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Review Article

NIOSOMES AS APOTENTIAL CARRIER SYSTEM: A REVIEW

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ABSTRACT
Niosomes are the non-ionic surfactant vesicles and like liposomes are bilayered structures, which can entrap both hydrophilic and lipophilic drugs either in an aqueous layer or in vesicular membrane, made up of lipids[1]. Niosomes are widely studied as an inexpensive alternative of non-biologicalorigin to liposomes or perhaps as carrier systems physically similar to liposomes, in vivo, with particular properties, which can be exploited to attain different drug distribution and release characteristics. They have all the advantages of liposomes but their low cost, greater stability, and resultant ease of storage has led to the exploitation of non-ionic surfactants (niosomes) as alternatives to phospholipids. Niosomes have been widely evaluated for controlled release and targeted delivery for the treatment of cancer, viral infections and other microbial diseases. Theoretically, niosome formulation requires presence of a particular class of amphiphile and an aqueous system. Cholesterol is added in order to prepare vesicles, which are less leaky. In addition, stabilizers may be included to prevent vesicle aggregation by repulsive, steric, or electrostatic effect. This review article focuses on the advantages, Disadvantages, preparation methods, factors affecting, characterizations, invitro methods, drug release kinetics, and applications of noisome.

Keywords: Niosomes, non-ionic, liposomes, vesicles, carrier system

1. INTRODUCTION
On admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media, microscopic lamellar structures formed are known as niosomes or non-ionic surfactant vesicles[2].Atpresent no available drug delivery system achieves the site specific delivery with controlled release kinetics of drug in predictable manner. Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes etc[3]. Among different carriers liposomes and niosomes are well documented drug delivery. 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 non target tissue[4].Niosomes are a novel drug delivery system in which both hydrophilic and hydrophobic drug is encapsulated in a vesicle[5]. Niosome can enhance bioavailability of encapsulated drug and provide therapeutic activity in a controlled manner for a prolonged period of time[6].

2. STRUCTURE OFA NIOSOME
In niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as Span – 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate[7,8]. A typical structure of niosome is shown in figure 1

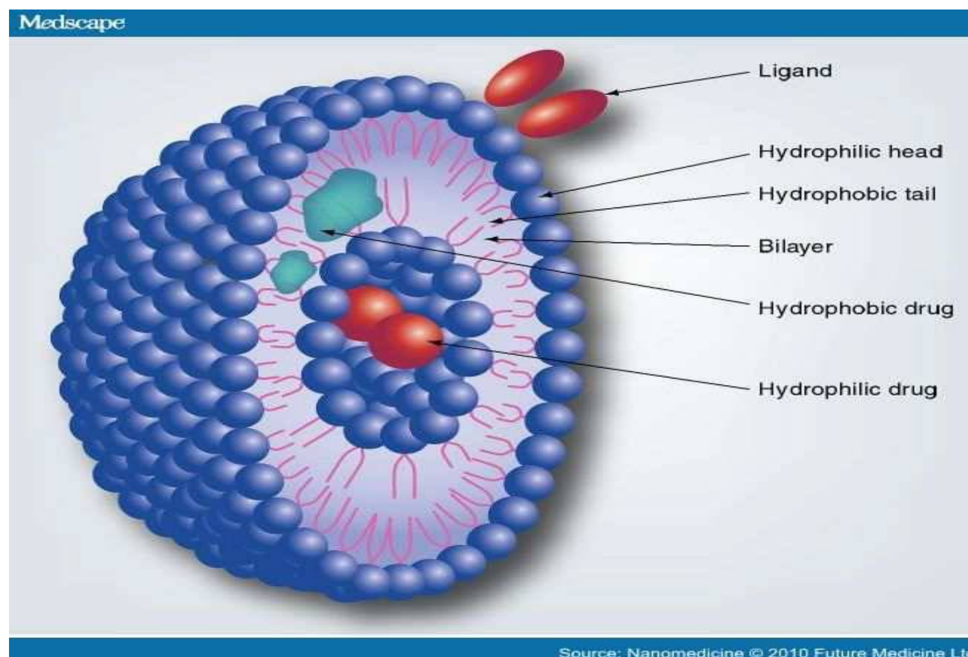

Fig. 1: structure of a niosome

A schematic representation of a drug targeting through its linkage to niosome via antibody is shown in figure 2.

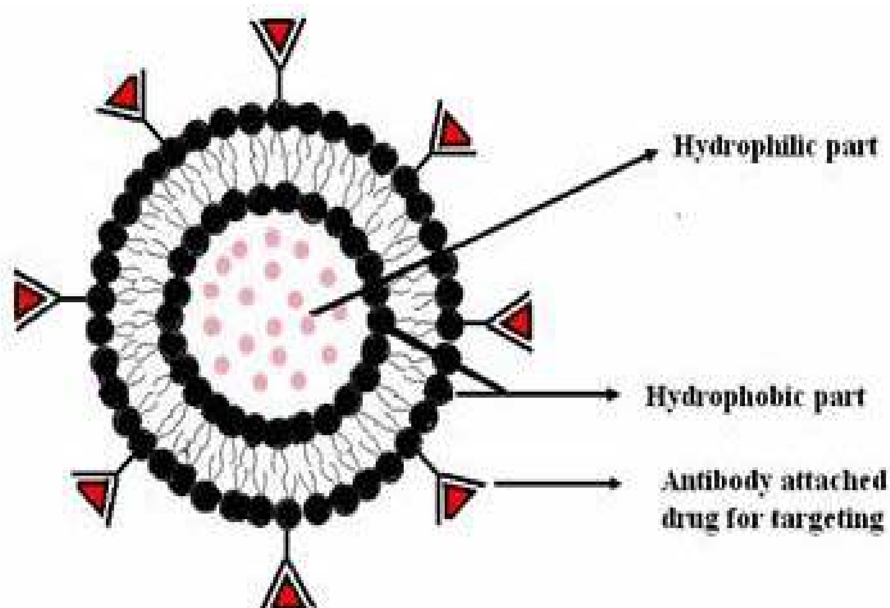

Fig. 2: structure of a niosome linked to an antibody

3. ADVANTAGES OF NIOSOMES

L'Oreal devised the first report of non-ionic surfactant vesicles came from the cosmetic applications[9]. The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic purpose may offer several advantages:

1) The vesicle suspension is water–based vehicle thus offers high patient compliance in comparison with oily dosage forms.
2) Due to the unique infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together they, as a result can accommodate drug molecules with a wide range of solubilities.

3) The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition,size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics.
4) The vesicles may act as a depot, releasing the drug in a controlled manner.

Niosomes in topical ocular delivery are preferred over other vesicular systems because:[10]

- They are chemically stable as compared to liposomes;
- can entrap both lipophilic and hydrophilic drugs;
- have low toxicity because of their non-ionic nature;
- unlike phosholipids, handling of surfactants requires no special precautions and conditions;
- They exhibit flexibility in their structural characterization, e.g. in their composition, fluidity, and size;
- can improve the performance of the drug via better availability and controlled delivery at a particular site;
- They are biodegradable, biocompatible, and non-immunogenic[11].

Additionally

- They are osmotically active and stable, and also they increase the stability of entrapped drug.
- Handling and storage of surfactants requires no special conditions.
- They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
- They can be made to reach the site of action by oral, parenteral as well as topical routes.

4. COMPONENTS OF A NIOSOME

Cholesterol

Cholesterol is a waxy steroid metabolite found in the cell membrane[6]. The incorporation of cholesterol into bilayer composition of noisome gives membranestability and decreases the leakiness of membrane. Hence incorporation of cholesterol into bilayer increases entrapment efficiency[12]. Cholesterol is added usually to the non ionic surfactants to give rigidity and orientational order to the niosomal bilayer[13]. Cholesterol is also known as abolish gel to liquid phase transition of niosomal system resulting in niosomes that are less leaky[8].

Non-ionic surfactants

Non-ionic surfactant possesses hydrophilic head group and hydrophobic tail. The hydrophobic moiety may consist of 1/2/3 alkyl chains or per fluro group or insome cases a single stearyl group[3]. Hydrophilic head group affects the entrapment efficiency of drug. As HLB value increasesi.e alkyl chain increases, thesize of noisome increases[14].Hence HLB value 14-17 is not suitable for niosome formulation. HLB value 8.6 has highest entrapment efficiency[15]. HLB number between 4 and 8 was found to be compatible with vesicle formation[16]. The following non-ionic surfactants are generally usedfor the preparation of niosomes.

- Spans (span 60, 40, 20, 85, 80)
- Tweens (tween 20, 40, 60, 80) and
- Brijs (brij 30, 35, 52, 58, 72, 76).

Other additives

Other additives include charge inducers which increase surface charge density and prevent vesicles flocculation, aggregation and fusion. Both negatively and positively charged molecules are used for induction of chargein niosomes. Dicetylphosphate (DCP) and stearyl amine (SA) induces negative or positive charge on membrane and thereby help to stabilize the formulation[17].

5. TYPES OF NIOSOMES[18]

Niosomes can be divided into three groups on the basis of their vesicles size:
(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).

6. METHODS OF PREPARATION[18]

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

(i) Preparation of Small Unilamellar Vesicles

(a) Sonication

The aqueous phase containing drug is added to the mixture of surfactant and cholesterol in ascintillation vial[19]. The mixture is probe sonicated at 60°C for 3 minutes to produce small and uniform in sizeniosomes.

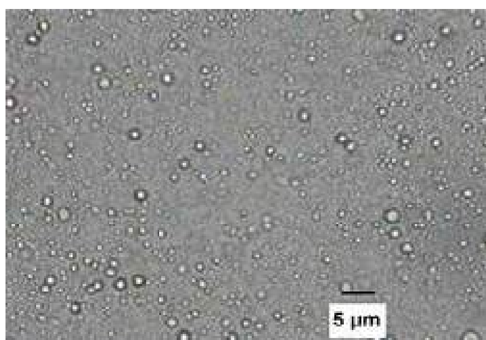

Fig. 3: Photomicrograph of Niosomes after Sonication[19]

(b) Micro fluidization: Micro fluidization is a recent technique to prepare unilamellar vesicles of defined sizedistribution. This method is based on submerged jet principle in which two fluidized streams interact at ultrahigh velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquidsheet along a common front is arranged such that the energy supplied to the system remains within the area ofniosomes formation. The result is a greater uniformity, smaller size and better reproducibility of niosomes formed[20].

(ii) Preparation of Multilamellar Vesicles

(a) Hand shaking method (Thin film hydration technique): In the hand shaking method, surfactant andcholesterol are dissolved in a volatile organic solvent (such as diethyl ether, chloroform or methanol) in around bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leavinga thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film is hydrated with aqueousphase containing drug at 50-60°C with gentle agitation. This process forms typical multilamellar niosomes[19].

(b) Trans-membrane pH gradient (inside acidic) drug uptake process (remote loading): Surfactant andcholesterol are dissolved in chloroform[21]. The solvent is then evaporated under reduced pressure to obtain a thinfilm on the wall of the round-bottom flask. The film ishydrated with 300 mm citric acid (pH 4.0) by vortexmixing. The multilamellar vesicles are frozen and thawedthree times and later sonicated. To this niosomalsuspension, aqueous solution containing 10 mg/ml ofdrug is added and vortexed. The pH of the sample is thenraised to 7.0-7.2 with 1M disodium phosphate. Thismixture is later heated at 60°C for 10 minutes to produce the desired multilamellar vesicles.

(iii) 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[22]. An aqueous phasecontaining 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.

(b) Ether injection method

The ether injection method is essentially based on slow injection of niosomal ingredients in diethyl ether through a 14-gauge needle at the rate of approximately 0.25 ml/min into a preheated aqueous phase maintained at 60°C[8,19]. The probable reason behind the formation of larger unilamellar vesicles is that the slow vaporization of solvent results in an ethergradient 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.

(iv) Miscellaneous

(a) Multiple membrane extrusion method

A mixture of surfactant, cholesterol, and diacetyl 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 a series for up to eight passages. This is a good method for controlling niosome size[20].

(b) 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[23,24]. The organic solvent is then evaporated, leaving niosomes dispersed in the aqueous phase.

(c) 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.

(d) The "bubble" method

It is novel technique for the one step preparation of liposome's 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[25].

(e) Formation of Niosomes from Proniosomes

Another method of producing niosomes is to coat a water-solublecarrier such as sorbitol with surfactant. The result of thecoating process is a dry formulation in which each watersolubleparticle is covered with a thin film of drysurfactant. This preparation is termed "Proniosomes".The niosomes are recognized by the addition of aqueousphase at T > Tm and brief agitation[26].

T = Temperature
Tm = Mean phase transition temperature.

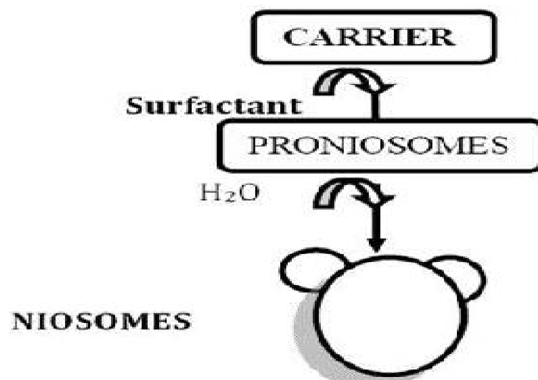

Fig. 4: Steps involved in formation of Niosomes[26]

7. SEPARATION OF UNENTRAPPED DRUG

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

(i) Dialysis

The aqueous niosomal dispersion is dialyzed in dialysistubing against phosphate buffer or normal saline orglucose solution[25].

(ii) Gel Filtration

The unentrapped drug is removed by gel filtration ofniosomal dispersion through a Sephadex-G-50 column and elution with phosphate buffered saline or normalsaline[27,28].

(iii) Centrifugation

The niosomal suspension is centrifuged and thesupernatant is separated. The pellet is washed and thenresuspended to obtain a niosomal suspension free fromunentrapped drug[29,30].

8. CHARACTERIZATION OF NIOSOMES

(i) Size

Shape of niosomal vesicles is assumed to be spherical,and their mean diameter can be determined by usinglaser light scattering method[31]. Also, diameter of thesevesicles can be determined by using electron microscopy,molecular sieve chromatography, ultracentrifugation, photon correlation microscopy, optical microscopy andfreeze fracture electronmicroscopy[3,32]. Freeze thawing(keeping vesicles suspension at -20°C for 24 hrs and thenheating to ambient temperature) of Niosomes increasesthe vesicle diameter, which might be attributed to fusionof vesicles during the cycle[20].

(ii) Bilayer Formation

Assembly of non-ionic surfactants to form a bilayervesicle is characterized by an X-cross formation under light polarization microscopy[33].

(iii) Number of Lamellae

This is determined by using nuclear magnetic resonance(NMR) spectroscopy, small angle X-ray scattering andelectron microscopy[3].

(iv)Membrane Rigidity

Membrane rigidity can be measured by means of mobilityof fluorescence probe as a function of temperature[33].

(v) Entrapment Efficiency

After preparing niosomal dispersion, unentrapped drug isseparated by dialysis, centrifugation, or gel filtration asdescribed above and the drug remained entrapped inNiosomes is determined by complete vesicle disruptionusing 50% n-propanol or 0.1% Triton X-100 and analyzingthe resultant solution by appropriate assay method forthe drug[34].

Entrapment efficiency = (Amount entrapped / totalamount) x 100

(vi) *In Vitro* Release Study

A method of *in vitro* release rate study has been reportedwith the help of dialysis tubing[27]. A dialysis sac is washedand soaked in distilled water. The vesicle suspension ispipetted into a bag made up of the tubing and sealed. Thebag containing the vesicles is then placed in 200 ml buffersolution in a 250 ml beaker with constant shaking at 25°Cor 37°C. At various time intervals, the buffer is analyzedfor the drug content by an appropriate assay method. Inanother method, isoniazid-encapsulated niosomes areseparated by gel filtration on Sephadex G-50 powder keptin double distilled water for 48 h for swelling[35]. At first, 1ml of prepared niosome suspension is placed on the topof the column and elution is carried out using normalsaline. Niosomes encapsulated isoniazid elutes out first asa slightly dense, white opalescent suspension followed byfree drug. Separated niosomes are filled in a dialysis tubeto which a sigma dialysis sac is attached to one end. Thedialysis tube is suspended in phosphate buffer of pH (7.4),stirred with a magnetic stirrer, and samples arewithdrawn at specific time intervals and analyzed usinghigh-performance liquid chromatography (HPLC) method.

(vii) *In Vivo* Release Study

Albino rats are used for this study. These rats aresubdivided with groups. Niosomal suspension used for *invivo* study is injected intravenously (through tail vein)using appropriate disposal syringe.

9. FACTORS AFFECTING PHYSICO-CHEMICAL PROPERTIES OF NIOSOMES

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

(i) Nature of Surfactants

A surfactant used for preparation of niosomes must havea hydrophilic head and hydrophobic tail. The hydrophobictail may consist of one or two alkyl or perfluoroalkylgroups or in some cases a single steroidal group[24]. Theether type surfactants with single chain alkyl ashydrophobic tail is more toxic than corresponding dialkylether chain[36].The ester type surfactants are chemicallyless stable than ether type surfactants and the former isless toxic than the latter due to ester-linked surfactantdegraded by esterase's to triglycerides and fatty acid *invivo*[36]. The surfactants with alkyl chain length from C12-C18 are suitable for preparation of niosomes[37,38].Surfactants such as C16EO5 (poly-oxyethylene cetylether) or C18EO5 (polyoxyethylene steryl ether) are usedfor preparation of polyhedral vesicles[39]. Span seriessurfactants having HLB number of between 4 and 8 canform vesicles[27].

Table 1: showing different types of non-ionic surfactants[27]

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

(ii) Structure of Surfactants

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

CPP (Critical Packing Parameters) = v/lc ×a0

Where v = hydrophobic group volume, lc = the critical hydrophobic group length,
a0= 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 of inverted micelles.

(iii) Amount and type of surfactant

The mean size of niosomes increases proportionally withincrease 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[27]. 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)[40]. Phase transition temperature (TC) of surfactant also effects entrapment efficiency i.e. Span 60 having higher TC, provides better entrapment.

(iv) Membrane Composition

The stable niosomes can be prepared with addition ofdifferent additives along with surfactants and drugs. Niosomes formed have a number of morphologies andtheir permeability and stability properties can be alteredby manipulating membrane characteristics by differentadditives. In case of polyhedral niosomes formed fromC16G2, the shape of these polyhedral niosome remainsunaffected by adding low amount of solulan C24(cholesteryl poly-24-oxyethylene ether), which prevents aggregation due to development of steric hindrance[41].The mean size of niosomes is influenced by membranecomposition 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 byC16G2: cholesterol: solulan C24 in ratio (49:49:2)(6.6±0.2mm). Addition of cholesterol molecule toniosomal system provides rigidity to the membrane andreduces the leakage of drug from niosome[13].Inclusion of cholesterol in niosomes increases

itshydrodynamic 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 liquidordered phase[30].An increase in cholesterol content of the bilayers resultedin a decrease in the release rate of encapsulated materialand therefore an increase of the rigidity of the bilayersobtained[30,42]. Presence of charge tends to increase theinterlamellar distance between successive bilayers inmultilamellar vesicle structure and leads to greateroverall entrapped volume.

(v) Nature of Encapsulated Drug
The physico-chemical properties of encapsulated druginfluence charge and rigidity of the niosome bilayer. Thedrug interacts with surfactant head groups and developsthe charge that creates mutual repulsion betweensurfactant bilayers and hence increases vesicle size[43]. Theaggregation of vesicles is prevented due to the chargedevelopment on bilayer. In polyoxyethylene glycol (PEG)coated vesicles, some drug is entrapped in the long PEGchains, thus reducing the tendency to increase the size[29].The hydrophilic lipophilic balance of the drug affectsdegree of entrapment.

Table 2: showing the effect of nature of drug on the formation of niosomes[29]

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
Macromolecules	Decreased	Increased	-

(vi) Temperature of Hydration
Hydration temperature influences the shape and size ofthe niosome. For ideal condition it should be above thegel to liquid phase transition temperature of system.Temperature change of niosomal system affects assemblyof surfactants into vesicles and also induces vesicle shapetransformation[32,41]. Arunothayanun *et al.* reported that apolyhedral vesicle formed by C16G2: solulan C24 (91:9) at25°C which on heating transformed into spherical vesicleat 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 contrast vesicle formed by C16G2: cholesterol: solulan C24 (49:49:2) shows no shape transformation on heating or cooling[41,44]. Along with the above mentioned factors, volume of hydration medium and time of hydration of niosomes are also critical factors. Improper selection of these factors may result in formation of fragile niosomes or creation of drug leakage problems.

(vii) Method of Preparation
Hand shaking method forms vesicles with greaterdiameter (0.35-13 nm) compared to the ether injection method (50-1000 nm)[20]. Small sized niosomes can be produced by Reverse Phase Evaporation method[22,45]. Micro fluidization method gives greater uniformity and small size vesicles[20]. Niosomes obtained by Trans membrane pH gradient (inside acidic) drug uptake process showed greater entrapment efficiency and better retention of drug.

(viii) Resistance to Osmotic Stress
Addition of a hypertonic salt solution to a suspension ofniosomes brings about reduction in diameter. Inhypotonic salt solution, there is initial slow release withslight swelling of vesicles probably due to inhibition ofeluting fluid from vesicles, followed by faster release,which may be due to mechanical loosening of vesiclesstructure under osmotic stress[2,46].

10. THERAPEUTIC APPLICATIONS OF NIOSOMES
Niosomal drug delivery is potentially applicable to manypharmacological agents for their action against variousdiseases. Some of their therapeutic applications arediscussed below:-

Ophthalmic drug delivery
It is difficult to achieve excellent bioavailability of drug from ocular dosage form like ophthalmic solution, suspension and ointment due to tear production, impermeability of corneal epithelium, non-productive absorption and transient residence time. But to achieve good bioavailability of drug niosomal vesicular systems have been proposed.

ACETAZOLAMIDE
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).

BRIMONIDINE TARTRATE
Prabhu et al[47]formulated and evaluated Brimonidine tartrate loaded niosomes for *in vitro* and *in vivo* intra ocular pressure lowering activity. *In vivo* intra ocular pressure lowering activity of the selected niosomal preparations were conducted on male albino rabbits.

NALTREXONE
Nanosized niosomal vesicles encapsulating naltrexone developed and optimized by Abdelkader et al[48]were found to possess better ocular tolerability and less ocular irritation.

TIMOLOL MALEATE
Vyas et al. (1998)[49] reported that there was about2.48 times increase in the ocular bioavailability oftimolol maleate (a water-soluble drug) encapsulatedin niosomes as compared to timolol maleate solution.

OFLOXACIN
Gupta et al[50] concluded that, the niosomal systems represent a system that is capable enough in delivering ofloxacin in a controlled manner efficiently, with improved corneal penetration and bioavailability.

Targeting of Bioactive Agents
(a) To reticulo-endothelial system (RES)
The cells of RES preferentially take up the vesicles. Theuptake of niosomes by the cells is also by circulatingserum factors known as opsonins, which mark them forclearance. Such localized drug accumulation has,however, been exploited in treatment of animal tumoursknown to metastasize to the liver and spleen and inparasitic infestation of liver[2].
(b) To organs other than RES
It has been suggested that carrier system can be directedto specific sites in the body by use of antibodies.Immunoglobulins seem to bind quite readily to the lipidsurface, thus offering a convenient means for targeting ofdrug carrier[44]. Many cells possess the intrinsic ability torecognize and bind particular carbohydrate determinantsand this can be exploited to direct carriers system toparticular cells.

Anti-tumour agents[51]
DAUNORUBICIN HCl[34]
Niosomal daunorubicin hydrochloride exhibited an enhanced anti-tumor efficacy when compared to free drug. The niosomal formulation was able to destroy the Dalton'sascitic lymphoma cells in the peritoneum within the third day of treatment, while free drug took around six days and the process was incomplete. The hematological studies also prove that the niosomal formulation was superior to free drug treatment. An enhanced mean survival time was achieved by the niosomal formulation that finally substantiates the overall efficacy of the niosomal formulation.

DOXORUBICIN
Rogerson et al[8]., studied distribution of niosomal doxorubicin prepared from C16 monoalkyl glycerol ether with or without cholesterol. Niosomal formulation exhibited an increased level of doxorubicin in tumor cells, serum and lungs, but not in liver and spleen. Doxorubicinloaded cholesterol-free niosomes decreased the rate of proliferation of tumor and increased life span of tumorbearing mice. The cardio toxicity effect of doxorubicin was reduced by niosomal formulation. Niosomal formulation changes the general metabolic pathway of doxorubicin.

METHOTREXATE
Azmin et al[32]., quoted in their research article that niosomal formulation of methotrexate exhibits higher AUC as compared to methotrexate solution, administered either intravenously or orally. Tumoricidal activity of niosomally-formulated methotrexate is higher as compared to plain drug solution.

BLEOMYCIN
Niosomal formulation ofbleomycin containing 47.5% cholesterol exhibited higher level drug in the liver, spleen and tumour as compared to plain drug solution in tumor bearing mice. There was no significant difference in drug concentration with niosomal formulation in lung as compared to plain drug solution. Also, there was less accumulation of drug in gut and kidney in case of niosomal formulation.

VINCRISTINE
Niosomal formulation of vincristine exhibited higher tumoricidal efficacy as compared to plain drug formulation (Parthasarathi G et al., 1994)[45]. Also, niosomal formulation of carboplatin exhibited higher tumoricidal efficacy in S-180 lung carcinoma-bearing mice as compared to plain drug solution and also less bone marrow toxic effect.

Leishmaniasis[19]
Sodium stibogluconate is a drug of choice for treatment of visceral leishmaniasis which is a protozoan infection ofreticulo-endothelial system. Niosomal formulation of sodium stibo-gluconate exhibited higher levels of antimony as compared to free drug solution in liver. Niosomal formulation of rifampicin exhibits better antitubercular activity as compared to plain drug.

Delivery of Peptide Drugs
Yoshida *et al* investigated oral delivery of 9-desglycinamide, 8-arginine vasopressin entrapped inniosomes in an *in-vitro* intestinal loop model andreported that stability of peptide increased significantly[42].

Anti-inflammatory agents
Niosomal formulation of diclofenac sodium with 70% cholesterol exhibited greater anti-inflammation activity as compared to free drug. Niosomal formulation of nimesulide and flurbiprofen also exhibited greater anti-inflammation activity as compared to free drug[22].

Transdermal drug delivery
Administration of drugs by the transdermal route has advantages such as avoiding the first pass effect, but it has one important drawback, the slow penetration rate of drugs through the skin. Various approaches have been made to overcome slow penetration rate, one such approach was niosomal formulation. Alsarra et al,[52] studied transdermal delivery of pro-niosomal formulation of ketorolac prepared from span 60 and it exhibited a higher ketorolac flux across the skin than those proniosome prepared from tween20. It has also been identified in literature that the bioavailability and therapeutic efficacy of drug like diclofenac, flurbiprofen and nimesulide are increased with niosomal formulation .

Immunological Application of Niosomes
Niosomes have been used for studying the nature of theimmune response provoked by antigens. Brewer andAlexander have reported niosomes as potent adjuvant interms of immunological selectivity, low toxicity andstability.

Diagnostic imaging with niosomes
Niosomal system can 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.

Other Applications
(a) Sustained Release
Sustained release action of niosomes can be applied todrugs with low therapeutic index and low water solubilitysince those could be maintained in the circulation vianiosomal encapsulation.
(b) Localized Drug Action
Drug delivery through niosomes is one of the approachesto achieve localized drug action, since their size and lowpenetrability through epithelium and connective tissuekeeps the drug localized at the site of administration.Localized drug action results in enhancement of efficacyof potency of the drug and at the same time reduces itssystemic toxic effects e.g. Antimonials encapsulatedwithin niosomes are taken up by mononuclear cellsresulting in localization of drug, increase in potency andhence decrease both in dose and toxicity.

Table 3: Showing delivery of drugs via Niosomes with their reported preclinical and clinical studies[53]

Drug	Route of delivery	Preclinical and clinical study	Inference
Methotrexate	Oral	In vivo absorption study	Enhanced absorption
Flurbiprofen and Piroxicam	Oral & transdermal	Bioavailability & in vivo anti-inflammatory activity	Enhanced bioavailability & effective anti-inflammatory activity
Erythromycin	Topical	In vivo CLSM	Enhanced penetration
Sumatriptine Succinate	Nasal	In vitro release & ex-vivo study	Enhanced nasal absorption & prolonged release.
Insulin	Vaginal	In vivo Hypoglycaemic activity	Insulin became active and therapeutically effective for vaginal delivery,
Propylthiouracil	Topical	In vitro drug release	Controlled drug delivery from Niosomes
Clobetasol Propionate	Topical	In vivo pharmacodynamic study (anti-inflammatory activity).	Enhancement in the % reduction in paw oedema exhibited by niosomal gel.
Lornoxicam	Transdermal	In vitro permeation & in vivo inflammatory activity.	Enhanced permeation and better anti-inflammatory activity as compared to solution of drug.
Silymarin	Hepatic	In vivo hepatoprotective activity & histopathological study.	Improved hepatoprotective efficiency & was found to be safe.

11. CONCLUSION

There is lot of scope to encapsulate toxic anti-cancerdrugs, anti-infective drugs, anti-AIDS drugs, anti-inflammatory drugs, anti-viral drugs, etc. in niosomes andto use them as promising drug carriers to achieve betterbioavailability and targeting properties and for reducingthe toxicity and side effects of the drugs. The ionic drugcarriers are relatively toxic and unsuitable whereasniosomal carriers are safer. Also handling and storageof niosomes require no special conditions. Vesicular drugcarriers like niosomes can be transported bymacrophages which are known to infiltrate tumour cells.It may be possible to take advantage of these activatedmacrophage system in delivering the anti-tumour agentswithin vesicles more quantitatively to tumour sites. So faronly animal experimentation of this targeted drugdelivery system is reported but further clinicalinvestigations in human volunteers, pharmacological andtoxicological investigations in animals and humanvolunteers may help to exploit niosomes as prosperousdrug carriers for targeting drugs more efficiently, fortreating cancer, infection and AIDS etc.

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