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Review Article

Niosomes: An approach to current drug delivery-A Review

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Abstract

Niosomes are a novel drug delivery system (NDDS), in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. The niosomes are very small, and microscopic in size. Their size lies in the nanometric scale. Although structurally similar to liposomes, they offer several advantages over them. It has been a study interest in the development of a NDDS. NDDS has an object to deliver the drug at a rate directed by the needs of the body during the period of treatment of a disease, and reach the active ingredient to the site of action. A number of NDDS have been reported through various routes of administration, to achieve controlled and targeted drug delivery. Encapsulation of the drug in vesicular structures is one of the most important systems, which can be predicted to prolong the existence of the drug in systemic circulation and reduce the toxicity, if prescribed uptake can be achieved. Consequently a number of vesicular drug delivery systems such as liposomes, niosomes, transfersomes, and pharmacosomes were developed. Advances have since been made in the area of vesicular drug delivery, leading to the development of systems that allow drug targeting and the sustained or controlled release of conventional medicines. The focus of this review is to the various method of preparations, characterization of niosomes, advantages and brings out the application vesicular systems.

Keywords: Niosomes, NDDS, Vesicles, Systemic circulation, Controlled drug release.

1. Introduction

Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids.[1] They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. One of the reasons for preparing niosomes is assumed higher chemical stability of the surfactants than that of phospholipids, which are used in the preparation of liposomes. Due to the presence of ester bond, phospholipids are easily hydrolysed.[2] Unreliable reproducibility arising from the use of lecithin in liposomes leads to additional problems and has led scientist to search for vesicles prepared from other material, such as nonionic surfactants. Niosomes are promising vehicle for drug delivery and being nonionic; it is less toxic and improves the therapeutic index of drug by restricting its action to target cells. Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media.[3] In niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as Span – 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate.

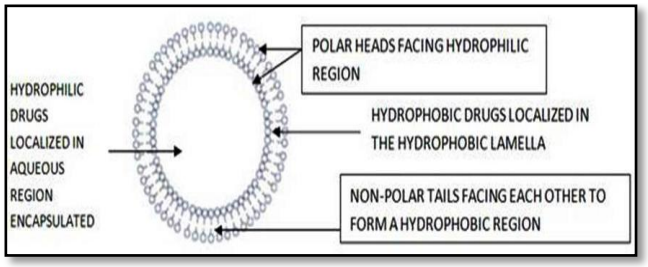


Fig 1: Structure of Niosome (Copied from google.co.in)

1.1 Salient Features of Niosomes;

- Niosomes can entrap solute in a manner analogous to Liposome.
- Niosomes osmoticaly active and stable.
- Niosomes possess an infra structure consisting of hydrophobic and hydrophilic mostly together and so also accommodate the drug molecule with a wide range of solubility.
- Niosomes exhibit flexibility in their structural charecterestics (composition, fluidity and size) and can be designed according to their desired situation.
- Niosomes can improve the performance of drug molecule.
- Better availability to the particular site, just by protecting the drug from biological environment.
- Niosomes surfactants are biodegradable, biocompatible and nonimmunogenic.[1]

1.2 Advantages of Niosomes

Use of niosomes in cosmetics was first done by L'Oreal as they offered the following advantages [4]:

- The vesicle suspension being water based offers greater patient compliance over oil based systems since the structure of the niosome offers place to accommodate hydrophilic, lipophilic as well as ampiphilic drug moieties, they can be used for a variety of drugs.
- The characteristics such as size, lamellarity etc. of the vesicle can be varied depending on the requirement.
- The vesicles can act as a depot to release the drug slowly and offer a controlled release.
- They increase the stability of the entrapped drug
- Handling and storage of surfactants do not require any special conditions.
- Can increase the oral bioavailability of drugs.
- Can enhance the skin penetration of drugs.
- They can be used for oral, parenteral as well topical use.
- Improve the therapeutic performance of the drug by protecting it from the biological environment and restricting effects to target cells, thereby reducing the clearance of the drug.
- The niosomal dispersions in an aqueous phase can be emulsified in a non-aqueous phase to control the release rate of the drug and administer normal vesicles in external non-aqueous phase.

2. Method of preparation

2.1 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 1000 nm. [5,6]

2.2 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. Thermo sensitive niosomes were prepared by *evaporating the organic solvent at 60°C and leaving a thin film of lipid on the wall of rotary flash evaporator. The aqueous phase containing drug was added slowly with intermittent shaking of flask at room temperature followed by sonication.* [6,7]

2.3 Sonication

A typical method of production of the vesicles is by Sonication of solution as described by Cable. 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 60°C for 3 minutes using a sonicater with a titanium probe to yield niosomes.[6,8]

2.4 Micro fluidization

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.[9]

2.5 Multiple membrane extrusion method

Polycarbonate membranes, which are placed in series for upto 8 passages. It is a good method for controlling niosome size. 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 which are placed in series for upto 8 passages. It is a good method for controlling niosome size.[9]

2.6 Reverse Phase Evaporation Technique

Cholesterol and surfactant (1:1) 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 4-5°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The 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. It also have been reported the preparation of Diclofenac Sodium niosomes using Tween 85 by this method.[7]

2.7 Trans membrane pH gradient 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 300 ml 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.[10]

2.8 The "Bubble" Method

It is novel 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 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.[11]

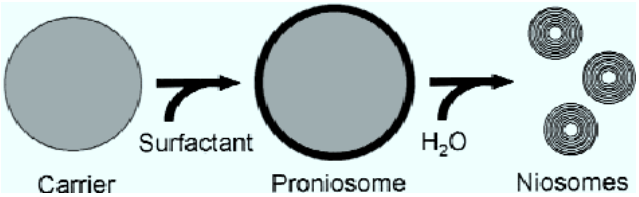
2.9 Formation of niosomes from proniosomes

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 > Tm and brief agitation.[12]

T = Temperature.

Tm = mean phase transition temperature.



It has been 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.[12]

3. Separation of unentrapped drug

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

3.1 Dialysis

The aqueous niosomal dispersion is dialyzed in a dialysis tubing against phosphate buffer or normal saline or glucose solution.[13]

3.2 Gel Filtration

The unentrapped drug is removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution with phosphate buffered saline or normal saline.[14,15]

3.3 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 unentrapped drug.[16,17]

4. Characterization and factors affecting formation of niosomes

4.1 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[18]. 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.[19] The surfactants with alkyl chain length from C12-C18 are suitable for preparation of noisome [20,21].

4.2 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*a0where v = hydrophobic group volume, lc = the critical hydrophobic group length, a0 = the area of hydrophilic head group.

From the critical packing parameter 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,

If CPP > 1 formation inverted micelles.[22]

4.3 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 solution C24 (cholesteryl poly-24-oxyethylene ether), which prevents aggregation due to development of steric hindrance[23].

4.4 Nature of encapsulated drug

The physicochemical 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.[24]

4.5 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.[25]

4.6 Bilayer formation

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

4.7 Number of lamellae

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

4.8 Membrane rigidity

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

4.9 Entrapment efficiency (EE)

The entrapment efficiency (EE) is expressed as EE = amount entrapped/total amount added 100. It is determined after separation of unentrapped 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[28]. 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 at1:1 ratio has highest entrapment efficiency for water soluble drugs[26]. 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.[29]

4.10 Cholesterol contents

The incorporation of cholesterol into bilayer composition of niosome induces membrane stabilizing activity and decreases the leakiness of membrane.[30] Hence, incorporation of cholesterol into bilayer increases entrapment efficiency. The permeability of vesicle bilayer to 5, 6-carboxy flourescein (CF) is reduced by 10 times due to incorporation of cholesterol.[31]

5. Applications of niosomes

5.1 Niosomes as Drug Carriers

A number of workers have reported the preparation, characterization and use of niosomes as drug carriers. Niosomes containing anti-cancer drugs, if suitably designed, will be expected to accumulate within tumors in a similar manner to liposomes. The niosomal encapsulation of Methotrexate and Doxorubicin increases drug delivery to the tumor and tumoricidal activity of the drug. Doxorubicin niosomes possessing muramic acid and triglycerol surfaces were not taken up significantly by liver. The triglycerol niosomes accumulated in the tumor and muramic acid vesicles accumulated in the spleen. Those vesicles with polyoxyethylene surface were rapidly taken up by the liver and accumulated to a lesser extent in tumor. Baillie *et al*[32] investigated the encapsulation and retention of entrapped solute 5,6-carboxy fluorescence (CF) in niosomes. They observed that stable vesicles could not be formed in the absence of cholesterol but were more permeable to entrapped solute. The physical characteristics of the vesicles were found to be dependent on the method of production. Chandraprakash *et al*[33] reported the formation and pharmacokinetic evaluation of Methotrexate niosomes in tumor bearing mice. Cable *et al*[34] modified the surface of niosomes by incorporating polyethylene alkyl ether in the bilayered structure. They compared the release pattern and plasma level of Doxorubicin in niosomes and Doxorubicin mixed with empty niosomes and observed a sustained and higher plasma level of doxorubicin from niosomes in mice. D' Souza *et al*[35] studied absorption of Ciprofloxacin and Norfloxacin when administered as niosome encapsulated inclusion complexes. Raja Naresh *et al*[36] reported the anti-inflammatory activity of niosome encapsulated Diclofenac sodium in arthritic rats. It was found that the niosomal formulation prepared by employing a 1:1 combination of Tween 85 elicited a better consistent anti-inflammatory activity for more that 72 hrs after administration of single dose. Carter *et al*[37] reported that

multiple dosing with sodium stibogluconate loaded niosomes was found to be effective against parasites in the liver, spleen and bone marrow as compared to simple solution of sodium stibogluconate. Namdeo *et al*[38] reported the formulation and evaluation of Indomethacin loaded niosomesand showed that therapeutic effectiveness increased and simultaneously toxic side effect reduced as compared with free Indomethacin in paw edema bearing rats. Parthasarthi *et al*[39] prepared niosomes of vincristine sulfate which had lesser toxicity and improved anticancer activity. Jagtap and Inamdar prepared niosomes of Pentoxifylline and studied the in-vivo bronchodilatory activity in guinea pigs. The entrapment efficiency was found to be 9.26 ± 1.93% giving a sustained release of drug over a period of 24 hrs. Azmin *et al*[40] reported the preparation and oral as well as intravenous administration of Methotrexate loaded niosomes in mice. They observed significant prolongation of plasma levels and high uptake of Methotrexate in liver from niosomes as compared to free drug solution.

5.2 Diagnostic imaging with niosomes

Niosomal system can be used as diagnostic agents. Conjugated niosomal formulation of gadobenatedimeglcemine with [N-palmitoylglucosamine (NPG)], PEG 4400, and both PEG and NPG exhibit significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging.[41]

5.3 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 chitosancoatedniosomal 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.[42]

6. Targeting of bioactive agents

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 known to metastasize to the liver and spleen and in parasitic infestation of liver.[43]

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.[44] 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.

Delivery of peptide drugs

Yoshida *et al*[45] 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.

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 [58]. 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 [46,47]. Immunological application of niosomes. Niosomes have been used for studying the nature of the immune response provoked by antigens. Brewer and Alexander [48] have reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability.

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*[49] 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.

Niosome formulation as a brain targeted

Niosomaldelivery system for the vasoactive intestinal peptide (VIP)Radiolabelled (I125) VIP-loaded glucosebearing niosomes were injected intravenously to mice. Encapsulated VIP within glucosebearing niosomes exhibits higher VIP brain uptake as compared to control.[50]

Niosomes as carriers for Hemoglobin.

Niosomes can be used as a carrier for hemoglobin. Niosomal suspension shows a visible spectrum superimposable onto that of free hemoglobin. Vesicles are permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin.[51,52]

Table 1: Drugs Incorporated into Niosomes by Various Methods

Method of Preparation	Drug Incorporated
Ether Injection	Sodium stibogluconate [53,54], Doxorubicin
Hand Shaking	Methotrexate[55],Doxorubicin
Sonication	9desglycinamide,arginine,Vasopressin,Oestradiol[56]

7. Comparison between niosomes and liposome

Niosomes are made of non-ionic surfactants and cholesterol. Most surfactants have a single hydrophobic tail, eg: sodium dodecyl sulphate. On the other hand liposomes are made of phospholipids, they may or may not contain cholesterol. Phospholipids have two hydrophobic tails.[3]

Since niosomes are prepared from uncharged single-chain surfactant and cholesterol, whereas liposomes are prepared from double-chain phospholipids (neutral or charged). The concentration of cholesterol in liposomes is much more than that in niosomes. As a result, drug entrapment efficiency of liposomes becomes lesser than niosomes because the intercalation of cholesterol in the bilayers decreases the entrapment volume during formulation and thus entrapment efficiency.[57]

Niosomes behave *in vivo* like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability.[58]

Due to presence of hydrophilic, amphiphilic and lipophilic moieties in the structure, these can accommodate drug molecules with a wide range of solubility comparision to liposome.[59]

Niosomes are usually more stable towards oxidative degradation because liposome's phospholipids are more prone to oxidative degradation.

Niosomes are inexpensive and easier to make and store whereas liposomes are expensive and they require special storage and handling.[60]

8. 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, antiinfectiveagents. Drug delivery potential of niosome can enhance by using novel concepts like proniosomes, discomes and aspasome. 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 present 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 candidate 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, parenteral.

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