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Review on Niosomes - A novel approach for drug targeting

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Abstract

This is a general review on niosome as a drug carrier, which improves the bioavailability of drugs, increases penetration through the skin, releases the drug in a controlled or sustained manner, and used for targeting of drugs to specific sites in the body. Niosomal drug delivery system can be considered as an emerging novel drug delivery system, which consists of microscopic non-ionic vesicles composed of non-ionic surfactants. These are biodegradable, relatively nontoxic, more stable and inexpensive, and an alternative to liposomes. Methods of preparation, characterization, and application of niosomes have been reviewed. Niosome has the potential to reduce the side effects of drugs and increase therapeutic effectiveness in various diseases. It can also be used as a carrier to deliver drugs topically. This review presents an overview of the types of niosomes, techniques of preparation of niosome characterization and their applications.
Keywords: Niosome; non-ionic surfactant; drug entrapment; novel drug delivery system.

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1. Introduction

Since past many years, research is going on for finding unique and better alternatives of drug delivery system and this will continue until the drug delivery system have no side effects with optimum therapeutic action. Conventional dosage forms are still in use because of high patient compliance, though they are having side effects. Recently, vesicular systems which have a lot of advantages over other drug delivery systems are being extensively explored. The vesicular system includes niosome, liposome, transferosomes. Niosome or nonionic surfactant vesicles are those which act as a drug carrier to deliver the drug to the site of action. Niosomes are vesicular carriers of non-ionic surfactants with size range between 10 and 1000 nm, the wherein the aqueous phase is enclosed in a highly ordered bilayer of non-ionic surfactants with or without cholesterol and dicetyl phosphate. Niosomes can be used for entrapping both hydrophilic and hydrophobic drugs (Fig 1).

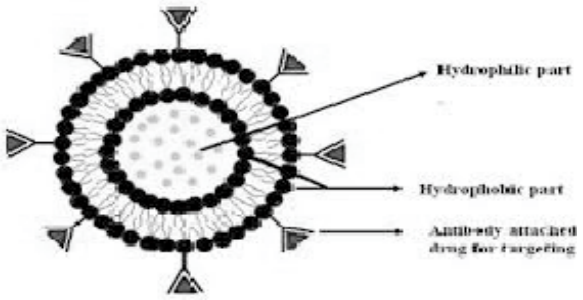

Fig. 1: Structure of Niosomes

Niosomes are novel drug delivery system, preferred over another vesicular system because of its low toxicity, nonionic nature, bio-degradable, better availability of the drug at the site, and good intrinsic skin penetration. Encapsulating the drug in the noisome can protect the drug from acidic and enzymatic degradation after administration. [1]

Many attempts have been made in the research of niosomes to encapsulate various NSAIDs for better bioavailability, and better permeation through the skin. Novel drug delivery system has limitations such as high cost, which makes it difficult for production and have problem with dose adjustments. So this problem can be overcome by using vesicular drug delivery system like niosomes, which may prolong the existence of the drug in the systemic circulation, increase permeation through the skin and reduce toxicity.[2]

1.1 Advantages of Niosomes

- Niosomes can act as a carrier for drugs which have a wide range of solubility as it has both hydrophilic and hydrophobic part.
- Surfactants used in niosome are bio-degradable, biocompatible, and nonimmunogenic.
- Niosomes of desired property can be prepared by altering vesicle characteristics such as vesicle composition, size, lamellarity, tapped volume, surface charge.
- Niosomes can also be used as a depot formulation.
- As ribosomal suspension has a hydrophilic tail, therefore it can be considered to provide better patient compliance than oil-based formulations.
- Niosomes not only have good stability but also have an osmotic property which makes it superior to oil-based formulations and also increases the entrapment efficiency.
- Niosomes are considered to be versatile as they can be given by oral, parenteral as well as topical routes.
- Niosomes are proposed to penetrate through the cornea i.e. it can be used for ocular drug delivery.[3, 4]

1.2 Disadvantages of Niosomes

Niosomal aqueous suspensions owe limited shelf life due to fusion, aggregation, leaking of entrapped drugs, and hydrolysis of encapsulated drugs.

The techniques involved in the niosomal formulation such as extrusion, sonication are time-consuming and requires specialized equipment for processing.[5]

1.3 Various Types of Niosome

Niosomes can be divided into three groups based on the vesicle size.

These are –

Small unilamellar vesicles= 0.025- 0.05 µm.

Multilamellar vesicles = >0.05 µm.

Large unilamellar vesicles= >0.10 µm.

2. Methods of preparation

Niosomes are prepared by various methods and they are:

2.1 Preparation of Small Unilamellar Vesicles

2.1.1 Sonication:

This method involves the addition of surfactant/cholesterol in organic solvent and drug in aqueous solution. This aqueous solution of the drug is mixed with a surfactant solution and further homogenized for 3 minutes at a temperature of 60°C.[6]

2.1.2 Micro fluidization:

The submerged jet principle is adopted for niosome formulation. Fluidized stream of drug and surfactant is allowed to interact at ultra high-speed velocities through microchannel within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy utilized by the system remains within the area of niosome formation. The method results in the formation of niosomes of greater uniformity, smaller size and better reproducibility.[5]

2.2 Preparation of Multilamellar Vesicles

2.2.1 Handshaking method (Thin film hydration technique):

This method involves the formation of the thin dried layer in the rota ask. In this method, surfactant and cholesterol are dissolved in an organic solvent. Both the solutions are mixed and the mixture is evaporated under reduced pressure at a definite temperature to form a thin layer on the inner wall of the ask. After evaporation, hydration is carried out with sonication to form niosomes. [6]

2.2.2 Trans-membrane pH gradient drug uptake process:

This method utilizes a thin film hydration technique. In this method, a definite ratio of cholesterol and surfactant is dissolved in organic solvents like ether or chloroform and evaporated under reduced pressure to form a thin dried film. The resultant film is hydrated with 300 mM citric acid (pH 4.0) by vortex mixing. The vesicles formed are allowed for freezing and thawing several times and sonicated to get niosomes. An aqueous solution of the drug is added to the above niosomal suspension and is vortexed. The pH of niosomal suspension is adjusted to 7.0-7.2 with 1 M disodium phosphate, heated to 60°C for 10 minutes to form the desired multilamellar vesicles.[7]

2.3 Preparation of Large Unilamellar Vesicles

2.3.1 Reverse phase evaporation technique (REV):

In this method, a definite ratio of cholesterol and surfactant is dissolved in organic solvents like ether or chloroform and evaporated under reduced pressure to form a thin dried film. The resultant film is hydrated with 300 mM citric acid (pH 4.0) by vortex mixing. The gel formed is further sonicated after addition of a small amount of phosphate buffer solution and the organic phase present is removed at 40°C which forms niosomes having high viscosity. This viscous niosome is diluted with phosphate buffer saline which is maintained at 60°C for 10-15 minutes.[8]

2.3.2 Ether injection method:

This method is used in the preparation of large unilamellar vesicles, where the density ratio of cholesterol and surfactant is dissolved in an organic solvent. To the above mixture, the organic solution of the drug is added and injected to the aqueous solution positioned at magnetic stirrer maintained at 60º with continuous stirring forming a niosomal suspension.[9]

2.4 Miscellaneous

2.4.1 Multiple membrane extrusion methods:

In this method surfactant and cholesterol are dissolved in organic solvent i.e. chloroform. Then dicetyl phosphate is added to the organic solution of surfactant/cholesterol, and the resultant solution is evaporated under reduced pressure to form a thin film. The film formed is rehydrated with an aqueous solution of the drug. The resultant suspension is extruded through polycarbonate membrane, placed in a series for up to eight passages. Size of the liposomal formulation can be controlled by this method. [10]

2.4.2 Emulsion method:

An aqueous solution of the drug is prepared separately and this solution is added to the solution of surfactant and cholesterol dissolved in an organic solvent, forming oil in water emulsion. The organic solvent is then evaporated leaving niosomes dispersed in the aqueous phase. [11]

2.4.3 Lipid Injection Method:

This method uses lipids along with surfactants. Lipids and surfactants are melt and the mixture is injected into an aqueous solution of drug which is heated. Another method involves the addition of drug in lipids and melting. The molten solution is injected into an aqueous solution of surfactant which is heated to form niosomes.[12]

2.4.4 The bubble method:

This is a one-step technique for the preparation of noisome without the use of organic solvent. The bubbling unit has a round-bottomed flask with three necks positioned in a water bath for controlling the temperature. In the neck, water cooled reflux is placed, thermometer placed in the second and nitrogen supply is provided through the third neck. Dispersion of niosomes is prepared by adding cholesterol and surfactant in phosphate buffer pH 7.4 which is maintained at 70º and using high shear homogenizer the dispersion formed is mixed for 15 seconds, then it is bubbled using nitrogen gas at 70º.[13]

3. Separation of unentrapped drug

The unentrapped drug can be separated by various techniques:

3.1 Dialysis:

The free drug is separated from niosomal dispersion by using a dialysis bag in phosphate buffer as media.

3.2 Gel Filtration:

The unentrapped drug in niosomal dispersion is removed by using gel filtration by passing through Sephadex G-50 column and eluted with phosphate buffer or normal saline.

3.3 Centrifugation:

Here the separation of the free drug is achieved by centrifugation of the niosomal suspension for 30 minutes. The supernatant solution is decanted, and the precipitate is washed and resuspended in phosphate buffer to obtain a liposomal suspension free from the unentrapped drug.[14]

4. Characterization of niosomes

4.1 Vesicle diameter:

The shape of niosomes is spherical in nature and the size ranges from 20 nm to 50 nm. Vesicular form and size distribution can be determined by light microscopy. Another method used for determination of diameter and size of niosome is freeze-fracture electron microscopy.[15]

4.2 Vesicle charge:

Vesicle charge is determined by measuring zeta potential. Charged niosomes are more stable than uncharged liposomal dispersion. Hence, during the preparation, charged vehicles like diacetyl phosphate are added to the surfactant/cholesterol mixture.[16]

4.3 Bilayer formation & number of lamellae:

Bilayer formation of niosomes is characterized by X-cross formation. NMR spectroscopy, electron microscopy, and small angle X-ray scattering are used to characterize the number of lamellae.

4.4 Membrane rigidity and homogeneity:

The rigidity of membrane affects bio-degradation and bio-distribution of niosomes. Determination of rigidity of niosomal suspension is done by fluorescence probe as a function of temperature. P-NMR, differential scanning calorimetry (DSC), Fourier transform-infra red spectroscopy (FTIR) and fluorescence resonance energy transfer (FRET) are used to determine the membrane homogeneity.[18]

4.5 Encapsulation efficiency:

It can be done by separating the unentrapped drug in the niosomal dispersion by using various methods like centrifugation, gel filtration and dialysis. Another method of separation includes complete disruption of vesicle using 50% n-propanol or 0.1% Triton X-100. Then the required disrupted vesicle is analyzed for the drug content and hence entrapment efficiency.[19]

Entrapment efficiency (EF) =

(Amount entrapped/ total amount) x100

4.6 In vitro drug release:

In vitro drug release of niosomes can be characterized by the following methods:

1). Dialysis; 2). Franz diffusion cell

4.6.1 Dialysis:

Dialysis is carried out by placing niosomal dispersion in dialysis bag which is pre-washed and presoaked and are tied at both the ends. The dialysis bag is suspended into a dissolution media maintained at 37 °C with continuous stirring. Samples are withdrawn at a regular time interval and replaced with a fresh sample. The withdrawn samples are analyzed for the drug content. [20]

4.6.2 Franz diffusion cell:

This cell assembly consists of the donor and receptor compartment which is separated by cellophane membrane or dialysis membrane. Niosomal dispersion is placed at donor compartment and dissolution media i.e. phosphate buffer is placed in receptor compartment maintained at 37°C with continuous stirring by a magnetic stirrer. The samples are taken out at suitable time intervals, replaced with fresh media and analyzed for drug content.[21]

4.6.3 In vivo study:

The *in vivo* study is carried out in albino Wistar male rats weighing 150-200 gm. The animals are divided into 3 groups, each group containing 6 animals. Group I is treated as treatment control, group II with pure drug solution, and group III with the liposomal formulation of the drug, (dose to be determined). Blood samples are collected from the rats at the interval of 0.5h, 2h, 4h, 8h, 12h, and 16 h, from the catheter, which is implanted in the femoral artery. The catheter is continuous with physiological saline. The collected blood samples are centrifuged in a cooling centrifuge at 12,000 rpm for 3min and blood plasma is separated. The separated blood plasma is stored in a freezer at -4^{o}C until it is analyzed by HPLC or any other precise method.[22]

4.6.4 Stability of niosomes:

Niosomes are stored at two different conditions, usually 4±1° and 25±2°. The constant particle size and constant concentration of entrapped drug indicate the stability of niosomes. The concentration and type of surfactant, cholesterol also affects niosome stability. The light microscope is used for the determination of vesicle size and the number of vesicles per cubic mm.[23]

5. Factors governing niosome formation

5.1 Choice of surfactants and additives:

Non-ionic surfactants are employed for the formation of niosome vesicles. Surfactants having hydrophobic tail may consist of one or two alkyls or per fluoroalkyl groups or, in some cases, a single steroidal group. The ether-type surfactants with mono alkyl chain are more toxic than ester-type surfactants. When stability comes into consideration, ester type surfactant is less stable than ether-type surfactants and it is because, ester-linked surfactants get degraded by esterase into triglycerides and fatty acid, *in vivo*. The surfactants with an alkyl chain length from C to C are suitable for preparation of 12-18 niosome. Niosome vesicle formation suitability in surfactants having HLB value between 4 and 8. [24, 25]

5.2 Surfactant and lipid level:

Generally surfactant/lipid level which is essential for niosomal formulation is kept between 10-30 mM (1-2.5% w/w). The niosomal dispersion is affected by alteration of surfactant, water ratio during the hydration step. By increasing the surfactant/lipid level the total amount of drug encapsulated also increases. [26]

5.3 Composition of the membrane:

Stabilisation of niosomes can be achieved by adding different additives to the surfactant mixture. One main disadvantage of niosome formulation is the leakage of drug from the vesicles which can be controlled by the addition of cholesterol. Cholesterol confers better rigidity to the membrane and therefore leakage of the drug is reduced.[13]

5.4 Nature of encapsulated drug:

Niosomal formulation is influenced by the nature of the drug being encapsulated. The interaction of the surfactant head groups lead to entrapment of drug in vesicles and cause an increase in charge. The formation of charge creates mutual repulsion of the surfactant bilayer and thus increases vesicle size. The HLB of the drug also affects the degree of entrapment.[27]

5.5 The temperature of hydration:

The shape and size of noisome are influenced by hydration temperature. Variation in temperature affects surfactants to assemble into vesicles and therefore, affects niosomal vesicle formation. The hydration temperature for niosome formation should be above the gel to the liquid phase transition temperature of the system.[23,24]

5.6 Cholesterol content:

Addition of cholesterol in niosomal formulation improves entrapment efficiency and thereby provides rigidity to the vesicles. It also increases the hydrodynamic diameter of the niosomal vesicles. Cholesterol also increases the chain order of liquid state bilayers and decreases the chain order of gel state bilayers. Gel-state bilayers can be converted into a liquid state by increasing the concentration of cholesterol.[28]

5.7 Charge:

In a multilamellar vesicle structure, the interlamellar distance between successive bilayers increases due to the presence of charge. This results in greater overall entrapped volume.[20]

6. Applications

Generally, peptide drugs have stability problem so it is difficult to formulate in the form of tablets, parenteral. Therefore, using niosome as a drug carrier can improve the stability of peptide drugs.[29, 30]

Nowadays due to various disadvantages of oral drug delivery system, research is going on for transdermal drug delivery and this has achieved a good response. Niosome as a drug carrier has good penetration capacity. Therefore, niosome can be used as transdermal drug delivery for various drugs. [31]

Niosomes can be used as a suitable drug delivery system for the administration of anticancer drugs such as 5-FU cancer therapy. It is also used for increasing the efficacy of the drug by incorporating it into niosome.[32]

Niosomal suspension shows a visible spectrum which is superimposable onto that of free hemoglobin; therefore it can be used as a carrier for hemoglobin. [33]

Niosomal system can encapsulate drugs which have a low therapeutic index and low water solubility and this can be maintained in the circulation showing sustained release action.[33]

The treatment of leishmaniasis is mostly achieved by antimony derivatives. It has side effects at higher concentrations which may cause liver, cardiac and kidney damage. These side effects at higher concentration can be overcome by niosomes as a drug carrier.[33]

Niosomal system also finds use in diagnostic agents. It can also act as a carrier for radio-pharmaceuticals.[34] Niosomal formulation of diclofenac sodium prepared with 70% cholesterol showed a greater anti-inflammatory effect as compared to the free drug. Similarly, nimesulide and ibuprofen showed greater activity than the free drug.[35]

7. Recent Developments

Various studies have been carried out in the field of niosomes. Attempts were made to improve the oral bioavailability of Cefdinir by incorporating into niosomes and study revealed that formulated niosome showed higher release and improved permeability across animal intestinal membrane than plain drug formulation and marketed formulation.[36]

Research carried out to increase the solubility of BCS class II drug valproic acid by incorporating into a niosomal gel concluded that niosomal entrapped gel had better *in vitro* release across the animal nasal membrane and hence it can be used as an efficient carrier for valproic acid.[37]

Oxcarbazepine niosomes were formulated and evaluated to explore the advantage over the conventional dosage forms. Pharmacokinetic studies have shown that oxcarbazepine niosomes have increased elimination half-life and the area under the curve also higher when compared with pure oxcarbazepine, which justifies their potential in strengthening the efficacy and safety profile of the drug.[22]

8. Conclusion

The field of vesicular drug delivery system is still in its infancy and increasing gradually during the past few decades. It is expected that this trend will continue to increase further. Niosome is a promising vesicular delivery system compared to liposomes because of its low cost, stability and the ability to encapsulate the different type of drugs. Researches have shown that it is useful in the delivery of anti-cancer, antiepileptic and anti-inflammatory agents. It also targets certain areas of the mammalian anatomy and hence exploited as a diagnostic imaging agent. It has expanded to various areas like vaccine delivery system, tumor targeting agents, ophthalmic, and transdermal delivery systems. Hence, further research has to be carried out to extract out the full potential of niosomes.

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