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A Review on Niosomes

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ABSTRACT
Niosomes are lamellar structures that are microscopic in size. Niosomes constitute a non-ionic surfactant of the alkyl or dialkylpolyglycerol ether class and cholesterol with subsequent hydration in aqueous medium. Niosomes are hydrophilic, amphiphilic and lipophilic in nature. They are biodegradable, biocompatible and non-immunogenic. They are stable dosage forms, they used as both controlled and sustained release dosage forms. They can be used as drug carriers; they are used in targeted delivery of drugs to a specified target tissue or cell. They serve better as diagnostic and imaging and a vaccine adjuvant. The review focuses on various methods of preparation of niosomes, characterization, factors affecting and applications.

KEYWORDS: Niosomes, non-ionic surfactants, cholesterol, vesicles, characterization, applications, method of preparation and characterization.

INTRODUCTION

[1,3].Paul Ehrlich, in 1909, initiated the era of development of targeted drug delivery of drugs that would directly target the desired organ, tissue or cell. Drug targeting can be defined as the ability to direct a therapeutic agent specifically to the desired site of action with little or no interaction with non- target tissue. Such delivery of drugs received much attention in recent years. Nanotechnology has provided the development of multifunctional nanoparticles that act as drug carriers, and can be loaded with different drugs.

Niosomes are promising drug carriers that have bilayer structure and are self-associating structures of non-ionic surfactants and cholesterol in aqueous phase. They are biocompatible, not immunogenic and biodegradable. They are stable, have long shelf life, and enable to deliver the drug to targeted sites of action, and also deliver the drug in controlled or sustained released patterns. Over the time various studies have been conducted on niosomes and various types of niosomes have been reported to enable the entrapment of a large number of drugs with a wide range of solubility.

The aim of the review is to provide a view over the various methods of preparation of niosomes, characterization, factors affecting and applications.

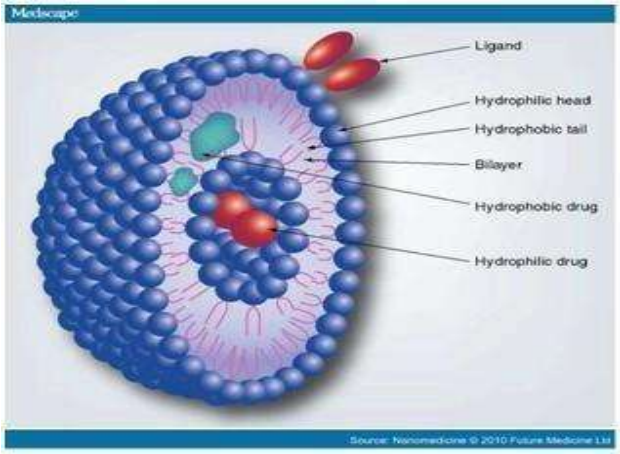

Fig1: structure of niosome [2]

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COMPOSITION OF NIOSOMES

- [2,4].Niosomes mainly contain following components
- **Non-ionic surfactants:** the non-ionic surfactants arrange themselves in bilayer lattice. Where the polar or hydrophilic head is facing towards the aqueous media and the hydrophobic head is arranged in such a way that it's contact with the aqueous media is limited. To attain thermodynamic stability, every bilayer forms a vesicle so that the hydrocarbon/water interface remains no more exposed.

Mainly following types of non-ionic surfactants are used:

- **Alkyl Ethers:** L'Oreal described some surfactants used for niosomes as, Surfactant-I (MW 473) where C_{16} mono alkyl glycerol ether with average of three glycerol units, surfactant-II (MW 972) diglycerol ether with average of seven glycerol units and surfactants-III (MW 393) ester linked surfactant. Poly hydroxyl head groups other than alkyl glycosides and alkyl ethers are used in the formulation.
- **Alkyl Ethers:** Sorbitan is the most preferred out of all surfactants. SorbitanMonolaurate surfactants are more soluble. E.g., polyoxyethylene is used in encapsulation of diclofenac sodium. A mixture of polyoxyethylene-10-stearyl ether: glyceryl laureate: cholesterol (27: 15:57) has been used in TDDS of cyclosporine -A.
- **Alkyl Amides:**galactosides and glucosides are used in production of niosomes.
- **Fatty acid and amino acid compounds:**long fatty acid chains and amino acids are used.

- **Cholesterol:**steroids are an important component of the cells and they affect the bilayer fluidity and permeability. Cholesterol may not play a role in bilayer formation but it is important in manipulation of layer characteristics and cannot be discarded. In the preparation of niosomes cholesterol affects the properties such as membrane permeability, rigidity, encapsulation efficiency, ease of rehydration of freeze dried niosomes and their toxicity. The prevent aggregation of niosomes by repulsive steric or electrostatic forces that cause the transition from gel to liquid phase in noisome systems. As a result, the niosomesbecome less leaky.
- **Chargedmolecule:** Some of the charged molecules prevent coalescence by increasing electrostatic repulsion. Only 2.5-5 mol % concentration of charged molecules is tolerable because high concentration can inhibit formation of niosomes. The negative charged molecules used are diacetyl phosphate and phosphatidic acid. STR and stearylpyridinium chloride are known positively charged molecules.

TYPES OF NIOSOMES:

[2].**Small Unilamellar Vesicles:** The size ranges from 0.025-0.05µm diameter. They are usually created by sonication and French press systems. Ultrasonic electro capillary emulsification or solvent dilution technique can be used to prepare SUVs.

Multi Lamellar Vesicles: The size ranges from 0.5-10 µm diameter. It comprises bilayers encompassing the aqueous lipid compartment independently and displays expanded trapped volume and equilibrium solute distribution, and requires hand-shaking method.

Large Unilamellar Vesicles: The size is more than 0.10 µm. LUV are prepared by reverse phase evaporation, or by solubilization method.

Fig 2: types of niosomes

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METHODS OF PREPARATION OF NIOSOMES:

[6, 1, 4].**Thin Film Hydration Method (TFH):**It is the simplest method. The surfactants, cholesterol and some additives are dissolved in organic solvent in a round bottom flask. Then the organic solvent is removed by a rotary evaporator. A thin film is formed inside the wall of the flask. Aqueous solution of the drug above the transition temperature of the surfactant is added to the dry film in the RBF. Multilamellarniosomes are formed by this method.

Ether Injection Method (EIM): In this method surfactants with additives are dissolved in diethyl ether and injected slowly through a needle in an aqueous drug solution maintained at constant temperature, which is above the boiling point of organic solvent. The organic solvent is evaporated using a rotary evaporator. Single layered vesicles are formed by this method.

Reverse Phase Evaporation Method (REV): The niosomal ingredients required are dissolved in a mixture of ether and chloroform. This mixture is added to the aqueous solution containing the drug. The mixture is then sonicated to form an emulsion and the organic phase is evaporated. Large unilamellar vesicles are formed during the evaporation of the organic solvent.

Micro fluidization Method: It is based on submerged jet principle. In this method the surfactant fluidized streams interact at ultrahigh velocities, in precisely defined micro channels within the interaction chamber. The high speed and the energy led to the formation of niosomes. The formed niosomes by this method offer a great uniformity, smaller size, unilamellar vesicles and high reproducibility in the formulation of niosomes.

Supercritical Carbon Dioxide Fluid ($scCO_2$): This method is described by Manosroi et al. for the formation of niosomes. Tween 61, cholesterol, glucose, PBS and ethanol is added into the view cell and the CO_2 gas is introduced into the view cell, it is magnetically stirred until equilibrium and then the pressure is released and the niosomal dispersion is obtained.

Proniosomes: This technique involves coating of a water-soluble carrier such as sorbitol and mannitol with surfactant. Coating results in the formation of dry formulation. This method is termed as "proniosomes" which require rehydration with aqueous phase before use. This method helps to reduce problems related to stability like aggregation, leaking and fusion problems and provides convenience in dosing, distribution, transportation and storage showing results than conventional methods.

Transmembrane pH Gradient: surfactants and cholesterol are dissolved in chloroform and evaporated to form a thin film on the wall of a round bottom flask. This is hydrated by citric acid in vortex mixing and the resultant process is freeze-thawed for niosomal formation. The aqueous solution is added to this niosomal suspension and then the pH is maintained between 7.0-7.2 by adding phosphate buffer. According to the method the interior of the noisome is more acidic pH than the outer medium. The unionized drug passes through the niosomal membrane and enters into the noisome. The drug gets ionized in the acidic medium and cannot escape.

Heating Method: This is a patented method developed by Mozafari et al. In this method the cholesterol and surfactants are separately hydrated in a buffer and the solution is heated to 120^0C until the cholesterol dissolves with constant stirring. The temperature of the buffer solution is cooled and then to it surfactants and other additives are added with constant stirring. This results in the formation of niosomes and the formed niosomes are stored at room temperature, and then stored at 4-5^0 C under nitrogen atmosphere until use.

The "Bubble" method: In a glass jar containing three necks surfactants, additives and buffers are added. Niosomes are dispersed at 70^0C and the dispersion is mixed with homogenizer. The beth is placed immediately in the water bath followed by the bubbling of nitrogen gas at 70^0 C. The sample is made to pass through the nitrogen gas, resulting in the formation of large unilamellar vesicles.

FACTORS EFFECTING NIOSOMAL FORMULATION:

[5, 4]**Drug:** Entrapment of drug in niosomes increases the size of vesicle, probably by interaction of solute with surfactant head groups, increasing the charge and mutual repulsion of the surfactant bilayers, thereby increasing vesicle size. In PEG coated vesicles, some drug is entrapped in long PEG chains, thus reducing the tendency to increase the size. The hydrophilic balance of drugs affects the degree of entrapment.

Amount and type of surfactant: The means size of niosomes increase with increase in the HLB

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surfactants because the surface free energy decreases with an increase in hydrophobicity of surfactant. The vesicle is either in the so-called liquid or in gel state, depending on the temperature, type of liquid or surfactant and the presence of other components such as cholesterol. In the gel state, alkyl chains are present in well-ordered structures of bilayers that are more disordered. The gel-liquid phase transition temperature is used to characterize the surfactants and lipids. The surfactant also affects entrapment efficiency i.e. span 60 having higher TC, provides better entrapment.

Cholesterol content and charge: inclusion of cholesterol in niosomes increases its hydrodynamic diameter and entrapment efficiency. Cholesterol folds into two folds, on one hand, cholesterol increases chain order of liquid-state bilayer and on the other hand cholesterol decreases the chain order of gel state bilayers. High cholesterol concentration, the gel state is transformed to a liquid ordered phase. Decrease in the release rate of the rigidity of the bilayers is observed due to the increase in cholesterol. Charge tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle structure and leads to greater overall entrapped volume.

Resistance to osmotic stress:hypertonic salts solution causes reduction in diameter. Hypertonic salt solution causes release of drug in smaller rate and faster later due to the mechanical loosening of vesicles structure under osmotic stress.

Membrane composition:niosomes are prepared by adding different drugs and surfactants. Niosomes are in the form of different morphologies. Their permeability and stability can be modified by different additives. In case of polyhedral niosomes formed remains unaffected by adding low amount of solulan C24 which prevents aggregation due to development of steric hindrance.

CHARACTERIZATIONOF NIOSOMES:

[1].Size and Morphology: Dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), freeze fracture replication electron microscopy (FF-TEM) and cryo transmission electron microscopy (cryo-TEM) are the most used method to determine the size and morphology. DLS gives simultaneous information of particle size and valuable information on the homogeneity of the solution. A single peak in DLS implies the existence of a single population of scatters. The microscopic approaches are generally used to characterize the morphology of the niosomes. The PI is helpful in this respect. Less than 0.3 corresponds to a homogenous population for colloidal systems.

[4].Entrapment Efficiency (EE %): It is defined as the portion of applied drug which is entrapped by the niosomes. For the determination of entrapment efficiency, the free drug or unencapsulated drug is removed from the solution by centrifugation, gel chromatography or dialysis method. The solution is then separated and supernatant liquid is collected, this liquid is then diluted as specified and estimated using appropriate methods.

$$EE=\frac{\text{AmountOfEntrappedDrug}}{\text{TotalAmountAdded}}\times 100$$

After this step the loaded rug can be released from niosomes by destruction of vesicles. The niosomes can be destroyed by 0.1% Triton x-199 or methanol. The loaded and free drug concentration can be known by spectrophotometer or HPLC.

[4].Transmission Electron Microscopy (TEM):TEM is used to determine the size, shape and lamellarity of niosomes. A suspension is prepared and mixed with 1% phosphotungstic acid. On the carbon coated grid, a drop of resultant is added, draining off the excess and then it is observed and images are taken under suitable TEM after complete drying.

[4].Freeze Fracture Microscopy: depending on the drug entrapment, nature of the drug and the nature of the surfactant the size and shape of niosomes are known. The vesicles are freeze thawed and are seen under the freeze fracture electron microscope for determination of size. For cryo-fixation of vesicular suspension liquid propane is used at low pressure. Thecryofixed vesicles are fractured at a specified angle. The surface is shadowed using carbon or platinum vapours at 45^0 angles. Carbon coating strengthens the replica formed. The replica is observed and examined under TEM after cleaning.

[1].Zeta Potential: zeta sizer and DLS are used to determine the surface zeta potential of the niosomes. The behaviour of niosomes depends on the charge of the niosomes. Charged niosomes are more stable than the uncharged niosomes. Bayindir and yukul found the negative zeta potential values ranging between -41.7 and -58.4mV of paclitaxel loaded niosomes are sufficiently high for electrostatic stabilization of niosomes.

[1,4].Stability: Two different conditions are used to do the stability conditions of the niosomes, usually $4+1^0$C and 25 ± 2^0C. The formulation size,

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shape and number of vesicles per cubic mm are assessed before and after storing for 30d. After 15-30d the residual matter can be measured. Light microscope is used for determination of size of vesicles and the number of vesicles per cubic mm and are measure by haemocytometer.

Number of niosomes per cubic $mm = \frac{TotalNumberOfNiosomes \times DilutionFactor}{TotalNumbe\ rOfSmallsquarescounted} \times 400$

[1].In vitro release: dialysis tubing is the often-applied method for in vitro release. A dialysis bag is washed and soaked in distilled water. After 30 mins, the niosomal suspension loaded with drugs is added into the bag. This bag is immersed into the buffer solution with constant shaking at 25^0C or 37^0C. Samples are collected at specified time intervals, the sample removed from the buffer is replaced with a fresh buffer of the same volume. The samples collected are analysed for drug content by appropriate assay method.

[4].Number of Lamella:NMR spectroscopy, small angle X-ray spectroscopy and electron microscopy are used to determine number of lamellae.

[4].Membrane rigidity: mobility of fluorescence probe as a function of temperature has been used to determine membrane rigidity.

[4].Vesicular Surface Charge: niosomes are generally prepared by inclusion of charged molecules in bilayer to prevent molecular aggregation, the charge on vesicles is expressed in terms of zeta potential and calculated using Henry's equation.

ADVANTAGES OF NIOSOMES:

- **[5].**Niosomal aqueous phase is emulsified in a non-aqueous phase to regulate the delivery of the drug and the normal vesicle is administered in an external non-aqueous phase.
- Water based vehicles offer higher patient compliance than oily dosage forms.
- They are osmotically active and stable.
- They increase the stability of entrapped drugs.
- No special conditions are required to store and handle the surfactants.
- Improve oral bioavailability and skin penetration of drugs.
- Oral and topical routes of administration are possible.
- The surfactants are non-immunogenic, biodegradable and biocompatible.
- Improve therapeutic performance of the drug by delayed clearance from circulation and restricting effects to target cells.
- Niosomes possess hydrophobic, amphiphilic and lipophilic moieties as a result it can accommodate a wide range of solubilities.
- The vesicle formulation characteristics are controllable and variable.
- Altering vesicle composition size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics.
- Depot release of formulation is possible, the drug is released in a controlled manner.

DISADVANTAGES:

- **[3].**Fusion
- Aggregation of particles
- Leaking of the entrapped drug from the vesicles.
- Physical instability.
- Hydrolysis of encapsulated drugs which is limiting the shelf life of the dispersion.

APPLICATIONS OF NIOSOMES:

[7, 1, 4]. The application of niosomal technology is widely varied and can be to treat a number of diseases.

- ❖ To improve the stability and physical properties.
- To increase oral bioavailability.
- To modify the physicochemical properties of drugs.
- For improvement of stability of peptide drugs:
- To promote transdermal delivery of drugs.
- As a tool for improvement of stability of immunological products.
- To improve anti- inflammatory activity.
- ❖ For controlled release of drugs:
- To prolong the release of the drug.
- In ophthalmic drug delivery.
- ❖ For targeting and retention of drug in blood circulation:
- For increased uptake by A431 cells.
- For liver targeting.
- To improve the efficacy of drugs in cancer.
- In treatment of localized psoriasis.
- In Leishmaniasis.
- In diagnostic imaging.
- Carrier of haemoglobin.

Application of niosomes and methods used:

[7, 1, 4]. As drug carrier-Thin layer evaporation technique To increase bioavailability-Film hydration method

For brain targeting-Probe sonication method

To prolong the release time-Reverse phase evaporation method

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For drug targeting-Sonication method
In leishmaniasis-Solvent evaporation method
For anti-inflammatory effect-Reverse phase evaporation method
In anti-cancer therapy-Sonication method
In localized psoriasis-Lipid layer hydration method
In oral delivery of peptide drugs-Film hydration method
In diagnostic imaging-Ether injection method
In ophthalmic drug delivery-Sonication method
In thrombotic disease-Film hydration
For stability improvement-Ether injection method

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