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Non Ionic Surfactant Vesicles – A Review

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ABSTRACT

There has been keen interest in the development of a novel drug delivery system which aims to deliver the drug at a rate directed by the needs of the body during the treatment periodand channel the active entity to the site of action. Consequently a number of vesicular drug delivery systems such as liposomes, niosomes, transfersomes, and pharmacosomes were developed. Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids and can be used as carriers of amphiphilic and lipophilic drugs. Niosomes alike liposomes are biodegradable, biocompatible and non-immunogenic in nature and exhibit flexibility in their structural characterization and storage. Niosomes are now widely studied as an alternative to liposomes because they alleviate the drawbacks like chemical instability, variable purity of phospholipids and high cost.Recently, niosomes have been studied by many researchers as a choice of oral drug delivery system to provide better oral bioavailability consideration, high penetration property of the niosome encapsulated agents through biological membrane and their stability. The aim of this article is to bring out the structural composition, advantages, and various methods of preparations, drawbacks and applications of Niosomes.

Keywords: Niosomes, Non- Ionic Surfactant vesicles, Novel drug delivery system, Vesicular carriers.

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INTRODUCTION

The ideal drug delivery system delivers drug at rate dictated by the need of the body over the period of treatment and it channels the active entity solely to the site of action. Drug targeting can be defined as the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with non-target tissue [2]. Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes etc [1]. Niosomes are important from a technical viewpoint as they possess greater stability and avoid some disadvantages associated with liposomes such as variable purity of phospholipids and high cost. Another advantage of niosomes is the development of a simple practical method for the routine and large-scale production without the use of pharmaceutically unacceptable solvents. In recent years, niosomes have been extensively studied for their potential to serve as carriers for delivery of drugs, antigens, hormones and other bioactive agents.

Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkylpolyglycerol ether class and cholesterol with subsequent hydration in aqueous media [3]. Niosomes are promising vehicle for drug delivery and being non-ionic, it is less toxic and improves the therapeutic index of drug by restricting its action to target cells. The focus of this review is to bring out the various methods of preparation, characterizations, factors affecting, advantages and applications of niosomes. 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.

Advantages of niosomes

- The vesicle suspension is water–based vehicle. This offers high patient compliance in comparison with oily dosage forms.
- They possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities.
- The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, tapped 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.

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- The surfactants are biodegradable, biocompatible and non-immunogenic.
- They 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.
- Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-aqueous phase.

NIOSOMES VS LIPOSOMES

- Niosomes are now widely studied as an alternative to liposomes, which exhibit certain disadvantages such as –they are expensive, their ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they require special storage and handling and purity of natural phospholipids is variable.
- Differences in characteristics exist between liposomes and niosomes, especially since niosomes are prepared from uncharged single-chain surfactant and cholesterol whereas liposomes are prepared from double-chain phospholipids (neutral or charged). Niosomes behave in-vivo like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability. Encapsulation of various anti neoplastic agents in these carrier vesicles has been shown to decrease drug induced toxic side effects, while maintaining, or in some instances, increasing the anti-tumor efficacy. Such vesicular drug carrier systems alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug. They can be expected to target the drug to its desired site of action and/or to control its release.
- As with liposomes, the properties of niosomes depends both on the composition of the bilayer and on method of their production. The intercalation of cholesterol in the bilayers decreases the entrapment volume during formulation and thus entrapment efficiency. As the concentration of cholesterol increases, entrapment efficiency decreases.
- The entrapment efficiency increases with increase in the concentration and lipophilicity of surfactant. It was also observed that as HLB value of surfactant decreased, the mean size was reduced. Chandraprakashet al made Methotrexate loaded non-ionic surfactant vesicles using lipophilic surfactants like Span 40, Span 60 and Span 80 and found that Span 60 (HLB = 4.7) gave highest percent entrapment while Span 85 (HLB = 9.8) gave least entrapment [4-11].

Method of preparation

- **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.

- **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.

- **Sonication**

A typical method of production of the vesicles is by sonication of solution as described by Cable [32]. 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.

- **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.

- **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.

- **Reverse Phase Evaporation Technique (REV)**

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.

- **Remote loading / 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 M 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.

- **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.

- **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" [12-19].

SEPARATION OF UNENTRAPPED DRUG

- **Dialysis:** The aqueous niosomal dispersion is dialyzed in a dialysis tubing against phosphate buffer or normal saline or glucose solution.
- **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.
- **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.

CHARACTERIZATION OF NIOSOMES

a) Entrapment efficiency

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After preparing niosomal dispersion, unentrapped drug is separated by dialysis, centrifugation, or gel filtration and the drug remained 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.

$$\text{Entrapment efficiency} = \frac{(\text{Amount of drug entrapped}) \times 100}{(\text{Amount of total drug taken})}$$

b) Vesicle diameter

Niosomes assume spherical shape and so their diameter can be determined using light microscopy, photon correlation microscopy and freeze fracture electron microscopy.

c) 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 [20-23].

FACTORS AFFECTING NIOSOMAL CHARACTERISTICS

- **Drug**

Entrapment of drug in niosomes increases vesicle size, probably by interaction of solute with surfactant head groups, increasing the charge and mutual repulsion of the surfactant bilayers, thereby increasing vesicle size. In polyoxyethylene glycol (PEG) coated vesicles, some drug is entrapped in the long PEG chains, thus reducing the tendency to increase the size. The hydrophilic lipophilic balance of the drug affects degree of entrapment [24-26].

- **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. 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 phase transition temperature (TC). Phase transition temperature (TC) of surfactant also effects entrapment efficiency i.e. Span 60 having higher TC, provides better entrapment [27-33].

❖ **Cholesterol content and charge**

Inclusion of cholesterol in niosomes increases its hydrodynamic diameter and entrapment efficiency. In general, the action of cholesterol is two folds; on one hand, cholesterol increases the chain order of liquid-state bilayers and on the other, cholesterol decreases the chain order of 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 the rigidity of the bilayers obtained. Presence of charge tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle structure and leads to greater overall entrapped volume.

❖ **Methods of preparation**

Methods of preparation of niosomes such as hand shaking, ether injection and sonication have been reviewed by Khandareet al . Hand shaking method forms vesicles with greater diameter (0.35-13nm)compared to the ether injection method (50-1000nm). Small sized niosomes can be produced by Reverse Phase Evaporation (REV) method. Microfluidization method gives greater uniformity and small size vesicles. Niosomes obtained by trans membrane pH gradient (inside acidic) drug uptake process method showed greater entrapment efficiency and better retention of drug.

❖ **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 with slight swelling of vesicles probably due to inhibition of eluting fluid from vesicles, followed by faster release, which may be due to mechanical loosening of vesicles structure under osmotic stress.

APPLICATIONS

❖ **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.
- 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 **[**34-41**]**.

❖ **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 [38]. 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 [42-44].

❖ **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 they damage the heart, liver and kidney [45].

❖ **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 Yoshida et al, oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide [46-49].

❖ **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.

❖ **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 [50,51].

❖ **Transdermal Drug Delivery Systems Utilizing Niosomes**

One of the most useful aspects of niosomes is that they greatly enhance the uptake of drugs through the skin. Transdermal drug delivery utilizing niosomal technology is widely used in cosmetics, in fact, it was one of the first uses of the niosomes. Topical use of niosome entrapped antibiotics to treat acne is done. The penetration of the drugs through the skin is greatly increased as compared to un-entrapped drug. Recently, transdermal vaccines utilizing niosomal technology is also being researched. A study conducted by P. N. Gupta et al has shown that niosomes (along with liposomes and transfersomes) can be utilized for topical immunization using tetanus toxoid. However, the current technology in niosomes allows only a weak immune response, and thus more research needs to be done in this field [52-61].

❖ **Other Applications**

Niosomes can also be utilized for sustained drug release and localized drug action to greatly increase the safety and efficacy of many drugs. Toxic drugs which need higher doses can possibly be delivered safely using niosomal encapsulation.

MARKETED PRODUCTS

Lancome has come out with a variety of anti-ageing products which are based on niosome formulations. L'Oreal is also conducting research on anti-ageing cosmetic products.

UNITED STATES PATENT 4830857

The invention is related to cosmetic and pharmaceutical compositions containing niosomes and a water-soluble polyamide, and a process for preparing these compositions

CONCLUSION

Over the years, there has been a great evolution in drug delivery technologies. The technology utilized in niosomes is still greatly in its infancy. , and already it is showing promise in the fields of cancer and infectious disease treatments; also for various cosmetic products. The concept of incorporating the drug into niosomes for a better targeting at appropriate tissue destination is widely accepted by researchers and academicians. Niosomes are thoughts to be better candidates 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, parentral, etc. Niosomes represent a promising drug delivery moduleand much research has to be inspired in this to extract out all the potential in this novel drug delivery system.

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