Review Article

Niosome: A future of targeted drug delivery systems

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Abstract

Over the past several years, treatment of infectious diseases and immunisation has undergone a revolutionary shift. With the advancement of biotechnology and genetic engineering, not only a large number of disease-specific biological have been developed, but also emphasis has been made to effectively deliver these biologicals. Niosomes are vesicles composed of non-ionic surfactants, which are biodegradable, relatively nontoxic, more stable and inexpensive, an alternative to liposomes. This article reviews the current deepening and widening of interest of niosomes in many scientific disciplines and, particularly its application in medicine. This article also presents an overview of the techniques of preparation of niosome, types of niosomes, characterisation and their applications.

Key words: Bilayer, drug entrapment, lamellar, niosomes, surfactants

INTRODUCTION

The concept of targeted drug delivery is designed for attempting to concentrate the drug in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. As a result, drug is localised on the targeted site. Hence, surrounding tissues are not affected by the drug. In addition, loss of drug does not happen due to localisation of drug, leading to get maximum efficacy of the medication. Different carriers have been used for targeting of drug, such as immunoglobulin, serum proteins, synthetic polymers, liposome, microspheres, erythrocytes and niosomes.[1]

Niosomes are one of the best among these carriers. The self-assembly of non-ionic surfactants into vesicles was first reported in the 70s by researchers in the cosmetic industry. Niosomes (non-ionic surfactant vesicles) obtained on hydration are microscopic lamellar structures formed upon combining non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class with cholesterol.[2] The non-ionic surfactants form a closed bilayer vesicle in aqueous media based on its amphiphilic nature using some energy for instance heat, physical agitation to form this structure. In the bilayer structure, hydrophobic parts are oriented away from the aqueous solvent, whereas the hydrophilic heads remain in contact with the aqueous solvent. The properties of the vesicles can be changed by varying the composition of the vesicles, size, lamellarity, tapped volume, surface charge and concentration. Various forces act inside the vesicle, eg, van der Waals forces among surfactant molecules, repulsive forces emerging from the electrostatic interactions among charged groups of surfactant molecules, entropic repulsive forces of the head groups of surfactants, short-acting repulsive forces, etc. These forces are responsible for maintaining the vesicular structure of niosomes. But, the stability of niosomes are affected by type of surfactant, nature of encapsulated drug, storage temperature, detergents, use of membrane spanning lipids, the interfacial polymerisation of surfactant monomers *in situ*, inclusion of charged molecule. Due to presence of hydrophilic, amphiphilic and lipophilic moieties in the structure, these can accommodate drug molecules with a wide range of solubility.[3] These may act as a depot, releasing the drug in a controlled manner. The therapeutic performance of the drug molecules can also be improved by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.[4] Noisome made of alpha, omega-hexadecyl-bis-(1-aza-18-crown-6) (Bola-surfactant)-Span 80-cholesterol (2:3:1 molar ratio) is named as Bola-Surfactant containing noisome.[5] The surfactants used in niosome preparation should be biodegradable, biocompatible and non-immunogenic. A dry product known as proniosomes may

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be hydrated immediately before use to yield aqueous niosome dispersions. The problems of niosomes such as aggregation, fusion and leaking, and provide additional convenience in transportation, distribution, storage, and dosing.[6]

Niosomes behave *in vivo* like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability.[7] As with liposomes, the properties of niosomes depend on the composition of the bilayer as well as method of their production. It is reported that the intercalation of cholesterol in the bilayers decreases the entrapment volume during formulation, and thus entrapment efficiency.[8]

However, 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). The concentration of cholesterol in liposomes is much more than that in niosomes. As a result, drug entrapment efficiency of liposomes becomes lesser than niosomes. Besides, liposomes are expensive, and its ingredients, such as phospholipids, are chemically unstable because of their predisposition to oxidative degradation; moreover, these require special storage and handling and purity of natural phospholipids is variable.

Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. It can also be used as vehicle for poorly absorbable drugs to design the novel drug delivery system. It enhances the bioavailability by crossing the anatomical barrier of gastrointestinal tract via transcytosis of M cells of Peyer's patches in the intestinal lymphatic tissues.[9] The niosomal vesicles are taken up by reticulo-endothelial system. Such localised drug accumulation is used in treatment of diseases, such as leishmaniasis, in which parasites invade cells of liver and spleen.[10,11] Some non-reticulo-endothelial systems like immunoglobulins also recognise lipid surface of this delivery system.[2-8,10-12] Encapsulation of various anti-neoplastic agents in this carrier vesicle has minimised drug-induced toxic side effects while maintaining, or in some instances, increasing the anti-tumour efficacy.[13] Doxorubicin, the anthracycline antibiotic with broad-spectrum anti-tumour activity, shows a dose-dependent irreversible cardio-toxic effect.[14,15] Niosomal delivery of this drug to mice bearing S-180 tumour increased their life span and decreased the rate of proliferation of sarcoma. Intravenous administration of methotrexate entrapped in niosomes to S-180 tumour bearing mice resulted in total regression of tumour and also higher plasma level and slower elimination. It has good control over the release rate of drug, particularly for treating brain malignant cancer.[16] Niosomes have been used for studying the nature of the immune response provoked by antigens.[17] Niosomes can be used as a carrier for haemoglobin.[18,19] Vesicles are permeable to oxygen and haemoglobin dissociation curve can be modified similarly to non-encapsulated haemoglobin. Slow penetration of drug through skin is the major drawback of transdermal route of delivery.[20] Certain anti-inflammatory drugs like flurbiprofen and piroxicam and sex hormones like estradiol and levonorgestrel are frequently administered through niosome via transdermal route to improve the therapeutic efficacy of these drugs. This vesicular system also provides better drug concentration at the site of action administered by oral, parenteral and topical routes. Sustained release action of niosomes can be applied to drugs with low therapeutic index and low water solubility. Drug delivery through niosomes is one of the approaches to achieve localised drug action in regard to their size and low penetrability through epithelium and connective tissue, which keeps the drug localised at the site of administration. Localised drug action enhances efficacy of potency of the drug and, at the same time, reduces its systemic toxic effects, eg, antimonials encapsulated within niosomes are taken up by mononuclear cells, resulting in localisation of drug, increase in potency, and hence decrease in dose as well as toxicity.[13] The evolution of niosomal drug delivery technology is still at the stage of infancy, but this type of drug delivery system has shown promise in cancer chemotherapy and anti-leishmanial therapy.

VARIOUS TYPES OF NIOSOME

Based on the vesicle size, niosomes can be divided into three groups. These are small unilamellar vesicles (SUV, size=0.025-0.05 μm), multilamellar vesicles (MLV, size=>0.05 μm), and large unilamellar vesicles (LUV, size=>0.10 μm).

Methods of Preparation

Niosomes are prepared by different methods based on the sizes of the vesicles and their distribution, number of double layers, entrapment efficiency of the aqueous phase and permeability of vesicle membrane.

Preparation of small unilamellar vesicles

Sonication

The aqueous phase containing drug is added to the mixture of surfactant and cholesterol in a scintillation vial.[11] The mixture is homogenised using a sonic probe at 60°C for 3 minutes. The vesicles are small and uniform in size.

Micro fluidisation

Two fluidised streams move forward through precisely defined micro channel and interact at ultra-high velocities within the interaction chamber.[21] 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.

Preparation of multilamellar vesicles

Hand shaking method (Thin film hydration technique)

In the hand shaking method, surfactant and cholesterol are dissolved in a volatile organic solvent such as diethyl ether, chloroform or methanol in a rotary evaporator, leaving a thin layer of solid mixture deposited on the wall of the flask.[11] The dried layer is hydrated with aqueous phase containing drug at normal temperature with gentle agitation.

Trans-membrane pH gradient (inside acidic) drug uptake process (remote Loading)

Surfactant and cholesterol are dissolved in chloroform.[22] The solvent is then evaporated under reduced pressure to obtain a thin film on the wall of the round-bottom flask. The film is hydrated with 300 mM citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed three 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 produce the desired multilamellar vesicles.

Preparation of large unilamellar vesicles

Reverse phase evaporation technique (REV)

In this method, cholesterol and surfactant are dissolved in a mixture of ether and chloroform.[23] 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. The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with phosphate-buffered saline and heated in a water bath at 60°C for 10 min to yield niosomes.

Ether injection method

The ether injection method is essentially based on slow injection of niosomal ingredients in ether through a 14-gauge needle at the rate of approximately 0.25 ml/min into a preheated aqueous phase maintained at 60°C.[11,24] The probable reason behind the formation of larger unilamellar vesicles is that the slow vapourisation of solvent results in an ether gradient extending towards the interface of aqueous-nonaqueous interface. The former may be responsible for the formation of the bilayer structure. The disadvantages of this method are that a small amount of ether is frequently present in the vesicles suspension and is difficult to remove.

Miscellaneous

Multiple membrane extrusion method

A mixture of surfactant, cholesterol, and diacetyl phosphate in chloroform is made into thin film by evaporation.[20] The film is hydrated with aqueous drug solution and the resultant suspension extruded through polycarbonate membranes, which are placed in a series for up to eight passages. This is a good method for controlling niosome size.

Niosome preparation using polyoxyethylene alkyl ether

The size and number of bilayer of vesicles consisting of polyoxyethylene alkyl ether and cholesterol can be changed using an alternative method.[25] Temperature rise above 60°C transforms small unilamellar vesicles to large multilamellar vesicles (>1 μm), while vigorous shaking at room temperature shows the opposite effect, ie, transformation of multilamellar vesicles into unilamellar ones. The transformation from unilamellar to multilamellar vesicles at higher temperature might be the characteristic for polyoxyethylene alkyl ether (ester) surfactant, since it is known that polyethylene glycol (PEG) and water remix at higher temperature due to breakdown of hydrogen bonds between water and PEG moieties. Generally, free drug is removed from the encapsulated drug by gel permeation chromatography dialysis method or centrifugation method. Often, density differences between niosomes and the external phase are smaller than that of liposomes, which make separation by centrifugation very difficult. Addition of protamine to the vesicle suspension facilitates separation during centrifugation.

Emulsion method

The oil in water (o/w) emulsion is prepared from an organic solution of surfactant, cholesterol, and an aqueous solution of the drug.[26,27] The organic solvent is then evaporated, leaving niosomes dispersed in the aqueous phase.

Lipid injection method

This method does not require expensive organic phase. Here, the mixture of lipids and surfactant is first melted and then injected into a highly agitated heated aqueous phase containing dissolved drug. Here, the drug can be dissolved in molten lipid and the mixture will be injected into agitated, heated aqueous phase containing surfactant.

Niosome preparation using Micelle

Niosomes may also be formed from a mixed micellar solution by the use of enzymes. A mixed micellar solution of C16 G2, dicalcium hydrogen phosphate, polyoxyethylene cholesteryl sebacetate diester (PCSD) converts to a niosome dispersion when incubated with esterases. PCSD is cleaved by the esterases to yield polyoxyethylene, sebacic acid and cholesterol. Cholesterol in combination with C16 G2 and DCP then yields C16 G2 niosomes.

Characterisation of niosomes

Size

Shape of niosomal vesicles is assumed to be spherical, and their mean diameter can be determined by using laser light scattering method.[28] Also, diameter of these vesicles can be determined by using electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation

microscopy and optical microscopy[29,30] and freeze fracture electron microscopy. Freeze thawing of niosomes increases the vesicle diameter, which might be attributed to a fusion of vesicles during the cycle.

Bilayer formation

Assembly of non-ionic surfactants to form a bilayer vesicle is characterised by an X-cross formation under light polarisation microscopy.[31]

Number of lamellae

This is determined by using nuclear magnetic resonance (NMR) spectroscopy, small angle X-ray scattering and electron microscopy.[29]

Membrane rigidity

Membrane rigidity can be measured by means of mobility of fluorescence probe as a function of temperature.[31]

Entrapment efficiency

After preparing niosomal dispersion, unentrapped drug is separated 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.[32] It can be represented as:

Entrapment efficiency (EF) = (Amount entrapped / total amount) × 100

In vitro Release Study

A method of *in vitro* release rate study was reported with the help of dialysis tubing.[33] A dialysis sac was washed and soaked in distilled water. The vesicle suspension was pipetted into a bag made up of the tubing and sealed. The bag containing the vesicles was then placed in 200 ml buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. At various time intervals, the buffer was analysed for the drug content by an appropriate assay method. In another method, isoniazid-encapsulated niosomes were separated by gel filtration on Sephadex G- 50 powder kept in double distilled water for 48 h for swelling.[34] At first, 1 ml of prepared niosome suspension was placed on the top of the column and elution was carried out using normal saline. Niosomes encapsulated isoniazid elutes out first as a slightly dense, white opalescent suspension followed by free drug. Separated niosomes were filled in a dialysis tube to which a sigma dialysis sac was attached to one end. The dialysis tube was suspended in phosphate buffer of pH (7.4), stirred with a magnetic stirrer, and samples were withdrawn at specific time intervals and analysed using high-performance liquid chromatography (HPLC) method.

In vivo Release Study

Albino rats were used for this study. These rats were subdivided with groups. Niosomal suspension used for *in vivo* study was injected intravenously (through tail vein) using appropriate disposal syringe.

Factors Affecting Physico-Chemical Properties of Niosomes

Various factors that affect the physico-chemical properties of niosomes are discussed further.

Choice of surfactants and main additives

A surfactant used for preparation of niosomes must have a hydrophilic head and a hydrophobic tail. The hydrophobic tail may consist of one or two alkyl or perfluoroalkyl groups or, in some cases, a single steroidal group.[35] The ether-type surfactants with single-chain alkyl tail is more toxic than corresponding dialkyl ether chain. The ester-type surfactants are chemically less stable than ether-type surfactants and the former is less toxic than the latter due to ester-linked surfactant degraded by esterases to triglycerides and fatty acid *in vivo*.[36] The surfactants with alkyl chain length from C12 to C18 are suitable for preparation of noisome. Span series surfactants having HLB number between 4 and 8 can form vesicles.[37] Different types of non-ionic surfactants with examples are given in Table 1.[38]

The stable niosomes can be prepared with addition of different additives along with surfactants and drugs. The niosomes formed have a number of morphologies and their permeability and stability properties can be altered by manipulating membrane characteristics by different additives. In case of polyhedral niosomes formed from C16G2, the shape of these polyhedral niosomes remains unaffected by adding low amount of *solulan* C24 (cholesteryl poly-24-oxyethylene ether), which prevents aggregation due to development of steric hindrance. In contrast, addition of C16G2:cholesterol:solulan (49:49:2) results in formation of spherical niosomes.[39] The mean size of niosomes is influenced by membrane composition. Addition of cholesterol molecule to niosomal system makes the membrane rigid and reduces leakage of drug from the noisome.[40]

Temperature of hydration

Hydration temperature influences the shape and size of the niosome. For ideal condition, it should be above the gel to liquid phase transition temperature of system.

Table 1: Different types of non-ionic surfactants

Type of non-ionic surfactant	Examples
Fatty alcohol	Cetyl alcohol, stearyl alcohol, cetostearyl alcohol, oleyl alcohol
Ethers	Brij, Decyl glucoside, Lauryl glucoside, Octyl glucoside, Triton X-100, Nonoxynol-9
Esters	Glyceryl laurate, Polysorbates, Spans
Block copolymers	Poloxamers

Temperature change in the niosomal system affects assembly of surfactants into vesicles and also induces vesicle shape transformation.[35,39] A polyhedral vesicle formed by C16G2:solulan C24 (91:9) at 25°C, on heating, transforms into spherical vesicle at 48°C, but on cooling from 55°C, the vesicle produces a cluster of smaller spherical niosomes at 49°C before changing into polyhedral structures at 35°C. In contrast, the vesicle formed by C16G2:cholesterol:solulan C24 (49:49:2) shows no shape transformation on heating or cooling.[27] Along with the above-mentioned factors, the volume of hydration medium and time of hydration of niosomes are also critical factors. Improper selection of these factors may result in the formation of fragile niosomes or creation of drug leakage problems.

Nature of encapsulated drug

The physico-chemical properties of encapsulated drug influence charge and rigidity of the niosome bilayer. The drug interacts with surfactant head groups and develops the charge that creates mutual repulsion between surfactant bilayers, and hence increases vesicle size.[29] The aggregation of vesicles is prevented due to the charge development on bilayer. The effect of the nature of drug on formation vesicle is given in Table 2.

Factors affecting vesicles size, entrapment efficiency, and release 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 the degree of entrapment.

Amount and type of surfactant

The mean size of niosomes increases proportionally with increase in the hydrophilic-lipophilic balance (HLB) of surfactants such as Span 85 (HLB 1.8) to Span 20 (HLB 8.6) because the surface free energy decreases with an increase in hydrophobicity of surfactants.[41] 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 characterised by the gel-liquid phase transition temperature (TC). Phase transition temperature (TC) of surfactants also affects entrapment efficiency, ie, Span 60 having higher TC provides better entrapment.

Table 2: Effect of the nature of drug on the formation of niosomes

Nature of the drug	Leakage from the vesicle	Stability	Other properties
Hydrophobic drug	Decreased	Increased	Improved trans-dermal delivery
Hydrophilic drug	Increased	Decreased	–
Amphiphilic drug	Decreased	–	Increased encapsulation, altered electrophoretic mobility
Macromolecule	Decreased	Increased	–

Cholesterol content and charge

Inclusion of cholesterol in niosomes increases its hydrodynamic diameter and entrapment efficiency. In general, the action of cholesterol is twofold. On one hand, cholesterol increases the chain order of liquid state bilayers, and, on the other, it 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 in the rigidity of the resulting bilayers. The presence of charge tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle structure and leads to greater overall entrapped volume.[41]

Methods of Preparation

Hand shaking method forms vesicles with greater diameter (0.35-13 nm) compared to the ether injection method (50-1,000 nm). Small-sized niosomes can be produced by Reverse Phase Evaporation (REV) method. Microfluidisation method gives greater uniformity and small-sized vesicles.

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.[2,42]

Table 3 lists drugs that have been used in animal study through different routes.

CONCLUSION

Recent advancements in the field of scientific research have resulted in the endorsement of small molecules such as proteins and vaccines as a major class of therapeutic agents. These, however, pose numerous drug-associated challenges such as poor bioavailability, suitable route of drug delivery, physical and chemical instability and potentially serious side effects. Opinions of the usefulness of niosomes in the

Table 3: Drugs used in niosomal delivery

Routes of drug administration	Examples of Drugs
Intravenous route	Doxorubicin, methotrexate, sodium stibogluconate, iopromide, vincristine, diclofenac sodium, flurbiprofen, centchroman, indomethacin, colchicine, rifampicin, tretinoin, transferrin and glucose ligands, zidovudine, insulin, cisplatin, amarogentin, daunorubicin, amphotericin B, 5-fluorouracil, camptothecin, adriamycin, cytarabine hydrochloride
Peroral route	DNA vaccines, proteins, peptides, ergot alkaloids, ciprofloxacin, norfloxacin, insulin
Transdermal route	Flurbiprofen, piroxicam, estradiol, levonorgestrol, nimesulide, dithranol, ketoconazole, enoxacin, ketorolac
Ocular route	Timolol maleate, cyclopentolate
Nasal route	Sumatriptan, influenza viral vaccine
Inhalation	All-trans retinoic acids

delivery of proteins and biologicals can be unsubstantiated with a wide scope in encapsulating toxic drugs such as anti-AIDS drugs, anti-cancer drugs, and anti-viral drugs. It provides a promising carrier system in comparison with ionic drug carriers, which are relatively toxic and unsuitable. However, the technology utilised in niosomes is still in its infancy. Hence, researches are going on to develop a suitable technology for large production because it is a promising targeted drug delivery system.

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