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Review Article

Promising Drug Delivery System: A Niosomes

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Abstract

Niosomes are vesicles composed of non-ionic surfactants, which are biodegradable, comparatively nontoxic, more stable and cheap, an alternative to liposomes. They existing a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes. The niosome ability to encapsulate different type of drugs within their multi environmental structure. These review article emphases on the structure of niosome, advantages of niosomes, methods of preparation, characterization of niosomes, application of niosomes.

Keywords: Niosomes, Vesicles, Applications, Methods, Characterization.

1. Introduction[1,2,3]

Niosomes are a novel drug delivery system, in which the drug 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 extremely small, and microscopic in size. Their size lies in the nanometric scale. Although structurally similar to liposomes, 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.

1.1 Salient features of niosomes[3]

- Niosomes can entrap solutes in manner equivalent to liposomes.
- Niosomes are osmotically active and stable.
- Niosomes exhibit flexibility in their structural characteristics.
- Niosomes can improve the performance of drug molecules.
- Better availability to particular site just by protecting drug from biological environment.

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1.2 Advantages of Niosomes[1,2]

- They improve therapeutics efficiency of drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.
- The vesicle suspension is water-based vehicle. This gives high patient compliance in comparison with oily dosage forms.
- The vesicles may act as a depot, releasing the drug in a controlled way.
- They can reduce drug toxicity because of their non-ionic nature.
- They have an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities.

1.3 Structure of Niosomes[4]

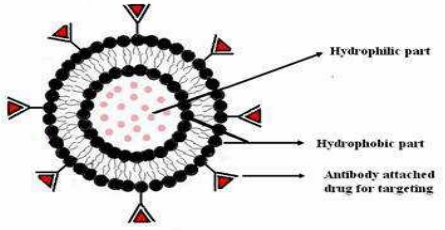

Fig.1: Structure of niosome.

Structurally, niosomes are analogous to liposomes, in that they are also made up of a bilayer. However, the bilayer in the case of niosomes is made up of non-ionic surface active agents rather than phospholipids as seen in the case of liposomes. Most surface active agents when immersed in water yield micellar structures however some surfactants can yield bilayer vesicles which are niosomes. Niosomes may be unilamellar or multilamellar depending on the method used to prepare them. The niosome is prepared of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicle, while the hydrophobic chains face each other within the bilayer. Hence, the vesicle holds hydrophilic drugs within the space enclosed in the vesicle, while hydrophobic drugs are embedded within the bilayer itself. The figure above will give a better idea of what a niosome looks like and where the drug is located within the vesicle.

1.4 Types of niosomes[5]

Types of Niosomes Based on the vesicle size, niosomes can be divided into three groups:

1. Small Unilamellar Vesicles (SUV, Size=0.025-0.05 µm)

These small unilamellar vesicles are generally prepared from multilamellar vesicles by sonication method, French press extrusion electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes.

2. Multilamellar Vesicles (MLV, Size=>0.05 µm)

It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.05-10 µm diameter. Multilamellar vesicles are the most widely used niosomes. It is simple to make and are mechanically stable upon storage for long periods.

3. Large Unilamellar Vesicles (LUV, Size=>0.10 µm).

Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids.

2. Methods of preparation of Niosomes

2.1 Ether injection method[6]

This method involves 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.

2.2 Hand shaking (film) method[7]

The mixture of surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask these two are vesicle forming agents. Then 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. Finally Sonicate the niosomes obtained and it should be kept in overnight. Large multilamellar vesicles are prepared.

2.3 Reverse phase evaporation[8]

The new thing in this method is the removal of solvent from an emulsion by evaporation. The surfactant and cholesterol are dissolved in ether or chloroform or in a mixture of chloroform and ether chloroform with or without drug. The resulting two-phase system is then homogenized using homogenizer. The organic phase is removed under reduced pressure to form niosomes dispersed in aqueous phase. In some cases, resulting suspensions must be further hydrated or homogenized to yield niosomes.

2.4 Micro fluidization[9]

Two fluidized streams move forward through precisely defined micro channel and interact at ultra-high velocities within the interaction chamber. Here, a common gateway 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.

2.5 Extrusion method[10]

The mixture of cholesterol and diacetyl phosphate is prepared and solvent is then evaporated using rotary vacuum evaporator to leave a thin film. The film is then hydrated with aqueous drug solution and the suspension thus obtained is extruded through the polycarbonate membrane (mean pore size 0.1 nm) and then placed in series up to eight passages to obtain uniform size niosomes.

2.6 Sonication method[10]

The mixture of surfactant and cholesterol is dispersed primarily in the aqueous phase. This dispersion is then probe sonicated for 10 min at 60 °C, which leads to the formation of multilameller vesicles (MLV). These MLVs are further ultrasonicated either by probe sonicator or bath sonicator, which leads to the formation of unilameller vesicles.

2.7 The "Bubble" Method[10]

It is one of the new techniques used for preparation of 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.

3. Separation of Unentrapped Drug[11,12]

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

1. Dialysis:

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

2. Gel Filtration:

The unentrapped drug is detached by gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution with phosphate buffered saline or normal saline.

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.

4. Evaluation of niosomes

4.1. Entrapment Efficiency[13]

After preparing niosomes, unentrapped drug is separated by dialysis, centrifugation or gel filtration as described above and the drug remained entrapped in niosomes is determined by whole vesicle disruption using 0.1% Triton X-100 and analyzing the resultant solution by appropriate assay method for the drug .Where,

Entrapment efficiency = Amount entrapped / Total amount used in preparation × 100.

4.2. Vesicle Diameter[13]

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

4.3. Number of Lamellae[13]

No of lamellae is determined by using nuclear magnetic resonance (NMR) spectroscopy, small angle X-ray scattering and electron microscopy.

4.4. Vesicle charge[14]

The vesicle surface charge can participate an important role in the behavior of niosomes in vivo and in vitro. Generally, charged niosomes are more stable against aggregation and fusion than uncharged vesicles. In order to obtain an estimate of the surface potential, the zeta potential of individual niosomes can be measured by micro electrophoresis. An alternative approach is the use of pHsensitive fluorophores. More recently, dynamic light scattering have been used to measure the zeta potential of niosomes.

4.5. Bilayer Rigidity and Homogeneity[14]

The biodistribution and biodegradation of niosomes are inclined by rigidity of the bilayer. In omogeneity can occur both within niosome structures themselves and between niosomes

in dispersion and could be identified via. P-NMR, differential scanning calorimetry (DSC) and Fourier transform-infra red spectroscopy (FT-IR) techniques. Recently, fluorescence resonance energy.

4.6. Viscosity[15]

Viscosity can be determined by using Ostwald viscometer. The niosomal formulation is poured in to the apparatus through the left arm up to the mark A. The formulation is was sucked in to the right arm slightly above the point B and the left arm is closed with the thumb to keep the liquid without dropping down. The apparatus is clamped vertically and then thumb is removed so as to allow the liquid to fall through the capillary under gravity then note down the time taken for the formulation to drop down from the point B to C. Then calculate the viscosity 14 by using poisulles equation as.

$$\eta l = \eta w \times tl \times dl / tw \times dw.$$

4.7. Stability studies[16]

To carry out the stability of niosomes, the optimized batch is stored in airtight sealed vials at different temperatures. Surface characteristics and percentage drug retained in niosomes should be selected as parameters for evaluation of the stability, since instability of the formulation would reflect in drug leakage and a decrease. In the percentage drug retained. The niosomes were sample at regular intervals of time (0, 1, 2, and 3months), observed for color change, surface characteristics and tested for the percentage drug retained.

Table.1: Evaluation of Niosomes.

Evaluation Parameter	Method
Morphology	SEM, TEM, freeze fracture technique
Size distribution, polydispersity index	Dynamic light scattering particle size analyzer
Viscosity	Ostwald viscometer
Membrane thickness	X-ray scattering analysis
Thermal analysis	DSC
Turbidity	UV-Visible diode array spectrophotometer
Entrapment efficacy	Centrifugation, dialysis, gel chromatography
In-vitro release study	Dialysis membrane
Permeation study	Dialysis membrane

4.8. Niosomal drug release[16]

The simple method to determine in vitro release kinetics of the loaded drug is by incubating a known quantity of drug loaded niosomes in a buffer of suitable pH at 37^0C with continuous stirring, withdrawing samples at some interval and analyzed the amount of drug by suitable analytical technique. Dialysis bags or dialysis membranes are commonly used to minimize interference.

4.9. Transmission electron microscopy (TEM)[17]

TEM is used to determine the size, shape and lamellarity of niosome. In this a suspension is prepared and mixed with 1% phosphotungstic acid (in sufficient amount). A drop of resultant was then used on carbon coated grid, draining off the excess and then the grid was observed and images are taken under suitable magnification under TEM after complete drying (Philips TEM).

5. Applications of Niosomes[18,19]

1. Ophthalmic drug delivery

A niosomal drug delivery system can be used for ophthalmic delivery. Cyclopentolate was encapsulated within niosomes prepared from polysorbate 20 and cholesterol and found to penetrate the cornea in a pH dependant manner within these niosomes. The increased absorption of cyclopentolate may be due to the altered permeability characteristics of the conjuctival and scleral membranes.

2. Diagnostic imaging with niosomes

Niosomes can be used as diagnostic agents. Conjugated niosomal formulation of gadobenate dimeglcemine with [N-palmitoyl-glucosamine (NPG)], PEG 4400, and both PEG and NPG exhibit significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging.

3. Niosomes as Drug Carriers

Niosomes are also used as carriers for iobitridol, a diagnostic agent used for Xray 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.

4. Anti-neoplastic Treatment

Niosomes can alter the metabolism; prolong circulation and half life of the drug, thus decreasing the side effects of the drugs. Niosomes is decreased rate of proliferation of tumor and higher plasma levels accompanied by slower elimination.

5. Niosomes as carriers for Hemoglobin

Niosomes are also used as a carrier for hemoglobin. Niosomal suspensions show a visible spectrum super imposable on top of that of free hemoglobin. Vesicles are permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin.

6. Leishmaniasis

Niosomes are also used to target 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. Baillie et al reported increased sodium stibogluconate efficacy of niosomal formulation and that the effect of two doses given on successive days was additive.

7. Localized Drug Action

Drug delivery through niosomes is one of the important approach 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

Niosomes are 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. Differrent methods are used for preparation of niosomes. Niosomes can be used for various purposes. It can be used as carrier for haemoglobin, targeting, localized action and all other.

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