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Niosomes in Targeted Drug Delivery – A Review

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ABSTRACT

Over the past several years, treatment of infectious diseases and immunization has undergone a paradigm shift. Stemming from the nanobiotechnology research, not only a large number of disease-specific biologicals have been developed, but also enormous efforts have been made to effectively deliver these biologicals. Non-ionic surfactant vesicles (or niosomes) are now widely studied as alternates to liposomes. 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 and liposomes are equiactive In drug delivery potential and both increase drug efficacy as compared with that of free Drug. Niosomes are preferred over liposomes because the former exhibit high chemical Stability and economy. Niosomes are self assembled vesicles composed primarily of synthetic surfactants and cholesterol. They are analogous in structure to the more widely studied liposomes formed from biologically derived phospholipids. Niosomes represent an emerging class of novel vesicular systems. Niosome formation requires the presence of a particular class of amphiphile and aqueous solvent. In recent years a comprehensive research carried over niosome as a drug carrier. Various drugs are enlisted and tried in niosome surfactant vesicles. Niosome appears to be a Well preferred drug delivery system over liposome as niosome being stable and economic. Also niosomes have great drug delivery potential for targeted delivery of anti-cancer, Anti-infective agents. Drug delivery potential of niosome can enhance by using novel Concepts like proniosomes, discomes and aspasome. Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant.

KEYWORDS

Niosomes, Liposomes, Non-Ionic Surfactants, Nanocarriers, Encapsulation, Proniosomes.

INTRODUCTION

At present 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. 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. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include immune globulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes etc. 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.

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Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. The niosomes are very small, and microscopic in size. Their size lies in the nanometric scale. Although structurally similar to liposomes, they offer several advantages over them. Niosomes have recently been shown to greatly increase transdermal drug delivery and also can be used in targeted drug delivery, and thus increased study in these structures can provide new methods for drug delivery.[1]

SALIENT FEATURES OF NIOSOMES

1. Niosomes can entrap solutes in a manner analogous to liposomes.
2. Niosomes are osmotically active and stable.
3. Niosomes possess an infra structure consisting of hydrophobic and hydrophilic mostly together and so also accommodate the drug molecules with a wide range of solubility.
4. Niosomes exhibits flexibility in their structural characteristics (composition, fluidity and size) and can be designed according to the desired situation.
5. Niosomes can improve the performance of the drug molecules.
6. Better availability to the particular site, just by protecting the drug from biological environment.
7. Niosomes surfactants are biodegradable, biocompatible and non-immunogenic.

STRUCTURE OF NIOSOMES

Niosomes are lamellar structures that are microscopic in size. They constitute of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media2. The surfactant molecules tend to orient themselves 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. The figure in this article on Niosomes gives a better idea of the lamellar structures, which are formed on the admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. Structurally, noisomes are similar to liposomes, in that they are also made up of a bilayer. The Structure of Niosomes is shown in Fig. 1 below.

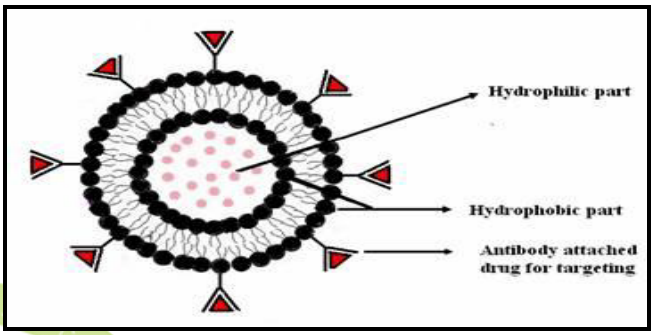

Fig 1: Structure of Niosomes

However, the bilayer in the case of niosomes is made up of non-ionic surface active agents rather than phospholipids as seen in the case of liposomes[3]. Most surface active agents when immersed in water yield micellar structures, however some surfactants can yield bilayer vesicles which are niosomes. Niosomes may be unilamellar or multilamellar depending on the method used to prepare them. The niosome is made of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicle, while the hydrophobic chains face each other within the bilayer. The schematic representation of drug loaded noisome is shown in Fig. 2 below.

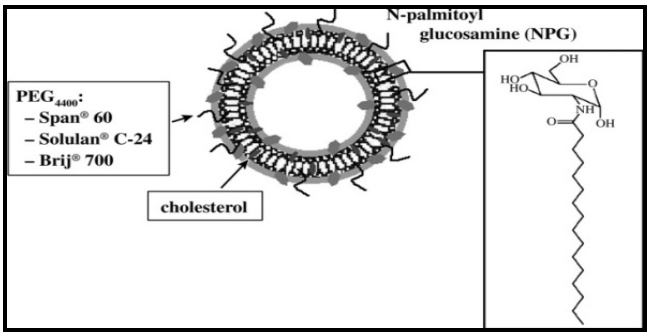

Fig 2: Schematic Representation of Drug Loaded Noisome

ADVANTAGES OF NIOSOMES

A. The vesicle suspension is water- based vehicle. This offers high patient compliance in comparison with oily dosage forms.

B. They possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities4.

C. 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.

D. The vesicles may act as a depot, releasing the drug in a controlled manner.

E. They can reduce drug toxicity because of their non-ionic nature.

OTHER ADVANTAGES OF NIOSOMES INCLUDE:

A. They are osmotically active and stable, as well as they increase the stability of entrapped drug.

B. Handling and storage of surfactants requires no special conditions.

C. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs[5].

D. They can be made to reach the site of action by oral, parenteral as well as topical routes.

E. The surfactants are biodegradable, biocompatible and non-immunogenic.

F. They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.

G. Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-aqueous phase.

RATIONALE FOR SITE SPECIFIC DRUG DELIVERY

1) To reach previously inaccessible domains e.g. intracellular site, bacteria, viruses, parasites etc[6].

2) Exclusive drug delivery to the specific cells or diseased site in the body.

3) Reduction in the drug dose and side effects.

4) To control the rate and frequency of drug delivery at the pharmacological receptor.

5) To protect the drug and the body from one another until it reaches at the desired site of action[8].

TYPES OF NIOSOMES

The niosomes are classified as a function of the number of bilayer (e.g. MLV, SUV) or as a function of size. (e.g. LUV, SUV) or as a function of the method of preparation (e.g. REV, DRV)[9]. The various types of niosomes are described below:

i) Multi lamellar vesicles (MLV),

ii) Large unilamellar vesicles (LUV),

iii) Small unilamellar vesicles (SUV).

1. **MULTILAMELLAR VESICLES (MLV):** It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 μm diameter. Multilamellar vesicles are the most widely used niosomes. It is simple to make and are mechanically stable upon storage for long periods. These vesicles are highly suited as drug carrier for lipophilic compounds.

2. **LARGE UNILAMELLAR VESICLES (LUV):** Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids.

3. **SMALL UNILAMELLAR VESICLES (SUV):** These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion

method or, homogenization method. The approximate sizes of small unilamellar vesicles are 0.025-0.05 µcm diameter. They are thermodynamically unstable and are susceptible to aggregation and fusion. Their entrapped volume is small and percentage entrapment of aqueous solute is correspondingly low.

Table 1: Patents in the field of noisome delivery

Sr. No	Title	Patent No.
1	Niosome-hydrogel drug delivery system	US Patent application 20100068264
2	Niosome-hydrogel drug delivery	European Patent application EP2012755
3	Niosome having metal porphyrin complex embedded therein, process for producing the same and drug with the use thereof	US Patent 20080269184
4	Cosmetic and pharmaceutical compositions containing niosomes and a water-soluble polyamide, and a process for preparing these composition	US Patent 4830854
5	Immunotargeting of non-ionic surfactant vesicles	US Patent 20070172520
6	Non-ionic surfactant emulsion vehicles and their use for deposition of drug into and across skin	US Patent 5720948

FACTORS GOVERNING NIOSOME FORMATION

I. Non-ionic surfactant structure: Theoretically niosome formation requires the presence of a particular class of amphiphile and aqueous solvent. In certain cases cholesterol is required in the formulation and vesicle aggregation for example may be prevented by the inclusion of molecules that stabilize the system against the formation of aggregates by repulsive steric or electrostatic effects. An example of steric stabilisation is the inclusion of Solulan C24 (a cholesteryl poly-24-oxyethylene ether) in doxorubicin (DOX) sorbitan monostearate (Span 60) niosome formulations**.** An example of electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes[11].

II. Surfactant and lipid level: The level of surfactant/lipid used to make niosomal dispersions is generally 10-30 mM (1- 2.5% w/w). Altering the surfactant: water ratio during the hydration step may affect the system's microstructure and hence the system's properties. However increasing the surfactant/lipid level also increases the total amount of drug encapsulated, although highly viscous systems result, if the level of surfactant/lipid is too high.

III. Nature of the encapsulated Bioactive drug: Another factor often overlooked is the influence of an amphiphilic drug on vesicle formation, when encapsulation of the amphipathic drug DOX was attempted. A steric stabilizer Solulan C24 (poly- 24-oxyethylene cholesteryl ether) must be added to the formulation to ensure a homogenous formulation devoid of aggregates**.** DOX has been shown to alter the electrophoretic mobility of hexadecyl diglycerol ether (C16G2) niosomes in a pH dependent manner, an indication that the amphipathic drug is incorporated in the vesicle membrane[10].

A variety of drugs/active agents have been encapsulated in Niosomes shown in table 2.

Table 2: Various instrumentation required for preparation of niosomes

Sr. No.	Equipment
1.	UV-Visible Spectrophotometer
2.	Digital pH meter
3.	Electronic Balance
4.	Rotary vacuum evaporator
5.	Microscope
6.	Vacuum Pump
7.	Magnetic Stirrer with hot plate
8	Research Centrifuge
9.	Digital Vernier Caliper
10.	Transmission electron microscope
11.	Water Bath
12.	Diffusion Cell

IV. 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 can predicate geometry of vesicle to be formed. Critical packing parameters can be defined using following equation, $CPP = \frac{v}{lc \times \alpha c}$

CPP ≤ 0.5 micelles form

CPP – (0.5-1.0) spherical vesicles form

CPP ≥ 1.0 inverted micelles form

Where v = hydrophobic group volume, lc = the critical hydrophobic group length,, a0= the area of hydrophilic head group.

V. Temperature of hydration: Hydration temperature influences the shape and size of the noisome. The hydrating temperatures used to make niosomes should usually be above the gel to liquid phase transition temperature of the system[12, 13].

METHOD OF PREPARATION OF NIOSOMES

Niosomes widely differ in their properties depending on the method used for production and composition of bilayer. The method of preparation of niosome is based on liposome technology. The basic process of preparation is the same i.e. hydration by aqueous phase of the lipid phase which may be either a pure surfactant or a mixture of surfactant with

Table 3: Various agents encapsulated in niosomes and the corresponding results

Drug	Result
Estradiol	Enhanced in vitro skin permeation of pronisome formulations.
Iopromide	Targeting of lopromide entrapped in MLV to the Kidney.
Flurbi profen	Enhanced bio-availability and anti- inflammatory activity of niosome encapsulated formulations as compared to conventional ointment base.
Timolol maleate	Sustained activity on ocular administration
Cytarabine Hydrochloride	Niosomal encapsulation provides sustained release delivery.
Rifampicin	Prolonged drug release
Cisplatin	Significant antimetastatic activity
Cytosine arabinoside	Effective release in acid environment
Tretinoin	Span 20 and Tween 80, Span 60 and Tween 80 combination gives good entrapment
Daunorubicin Hydrochloride	Improved therapeutic efficacy
Colchicine	Sustain release & reduced toxic side effects
Insulin	Sustained release after oral dosage form Enhancing effect on vaginal delivery of insulin Improved stability against proteolytic enzyme
Finasteride	Enhance drug concentration by topical application
Hydroxycamphothecin	Enhanced stability and antitumor activity.
Acetazolamide	Prolonged effect and decrease in Intraocular pressure
Clotrimazole	Sustain and controlled release of clotrimazale for local vaginal therapy
Timolol maleate	Improved pharmacodynamics
Tetanous Toxoide	Mannosylated niosomes were found to be useful oral vaccine delivery carrier.
Propylthiouracil	Control the release of propyl thiouracil.

cholesterol. The bioactive material, which is to be entrapped, is dissolved in the aqueous phase/organic phase. The methods used for preparation of niosomes are listed as follows:

A. Ether Injection method: This method was reported in 1976 by Deamer and Bangham, in which a lipid solution in di-ethyl ether is slowly introduced into warm water typically the lipid mixture is injected into an queous solution of the material to be encapsulated (using syringe type infusion pump) at 55-65^{o}C and under reduced pressure. Vaporization of ether leads to the formation of single layered vesicles (SLVs) depending upon the conditions used, the diameter of vesicles varies. Baillie et al., used this method for entrapment of 5, 6 carboxy florescein whereas, Hunter et al., and Carter et al., used it for the entrapment of sodium stibogluconate (pentosam).

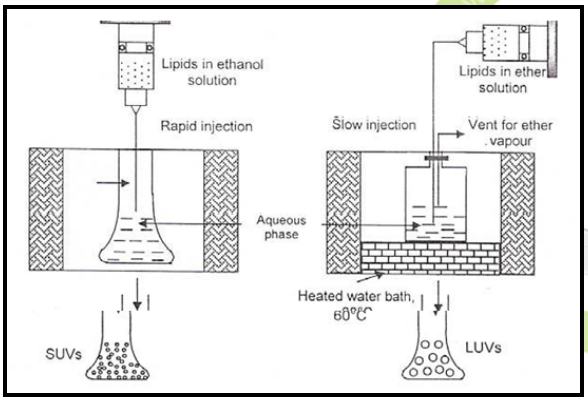

Fig 3: Ether injection method

B. Lipid Film Formation (Hand Shaking Method): Surfactant/cholesterol mixture was dissolved in di-ethyl ether in a round bottom flask and ether was removed at room temperature under reduced pressure, in a rotary evaporator. The dried surfactant film was hydrated with aqueous phase at 50 - 60°C with gentle agitation; this method produces multilamellar vesicles (ML V) with large diameter.Baillie et al reported Hand shaking method for the entrapment of 5, 6 carboxy fluorescein[14]. Chandraprakash et al entrapped methotrexate in niosomes prepared by Hand shaking method using lipophilic surfactants like span 40, span 60 and span 80, cholesterol and di-cetyl phosphate in ratio of 47.5: 47.5: 5. The tissue distribution of methotrexate was improved after entrapping with niosomes[15].

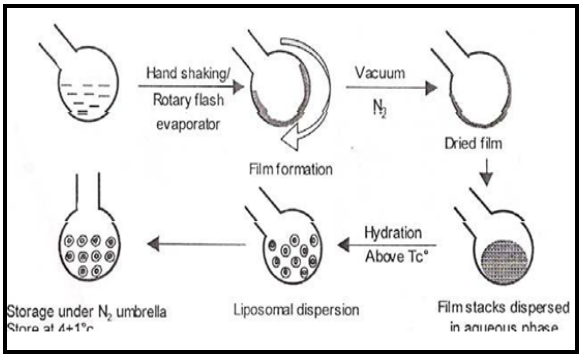

Fig 4: Hand Shaking Method of Niosomes Preparation

Rogerson et al prepared doxorubicin entrapped niosomes using pure surfactant or a mixture of surfactants and cholesterol[16]. Azmin et al modified this method for preparation of methotrexate entrapped niosomes[17].

C. Sonication Method: Aqueous phase was added to the surfactant/cholesterol mixture and the mixture was probe sonicated at 60° C for 3 minutes to produce niosomes.Baillie et al prepared 5,6 carboxy fluorescein in entrapped niosomes by sonication method[3].Carter et al prepared sonicated niosomes by sonication of multilamellar niosomes being prepared by Ether injection method[18]**.** Yoshida et al modified this method for entrapment of 9-desglycinamide 8-arginine vasopressin (DGA VP)[19]. Hofland et al prepared niosomes by sonication of transdermal delivery of estradiol by niosomes in vitro[20].

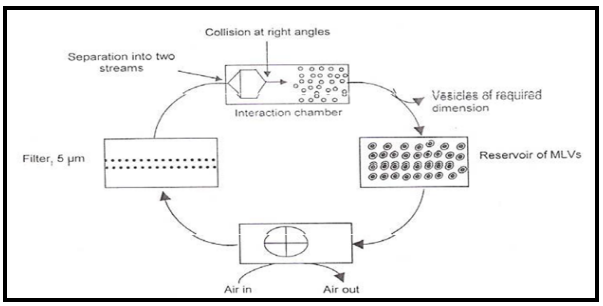

Fig 5: Microfludisation

D. **Microfludisation:** This is a recent technique to prepare small MLVS. A Microfludizer is used to pump the fluid at a very high pressure (10,000 psi) through a 5 pm screen. Thereafter; it is forced along defined micro channels, which direct two streams of fluid to collide together at right angles, thereby affecting a very efficient transfer of energy. The lipids can be introduced into the fluidizer. The fluid collected can be recycled through the pump until vesicles of spherical dimensions are obtained. This results in greater uniformity, small size and better reproducible niosomes[21].

E. **Reverse phase evaporation (REV):** The novel key in this method is the removal of solvent from an emulsion by evaporation. Water in oil emulsion is formed by bath sonication of a mixture of two phases, and then the emulsion is dried to a semi-solid gel in a rotary evaporator under reduced pressure. The next step is to bring about the collapse of certain portion of water droplets by vigorous mechanical shaking with a vortex mixture. In these circumstances, the lipid monolayer, which encloses the collapse vesicles, is contributed to adjacent intact vesicles to form the outer leaflet of the bilayer of large unilamellar niosomes. The vesicles formed are unilamellar and have a diameter of 0.5 μm. Recently a great deal of interest is being shown in formulation of proniosomes. Proniosomes are dry formulations of surfactantcoated carrier, which on rehydration and mild agitation give niosomes.

Proniosomes have the advantage of circumventing the problems of physical stability such as aggregation, fusion and leaking, chemical stability such as hydrolysis, providing the convenience of transportation, distribution, storage and dosing. Proniosomes are usually prepared by dissolving spray coated surfactant in a organic solvent on to inert carriers such as sorbitol and maltodextrin[22,23].

F. **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 polycarbonate membranes, solution and the resultant suspension extruded through which are placed in series for upto 8 passages. It is a good method for controlling niosome size[24].

G. **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 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[25].

H. **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[26].

I. **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 agitation.

T=Temperature.

Tm = mean phase transition temperature[27].

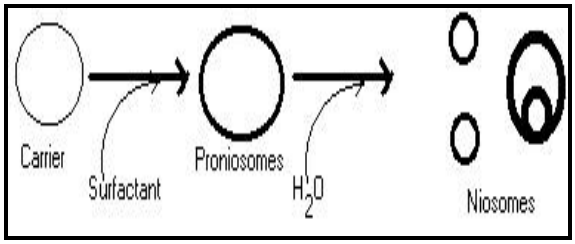

Fig 6: Proniosome Method

SEPARATION OF UNENTRAPPED DRUG

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

1) DIALYSIS[28]:

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

2) GEL FILTRATION[29]:

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.

3) CENTRIFUGATION[30]:

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.

CHARACTERIZATION OF NIOSOMES

1. Entrapment efficiency

After preparing niosomal dispersion, unentrapped drug is separated by dialysis[31], centrifugation[36,37], or gel filtration[35] as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analysing the resultant solution by appropriate assay method for the drug. Where,

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

2. Vesicle diameter

Niosomes diameter can be determined using light microscopy, photon correlation microscopy and freeze fracture electron microscopy. Freeze thawing[32] (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 cycle.

3. 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 method[34].

4. Vesicle charge

The vesicle surface charge can play an important role in the behavior of niosomes in vivo and in vivo. In general, charged niosomes are more stable against aggregation and fusion than uncharged vesicles. In order to obtain an estimate of the surface potential, the zeta potential of individual niosomes can be measured by microelectrophoresis. An alternative approach is the use of pH-sensitive fluorophores. More recently, dynamic light scattering have been used to measure the zeta potential of niosomes.

5. Bilayer Rigidity and Homogeneity

The biodistribution and biodegradation of niosomes are influenced by rigidity of the bilayer. In omogeneity can occur both within niosome structures themselves and between niosomes in dispersion and could be identified via. 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.

6. Niosomal drug loading and encapsulation efficiency

To determine drug loading and encapsulation efficiency, the niosomal aqueous suspension was ultracentrifuged, supernatant was removed and sediment was washed twice with distilled water in order to remove the adsorbed drug. The niosomal recovery was calculated as:

$$\text{Niosome recovery (\%)} = \frac{\text{Amount of niosomes recovered} \times 100}{\text{Amount of polymer + drug + excipient}}$$

The entrapment efficiency (EE) was then calculated using formula:

$$\text{Entrapment Efficiency (\%)} = ((\text{Amount of drug in niosomes} \times 100))/(\text{Amount of drug used})$$

The drug loading was calculated as:

$$\text{Drug loading (\%)} = \left(\frac{\text{Amount of drug in niosomes}}{(\text{Amount of niosomes recovered})}\right)$$

7. Niosomal drug release

Recently, FRET was used to monitor release of encapsulated matters in niosomes by using separate niosomal suspensions incorporating donor and acceptor. The simplest method to determine in vitro release kinetics of the loaded drug is by incubating a known quantity of drug loaded niosomes in a buffer of suitable pH at 37ƒC with continuous stirring, withdrawing samples periodically and analyzed the amount of drug by suitable analytical technique. Dialysis bags or dialysis membranes are commonly used to minimize interference[10].

MODIFIED NONIONIC SURFACTANTS:

Different types of modified nonionic surfactant vesicles, which are discussed below.

- Sterically Stabilized Niosomes
- Polymerized Nonionic Surfactant Vesicles
- Emulsified Niosomal Dispersion

➢ Sterically Stabilized Niosomes

Colloidal carriers are removed from circulation mainly by cells of mononuclear phagocytic system (MPS). Modifying the surface properties by coating the carrier with polymers is known to alter the rate of uptake by the MPS[33]. Chouhan and Lowrence synthesized a non-ionic surfactant polyoxyethylene 20 glycerol 1, 2 distearoyl ether bearing polyoyethylene glycol (PEG) as its hydrophilic chain and determined volume and diameter of niosomes prepared by different methods[38]. The presence of PEG, by increasing the steric stabilization of the particles, should reduce its uptake by cells of the MPS. Incorporation of cholesterol, polyoxyethylene ether (soluans) also provides sterical stability and modifies surface properties. Cablew reported sustained and higher plasma level of doxorubicin administered in solulan modified niosomes[32].

➢ Polymerized nonionic surfactant vesicles

Since vesicle system are more or less thermodynamically unstable, proximity and regular orientation of surface-active molecules at interface has been exploited to increase stability by controlled polymerization at vesicular bilayer made up of non-ionic surfactant bearing a polymerizable residue. Polymerizable surfactant used were:

(a) Diamethyl-n-hexadecyl [{(1-iso-cynoethyl) carbonyloxy} methyl] ammonium bromide.

(b) N, N (dihexadecanoyloxyethyl) maleyl amide.

(c) Dihexadecyl N, methyl N, maleyl ammonium bromide.

The vesicles formed from these surfactants were polymerized by radiation or radical initiation. Kippenberger observed that UV exposure brought closing of both surfaces while additions of radical initiator lead to selective “Zipping up” of outer surfaces only[39]. This allows for selective polymerization of surface. Polymerization restricts mobility of hydrocarbon core and improves the stability of niosomes, size of the vesicles on polymerization

remains unchanged but change in appearance depends upon location of polymerizable group. The combine advantage of polymer and membrane is that, they have stabilities and intriguing structural properties like polymers while retaining beneficial fluidity and organizational abilities of membrane. In terms of drug delivery they might serve as unique poly-disperse, timed release carriers.

- **Emulsified niosomal dispersion**

Yoshioka formulated a range of double emulsion (V/W/O emulsion) from niosomes made from spans(20,40,60,80) in the size range 600 nm to 3.4 um, dispersed in water droplet of around 5-25 um, themselves dispersed in oil (octane, hexadecane, isopropyl myristate)[5]. This system showed release of CF slower than vesicle suspension and W/O emulsion. On increasing hydrophobicity of surfactant used the release rate decreased until HLB 4.7 (span 60) and then increased. Also the nature of oil affected the release depending upon the partitioning behavior of solute. Faster release was observed at higher temperature but span 60 formulations were unaffected due to maintenance of gel phase. Thus, delivery rate of a drug can be regulated by appropriate choice of surfactant, oil and temperature of dialysis media. This system allows administration or application of vesicles in an external non-aqueous phase while maintaining normal vesicular structure in an aqueous phase and can be of potential use in drug delivery or a vaccine vesicle. Albert has patented a similar system for cosmetic application [41].

Table 4: Various agents encapsulated in niosomes and the routes of administration

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

APPLICATIONS OF NIOSOMES

The application of niosomal technology is widely varied and can be used to treat a number of diseases.

1. **Niosomes as Drug Carriers**

   Niosomes have also been used as carriers for iobitridol, a diagnostic agent used for Xray imaging. Topical niosomes may serve as solubilization matrix, as a local depot for sustained release of dermally active compounds, as penetration enhancers, or as rate-limiting membrane barrier for the modulation of systemic absorption of drugs[46.]

2. **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[42].

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[43]. Immunoglobulins seem to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier.Many cells possess the intrinsic ability to recognize and bind particular carbohydrate determinants[44] and this can be exploited to direct carriers system to particular cells.

3. **Anti-neoplastic Treatment**

Most antineoplastic drugs cause severe side effects. Niosomes can alter the metabolism; prolong circulation and half life of the drug, thus decreasing the side effects of the drugs. Niosomes, is decreased rate of proliferation of tumor and higher plasma levels accompanied by slower elimination[46.]

4. Leishmaniasis

Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells of the liver and spleen. Use of niosomes in tests conducted showed that it was possible to administer higher levels of the drug without the triggering of the side effects, and thus allowed greater efficacy in treatment[47.]

5. Delivery of Peptide Drugs

Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. In an invitro study conducted by oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide[48.]

6. Use in Studying Immune Response

Due to their immunological selectivity, low toxicity and greater stability; niosomes are being used to study the nature of the immune response provoked by antigens. Non-ionic surfactant vesicles have clearly demonstrated their ability to function as adjuvants following parenteral administration with a number of different antigens and peptides.

7. 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.

8. 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[48].

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[49,50].

c) Niosome formulation as a brain targeted delivery system for the vasoactive intestinal peptide (VIP)

Radiolabelled (I^{125}) VIP-loaded glucosebearing niosomes were injected intravenously to mice. Encapsulated VIP within glucosebearing niosomes exhibits higher VIP brain uptake as compared to control[51].

d) Niosomes as carriers 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 hemoglobin[52,53]

CONCLUSION

It is obvious that niosome appears to be a well preferred drug delivery system over liposome as niosome being stable and economic. Also niosomes have great drug delivery potential for targeted delivery of anti-cancer, anti-infective agents. Drug delivery potential of niosome can enhance by using novel concepts like proniosomes, discomes andaspasome.Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant. Thus these areas need further exploration and research so as to bring out commercially available niosomal preparation. 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 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 multienvironmental structure. Niosomes are thoughts to be better candidates drug delivery as compared to liposomes due to various factors like cost, stability etc. Various types of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parentral.

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