altered by routes such as topical delivery has been widely explored.. Most of the drugs which are developed from contemporary drug delivery system are hydrophobic in nature which then requires delivering drugs in a modified form to enhance the bioavailability of the drug. Niosomes and proniosomes can enhance the bioavailability of encapsulated drug and also provide the drug release in a controlled manner for prolonged period of time.⁴ Niosomes are novel surfactant vesicles, which are microscopic lamellar structures of size range 10-1000 nm formed on admixture of non-ionic surfactant of alkyl or dialkylpolyglycerol ether class and cholesterol with subsequent hydration in aqueous media.^{5,6} The properties of non-ionic surfactant vesicles can be modified by incorporation of various ingredients into the membrane, e.g., cholesterol imparts rigidity and orientational order to the niosomal bilayer resulting in stable and less leaky vesicles^{4,6}. Charge inducing agents like dicetyl phosphate, diacylglycerol and stearylamine

provide electrostatic stabilization of vesicles and thus show increased entrapment efficiency of vesicles.⁴ Proniosomes are also known as amphiphilic vesicles allow the encapsulation of hydrophilic drug in the core cavity and hydrophobic drugs in non-polar region within the bilayer⁸. The vesicles act as a depot and release the drug in controlled manner¹⁰. The therapeutic performance of drug molecules can be improved by delayed clearance from transmission, protecting the drug from biological environment thus providing targeted drug delivery. They provide enhanced drug concentration at the site of action after oral, parenteral and topical administration, thus minimize the side-effects. They release the drug by diffusion controlled mechanism.

NIOSOME: - By reaction of a non ionic surfactant, cholesterol and a charge inducing agent with subsequent hydration in aqueous media and formed microscopic lamellar structures called niosomes.⁸⁻⁹ it has property to entrap solutes in a manner analogous to liposomes and improves the stability of the entrapped drugs. These are polymeric biodegradable, biocompatible and non-immunogenic preparation in nature.¹⁰⁻¹¹

STRUCTURE AND TYPES OF NIOSOME

Niosomes are microscopic lamellar structures in size and constitute of nonionic surfactant of the alkyl or dialkyl poly glycerol ether class and cholesterol with subsequent hydration in aqueous media. Structurally, niosomes are similar to liposomes, in that they are also made up of a bilayer. However, the bilayer of niosomes is made up of non-ionic surface active agents rather than phospholipids of liposomes. The niosomes are classified as multi lamellar vesicles, large unilamellar vesicles and small unilamellar vesicles niosomes. The various types of niosomes are described below:

1. Multi lamellar Vesicles (MLV):- It consist a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 μm diameter. These vesicles are highly suited as drug carrier for lipophilic compounds.

2. Large Unilamellar Vesicles (LUV):- Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids.

3. Small Unilamellar Vesicles (SUV):- These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion method or, homogenization method. The approximate sizes of small unilamellar vesicles are 0.025-0.05 μm diameter. They are thermodynamically unstable and are susceptible to aggregation and fusion. Their entrapped volume is small and percentage entrapment of aqueous solute is correspondingly low.¹²⁻¹⁴

ADVANTAGES OF NIOSOME

1. The vesicle suspension is water-based vehicle. This offers high patient compliance in comparison with oily dosage forms and possesses an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together.

2. The characteristics of the vesicle formulation are variable and controllable. The vesicles may act as a depot, releasing the drug in a controlled manner.

3. They are osmotically active and stable, as well as they increase the stability of entrapped drug and improve oral bioavailability of poorly absorbed drugs, therapeutic performance of the drug molecules.¹⁵⁻¹⁶

COMPOSITIONS OF NIOSOMES:-

The two major ingredients or components are used for the preparation of niosomes:

1. Cholesterol: - It provides rigidity and proper shape, conformation to the niosomes preparations.

2. The characteristics of the vesicle formulation are variable and controllable. The vesicles may act as a depot, releasing the drug in a controlled manner.

3. They are osmotically active and stable, as well as they increase the stability of entrapped drug and improve oral

bioavailability of poorly absorbed drugs, therapeutic performance of the drug molecules.¹⁵⁻¹⁶

The non ionic surfactants possess a hydrophilic head and a hydrophobic tail.¹⁷⁻²⁰

METHOD OF PREPARATION

Some important methods that are used to formulate niosomes are as follows:

1) **Ether injection method:** - In this method the niosomes are prepared by a slowly mixing of cholesterol and surfactant in ether into the preheated aqueous solution in particular ratio. The drugs conserved at 60° C by the specified gauge needle and the unilamellar vesicles of the surfactants including drug formed due to the vaporization of ether and The size of niosomes resulted by this method alter between 50-1000 μm , which mainly based on the method of preparation, experimental procedure and conditions.²¹⁻²³

2) **Hand shaking method:** - in this method lipid cholesterol and surfactant allow dissolving in some organic solvent (like ether, chloroform, benzene etc.) followed by the solvent evaporation under reduced pressure, which help to removing the solution mixture of solid surfactant and cholesterol on the round bottom flask's wall. The resulting layer (solid surfactant and cholesterol) then rehydrates with drug loaded aqueous solution with continuous shaking, results to Swelling of amphiphiles eventually which folds and form vesicles which entrap the drugs. The liquid volume entrapped in vesicles was found to be small i.e.5-10%.^{21-22 24}

3) **Sonication method:** - In this method, the surfactant-cholesterol solution mixture is allow to disperse in the aqueous phase firstly with sonication for 10 minute at 60°C, which results to the formulation of multilamellar vesicles (MLV), These are further ultrasonicated either by probe sonicator or bath sonicator, which in turn leads to the formation of unilamellar vesicles.²¹⁻²⁴

4) **Reverse phase evaporation method:** - in a mixture of ether and chloroform (1:1) the solution of cholesterol and surfactant is prepared and the drug containing aqueous solution is added and allow to sonicate at temperature 45°C in it and The solution obtained by this further sonicated with addition of phosphate buffer saline (PBS) which results to the formation of gel. This gel formation allows to heat with addition of PBS on water bath at 60°C for 10 minute to yield niosomes.²⁴⁻²⁵

5) **Trans membrane pH gradient drug uptake process (Remote Loading):** - this method principles, that the interior of niosome has the low pH value (acidic pH) as compare to the outer side and the added unionized basic drug crosses the membrane but after entering into the niosome it gets ionized in acidic medium and is unable to leave the niosome and thus this method increases the entrapment efficiency of such drugs. The acidic pH towards the interior of Niosomes acts as an intravascular trap for the drugs.²⁶

6) **Micro fluidization method:** - In this method two fluidized streams solution (one containing drug and the other surfactant) reacts together 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 and this is known as submerged jet principle. It results in better uniformity, smaller size and reproducibility in the formulation of niosomes²⁷⁻²⁹.

7) **Multiple membrane extrusion method:** - In this method, the niosome's size is decreased/reduced by passing them by membrane filter. It can be used for production of multi lamellar vesicles as well as large unilamellar vesicles and it is found as a good method for controlling niosomal size.²⁹⁻³⁰

8) **Ethanol injection method:** - in ethanol injection method an alcoholic (ethanol) solution of surfactant is employed to inject rapidly by the help of a fine needle into excess of saline or other aqueous medium, then the vaporization of ethanol results to the formation of vesicles. It has been reported as one of the alternatives used for the preparation of small unilamellar vesicles (SUVs) without sonication.³⁰⁻³¹

PRONIOSOMES

Proniosomes: are dry formulations which make use of carriers coated with non-ionic surfactants and can be converted into niosomes immediately before use by hydration. Proniosomes minimize problems of niosomes physical stability such as aggregation, fusion, and leaking, and provide additional convenience in transportation, distribution, storage and dosing⁴⁸. Proniosomes-derived niosomes are as good as or even better than conventional niosomes. Proniosomes offer a versatile vesicle drug delivery concept with potential for delivery of drugs via transdermal route. This would be possible if proniosomes form niosomes upon hydration with water from skin following topical application under occlusive conditions⁴⁹. Transdermal therapeutic system have generated an interest as they provide considerable advantage of a non-invasive parenteral route for drug therapy, avoidance of first pass gut and hepatic metabolism, decreased side effects and relative ease of drug input termination in problematic case. Colloidal particulate carriers such as liposomes or niosomes have been widely employed in drug delivery systems and producing them from proniosomes provides them a distinctive advantage. These carriers act as drug reservoirs and the rate of drug release can be controlled by modification of their composition. To get the desired characteristics of a particular proniosome formulation, it is important to select the surfactant of suitable Hydrophilic Lipophilic Balance (HLB) number in the formulation of proniosome. The studies on vesicles systems till date open the door for the future use of different carrier with biocompatibility and suitability for the preparation of proniosomes.

Method of Preparation

Three different methods were reported for the preparation of proniosomes as described below:

Slurry Method

By this method proniosomes can be prepared from a stock solution of surfactants and cholesterol in a suitable solvent. The required volume of surfactant and cholesterol stock solution per gram of carrier and drug are firstly dissolved in the solvent in 100 ml round bottom flask containing the carrier (maltodextrin or lecithin). Additional chloroform can be added to form the slurry in case of lower surfactant loading. Further, the flask has to be attached to a rotary flash evaporator to evaporate solvent at 50–60 rpm at a temperature of $45 \pm 2^\circ\text{C}$ and at a reduced pressure of 600 mm Hg until the mass in the flask becomes a dry free flowing product. The formulation should be stored in a tightly closed container under refrigeration under light⁵¹.

Coacervation Phase Separation Method

This method is widely adopted to prepare proniosomal gel. Precisely weighed amounts of surfactant, lipid and drug are taken in a clean and dry wide mouthed glass vial of 5.0 ml capacity and alcohol (0.5 ml) is added to it. After warming, all the ingredients are mixed well with a glass rod, the open end of the glass bottle is covered with a lid to prevent the loss of solvent from it and warmed over water bath at 60-70°C for about 5 min until the surfactant mixture is dissolved completely. Then the aqueous phase (phosphate buffer pH 7.4) is added and warmed on a water bath till a clear solution is formed which is then converted into proniosomal gel on cooling⁵².

Slow Spray-Coating Method

This method involves preparation of proniosomes by spraying surfactant in organic solvent onto carrier material and then evaporating the solvent. Since, the carrier is soluble in the organic solvent, the process is repeated until the desired surfactant loading has been achieved. The surfactant coating on the carrier is very thin and hydration of this coating allows multilamellar vesicles to form as the carrier dissolves. The resulting niosomes are very similar to those produced by conventional methods and the size distribution is more uniform⁵³.

Advantage of Proniosome⁵⁴

- 1 Avoiding problem of physical stability like aggregation, fusion, leaking of niosomes
- 2 Avoiding hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion.
- 3 Avoid first pass metabolism
- 4 Minimize side effect
- 5 improve bioavailability and stability problems

APPLICATIONS OF NIOSOMES AND PRONIOSOMES

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

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 drugs³².

Drug Targetting

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.

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, decreases rate of proliferation of tumor and higher plasma levels accompanied by slower elimination³².

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 invitro study conducted by oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide³³.

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. Non-ionic surfactant vesicles have clearly demonstrated their ability to function as adjuvants following parenteral administration with a number of different antigens and peptides.

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 anemic patients.

Leishmaniasis

Leishmaniasis is a disease in which a parasite of the genus *Leishmania* invades the cells of the liver and spleen. 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 (RES). The commonly prescribed drugs are antimonials, which are related to arsenic, and at high concentration they damage the heart, liver and kidney.³⁴ It was reported that increased sodium stibogluconate efficacy of niosomal formulation and that the effect of two doses given on successive days was additive.³⁵ Pawar SD et al reported that the use of niosomes to administer higher levels of the drug without triggering of the side effects, and thus allowed greater efficacy in treatment³⁶.

Transdermal drug delivery delivery

The major drawback of transdermal route of delivery is slow penetration of drug through skin, and increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes.³⁷

Cosmetic delivery

The first report of non-ionic surfactant vesicles came from the cosmetic applications devised by L'Oreal. Niosomes were developed and patented by L'Oréal in the 1970s and 80s. The first product 'Niosome' was introduced in 1987 by Lancôme. The advantages of using niosomes in cosmetic and skin care applications include their ability to increase the stability of entrapped drugs, improved bioavailability of poorly absorbed ingredients and enhanced skin penetration.³⁸

Hormone delivery

The in-vitro permeation of estradiol from vesicular formulations through human stratum corneum was studied. The vesicles were composed of non-ionic n-alkyl polyoxyethylene ether surfactants (CnEOm). Two mechanisms are proposed to play an important role in vesicle-skin interactions, i.e., the penetration enhancing effect of surfactant molecules and the effect of the vesicular structures caused by their adsorption at the stratum corneum suspension interface³⁹.

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.⁴⁰⁻⁴²

Vaccine delivery

An interesting group of vaccine carrier systems are formulations based on non-ionic surfactant vesicles (niosomes) which themselves are only weakly immunogenic. Niosomes are gaining wide attention as per oral vaccine delivery system and for topical immunization. Influence of the varying proportion of surfactant, cholesterol, and dicetyl phosphate on the morphology, particle size, entrapment efficiency, and in-vitro antigen release from niosomes was investigated. The immune stimulating activity was investigated and it was observed that topical niosomes elicited a comparable serum antibody titer and endogenous cytokines levels as compared to intramuscular recombinant HBsAg and topical liposome's.⁴³⁻⁴⁴

Other Applications

a) Sustained Release

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 encapsulation⁴⁵.

b) 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 localized at the site of administration⁴⁶⁻⁴⁷

CONCLUSION

Proniosomes niosomes are very promising as drug carriers. Compared to liposomes of natural or synthetic phospholipids, niosomes have the advantage that chemical degradation problems, such as oxidation and hydrolysis, may be largely alleviated. Compared to liposome or niosome suspensions, proniosomes represent a significant improvement by eliminating physical stability problems, such as aggregation or fusion of vesicles and leaking of entrapped drugs during long-term storage. Compared to niosomes prepared by conventional means, proniosome-derived niosomes are superior in their convenience of storage, transport and dosing. The release data indicate that proniosome-derived niosomes are at least as effective as conventional niosomes in their release characteristics, and may therefore offer improved bioavailability of some drugs with poor solubility, controlled release formulations, or reduced adverse effects of some drugs. Because proniosomes are a dry powder, further processing is possible. To provide convenient unit dosing, the proniosome powder may be processed to make beads, tablets, gel or capsules. one of the greatest advances offered by proniosomes is their ease of use. The hydration of proniosome powder is much easier than the long shaking process required to hydrate surfactants in the conventional dry film method and can be implemented in a 'point-of-use' application. Proniosome derived niosome suspensions appear to be as good as or better than conventional niosome preparations, and may be an appropriate preparation to use as a hydrophobic drug carrier.

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