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Niosome: A Targeted Drug Delivery System

Darshan Kamani[*1], Hiral Shah[1],Ragin Shah[1], Jignesh Solanki[1], Sunita Chaudhary[1], kinjal Sanghvi[1]

1.Arihant school of pharmacy and BRI, Adalaj, Gandhinagar, Gujarat

ABSTRACT

Drug targeting is the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with nontarget tissue. Niosomes are one of the best carriers for drug targeting. Niosomes are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. Niosomes are biodegradable, relatively nontoxic, more stable and inexpensive, an alternative to liposomes. Niosomes can be SUV (Small Unilamellar Vesicles), MLV (Multilamellr Vesicles) or LUV (Large Unilamellar Vesicles). The method of preparation of niosome is the based on liposome technology. The basic process of preparation is the same i.e. hydration of the lipid phase by aqueous phase. Niosomes are characterized by vesicle size, bilayer formation, number of lamellae, membrane rigidity and entrapment efficiency. A method of *in-vitro* release rate study includes the use of dialysis tubing. Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases including cancer and leishmaniasis.

Keywords: Niosome, Surfactant, liposome, targeting.

*Corresponding Author Email: darshankamani@yahoo.com

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INTRODUCTION

The ideal drug delivery system delivers drug at rate decided by the need of the body throughout the period of treatment and it provides the active entity solely to the site of action. 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 localized on the targeted site. Hence, surrounding tissues are not affected by the drug. In addition, loss of drug does not happen due to localization 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. Niosomes are one of the best among these carriers.[1]

Niosomes (non-ionic surfactant vesicles) are microscopic lamellar structures obtained on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media.[2]

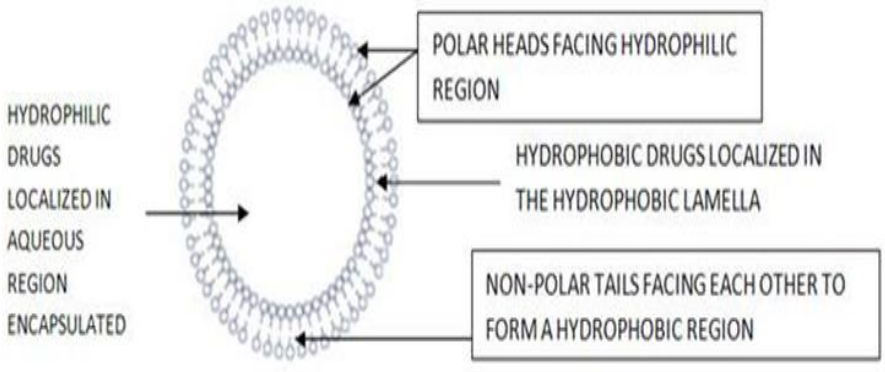

Figure 1: Structure of noisome

Advantages of Niosomes

- Since the structure of the niosome offers place to accommodate hydrophilic, lipophilic as well as ampiphilic drug moieties, they can be used for a variety of drugs.
- Niosomes exhibits flexibility in their structural characteristics (composition, fluidity and size) and can be designed according to the desired situation.
- They improve the therapeutic performance of the drug by protecting it from the biological environment and restricting effects to target cells, thereby reducing the clearance of the drug.
- Niosomes can act as a depot to release the drug slowly and offer a controlled release.
- They can increase the oral bioavailability of drugs.
- They are osmotically active and stable.

- They increase the stability of the entrapped drug.
- They can enhance the skin penetration of drugs.
- They can be made to reach the site of action by oral, parenteral as well as topical routes.
- The surfactants are biodegradable, biocompatible, and non-immunogenic
- The niosomal dispersions in an aqueous phase can be emulsified in a non-aqueous phase to control the release rate of the drug and administer normal vesicles in external non-aqueous phase.
- Handling and storage of surfactants do not require any special conditions.
- The vesicle suspension being water based offers greater patient compliance over oily dosage forms.[3]

Comparison of Niosomes Vs Liposomes

Niosomes are now widely studied as an alternative to liposomes, which exhibit certain disadvantages such as –they are expensive, their ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they require special storage and handling and purity of natural phospholipids is variable. Niosomes are prepared from uncharged single-chain surfactant and cholesterol whereas liposomes are prepared from doublechain phospholipids (neutral or charged). Niosomes behave *in-vivo* like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability. Encapsulation of various anti neoplastic agents in these carrier vesicles has been shown to decrease drug induced toxic side effects, while maintaining, or in some instances, increasing the anti-tumor efficacy. Such vesicular drug carrier systems alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug[4].

Types of Niosomes

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

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

(ii) Multilamellar Vesicles (MLV, Size=>0.05 μm)

(iii) Large Unilamellar Vesicles (LUV, Size=>0.10 μm).[5]

FACTORS AFFECTING PHYSICO-CHEMICAL PROPERTIES OF NIOSOMES

Nature of Surfactants

A surfactant used for preparation of niosomes must have a hydrophilic head and hydrophobic tail. The hydrophobic tail may consist of one or two alkyl or perfluoroalkyl groups or in some cases a single steroidal group.[6]The ether type surfactants with single chain alkyl as hydrophobic

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*.[7]The surfactants with alkyl chain length from C12-C18 are suitable for preparation of niosomes.[8] Span series surfactants having HLB number of between 4 and 8 can form vesicles.[9]

Table 1: Different Types of Non-Ionic Surfactant

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

Structure of surfactants

The geometry of vesicle to be formed from surfactants is affected by its structure, which is related to critical packing parameters. On the basis of critical packing parameters of surfactants, we can predicate geometry of vesicle to be formed. Critical packing parameters can be defined using following equation,

CPP (Critical Packing Parameters) = $v/lc \times a_0$

Where v = hydrophobic group volume, lc = the critical hydrophobic group length, a_0= the area of hydrophilic head group.

From the critical packing parameter value type of miceller structure formed can be ascertained as given below,

If CPP < ½, then formation of spherical micelles,

If ½ < CPP < 1, then formation of bilayer micelles,

If CPP > 1, then formation inverted micelles.

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.[9]

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)[10] Phase transition temperature (TC) of surfactant also effects entrapment efficiency i.e. Span 60 having higher TC, provides better entrapment.

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.[13] 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 ± 0.03mm) than spherical/tubular niosomes formed by C16G2: cholesterol: solulan C24 in ratio (49:49:2) (6.6±0.2mm).[11] Addition of cholesterol molecule to niosomal system provides rigidity to the membrane and reduces the leakage of drug from niosome.[12]

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 phase.[13]

An increase in cholesterol content of the bilayers resulted in a decrease in the release rate of encapsulated material and therefore an increase of the rigidity of the bilayers obtained.[13,14] Presence of charge tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle structure and leads to greater overall entrapped volume.

Nature of Encapsulated Drug

The physico-chemical properties of encapsulated drug influencecharge and rigidity of the niosome bilayer. The drug interacts withsurfactant head groups and develops the charge that creates mutualrepulsion between surfactant bilayers and hence increases vesicle size. The aggregation of vesicles is prevented due to the charge development on bilayer. In polyoxyethylene glycol (PEG) coated vesicles, some drug is entrapped in the long PEG chains, thus reducing the tendency to increase the size.[15] The hydrophilic lipophilic balance of the drug affects degree of entrapment.

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

Nature of the drug	Leakage from the vesicles	Stability	Other properties
Hydrophobic drug	Decreased	Increased	Improved transdermal delivery
Hydrophobic drug	Increased	Decreased	-
Amphiphilic drug	Decreased	-	Increased encapsulation, Altered elecrophoretic mobility

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 transformation.[6,13]Arunothayanun et al. reported that a polyhedral vesicle formed by C16G2: solulan C24 (91:9) at 25°C which on heating transformed into spherical vesicle at 48°C, but on cooling from 55°C, the vesicle produced a cluster of smaller spherical niosomes at 49°C before changing to the polyhedral structures at 35°C. In contrastvesicle formed by C16G2: cholesterol: solulanC24 (49:49:2) shows no shape transformation on heating or cooling.[16] Along with the above mentioned factors, volume of hydration medium and time of hydration of niosomes are also critical factors. Improper selection ofthese factors may result in formation of fragile niosomes or creation of drug leakage problems.

Methods of Preparation

Hand shaking method forms vesicles with greater diameter (0.35-13 nm) compared to the ether injection method (50-1000 nm).[17] Small sized niosomes can be produced by Reverse Phase Evaporation method.[18] Micro fluidization method gives greater uniformity and small size vesicles.[19]Niosomes obtained by trans membrane pH gradient (inside acidic) drug uptake process showed greater entrapment efficiency and better retention of drug.[19]

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.[20]

METHOD OF PREPRATION

Ether injection method

This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The surfactant mixture

in ether is injected through 14-gauge needle into an aqueous solution of material. Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used, the diameter of the vesicle range from 50 to 1000 nm.[12]

Hand shaking method (Thin film hydration technique)

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar niosomes film of lipid on the wall of rotary flash evaporator. The aqueous phase containing drug was added slowly with intermittent shaking of flask at room temperature followed by sonication.[12]

Sonication

A typical method of production of the vesicles is by sonication of solution as described by Cable. In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10-ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes.[12]

Micro fluidization

Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front 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 of niosomes formed.[12]

Multiple membrane extrusion method

Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug solution and the resultant suspension extruded through polycarbonate membranes, which are placed in series for upto 8 passages. It is a good method for controlling niosome size.[12]

Reverse Phase Evaporation Technique

Cholesterol and surfactant (1:1) 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 (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes. Raja Naresh et al have reported the preparation of Diclofenac Sodium niosomes using Tween 85 by this method.[21]

Trans membrane pH gradient(inside acidic)Drug Uptake Process:

Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get 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 3 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 give niosomes.[22]

The Bubble Method

It is novel technique for the one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.[23]

Formation of niosomes from proniosomes

Another method of producing niosomes is to coat a water-soluble carrier such as sorbitol with surfactant. The result of the coating process is a dry formulation. In which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed "Proniosomes". The niosomes are recognized by the addition of aqueous phase at T > Tm and brief agitatiation.[24]

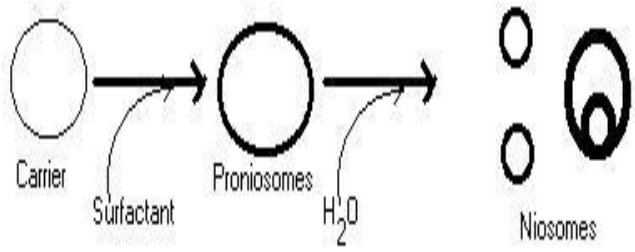

Figure 2: Formation of noisome from proniosome

Separation of Unentrapped Drug

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

Dialysis

The aqueous niosomal dispersion is dialyzed in dialysis tubing against phosphate buffer or normal saline or glucose solution.[23]

Gel Filtration

The unentrapped drug is removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution with phosphate buffered saline or normal saline.[9,25]

Centrifugation

The niosomal suspension is centrifuged and the supernatant is separated. The pellet is washed and then resuspended to obtain a niosomal suspension free from unentrapped drug.[13,15]

CHARACTERIZATION OF NOISOME

Entrapment efficiency

After preparing niosomal dispersion, unentrapped drug is separated by dialysis centrifugation and gel filtration. The drug remain entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzed resultant solution by appropriate assay method using following equation.[12,13]

Particle size analysis

Particle size analysis was done by scanning electronic microscopy (SEM) using JEOL JSM-T330A scanning microscope brass stab. The stabs were placed briefly in a drier and then coated with gold in an ion sputter. Pictures of niosomes were taken by random scanning of the stub and count. The diameter is about 30 niosomes was measured from the photomicrographs of each batch. Finally, average mean diameters were taken into consideration.[12,14]

Bilayer formation

Assembly of non-ionic surfactants to form a bilayer vesicle is characterized by an X-cross formation under light polarization microscopy.[26]

Number of lamellae

This is determined by using nuclear magnetic resonance (NMR) spectroscopy, small angle X-ray scattering and electron microscopy.[27]

Membrane Rigidity

Membrane rigidity can be measured by means of mobility of fluorescence probe as a function of temperature.[26]

In-vitro release study

Human cadaver skin (HCS) was obtained from ventral part of forearm of 35 years old male corpse and was stored at 4°C. HCS membrane was spread and punches it at approximately 3 cm^2

area. Trimmed away the excessfat and sliced to 500 □ m thickness using a Daw's derma tone. These slices were hydrated in pH 7.4 PBS for 24 hrs prior to use. The HCS were attached to Khesary cell (K.C., filled with 100 ml of PBS) and add 10 mg niosomal suspension on it. Finally, cell was immersed into the receptor compartment. The dermal surface was just flush to the surface of permeation fluid (PBS), which was maintain at 37°C 0.50°C and stirred magnetically at 50 r.p.m., aliquots were withdraw and replaced with the same volume of fresh buffer, at every sampling points and analyzed by UV. Spectrophotometer method at 294 nm.[12,13]

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[5.]

Stability study

All niosomal formulations were subjected to stability studies by storering at 4°C, 25°C and 37°C in thermostatic oven for the period of three ssmonths. After one month, drug content of all the formulations were checked by method discussed previously in entrapped efficiency parameter. In-vitro release studies of selected formulations were also carried out.[14]

Therapeutic Applications 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.

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 clearance. Such localized drug accumulation has, however, been exploited in treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of liver.[2]

(b) To organs other than RES

It has been suggested that carrier system can be directed to specific sites in the body by use of antibodies.[28] Immunoglobulins seem to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier.[16] Many cells possess the intrinsic ability to recognize and bind particular carbohydrate determinants and this can be exploited to direct carriers system to particular cells.

Neoplasia

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 sarcoma.[29] 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 elimination.[30]

Leishmaniasis

Niosomes can be used for targeting of drug in the treatment of diseases in which the infecting organism resides in the organ of reticulo-endothelial system. Leishmaniasis is such a disease in which parasite invades cells of liver and spleen. The commonly prescribed drugs are antimonials, which are related to arsenic, and at high concentration they damage the heart, liver and kidney. The study of antimony distribution in mice, performed by Hunter et al showed high liver level after intravenous administration of the carriers forms of the drug.[7]

Delivery of Peptide Drugs

Yoshida et al investigated oral delivery of 9-desglycinamide, 8-arginine vasopressin entrapped in niosomes in an *in-vitro* intestinal loop model and reported that stability of peptide increased significantly.[14]

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 stability.[31]

Niosomes as a Carrier for Hemoglobin

Niosomes can be used as a carrier for hemoglobin. Niosomal suspension shows a visible spectrum superimposable onto that of free hemoglobin. Vesicles are permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated haemoglobin.[32]

Transdermal Delivery of Drugs by Niosomes

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 niosomes.

Other applications

a) **Sustained Release**

Sustained release action of niosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via niosomal encapsulation.

b) Localized Drug Action

Drug delivery through niosomes is one of the approaches to achieve localized drug action, since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration.

Localized drug action results in enhancement of efficacy of potency of the drug and at the same time reduces its systemic toxic effects e.g. Antimonials encapsulated within noisome are taken up by mononuclear cells resulting in localization of drug, increase in potency and hence decrease both in dose and toxicity.[7]

NIOSOME AS DRUG CARRIER

A number of scientist have reported the preparation, characterization and use of niosomes as drug carriers. Niosomes containing anti-cancer drugs, if suitably designed, will be expected to accumulate within tumors in a similar manner to liposomes. The niosomal encapsulation of Methotrexate and Doxorubicin increases drug delivery to the tumor and tumoricidal activity of the drug. Doxorubicin niosomes possessing muramic acid and triglycerol surfaces were not taken up significantly by liver. The triglycerol niosomes accumulated in the tumor and muramic acid vesicles accumulated in the spleen. Those vesicles with polyoxyethylene surface were rapidly taken up by the liver and accumulated to a lesser extent in tumor. Baillie et al investigated the encapsulation and retention of entrapped solute 5,6-carboxy fluorescence (CF) in niosomes. They observed that stable vesicles could not be formed in the absence of cholesterol but were more permeable to entrapped solute. The physical characteristics of the vesicles were found to be dependent on the method of production.[21]

Carter et al reported that multiple dosing with sodium stibogluconate loaded niosomes was found to be effective against parasites in the liver, spleen and bone marrow as compared to simple solution of sodium stibogluconate.[33]

Azmin *et al* reported the preparation and oral as well as intravenous administration of Methotrexate loaded niosomes in mice. They observed significant prolongation of plasma levels and high uptake of Methotrexate in liver from niosomes as compared to free drug solution.[4] D'Souza et al studied absorption of Ciprofloxacin and Norfloxacin when administered as niosome encapsulated inclusion complexes.[34] Namdeo et al reported the formulation and evaluation of Indomethacin loaded niosomes and showed that therapeutic effectiveness increased and simultaneously toxic side effect reduced as compared with free Indomethacin in pawoedema bearing rats.[35] Parthasarthi et al prepared niosomes of vincristine sulfate which had lesser

toxicity and improved anticancer activity.[19] Jagtap et al prepared niosomes of Pentoxifylline and studied the *in-vivo* bronchodilatory activity in guinea pigs. The entrapment efficiency was found to be 9.26 ± 1.93% giving a sustained release of drug over a period of 24 hrs.[36] Raja Naresh et al reported the anti-inflammatory activity of niosome encapsulated Diclofenac sodium in arthritic rats. It was found that the niosomal formulation prepared by employing a 1:1 combination of Tween 85 elicited a better consistent anti-inflammatory activity for more that 72 hrs after administration of single dose.[37]

Marketed Preparation

Lancome has come out with a variety of anti-ageing products which are based on niosome formulations. L'Oreal is also conducting research on anti-ageing cosmetic products.

CONCLUSION

The concept of incorporating the drug into liposomes or niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. Niosomes represent a promising drug delivery module. They presents a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multienvironmental structure. Niosomes are thoughts to be better candidate's drug delivery as compared to liposomes due to various factors like cost, stability etc. Various type of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parentral, etc. Niosomal drug delivery system is the one of the best targeted drug delivery system. However, the technology utilized 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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