



NIOSOMES AS TARGETED DRUG DELIVERY SYSTEMS

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ABSTRACT

Niosomes are globular, submicroscopic vesicles obtained on hydration of synthetic nonionic surfactants with incorporation of cholesterol or other lipids. They may be unilamellar or multilamellar with size range of 100nm-2 μ . They are vesicular systems similar to liposomes that can be used as carriers of both hydrophilic and lipophilic drugs. Being non-ionic, it is less toxic and improves the therapeutic index of drug by restricting its action to target cells.

Keywords: Niosomes, Liposomes, Targeted delivery system.

INTRODUCTION

In 1909, Paul Ehrlich introduced the concept of targeted delivery and defined first order, second order and third order approach. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include antibodies, serum proteins, synthetic polymers, liposomes, microspheres, nanoparticles, resealed erythrocytes, niosomes etc¹.

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 media². These are called lamellar because surfactant micelles are arranged in lamellar fashion rather than spherical. Most surface active agents when immersed in water yield micellar structures, however some surfactants can yield bilayer vesicles which are niosomes.

Schematic representation of a drug targeting through its linkage to niosome via antibody is shown in figure 1.

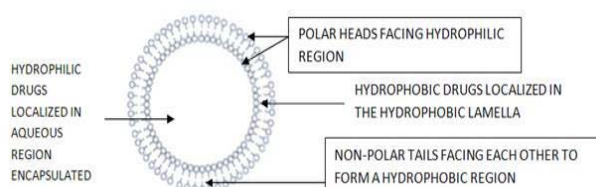


Figure 1: Niosome Structure

METHOD OF PREPARATION

A. Ether injection method

In this method, surfactant and cholesterol solution is made in a volatile solvent (eg. diethyl ether). The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of drug at 60°C. 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 nm³. This

method yields small sized vesicles, however it cannot be used for lipophilic and thermolabile drugs. Eg. Sodium stilboglucuronate, doxorubicin.

B. 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 niosomes⁴. This method can be used for heat sensitive drugs but forms larger sized vesicles. Eg. MTX, doxorubicin.

Protein and peptide drugs can be formulated by evaporating solvent using rotary vacuum evaporator (evaporation at low temperature)⁵. Along with this, fluorinated hydrocarbons (freons with low BP) can also be used instead of ether.

C. Sonication⁵

A typical method of production of the vesicles is by sonication of solution. 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. Probe diameter governs the vesicle size. Eg. 8-arginine, vasopressin, oestradiol.

D. Micro fluidization

This is a recent technique to prepare small multilamellar vesicles. A microfluidizer is used to pump the fluid at a very high pressure (10,000 psi) through a 5 μ m 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 fluidizer⁶. 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. It consists of expensive equipment but yet used commercially.

E. Multiple membrane extrusion method⁶

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 (pore size 1μ), which are placed in series for up to 8 passages. It is a good method for controlling niosome size.

Size of niosome can be reduced to nano range (140 nm) by extrusion of niosome through nucleopore filters of pore size 100 nm.

F. Reverse Phase Evaporation Technique (REV)

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 niosomes⁵. The vesicles formed are unilamellar and have a diameter of 0.5 μ m. Temperature change may vary with type of surfactant used.

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 causes the drug which is outside the vesicle to become non-ionic and can then cross the niosomal membrane, and once inside it is again ionized thus not allowing it to exit the vesicle). This mixture is later heated at 60°C for 10 minutes to give niosomes⁷. It Offers max. entrapment efficiency but can be used for basic drugs only.

H. The bubble method⁸

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

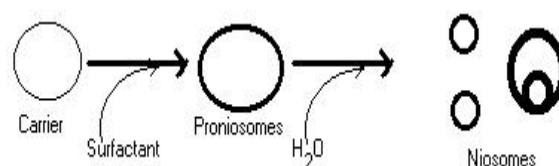
supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.

I. Formation of niosomes from proniosomes

Another method of producing niosomes is to coat a water-soluble carrier such as sorbitol with surfactant. The coating is done by preparing a solution of the surfactant with cholesterol in a volatile organic solvent, which is sprayed onto the powder of sorbitol kept in a rotary evaporator. 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"⁹. The niosomes are recognized by the addition of aqueous phase at $T > T_m$ and brief agitation.

T=Temperature.

T_m = mean phase transition temperature.



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 dosing¹⁰.

SEPARATION OF UNENTRAPPED DRUG

The removal of untrapped solute from the vesicles is important as it may cause undesirable side effects and may add charge to niosomes leading to physical instability. This can be accomplished by various techniques, which include:

1. Dialysis

The aqueous niosomal dispersion is dialyzed in dialysis tubing against phosphate buffer or normal saline or glucose solution⁸.

2. Gel Filtration

The untrapped drug is removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution with phosphate buffered saline or normal saline^{11, 12}.

3. 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 untrapped drug^{13, 14}.

CHARACTERIZATION OF NIOSOMES

a) Entrapment efficiency

After preparing niosomal dispersion, untrapped drug is separated by dialysis, centrifugation, or gel filtration 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.

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

b) Vesicle diameter

Niosomes, similar to liposomes, assume spherical shape and so their diameter can be determined using light microscopy, photon correlation microscopy, molecular sieve chromatography, ultracentrifugation. Liquid state products are characterized by TEM and freeze thaw microscopy while solid products are studied using SEM.

Freeze thawing¹⁵ (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.

c) Number of lamellae

It is determined by using NMR spectroscopy, small angle X-ray scattering and electron microscopy¹⁶.

d) Membrane rigidity¹⁷

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

e) Bilayer formation¹⁷

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

f) 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 method¹¹.

FACTORS AFFECTING VESICLES SIZE, ENTRAPMENT EFFICIENCY AND RELEASE CHARACTERISTICS

a) Drug

Molecular weight of drug affects EF. Higher the molecular weight, lower the EF. The physico-chemical properties of encapsulated drug influence charge and rigidity of the niosome bilayer. Entrapment of drug in niosomes increases vesicle size, probably by interaction of solute with surfactant head groups, increasing the charge and

mutual repulsion of the surfactant bilayers, thereby increasing vesicle size. The hydrophilic lipophilic balance of the drug affects degree of entrapment¹⁸.

b) Amount and type of surfactant

The bilayers of the vesicles are either in the so-called liquid state or in gel state, depending on the temperature, the type of lipid or surfactant and the presence of other components such as cholesterol. In the gel state, alkyl chains are present in a well-ordered structure, and in the liquid state, the structure of the bilayers is more disordered. The surfactants and lipids are characterized by the gel-liquid phase transition temperature (TC). Phase transition temperature (TC) of surfactant also effects entrapment efficiency i.e. Span 60 having higher TC, provides better entrapment²⁰.

The ether type surfactants with single chain alkyl as hydrophobic tail is more toxic than corresponding dialkylether 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*. The surfactants with alkyl chain length from C12-C18 are suitable for preparation of niosome. Span series surfactants having HLB number of between 4 and 8 can form vesicles¹⁹.

Critical packing parameters²¹ can be defined using following equation,

CPP (Critical Packing Parameters) = $v \cdot l / a$

Where v = hydrophilic group volume, l = the hydrophilic group length,,

a = the area of hydrophobic group.

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

If $CPP < \frac{1}{2}$ then formation of spherical micelles,

If $\frac{1}{2} < CPP < 1$ formation of bilayer micelles,

c) Cholesterol content and charge

Inclusion of cholesterol in niosomes increases its hydrodynamic diameter and entrapment efficiency. In general, the action of cholesterol is two folds; on one hand, cholesterol increases the chain order of liquid-state bilayers and on the other, cholesterol decreases the chain order of gel state bilayers. At a high cholesterol concentration, the gel state is transformed to a liquid-ordered phase¹⁴.

An increase in cholesterol content of the bilayers resulted in a decrease in the release rate of encapsulated material and reduction in EF and therefore an increase of the rigidity of the bilayers obtained²². Presence of charge tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle structure and leads to greater overall entrapped volume.



d) Methods of preparation

Methods of preparation of niosomes such as hand shaking, ether injection and sonication yields different sized vesicles. Hand shaking method forms vesicles with greater diameter compared to the ether injection method (50-1000nm)⁶.

Small sized niosomes can be produced by Reverse Phase Evaporation (REV) method. Microfluidization method gives greater uniformity and small size vesicles. Niosomes by transmembrane pH gradient (inside acidic) drug uptake process showed greater entrapment efficiency and better retention of drug²³.

e) 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 stress²⁴.

f) 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^{25, 26}.

FORMULATION ADDITIVES

Surfactants: Non-ionic surfactants of low HLB value are suitable candidates²⁷. They are classified as :

- Higher fatty acids and LMW amino acids.
- Alkyl amides: galactosides and glucosides.
- Alkyl esters: spans (sorbitan esters)
- Alkyl ethers: monoalkyl glycerol ethers (surfactant 1), dialkyl glycerol ether (surfactant 2), ester linked chains (surfactant 3).

Cholesterol: It provides rigidity, fluidity and permeability to cell membrane which is not provided by surfactant alone (brittle otherwise). It stabilizes niosomes against destabilizing effects of plasma and serum proteins and decreases the permeability of vesicles to entrapped solute preventing leakage^{28, 29}.

Charged solutes³⁰: These are added to overcome aggregation of vesicles by creating electrostatic repulsion. Zeta potential of 30mV is desirable. Charge of niosomes can also alter their in vivo distribution pattern.

- +ve charge: stearylamine, cetyl pyridinium chloride.
- ve charge: dicetyl phosphate, phosphatidic acid.

ADVANTAGES OF NIOSOMES

The application of vesicular systems in cosmetics and for therapeutic purpose³¹ may offer several advantages:

- The vesicle suspension is water-based vehicle. This offers high patient compliance in comparison with oily dosage forms.
- 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 solubilities.
- 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.
- The vesicles may act as a depot, releasing the drug in a controlled manner.
- They are osmotically active and stable, as well as 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 and delayed clearance from body.
- They can be made to reach the site of action by oral, parenteral as well as topical routes³².
- The surfactants are biodegradable, biocompatible and non-immunogenic.
- 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.
- 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.

DISADVANTAGES

- They may fuse with one another on standing.
- They are not suitable for oral administration as they can't survive action of bile salts and phospholipase.
- Hydrolysis of vesicles and leakage of drug may be a limitation.

COMPARISON OF NIOSOMES AND LIPOSOMES

a) 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.

b) Differences in characteristics exist between liposomes and niosomes, especially since niosomes are prepared from uncharged single-chain surfactant and cholesterol whereas liposomes are prepared from double-chain phospholipids (neutral or charged)⁵.

c) Niosomes behave *in-vivo* like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability³². Encapsulation of various anti neoplastic agents in these carrier vesicles has been shown to decrease drug induced toxic side effects and increased efficacy³³. Such systems alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug^{34, 35}. They can be expected to target the drug to its desired site of action and/or to control its release³⁶.

d) As with liposomes, the properties of niosomes depends both on the composition of the bilayer and on method of their production³⁷. It was observed by Baillie *et al* that the intercalation of cholesterol in the bilayers decreases the entrapment volume during formulation and thus entrapment efficiency. As the concentration of cholesterol increases, entrapment efficiency decreases.

e) The entrapment efficiency increases with increase in the concentration and lipophilicity of surfactant. Chandraprakash *et al*³⁸ made Methotrexate loaded non-ionic surfactant vesicles using lipophilic surfactants like Span 40, Span 60 and Span 80 and found that Span 60 (HLB = 4.7) gave highest percent entrapment while Span 85 (HLB = 9.8) gave least entrapment. They also observed that as HLB value of surfactant decreased, the mean size was reduced.

APPLICATIONS

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

1. Targeting of bioactive agents

a) To reticulo-Endothelial System (RES)

The cells of RES preferentially take up the vesicles. The uptake of niosomes by the cells is also by circulating serum factors known as opsonins², 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.

b) To organs other than RES

It has been suggested that carrier system (antibodies) are attached to direct niosomes to specific sites in the body. Immunoglobulins³⁹ 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 and this can be exploited to direct carriers system to particular cells⁴⁰.

2. Anti-neoplastic therapy

Doxorubicin, the anthracyclic antibiotic with broad spectrum anti tumor activity, shows a dose dependant irreversible cardio toxic effect. Niosomal delivery of this drug to mice bearing S-180 tumor increased their life span and decreased the rate of proliferation of sarcoma⁴¹. 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 elimination⁴².

Niosomes have great potential in drug nanoformulations for melanoma therapy owing to their advantages, such as relatively higher chemical stability, improved purity and relatively lower cost in comparison with liposomes.

3. 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 drug⁴³.

Baillie *et al* reported increased sodium stibogluconate efficacy of niosomal formulation and that the effect of two doses given on successive days was additive.

4. 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 Yoshida *et al*, oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide:

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.

5. 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 stability⁴⁴.



6. 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^{45, 46}.

7. 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 niosomes⁴⁷. Adsorption and fusion of niosomes via skin is due to high thermodynamic gradient at the interface acting as driving force for permeation of LPL drugs. Using confocal microscopy, it was seen that non-ionic vesicles could be formulated to target pilosebaceous glands.

Topical use of niosome entrapped antibiotics to treat acne is done. Recently, transdermal vaccines utilizing niosomal technology is also being researched. A study conducted by P. N. Gupta *et al* has shown that niosomes (along with liposomes and transfersomes) can be utilized for topical immunization using tetanus toxoid. However, the current technology in niosomes allows only a weak immune response, and thus more research needs to be done in this field. Niosomes containing DNA encoding Hepatitis B surface Antigen (HBsAg) have been prepared as DNA carriers for effective topical immunization.

Eg. Nimesulide, levonorgesterol, MTX, ketorolac, captopril, celecoxib etc.

8. Ophthalmics⁴⁸: 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).

9. Niosome formulation as a brain targeted delivery system for the vasoactive intestinal peptide (VIP): Radiolabelled (125) VIP-loaded glucose-bearing niosomes were injected intravenously to mice. Encapsulated VIP within glucose-bearing niosomes exhibits higher VIP brain uptake as compared to control⁴⁹.

10. Niosomal system can be used as diagnostic agents. Conjugated niosomal formulation of gadobenate dimeglumine with [N-Palmitoyl-Glucosamine (NPG)], PEG 4400, and both PEG and NPG exhibit significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging⁵⁰.

10. Other Applications

a. Azmin *et al* suggested the role of liver as a depot for methotrexate after niosomes are taken up by the liver cells. 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. 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.

c. 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 niosomes are taken up by mononuclear cells resulting in localization of drug, increase in potency and hence decrease both in dose and toxicity .

d. The evolution of niosomal drug delivery technology is still at an infancy stage, but this type of drug delivery system has shown promise in cancer chemotherapy and anti-leishmanial therapy.

MARKETED PRODUCTS

Lancome has come out with a variety of anti-ageing products which are based on niosome formulations. Foundation and skin whitening creams are also developed. L'Oreal is also conducting research on anti-ageing cosmetic products. 1st niosomal formulation was dev and patented by L'Oreal in 1975.

Aspasomes (Ascorbyl palmitate vesicles)⁵¹

Rambhau *et al.*, reported that ascorbyl palmitate in combination with cholesterol and negatively charged lipid diacetyl phosphate forms vesicles called aspasome. The film hydration method was used for preparation of aspasomes, followed by sonication. The aqueous solution of azidothymidine was entrapped in aqueous region of bilayers. The cholesterol content in aspasomes exhibits very less effect for vesicle size and percent entrapment that affect release rate of azidothymidine. Aspasome with 45% of cholesterol shows maximum retardation in release rate than other composition. Aspasomes have inherent antioxidant properties that have potential applications toward disorder caused by reactive oxygen species. Transdermal permeation of aspasomal drug is much higher than aqueous dispersion and aqueous solution of drug.

Vesicles in water and oil system (V/W/O)

Yoshioka *et al.*, reported that the emulsification of an aqueous niosomes into an oil phase form vesicle in water in oil emulsion (V/W/O). On addition of niosomes suspension formed from mixture of sorbitol mono stearate, cholesterol and solulan C24 to oil phase at 60°C⁵². There is formation of vesicle in water in oil emulsion but cooling to room temperature forms vesicle in water in oil gel (V/W/O)⁵³. The (V/W/O gel) can entrap protein and also protect it from enzymatic degradation after oral administration and controlled release. The release of entrap material is lowest in case of V/W/O gel as compared to W/O gel and niosomal suspension.



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