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REVIEW ARTICLE

Niosomes as an emerging formulation tool for drug delivery

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ABSTRACT

Niosomes are a novel drug delivery system, 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 liposome's, they offer several advantages over them. Niosomes have recently been shown to greatly increase transdermal drug delivery and also can be used in targeted drug delivery, and thus increased study in these structures can provide new methods for drug delivery. In recent years, niosomes have been extensively studied for their potential to serve as a carrier for the delivery of drugs, antigens, hormones and other bioactive agents. Besides this, noisome have been used to solve the problem of insolubility, instability and rapid degradation of drugs.

INTRODUCTION

Niosomes are a novel excellent tool for drug delivery, in which the medication is encapsulated in a vesicle. The main components of niosomes are mostly formed by non-ionic surfactant and cholesterol [1]. Niosomes are also made up of bilayer, as like liposomes. In the case of niosomes the bilayer is made up of non-ionic surfactants rather than phospholipids as seen in the case of liposomes. 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. Addition of cholesterol in the formation of niosomes provided rigidity to the bilayer and thus results in limited drug leakage from them Niosome contains major component that is non-ionic surfactant which give more stability to niosomes when compared to liposomes, thus overcoming the problems associated with liposomes i.e. susceptibility to oxidation, high price and stability [2, 3].

Merits of Niosomes [4, 5]

1. The vesicles may act as a depot, releasing the drug in a sustained manner.
2. They are osmotically active and stable, and they also increase the stability of entrapped drug.
3. Niosomes have been widely used in various drug delivery systems like drug targeting, controlled release and permeation enhancement of drugs.
4. The surfactants used are biodegradable, biocompatible and non-immunogenic.
5. Niosomes entrap solute in manner analogous to liposomes.
6. Handling and storage of niosomes required no special conditions.
7. Niosomes possess an intra structure consisting of hydrophobic and hydrophilic moieties together and as result can accommodate drug molecules with a wide range of solubilitys.
8. Niosomes exhibit flexibility in their structural characteristic (composition, fluidity, size) and can be designed according to the desired situation.

9. They can be made to reach the site of action by oral, parenteral as well as topical routes.
10. Niosomes improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.

Demerits of Niosomes [6]

1. Physical instability
2. Aggregation
3. Fusion
4. Leaking of entrapped drug
5. Hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion

Composition of Niosomes

Niosomes contain two major component, Cholesterol and Nonionic surfactants. Cholesterol is used to provide rigidity and proper shape to the niosomes. Surfactants play a major role in the formation of niosomes. The following non-ionic surfactants are generally used for the preparation of niosomes the spans (span 60, 40, 20, 85, 80), tweens (tween 20, 40, 60, 80) and brijs (brij 30, 35, 52, 58, 72, 76). The non ionic surfactants possess a hydrophillic head and a hydrophobic tail [7, 8].

1. Main component : Non-ionic surfactant
2. Membrane additives: Cholesterol
3. Stabilizer- Charged molecule
4. Drug candidate

Non- Ionic Surfactants [9, 10]

Non-ionic surfactants are uncharged amphiphilic compounds like lipids the non-ionic surfactants also orient in an aqueous medium as planar bilayer lattices wherein polar (or) hydrophilic heads align facing aqueous bulk while hydrocarbon segments are so aligned that their interaction with aqueous media is minimized. Every bilayer folds over itself to be a continuous membrane that forms vesicles so that hydrocarbon/water interface remains no more exposed. Examples of non-ionic surfactants forming vesicles are, polyoxy ethylene fatty acid esters, polyoxy ethylene alkyl esters (including ethers of fatty alcohols) polyoxy ethylene sorbitan esters, polyoxy ethylene glyceryl mono and diesters, sucrose diester, propylene glycol stearate, Long chain acyl amide, C12-C22 fatty alcohols etc., BRIJTM (polyoxy ethylene fatty acid esters), SPANTM (sorbitan fatty acid esters) and TWEENTM (polyoxy ethylene derivatives of sorbitan fatty acid esters.) are commercially available amphiphile surfactants. The choice of non-ionic surfactant on vesicle formation depends on hydrophilic lipophilic balance (HLB), critical micellar concentration (CMC) and critical packing parameter of amphiphiles.

Cholesterol [11]

Steroids are important components of cell membrane bring bilayer fluidity and permeability. The most common additive found in niosomal systems is cholesterol which is known to abolish the gel to liquid phase transition of liposomal and niosomal systems, resulting in less leakiness of the vesicles. However, it may have effects on membrane permeability, encapsulation efficiency, bilayer rigidity, ease of rehydration of freeze dried niosomes and toxicity. In general, it has been found that a molar ratio of 1:1 between cholesterol and non-ionic surfactants is an optimal ratio for the formulation of physically stable niosomal vesicles cholesterol can be incorporated in bilayers at significantly higher molar ratio, however by itself does not form niosomal bilayer. Its -OH group orients towards aqueous phase while aliphatic chains parallel to the hydrocarbon chain of surfactants. Cholesterol is known to have important modulatory effect on the bilayer membrane. Cholesterol acts as '*fluidity buffer*', since below the phase transition it tend to make the membrane less ordered while above the transition it tends to make the membrane more ordered, thus suppressing the tilts and shift in membrane structure specifically at the phase transition.

Role of Cholesterol in Bilayer Formation:

- Acts as a fluidity buffer.
- After intercalation with phospholipid molecules alters the freedom of motion of carbon molecules in the acyl chain.
- Restricts the transformations of *trans- to gauche-* conformations.

Drug Candidate [12]

Ciclopirox olamine (CPO), a broad-spectrum antifungal, is a hydroxypyridone derivative used for topical dermatologic treatment of superficial mycoses. It has a broad spectrum of action against dermatophytes, yeasts, filamentous fungi, and bacteria. Biological half-life of Ciclopirox Olamine is 1.7 h and bioavailability of <5% with prolonged use. It inhibits all clinically relevant dermatophytes, yeasts and molds, including the frequently azole-resistant Candida species. In addition, it acts against a wide range of bacteria, such many Gram-positive and Gram-negative

bacteria that are pathogenic for humans and may be associated to the fungal infection. CPO is presented in a variety of topical formulations; however an oral formulation is not currently available. The usual concentration of CPO in topical dosage forms is 1%, but its effective concentration range from 0.1%, for solutions against tinea versicolor, to 8% in nail lacquer solutions for the treatment of mild to moderate onychomycosis.

Types of Niosomes [13, 14]

a. Small Unilamellar Vesicles (SUV)

SUV are commonly produced by sonication, and French Press procedures.Ultrasonic electro capillary emulsification or solvent dilution techniques can be used to prepare SUVs. (size - 0.025-0.05 µm).

b. Multilamellar Vesicles (MUV)

Exhibit increased-trapped volume and equilibrium solute distribution, and require hand-shaking method. They show variations in lipid compositions. (size >0.05 µm).

c. Large Unilamellar Vesicles (LUV)

The injections of lipids solubilised in an organic solvent into an aqueous buffer, can result in spontaneous formation of LUV, but the better method of preparation of LUV is Reverse phase evaporation, or by Detergent solubilisation method. (size > 0.10 µm).

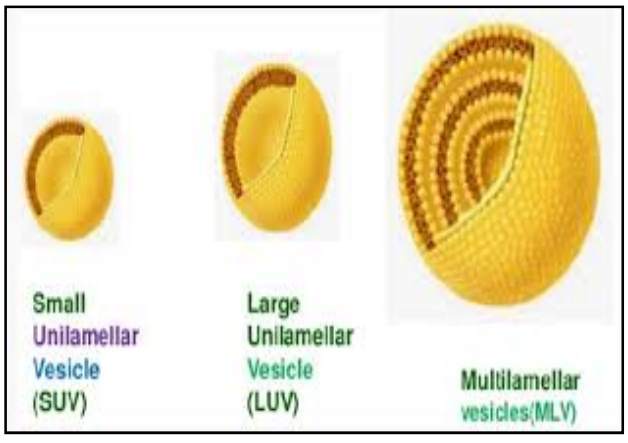

Figure 1: Types of Niosomes

Method of Preparation [15-21]

a. Ether Injection Method
b. Hand Shaking Method (Thin film hydration technique)
c. Sonication
d. Microfludization
e. Multiple Membrane Extrusion method
f. Reverse Phase Evaporation Technique (REV)
g. Trans membrane pH gradient (inside acidic) Drug Uptake Process (remote loading)
h. The "Bubble" Method
i. Ethanol injection method
j. Formation of niosomes from proniosomes

a. Ether Injection Method

This method provides a means of making Niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warmwater maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into anaqueous 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.

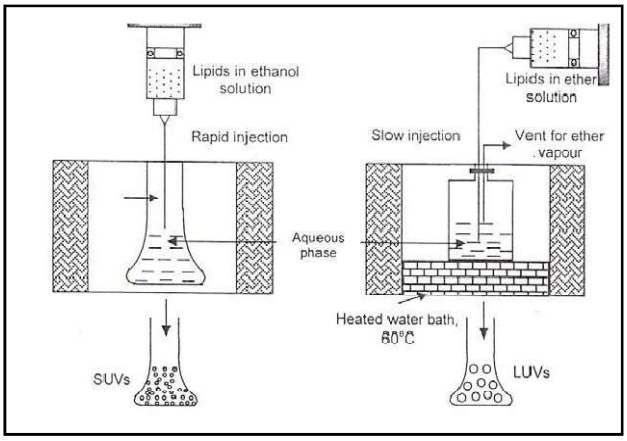

Figure 2: Ether Injection Method

b. 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 round bottom flak. The solvent is evaporated at a temperature (200C) using a 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 maintained at 0-60º C with gentle agitation.

c. Sonication

A typical method of production of the vesicles is by Sonication of solution was introduced. 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 sonicator with a titanium probe to yield Niosomes.

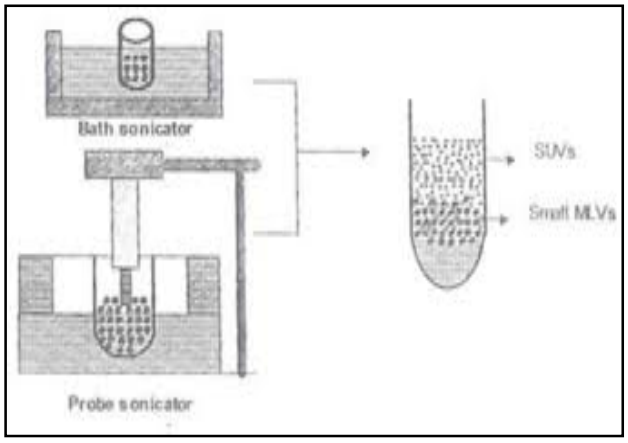

Figure 3: Sonication method

d. Microfluidization

It 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 smaller size, greater uniformity and better reproducibility of niosomes formed.

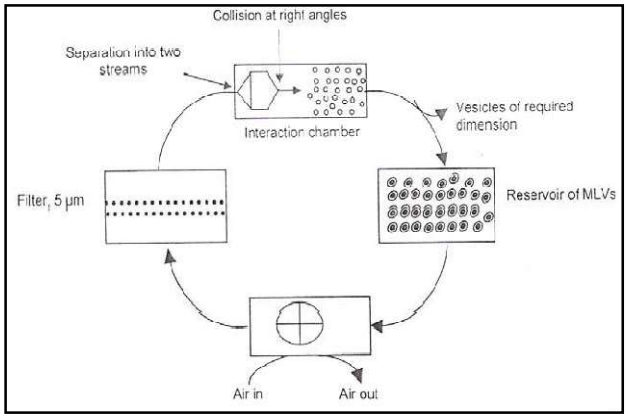

Figure 4: Microfluidization

e. Multiple Membrane Extrusion Method

Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug polycarbonate membranes, 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.

f. Reverse Phase Evaporation Technique (REV)

The novel key in this method is the removal of solvent from an emulsion by evaporation. 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 phase system is 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 minutes to yield niosomes.

g. Trans Membrane pH Gradient (Inside Acidic) Drug Uptake Process (Remote Loading)

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 (pH 4.0) by vortex mixing. The resulting multilamellar vesicles are then treated to three freeze thaw cycles and sonicated. To this niosomal suspension, aqueous solutions containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with the addition of 1M disodium phosphate (this causes the drug which is outside the vesicle to become non-ionic and can then cross the niosomal membrane, and once inside it is again ionized thus not allowing it to exit the vesicle). This mixture is later heated at 60°C for 10 minutes to give niosomes.

h. The "Bubble" Method

It is novel technique for the 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.

i. Ethanol Injection Method

This method has been reported as one of the alternatives used for the preparation of small unilamellar vesicles (SUVs) without sonication. In this method, an ethanol solution of surfactant is injected rapidly through a fine needle into excess of saline or other aqueous medium. Vaporization of ethanol leads to the formation of vesicles.

j. 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 termed as "proniosomes". The niosomes are recognized by the addition of aqueous phase at T > Tm and brief agitation.

T – Temperature
Tm – Mean phase transition temperature

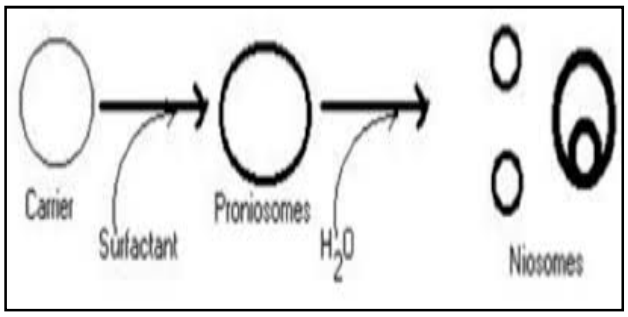

Figure 5: Formation of niosomes from proniosomes

Applications of Niosomes [22]

The application of niosomal technology is widely varied and can be used to treat a number of diseases.

1. 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 drugs.

2. Drug Targeting

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.

3. 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 are decreased rate of proliferation of tumor and higher plasma levels accompanied by slower elimination.

4. Leishmaniasis

Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells of the liver and spleen. Use of niosomes in tests conducted showed that it was possible to administer higher levels of the drug without the triggering of the side effects, and thus allowed greater efficacy in treatment.

5. 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 *in vitro* study conducted by oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide.

6. 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. Nonionic surfactant vesicles have clearly demonstrated their ability to function as adjuvant following parenteral administration with a number of different antigens and peptides.

7. 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 anaemic patients.

8. 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 encapsulation.

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 administration.

CONCLUSION

One of the best examples of significant advances in drug delivery technology and nanotechnology is the Niosomal dru delivery system. Niosomas seem to be a favored drug delivery mechanism rather than another dosage type as niosomes that are mostly stable in nature and economically. The goal is to encapsulate and use niosomes as promising drug carriers to improve bioavailability and targeted properties and to reduce the toxicity and side-effects of medicines. The purpose is a great deal of anti-cancer, anti-infective medicines, anti-AIDS, anti-inflammatory medications, anti-virals and other toxicants. These areas need therefore to be considered and examined more thoroughly to increase trade. Researchers and academics generally support the idea of integrating the medication in or niosomes for enhanced drug targeting at the required tissue destination. The carriers of ionic drugs are relative hazardous and inappropriate, while they are safer. And there are no special conditions for the handling and storage of niosomes. Niosomes are a promising module for drug delivery. They have a similar structure to liposome and therefore little similar property, and because of the niosomic ability to encapsulate different drug type within their multi-environmental structures, they may represent an alternative vesicular system for liposomes.

Niosomes are the concept of better drug delivery than liposomes because of several factors such as cost, stability etc. In different types of drug products niosomes play an important and important role; as targeting, topical, ophthalmic and parenteral. Niosomes are valuable to the pharmaceutical industry in the bright future. Further research in human volunteers, pharmacological and toxicological studies on animals and human volunteers can lead to using niosomes more effectively as prosperous drug carers to target drugs for the treatment of other diseases. Currently only animals are experimented with this target-specific drug-delivery method.

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