

Niosome: as dermal drug delivery tool

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Abstract: *The design of proper dosage regimen is an important element to achieve a steady state blood or tissue level that is therapeutically effective and nontoxic for an extended period. Recently niosomes are becoming popular in the field of topical drug delivery due to its outstanding characteristics like enhancing the penetration of drugs, providing a sustained pattern of drug release and ability to carry both hydrophilic and lipophilic drugs. Niosome are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or their lipids. The sizes of niosomes are microscopic and lie in nanometric scale. The particle size ranges from 10nm-100nm. This review article focuses on the structure, advantages, Disadvantages, preparation methods, factors affecting, characterizations, and applications of niosome.*

Key words: *Cholesterol, Hydrophilic and lipophilic drugs, Niosome, Surfactant,*

I. Introduction

The development for targeted delivery was initiated by Paul Ehrlich, in 1909 when he envisaged a drug delivery mechanism that would target directly to diseased cell. 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. Some modified vesicles possessed properties that allowed them to successfully deliver drugs in deeper layers of skin which was one of the major advances in vesicle research. Dermal delivery is important because it is a noninvasive procedure for drug delivery as well as avoids the problem of drug degradation by digestive enzymes after oral administration. Further, it also helps to avoid discomfort associated with parenteral drug administration [1]. Niosomes are promising vehicle for drug delivery because it is less toxic and improves the therapeutic index of drug by restricting its action to target cells[2]. Niosomes are microscopic lamellar structures composed of non-ionic surfactants and cholesterol.[3]. In niosome, non-ionic surfactant is used as vesicles forming amphiphile stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate[4]. Using of Non-ionic surfactants are better than than the phospholipids. Because Non-ionic surfactants are more economical and are chemically more stable as they are not easily hydrolysed or oxidised during storage. Sustained or controlled delivery of drug can be obtained by modifying the vesicular structure of niosome[5]. Niosomes have been investigated for drug delivery through the most common routes of administration, such as intramuscular, intravenous, subcutaneous, ocular, oral and transdermal.

II. Structure

Structurally, niosomes are made up of a bilayer which is consisted of non-ionic surface active agents. Depending on method of preparation, niosomes may be unilamellar or multilamellar. Most surface active agents are immersed in water yield micellar structures and bilayer vesicles can be made by some surfactants which are niosomes. Hydrophobic drugs are embedded within the bilayer, while the vesicle holds hydrophilic drugs within the space enclosed in the vesicle. A typical niosome consists of non-ionic surfactant such as Span- 60. Cholesterol and a small amount of non- ionic surfactant such as diacetyl phosphate are used to stabilize the vesicle [6,7,8].

III. Type Of Niosome

Niosome can be classified based on the vesicle size and divided into three groups:

1. Small Unilamellar Vesicles (SUV, Size=0.025-0.05 μm)
2. Multilamellar Vesicles (MLV, Size=>0.05 μm)
3. Large Unilamellar Vesicles (LUV, Size=>0.10 μm)[9]

IV. Advantages

- Niosome can accommodate variety of drug moieties such as hydrophilic, lipophilic, as well as amphiphilic drugs.
- Niosomes can be designed according to the desired situation because of its flexibility in their structural characteristics (composition, fluidity and size).
- Therapeutic performances can be improved by restricting effects to target cells and protecting drugs from biological environment.
- Niosomes can offer control release of drugs
- Oral bioavailability can be increased if the drug is incorporate in niosomes.
- Niosomes are osmotically active and stability of entrapped drug can be increased by niosomal preparation.
- Niosomes can enhance the skin penetration of drug through skin.
- They offer to reach the drug at the site of action by multiple routes such as oral, parenteral as well as topical routes.
- Surfactants used in niosomes are non-immunogenic, biodegradable and biocompatible.
- No special conditions are not required for handling and storage of surfactants[10].
- Niosomes are colloidal vesicular carriers and these vesicles can act as drug reservoirs and the rate of drug release can be modified by changing of their composition.
- Niosomes can encapsulate both hydrophilic drugs (by loading in inner space) and hydrophobic drugs (in lipid area). That's why it is used in various drug delivery systems like drug targeting, controlled release and permeation enhancement of drugs[11].

V. Disadvantages

- Physical instability
- Aggregation
- Fusion
- Leaking of entrapped drug
- Hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion[12].

VI. Components

Non-ionic surfactants: The main component in niosomal formulations is Non-ionic surfactants which possess hydrophilic head group and a hydrophobic tail. The hydrophobic moiety may consist of 1/2/3 alkyl chains(chain length is from C12- C18) or perfluoro group(chain length having C10) or in certain cases a single stearyl group. Most commonly used surfactants found in literature are Sorbitan fatty acid esters. Spans series specially Span 20, 40, 60, 65, 80, and 85 are most commonly used. All Span types have the same head group and different alkyl chain length and increasing alkyl chain length leads to high entrapment efficiency of drug[13]. Tweens are polysorbates derived from PEGylated sorbitan esterified with fatty acids are also used in niosomal formulations. Tween 20, Tween 40, and Tween 60 are most commonly reported Tweens in niosomal preparations[14]. Spherical, tubular or polyhedral niosomal vesicles could be formed by using solulan C24 poly-24-oxethylene cholesteryl ether.[15] Bilayer vesicles can be prepared by using polyoxyethylene alkyl ethers (CnEOm, Brij TM) surfactants when mixed with cholesterol. The different grades of Brij used for vesicle formation are Brij 30, 35, 52, 58, 72, 76, 92, and 97[16]. Recently bola surfactants have been synthesized to prepare innovative niosomal systems. Bola forms amphiphiles are composed of two identical AZA- Crown ether units, as polar heads, linked to a long alkyl chain. Bola surfactants are able to assemble in colloidal structures if associated with cholesterol[17]. Ovalbumin niosomes can be prepared by using another category of biodegradable and very low toxic surfactants Wasag®7 (70% stearate sucrose ester, 30% palmitate sucrose ester) and Wasag® 15 (70% stearate sucrose ester, 30% palmitate sucrose ester). They are able to form gel state bilayer at 37°C[18].

Cholesterol; In niosomes, nonionic surfactant is usually stabilized by addition of cholesterol. Rigidity and proper shape and conformation of the niosomes preparations can be achieved by using Cholesterol.

Other additives: Dicapryl phosphate (DCP) and stearyl amine (SA) are used as membrane additives which induces negative or positive charge in niosomes because they increase surface charge density and prevent vesicles flocculation, aggregation and fusion[19].

VII. Methods Of Preparation

The preparation method of niosomes affects the size, size distribution, number of bilayers, and entrapment efficiency of the aqueous phase and the membrane permeability of the vesicles. It also depends on the use of niosomes.

Ether injection method: In this method a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C by slowly. Using a 14-gauge needle, the surfactant mixture in ether is injected into an aqueous solution of material. Single layered vesicles are formed after vaporization of ether[20].

Sonication Method: Sonication is atypical method for the production of vesicles. In this method a mixture is prepared by adding drug solution in buffer into the surfactant/cholesterol which can be taken in 10-ml glass vial. Using a sonicator this mixture is sonicated at 60°C for 3 minutes with a titanium probe to yield niosomes[21].

Micro fluidization Method: Recently, Micro fluidization method is used to prepare unilamellar vesicles of defined size distribution. This method works according to the submerged jet principle. According to this principle two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The energy supplied to the system remains within the area where niosomes is formed. The impingement of thin liquid sheet along a common front is arranged in such a way that the energy is supplied only the niosomes forming area. A greater uniformity, smaller size and better reproducibility of niosomes is formed by this method[22].

Multiple membrane extrusion method: A thin film is made from the mixture of surfactant, cholesterol and dicetyl phosphate in chloroform 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. Niosome size is suitably controlled by this method[23].

Reverse Phase Evaporation Technique (REV): Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. Then aqueous phase which contain drug is added to the mixture. Final mixture contains two phases that are sonicated at 4-5°C. The clear gel is formed where small amount of phosphate buffered saline (PBS) is added here then further sonicated. After sonication 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[24].

Hand shaking method (thin film hydration technique): Surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. A thin layer of solid mixture deposited on the wall of the flask after removing organic solvent at room temperature (20°C) using rotary evaporator. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. Typical multilamellar niosomes is formed by this process[25].

Transmembrane pH gradient Drug Uptake Process (Remote Loading): A solution of surfactant and cholesterol is made in chloroform. A thin film on the wall of the round bottom flask is formed after evaporating the solvent under reduced pressure, similar to the hand shaking method. Hydration of this solution is done by using citric acid solution with help of vortex mixing. Multilamellar vesicles are formed then treated to three freeze thaw cycles and sonicated. Aqueous solution containing 10mg/ml of drug is added to the niosomal suspension and vortexed. 1M disodium phosphate is used to raise the pH of the sample to 7.0-7.2 and mixture is later heated at 60°C for 10 minutes to give niosomes[26].

The “Bubble” Method: Recently the “Bubble” method has been developed and this method allow the preparation of niosomes without the use of organic solvents. The bubbling unit consists of a round bottom flask with three necks which is placed in a water bath to control the temperature. Among the three necks, water-cooled reflux and thermometer is positioned in the first and second neck and the third neck is used to supply nitrogen. Cholesterol and surfactant are dispersed together in a buffer (pH 7.4) at 70°C and mixed for a period of 15 seconds with high shear homogenizer and immediately afterwards, it is bubbled at 70°C using the nitrogen gas to yield niosomes[27].

Formation of Niosomes from Proniosomes: Proniosome is a dry formulation in which each water-soluble particle was covered with a thin film of dry surfactant. The niosomes were recognized by the adding aqueous phase at $T > T_m$ with brief agitation. T is the Temperature and T_m is the mean phase transition temperature.[28]

Method of Handjani-Vila: The equivalent amounts of synthetic non-ionic lipids were mixed with the aqueous solution of active substance that was encapsulated. Homogenous lamellar film was formed through shaking. Using ultra-centrifugation and agitation, the resultant mixture was then homogenized at a controlled temperature[29].

Heating Method: This method was one-stepped, scalable and non-toxic and also based on the patented procedure. A suitable aqueous medium such as buffer distilled, H₂O, etc in which Mixtures of non-ionic surfactants, cholesterol and/or charge inducing molecules are added in the presence of the polyol like as glycerol. The mixture was heated with (at low shear forces) until vesicles were formed[30].

VIII. Factors Affecting Niosomes Formulations

Drug: Degree of entrapment can be affected by hydrophilic lipophilic balance of the drug. Entrapment of drug in niosomes increases vesicle size and it can be reduced by entrapping drug with long polyoxyethylene glycol (PEG) chains.

Amount and type of surfactant: Entrapment efficiency of formulations depends on concentration and nature of surfactants[31]. HLB value of surfactants may affect the mean size of niosomes. Higher HLB surfactants may increase the mean size of niosomes. Some factors such as temperature, the type of lipid or surfactant and the presence of other components such as cholesterol may affect the bilayers of the vesicles either in liquid state or in gel state.

Cholesterol content and charge: Hydrodynamic diameter and entrapment efficiency of niosomes depends on the inclusion of cholesterol. Cholesterol increases the chain order of liquid-state bilayers and decreases the chain order of gel state bilayers. The release rate of encapsulated material can be decreased by increasing cholesterol content because high cholesterol content increases the rigidity of the bilayers.

Resistance to osmotic stress: Vesicles diameter and release pattern also depends on the addition of hypertonic or hypotonic salt solution. Diameter can be reduced by addition of hypertonic salt solution where as initial slow release due to the inhibition of eluting fluid from vesicles followed by faster release due to mechanical loosening of vesicles structure under osmotic stress obtained by addition of hypotonic salt solution.

Membranes Composition: The stable niosomes can be prepared with addition of different additives along with surfactants and drugs. The shape of polyhedral niosomes can be protected by adding low amount of solulan C24 (cholesterol poly-24- oxyethylene ether), which prevents aggregation due to development of stearic unhydrance. Rigidity to the membrane can be obtained by addition of cholesterol molecule to niosomal system and also reduces the leakage of drug from niosomes[32].

IX. Characterization

Measurement of Angle of repose: Funnel method is used to measure angle of repose of dry niosomes powder. A funnel is fixed stand and pour the niosomes powder into funnel. A cone on the surface is formed when powder flows down from the funnel. The angle of repose is then calculated by measuring the height of the cone and the diameter of its base by using following equation.

$$\tan \alpha = H/R \text{ or } \alpha = \tan^{-1} H/R$$

Where α = Angle of repose H= Height of the granules R = Radius of the granules

Particle size: Scanning Electron Microscopy (SEM) is used to study the surface morphology (roundness, smoothness, and formation of aggregates) and the size distribution of niosomes. A gaseous secondary electron detector is to observe the morphological character of niosomes.

Measurement of vesicle size: Particle size analyzer is used to measure the Vesicle size. Before determining the vesicle size the sample is stirred using a stirrer.

Osmotic shock: Niosomes formulations are incubated with hypotonic, isotonic, hypertonic solutions for 3 hours to determine the change of vesicle size by osmotic studies. Optical microscope is used to observe the changes in the size of vesicles in the formulations.

Zeta potential analysis: Zeta potential analyzer based on electrophoretic light scattering and laser Doppler velocimetry method is used to analyze the Zeta potential which is done for determining the colloidal properties of the prepared formulations. The temperature is set at 25°C[33,34,35,36,37].

Entrapment efficiency

Method 1: Untrapped drug is separated by dialysis, centrifugation, or gel filtration from niosomal dispersion. Vesicle is disrupted by using 50% n-propanol or 0.1% Triton X-100 and the resultant solution is analyzed by appropriate assay method for the drug. Following equation is used to determine the % Entrapment efficiency.

% Entrapment efficiency (% EF) = (Amount of drug entrapped/ total amount of drug) x 100 [38].

Method 2: Separation of untrapped drug is done by dialysis, centrifugation, or gel filtration method. The supernatant was diluted with 5 ml of phosphate buffer pH 7.4. From the above solution, 1 ml is taken and transferred to 10 ml standard flask and made up to 10 ml with phosphate buffer pH 7.4. The resultant solution is analyzed by appropriate assay method using phosphate buffer pH 7.4 as blank. The percentage of drug encapsulation was calculated by the following equation:

$EE (\%) = [(C_t - C_f)/C_t] 100$

Where C_t is the concentration of total drug and C_f is the concentration of untrapped drug[39].

In vitro release:

Method 1: Glass tube of diameter 2.5cm with an effective length of 8cm which is previously covered with cellophane membrane is used to determine the in vitro release rate. Measured amount of niosomes are placed in the cylinder which is placed in 100 ml of phosphate buffer saline, pH 7.4. This phosphate buffer saline acts as receptor compartment. The temperature of receptor medium was maintained at $37 \pm 1^\circ\text{C}$ and agitated at 100rpm speed using magnetic stirrer. Aliquots of 5ml sample are withdrawn from receptor compartment at intervals of 24 h for 3 days. An equal volume of phosphate buffer saline, pH 7.4 is added to receptor compartment to maintain its volume in each sampling time. The drug in withdrawn samples is estimated by the reported assay method using medium as blank[40].

Method 2: Method of in-vitro release is studied by the use of dialysis bag (pore size of dialysis bag depends on MW of drug) After separating the untrapped drug, the niosomal suspension containing drug equivalent to drug content is pipette into dialysis bag which is previously soaked and washed several times with distilled water. This is placed in 100 ml of phosphate buffer saline pH 7.4 and kept with constant agitation on a magnetic stirrer maintaining a temperature of 37°C . In each periodical time the reported amount of sample is withdrawn and same volume of fresh sample is replaced. Then samples is assayed reported assay method using medium as blank. The release was compared with pure drug solution[41].

Stability studies:

PH stability: The niosomal dispersion (1 mg drug entrapped niosome / 5ml of pH 7.4 phosphate buffer) are kept in air tight containers and stored at different pH condition for 2 hours and the then sample are withdrawn. The supernatant are analyzed by reported assay method after centrifugation[41].

Temperature Stability: The drug retain ability of vesicle was assessed by keeping the niosomal formulation at different temperature conditions i.e. such as refrigeration temperature ($2^\circ\text{-}8^\circ\text{C}$), room temperature ($25^\circ \pm 0.5^\circ\text{C}$) and elevated temperature ($45^\circ \pm 0.5^\circ\text{C}$) from a period of 1 month to 3 months. Niosome formulations were stored in aluminum foil sealed glass vials and the samples were withdrawn at different time intervals over a period of time. Drug leakage from the formulations was analyzed for drug content by spectrophotometrically[42].

X. Application

Drug Carriers: Niosomes have also been used as carriers for example iobitridol, a diagnostic agent used for Xray imaging. Topical niosomes may be used for sustained release of dermally active compounds, as penetration enhancers, or as rate-limiting membrane barrier for the modulation of systemic absorption of drugs.

Drug Targetting: Niosomes can be utilized for organ specific drugs targeting. Specific drugs are attached to niosomes to target them to specific organs. For example antibodies such as immunoglobulin's bind readily to the lipid surface of the niosome.

Anti-neoplastic Treatment: The side effects of the antineoplastic drugs are common phenomenon. Side effects of antineoplastic drugs can be reduced by altering the metabolism; prolong circulation and half life of the drug.

Leishmaniasis: Leishmaniasis is a disease in which parasite invades cells of liver and spleen. High level of antimonials is commonly prescribed for the treatment of leishmaniasis. But antimonials are closely related to arsenic and heart, liver and kidney may be damaged at high concentration of antimonials.

Delivery of Peptide Drugs: Oral peptide drugs are breakdown by some enzymes present in gastrointestinal tract that can be avoided by using of niosomes. Sometimes stability of the peptide drug can be increased by entrapping drug in niosomes.

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.

Niosomes as Carriers for Haemoglobin; Niosomes can be used as carriers for haemoglobin in anaemic patients. Oxygen is permeable to niosomal vesicle and hence act as carrier for haemoglobin within the blood [43,44,45,46].

Other applications:

- Transdermal applications of drugs allow to protecting the drugs from the hepatic first pass effect.
- Parenteral administration of niosomes is possible for its sub-micron particle size.
- The oral use of niosomal formulations appears that there is enhanced drug absorption.
- Niosomes are also used for radiopharmaceuticals purpose. For example, 131-I labeled iopromide niosomes with positive charge was prepared in 1996 by Erdogan [47, 48].

XI. Conclusion

Niosomal drug delivery systems to be a promising controlled drug delivery systems to the target area. Niosomes are relatively non-toxic and stable and offer successful drug localization in skin. Physical and chemical instability of active drug can be protected by vesicular carriers. Among the all of these advantages there are still some challenges in this area. The type of surfactant is the main parameter because it affects the formation of the vesicles, their toxicity and stability. So the researchers should be more alert in the selection of suitable surfactant for niosome preparation.

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