



UNIQUE JOURNAL OF PHARMACEUTICAL AND BIOLOGICAL SCIENCES

Available online: www.ujconline.net

Review Article

RECENT TRENDS IN NIOSOMES AS NANOCARRIERS

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Received 07-08-2013; Revised 29-08-2013; Accepted 13-09-2013

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ABSTRACT

Novel drug delivery system aims to deliver the drug at a rate directed by the needs of the body during the period of treatment, and channel the active entity to the site of action. The article focuses on various advantages of vesicular systems (niosomes) to develop the effective delivery system to achieve maximum effective concentration. Niosomes, nonionic surfactant vesicles with lamellar structure which may be unilamellar and multilamellar serve to be efficient in providing these required advantages. The bilayer structure of niosomes being amphiphilic in nature can be used to deliver hydrophilic drugs in its aqueous core and lipophilic drugs in the bilayer made up of surfactants. Niosomes are vesicles composed of non-ionic surfactants, which are biodegradable, relatively nontoxic, more stable and inexpensive, an alternative to liposomes. They present 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 multi environmental structure. Niosomes are thoughts to be better candidate's drug delivery as compared to liposomes due to various factors like cost, stability etc. Various types of drug deliveries can be possible using niosomes for example ophthalmic, topical, parenteral etc. drug deliveries. On the basis of above information, the niosomes have been thoroughly exploited for the drug delivery system and still offer scope for research on various drugs for their maximum therapeutic utilization in management and treatment of various dreadful diseases.

Keywords: Novel drug delivery system, Niosomes, Vesicles, Non ionic surfactant, Amphiphilic nature, Liposomes

INTRODUCTION

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 nontarget tissue¹. Different novel approaches used for delivering these drugs include liposomes, microspheres, nanotechnology, micro emulsions, antibody-loaded drug delivery, magnetic microcapsules, implantable pumps and niosomes. Niosomes proved to be a promising drug carrier and has potential to reduce the side effects of drugs and increased therapeutic effectiveness in various diseases². Niosomes are the highly ordered vesicular bilayer membrane made up of non – ionic surfactant with or without incorporation of cholesterol and dicetyl phosphate. The closed bilayer vesicular structure of niosome formed by the self assembling of non – ionic surfactants in the presence of aqueous media^{3,4}. Niosomes can entrap both hydrophilic and lipophilic drugs in aqueous layer and vesicular membrane respectively. The bilayers of niosomes have both inner and outer surfaces to be hydrophilic with sandwiched lipophilic area in between. Thus a large number of drugs and other materials can be delivered using niosomes⁵.

SILENT FEATURES OF NIOSOMES

1. Niosomes are osmotically active and stable.
2. Niosomes surfactants are biodegradable, biocompatible and nonimmunogenic.
3. Niosomes possess infrastructure consisting of hydrophilic and hydrophobic mostly together and so accommodate the drug molecules with a wide range of solubility.
4. The bilayers of the niosomes protect the enclosed active pharmaceutical ingredient from the deterogenous factors present both inside and outside the body. So niosomes can be used for the delivery of labile and sensitive drugs.
5. Niosomes exhibit flexibility in their structural characteristics and can be designed according to the desired situation.
6. Better availability at the particular site, just by protecting the drug from biological environment.
7. The formulation is in the form of aqueous vehicle based suspension having greater patient compliance when compared to oily dosage forms.
8. Niosomal dispersion being aqueous can be emulsified in a non aqueous phase to regulate the drug release rate and to administer the vesicles in non-aqueous phase⁶⁻⁸.

ADVANTAGES

1. Niosomes can improve oral bioavailability of poorly absorbed drugs.
2. Niosomes can enhance the skin penetration of drugs.
3. Niosomes act as a depot for short acting peptide drugs and releases the drug in a controlled rate and increases the stability of entrapped drug.
4. Niosomes prolong the circulation of entrapped drug and altering its organ distribution and metabolic stability.
5. Niosomes can entrap hydrophilic, amphiphilic and lipophilic drugs and the entrapment efficiency drug increases by increasing the concentration and lipophilicity of surfactant.
6. Surfactants used in the preparation of niosomes are nontoxic, biodegradable, biocompatible and non-immunogenic and they don't require special conditions for handling and storage.
7. Niosomes are chemically stable as compare to liposomes.
8. Niosomes acts as carriers for enhanced delivery of drugs to specific cells and improves their therapeutic index by restricting drug effects to target cells only.
9. The release of drug from the reservoir is slow which may reduces the systemic toxicity of the drug⁹⁻¹³.

STRUCTURAL COMPONENTS OF NIOSOMES

The two major components used for the preparation of niosomes are, Cholesterol Nonionic surfactants. Cholesterol is used to provide rigidity and proper shape, conformation to the niosomes. The surfactant plays a major role in the formation of niosomes. The following non-ionic surfactants are generally used for the preparation of niosomes the spans (span 60,40,20,85,80), tweens (tween 20,40,60,80) and brij (brij 30,35,52,58,72,76). The non ionic surfactants possess a hydrophilic head and a hydrophobic tail^{14,15}. Entrapment of drug in structure of niosome is shown in Fig no.1¹⁶.

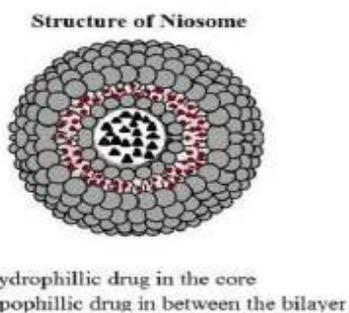


Figure 1: Entrapment of drug in structure of niosome

Surfactants used in formation of Niosomes:

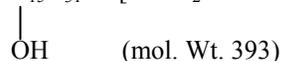
Niosomes are non-ionic surfactant unilamellar or multilamellar vesicles formed from synthetic non-ionic surfactants. The surfactants that are reported to form niosomes are as follows:

1. Ether linked surfactant

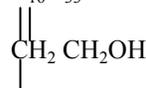
These are surfactants in which the hydrophilic hydrophobic moieties are ether linked, polyoxyethylene alkyl ethers with the general formula (C_nE_m), where n; i.e. number of carbon atoms varies between 12 and 18 and m; i.e. number of oxyethylene unit varies between 3 and 7¹⁷. Surfactants with polyhydroxyl head and ethylene oxide units are also reported to be used in niosomes formation¹⁸.

2. Ester linked surfactant

These surfactants have ester linkage between hydrophilic and hydrophobic groups and have been studied for its use in the preparation and delivery of sodium stibogluconate to the experimental marine visceral leishmaniasis^{18,19}.

**3. Di-alkyl chain surfactant**

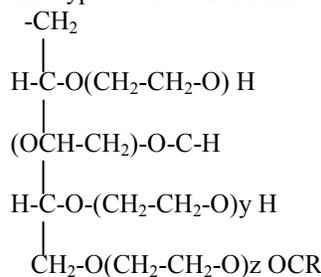
Surfactant was used as a principal component of niosomal preparation of stibogluconate and its potential in delivering sodium stibogluconate in experimental marine visceral leishmaniasis has been explored¹⁸.

**4. Sorbitan esters**

These are most widely used ester linked surfactants especially in food industry. The commercial sorbitan esters are mixtures of the partial esters of sorbitol and its mono and di-anhydrides with oleic acid. These have been used to entrap wide range of drugs viz doxorubicin²⁰.

5. Poly-sorbates

The typical structural formula of polysorbates is



When $n = x + y + z + 2$ and R is an alkyl chain this series of surfactants has been used to study the pharmacokinetics of niosomal entrapped methotrexate.

Charge inducers increase the stability of the vesicles by induction of charge on the surface of the prepared vesicles. It act by preventing the fusion of vesicles due to repulsive forces of the same charge and provide higher values of zeta potential. The commonly used negative charge inducers are dicetyl phosphate, dihexadecyl phosphate and lipoamine acid and positive charge inducers are sterylamine and cetyl pyridinium chloride^{21,22}.

FORMULATION OF NIOSOMES**1. Preparation of small unilamellar vesicles****a. Sonication:**

The aqueous phase containing drug is added to the mixture of surfactant and cholesterol in a scintillation vial. The mixture is homogenised using a sonic probe at 60°C for 3 minutes. The vesicles are small and uniform in size (Fig no.2)^{23,24}.

b. Micro fluidization:

Two fluidised 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 reproducibility²⁵.

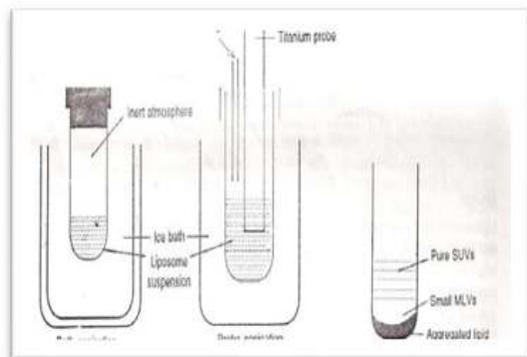


Figure 2: Formulation of niosome by sonication method

2. Preparation of multilamellar vesicles

a. 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. The dried layer is hydrated with aqueous phase containing drug at normal temperature with gentle agitation (Fig no.3)^{23,24,26}.

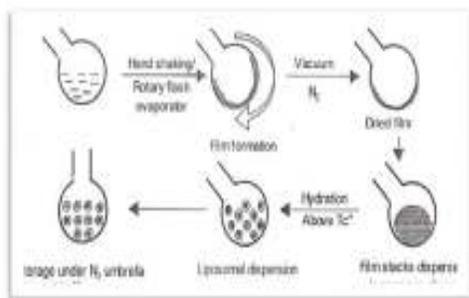


Figure 3: Formulation of niosome by hand shaking method

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

Surfactant and cholesterol are dissolved in chloroform. 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 vesicles²⁷.

3. Preparation of large unilamellar vesicles

a. Reverse phase evaporation technique (REV):

In this method, cholesterol and surfactant are dissolved in a mixture of ether and chloroform. 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 (Fig no.4)^{23,28}.

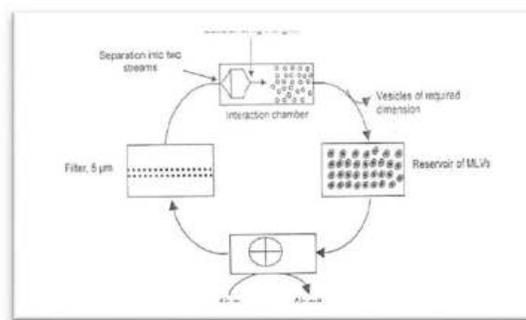


Figure 4: Formulation of niosome by reverse phase evaporation method

b. 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. 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 disadvantage of this method is that a small amount of ether is frequently present in the vesicles suspension and is difficult to remove (Fig no.5)^{23,24,26}.

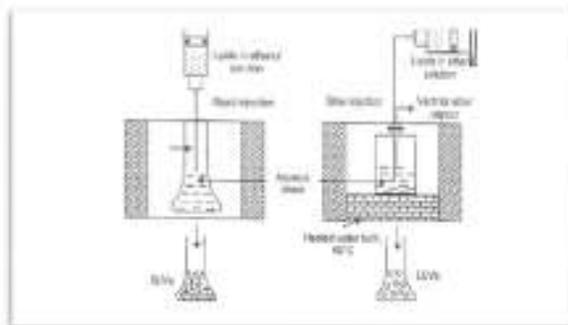


Figure 5: Formulation of niosome by ether injection method

CHARACTERIZATION OF NIOSOMES

1. Entrapment efficiency (EE)

The entrapment efficiency (EE) is expressed as

$$EE = (\text{amount entrapped} / \text{total amount added}) \times 100$$

It is determined after separation of unentrapped drug, on complete vesicle disruption by using about 1ml of 2.5% sodium lauryl sulfate, briefly homogenized and centrifuged and supernatant assayed for drug after suitable dilution²⁹.

2. Vesicle diameter

Niosomes, similar to liposomes, assume spherical shape and so their diameter can be determined using light microscopy, photon correlation microscopy, molecular sieve chromatography and ultracentrifugation. Liquid state products are characterized by TEM and freeze thaw microscopy while solid products are studied using SEM. Freeze thawing (keeping vesicles suspension at -20°C for 24 hrs and then heating to ambient temperature) of niosomes increases the

vesicle diameter, which might be attributed to fusion of vesicles during the cycle²⁵.

3. Number of lamellae

It is determined by using NMR spectroscopy, small angle X-ray scattering and electron microscopy³⁰.

4. Membrane rigidity

Membrane rigidity can be measured by means of mobility of fluorescence probe as function of temperature³¹.

5. Bilayer formation

Assembly of non-ionic surfactants to form bilayer vesicle is characterized by X-cross formation under light polarization microscopy³¹.

6. *In-vitro* release

A method of *in-vitro* release rate study includes the use of dialysis tubing. A dialysis sac is washed and soaked in distilled water. The vesicle suspension is pipetted into a bag made up of the tubing and sealed. The bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. At various time intervals, the buffer is analyzed for the drug content by an appropriate assay method³².

FACTORS AFFECTING FORMULATION OF NIOSOMES

1. Nature of encapsulated 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 degree of entrapment^{15,33}.

2. Amount and type of surfactant

The mean size of niosomes increases proportionally with increase in the HLB of surfactants like Span 85 (HLB 1.8) to Span 20 (HLB 8.6) because the surface free energy decreases with an increase in hydrophobicity of surfactant^{15,25}. 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 characterized by the gel-liquid phase transition temperature (TC). Phase transition temperature (TC) of surfactant also effects entrapment efficiency i.e. Span 60 having higher TC, provides better entrapment²⁵.

3. Cholesterol content and charge

Inclusion of cholesterol in niosomes increases its hydrodynamic diameter and entrapment efficiency. In general, the action of cholesterol is two folds; on one hand, cholesterol increases the chain order of liquid-state bilayers and on the other, cholesterol decreases the chain order of gel state bilayers. At a high cholesterol concentration, the gel state is transformed to a liquid-ordered phase³⁴.

4. 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. Temperature

change of niosomal system affects assembly of surfactants into vesicles and also induces vesicle shape transformation³⁵.

5. 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 stress³⁶.

6. Membrane Composition

The stable niosomes can be prepared with addition of different additives along with surfactants and drugs. 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 niosome 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 spherical Niosomes are formed by C16G2: cholesterol:solulan (49:49:2). The mean size of niosomes is influenced by membrane composition such as Polyhedral niosomes formed by C16G2: solulan C24 in ratio (91:9) having bigger size ($8.0 \pm 0.03\text{mm}$) than spherical/tubular niosomes formed by C16G2: cholesterol:solulan C24 in ratio (49:49:2) ($6.6 \pm 0.2\text{mm}$). Addition of cholesterol molecule to niosomal system provides rigidity to the membrane and reduces the leakage of drug from niosome³⁷.

APPLICATION OF NIOSOMES

Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Some of their therapeutic applications are discussed below.

1. Targeting of bioactive agents

a. To reticulo-Endothelial System (RES):

The cells of RES preferentially take up the vesicles. The uptake of niosomes by the cells is also by circulating serum factors known as opsonins, which mark them for clearance³⁶.

b. To organs other than RES:

It has been suggested that carrier system (antibodies) are attached to direct niosomes to specific sites in the body. Immunoglobulins seem to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier³⁸.

2. Anti-neoplastic therapy

Doxorubicin, the anthracyclic antibiotic with broad spectrum anti tumor activity, shows a dose dependant irreversible cardio toxic effect. Niosomal delivery of this drug to mice bearing S-180 tumor increased their life span and decreased the rate of proliferation of sarcoma³⁹. Niosomal entrapment increased the half-life of the drug, prolonged its circulation and altered its metabolism. Intravenous administration of methotrexate entrapped in niosomes to S-180 tumor bearing mice resulted in total regression of tumor and also higher plasma level and slower elimination⁴⁰.

3. Immunological application of niosomes

Niosomes have been used for studying the nature of the immune response provoked by antigens. Brewer and

Alexander have reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability⁴¹.

4. Niosomes as carriers for Haemoglobin

Niosomes can be used as carriers for haemoglobin within the blood. The niosomal vesicle is permeable to oxygen and hence can act as a carrier for haemoglobin in anemic patients^{42,43}.

5. Transdermal delivery of drugs

Slow penetration of drug through skin is the major drawback of transdermal route of delivery. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes⁴⁴.

6. Ophthalmics

Bioadhesive-coated niosomal formulation of acetazolamide prepared from span 60, cholesterol stearylamine or dicetyl phosphate exhibits more tendency for reduction of intraocular pressure as compared to marketed formulation (Dorzolamide)⁴⁵.

7. Niosome formulation as a brain targeted delivery system

For the vasoactive intestinal peptide (VIP): Radiolabelled (I125) VIP-loaded glucose-bearing niosomes were injected intravenously to mice. Encapsulated VIP within glucose-bearing niosomes exhibits higher VIP brain uptake as compared to control⁴⁶.

8. Niosomal system can be used as diagnostic agents

Conjugated niosomal formulation of gadobenate dimeglumine 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 50⁴⁷.

CONCLUSION

Niosomes represent a promising drug delivery module. The concept of incorporating the drug into niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. Niosomes are superior systems when compared to other carriers with respect to stability, toxicity and cost-effectiveness. The problem of drug loading remain to be addressed and although some new approaches have been developed to overcome this problem, it is still necessary to increase encapsulation efficiencies as it is important to maintain the biological potential of the formulations. More concerted research efforts, however, are still required to realize the full potential of these novel systems.

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Source of support: Nil, Conflict of interest: None Declared