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Research Article

# RECENT TRENDS IN DRUG DELIVERY BY NIOSOMES: A REVIEW

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## ABSTRACT

*Niosomes or non ionic surfactant are microscopic lamellar structures which may be unilamellar or multilamellar. These are amphiphillic in nature, hence capable of entrapping both hydrophilic and lipophilic drugs for their controlled delivery. Niosomes are formulated by hydration of the lipid by the aqueous phase which may be either single surfactant or a mixture of surfactant with cholesterol. Stability of niosomes is greater as compared with other novel drug delivery techniques. Niosomes are widely used for delivery of many drugs especially in treatment of life threatening diseases, site specific targeting can be achieved with niosomes, and they are also used in diagnostic imaging purpose. This study is based upon the recent advances by which niosomes can be formulated and their application in controlled and effective delivery of various drugs.*

***Key words:*** *Cholesterol, controlled delivery, niosomes, non-ionic surfactant.*

## INTRODUCTION

As it known that, it is essential to take medication various times for the treatment of chronic diseases; this may lead to fluctuating drug level in body. So, in order to avoid frequent drug administration and maintain therapeutic drug level in body it is important to administer drug by controlled release system [1]. Controlled drug delivery system is designed to obtain desirable drug release profile for a longer period of time. There are various techniques to obtain controlled release system; one of them is by formulating niosomes. Niosomes are non-ionic, surfactant vesicles with microscopic lamellar bilayer structure formed by self association of hydrated surfactant monomers.

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The multilamellar or unilamellar structure of niosomes are formed by mixing nonionic surfactant, cholesterol and diethyl ether along with subsequent hydration in aqueous media [2].Niosomes formulation as a carrier controlled drug deliver, can entrap both hydrophilic and lipophilic drugs in aqueous layer and vesicular membrane respectively. Structurally, niosomes have inner and outer hydrophilic layer with sandwiched lipophilic layer in between. So, by this method various numbers of drugs and other substances can be delivered using niosomes [3].

## SALIENT FEATURES OF NIOSOMES

Niosomes formulations have wide area of applications, they can be administered by various modes of administration like intramuscular [4] intravenous [5] peroral [6] and transdermal[7]. In addition, as drug delivery vesicles niosomes have been shown to enhance absorption of some drugs across

cell membranes to localize in targeted organs [8,9].

Niosomes are amphiphillic in nature, so they can accommodate a large number of drugs with a wide range of solubilities hence the bioavailability of poorly soluble drugs is enhanced. Niosomes formulationare preferred over other vesicular systems as its vesicle suspension is aqueous in nature, so high patient compliance is achieved as compared with other non aqueous formulations. Drug depots are formed on administration of niosomes in body which release the drug in a controlled manner through its bilayer system [10].

Niosomes are one of the most suitable drug delivery system for obtaining controlled delivery of drug as the therapeutic efficacy of the drug is improved since its clearance rate is reduced, site specific drug targeting helps in reduction of dose [11,12] they are osmotically active and stable so the stability of the entrapped drug is also enhanced.

## STRUCTURE OF NIOSOMES

Niosomes are microscopic, lamellar structures that are biodegradable, biocompatible and non-immunogenic consists of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. The surfactant molecules are arranged in such a way that the hydrophilic ends of the non-ionic surfactant point outwards, while the hydrophobic ends face each other to form the bilayer, this arrangement of surfactant results due to self orientation of molecules.

The schematic representation of drug loaded noisome is shown in Figure 1 below.

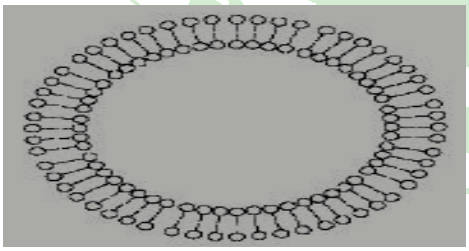

**Figure 1:** Structure of Niosome. Here "o" represents "Hydrophilic head group" and "—" represents "Hydrophobic tail"

## STRUCTURAL COMPONENTS OF NIOSOMES

### *Surfactants*

Surfactants are one of the most essential component of niosomes, different types and their combinations are used to entrap various drugs to form niosomes [13]. The surfactants are amphiphilic, biodegradable, biocompatible and non- immunogenic in nature. The characteristics of formulated niosomes are based on composition, additives concentration, size, lamellarity and surface charge of vesicles [14,15].

### *Ether linked surfactants*

These are polyoxyethylene alkyl ethers which have hydrophilic and hydrophobic groups linked with ether. The general formula of this group is (CnEOm), where n can be 12-18 and m can be 3 to 7. Surfactants with polyhydroxyl head and ethylene oxide units are also used in niosomes formulation [16].

### *Ester linked surfactants*

They have ester linkage between hydrophilic and hydrophobic moieties and have been investigated for its use in formulation and delivery of sodium stibogluconate [17].

### *Sorbitan Esters*

These are most commonly used ester linked surfactants particularly used in food industry. Commercial these are available as mixtures of partial esters of sorbital and its mono and di-an hydrides with oleic acid. Various drugs like doxorubicin have been used in niosomes preparation [18].

### *Alkyl Amides*

In alkyl amides, the alkyl galactosides and glucosides are incorporated with amino acid spacers. The alky groups are fully or partially saturated $C^{12}$ to $C^{22}$ hydrocarbons with some novel amide compounds having fluorocarbon chains.

### *Fatty Acids and Amino Acid Compounds*

These amino acids are made amphiphilic by addition of hydrophobic alkyl side chains and long chain fatty acids which form "Ufasomes vesicles,whic are formed from fatty acid bilayers.

### *Cholesterol*

Cholesterol is a waxy steroid metabolite which is frequently added to non-ionic surfactants to provide rigidity, it is amphiphilic in nature. Rigidity is obtained by alternative position of steroidal skeleton with surfactant

molecules in bilayer. Cholesterol is also known to prevent leakage by abolishing gel to liquid phase transition [19].

***Charge Inducers***

These help to induce surface charge to the prepared vesicles, they increases the stability of the vesicles 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 [20,21].

**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 OF NIOSOMES** [22]

**Preparation of small unilamellar vesicles**

***Sonication*:**

Sonication [23, 24] is the most commonly used technique for the production of niosomes. In this technique, desirable amount of drug solution is taken in buffer media, and then it is added to the surfactant/cholesterol mixture in a 10-ml glass vial. Then this mixture is solicited for 3 minutes at 60°C with a titanium probe to form niosomes.

***Micro fluidization*** [25]:

This method of niosomes formation is a recent technique used to formulate unilamellar vesicles of desirable size. It is based on submerged jet method in which two fluidize streams interact with each other at very high speed in defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged in such a manner that the energy supplied to the system remains within the area of niosomes formation. So, by this method noisome are formed by micro fluidization technique.

***Preparation of multilamellar vesicles***

***Trans membrane pH gradient Drug Uptake Process:*** [26]

In trans membrane pH gradient drug uptake process the solution of surfactant and cholesterol is formed in chloroform, then the solvent is evaporated under reduced pressure to obtained a thin film on the walls of the round bottom flask. Then this film is hydrated with citric acid. The multilamellar vesicles are formed by freeze thaw method and finally sonicated. Lastly, to this niosomes suspension, aqueous solution of 10 mg/ml of drug is added and vortexed, then pH is increased to 7.0-7.2 with 1M disodium phosphate. This mixture is finally heated for 10 minutes at 60°C to give niosomes.

***Hand shaking method:***

In this method the mixture of surfactant and cholesterol was dissolved in a volatile organic solvent like diethyl ether, chloroform or methanol, then the volatile solvent is removed by evaporation, at room temperature (20°C) using rotary evaporator which leaves a thin layer of solid mixture deposited on the wall of the flask. Then the dried surfactant film is rehydrated with aqueous phase with gentle agitation, this leads to the formation of multilamellar niosomes.

**Preparation of large unilamellar vesicles**

***Ether Injection:***

In Ether Injection method the mixture of Surfactant along with other components is formed by dissolving in a and other components are dissolved in ether and it is then slowly injected into aqueous solution maintained at 60°C with the help of needle, then the volatile solvent is evaporated which gives formation of single layered vesicles. In this method the size of niosomes is very efficiently regulated with the help of needle. The major disadvantage of formulating niosomes by this technique is minimum

solubility of substances in ether and finally the removal of ether from the formulation [27, 28].

***Reverse phase evaporation technique*:**

In Reverse phase evaporation technique the mixture of this method, surfactant and cholesterol is formed by dissolving them in combination of volatile solvents i.e. ether and chloroform [29]. Then the aqueous phase containing drug is added to this and the resulting two phases are sonicated, this leads to the formation of a clear gel which is further sonicated after the addition of little amount of phosphate buffered saline. Finally, the volatile phase is removed by evaporation under low pressure at 40°C. Then the resulting niosomes suspension is diluted further with phosphate-buffer saline and heated in a water bath at 60°C for 10 min to give niosomes.

**Other techniques**

***The Bubble Method:***

This is a single step technique to form niosomes in which no organic solvent is used. In Bubble Method all the components are dispersed in a buffered system which is placed in a round bottom flask immersed temperature regulated water bath system. This method prepares niosomes in one step without the use of organic solvent. The round bottom flask is specially designed in such a way that it has three necks, which are attached to water cooled reflux, thermometer and nitrogen supply respectively. The resulting dispersion is mixed with the help of shear homogenizer for 15 seconds and then bubbled with nitrogen to form niosomes [30].

***Multiple Membrane Extrusion*:**

In this method of niosomes formation the basic technique includes extrusion of mixture of components which is then passed through polycarbonate membranes repeatedly to obtain niosomes of required size. The volatile phase is dried in a rotary evaporator and is hydrated by aqueous phase, the resultant is extruded through the membrane to give niosomes.

***Formation of niosomes from proniosomes*:**

As the name suggests, in this method the niosomes are prepared from proniosomes. Here coating of water soluble carrier is done with the help of a surfactant molecules, this leads to the formation of a dry formulation in which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is known as proniosomes, hence from these proniosomes niosomes are prepared [31].

***Active Trapping Techniques*:**

In this method, the drug loading is done when the niosomes are formed; it is done by maintaining the pH gradient which helps in drug uptake by niosomes. This technique of niosomes formulation is highly advantageous as it offers complete drug entrapment, drug-lipid ratio is high, it is cost effective and chances of drug leakage will be minimum.

***Emulsion method*:**

This is a simple method to form niosome in which oil in water (o/w) emulsion is prepared from an organic solution of surfactant, cholesterol, and an aqueous solution of the drug. Finally, the organic solvent is evaporated leaving niosomes dispersed in the aqueous phase [32].

**CHARACTERIZATION OF NIOSOMES**

***Size*:**

In general, the niosomes are spherical in shape, their mean diameter can be determined with the help of laser light scattering method. It can also be estimated using electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation microscopy and optical microscopy and freeze fracture electron microscopy [33, 34]

***Bilayer formation:***

Niosomes are formed by association of surfactants to form bilayer vesicles, which is characterized by X-cross formation under light polarization microscopy [35].

***Number of lamellae:***

Number of lamellae of niosomes are determined by nuclear magnetic resonance

(NMR) spectroscopy, X-ray scattering and electron microscopy

***Vesicle charge:***

The surface charge plays an essential role in stability of niosomes, in general the charged niosomes are more stable as compared with uncharged vesicles. The charge of vesicles are determined by estimating zeta potential, it is calculated by micro electrophoresis, or zeta potential can also be estimated by pH-sensitive fluorophores or dynamic light scattering technique.

***Bilayer Rigidity and Homogeneity*:**

In niosomes the bilayer which is formed should be rigid to maintain its definite shape and it should also be homogeneous in nature, so that proper drug distribution can be obtained. So, this bilayer rigidity and structural homogeneity can be determined by p-NMR, differential scanning calorimetry (DSC) and Fourier transform-infra red spectroscopy (FT- IR) techniques. Recently, fluorescence resonance energy transfer (FRET) was used to obtain deeper insight about the shape, size and structure of the niosomes [36,37,38].

***Entrapment efficiency*:**

Drug entrapment efficiency test is performed to check the amount of drug entrapped in formulated niosomes**.** When niosomes are formed, the unentrapped drug is separated by dialysis, centrifugation or gel filtration and the drug entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzing the resultant solution by appropriate assay method for the drug. The drug entrapment efficiency is determined using the following formula:[39,40,41].

Entrapment efficiency (% EF) = (Amount of drug entrapped/ total amount of drug) x 100

***In vitro* release**:

The *in-vitro* drug release study is determined by dialysis method, a dialysis sac is used which is cleaned, washed and soaked in distilled water, then the niosomes suspension is pipette into a bag made up of the tubing and sealed. The bag containing 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 appropriate assay method.

## APPLICATIONS OF NIOSOMES

***Targeting of bioactive agents***

***To reticulo-endothelial system***

The reticulo-endothelial cells have the tendency to take the niosomes, so these are up taken by cells with the help of circulating serum factors known as opsonins, which mark them for clearance. This type of drug targeting helps in localized accumulation drug, hence used in drug targeting, however, been exploited in treatment of various types of tumors, which are known to metastasize to the liver and spleen and in parasitic infestation of liver [42].

***To organs other than reticulo-endothelial system***

As it is known that various types of carrier system are used for site specific drug targeting in body by the use of antibodies [43] immunoglobulins have also been found to bind with the lipid surface, thus it offers a convenient means for targeting of drug carrier system [44].

***Niosomes used in neoplasia***

Niosomes are very effective mode of controlled drug delivery system, various drugs like Doxorubicin, the anthrax cyclic antibiotic with broad spectrum anti tumor activity, is widely used for its controlled delivery. Doxorubicin has dose dependant irreversible cardio toxic effect, its niosomal formulation in mice bearing S-180 tumor has increased their life span and decreased the rate of proliferation of sarcoma [45]. Niosomal entrapment increased the half-life of the drug, prolonged its circulation and altered its metabolism. Intrave nous 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 elimination [46].

***Treatment of leishmaniasis***

As it is known that niosomes are widely used for drug targeting, Leishmaniasis is such a disease in which parasite invades cells of liver and spleen, so niosomal preparation of antimonials class of drugs are widely used in its treatment.

***Delivery of peptide drugs***

Various drugs for which oral controlled delivery is designed by niosomes formulation are 9-desglycinamide, 8- arginine vasopressin etc formulated as niosomes has shown to enhance the stability of peptide drugs.

***Immunological application of niosomes***

Niosomes have been used to study the antigen-antibody response provoked by antigens. It has been found that niosomes act as a potent adjuvant related with immunological selectivity, minimum toxicity and maximum stability [47].

***Niosomes as Hemoglobin carrier***

Hemoglobin cab be carried with help of niosomes, niosomal suspension shows a visible spectrum that is super imposable over free hemoglobin. These vesicles are permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin [48].

***Transdermal drug delivery by niosomes***

The major drawback of transdermal drug delivery system is its slow penetration of drug through skin, this drawback can be overcome by transdermal delivery of drug incorporated in niosomes. It has been studied that on transdermal delivery, the rate of penetration of erythromycin on hairless mouse was increased when administerd as niosomes [49]. The data obtained by various evaluating parameters and the confocal microscopy study revealed that non-ionic vesicles targeted the drug to the pilo sebaceous glands, hence earlier effect is achieved.

***Use in diagnosis***

Niosomes can also 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 [50].

***Ophthalmic delivery of drug***

Niosome have been used for ophthalmic drug delivery by using various bioadhesive polymers, for example bioadhesive-coated niosomal formulation of acetazolamide formulated with span 60, cholesterol stearylamine or dicetyl phosphate shows enhanced reduction of reduction of intraocular pressure as compared with marketed formulation. Similar results were obtained with chitosan- coated niosomal formulation of timolol maleate [51].

***Niosomes as Carrier for Drugs***

Niosomes are widely used as carriers for various types of anti cancer drugs like, Methotrexate, Doxorubicin etc.

***Niosomes used in Cosmetic formulations***

Various cosmetic preparations are prepared as niosomes because both hydrophilic and hydrophobic drugs in topical formulations are easily prepared. N-acetyl glucosamine (NAG) has been considered in the treatment of thyrosinase enzymes in melanocytes. Prepared formulations improved the extent of drug localized in the skin, as needed in hyperpigmentation disorders [52]. In the formulation of anti aging preparation of niosomes both types of elastic and non-elastic niosomes were prepared, the elastic niosomes showed better permeation rate through the skin which yields better topical anti-aging effect [53]. One of the potent antioxidant i.e. Ellagic acid, a phytochemical substance with limited use due to its poor biopharmaceutical properties, low solubility and low permeability had limited use. But when it is formulated as niosomes with various, its permeation rate through the skin was enhanced [54].

## STABILITY AND TOXICITY OF NIOSOMES

Niosomes are one of stable formulations among various available controlled drug delivery systems, when compared with liposomes, niosomes are relatively more stable. The only reason that may lead to instability of niosomes is the nature of surfactants used in its formulation, but till now no such reports have been available yet. There are no reports available on the *in vivo* toxicity of niosomes linked with the concentration of ether or esters surfactants used in the preparation of vesicles [55].

## CONCLUSION

Niosomes are novel drug delivery system that has a wide range of advantages when compared with other conventional and vesicular delivery systems, like with niosomes drug targeting is done; controlled drug delivery of drug products is formulated. In various formulations the stability of formulation was enhanced when prepared as niosomes, their toxicity is reduced etc. From the above compilation of work it can be concluded that niosomes have suitability for encapsulating various types of drugs. Niosomes have been used for many chronic diseases with effective treatment efficiently with reduced side effects and better patient compliance. Thus niosomes can be used with wider applications in the field of disease management.

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